

		F468의 카르복실기 다음을 전달한다.	HLWGYLFPDCYNHHYKPGYNGSCFNVEIKRND DLSWLWNESTALYPSIYLNQQSPVAATLYVRNRVR EAIKRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDEL VYTFGETVALGASGMWGTLSITRTKESCAIKEYM <u>DTTLN</u> PYIINVTLAAKMCSQVLCQEQGVCIRKNW NSSDYLHLNPDNFAIQLEKGGKFTVRGKPTLEDLEQ FSEKFCSCYSTLSCKEKADVKTDAVDVCIADGVCI DAF
HM16	74	M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 11개 아미노산을 치환하고, P471의 카르복실기 다음을 절단한다.	LNFRAPPVIPNVFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTFYVDRLGYYPIDSITGV TVNGGIPQKISLQDHLDAKAKDITFYMPVDNLGMA VIDWEEWRPTWARNWKPKDVYKNRSIELVQQQN VQLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPN HLWGYLFPDCYNHHYKPGYNGSCFNVEIKRND DLSWLWNESTALYPSIYLNQQSPVAATLYVRNRVR EAIKRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDEL VYTFGETVALGASGMWGTLSITRTKESCAIKEYM <u>DTTLN</u> PYIINVTLAAKMCSQVLCQEQGVCIRKNW NSSDYLHLNPDNFAIQLEKGGKFTVRGKPTLEDLEQ FSEKFCSCYSTLSCKEKADVKTDAVDVCIADGVCI DAFLKP
HM17	75	L36~V47의 아미노산을	<u>FRGPLLPNR</u> PFLWAWNAPSEFCLGKFDEPLDMSLF

[0150]

		FRGPLLPNR로 치환하고, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 11개 아미노산을 치환한다.	SFIGSPRINATGQGVTFYVDRLGYYPYIDSTITGVTVN GGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVID WEEWRPTWARNWPKDVKYKNRSIELVQQQNVQL SLTEATEKAKQEFKAGKDFIVETIKLGKLLRPNHLW GYLFPDCYNHHYKPGYNGSCFNVEIKRNDLS WLWNESTALYPSIYLTQQSPVAATLYVRNRVREAI RVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDELVYT FGETVALGASGMWGTLSITRTKESCAIKEYMDT TLNPYIINVTLAAKMCSQVLCQEQGVCIRKNWNSS DYLHLNPDNFAIQLEKGGKFTVRGKPTLEDLEQFSE KFYCSCYSTLSCKEKADVKTDAVDVCIADGVCIDA FLKPPMETEEPQIFYNASPSTLS
HM18	76	L36~A52의 아미노산을 FRGPLLPNRPFITV로 치환하고, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 11개 아미노산을 치환한다.	FRGPLLPNRPFITV WNAPSEFCLGKFDEPLDMSLF SFIGSPRINATGQGVTFYVDRLGYYPYIDSTITGVTVN GGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVID WEEWRPTWARNWPKDVKYKNRSIELVQQQNVQL SLTEATEKAKQEFKAGKDFIVETIKLGKLLRPNHLW GYLFPDCYNHHYKPGYNGSCFNVEIKRNDLS WLWNESTALYPSIYLTQQSPVAATLYVRNRVREAI RVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDELVYT FGETVALGASGMWGTLSITRTKESCAIKEYMDT TLNPYIINVTLAAKMCSQVLCQEQGVCIRKNWNSS

[0151]

			DYHLNPDNFAIQLEKGGKFTVRGKPTLEDLEQFSE KFYCSCYSTLSCKEKADVKTDAVDVCIADGVCIDA FLKPPMETEEPQIFYNASPSTLS
HM19	77	L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 14개 아미노산 잔기를 치환하고, N-말단의 F38 잔기 앞에서 절단되고, C-말단의 K470 잔기 다음에서 절단된다.	FRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTFYVDRLGYYPYIDSITGVTV NGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVI DWEEWRPTWARNWPKDVYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPNH LWGYLFPDCYNHHYKPGYNGSCFNVEIKRND LSWLWNESTALYPSIYLNQQSPAATLYVRNRVR EAIKRVSKIPDAKSLPVFAYTRIVFTDQVLKFLSQDEL VYTFGETVALGASGMWGTWENTRTKESCQAIKE YMDITLNPYINVTIAAKMCSQVLCQEQGVCIRKN WNSSDYHLNPDNFAIQLEKGGKFTVRGKPTLEDL EQFSEKFYCSCYSTLSCKEKADVKTDAVDVCIADG VCIDAFK
HM20	78	L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 14개 아미노산 잔기를	FRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTFYVDRLGYYPYIDSITGVTV NGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVI DWEEWRPTWARNWPKDVYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPNH LWGYLFPDCYNHHYKPGYNGSCFNVEIKRND

[0152]

		치환하고, N-말단의 F38 잔기 앞에서 절단되며, C-말단의 F468 잔기 다음에서 절단된다.	LSWLWNESTALYPSIYLTQQSPVAATLYVRNRVR EAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDEL VYTFGETVALGASGMWGT <u>WENTRTKESCQAIKE</u> YMD <u>DTT</u> INPYIINVTLAAKMCSQVLCQEQGVCIRKN WNSSDYHLNPDNFAIQLEKGGKFTVRGKPTLEDL EQFSEKFCSCYSTLSCKEKADVKTDAVDVCIADG VCIDAF
HM21	79	T341S, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 15개 아미노산 잔기를 치환한다.	LNFRAPPVIPNPFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTFYVDRLGYYPIDSITGV TVNGGIPQKISLQDHLDAKAKDITFYMPVDNLGM AVIDWEEWRPTWARNWPKPDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRP NHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKRN DDLWLWNESTALYPSIYLTQQSPVAATLYVRNR VREAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQ DELVYTFGETVALGASGMWGT <u>SWENTRTKESCQA</u> <u>IKEYMDTT</u> INPYIINVTLAAKMCSQVLCQEQGVC RKNWNSSDYHLNPDNFAIQLEKGGKFTVRGKPTL EDLEQFSEKFCSCYSTLSCKEKADVKTDAVDVCI ADGVCIDAFKPPMETEEPQIFYNASPSTLS
HM24	80	M345T, S347T, M348K, K349E, L352Q, L353A,	APPVIPNPFLWAWNAPSEFCLGKFDEPLDMSLFS FIGSPRINATGQGVTFYVDRLGYYPIDSITGVTVN

[0153]

		L354I, D355K, N356E, E359D, I361T로 11개 아미노산 잔기를 치환하고, N-말단의 A40 잔기 앞에서 절단된다.	GGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVID WEEWRPTWARNWKPKDVYKNRSIELVQQQNVQ LSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPNHL WGYYLFPDCYNHHYKPGYNGSCFNVEIKRNDL SWLWNESTALYPSIYINTQQSPVAATLYVRNRVRE AIRVSKIPDAKSPLPVFAYTRMFTDQVLKFLSQDELV YTFGETVALGASGIMWGTLSITRTKESCQAIKEYM DTTLNPIYIINVTLAAKMCSQVLCQEQQVCIRKNW NSSDYLHLNPDNFAIQLEKGGKFTVRGKPTLEDLE QFSEKFYCSCYSTLSCKEADVKTDAVDVCIADG VCIDAFLKPPMETEEPQIFYNASPSTLS
HM25	81	M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 11개 아미노산을 치환하고, N-말단의 P42 잔기 앞에서 절단된다.	PVIPNVPLWAWNAPSEFCIGKFDEPLDMSLFSFIG SPRINATGQGVTFYVDRLGYYPYIDSITGVTNNGGI PQKISLQDHLDKAKKDITFYMPVDNLGMAVIDWE EWRPTWARNWKPKDVYKNRSIELVQQQNVQLSL TEATEKAKQEFKAGKDFLVETIKLGKLLRPNHLWG YYLFPDCYNHHYKPGYNGSCFNVEIKRNDLSDW LWNESTALYPSIYINTQQSPVAATLYVRNRVREAIR VSKIPDAKSPLPVFAYTRMFTDQVLKFLSQDELVYT FGETVALGASGIMWGTLSITRTKESCQAIKEYMDT TLNPIYIINVTLAAKMCSQVLCQEQQVCIRKNWNSS DYLHLNPDNFAIQLEKGGKFTVRGKPTLEDLEQFSE

[0154]

			KFYCSCYSTLSCKEKADVKTDAVDVCIADGVCID AFLKPPMETEEPQIFYNASPSTLS
HM29	82	L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 14개 아미노산 잔기를 치환하고, N-말단의 L36 잔기 앞에서 절단하고, C-말단의 A467 잔기 다음에서 절단한다.	LNFRAPPVIPNVPFLWAWNAPSECLGKFDEPLDM SLFSFIGSPRINATGQGVTFYVDRLGYYPIDSITGV TVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGM AVIDWEEWRPTWARNWPKDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRP NHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKRN DDLWLWNESTALYPSIYLNNTQQSPVAATLWRNR VREAIRVSKIPDAKSPLPVFAYTRVFTDQVLKFLSQ DELVYTFGETVALGASGMWGT <u>WENTRTKESCQA</u> <u>IKEYMDIT</u> LNPIINVTLAAKMCSQVLCQEKGVC RKNWNSSDYLHNPDNFAIQLEKGGKFTVRGKPTL EDLEQFSEKFYCSCYSTLSCKEKADVKTDAVDVCI ADGVCIDA
HM30	83	L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 14개 아미노산 잔기를 치환하고, N-말단의	LNFRAPPVIPNVPFLWAWNAPSECLGKFDEPLDM SLFSFIGSPRINATGQGVTFYVDRLGYYPIDSITGV TVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGM AVIDWEEWRPTWARNWPKDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRP NHLWGYYLFPDCYNHHYKPGYNGSCFNVEIKRN DDLWLWNESTALYPSIYLNNTQQSPVAATLWRNR

[0155]

		L36 잔기 앞에서 절단되고, C-말단의 C464 잔기 다음에서 절단된다.	VREAIRVSKIPDAKSPLPVFAYTRMFTDQVLKFLSQ DELVYTFGETVALGASGMWGT <u>WENTRTKESCQA</u> <u>IKEYMDIT</u> LNPIYINVTLAAKMCSQVLCQEQGVCI RKNWNSSDYHLNPDNFAIQLEKGGKFTVRGKPTL EDLEQFSEKFCSCYSTLSCKEKADVKTDAVDVCI ADGVC
HM31	84	L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 14개 아미노산 잔기를 치환하고, N-말단의 L36 잔기 앞에서 절단되고, C-말단의 D461 잔기 다음에서 절단된다.	LNFRAPPVIPNVPLWAWNAPSEFC LGKFDEPLDM SLFSFIGSPRINATGQGVTFYVDR LGYYPYIDSITGV TVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGM AVIDWEEWRPTWARNWPKDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRP NHLWGYLFPDCYNHHYKPGYNGSCFNVEIKRN DDLWLWNESALYPSIYLNQQSPVAATLVVRNR VREAIRVSKIPDAKSPLPVFAYTRMFTDQVLKFLSQ DELVYTFGETVALGASGMWGT <u>WENTRTKESCQA</u> <u>IKEYMDIT</u> LNPIYINVTLAAKMCSQVLCQEQGVCI RKNWNSSDYHLNPDNFAIQLEKGGKFTVRGKPTL EDLEQFSEKFCSCYSTLSCKEKADVKTDAVDVCI AD
HM32	85	L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A,	LNFRAPPVIPNVPLWAWNAPSEFC LGKFDEPLDM SLFSFIGSPRINATGQGVTFYVDR LGYYPYIDSITGV TVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGM

[0156]

		L354I, D355K, N356E, E359D, I361T로 14개 아미노산 잔기를 치환하고, N-말단의 L36 잔기 앞에서 절단되고, C-말단의 C458 잔기 다음에서 절단된다.	AVIDWEEWRPTWARNWPKPDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRP NHLWGYLFPDCYNHHYKKPGYNGSCFNVEIKRN DDLSWLWNESTALYPSTYLNQQSPVAATLWRNR VREAIRVSKIPDAKSPLPVFAYTRVFTDQVLKFLSQ DELVYTFGETVALGASGMIWGT <u>WENTRTKESCQA</u> <u>IKEYMDTT</u> LNPIYINVTIAAKMCSQVLCQEQGVCI RKNWNSSDYHLNPDNFAIQLEKGGKFTVRGKPTL EDLEQFSEKFCSCYSTLSCKEKADVKTDAVDVC
HM33	86	L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 14개 아미노산 잔기를 치환하고, N-말단의 L36 잔기 앞에서 절단되고, C-말단의 V455 잔기 다음에서 절단된다.	LNFRAPPVIPNPFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTFYVDRLGYYPIDSTIGV TVNGGIPQKISLQDHLDAKAKDITFYMPVDNLGM AVIDWEEWRPTWARNWPKPDVYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRP NHLWGYLFPDCYNHHYKKPGYNGSCFNVEIKRN DDLSWLWNESTALYPSTYLNQQSPVAATLWRNR VREAIRVSKIPDAKSPLPVFAYTRVFTDQVLKFLSQ DELVYTFGETVALGASGMIWGT <u>WENTRTKESCQA</u> <u>IKEYMDTT</u> LNPIYINVTIAAKMCSQVLCQEQGVCI RKNWNSSDYHLNPDNFAIQLEKGGKFTVRGKPTL EDLEQFSEKFCSCYSTLSCKEKADVKTDAV
HP34	87	T341S, L342W, S343E,	FRAPPVIPNPFLWAWNAPSEFCLGKFDEPLDMSL

[0157]

		<p>I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 15개 아미노산 잔기를 치환하고, N-말단의 F38 잔기 앞에서 절단되며, C-말단의 K470 잔기 다음에서 절단된다.</p>	<p>FSFIGSPRINATGQGVTIFYVDRLGYYPYIDSITGVTV NGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVI DWEEWRPTWARNWPKDVYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPNH LWGYLFPDCYNHHYKKPGYNGSCFNVEIKRNDD LSWLWNESTALYPSIYLNTQQSPVAATLWRNRVR EAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDEL VYTFGETVALGASGIMWGSWENTRTKESCQAIKE YMDTTLNPIYINVTLAAKMCSQVLCQEQQVCIRKN WNSSDYHLINPDNFAIQLEKGGKFTVRGKPTLEDL EQFSEKFCSCYSTLSCKEKADVKTDAVDVCIADG VCIDAFLK</p>
HM35	88	<p>L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 14개 아미노산 잔기를 치환하고, N-말단의 F38 잔기 앞에서 절단되며, C-말단의 P472 잔기 다음에서</p>	<p>FRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTIFYVDRLGYYPYIDSITGVTV NGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVI DWEEWRPTWARNWPKDVYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPNH LWGYLFPDCYNHHYKKPGYNGSCFNVEIKRNDD LSWLWNESTALYPSIYLNTQQSPVAATLWRNRVR EAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDEL VYTFGETVALGASGIMWGTWENTRTKESCQAIKE YMDTTLNPIYINVTLAAKMCSQVLCQEQQVCIRKN</p>

[0158]

		절단된다.	WNSSDYLHLPDNFAIQLEKGGKFTVRGKPTLEDL EQFSEKFCSCYSTLSCKEKADVKTDAVDVCIADG VCIDAFKPP
HM36	89	L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 14개 아미노산 잔기를 치환하고, N-말단의 F38 잔기 앞에서 절단되며, C-말단의 M473 잔기 다음에서 절단된다.	FRAPPVIPNPFLWAWNAPSEFLGKFDEPLDMSL FSFIGSPRINATGQGVTFYVDRLGYYPIDSGVTV NGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVI DWEEWRPTWARNWPKDVYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPNH LWGYLFPDCYNHHYKPGYNGSCFNVEIKRND LSWLWNESTALYPSIYINTQQSPVAATLWRNRVR EAIKRVSKIPDAKSLPVFAYTRIVFTDQVLKFLSQDEL VYTFGETVALGASGMWGTWENTRTKESCQAIKE YMDTTLNPIINVTAAKMCQVLCQEQGVCIRKN WNSSDYLHLPDNFAIQLEKGGKFTVRGKPTLEDL EQFSEKFCSCYSTLSCKEKADVKTDAVDVCIADG VCIDAFKPPM
HM37	90	L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 14개 아미노산 잔기를	FRAPPVIPNPFLWAWNAPSEFLGKFDEPLDMSL FSFIGSPRINATGQGVTFYVDRLGYYPIDSGVTV NGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVI DWEEWRPTWARNWPKDVYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPNH LWGYLFPDCYNHHYKPGYNGSCFNVEIKRND

[0159]

		치환하고, N-말단의 F38 잔기 앞에서 절단되며, C-말단의 E474 잔기 다음에서 절단된다.	LSWLWNESTALYPSIYLNTQQSPVAATLYVRNRVR EAIKRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDEL VYTFGETVALGASGIMTWGT <u>WENTRTKESCQAIKE</u> YMD <u>DTT</u> LNPIYINVTLAAMCSQVLCQEQGVCIRKN WNSSDYHLNPDNFAIQLEKGGKFTVRGKPTLEDL EQFSEKFYCSCYSTLSCKEKADVKTDAVDVCIADG VCIDAFKPPME
HM38	91	L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 14개 아미노산 잔기를 치환하고, N-말단의 F38 잔기 앞에서 절단되며, C-말단의 T475 잔기 다음에서 절단된다.	FRAPPVIPNPFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTFYVDRLGYYPYIDSITGVTV NGGIPQKISLQDHLKAKKDITFYMPVDNLGMAVI DWEEWRPTWARNWPKDVKYKRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGLLRPNH LWGYLFPDCYNHHYKPGYNGSCFNVEIKRND LSWLWNESTALYPSIYLNTQQSPVAATLYVRNRVR EAIKRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDEL VYTFGETVALGASGIMTWGT <u>WENTRTKESCQAIKE</u> YMD <u>DTT</u> LNPIYINVTLAAMCSQVLCQEQGVCIRKN WNSSDYHLNPDNFAIQLEKGGKFTVRGKPTLEDL EQFSEKFYCSCYSTLSCKEKADVKTDAVDVCIADG VCIDAFKPPMET
HM39	92	L342W, S343E, I344N, M345T, S347T, M348K,	FRAPPVIPNPFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTFYVDRLGYYPYIDSITGVTV

[0160]

		<p>K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 14개 아미노산 잔기를 치환하고, N-말단의 F38 잔기 앞에서 절단되며, C-말단의 E476 잔기 다음에서 절단된다.</p>	<p>NGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVI DWEWRPTWARNWPKDVKYKRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPNH LWGYLFPDCYNHHYKPGYNGSCFNVEIKRND LSWLWNESTALYPSIYLN TQQSPVAATLYVRNRVR EAIKRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDEL VYTFGETVALGASGMVWGTWENTRTKESCAIKE YMDTTLNPIYIINVTLAAKMCSQVLCQEQQVCIRKN WNSSDYLHLNPDNFAIQLEKGGKFTVRGKPTLEDL EQFSEKFCSCYSTLSCKEKADV KDTDAVDVCIADG VCIDAF LKPPMETE</p>
HM40	93	<p>M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 11개 아미노산 잔기를 치환하고, N-말단의 N37 잔기 앞에서 절단된다.</p>	<p>NFRAPPVIPNVPLWAWNAPSEFCLGKFDEPLDMS LFSFIGSPRINATGQGVTFYVDRLGYYPIYDSITGVT VNGGIPQKISLQDHLDKAKKDITFYMPVDNLGMA VIDWEWRPTWARNWPKDVKYKRSIELVQQQNV VQLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPN HLWGYLFPDCYNHHYKPGYNGSCFNVEIKRND DLSWLWNESTALYPSIYLN TQQSPVAATLYVRNRV REAIKRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDE LVYTFGETVALGASGMVWGTLSITRTKESCAIKEY MDTTLNPIYIINVTLAAKMCSQVLCQEQQVCIRKN WNSSDYLHLNPDNFAIQLEKGGKFTVRGKPTLEDL</p>

[0161]

			EQFSEKFCSCYSTLSCKEKADVKTDAVDVCIADG VCIDAFKPPMETEEPQIFYNASPSTLS
HM41	94	M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 11개 아미노산 잔기를 치환하고, N-말단의 R39 잔기 앞에서 절단된다.	RAPPVIPNPFLWAWNAPSEFCLGKFDEPLDMSLF SFIGSPRINATGQGVTFWDRLGYYPYIDSITGVTV NGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVI DWEEWRPTWARNWPKDVYKNRSIELVQQQNV QLSLTEATEKAKQEFEKAGKDFLVETIKLGKLLRPNH LWGYLFPDCYNHHYKPGYNGSCFNVEIKRND LSWLWNESTALYPSIYLNNTQQSPVAATLYVRNRVR EAIKRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDEL VYTFGETVALGASGMWGTLSITR <u>TKESCQAIKEY</u> <u>MDIT</u> LNPIYINVTLAAKMCQVLCQEQQGVCIRKN WNSSDYLHLPDNPFAIQLEKGGKFTVRGKPTLEDL EQFSEKFCSCYSTLSCKEKADVKTDAVDVCIADG VCIDAFKPPMETEEPQIFYNASPSTLS
HM42	95	M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 11개 아미노산 잔기를 치환하고, N-말단의 P41 잔기 앞에서	PPVIPNPFLWAWNAPSEFCLGKFDEPLDMSLFSFI GSPRINATGQGVTFWDRLGYYPYIDSITGVTVNG GIPQKISLQDHLDKAKKDITFYMPVDNLGMAVIDW EEWRPTWARNWPKDVYKNRSIELVQQQNVQLS LTEATEKAKQEFEKAGKDFLVETIKLGKLLRPNHLW GYLFPDCYNHHYKPGYNGSCFNVEIKRNDLS WLWNESTALYPSIYLNNTQQSPVAATLYVRNRVREA

[0162]

		절단된다.	IRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDELVY TFGETVALGASGVIWGTLSITRTKESCQAIKEYMD TTLNPHYINVTAAKMCSQVLCQEQGVCIRKNWNS SDYLHLNPDNFAIQLEKGGKFTVRGKPTLEDLEQFS EKFYCSCYSTLSCKEKADVKTDAVDVCIADGVCI AFLKPPMETEEPQIFYNASPSTLS
HM43	96	L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 14개 아미노산 잔기를 치환 하고, N-말단의 F38 잔 기 앞에서 절단되며, C- 말단의 I465 잔기 다음 에서 절단된다.	FRAPPVIPNPFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTFYVDRLGYYPIDSTIGVTV NGGIPQKISLQDHLDAKAKDITFYMPVDNLGMAVI DWEEWRPTWARNWPKDVYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFIVETIKGLLRPNHL WGYLFPDCYNHHYKPGYNGSCFNVEIKRNDL SWLWNESTALYPSIYLNITQQSPVAATLYVRNRVREA IRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDELVY TFGETVALGASGVIWGSWENTRTKESCQAIKEYM DTTLNPHYINVTAAKMCSQVLCQEQGVCIRKNW NSSDYLHLNPDNFAIQLEKGGKFTVRGKPTLEDLEQ FSEKFYCSCYSTLSCKEKADVKTDAVDVCIADGVCI
HM44	97	L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E,	FRAPPVIPNPFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTFYVDRLGYYPIDSTIGVTV NGGIPQKISLQDHLDAKAKDITFYMPVDNLGMAVI DWEEWRPTWARNWPKDVYKNRSIELVQQQNV

[0163]

		E359D, I361T로 14개 아미노산 잔기를 치환 하고, N-말단의 F38 잔 기 앞에서 절단되며, C- 말단의 D466 잔기 다 음에서 절단된다.	QLSLTEATEKAKQEFKAGKDFLVEITIKLGKLLRPNHL WGYYLFPDCYNHHYKKPGYNGSCFNVEIKRNDL SWLWNESTALYPSIYLNLTQQSPAATLYVRNRVREA IRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDELVY TFGETVALGASGVTWGSWENTRTKESCAIKEYM DTTLNPIYINVTLAAKMCSQVLCQEQGVCIRKNW NSSDYLHLNPDNFAIQLEKGGKFTVRGKPTLEDLEQ FSEKFCSCYSTLSCKEKADVKTDAVDVCIADGVCI D
HM45	98	L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 14개 아미노산 잔기를 치환 하고, N-말단의 F38 잔 기 앞에서 절단되며, C- 말단의 A467 잔기 다 음에서 절단된다.	FRAPPVIPNVPFLWAWNAPSEFLGKFDEPLDMSL FSFIGSPRINATGQGVTFYVDRLGYYPIDSGVTV NGGIPQKISLQDHLDKAKDITFYMPVDNLGMAVI DWEEWRPTWARNWPKDVYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVEITIKLGKLLRPNHL WGYYLFPDCYNHHYKKPGYNGSCFNVEIKRNDL SWLWNESTALYPSIYLNLTQQSPAATLYVRNRVREA IRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDELVY TFGETVALGASGVTWGSWENTRTKESCAIKEYM DTTLNPIYINVTLAAKMCSQVLCQEQGVCIRKNW NSSDYLHLNPDNFAIQLEKGGKFTVRGKPTLEDLEQ FSEKFCSCYSTLSCKEKADVKTDAVDVCIADGVCI DA

[0164]

HP46	99	T341S, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 15개 아미노산 잔기를 치환하고, N-말단의 F38 잔기 앞에서 절단되며, C-말단의 F468 잔기 다음에서 절단된 다.	FRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTFYVDRLGYPYIDSTIGVTV NGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVI DWEEWRPTWARNWPKDVYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPNHL WGYYLFPDCYNHHYKPGYNGSCFNVEIKRNDL SWLWNESTALYPSIYLN TQQSPVAATLYVRNRVREA IRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDELVY TFGETVALGASGIMWGSWENTRTKESCQAIKEYM DTTLNPIYINVTLAAKMCSQVLCQEQQVCIRKNW NSSDYHLNPDNFAIQLEKGGKFTVRGKPTLEDLEQ FSEKFYCSCYSTLSCKEKADVKTDAVDVCIADGVC DAF
HM47	100	L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 14개 아미노산 잔기를 치환하고, N-말단의 F38 잔기 앞에서 절단되며, C-말단의	FRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTFYVDRLGYPYIDSTIGVTV NGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVI DWEEWRPTWARNWPKDVYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPNH LWGYYLFPDCYNHHYKPGYNGSCFNVEIKRNDL LSWLWNESTALYPSIYLN TQQSPVAATLYVRNRVR EAI RSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDEL VYTFGETVALGASGIMWGTWENTRTKESCQAIKE

[0165]

		P478 잔기 다음에서 절단된다.	YMDTTLN PI INVTLAAKMCSQVLCQEQGVCIRKN WNSSDY LH LNPDNFAIQLEKGGKFTVRGKPTLEDL EQFSEK FC SCYSTLSCKEKADV KD TD AV DVCIADG VCIDAF LK PPMETEEP
HM48	101	L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 14개 아미노산 잔기를 치환하고, N-말단의 F38 잔기 앞에서 절단되며, C-말단의 I480 잔기 다음에서 절단된다.	FRAPPVIPNPFLWAWNAPSEFC L GKFDEPLDMSL FSFIGSPRINATGQGV T IFYVDRLGYYPYIDSITGVTV NGGIPQKISLQDHL D KAKKDITFYMPVDN L GMAVI DWEEWRPTWAR N WPKDVYKNRSIELVQQQNV QLSLTEATEKAKQEF E KAGKDFLVETIKL G LLRPNH LWGYLFPDCYNH H YKPGYNGSCFNVEIKRND LSWLWNESTALYPSI V LN T QQSPVAATLYVRN R VR EAIRVSKIPDAKSP L PVFAYTRIVFTDQVLK F LSQDEL VYTFGETVALGASG M WTG T WENTRT K ESCQAIKE YMDTTLN PI INVTLAAKMCSQVLCQEQGVCIRKN WNSSDY LH LNPDNFAIQLEKGGKFTVRGKPTLEDL EQFSEK FC SCYSTLSCKEKADV KD TD AV DVCIADG VCIDAF LK PPMETEEPQI
HM49	102	L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 14개	FRAPPVIPNPFLWAWNAPSEFC L GKFDEPLDMSL FSFIGSPRINATGQGV T IFYVDRLGYYPYIDSITGVTV NGGIPQKISLQDHL D KAKKDITFYMPVDN L GMAVI DWEEWRPTWAR N WPKDVYKNRSIELVQQQNV QLSLTEATEKAKQEF E KAGKDFLVETIKL G LLRPNH

[0166]

		아미노산 잔기를 치환하고, N-말단의 F38 잔기 앞에서 절단되며, C-말단의 Y482 잔기 다음에서 절단된다.	LWGYLFPDCYNHHYKPGYNGSCFNVEIKRND LSWLWNESTALYPSIYLNQQSPVAATLYVRNRVR EAIKRVSKIPDAKSPVPVFAITRIVFTDQVLKFLSQDEL VYTFGETVALGASGMVWGTWENTRTKESCQAIKE YMDTTLNPIYINVTLAAMCSQVLCQEQGVCIRKN WNSSDYLHLPNDNFQIQLEKGGKFTVRGKPTLEDL EQFSEKFCSCYSTLSCKEADVKTDAVDVCIADG VCIDAFKPPMETEEPQIFY
HM50	103	L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 14개 아미노산 잔기를 치환하고, N-말단의 F38 잔기 앞에서 절단되며, C-말단의 A484 잔기 다음에서 절단된다.	FRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTFYVDRLGYYPIDSITGVTV NGGIPQKISLQDHLKAKKDITFYMPVDNLGMAVI DWEEWRPTWARNWPKDVKYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGLLRPNH LWGYLFPDCYNHHYKPGYNGSCFNVEIKRND LSWLWNESTALYPSIYLNQQSPVAATLYVRNRVR EAIKRVSKIPDAKSPVPVFAITRIVFTDQVLKFLSQDEL VYTFGETVALGASGMVWGTWENTRTKESCQAIKE YMDTTLNPIYINVTLAAMCSQVLCQEQGVCIRKN WNSSDYLHLPNDNFQIQLEKGGKFTVRGKPTLEDL EQFSEKFCSCYSTLSCKEADVKTDAVDVCIADG VCIDAFKPPMETEEPQIFYNA
HM51	104	L342W, S343E, I344N,	FRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSL

[0167]

		<p>M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 14개 아미노산 잔기를 치환하고, N-말단의 F38 잔기 앞에서 절단되며, C-말단의 P486 잔기 다음에서 절단된다.</p>	<p>FSFIGSPRINATGQGVTFYVDRLGYYPYIDSITGTV NGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVI DWEEWRPTWARNWPKDVKYKRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPNH LWGYLFPDCYNHHYKPGYNGSCFNVEIKRND LSWLWNESTALYPSIYLNLTQQSPVAATLWRNRVR EAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDEL VYTFGETVALGASGMWGT<u>WENTRTKESCQAIKE</u> YMD<u>DTT</u>LNPIYINVTLAAKMCSQVLCQEQGVCIRKN WNSSDYLHLNPDNFAIQLEKGGKFTVRGKPTLEDL EQFSEKFCSCYSTLSCKEKADVKTDAVDVCIADG VCIDAFKPPMETEEPQIFYNASP</p>
HM52	105	<p>L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 14개 아미노산 잔기를 치환하고, N-말단의 F38 잔기 앞에서 절단되며, C-말단의 T488 잔기 다음에서</p>	<p>FRAPPVIPNPFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTFYVDRLGYYPYIDSITGTV NGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVI DWEEWRPTWARNWPKDVKYKRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPNH LWGYLFPDCYNHHYKPGYNGSCFNVEIKRND LSWLWNESTALYPSIYLNLTQQSPVAATLWRNRVR EAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDEL VYTFGETVALGASGMWGT<u>WENTRTKESCQAIKE</u> YMD<u>DTT</u>LNPIYINVTLAAKMCSQVLCQEQGVCIRKN</p>

[0168]

		절단된다.	WNSSDYLHLNPDNFAIQLEKGGKFTVRGKPTLEDL EQFSEKFCSCYSTLSCKEKADVKTDAVDVCIADG VCIDAFKPPMETEEPQIFYNASPST
HM53	106	T341G, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 15개의 아미노산 잔기를 치환하고, N말단의 L36잔기 앞에서 절단되며, C말단의 S490 잔기 다음에서 절단된다.	LNFRAPPVIPNPFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTFYVDRLGYYPYIDSITGV TVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGM AVIDWEEWRPTWARNWPKDVKYKNSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRP NHLWGYLFPDCYNHHYKPGYNGSCFNVEIKRN DDLWLWNESALYPSIYLNQQSPVAATLVRNR VREAIRVSKIPDAKSLPVFAYTRMFTDQVLKFLSQ DELVYTFGETVALGASGMWGGWENTRTKESQ AIKEYMDITLNPYIINVTAAKMCSQVLCQEQGVC IRKNWNSSDYLHLNPDNFAIQLEKGGKFTVRGKPT LEDLEQFSEKFCSCYSTLSCKEKADVKTDAVDVC IADGVCIDAFKPPMETEEPQIFYNASPSTLS
HM54	107	T341A, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 15개의 아미노산	LNFRAPPVIPNPFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTFYVDRLGYYPYIDSITGV TVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGM AVIDWEEWRPTWARNWPKDVKYKNSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRP NHLWGYLFPDCYNHHYKPGYNGSCFNVEIKRN

[0169]

		잔기를 치환하고, N말단의 L36잔기 앞에서 절단되며, C말단의 S490 잔기 다음에서 절단된다.	DDLSWLWNESTALYPSTYLNQQSPVAATLWRNR VREAIRVSKIPDAKSPVPFAYTRMFTDQVLKFLSQ DELVYTFGETVALGASGMIWG <u>AWENTRTKESCQ</u> <u>AIKEYMDTT</u> LNPIIINVTAAKMCSQVLCQEQGVC IRKNWNSSDYHLNPDNFAIQLEKGGKFTVRGKPT LEDLEQFSEKFCSCYSTLSCKEKADVKTDAVDVC IADGVCIDAFKPPMETEEPQIFYNASPSTLS
HM55	108	T341C, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 15개의 아미노산 잔기를 치환하고, N말단의 L36잔기 앞에서 절단되며, C말단의 S490 잔기 다음에서 절단된다.	LNFRAPPVIPNPFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTFYVDRLGYYPYIDSITGV TVNGGIPQKISLQDHLKAKKDITFYMPVDNLGM AVIDWEEWRPTWARNWPKDVKYKNRSIELVQQQ NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRP NHLWGYLFPDCYNHHYKPGYNGSCFNVEIKRN DDLSWLWNESTALYPSTYLNQQSPVAATLWRNR VREAIRVSKIPDAKSPVPFAYTRMFTDQVLKFLSQ DELVYTFGETVALGASGMIWG <u>CWENTRTKESCQA</u> <u>IKEYMDTT</u> LNPIIINVTAAKMCSQVLCQEQGVC RKNWNSSDYHLNPDNFAIQLEKGGKFTVRGKPTL EDLEQFSEKFCSCYSTLSCKEKADVKTDAVDVCI ADGVCIDAFKPPMETEEPQ109IFYNASPSTLS
HM56	109	T341D, L342W, S343E, I344N, M345T, S347T,	LNFRAPPVIPNPFLWAWNAPSEFCLGKFDEPLDM SLFSFIGSPRINATGQGVTFYVDRLGYYPYIDSITGV

[0170]

		<p>M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로</p> <p>15개의 아미노산 잔기를 치환하고, N말단의 L36잔기 앞에서 절단되며, C말단의 S490 잔기 다음에서 절단된다.</p>	<p>TVNGGIPQKISLQDHLDKAKKDITFYMPVDNLGM</p> <p>AVIDWEEWRPTWARNWPKDVYKNRSIELVQQQ</p> <p>NVQLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRP</p> <p>NHLWGYLFPDCYNHHYKPGYNGSCFNVEIKRN</p> <p>DDLSWLWNESTALYPSIYINTQQSPVAATLVRNR</p> <p>VREAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQ</p> <p>DELVYTFGETVALGASGIMWGDWENTRTKESCQ</p> <p>AIKEYMDITLNPYIINVTLAAKMCSQVLCQEQGVC</p> <p>IRKNWNSSDYLHLPDNPFAIQLEKGGKFTVRGKPT</p> <p>LEDLEQFSEKFCSCYSTLSCKEKADVKTDAVDVC</p> <p>IADGVCIDAFKPPMETEEPQIFYNASPSTLS</p>
HP57	110	<p>I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로</p> <p>12개의 아미노산 잔기를 치환하고, N말단의 F38잔기 앞에서 절단되며, C말단의 F468 잔기 다음에서 절단된다.</p>	<p>FRAPPVIPNPFLWAWNAPSEFCLGKFDPLDMSL</p> <p>FSFIGSPRINATGQGVTFYVDRLGYYPYIDSITGVTV</p> <p>NGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVI</p> <p>DWEEWRPTWARNWPKDVYKNRSIELVQQQNV</p> <p>QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPNH</p> <p>LWGYLFPDCYNHHYKPGYNGSCFNVEIKRNDD</p> <p>LSWLWNESTALYPSIYINTQQSPVAATLVRNRVR</p> <p>EAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDEL</p> <p>VYTFGETVALGASGIMWGTLSNTRTKESCQAIKEY</p> <p>MDITLNPYIINVTLAAKMCSQVLCQEQGVCIRKN</p> <p>WNSSDYLHLPDNPFAIQLEKGGKFTVRGKPTLEDL</p>

[0171]

			EQFSEKFCSCYSTLSCKEKADVKTDAVDVCIADG VCIDAF
HP58	111	S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 13개의 아미노산 잔기를 치환하고, N말단의 F38잔기 앞에서 절단되며, C말단의 F468 잔기 다음에서 절단된다.	FRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTFYVDRLGYYPYIDSITGVTV NGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVI DWEEWRPTWARNWPKDVYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPNH LWGYLFPDCYNHHYKPGYNGSCFNVEIKRNDD LSWLWNESTALYPSIYINTQQSPVAATLYVRNRVR EAIKRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDEL VYTFGETVALGASGMIWGTLENTRTKESQAIKEY MDTTLNPIIINVTLAAKMCSQVLCQEQQVCIRKN WNSSDYHLNPDNFAIQLEKGGKFTVRGKPTLEDL EQFSEKFCSCYSTLSCKEKADVKTDAVDVCIADG VCIDAF
HP59	112	T341A, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 15개의 아미노산 잔기를 치환하고,	FRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTFYVDRLGYYPYIDSITGVTV NGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVI DWEEWRPTWARNWPKDVYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPNH LWGYLFPDCYNHHYKPGYNGSCFNVEIKRNDD LSWLWNESTALYPSIYINTQQSPVAATLYVRNRVR

[0172]

		N말단의 F38잔기 앞에서 절단되며, C말단의 F468 잔기 다음에서 절단된다.	EAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDEL VYTFGETVALGASGMIWG <u>AWENTRTKESCQAIKE</u> YMD <u>DTT</u> LNPIYINVTLAAKMCSQVLCQEQQGVCIRKN WNSSDYHLNPDNFAIQLEKGGKFTVRGKPTLEDL EQFSEKFYCSCYSTLSCKEKADVKTDAVDVCIADG VCIDAF
HP60	113	T341G, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 15개의 아미노산 잔기를 치환하고, N말단의 F38잔기 앞에서 절단되며, C말단의 F468 잔기 다음에서 절단된다.	FRAPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTFYVDRLGYYPIDSITGVTV NGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVI DWEEWRPTWARNWPKDVYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPNH LWGYLFPDCYNHHYKPGYNGSCFNVEIKRND LSWLWNESTALYPSIYLNQQSPVAATLYVRNRVR EAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDEL VYTFGETVALGASGMIWG <u>GWENTRTKESCQAIKE</u> YMD <u>DTT</u> LNPIYINVTLAAKMCSQVLCQEQQGVCIRKN WNSSDYHLNPDNFAIQLEKGGKFTVRGKPTLEDL EQFSEKFYCSCYSTLSCKEKADVKTDAVDVCIADG VCIDAF
HP61	114	A40G, T341S, L342W, S343E, I344N, M345T, S347T, M348K, K349E,	FRGPPVIPNVPFLWAWNAPSEFCLGKFDEPLDMSL FSFIGSPRINATGQGVTFYVDRLGYYPIDSITGVTV NGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVI

[0173]

		L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 16개의 아미노산 잔기를 치환하고, N말단의 F38잔기 앞에서 절단되며, C말단의 F468 잔기 다음에서 절단된다.	DWEEWRPTWARNWPKDVYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGKLLRPNH LWGYLFPDCYNHHYKPGYNGSCFNVEIKRND LSWLWNESTALYPSIYLNQQSPVAATLYVRNRVR EAIRVSKIPDAKSPLPVFAYTRIVFTDQVLKFLSQDEL VYTFGETVALGASGMIWG <u>SWENTRTKESCQAIKE</u> YMD <u>DTT</u> LNPIYINVTLAAKMCSQVLCQEQQGVCIRKN WNSSDYHLNPDNFAIQLEKGGKFTVRGKPTLEDL EQFSEKFYCSCYSTLSCKEKADVKTDAVDVCIADG VCIDAF
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[0174]

HP62	115	P42를 제거하고, T341S, L342W, S343E, I344N, M345T, S347T, M348K, K349E, L352Q, L353A, L354I, D355K, N356E, E359D, I361T로 15개의 아미노산 잔기를 치환하며, 말단의 F38잔기 앞에서 절단하고, C말단의 F468 잔기 다음에서 절단된다.	FRGPPVPNPVFLWAWNAPSEFLGKFDEPLDMSL FSFIGSPRINATGQGVTFYVDRLGYYPYIDSITGVTV NGGIPQKISLQDHLDKAKKDITFYMPVDNLGMAVI DWEEWRPTWARNWPKDVYKNRSIELVQQQNV QLSLTEATEKAKQEFKAGKDFLVETIKLGLLRPNH LWGYLFPDCYNHHYKPGYNGSCFNVKRNDD LSWLWNESTALYPSIYLNTQQSPVAATLYVRNRVR EAIRVSKIPIAKSPLPVFAYTRIVFTDQVLKFLSQDEL VYTFGETVALGASGIMWGSWENTRTKESCAIKE YMDITLNPYIINVTAAKMCQVLCQEQQVCIRKN WNSSDYLHLNPDNFALQLEKGGKFTVRGKPTLEDL EQFSEKFYCSYSTLSCKEKADVKTDAVDVCIADG VCIDAF
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[0175]

[0176] 실시예 2. PH20의 변이체 HM1과 HM6의 제작

[0177] PH20의 아미노산 서열 M345~N363은 <도 1B>에 나타난 것과 같이 단백질 3차구조 모델에서 알파나선 8 부위 및 알파나선 7과 알파나선 8 연결 부위에 해당한다. 알파나선 8의 아미노산 중 C351은 알파나선 1의 C60과 이황화 결합을, Y357은 알파나선 7의 F315와 소수성 상호작용을, N363은 알파나선 1의 D69와 수소결합을 형성하여 알파나선 8과 이웃한 2차구조를 안정화 시키고 있다(도 1C).

[0178] PH20의 알파나선 8 부위 및 알파나선 7과 알파나선 8 연결 부위에 위치한 아미노산을 치환하여 WT보다 효소 활성과 열 안정성이 높은 변이체를 제작하기 위하여 M345~N363 구간에서 12개의 아미노산을 치환한 변이체 HM1과 Y365~V379 구간에서 7개의 아미노산을 치환한 HM2, M345~V379 구간의 아미노산 19개를 치환한 HM3를 각각 제작하였다. PH20의 알파나선 8에 위치한 아미노산 중 이황화 결합에 관여하는 C351과 소수성 상호작용에 관여하는 Y357은 치환하지 않았다. 변이체 HM1, HM2, HM3에서 치환한 아미노산의 서열은 표11에 표시되어 있다. 변이체 HM1, HM2, HM3의 유전자가 포함된 pcDNA3.4-TOPO 플라스미드로 ExpiCHO 세포에 형질주입 하였을 때, 변이체 HM1은 ExpiCHO 세포에서 발현되었고(도 3A), 변이체 HM2와 HM3는 발현되지 않았다. 단백질 발현 여부는 효소 활성 측정뿐만 아니라 인간 PH20에 대한 항체(Abcam, ab193009)를 이용하여 웨스턴 블롯(Western blot)으로도 확인하였다. 항체의 epitope은 Q173-P222 구간이다. 이 실험결과는 알파나선 8의 아미노산 서열 중에서도 변이체 HM2, HM3 제작에 사용한 Y365~V379 구간의 아미노산 치환은 단백질 구조에 심각한 영향을 초래하여 변이체 HM2, HM3의 단백질 발현이 되지 않은 것으로 여겨진다. 변이체 HM1은 야생형 WT보다 발현량이 3.4배 높았다(도 2). 변이체 HM1은 N363을 글리신으로 치환하여 알파나선 8의 N363과 알파나선 1의 D69 사이의 수소결합을 제거한 것이다(도 1C). N363과 D69 사이의 수소결합을 복원하기 위해 HM1에서 G363을 아스파라진으로 치환한 변이체 HM6를 제작하였다. 변이체 HM6에서 치환한 아미노산은 표 11에 표시되어 있다.

[0179] 변이체 HM6는 ExpiCHO 세포에서 발현되었으며 발현량은 변이체 HM1과 유사하였다(WT보다 3.4배 발현량 많음)(도 2). Turbidimetric assay 방법으로 효소 활성을 측정하였을 때 변이체 HM6는 WT보다 효소 활성이 1.3배 증가하였다(도 3B). Substrate-gel assay는 일반적으로 SDS-PAGE 후 2.5% Triton X-100 (w/v)을 이용해서 SDS를 제거하고 37 °C에서 1~4 시간 동안 반응하면서 히알루로니다제가 히알루론산을 가수분해하는 정도를 Alcian blue 염색약을 이용해서 측정한다. Substrate gel에서 SDS가 제거되면 단백질의 접힘(refolding)이 바로 일어나며, substrate이 단백질 접힘에는 영향을 주지 않는 것으로 알려져 있다. WT와 변이체 HM1, HM6의 효소 활성을 substrate-gel assay 방법으로 37 °C에서 1~4시간 동안 측정하였을 때 HM6는 WT 및 변이체 HM1보다 높은 효소 활성을 나타내었다(도 3C). 이 결과는 변이체 HM1과 HM6의 단백질 접힘(refolding)과 이로 인한 renaturation이 WT보다 빠르며, 제작한 변이체들이 WT보다 높은 효소 활성을 나타낸다는 것을 제시한다. PH20 자체의 신호 펩티드를 이용했을 때는 ExpiCHO 세포에서 단백질 발현량이 낮았으며, 이를 해결하기 위해 인간 혈청 알부민 또

는 인간 Hyal1의 신호 펩티드 서열을 사용하였다. 도 3C에서 나타난 것과 같이 변이체 HM1의 신호 펩티드로 인간 혈청 알부민과 인간 Hyal1의 신호 펩티드를 사용했을 때 단백질 발현이 증가하였으며, 두 종류의 신호 펩티드 사이에 큰 차이는 없었다. Substrate-gel assay 방법으로 효소 활성을 측정하였을 때 인간 혈청 알부민 신호 펩티드를 가진 WT와 인간 혈청 알부민 또는 Hyal1의 신호 펩티드를 가진 변이체 HM1은 pH 5-8 구간에서 효소 활성을 나타내었다 (도 3D). 본 발명에서 HM1 이후에 제작한 변이체의 신호 펩티드로 인간 혈청 알부민의 신호 펩티드를 사용하였다.

- [0180] WT와 변이체 HM1, HM6의 열 안정성을 응집온도로 비교하면 각각 46.5 °C, 53.0 °C, 50.5 °C로 변이체 HM1과 HM6의 응집온도가 WT보다 각각 6.5 °C와 4.0 °C 더 높다 (도 10). 응집온도 측정 결과는 substrate-gel assay에서 나타난 단백질 refolding 결과와 일치한다. 이 결과들은 알파나선 8의 N363 잔기가 이루는 수소결합이 단백질 구조의 열 안정성과 효소 활성에 중요한 역할을 함을 처음으로 제시한다.
- [0181] 또한 Phenyl 컬럼을 이용하여 WT와 변이체 HM1, HM6의 친수성/소수성 특성을 비교하였을 때, HM1과 HM6는 모두 WT보다 더 앞쪽에서 용출되었으며 이는 변이체 HM1과 HM6가 아미노산의 치환으로 인해 WT보다 더 친수성 성질을 가짐을 제시한다. 그렇지만 Phenyl 컬럼에서 용출된 변이체 HM1과 HM6는 WT와는 달리 2개의 피크가 존재하며 PNGase F를 처리하였을 때 동일한 분자량을 나타내었다. 이는 N-당화에 의한 차이로 사료된다 (도 3E).
- [0182] 실시예 3. PH20 변이체 HM4, HM7, HM8, HM9, HM 10, HM11, HM12의 제작
- [0183] 실시예 2에서 변이체 HM1과 HM6의 제작으로 M345-N363과 M345-I361 구간의 아미노산 치환이 PH20의 효소 활성과 열 안정성을 모두 증가시킨 것은 단백질 공학 관점에서 큰 진전을 이룬 것으로 여겨진다. 따라서 변이체 HM1과 HM6를 기반으로 N-말단과 C-말단 방향으로 더 확장하여 추가적으로 아미노산을 치환하였다.
- [0184] 먼저, 변이체 HM1과 HM6에서 치환한 아미노산을 포함하고 추가적으로 G340-I344 사이의 아미노산을 G340V, T341S, L342W, S343E, I344N으로 치환한 변이체 HM4, HM7을 각각 제작하였다. 변이체 HM4와 HM7에서 치환한 아미노산의 서열은 표11에 표시되어 있다. 변이체 HM4와 HM7은 ExpiCHO 세포에서 발현되었다. HM7에 대한 단백질 정제 결과는 도 5A에 나타나 있다. HM4, HM7은 단백질 발현이 WT보다 모두 6.3배 증가하였고, 응집온도는 각각 10 °C와 11.5 °C 증가하였다. 그렇지만 turbidimetric assay 방법으로 측정한 HM4와 HM7의 효소 활성은 WT와 비교하여 대략 15%에 불과하였다 (도 5B). 일반적으로 효소 활성과 열 안정성은 교환(trade-off)의 관계가 성립하지만, 본 발명에서는 변이체 HM1과 HM6에서 도입한 치환에 의해서는 효소 활성은 유지되면서 열 안정성이 증가하였고, 변이체 HM4와 HM7에서는 과도한 열 안정성 증가로 인해 효소 활성이 감소한 것으로 여겨진다. 단백질 공학 관점에서 변이체 HM4, HM7에서 나타난 11.5 °C의 응집온도 증가는 매우 의미 있는 결과이다. Stern-Volmer plot으로 단백질의 구조 유연성을 분석하였을 때 알파나선 8과 그 연결 부위를 치환한 HM1, HM6, HM4, HM7은 모두 WT보다 구조 유연성이 높았다(도 11A). 이 결과는 국소적 열 안정성의 증가가 단백질 구조 전체의 유연성을 증가 시켰음을 제시한다.
- [0185] 변이체 HM6와 HM7의 차이점은 G340-I344 사이의 아미노산이다. 변이체 HM7의 열 안정성 증가에 관여하는 아미노산을 알아보기 위해 변이체 HM6를 기반으로 I344N이 치환된 HM8, S343과 I344N이 치환된 HM9, L342W, S343E, I344N이 치환된 HM10, T341S, L342W, S343E 및 I344N이 치환된 HM21을 각각 제작하였다. 변이체 HM8, HM9, HM10, HM21에서 치환한 아미노산의 서열은 표11에 표시되어 있다. 변이체 HM8, HM9, HM10, HM21은 ExpiCHO 세포에서 발현되었다 (도 5A). 변이체 HM6를 기반으로 알파나선 8의 N-말단 방향으로 I344N, S343E, L342W 돌연변이를 도입할수록 변이체 HM8, HM9, HM10의 응집온도가 각각 52.5 °C, 53 °C, 55.5 °C로 증가하였다 (도 10). 그렇지만 변이체 HM8, HM9, HM10에서는 WT와 유사한 효소 활성이 유지되었다 (도 5B). 이 결과는 변이체 HM8, HM9, HM10에서 도입된 아미노산 치환이 효소의 열 안정성에는 국소적인 영향을 주었지만, 효소 활성에는 큰 영향을 주지 않음을 제시한다. 그렇지만 HM21은 HM10보다 열 안정성이 감소하였지만, pH 7.0에서 WT보다 2배 높은 특성을 나타내었다. Substrate-gel assay에서 1 시간 동안 WT와 각 변이체를 기질과 반응시켰을 때 효소 활성은 HM21 > HM10 > HM9 > HM8 > HM6 > WT순으로 나타났다 (도 5C).
- [0186] Phenyl 컬럼을 이용하여 변이체 HM7, HM8, HM9, HM10, HM21을 물성을 조사하였을 때, 이들 PH20 변이체들은 WT보다 더 빨리 용출되어 모두 친수성 성질이 있음을 제시한다. 그렇지만 아미노산 치환 위치에 주 피크의 패턴이 다르게 나타나는 특성을 보였다 (도 5D).
- [0187] 변이체 HM7의 경우에도 변이체 HM1, HM6와 마찬가지로 Phenyl 컬럼에서 2개의 피크로 나타나 2종류의 형태가 존재함을 제시한다.
- [0188] 등전점에 따른 WT와 변이체의 이동 양상을 알아보기 위해 등전위점 초점화(Isoelectric focusing, 이하 IEF라고

함) 분석을 실시하였다 (도 5E). IEF gel에서 WT와 변이체 HM6, HM8은 비슷한 이동 양상을 보이고, S343E 돌연 변이가 포함된 변이체 HM9, HM10, HM21, HM7은 더 산성(acidic)쪽으로 이동하였다. 이 결과는 G340-I344 사이의 아미노산 중 S344E 치환에 의한 글루탐산의 도입으로 인해 단백질의 등전점에 변화가 일어남을 보인다.

[0189] 그리고 변이체 HM6를 기반으로 알파나선 8의 C-말단 방향으로 확장하여 아미노산을 치환하여 변이체 HM11, HM12를 제작하였다. 변이체 HM11과 HM12에서 치환한 아미노산의 서열은 표 11에 표시되어 있다. 변이체 HM11는 ExpiCHO 세포에서 발현되었으나 발현량이 야생형 WT보다 낮았으며 (도 2), 변이체 HM12는 ExpiCHO 세포에서 발현되지 않았다. 변이체 HM11은 WT와 비교하여 32%의 활성을 나타내었다 (도 6B).

[0190] 실시예 4. N-말단이 절단된 HM6 기반의 변이체 제작

[0191] PH20의 C-말단 부위는 PH20의 발현과 효소 활성에 중요한 역할을 하는 것으로 이미 알려져 있지만, PH20의 N-말단 부위 아미노산의 역할은 잘 알려져 있지 않다. PH20의 N-말단 부위 아미노산의 절단이 효소 활성에 어떤 영향을 주는지를 알아보기 위해 변이체 HM6를 기반으로, N-말단이 N37, F38, R39, A40, P41, P42에서 절단된 변이체 HM40, HM13, HM41, HM24, HM42 및 HM25을 제작하였다 (표 11). 그리고, 추가적으로 N-말단의 아미노산에 변형을 가한 HP61, HP62를 제작하였다.

[0192] HM40, HM13, HM41, HM24, HM42, HP61, HP62는 ExpiCHO 세포에서 발현되었으나 HM25는 발현되지 않았다(도 7A 및 도 7B). N-말단이 절단된 PH20 변이체들은 N 말단 시작하는 위치에 따라 효소 활성의 차이를 나타내었다. 아미노산 1~3개가 절단된 변이체 HM40, HM13, HM41은 주형인 HM6와 비교하여 효소 활성이 유사하지만, 아미노산의 4~5개 절단된 HM24와 HM42는 활성이 HM6 보다 조금 감소하였다 (도 7C). 그렇지만 6개의 아미노산이 절단된 HM25는 ExpiCHO에서 발현이 거의 안되었을 뿐만 아니라 효소 활성도 3.5 U/ μ g으로 현저히 낮았다. N-말단의 아미노산에 변형을 가한 HP61과 HP62에서는 효소 활성의 변화가 크지 않은 것으로 보인다.

[0193] Substrate-gel assay 방법(1시간 반응)으로 측정한 N-말단 절단 변이체의 효소 활성은 HM40, HM13, HM41의 경우 주형인 HM6의 효소 활성과 유사하였지만, HM24, HM42는 HM6의 효소 활성 보다 감소하였다 (도 7D). 6개의 아미노산이 절단된 HM25는 단백질량이 적어 분석하지 못하였다.

[0194] Phenyl 컬럼을 이용하여 변이체 HM40, HM13, HM41, HM24, HM42의 물성을 분석하였을 때, 이들 변이체들은 WT보다 먼저 컬럼에서 용출되어 친수성 성질을 나타내었다 (도 7E). 이 결과는 변이체 HM40, HM13, HM41, HM24, HM42이 변이체 HM6에 기반하여 제작되었고 L36-A40 잔기의 특성을 고려할 때, HM6의 친수성 특성을 따른 것으로 여겨진다.

[0195] DLS로 측정된 N-말단 절단 변이체의 응집온도는 아미노산이 시작하는 위치에 따라 변이체 간의 차이가 나타났다 (도 7F). 변이체 HM40, HM13, HM41, HM42는 N-말단이 절단되었음에도 50℃ 이상의 응집온도를 나타내어 주형인 HM6의 특성이 그대로 유지되었다. 그 중에서도 HM40과 HM42는 HM6 보다 3~4℃ 높은 응집온도를 나타내어 열 안정성이 증가한 것으로 사료된다. 또한, PH20의 N-말단 부위에 위치한 아미노산을 치환하였을 때 단백질 발현과 효소 활성에 미치는 영향을 알아보기 위해 PH20의 N-말단 아미노산 서열 36~47 (LNFRAAPPVIPNV)를 FRGPLLPNR로 치환한 변이체 HM17과 PH20의 N-말단 아미노산 서열 36~52 (LNFRAAPPVIPNVPFLWA)를 FRGPLLPNRPFTTV로 치환한 변이체 HM18을 제작하였다. 변이체 HM17과 HM18에서 치환한 아미노산의 서열은 표 11에 표시되어 있다. 변이체 HM17과 HM18은 ExpiCHO 세포에서 발현되지 않았다. N-말단에 위치한 5개 아미노산까지 절단되더라도 단백질 발현과 효소 활성을 보였으나 36~47 또는 36~52와 같이 더 많은 아미노산 서열의 치환은 단백질 접힘에 영향을 준다는 것을 제시한다.

[0196] 실시예 5. PH20의 C-말단이 절단된 HM6 기반의 변이체 HM14, HM15, HM16 제작

[0197] PH20의 C-말단은 단백질 발현과 효소 활성에 중요한 부위로 알려져 있다. 본 발명에서는 변이체 HM6를 기반으로 C-말단의 아미노산을 각각 I465, F468, K471에서 절단한 변이체 HM14, HM15, HM16을 제작하였다. 변이체 HM14, HM15, HM16에서 치환한 아미노산의 서열은 표11에 표시되어 있다. 변이체 HM14, HM15, HM16은 ExpiCHO 세포에서 발현되었으며 (도 8A), 단백질 발현량은 HM16 > HM15 > HM14 순서로 C-말단의 아미노산이 많이 절단될수록 단백질 발현량이 감소하였다 (도 8A). 그렇지만 변이체 HM14, HM15, HM16의 효소 활성은 HM16 > HM14 (≡WT) > HM15 순서이었다(도 8B). Frost 등에 의하면 PH20의 C-말단 477~483 부위는 soluble expression에 필요하고, C-말단이 C467에서 절단될 경우 효소 활성은 C-말단이 477~483에서 절단된 PH20 변이체에 비해 10%에 불과하고, C-말단이 467보다 앞에서 절단될 경우 효소 활성이 없었다. 그렇지만 본 발명에서 제작한 C-말단이 절단된 변이체(HM14, HM15, HM16)들은 변이체 HM6를 기반으로 제작하여 M345-I361 구간의 아미노산 치환으로 인해 단백질 접힘이 증가하고, 이로 인해 열 안정성이 증가하였기 때문에 C-말단의 I465, F468, P471 다음에서 절단되더라도

WT와 효소 활성이 유사하였고, 현저한 효소 활성의 감소는 없었다.

- [0198] WT와 변이체 HM14, HM15, HM16의 구조 유연성을 아크릴아마이드를 이용한 형광 quenching으로 조사하였다(도 11B). 변이체 HM14, HM15, HM16은 모두 WT보다 구조가 유연하였다. 이 결과는 변이체 HM6를 기반으로 제작한 C-말단 절단 변이체의 경우에도 구조 유연성을 유지함을 알 수 있다.
- [0199] Turbidimetric assay 방법으로 측정된 변이체 HM14, HM15, HM16의 효소 활성은 substrate-gel assay에서도 확인되었다(도 8C).
- [0200] Phenyl 컬럼을 이용하여 C-말단이 절단된 변이체의 물성을 분석하였을 때 변이체 HM14, HM15, HM16은 모두 WT보다 먼저 용출되어 친수성 성질을 나타내며 변이체들 사이의 친수성은 변이체 HM16 > HM14 > HM15 순이다(도 8D).
- [0201] 실시예 6. N-말단과 C-말단 아미노산 절단을 포함하는 HM10 기반의 변이체 HM19, HM20 제작.
- [0202] 본 발명에서 제작한 PH20 변이체들은 HM6를 기반으로 하고 G340~I344의 아미노산 추가 치환한 HM8, HM9, HM10이 WT보다 단백질 발현량, 효소 활성, 열 안정성 면에서 우수한 성능을 보였다. HM8, HM9, HM10 중에서 효소 활성과 열 안정성이 높은 HM10을 기반으로 N-말단이 F38에서 절단되고, C-말단이 K470 또는 F468에서 절단된 변이체 HM19와 HM20을 제작하였다. HM19와 HM20은 모두 ExpiCHO 세포에서 발현되었고, HisTrap 컬럼을 이용하여 정제되었다(도 9A). Turbidimetric assay 방법으로 효소 활성을 측정하였을 때, HM19와 HM20은 WT보다 10% 높은 효소 활성을 나타내었다(도 9B). Substrate-gel assay에서도 HM19와 HM20은 WT보다 높은 효소 활성을 나타내었다(도 9C).
- [0203] 실시예 7. HM10 기반의 PH20 변이체 특성 분석
- [0204] HM10 기반의 C-말단 절단 변이체들은 C-말단의 길이가 짧아질 수록 ExpiCHO 세포에서 발현량이 감소하는 경향을 보였으며, C-말단의 길이가 C464 이하인 경우 발현 되지 않았다 (도 12). C464는 C437과 이황화 결합을 형성하여 단백질 구조 유지에 중요하기 때문에 반드시 필요하다.
- [0205] C-말단이 464에서 절단되거나 또는 더 짧은 경우 ExpiCHO에서 발현이 되지 않는지를 확인하기 위해 Western blot 실험을 하였다. 도 13과 같이 HM30, HM31, HM32, HM33 변이체는 Western blot에서 탐지되지 않았다.
- [0206] Turbidimetric assay 방법으로 측정된 HM10 기반의 C-말단 절단 변이체의 효소 활성은 도 14A와 도 14B에 나타나 있다. C-말단 절단 변이체들은 WT과 비교하여 $\pm 20\%$ 의 효소 활성을 나타내었다. C-말단이 I480 이후에서 절단될 경우 효소 활성은 전반적으로 증가하였다. 그리고 HM19와 HM20에서 6xHis-tag을 제거한 변이체인 HP19와 HP20은 6xHis-tag이 있을 때 보다 효소 활성이 각각 23%, 9.6% 감소하는 것으로 나타나 6His-tag이 효소 활성에 영향을 주는 것으로 사료된다.
- [0207] Substrate-gel assay 방법으로 HM10 기반의 C-말단 절단 변이체에 대한 효소 활성을 측정하였을 때 이들 변이체들은 WT 보다 높은 효소 활성을 나타내었으며, 주형인 HM10의 효소 활성과 유사하여 C-말단 길이에 따른 차이는 크지 않았다 (도 14C).
- [0208] 실시예 8. HM21 기반의 PH20 변이체 특성 분석
- [0209] 변이체 HP34는 4 단계의 컬럼을 거쳐 정제하였고 (도 15A), HP46은 3 단계의 컬럼을 거쳐 정제하였다 (도 15B). HP34와 HP46의 생산량은 각각 1.73 mg/L와 25.6 mg/L이었다. HP34와 HP46은 6xHis-tag이 없는 변이체로 6xHis-tag이 있는 변이체들과는 정제 과정이 달라 단백질의 발현량을 비교하는 것은 어렵다.
- [0210] Turbidimetric assay에서 HP34와 HP46의 활성은 각각 45.6 U/ μ g과 47.2 U/ μ g으로 WT 보다 약 2배 높은 활성을 보였으며, 주형인 HM21 보다도 대략 10% 정도 활성이 증가하였다 (도 16A).
- [0211] Morgan-Elson assay로 각 변이체의 kinetics를 측정하여 도 16B에 나타내었다. HP34와 HP46 촉매효율(k_{cat}/K_m)은 야생형 HW2 보다 1.7~2배 높아 specific activity가 WT 보다 높은 결과와 상통한다. Michaelis 상수(K_m)는 이들 변이체가 HW2 보다 낮아 기질에 대한 친화도가 증가한 것으로 사료된다. 이 결과들로부터 HM21, HP34, HP46 변이체들은 기질과 강하게 결합할 뿐만 아니라 기질을 생성물로 바꾸는 효율 또한 높은 특성을 지닌 것으로 결론 내릴 수 있다. 이런 특성은 T341을 세린으로 치환한 효과이다. 341번에 위치한 트레오닌을 알라닌, 글리신, 아스파르트산 등의 아미노산으로 치환 할 경우 효소 활성에 영향을 미치는 것을 예측할 수 있다.
- [0212] DLS로 측정된 HP34와 HP46의 응집온도는 각각 51.5°C와 51.0°C으로 나타나 주형인 HM21과 유사하였으며, HW2 보

다 대략 5°C 높은 열 안정성을 나타내었다 (도 17A). Substrate-gel assay로 측정한 변이체 HP34의 활성은 HP20와 유사하게 나타난 반면, HP46은 HP20 보다 높은 효소 활성을 나타내어 주형으로 HM10 보다 HM21의 단백질 접힘이 더 뛰어난 것으로 여겨진다 (도 17B).

- [0213] 야생형 HW2와 변이체 HP46를 pH 7.0과 pH 3.0 조건에서 하룻밤 동안 방치한 후 substrate-gel assay로 효소 활성을 비교하였을 때 HP46는 pH 7.0 뿐만 아니라 pH 3.0에서도 높은 활성을 나타내어 뛰어난 안정성을 보여 주었다 (도 17C).
- [0214] HM53, HM54, HM55, HM56, HP59, HP60은 HM21 기반의 변이체 중 341번 위치의 아미노산에 대해 변이를 갖고 있는 변이체이다. 341번 위치의 아미노산이 변이됨에 따라 그 발현 정도와 활성에 다양한 영향을 미치는 것을 확인하였다 (도 17D, 도 17E).
- [0215] 실시예 9. PH20 변이체의 in vitro 면역 원성 분석
- [0216] 저분자 화학합성물질에 비해 큰 분자량을 갖는 바이오의약품은 인체내로 들어갔을 때 의도하지 않은 면역반응을 일으킬 위험성을 가지고 있다. 큰 분자량 바이오물질의 2차 구조나, 3차구조에서 접힘이나 인접 도메인과의 상호작용에 의해 만들어지는 외부와의 접촉면은 인체내의 면역작용계에 항원결정기(epitope)을 제공함으로써 바이오 물질에 대한 면역반응을 촉진시킬 수 있다. 이러한 면역반응은 약물에 대한 항체(anti-drug antibody: ADA)를 생성시킬 수 있으며, 이러한 반응에 의해 약물의 효능성을 저해시키거나, 약물에 대한 과민반응을 유발하거나, 약물의 인체내에서의 제거(clearance)를 촉진할 수 있다. 약물에 대한 면역반응은 따라서 임상 시험에서의 결과에 영향을 미칠 수 있으며, 장기간 사용시에 중대한 이상 반응을 유발할 수 있다. 이러한 면역 반응에는 여러 가지 요인들이 영향을 미칠 수 있는데, 약물 자체나 질병에 특이적 반응, 또는 투약 방법이나 개개인의 환자에 따른 요인에 의해 유발될 수 있다. 약물 자체에 의한 요인으로는 바이오 의약품의 인체내 펩타이드와의 유사/비유사성, posttranslational modification, 불순물, 응집체 형성, 제형의 특성 등이 있다. 환자 개개인에 따른 요인으로는 성별이나, 복용하고 있는 다 약물과의 반응성, HLA (human leukocyte antigen) type에 따른 유전적 요인 등이 있다.
- [0217] 이러한 면역원성 반응은 면역반응의 생성 원인에 관계없이 항원결정기를 인식하는 CD4+ T cell이나 CD8+ T cell에 의해 진행된다. 개개인에 있어서의 HLA class II 유전자 다양성 때문에, CD4+ T cell의 항원결정기는 개개인 간에 차이가 있고, 따라서 건강한 기증자에 의해 제공된 각각의 혈액내 CD4+ T cell에서의 바이오 약물에 반응성은 임상과정에서 생겨날 수 있는 면역 반응성을 평가하는데 있어서 매우 중요한 판단기준이 될 수 있다. CD4+ T cell은 항원제시세포(antigen presenting cell; APC)가 자신의 II형 MHC(major histocompatibility complex)를 통해 제시된 항원을 인식하여 활성화된다. 활성화된 CD4+ T cell은 사이토카인을 방출하여 대식세포, 세포독성 T 세포, B 세포를 활성화시켜, 결과적으로 항체가 많이 생산되도록 한다. 이와는 달리 CD8+ T cell은 직접적인 세포독성을 가지고 있으며 항원에 감염된 세포, 손상되거나 제 기능을 상실한 세포를 직접 제거한다. CD8+ T cell은 T 세포 수용체를 가지고 있어, 모든 세포의 표면에 위치한 I형 MHC 분자에 붙어있는 특정한 항원의 펩타이드를 인식할 수 있다. CD8+ T cell은 또한 항원제시세포에 의해서 제시된 항원을 인식하여 활성화될 수 있으며, 이러한 활성화는 CD4+ T cell의 사이토카인에 더욱 증진될 수 있다. 따라서 in vitro에서 신규 바이오물질의 CD4+ T cell과 CD8+ T cell의 활성화 정도를 측정함으로써 임상과정에서 유발될 수 있는 면역원성 반응을 예측할 수 있다. 본 실시예에서는 PBMC로부터 CD4+ T cell과 CD8+ T cell을 분리한 후, 대조물질인 PH20과 PH20변이체 (HP46)를 각각 1.5 ng/mL과 15 ng/mL로 처리한 후, 활성화된 CD4+ T cell과 CD8+ T cell의 분포를 측정함으로써 대조물질과 비교하여 PH20변이체의 면역원성을 예측하고자 하였다. 각 T cell의 활성화 정도는 Stimulating Index를 이용하여 측정하였으며, Stimulating Index (SI)는 아래와 같이 정의된다. SI 값이 2 이상인 경우에 유의적 수준에서 활성화되었다고 판단할 수 있다.
- [0218] Stimulating Index (SI) = (시험시료를 처리 후의 T cell 활성화도) /
- [0219] (vehicle 처리 후의 T cell 활성화도)
- [0220] 면역원성 반응은 HLA type에 따라 달라질 수 있으며, 따라서 보다 다양한 HLA type에서의 반응을 측정하기 위해 실험은 10명의 healthy donor로부터 받은 PBMC에서 분리한 T cell을 이용하여 수행하였다. 사용된 10개 PBMC의 HLA type은 아래의 표 12 와 같다.

표 12

테스트된 PBMC의 HLA type

No	HLA A		HLA B		HLA C1		DRB1		DQB1		DPB1	
1	0206	3303	3501	5801	0302	0801	1405	1501	0303	0602	0201	0301
2	0201	0207	4601	5101	0102	1502	0803	1101	0301	0601	0201	0202
3	0206	3101	1501	3501	0304	0401	0803	0901	0303	0601	0201	0501
4	0101	3101	1501	1517	0303	0701	1302	1501	0602	0604	0401	0501
5	0201	3101	5101	6701	0702	1402	0401	0403	0301	0302	0201	0401
6	0201	1101	1501	3901	0401	0702	0102	0901	0402	0501	0101	1401
7	0201	0206	4002	5502	0102	0304	0802	1454	0302	0502	0402	0501
8	0201	0201	1501	4001	0303	0304	0802	1406	0301	0302	0501	1301
9	1101	2402	4006	5101	0801	1502	0701	0901	0202	0303	0201	1301
10	2602	3101	4002	5101	0304	1502	0405	1501	0401	0602	0201	0501

[0221]

[0222] PH20과 PH20변이체에서의 CD4+와 CD8+ T cell의 활성화도 측정 결과는 표 13에 정리된 것과 같다. CD4+과 CD8+ T cell의 활성화도 측정 결과를 보면, PH20과 PH20 변이체 모두, 활성화도가 비교적 낮은 수준으로 판단된다. PH20의 경우, 2개의 실험에서 CD4+ T cell의 활성화도가 2 이상으로 측정되었으며, PH20변이체의 경우는 CD4+ T cell의 활성화가 측정되지 않았다. CD8+ T cell의 경우는 PH20에서 1개의 실험에서 활성화가 측정되었으며, PH20변이체의 경우도 1개의 실험에서 활성화가 측정되었다. 그러나 PH20의 경우는 1.5 ng/mL과 15 ng/mL 모두에서 SI값이 2 이상으로 측정되었으나 PH20변이체의 경우는 1.5 ng/mL에서의 2 이하의 SI값이, 15 ng/mL에서는 2 이상의 SI 값이 측정되었다(도 18 및 도 19 참조).

[0223] 따라서 낮은 농도에서는 CD8+ T cell의 활성화도가 PH20변이체에서는 낮은 것으로 관찰되며, PH20변이체에 비해 PH20에서의 CD8+ T cell의 활성화도가 높은 것으로 판단된다. 위와 같은 결과에서 도출되는 결론은,

[0224] 1) PH20과 PH20변이체의 CD4+ T cell 및 CD8+ T cell의 활성화도가 비교적 낮으며

[0225] 2) PH20보다 PH20변이체에서의 CD4+ T cell과 CD8+ T cell의 활성화 가능성이 낮은 것으로 판단된다.

[0226] 이와 같은 결과에서 PH20변이체의 임상에서의 면역원성 반응을 유발할 가능성은 PH20보다 낮을 것으로 예상된다.

표 13

In vitro 면역원성 분석(immunogenicity assay)결과로부터 측정된

자극 인덱스(Stimulating Index (SI))

PBMC No.	CD4				CD8			
	PH20 (ng/mL)		PH20변이체 (ng/mL)		PH20 (ng/mL)		PH20변이체 (ng/mL)	
	1.5	15	1.5	15	1.5	15	1.5	15
1	1.03	0.859	0.728	1.176	1.38	1.42	1.22	1.60
2	1.05	0.09	0.596	0.922	1.20	1.11	1.00	1.07
3	1.90	1.44	1.56	1.12	1.43	1.31	1.59	1.35
4	2.51	2.79	0.788	1.82	1.28	1.90	0.579	0.974
5	1.27	1.47	1.09	1.14	0.987	0.932	0.972	1.02
6	0.825	0.834	0.998	0.946	0.904	1.13	1.09	0.986
7	2.07	2.07	1.43	1.90	2.08	2.34	1.30	2.46
8	0.898	1.079	0.967	0.822	0.926	1.06	0.896	0.813
9	0.882	0.957	0.895	0.941	0.853	0.993	0.950	1.09
10	0.983	0.970	1.12	1.13	1.15	1.08	1.15	1.24

[0227]

산업상 이용가능성

[0228] 본 발명에 따른 PH20 변이체 또는 이의 절편들은 성숙된 야생형 PH20과 비교하여 ExpiCHO 세포에서 발현되었을 때 단백질 발현량이 증가하였으며, 단백질 응집온도는 4~11.5 °C 정도 증가하여, 높은 열 안정성을 가지면서 또한 효율적으로 생산될 수 있는 효과가 있다.

[0229] 또한, 본 발명에 따른 PH20 변이체 또는 이의 절편들은 히알루로니다제의 활성을 측정하는 실험 중의 하나인 substrate-gel assay의 결과에서 단백질의 접힘(refolding)이 향상되어 성숙된 야생형 PH20보다 빨리 renaturation이 되는 효과가 있으며, C-말단의 절단위치에 상관없이 원래의 효소 활성을 유지하는 효과가 있다.

[0230] 나아가 본 발명에 따른 PH20 변이체 또는 이의 절편들은 낮은 면역원성을 가지고 있어, 인체에 반복 투여하는 것이 가능하다.

[0231] 참고문헌

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[0233] Bookbinder, L.H., Hofer, A., Haller, M.F., Zepeda, M.L., Keller, G.A., Lim, J.E., Edgington, T.S., Shepard, H.M., Patton, J.S., and Frost, G.I. (2006). A recombinant human enzyme for enhanced interstitial transport of therapeutics. *J Control Release* **114**, 230-241.

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[0235] Frost, G.I. (2007). Recombinant human hyaluronidase (rHuPH20): an enabling platform for subcutaneous

drug and fluid administration. Expert Opin Drug Deliv 4, 427-440.

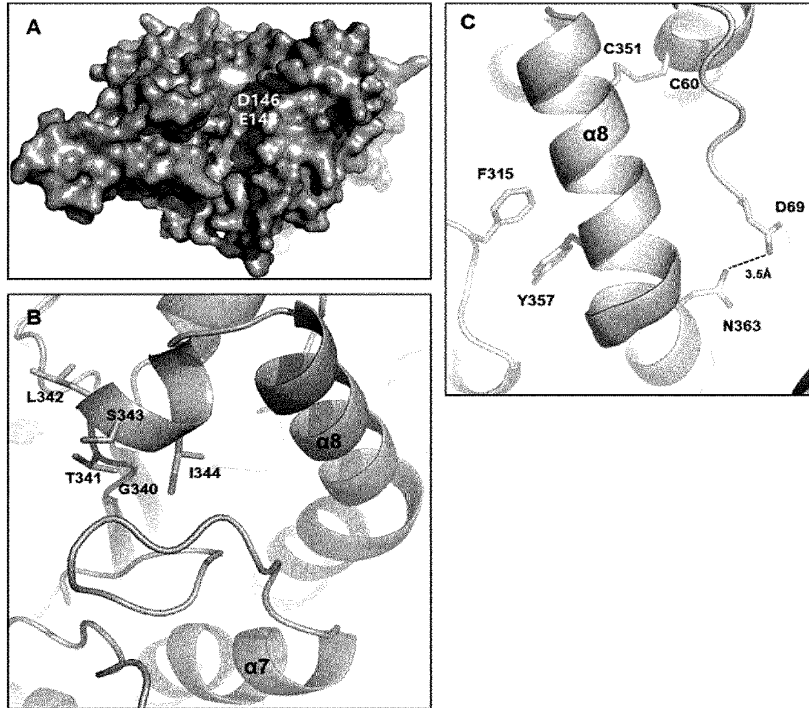
시열목록 자유텍스트

[0237]

전자파일 첨부하였음.

도면

도면1



도면2

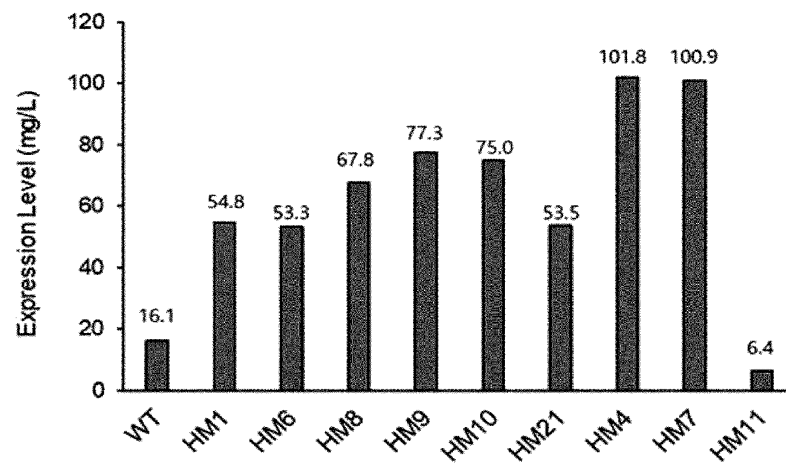


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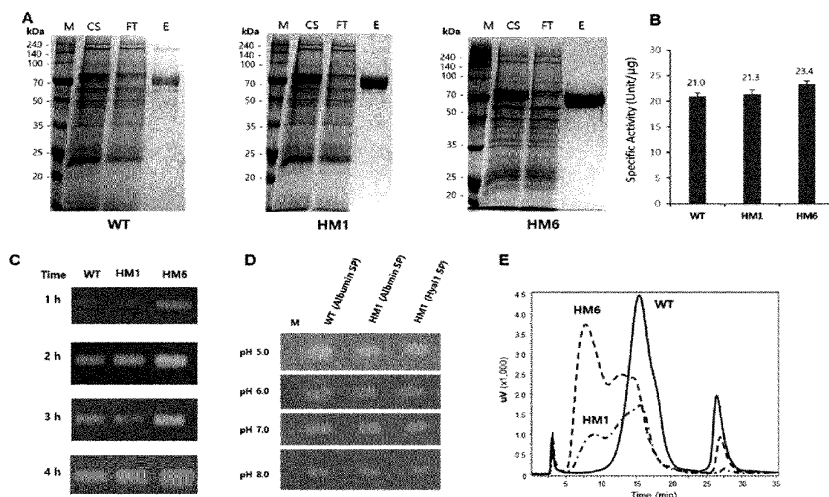
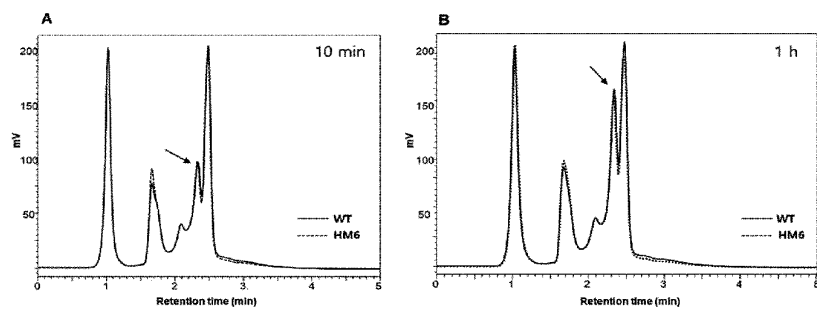
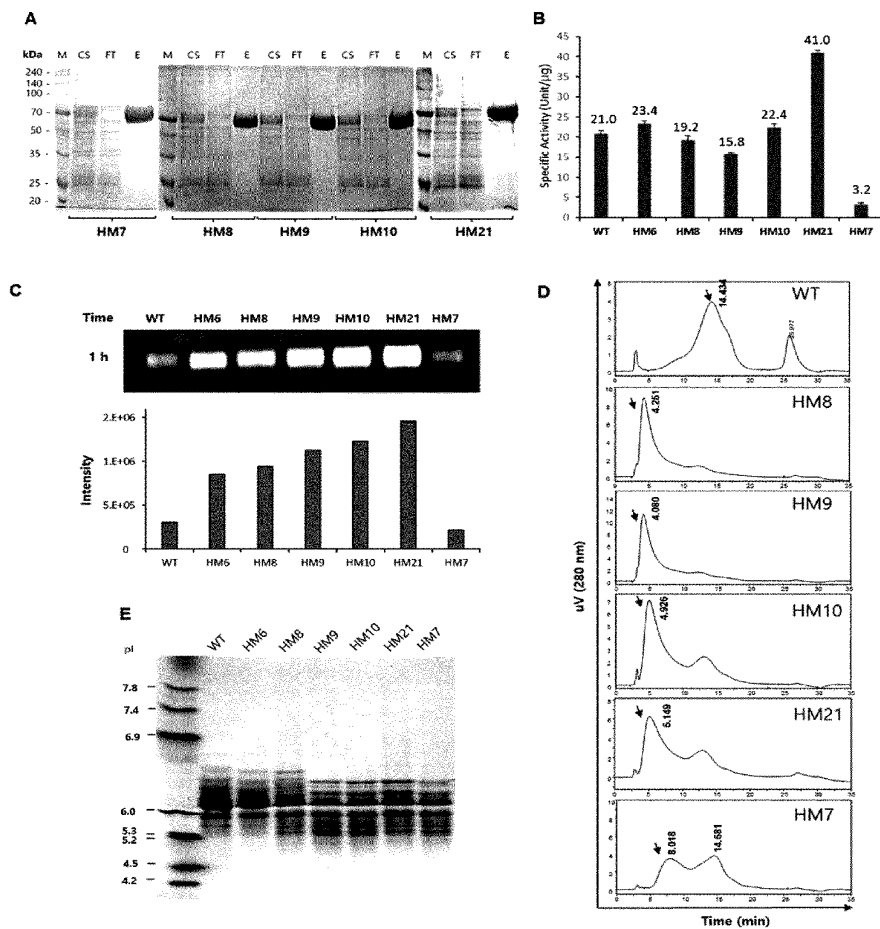


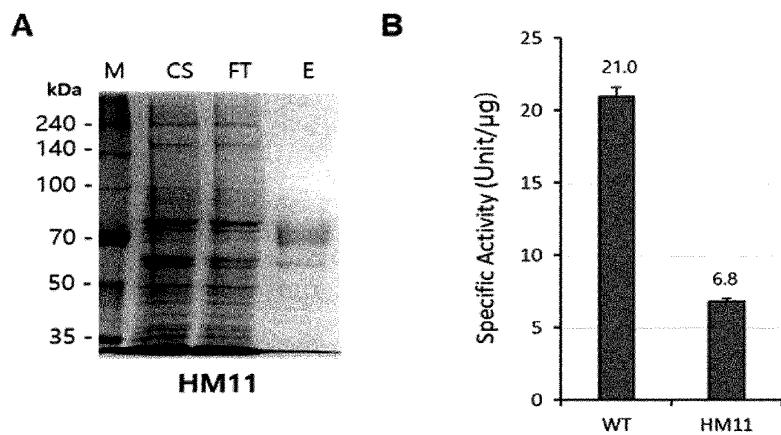
Figure 4



제 9/5



제 9/6



10/7

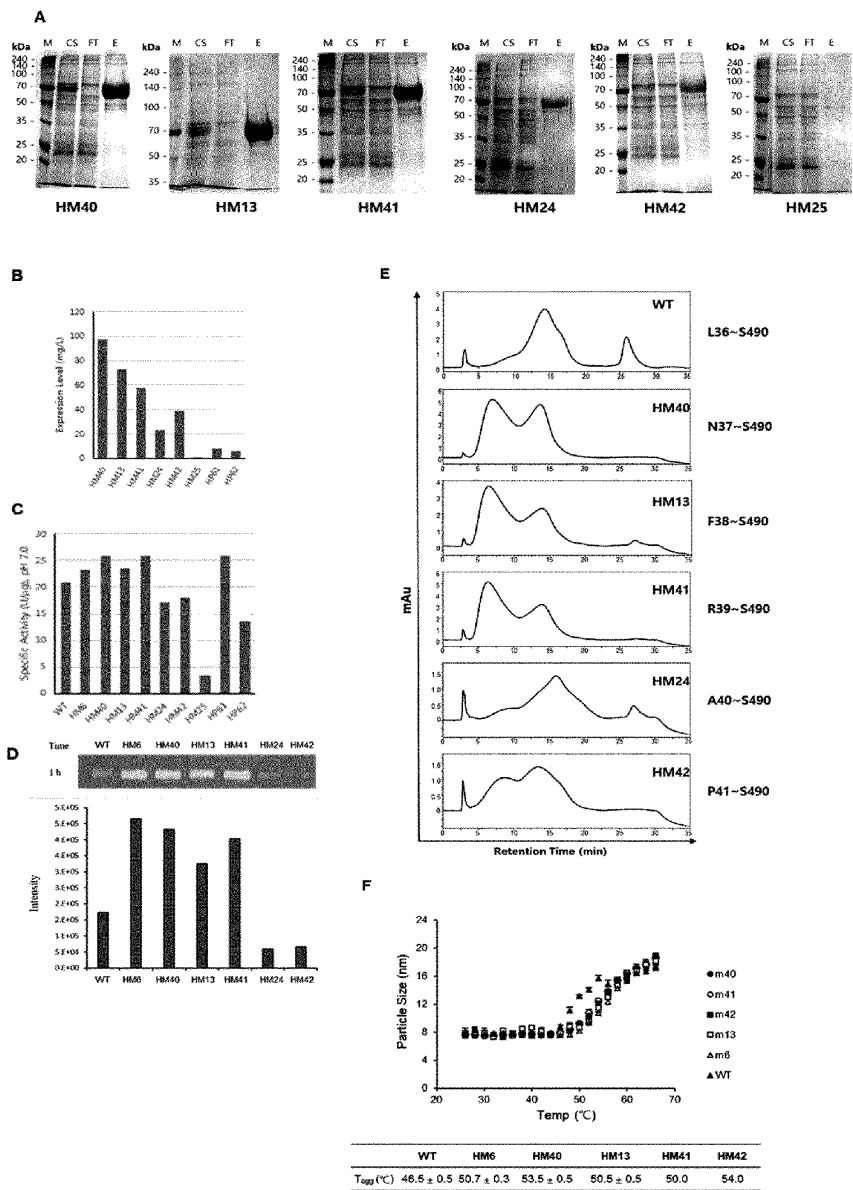


Figure 1

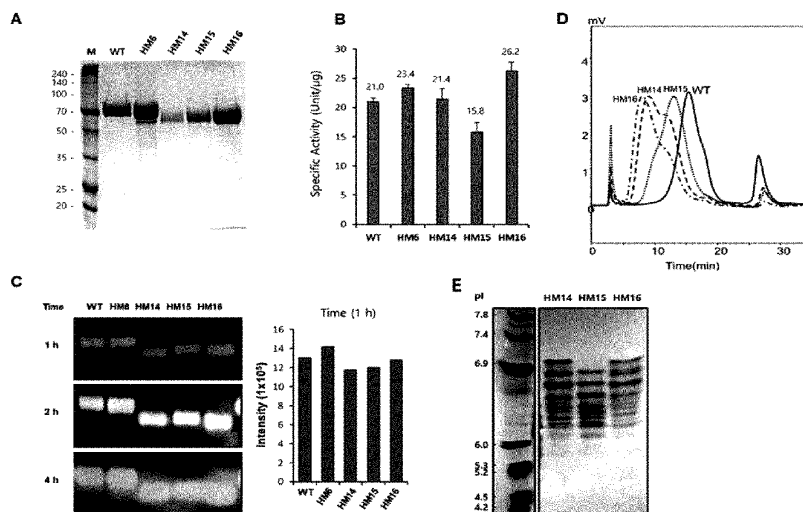


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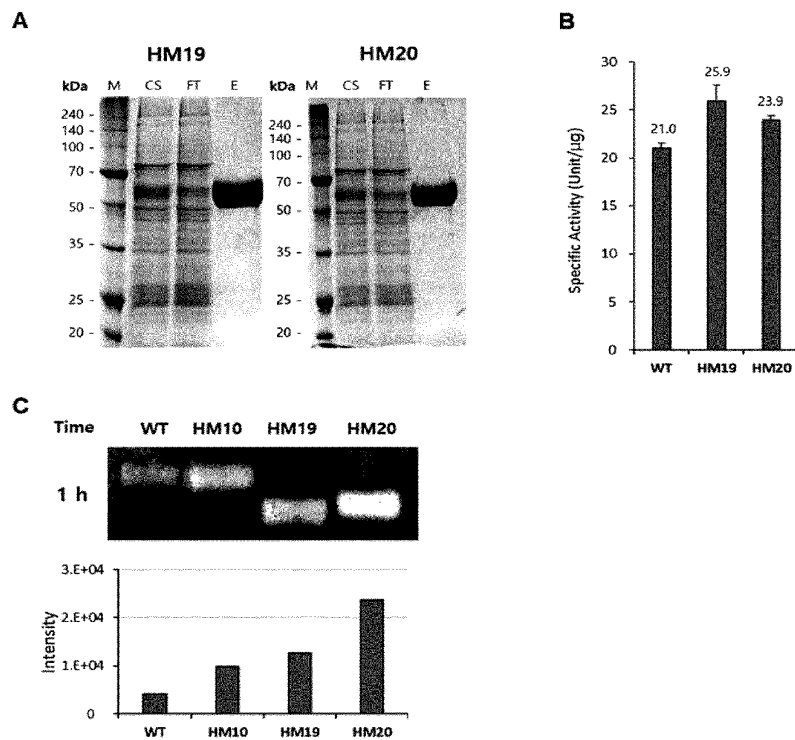


표 10

	응집온도 (°C)
WT	46.5 ± 0.5
HM1	53.0 ± 1.2
HM4	56.5 ± 1.5
HM6	50.5 ± 0.5
HM7	58.0 ± 1.0
HM8	52.5 ± 0.5
HM9	53.0 ± 1.0
HM10	55.5 ± 0.5
HM13	50.5 ± 0.5
HM14	51.0 ± 1.0
HM15	49.0 ± 1.0
HM16	51.0 ± 1.0
HM19	53.0 ± 1.0
HM20	51.0 ± 1.0
HM21	51.7 ± 0.7

표 11

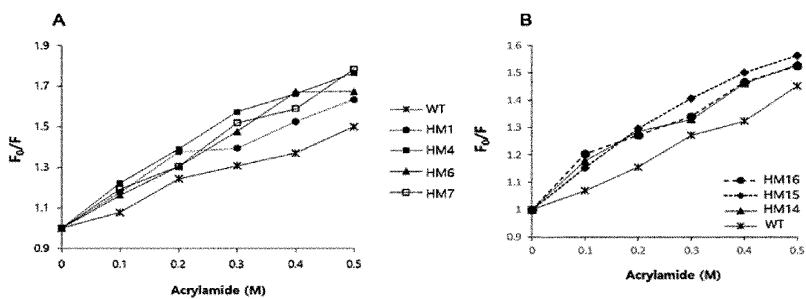


FIG 12

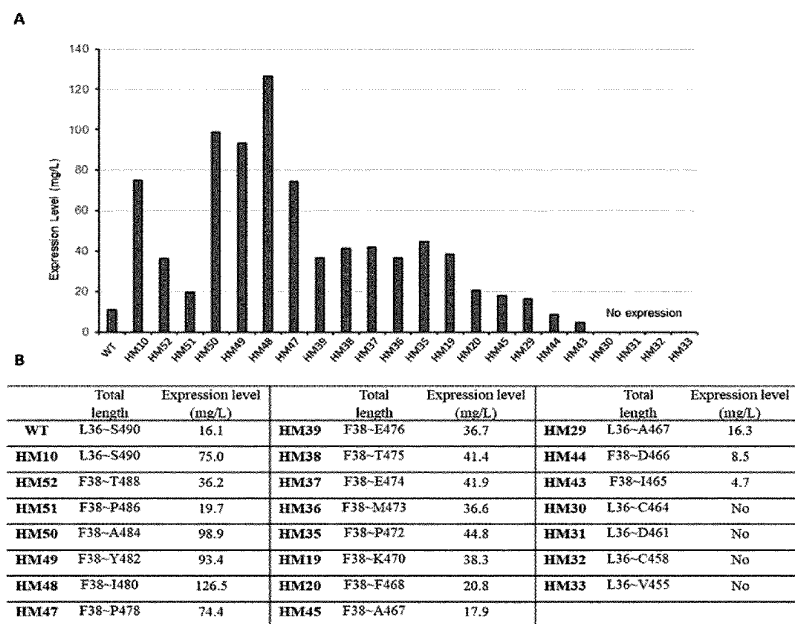


FIG 13

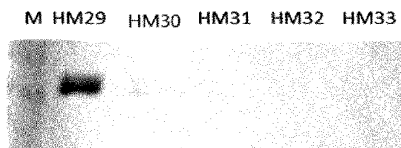


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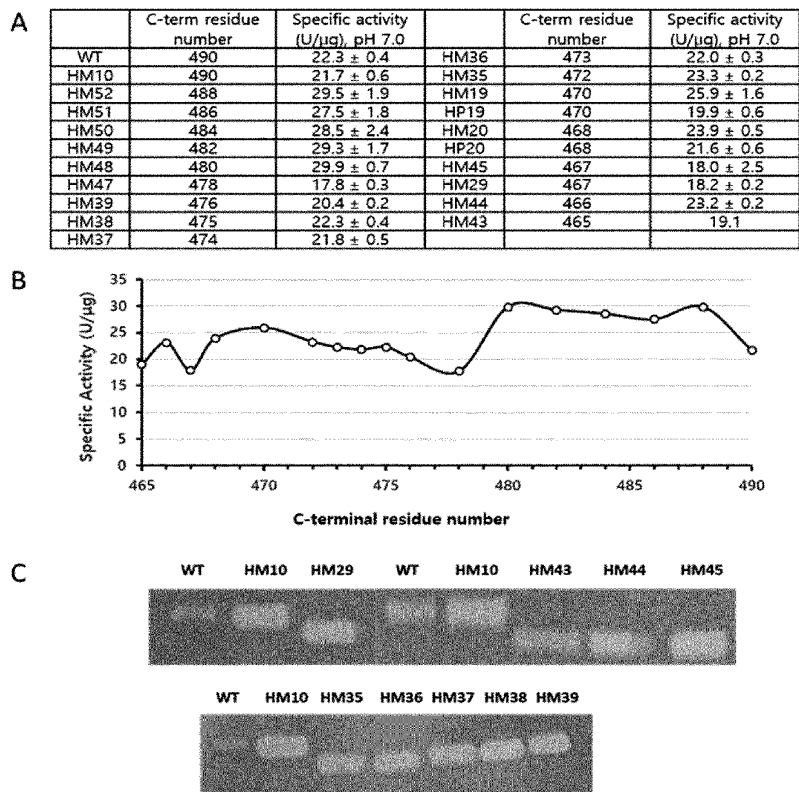


Figure 15

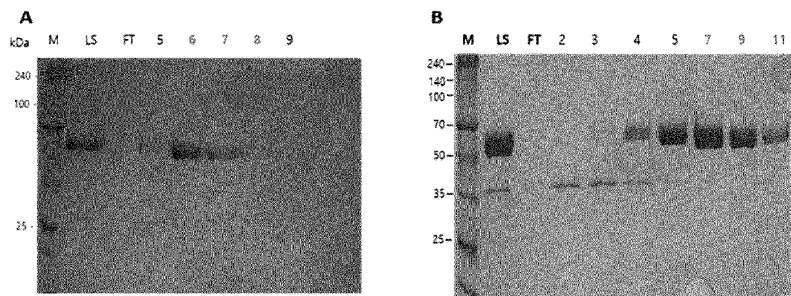


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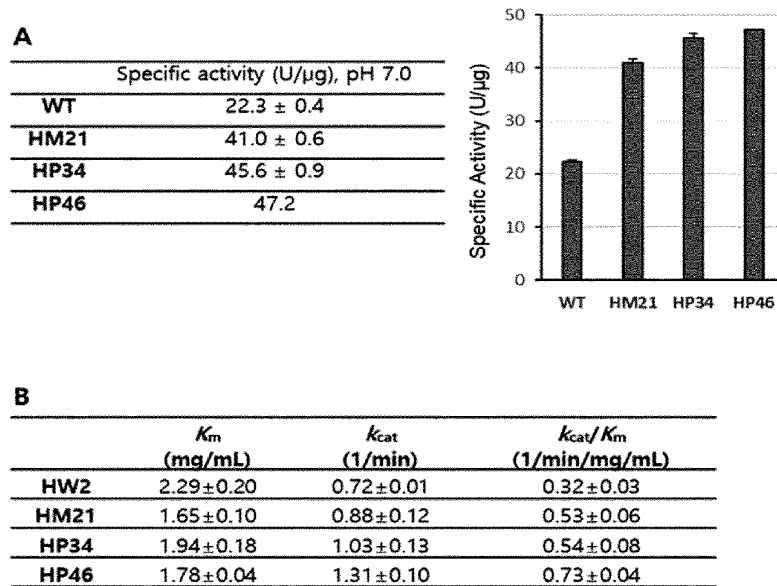
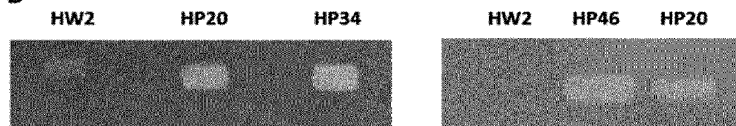


Figure 17

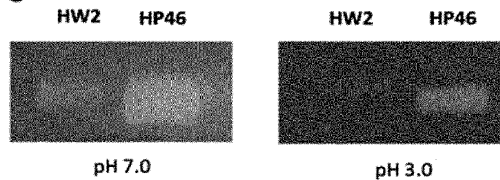
A

	T_{agg} (°C)
HW2	46.5
HM21	51.7
HP34	51.5
HP46	51.0

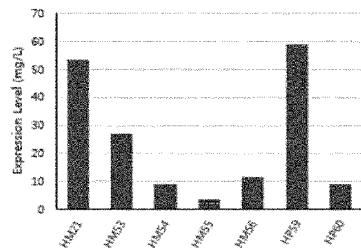
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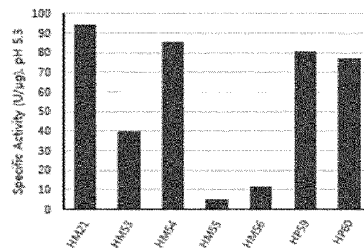
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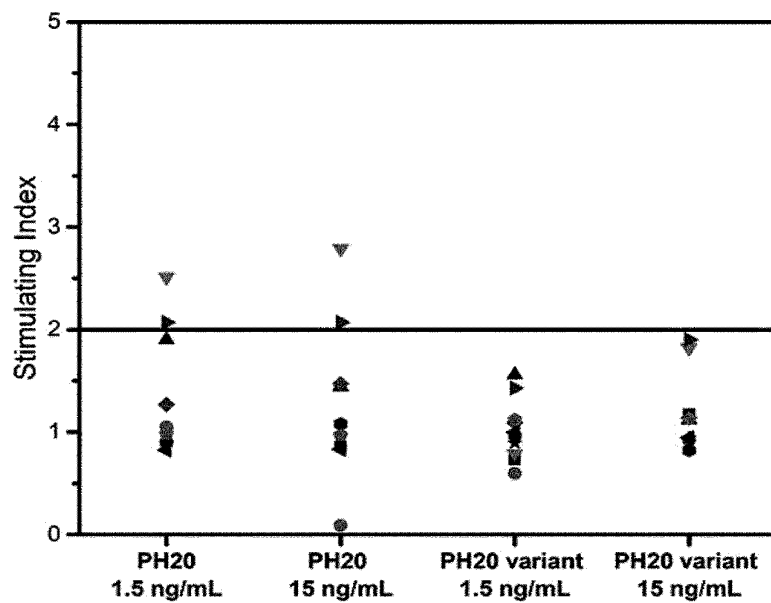
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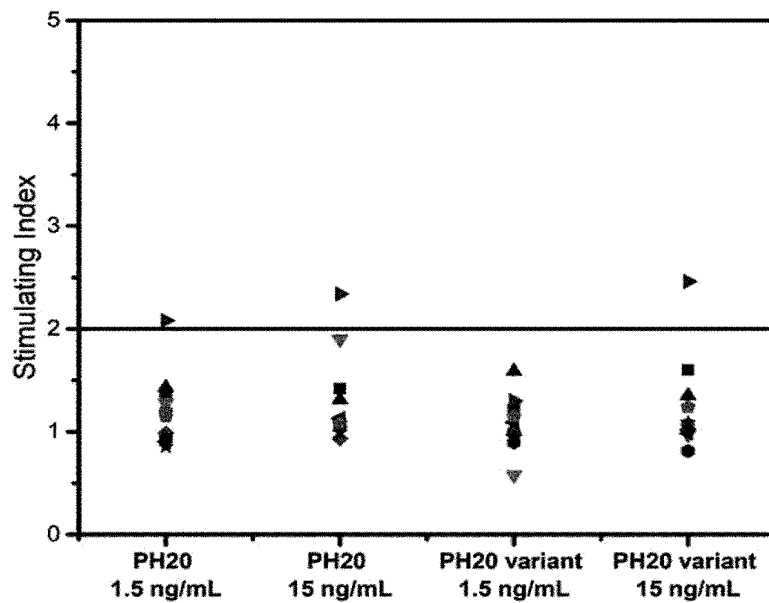
E



도 18



도 19



Alteogen Inc.

Alteogen Inc.

Novel Hyaluronidase Variants and Pharmaceutical Composition
Comprising the Same

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 100 105 110
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 115 120 125
 Lys Asp Ile Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val
 130 135 140
 Ile Asp Trp Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro

145	150	155	160
Lys Asp Val Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn			
	165	170	175
Val Gln Leu Ser Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe			
	180	185	190
Glu Lys Ala Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys			
	195	200	205
Leu Leu Arg Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys			
	210	215	220
Tyr Asn His His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn			
225	230	235	240
Val Glu Ile Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser			
	245	250	255
Thr Ala Leu Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val			
	260	265	270
Ala Ala Thr Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val			
	275	280	285
Ser Lys Ile Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr			
	290	295	300
Arg Ile Val Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu			
305	310	315	320
Leu Val Tyr Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile			
	325	330	335
Val Ile Trp Gly Thr Leu Ser Ile Met Arg Ser Met Lys Ser Cys Leu			
	340	345	350
Leu Leu Asp Asn Tyr Met Glu Thr Ile Leu Asn Pro Tyr Ile Ile Asn			
	355	360	365
Val Thr Leu Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln			
370	375	380	
Gly Val Cys Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu			
385	390	395	400

Asn Pro Asp Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr
405 410 415
Val Arg Gly Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys
420 425 430
Phe Tyr Cys Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp
435 440 445
Val Lys Asp Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys
450 455 460
Ile Asp Ala Phe Leu Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile
465 470 475 480
Phe Tyr Asn Ala Ser Pro Ser Thr Leu Ser Ala Thr Met Phe Ile Val
485 490 495
Ser Ile Leu Phe Leu Ile Ile Ser Ser Val Ala Ser Leu
500 505
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Asp Met Ala Gln Gly Phe Arg Gly Pro Leu Leu Pro Asn Arg Pro Phe
20 25 30
Thr Thr Val Trp Asn Ala Asn Thr Gln Trp Cys Leu Glu Arg His Gly
35 40 45
Val Asp Val Asp Val Ser Val Phe Asp Val Val Ala Asn Pro Gly Gln
50 55 60
Thr Phe Arg Gly Pro Asp Met Thr Ile Phe Tyr Ser Ser Gln Leu Gly
65 70 75 80
Thr Tyr Pro Tyr Tyr Thr Pro Thr Gly Glu Pro Val Phe Gly Gly Leu
85 90 95

Pro Gln Asn Ala Ser Leu Ile Ala His Leu Ala Arg Thr Phe Gln Asp
100 105 110
Ile Leu Ala Ala Ile Pro Ala Pro Asp Phe Ser Gly Leu Ala Val Ile
115 120 125
Asp Trp Glu Ala Trp Arg Pro Arg Trp Ala Phe Asn Trp Asp Thr Lys
130 135 140
Asp Ile Tyr Arg Gln Arg Ser Arg Ala Leu Val Gln Ala Gln His Pro
145 150 155 160
Asp Trp Pro Ala Pro Gln Val Glu Ala Val Ala Gln Asp Gln Phe Gln
165 170 175
Gly Ala Ala Arg Ala Trp Met Ala Gly Thr Leu Gln Leu Gly Arg Ala
180 185 190
Leu Arg Pro Arg Gly Leu Trp Gly Phe Tyr Gly Phe Pro Asp Cys Tyr
195 200 205
Asn Tyr Asp Phe Leu Ser Pro Asn Tyr Thr Gly Gln Cys Pro Ser Gly
210 215 220
Ile Arg Ala Gln Asn Asp Gln Leu Gly Trp Leu Trp Gly Gln Ser Arg
225 230 235 240
Ala Leu Tyr Pro Ser Ile Tyr Met Pro Ala Val Leu Glu Gly Thr Gly
245 250 255
Lys Ser Gln Met Tyr Val Gln His Arg Val Ala Glu Ala Phe Arg Val
260 265 270
Ala Val Ala Ala Gly Asp Pro Asn Leu Pro Val Leu Pro Tyr Val Gln
275 280 285
Ile Phe Tyr Asp Thr Thr Asn His Phe Leu Pro Leu Asp Glu Leu Glu
290 295 300
His Ser Leu Gly Glu Ser Ala Ala Gln Gly Ala Ala Gly Val Val Leu
305 310 315 320
Trp Val Ser Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile
325 330 335
Lys Glu Tyr Met Asp Thr Thr Leu Gly Pro Phe Ile Leu Asn Val Thr

340 345 350
 Ser Gly Ala Leu Leu Cys Ser Gln Ala Leu Cys Ser Gly His Gly Arg
 355 360 365
 Cys Val Arg Arg Thr Ser His Pro Lys Ala Leu Leu Leu Leu Asn Pro
 370 375 380
 Ala Ser Phe Ser Ile Gln Leu Thr Pro Gly Gly Gly Pro Leu Ser Leu
 385 390 395 400
 Arg Gly Ala Leu Ser Leu Glu Asp Gln Ala Gln Met Ala Val Glu Phe
 405 410 415

 Lys Cys Arg Cys Tyr Pro Gly Trp Gln Ala Pro Trp Cys Glu Arg Lys
 420 425 430
 Ser Met Trp
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 <211> 26
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 1 5 10 15
 Cys Leu Pro Trp Leu Gln Glu Gly Ser Ala
 20 25
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 212> PRT
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 1 5 10 15
 Tyr Ser

<210> 5
 <211> 21
 <212> PRT
 <213> Artificial Sequence
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 1 5 10 15
 Asp Met Ala Gln Gly
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<210> 6
 <211> 33
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 <400> 6
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<210> 7
 <211> 55
 <212> DNA
 <213> Artificial Sequence
 <220><223> Synthetic Sequence
 <400> 7
 ctaattgcgg ccgctcatta gtggtgatgg tgatgatgga agaaaccaat tctgc 55

<210> 8
 <211> 41
 <212> DNA
 <213> Artificial Sequence
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 <400>
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 taacaggagg tgctctgaaa ttcagagagt aagcagagga g 41
 <210> 9
 <211> 98

<212> DNA
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 ggacactaca ctggggccct acataatcaa cgtcacac 98
 <210> 10
 <211> 89
 <212> DNA
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 <220><223> Synthetic Sequence
 <400> 10
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 caagccctgt gccaggagca aggagtgtg 89
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 <211> 89
 <212> DNA
 <213> Artificial Sequence
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 caagccctgt gccaggagca aggagtgtg 89
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 <211> 74
 <212> DNA
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 aaggaatcat gtca 74
 <210> 13
 <211> 61
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<213> Artificial Sequence

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<400> 13

agcaaggagt gtgtataagg aaaaccagcc acccaaaaga ctatcttcac ctcaaccag 60

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<210> 14

<211> 43

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<400> 14

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<210> 15

<211> 44

<212> DNA

<213> Artificial Sequence

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<400> 15

attgtaatat ggggaaccct cagtaataca agaaccaagg aatc 44

<210> 16

<211> 44

<212> DNA

<213> Artificial Sequence

<220><223> Synthetic Sequence

<400> 16

attgtaatat ggggaaccct cgaaaataca agaaccaagg aatc 44

<210> 17

<211> 44

<212> DNA

<213> Artificial Sequence

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<400> 17

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<210>	19	
<211>	63	
<212>	DNA	
<213>	Artificial Sequence	
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	acactacact gaacccttc atactcaacg tcacctatc aggcaaatg ttagccaag	60
	tgc	63
<210>	20	
<211>	35	
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<400>	20	
	taacaggagg tgctctgaaa gagtaagcag aggag	35
<210>	21	
<211>	56	
<212>	DNA	
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<400>	21	
	ctaattgcgg ccgctcatta gtggtgatgg tgatgatgta tacagacacc atcagc	56
<210>	22	
<211>	59	
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<220><223> Synthetic Sequence

<400> 22

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59

<210> 23

<211> 61

<212> DNA

<213> Artificial Sequence

<220><223> Synthetic Sequence

<400> 23

ctaattgcgg ccgctcatta gtggtgatgg tgaatgatgag gtttagaaa agcatctata

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61

<210> 24

<211> 62

<212> DNA

<213> Artificial Sequence

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<400> 24

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60

ag

62

<210> 25

<211> 75

<212> DNA

<213> Artificial Sequence

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60

gagtaagcag aggag

75

<210> 26

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<210> 27

<211> 41

<212> DNA

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<400> 27

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<210> 28

<211> 35

<212> DNA

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<400> 28

aattgtaata tggggaagct gggaaaatac aagaa 35

<210> 29

<211> 35

<212> DNA

<213> Artificial Sequence

<220><223> Synthetic Sequence

<400> 29

tgggaataaca ggaggtgcag agtaagcaga ggaga 35

<210> 30

<211> 31

<212> DNA

<213> Artificial Sequence

<220><223> Synthetic Sequence

<400> 30

tttgggaataa caggagagta agcagaggag a 31

<210> 31

<211> 77

<212> DNA

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 ggggtgcttct ggaattg 77

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<210> 33
 <211> 48
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 attcctttct caagatgaac ttgagcacag ctttggcgaa actgttgc 48

<210> 34
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<210> 35
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<210> 36

<211> 56
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 <210> 37
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 <210> 38
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 <212> DNA
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 <210> 39
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 <212> DNA
 <213> Artificial Sequence
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 <400> 39
 gttatagcgg ccgctcatta gggagggtttt agaaaagcat c 41
 <210> 40
 <211> 44
 <212> DNA
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 <400> 40

gttatagcgg ccgctcatta catgggaggt tttagaaaag catc 44

<210> 41

<211> 44

<212> DNA

<213> Artificial Sequence

<220><223> Synthetic Sequence

<400> 41

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<210> 42

<211> 41

<212> DNA

<213> Artificial Sequence

<220><223> Synthetic Sequence

<400> 42

gttatagcgg ccgctcatta tgtctccatg ggaggtttta g 41

<210> 43

<211> 38

<212> DNA

<213> Artificial Sequence

<220><223> Synthetic Sequence

<400> 43

taacaggagg tgctctgaaa ttagagtaag cagaggag 38

<210> 44

<211> 37

<212> DNA

<213> Artificial Sequence

<220><223> Synthetic Sequence

<400> 44

tggaataaca ggaggtgctc tagagtaagc agaggag 37

<210> 45

<211>

> 33

<212> DNA

<213> Artificial Sequence

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<210>	46	
<211>	59	
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ctaattgcgg	ccgctcatta gtggtgatgg tgatgatgat ctatacagac accatcagc	59
<210>	47	
<211>	59	
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gataaatgcgg	ccgctcatta gtggtgatgg tgatgatgag gtctctctgt ctccatggg	59
<210>	48	
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gataaatgcgg	ccgctcatta gtggtgatgg tgatgatgaa tttagaggttc ttctgtctcc	60
<210>	49	
<211>	61	
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	tc	62
<210>	51	
<211>	65	
<212>	DNA	
<213>	Artificial Sequence	
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	gataatgcgg ccgctcatta gtggatgatgg tgatgatggg gtgaagcatt gtagaaaatt	60
	tgagg	65
<210>	52	
<211>	60	
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	gataatgcgg ccgctcatta gtggatgatgg tgatgatgtg tggaggggtga agcattgtag	60
		60
<210>	53	
<211>	58	
<212>	DNA	
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	ctaattgcgg ccgctcatta gtggatgatgg tgatgatgtt ttagaaaagc atctatac	58
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<210> 55

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<212> DNA

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tc 62

<210> 56

<211> 62

<212> DNA

<213> Artificial Sequence

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<400> 56

gttatagcgg ccgctcatta gtggtgatgg tgatgatgct ccatgggagg ttttagaaaa 60

gc 62

<210> 57

<211> 59

<212> DNA

<213> Artificial Sequence

<220><223> Synthetic Sequence

<400> 57

gttatagcgg ccgctcatta gtggtgatgg tgatgatgtg tctccatggg aggttttag 59

<210> 58

<211> 56

<212> DNA

<213> Artificial Sequence

<220><223> Synthetic Sequence

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 <210> 59
 <211> 38
 <212> DNA
 <213> Artificial Sequence
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 <400> 59
 gttatagcgg ccgctcatta ttctgtctcc atgggagg 38
 <210> 60
 <211> 455
 <212> PRT
 <213> Artificial Sequence
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 <400> 60
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 Ala Trp Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro
 20 25 30
 Leu Asp Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala
 35 40 45
 Thr Gly Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr
 50 55 60
 Pro Tyr Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro
 65 70 75 80
 Gln Lys Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile
 85 90 95
 Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp
 100 105 110
 Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val
 115 120 125
 Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu
 130 135 140

Ser Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala
145 150 155 160

Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg
165 170 175

Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His
180 185 190

His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile
195 200 205

Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu
210 215 220

Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr
225 230 235 240

Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile
245 250 255

Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val
260 265 270

Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr
275 280 285

Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp
290 295 300

Gly Thr Leu Ser Ile Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys
305 310 315 320

Glu Tyr Met Asp Thr Thr Leu Gly Pro Tyr Ile Ile Asn Val Thr Leu
325 330 335

Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys
340 345 350

Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp
355 360 365

Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly
370 375 380

Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys

385 390 395 400
 Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp
 405 410 415
 Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala
 420 425 430
 Phe Leu Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr Asn
 435 440 445

Ala Ser Pro Ser Thr Leu Ser

450 455
 <210> 61
 <211> 455
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 <400> 61

Leu Asn Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp
 1 5 10 15
 Ala Trp Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro
 20 25 30
 Leu Asp Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala
 35 40 45

Thr Gly Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr
 50 55 60
 Pro Tyr Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro
 65 70 75 80
 Gln Lys Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile
 85 90 95
 Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp
 100 105 110
 Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val
 115 120 125
 Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu

130	135	140	
Ser Leu Thr Glu Ala Thr	Glu Lys Ala Lys Gln Glu Phe	Glu Lys Ala	
145	150	155	160
Gly Lys Asp Phe Leu Val	Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg		
165	170	175	
Pro Asn His Leu Trp Gly Tyr Tyr	Leu Phe Pro Asp Cys Tyr Asn His		
180	185	190	
His Tyr Lys Lys Pro Gly Tyr	Asn Gly Ser Cys Phe Asn Val Glu Ile		
195	200	205	
Lys Arg Asn Asp Asp Leu Ser Trp	Leu Trp Asn Glu Ser Thr Ala Leu		
210	215	220	
Tyr Pro Ser Ile Tyr Leu Asn Thr	Gln Gln Ser Pro Val Ala Ala Thr		
225	230	235	240
Leu Tyr Val Arg Asn Arg Val Arg	Glu Ala Ile Arg Val Ser Lys Ile		
245	250	255	
Pro Asp Ala Lys Ser Pro Leu Pro	Val Phe Ala Tyr Thr Arg Ile Val		
260	265	270	
Phe Thr Asp Gln Val Leu Lys Phe	Leu Ser Gln Asp Glu Leu Val Tyr		
275	280	285	
Thr Phe Gly Glu Thr Val Ala Leu	Gly Ala Ser Gly Ile Val Ile Trp		
290	295	300	
Gly Thr Leu Ser Ile Thr Arg Thr	Lys Glu Ser Cys Gln Ala Ile Lys		
305	310	315	320
Glu Tyr Met Asp Thr Thr Leu Asn	Pro Phe Ile Leu Asn Val Thr Ser		
325	330	335	
Gly Ala Leu Leu Cys Ser Gln Ala	Leu Cys Gln Glu Gln Gly Val Cys		
340	345	350	
Ile Arg Lys Asn Trp Asn Ser Ser	Asp Tyr Leu His Leu Asn Pro Asp		
355	360	365	
Asn Phe Ala Ile Gln Leu Glu Lys	Gly Gly Lys Phe Thr Val Arg Gly		
370	375	380	
Lys Pro Thr Leu Glu Asp Leu Glu	Gln Phe Ser Glu Lys Phe Tyr Cys		

385 390 395 400
Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp

 405 410 415
Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala

 420 425 430
Phe Leu Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr Asn

 435 440 445
Ala Ser Pro Ser Thr Leu Ser

 450 455
<210> 62

<211> 455
<212> PRT

<213> Artificial Sequence
<220><223> Synthetic Sequence

<400> 62
Leu Asn Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp

 1 5 10 15
Ala Trp Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro

 20 25 30
Leu Asp Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala

 35 40 45
Thr Gly Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr

 50 55 60
Pro Tyr Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro

 65 70 75 80

Gln Lys Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile
 85 90 95

Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp
 100 105 110

Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val
 115 120 125

Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu

130 135 140
 Ser Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala

 145 150 155 160
 Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg

 165 170 175
 Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His

 180 185 190
 His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile

 195 200 205
 Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu

 210 215 220

 Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr
 225 230 235 240
 Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile

 245 250 255
 Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val

 260 265 270
 Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr

 275 280 285
 Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp

 290 295 300
 Gly Thr Leu Ser Ile Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys
 305 310 315 320
 Glu Tyr Met Asp Thr Thr Leu Gly Pro Phe Ile Leu Asn Val Thr Ser

 325 330 335
 Gly Ala Leu Leu Cys Ser Gln Ala Leu Cys Gln Glu Gln Gly Val Cys

 340 345 350
 Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp

 355 360 365

 Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly
 370 375 380

Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys
 385 390 395 400
 Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp
 405 410 415
 Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala
 420 425 430
 Phe Leu Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr Asn
 435 440 445
 Ala Ser Pro Ser Thr Leu Ser
 450 455
 <210> 63
 <211> 455
 <212> PRT
 <213> Artificial Sequence
 <220><223> Synthetic Sequence
 <400> 63
 Leu Asn Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp
 1 5 10 15
 Ala Trp Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro
 20 25 30
 Leu Asp Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala
 35 40 45
 Thr Gly Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr
 50 55 60
 Pro Tyr Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro
 65 70 75 80
 Gln Lys Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile
 85 90 95
 Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp
 100 105 110
 Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val
 115 120 125

Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu
 130 135 140
 Ser Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala
 145 150 155 160
 Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg
 165 170 175
 Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His
 180 185 190
 His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile
 195 200 205
 Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu
 210 215 220
 Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr
 225 230 235 240
 Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile
 245 250 255
 Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val
 260 265 270
 Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr
 275 280 285
 Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp
 290 295 300
 Val Ser Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys
 305 310 315 320
 Glu Tyr Met Asp Thr Thr Leu Gly Pro Tyr Ile Ile Asn Val Thr Leu
 325 330 335
 Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys
 340 345 350
 Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp
 355 360 365
 Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly
 370 375 380

Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys
385 390 395 400

Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp
405 410 415

Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala
420 425 430

Phe Leu Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr Asn
435 440 445

Ala Ser Pro Ser Thr Leu Ser
450 455

<210> 64

<211> 455

<212> PRT

<213> Artificial Sequence

<220><

223> Synthetic Sequence

<400> 64

Leu Asn Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp
1 5 10 15

Ala Trp Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro
20 25 30

Leu Asp Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala
35 40 45

Thr Gly Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr
50 55 60

Pro Tyr Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro
65 70 75 80

Gln Lys Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile
85 90 95

Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp
100 105 110

Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val
115 120 125

Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu

130	135	140	
Ser Leu Thr Glu Ala Thr	Glu Lys Ala Lys Gln Glu Phe	Glu Lys Ala	
145	150	155	160
Gly Lys Asp Phe Leu Val	Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg		
	165	170	175
Pro Asn His Leu Trp Gly Tyr Tyr	Leu Phe Pro Asp Cys Tyr Asn His		
	180	185	190
His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile			
195	200	205	

Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu			
210	215	220	
Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr			
225	230	235	240
Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile			
	245	250	255
Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val			
	260	265	270
Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr			

275	280	285	
Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp			
290	295	300	
Gly Thr Leu Ser Ile Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys			
305	310	315	320
Glu Tyr Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu			
	325	330	335
Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys			
340	345	350	

Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp			
355	360	365	
Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly			

370 375 380
 Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys
 385 390 395 400
 Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp
 405 410 415
 Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala

 420 425 430
 Phe Leu Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr Asn
 435 440 445
 Ala Ser Pro Ser Thr Leu Ser
 450 455
 <210> 65
 <211> 455
 <212> PRT
 <213> Artificial Sequence
 <220><223> Synthetic Sequence
 <400> 65
 Leu Asn Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp
 1 5 10 15
 Ala Trp Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro

 20 25 30
 Leu Asp Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala
 35 40 45
 Thr Gly Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr
 50 55 60
 Pro Tyr Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro
 65 70 75 80
 Gln Lys Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile
 85 90 95

 Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp
 100 105 110
 Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val

115	120	125	
Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu			
130	135	140	
Ser Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala			
145	150	155	160
Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg			
	165	170	175
Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His			
180	185	190	
His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile			
195	200	205	
Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu			
210	215	220	
Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr			
225	230	235	240
Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile			
245	250	255	
Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val			
260	265	270	
Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr			
275	280	285	
Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp			
290	295	300	
Val Ser Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys			
305	310	315	320
Glu Tyr Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu			
325	330	335	
Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys			
340	345	350	
Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp			
355	360	365	
Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly			

370	375	380
Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys		
385	390	395
Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp		
405	410	415
Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala		
420	425	430
Phe Leu Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr Asn		
435	440	445
Ala Ser Pro Ser Thr Leu Ser		

	450	455
<210>	66	
<211>	455	
<212>	PRT	
<213>	Artificial Sequence	
<220><223>	Synthetic Sequence	
<400>	66	

Leu	Asn	Phe	Arg	Ala	Pro	Pro	Val	Ile	Pro	Asn	Val	Pro	Phe	Leu	Trp
1				5					10					15	
Ala	Trp	Asn	Ala	Pro	Ser	Glu	Phe	Cys	Leu	Gly	Lys	Phe	Asp	Glu	Pro
				20				25						30	
Leu	Asp	Met	Ser	Leu	Phe	Ser	Phe	Ile	Gly	Ser	Pro	Arg	Ile	Asn	Ala
				35				40						45	

Thr	Gly	Gln	Gly	Val	Thr	Ile	Phe	Tyr	Val	Asp	Arg	Leu	Gly	Tyr	Tyr		
50					55					60							
Pro	Tyr	Ile	Asp	Ser	Ile	Thr	Gly	Val	Thr	Val	Asn	Gly	Gly	Ile	Pro		
65					70					75						80	
Gln	Lys	Ile	Ser	Leu	Gln	Asp	His	Leu	Asp	Lys	Ala	Lys	Lys	Asp	Ile		
					85					90					95		
Thr	Phe	Tyr	Met	Pro	Val	Asp	Asn	Leu	Gly	Met	Ala	Val	Ile	Asp	Trp		
100					105					110							

Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val

115	120	125
Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu		
130	135	140
Ser Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala		
145	150	155
Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg		
165	170	175
Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His		
180	185	190

195	200	205
His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile		
210	215	220
Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu		
225	230	235
Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr		
245	250	255
Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile		
260	265	270
Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val		

275	280	285
Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr		
290	295	300
Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp		
305	310	315
Gly Thr Leu Ser Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys		
325	330	335
Glu Tyr Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu		

340	345	350
Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys		
Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp		

355 360 365
 Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly
 370 375 380
 Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys
 385 390 395 400
 Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp

405 410 415
 Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala
 420 425 430
 Phe Leu Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr Asn
 435 440 445
 Ala Ser Pro Ser Thr Leu Ser
 450 455

<210> 67

<211> 455

<212> PRT

<213> Artificial Sequence

<220><223> Synthetic Sequence

<400> 67

Leu Asn Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp

1 5 10 15
 Ala Trp Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro
 20 25 30
 Leu Asp Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala
 35 40 45
 Thr Gly Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr
 50 55 60
 Pro Tyr Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro
 65 70 75 80
 Gln Lys Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile
 85 90 95
 Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp

100	105	110	
Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val			
115	120	125	
Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu			
130	135	140	
Ser Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala			
145	150	155	160
Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg			
165	170	175	
Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His			
180	185	190	
His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile			
195	200	205	
Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu			
210	215	220	
Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr			
225	230	235	240
Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile			
245	250	255	
Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val			
260	265	270	
Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr			
275	280	285	
Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp			
290	295	300	
Gly Thr Leu Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys			
305	310	315	320
Glu Tyr Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu			
325	330	335	
Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys			
340	345	350	
Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp			

355 360 365
 Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly
 370 375 380
 Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys
 385 390 395 400
 Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp
 405 410 415
 Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala
 420 425 430
 Phe Leu Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr Asn
 435 440 445
 Ala Ser Pro Ser Thr Leu Ser
 450 455
 <210> 68
 <211> 455
 <212> PRT
 <213> Artificial Sequence
 <220><223> Synthetic Sequence
 <400> 68
 Leu Asn Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp
 1 5 10 15
 Ala Trp Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro
 20 25 30
 Leu Asp Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala
 35 40 45
 Thr Gly Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr
 50 55 60
 Pro Tyr Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro
 65 70 75 80
 Gln Lys Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile
 85 90 95
 Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp

100	105	110	
Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val			
115	120	125	
Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu			
130	135	140	
Ser Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala			
145	150	155	160
Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg			
165	170	175	
Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His			
180	185	190	
His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile			
195	200	205	
Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu			
210	215	220	
Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr			
225	230	235	240
Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile			
245	250	255	
Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val			
260	265	270	
Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr			
275	280	285	
Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp			
290	295	300	
Gly Thr Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys			
305	310	315	320
Glu Tyr Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu			
325	330	335	
Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys			
340	345	350	

Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp
355 360 365

Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly
370 375 380

Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys
385 390 395 400

Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp
405 410 415

Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala
420 425 430

Phe Leu Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr Asn
435 440 445

Ala Ser Pro Ser Thr Leu Ser
450 455

<210> 69
<211> 455
<212> PRT
<213> Artificial Sequence
<220><
223> Synthetic Sequence
<400> 69

Leu Asn Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp
1 5 10 15

Ala Trp Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro
20 25 30

Leu Asp Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala
35 40 45

Thr Gly Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr
50 55 60

Pro Tyr Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro
65 70 75 80

Gln Lys Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile
85 90 95

Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp
 100 105 110
 Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val
 115 120 125
 Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu
 130 135 140
 Ser Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala
 145 150 155 160
 Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg
 165 170 175
 Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His
 180 185 190
 His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile
 195 200 205
 Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu
 210 215 220
 Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr
 225 230 235 240
 Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile
 245 250 255
 Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val
 260 265 270
 Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr
 275 280 285
 Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp
 290 295 300
 Gly Thr Leu Ser Ile Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys
 305 310 315 320
 Glu Tyr Met Asp Thr Thr Leu Asn Pro Phe Ile Leu Asn Val Thr Leu
 325 330 335
 Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys

340 345 350
 Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp
 355 360 365
 Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly
 370 375 380
 Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys
 385 390 395 400
 Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp
 405 410 415
 Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala

 420 425 430
 Phe Leu Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr Asn
 435 440 445
 Ala Ser Pro Ser Thr Leu Ser
 450 455
 <210> 70
 <211> 455
 <212> PRT
 <213> Artificial Sequence
 <220><223> Synthetic Sequence
 <400> 70
 Leu Asn Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp
 1 5 10 15
 Ala Trp Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro

 20 25 30
 Leu Asp Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala
 35 40 45
 Thr Gly Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr
 50 55 60
 Pro Tyr Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro
 65 70 75 80
 Gln Lys Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile

85	90	95
Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp		
100	105	110
Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val		
115	120	125
Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu		
130	135	140
Ser Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala		
145	150	155
Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg		
165	170	175
Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His		
180	185	190
His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile		
195	200	205
Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu		
210	215	220
Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr		
225	230	235
240		
Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile		
245	250	255
Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val		
260	265	270
Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr		
275	280	285
Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp		
290	295	300
Gly Thr Leu Ser Ile Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys		
305	310	315
320		
Glu Tyr Met Asp Thr Thr Leu Asn Pro Phe Ile Leu Asn Val Thr Ser		
325	330	335

Gly Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys
340 345 350

Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp
355 360 365

Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly
370 375 380

Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys
385 390 395 400

Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp
405 410 415

Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala
420 425 430

Phe Leu Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr Asn
435 440 445

Ala Ser Pro Ser Thr Leu Ser

450 455

<210> 71
<211> 453
<212> PRT
<213> Artificial Sequence
<220><223> Synthetic Sequence
<400> 71

Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp Ala Trp
1 5 10 15

Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro Leu Asp
20 25 30

Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala Thr Gly
35 40 45

Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr
50 55 60

Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys
65 70 75 80

Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe
85 90 95
Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu
100 105 110
Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys
115 120 125
Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu Ser Leu
130 135 140
Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala Gly Lys
145 150 155 160
Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn
165 170 175
His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr
180 185 190
Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg
195 200 205
Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro
210 215 220
Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr
225 230 235 240
Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp
245 250 255
Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr
260 265 270
Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe
275 280 285
Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Thr
290 295 300
Leu Ser Ile Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr
305 310 315 320
Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala

325 330 335
 Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg
 340 345 350
 Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe
 355 360 365
 Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro
 370 375 380
 Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys
 385 390 395 400
 Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp

 405 410 415
 Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala Phe Leu
 420 425 430
 Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr Asn Ala Ser
 435 440 445
 Pro Ser Thr Leu Ser
 450
 <210> 72
 <211> 430
 <212> PRT
 <213> Artificial Sequence
 <220><223> Synthetic Sequence
 <400> 72
 Leu Asn Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp

 1 5 10 15
 Ala Trp Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro
 20 25 30
 Leu Asp Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala
 35 40 45
 Thr Gly Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr
 50 55 60
 Pro Tyr Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro

65	70	75	80
Gln Lys Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile			
	85	90	95
Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp			
	100	105	110
Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val			
	115	120	125
Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu			
	130	135	140
Ser Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala			
145	150	155	160
Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg			
	165	170	175
Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His			
	180	185	190
His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile			
	195	200	205
Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu			
	210	215	220
Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr			
225	230	235	240
Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile			
	245	250	255
Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val			
	260	265	270
Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr			
	275	280	285
Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp			
290	295	300	
Gly Thr Leu Ser Ile Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys			
305	310	315	320

Glu Tyr Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu
325 330 335

Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys
340 345 350

Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp
355 360 365

Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly
370 375 380

Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys
385 390 395 400

Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp
405 410 415

Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile
420 425 430

<210> 73
<211> 433

<212> PRT
<213> Artificial Sequence
<220><223> Synthetic Sequence
<400> 73

Leu Asn Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp
1 5 10 15

Ala Trp Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro
20 25 30

Leu Asp Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala
35 40 45

Thr Gly Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr
50 55 60

Pro Tyr Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro
65 70 75 80

Gln Lys Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile
85 90 95

Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp
100 105 110

Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val
115 120 125

Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu
130 135 140

Ser Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala
145 150 155 160

Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg
165 170 175

Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His
180 185 190

His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile
195 200 205

Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu
210 215 220

Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr
225 230 235 240

Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile
245 250 255

Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val
260 265 270

Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr
275 280 285

Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp
290 295 300

Gly Thr Leu Ser Ile Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys
305 310 315 320

Glu Tyr Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu
325 330 335

Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys

340 345 350
 Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp
 355 360 365
 Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly
 370 375 380
 Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys
 385 390 395 400
 Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp
 405 410 415

Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala
 420 425 430
 Phe

<210> 74
 <211> 436
 <212> PRT
 <213> Artificial Sequence
 <220><223> Synthetic Sequence
 <400> 74

Leu Asn Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp
 1 5 10 15
 Ala Trp Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro
 20 25 30
 Leu Asp Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala

35 40 45
 Thr Gly Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr
 50 55 60
 Pro Tyr Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro
 65 70 75 80
 Gln Lys Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile
 85 90 95
 Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp

100	105	110	
Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val			
115	120	125	
Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu			
130	135	140	
Ser Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala			
145	150	155	160
Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg			
165	170	175	
Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His			
180	185	190	
His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile			
195	200	205	
Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu			
210	215	220	
Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr			
225	230	235	240
Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile			
245	250	255	
Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val			
260	265	270	
Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr			
275	280	285	
Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp			
290	295	300	
Gly Thr Leu Ser Ile Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys			
305	310	315	320
Glu Tyr Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu			
325	330	335	
Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys			
340	345	350	

Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp
 355 360 365
 Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly
 370 375 380
 Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys
 385 390 395 400

Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp
 405 410 415
 Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala
 420 425 430

Phe Leu Lys Pro
 435

<210> 75

<211> 452

<212> PRT

<213> Artificial Sequence

<220><223> Synthetic Sequence

<400> 75

Phe Arg Gly Pro Leu Leu Pro Asn Arg Pro Phe Leu Trp Ala Trp Asn
 1 5 10 15

Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro Leu Asp Met
 20 25 30

Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala Thr Gly Gln
 35 40 45

Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr Ile
 50 55 60

Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys Ile
 65 70 75 80

Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe Tyr

85 90 95
 Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu Trp
 100 105 110

Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys Asn
 115 120 125
 Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu Ser Leu Thr
 130 135 140
 Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala Gly Lys Asp
 145 150 155 160

 Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn His
 165 170 175
 Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr Lys
 180 185 190
 Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg Asn
 195 200 205
 Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro Ser
 210 215 220
 Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr Val

 225 230 235 240
 Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp Ala
 245 250 255
 Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr Asp
 260 265 270
 Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe Gly
 275 280 285
 Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Thr Leu
 290 295 300

 Ser Ile Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr Met
 305 310 315 320
 Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala Lys
 325 330 335
 Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg Lys
 340 345 350
 Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe Ala
 355 360 365

Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro Thr

370	375	380
Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys Tyr		
385	390	395
Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp Ala		
405	410	415
Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala Phe Leu Lys		
420	425	430
Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr Asn Ala Ser Pro		
435	440	445

Ser Thr Leu Ser

450

<210> 76

<211> 452

<212> PRT

<213> Artificial Sequence

<220><223> Synthetic Sequence

<400> 76

Phe Arg Gly Pro Leu Leu Pro Asn Arg Pro Phe Thr Thr Val Trp Asn
1 5 10 15
Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro Leu Asp Met
20 25 30
Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala Thr Gly Gln
35 40 45

Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr Ile
50 55 60
Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys Ile
65 70 75 80
Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe Tyr
85 90 95
Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu Trp
100 105 110

Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys Asn

115	120	125
Arg Ser Ile Glu Leu Val	Gln Gln Gln Asn Val	Gln Leu Ser Leu Thr
130	135	140
Glu Ala Thr Glu Lys Ala Lys	Gln Glu Phe Glu Lys Ala Gly Lys Asp	
145	150	155
160		
Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn His		
165	170	175
Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr Lys		
180	185	190

Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg Asn
195
200
205
Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro Ser
210
215
220
Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr Val
225
230
235
240
Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp Ala
245
250
255
Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr Asp

260	265	270
Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe Gly		
275	280	285
Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Thr Leu		
290	295	300
Ser Ile Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr Met		
305	310	315
320		
Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala Lys		
325	330	335

Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg Lys
340
345
350
Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe Ala

355 360 365
 Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro Thr
 370 375 380
 Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys Tyr
 385 390 395 400
 Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp Ala

 405 410 415
 Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala Phe Leu Lys
 420 425 430
 Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr Asn Ala Ser Pro
 435 440 445
 Ser Thr Leu Ser
 450
 <210> 77
 <211> 433
 <212> PRT
 <213> Artificial Sequence
 <220><223> Synthetic Sequence
 <400> 77
 Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp Ala Trp

 1 5 10 15
 Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro Leu Asp
 20 25 30
 Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala Thr Gly
 35 40 45
 Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr
 50 55 60
 Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys
 65 70 75 80

 Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe
 85 90 95
 Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu

100	105	110	
Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys			
115	120	125	
Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu Ser Leu			
130	135	140	
Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala Gly Lys			
145	150	155	160
Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn			
165	170	175	
His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr			
180	185	190	
Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg			
195	200	205	
Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro			
210	215	220	
Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr			
225	230	235	240
Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp			
245	250	255	
Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr			
260	265	270	
Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe			
275	280	285	
Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Thr			
290	295	300	
Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr			
305	310	315	320
Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala			
325	330	335	
Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg			
340	345	350	
Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe			

355 360 365
Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro
370 375 380
Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys
385 390 395 400
Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp
405 410 415
Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala Phe Leu
420 425 430
Lys

<

<210> 78

<211> 431

<212> PRT

<213> Artificial Sequence

<220><223> Synthetic Sequence

<400> 78

Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp Ala Trp
1 5 10 15
Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro Leu Asp
20 25 30
Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala Thr Gly
35 40 45
Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr
50 55 60
Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys
65 70 75 80
Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe
85 90 95
Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu
100 105 110
Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys

115	120	125
Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu Ser Leu		
130	135	140
Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala Gly Lys		
145	150	155
160		
Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn		
165	170	175
His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr		
180	185	190
Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg		
195	200	205
Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro		
210	215	220
Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr		
225	230	235
240		
Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp		
245	250	255
Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr		
260	265	270
Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe		
275	280	285
Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Thr		
290	295	300
Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr		
305	310	315
320		
Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala		
325	330	335
Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg		
340	345	350
Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe		
355	360	365

Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro
 370 375 380
 Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys
 385 390 395 400
 Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp
 405 410 415

Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala Phe
 420 425 430

<210> 79

<211> 455

<212> PRT

<213> Artificial Sequence

<220><223> Synthetic Sequence

<400> 79

Leu Asn Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp
 1 5 10 15
 Ala Trp Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro
 20 25 30
 Leu Asp Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala

35 40 45
 Thr Gly Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr
 50 55 60
 Pro Tyr Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro
 65 70 75 80
 Gln Lys Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile
 85 90 95
 Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp
 100 105 110

Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val
 115 120 125
 Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu
 130 135 140

Ser Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala
 145 150 155 160
 Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg
 165 170 175
 Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His
 180 185 190
 His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile
 195 200 205
 Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu
 210 215 220
 Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr
 225 230 235 240
 Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile
 245 250 255

 Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val
 260 265 270
 Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr
 275 280 285
 Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp
 290 295 300
 Gly Ser Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys
 305 310 315 320
 Glu Tyr Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu

 325 330 335
 Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys
 340 345 350
 Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp
 355 360 365
 Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly
 370 375 380
 Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys

385 390 395 400

Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp
 405 410 415

Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala
 420 425 430

Phe Leu Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr Asn
 435 440 445

Ala Ser Pro Ser Thr Leu Ser
 450 455

<210> 80

<211> 451

<212> PRT

<213> Artificial Sequence

<220><

223> Synthetic Sequence

<400> 80

Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp Ala Trp Asn Ala
 1 5 10 15

Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro Leu Asp Met Ser
 20 25 30

Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala Thr Gly Gln Gly
 35 40 45

Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr Ile Asp
 50 55 60

Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys Ile Ser
 65 70 75 80

Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe Tyr Met
 85 90 95

Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu Trp Arg
 100 105 110

Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys Asn Arg
 115 120 125

Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu Ser Leu Thr Glu

130	135	140	
Ala Thr Glu Lys	Ala Lys Gln Glu Phe Glu Lys	Ala Gly Lys Asp Phe	
145	150	155	160
Leu Val Glu Thr	Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn His Leu		
	165	170	175
Trp Gly Tyr Tyr	Leu Phe Pro Asp Cys Tyr Asn His His Tyr Lys Lys		
	180	185	190
Pro Gly Tyr Asn Gly Ser	Cys Phe Asn Val Glu Ile Lys Arg Asn Asp		
195	200	205	

Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro Ser Ile		
210	215	220
Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr Val Arg		
225	230	235
240		
Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp Ala Lys		
	245	250
	255	
Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr Asp Gln		
260	265	270
Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe Gly Glu		

275	280	285	
Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Thr Leu Ser			
290	295	300	
Ile Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr Met Asp			
305	310	315	320
Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala Lys Met			
	325	330	335
Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg Lys Asn			
340	345	350	

Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe Ala Ile		
355	360	365
Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro Thr Leu		

370 375 380
 Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys Tyr Ser
 385 390 395 400
 Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp Ala Val
 405 410 415
 Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala Phe Leu Lys Pro

 420 425 430
 Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr Asn Ala Ser Pro Ser
 435 440 445
 Thr Leu Ser
 450
 <210> 81
 <211> 449
 <212> PRT
 <213> Artificial Sequence
 <220><223> Synthetic Sequence
 <400> 81
 Pro Val Ile Pro Asn Val Pro Phe Leu Trp Ala Trp Asn Ala Pro Ser
 1 5 10 15
 Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro Leu Asp Met Ser Leu Phe

 20 25 30
 Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala Thr Gly Gln Gly Val Thr
 35 40 45
 Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr Ile Asp Ser Ile
 50 55 60
 Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys Ile Ser Leu Gln
 65 70 75 80
 Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe Tyr Met Pro Val
 85 90 95

 Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu Trp Arg Pro Thr
 100 105 110
 Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys Asn Arg Ser Ile

115	120	125	
Glu Leu Val Gln Gln Gln Asn Val	Gln Leu Ser Leu Thr	Glu Ala Thr	
130	135	140	
Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala Gly Lys Asp Phe Leu Val			
145	150	155	160
Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn His Leu Trp Gly			
165	170	175	
Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr Lys Lys Pro Gly			
180	185	190	
Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg Asn Asp Asp Leu			
195	200	205	
Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro Ser Ile Tyr Leu			
210	215	220	
Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr Val Arg Asn Arg			
225	230	235	240
Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp Ala Lys Ser Pro			
245	250	255	
Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr Asp Gln Val Leu			
260	265	270	
Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe Gly Glu Thr Val			
275	280	285	
Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Thr Leu Ser Ile Thr			
290	295	300	
Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr Met Asp Thr Thr			
305	310	315	320
Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala Lys Met Cys Ser			
325	330	335	
Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg Lys Asn Trp Asn			
340	345	350	
Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe Ala Ile Gln Leu			
355	360	365	
Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro Thr Leu Glu Asp			

[illegible]

<210>	82
<211>	432
<212>	PRT
<213>	Artificial Sequence
<220><223>	Synthetic Sequence
<400>	82

Leu	Asn	Phe	Arg	Ala	Pro	Pro	Val	Ile	Pro	Asn	Val	Pro	Phe	Leu	Trp
1				5					10					15	
Ala	Trp	Asn	Ala	Pro	Ser	Glu	Phe	Cys	Leu	Gly	Lys	Phe	Asp	Glu	Pro
				20				25						30	
Leu	Asp	Met	Ser	Leu	Phe	Ser	Phe	Ile	Gly	Ser	Pro	Arg	Ile	Asn	Ala
				35				40						45	
Thr	Gly	Gln	Gly	Val	Thr	Ile	Phe	Tyr	Val	Asp	Arg	Leu	Gly	Tyr	Tyr
				50				55						60	
Pro	Tyr	Ile	Asp	Ser	Ile	Thr	Gly	Val	Thr	Val	Asn	Gly	Gly	Ile	Pro
65					70					75					80
Gln	Lys	Ile	Ser	Leu	Gln	Asp	His	Leu	Asp	Lys	Ala	Lys	Lys	Asp	Ile
					85					90				95	
Thr	Phe	Tyr	Met	Pro	Val	Asp	Asn	Leu	Gly	Met	Ala	Val	Ile	Asp	Trp
				100				105						110	
Glu	Glu	Trp	Arg	Pro	Thr	Trp	Ala	Arg	Asn	Trp	Lys	Pro	Lys	Asp	Val

115	120	125
Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu		
130	135	140
Ser Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala		
145	150	155
Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg		
165	170	175
Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His		
180	185	190
His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile		
195	200	205
Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu		
210	215	220
Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr		
225	230	235
Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile		
245	250	255
Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val		
260	265	270
Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr		
275	280	285
Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp		
290	295	300
Gly Thr Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys		
305	310	315
Glu Tyr Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu		
325	330	335
Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys		
340	345	350
Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp		
355	360	365

Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly
 370 375 380
 Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys
 385 390 395 400
 Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp
 405 410 415

Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala
 420 425 430

<210> 83

<211> 429

<212> PRT

<213> Artificial Sequence

<220><223> Synthetic Sequence

<400> 83

Leu Asn Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp
 1 5 10 15
 Ala Trp Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro
 20 25 30
 Leu Asp Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala

35 40 45
 Thr Gly Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr
 50 55 60
 Pro Tyr Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro
 65 70 75 80
 Gln Lys Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile
 85 90 95
 Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp
 100 105 110

Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val
 115 120 125
 Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu
 130 135 140

Ser Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala
 145 150 155 160
 Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg
 165 170 175
 Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His
 180 185 190
 His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile
 195 200 205
 Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu
 210 215 220
 Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr
 225 230 235 240
 Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile
 245 250 255

 Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val
 260 265 270
 Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr
 275 280 285
 Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp
 290 295 300
 Gly Thr Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys
 305 310 315 320
 Glu Tyr Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu

 325 330 335
 Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys
 340 345 350
 Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp
 355 360 365
 Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly
 370 375 380
 Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys

385						390						395						400
Ser	Cys	Tyr	Ser	Thr	Leu	Ser	Cys	Lys	Glu	Lys	Ala	Asp	Val	Lys	Asp			
405					410					415								
Thr	Asp	Ala	Val	Asp	Val	Cys	Ile	Ala	Asp	Gly	Val	Cys						
420					425													
<210>	84																	
<211>	426																	
<212>	PRT																	
<213>	Artificial Sequence																	
<220><223>	Synthetic Sequence																	
<400>	84																	
Leu	Asn	Phe	Arg	Ala	Pro	Pro	Val	Ile	Pro	Asn	Val	Pro	Phe	Leu	Trp			
1	5				10				15									
Ala	Trp	Asn	Ala	Pro	Ser	Glu	Phe	Cys	Leu	Gly	Lys	Phe	Asp	Glu	Pro			
20					25					30								
Leu	Asp	Met	Ser	Leu	Phe	Ser	Phe	Ile	Gly	Ser	Pro	Arg	Ile	Asn	Ala			
35					40					45								
Thr	Gly	Gln	Gly	Val	Thr	Ile	Phe	Tyr	Val	Asp	Arg	Leu	Gly	Tyr	Tyr			
50					55					60								
Pro	Tyr	Ile	Asp	Ser	Ile	Thr	Gly	Val	Thr	Val	Asn	Gly	Gly	Ile	Pro			
65					70					75					80			
Gln	Lys	Ile	Ser	Leu	Gln	Asp	His	Leu	Asp	Lys	Ala	Lys	Lys	Asp	Ile			
85					90					95								
Thr	Phe	Tyr	Met	Pro	Val	Asp	Asn	Leu	Gly	Met	Ala	Val	Ile	Asp	Trp			
100					105					110								
Glu	Glu	Trp	Arg	Pro	Thr	Trp	Ala	Arg	Asn	Trp	Lys	Pro	Lys	Asp	Val			
115					120					125								
Tyr	Lys	Asn	Arg	Ser	Ile	Glu	Leu	Val	Gln	Gln	Gln	Asn	Val	Gln	Leu			
130					135					140								
Ser	Leu	Thr	Glu	Ala	Thr	Glu	Lys	Ala	Lys	Gln	Glu	Phe	Glu	Lys	Ala			
145					150					155					160			

Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg

	165	170	175
Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His			
180	185	190	
His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile			
195	200	205	
Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu			
210	215	220	
Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr			
225	230	235	240

Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile			
245	250	255	
Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val			
260	265	270	
Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr			
275	280	285	
Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp			
290	295	300	
Gly Thr Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys			

305	310	315	320
Glu Tyr Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu			
325	330	335	
Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys			
340	345	350	
Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp			
355	360	365	
Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly			
370	375	380	

Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys			
385	390	395	400
Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp			

405 410 415
 Thr Asp Ala Val Asp Val Cys Ile Ala Asp
 420 425
 <210> 85
 <211> 423
 <212> PRT
 <213> Artificial Sequence
 <220><223> Synthetic Sequence
 <400> 85
 Leu Asn Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp

 1 5 10 15
 Ala Trp Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro
 20 25 30
 Leu Asp Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala
 35 40 45
 Thr Gly Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr
 50 55 60
 Pro Tyr Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro
 65 70 75 80

 Gln Lys Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile
 85 90 95
 Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp
 100 105 110
 Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val
 115 120 125
 Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu
 130 135 140
 Ser Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala

 145 150 155 160
 Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg
 165 170 175
 Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His

180	185	190
His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile		
195	200	205
Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu		
210	215	220
Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr		
225	230	235
240		
Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile		
245	250	255
Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val		
260	265	270
Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr		
275	280	285
Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp		
290	295	300
Gly Thr Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys		
305	310	315
320		
Glu Tyr Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu		
325	330	335
Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys		
340	345	350
Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp		
355	360	365
Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly		
370	375	380
Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys		
385	390	395
400		
Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp		
405	410	415
Thr Asp Ala Val Asp Val Cys		
420		
<210>	86	

<211> 420

<212> PRT

<213> Artificial Sequence

<220

><223> Synthetic Sequence

<400> 86

Leu Asn Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp

1 5 10 15

Ala Trp Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro

20 25 30

Leu Asp Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala

35 40 45

Thr Gly Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr

50 55 60

Pro Tyr Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro

65 70 75 80

Gln Lys Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile

85 90 95

Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp

100 105 110

Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val

115 120 125

Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu

130 135 140

Ser Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala

145 150 155 160

Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg

165 170 175

Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His

180 185 190

His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile

195 200 205

Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu
 210 215 220
 Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr
 225 230 235 240
 Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile
 245 250 255
 Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val
 260 265 270
 Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr
 275 280 285
 Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp
 290 295 300
 Gly Thr Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys
 305 310 315 320
 Glu Tyr Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu
 325 330 335
 Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys
 340 345 350
 Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp
 355 360 365
 Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly
 370 375 380
 Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys
 385 390 395 400
 Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp
 405 410 415
 Thr Asp Ala Val
 420

<210> 87
 <211> 433
 <212> PRT
 <213> Artificial Sequence

<220><223> Synthetic Sequence

<400> 87

Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp Ala Trp

1 5 10 15

Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro Leu Asp

20 25 30

Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala Thr Gly

35 40 45

Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr

50 55 60

Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys

65 70 75 80

Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe

85 90 95

Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu

100 105 110

Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys

115 120 125

Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu Ser Leu

130 135 140

Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala Gly Lys

145 150 155 160

Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn

165 170 175

His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr

180 185 190

Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg

195 200 205

Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro

210 215 220

Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr

225 230 235 240

Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp
245 250 255
Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr
260 265 270
Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe
275 280 285
Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Ser
290 295 300
Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr
305 310 315 320
Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala
325 330 335
Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg
340 345 350
Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe
355 360 365
Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro
370 375 380
Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys
385 390 395 400
Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp
405 410 415
Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala Phe Leu
420 425 430
Lys

<210> 88
<211> 435
<212> PRT
<213> Artificial Sequence
<220><223> Synthetic Sequence
<400> 88

Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp Ala Trp
 1 5 10 15
 Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro Leu Asp
 20 25 30
 Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala Thr Gly
 35 40 45
 Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr
 50 55 60
 Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys
 65 70 75 80
 Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe
 85 90 95
 Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu
 100 105 110
 Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys
 115 120 125
 Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu Ser Leu
 130 135 140
 Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala Gly Lys
 145 150 155 160
 Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn
 165 170 175
 His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr
 180 185 190
 Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg
 195 200 205
 Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro
 210 215 220
 Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr
 225 230 235 240
 Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp

245 250 255
 Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr
 260 265 270
 Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe
 275 280 285
 Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Thr
 290 295 300
 Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr

 305 310 315 320
 Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala
 325 330 335
 Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg
 340 345 350
 Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe
 355 360 365
 Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro
 370 375 380

 Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys
 385 390 395 400
 Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp
 405 410 415
 Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala Phe Leu
 420 425 430
 Lys Pro Pro
 435
 <210> 89
 <211> 436
 <212> PRT
 <213> Artificial Sequence
 <220><223> Synthetic Sequence

 <400> 89
 Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp Ala Trp

1	5	10	15												
Asn	Ala	Pro	Ser	Glu	Phe	Cys	Leu	Gly	Lys	Phe	Asp	Glu	Pro	Leu	Asp
	20	25	30												
Met	Ser	Leu	Phe	Ser	Phe	Ile	Gly	Ser	Pro	Arg	Ile	Asn	Ala	Thr	Gly
	35	40	45												
Gln	Gly	Val	Thr	Ile	Phe	Tyr	Val	Asp	Arg	Leu	Gly	Tyr	Tyr	Pro	Tyr
	50	55	60												
Ile	Asp	Ser	Ile	Thr	Gly	Val	Thr	Val	Asn	Gly	Gly	Ile	Pro	Gln	Lys
65	70	75	80												
Ile	Ser	Leu	Gln	Asp	His	Leu	Asp	Lys	Ala	Lys	Lys	Asp	Ile	Thr	Phe
	85	90	95												
Tyr	Met	Pro	Val	Asp	Asn	Leu	Gly	Met	Ala	Val	Ile	Asp	Trp	Glu	Glu
	100	105	110												
Trp	Arg	Pro	Thr	Trp	Ala	Arg	Asn	Trp	Lys	Pro	Lys	Asp	Val	Tyr	Lys
	115	120	125												
Asn	Arg	Ser	Ile	Glu	Leu	Val	Gln	Gln	Gln	Asn	Val	Gln	Leu	Ser	Leu
	130	135	140												
Thr	Glu	Ala	Thr	Glu	Lys	Ala	Lys	Gln	Glu	Phe	Glu	Lys	Ala	Gly	Lys
145	150	155	160												
Asp	Phe	Leu	Val	Glu	Thr	Ile	Lys	Leu	Gly	Lys	Leu	Leu	Arg	Pro	Asn
	165	170	175												
His	Leu	Trp	Gly	Tyr	Tyr	Leu	Phe	Pro	Asp	Cys	Tyr	Asn	His	His	Tyr
	180	185	190												
Lys	Lys	Pro	Gly	Tyr	Asn	Gly	Ser	Cys	Phe	Asn	Val	Glu	Ile	Lys	Arg
	195	200	205												
Asn	Asp	Asp	Leu	Ser	Trp	Leu	Trp	Asn	Glu	Ser	Thr	Ala	Leu	Tyr	Pro
210	215	220													
Ser	Ile	Tyr	Leu	Asn	Thr	Gln	Gln	Ser	Pro	Val	Ala	Ala	Thr	Leu	Tyr
225	230	235	240												
Val	Arg	Asn	Arg	Val	Arg	Glu	Ala	Ile	Arg	Val	Ser	Lys	Ile	Pro	Asp
	245	250	255												
Ala	Lys	Ser	Pro	Leu	Pro	Val	Phe	Ala	Tyr	Thr	Arg	Ile	Val	Phe	Thr

260 265 270
 Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe
 275 280 285

 Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Thr
 290 295 300
 Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr
 305 310 315 320
 Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala
 325 330 335
 Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg
 340 345 350
 Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe

 355 360 365
 Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro
 370 375 380
 Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys
 385 390 395 400
 Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp
 405 410 415
 Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala Phe Leu
 420 425 430

 Lys Pro Pro Met
 435
 <210> 90
 <211> 437
 <212> PRT
 <213> Artificial Sequence
 <220><223> Synthetic Sequence
 <400> 90
 Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp Ala Trp
 1 5 10 15
 Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro Leu Asp

20	25	30
Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala Thr Gly		
35	40	45
Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr		
50	55	60
Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys		
65	70	75
Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe		
85	90	95
Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu		
100	105	110
Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys		
115	120	125
Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu Ser Leu		
130	135	140
Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala Gly Lys		
145	150	155
Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn		
165	170	175
His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr		
180	185	190
Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg		
195	200	205
Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro		
210	215	220
Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr		
225	230	235
Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp		
245	250	255
Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr		
260	265	270

Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe
 275 280 285
 Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Thr
 290 295 300
 Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr
 305 310 315 320
 Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala
 325 330 335

 Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg
 340 345 350
 Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe
 355 360 365
 Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro
 370 375 380
 Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys
 385 390 395 400
 Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp

 405 410 415
 Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala Phe Leu
 420 425 430
 Lys Pro Pro Met Glu
 435
 <210> 91
 <211> 438
 <212> PRT
 <213> Artificial Sequence
 <220><223> Synthetic Sequence
 <400> 91
 Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp Ala Trp
 1 5 10 15
 Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro Leu Asp
 20 25 30

Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala Thr Gly
35 40 45

Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr
50 55 60

Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys
65 70 75 80

Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe
85 90 95

Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu
100 105 110

Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys
115 120 125

Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu Ser Leu
130 135 140

Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala Gly Lys
145 150 155 160

Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn
165 170 175

His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr
180 185 190

Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg
195 200 205

Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro
210 215 220

Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr
225 230 235 240

Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp
245 250 255

Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr
260 265 270

Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe
275 280 285

Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Thr
290 295 300

Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr

305 310 315 320

Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala
325 330 335

Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg
340 345 350

Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe
355 360 365

Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro
370 375 380

Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys
385 390 395 400

Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp
405 410 415

Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala Phe Leu
420 425 430

Lys Pro Pro Met Glu Thr
435

<210> 92

<211> 439

<212> PRT

<213> Artificial Sequence

<220

><223> Synthetic Sequence

<400> 92

Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp Ala Trp
1 5 10 15

Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro Leu Asp
20 25 30

Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala Thr Gly
35 40 45

Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr
50 55 60

Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys
65 70 75 80

Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe
85 90 95

Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu
100 105 110

Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys
115 120 125

Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu Ser Leu
130 135 140

Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala Gly Lys
145 150 155 160

Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn
165 170 175

His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr
180 185 190

Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg
195 200 205

Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro
210 215 220

Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr
225 230 235 240

Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp
245 250 255

Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr
260 265 270

Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe
275 280 285

Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Thr

290 295 300
 Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr
 305 310 315 320
 Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala
 325 330 335
 Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg
 340 345 350

 Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe
 355 360 365
 Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro
 370 375 380
 Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys
 385 390 395 400
 Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp
 405 410 415
 Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala Phe Leu

 420 425 430
 Lys Pro Pro Met Glu Thr Glu
 435
 <210> 93
 <211> 454
 <212> PRT
 <213> Artificial Sequence
 <220><223> Synthetic Sequence
 <400> 93
 Asn Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp Ala
 1 5 10 15
 Trp Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro Leu
 20 25 30
 Asp Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala Thr

 35 40 45
 Gly Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro

50 55 60
 Tyr Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln
 65 70 75 80
 Lys Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr
 85 90 95
 Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu
 100 105 110

 Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr
 115 120 125
 Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu Ser
 130 135 140
 Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala Gly
 145 150 155 160
 Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro
 165 170 175
 Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His

 180 185 190
 Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys
 195 200 205
 Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr
 210 215 220
 Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu
 225 230 235 240
 Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro
 245 250 255

 Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe
 260 265 270
 Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr
 275 280 285
 Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly
 290 295 300
 Thr Leu Ser Ile Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu

305 310 315 320
Tyr Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala

 325 330 335
Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile

 340 345 350
Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn

 355 360 365
Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys

 370 375 380
Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser

385 390 395 400

Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr

 405 410 415
Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala Phe

 420 425 430
Leu Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr Asn Ala

 435 440 445
Ser Pro Ser Thr Leu Ser

450

<210> 94

<211> 452

<212> PRT

<213> Artificial Sequence

<220><223> Synthetic Sequence

<400> 94

Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp Ala Trp Asn

1 5 10 15
Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro Leu Asp Met

 20 25 30
Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala Thr Gly Gln

 35 40 45
Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr Ile

50 55 60
 Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys Ile

 65 70 75 80
 Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe Tyr
 85 90 95
 Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu Trp
 100 105 110
 Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys Asn
 115 120 125
 Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu Ser Leu Thr
 130 135 140

 Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala Gly Lys Asp
 145 150 155 160
 Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn His
 165 170 175
 Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr Lys
 180 185 190
 Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg Asn
 195 200 205
 Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro Ser

 210 215 220
 Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr Val
 225 230 235 240
 Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp Ala
 245 250 255
 Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr Asp
 260 265 270
 Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe Gly
 275 280 285

 Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Thr Leu
 290 295 300

Ser Ile Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr Met
305 310 315 320
Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala Lys
325 330 335
Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg Lys
340 345 350
Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe Ala
355 360 365
Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro Thr
370 375 380
Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys Tyr
385 390 395 400
Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp Ala
405 410 415
Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala Phe Leu Lys
420 425 430
Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr Asn Ala Ser Pro
435 440 445
Ser Thr Leu Ser
450
<210> 95
<211> 450
<212> PRT
<213> Artificial Sequence
<220><223> Synthetic Sequence
<400> 95
Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp Ala Trp Asn Ala Pro
1 5 10 15
Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro Leu Asp Met Ser Leu
20 25 30
Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala Thr Gly Gln Gly Val
35 40 45

Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr Ile Asp Ser
 50 55 60
 Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys Ile Ser Leu
 65 70 75 80
 Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe Tyr Met Pro
 85 90 95
 Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu Trp Arg Pro
 100 105 110
 Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys Asn Arg Ser
 115 120 125
 Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu Ser Leu Thr Glu Ala
 130 135 140
 Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala Gly Lys Asp Phe Leu
 145 150 155 160
 Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn His Leu Trp
 165 170 175
 Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr Lys Lys Pro
 180 185 190
 Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg Asn Asp Asp
 195 200 205
 Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro Ser Ile Tyr
 210 215 220
 Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr Val Arg Asn
 225 230 235 240
 Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp Ala Lys Ser
 245 250 255
 Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr Asp Gln Val
 260 265 270
 Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe Gly Glu Thr
 275 280 285
 Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Thr Leu Ser Ile
 290 295 300

Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr Met Asp Thr
305 310 315 320

Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala Lys Met Cys
325 330 335

Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg Lys Asn Trp
340 345 350

Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe Ala Ile Gln
355 360 365

Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro Thr Leu Glu
370 375 380

Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys Tyr Ser Thr

385 390 395 400

Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp Ala Val Asp
405 410 415

Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala Phe Leu Lys Pro Pro
420 425 430

Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr Asn Ala Ser Pro Ser Thr
435 440 445

Leu Ser

450

<210> 96

<211> 428

<212> PRT

<213> Artificial Sequence

<220><223> Synthetic Sequence

<400> 96

Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp Ala Trp
1 5 10 15

Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro Leu Asp
20 25 30

Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala Thr Gly
35 40 45

Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr
50 55 60

Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys
65 70 75 80

Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe
85 90 95

Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu
100 105 110

Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys
115 120 125

Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu Ser Leu
130 135 140

Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala Gly Lys
145 150 155 160

Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn
165 170 175

His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr
180 185 190

Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg
195 200 205

Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro
210 215 220

Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr
225 230 235 240

Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp
245 250 255

Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr
260 265 270

Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe
275 280 285

Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Ser

290 295 300
 Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr
 305 310 315 320
 Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala
 325 330 335
 Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg
 340 345 350

 Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe
 355 360 365
 Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro
 370 375 380
 Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys
 385 390 395 400
 Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp
 405 410 415
 Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile

 420 425
 <210> 97
 <211> 429
 <212> PRT
 <213> Artificial Sequence
 <220><223> Synthetic Sequence
 <400> 97
 Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp Ala Trp
 1 5 10 15
 Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro Leu Asp
 20 25 30
 Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala Thr Gly
 35 40 45

 Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr
 50 55 60
 Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys

65						70						75				80
Ile	Ser	Leu	Gln	Asp	His	Leu	Asp	Lys	Ala	Lys	Lys	Asp	Ile	Thr	Phe	
				85					90						95	
Tyr	Met	Pro	Val	Asp	Asn	Leu	Gly	Met	Ala	Val	Ile	Asp	Trp	Glu	Glu	
			100					105					110			
Trp	Arg	Pro	Thr	Trp	Ala	Arg	Asn	Trp	Lys	Pro	Lys	Asp	Val	Tyr	Lys	
			115					120					125			
Asn	Arg	Ser	Ile	Glu	Leu	Val	Gln	Gln	Gln	Asn	Val	Gln	Leu	Ser	Leu	
	130						135					140				
Thr	Glu	Ala	Thr	Glu	Lys	Ala	Lys	Gln	Glu	Phe	Glu	Lys	Ala	Gly	Lys	
145					150					155					160	
Asp	Phe	Leu	Val	Glu	Thr	Ile	Lys	Leu	Gly	Lys	Leu	Leu	Arg	Pro	Asn	
			165						170					175		
His	Leu	Trp	Gly	Tyr	Tyr	Leu	Phe	Pro	Asp	Cys	Tyr	Asn	His	His	Tyr	
		180							185					190		
Lys	Lys	Pro	Gly	Tyr	Asn	Gly	Ser	Cys	Phe	Asn	Val	Glu	Ile	Lys	Arg	
		195						200					205			
Asn	Asp	Asp	Leu	Ser	Trp	Leu	Trp	Asn	Glu	Ser	Thr	Ala	Leu	Tyr	Pro	
	210							215				220				
Ser	Ile	Tyr	Leu	Asn	Thr	Gln	Gln	Ser	Pro	Val	Ala	Ala	Thr	Leu	Tyr	
225					230					235					240	
Val	Arg	Asn	Arg	Val	Arg	Glu	Ala	Ile	Arg	Val	Ser	Lys	Ile	Pro	Asp	
			245						250					255		
Ala	Lys	Ser	Pro	Leu	Pro	Val	Phe	Ala	Tyr	Thr	Arg	Ile	Val	Phe	Thr	
			260						265				270			
Asp	Gln	Val	Leu	Lys	Phe	Leu	Ser	Gln	Asp	Glu	Leu	Val	Tyr	Thr	Phe	
		275							280				285			
Gly	Glu	Thr	Val	Ala	Leu	Gly	Ala	Ser	Gly	Ile	Val	Ile	Trp	Gly	Ser	
	290						295					300				
Trp	Glu	Asn	Thr	Arg	Thr	Lys	Glu	Ser	Cys	Gln	Ala	Ile	Lys	Glu	Tyr	
305					310					315					320	
Met	Asp	Thr	Thr	Leu	Asn	Pro	Tyr	Ile	Ile	Asn	Val	Thr	Leu	Ala	Ala	

325 330 335
 Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg
 340 345 350
 Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe
 355 360 365
 Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro
 370 375 380
 Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys
 385 390 395 400
 Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp

 405 410 415
 Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp
 420 425
 <210> 98
 <211> 430
 <212> PRT
 <213> Artificial Sequence
 <220><223> Synthetic Sequence
 <400> 98
 Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp Ala Trp
 1 5 10 15
 Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro Leu Asp
 20 25 30

 Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala Thr Gly
 35 40 45
 Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr
 50 55 60
 Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys
 65 70 75 80
 Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe
 85 90 95

Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu

100 105 110
Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys
115 120 125
Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu Ser Leu
130 135 140
Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala Gly Lys
145 150 155 160
Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn
165 170 175

His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr
180 185 190
Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg
195 200 205
Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro
210 215 220
Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr
225 230 235 240
Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp

245 250 255
Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr
260 265 270
Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe
275 280 285
Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Ser
290 295 300
Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr
305 310 315 320

Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala
325 330 335
Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg

340 345 350
 Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe
 355 360 365
 Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro
 370 375 380
 Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys

 385 390 395 400
 Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp
 405 410 415
 Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala
 420 425 430
 <210> 99
 <211> 431
 <212> PRT
 <213> Artificial Sequence
 <220><223> Synthetic Sequence
 <400> 99
 Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp Ala Trp
 1 5 10 15

 Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro Leu Asp
 20 25 30
 Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala Thr Gly
 35 40 45
 Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr
 50 55 60
 Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys
 65 70 75 80
 Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe

 85 90 95
 Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu
 100 105 110
 Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys

115	120	125	
Asn Arg Ser Ile Glu Leu Val	Gln Gln Gln Asn Val	Gln Leu Ser Leu	
130	135	140	
Thr Glu Ala Thr Glu Lys Ala	Lys Gln Glu Phe Glu Lys Ala	Gly Lys	
145	150	155	160
Asp Phe Leu Val Glu Thr Ile	Lys Leu Gly Lys Leu Leu Arg	Pro Asn	
165	170	175	
His Leu Trp Gly Tyr Tyr Leu	Phe Pro Asp Cys Tyr Asn His	His Tyr	
180	185	190	
Lys Lys Pro Gly Tyr Asn Gly	Ser Cys Phe Asn Val Glu Ile	Lys Arg	
195	200	205	
Asn Asp Asp Leu Ser Trp Leu	Trp Asn Glu Ser Thr Ala Leu	Tyr Pro	
210	215	220	
Ser Ile Tyr Leu Asn Thr Gln	Gln Ser Pro Val Ala Ala Thr	Leu Tyr	
225	230	235	240
Val Arg Asn Arg Val Arg Glu	Ala Ile Arg Val Ser Lys Ile	Pro Asp	
245	250	255	
Ala Lys Ser Pro Leu Pro Val	Phe Ala Tyr Thr Arg Ile Val	Phe Thr	
260	265	270	
Asp Gln Val Leu Lys Phe Leu	Ser Gln Asp Glu Leu Val Tyr	Thr Phe	
275	280	285	
Gly Glu Thr Val Ala Leu Gly	Ala Ser Gly Ile Val Ile Trp	Gly Ser	
290	295	300	
Trp Glu Asn Thr Arg Thr Lys	Glu Ser Cys Gln Ala Ile Lys	Glu Tyr	
305	310	315	320
Met Asp Thr Thr Leu Asn Pro	Tyr Ile Ile Asn Val Thr Leu	Ala Ala	
325	330	335	
Lys Met Cys Ser Gln Val Leu	Cys Gln Glu Gln Gly Val Cys	Ile Arg	
340	345	350	
Lys Asn Trp Asn Ser Ser Asp	Tyr Leu His Leu Asn Pro Asp	Asn Phe	
355	360	365	

Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro

370 375 380
 Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys
 385 390 395 400
 Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp
 405 410 415
 Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala Phe
 420 425 430

<210> 100

<211> 441

<212> PRT

<213> Artificial Sequence

<220><223

> Synthetic Sequence

<400> 100

Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp Ala Trp
 1 5 10 15
 Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro Leu Asp
 20 25 30
 Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala Thr Gly
 35 40 45
 Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr
 50 55 60

Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys
 65 70 75 80
 Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe
 85 90 95
 Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu
 100 105 110
 Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys
 115 120 125
 Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu Ser Leu

130	135	140	
Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala Gly Lys			
145	150	155	160
Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn			
	165	170	175
His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr			
	180	185	190
Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg			
195	200	205	
Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro			
210	215	220	
Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr			
225	230	235	240
Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp			
	245	250	255
Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr			
260	265	270	
Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe			
275	280	285	
Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Thr			
290	295	300	
Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr			
305	310	315	320
Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala			
	325	330	335
Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg			
340	345	350	
Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe			
355	360	365	
Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro			
370	375	380	
Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys			

385 390 395 400
 Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp
 405 410 415
 Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala Phe Leu

 420 425 430
 Lys Pro Pro Met Glu Thr Glu Glu Pro
 435 440
 <210> 101
 <211> 443
 <212> PRT
 <213> Artificial Sequence
 <220><223> Synthetic Sequence
 <400> 101
 Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp Ala Trp
 1 5 10 15
 Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro Leu Asp
 20 25 30
 Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala Thr Gly

 35 40 45
 Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr
 50 55 60
 Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys
 65 70 75 80
 Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe
 85 90 95
 Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu
 100 105 110

 Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys
 115 120 125
 Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu Ser Leu
 130 135 140
 Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala Gly Lys

145 150 155 160
 Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn
 165 170 175
 His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr

 180 185 190
 Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg
 195 200 205
 Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro
 210 215 220
 Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr
 225 230 235 240
 Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp
 245 250 255

 Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr
 260 265 270
 Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe
 275 280 285
 Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Thr
 290 295 300
 Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr
 305 310 315 320
 Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala

 325 330 335
 Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg
 340 345 350
 Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe
 355 360 365
 Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro
 370 375 380
 Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys
 385 390 395 400

Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp
405 410 415

Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala Phe Leu
420 425 430

Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile
435 440

<210> 102

<211> 445

<212> PRT

<213> Artificial Sequence

$\langle 220 \rangle \langle 223 \rangle$ Synthetic Sequence

<400> 102

Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp Ala Trp

1 5 10 15

Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro Leu Asp

Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala Thr Gly

Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr

Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys

65 70 75 80

Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe
85 90 95

Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu

100 105 110

Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys

115 120 125

Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu Ser Leu

130 135 140

Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala Gly Lys

145 150 155 160

Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn
 165 170 175
 His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr
 180 185 190
 Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg
 195 200 205
 Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro
 210 215 220

 Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr
 225 230 235 240
 Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp
 245 250 255
 Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr
 260 265 270
 Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe
 275 280 285
 Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Thr

 290 295 300
 Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr
 305 310 315 320
 Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala
 325 330 335
 Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg
 340 345 350
 Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe
 355 360 365

 Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro
 370 375 380
 Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys
 385 390 395 400
 Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp
 405 410 415

Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala Phe Leu
420 425 430

Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr

435 440 445

<210> 103

<211> 447

<212> PRT

<213> Artificial Sequence

<220><223> Synthetic Sequence

<400> 103

Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp Ala Trp

1 5 10 15

Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro Leu Asp

20 25 30

Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala Thr Gly

35 40 45

Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr

50 55 60

Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys

65 70 75 80

Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe

85 90 95

Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu

100 105 110

Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys

115 120 125

Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu Ser Leu

130 135 140

Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala Gly Lys

145 150 155 160

Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn

165 170 175

His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr
 180 185 190

 Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg
 195 200 205
 Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro
 210 215 220
 Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr
 225 230 235 240
 Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp
 245 250 255
 Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr
 260 265 270
 Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe
 275 280 285
 Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Thr
 290 295 300
 Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr
 305 310 315 320
 Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala
 325 330 335

 Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg
 340 345 350
 Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe
 355 360 365
 Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro
 370 375 380
 Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys
 385 390 395 400
 Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp
 405 410 415
 Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala Phe Leu

420 425 430
 Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr Asn Ala
 435 440 445
 <210> 104
 <211> 449
 <212> PRT
 <213> Artificial Sequence
 <220><223> Synthetic Sequence
 <400> 104
 Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp Ala Trp
 1 5 10 15

 Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro Leu Asp
 20 25 30
 Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala Thr Gly
 35 40 45
 Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr
 50 55 60
 Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys
 65 70 75 80
 Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe

 85 90 95
 Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu
 100 105 110
 Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys
 115 120 125
 Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu Ser Leu
 130 135 140
 Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala Gly Lys
 145 150 155 160

 Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn
 165 170 175
 His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr

180	185	190	
Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg			
195	200	205	
Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro			
210	215	220	
Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr			
225	230	235	240
Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp			
245	250	255	
Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr			
260	265	270	
Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe			
275	280	285	
Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Thr			
290	295	300	
Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr			
305	310	315	320
Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala			
325	330	335	
Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg			
340	345	350	
Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe			
355	360	365	
Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro			
370	375	380	
Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys			
385	390	395	400
Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp			
405	410	415	
Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala Phe Leu			
420	425	430	
Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr Asn Ala Ser			

435

440

445

Pro

<210> 105

<211> 451

<212> PRT

<213> Artificial Sequence

<220><223> Synthetic Sequence

<400> 105

Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp Ala Trp

1 5 10 15

Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro Leu Asp

20 25 30

Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala Thr Gly

35 40 45

Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr

50 55 60

Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys

65 70 75 80

Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe

85 90 95

Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu

100 105 110

Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys

115 120 125

Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu Ser Leu

130 135 140

Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala Gly Lys

145 150 155 160

Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn

165 170 175

His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr

180 185 190
 Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg

 195 200 205
 Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro
 210 215 220
 Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr
 225 230 235 240
 Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp
 245 250 255
 Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr
 260 265 270

 Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe
 275 280 285
 Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Thr
 290 295 300
 Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr
 305 310 315 320
 Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala
 325 330 335
 Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg

 340 345 350
 Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe
 355 360 365
 Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro
 370 375 380
 Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys
 385 390 395 400
 Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp
 405 410 415

 Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala Phe Leu
 420 425 430

Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr Asn Ala Ser
435 440 445

Pro Ser Thr
450

<210> 106
<211> 455
<212> PRT
<213> Artificial Sequence
<220><223> Synthetic Sequence
<400> 106

Leu Asn Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp
1 5 10 15

Ala Trp Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro
20 25 30

Leu Asp Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala
35 40 45

Thr Gly Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr
50 55 60

Pro Tyr Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro
65 70 75 80

Gln Lys Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile
85 90 95

Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp
100 105 110

Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val
115 120 125

Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu
130 135 140

Ser Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala
145 150 155 160

Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg
165 170 175

Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His
180 185 190

His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile
195 200 205

Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu
210 215 220

Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr
225 230 235 240

Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile
245 250 255

Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val
260 265 270

Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr
275 280 285

Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp
290 295 300

Gly Gly Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys
305 310 315 320

Glu Tyr Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu
325 330 335

Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys
340 345 350

Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp
355 360 365

Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly
370 375 380

Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys
385 390 395 400

Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp
405 410 415

Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala
420 425 430

Phe Leu Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr Asn
435 440 445

Ala Ser Pro Ser Thr Leu Ser
450 455

<210> 107

<211> 455

<212> PRT

<213> Artificial Sequence

<220><223> Synthetic Sequence

<400> 107

Leu Asn Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp
1 5 10 15
Ala Trp Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro
20 25 30
Leu Asp Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala
35 40 45

Thr Gly Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr
50 55 60
Pro Tyr Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro
65 70 75 80
Gln Lys Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile
85 90 95
Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp
100 105 110
Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val

115 120 125
Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu
130 135 140
Ser Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala
145 150 155 160
Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg
165 170 175

Pro Asn His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His
180 185 190

His Tyr Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile
195 200 205

Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu
210 215 220

Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr
225 230 235 240

Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile
245 250 255

Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val
260 265 270

Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr
275 280 285

Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp
290 295 300

Gly Ala Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys
305 310 315 320

Glu Tyr Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu
325 330 335

Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys
340 345 350

Ile Arg Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp
355 360 365

Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly
370 375 380

Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys
385 390 395 400

Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp
405 410 415

Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala

420 425 430
 Phe Leu Lys Pro Pro Met Glu Thr Glu Glu Pro Gln Ile Phe Tyr Asn
 435 440 445
 Ala Ser Pro Ser Thr Leu Ser
 450 455
 <210> 108
 <211> 455
 <212> PRT
 <213> Artificial Sequence
 <220><223> Synthetic Sequence
 <400> 108
 Leu Asn Phe Arg Ala Pro Pro Val Ile Pro Asn Val Pro Phe Leu Trp

 1 5 10 15
 Ala Trp Asn Ala Pro Ser Glu Phe Cys Leu Gly Lys Phe Asp Glu Pro
 20 25 30
 Leu Asp Met Ser Leu Phe Ser Phe Ile Gly Ser Pro Arg Ile Asn Ala
 35 40 45
 Thr Gly Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr
 50 55 60
 Pro Tyr Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro
 65 70 75 80

 Gln Lys Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile
 85 90 95
 Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp
 100 105 110
 Glu Glu Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val
 115 120 125
 Tyr Lys Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu
 130 135 140
 Ser Leu Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala

 145 150 155 160
 Gly Lys Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg

	165	170	175
Pro	Asn	His	Leu
Tyr	Trp	Gly	Tyr
Tyr	Leu	Phe	Pro
Asp	Cys	Tyr	Asn
His			
	180	185	190
His	Tyr	Lys	Lys
Pro	Gly	Tyr	Asn
Gly	Ser	Cys	Phe
Asn	Val	Glu	Ile
	195	200	205
Lys	Arg	Asn	Asp
Asp	Leu	Ser	Trp
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Leu	Ser	Gln	Asp
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Ile	Val	Ile	Trp
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Gly	Cys	Trp	Glu
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Glu	Tyr	Met	Asp
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Asn	Val	Thr	Leu
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Cys	Ser	Gln	Val
Leu	Cys	Gln	Glu
Gln	Gly	Val	Cys
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Trp	Asn	Ser	Ser
Asp	Tyr	Leu	His
Leu	Asn	Pro	Asp
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Gln	Leu	Glu	Lys
Gly	Gly	Lys	Phe
Thr	Val	Arg	Gly
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Gln	Phe	Ser	Glu
Lys	Phe	Tyr	Cys
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Thr	Leu	Ser	Cys
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Asp	Val	Lys	Asp
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 Thr Phe Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp
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 195 200 205
 Lys Arg Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu
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 Tyr Pro Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr
 225 230 235 240
 Leu Tyr Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile
 245 250 255

 Pro Asp Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val
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 Phe Thr Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr
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 Thr Phe Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp
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 Gly Asp Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys
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 Ala Ala Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys
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 Asn Phe Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly
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 Lys Pro Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys
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 Ser Cys Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp
 405 410 415

Thr Asp Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala
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35 40 45

Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr
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Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys
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Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe
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Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu
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Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys
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Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu Ser Leu
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Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala Gly Lys
145 150 155 160

Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn
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His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr
180 185 190

Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg
195 200 205

Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro
210 215 220

Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr
225 230 235 240

Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp
245 250 255

Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr
260 265 270

Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe
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Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Thr
290 295 300

Leu Ser Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr
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Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala
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Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg
340 345 350

Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe
355 360 365

Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro
370 375 380

Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys
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Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp
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 65 70 75 80
 Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe
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 Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu
 100 105 110
 Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys

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 Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu Ser Leu
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 Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala Gly Lys
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 Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn
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 His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr

180	185	190	
Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg			
195	200	205	
Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro			
210	215	220	
Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr			
225	230	235	240
Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp			
245	250	255	
Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr			
260	265	270	
Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe			
275	280	285	
Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Thr			
290	295	300	
Leu Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr			
305	310	315	320
Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala			
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Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg			
340	345	350	
Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe			
355	360	365	
Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro			
370	375	380	
Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys			
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 35 40 45
 Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr
 50 55 60
 Ile Asp Ser Ile Thr Gly Val Thr Val Asn Gly Gly Ile Pro Gln Lys
 65 70 75 80
 Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe
 85 90 95
 Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu
 100 105 110
 Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys
 115 120 125
 Asn Arg Ser Ile Glu Leu Val Gln Gln Gln Asn Val Gln Leu Ser Leu
 130 135 140
 Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala Gly Lys
 145 150 155 160
 Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn
 165 170 175
 His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr
 180 185 190
 Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg
 195 200 205

Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro
 210 215 220
 Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr
 225 230 235 240
 Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp

 245 250 255
 Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr
 260 265 270
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 Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Ala
 290 295 300
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 305 310 315 320

 Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala
 325 330 335
 Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg
 340 345 350
 Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe
 355 360 365
 Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro
 370 375 380
 Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys

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Gln Gly Val Thr Ile Phe Tyr Val Asp Arg Leu Gly Tyr Tyr Pro Tyr

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Ile Ser Leu Gln Asp His Leu Asp Lys Ala Lys Lys Asp Ile Thr Phe

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Tyr Met Pro Val Asp Asn Leu Gly Met Ala Val Ile Asp Trp Glu Glu

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Trp Arg Pro Thr Trp Ala Arg Asn Trp Lys Pro Lys Asp Val Tyr Lys

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Thr Glu Ala Thr Glu Lys Ala Lys Gln Glu Phe Glu Lys Ala Gly Lys

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Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn

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His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr

180 185 190

Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg

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Asn Asp Asp Leu Ser Trp Leu Trp Asn Glu Ser Thr Ala Leu Tyr Pro

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Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr

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 Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp
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 260 265 270
 Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe
 275 280 285
 Gly Glu Thr Val Ala Leu Gly Ala Ser Gly Ile Val Ile Trp Gly Gly
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 Trp Glu Asn Thr Arg Thr Lys Glu Ser Cys Gln Ala Ile Lys Glu Tyr
 305 310 315 320
 Met Asp Thr Thr Leu Asn Pro Tyr Ile Ile Asn Val Thr Leu Ala Ala
 325 330 335
 Lys Met Cys Ser Gln Val Leu Cys Gln Glu Gln Gly Val Cys Ile Arg
 340 345 350
 Lys Asn Trp Asn Ser Ser Asp Tyr Leu His Leu Asn Pro Asp Asn Phe
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 Ala Ile Gln Leu Glu Lys Gly Gly Lys Phe Thr Val Arg Gly Lys Pro

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Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr			

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Asp Phe Leu Val Glu Thr Ile Lys Leu Gly Lys Leu Leu Arg Pro Asn		
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His Leu Trp Gly Tyr Tyr Leu Phe Pro Asp Cys Tyr Asn His His Tyr		
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Lys Lys Pro Gly Tyr Asn Gly Ser Cys Phe Asn Val Glu Ile Lys Arg		
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Ser Ile Tyr Leu Asn Thr Gln Gln Ser Pro Val Ala Ala Thr Leu Tyr		
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Val Arg Asn Arg Val Arg Glu Ala Ile Arg Val Ser Lys Ile Pro Asp		
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Ala Lys Ser Pro Leu Pro Val Phe Ala Tyr Thr Arg Ile Val Phe Thr		
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Asp Gln Val Leu Lys Phe Leu Ser Gln Asp Glu Leu Val Tyr Thr Phe		
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 Thr Leu Glu Asp Leu Glu Gln Phe Ser Glu Lys Phe Tyr Cys Ser Cys
 385 390 395 400
 Tyr Ser Thr Leu Ser Cys Lys Glu Lys Ala Asp Val Lys Asp Thr Asp

 405 410 415
 Ala Val Asp Val Cys Ile Ala Asp Gly Val Cys Ile Asp Ala Phe
 420 425 430

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Wei *et al.* Art Unit : 1656
Serial No. : 15/226,489 Examiner : Liu, Samuel W.
Filed : August 02, 2016 Conf. No. : 9968
Cust. No. : 13565
Title : **PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES
THEREOF**

Mail Stop Amendment

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT TRANSMITTAL
LETTER**

Dear Sir:

Transmitted herewith are a Supplemental Information Disclosure Statement (2 pages), Form PTO-1449 (1 page), and cited non-U.S. patent documents in connection with the above-identified application. Because this Supplemental Information Disclosure Statement is filed after the receipt of a First Office Action on the Merits for the above-captioned application, the Commissioner is authorized to charge Deposit Account No. 50-0911.

☒ The Commissioner is hereby authorized to charge any fees that may be due in connection with this paper or with this application during its entire pendency to Deposit Account No. 50-0911.

Respectfully submitted,

/Stephanie Seidman/

Stephanie Seidman

Reg. No. 33,779

Attorney Docket No.: 33320.03087.US25/3087B

Address all correspondence to: 13565

Stephanie Seidman

Dentons US LLP

4655 Executive Drive, Ste. 700

San Diego, California 92121

Telephone: (619) 595-8010

Facsimile: (619) 595-8135

email: stephanie.seidman@dentons.com

CERTIFICATE OF TRANSMISSION VIA EFS-WEB

I hereby certify that this paper is being transmitted via the Electronic Filing System (EFS-WEB) to the United States Patent and Trademark Office on **April 24, 2020**.

/Hyun Jeung Ji/

Hyun Jeung Ji

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Wei *et al.* Art Unit : 1656
Serial No. : 15/226,489 Examiner : Liu, Samuel W.
Filed : August 02, 2016 Conf. No. : 9968
Cust. No. : 13565
Title : **PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES
THEREOF**

Mail Stop Amendment

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT IN
ACCORDANCE WITH 37 C.F.R. §§ 1.97-1.98**

Dear Sir:

This Supplemental Information Disclosure Statement is filed pursuant to 37 C.F.R. § 1.97(c) and includes a Statement in accordance with 37 C.F.R. § 1.97(e) and a Statement in accordance with 37 C.F.R. § 1.704(d). The Statements apply to a Hearing Notice issued by the Indian Patent Office. Because this Supplemental Information Disclosure Statement is accompanied by a Statement pursuant to 37 C.F.R. § 1.97(e), a fee is not required. If a fee for filing these papers is required, the Commissioner is authorized to charge Deposit Account No. 50-0911.

In accordance with the duty of disclosure imposed by 37 C.F.R. § 1.56 to inform the Patent Office of all information known by Applicant or Applicant's representative that may be material to the examination of the subject application, Applicant's representative hereby provides this Supplemental Information Disclosure Statement that is prepared in accordance with 37 C.F.R. §§ 1.97-1.98. A Form PTO-1449 (1 page) and copies of the non-U.S. patent documents listed thereon are provided herewith in connection with the above-captioned application.

The documents cited on the Form PTO-1449 are in the English language. Hence, in accordance with the requirements of 37 C.F.R. § 1.98, no further explanation of the listed items is necessary.

The communication provided herewith was issued by a foreign patent office, in a corresponding foreign application, and was not received by any individual designated in 37 C.F.R. § 1.56(c) more than thirty (30) days prior to the filing of this Supplemental Information Disclosure Statement. A Statement to this effect is provided.

CERTIFICATE OF TRANSMISSION VIA EFS-WEB

I hereby certify that this paper is being transmitted via the Electronic Filing System (EFS-WEB) to the United States Patent and Trademark Office on **July 08, 2020**.

/Hyun Jeung Ji/

Hyun Jeung Ji

Applicant : Wei *et al.*
Serial No. : 15/226,489
Filed : August 02, 2016

Attorney Docket No.: 33320.03087.US25/3087B
Supplemental Information Disclosure Statement

The Hearing Notice, listed on the attached Form PTO-1449 as Item AB was issued by the Indian Patent Office on June 17, 2020, in connection with Indian Patent Application No. 6272/DELNP/2014, was received June 18, 2020, and a copy is provided herewith. The Indian Patent Application, for which this communication was issued, is a National Stage of International Patent Application No. PCT/US2012/072182, which claims priority to US 61/631,313 and 61/796,208, as does the instant application.

Although these documents and applications are made known to the Patent and Trademark Office in compliance with Applicant's duty of disclosure, such disclosure is not to be construed as an admission by Applicant or Applicant's representative that any of the documents, singly or in any combination thereof, is effective as prior art against the subject application. In accordance with 37 C.F.R. § 1.97(g) and (h), the filing of this Supplemental Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 C.F.R. § 1.56(b) exists.

Applicant respectfully requests that the Examiner review the foregoing documents and they be made of record in the file history of the above-captioned application.

Respectfully submitted,

/Stephanie Seidman/
Stephanie Seidman
Reg. No. 33,779

Attorney Docket No.: 33320.03087.US25/3087B
Address all correspondence to: 13565
Stephanie Seidman
Dentons US LLP
4655 Executive Dr., Ste. 700
San Diego, California 92121
Telephone: (619) 595-8010
Facsimile: (619) 595-8135
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Wei *et al.* Art Unit : 1656
Serial No. : 15/226,489 Examiner : Liu, Samuel W.
Filed : August 02, 2016 Conf. No. : 9968
Cust. No. : 13565
Title : **PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES
THEREOF**

Mail Stop Amendment

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**STATEMENT FOR SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT
IN ACCORDANCE WITH 37 C.F.R. § 1.704(d)**

Dear Sir:

1. This Statement is being made for the Supplemental Information Disclosure Statement accompanying this certification.

2. I, Stephanie Seidman, hereby state that the item of information in the Supplemental Information Disclosure Statement, listed as Item AB on the attached PTO-1449 Form, is a communication from a foreign patent office or was first cited in any communication from a foreign patent office in a counterpart foreign application and the communication was not received by any individual designated in C.F.R. §1.56(c) more than thirty days prior to the filing of the Supplemental Information Disclosure Statement.

The above-referenced communication, listed on the attached Form PTO-1449 as Item AB, was issued from the Indian Patent Office on June 17, 2020 and was received on June 18, 2020, in connection with Indian Patent Application No. 6272/DELNP/2014. This Indian Patent Application is a National Stage of International Patent Application No. PCT/US2012/072182, which claims priority to US 61/631,313 and 61/796,208, as does the instant application.

3. The written disclosure of the Supplemental Information Disclosure Statement filed herewith is listed on the attached PTO-1449 Form as Item AA for purposes of Patent Application Information Retrieval (PAIR) classification and entry into the file history of the instant application.

CERTIFICATE OF TRANSMISSION VIA EFS-WEB

I hereby certify that this paper is being transmitted via the Electronic Filing System (EFS-WEB) to the United States Patent and Trademark Office on **July 08, 2020**.

/Hyun Jeung Ji/

Hyun Jeung Ji

Applicants : Wei *et al.*
Serial No. : 15/226,489
Filed : August 02, 2016

Attorney Docket No.: 33320.03087.US25/3087B
Statement in Accordance with 37 C.F.R. § 1.704(d)

4. The person making this Statement is a registered practitioner and signs below on the basis of information in the attorney's file.

Respectfully submitted,

/Stephanie Seidman/

Stephanie Seidman

Reg. No. 33,779

Attorney Docket No.: 33320.03087.US25/3087B

Address all correspondence to: 13565

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	: Wei <i>et al.</i>	Art Unit	: 1656
Serial No.	: 15/226,489	Examiner	: Liu, Samuel W.
Filed	: August 02, 2016	Conf. No.	: 9968
		Cust. No.	: 13565
Title	: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		

Mail Stop Amendment

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**STATEMENT FOR SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT
IN ACCORDANCE WITH 37 C.F.R. § 1.97(e)**

Dear Sir:

1. This Statement is being made for the Supplemental Information Disclosure Statement accompanying this certification.

2. I, Stephanie Seidman, hereby state that the item of information contained in the Supplemental Information Disclosure statement, listed as Item AB on the attached PTO-1449 Form and provided herewith in the Supplemental Information Disclosure Statement, is a communication from a foreign patent office in a counterpart foreign application, or was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the Supplemental Information Disclosure Statement.

The above-referenced communication, listed on the attached Form PTO-1449 as Item AB, was issued from the Indian Patent Office on June 17, 2020 and was received on June 18, 2020, in connection with Indian Patent Application No. 6272/DELNP/2014. This Indian Patent Application is a National Stage of International Patent Application No. PCT/US2012/072182, which claims priority to US 61/631,313 and 61/796,208, as does the instant application.

3. The written disclosure of the Supplemental Information Disclosure Statement filed herewith is listed on the attached PTO-1449 Form as Item AA for purposes of Patent Application Information Retrieval (PAIR) classification and entry into the file history of the instant application.

CERTIFICATE OF TRANSMISSION VIA EFS-WEB

I hereby certify that this paper is being transmitted via the Electronic Filing System (EFS-WEB) to the United States Patent and Trademark Office on **July 08, 2020**.

/Hyun Jeung Ji/

Hyun Jeung Ji

Applicants : Wei *et al.*
Serial No. : 15/226,489
Filed : August 02, 2016

Attorney Docket No.: 33320.03087.US25/3087B
Statement in Accordance with 37 C.F.R. § 1.97(c)

4. The person making this Statement is a registered practitioner and signs below on the basis of information in the attorney's file.

Respectfully submitted,

/Stephanie Seidman/

Stephanie Seidman

Reg. No. 33,779

Attorney Docket No.: 33320.03087.US25/3087B

Address all correspondence to: 13565

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Substitute Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. 33320.03087.US25/3087B	Application No. 15/226,489
List of Patents and Publications for Applicant's Information Disclosure Statement (37 CFR §1.98(b))		Applicants <i>Wei et al.</i>	
		Filing Date August 02, 2016	Group Art Unit 1656

U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
None							

Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Translation	
					Yes	No
None						

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document
	AA	Letter/Written Disclosure of the Supplemental Information Disclosure Statement for the above-referenced application, filed herewith on July 08, 2020, 3 pages.
	AB	Hearing Notice, issued Jun. 17, 2020, in connection with Indian Patent Application No. 6272/DELNP/2014, 2 pages.

Examiner Signature	Date Considered
EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

Electronic Acknowledgement Receipt	
EFS ID:	39949457
Application Number:	15226489
International Application Number:	
Confirmation Number:	9968
Title of Invention:	PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF
First Named Inventor/Applicant Name:	Ge Wei
Customer Number:	13565
Filer:	Stephanie L. Seidman/Laura Westergard
Filer Authorized By:	Stephanie L. Seidman
Attorney Docket Number:	33320.03087.US25 / 3087B
Receipt Date:	08-JUL-2020
Filing Date:	02-AUG-2016
Time Stamp:	21:17:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment		no			
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	3087Btra.pdf	26592	no	1
			0149af103f415dfc7155d57e4d2efdb6d7f4cba8		
Warnings:					

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	3087Bids.pdf	32082	no	2
			25269d706f96eaaa55584d7522c1a8438999abd2		
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Patent Term Adjustment Stmt Under 37CFR1.704(d)	3087Bsta1704d.pdf	28918	no	2
			09bd2b14225adb6a1c856d3a51aba386240284f5		
Warnings:					
Information:					
4	Transmittal Letter	3087Bsta197e.pdf	29033	no	2
			872e375fbc2c5b347801094fd207ed6be607e0f4		
Warnings:					
Information:					
5	Information Disclosure Statement (IDS) Form (SB08)	3087Bp49.pdf	29804	no	1
			159159233ef7f4cf52ce2172533e5f01d937984f		
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
6	Non Patent Literature	AA.pdf	103897	no	2
			8b79ad20684fe736b7dde120b8f4ad1c1b5568d7		
Warnings:					
Information:					
7	Non Patent Literature	AB.pdf	1672487	no	2
			43b17134d0cc03a32a96d8c6cb49169c6e596a9a		
Warnings:					
Information:					
Total Files Size (in bytes):			1922813		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Wei *et al.* Art Unit : 1656
Serial No. : 15/226,489 Examiner : Liu, Samuel W.
Filed : August 02, 2016 Conf. No. : 9968
Cust. No. : 13565
Title : **PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES
THEREOF**

Mail Stop Amendment

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT TRANSMITTAL
LETTER**

Dear Sir:

Transmitted herewith are a Supplemental Information Disclosure Statement (2 pages), a Statement for Supplemental Information Disclosure Statement in Accordance with 37 C.F.R. § 1.97(e) (2 pages), a Statement for Supplemental Information Disclosure Statement in Accordance with 37 C.F.R. § 1.704(d) (2 pages), Form PTO-1449 (1 page), and cited non-U.S. patent documents in connection with the above-identified application. Because this Supplemental Information Disclosure Statement is accompanied by a Statement pursuant to 37 C.F.R. § 1.97(e), a fee is not required. If a fee for filing these papers is required, the Commissioner is authorized to charge Deposit Account No. 50-0911, as stated below:

☒ The Commissioner is hereby authorized to charge any fees that may be due in connection with this paper or with this application during its entire pendency to Deposit Account No. 50-0911.

Respectfully submitted,

/Stephanie Seidman/
Stephanie Seidman
Reg. No. 33,779

Attorney Docket No.: 33320.03087.US25/3087B

Address all correspondence to: 13565

Stephanie Seidman
Dentons US LLP
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Telephone: (619) 595-8010
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email: stephanie.seidman@dentons.com

CERTIFICATE OF TRANSMISSION VIA EFS-WEB

I hereby certify that this paper is being transmitted via the Electronic Filing System (EFS-WEB) to the United States Patent and Trademark Office on **July 08, 2020**.

/Hyun Jeung Ji/

Hyun Jeung Ji



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

13565 7590 07/16/2020
Dentons US LLP
4655 Executive Drive
Suite 700
San Diego, CA 92121

EXAMINER

LIU, SAMUEL W

ART UNIT

PAPER NUMBER

1656

DATE MAILED: 07/16/2020

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/226,489	08/02/2016	Ge Wei	33320.03087.US25 / 3087B	9968

TITLE OF INVENTION: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1000	\$0.00	\$0.00	\$1000	10/16/2020

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

13565 7590 07/16/2020
Dentons US LLP
4655 Executive Drive
Suite 700
San Diego, CA 92121

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/226,489	08/02/2016	Ge Wei	33320.03087.US25 / 3087B	9968

TITLE OF INVENTION: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1000	\$0.00	\$0.00	\$1000	10/16/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
LIU, SAMUEL W	1656	424-094620

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

1 _____

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☐ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment: (Please first reapply any previously paid fee shown above)

☐ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. Change in Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment. NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/226,489	08/02/2016	Ge Wei	33320.03087.US25 / 3087B	9968
13565	7590	07/16/2020	EXAMINER	
Dentons US LLP 4655 Executive Drive Suite 700 San Diego, CA 92121			LIU, SAMUEL W	
			ART UNIT	PAPER NUMBER
			1656	
DATE MAILED: 07/16/2020				

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.** Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b) (2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 15/226,489	Applicant(s) Wei, Ge	
	Examiner SAMUEL W LIU	Art Unit 1656	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 4/24/2020 & 7/3/2020.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are 1-14,19,23 and 27-28. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov**.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some *c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892) 2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date <u>4/24/2020</u> . 3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____. 4. ☒ Interview Summary (PTO-413), Paper No./Mail Date. <u>7/3/2020</u> .	5. ☒ Examiner's Amendment/Comment 6. ☒ Examiner's Statement of Reasons for Allowance 7. ☐ Other _____.
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/SAMUEL W LIU/ Examiner, Art Unit 1656	/MANJUNATH N RAO/ Supervisory Patent Examiner, Art Unit 1656
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Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

The amendment filed 4/24/2020 which amends claims 1 and 3-5, and adds new claim 28 has been entered. Claims 15-18 were canceled by the amendment filed 3/8/2019. The new claims 27-28 are drawn to the examined invention. The following office action is applied to claims 1-14, and 19-28.

The references cited in the information disclosure statement (IDS) filed 4/24/2020 have been considered by Examiner.

EXAMINER'S AMENDMENT

An Examiner's Amendment to the record appears below. Should the change and/or additions be unacceptable to Applicant, an amendment may be filed as provided by 37 C.F.R. § 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than payment of the Issue Fee. Authorization for this Examiner's Amendment was given in a telephone interview with Stephanie Seidman on 7/3/2020. Applicants agreed the Examiner proposed amendment to claims 1, 3-5, 27 and 28, and agreed to cancel claims 20-22 and 24-26.

Claim 1 (Currently amended). A modified PH20 polypeptide, comprising one or more amino acid replacements in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NOS: 3, 7 and 32-66;

the modified PH20 polypeptide exhibits increased hyaluronidase activity that is at least 120% of the hyaluronidase activity compared to the unmodified PH20 polypeptide not containing the amino acid replacements); wherein:

the activity of the unmodified PH20 polypeptide not containing the replacement(s) is 100%;

hyaluronidase activity of the modified PH20 polypeptide and hyaluronidase activity of the unmodified PH20 polypeptide ~~is~~ are measured under identical conditions;

the amino acid replacement(s) confer(s) the increased hyaluronidase activity; at least one amino acid replacement(s) is/are at a position corresponding to a position selected from ~~among~~ 1, 15, 24, 27, 29, 30, 31, 32, 33, 37, 39, 48, 63, 67, 69, 71, 72, 73, 75, 87, 92, 93, 94, 118, 120, 135, 141, 147, 148, 150, 151, 152, 155, 156, 163, 164, 165, 170, 198, 209, 212, 215, 219, 233, 236, 247, 257, 259, 260, 263, 269, 271, 272, 276, 278, 282, 293, 305, 308, 313, 320, 324, 325, 326, 328, 353, 359, 371, 377, 380, 389, 392, 395, 405, 409, 410, 418, 425, 436, 437, 438, 441, 442,

446 and 447 with reference to amino acid positions set forth in SEQ ID NO:3, which confers the increased hyaluronidase activity;

corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the sequence of amino acids set forth as SEQ ID NO:3, with the proviso that if the modified PH20 polypeptide includes only a single amino acid replacement, the replacement does not correspond to amino acid replacement N219A with reference to amino acid positions set forth in SEQ ID NO:3; and

the modified PH20 polypeptide has at least **95%** sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7 and 32-66.

Claim 3 (Currently amended). A modified PH20 polypeptide, comprising one or more amino acid replacements in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NOS: 3, 7 and 32-66; the modified PH20 polypeptide exhibits increased hyaluronidase activity that is at least 120% of the hyaluronidase activity compared to the unmodified PH20 polypeptide not containing the amino acid replacements); wherein:

the activity of the unmodified PH20 polypeptide not containing the replacement(s) is 100%;

hyaluronidase activity of the modified PH20 polypeptide and hyaluronidase activity of the unmodified PH20 polypeptide ~~is~~ are measured under identical conditions:

at least one amino acid replacement confers the increased hyaluronidase activity, and is selected from ~~among~~ E at a position corresponding to position 12; E at a position corresponding to position 26; K at a position corresponding to position 26; R at a position corresponding to position 46; Q at a position corresponding to position 52; Q at a position corresponding to position 58; H at a position corresponding to position 68; Q at a position corresponding to position 68; A at a position corresponding to position 70; C at a position corresponding to position 70; F at a position corresponding to position 70; G at a position corresponding to position 70; H at a position corresponding to position 70; K at a position corresponding to position 70; L at a position corresponding to position 70; N at a position corresponding to position 70; P at a position corresponding to position 70; R at a position corresponding to position 70; S at a position corresponding to position 70; T at a position corresponding to position 70; A at a position corresponding to position 74; C at a position corresponding to position 74; G at a position corresponding to position 74; N at a position corresponding to position 74; P at a position corresponding to position 74; R at a position corresponding to position 74; S at a position corresponding to position 74; V at a position corresponding to position 74; W at a position corresponding to position 74; G at a position corresponding to position 84; R at a position corresponding to position 84; G at a position corresponding to position 97; H at a position corresponding to position 127; N at a position corresponding to position 127; G at a position

corresponding to position 131; V at a position corresponding to position 131; R at a position corresponding to position 142; A at a position corresponding to position 166; F at a position corresponding to position 166; H at a position corresponding to position 166; L at a position corresponding to position 166; R at a position corresponding to position 166; Y at a position corresponding to position 166; K at a position corresponding to position 174; K at a position corresponding to position 206; M at a position corresponding to position 213; N at a position corresponding to position 213; E at a position corresponding to position 237; S at a position corresponding to position 238; N at a position corresponding to position 261; R at a position corresponding to position 277; T at a position corresponding to position 277; L at a position corresponding to position 309; N at a position corresponding to position 309; Q at a position corresponding to position 309; R at a position corresponding to position 309; T at a position corresponding to position 309; A at a position corresponding to position 310; G at a position corresponding to position 310; H at a position corresponding to position 315; I at a position corresponding to position 317; K at a position corresponding to position 317; R at a position corresponding to position 317; M at a position corresponding to position 318; G at a position corresponding to position 347; S at a position corresponding to position 347; M at a position corresponding to position 399; T at a position corresponding to position 399; W at a position corresponding to position 399; D at a position corresponding to position 407; Q at a position corresponding to position 407; F at a position corresponding to position 419; I at a position corresponding to position 419; R at a position corresponding to position 419; S at a position corresponding to position 419; K at a position corresponding to position 421; N at a position corresponding to position 421; Q at a position corresponding to position 421; R at a position corresponding to position 421; S at a position corresponding to position 421; A at a position corresponding to position 431; H at a position corresponding to position 431; K at a position corresponding to position 431; Q at a position corresponding to position 431; R at a position corresponding to position 431; S at a position corresponding to position 431; V at a position corresponding to position 431; L at a position corresponding to position 433; R at a position corresponding to position 433; V at a position corresponding to position 439; H at a position corresponding to position 440; R at a position corresponding to position 440; A at a position corresponding to position 443; M at a position corresponding to position 443; M at a position corresponding to position 445, with P at a position corresponding to position 445, with reference to amino acid positions set forth in SEQ ID NO:3; and

the modified PH20 polypeptide has at least **95%** sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7, and 32-66.

Claim 4 (Currently amended). A The modified PH20 polypeptide of claim 3, comprising the amino acid sequence selected from the group consisting of ~~set forth as any of~~ SEQ ID NOs: 73, 78, 91, 95, 96, 105, 106, 108, 109, 111, 112, 113, 115, 117, 118, 119, 120, 123-126, 128-136,

139-141, 149, 154, 155, 164, 165, 167, 191, 192, 196, 197, 199-205, 207, 208, 225, 226, 228, 229, 231, 233, 237, 253, 254, 256, 257, 277, 283, 293, 295, 296, 298, 300, 303, 316, 318, 321, 322, 338-340, 344, 348, 367, 369, 371, 377, 384-388, 394, 398, 399, 401, 406-408, 410, 412, 414, 416, 431, 448, 459, 465, 469, 478, 479, 482, 493, 497, 501, 503, 507, 508, 510-512, 514, 518, 522, 523, 537-543, 545, 558, 559, 561, 563-566, 569, 572, 574, 594, 596, 618-620, 624-634, 637, 640-644, 652, 657, 675, 695, 698, 699, 700, 712, 717, 725, 738, 748-750, 757, 775, 799-801, 807, 822, 825, 844, 847, 85C and 853, or an amino acid sequence that has exhibits at least 96% sequence identity to a the amino acid sequence of amino acids set forth as any of selected from the group consisting of SEQ ID NOs: 73, 78, 91, 95, 96, 105, 106, 108, 109, 111, 112, 113, 115, 117, 118, 119, 120, 123-126, 128-136, 139-141, 149, 154, 155, 164, 165, 167, 191, 192, 196, 197, 199-205, 207, 208, 225, 226, 228, 229, 231, 233, 237, 253, 254, 256, 257, 277, 283, 293, 295, 296, 298, 300, 303, 316, 318, 321, 322, 338-340, 344, 348, 367, 369, 371, 377, 384-388, 394, 398, 399, 401, 406-408, 410, 412, 414, 416, 431, 448, 459, 465, 469, 478, 479, 482, 493, 497, 501, 503, 507, 508, 510-512, 514, 518, 522, 523, 537-543, 545, 558, 559, 561, 563-566, 569, 572, 574, 594, 596, 618-620, 624-634, 637, 640-644, 652, 657, 675, 695, 698, 699, 700, 712, 717, 725, 738, 748-750, 757, 775, 799-801, 807, 822, 825, 844, 847, 851 and 853, and that contains the amino acid replacement as compared to corresponding positions in a polypeptide of any of SEQ ID NOs:3, 7, and 32-66.

Claim 5 (Currently amended). ~~A~~ The modified PH20 polypeptide of claim 3 comprising the amino acid sequence set forth as any of selected from the group consisting of SEQ ID NOs: 86, 89, 99, 100, 159, 173, 181, 193, 195, 209-220, 238, 239, 242, 247-252, 267, 269, 277, 308, 324, 325, 330, 335, 355, 419, 421-423, 425, 428, 435, 455, 456, 462, 463, 484, 490, 506, 531, 533, 579, 581-583, 585, 587, 588, 602, 605, 606, 609, 613, 648, 731, 732, 734, 742, 746, 760, 762, 764, 765, 769-773, 779, 782, 783, 786-789, 794, 795, 814, 816, 819, 826, 830, 836, and 838, or an amino acid sequence that has exhibits at least 96% sequence identity to a the amino acid sequence of amino acids set forth as any of selected from the group consisting of SEQ ID NOs: 86, 89, 99, 100, 159, 173, 181, 193, 195, 209-220, 238, 239, 242, 247-252, 267, 269, 277, 308, 324, 325, 330, 335, 355, 419, 421-423, 425, 428, 435, 455, 456, 462, 463, 484, 490, 506, 531, 533, 579, 581-583, 585, 587, 588, 602, 605, 606, 609, 613, 648, 731, 732, 734, 742, 746, 760, 762, 764, 765, 769-773, 779, 782, 783, 786-789, 794, 795, 814, 816, 819, 826, 830, 836 and 838 and that contains the amino acid replacement as compared to corresponding positions in a polypeptide of any of SEQ ID NOs:3, 7, and 32-66.

Cancel claims 20-22 and 24-26.

Claim 27 (Currently amended). The modified PH20 polypeptide of claim 2, wherein [[:]] the modified PH20 polypeptide is a soluble PH20 polypeptide; and the unmodified polypeptide consists of the amino acid sequence set forth in any of SEQ ID NOs: 3 or 32-66.

Claim 28 (Currently amended). The modified PH20 polypeptide of claim 3, wherein [[:]] the modified PH20 polypeptide is a soluble PH20 polypeptide; and the unmodified polypeptide consists of the amino acid sequence set forth in any of SEQ ID NOs: 3 or 32-66.

The following is an examiner's statement of reasons for allowance:

[1] The 101 rejection of claims 1-10, 13 and 14 is withdrawn in light of the amendment of claims 1 and 3, and in light of that now the amended claims set forth that the **modified** PH20 polypeptide has at least **95% sequence identity** to SEQ ID NO: 7 or to any of SEQ ID NOs: 3 and 32-66 (*wherein SEQ ID NO:7 is the full-length human PH20 polypeptide, SEQ ID NO:3 and 32-66 is C-terminal truncated variant forms of SEQ ID NO:7*); there is no naturally-occurring PH20 polypeptide (genetic variant) or naturally occurring counterparts thereof has its amino acid sequence which has 95% sequence identity to any of SEQ ID NO: 3, 7 and 32-66 and has increased hyaluronidase enzymatic activity compared to unmodified PH20 polypeptide (one of SEQ ID NO: 3, 7 and 32-66) which activity is set forth as "100%" (see the amended claims 1, 3). Thus, claims 1-10, 13 and 14 are not directed to the judicial exception (*Step 2A: NO*); and thereof, the claims are eligible.

[2] The 112(b) of claims 1-3, 5-14, 19 and 23 is withdrawn in light of the amendment of claims 1 and 3.

[3] The 102 reaction of claims 1-10, 13 and 14 by Prothmann et al. is withdrawn in light of the amendment of claims 1 and 3; wherein the amended claims 1 and 3 now recites that the modified PH20 polypeptide has at least **95%** sequence identity to SEQ ID NO: 7 or any of SEQ ID NOs: 3 and 32-66.

[4] The 103 rejection of claims 19 and 23 and the 103 rejection of claims 10-12 by Prothmann in view of Lin et al. and US 20100143457 ('457) are withdrawn in light of the amendment of claims 1 and 3, and in light of that none of the cited references Prothmann, Lin and '457 or combination thereof reasonably renders claim 1 and/or 3 (from which claims 10-12, 19 and/or 23 depend) and claims 10-12, 19 and 23 obvious.

Therefore, claims 1-14, 19, 23, 27 and 28 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Liu whose telephone number is (571) 272-0949. The examiner can normally be reached on Monday-Friday, 9 am to 5:30 pm. If attempts to reach the examiner by

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Art Unit: 1656

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telephone are unsuccessful, the examiner's supervisor Manjunath N. Rao can be reached on 571-272-0939.

/Samuel Wei Liu/
Patent Examiner, Art Unit 1656
July 3, 2020

/MANJUNATH N RAO/
Supervisory Patent Examiner, Art Unit 1656

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments:

Discussed allowability of the amended claims 1-14, 19, 23, 27 and 28. Examiners indicated that the amendment (filed 4/2/4/2020) overcomes the 101 rejection and 112(b), 102 and 103 rejections of record. Examiners pointed that, however, new claims 27-28 have 112(b) issue because the claims do not make it clear which form PH20 polypeptide "modified" or/and "unmodified" PH20 polypeptide is soluble, and that for considering allowability, claims 1 and 3-5 need to be further amended (see the section "Examiner's Amendment" in Allowability Notice). In addition, Examiners pointed out that the process claims 20-22 and 24-26 (which are directed to treatment of disease/disorder including a tumor, a cardiovascular disorder or/and an ophthalmic disorder using a composition comprising a modified PH20 polypeptide) previously withdrawn from further consideration should be canceled in order to considered allowability of this case. Applicants' representative accepted the examiners proposed amendment (see "Examiner's Amendment" in Allowability Notice) and agreed to cancel claims 20-22 and 24-26.

Issue Classification 	Application/Control No. 15/226,489	Applicant(s)/Patent Under Reexamination Wei, Ge	
	Examiner SAMUEL W LIU	Art Unit 1656	

CPC						
Symbol					Type	Version
C12N	/	9	/	2474	F	2013-01-01
A61K	/	38	/	47	I	2013-01-01
A61K	/	38	/	28	I	2013-01-01
A61K	/	45	/	06	I	2013-01-01
C12Y	/	302	/	01035	I	2013-01-01
A61K	/	9	/	0019	I	2013-01-01
A61K	/	47	/	10	I	2013-01-01
C12Q	/	1	/	34	I	2013-01-01
G01N	/	2333	/	926	A	2013-01-01
G01N	/	2333	/	928	A	2013-01-01
Y02A	/	50	/	463	A	2018-01-01
A61K	/	38	/	00	A	2013-01-01

CPC Combination Sets								
Symbol					Type	Set	Ranking	Version
A61K	/	38	/	28	I	1	1	2013-01-01
A61K	/	2300	/	00	I	1	2	2013-01-01
A61K	/	38	/	47	I	2	1	2013-01-01
A61K	/	2300	/	00	I	2	2	2013-01-01

/SAMUEL W LIU/ Examiner, Art Unit 1656 (Assistant Examiner)	04 July 2020 (Date)	Total Claims Allowed: 18	
/MANJUNATH N RAO/ Supervisory Patent Examiner, Art Unit 1656 (Primary Examiner)	06 July 2020 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Issue Classification 	Application/Control No. 15/226,489	Applicant(s)/Patent Under Reexamination Wei, Ge
	Examiner SAMUEL W LIU	Art Unit 1656

INTERNATIONAL CLASSIFICATION			
CLAIMED			
A12N		9	2474
A12N		15	11
NON-CLAIMED			
A61K		38	00

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

/SAMUEL W LIU/ Examiner, Art Unit 1656 (Assistant Examiner)	04 July 2020 (Date)	Total Claims Allowed: 18	
/MANJUNATH N RAO/ Supervisory Patent Examiner, Art Unit 1656 (Primary Examiner)	06 July 2020 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Issue Classification 	Application/Control No. 15/226,489	Applicant(s)/Patent Under Reexamination Wei, Ge
	Examiner SAMUEL W LIU	Art Unit 1656

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47															
CLAIMS															
Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	10	10												
2	2	15	11												
14	3	11	12												
4	4	12	13												
5	5	16	14												
6	6	13	19												
7	7	17	23												
8	8	3	27												
9	9	18	28												

/SAMUEL W LIU/ Examiner, Art Unit 1656 (Assistant Examiner)	04 July 2020 (Date)	Total Claims Allowed: 18	
/MANJUNATH N RAO/ Supervisory Patent Examiner, Art Unit 1656 (Primary Examiner)	06 July 2020 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

<i>Search Notes</i> 	Application/Control No. 15/226,489	Applicant(s)/Patent Under Reexamination Wei et al.
	Examiner SAMUEL W LIU	Art Unit 1656

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

/SAMUEL W LIU/ Examiner, Art Unit 1656	
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<i>Search Notes</i> 	Application/Control No. 15/226,489	Applicant(s)/Patent Under Reexamination Wei et al.
	Examiner SAMUEL W LIU	Art Unit 1656

Search Notes		
Search Notes	Date	Examiner
STIC sequence search for SEQ ID NOs:3, 86, 89, 99-100, 159, 173, 181, 193, 195, 196 and 209-220.	07/02/2020	SWL
STIC E2D2 databases search and WEST search for PH20 or SPerm Adhesion Molecule 1 or SPAM1 or posterior head protein 20 / (variant or mutant or substitution) or modified PH20 or engineered or recombinant PH20/ enhanced or increased hyaluronidase activity/ the amino acid substitutions: G27 or F29 or D30 or E31 or P32 or A48 or Y63 or I67 or T71 or G72 or V73 or V75 or D87 or A92 or K93 or K94 or T118 or A120 or E135 or N141 or T147 or E148 or T150 or E151 or K152 or E155 or E156 or D163 or F164 or K170 or G198 or K209 or D212 or N219 or Q233 or P236 or V247 or P257 or A259 or K260 or T269 or I271 or V272 or Q276 or T293 or G305 or M313 or D320 or E324 or T325 or I326 or N328 or I353 or A371 or G377 or F380 or E389 or E392 or T405 or K409 or E410 or D418 or A425 or P436 or P437 or M438 or E441 or E442 or F446 or/and Y447.	07/01/2020	SWL
PALM inventor name search; and reviewed US Pat. No.9447401.	07/01/2020	SWL

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	PGPUB text search for PH20 or SPerm Adhesion Molecule 1 or SPAM1 or posterior head protein 20 / (variant or mutant or substitution) or modified PH20 or engineered or recombinant PH20/ enhanced or increased hyaluronidase activity/ the amino acid substitutions: G27 or F29 or D30 or E31 or P32 or A48 or Y63 or I67 or T71 or G72 or V73 or V75 or D87 or A92 or K93 or K94 or T118 or A120 or E135 or N141 or T147 or E148 or T150 or E151 or K152 or E155 or E156 or D163 or F164 or K170 or G198 or K209 or D212 or N219 or Q233 or P236 or V247 or P257 or A259 or K260 or T269 or I271 or V272 or Q276 or T293 or G305 or M313 or D320 or E324 or T325 or I326 or N328 or I353 or A371 or G377 or F380 or E389 or E392 or T405 or K409 or E410 or D418 or A425 or P436 or P437 or M438 or E441 or E442 or F446 or/and Y447.	07/01/2020	SWL

/SAMUEL W LIU/ Examiner, Art Unit 1656	
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<i>Search Notes</i> 	Application/Control No. 15/226,489	Applicant(s)/Patent Under Reexamination Wei et al.
	Examiner SAMUEL W LIU	Art Unit 1656

/SAMUEL W LIU/ Examiner, Art Unit 1656	
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Substitute Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. 33320.03087.US25/ 3087B	Application No. 15/226,489
List of Patents and Publications for Applicant's Information Disclosure Statement		Applicant <i>Wei et al.</i>	
		Filing Date August 02, 2016	Group Art Unit 1656
(37 CFR §1.98(b))			

U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	AA	10,328,130	06/25/2019	Frost et al.	424	094.620	02/22/2012
	AB	10,588,983	03/17/2020	Bookbinder et al.	435	069.100	02/23/2018
	AC	2019/0336587	11/07/2019	Frost et al.	424	078.170	05/21/2019

Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Translation	
					Yes	No
	AD	KR 10-2020-0017538	02/18/20	KR	X	

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document
	AE	Letter/Written Disclosure of the Supplemental Information Disclosure Statement for the above-referenced application, filed herewith on Apr. 24, 2020, 2 pages.
	AF	Infante et al., "Phase 1 trials of PEGylated recombinant human hyaluronidase PH20 in patients with advanced solid tumours," Br J Cancer 118(2):153-161 (2018).
	AG	Jadin et al., "A comprehensive model of hyaluronan turnover in the mouse," Matrix Biol 31(2):81-89 (2012).
	AH	Locke et al., "ENHANZE® drug delivery technology: a novel approach to subcutaneous administration using recombinant human hyaluronidase PH20," Drug Deliv 26(1):98-106 (2019).
	AI	NCBI Reference Sequence XP_011728213.1, Macaca nemestrina (pig-tailed macaque) PH-20 hyaluronidase. Published on Apr. 24, 2018. Retrieved from URL:<ncbi.nlm.nih.gov/protein/795324051/ [retrieved on Apr. 20, 2020], 2 pages.
	AJ	News Release, Halozyne Therapeutics, Inc., "Halozyne Announces Actions To Focus Strategy On ENHANZE® Drug Delivery Technology," Published Nov. 04, 2019 [online]. Retrieved from: <URL: halozyne.com/investors/news-releases/news-release-details/2019/Halozyne-Announces-Actions-To-Focus-Strategy-On-ENHANZE-Drug-Delivery-Technology/default.aspx [retrieved on Nov. 11, 2019], 4 pages.
	AK	News Release, Halozyne Therapeutics, Inc., "Halozyne Announces HALO-301 Phase 3 Study Fails To Meet Primary Endpoint," Published Nov. 04, 2019 [online]. Retrieved from: <URL: halozyne.com/investors/news-releases/news-release-details/2019/Halozyne-Announces-HALO-301-Phase-3-Study-Fails-To-Meet-Primary-Endpoint/default.aspx [retrieved on Nov. 11, 2019], 3 pages.
	AL	English translation of News Article, "Alteogen files a PCT application for subcutaneous pharmaceutical composition," Published on Mar. 24, 2020 [online], retrieved from <URL: medipana.com/news/news_viewer.asp?NewsNum=254556&MainKind=A&NewsKind=5&vCount=12&vKind [retrieved on Mar. 26, 2020], 2 pages.
	AM	Notice of Acceptance, dated Mar. 10, 2020, issued in connection with New Zealand Patent Application No. 720075, 1 page.
	AN	English translation of Official Action, issued Mar. 20, 2020, in connection with Korean Application No. 10-2020-7002955, 6 pages.

Examiner Signature /SAMUEL W LIU/	Date Considered 05/05/2020
EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

WEST Search History for Application 15226489

Creation Date: 2020070216:38

Prior Art Searches

Query	DB	Hits	Op.	Plur.	Thes.	Date
(variant or mutant or substitution or modified or engineered or recombinant) with (SPERM Adhesion Molecule 1 or SPAM1 or posterior head protein 20 or PH20)	PGPB, USPT, USOC	258	ADJ	YES		07-02-2020
((variant or mutant or substitution or modified or engineered or recombinant) with (SPERM Adhesion Molecule 1 or SPAM1 or posterior head protein 20 or PH20)) and (enhanced or increased) with PH20 with activity	PGPB, USPT, USOC	18	ADJ	YES		07-02-2020
((variant or mutant or substitution or modified or engineered or recombinant) with (SPERM Adhesion Molecule 1 or SPAM1 or posterior head protein 20 or PH20) and (enhanced or increased) with PH20 with activity) and PH20 with (polypeptide or protein)	PGPB, USPT, USOC	16	ADJ	YES		07-02-2020
((variant or mutant or substitution or modified or engineered or recombinant) with (SPERM Adhesion Molecule 1 or SPAM1 or posterior head protein 20 or PH20) and (enhanced or increased) with PH20 with activity and PH20 with (polypeptide or protein)) and amino acid substitution\$1 and (G27 or F29 or D30 or E31 or P32 or A48 or Y63 or I67 or T71 or G72 or V73 or V75 or D87 or A92 or K93 or K94 or T118 or A120 or E135 or N141 or T147 or E148 or T150 or E151 or K152 or E155 or E156 or D163 or F164 or K170 or G198 or K209 or D212 or N219 or Q233 or P236 or V247 or P257 or A259 or K260 or T269 or I271 or V272 or Q276 or T293 or G305 or M313 or D320 or E324 or T325 or I326 or N328 or I353 or A371 or G377 or F380 or E389 or E392 or T405 or K409 or E410 or D418 or A425 or P436 or P437 or M438 or E441 or E442 or F446 or Y447)	PGPB, USPT, USOC	8	ADJ	YES		07-02-2020



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BIB DATA SHEET

CONFIRMATION NO. 9968

SERIAL NUMBER 15/226,489	FILING or 371(c) DATE 08/02/2016 RULE	CLASS 424	GROUP ART UNIT 1656	ATTORNEY DOCKET NO. 33320.03087.US25 / 3087B		
APPLICANTS HALOZYME, INC., San Diego, CA; INVENTORS Ge Wei, San Diego, CA; H. Michael Shepard, San Diego, CA; Qiping Zhao, San Diego, CA; Robert James Connor, Oceanside, CA; ** CONTINUING DATA ***** This application is a DIV of 13/694,731 12/28/2012 PAT 9447401 which claims benefit of 61/796,208 11/01/2012 and claims benefit of 61/631,313 12/30/2011 ** FOREIGN APPLICATIONS ***** ** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** 08/15/2016						
Foreign Priority claimed ☐ Yes ☒ No 35 USC 119(a-d) conditions met ☐ Yes ☒ No Verified and Acknowledged // <u> </u> Examiner's Signature		☐ Met after Allowance <u> </u> Initials	STATE OR COUNTRY CA	SHEETS DRAWINGS 13	TOTAL CLAIMS 22	INDEPENDENT CLAIMS 3
ADDRESS Dentons US LLP 4655 Executive Drive Suite 700 San Diego, CA 92121 UNITED STATES						
TITLE PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF						
FILING FEE RECEIVED 4020	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:			☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit		



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/226,489	08/02/2016	Ge Wei	33320.03087.US25 / 3087B	9968
13565	7590	08/27/2020	EXAMINER	
Dentons US LLP 4655 Executive Drive Suite 700 San Diego, CA 92121			LIU, SAMUEL W	
			ART UNIT	PAPER NUMBER
			1656	
			NOTIFICATION DATE	DELIVERY MODE
			08/27/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

MLAIPSD@Dentons.com
lucy.begalla@dentons.com
rosalind.smith@dentons.com



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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR/ PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
15/226,489	08/02/2016	Wei et al.	33320.03087.US25

Dentons US LLP 4655 Executive Drive Suite 700 San Diego, CA 92121		EXAMINER	
		SAMUEL W LIU	
		ART UNIT	PAPER
		1656	20200822

DATE MAILED: _____

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Commissioner for Patents

The references cited in the IDS filed 7/8/2020 have been considered by Examiner.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Samuel Wei Liu, Ph.D. whose telephone number is (571) 272-0949. The Examiner can normally be reached daily M-F from 8:30 am to 5:30 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor Manjunath N. Rao can be reached at (571) 272-0939. The official fax number for Technology Center 1600 is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology Center 1600 receptionist whose telephone number is (703)308-0196.

/SAMUEL W LIU/
Examiner, Art Unit 1656

/MANJUNATH N RAO/
Supervisory Patent Examiner, Art Unit 1656

Substitute Form PTO-1449 (Modified)		U.S. Department of Commerce Patent and Trademark Office		Attorney Docket No. 33320.03087.US25/3087B		Application No. 15/226,489	
List of Patents and Publications for Applicant's Information Disclosure Statement (37 CFR §1.98(b))				Applicants <i>Wei et al.</i>			
				Filing Date August 02, 2016		Group Art Unit 1656	
U.S. Patent Documents							
Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
None							

Foreign Patent Documents or Published Foreign Patent Applications						
Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Translation	
					Yes	No
None						

Other Documents (include Author, Title, Date, and Place of Publication)		
Examiner Initial	Desig. ID	Document
	AA	Letter/Written Disclosure of the Supplemental Information Disclosure Statement for the above-referenced application, filed herewith on July 08, 2020, 3 pages.
	AB	Hearing Notice, issued Jun. 17, 2020, in connection with Indian Patent Application No. 6272/DELNP/2014, 2 pages.

Examiner Signature /SAMUEL W LIU/	Date Considered 08/22/2020
EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.W.L/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	Wei <i>et al.</i>	Art Unit	: 1656
Serial No.:	15/226,489	Examiner	: Liu, Samuel W.
Filed	: August 02, 2016	Conf. No.	: 9968
		Cust. No.	: 13565
Title	: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		

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**COMMENTS ON EXAMINER'S REASONS FOR ALLOWANCE AND
AMENDMENT PURSUANT TO 37 C.F.R. §1.312**

Dear Sir:

Entry of the following amendment and consideration of the following remarks respectfully are requested. This amendment is filed concurrently with the payment of the issue fee.

Responsive to the Examiner's Reasons for Allowance, set forth with the *Notice of Allowance*, mailed July 16, 2020, entry of the following comments into the file history of the above-captioned application respectfully is requested.

Amendments to the claims begin on page 2 of this paper.

Remarks begin on page 11 of this paper.

CERTIFICATE OF TRANSMISSION VIA EFS-WEB

I hereby certify that this paper is being transmitted via the Electronic Filing System (EFS-WEB) to the United States Patent and Trademark Office on **October 01, 2020**.

/Rosalind E. Smith/

Rosalind E. Smith

AMENDMENTS TO THE CLAIMS:

Please amend claims 1-5, as indicated below. This listing of claims replaces all prior versions and listing of claims in the application.

LISTING OF CLAIMS:

1. (Currently Amended) A modified PH20 polypeptide, comprising one or more amino acid replacements in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NOS: 3, 7, and 32-66;

the modified PH20 polypeptide exhibits increased hyaluronidase activity that is at least 120% of the hyaluronidase activity compared to the unmodified PH20 polypeptide not containing the amino acid replacement(s); wherein:

the activity of the unmodified PH20 polypeptide not containing the replacement(s) is 100%;

hyaluronidase activity of the modified PH20 polypeptide and hyaluronidase activity of the unmodified PH20 polypeptide are measured under identical conditions;

the amino acid replacement(s) confer(s) the increased hyaluronidase activity;

at least one amino acid replacement(s) confers the increased hyaluronidase activity, and is/are at a position corresponding to a position selected from 1, 15, 24, 27, 29, 30, 31, 32, 33, 37, 39, 48, 63, 67, 69, 71, 72, 73, 75, 87, 92, 93, 94, 118, 120, 135, 141, 147, 148, 150, 151, 152, 155, 156, 163, 164, 165, 170, 198, 209, 212, 215, 219, 233, 236, 247, 257, 259, 260, 263, 269, 271, 272, 276, 278, 282, 293, 305, 308, 313, 320, 324, 325, 326, 328, 353, 359, 371, 377, 380, 389, 392, 395, 405, 409, 410, 418, 425, 436, 437, 438, 441, 442, 446, and 447, with reference to amino acid positions set forth in SEQ ID NO:3, ~~which confers the increased hyaluronidase activity;~~

corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the sequence of amino acids set forth as SEQ ID NO:3, with the proviso that if the modified PH20 polypeptide includes only a single amino acid replacement, the replacement does not correspond to amino acid replacement N219A with reference to amino acid positions set forth in SEQ ID NO:3; and

the modified PH20 polypeptide has at least 95% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOS: 3, 7, and 32-66.

2. (Currently Amended) The modified PH20 polypeptide of claim 1, comprising at least one amino acid replacement selected from among replacement with:

~~histidine (H)~~ at a position corresponding to position 1; Q at a position corresponding to position 1; V at a position corresponding to position 15; E at a position corresponding to position 24; H at a position corresponding to position 24; K at a position corresponding to position 27; R at a position corresponding to position 27; E at a position corresponding to position 29; I at a position corresponding to position 29; L at a position corresponding to position 29; M at a position corresponding to position 29; P at a position corresponding to position 29; S at a position corresponding to position 29; V at a position corresponding to position 29; G at a position corresponding to position 30; H at a position corresponding to position 30; K at a position corresponding to position 30; M at a position corresponding to position 30; R at a position corresponding to position 30; S at a position corresponding to position 30; A at a position corresponding to position 31; C at a position corresponding to position 31; H at a position corresponding to position 31; I at a position corresponding to position 31; K at a position corresponding to position 31; L at a position corresponding to position 31; P at a position corresponding to position 31; R at a position corresponding to position 31; S at a position corresponding to position 31; T at a position corresponding to position 31; V at a position corresponding to position 31; F at a position corresponding to position 32; G at a position corresponding to position 32; H at a position corresponding to position 32; W at a position corresponding to position 33; F at a position corresponding to position 37; N at a position corresponding to position 39; T at a position corresponding to position 39; F at a position corresponding to position 48; H at a position corresponding to position 48; N at a position corresponding to position 48; W at a position corresponding to position 63; V at a position corresponding to position 67; A at a position corresponding to position 69; C at a position corresponding to position 69; F at a position corresponding to position 69; G at a position corresponding to position 69; I at a position corresponding to position 69; L at a position corresponding to position 69; M at a position corresponding to position 69; P at a position corresponding to position 69; R at a position corresponding to position 69; W at a position corresponding to position 69; Y at a position corresponding to position 69; R at a position corresponding to position 71; S at a position corresponding to position 71; M at a position corresponding to position 72; Q at a position corresponding to position 72; H at a position corresponding to position 73; L at a position corresponding to position 73; W at a position corresponding to position 73; F at a position corresponding to position 75; L at a position corresponding to position 75; R at a position corresponding to position 75; T at a position corresponding to position 75; C at a position corresponding to

position 87; T at a position corresponding to position 87; Y at a position corresponding to position 87; C at a position corresponding to position 92; I at a position corresponding to position 93; L at a position corresponding to position 93; R at a position corresponding to position 93; T at a position corresponding to position 93; R at a position corresponding to position 94; Q at a position corresponding to position 118; F at a position corresponding to position 120; V at a position corresponding to position 120; Y at a position corresponding to position 120; D at a position corresponding to position 135; G at a position corresponding to position 135; R at a position corresponding to position 135; H at a position corresponding to position 141; Y at a position corresponding to position 141; R at a position corresponding to position 147; V at a position corresponding to position 147; K at a position corresponding to position 148; G at a position corresponding to position 150; K at a position corresponding to position 151; L at a position corresponding to position 151; M at a position corresponding to position 151; Q at a position corresponding to position 151; R at a position corresponding to position 151; R at a position corresponding to position 152; G at a position corresponding to position 155; K at a position corresponding to position 155; D at a position corresponding to position 156; A at a position corresponding to position 163; E at a position corresponding to position 163; K at a position corresponding to position 163; R at a position corresponding to position 163; M at a position corresponding to position 164; D at a position corresponding to position 165; N at a position corresponding to position 165; R at a position corresponding to position 170; D at a position corresponding to position 198; N at a position corresponding to position 212; M at a position corresponding to position 215; S at a position corresponding to position 219; K at a position corresponding to position 233; R at a position corresponding to position 233; R at a position corresponding to position 236; I at a position corresponding to position 247; T at a position corresponding to position 257; P at a position corresponding to position 259; Y at a position corresponding to position 260; K at a position corresponding to position 263; R at a position corresponding to position 263; A at a position corresponding to position 269; L at a position corresponding to position 271; M at a position corresponding to position 271; T at a position corresponding to position 272; D at a position corresponding to position 276; S at a position corresponding to position 276; Y at a position corresponding to position 276; H at a position corresponding to position 278; K at a position corresponding to position 278; N at a position corresponding to position 278; R at a position corresponding to position 278; S at a position corresponding to position 278; T at a position corresponding to position 278; Y at a position corresponding to position 278; M at a position corresponding to

position 282; A at a position corresponding to position 293; C at a position corresponding to position 293; F at a position corresponding to position 293; M at a position corresponding to position 293; P at a position corresponding to position 293; Q at a position corresponding to position 293; V at a position corresponding to position 293; E at a position corresponding to position 305; G at a position corresponding to position 308; N at a position corresponding to position 308; K at a position corresponding to position 313; R at a position corresponding to position 313; H at a position corresponding to position 320; K at a position corresponding to position 320; R at a position corresponding to position 320; R at a position corresponding to position 324; A at a position corresponding to position 325; D at a position corresponding to position 325; E at a position corresponding to position 325; G at a position corresponding to position 325; H at a position corresponding to position 325; K at a position corresponding to position 325; M at a position corresponding to position 325; N at a position corresponding to position 325; Q at a position corresponding to position 325; S at a position corresponding to position 325; V at a position corresponding to position 326; I at a position corresponding to position 328; K at a position corresponding to position 328; L at a position corresponding to position 328; S at a position corresponding to position 328; Y at a position corresponding to position 328; V at a position corresponding to position 353; T at a position corresponding to position 359; R at a position corresponding to position 371; P at a position corresponding to position 377; T at a position corresponding to position 377; W at a position corresponding to position 380; Y at a position corresponding to position 380; K at a position corresponding to position 389; M at a position corresponding to position 392; R at a position corresponding to position 395; G at a position corresponding to position 405; A at a position corresponding to position 409; Q at a position corresponding to position 409; T at a position corresponding to position 410; P at a position corresponding to position 418; K at a position corresponding to position 425; K at a position corresponding to position 436; I at a position corresponding to position 437; M at a position corresponding to position 437; T at a position corresponding to position 438; F at a position corresponding to position 441; R at a position corresponding to position 442; A at a position corresponding to position 446; D at a position corresponding to position 447; N at a position corresponding to position 447; and/or ~~with~~ Q at a position corresponding to position 447, with reference to amino acid positions set forth in SEQ ID NO:3.

3. (Currently Amended) A modified PH20 polypeptide, comprising one or more amino acid replacements in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NOS: 3, 7, and 32-66;

the modified PH20 polypeptide exhibits increased hyaluronidase activity that is at least 120% of the hyaluronidase activity compared to the unmodified PH20 polypeptide not containing the amino acid replacement(s); wherein:

the activity of the unmodified PH20 polypeptide not containing the replacement(s) is 100%;

hyaluronidase activity of the modified PH20 polypeptide and hyaluronidase activity of the unmodified PH20 polypeptide are measured under identical conditions;

at least one amino acid replacement confers the increased hyaluronidase activity, and is selected from E at a position corresponding to position 12; E at a position corresponding to position 26; K at a position corresponding to position 26; R at a position corresponding to position 46; Q at a position corresponding to position 52; Q at a position corresponding to position 58; H at a position corresponding to position 68; Q at a position corresponding to position 68; A at a position corresponding to position 70; C at a position corresponding to position 70; F at a position corresponding to position 70; G at a position corresponding to position 70; H at a position corresponding to position 70; K at a position corresponding to position 70; L at a position corresponding to position 70; N at a position corresponding to position 70; P at a position corresponding to position 70; R at a position corresponding to position 70; S at a position corresponding to position 70; T at a position corresponding to position 70; A at a position corresponding to position 74; C at a position corresponding to position 74; G at a position corresponding to position 74; N at a position corresponding to position 74; P at a position corresponding to position 74; R at a position corresponding to position 74; S at a position corresponding to position 74; V at a position corresponding to position 74; W at a position corresponding to position 74; G at a position corresponding to position 84; R at a position corresponding to position 84; G at a position corresponding to position 97; H at a position corresponding to position 127; N at a position corresponding to position 127; G at a position corresponding to position 131; V at a position corresponding to position 131; R at a position corresponding to position 142; A at a position corresponding to position 166; F at a position corresponding to position 166; H at a position corresponding to position 166; L at a position corresponding to position 166; R at a position corresponding to position 166; Y at a position corresponding to position 166; K at a position corresponding to position 174; K at a position corresponding to position 206; M at a position corresponding to

position 213; N at a position corresponding to position 213; E at a position corresponding to position 237; S at a position corresponding to position 238; N at a position corresponding to position 261; R at a position corresponding to position 277; T at a position corresponding to position 277; L at a position corresponding to position 309; N at a position corresponding to position 309; Q at a position corresponding to position 309; R at a position corresponding to position 309; T at a position corresponding to position 309; A at a position corresponding to position 310; G at a position corresponding to position 310; H at a position corresponding to position 315; I at a position corresponding to position 317; K at a position corresponding to position 317; R at a position corresponding to position 317; M at a position corresponding to position 318; G at a position corresponding to position 347; S at a position corresponding to position 347; M at a position corresponding to position 399; T at a position corresponding to position 399; W at a position corresponding to position 399; D at a position corresponding to position 407; Q at a position corresponding to position 407; F at a position corresponding to position 419; I at a position corresponding to position 419; R at a position corresponding to position 419; S at a position corresponding to position 419; K at a position corresponding to position 421; N at a position corresponding to position 421; Q at a position corresponding to position 421; R at a position corresponding to position 421; S at a position corresponding to position 421; A at a position corresponding to position 431; H at a position corresponding to position 431; K at a position corresponding to position 431; Q at a position corresponding to position 431; R at a position corresponding to position 431; S at a position corresponding to position 431; V at a position corresponding to position 431; L at a position corresponding to position 433; R at a position corresponding to position 433; V at a position corresponding to position 439; H at a position corresponding to position 440; R at a position corresponding to position 440; A at a position corresponding to position 443; M at a position corresponding to position 443; M at a position corresponding to position 445; and/or ~~with~~ P at a position corresponding to position 445, with reference to amino acid positions set forth in SEQ ID NO:3; and

the modified PH20 polypeptide has at least 95% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOS: 3, 7, and 32-66.

4. (Currently Amended) The modified PH20 polypeptide of claim 23, comprising the amino acid sequence selected from the group consisting of SEQ ID NOS: 73, 78, 91, 95, 96, 105, 106, 108, 109, 111, 112, 113, 115, 117, 118, 119, 120, 123-126, 128-136, 139-141, 149, 154, 155, 164, 165, 167, 191, 192, 196, 197, 199-205, 207, 208, 225, 226, 228, 229, 231,

233, 237, 253, 254, 256, 257, 277, 283, 293, 295, 296, 298, 300, 303, 316, 318, 321, 322, 338-340, 344, 348, 367, 369, 371, 377, 384-388, 394, 398, 399, 401, 406-408, 410, 412, 414, 416, 431, 448, 459, 465, 469, 478, 479, 482, 493, 497, 501, 503, 507, 508, 510-512, 514, 518, 522, 523, 537-543, 545, 558, 559, 561, 563-566, 569, 572, 574, 594, 596, 618-620, 624-634, 637, 640-644, 652, 657, 675, 695, 698, 699, 700, 712, 717, 725, 738, 748-750, 757, 775, 799-801, 807, 822, 825, 844, 847, 851, and 853, or an amino acid sequence that has at least 96% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOS: 73, 78, 91, 95, 96, 105, 106, 108, 109, 111, 112, 113, 115, 117, 118, 119, 120, 123-126, 128-136, 139-141, 149, 154, 155, 164, 165, 167, 191, 192, 196, 197, 199-205, 207, 208, 225, 226, 228, 229, 231, 233, 237, 253, 254, 256, 257, 277, 283, 293, 295, 296, 298, 300, 303, 316, 318, 321, 322, 338-340, 344, 348, 367, 369, 371, 377, 384-388, 394, 398, 399, 401, 406-408, 410, 412, 414, 416, 431, 448, 459, 465, 469, 478, 479, 482, 493, 497, 501, 503, 507, 508, 510-512, 514, 518, 522, 523, 537-543, 545, 558, 559, 561, 563-566, 569, 572, 574, 594, 596, 618-620, 624-634, 637, 640-644, 652, 657, 675, 695, 698, 699, 700, 712, 717, 725, 738, 748-750, 757, 775, 799-801, 807, 822, 825, 844, 847, 851, and 853, and that contains the amino acid replacement as compared to corresponding positions in a polypeptide of any of SEQ ID NOS: 3, 7, and 32-66.

5. (Currently Amended) The modified PH20 polypeptide of claim 3, comprising the amino acid sequence selected from the group consisting of SEQ ID NOS: 86, ~~89-99~~, 100, 159, 173, 181, 193, 195, 209-220, 238, 239, 242, 247-252, 267, 269, ~~277-308~~, 324, 325, 330, 335, 355, 419, 421-423, 425, 428, 435, 455, ~~456-462~~, 463, 484, 490, 506, 531, 533, 579, 581-583, 585, 587, 588, 602, 605, 606, 609, 613, 648, 731, 732, 734, 742, 746, 760, 762, 764, 765, 769-773, 779, 782, 783, 786-789, 794, 795, 814, 816, 819, 826, 830, 836, and 838, or an amino acid sequence that has at least 96% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOS: 86, ~~89-99~~, 100, 159, 173, 181, 193, 195, 209-220, 238, 239, 242, 247-252, 267, 269, ~~277-308~~, 324, 325, 330, 335, 355, 419, 421-423, 425, 428, 435, 455, ~~456-462~~, 463, 484, 490, 506, 531, 533, 579, 581-583, 585, 587, 588, 602, 605, 606, 609, 613, 648, 731, 732, 734, 742, 746, 760, 762, 764, 765, 769-773, 779, 782, 783, 786-789, 794, 795, 814, 816, 819, 826, 830, 836, and 838, and that contains the amino acid replacement as compared to corresponding positions in a polypeptide of any of SEQ ID NOS: 3, 7, and 32-66.

6. (Original) The modified PH20 polypeptide of claim 1 that exhibits at least 2.0-fold of the hyaluronidase activity compared to the PH20 polypeptide not containing the amino acid replacement(s).
7. (Original) The modified PH20 polypeptide of claim 1 that comprises one or more of a modification selected from among glycosylation, sialation, albumination, farnesylation, carboxylation, hydroxylation and phosphorylation.
8. (Original) The modified PH20 polypeptide of claim 1 that comprises at least an N-acetylglucosamine moiety linked to each of at least three asparagine (N) residues.
9. (Original) The modified PH20 polypeptide of claim 8, wherein the three asparagine residues correspond to amino acid residues 200, 333 and 358 of SEQ ID NO:3.
10. (Original) The modified PH20 polypeptide of claim 1 that is conjugated to a polymer.
11. (Original) The modified PH20 polypeptide of claim 3 that is conjugated to a polymer.
12. (Original) The modified PH20 polypeptide of claim 10, wherein the polymer is dextran or PEG.
13. (Original) The modified PH20 polypeptide of claim 1, comprising up to 10 amino acid modifications selected from among amino acid replacements, insertions and deletions.
14. (Original) The modified PH20 polypeptide of claim 3, comprising up to 10 amino acid modifications selected from among amino acid replacements, insertions and deletions.
- 15.-18. (Cancelled).
19. (Original) A pharmaceutical composition, comprising a modified PH20 polypeptide of claim 1.
- 20.-22. (Cancelled).
23. (Previously Presented) A pharmaceutical composition, comprising a modified PH20 polypeptide of claim 3.
- 24.-26. (Cancelled).
27. (Previously Presented) The modified PH20 polypeptide of claim 2, wherein the modified PH20 polypeptide is a soluble PH20 polypeptide; and the unmodified polypeptide consists of the amino acid sequence set forth in any of SEQ ID NOs: 3 or 32-66.

Inventor(s): Wei *et al.*
Serial No. : 15/226,489
Filed : August 02, 2016

Attorney Docket No.: 33320.03087.US25/3087B
**Comments on Reasons for Allowance and
Amendment Pursuant to 37 C.F.R. §1.312**

28. (Previously Presented) The modified PH20 polypeptide of claim 3, wherein the modified PH20 polypeptide is a soluble PH20 polypeptide; and the unmodified polypeptide consists of the amino acid sequence set forth in any of SEQ ID NOs: 3 or 32-66.

Inventor(s): Wei *et al.*
Serial No. : 15/226,489
Filed : August 02, 2016

Attorney Docket No.: 33320.03087.US25/3087B
**Comments on Reasons for Allowance and
Amendment Pursuant to 37 C.F.R. §1.312**

REMARKS

Any fees that may be due in connection with this paper or this application during its entire pendency should be charged to Deposit Account No. 50-0911. If a Petition for extension of time is needed, this paper is to be considered such Petition.

Amendment of the Claims:

Applicant acknowledges the *Notice of Allowance*, mailed July 16, 2020, in which claims 1-14, 19, 23, 27, and 28 are allowed. In reviewing the claims for payment of the issue fee, minor obvious typographical and grammatical errors were noted. Claims 1-5 are amended to correct these minor obvious errors. For example, claim 1 is amended to recite that “at least one amino acid replacement confers the increased hyaluronidase activity, and is at a position corresponding to...,” for clarity and consistency with the language in claim 3. Claim 2 is amended to replace the recitation of “histidine (H)” with “H” for clarity and consistency with the other replacements recited in the claims. Claims 2 and 3 are amended to delete the recitation of the extraneous term “with,” for clarity. Claim 4 is amended, for clarity, to depend on claim 2 instead of claim 3, because the SEQ ID NOS listed in claim 4 set forth sequences of modified PH20 polypeptides with replacements that are recited in claim 2, and not in claim 3. For example, the modified PH20 polypeptides of SEQ ID NOS: 73, 78, and 91 contain the replacements H at a position corresponding to position 1, Q at a position corresponding to position 1, and V at a position corresponding to position 15, respectively; these replacements are recited in claim 2, and not in claim 3. For clarity, claim 5, which depends on claim 3, is amended to delete the recitations of SEQ ID NOS: 89, 277, and 456, which correspond to sequences of modified PH20 polypeptides comprising replacements that are not recited in claim 3. Claims 4 and 5 had been independent claims that were amended to be dependent claims by the Examiner’s amendment in the *Notice of Allowance*, issued on July 16, 2020. Upon review of the sequences recited in claims 4 and 5, it was noted that the Examiner’s amendment rendered claim 4 improperly dependent. Since claims 1 and 2 are allowed, amending claim 4 to depend on claim 2 does not raise any issues of patentability. Since the amendments correct obvious minor errors, they do not affect patentability of the claims. No new matter is added.

Comments on Statement of Reasons for Allowance:

The Examiner provides comments and states that:

[1] The 101 rejection of claims 1-10, 13 and 14 is withdrawn in light of the amendment of claims 1 and 3, and in light of that now the amended claims set forth that the **modified** PH20 polypeptide has at least 95% sequence identity to SEQ ID NO: 7 or

to any of SEQ ID Nos: 3 and 32-66 (*wherein SEQ ID NO:7 is the full-length human PH20 polypeptide, SEQ ID NO:3 and 32-66 is C-terminal truncated variant forms of SEQ ID NO:7*); there is no naturally-occurring PH20 polypeptide (genetic variant) or naturally occurring counterparts thereof has its amino acid sequence which has 95% sequence identity to any of SEQ ID NO: 3, 7 and 32-66 and has increased hyaluronidase enzymatic activity compared to unmodified PH20 polypeptide (one of SEQ ID NO: 3, 7 and 32-66) which activity is set forth as “100%” (see the amended claims 1, 3). Thus, claims 1-10, 13 and 14 are not directed to the judicial exception (*Step 2A: NO*); and thereof, the claims are eligible.

[2] The 112(b) [rejection] of claims 1-3, 5-14, 19 and 23 is withdrawn in light of the amendment of claims 1 and 3.

[3] The 102 [rejection] of claims 1-10, 13 and 14 by Prothmann *et al.* is withdrawn in light of the amendment of claims 1 and 3; wherein the amended claims 1 and 3 now recites that the modified PH20 polypeptide has at least **95%** sequence identity to SEQ ID NO: 7 or any of SEQ ID NOS: 3 and 32-36.

[4] the 103 rejection of claims 19 and 23 and the 103 rejection of claims 10-12 by Prothmann in view of Lin *et al.* and US 20100143457 (‘457) are withdrawn in light of the amendment of claims 1 and 3, and in light of that none of the cited references Prothmann, Lin and ‘457 or combination thereof reasonably renders claim 1 and/or 3 (from which claims 10-12, 19 and/or 23 depend) and claims 10-12, 19 and 23 obvious.

Therefore, claims 1-14, 19, 23, 27 and 28 are allowed.

In accord with MPEP §1302.14, the Examiner’s reasons for allowance need not set forth all of the details why the claims are allowed. Applicant does not concede that the Examiner’s stated reasons for allowance are the only reasons for which the claims are allowable. As discussed below, the claims may be patentable for additional reasons.

Independent claim 1 and dependent claims

Claim 1 and its dependent claims are directed to modified PH20 polypeptides comprising one or more amino acid replacements at specified positions with reference to SEQ ID NO:3, in an unmodified PH20 polypeptide that consists of the amino acid sequence selected from among SEQ ID NOS: 3, 7, and 32-66, where the amino acid replacements confer increased hyaluronidase activity, such that the modified PH20 polypeptide exhibits increased hyaluronidase activity that is at least 120% of the hyaluronidase activity of the unmodified PH20 polypeptide not containing the amino acid replacement(s); the activity of the unmodified PH20 polypeptide not containing the replacement(s) is 100%; the hyaluronidase activities of the modified PH20 polypeptide and of the unmodified PH20 polypeptide are measured under identical conditions; and the modified PH20 polypeptide has at least 95% sequence identity to the amino acid sequence selected from among SEQ ID NOS: 3, 7, and 32-66. Dependent claims recite particular replacements at the positions recited in claim 1, and SEQ ID NOS that correspond to sequences of modified PH20 polypeptides containing these replacements; recite that the modified PH20 polypeptide exhibits at least

2.0-fold of the hyaluronidase activity compared to the PH20 polypeptide not containing the amino acid replacement(s); recite modifications to the modified PH20 polypeptides, including glycosylation, sialation, albumination, farnesylation, carboxylation, hydroxylation, phosphorylation, and conjugation to a polymer such as dextran or PEG; and also recite that the modified PH20 polypeptide comprises up to 10 amino acid modifications, selected from among amino acid replacements, insertions and deletions, relative to the unmodified C-terminally truncated PH20 polypeptides and to the full length unmodified PH20 polypeptide, and that the modified PH20 polypeptide is a soluble PH20 polypeptide. Dependent claim 4 recites SEQ ID NOS that correspond to sequences of modified PH20 polypeptides containing replacements at the amino acid positions recited in claim 1. The claims also are directed to pharmaceutical compositions comprising the modified PH20 polypeptides.

Independent claim 3 and dependent claims

Claim 3 and dependent claims are directed to modified PH20 polypeptides comprising one or more particular amino acid replacements in an unmodified PH20 polypeptide that consists of the amino acid sequence selected from among SEQ ID NOS: 3, 7, and 32-66, where the recited amino acid replacements confer increased hyaluronidase activity, such that the modified PH20 polypeptide exhibits increased hyaluronidase activity that is at least 120% of the hyaluronidase activity of the unmodified PH20 polypeptide not containing the amino acid replacement(s); the activity of the unmodified PH20 polypeptide not containing the replacement(s) is 100%; the hyaluronidase activities of the modified PH20 polypeptide and of the unmodified PH20 polypeptide are measured under identical conditions; and the modified PH20 polypeptide has at least 95% sequence identity to the amino acid sequence selected from among SEQ ID NOS: 3, 7, and 32-66. Dependent claims recite SEQ ID NOS that correspond to sequences of modified PH20 polypeptides containing the replacements recited in claim 3; recite that the modified PH20 polypeptide is conjugated to a polymer; and recite that the modified PH20 polypeptide comprises up to 10 amino acid modifications, selected from among amino acid replacements, insertions and deletions, and that the modified PH20 polypeptide is a soluble PH20 polypeptide. Dependent claim 5 recites SEQ ID NOS that correspond to sequences of modified PH20 polypeptides containing the replacements recited in claim 3. The claims also are directed to pharmaceutical compositions comprising the modified PH20 polypeptides.

Analysis

The claims are directed to modified PH20 polypeptides, with amino acid replacements that confer increased hyaluronidase activity, that are not found in nature. The modified PH20 polypeptides have at least 95% sequence identity to the amino acid sequence selected from among SEQ ID NOS: 3, 7, and 32-66; SEQ ID NO:7 corresponds to the full-length sequence of the unmodified, mature human PH20 polypeptide, and SEQ ID NOS: 3 and 32-66 correspond to C-terminally truncated forms of the full-length amino acid sequence of SEQ ID NO:7.

Applicant agrees with the Examiner that no art of any record, including Prothmann *et al.* (*Mol. Phylogenet. Evol.* 63:52-63 (2012)), Lin *et al.* (*Proc. Natl. Acad. Sci. U.S.A.* 90:10071-10075 (1993)), and U.S. Patent Publication No. 2010/0143457 (the '457 patent), singly or in any combination, discloses, teaches or suggests mutations that increase hyaluronidase activity, and none, singly or in any combination, discloses, teaches or suggests the instantly claimed modified PH20 polypeptides, nor the properties thereof.

The instantly claimed modified PH20 polypeptides containing the replacement(s) identified in the application demonstrate markedly increased hyaluronidase activity, such as hyaluronidase activity that is at least 120% of the activity of an unmodified PH20 polypeptide not containing the amino acid replacement(s). These results are taught in the extensive working examples provided in the instant application; the working examples provide a structure/function survey of PH20. For example, Example 4 provides the results of testing more than 6,700 modified PH20 polypeptides (see, *e.g.*, Table 8) for hyaluronidase activity. The tested variants were identified as active (see, *e.g.*, Table 9) or inactive (see, *e.g.*, Table 10). The results in Table 9 show that, of about 7,000 mutants that were tested, there are many mutations that confer activity that is increased compared to wild-type; among these are about 536 mutations that confer 120% or greater than 120% of the hyaluronidase activity of wild-type PH20. The instant claims are directed to those mutations and the resulting polypeptides that exhibit increased activity. There is no disclosure, teaching or suggestion in the cited references, singly or in any combination, of a modified PH20 polypeptide that exhibits such increased hyaluronidase activity, nor any reason to generate such a polypeptide, nor to modify (*i.e.*, with a polymer, *e.g.*, PEGylate) such modified PH20 polypeptides, nor to provide such polypeptides in a pharmaceutical composition. Thus, for these and other reasons, the claimed modified PH20 polypeptides are novel and unobvious.

* * *

Inventor(s): Wei *et al.*
Serial No. : 15/226,489
Filed : August 02, 2016

Attorney Docket No.: 33320.03087.US25/3087B
**Comments on Reasons for Allowance and
Amendment Pursuant to 37 C.F.R. §1.312**

Entry of the amendments and remarks into the file history of the above-captioned application respectfully is requested.

Respectfully submitted,

/Stephanie Seidman/

Stephanie Seidman

Reg. No. 33,779

Attorney Docket No.: 33320.03087.US25/3087B

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Electronic Patent Application Fee Transmittal				
Application Number:		15226489		
Filing Date:		02-Aug-2016		
Title of Invention:		PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		
First Named Inventor/Applicant Name:		Ge Wei		
Filer:		Stephanie L. Seidman/Rosalind Smith		
Attorney Docket Number:		33320.03087.US25 / 3087B		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
UTILITY APPL ISSUE FEE	1501	1	1000	1000
Extension-of-Time:				
Miscellaneous:				
PRINTED COPY OF PATENT - NO COLOR	8001	14	3	42
Total in USD (\$)				1042

Electronic Acknowledgement Receipt	
EFS ID:	40729119
Application Number:	15226489
International Application Number:	
Confirmation Number:	9968
Title of Invention:	PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF
First Named Inventor/Applicant Name:	Ge Wei
Customer Number:	13565
Filer:	Stephanie L. Seidman/Rosalind Smith
Filer Authorized By:	Stephanie L. Seidman
Attorney Docket Number:	33320.03087.US25 / 3087B
Receipt Date:	01-OCT-2020
Filing Date:	02-AUG-2016
Time Stamp:	14:18:54
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$1042
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	3087Btra_10-01-20.pdf	166656	no	1
			e35d49b3ab69ae7baa3cee025c1dc94eae e3bbe		
Warnings:					
Information:					
2	Issue Fee Payment (PTO-85B)	3087Bifp_10-01-20.pdf	318489	no	2
			04b416cae824186d50de42b4acff32bafa99 301a		
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3		3087Bcra-312_10-01-20.pdf	194240	yes	15
			c4e514ba6cacda185b4bde365613ac0ceae 5b4b4		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Amendment after Notice of Allowance (Rule 312)		1	1	
	Claims		2	10	
	Applicant Arguments/Remarks Made in an Amendment		11	15	
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	33844	no	2
			cbd4fd905bd04bf449a6757764e0204868f 7598		
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Total Files Size (in bytes):			713229		

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	Ge Wei <i>et al.</i>	Art Unit	: 1656
Serial No.:	15/226,489	Examiner	: Samuel W. Liu
Filed	: August 02, 2016	Conf. No.	: 9968
		Cust. No.	: 13565
Title	: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		

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TRANSMITTAL LETTER

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Transmitted herewith are *Comments Responsive to the Statement of Reasons for Allowance and Amendment Pursuant to 37 C.F.R. § 1.312* (15 pages), a *PTOL-85 Part B-Fee Transmittal Form* (1 page in duplicate), with an authorization to charge the Deposit Account for the issue fee, publication fee, and order for 14 copies of the patent (Large Entity Status), for filing in connection with the above-identified application.

☒ The Commissioner is hereby authorized to charge any fees that may be due in connection with this paper or with this application during its entire pendency to Deposit Account No. 50-0911.

Respectfully submitted,

/Stephanie Seidman/
Stephanie Seidman
Reg. No. 33,779

Attorney Docket No. 33320.03087.US25/3087B
Address all correspondence to: 13565
Stephanie Seidman
Dentons US LLP
4655 Executive Drive, Ste. 700
San Diego, California 92121
Telephone: (619) 595-8010
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email: stephanie.seidman@dentons.com

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October 01, 2020	(Date)

APPLICATION NO. 15/226,489	FILING DATE 08/02/2016	FIRST NAMED INVENTOR Ge Wei	ATTORNEY DOCKET NO. 33320.03087,US25/3087B	CONFIRMATION NO. 9968
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TITLE OF INVENTION: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF

APPLN. TYPE NONPROVISIONAL	ENTITY STATUS UNDISCOUNTED	ISSUE FEE \$1000	PUBLICATION FEE \$0	PREV. PAID ISSUE FEE \$0	TOTAL FEE(S) DUE \$1000	DATE DUE 10/16/2020
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EXAMINER LIU, SAMUEL W.	ART UNIT 1656	CLASS-SUBCLASS 424-094620
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1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

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☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

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- Dentons US LLP**
- Stephanie Seidman**
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(A) NAME OF ASSIGNEE
(B) RESIDENCE (CITY AND STATE OR COUNTRY)

Halozyme, Inc.

San Diego, California

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ individual ☒ corporation or other private group entity ☐ government

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5. Change in Entity Status (from status indicated above)

- ☐ a. Applicant claims MICRO ENTITY status. See 37 CFR 1.29.
☐ b. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
☐ c. Applicant changing to regular UNDISCOUNTED fee status.

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(Authorized Signature) /Stephanie Seidman/

(Date) October 01, 2020

Typed or Printed Name Stephanie Seidman

Registration No. 33,779

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Rosalind E. Smith	(Depositor's name)
/Rosalind E. Smith/	(Signature)
October 01, 2020	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/226,489	08/02/2016	Ge Wei	33320.03087,US25/3087B	9968

TITLE OF INVENTION: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF

APPLN. TYPE	ENTITY STATUS	ISSUE FEE	PUBLICATION FEE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
NONPROVISIONAL	UNDISCOUNTED	\$1000	\$0	\$0	\$1000	10/16/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
LIU, SAMUEL W.	1656	424-094620

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
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- Dentons US LLP**
- Stephanie Seidman**
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3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

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(A) NAME OF ASSIGNEE (B) RESIDENCE (CITY AND STATE OR COUNTRY)

Halozyme, Inc.

San Diego, California

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ individual ☒ corporation or other private group entity ☐ government

4a. The following fee(s) are enclosed:

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☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number **50-0911**, (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

- ☐ a. Applicant claims MICRO ENTITY status. See 37 CFR 1.29.
☐ b. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
☐ c. Applicant changing to regular UNDISCOUNTED fee status.

- a. NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
b. NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
c. NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

The Director of the USPTO is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.
NOTE: The issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant, a registered agent or, or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

(Authorized Signature) **/Stephanie Seidman/**

(Date) **October 01, 2020**

Typed or Printed Name **Stephanie Seidman**

Registration No. **33,779**

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/226,489	08/02/2016	Ge Wei	33320.03087.US25 / 3087B	9968
13565	7590	10/16/2020	EXAMINER	
Dentons US LLP 4655 Executive Drive Suite 700 San Diego, CA 92121			LIU, SAMUEL W	
			ART UNIT	PAPER NUMBER
			1656	
			NOTIFICATION DATE	DELIVERY MODE
			10/16/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

MLAIPSD@Dentons.com
lucy.begalla@dentons.com
rosalind.smith@dentons.com

Response to Rule 312 Communication	Application No. 15/226,489	Applicant(s) Wei et al.	
	Examiner SAMUEL W LIU	Art Unit 1656	AIA (FITF) Status No
<p align="center">-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --</p> <p>1. ☒ The amendment filed on <u>01 October 2020</u> under 37 CFR 1.312 has been considered, and has been:</p> <p>a) ☒ entered.</p> <p>b) ☒ entered as directed to matters of form not affecting the scope of the invention.</p> <p>c) ☐ disapproved because the amendment was filed after the payment of the issue fee. Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.</p> <p>d) ☐ disapproved. See explanation below.</p> <p>e) ☐ entered in part. See explanation below.</p> <p>_____</p>			
/SAMUEL W LIU/ Examiner, Art Unit 1656		/MANJUNATH N RAO/ Supervisory Patent Examiner, Art Unit 1656	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): Wei *et al.* Art Unit : 1656
Serial No. : 15/226,489 Examiner : Liu, Samuel W.
Filed : August 02, 2016 Conf. No. : 9968
Cust. No. : 13565
Title : **PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES
THEREOF**

Mail Stop ISSUE FEE

Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

**COMMENTS ON EXAMINER'S REASONS FOR ALLOWANCE AND
AMENDMENT PURSUANT TO 37 C.F.R. §1.312**

Dear Sir:

Entry of the following amendment and consideration of the following remarks respectfully are requested. This amendment is filed concurrently with the payment of the issue fee.

Responsive to the Examiner's Reasons for Allowance, set forth with the *Notice of Allowance*, mailed July 16, 2020, entry of the following comments into the file history of the above-captioned application respectfully is requested.

Amendments to the claims begin on page 2 of this paper.

Remarks begin on page 11 of this paper.

CERTIFICATE OF TRANSMISSION VIA EFS-WEB

I hereby certify that this paper is being transmitted via the Electronic Filing System (EFS-WEB) to the United States Patent and Trademark Office on **October 01, 2020**.

/Rosalind E. Smith/

Rosalind E. Smith

Issue Classification 	Application/Control No. 15/226,489	Applicant(s)/Patent Under Reexamination Wei, Ge
	Examiner SAMUEL W LIU	Art Unit 1656

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47															
CLAIMS															
Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	10	10												
2	2	15	11												
3	3	11	12												
4	4	12	13												
5	5	16	14												
6	6	13	19												
7	7	17	23												
8	8	3	27												
9	9	18	28												

Change(s) applied
to document,
/M.A.P./
8/20/2020

/SAMUEL W LIU/ Examiner, Art Unit 1656 (Assistant Examiner)	04 July 2020 (Date)	Total Claims Allowed: 18	
/MANJUNATH N RAO/ Supervisory Patent Examiner, Art Unit 1656 (Primary Examiner)	06 July 2020 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none



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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/226,489	12/15/2020	10865400	33320.03087.US25 / 3087B	9968

13565 7590 11/24/2020
Dentons US LLP
4655 Executive Drive
Suite 700
San Diego, CA 92121

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (application filed on or after May 29, 2000)

The Patent Term Adjustment is 722 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site <http://pair.uspto.gov> for additional applicants):

Ge Wei, San Diego, CA;
HALOZYME, INC., San Diego, CA;
H. Michael Shepard, San Diego, CA;
Qiping Zhao, San Diego, CA;
Robert James Connor, Oceanside, CA;

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors : Ge Wei *et al.*
Patent No. : 10,865,400
Issue Date : December 15, 2020
Serial No. : 15/226,489
Filed : August 02, 2016
Title : **PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF**

Art Unit : 1656
Examiner : Samuel W. Liu
Conf. No. : 9968
Cust. No. : 13565

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APPLICATION FOR PATENT TERM ADJUSTMENT
UNDER 37 C.F.R. § 1.705(b)

Dear Sir:

Patentee hereby files this *Application for Patent Term Adjustment Under 37 C.F.R. 1.705(b)* respectfully requesting reconsideration of the Patent Term Adjustment (PTA) accorded to U.S. Patent No. 10,865,400. The Determination of Patent Term Adjustment under 35 U.S.C. § 154(b) printed on the face of the patent, issued December 15, 2020, states that the Total PTA is 722 days. **Reconsideration of the PTA Determination to increase Total PTA from 722 days to 794 days, respectfully is requested.**

Patentee hereby provides a statement of facts involved, specifying the correct PTA, the basis under 37 C.F.R. § 1.702 for adjustment, the relevant dates for which the adjustment is sought, and the adjustment to which the patent is entitled.

CERTIFICATE OF TRANSMISSION VIA EFS-WEB

I hereby certify that this paper is being transmitted via the Electronic Filing System (EFS-WEB) to the United States Patent and Trademark Office on **December 30, 2020**.

/Rosalind E. Smith/
Rosalind E. Smith

Inventors : Ge Wei *et al.*
Patent No. : **10,865,400**
Issue Date : December 15, 2020
Serial No. : 15/226,489
Filed : August 02, 2016

Attorney Docket: 33320.03087.US25/3087B
Application for Patent Term Adjustment
Under 35 C.F.R. § 1.705(b)

STATEMENT OF FACTS

U.S. Application Serial No. 15/226,489 issued as U.S. Patent No. 10,865,400 on December 15, 2020. Patentee is filing this *Application for Reconsideration of Patent Term Adjustment* within two months of the patent grant. The *Determination of Patent Term Adjustment Under 35 U.S.C. 154(b)* as printed on the face of the instant patent, issued on December 15, 2020, states that the Total Patent Term Adjustment at issuance is “722” days. Patentee respectfully requests reconsideration of patent term adjustment as provided below.

Time Period 1: October 15, 2019 to October 18, 2019

On October 15, 2019, Applicant filed its *Response to the Non-Final Office Action* of May 15, 2019. **The Patent Office accorded 61 days of Applicant Delay to the *Response*. Applicant does not dispute this adjustment.**

On October 18, 2019, Applicant filed a *Request for Corrected Filing Receipt* with an updated Application Data Sheet, correcting the relationship of this application as provided in the amendment to the specification filed with the response to the Non-Final Office Action. **The Patent Office accorded 0 days of Applicant Delay to this submission. Applicant submits that it may be appropriate to accord 3 days of Applicant Delay under 37 CFR 1.704(c)(8) as a supplemental submission after the response to the Office action.**

Time Period 2: April 24, 2020 to July 8, 2020

On April 24, 2020, Applicant filed its *Response to Non-Final Office Action* of January 23, 2020. **The Patent Office accorded 1 day of Applicant Delay to the *Response*. Applicant does not dispute this adjustment.**

On July 8, 2020, Applicant filed an IDS with the *Safe Harbor Statement under 37 C.F.R. 1.704(d)* that the IDS was a submission filed within 30 days of receipt of a communication received from a counterpart foreign application. **The Patent Office accorded 75 days of Applicant Delay to the *IDS*. Applicant disputes this adjustment.**

The U.S. Patent and Trademark Office (USPTO) has treated the *IDS*, filed July 8, 2020, as a supplemental paper under 1.704(c)(8). The USPTO has accorded Applicant Delay beginning the patent term reductions on April 24, 2020, the day after the *Response to Non-Final Office Action* was filed, and ending on July 8, 2020, the date the *IDS* was filed, for 75 days of Applicant Delay. Information disclosure statements filed as a result of the citation of information that is promptly filed with the Office within 30 days of receipt, when

Inventors : Ge Wei *et al.*
Patent No. : **10,865,400**
Issue Date : December 15, 2020
Serial No. : 15/226,489
Filed : August 02, 2016

Attorney Docket: 33320.03087.US25/3087B
Application for Patent Term Adjustment
Under 35 C.F.R. § 1.705(b)

accompanied by a statement pursuant to 37 C.F.R. § 1.704(d), are **exempt from patent term reductions** under 37 C.F.R. § 1.704(c)(6), (c)(8), (c)(9), and (c)(10).

The *IDS* filed on July 8, 2020, provides the Office with the requisite statement under 1.704(d) that the communication was issued by a counterpart foreign application and was not received by any individual designated in § 1.56(c) more than 30 days prior to filing the *IDS* of July 8, 2020, and the statement provides the Office with the date the communication was received by U.S. counsel (received on June 18, 2020). **Applicant submits that it complied with 37 C.F.R. § 1.704(d) and that the 75 days of Applicant Delay accorded to the *IDS* of July 8, 2020, is improper and should be removed.**

Adjustments Not in Dispute

Applicant does not dispute the following patent term adjustments: the 28 days of Applicant Delay accorded to the *Response to Restriction Requirement*, filed March 8, 2019; the 61 days of Applicant Delay accorded to the *Response to Non-Final Office Action*, filed October 15, 2019; the 1 day of Applicant Delay accorded to the *Response to Non-Final Office Action*, filed April 24, 2020; the 16 days of Applicant Delay accorded to the *312 Amendment*, filed October 1, 2020; the 402 days of USPTO “A” Delay accorded to the *Restriction Requirement*, mailed November 8, 2018; nor the 501 days of USPTO “B” Delay days.

REMARKS

In consideration of the events described above, Applicant submits the Total PTA calculation of 722 days is ***understated*** as of the date of patent issuance. Applicant respectfully requests reconsideration of the patent term adjustment in the following manner:

1. **USPTO Delay:** 903 days – correct as stated;
2. Reduce **Applicant Delay** from 181 days to 109 days;
(181 - 75 + 3 = 109 days)
3. Increase **Total PTA** days from 722 days to 794 days.
(903 - 109 = 794 days)

U.S. Patent No. 10,865,400 is not subject to a Terminal Disclaimer.

Any fees that may be due in connection with the filing of this paper or with this patent application should be charged to Deposit Account No. 50-0911. If a Petition for Extension of Time is needed, this paper is to be considered such Petition.

* * *

Inventors : Ge Wei *et al.*
Patent No. : **10,865,400**
Issue Date : December 15, 2020
Serial No. : 15/226,489
Filed : August 02, 2016

Attorney Docket: 33320.03087.US25/3087B
Application for Patent Term Adjustment
Under 35 C.F.R. § 1.705(b)

If there are any questions, please contact the undersigned. Thank you for your
courtesy and consideration.

Respectfully submitted,

/Stephanie Seidman/
Stephanie Seidman
Reg. No. 33,779

Attorney Docket No. 33320.03087.US25/3087B
Address all correspondence to:
Customer No. 13565
Stephanie Seidman
Dentons US LLP
4655 Executive Drive, Suite 700
San Diego, California 92121
Telephone: (619) 595-8010
Facsimile: (619) 595-8135
email: stephanie.seidman@dentons.com

Inventors : Ge Wei *et al.*
Patent No. : **10,865,400**
Issue Date : December 15, 2020
Serial No. : 15/226,489
Filed : August 02, 2016

Attorney Docket: 33320.03087.US25/3087B
Application for Patent Term Adjustment
Under 35 C.F.R. § 1.705(b)

Attachment 1
Copy of Patent Term Adjustment Screen from PAIR

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15/226,489 PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF 33320.03087.US25 / 3087B

Select New Case Application Data Transaction History Image File Wrapper Patent Term Adjustments Continuity Data Fees Published Documents Address & Attorney/Agent Supplemental Assignments Content Display References

Patent Term Adjustment
Filing or 371(c) Date: 08-02-2016 Overlapping Days Between {A and B} or {A and C}: 0
Issue Date of Patent: 12-15-2020 Non-Overlapping USPTO Delays: 903 OK
A Delays: 402 OK PTO Manual Adjustments: 0
B Delays: 501 OK Applicant Delays: (181 - 75 + 3 = 109 days) 181 NO
C Delays: 0 Total PTA Adjustments: (903 - 109 = 794 days) 722 NO

Patent Term Adjustment History

Number	Date	Explanation Of Calculations Contents Description	PTO(Days)	APPL(Days)	Start
135.5	12-15-2020	PTA 36 Months	501		0.5 OK
135	12-15-2020	Patent Issue Date Used in PTA Calculation			0
134	11-11-2020	Export to Final Data Capture			0
133	11-09-2020	Finished Initial Data Capture			0
132	11-10-2020	Dispatch to FDC			0
131	11-10-2020	Application Is Considered Ready for Issue			0
130	07-08-2020	Information Disclosure Statement considered			0
129	10-16-2020	Email Notification			0
128	10-16-2020	Mail Response to 312 Amendment (PTO-271)		16	123 OK
127	10-11-2020	Office Action Review			0
126	10-09-2020	Response to Amendment under Rule 312			0
125	10-09-2020	Printer Rush- No mailing			0
124	10-08-2020	Pubs Case Remand to TC			0
123	10-01-2020	Amendment after Notice of Allowance (Rule 312)			0
122	10-01-2020	Issue Fee Payment Verified			0
121	10-01-2020	Issue Fee Payment Received			0
120	08-27-2020	Email Notification			0
119	08-27-2020	Mail Miscellaneous Communication to Applicant			0
118	08-22-2020	Printer Rush- No mailing			0
117	08-22-2020	Miscellaneous Communication to Applicant - No Action Count			0
116	08-22-2020	Information Disclosure Statement considered			0
115	08-21-2020	Pubs Case Remand to TC			0
114	07-22-2020	Sequence Forwarded to Pubs on Tape			0
113	07-15-2020	Export to Initial Data Capture			0
112	07-16-2020	Electronic Review			0
111	07-16-2020	Email Notification			0
110	07-16-2020	Mail Notice of Allowance			0 OK
109	07-13-2020	Office Action Review			0
108	07-13-2020	Office Action Review			0
107	07-13-2020	Office Action Review			0
106	07-13-2020	Office Action Review			0
105	07-08-2020	Information Disclosure Statement (IDS) Filed			0
104	07-13-2020	Issue Revision Completed			0
103	07-13-2020	Document Verification			0
102	07-13-2020	Notice of Allowance Data Verification Completed			0
101	07-08-2020	Information Disclosure Statement (IDS) Filed			0
100	07-08-2020	Information Disclosure Statement (IDS) Filed			0
99	07-06-2020	Examiner's Amendment Communication			0
98	07-06-2020	Reasons for Allowance			0
97	07-06-2020	Interview Summary - Examiner Initiated - Telephonic			0
96	07-06-2020	Allowability Notice			0
95	08-29-2018	Information Disclosure Statement considered			0
94	10-15-2019	Information Disclosure Statement considered			0
93	03-08-2019	Information Disclosure Statement considered			0

PTO ignored the Safe Harbor Statement under 1.704(d), which was present for this IDS.

IDS contains Safe Harbor Statement under 1.704(d) and should not have been accorded applicant delay.

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12/15/2020

https://ppair-my.uspto.gov/pair/PrivatePair

Petitioner Merck, Ex. 1002, p. 1015

	92	04-24-2020	Information Disclosure Statement considered		0	
	80	05-05-2020	Information Disclosure Statement considered		0	
	79	04-24-2020	Information Disclosure Statement (IDS) Filed		0	
	78	04-27-2020	Date Forwarded to Examiner		0	
	77	04-24-2020	Response after Non-Final Action	1	73	OK
	76	04-24-2020	Request for Extension of Time - Granted		0	
	75	04-24-2020	Information Disclosure Statement (IDS) Filed		0	
	74	04-24-2020	Information Disclosure Statement (IDS) Filed		0	
	73	01-23-2020	Mail Non-Final Rejection		0	
	72	01-17-2020	Non-Final Rejection		0	
10/18/2019 - Request for Corrected Filing Receipt filed - 3 days after the response, correcting the "relationship" from "CON" to "DIV" as per amendment to the specification made on 10/15/2020 in response to the Office action. Possible 3 days of application delay as a supplemental submission after a response had already been filed, under 37 CFR 1.704(c)(8).	70	10-22-2019	Filing Receipt - Corrected		0	
	69	10-15-2019	Information Disclosure Statement (IDS) Filed	(3 days?)	0	
	68	10-20-2019	Date Forwarded to Examiner		0	
	67	10-15-2019	Response after Non-Final Action	61	57	OK
	66	10-15-2019	Request for Extension of Time - Granted		0	
	65	10-15-2019	Information Disclosure Statement (IDS) Filed		0	
	63	10-15-2019	Mail-Petition Decision - Granted		0	
	62	09-27-2019	Petition Decision - Granted		0	
	61	09-27-2019	Mail TC Petition Granted		0	
	60	09-26-2019	Office Action Review		0	
	59	09-23-2019	TC Petition Granted		0	
	58	08-09-2019	Petition Entered		0	
	57	05-15-2019	Mail Non-Final Rejection		0	
	56	05-09-2019	Non-Final Rejection		0	
	53	04-26-2019	Information Disclosure Statement considered		0	
	52	04-26-2019	Information Disclosure Statement considered		0	
	48	03-08-2019	Information Disclosure Statement (IDS) Filed		0	
	43	03-20-2019	Date Forwarded to Examiner		0	
	42	03-08-2019	Response to Election / Restriction Filed	28	38	OK
	41	03-08-2019	Request for Extension of Time - Granted		0	
	40	03-08-2019	Information Disclosure Statement (IDS) Filed		0	
	38	11-08-2018	Mail Restriction Requirement	402	0.5	OK
	37	11-05-2018	Restriction/Election Requirement		0	
	35	08-29-2018	Information Disclosure Statement (IDS) Filed		0	
	34	08-29-2018	Information Disclosure Statement (IDS) Filed		0	
	33	08-29-2018	Information Disclosure Statement (IDS) Filed		0	
	31	09-15-2017	Electronic Information Disclosure Statement		0	
	30	09-15-2017	Electronic Information Disclosure Statement		0	
	28	09-15-2017	Information Disclosure Statement (IDS) Filed		0	
	27	12-15-2016	Application ready for PDX access by participating foreign offices		0	
	26	12-15-2016	PG-Pub Issue Notification		0	
	25	08-02-2016	Oath or Declaration Filed (Including Supplemental)		0	
	24	08-29-2016	Miscellaneous Incoming Letter		0	
	23	09-23-2016	Change in Power of Attorney (May Include Associate POA)		0	
	22	08-31-2016	CRF Is Good Technically / Entered into Database		0	
	21	09-06-2016	Case Docketed to Examiner in GAU		0	
	20	09-06-2016	Application Dispatched from OIPE		0	
	19	09-06-2016	FITF set to NO - revise initial setting		0	
	18	08-29-2016	Patent Term Adjustment - Ready for Examination		0	
	17	09-06-2016	Application Is Now Complete		0	
	16	09-06-2016	Filing Receipt - Updated		0	
	15	08-29-2016	Additional Application Filing Fees		0	
	14	08-29-2016	CRF Disk Has Been Received by Preexam / Group / PCT		0	
	12	08-24-2016	Information Disclosure Statement (IDS) Filed		0	
	11	08-10-2016	CRF Is Flawed Technically / Not Entered into Database		0	
	10	08-15-2016	Filing Receipt		0	
	9	08-15-2016	SEQUENCE ERRORS		0	
	8	08-02-2016	PTO/SB/69-Authorize EPO Access to Search Results		0	
	7	08-02-2016	Applicants have given acceptable permission for participating foreign		0	
	6	08-02-2016	CRF Disk Has Been Received by Preexam / Group / PCT		0	
	5	08-03-2016	Cleared by L&R (LARS)		0	
	4	08-03-2016	Referred to Level 2 (LARS) by OIPE CSR		0	
	3	08-02-2016	IFW Scan & PACR Auto Security Review		0	
	2	08-02-2016	ENTITY STATUS SET TO UNDISCOUNTED (INITIAL DEFAULT SETTING OR STATUS CHANGE)		0	
	1	08-02-2016	Initial Exam Team nn		0	
	0.5	08-02-2016	Filing date		0	

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Electronic Patent Application Fee Transmittal				
Application Number:		15226489		
Filing Date:		02-Aug-2016		
Title of Invention:		PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		
First Named Inventor/Applicant Name:		Ge Wei		
Filer:		Stephanie L. Seidman/Rosalind Smith		
Attorney Docket Number:		33320.03087.US25 / 3087B		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
APPLICATION FOR PATENT TERM ADJUSTMENT	1455	1	210	210
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				210

Electronic Acknowledgement Receipt	
EFS ID:	41522312
Application Number:	15226489
International Application Number:	
Confirmation Number:	9968
Title of Invention:	PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF
First Named Inventor/Applicant Name:	Ge Wei
Customer Number:	13565
Filer:	Stephanie L. Seidman/Rosalind Smith
Filer Authorized By:	Stephanie L. Seidman
Attorney Docket Number:	33320.03087.US25 / 3087B
Receipt Date:	30-DEC-2020
Filing Date:	02-AUG-2016
Time Stamp:	14:11:58
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$210
RAM confirmation Number	E2020BTE13010091
Deposit Account	500911
Authorized User	Rosalind Smith
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

37 CFR 1.19 (Document supply fees)
 37 CFR 1.20 (Post Issuance fees)
 37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	3087Btra_12-30-20.pdf	144507	no	1
			ca9785e0e5db82527962d2e2f3ff6478f39d3226		

Warnings:

Information:

2	Patent Term Adjustment Petition	3087Bpta_12-30-20.pdf	416139	no	8
			89c20b2997a91b728fb782ef13dcb6f30f244f33		

Warnings:

Information:

3	Fee Worksheet (SB06)	fee-info.pdf	30769	no	2
			1018431f344459d581739e952f26a6f75e5f5373		

Warnings:

Information:

Total Files Size (in bytes):			591415
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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors : Ge Wei *et al.*
Patent No. : 10,865,400
Issue Date : December 15, 2020
Serial No. : 15/226,489
Filed : August 02, 2016
Title : **PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF**

Art Unit : 1656
Examiner : Samuel W. Liu
Conf. No. : 9968
Cust. No. : 13565

Mail Stop PATENT EXT.
Commissioner for Patents
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Dear Sir:

Transmitted herewith is an *Application for Patent Term Adjustment Under 37 C.F.R. § 1.705(b)* (4 pages) and 1 attachment, in response to the *Determination of Patent Term Adjustment Under 35 U.S.C. § 154(b)*, as printed on the face of U.S. Patent No. 10,865,400, which issued December 15, 2020, for filing in connection with the above-identified application.

☒ **Fee set forth in § 1.18(e) for application for patent term adjustment: \$210.00**

☒ The Commissioner is hereby authorized to charge the fee for this Application for Patent Term Adjustment and any other fee that may be due in connection with this and the attached papers, or with this application during its entire pendency, or to credit any overpayment, to Deposit Account No. 50-0911.

Respectfully submitted,

/Stephanie Seidman/

Stephanie Seidman

Reg. No. 33,779

Attorney Docket No. 33320.03087.US25/3087B

Address all correspondence to:

Customer No. 13565

Stephanie Seidman

Dentons US LLP

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Telephone: (619) 595-8010

Facsimile: (619) 595-8135

email: stephanie.seidman@dentons.com

CERTIFICATE OF TRANSMISSION BY EFS-WEB

I hereby certify that this paper is being transmitted via the Electronic Filing System (EFS-WEB) to the United States Patent and Trademark Office on **December 30, 2020.**

/Rosalind E. Smith/

Rosalind E. Smith



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/226,489	08/02/2016	Ge Wei	33320.03087.US25 / 3087B	9968
13565	7590	09/01/2021	EXAMINER	
Dentons US LLP 4655 Executive Drive Suite 700 San Diego, CA 92121			LIU, SAMUEL W	
			ART UNIT	PAPER NUMBER
			1656	
			NOTIFICATION DATE	DELIVERY MODE
			09/01/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

MLAIPSD@Dentons.com
lucy.begalla@dentons.com
rosalind.smith@dentons.com



UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

In re Patent No. 10,865,400 :
Issue Date: 15 Dec 2020 : REDETERMINATION OF
Application No. 15/226,489 : PATENT TERM
Filing or 371(c) Date: 2 Aug 2016 : ADJUSTMENT
Attorney Docket No. 33320.03087.US25 / :
3087B :

This is a decision on the “APPLICATION FOR PATENT TERM ADJUSTMENT UNDER 37 C.F.R. § 1.705(b)” (“Request”), filed December 30, 2020. Applicant requests the United States Patent and Trademark Office (“Office”) correct the patent term adjustment determination (“PTA”) set forth on the patent from seven hundred twenty-two (722) days to seven hundred ninety-four (794) days. The Office’s redetermination of the PTA indicates the correct PTA is **seven hundred thirty-three (733) days**.

This redetermination of the PTA is NOT a “Director’s decision on the applicant’s request for reconsideration” within the meaning of 35 U.S.C. § 154(b)(4), and the issuance of this redetermination does *not* start the 180-day period set forth in 35 U.S.C. § 154(b)(4) to commence a civil action.

Relevant Procedural History

The patent issued with a PTA determination of 722 days on December 15, 2020. Applicant timely submitted the present Request with \$200 petition fee on December 30, 2020.

Decision

The patent sets forth a PTA based on the following calculations previously made by the Office:

- (1) The period of delay under 35 U.S.C. § 154(b)(1)(A) (“A Delay”) is 402 days;
- (2) The period of delay under 35 U.S.C. § 154(b)(1)(B) (“B Delay”) is 501 days;
- (3) The period of delay under 35 U.S.C. § 154(b)(1)(C) (“C Delay”) is 0 days;
- (4) The number of days of overlapping delay (“Overlap”) between the periods of A Delay, B Delay, and C Delay is 0 days; and
- (5) The period of delay under 35 U.S.C. § 154(b)(2)(C) (“Applicant Delay”) is 181 days.

The PTA is the sum of the days of A Delay, B Delay, and C Delay reduced by the number of days of Overlap and Applicant Delay. In other words, the following formula may be used to calculate the PTA:

$$\text{PTA} = \text{A Delay} + \text{B Delay} + \text{C Delay} - \text{Overlap} - \text{Applicant Delay}$$

The PTA is 722 days (402 days of A Delay + 501 days of B Delay + 0 days of C Delay - 0 days of Overlap - 181 days of Applicant Delay).

Regarding the period of Applicant Delay: The Request discloses the Office failed to enter a 3 day period of reduction under 37 CFR 1.704(c)(8) for the supplemental paper filed on October 18, 2019, after a reply was filed on October 15, 2019. The Request argues no reduction, rather than a 75 day period of reduction is warranted under 37 CFR 1.704(c)(8) for the filing of an Information Disclosure Statement (“IDS”) on July 8, 2020, after a reply had been filed on April 24, 2020, because the IDS was accompanied by a statement under 37 CFR 1.704(d). The Request asserts the period of Applicant Delay is 109 (28 + 61 + 3 + 1 + 16) days.

The Request asserts the correct PTA is 794 days (402 days of A Delay + 501 days of B Delay + 0 days of C Delay – 0 days of Overlap – 109 days of Applicant Delay).

As will be discussed, the Office concurs that a 3 day period of reduction is warranted under 37 CFR 1.704(c)(8) for the filing of a supplemental paper on October 18, 2019 after a reply was filed on October 15, 2019. In addition, the Office concurs no reduction is warranted under 37 CFR 1.704(c)(8) for the filing of an IDS on July 8, 2020 after a reply was filed on April 24, 2020, because the IDS was accompanied by a safe harbor statement under 37 CFR 1.704(d).

An audit of PTA calculations has revealed an error in the calculation of applicant delay under 37 CFR 1.704(c)(10) in connection with the filing of an amendment under 37 CFR 1.312 on October 1, 2020, after a notice of allowance was mailed on July 16, 2020. A 77 day period of reduction, not a 16 day period of reduction is warranted.

Therefore, the Office finds that the period of Applicant Delay is 170 (28 + 61 + 3 + 1 + 77), and the correct PTA is 733 days (402 days of A Delay + 501 days of B Delay + 0 days of C Delay – 0 days of Overlap – 170 days of Applicant Delay).

A Delay

The Request does not dispute the Office’s prior determination the period of A Delay is 402 days. The Office has recalculated the period of A Delay as part of the Office’s redetermination of the PTA and confirmed the period of A Delay is 402 days.

B Delay

The Request does not dispute the Office’s prior determination the period of B Delay is 501 days. The Office has recalculated the period of B Delay as part of the Office’s redetermination of the PTA and confirmed the period of B Delay is 501 days.

C Delay

The Request does not dispute the Office's prior determination the period of C Delay is 0 days. The Office has recalculated the period of C Delay as part of the Office's redetermination of the PTA and confirmed the period of C Delay is 0 days.

Overlap

The Request does not dispute the Office's prior determination the number of days of Overlap is 0 days. The Office has recalculated the number of days of Overlap as part of the Office's redetermination of the PTA and confirmed the number of days of Overlap is 0 days.

Applicant Delay

The Request disputes the Office's prior determination the number of days of Applicant Delay is 170 days. The Office has recalculated the number of days of Applicant Delay as part of the Office's redetermination of the PTA and determined the number of days of Applicant Delay is 170 days.

The Request discloses a previously unidentified period of applicant delay under 37 CFR 1.704(c)(8).

37 CFR 1.704(c)(8), provides:

Circumstances that constitute a failure of the applicant to engage in reasonable efforts to conclude processing or examination of an application also include the following circumstances, which will result in the following reduction of the period of adjustment set forth in § 1.703 to the extent that the periods are not overlapping:

...

Submission of a supplemental reply or other paper, other than a supplemental reply or other paper expressly requested by the examiner, after a reply has been filed, in which case the period of adjustment set forth in § 1.703 shall be reduced by the number of days, if any, beginning on the day after the date the initial reply was filed and ending on the date that the supplemental reply or other such paper was filed; ...

The Office mailed a non-final Office action on May 15, 2019. Applicants were assessed a 61 day period of reduction under 37 CFR 1.704(b) for the reply filed on October 15, 2019. Applicant filed a supplemental reply/other paper on October 18, 2019. The supplemental reply/other paper does not appear to have been expressly requested by the examiner. A 3 day period of reduction under 37 CFR 1.704(c)(8) is warranted, beginning on October 16, 2019, the day after the filing of the October 15, 2019 reply, and ending with the filing of the supplemental reply/other paper on October 18, 2019. Accordingly, a 3 day period of reduction has been entered.

The Request asserts no reduction, not a 75 day period of reduction, is warranted under 37 CFR 1.704(c)(8) for the filing of an Information Disclosure Statement (“IDS”) on July 8, 2020, after a reply was filed on April 24, 2020, because the IDS was accompanied by a statement under 37 CFR 1.704(d).

The Office concurs.

37 CFR 1.704(d)(1) states, in pertinent part:

(d)(1) A paper containing only an information disclosure statement in compliance with §§ 1.97 and 1.98 will not be considered a failure to engage in reasonable efforts to conclude prosecution (processing or examination) of the application under paragraphs (c)(6), (c)(8), (c)(9), or (c)(10) of this section, and a request for continued examination in compliance with § 1.114 with no submission other than an information disclosure statement in compliance with §§ 1.97 and 1.98 will not be considered a failure to engage in reasonable efforts to conclude prosecution (processing or examination) of the application under paragraph (c)(12) of this section, if the paper or request for continued examination is accompanied by a statement that each item of information contained in the information disclosure statement:

- (i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement or
- (ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

The IDS filed on July 8, 2020 was accompanied by a STATEMENT FOR SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT IN ACCORDANCE WITH 37 C.F.R. §1.704 (d), which included a statement complying with 37 CFR 1.704(d)(1)(i) and (ii). Accordingly, the Office concurs no reduction, not a 75 day period of reduction, is warranted pursuant to 37 CFR 1.704(c)(8) in connection with filing of the IDS on July 8, 2020, after reply was filed on April 24, 2020. The 75 day period of reduction under 37 CFR 1.704(c)(8) assessed in connection with the July 8, 2020 IDS has been removed.

An audit of PTA calculations has revealed an error in the calculation of delay under 37 CFR 1.704(c)(10) in connection with the filing of a COMMENT ON EXAMINER’S REASONS FOR ALLOWANCE AND AMENDMENT UNDER 37 C.F.R. §1.312 on October 1, 2020, after a notice of allowance was mailed July 16, 2020.

Supernus Pharm., Inc. v. Iancu, 913 F.3d 1351, 129 USPQ2d 1240 (Fed. Cir. 2019) impacted 37 CFR 1.704(c)(10). See, the Federal Register notice, *Patent Term Adjustment Reductions in View of the Federal Circuit Decision in Supernus Pharm., Inc. v. Iancu* 85 Fed. Reg. 36335 (June 16,

2020). Relevant PTA rules have been revised to focus on the delay due to applicant's action rather than the consequences to the Office due to the applicant's actions. The changes in this final rule apply to original utility and plant patents issuing from applications filed on or after May 29, 2000, in which a notice of allowance was mailed on or after July 16, 2020. A Notice of Allowance was mailed in this application on July 16, 2020. Therefore, new 37 CFR 1.704(c)(10) applies.

37 CFR 1.704(c)(10) provides:

(c) Circumstances that constitute a failure of the applicant to engage in reasonable efforts to conclude processing or examination of an application also include the following circumstances, which will result in the following reduction of the period of adjustment set forth in § 1.703 to the extent that the periods are not overlapping:

...

(10) Submission of an amendment under § 1.312 or other paper, other than an amendment under § 1.312 or other paper expressly requested by the Office or a request for continued examination in compliance with § 1.114, after a notice of allowance has been given or mailed, in which case the period of adjustment set forth in § 1.703 shall be reduced by the number of days, if any, beginning on the day after the date of mailing of the notice of allowance under 35 U.S.C. 151 and ending on the date the amendment under § 1.312 or other paper was filed.

Turning to the facts of this case: A Notice of Allowance was mailed on July 16, 2020. The October 1, 2020 filing included a Rule 312 amendment that was not expressly requested by the examiner.

Pursuant to 37 CFR 1.704(c)(10), a 77 day period of reduction, beginning on July 17, 2020, the day after the date of the mailing of the notice of allowance under 35 U.S.C. 151, and ending on October 1, 2020, the date the amendment under § 1.312 was filed, is warranted. A 77 day period of reduction has been entered. The 16 day period of reduction has been removed.

The period of Applicant Delay is 170 (28 + 61 + 3 + 1 + 77).

Conclusion

The Request asserts the correct PTA is 794 days (402 days of A Delay + 501 days of B Delay + 0 days of C Delay – 0 days of Overlap – 109 days of Applicant Delay).

As previously discussed, the correct period of Applicant Delay is 170 days.

Therefore, the correct PTA is 733 days (402 days of A Delay + 501 day of B Delay + 0 days of C Delay - 0 days of Overlap - 170 days of Applicant Delay).

A request for reconsideration of the instant redetermination of PTA may be filed if patentee disagrees with the Office's determination the correct PTA is 733 days. Such a request must be filed within TWO MONTHS of the issuance date of the instant redetermination of PTA. Extensions of the two-month time period may be obtained under 37 C.F.R. § 1.136(a). The request for reconsideration does not need to include a fee if the request is filed within two months of the issuance date of the instant redetermination. If the request is filed more than two months after the issuance date of this decision, the request must include the appropriate extension of time fee. If a request for reconsideration is not filed within the maximum extendable period to file the request, the Office will *sua sponte* issue a certificate of correction adjusting the PTA to seven hundred thirty-three (733) days.

Further correspondence with respect to this matter may be submitted as follows:

By Internet: A request for reconsideration may be filed electronically using EFS Web. Document Code "PET.OP" should be used if the request is filed electronically.

By mail: Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

By facsimile: (571) 273-8300
Attn: Office of Petitions

By hand: U.S. Patent and Trademark Office
Customer Service Window
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Telephone inquiries specific to this decision should be directed to the undersigned at (571) 272-3230.

/SHIRENE W BRANTLEY/
Attorney Advisor, OPET

Enclosure: Draft Certificate of Correction

DRAFT COPY

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT : 10,865,400 B2
DATED : December 15, 2020
INVENTOR(S) : Wei et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the cover page,

[*] Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 722 days.

Delete the phrase “by 722 days” and insert – by 733 days--

Electronic Patent Application Fee Transmittal				
Application Number:		15226489		
Filing Date:		02-Aug-2016		
Title of Invention:		PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		
First Named Inventor/Applicant Name:		Ge Wei		
Filer:		Stephanie L. Seidman/Anh Nguyen		
Attorney Docket Number:		33320.03087.US25 / 3087B		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
CERTIFICATE OF CORRECTION	1811	1	160	160

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				160

Electronic Acknowledgement Receipt	
EFS ID:	43778222
Application Number:	15226489
International Application Number:	
Confirmation Number:	9968
Title of Invention:	PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF
First Named Inventor/Applicant Name:	Ge Wei
Customer Number:	13565
Filer:	Stephanie L. Seidman/Anh Nguyen
Filer Authorized By:	Stephanie L. Seidman
Attorney Docket Number:	33320.03087.US25 / 3087B
Receipt Date:	16-SEP-2021
Filing Date:	02-AUG-2016
Time Stamp:	17:37:48
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$160
RAM confirmation Number	E20219FH39171006
Deposit Account	500911
Authorized User	Anh Nguyen
<p>The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:</p> <p>37 CFR 1.21 (Miscellaneous fees and charges)</p> <p>37 CFR 1.20 (Post Issuance fees)</p>	

37 CFR 1.19 (Document supply fees)
 37 CFR 1.17 (Patent application and reexamination processing fees)
 37 CFR 1.16 (National application filing, search, and examination fees)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	3087Btra.pdf	136314	no	1
			c2ab56a0c442b282f8878f12967f8c4bcafc 772		
Warnings:					
Information:					
2	Request for Certificate of Correction	3087Brcc.pdf	264740	no	19
			87cf0335f6921c6be7ee1cc3f2665bae09f54 e34		
Warnings:					
Information:					
3	Miscellaneous Incoming Letter	3087Bcoc.pdf	441084	no	29
			55f5a80b305deb0c0f87d3806641573e64b d0a7c		
Warnings:					
Information:					
4	Miscellaneous Incoming Letter	3087Bspec.pdf	13308761	no	12
			f954238ff348c24f82b4930bec73965f51383 f22		
Warnings:					
Information:					
5	Miscellaneous Incoming Letter	3087Bp49.pdf	1094882	no	2
			4fba842ee973b65952696903d473c664f57 e8ceb		
Warnings:					
Information:					
6	Miscellaneous Incoming Letter	3087B312.pdf	6180050	no	8
			d34f5de3a32b1c7ccb7d7ca81e4fa4680927c a3c1		
Warnings:					
Information:					

7	Fee Worksheet (SB06)	fee-info.pdf	<div>38224</div> <div>f0ad1e7d0e1cf69d5e925aab15f130ea37666fbf</div>	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			21464055		
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>					

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	Wei <i>et al.</i>	Art Unit	: 1656
Patent No. :	10,865,400	Examiner	: Liu, Samuel W.
Issue Date :	December 15, 2020	Conf. No.	: 9968
Serial No. :	15/226,489	Cust. No.	: 13565
Filed	: August 02, 2016		
Title	: PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF		

Attn: Certificate of Correction Branch

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Dear Sir:

Transmitted herewith are a Request for Certificate of Correction (19 pages); a Certificate of Correction (28 pages); a copy of page 9 of the Form PTO-1449 filed August 24, 2016, as initialed by the examiner on April 26, 2019; copies of pages 15, 26, 63, 82, 83, 98, 190, 198, 276, 277, and 315 of the Specification as originally filed on August 02, 2016 (11 pages); and copies of pages 2-4 and 6-9 of Amendment Pursuant to 37 C.F.R. § 1.312 filed on October 01, 2020 (7 pages). Since not all the errors are those of the Patent Office, the Commissioner is authorized to charge the fee for filing these papers to Deposit Account No. 50-0911.



The Commissioner is hereby authorized to charge any fees that may be due in connection with this and the attached papers or with this application during its entire pendency to Deposit Account No. 50-0911.

Respectfully submitted,

/Stephanie Seidman/

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Reg. No. 33,779

Attorney Docket No.: 33320.03087.US25/3087B

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CERTIFICATE OF TRANSMISSION VIA EFS-WEB

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/Anh Nguyen/
Anh Nguyen

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): Wei <i>et al.</i>	Art Unit : 1656
Patent No. : 10,865,400	Examiner : Liu, Samuel W.
Issue Date : December 15, 2020	Conf. No. : 9968
Serial No. : 15/226,489	Cust. No. : 13565
Filed : August 02, 2016	
Title : PH20 POLYPEPTIDE VARIANTS, FORMULATIONS AND USES THEREOF	

Attn.: Certificate of Correction Branch

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION

Dear Sir:

Pursuant to 37 C.F.R. §§ 1.322 and 1.323, the patentee respectfully requests that a issuance of a Certificate of Correction for the above referenced patent to correct the following errors:

IN THE TITLE PAGES:

In Item (56) References Cited, in U.S. PATENT DOCUMENTS, on page 1, 2nd column, line 31, please replace the inventor "Greennnwald" with —Greenwald—;

In Item (56) References Cited, in OTHER PUBLICATIONS, on page 3, 1st column, line 26, please replace "claimed" with —claims—;

In Item (56) References Cited, in OTHER PUBLICATIONS, on page 4, 1st column, line 60, please replace "Rearch" with —Research—;

In Item (56) References Cited, in OTHER PUBLICATIONS, on page 5, 2nd column, line 20, please replace the author "Harahan" with —Hanahan—;

IN THE SPECIFICATION:

At column 13, line 15, please replace "Mat" with —M at—;

At column 22, line 36, please replace "Mat" with —M at—;

At column 53, lines 7-8, please replace "poly-propylene oxide)" with —poly(propylene oxide)—;

At column 69, line 2, please replace "w-site" with —ω-site—;

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At column 69, line 5, please replace "w-site" with —ω-site—;

At column 69, line 10, please replace "w-site" with —ω-site—;

At column 69, line 46, please replace "w-site" with —ω-site—;

At column 69, line 53, please replace "w-site" with —ω-site—;

At column 90, line 40, please replace "179" with —I79—;

At column 90, line 49, please replace "5235" with —S235—;

From column 120, line 46 to column 133, line 36, please replace Table 5 with the following amended Table:

TABLE 5: Inactive Mutants					
Corres- ponding Position	Replacement	Corres- ponding Position	Replacement	Corres- ponding Position	Replacement
2	HKWY	3	AGKPTV	4	DEFGLPWY
5	DGILMNPQR TVWY	6	EFTVY	7	CDFGHIKLQ RSTWY
8	DEGHNRSW	9	CDEGNP	10	FILMY
11	ACFILPTWY	12	GHW	13	EGILMV
14	AEGHKNPQW	15	EFGKNPQRS Y	16	ACDEFGHK MPRSTY
17	DEGHILNPQ RSTVWY	18	CDFGHILMP QSTVY	19	ACFGHILMP QRSVWY
20	DEFHKLNPR TVY	21	ACDEGHILM RSTVW	22	CEGKP
23	AFLMNPRST V	25	DEFGHIKLN PRSTVY	27	C
33	CDHNVY	34	ILNSTV	35	ADGPRS
36	CFVWY	37	CEGNS	38	EGKLNQRT W
39	CDFW	40	ADEGKNRST V	41	Q
42	DEHIKLMPQ RSTV	43	AEFGIKLQR V	44	ACFGHILNQ RSTWY
45	ADFGPW	46	PW	47	V
48	P	49	CDGHP	50	V
51	CFIMPTWY	52	CEFWY	53	ACDEGHLNP QRSTWY
54	DEGPRY	55	ADGHNPNQRT VY	56	ACEGHIKLP RSTVW
57	ADFGIMPQR VW	58	A	59	AEILMPRTV WY
60	ADFGHILNPQ STVY	61	AEFGHNPQR TWY	62	ACDFIKLMP QRSTVY
63	CGP	64	ACDEFGHIK LPQRSTVW	65	ACDGHIKNR STVWY
66	ACDEGIKLN STV	67	DEGPRTW	68	ACGILPVY

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69	NT	70	Q	71	P
72	CFHIPVW	73	P	75	DGP
76	ACFGIKLPQ RSTVW	77	DELPQRTV	78	ADIMPTY
79	ADFGHKNPS WY	80	ADEF GIKLM NRSTVY	81	ACEGHLNPS VWY
82	YEK	84	Y	85	ACDEFGHNQ ST
86	CP	87	P	88	ACEFGIKLM PRSTVY
89	ADEGQSTWY	90	CG	91	DEFGHILT
92	EFHKPQRWY	94	GP	95	ACEFGHKLM PQSVWY
96	SVHPRSTW	98	P	99	CEGINPVW
100	CEFGNPRST WY	101	ACFHIKLMN QRST	102	P
103	AEFGHILQRT VWY	104	FPW	105	CMN
106	ACDFHLMNP SWY	107	ACHKPQSVW	108	DEFKLMPQT VY
109	CDELMRTW	110	FKLMPW	111	HIQ
112	CEGHLNPS	113	RV	114	ILPTV
115	ACDFGHIKL MRSVY	116	ACDEGHILN PQSVW	117	DGIKNQRSV W
118	CDEGPRWY	119	AKILNPR	121	ACEFGHKLM PWY
122	A CEFIKQRS TV	123	ACDEHLMPQ RSTVY	124	CDEFN
125	CDGLNW	126	FHILNPY	127	K
128	EP	129	ACDEGHLPQ STVW	130	CDGHLNST WY
131	P	132	P	133	DEFGHLMNP RTVW
134	ACDFGHKPQ RSW	135	P	136	P
137	FGHNPRWY	138	V	139	P
143	CHPRST	144	AEFIKPQSVY	145	TW
149	E	149	P	150	V
152	L	153	EFMPRTV	154	DEGPSWY
155	PY	156	P	157	ACDEGHIKL M PQRSTV
158	DKPRY	159	WY	161	W
163	CP	164	ACDEGHNPQ R	165	CHPT
166	D	167	V	168	ACDEFGKLP RSVWY
169	ADFGHKNPQ STY	170	CDEGMPWY	171	CDHMNRSW Y
172	DEILPQTVW Y	173	DEGHILMPS VWY	174	P
175	CDGKPRS	176	ACEFGHIPQS TVW	177	ACDFGHLM QRSTVW
178	EILVW	180	ACEPRS	181	ACDEFHIKL RS

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182	ACDEHNPQR STVY	183	CDEGIKNPQ RSV	184	ACDEFGHKL MPRSV
185	ADEFGIKPRS TVWY	186	ADGHIKLN QRSVW	187	AFGHILMNQ RSTVWY
188	ACFGHLMNP QRSTVW	189	AEGHKLMNP RSTVWY	190	CEFGHKLNQ RSTVW
191	ADEFGKLMNP RSTVWY	192	CFGKLMNPQ RVWY	193	ADKLMPV
194	ACILPSTV	195	S	197	C
198	VW	199	EGHIKLPRS W	200	AFGHKLMNP RSWY
201	AFLMNPQRST VW	202	ADEFGHKNPQ RVWY	203	ADEGHLMN QRSTV
204	ACEGHKQR ST	206	CDFGPY	207	AFGMPQRST VW
208	DGPW	209	CP	210	ACDEGKMN PSTVWY
211	CFGHIKMPR STVW	212	AGHIKLMPV W	213	PS
214	ACDEGHKNP RSTY	215	CP	216	DEGHIKLMN PQRTV
217	ACGHPQSTV W	218	AIKLPSV	219	P
220	GKNPRW	221	DEHKPR	222	PY
223	CDEGHKLPQ RSTVWY	224	ADEFGMPQR STWY	225	ADEGHKPNR TVW
226	ACDEFGLNQ RSTVWY	227	AFGHIKLMP QRTVWY	228	ADEGHLMNP RSTW
229	DEFGKLPQTV W	230	AEGHKMNPR STVWY	231	ACDFGHIKL PQRSV
232	CGHKLNPPQV Y	233	DIPST	234	ADEGHNPST VW
235	FLMRWY	236	CILNQTY	238	FGLPVWY
239	CFGHILPRST VWY	240	EFGNWX	241	ACDEGIPRS TVW
242	ACDGILMPR STVW	243	CDFGHLMPQ RSWY	244	ADGIVY
245	ACFLPQRSTV	246	ACDEGHKLN MPSTVW	247	ACFHNPNRS TWY
248	CDEGIMPT	249	AGHIKMQSY	250	CFGHKLMPN QRSTVW
251	DFGHKPNSTW	252	ADEFGHIKL NPSTY	253	ADEGHLMN QRSW
254	CDEGIKLPQR TVWY	255	CDLPVW	256	CDEGP
257	D	258	LPVW	260	CP
261	P	262	ADEGHKQR STVWY	263	EFPQW
264	DEFGLMRTV WY	265	ADFGHKLMP QRS	266	ACGHMPQRS TVW
267	DGHKLNRSW	268	ACFGHKLN QSTVW	269	EKLMNPQR
270	ACEFGHIPY	271	ADEHKTW	272	HLNPW
273	ACDGILPQSV W	274	CEGHNQWY	275	AFGIKLMQT VW

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276	FPW	278	MP	279	ACFGLWY
280	DI MNRSTVW	281	AD GHIKNPQ RSVW	282	FLVWY
283	ACDFW	284	CDFW	284	CIP
285	KPRTV	286	ACDFHKMPT Y	287	ACDEGKLN PQRS
288	DEFGHIKPRT	289	ACEGHL PQRSY	290	DQY
291	ACDEFMNTW Y	292	ILT	293	EN
294	AEGHKLNPQ RSTW	295	CGHILNP TVY	296	CFGIKMQRS TVWY
297	CEHLNPQRS TY	298	CELMNPQST WY	299	ACDFGHLMP QT
300	ACDEFMLNP QSTVW	301	EGHKMNPQR SWY	302	CDEFGHLMP RSTY
303	ACDEFGKLM RWY	304	ACDGINNPQ STVY	305	LPQRSTVY
306	ACHILVWY	307	CIP	308	CFLMVWY
310	CEFKL	311	CEFILPVW	312	CEMVW
313	C	314	CLW	315	CIV
316	EGIKLMPRST VWY	317	G P	318	CPW
319	CEFGHIKMP QRSVWY	320	CPV	321	EMP
322	CDEGILNPRS TVW	323	ACEGHKNRS TV	324	CFPVWY
325	CREGHNW	327	AEFGHNQRS TVWY	329	CFGHIKLNQ RSTVWY
330	ACDEGILMN PRSVW	331	ACDEFHKQR STWY	332	ACDEFGHKL NPRSTY
333	GHIKPRSTW Y	334	ACDEGMNRS	335	FGHIKLPVW Y
336	AEFGKNPRS TVWY	337	CFGIKLMRT W	338	CDEFGHIKL PRTV
339	DEFGHLNPST VWY	340	ACDEFGHKP RSTVW	341	AEGHKL MNQRSTVY
342	DEFHKLMPQ RTY	343	CDFIPW	344	FGHLMNPQR STWY
345	A CEHKNQRT VY	346	ADFGIKLMP RSTVW	347	CFIPTVW
348	CHILPQRTV WY	349	DFGPVWY	350	ADEFHKL MNPRSTVY
351	CDEFHNRWY	352	ADEFGKMPQ RSTVWY	353	CFGHKLMQ RSW
354	CDEGHIKLM PQSVWY	355	DFGHLMN PQRSTVWY	356	CGKLPRTVW
357	DEFGLMQR	358	EHIK PQRW	359	AFGLPW
360	ACEFGIKLMP QRV	361	ACEGMNPQR SVW	362	ACEGHKL MNPRSTVW
363	ACDEFGHIPQ RSTVW	364	ACDEFGKLM PRSTVY	365	ACDEGMNP QRSTWY
366	ACEFGKMPQ RTW	367	EFILMQV	368	CPW

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369	CEFIKLPQV W	370	ADEGHKLN P Q R S V Y	371	P
372	ADEFGHKL N P R S T V W	373	CPW	374	DE
375	CFPVY	376	IPW	377	CILV
378	DEFILMQT W Y	379	ACEFILMW	380	CDEGQRS
381	GLPWY	382	EGHKLMNP Q R S T W Y	383	GP
384	CFMQST	385	CLMPWY	386	ACFGHILMN Q R S T V Y
387	CEFGHILMN V W Y	388	CGPQ	389	FV
390	ACEFGHLNP R S T V W Y	391	ADGHKNPQR S T V W Y	392	CP
393	CP	394	ADEGIKNPQ R S T V	395	CLMP
396	CFGIPY	397	ACEFGILMP Q T V	398	ACEGHILNP R S T V W Y
399	DP	400	ADEFGILMP Q R S T V Y	401	CFHKRWY
402	ADEFLMPQR S T V W Y	403	ACEGHKLMN P Q R T	404	CDFGHLMN R V W Y
405	CIV	406	PR	408	AEFGIKLPR S T V W Y
410	W	411	DEFG	412	EH
413	HIKLP	414	ADEGHKRST	415	CDEP
416	CS	417	ADEFGHKMP Q R	419	DP
420	ADFGHKLNR S T W Y	422	CDGHLMNQ R S Y	423	ADEFGHLMP Q R S T V W
424	ACEGHNQRS W Y	425	ELPWY	426	CFMR
427	ACFLPVWY	428	ACDEGHNRS Y	429	ADKLNPS T V W Y
430	ADELMNSTV	431	P	432	CFIKLMPY
434	HKPQRW	437	T	438	Y
439	NR	440	Q	441	R
442	MNS	443	D		

;

At column 178, line 28, please replace "f 15%" with —± 15%—;

At column 185, line 25, please replace "U520100074885" with —US20100074885—;

At column 293, line 25, please replace "Jasco J-810-1505" with —Jasco J-810-150S—;

At column 293, line 26, please replace "PTC-4245" with —PTC-424S—.

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IN THE CLAIMS:

From column 299, line 36 to column 300, line 44, please replace claim 1 with the following amended claim:

1. A modified PH20 polypeptide, comprising one or more amino acid replacements in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NOS: 3, [[7]]7, and 32-66;

the modified PH20 polypeptide exhibits increased hyaluronidase activity that is at least 120% of the hyaluronidase activity compared to the unmodified PH20 polypeptide not containing the amino acid ~~replacements~~replacement(s); wherein:

the activity of the unmodified PH20 polypeptide not containing the replacement(s) is 100%;

hyaluronidase activity of the modified PH20 polypeptide and hyaluronidase activity of the unmodified PH20 polypeptide are measured under identical conditions;

the amino acid replacement(s) confer(s) the increased hyaluronidase activity;

at least one amino acid replacement confers the increased hyaluronidase activity, and is at a position corresponding to a position selected from 1, 15, 24, 27, 29, 30, 31, 32, 33, 37, 39, 48, 63, 67, 69, 71, 72, 73, 75, 87, 92, 93, 94, 118, 120, 135, 141, 147, 148, 150, 151, 152, 155, 156, 163, 164, 165, 170, 198, 209, 212, 215, 219, 233, 236, 247, 257, 259, 260, 263, 269, 271, 272, 276, 278, 282, 293, 305, 308, 313, 320, 324, 325, 326, 328, 353, 359, 371, 377, 380, 389, 392, 395, 405, 409, 410, 418, 425, 436, 437, 438, 441, 442, [[446]]446, and 447, with reference to amino acid positions set forth in SEQ ID NO:3;

corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the sequence of amino acids set forth as SEQ ID NO:3, with the proviso that if the modified PH20 polypeptide includes only a single amino acid replacement, the replacement does not correspond to amino acid replacement N219A with reference to amino acid positions set forth in SEQ ID NO:3; and

the modified PH20 polypeptide has at least 95% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOS: 3, [[7]]7, and 32-66.

From column 300, line 45 to column 303, line 11, please replace claim 2 with the following amended claim:

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2. The modified PH20 polypeptide of claim 1, comprising at least one amino acid replacement selected from among replacement with: H at a position corresponding to position 1; Q at a position corresponding to position 1; V at a position corresponding to position 15; E at a position corresponding to position 24; H at a position corresponding to position 24; K at a position corresponding to position 27; R at a position corresponding to position 27; E at a position corresponding to position 29; I at a position corresponding to position 29; L at a position corresponding to position 29; M at a position corresponding to position 29; P at a position corresponding to position 29; S at a position corresponding to position 29; V at a position corresponding to position 29; G at a position corresponding to position 30; H at a position corresponding to position 30; K at a position corresponding to position 30; M at a position corresponding to position 30; R at a position corresponding to position 30; S at a position corresponding to position 30; A at a position corresponding to position 31; C at a position corresponding to position 31; H at a position corresponding to position 31; I at a position corresponding to position 31; K at a position corresponding to position 31; L at a position corresponding to position 31; P at a position corresponding to position 31; R at a position corresponding to position 31; S at a position corresponding to position 31; T at a position corresponding to position 31; V at a position corresponding to position 31; F at a position corresponding to position 32; G at a position corresponding to position 32; H at a position corresponding to position 32; W at a position corresponding to position 33; F at a position corresponding to position 37; N at a position corresponding to position 39; T at a position corresponding to position 39; F at a position corresponding to position 48; H at a position corresponding to position 48; N at a position corresponding to position 48; W at a position corresponding to position 63; V at a position corresponding to position 67; A at a position corresponding to position 69; C at a position corresponding to position 69; F at a position corresponding to position 69; G at a position corresponding to position 69; I at a position corresponding to position 69; L at a position corresponding to position 69; M at a position corresponding to position 69; P at a position corresponding to position 69; R at a position corresponding to position 69; W at a position corresponding to position 69; Y at a position corresponding to position 69; R at a position corresponding to position 71; S at a position corresponding to position 71; M at a position corresponding to position 72; Q at a position corresponding to position 72; H at a position corresponding to position 73; L at a position corresponding to position 73; W at a position corresponding to

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position 73; F at a position corresponding to position 75; L at a position corresponding to position 75; R at a position corresponding to position 75; T at a position corresponding to position 75; C at a position corresponding to position 87; T at a position corresponding to position 87; Y at a position corresponding to position 87; C at a position corresponding to position 92; I at a position corresponding to position 93; L at a position corresponding to position 93; R at a position corresponding to position 93; T at a position corresponding to position 93; R at a position corresponding to position 94; Q at a position corresponding to position 118; F at a position corresponding to position 120; V at a position corresponding to position 120; Y at a position corresponding to position 120; D at a position corresponding to position 135; G at a position corresponding to position 135; R at a position corresponding to position 135; H at a position corresponding to position 141; Y at a position corresponding to position 141; R at a position corresponding to position 147; V at a position corresponding to position 147; K at a position corresponding to position 148; G at a position corresponding to position 150; K at a position corresponding to position 151; L at a position corresponding to position 151; M at a position corresponding to position 151; Q at a position corresponding to position 151; [[Rat]]R at a position corresponding to position 151; [[Rat]]R at a position corresponding to position 152; G at a position corresponding to position 155; K at a position corresponding to position 155; D at a position corresponding to position 156; A at a position corresponding to position 163; E at a position corresponding to position 163; K at a position corresponding to position 163; R at a position corresponding to position 163; M at a position corresponding to position 164; D at a position corresponding to position 165; N at a position corresponding to position 165; R at a position corresponding to position 170; D at a position corresponding to position 198; N at a position corresponding to position 212; M at a position corresponding to position 215; S at a position corresponding to position 219; K at a position corresponding to position 233; R at a position corresponding to position 233; R at a position corresponding to position 236; I at a position corresponding to position 247; T at a position corresponding to position 257; P at a position corresponding to position 259; Y at a position corresponding to position 260; K at a position corresponding to position 263; R at a position corresponding to position 263; A at a position corresponding to position 269; L at a position corresponding to position 271; M at a position corresponding to position 271; T at a position corresponding to position 272; D at a position corresponding to position 276; S at a position corresponding to position 276; Y at a position corresponding to position 276; H at a position

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corresponding to position 278; K at a position corresponding to position 278; N at a position corresponding to position 278; R at a position corresponding to position 278; S at a position corresponding to position 278; T at a position corresponding to position 278; Y at a position corresponding to position 278; M at a position corresponding to position 282; A at a position corresponding to position 293; C at a position corresponding to position 293; F at a position corresponding to position 293; M at a position corresponding to position 293; P at a position corresponding to position 293; Q at a position corresponding to position 293; V at a position corresponding to position 293; E at a position corresponding to position 305; G at a position corresponding to position 308; N at a position corresponding to position 308; K at a position corresponding to position 313; R at a position corresponding to position 313; H at a position corresponding to position 320; K at a position corresponding to position 320; R at a position corresponding to position 320; R at a position corresponding to position 324; A at a position corresponding to position 325; D at a position corresponding to position 325; E at a position corresponding to position 325; G at a position corresponding to position 325; H at a position corresponding to position 325; K at a position corresponding to position 325; M at a position corresponding to position 325; N at a position corresponding to position 325; Q at a position corresponding to position 325; S at a position corresponding to position 325; V at a position corresponding to position 326; I at a position corresponding to position 328; K at a position corresponding to position 328; L at a position corresponding to position 328; S at a position corresponding to position 328; Y at a position corresponding to position 328; V at a position corresponding to position 353; T at a position corresponding to position 359; R at a position corresponding to position 371; P at a position corresponding to position 377; T at a position corresponding to position 377; W at a position corresponding to position 380; Y at a position corresponding to position 380; K at a position corresponding to position 389; M at a position corresponding to position 392; R at a position corresponding to position 395; G at a position corresponding to position 405; A at a position corresponding to position 409; Q at a position corresponding to position 409; T at a position corresponding to position 410; P at a position corresponding to position 418; K at a position corresponding to position 425; K at a position corresponding to position 436; I at a position corresponding to position 437; M at a position corresponding to position 437; T at a position corresponding to position 438; F at a position corresponding to position 441; R at a position corresponding to position 442; A at a position corresponding to position 446; D at a position corresponding to position 447; N at a position

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corresponding to position 447; and/or Q at a position corresponding to position 447, with reference to amino acid positions set forth in SEQ ID NO:3.

At column 303, lines 12-16, please replace claim 3 with the following amended claim:

3. The modified PH20 polypeptide of claim 2, wherein ~~PM~~ the modified PH20 polypeptide is a soluble PH20 polypeptide; and the unmodified polypeptide consists of the amino acid sequence set forth in any of SEQ ID NOS: 3 or 32-66.

From column 303, line 17 to column 304, line 54, please replace claim 4 with the following amended claim:

4. A modified PH20 polypeptide, comprising one or more amino acid replacements in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NOS: 3, ~~[[7]]~~7, and 32-66;

the modified PH20 polypeptide exhibits increased hyaluronidase activity that is at least 120% of the hyaluronidase activity compared to the unmodified PH20 polypeptide not containing the amino acid ~~replacements~~replacement(s); wherein:

the activity of the unmodified PH20 polypeptide not containing the replacement(s) is 100%;

hyaluronidase activity of the modified PH20 polypeptide and hyaluronidase activity of the unmodified PH20 polypeptide are measured under identical ~~conditions~~conditions;

at least one amino acid replacement confers the increased hyaluronidase activity, and is selected from E at a position corresponding to position 12; E at a position corresponding to position 26; K at a position corresponding to position 26; R at a position corresponding to position 46; Q at a position corresponding to position 52; Q at a position corresponding to position 58; H at a position corresponding to position 68; Q at a position corresponding to position 68; A at a position corresponding to position 70; C at a position corresponding to position 70; F at a position corresponding to position 70; G at a position corresponding to position 70; H at a position corresponding to position 70; K at a position corresponding to position 70; L at a position corresponding to position 70; N at a position corresponding to position 70; P at a position corresponding to position 70; R at a position corresponding to position 70; S at a position corresponding to position 70; T at a position corresponding to position 70; A at a position corresponding to position 74; C at a position corresponding to

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position 74; G at a position corresponding to position 74; N at a position corresponding to position 74; P at a position corresponding to position 74; R at a position corresponding to position 74; S at a position corresponding to position 74; V at a position corresponding to position 74; W at a position corresponding to position 74; G at a position corresponding to position 84; R at a position corresponding to position 84; G at a position corresponding to position 97; H at a position corresponding to position 127; N at a position corresponding to position 127; G at a position corresponding to position 131; V at a position corresponding to position 131; R at a position corresponding to position 142; A at a position corresponding to position 166; F at a position corresponding to position 166; H at a position corresponding to position 166; L at a position corresponding to position 166; R at a position corresponding to position 166; Y at a position corresponding to position 166; K at a position corresponding to position 174; K at a position corresponding to position 206; M at a position corresponding to position 213; N at a position corresponding to position 213; E at a position corresponding to position 237; S at a position corresponding to position 238; N at a position corresponding to position 261; R at a position corresponding to position 277; T at a position corresponding to position 277; L at a position corresponding to position 309; N at a position corresponding to position 309; Q at a position corresponding to position 309; R at a position corresponding to position 309; T at a position corresponding to position 309; A at a position corresponding to position 310; G at a position corresponding to position 310; H at a position corresponding to position 315; I at a position corresponding to position 317; K at a position corresponding to position 317; R at a position corresponding to position 317; M at a position corresponding to position 318; G at a position corresponding to position 347; S at a position corresponding to position 347; M at a position corresponding to position 399; T at a position corresponding to position 399; W at a position corresponding to position 399; D at a position corresponding to position 407; Q at a position corresponding to position 407; F at a position corresponding to position 419; I at a position corresponding to position 419; R at a position corresponding to position 419; S at a position corresponding to position 419; K at a position corresponding to position 421; N at a position corresponding to position 421; Q at a position corresponding to position 421; R at a position corresponding to position 421; S at a position corresponding to position 421; A at a position corresponding to position 431; H at a position corresponding to position 431; K at a position corresponding to position 431; Q at a position corresponding to position 431; R at a position corresponding to position 431; S at a position corresponding to

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position 431; V at a position corresponding to position 431; L at a position corresponding to position 433; R at a position corresponding to position 433; V at a position corresponding to position 439; H at a position corresponding to position 440; R at a position corresponding to position 440; A at a position corresponding to position 443; M at a position corresponding to position 443; M at a position corresponding to position ~~[[445,]]445~~ and/or P at a position corresponding to position 445, with reference to amino acid positions set forth in SEQ ID NO:3; and

the modified PH20 polypeptide has at least 95% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7, and 32-66.

From column 304, line 55 to column 305, line 7, please replace claim 5 with the following amended claim:

5. The modified PH20 polypeptide of claim ~~[[3]]~~4 comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 86, 99, 100, 159, 173, 181, 193, 195, 209-220, 238, 239, 242, 247-252, 267, 269, 308, 324, 325, 330, 335, 355, 419, 421-423, 425, 428, 435, 455, 462, 463, 484, 490, 506, 531, 533, 579, 581-583, 585, 587, 588, 602, 605, 606, 609, 613, 648, 731, 732, 734, 742, 746, 760, 762, 764, 765, 769-773, 779, 782, 783, 786-789, 794, 795, 814, 816, 819, 826, 830, 836, and 838, or an amino acid sequence that has at least 96% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 86, 99, 100, 159, 173, 181, 193, 195, 209-220, 238, 239, 242, 247-252, 267, 269, 308, 324, 325, 330, 335, 355, 419, 421-423, 425, 428, 435, 455, 462, 463, 484, 490, 506, 531, 533, 579, 581-583, 585, 587, 588, 602, 605, 606, 609, 613, 648, 731, 732, 734, 742, 746, 760, 762, 764, 765, 769-773, 779, 782, 783, 786-789, 794, 795, 814, 816, 819, 826, 830, ~~[[836]]~~836, and 838, and that contains the amino acid replacement as compared to corresponding positions in a polypeptide of any of SEQ ID NOs:3, 7, and 32-66.

From column 305, line 31 to column 306, line 25, please replace claim 14 with the following amended claim:

14. The modified PH20 polypeptide of claim 2, comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 73, 78, 91, 95, 96, 105, 106, 108, 109, 111, 112, 113, 115, 117, 118, 119, 120, 123-126, 128-136, 139-141, 149, 154, 155, 164, 165, 167, 191, 192, 196, 197, 199-205, 207, 208, 225, 226, 228, 229, 231, 233, 237, 253, 254, 256, 257, 277, 283, 293, 295, 296, 298, 300, 303, 316, 318, 321, 322, 338-340, 344, 348,

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367, 369, 371, 377, 384-388, 394, 398, 399, 401, 406-408, 410, 412, 414, 416, 431, 448, 459, 465, 469, 478, 479, 482, 493, 497, 501, 503, 507, 508, 510-512, 514, 518, 522, 523, 537-543, 545, 558, 559, 561, 563-566, 569, 572, 574, 594, 596, 618-620, 624-634, 637, 640-644, 652, 657, 675, 695, 698, 699, 700, 712, 717, 725, 738, 748-750, 757, 775, 799-801, 807, 822, 825, 844, 847, [[85C]]851, and 853, or an amino acid sequence that has at least 96% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 73, 78, 91, 95, 96, 105, 106, 108, 109, 111, 112, 113, 115, 117, 118, 119, 120, 123-126, 128-136, 139-141, 149, 154, 155, 164, 165, 167, 191, 192, 196, 197, 199-205, 207, 208, 225, 226, 228, 229, 231, 233, 237, 253, 254, 256, 257, 277, 283, 293, 295, 296, 298, 300, 303, 316, 318, 321, 322, 338-340, 344, 348, 367, 369, 371, 377, 384-388, 394, 398, 399, 401, 406-408, 410, 412, 414, 416, 431, 448, 459, 465, 469, 478, 479, 482, 493, 497, 501, 503, 507, 508, 510-512, 514, 518, 522, 523, 537-543, 545, 558, 559, 561, 563-566, 569, 572, 574, 594, 596, 618-620, 624-634, 637, 640-644, 652, 657, 675, 695, 698, 699, 700, 712, 717, 725, 738, 748-750, 757, 775, 799-801, 807, 822, 825, 844, 847, [[851]]851, and 853, and that contains the amino acid replacement as compared to corresponding positions in a polypeptide of any of SEQ ID NOs: 3, 7, and 32-66.

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REMARKS

A Certificate of Correction (Form PTO/SB/44) incorporating the above changes is included with this Request. Since not all the errors are those of the Patent Office, the Office is hereby authorized to charge the fee to Deposit Account No. 50-0911.

IN THE TITLE PAGES

This Certificate of Correction seeks to correct typographical errors in the References Cited. In Item (56), in U.S. PATENT DOCUMENTS, on page 1, 2nd column, line 31, the typographical error is corrected by replacing “Greennnwald” with “Greenwald,” to correct the inventor of cited patent. In Item (56), in OTHER PUBLICATIONS, on page 3, 1st column, line 26, the error is corrected by replacing “claimed deemed allowable” with “claims deemed allowable,” to correct the noun verb agreement.

This Certificate of Correction also seeks to correct a spelling error in the References Cited. In Item (56), in OTHER PUBLICATIONS, on page 4, 1st column, line 60, the obvious spelling error is corrected by replacing “Rearch” with “Research.”

This Certificate of Correction also seeks to correct a typographical error introduced by the PTO in the References Cited. In Item (56), in OTHER PUBLICATIONS, on page 5, 2nd column, line 20, the error is corrected by replacing “Harahan” with “Hanahan,” to correct the author of the cited publication. The reference was listed on a PTO-1449 Form as Item IR and provided to the Patent Office with an Information Disclosure Statement on August 24, 2016. A copy of page 9 of the Examiner-initialed PTO-1449 Form, considered by the Examiner on April 26, 2019, and mailed to the Applicant on May 15, 2019, is provided to show the correct citation.

IN THE SPECIFICATION

This Certificate of Correction seeks to correct typographical errors introduced by the PTO in the specification. At column 13, line 15, and at column 22, line 36, the errors are corrected by replacing “Mat” with “M at,” to correct the recited amino acid replacement. Basis for these corrections can be found at page 15, line 30, and at page 26, line 26 of the specification as originally filed on August 02, 2016. Copies of pages 15 and 26 of the specification as originally filed on August 02, 2016, are attached as evidence.

This Certificate of Correction also seeks to a correct typographical error introduced by the PTO in the specification, at column 53, lines 7-8. The error is corrected by replacing “poly-propylene oxide)” with “poly(propylene oxide),” to insert the omitted parenthesis, and

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correct the obvious typographical error. Basis for this correction can be found at page 63, lines 11-12 of the specification as originally filed on August 02, 2016. A copy of page 63 of the specification as originally filed on August 02, 2016, is attached as evidence.

This Certificate of Correction also seeks to correct typographical errors introduced by the PTO in the specification at column 69, lines 2, 5, 10, 46, and 53. The errors are corrected by replacing “w-site” with “ω-site” to insert the correct Greek symbol and, thus, correct the reference to a specific amino acid position. Basis for these corrections can be found at page 82, line 22; page 82, line 24; page 82, line 27; page 83, line 14; and page 83, line 19, of the specification as originally filed on August 02, 2016. Copies of pages 82 and 83 of the specification as originally filed on August 02, 2016, are attached as evidence.

This Certificate of Correction also seeks to correct typographical errors introduced by the PTO in the specification at column 90. At line 40, the error is corrected by replacing “179” with “I79” to correct the amino acid residue at position 79. At line 49, the error is corrected by replacing “5235” with “S235” to correct the amino acid residue at position 235. Basis for these corrections can be found at page 98, lines 3 and 8, of the specification as originally filed on August 02, 2016. A copy of page 98 of the specification as originally filed on August 02, 2016, is attached as evidence.

This Certificate of Correction also seeks typographical errors in the specification at Table 5, from column 120, line 46 to column 133, line 36. The error is corrected by replacing the replacements “C ; , [” at corresponding position 395 with the replacements “C L M P,” to correct the obvious typographical error. Basis for this correction can be found in Table 10: Inactive mutants from page 273, lines 6 to page 282, in the specification as originally filed on August 02, 2016. Table 10 lists the amino acid replacements that yielded inactive mutants; specifically, at page 276, lines 19-22, the table lists the mutants S395C, S395L, S395M and S395P. The replacements “C L M P” at corresponding position 395 yield inactive mutants; thus, the amendment corrects an obvious typographical error. Another error is corrected by replacing the replacements “ C D E G [” at corresponding position 256 with the replacements “C D E G P,” to correct the obvious typographical error. Basis for this correction can be found for this correction can be found in Table 10: Inactive mutants from page 273, lines 6 to page 282, in the specification as originally filed on August 02, 2016. Table 10 lists the amino acid replacements that yielded inactive mutants; specifically, at page 277, lines 37-41, the table lists the mutants I256C, I256D, I256E, I256G and I256P. The replacements “C D E G

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P” at corresponding position 256 yield inactive mutants; thus, the amendment corrects an obvious typographical error. Copies of pages 276 and 277 of the specification as originally filed on August 02, 2016, are attached as evidence.

This Certificate of Correction also seeks to correct a typographical error introduced by the PTO in the specification, at column 178, line 28. The error is corrected by replacing “f 15%” with “ $\pm$ 15%,” to insert the plus-minus sign and, thus, correct the obvious typographical error. Basis for this correction can be found at page 190, line 9 of the specification as originally filed on August 02, 2016. A copy of page 190 of the specification as originally filed on August 02, 2016, is attached as evidence.

This Certificate of Correction also seeks to correct a typographical error introduced by the PTO in specification, at column 185, line 25. The error is corrected by replacing “U520100074885” with “US20100074885,” to correct the cited U.S. Publication No.. Basis for this correction can be found at page 198, line 18 of the specification as originally filed on August 02, 2016. A copy of page 198 of the specification as originally filed on August 02, 2016, is attached as evidence.

This Certificate of Correction also seeks to correct typographical errors introduced by the PTO in the specification, at column 293. The error at line 25 is corrected by replacing “Jasco J-810-1505” with “Jasco J-810-150S” to correct the name of the equipment used for CD spectral measurement. The error at line 26 is corrected by replacing “PTC-4245” with “PTC-424S” to correct the name of the equipment used for CD spectral measurement. Basis for these corrections can be found at page 315, line 21 of the specification as originally filed on August 02, 2016. A copy of page 315 of the specification as originally filed on August 02, 2016, is attached as evidence.

IN THE CLAIMS

This Certificate of Correction seeks to correct typographical errors introduced by the PTO in claim 1, from column 299, line 36 to column 300, line 44. The errors are corrected by replacing “replacements)” with “replacement(s) at column 299, line 46, and by adding the omitted commas at column 299, lines 41 and 63, and at column 300, line 44. These corrections can be found at page 2, lines 11, 8, 22, and 31, respectively, in the Amendment Pursuant to 37 C.F.R. § 1.312 filed on October 01, 2020, which was entered into the record on October 16, 2020. A copy of page 2 of the Amendment Pursuant to 37 C.F.R. § 1.312 filed on October 01, 2020, is provided as evidence.

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This Certificate of Correction also seeks to correct typographical errors introduced by the PTO in claim 2, from column 300, line 45 to column 303, line 11. The errors are corrected by inserting the omitted “H” at column 300, line 48, and by replacing “Rat” with “R at” at column 301, lines 57 and 58. Basis for these corrections can be found at page 3, line 1 and page 4, lines 13-14, respectively, in the Amendment Pursuant to 37 C.F.R. § 1.312 filed on October 01, 2020 and entered into the record on October 16, 2020. Copies of pages 3 and 4 of the Amendment Pursuant to 37 C.F.R. § 1.312 filed on October 01, 2020, are provided as evidence.

This Certificate of Correction also seeks to correct a typographical error introduced by the PTO in claim 3, at column 303, line 12-16. The error is corrected by removing “[M]” at column 303, line 13. Basis for this correction can be found in the Amendment Pursuant to 37 C.F.R. § 1.312 filed on October 01, 2020, which was entered into the record on October 16, 2020, in claim 27, renumbered to claim 3 in the issued patent, at page 9, line 30. A copy of page 9 of the Amendment Pursuant to 37 C.F.R. § 1.312 filed on October 01, 2020, is provided as evidence.

This Certificate of Correction seeks to correct typographical errors introduced by the PTO in claim 4, from 303, line 17 to column 304, line 54. The errors are corrected by inserting the omitted comma after SEQ ID NO:7 at column 303, line 22, replacing “replacements”)” with “replacement(s)” at line 27 of column 303, and by replacing a colon after the recitation “conditions” and a comma after the recitation “position 445” with semicolons at column 303, line 32 and column 304, line 49, respectively. Basis for these corrections can be found in the Amendment Pursuant to 37 C.F.R. § 1.312 filed on October 01, 2020, which was entered into the record on October 16, 2020, in claim 3, renumbered to claim 4 in the issued patent, at page 6, lines 2, 5 and 9, and page 7, line 25, respectively. Copies of pages 6 and 7 of the Amendment Pursuant to 37 C.F.R. § 1.312 filed on October 01, 2020, are provided as evidence.

This Certificate of Correction also seeks to correct typographical errors introduced by the PTO in claim 5, from column 304, line 55 to column 305, line 7. The errors are corrected by replacing “claim 3” with “claim 4” at column 304, line 55 to correct claim dependency, and by inserting the omitted comma after SEQ ID NO:836 at column 305, line 5. Basis for these corrections can be found in the Amendment Pursuant to 37 C.F.R. § 1.312 filed on October 01, 2020 and entered into the record on October 16, 2020, at page 8, line 18, and at

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page 8, line 29, respectively. In the Amendment Pursuant to 37 C.F.R. § 1.312, claim 5 was dependent on claim 3 (see, page 8, line 18); in the issued patent, claim 3 was renumbered to claim 4. A copy of page 8 of the Amendment Pursuant to 37 C.F.R. § 1.312 filed on October 01, 2020, is provided as evidence.

This Certificate of Correction also seeks to correct typographical errors introduced by the PTO in claim 14 from column 305, line 31 to column 306, line 25. The errors are corrected by replacing “85C” with “851” at column 306, line 8, and by inserting the omitted commas after SEQ ID NO:851 at column 306, lines 8 and 22. Basis for these corrections can be found in the Amendment Pursuant to 37 C.F.R. § 1.312 filed on October 01, 2020, which was entered into the record on October 16, 2020, in claim 4, renumbered to claim 14 in the issued patent, at page 8, lines 6 and 15. A copy of page 8 of the Amendment Pursuant to 37 C.F.R. § 1.312 filed on October 01, 2020, is provided as evidence.

* * *

These changes do not constitute new matter. Patentee respectfully requests correction of these errors by issuance of a Certificate of Correction.

Respectfully submitted,

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CERTIFICATE OF CORRECTION

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UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

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PATENT NO. .: 10,865,400
APPLICATION NO. .: 15/226,489
DATED .: DECEMBER 15, 2020
INVENTOR(S) .: WEI *ET AL.*

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

IN THE TITLE PAGES:

In Item (56) References Cited, in U.S. PATENT DOCUMENTS, on page 1, 2nd column, line 31, please replace the inventor "Greennnwald" with —Greenwald—;

In Item (56) References Cited, in OTHER PUBLICATIONS, on page 3, 1st column, line 26, please replace "claimed" with —claims—;

In Item (56) References Cited, in OTHER PUBLICATIONS, on page 4, 1st column, line 60, please replace "Rearch" with —Research—;

In Item (56) References Cited, in OTHER PUBLICATIONS, on page 5, 2nd column, line 20, please replace the author "Harahan" with —Hanahan—;

IN THE SPECIFICATION:

At column 13, line 15, please replace "Mat" with —M at—;

At column 22, line 36, please replace "Mat" with —M at—;

At column 53, lines 7-8, please replace "poly-propylene oxide)" with —poly(propylene oxide)—;

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CERTIFICATE OF CORRECTION

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PATENT NO. .: 10,865,400
 APPLICATION NO. .: 15/226,489
 DATED .: DECEMBER 15, 2020
 INVENTOR(S) .: WEI *ET AL.*

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

At column 69, line 2, please replace "w-site" with —ω-site—;

At column 69, line 5, please replace "w-site" with —ω-site—;

At column 69, line 10, please replace "w-site" with —ω-site—;

At column 69, line 46, please replace "w-site" with —ω-site—;

At column 69, line 53, please replace "w-site" with —ω-site—;

At column 90, line 40, please replace "I79" with —I79—;

At column 90, line 49, please replace "5235" with —S235—;

From column 120, line 46 to column 133, line 36, please replace Table 5 with the following amended Table:

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CERTIFICATE OF CORRECTION

Page 3 of 28

PATENT NO. : 10,865,400
 APPLICATION NO. : 15/226,489
 DATED : DECEMBER 15, 2020
 INVENTOR(S) : WEI ET AL.

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

TABLE 5: Inactive Mutants					
Corres- ponding Position	Replacement	Corres- ponding Position	Replacement	Corres- ponding Position	Replacement
2	HKWY	3	AGKPTV	4	DEFGLPWY
5	DGILMNPQR TVWY	6	EFTVY	7	CDFGHIKLQ RSTWY
8	DEGHNRSW	9	CDEGNP	10	FILMY
11	ACFILPTWY	12	GHW	13	EGILMV
14	AEGHKNPQW	15	EFGKNPQRS Y	16	ACDEFGHK MPRSTY
17	DEGHILNPQ RSTVWY	18	CDFGHILMP QSTVY	19	ACFGHILMP QRSVWY
20	DEFHKLNPR TVY	21	ACDEGHILM RSTVW	22	CEGKP
23	AFLMNPRST V	25	DEFGHIKLN PRSTVY	27	C
33	CDHNVY	34	ILNSTV	35	ADGPRS
36	CFVWY	37	CEGNS	38	EGKLNQRT W
39	CDFW	40	ADEGKNRST V	41	Q
42	DEHIKLMPQ RSTV	43	AEFGIKLQR V	44	ACFGHILNQ RSTWY
45	ADFGPW	46	PW	47	V
48	P	49	CDGHP	50	V

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PATENT No. : 10,865,400
 APPLICATION No. : 15/226,489
 DATED : DECEMBER 15, 2020
 INVENTOR(S) : WEI ET AL.

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

51	CFIMPTWY	52	CEFWY	53	ACDEGHLNP QRSTWY
54	DEGPRY	55	ADGHN PQRT VY	56	ACEGHIKLP RSTVW
57	ADFGIMPQR VW	58	A	59	AEILMPRTV WY
60	ADFGHILNPQ STVY	61	AEFGHNPQR TWY	62	ACDFIKLMP QRSTVY
63	CGP	64	ACDEFGHIK LPQRSTVW	65	ACDGHKINR STVWY
66	ACDEGIKLN STV	67	DEGPRTW	68	ACGILPVY
69	NT	70	Q	71	P
72	CFHIPVW	73	P	75	DGP
76	ACFGIKLPQ RSTVW	77	DELPQRTV	78	ADIMPTY
79	ADFGHKNPS WY	80	ADEFGIKLM NRSTVY	81	ACEGHLNPS VWY
82	YEK	84	Y	85	ACDEFGHNQ ST
86	CP	87	P	88	ACEFGIKLM PRSTVY
89	ADEGQSTWY	90	CG	91	DEFGHILT
92	EFHKPQRWY	94	GP	95	ACEFGHKLM PQSVWY
96	SVHPRSTW	98	P	99	CEGINPVW

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CERTIFICATE OF CORRECTION

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PATENT NO. : 10,865,400
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 DATED : DECEMBER 15, 2020
 INVENTOR(S) : WEI ET AL.

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

100	CEFGNPRST WY	101	ACFHIKLMN QRST	102	P
103	AEFGHILQRT VWY	104	FPW	105	CMN
106	ACDFHLMNP SWY	107	ACHKPQSVW	108	DEFKLMPT VY
109	CDELMRTW	110	FKLMPW	111	HIQ
112	CEGHLNPS	113	RV	114	ILPTV
115	ACDFGHIKL MRSVY	116	ACDEGHILN PQSVW	117	DGIKNQRSV W
118	CDEGPRWY	119	AKILNPR	121	ACEFGHKLM PWY
122	A CEFIKQRS TV	123	ACDEHLMPQ RSTVY	124	CDEFN
125	CDGLNW	126	FHILNPY	127	K
128	EP	129	ACDEGHL PQ STVW	130	CDGHLNST WY
131	P	132	P	133	DEFGHLMNP RTVW
134	ACDFG HKPQ RSW	135	P	136	P
137	F GHNPRWY	138	V	139	P
143	CHPRST	144	AEFIKPQSVY	145	TW
149	E	149	P	150	V
152	L	153	EFMPRTV	154	DEGPSWY
155	PY	156	P	157	ACDEGHIKL M PQRSTV

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CERTIFICATE OF CORRECTION

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PATENT NO. : 10,865,400
 APPLICATION NO. : 15/226,489
 DATED : DECEMBER 15, 2020
 INVENTOR(S) : WEI ET AL.

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

158	DKPRY	159	WY	161	W
163	CP	164	ACDEGHNPQR	165	CHPT
166	D	167	V	168	ACDEFGKLP RSVWY
169	ADFGHKNPQ STY	170	CDEGMPWY	171	CDHMNRSW Y
172	DEILPQTVW Y	173	DEGHILMPS VWY	174	P
175	CDGKPRS	176	ACEFGHIPQS TVW	177	ACDFGHLM QRSTVW
178	EILVW	180	ACEPRS	181	ACDEFHIKL RS
182	ACDEHNPQR STVY	183	CDEGIKNPQ RSV	184	ACDEFGHKL MPRSV
185	ADEFGIKPRS TVWY	186	ADGHIKLP QRSVW	187	AFGHILMNQ RSTVWY
188	ACFGHLMNP QRSTVW	189	AEGHKLMPN RSTVWY	190	CEFGHKLNQ RSTVW
191	ADEFGKLPQ RSTVWY	192	CFGKLMNPQ RVWY	193	ADKLMPV
194	ACILPSTV	195	S	197	C
198	VW	199	EGHIKLPRS W	200	AFGHKLMPQ RSWY
201	AFLMNPQRST VW	202	AEFGHKNPQ RVWY	203	ADEGHLMN QRSTV
204	ACEGHIKQR ST	206	CDFGPY	207	AFGMPQRST VW

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PATENT NO. : 10,865,400
 APPLICATION NO. : 15/226,489
 DATED : DECEMBER 15, 2020
 INVENTOR(S) : WEI ET AL.

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

208	D G P W	209	C P	210	A C D E G K M N P S T V W Y
211	C F G H I K M P R S T V W	212	A G H I K L M P V W	213	P S
214	A C D E G H K N P R S T Y	215	C P	216	D E G H I K L M N P Q R T V
217	A C G H P Q S T V W	218	A I K L P S V	219	P
220	G K N P R W	221	D E H K P R	222	P Y
223	C D E G H K L P Q R S T V W Y	224	A D E F G M P Q R S T W Y	225	A D E G H K P Q R T V W
226	A C D E F G L N Q R S T V W Y	227	A F G H I K L M P Q R T V W Y	228	A E F G H L M N P R S T W
229	E F G K L P Q T V W	230	A E G H K M N P R S T V W Y	231	A C D F G H I K L P Q R S V
232	C G H K L N P Q V Y	233	D I P S T	234	A D E G H N P S T V W
235	F L M R W Y	236	C I L N Q T Y	238	F G L P V W Y
239	C F G H I L P R S T V W Y	240	E F G N W Y	241	A C D E G I P R S T V W
242	A C D G I L M P R S T V W	243	C D F G H L M P Q R S W Y	244	A D G I V Y
245	A C F L P Q R S T V	246	A C D E G H I K L M P S T V W	247	A C F H N P Q R S T W Y
248	C D E G I M P T	249	A G H I K M Q S Y	250	C F G H K L M N P Q R S T V W
251	D F G H K P S T W	252	A D E F G H I K L N P S T Y	253	A D E G H L M N Q R S W

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PATENT NO. : 10,865,400
 APPLICATION NO. : 15/226,489
 DATED : DECEMBER 15, 2020
 INVENTOR(S) : WEI ET AL.

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

254	CDEGIKLPQR TVWY	255	CDLPVW	256	CDEGP
257	D	258	LPVW	260	CP
261	P	262	ADE GHIKQR STVWY	263	EF PQW
264	DEFG LMRTV WY	265	ADFGHKLMN QRS	266	ACGHMPQRS TVW
267	DGHIKNRSW	268	ACFGHKLNP QSTVW	269	EKLMNPQR
270	ACEFGHIPY	271	ADEHKTW	272	HLNPW
273	ACDGILPQSV W	274	CEGHNQWY	275	AFGIKLMQT VW
276	FPW	278	MP	279	ACFGLWY
280	DI MNRSTVW	281	ADGHIKNPQ RSVW	282	FLVWY
283	ACDFW	284	CDFW	284	CIP
285	KPRTV	286	ACDFHKMPT Y	287	ACDEGKLN PQRS
288	DEFGHIKPRT	289	ACEGHL PQR SY	290	DQY
291	ACDEFMNTW Y	292	ILT	293	EN
294	AEGHKLN PQ RSTW	295	CGHILNPTV Y	296	CFGIKMQRS TVWY
297	CEHLNPQRS TY	298	CELMNPQST WY	299	ACDFGHLMP QT

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PATENT NO. : 10,865,400
 APPLICATION NO. : 15/226,489
 DATED : DECEMBER 15, 2020
 INVENTOR(S) : WEI ET AL.

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

300	ACDEFLMNP QSTVW	301	EGHKMNPQR SWY	302	CDEFGHLM P RSTY
303	ACDEFGKLM RWY	304	ACDGIMNPQ STVY	305	LPQRSTVY
306	ACHILVWY	307	CIP	308	CFLMVWY
310	CEFKL	311	CEFILPVW	312	CEMVW
313	C	314	CLW	315	CIV
316	EGIKLMPRST VWY	317	G P	318	CPW
319	CEFGHIKMP QRSVWY	320	CPV	321	EMP
322	CDEGILNPRS TVW	323	ACEGHKNRS TV	324	CFPVWY
325	CREGHNW	327	AEFGHNQRS TVWY	329	CFGHIKLNQ RSTVWY
330	ACDEGILMN PRSVW	331	ACDEFHKQR STWY	332	ACDEFGHKL NPRSTY
333	GHIKPRSTW Y	334	ACDEGMNRS	335	FGHIKLPVW Y
336	AEFGKNPRS TVWY	337	CFGIKLMRT W	338	CDEFGHIKL PRTV
339	DEFGHLNPST VWY	340	ACDEFGHKP RSTVW	341	AEGHKLMN QRSTVY
342	DEFHKLMPQ RTY	343	CDFIPW	344	FGHLMNPQR STWY
345	ACEHKNQRT VY	346	ADFGIKLMP RSTVW	347	CFIPTVW

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Page 10 of 28

PATENT NO. : 10,865,400
 APPLICATION NO. : 15/226,489
 DATED : DECEMBER 15, 2020
 INVENTOR(S) : WEI ET AL.

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

348	CHILPQRTV WY	349	DFGPVWY	350	ADEFHKLM NPRSTVY
351	CDEFHNRWY	352	ADEFGKMPQ RSTVWY	353	CFGHKLMQ RSW
354	CDEGHIKLM PQSVWY	355	DFGHLMPNPQ RSTVWY	356	CGKLPRTVW
357	DEFGMLQR	358	EHKPPQRW	359	AFGLPW
360	ACEFGIKLMP QRV	361	ACEGMNPQR SVW	362	ACEGHKLM NPRSTVW
363	ACDEFGHIPQ RSTVW	364	ACDEFGKLM PRSTVY	365	ACDEGMNP QRSTWY
366	ACEFGKMPQ RTW	367	EFILMQV	368	CPW
369	CEFIKLPQV W	370	ADEGHKLN QRSVY	371	P
372	ADEFGHKL NPRSTVW	373	CPW	374	DE
375	CFPVY	376	IPW	377	CILV
378	DEFILMQTW Y	379	ACEFILMW	380	CDEGQRS
381	GLPWY	382	EGHKLMNPQ RSTWY	383	GP
384	CFMQST	385	CLMPWY	386	ACFGHILMN QRSTVY
387	CEFGHILMN VWY	388	CGPQ	389	FV

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PATENT NO. : 10,865,400
 APPLICATION NO. : 15/226,489
 DATED : DECEMBER 15, 2020
 INVENTOR(S) : WEI ET AL.

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

390	ACEFGHLNP RSTVWY	391	ADGHKNPQR STVWY	392	CP
393	CP	394	ADEGIKNPQ RSTV	395	CLMP
396	CFGIPY	397	ACEFGILMP QTV	398	ACEGHLNP RSTVWY
399	DP	400	ADEFGILMP QRSTVY	401	CFHKRWY
402	ADEFLMPQR STVWY	403	ACEGHKLMN PQRT	404	CDFGHLMN RVWY
405	CIV	406	PR	408	AEFGIKLPR STVWY
410	W	411	DEFG	412	EH
413	HIKLP	414	ADEGHKRST	415	CDEP
416	CS	417	ADEFGHKMP QR	419	DP
420	ADFGHKLNR STWY	422	CDGHLMNQ RSY	423	ADEFGHLMP QRSTVW
424	ACEGHNQRS WY	425	ELPWY	426	CFMR
427	ACFLPVWY	428	ACDEGHNRS Y	429	ADKLN PSTV WY
430	ADELMNSTV	431	P	432	CFIKLMPY
434	HKPQRW	437	T	438	Y
439	NR	440	Q	441	R
442	MNS	443	D		

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PATENT NO. .: 10,865,400
APPLICATION NO. .: 15/226,489
DATED .: DECEMBER 15, 2020
INVENTOR(S) .: WEI *ET AL.*

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

At column 178, line 28, please replace "f 15%" with $\pm 15\%$;

At column 185, line 25, please replace "U520100074885" with —US20100074885—;

At column 293, line 25, please replace "Jasco J-810-1505" with —Jasco J-810-150S—;

At column 293, line 26, please replace "PTC-4245" with —PTC-424S—.

IN THE CLAIMS:

From column 299, line 36 to column 300, line 44, please replace claim 1 with the following amended claim:

1. A modified PH20 polypeptide, comprising one or more amino acid replacements in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NOS: 3, 7, and 32-66;

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PATENT NO. .: 10,865,400
 APPLICATION NO. .: 15/226,489
 DATED .: DECEMBER 15, 2020
 INVENTOR(S) .: WEI *ET AL.*

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

the modified PH20 polypeptide exhibits increased hyaluronidase activity that is at least 120% of the hyaluronidase activity compared to the unmodified PH20 polypeptide not containing the amino acid replacement(s); wherein:

the activity of the unmodified PH20 polypeptide not containing the replacement(s) is 100%;

hyaluronidase activity of the modified PH20 polypeptide and hyaluronidase activity of the unmodified PH20 polypeptide are measured under identical conditions;

the amino acid replacement(s) confer(s) the increased hyaluronidase activity;

at least one amino acid replacement confers the increased hyaluronidase activity, and is at a position corresponding to a position selected from 1, 15, 24, 27, 29, 30, 31, 32, 33, 37, 39, 48, 63, 67, 69, 71, 72, 73, 75, 87, 92, 93, 94, 118, 120, 135, 141, 147, 148, 150, 151, 152, 155, 156, 163, 164, 165, 170, 198, 209, 212, 215, 219, 233, 236, 247, 257, 259, 260, 263, 269, 271, 272, 276, 278, 282, 293, 305, 308, 313, 320, 324, 325, 326, 328, 353, 359, 371, 377, 380, 389, 392, 395, 405, 409, 410, 418, 425, 436, 437, 438, 441, 442, 446, and 447, with reference

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PATENT NO. .: 10,865,400
 APPLICATION NO. .: 15/226,489
 DATED .: DECEMBER 15, 2020
 INVENTOR(S) .: WEI *ET AL.*

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

to amino acid positions set forth in SEQ ID NO:3;

corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the sequence of amino acids set forth as SEQ ID NO:3, with the proviso that if the modified PH20 polypeptide includes only a single amino acid replacement, the replacement does not correspond to amino acid replacement N219A with reference to amino acid positions set forth in SEQ ID NO:3; and

the modified PH20 polypeptide has at least 95% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7, and 32-66.

From column 300, line 45 to column 303, line 11, please replace claim 2 with the following amended claim:

2. The modified PH20 polypeptide of claim 1, comprising at least one amino acid replacement selected from among replacement with: H at a position corresponding to position 1; Q at a position corresponding to position 1; V at a position corresponding to position 15; E at a position corresponding to position 24; H at a position corresponding to position 24; K at a

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Page 15 of 28

PATENT NO. .: 10,865,400
 APPLICATION NO. .: 15/226,489
 DATED .: DECEMBER 15, 2020
 INVENTOR(S) .: WEI *ET AL.*

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

position corresponding to position 27; R at a position corresponding to position 27; E at a position corresponding to position 29; I at a position corresponding to position 29; L at a position corresponding to position 29; M at a position corresponding to position 29; P at a position corresponding to position 29; S at a position corresponding to position 29; V at a position corresponding to position 29; G at a position corresponding to position 30; H at a position corresponding to position 30; K at a position corresponding to position 30; M at a position corresponding to position 30; R at a position corresponding to position 30; S at a position corresponding to position 30; A at a position corresponding to position 31; C at a position corresponding to position 31; H at a position corresponding to position 31; I at a position corresponding to position 31; K at a position corresponding to position 31; L at a position corresponding to position 31; P at a position corresponding to position 31; R at a position corresponding to position 31; S at a position corresponding to position 31; T at a position corresponding to position 31; V at a position corresponding to position 31; F at a position corresponding to position 32; G at a position corresponding to position 32; H at a position corresponding to position 32; W at a position corresponding to position 33; F at a

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CERTIFICATE OF CORRECTION**Page 16 of 28

PATENT NO. .: 10,865,400
APPLICATION NO. .: 15/226,489
DATED .: DECEMBER 15, 2020
INVENTOR(S) .: WEI *ET AL.*

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

position corresponding to position 37; N at a position corresponding to position 39; T at a position corresponding to position 39; F at a position corresponding to position 48; H at a position corresponding to position 48; N at a position corresponding to position 48; W at a position corresponding to position 63; V at a position corresponding to position 67; A at a position corresponding to position 69; C at a position corresponding to position 69; F at a position corresponding to position 69; G at a position corresponding to position 69; I at a position corresponding to position 69; L at a position corresponding to position 69; M at a position corresponding to position 69; P at a position corresponding to position 69; R at a position corresponding to position 69; W at a position corresponding to position 69; Y at a position corresponding to position 69; R at a position corresponding to position 71; S at a position corresponding to position 71; M at a position corresponding to position 72; Q at a position corresponding to position 72; H at a position corresponding to position 73; L at a position corresponding to position 73; W at a position corresponding to position 73; F at a position corresponding to position 75; L at a position corresponding to position 75; R at a position corresponding to position 75; T at a position corresponding to position 75; C at a

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PATENT NO. .: 10,865,400
APPLICATION NO. .: 15/226,489
DATED .: DECEMBER 15, 2020
INVENTOR(S) .: WEI *ET AL.*

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

position corresponding to position 87; T at a position corresponding to position 87; Y at a position corresponding to position 87; C at a position corresponding to position 92; I at a position corresponding to position 93; L at a position corresponding to position 93; R at a position corresponding to position 93; T at a position corresponding to position 93; R at a position corresponding to position 94; Q at a position corresponding to position 118; F at a position corresponding to position 120; V at a position corresponding to position 120; Y at a position corresponding to position 120; D at a position corresponding to position 135; G at a position corresponding to position 135; R at a position corresponding to position 135; H at a position corresponding to position 141; Y at a position corresponding to position 141; R at a position corresponding to position 147; V at a position corresponding to position 147; K at a position corresponding to position 148; G at a position corresponding to position 150; K at a position corresponding to position 151; L at a position corresponding to position 151; M at a position corresponding to position 151; Q at a position corresponding to position 151; R at a position corresponding to position 151; R at a position corresponding to position 152; G at a position corresponding to position 155; K at a position corresponding to position 155; D at a

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PATENT NO. .: 10,865,400
APPLICATION NO. .: 15/226,489
DATED .: DECEMBER 15, 2020
INVENTOR(S) .: WEI *ET AL.*

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

position corresponding to position 156; A at a position corresponding to position 163; E at a position corresponding to position 163; K at a position corresponding to position 163; R at a position corresponding to position 163; M at a position corresponding to position 164; D at a position corresponding to position 165; N at a position corresponding to position 165; R at a position corresponding to position 170; D at a position corresponding to position 198; N at a position corresponding to position 212; M at a position corresponding to position 215; S at a position corresponding to position 219; K at a position corresponding to position 233; R at a position corresponding to position 233; R at a position corresponding to position 236; I at a position corresponding to position 247; T at a position corresponding to position 257; P at a position corresponding to position 259; Y at a position corresponding to position 260; K at a position corresponding to position 263; R at a position corresponding to position 263; A at a position corresponding to position 269; L at a position corresponding to position 271; M at a position corresponding to position 271; T at a position corresponding to position 272; D at a position corresponding to position 276; S at a position corresponding to position 276; Y at a position corresponding to position 276; H at a position corresponding to position 278; K at a

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PATENT NO. .: 10,865,400
APPLICATION NO. .: 15/226,489
DATED .: DECEMBER 15, 2020
INVENTOR(S) .: WEI *ET AL.*

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

position corresponding to position 278; N at a position corresponding to position 278; R at a position corresponding to position 278; S at a position corresponding to position 278; T at a position corresponding to position 278; Y at a position corresponding to position 278; M at a position corresponding to position 282; A at a position corresponding to position 293; C at a position corresponding to position 293; F at a position corresponding to position 293; M at a position corresponding to position 293; P at a position corresponding to position 293; Q at a position corresponding to position 293; V at a position corresponding to position 293; E at a position corresponding to position 305; G at a position corresponding to position 308; N at a position corresponding to position 308; K at a position corresponding to position 313; R at a position corresponding to position 313; H at a position corresponding to position 320; K at a position corresponding to position 320; R at a position corresponding to position 320; R at a position corresponding to position 324; A at a position corresponding to position 325; D at a position corresponding to position 325; E at a position corresponding to position 325; G at a position corresponding to position 325; H at a position corresponding to position 325; K at a position corresponding to position 325; M at a position corresponding to position 325; N at a

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PATENT NO. .: 10,865,400
APPLICATION NO. .: 15/226,489
DATED .: DECEMBER 15, 2020
INVENTOR(S) .: WEI *ET AL.*

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

position corresponding to position 325; Q at a position corresponding to position 325; S at a position corresponding to position 325; V at a position corresponding to position 326; I at a position corresponding to position 328; K at a position corresponding to position 328; L at a position corresponding to position 328; S at a position corresponding to position 328; Y at a position corresponding to position 328; V at a position corresponding to position 353; T at a position corresponding to position 359; R at a position corresponding to position 371; P at a position corresponding to position 377; T at a position corresponding to position 377; W at a position corresponding to position 380; Y at a position corresponding to position 380; K at a position corresponding to position 389; M at a position corresponding to position 392; R at a position corresponding to position 395; G at a position corresponding to position 405; A at a position corresponding to position 409; Q at a position corresponding to position 409; T at a position corresponding to position 410; P at a position corresponding to position 418; K at a position corresponding to position 425; K at a position corresponding to position 436; I at a position corresponding to position 437; M at a position corresponding to position 437; T at a position corresponding to position 438; F at a position corresponding to position 441; R at a

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PATENT NO. .: 10,865,400
APPLICATION NO. .: 15/226,489
DATED .: DECEMBER 15, 2020
INVENTOR(S) .: WEI ET AL.

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

position corresponding to position 442; A at a position corresponding to position 446; D at a position corresponding to position 447; N at a position corresponding to position 447; and/or Q at a position corresponding to position 447, with reference to amino acid positions set forth in SEQ ID NO:3.

At column 303, lines 12-16, please replace claim 3 with the following amended claim:

3. The modified PH20 polypeptide of claim 2, wherein the modified PH20 polypeptide is a soluble PH20 polypeptide; and the unmodified polypeptide consists of the amino acid sequence set forth in any of SEQ ID NOS: 3 or 32-66.

From column 303, line 17 to column 304, line 54, please replace claim 4 with the following amended claim:

4. A modified PH20 polypeptide, comprising one or more amino acid replacements in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NOS: 3, 7, and 32-66;

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CERTIFICATE OF CORRECTION

Page 22 of 28

PATENT NO. .: 10,865,400
 APPLICATION NO. .: 15/226,489
 DATED .: DECEMBER 15, 2020
 INVENTOR(S) .: WEI *ET AL.*

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

the modified PH20 polypeptide exhibits increased hyaluronidase activity that is at least 120% of the hyaluronidase activity compared to the unmodified PH20 polypeptide not containing the amino acid replacement(s); wherein:

the activity of the unmodified PH20 polypeptide not containing the replacement(s) is 100%;

hyaluronidase activity of the modified PH20 polypeptide and hyaluronidase activity of the unmodified PH20 polypeptide are measured under identical conditions;

at least one amino acid replacement confers the increased hyaluronidase activity, and is selected from E at a position corresponding to position 12; E at a position corresponding to position 26; K at a position corresponding to position 26; R at a position corresponding to position 46; Q at a position corresponding to position 52; Q at a position corresponding to position 58; H at a position corresponding to position 68; Q at a position corresponding to position 68; A at a position corresponding to position 70; C at a position corresponding to position 70; F at a position corresponding to position 70; G at a position corresponding to position 70; H at a position corresponding to position 70; K at a position corresponding to

MAILING ADDRESS OF SENDER:

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Only**UNITED STATES PATENT AND TRADEMARK OFFICE
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PATENT NO. .: 10,865,400
APPLICATION NO. .: 15/226,489
DATED .: DECEMBER 15, 2020
INVENTOR(S) .: WEI *ET AL.*

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

position 70; L at a position corresponding to position 70; N at a position corresponding to position 70; P at a position corresponding to position 70; R at a position corresponding to position 70; S at a position corresponding to position 70; T at a position corresponding to position 70; A at a position corresponding to position 74; C at a position corresponding to position 74; G at a position corresponding to position 74; N at a position corresponding to position 74; P at a position corresponding to position 74; R at a position corresponding to position 74; S at a position corresponding to position 74; V at a position corresponding to position 74; W at a position corresponding to position 74; G at a position corresponding to position 84; R at a position corresponding to position 84; G at a position corresponding to position 97; H at a position corresponding to position 127; N at a position corresponding to position 127; G at a position corresponding to position 131; V at a position corresponding to position 131; R at a position corresponding to position 142; A at a position corresponding to position 166; F at a position corresponding to position 166; H at a position corresponding to position 166; L at a position corresponding to position 166; R at a position corresponding to position 166; Y at a position corresponding to position 166; K at a position corresponding to

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 APPLICATION NO. .: 15/226,489
 DATED .: DECEMBER 15, 2020
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It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

position 174; K at a position corresponding to position 206; M at a position corresponding to position 213; N at a position corresponding to position 213; E at a position corresponding to position 237; S at a position corresponding to position 238; N at a position corresponding to position 261; R at a position corresponding to position 277; T at a position corresponding to position 277; L at a position corresponding to position 309; N at a position corresponding to position 309; Q at a position corresponding to position 309; R at a position corresponding to position 309; T at a position corresponding to position 309; A at a position corresponding to position 310; G at a position corresponding to position 310; H at a position corresponding to position 315; I at a position corresponding to position 317; K at a position corresponding to position 317; R at a position corresponding to position 317; M at a position corresponding to position 318; G at a position corresponding to position 347; S at a position corresponding to position 347; M at a position corresponding to position 399; T at a position corresponding to position 399; W at a position corresponding to position 399; D at a position corresponding to position 407; Q at a position corresponding to position 407; F at a position corresponding to position 419; I at a position corresponding to position 419; R at a position corresponding to

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PATENT NO. .: 10,865,400
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 DATED .: DECEMBER 15, 2020
 INVENTOR(S) .: WEI *ET AL.*

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

position 419; S at a position corresponding to position 419; K at a position corresponding to position 421; N at a position corresponding to position 421; Q at a position corresponding to position 421; R at a position corresponding to position 421; S at a position corresponding to position 421; A at a position corresponding to position 431; H at a position corresponding to position 431; K at a position corresponding to position 431; Q at a position corresponding to position 431; R at a position corresponding to position 431; S at a position corresponding to position 431; V at a position corresponding to position 431; L at a position corresponding to position 433; R at a position corresponding to position 433; V at a position corresponding to position 439; H at a position corresponding to position 440; R at a position corresponding to position 440; A at a position corresponding to position 443; M at a position corresponding to position 443; M at a position corresponding to position 445; and/or P at a position corresponding to position 445, with reference to amino acid positions set forth in SEQ ID NO:3; and

the modified PH20 polypeptide has at least 95% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7, and 32-66.

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PATENT NO. .: 10,865,400
 APPLICATION NO. .: 15/226,489
 DATED .: DECEMBER 15, 2020
 INVENTOR(S) .: WEI *ET AL.*

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

From column 304, line 55 to column 305, line 7, please replace claim 5 with the following amended claim:

5. The modified PH20 polypeptide of claim 4 comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 86, 99, 100, 159, 173, 181, 193, 195, 209-220, 238, 239, 242, 247-252, 267, 269, 308, 324, 325, 330, 335, 355, 419, 421-423, 425, 428, 435, 455, 462, 463, 484, 490, 506, 531, 533, 579, 581-583, 585, 587, 588, 602, 605, 606, 609, 613, 648, 731, 732, 734, 742, 746, 760, 762, 764, 765, 769-773, 779, 782, 783, 786-789, 794, 795, 814, 816, 819, 826, 830, 836, and 838, or an amino acid sequence that has at least 96% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 86, 99, 100, 159, 173, 181, 193, 195, 209-220, 238, 239, 242, 247-252, 267, 269, 308, 324, 325, 330, 335, 355, 419, 421-423, 425, 428, 435, 455, 462, 463, 484, 490, 506, 531, 533, 579, 581-583, 585, 587, 588, 602, 605, 606, 609, 613, 648, 731, 732, 734, 742, 746, 760, 762, 764, 765, 769-773, 779, 782, 783, 786-789, 794, 795, 814, 816, 819, 826, 830, 836, and 838, and that contains the amino acid replacement as compared to corresponding positions in a polypeptide of any of SEQ ID NOs: 3, 7, and 32-66.

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 APPLICATION NO. .: 15/226,489
 DATED .: DECEMBER 15, 2020
 INVENTOR(S) .: WEI *ET AL.*

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

From column 305, line 31 to column 306, line 25, please replace claim 14 with the following amended claim:

14. The modified PH20 polypeptide of claim 2, comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 73, 78, 91, 95, 96, 105, 106, 108, 109, 111, 112, 113, 115, 117, 118, 119, 120, 123-126, 128-136, 139-141, 149, 154, 155, 164, 165, 167, 191, 192, 196, 197, 199-205, 207, 208, 225, 226, 228, 229, 231, 233, 237, 253, 254, 256, 257, 277, 283, 293, 295, 296, 298, 300, 303, 316, 318, 321, 322, 338-340, 344, 348, 367, 369, 371, 377, 384-388, 394, 398, 399, 401, 406-408, 410, 412, 414, 416, 431, 448, 459, 465, 469, 478, 479, 482, 493, 497, 501, 503, 507, 508, 510-512, 514, 518, 522, 523, 537-543, 545, 558, 559, 561, 563-566, 569, 572, 574, 594, 596, 618-620, 624-634, 637, 640-644, 652, 657, 675, 695, 698, 699, 700, 712, 717, 725, 738, 748-750, 757, 775, 799-801, 807, 822, 825, 844, 847, 851, and 853, or an amino acid sequence that has at least 96% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 73, 78, 91, 95, 96, 105, 106, 108, 109, 111, 112, 113, 115, 117, 118, 119, 120, 123-126, 128-136, 139-141, 149, 154, 155, 164, 165, 167, 191, 192, 196, 197, 199-205, 207, 208, 225, 226, 228, 229, 231, 233, 237, 253, 254,

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APPLICATION NO. .: 15/226,489
DATED .: DECEMBER 15, 2020
INVENTOR(S) .: WEI *ET AL.*

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

256, 257, 277, 283, 293, 295, 296, 298, 300, 303, 316, 318, 321, 322, 338-340, 344, 348, 367, 369, 371, 377, 384-388, 394, 398, 399, 401, 406-408, 410, 412, 414, 416, 431, 448, 459, 465, 469, 478, 479, 482, 493, 497, 501, 503, 507, 508, 510-512, 514, 518, 522, 523, 537-543, 545, 558, 559, 561, 563-566, 569, 572, 574, 594, 596, 618-620, 624-634, 637, 640-644, 652, 657, 675, 695, 698, 699, 700, 712, 717, 725, 738, 748-750, 757, 775, 799-801, 807, 822, 825, 844, 847, 851, and 853, and that contains the amino acid replacement as compared to corresponding positions in a polypeptide of any of SEQ ID NOs:3, 7, and 32-66.

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Inventor(s): Wei *et al.*
Patent No. : 10,865,400
Issue Date : December 15, 2020
Serial No. : 15/226,489
Filed : August 02, 2016

Attorney Docket No.: 33320.03087.US25/3087B
Request for Certificate of Correction Pursuant to
37 C.F.R. §§ 1.322 and 1.323

COPIES OF PAGES 15, 26, 63, 82, 83, 98, 190, 198, 276, 277, AND 315 OF THE
SPECIFICATION AS ORIGINALLY FILED ON AUGUST 02, 2016

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Attorney Docket No.: 33320.03087.US25/3087B

corresponding to position 70; R at a position corresponding to position 70; S at a position
corresponding to position 70; T at a position corresponding to position 70; V at a position
corresponding to position 70; R at a position corresponding to position 71; S at a position
corresponding to position 71; M at a position corresponding to position 72; Q at a position
5 corresponding to position 72; H at a position corresponding to position 73; L at a position
corresponding to position 73; W at a position corresponding to position 73; A at a position
corresponding to position 74; C at a position corresponding to position 74; G at a position
corresponding to position 74; N at a position corresponding to position 74; P at a position
corresponding to position 74; R at a position corresponding to position 74; S at a position
10 corresponding to position 74; V at a position corresponding to position 74; W at a position
corresponding to position 74; F at a position corresponding to position 75; L at a position
corresponding to position 75; R at a position corresponding to position 75; T at a position
corresponding to position 75; G at a position corresponding to position 84; R at a position
corresponding to position 84; A at a position corresponding to position 86; C at a position
15 corresponding to position 87; T at a position corresponding to position 87; Y at a position
corresponding to position 87; C at a position corresponding to position 92; I at a position
corresponding to position 93; L at a position corresponding to position 93; R at a position
corresponding to position 93; T at a position corresponding to position 93; R at a position
corresponding to position 94; G at a position corresponding to position 97; Q at a position
20 corresponding to position 118; F at a position corresponding to position 120; V at a position
corresponding to position 120; Y at a position corresponding to position 120; H at a position
corresponding to position 127; N at a position corresponding to position 127; G at a position
corresponding to position 131; R at a position corresponding to position 131; V at a position
corresponding to position 131; D at a position corresponding to position 135; G at a position
25 corresponding to position 135; R at a position corresponding to position 135, with H at a
position corresponding to position 141; Y at a position corresponding to position 141; R at a
position corresponding to position 142; R at a position corresponding to position 147; V at a
position corresponding to position 147; K at a position corresponding to position 148; G at a
position corresponding to position 150; K at a position corresponding to position 151; L at a
30 position corresponding to position 151; M at a position corresponding to position 151; Q at a
position corresponding to position 151; R at a position corresponding to position 151; R at a
position corresponding to position 152; G at a position corresponding to position 155; K at a
position corresponding to position 155; D at a position corresponding to position 156; A at a
position corresponding to position 163; E at a position corresponding to position 163; K at a
35 position corresponding to position 163; R at a position corresponding to position 163; M at a
position corresponding to position 164; D at a position corresponding to position 165; N at a
position corresponding to position 165; A at a position corresponding to position 166; F at a

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Attorney Docket No.: 33320.03087.US25/3087B

212; A at a position corresponding to position 213; M at a position corresponding to position
213; N at a position corresponding to position 213; H at a position corresponding to position
215; M at a position corresponding to position 215; I at a position corresponding to position
219; K at a position corresponding to position 219; S at a position corresponding to position
5 219; H at a position corresponding to position 220; I at a position corresponding to position
220; L at a position corresponding to position 220; V at a position corresponding to position
220; Q at a position corresponding to position 221; G at a position corresponding to position
222; F at a position corresponding to position 232; G at a position corresponding to position
233; K at a position corresponding to position 233; R at a position corresponding to position
10 233; M at a position corresponding to position 234; A at a position corresponding to position
235; R at a position corresponding to position 236; C at a position corresponding to position
237; E at a position corresponding to position 237; H at a position corresponding to position
237; Q at a position corresponding to position 237; T at a position corresponding to position
237; E at a position corresponding to position 238; H at a position corresponding to amino
15 acid position 238; S at a position corresponding to position 238; A at a position corresponding
to position 240; Q at a position corresponding to position 240; I at a position corresponding to
position 247; A at a position corresponding to position 248; V at a position corresponding to
position 249; G at a position corresponding to position 257; T at a position corresponding to
position 257; R at a position corresponding to position 257; N at a position corresponding to
20 position 258; S at a position corresponding to position 258; P at a position corresponding to
position 259; M at a position corresponding to position 260; Y at a position corresponding to
position 260; A at a position corresponding to position 261; K at a position corresponding to
position 261; N at a position corresponding to position 261; K at a position corresponding to
position 263; R at a position corresponding to position 263; T at a position corresponding to
25 position 267; A at a position corresponding to position 269; L at a position corresponding to
position 271; M at a position corresponding to position 271; D at a position corresponding to
position 272; T at a position corresponding to position 272; H at a position corresponding to
position 273; Y at a position corresponding to position 273; F at a position corresponding to
position 274; D at a position corresponding to position 276; H at a position corresponding to
30 position 276; M at a position corresponding to position 276; R at a position corresponding to
position 276; S at a position corresponding to position 276; Y at a position corresponding to
position 276; A at a position corresponding to position 277; E at a position corresponding to
position 277; H at a position corresponding to position 277; K at a position corresponding to
position 277; M at a position corresponding to position 277; N at a position corresponding to
35 position 277; Q at a position corresponding to position 277; R at a position corresponding to
position 277; S at a position corresponding to position 277; T at a position corresponding to
position 277; E at a position corresponding to position 278; F at a position corresponding to

-- 26 --

its head. A zwitterionic surfactant contains a head with two oppositely charged groups. Some examples of common surfactants include: Anionic (based on sulfate, sulfonate or carboxylate anions): perfluorooctanoate (PFOA or PFO), perfluorooctane sulfonate (PFOS), sodium dodecyl sulfate (SDS), ammonium lauryl sulfate, and other alkyl sulfate salts, sodium laureth sulfate (also known as sodium lauryl ether sulfate, or SLES), alkyl benzene sulfonate; 5 cationic (based on quaternary ammonium cations): cetyl trimethylammonium bromide (CTAB) a.k.a. hexadecyl trimethyl ammonium bromide, and other alkyltrimethylammonium salts, cetylpyridinium chloride (CPC), polyethoxylated tallow amine (POEA), benzalkonium chloride (BAC), benzethonium chloride (BZT); Zwitterionic (amphoteric): dodecyl betaine; 10 cocamidopropyl betaine; coco amphoteric glycinate; nonionic: alkyl poly(ethylene oxide), alkylphenol poly(ethylene oxide), copolymers of poly(ethylene oxide) and poly(propylene oxide) (commercially known as Poloxamers or Poloxamines), alkyl polyglucosides, including octyl glucoside, decyl maltoside, fatty alcohols (*e.g.*, cetyl alcohol and oleyl alcohol), cocamide MEA, cocamide DEA, polysorbates (Tween 20, Tween 80, *etc.*), Triton detergents, 15 and dodecyl dimethylamine oxide.

As used herein, a "buffer" refers to a substance, generally a solution, that can keep its pH constant, despite the addition of strong acids or strong bases and external influences of temperature, pressure, volume or redox potential. A buffer prevents change in the concentration of another chemical substance, *e.g.*, proton donor and acceptor systems that 20 prevent marked changes in hydrogen ion concentration (pH). The pH values of all buffers are temperature and concentration dependent. The choice of buffer to maintain a pH value or range can be empirically determined by one of skill in the art based on the known buffering capacity of known buffers. Exemplary buffers include but are not limited to, bicarbonate buffer, cacodylate buffer, phosphate buffer or Tris buffer. For example, Tris buffer 25 (tromethamine) is an amine based buffer that has a pKa of 8.06 and has an effective pH range between 7.9 and 9.2. For Tris buffers, pH increases about 0.03 unit per °C temperature decrease, and decreases 0.03 to 0.05 unit per ten-fold dilution.

As used herein, the residues of naturally occurring α -amino acids are the residues of those 20 α -amino acids found in nature which are incorporated into protein by the specific 30 recognition of the charged tRNA molecule with its cognate mRNA codon in humans.

As used herein, nucleic acids include DNA, RNA and analogs thereof, including peptide nucleic acids (PNA) and mixtures thereof. Nucleic acids can be single or double-stranded. When referring to probes or primers, which are optionally labeled, such as with a detectable label, such as a fluorescent or radiolabel, single-stranded molecules are 35 contemplated. Such molecules are typically of a length such that their target is statistically unique or of low copy number (typically less than 5, generally less than 3) for probing or priming a library. Generally a probe or primer contains at least 14, 16 or 30 contiguous

hyaluronidases and is similar to the heparin binding motif. Mutation of the arginine residue at position 176 (corresponding to the mature PH20 polypeptide set forth in SEQ ID NO:3 or 7) to a glycine results in a polypeptide with only about 1% of the hyaluronidase activity of the wild type polypeptide (Arming *et al.*, (1997) *Eur. J. Biochem.* 247:810-814).

5 PH20 polypeptides contain a glycosyl phosphatidylinositol (GPI) anchor attached to the C-terminus of the protein that anchors the protein to the extracellular leaflet of the plasma membrane of cells. At least human, monkey, mouse and guinea pig PH20 are strongly attached to the plasma membrane via the GPI anchor, which can be released by treating with phosphatidylinositol-specific phospholipase C (PI-PLC; see *e.g.*, Lin *et al.* (1994) *Journal of*
10 *Cell Biology*, 125:1157-1163; Lin *et al.* (1993) *Proc. Natl. Acad. Sci.*, 90:10071-10075). Other PH20 enzymes, such as bovine PH20, are loosely attached to the plasma membrane and are not anchored via a phospholipase sensitive anchor. As discussed below, soluble active forms that, when expressed, are not attached to the membrane but are secreted can be generated by removal of all of a portion of the GPI anchor attachment signal site (see *also*
15 U.S. Patent No. 7,767,429; U.S. Publication No. US20100143457). These include, for example, soluble PH20 polypeptides set forth in any of SEQ ID NOS: 3 or 32-66, or precursor forms thereof containing a signal sequence.

GPI-anchored proteins, for example human PH20, are translated with a cleavable N-terminal signal peptide that directs the protein to the endoplasmic reticulum (ER). At the C-terminus of these proteins is another signal sequence that directs addition of a preformed GPI-
20 anchor to the polypeptide within the lumen of the ER. Addition of the GPI anchor occurs following cleavage of the C-terminal portion at a specific amino acid position, called the ω -site (typically located approximately 20-30 amino acids from the C-terminus). Although there appears to be no consensus sequence to identify the location of the ω -site, GPI anchored
25 proteins contain a C-terminal GPI-anchor attachment signal sequence or domain that typically contains a predominantly hydrophobic region of 8-20 amino acids, preceded by a hydrophilic spacer region of 8-12 amino acids immediately downstream of the ω -site. This hydrophilic spacer region often is rich in charged amino acids and proline (White *et al.* (2000) *J. Cell Sci.* 113(Pt.4):721-727). There is generally a region of approximately 11 amino acids before the
30 ω -1 position that is characterized by a low amount of predicted secondary structure, a region around the cleavage site (ω -site), from ω -1 to ω +2 that is characterized by the presence of small side chain residues, the spacer region between positions ω +3 and ω +9, and a hydrophobic tail from ω +10 to the C-terminal end (Pierleoni *et al.*, (2008) *BMC Bioinformatics* 9:392).

35 Although there is no GPI-anchor attachment signal consensus sequence, various *in silico* methods and algorithms have been developed that can be used to identify such sequences in polypeptides (see, *e.g.*, Udenfriend *et al.* (1995) *Methods Enzymol.* 250:571-582;

Eisenhaber *et al.* (1999) *J. Mol. Chem.* 292: 741-758; Kronegg and Buloz, (1999),

"Detection/prediction of GPI cleavage site (GPI-anchor) in a protein (DGPI),"

129.194.185.165/dgpi/; Fankhauser *et al.* (2005) *Bioinformatics* 21:1846-1852;

Omaetxebarria *et al.* (2007) *Proteomics* 7:1951-1960; Pierleoni *et al.* (2008) *BMC*

- 5 *Bioinformatics* 9:392), including those that are readily available on bioinformatic websites, such as the ExPASy Proteomics tools site (expasy.ch/tools/). Thus, one of skill in the art can determine whether a PH20 polypeptide likely contains a GPI-anchor attachment signal sequence, and, therefore, whether the PH20 polypeptide is a GPI-anchored protein.

- The covalent attachment of a GPI-anchor to the C-terminus of human PH20 and, therefore, the membrane-bound nature of PH20, has been confirmed using phosphatidylinositol-specific phospholipase C (PI-PLC) hydrolysis studies (see *e.g.*, Lin *et al.*, (1994) *J. Biol. Chem.* 125:1157-1163). Phosphatidylinositol-specific phospholipase C (PI-PLC) and D (PI-PLD) hydrolyze the GPI anchor, releasing the PH20 polypeptide from the cell membrane. The prior art literature reports that a ω -site cleavage site of human PH20 is identified between Ser-490 and Ala-491 and for monkey PH20 is identified between Ser491 and Thr492 (Lin *et al.* (1993) *Proc. Natl. Acad. Sci.* (1993) 90:10071-10075). Thus, the literature reports that a GPI-anchor attachment signal sequence of human PH20 is located at amino acid positions 491-509 of the precursor polypeptide set forth in SEQ ID NO:6, and the ω -site is amino acid position 490. Thus, in this modeling of human PH20, amino acids 491-509 are cleaved following transport to the ER and a GPI anchor is covalently attached to the serine residue at position 490.
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2. Function

- PH20 is normally expressed in sperm from a single testis-specific gene. PH20 is a sperm-associated protein involved in fertilization. PH20 is normally localized on the sperm surface, and in the lysosome-derived acrosome, where it is bound to the inner acrosomal membrane. PH20 is multifunctional and exhibits hyaluronidase activity, hyaluronan (HA)-mediated cell-signaling activity, and acts as a sperm receptor for the zona pellucida surrounding the oocyte when present on acrosome reacted (AR) sperm. For example, PH20 is naturally involved in sperm-egg adhesion and aids penetration by sperm of the layer of cumulus cells by digesting hyaluronic acid. In addition to being a hyaluronidase, PH20 also appears to be a receptor for HA-induced cell signaling, and a receptor for the zona pellucida surrounding the oocyte. Due to the role of PH20 in fertilization, PH20 can be used as an antigen for immunocontraception.
- 25
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- PH20 is a neutral active hyaluronidase, although it can exhibit acid-active activity in some cases. The hyaluronidase activity of PH20 is exhibited by the plasma membrane- and inner acrosomal membrane-associated PH20. The plasma membrane PH20 exhibits hyaluronidase activity only at neutral pH, while the inner acrosomal membrane-associated
- 35

at position 1 (L1), P6, V8, I9, P10, N11, V12, F14, L15, A20, S22, F24, L26, G27, K28, F29, D30, E31, P32, L33, D34, M35, S36, L37, F38, S39, F40, I41, I46, N47, A48, T49, G50, G52, V58, D59, Y63, I67, D68, S69, I70, T71, G72, V73, T74, V75, I79, K82, I83, S84, G86, D87, L89, D90, A92, K93, K94, T97, V102, N104, M107, E114, T118, A120, D127, V128, 5 K130, N131, R132, E135, Q138, Q139, Q140, N141, V142, Q143, L144, L146, T147, E148, A149, T150, E151, K152, Q155, E156, E158, A160, K162, D163, F164, L165, V166, E167, I169, K170, G172, K173, L174, L175, N178, H179, H193, K195, K196, G198, F204, N205, V206, K209, D212, D213, S215, N219, E220, S221, T222, T232, Q233, Q234, S235, P236, V237, A238, T240, V247, R248, E249, P257, D258, A259, K260, S261, L263, A267, T269, 10 I271, V272, F273, T274, Q276, V277, L278, K279, S282, Q283, E285, V287, T289, G291, E292, T293, A298, G305, L307, S308, I309, M310, M313, K314, S315, L317, L318, D320, N321, E324, T325, I326, N328, T335, Q347, Q349, V351, I353, N356, S359, P367, D368, N369, A371, Q373, L374, E375, K376, G377, F380, T381, R383, K385, E389, E392, Q393, S395, E396, Y399, S401, S404, T405, L406, S407, K409, E410, A412, D416, D418, A419, 15 D421, A425, G427, A428, D431, F433, P436, P437, M438, E439, T440, E441, E442, P443, Q444, I445, F446 or Y447 with reference to amino acid positions set forth in SEQ ID NO:3.

Exemplary amino acid replacements in the modified PH20 polypeptides provided herein include, but are not limited, replacement with: histidine (H) at a position corresponding to position 1; A at a position corresponding to position 1; E at a position corresponding to position 1; G at a position corresponding to position 1; K at a position corresponding to position 1; Q at a position corresponding to position 1; R at a position corresponding to position 1; A at a position corresponding to position 6; M at a position corresponding to position 8; Q at a position corresponding to position 9; G at a position corresponding to position 10; H at a position corresponding to position 10; S at a position corresponding to position 11; E at a position corresponding to position 12; I at a position corresponding to position 12; K at a position corresponding to position 12; T at a position corresponding to position 12; V at a position corresponding to position 14; V at a position corresponding to position 15; M at a position corresponding to position 15; S at a position corresponding to position 20; T at a position corresponding to position 22; E at a position corresponding to position 24; H at a position corresponding to position 24; R at a position corresponding to position 24; A at a position corresponding to position 26; E at a position corresponding to position 26; K at a position corresponding to position 26; M at a position corresponding to position 26; Q at a position corresponding to position 26; R at a position corresponding to position 26; D at a position corresponding to position 27; K at a position corresponding to position 27; R at a position corresponding to position 27; R at a position corresponding to position 28; E at a position corresponding to position 29; I at a position corresponding to position 29; K at a position corresponding to position 29; L at a position corresponding to

buffering agent that maintains the pH range of between or about between 7.0 to 7.8; 0.1% to 0.4% preservative as a mass concentration (w/v). Optionally, a further stabilizing agent can be included. For example, the co-formulations provided herein contain 1 mM to 100 mM of a buffering agent. For example, the co-formulations provided herein contain 0.005% to 0.5% surfactant. Exemplary co-formulations provided herein also can contain less than 60 mM glycerin (glycerol) and 2 mM to or to about 50 mM of an antioxidant.

The following stable formulations are exemplary only and provide a platform from which minor adjustments can be made. It is understood that very small changes in the concentrations of the various excipients and other components (*e.g.*, $\pm 15\%$ of the stated concentrations), or small changes in pH, can be made while retaining some if not all of the insulin solubility and stability and PH20 stability. Further changes also can be made by adding or removing excipients. For example, the type of stabilizing surfactant can be changed.

For example, the exemplary co-formulations herein contain 100 U/mL to 1000 U/mL of a modified PH20 polypeptide, and in particular at least or about at least or about 600 U/mL of a modified PH20 polypeptide; 10 U/mL to 1000 U/mL of a fast-acting insulin, and in particular at least or about at least or about 100 U/mL of a fast-acting insulin; from or from about 10 mM to or to about 50 mM Tris (*e.g.*, from or from about 20 mM to 40 mM Tris, such as or as about 20 mM, 25 mM, 30 mM, 35 mM or 40 mM Tris); from or from about 80 mM to or to about 160 mM NaCl (*e.g.*, at or about 80 mM, 90 mM, 100 mM, 110 mM 120 mM, 130 mM, 140 mM, 150 mM or 160 mM NaCl); from or from about 2 mM to or to about 50 mM methionine (*e.g.*, at or about 5 mM, 10 mM, 20 mM, 30 mM, 40 mM or 50 mM methionine); from or from about 0 mM to or to about 50 mM glycerin (*e.g.*, at or about 5 mM, 10 mM, 20 mM, 30 mM, 40 mM or 50 mM glycerin); from or from about 0.005% to or to about 0.5% poloxamer 188, such as 0.01% to 0.05% (*e.g.*, at or about 0.01%, 0.02%, 0.03%, 0.04% or 0.05% poloxamer 188); from or from about 0.05% to or to about 0.25% phenol (*e.g.*, at or about 0.1%, 0.12%, 0.125%, 0.13%, 0.14%, 0.15%, 0.16% or 0.17% phenol); and from or from about 0.05% to or to about 0.4% m-cresol (*e.g.*, at or about 0.075%, 0.08%, 0.09%, 0.1%, 0.12%, 0.13%, 0.14%, 0.15%, 0.16% or 0.17% m-cresol). The formulations are prepared with a pH from or from about 7.0 to or to about 7.6 (*e.g.*, at or about pH 7.0, 7.1, 7.2, 7.3, 7.4, 7.5 or 7.6). In further examples, zinc is included at a concentration of or about 0.017 mg/100 U, 0.018 mg/100 U, 0.02 mg/100 U, 0.022 mg/100 U or 0.024 mg/100 U insulin.

In particular examples, the fast acting insulin is insulin aspart, insulin lispro or insulin glulisine. Exemplary co-formulations provided herein that contain a modified PH20 polypeptide and insulin lispro are those that contain from or about 25 mM to or to about 35 mM Tris (*e.g.*, at or about 30 mM Tris); from or from about 70 mM to or to about 100 mM

hyaluronidase. Hylenex® (Halozyme Therapeutics) is a human recombinant hyaluronidase produced by genetically engineered Chinese Hamster Ovary (CHO) cells containing nucleic acid encoding for soluble rHuPH20 (see e.g., U.S. Patent No. 7,767,429). Approved therapeutic uses for hyaluronidases include use as an adjuvant to increase the absorption and dispersion of other therapeutic agents for hypodermoclysis (subcutaneous fluid administration), and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents. In addition to these indications, hyaluronidases can be used as a therapeutic or cosmetic agent for the treatment of additional diseases and conditions. For example, hyaluronidase is commonly used, for example, for peribulbar block in local anesthesia prior ophthalmic surgery. The presence of the enzyme prevents the need for additional blocks and reduces the time to the onset of akinesia (loss of eye movement). Peribulbar and sub-Tenon's block are the most common applications of hyaluronidase for ophthalmic procedures. Hyaluronidase also can promote akinesia in cosmetic surgery, such as blepharoplasties and face lifts. It is understood that soluble PH20 hyaluronidases provided herein, including esPH20 hyaluronidases, can be used in any method of treatment or combination therapy for which a PH20 hyaluronidase is used (see e.g., U.S. Publication Nos. US20040268425; US20050260186; US20060104968; and U.S. Appl. Serial Nos. 12/381,844, published as U.S. Publication No. US20100074885; 12/386,249, published as U.S. Publication No. US20090311237; 12/387,225, published as U.S. Publication No. US20090304665; and 12/386,222, published as U.S. Publication No. US2010003238, each incorporated by reference in their entirety).

Exemplary, non-limiting, methods and uses are described in the following subsections.

1. Methods of Delivering Therapeutic Agents

As noted above, hyaluronidase is a spreading or diffusing substance that modifies the permeability of connective tissue through the hydrolysis of hyaluronic acid, a polysaccharide found in the intercellular ground substance of connective tissue, and of certain specialized tissues, such as the umbilical cord and vitreous humor. When no spreading factor is present, materials injected subcutaneously, such as drugs, proteins, peptides and nucleic acid, spread very slowly. Co-injection with hyaluronidase, however, can cause rapid spreading. The rate of diffusion is proportional to the amount of enzyme, and the extent of diffusion is proportional to the volume of solution.

Modified PH20 polypeptides provided herein can be used to promote or enhance the delivery agents and molecules to any of a variety of mammalian tissues *in vivo*. It can be used to facilitate the diffusion and, therefore, promote the delivery, of small molecule pharmacologic agents as well as larger molecule pharmacologic agents, such as proteins, nucleic acids and ribonucleic acids, and macromolecular compositions than can contain a

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TABLE 10: Inactive Mutants

A017G	G077L	L144Q	C203N	E249G	G300Q	Q347C	E392C
A017H	G077P	L144S	C203Q	E249H	G300S	Q347F	E392P
A017I	G077Q	L144V	C203R	E249I	G300T	Q347I	Q393C
A017L	G077R	L144Y	C203S	E249K	G300V	Q347P	Q393P
A017N	G077T	S145T	C203T	E249M	G300W	Q347T	F394A
A017P	G077V	S145W	C203V	E249Q	I301E	Q347V	F394D
A017Q	G078A	A149E	F204A	E249S	I301G	Q347W	F394E
A017R	G078D	A149P	F204C	E249Y	I301H	E348C	F394G
A017S	G078I	T150V	F204E	A250C	I301K	E348H	F394I
A017T	G078M	K152L	F204G	A250F	I301M	E348I	F394K
A017V	G078P	A153E	F204H	A250G	I301N	E348L	F394N
A017W	G078T	A153F	F204I	A250H	I301P	E348P	F394P
A017Y	G078Y	A153M	F204K	A250K	I301Q	E348Q	F394Q
W018C	I079A	A153P	F204Q	A250L	I301R	E348R	F394R
W018D	I079D	A153R	F204R	A250M	I301S	E348T	F394S
W018F	I079F	A153T	F204S	A250N	I301W	E348V	F394T
W018G	I079G	A153V	F204T	A250P	I301Y	E348W	F394V
W018H	I079H	K154D	V206C	A250Q	V302C	E348Y	S395C
W018I	I079K	K154E	V206D	A250R	V302D	Q349D	S395L
W018L	I079N	K154G	V206F	A250S	V302E	Q349F	S395M
W018M	I079P	K154P	V206G	A250T	V302F	Q349G	S395P
W018P	I079S	K154S	V206P	A250V	V302G	Q349P	E396C
W018Q	I079W	K154W	V206Y	A250W	V302H	Q349V	E396F
W018S	I079Y	K154Y	E207A	I251D	V302L	Q349W	E396G
W018T	P080A	Q155P	E207F	I251F	V302M	Q349Y	E396I
W018V	P080D	Q155Y	E207G	I251G	V302P	G350A	E396P
W018Y	P080E	E156P	E207M	I251H	V302R	G350D	E396Y
N019A	P080F	F157A	E207P	I251K	V302S	G350E	K397A
N019C	P080G	F157C	E207Q	I251P	V302T	G350F	K397C
N019F	P080I	F157D	E207R	I251S	V302Y	G350H	K397E
N019G	P080K	F157E	E207S	I251T	I303A	G350K	K397F
N019H	P080L	F157G	E207T	I251W	I303C	G350L	K397G
N019I	P080M	F157H	E207V	R252A	I303D	G350M	K397I
N019L	P080N	F157I	E207W	R252D	I303E	G350N	K397L
N019M	P080R	F157K	I208D	R252E	I303F	G350P	K397M
N019P	P080S	F157L	I208G	R252F	I303G	G350R	K397P
N019Q	P080T	F157M	I208P	R252G	I303K	G350S	K397Q
N019R	P080V	F157P	I208W	R252H	I303L	G350T	K397T
N019S	P080Y	F157Q	K209C	R252I	I303M	G350V	K397V
N019V	Q081A	F157R	K209P	R252K	I303R	G350Y	F398A
N019W	Q081C	F157S	R210A	R252L	I303W	V351C	F398C
N019Y	Q081E	F157T	R210C	R252N	I303Y	V351D	F398E
A020D	Q081G	F157V	R210D	R252P	W304A	V351E	F398G

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TABLE 10: Inactive Mutants							
A020E	Q081H	E158D	R210E	R252S	W304C	V351F	F398H
A020F	Q081L	E158K	R210G	R252T	W304D	V351H	F398I
A020H	Q081N	E158P	R210K	R252Y	W304G	V351N	F398L
A020K	Q081P	E158R	R210M	V253A	W304I	V351R	F398N
A020L	Q081S	E158Y	R210N	V253D	W304M	V351W	F398P
A020N	Q081V	K159W	R210P	V253E	W304N	V351Y	F398R
A020P	Q081W	K159Y	R210S	V253G	W304P	C352A	F398S
A020R	Q081Y	G161W	R210T	V253H	W304Q	C352D	F398T
A020T	K082W	D163C	R210V	V253L	W304S	C352E	F398V
A020V	K082Y	D163P	R210W	V253M	W304T	C352F	F398W
A020Y	I083E	F164A	R210Y	V253N	W304V	C352G	F398Y
P021A	I083K	F164C	N211C	V253Q	W304Y	C352K	Y399D
P021C	S084Y	F164D	N211F	V253R	G305L	C352M	Y399P
P021D	L085A	F164E	N211G	V253S	G305P	C352P	C400A
P021E	L085C	F164G	N211H	V253W	G305Q	C352Q	C400D
P021G	L085D	F164H	N211I	S254C	G305R	C352R	C400E
P021H	L085E	F164N	N211K	S254D	G305S	C352S	C400F
P021I	L085F	F164P	N211M	S254E	G305T	C352T	C400G
P021L	L085G	F164Q	N211P	S254G	G305V	C352V	C400I
P021M	L085H	F164R	N211R	S254I	G305Y	C352W	C400L
P021R	L085N	L165C	N211S	S254K	T306A	C352Y	C400M
P021S	L085Q	L165H	N211T	S254L	T306C	I353C	C400P
P021T	L085S	L165P	N211V	S254P	T306H	I353F	C400Q
P021V	L085T	L165T	N211W	S254Q	T306I	I353G	C400R
P021W	Q086C	V166D	D212A	S254R	T306L	I353H	C400S
S022C	Q086P	E167V	D212G	S254T	T306V	I353K	C400T
S022E	D087P	T168A	D212H	S254V	T306W	I353L	C400V
S022G	H088A	T168C	D212I	S254W	T306Y	I353M	C400Y
S022K	H088C	T168D	D212K	S254Y	L307C	I353Q	S401C
S022P	H088E	T168E	D212L	K255C		I353R	S401F
E023A	H088F	T168F	D212M	K255D	L307I	I353S	S401H
E023F	H088G	T168G	D212P	K255L	L307P	I353W	S401K
E023L	H088I	T168K	D212V	K255P	S308C	R354C	S401R
E023M	H088K	T168L	D212W	K255V	S308F	R354D	S401W
E023N	H088L	T168P	D213P	K255W	S308L	R354E	S401Y
E023P	H088M	T168R	D213S	I256C	S308M	R354G	C402A
E023R	H088P	T168S	L214A	I256D	S308V	R354H	C402D
E023S	H088R	T168V	L214C	I256E	S308W	R354I	C402E
E023T	H088S	T168W	L214D	I256G	S308Y	R354K	C402F
E023V	H088T	T168Y	L214E	I256P	M310C	R354L	C402L
C025D	H088V	I169A	L214G	P257D	M310E	R354M	C402M
C025E	H088Y	I169D	L214H	D258L	M310F	R354P	C402P
C025F	L089A	I169F	L214K	D258P	M310K	R354Q	C402Q

media containing 4 µg/mL hexadimethrine bromide at a final concentration of 4 µg/mL (Polybrene; SIGMA). Virus was added to each well at a multiplicity of infection (MOI) of 10 and the cells were incubated with shaking (120 rpm) at 37 °C and 5% CO₂ for 6 hours. The cells were then harvested and pelleted by low speed centrifugation (500 x g, 5 min). The transduction medium was removed and replaced with 10 mL of fresh CHO-S medium (Invitrogen) supplemented with GlutaMax (50 mL/liter) and transferred to a T-25 flask. Three days post infection, blasticidin (Invitrogen) was added to the growth medium at a concentration of 1 µg/mL. The medium was changed regularly at 3-4 day intervals, and the cells were transferred to a T75 flask for expansion. Two weeks after the initial infection, the cells were expanded to shaker flasks and maintained in culture using medium containing 1 µg/mL blasticidin. F204P-PH20 protein secreted into the CHO-S medium was collected and purified by affinity chromatography using an anti-rHuPH20 affinity column as described in Example 6. The protein was prepared in standard API buffer (10 mM Histidine, 130 mM NaCl, pH 6.5).

EXAMPLE 13

ANALYSIS OF SECONDARY STRUCTURE AND MELTING TEMPERATURE

The secondary structure and melting temperature of the PH20 variant F204P was tested and compared to wild-type rHuPH20 (generated as described in Example 1) to further assess stability of the variant. The secondary structure was tested by circular dichroism. A Jasco J-810-150S equipped with PTC-424S was employed for the CD spectral measurement and the CD spectra were collected by Spectra Manager (Version 1.5, Jasco). Procedures for instrumental set up and data collection are described in Table 24.

Table 24: CD Spectroscopy Operation Conditions	
Parameters	Conditions
Nitrogen flow rate	25 ft ³ /h
Sample temperature	30-75 °C
Sample concentration	Approx. 0.1 mg/mL
Cell pathlength	1 mm
Wavelength	220 nm
Data pitch	1 °C
Delay time	60 seconds
Temperature slope	1 °C/min
Sensitivity	standard
Response	4 seconds
Band width	1 nm

1. Sample Preparation and Measurement

Two hundred (200) µL of a 0.1 mg/mL protein sample diluted in Mcllvaine's buffer (Mcllvaine (1921) JBC 49:183) adjusted to pH 6.5 were prepared. A series of samples of the F204P variant were also generated that varied in pH by adjustment using Mcllvaine's buffer

Inventor(s): Wei *et al.*
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Request for Certificate of Correction Pursuant to
37 C.F.R. §§ 1.322 and 1.323

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THE EXAMINER ON APRIL 26, 2019 AND MAILED ON MAY 15, 2019

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Substitute Form PTO-1449 (Modified)		U.S. Department of Commerce Patent and Trademark Office		Attorney Docket No. 33320.03087.US25/ 3087B		Application No. 15/226,489	
List of Patents and Publications for Applicant's Information Disclosure Statement				Applicant Wei <i>et al.</i>			
				Filing Date August 02, 2016		Group Art Unit 1652	
(37 CFR §1.98(b))							
Other Documents (include Author, Title, Date, and Place of Publication)							
Examiner Initial	Desig. ID	Document					
	IF**	Girish et al., "Hyaluronidase inhibitors: a biological and therapeutic perspective," <i>Curr Med Chem</i> 16(18):2261-2288 (2009).					
	IG**	Gmachl et al., "The human sperm protein PH-20 has hyaluronidase activity," <i>FEBS</i> 336(3):545-548 (1993).					
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	II**	Grbskov et al., "Sigma factors from <i>E. coli</i> , <i>B. subtilis</i> , phage SP01, and phage T4 are homologous proteins," <i>Nucl. Acids Res.</i> 14(16):6745-6763 (1986).					
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	IT**	Hartman S. and R. Mulligan, "Two dominant-acting selectable markers for gene transfer studies in mammalian cells," <i>Proc Natl Acad Sci</i> 85:8047-8051 (1988).					
	IU**	Have et al., "Cloning and characterization of the cDNA encoding the PH20 protein in the European red fox <i>Vulpes vulpes</i> ," <i>Reproduct Fertil Dev</i> 10:165-172 (1998).					
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	JA**	Hooper et al., "Determination of glycosyl-phosphatidylinositol membrane protein anchorage" <i>Proteomics</i> 1:748-755 (2001)					
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Examiner Signature /SAMUEL W LIU/	Date Considered 04/26/2019
EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.W.L/

Inventor(s): Wei *et al.*
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Issue Date : December 15, 2020
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Request for Certificate of Correction Pursuant to
37 C.F.R. §§ 1.322 and 1.323

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1.312 SUBMITTED ON OCTOBER 01, 2020

AMENDMENTS TO THE CLAIMS:

Please amend claims 1-5, as indicated below. This listing of claims replaces all prior versions and listing of claims in the application.

LISTING OF CLAIMS:

1. (Currently Amended) A modified PH20 polypeptide, comprising one or more amino acid replacements in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NOS: 3, 7, and 32-66;

the modified PH20 polypeptide exhibits increased hyaluronidase activity that is at least 120% of the hyaluronidase activity compared to the unmodified PH20 polypeptide not containing the amino acid replacement(s); wherein:

the activity of the unmodified PH20 polypeptide not containing the replacement(s) is 100%;

hyaluronidase activity of the modified PH20 polypeptide and hyaluronidase activity of the unmodified PH20 polypeptide are measured under identical conditions;

the amino acid replacement(s) confer(s) the increased hyaluronidase activity;

at least one amino acid replacement(s) confers the increased hyaluronidase activity, and is/are at a position corresponding to a position selected from 1, 15, 24, 27, 29, 30, 31, 32, 33, 37, 39, 48, 63, 67, 69, 71, 72, 73, 75, 87, 92, 93, 94, 118, 120, 135, 141, 147, 148, 150, 151, 152, 155, 156, 163, 164, 165, 170, 198, 209, 212, 215, 219, 233, 236, 247, 257, 259, 260, 263, 269, 271, 272, 276, 278, 282, 293, 305, 308, 313, 320, 324, 325, 326, 328, 353, 359, 371, 377, 380, 389, 392, 395, 405, 409, 410, 418, 425, 436, 437, 438, 441, 442, 446, and 447, with reference to amino acid positions set forth in SEQ ID NO:3; ~~which confers the increased hyaluronidase activity;~~

corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the sequence of amino acids set forth as SEQ ID NO:3, with the proviso that if the modified PH20 polypeptide includes only a single amino acid replacement, the replacement does not correspond to amino acid replacement N219A with reference to amino acid positions set forth in SEQ ID NO:3; and

the modified PH20 polypeptide has at least 95% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOS: 3, 7, and 32-66.

2. (Currently Amended) The modified PH20 polypeptide of claim 1, comprising at least one amino acid replacement selected from among replacement with:

~~histidine (H)~~ at a position corresponding to position 1; Q at a position corresponding to position 1; V at a position corresponding to position 15; E at a position corresponding to position 24; H at a position corresponding to position 24; K at a position corresponding to position 27; R at a position corresponding to position 27; E at a position corresponding to position 29; I at a position corresponding to position 29; L at a position corresponding to position 29; M at a position corresponding to position 29; P at a position corresponding to position 29; S at a position corresponding to position 29; V at a position corresponding to position 29; G at a position corresponding to position 30; H at a position corresponding to position 30; K at a position corresponding to position 30; M at a position corresponding to position 30; R at a position corresponding to position 30; S at a position corresponding to position 30; A at a position corresponding to position 31; C at a position corresponding to position 31; H at a position corresponding to position 31; I at a position corresponding to position 31; K at a position corresponding to position 31; L at a position corresponding to position 31; P at a position corresponding to position 31; R at a position corresponding to position 31; S at a position corresponding to position 31; T at a position corresponding to position 31; V at a position corresponding to position 31; F at a position corresponding to position 32; G at a position corresponding to position 32; H at a position corresponding to position 32; W at a position corresponding to position 33; F at a position corresponding to position 37; N at a position corresponding to position 39; T at a position corresponding to position 39; F at a position corresponding to position 48; H at a position corresponding to position 48; N at a position corresponding to position 48; W at a position corresponding to position 63; V at a position corresponding to position 67; A at a position corresponding to position 69; C at a position corresponding to position 69; F at a position corresponding to position 69; G at a position corresponding to position 69; I at a position corresponding to position 69; L at a position corresponding to position 69; M at a position corresponding to position 69; P at a position corresponding to position 69; R at a position corresponding to position 69; W at a position corresponding to position 69; Y at a position corresponding to position 69; R at a position corresponding to position 71; S at a position corresponding to position 71; M at a position corresponding to position 72; Q at a position corresponding to position 72; H at a position corresponding to position 73; L at a position corresponding to position 73; W at a position corresponding to position 73; F at a position corresponding to position 75; L at a position corresponding to position 75; R at a position corresponding to position 75; T at a position corresponding to position 75; C at a position corresponding to

position 87; T at a position corresponding to position 87; Y at a position corresponding to position 87; C at a position corresponding to position 92; I at a position corresponding to position 93; L at a position corresponding to position 93; R at a position corresponding to position 93; T at a position corresponding to position 93; R at a position corresponding to position 94; Q at a position corresponding to position 118; F at a position corresponding to position 120; V at a position corresponding to position 120; Y at a position corresponding to position 120; D at a position corresponding to position 135; G at a position corresponding to position 135; R at a position corresponding to position 135; H at a position corresponding to position 141; Y at a position corresponding to position 141; R at a position corresponding to position 147; V at a position corresponding to position 147; K at a position corresponding to position 148; G at a position corresponding to position 150; K at a position corresponding to position 151; L at a position corresponding to position 151; M at a position corresponding to position 151; Q at a position corresponding to position 151; R at a position corresponding to position 151; R at a position corresponding to position 152; G at a position corresponding to position 155; K at a position corresponding to position 155; D at a position corresponding to position 156; A at a position corresponding to position 163; E at a position corresponding to position 163; K at a position corresponding to position 163; R at a position corresponding to position 163; M at a position corresponding to position 164; D at a position corresponding to position 165; N at a position corresponding to position 165; R at a position corresponding to position 170; D at a position corresponding to position 198; N at a position corresponding to position 212; M at a position corresponding to position 215; S at a position corresponding to position 219; K at a position corresponding to position 233; R at a position corresponding to position 233; R at a position corresponding to position 236; I at a position corresponding to position 247; T at a position corresponding to position 257; P at a position corresponding to position 259; Y at a position corresponding to position 260; K at a position corresponding to position 263; R at a position corresponding to position 263; A at a position corresponding to position 269; L at a position corresponding to position 271; M at a position corresponding to position 271; T at a position corresponding to position 272; D at a position corresponding to position 276; S at a position corresponding to position 276; Y at a position corresponding to position 276; H at a position corresponding to position 278; K at a position corresponding to position 278; N at a position corresponding to position 278; R at a position corresponding to position 278; S at a position corresponding to position 278; T at a position corresponding to position 278; Y at a position corresponding to position 278; M at a position corresponding to

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NOS: 3, 7, and 32-66;

the modified PH20 polypeptide exhibits increased hyaluronidase activity that is at least 120% of the hyaluronidase activity compared to the unmodified PH20 polypeptide not containing the amino acid replacement(s); wherein:

the activity of the unmodified PH20 polypeptide not containing the replacement(s) is 100%;

hyaluronidase activity of the modified PH20 polypeptide and hyaluronidase activity of the unmodified PH20 polypeptide are measured under identical conditions;

at least one amino acid replacement confers the increased hyaluronidase activity, and is selected from E at a position corresponding to position 12; E at a position corresponding to position 26; K at a position corresponding to position 26; R at a position corresponding to position 46; Q at a position corresponding to position 52; Q at a position corresponding to position 58; H at a position corresponding to position 68; Q at a position corresponding to position 68; A at a position corresponding to position 70; C at a position corresponding to position 70; F at a position corresponding to position 70; G at a position corresponding to position 70; H at a position corresponding to position 70; K at a position corresponding to position 70; L at a position corresponding to position 70; N at a position corresponding to position 70; P at a position corresponding to position 70; R at a position corresponding to position 70; S at a position corresponding to position 70; T at a position corresponding to position 70; A at a position corresponding to position 74; C at a position corresponding to position 74; G at a position corresponding to position 74; N at a position corresponding to position 74; P at a position corresponding to position 74; R at a position corresponding to position 74; S at a position corresponding to position 74; V at a position corresponding to position 74; W at a position corresponding to position 74; G at a position corresponding to position 84; R at a position corresponding to position 84; G at a position corresponding to position 97; H at a position corresponding to position 127; N at a position corresponding to position 127; G at a position corresponding to position 131; V at a position corresponding to position 131; R at a position corresponding to position 142; A at a position corresponding to position 166; F at a position corresponding to position 166; H at a position corresponding to position 166; L at a position corresponding to position 166; R at a position corresponding to position 166; Y at a position corresponding to position 166; K at a position corresponding to position 174; K at a position corresponding to position 206; M at a position corresponding to

position 213; N at a position corresponding to position 213; E at a position corresponding to position 237; S at a position corresponding to position 238; N at a position corresponding to position 261; R at a position corresponding to position 277; T at a position corresponding to position 277; L at a position corresponding to position 309; N at a position corresponding to position 309; Q at a position corresponding to position 309; R at a position corresponding to position 309; T at a position corresponding to position 309; A at a position corresponding to position 310; G at a position corresponding to position 310; H at a position corresponding to position 315; I at a position corresponding to position 317; K at a position corresponding to position 317; R at a position corresponding to position 317; M at a position corresponding to position 318; G at a position corresponding to position 347; S at a position corresponding to position 347; M at a position corresponding to position 399; T at a position corresponding to position 399; W at a position corresponding to position 399; D at a position corresponding to position 407; Q at a position corresponding to position 407; F at a position corresponding to position 419; I at a position corresponding to position 419; R at a position corresponding to position 419; S at a position corresponding to position 419; K at a position corresponding to position 421; N at a position corresponding to position 421; Q at a position corresponding to position 421; R at a position corresponding to position 421; S at a position corresponding to position 421; A at a position corresponding to position 431; H at a position corresponding to position 431; K at a position corresponding to position 431; Q at a position corresponding to position 431; R at a position corresponding to position 431; S at a position corresponding to position 431; V at a position corresponding to position 431; L at a position corresponding to position 433; R at a position corresponding to position 433; V at a position corresponding to position 439; H at a position corresponding to position 440; R at a position corresponding to position 440; A at a position corresponding to position 443; M at a position corresponding to position 443; M at a position corresponding to position 445; and/or ~~with~~ P at a position corresponding to position 445, with reference to amino acid positions set forth in SEQ ID NO:3; and

the modified PH20 polypeptide has at least 95% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOS: 3, 7, and 32-66.

4. (Currently Amended) The modified PH20 polypeptide of claim 23, comprising the amino acid sequence selected from the group consisting of SEQ ID NOS: 73, 78, 91, 95, 96, 105, 106, 108, 109, 111, 112, 113, 115, 117, 118, 119, 120, 123-126, 128-136, 139-141, 149, 154, 155, 164, 165, 167, 191, 192, 196, 197, 199-205, 207, 208, 225, 226, 228, 229, 231,

233, 237, 253, 254, 256, 257, 277, 283, 293, 295, 296, 298, 300, 303, 316, 318, 321, 322, 338-340, 344, 348, 367, 369, 371, 377, 384-388, 394, 398, 399, 401, 406-408, 410, 412, 414, 416, 431, 448, 459, 465, 469, 478, 479, 482, 493, 497, 501, 503, 507, 508, 510-512, 514, 518, 522, 523, 537-543, 545, 558, 559, 561, 563-566, 569, 572, 574, 594, 596, 618-620, 624-634, 637, 640-644, 652, 657, 675, 695, 698, 699, 700, 712, 717, 725, 738, 748-750, 757, 775, 799-801, 807, 822, 825, 844, 847, 851, and 853, or an amino acid sequence that has at least 96% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOS: 73, 78, 91, 95, 96, 105, 106, 108, 109, 111, 112, 113, 115, 117, 118, 119, 120, 123-126, 128-136, 139-141, 149, 154, 155, 164, 165, 167, 191, 192, 196, 197, 199-205, 207, 208, 225, 226, 228, 229, 231, 233, 237, 253, 254, 256, 257, 277, 283, 293, 295, 296, 298, 300, 303, 316, 318, 321, 322, 338-340, 344, 348, 367, 369, 371, 377, 384-388, 394, 398, 399, 401, 406-408, 410, 412, 414, 416, 431, 448, 459, 465, 469, 478, 479, 482, 493, 497, 501, 503, 507, 508, 510-512, 514, 518, 522, 523, 537-543, 545, 558, 559, 561, 563-566, 569, 572, 574, 594, 596, 618-620, 624-634, 637, 640-644, 652, 657, 675, 695, 698, 699, 700, 712, 717, 725, 738, 748-750, 757, 775, 799-801, 807, 822, 825, 844, 847, 851, and 853, and that contains the amino acid replacement as compared to corresponding positions in a polypeptide of any of SEQ ID NOS: 3, 7, and 32-66.

5. (Currently Amended) The modified PH20 polypeptide of claim 3, comprising the amino acid sequence selected from the group consisting of SEQ ID NOS: 86, ~~89~~-99, 100, 159, 173, 181, 193, 195, 209-220, 238, 239, 242, 247-252, 267, 269, ~~277~~-308, 324, 325, 330, 335, 355, 419, 421-423, 425, 428, 435, 455, ~~456~~-462, 463, 484, 490, 506, 531, 533, 579, 581-583, 585, 587, 588, 602, 605, 606, 609, 613, 648, 731, 732, 734, 742, 746, 760, 762, 764, 765, 769-773, 779, 782, 783, 786-789, 794, 795, 814, 816, 819, 826, 830, 836, and 838, or an amino acid sequence that has at least 96% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOS: 86, ~~89~~-99, 100, 159, 173, 181, 193, 195, 209-220, 238, 239, 242, 247-252, 267, 269, ~~277~~-308, 324, 325, 330, 335, 355, 419, 421-423, 425, 428, 435, 455, ~~456~~-462, 463, 484, 490, 506, 531, 533, 579, 581-583, 585, 587, 588, 602, 605, 606, 609, 613, 648, 731, 732, 734, 742, 746, 760, 762, 764, 765, 769-773, 779, 782, 783, 786-789, 794, 795, 814, 816, 819, 826, 830, 836, and 838, and that contains the amino acid replacement as compared to corresponding positions in a polypeptide of any of SEQ ID NOS: 3, 7, and 32-66.

6. (Original) The modified PH20 polypeptide of claim 1 that exhibits at least 2.0-fold of the hyaluronidase activity compared to the PH20 polypeptide not containing the amino acid replacement(s).
7. (Original) The modified PH20 polypeptide of claim 1 that comprises one or more of a modification selected from among glycosylation, sialation, albumination, farnesylation, carboxylation, hydroxylation and phosphorylation.
8. (Original) The modified PH20 polypeptide of claim 1 that comprises at least an N-acetylglucosamine moiety linked to each of at least three asparagine (N) residues.
9. (Original) The modified PH20 polypeptide of claim 8, wherein the three asparagine residues correspond to amino acid residues 200, 333 and 358 of SEQ ID NO:3.
10. (Original) The modified PH20 polypeptide of claim 1 that is conjugated to a polymer.
11. (Original) The modified PH20 polypeptide of claim 3 that is conjugated to a polymer.
12. (Original) The modified PH20 polypeptide of claim 10, wherein the polymer is dextran or PEG.
13. (Original) The modified PH20 polypeptide of claim 1, comprising up to 10 amino acid modifications selected from among amino acid replacements, insertions and deletions.
14. (Original) The modified PH20 polypeptide of claim 3, comprising up to 10 amino acid modifications selected from among amino acid replacements, insertions and deletions.
- 15.-18. (Cancelled).
19. (Original) A pharmaceutical composition, comprising a modified PH20 polypeptide of claim 1.
- 20.-22. (Cancelled).
23. (Previously Presented) A pharmaceutical composition, comprising a modified PH20 polypeptide of claim 3.
- 24.-26. (Cancelled).
27. (Previously Presented) The modified PH20 polypeptide of claim 2, wherein the modified PH20 polypeptide is a soluble PH20 polypeptide; and the unmodified polypeptide consists of the amino acid sequence set forth in any of SEQ ID NOs: 3 or 32-66.



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Patent No.: 10865400
Issue Date: 12/15/2020
Appl. No.: 15/226,489
Filed: 08/02/2016

PART (A) RESPONSE FOR CERTIFICATES OF CORRECTION

This is a decision on the Certificate of Correction request filed 16 September 2021.

The request for issuance of Certificate of Correction for the above-identified correction(s) under the provisions of 37 CFR 1.322 and/or 1.323 is hereby:

(Check one)

☒ Approved ☐ Approved in Part ☐ Denied

Comments: _____

PART (B) PETITION UNDER 37 CFR 1.324 OR 37 CFR 1.48

☐ This is a decision on the petition filed _____ to correct inventorship under 37 CFR 1.324.

☐ This is a decision on the request under 37 CFR 1.48, petition filed _____. In view of the fact that the patent has already issued, the request under 37 CFR 1.48 has been treated as a petition to correct inventorship under 37 CFR 1.324.

The petition is hereby: ☐ Granted ☐ Dismissed

Comment: _____

The patented filed is being forwarded to Certificate of Corrections Branch for issuance of a certificate naming only the actual inventor or inventors.

/MANJUNATH N RAO/
Supervisory Patent Examiner, Art Unit 1656
Technology Center 1600
Phone: (571)272-0939

Certificates of Correction Branch email: CustomerServiceCoC@uspto.gov CoC Central Phone Number: (703) 756-1814

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 10,865,400 B2
APPLICATION NO. : 15/226489
DATED : December 15, 2020
INVENTOR(S) : Wei et al.

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It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

In Item (56) References Cited, in U.S. PATENT DOCUMENTS, on page 1, 2nd Column, Line 31, please replace the inventor "Greennnwald" with --Greenwald--;

In Item (56) References Cited, in OTHER PUBLICATIONS, on page 3, 1st Column, Line 26, please replace "claimed" with --claims--;

In Item (56) References Cited, in OTHER PUBLICATIONS, on page 4, 1st Column, Line 60, please replace "Rearch" with --Research--;

In Item (56) References Cited, in OTHER PUBLICATIONS, on page 5, 2nd Column, Line 20, please replace the author "Harahan" with --Hanahan--;

In the Specification

At Column 13, Line 15, please replace "Mat" with --M at--;

At Column 22, Line 36, please replace "Mat" with --M at--;

At Column 53, Lines 7-8, please replace "poly-propylene oxide)" with --poly(propylene oxide)--;

At Column 69, Line 2, please replace "w-site" with --ω-site--;

At Column 69, Line 5, please replace "w-site" with --ω-site--;

At Column 69, Line 10, please replace "w-site" with --ω-site--;

At Column 69, Line 46, please replace "w-site" with --ω-site--;

Signed and Sealed this
Nineteenth Day of October, 2021



Drew Hirshfeld
*Performing the Functions and Duties of the
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office*

At Column 69, Line 53, please replace “w-site” with --ω-site--;

At Column 90, Line 40, please replace “179” with --I79--;

At Column 90, Line 49, please replace “5235” with --S235--;

From Column 120, Line 46 to Column 133, Line 36, please replace Table 5 with the following amended Table:

TABLE 5: Inactive Mutants					
Corres- ponding Position	Replacement	Corres- ponding Position	Replacement	Corres- ponding Position	Replacement
2	HKWY	3	AGKPTV	4	DEFGLPWY
5	DGILMNPQR TVWY	6	EFTVY	7	CDFGHIKLQ RSTWY
8	DEGHNRSW	9	CDEGNP	10	FILMY
11	ACFILPTWY	12	GHW	13	EGILMV
14	AEGHKNPQW	15	EFGKNPQRS Y	16	ACDEFGHK MPRSTY
17	DEGHILNPQ RSTVWY	18	CDFGHILMP QSTVY	19	ACFGHILMP QRSVWY
20	DEFHKLNPR TVY	21	ACDEGHILM RSTVW	22	CEGKP
23	AFLMNPRST V	25	DEFGHIKLN PRSTVY	27	C
33	CDIINVY	34	ILNSTV	35	ADGPRS
36	CFVWY	37	CEGNS	38	EGKLNQRT W
39	CDFW	40	ADEGKNRST V	41	Q
42	DEHIKLMPQ RSTV	43	AEFGIKLQR V	44	ACFGHIILNQ RSTWY
45	ADEGPW	46	PW	47	V
48	P	49	CDGHP	50	V

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51	CFIMPTWY	52	CEFWY	53	ACDEGHLNP QRSTWY
54	DEGPRY	55	ADGIINPQRT VY	56	ACEGHIKLP RSTVW
57	ADFGIMPQR VW	58	A	59	AEILMPRTV WY
60	ADFGHILNPQ STVY	61	A EFGHNPQR TWY	62	ACDFIKLMP QRSTVY
63	CGP	64	ACDEFGHIK LPQRSTVW	65	ACDGHKNR STVWY
66	ACDEGIKLN STV	67	DEGPRTW	68	ACGILPVY
69	NT	70	Q	71	P
72	CFHIPVW	73	P	75	DGP
76	ACFGIKLPQ RSTVW	77	DELPQRTV	78	ADIMPTY
79	ADFGHKNPS WY	80	ADEF GIKLM NRSTVY	81	ACEGHLNPS VWY
82	YEK	84	Y	85	ACDEFGIINQ ST
86	CP	87	P	88	ACEFGIKLM PRSTVY
89	ADEGQSTWY	90	CG	91	DEFGHILT
92	EFHKPQRWY	94	GP	95	ACEFGHIKLM PQSVWY
96	SVHPRSTW	98	P	99	CEGINPVW

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100	CEFGNPRST WY	101	ACFHIKLMN QRST	102	P
103	AEFGHILQRT VWY	104	FPW	105	CMN
106	ACDFIILMNP SWY	107	ACIIKPQSVW	108	DEFKLMPT VY
109	CDELMRTW	110	FKLMPW	111	HIQ
112	CEGHLNPS	113	RV	114	ILPTV
115	ACDFGHIKL MRSVY	116	ACDEGHILN PQSVW	117	DGIKNQRSV W
118	CDEGPRWY	119	AKILNPR	121	ACEFGHKLM PWY
122	ACEFIKQRS TV	123	ACDEHLMPQ RSTVY	124	CDEFN
125	CDGLNW	126	FHILNPY	127	K
128	EP	129	ACDEGHLPQ STVW	130	CDGHLNST WY
131	P	132	P	133	DEFGHLMNP RTVW
134	ACDFGHKPQ RSW	135	P	136	P
137	FGHNPRWY	138	V	139	P
143	CIIPRST	144	AEFIKPQSVY	145	TW
149	E	149	P	150	V
152	L	153	EFMPRTV	154	DEGPSWY
155	PY	156	P	157	ACDEGHIKL M PQRSTV

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158	DKPRY	159	WY	161	W
163	CP	164	ACDEGHNPQ R	165	CHPT
166	D	167	V	168	ACDEFGKLP RSVWY
169	ADFGHKNPQ STY	170	CDEGMPWY	171	CDHMNRSW Y
172	DEILPQTVW Y	173	DEGHILMPS VWY	174	P
175	CDGKPRS	176	ACEFGHIPQS TVW	177	ACDFGHL MQRSTVW
178	EILVW	180	ACEPRS	181	ACDEFHIKL RS
182	ACDEHNPQR STVY	183	CDEGIKNPQ RSV	184	ACDEFGHKL MPSV
185	ADEFGIKPRS TVWY	186	ADGHIKLP QRSVW	187	AFGHILMNQ RSTVWY
188	ACFGHLMNP QRSTVW	189	AEGHKLMNP RSTVWY	190	CEFGHKLNQ RSTVW
191	AEFGKLMPQ RSTVWY	192	CFGKLMNPQ RVWY	193	ADKLMPV
194	ACILPSTV	195	S	197	C
198	VW	199	EGHIKLPRS W	200	AFGHKLMPQ RSWY
201	AFLMNPRST VW	202	AEFGHKNPQ RVWY	203	ADEGHLMN QRSTV
204	ACEGHIKQR ST	206	CDFGPY	207	AFGMPQRST VW

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208	DGPW	209	CP	210	ACDEGKMNPSTVWY
211	CFGHIKMPRSTVW	212	AGHIKLMPVW	213	PS
214	ACDEGHIKNPRSTY	215	CP	216	DEGHIKLMNPQRTV
217	ACGHPQSTVW	218	AIKLPSV	219	P
220	GKNPRW	221	DEHKPR	222	PY
223	CDEGHKLPQRSTVWY	224	ADEFGMPQRSTWY	225	ADEGHKLPQRTVW
226	ACDEFGLNQRSTVWY	227	AFGHIKLMNPQRTVWY	228	AEFGHLMNPRSTW
229	EFGKLPQTVW	230	AEGHKMNPRSTVWY	231	ACDFGHIKLPQRSV
232	CGHKLNQPVY	233	DIPST	234	ADEGHNPSTVW
235	FLMRWY	236	CILNQTY	238	FGLPVWY
239	CFGHILPRSTVWY	240	EFGNWY	241	ACDEGIPRSTVW
242	ACDGILMPRSTVW	243	CDFGILMPQRSWY	244	ADGIVY
245	ACFLPQRSTV	246	ACDEGHIKLMPTVW	247	ACFHNPPQRSTWY
248	CDEGIMPT	249	AGHIKMQSY	250	CFGHKLMNPQRSTVW
251	DFGHIKPSTW	252	ADEFGHIKLNPNSTY	253	ADEGILMNORSW

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254	CDEGIKLPQR TVWY	255	CDLPVW	256	CDEGP
257	D	258	LPVW	260	CP
261	P	262	ADE GHIKQR STVWY	263	EFPQW
264	DEFG LMRTV WY	265	ADFGHKLMN QRS	266	ACGHMPQRS TVW
267	DGHIKNRSW	268	ACFGHKLNP QSTVW	269	EKLMNPQR
270	ACEFGHIPY	271	ADEHKTW	272	HLNPW
273	ACDGILPQSV W	274	CEGHNQWY	275	AFGIKLMQT VW
276	FPW	278	MP	279	ACFGLWY
280	DIMNRSTVW	281	ADGHIKNPQ RSVW	282	FLVWY
283	ACDFW	284	CDFW	284	CIP
285	KPRTV	286	ACDFHKMPT Y	287	ACDEGKLNP QRS
288	DEFGHIKPRT	289	ACEGHLPQR SY	290	DQY
291	ACDEFMNTW Y	292	ILT	293	EN
294	AEGHKLNPQ RSTW	295	CGHILNPTV Y	296	CFGIKMQRS TVWY
297	CEHLNPQRS TY	298	CELMNPQST WY	299	ACDFGHLMP QT

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300	ACDEFLMNP QSTVW	301	EGHKMNPQR SWY	302	CDEFGHLM P RSTY
303	ACDEFGKLM RWY	304	ACDGIMNPQ STVY	305	LPQRSTVY
306	ACHILVWY	307	CIP	308	CFLMVWY
310	CEFKL	311	CEFILPVW	312	CEMVW
313	C	314	CLW	315	CIV
316	EGIKLMPRST VWY	317	G P	318	CPW
319	CEFGHIKMP QRSVWY	320	CPV	321	EMP
322	CDEGILNPRS TVW	323	ACEGHKNRS TV	324	CFPVWY
325	CREGHNW	327	AEFGHNQRS TVWY	329	CFGHIKLNQ RSTVWY
330	ACDEGILMN PRSVW	331	ACDEFHKQR STWY	332	ACDEFGHKL NPRSTY
333	GHIKPRSTW Y	334	ACDEGMNRS	335	FGHIKLPVW Y
336	AEFGKNPRS TVWY	337	CFGIKLMRT W	338	CDEFGHIKL PRTV
339	DEFGHILNPST VWY	340	ACDEFGIHKP RSTVW	341	AEGHKLMN QRSTVY
342	DEFHKLMPQ RTY	343	CDFIPW	344	FGHLMNPQR STWY
345	ACEIKNQRT VY	346	ADFGIKLMP RSTVW	347	CFIPTVW

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348	CHILPQRTV WY	349	DFGPNVWY	350	ADEFHJKLM NPRSTVY
351	CDEFIINRWY	352	ADEFGKMPQ RSTVWY	353	CFGIIKLMQ RSW
354	CDEGHIKLM PQSVWY	355	DFGHLMNPNQ RSTVWY	356	CGKLPRTVW
357	DEFGMLQQR	358	EHIKPQRW	359	AFGLPW
360	ACEFGIKLMP QRV	361	ACEGMNPQR SVW	362	ACEGHKLM NPRSTVW
363	ACDEFGHIPQ RSTVW	364	ACDEFGKLM PRSTVY	365	ACDEGMNP QRSTWY
366	ACEFGKMPQ RTW	367	EFILMQV	368	CPW
369	CEFIKLPQV W	370	ADEGHKLNPN QRSVY	371	P
372	ADEFGHKLN PRSTVW	373	CPW	374	DE
375	CFPVY	376	IPW	377	CILV
378	DEFILMQTW Y	379	ACEFILMW	380	CDEGQRS
381	GLPWY	382	EGHKLMPNPQ RSTWY	383	GP
384	CFMQST	385	CLMPWY	386	ACFGHILMN QRSTVY
387	CEFGHILMN VWY	388	CGPQ	389	FV

390	ACEFGHLNP RSTVWY	391	ADGHKNPQR STVWY	392	CP
393	CP	394	ADEGIKNPQ RSTV	395	CLMP
396	CFGIPY	397	ACEFGILMP QTV	398	ACEGHILNP RSTVWY
399	DP	400	ADEFGILMP QRSTVY	401	CFHKRWY
402	ADEFLMPQR STVWY	403	ACEGHKLMN PQRT	404	CDFGHLMN RVWY
405	CIV	406	PR	408	AEFGIKLPR STVWY
410	W	411	DEFG	412	EH
413	HIKLP	414	ADEGHKRST	415	CDEP
416	CS	417	ADEFGHKMP QR	419	DP
420	ADFGHKLNR STWY	422	CDGHLMNQ RSY	423	ADEFGHLMP QRSTVW
424	ACEGHNQRS WY	425	ELPWY	426	CFMR
427	ACFLPVWY	428	ACDEGHNRS Y	429	ADKLN PSTV WY
430	ADELMNSTV	431	P	432	CFIKLMPY
434	HKPQRW	437	T	438	Y
439	NR	440	Q	441	R
442	MNS	443	D		

--;

At Column 178, Line 28, please replace “f 15%” with --± 15%--;

At Column 185, Line 25, please replace “U520100074885” with --US20100074885--;

At Column 293, Line 25, please replace “Jasco J-810-1505” with Jasco J-810-150S--;

At Column 293, Line 26, please replace “PTC-4245” with --PTC-424S--.

In the Claims

From Column 299, Line 36 to Column 300, Line 44, please replace claim 1 with the following amended claim:

1. A modified PH20 polypeptide, comprising one or more amino acid replacements in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NOS: 3, 7, and 32-66;

the modified PH20 polypeptide exhibits increased hyaluronidase activity that is at least 120% of the hyaluronidase activity compared to the unmodified PH20 polypeptide not containing the amino acid replacement(s); wherein:

the activity of the unmodified PH20 polypeptide not containing the replacement(s) is 100%;

hyaluronidase activity of the modified PH20 polypeptide and hyaluronidase activity of the unmodified PH20 polypeptide are measured under identical conditions;

the amino acid replacement(s) confer(s) the increased hyaluronidase activity;

at least one amino acid replacement confers the increased hyaluronidase activity, and is at a position corresponding to a position selected from 1, 15, 24, 27, 29, 30, 31, 32, 33, 37, 39, 48, 63, 67, 69, 71, 72, 73, 75, 87, 92, 93, 94, 118, 120, 135, 141, 147, 148, 150, 151, 152, 155, 156, 163, 164, 165, 170, 198, 209, 212, 215, 219, 233, 236, 247, 257, 259, 260, 263, 269, 271, 272, 276, 278, 282, 293, 305, 308, 313, 320, 324, 325, 326, 328, 353, 359, 371, 377, 380, 389, 392, 395, 405, 409, 410, 418, 425, 436, 437, 438, 441, 442, 446, and 447, with reference to amino acid positions set forth in SEQ ID NO:3;

corresponding amino acid positions are identified by alignment of the PH20 polypeptide with the polypeptide having the sequence of amino acids set forth as SEQ ID NO:3, with the proviso that if the modified PH20 polypeptide includes only a single amino acid replacement, the replacement does not correspond to amino acid replacement N219A with reference to amino acid positions set forth in SEQ ID NO:3; and

the modified PH20 polypeptide has at least 95% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7, and 32-66.

From Column 300, Line 45 to Column 303, Line 11, please replace claim 2 with the following amended claim:

2. The modified PH20 polypeptide of claim 1, comprising at least one amino acid replacement selected from among replacement with: H at a position corresponding to position 1; Q at a position corresponding to position 1; V at a position corresponding to position 15; E at a position corresponding to position 24; H at a position corresponding to position 24; K at a position corresponding to position 27; R at a position corresponding to position 27; E at a position corresponding to position 29; I at a position corresponding to position 29; L at a position corresponding to position 29; M at a position corresponding to position 29; P at a position corresponding to position 29; S at a position corresponding to position 29; V at a position corresponding to position 29; G at a position corresponding to position 30; H at a position corresponding to position 30; K at a position corresponding to position 30; M at a position corresponding to position 30; R at a position corresponding to position 30; S at a position corresponding to position 30; A at a position corresponding to position 31; C at a position corresponding to position 31; H at a position corresponding to position 31; I at a position corresponding to position 31; K at a position corresponding to position 31; L at a position corresponding to position 31; P at a position corresponding to position 31; R at a position corresponding to position 31; S at a position corresponding to position 31; T at a position corresponding to position 31; V at a position corresponding to position 31; F at a position corresponding to position 32; G at a position corresponding to position 32; H at a position corresponding to position 32; W at a position corresponding to position 33; F at a position corresponding to position 37; N at a position corresponding to position 39; T at a position corresponding to position 39; F at a position corresponding to position 48; H at a position corresponding to position 48; N at a position corresponding to position 48; W at a position corresponding to position 63; V at a position corresponding to position 67; A at a position corresponding to position 69; C at a position corresponding to position 69; F at a position corresponding to position 69; G at a position corresponding to position 69; I at a position corresponding to position 69; L at a position corresponding to position 69; M at a position corresponding to position 69; P at a position corresponding to position 69; R at a position

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corresponding to position 69; W at a position corresponding to position 69; Y at a position corresponding to position 69; R at a position corresponding to position 71; S at a position corresponding to position 71; M at a position corresponding to position 72; Q at a position corresponding to position 72; H at a position corresponding to position 73; L at a position corresponding to position 73; W at a position corresponding to position 73; F at a position corresponding to position 75; L at a position corresponding to position 75; R at a position corresponding to position 75; T at a position corresponding to position 75; C at a position corresponding to position 87; T at a position corresponding to position 87; Y at a position corresponding to position 87; C at a position corresponding to position 92; I at a position corresponding to position 93; L at a position corresponding to position 93; R at a position corresponding to position 93; T at a position corresponding to position 93; R at a position corresponding to position 94; Q at a position corresponding to position 118; F at a position corresponding to position 120; V at a position corresponding to position 120; Y at a position corresponding to position 120; D at a position corresponding to position 135; G at a position corresponding to position 135; R at a position corresponding to position 135; H at a position corresponding to position 141; Y at a position corresponding to position 141; R at a position corresponding to position 147; V at a position corresponding to position 147; K at a position corresponding to position 148; G at a position corresponding to position 150; K at a position corresponding to position 151; L at a position corresponding to position 151; M at a position corresponding to position 151; Q at a position corresponding to position 151; R at a position corresponding to position 151; R at a position corresponding to position 152; G at a position corresponding to position 155; K at a position corresponding to position 155; D at a position corresponding to position 156; A at a position corresponding to position 163; E at a position corresponding to position 163; K at a position corresponding to position 163; R at a position corresponding to position 163; M at a position corresponding to position 164; D at a position corresponding to position 165; N at a position corresponding to position 165; R at a position corresponding to position 170; D at a position corresponding to position 198; N at a position corresponding to position 212; M at a position corresponding to position 215; S at a position corresponding to position 219; K at a position corresponding to position 233; R at a position corresponding to position 233; R at a position corresponding to position 236; I at a position corresponding to position 247; T at a position corresponding to position 257; P at a position corresponding to position 259; Y at a position corresponding to position 260; K at a position corresponding to position 263; R at a position corresponding to position 263; A at a position corresponding to position 269; L at a position corresponding to position 271; M at a position corresponding to position 271; T at a position corresponding to position 272; D at a position corresponding to position 276; S at a position corresponding to position 276; Y at a position corresponding to position 276; H at a position corresponding to position 278; K at a position corresponding to position 278; N at a position corresponding to position 278; R at a position corresponding to position 278; S at a position corresponding to position 278; T at a position corresponding to position 278; Y at a position corresponding to position 278; M at a position corresponding to position 282; A at a position corresponding to position 293; C at a position corresponding to position 293; F at a position corresponding to position 293; M at a position corresponding to position 293; P at a position corresponding to position 293; Q at a position corresponding to position 293; V at a position corresponding to position 293; E at a position corresponding to position 305; G at a position corresponding to position 308; N at a position corresponding to position 308; K at a position corresponding to position 313; R at a position

corresponding to position 313; H at a position corresponding to position 320; K at a position corresponding to position 320; R at a position corresponding to position 320; R at a position corresponding to position 324; A at a position corresponding to position 325; D at a position corresponding to position 325; E at a position corresponding to position 325; G at a position corresponding to position 325; H at a position corresponding to position 325; K at a position corresponding to position 325; M at a position corresponding to position 325; N at a position corresponding to position 325; Q at a position corresponding to position 325; S at a position corresponding to position 325; V at a position corresponding to position 326; I at a position corresponding to position 328; K at a position corresponding to position 328; L at a position corresponding to position 328; S at a position corresponding to position 328; Y at a position corresponding to position 328; V at a position corresponding to position 353; T at a position corresponding to position 359; R at a position corresponding to position 371; P at a position corresponding to position 377; T at a position corresponding to position 377; W at a position corresponding to position 380; Y at a position corresponding to position 380; K at a position corresponding to position 389; M at a position corresponding to position 392; R at a position corresponding to position 395; G at a position corresponding to position 405; A at a position corresponding to position 409; Q at a position corresponding to position 409; T at a position corresponding to position 410; P at a position corresponding to position 418; K at a position corresponding to position 425; K at a position corresponding to position 436; I at a position corresponding to position 437; M at a position corresponding to position 437; T at a position corresponding to position 438; F at a position corresponding to position 441; R at a position corresponding to position 442; A at a position corresponding to position 446; D at a position corresponding to position 447; N at a position corresponding to position 447; and/or Q at a position corresponding to position 447, with reference to amino acid positions set forth in SEQ ID NO:3.

At Column 303, Lines 12-16, please replace claim 3 with the following amended claim:

3. The modified PH20 polypeptide of claim 2, wherein the modified PH20 polypeptide is a soluble PH20 polypeptide; and the unmodified polypeptide consists of the amino acid sequence set forth in any of SEQ ID NOs: 3 or 32-66.

From Column 303, Line 17 to Column 304, Line 54, please replace claim 4 with the following amended claim:

4. A modified PH20 polypeptide, comprising one or more amino acid replacements in an unmodified PH20 polypeptide, wherein:

the unmodified PH20 polypeptide consists of the amino acid sequence selected from the group consisting of SEQ ID NOS: 3, 7, and 32-66;

the modified PH20 polypeptide exhibits increased hyaluronidase activity that is at least 120% of the hyaluronidase activity compared to the unmodified PH20 polypeptide not containing the amino acid replacement(s); wherein:

the activity of the unmodified PH20 polypeptide not containing the replacement(s) is 100%;

hyaluronidase activity of the modified PH20 polypeptide and hyaluronidase activity of the unmodified PH20 polypeptide are measured under identical conditions;

at least one amino acid replacement confers the increased hyaluronidase activity, and is selected from E at a position corresponding to position 12; E at a position corresponding to position 26; K at a position corresponding to position 26; R at a position corresponding to position 46; Q at a position corresponding to position 52; Q at a position corresponding to position 58; H at a position

corresponding to position 68; Q at a position corresponding to position 68; A at a position corresponding to position 70; C at a position corresponding to position 70; F at a position corresponding to position 70; G at a position corresponding to position 70; H at a position corresponding to position 70; K at a position corresponding to position 70; L at a position corresponding to position 70; N at a position corresponding to position 70; P at a position corresponding to position 70; R at a position corresponding to position 70; S at a position corresponding to position 70; T at a position corresponding to position 70; A at a position corresponding to position 74; C at a position corresponding to position 74; G at a position corresponding to position 74; N at a position corresponding to position 74; P at a position corresponding to position 74; R at a position corresponding to position 74; S at a position corresponding to position 74; V at a position corresponding to position 74; W at a position corresponding to position 74; G at a position corresponding to position 84; R at a position corresponding to position 84; G at a position corresponding to position 97; H at a position corresponding to position 127; N at a position corresponding to position 127; G at a position corresponding to position 131; V at a position corresponding to position 131; R at a position corresponding to position 142; A at a position corresponding to position 166; F at a position corresponding to position 166; H at a position corresponding to position 166; L at a position corresponding to position 166; R at a position corresponding to position 166; Y at a position corresponding to position 166; K at a position corresponding to position 174; K at a position corresponding to position 206; M at a position corresponding to position 213; N at a position corresponding to position 213; E at a position corresponding to position 237; S at a position corresponding to position 238; N at a position corresponding to position 261; R at a position corresponding to position 277; T at a position corresponding to position 277; L at a position corresponding to position 309; N at a position corresponding to position 309; Q at a position corresponding to position 309; R at a position corresponding to position 309; T at a position corresponding to position 309; A at a position corresponding to position 310; G at a position corresponding to position 310; H at a position corresponding to position 315; I at a position corresponding to position 317; K at a position corresponding to position 317; R at a position corresponding to position 317; M at a position corresponding to position 318; G at a position corresponding to position 347; S at a position corresponding to position 347; M at a position corresponding to position 399; T at a position corresponding to position 399; W at a position corresponding to position 399; D at a position corresponding to position 407; Q at a position corresponding to position 407; F at a position corresponding to position 419; I at a position corresponding to position 419; R at a position corresponding to position 419; S at a position corresponding to position 419; K at a position corresponding to position 421; N at a position corresponding to position 421; Q at a position corresponding to position 421; R at a position corresponding to position 421; S at a position corresponding to position 421; A at a position corresponding to position 431; H at a position corresponding to position 431; K at a position corresponding to position 431; Q at a position corresponding to position 431; R at a position corresponding to position 431; S at a position corresponding to position 431; V at a position corresponding to position 431; L at a position corresponding to position 433; R at a position corresponding to position 433; V at a position corresponding to position 439; H at a position corresponding to position 440; R at a position corresponding to position 440; A at a position corresponding to position 443; M at a position corresponding to position 443; M at a position corresponding to position 445; and/or P at a position corresponding to position 445, with reference to amino acid positions set forth in SEQ ID NO:3; and

the modified PH20 polypeptide has at least 95% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 7, and 32-66.

From Column 304, Line 55 to Column 305, Line 7, please replace claim 5 with the following amended claim:

5. The modified PH20 polypeptide of claim 4 comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 86, 99, 100, 159, 173, 181, 193, 195, 209-220, 238, 239, 242, 247-252, 267, 269, 308, 324, 325, 330, 335, 355, 419, 421-423, 425, 428, 435, 455, 462, 463, 484, 490, 506, 531, 533, 579, 581-583, 585, 587, 588, 602, 605, 606, 609, 613, 648, 731, 732, 734, 742, 746, 760, 762, 764, 765, 769-773, 779, 782, 783, 786-789, 794, 795, 814, 816, 819, 826, 830, 836, and 838, or an amino acid sequence that has at least 96% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 86, 99, 100, 159, 173, 181, 193, 195, 209-220, 238, 239, 242, 247-252, 267, 269, 308, 324, 325, 330, 335, 355, 419, 421-423, 425, 428, 435, 455, 462, 463, 484, 490, 506, 531, 533, 579, 581-583, 585, 587, 588, 602, 605, 606, 609, 613, 648, 731, 732, 734, 742, 746, 760, 762, 764, 765, 769-773, 779, 782, 783, 786-789, 794, 795, 814, 816, 819, 826, 830, 836, and 838, and that contains the amino acid replacement as compared to corresponding positions in a polypeptide of any of SEQ ID NOs: 3, 7, and 32-66.

From Column 305, Line 31 to Column 306, Line 25, please replace claim 14 with the following amended claim:

14. The modified PH20 polypeptide of claim 2, comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 73, 78, 91, 95, 96, 105, 106, 108, 109, 111, 112, 113, 115, 117, 118, 119, 120, 123-126, 128-136, 139-141, 149, 154, 155, 164, 165, 167, 191, 192, 196, 197, 199-205, 207, 208, 225, 226, 228, 229, 231, 233, 237, 253, 254, 256, 257, 277, 283, 293, 295, 296, 298, 300, 303, 316, 318, 321, 322, 338-340, 344, 348, 367, 369, 371, 377, 384-388, 394, 398, 399, 401, 406-408, 410, 412, 414, 416, 431, 448, 459, 465, 469, 478, 479, 482, 493, 497, 501, 503, 507, 508, 510-512, 514, 518, 522, 523, 537-543, 545, 558, 559, 561, 563-566, 569, 572, 574, 594, 596, 618-620, 624-634, 637, 640-644, 652, 657, 675, 695, 698, 699, 700, 712, 717, 725, 738, 748-750, 757, 775, 799-801, 807, 822, 825, 844, 847, 851, and 853, or an amino acid sequence that has at least 96% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 73, 78, 91, 95, 96, 105, 106, 108, 109, 111, 112, 113, 115, 117, 118, 119, 120, 123-126, 128-136, 139-141, 149, 154, 155, 164, 165, 167, 191, 192, 196, 197, 199-205, 207, 208, 225, 226, 228, 229, 231, 233, 237, 253, 254, 256, 257, 277, 283, 293, 295, 296, 298, 300, 303, 316, 318, 321, 322, 338-340, 344, 348, 367, 369, 371, 377, 384-388, 394, 398, 399, 401, 406-408, 410, 412, 414, 416, 431, 448, 459, 465, 469, 478, 479, 482, 493, 497, 501, 503, 507, 508, 510-512, 514, 518, 522, 523, 537-543, 545, 558, 559, 561, 563-566, 569, 572, 574, 594, 596, 618-620, 624-634, 637, 640-644, 652, 657, 675, 695, 698, 699, 700, 712, 717, 725, 738, 748-750, 757, 775, 799-801, 807, 822, 825, 844, 847, 851, and 853, and that contains the amino acid replacement as compared to corresponding positions in a polypeptide of any of SEQ ID NOs: 3, 7, and 32-66.

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 10,865,400 B2
APPLICATION NO. : 15/226489
DATED : December 15, 2020
INVENTOR(S) : Wei et al.

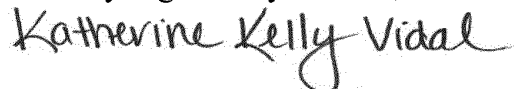
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

The first or sole Notice should read --

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b)
by 733 days.

Signed and Sealed this
Twenty-eighth Day of June, 2022


Katherine Kelly Vidal
Director of the United States Patent and Trademark Office