

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CHARLES RIVER LABORATORIES, INC.,
Petitioner,

v.

SEIKAGAKU CORPORATION,
Patent Owner.

Case No. PGR2025-00023

Patent No. 11,959,109

PATENT OWNER'S UPDATED EXHIBIT LIST

PATENT OWNER'S EXHIBITS (New Exhibits in Italics)

Exhibit No.	Description
2001	Disclaimer of Claim 10 in U.S. Patent 11,959,109
2002	Muta, et al., "Horseshoe Crab Coagulation Factor B, A Unique Serine Protease Zymogen Activated by Cleavage of an Ile-Ile Bond," (1993) J. Biol Chem., Vol. 268, No. 28, 21384-88
2003	Muta, et al., "Proclotting Enzyme from Horseshoe Crab Hemocytes, cDNA Cloning, Disulfide Locations, and Subcellular Localization," (1990) J. Biol Chem., Vol. 265, No. 36, 22426-33
2004	Declaration of Michael A. Frohman, M.D., Ph.D. and exhibits from Opposition to European Patent No. 3530670
2005	Novitsky, T.J., "Biomedical Applications of Limulus Amebocyte Lysate," in , J. Tancredi et al (eds.), <i>Biology and Conservation of Horseshoe Crabs</i> , Springer Science+Business Media, LLC (2010) pp. 315-329
2006	Notice of Opposition to European Patent No. 3530670
2007	Extract from the Register of European Patents for European Patent No. 4291648
2008	Ding, et al., "Molecular cloning and sequence analysis of Factor C cDNA from the Singapore horseshoe crab, <i>Carcinoscorpius rotundicauda</i> ," Molecular Marine Biology and Biotechnology (1995) 4(1), 90-103, submitted in Opposition to European Patent No. 3441466
2009	Ding, et al., "Molecular cloning and sequence analysis of Factor C cDNA from the Singapore horseshoe crab, <i>Carcinoscorpius rotundicauda</i> ," Molecular Marine Biology and Biotechnology (1995) 4(1), 90-103, submitted in U.S. Patent Application No. 17/650,803

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2010	Ding, et al., "Molecular cloning and sequence analysis of Factor C cDNA from the Singapore horseshoe crab, <i>Carcinoscorpius rotundicauda</i> ," Molecular Marine Biology and Biotechnology (1995) 4(1), 90-103, submitted in U.S. Patent Application No. 18/275,777
2011	Ding, et al., "Molecular cloning and sequence analysis of Factor C cDNA from the Singapore horseshoe crab, <i>Carcinoscorpius rotundicauda</i> ," Molecular Marine Biology and Biotechnology (1995) 4(1), 90-103, submitted in U.S. Patent Application No. 18/953,525
2012	Ding, et al., "Molecular cloning and sequence analysis of Factor C cDNA from the Singapore horseshoe crab, <i>Carcinoscorpius rotundicauda</i> ," Molecular Marine Biology and Biotechnology (1995) 4(1), 90-103, submitted in Opposition to European Patent No. 3530670
2013	Wang, et al., "Modular Arrangement and Secretion of a Multidomain Serine Protease," J. Biological Chemistry (2002), 277(39):36363-36372, submitted in Opposition to European Patent No. 3441466
2014	Wang, et al., "Modular Arrangement and Secretion of a Multidomain Serine Protease," J. Biological Chemistry (2002), 277(39):36363-36372, submitted in U.S. Patent Application No. 17/650,803
2015	Wang, et al., "Modular Arrangement and Secretion of a Multidomain Serine Protease," J. Biological Chemistry (2002), 277(39):36363-36372, submitted in U.S. Patent Application No. 18/275,777
2016	Wang, et al., "Modular Arrangement and Secretion of a Multidomain Serine Protease," J. Biological Chemistry (2002), 277(39):36363-36372, submitted in U.S. Patent Application No. 18/953,525
2017	Hossler, et al., "Optimal and consistent protein glycosylation in mammalian cell culture," Glycobiology (2009), 19(9): 936-949, submitted in Opposition to European Patent No. 3441466

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2018	Hossler, et al., "Optimal and consistent protein glycosylation in mammalian cell culture," Glycobiology (2009), 19(9): 936-949, submitted in U.S. Patent Application No. 17/650,803
2019	Hossler, et al., "Optimal and consistent protein glycosylation in mammalian cell culture," Glycobiology (2009), 19(9): 936-949, submitted in U.S. Patent Application No. 18/275,777
2020	Hossler, et al., "Optimal and consistent protein glycosylation in mammalian cell culture," Glycobiology (2009), 19(9): 936-949, submitted in U.S. Patent Application No. 18/953,525
2021	U.S. Patent Application Publication No. U.S. 2023/0258647 A1
2022	Thorne, et al., "Evaluation of the <i>Limulus</i> Amebocyte Lysate and Recombinant Factor C Assays for Assessment of Airborne Endotoxin," Appl. Environ. Microbiol. 76(15):4988-95 (2010)
2023	International Publication Number WO 2012/118226
2024	Ding, J.L. and Ho, B., "Endotoxin detection – from <i>Limulus</i> Amebocyte Lysate to Recombinant Factor C," pp. 187-208 (2010)
2025	English Translation of Hashiguchi, et al., "Expression of Recombinant Proteins in Cultured Human Cells Standard Protocol with 293 Strain Cells," (2008) Protein Science Society Archive 1, e017, submitted in Opposition to European Patent No. 3441466
2026	English Translation of Hashiguchi, et al., "Expression of Recombinant Proteins in Cultured Human Cells Standard Protocol with 293 Strain Cells," (2008) Protein Science Society Archive 1, e017, submitted in U.S. Patent Application No. 17/650,803
2027	Tamura, H., " <i>EC Bacteriol. Virol. Rsch.</i> 2016," available at https://ecronicon.net/assets/ecbvr/pdf/ECBVR-01-ECO-03.pdf
2028	U.S. Patent No. 6,391,570

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2029	Tokunaga, et al., "Further Studies on Lipopolysaccharide-Sensitive Serine Protease Zymogen (Factor C): Its Isolation from <i>Limulus polyphemus</i> Hemocytes and Identification as an Intracellular Zymogen Activated by α -Chymotrypsin, Not by Trypsin" (1991) J. Biochem, 109: 150-157, submitted in Opposition to European Patent No. 3441466
2030	Tokunaga, et al., "Further Studies on Lipopolysaccharide-Sensitive Serine Protease Zymogen (Factor C): Its Isolation from <i>Limulus polyphemus</i> Hemocytes and Identification as an Intracellular Zymogen Activated by α -Chymotrypsin, Not by Trypsin" (1991) J. Biochem, 109: 150-157, submitted in U.S. Patent Application No. 17/650,803
2031	Tokunaga, et al., "Further Studies on Lipopolysaccharide-Sensitive Serine Protease Zymogen (Factor C): Its Isolation from <i>Limulus polyphemus</i> Hemocytes and Identification as an Intracellular Zymogen Activated by α -Chymotrypsin, Not by Trypsin" (1991) J. Biochem, 109: 150-157, submitted in U.S. Patent Application No. 18/275,777
2032	Tokunaga, et al., "Further Studies on Lipopolysaccharide-Sensitive Serine Protease Zymogen (Factor C): Its Isolation from <i>Limulus polyphemus</i> Hemocytes and Identification as an Intracellular Zymogen Activated by α -Chymotrypsin, Not by Trypsin" (1991) J. Biochem, 109: 150-157, submitted in U.S. Patent Application No. 18/953,525
2033	Excerpt from file history for U.S. Application No. 14/650767 (issued as U.S. Patent No. 10,144,923)
2034	Excerpt from file history for U.S. Application No. 15/983725 (issued as U.S. Patent No. 10,982,202)
2035	Notice of Opposition to European Patent No. 3441466
2036	D19, "A comparison of <i>Limulus</i> Factor C expressed with and without terminal sialic acid glycosylation"

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2037	Iwanaga, S., "The limulus clotting reaction" (1993) Curr. Op. Immunol., 5(1):74-82
2038	Iwanaga, S., "Primitive Coagulation Systems and their Message to Modern Biology" (1993) Thromb. Haemost., 70(01):48-55
2039	Iwanaga, S. et al., "New Types of Clotting Factors and Defense Molecules Found in Horseshoe Crab Hemolymph: Their Structures and Functions" (1998) J. Biochem., 123:1-15
2040	Koshiba, et al., "A Structural Perspective on the Interaction between Lipopolysaccharide and Factor C, a Receptor Involved in Recognition of Gram-negative Bacteria," (2007) J. Biological Chemistry, 282(6): 3962-3967, submitted in Opposition to European Patent No. 3441466
2041	Koshiba, et al., "A Structural Perspective on the Interaction between Lipopolysaccharide and Factor C, a Receptor Involved in Recognition of Gram-negative Bacteria," (2007) J. Biological Chemistry, 282(6): 3962-3967, submitted in U.S. Patent Application No. 17/650,803
2042	Koshiba, et al., "A Structural Perspective on the Interaction between Lipopolysaccharide and Factor C, a Receptor Involved in Recognition of Gram-negative Bacteria," (2007) J. Biological Chemistry, 282(6): 3962-3967, submitted in U.S. Patent Application No. 18/275,777
2043	Koshiba, et al., "A Structural Perspective on the Interaction between Lipopolysaccharide and Factor C, a Receptor Involved in Recognition of Gram-negative Bacteria," (2007) J. Biological Chemistry, 282(6): 3962-3967, submitted in U.S. Patent Application No. 18/953,525
2044	English Translation of Hashiguchi, et al., "Expression of Recombinant Proteins in Cultured Human Cells Standard Protocol with 293 Strain Cells," (2008) Protein Science Society Archive 1, e017, submitted in U.S. Patent Application No. 18/275,777

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2045	English Translation of Hashiguchi, et al., "Expression of Recombinant Proteins in Cultured Human Cells Standard Protocol with 293 Strain Cells," (2008) Protein Science Society Archive 1, e017, submitted in U.S. Patent Application No. 18/953,525
2046	U.S. Patent No. 10,473,663
2047	U.S. Patent Application Publication No. 2003/0054432 A1
2048	Alwis, K.U. & Milton, D.K., "Recombinant Factor C Assay for Measuring Endotoxin in House Dust: Comparison with LAL, and (1→3)-β-D-Glucans," (2006) Am. J. Indus. Med. 49:296-300
2049	Mustopa, A.Z. et al., "Characterization, protein modeling, and molecular docking of factor C from Indonesian horseshoe crab (<i>Tachypleus gigas</i>)," J. Genetic Eng'g and Biotechnology, (2023) 21:44
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2053	Excerpts from Japanese Pharmacopoeia-XV, "4.01 Bacterial Endotoxins Test" (March 31, 2006)
2054	Dubczak, J., "Standing Guard," Charles River Laboratories, PDA Letter (Sept. 26, 2018)
2055	U.S. Patent Application Publication No. 2009/0208995 A1
2056	U.S. Patent No. 9,040,254

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2057	Iwanaga, S., "Biochemical principle of <i>Limulus</i> test for detecting bacterial endotoxins," Proc. Jpn. Acad., Ser. B (2007), 83:110-119
2058	Kawabata, S., et al., "The lipopolysaccharide-activated innate immune response network of the horseshoe crab," Invertebrate Survival J. (2009), 6(1):59-77
2059	Iwanaga, S. and Lee, B.K., "Recent Advances in the Innate Immunity of Invertebrate Animals," J Biochem. and Mol. Biol. (2005), 38(2):128-150
2060	D'Amato A., et al., "In Depth Exploration of the Hemolymph of <i>Limulus polyphemus</i> via Combinatorial Peptide Ligand Libraries," J. Proteome Rsch. (2010), 9:3260-3269
2061	RESERVED
2062	Declaration of Brian C. Schaefer, Ph.D.
2063	Curriculum vitae of Brian C. Schaefer, Ph.D.
2064	Declaration of Wan-Shon Lo
2065	Obst M, et al., Molecular phylogeny of extant horseshoe crabs (Xiphosura, Limulidae) indicates Paleogene diversification of Asian species. Molecular Phylogenetics and Evolution (2012) 62:21-26
2066	TJ Novitsky and H Donald Hochstein, Limulus Endotoxin Test, in Rapid Microbial Methods in the Pharmaceutical Industry, Martin C. Easter, ed. (2005)
2067	Iwanaga S et al., Molecular Mechanism of Hemolymph Clotting System in <i>Limulus</i> , Thromb Res (1992) 68:1-32
2068	T Nakamura and S Iwanaga, Lipopolysaccharide-sensitive serine-protease zymogen (factor C) found in Limulus hemocytes: isolation and characterization, Eur J Biochem (1986) 154:511-521

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2069	Tokunaga F et al., Lipopolysaccharide-sensitive serine-protease zymogen (factor C) of horseshoe crab hemocytes, Eur J Biochem (1987) 167:405-416
2070	Loverock, B et al., A Recombinant Factor C Procedure for the Detection of Gram-negative Bacterial Endotoxin, Pharmacopoeial Forum [Nov.-Dec. 2009] 35(6): 1613-1621.
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2072	NCBI BioProject PRJNA178588 https://www.ncbi.nlm.nih.gov/bioproject/PRJNA178588/
2073	NCBI Sequence Read Archive SRX202160 from BioProject PRJNA178588 https://www.ncbi.nlm.nih.gov/sra?LinkName=bioproject_sra_all&from_uid=178588
2074	NCBI Sequence Read Archive Run SRR610305 for Horseshoe Crab Transcriptome (metadata and data access tabs) https://trace.ncbi.nlm.nih.gov/Traces/?view=run_browser&acc=SRR610305
2075	NCBI SRA link from BioProject 178587 and entries for SRX202152 and SRX202154 (combined) https://www.ncbi.nlm.nih.gov/sra/?term=srx202152 https://www.ncbi.nlm.nih.gov/sra/?term=srx202154
2076	NCBI BioProjects FAQ https://www.ncbi.nlm.nih.gov/bioproject/docs/faq/
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2082	Pharmacopoeial Discussion Group https://www.usp.org/harmonized-standards/pdg
2083	Bolden J et al., Currently Available Recombinant Alternatives to Horsehoe Crab blood Lysates: Are they Comparable for the Detection of Environmental Bacterial Endotoxins? A Review. PDA J Pharm Sci and Tech (2020) 74:602-611.
2084	FDA Guidance for Industry Pyrogen and Endotoxins Testing: Questions and Answers, June 2012.
2085	U.S. Patent Application Publication No. 2024/0125789
2086	ORCID entry for Shun-ichiro Kawabata https://orcid.org/0000-0002-8772-7522
2087	B. Schaefer, Revolutions in Rapid Amplification of cDNA Ends: New Strategies for Polymerase Chain Reaction Cloning of Full-Length cDNA Ends, Anal Biochem (1995) 227(2):255-273.
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2093	BLAST hits and CD-Search results for Factor C, Factor B, and Pro-clotting enzyme against SRR610305
2094	Clustal alignments of T. tridentatus, L. polyphemus and C. rotundicauda Factor C and T. tridentatus and L. polyphemus Factor B and Pro-clotting enzyme
2095	Sievers F et al., Fast, scalable generation of high-quality protein multiple sequence alignments using Clustal Omega, Molecular Systems Biology 7:539
2096	JL Ding and B Ho, A new era in pyrogen testing, TRENDS Biotech (2001) 19(8):277-281
2097	Vaseeharan B et al., Cloning and characterization of a serine proteinase from the haemocytes of mud crab Scylla serrata, Fish & Shellfish Immunology (2006) 21:20-31
2098	Nguyen et al., The amino acid sequence of Limulus C-reactive protein. Evidence of polymorphism, J. Biol Chem (1986) 261(22): 10456-10465
2099	Muta et al., Primary structure of anti-lipopolysaccharide factor from American horseshoe crab, Limulus polyphemus, J Biochem (1987) 101(6): 1321-1330
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2101	Liu T et al., Limunectin: A phosphocholine-binding protein from Limulus ameobocytes with adhesion-promoting properties, J Biol Chem (1991) 266:14813-13821
2102	Fujii N et al., Isolation, cDNA cloning, and characterization of an 18-kDa hemagglutinin and ameobocyte aggregation factor from Limulus polyphemus, J Biol Chem. (1992) 267(31): 22452-22459
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2104	SJ Strong and WR Ellington, Isolation and sequence analysis of the gene for arginine kinase from the chelicerate arthropod, Limulus polyphemus: insights into catalytically important residues, Biochim Biophys Acta (1995) 1246(2): 197-200
2105	Munger SD et al., Molecular and immunological characterization of a Gq protein from ventral and lateral eye of the horseshoe crab Limulus polyphemus, Invert Neurosci. (1996) 2(3):1 75-182
2106	Chen FH et al., Molecular cloning of a putative cyclic nucleotide-gated ion channel cDNA from Limulus polyphemus, J Neurochem. (1999) 72(2): 461-471 (1999)
2107	Reid EA et al., Molecular cloning and identification of a putative PKC epsilon cDNA from Limulus polyphemus brain, Life Sci (2003) 72(8): 961-976
2108	Blackburn DC et al., Isolation and Expression of Pax6 and atonal Homologues in the American Horseshoe Crab, Limulus polyphemus, Dev Dyn (2008) 237(8): 2209-19
2109	NCBI Nucleotide search results for limulus polyphemus released prior to December 10, 2013
2110	AL Demain and P Vaishnav, Production of recombinant proteins by microbes and higher organisms. Biotech Adv (2009) 27:297-306
2111	Opponent's November 21, 2025 Submission in the Opposition against European Patent EP 3530670

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2112	Predicted 3-D structure comparisons for <i>Limulus polyphemus</i> and <i>Tachypleus tridentatus</i> Factor C, Factor B and Pro-clotting enzyme
2113	A Yoneda and T Kurokawa, A sensitive sandwich ELISA to measure (1→3)-β-D-glucan levels in blood, J Immun Meth (2011) 365:158-165
2114	Graphical depiction of Clustal alignment of <i>L. polyphemus</i> , <i>C. rotundicauda</i> , and <i>T. tridentatus</i> Factor C sequences
2115	<i>Patent Owner's Oral Hearing Demonstratives</i>

Respectfully Submitted,

Dated: June 4, 2026

/s/ Alexander B. Stein
Alexander B. Stein, Reg. No. 71,397

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e)(4), lead counsel for Patent Owner hereby certifies that on April 13, 2026, a copy of this PATENT OWNER'S UPDATED EXHIBIT LIST was served via the email correspondence address of record for Petitioner's counsel of record:

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Respectfully Submitted,

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