

Munich, December 6, 2023

Our Ref.: 257 443 m10/m30/liw
EP Application No. 23 191 930.9
Halozyne, Inc.

We write in response to the communication under Article 94(3) EPC of October 17, 2023.

1 Amendments and basis (Art. 76(1) and 123(2) EPC)

An amended set of claims is enclosed. A marked-up copy indicating the amendments made is also enclosed. All amendments to the application are made without prejudice to any of the Applicant's rights. No subject matter is abandoned. The Applicant reserves all rights under the EPC to reinstate subject matter contained in the application as originally filed in the present application or divisional applications.

Claim 1 has been amended to remove the reference to SEQ ID NO: 9, i.e., to refer to SEQ ID NOs: 4-8. The removal of SEQ ID NO: 9 does not generate any new information. Page

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111 of the Original Disclosure,¹ for example, confirms unambiguously that SEQ ID NO: 9 is indeed not necessarily present in mixtures of species of polypeptides according to the invention. A presence of SEQ ID NO: 9 is therefore not intrinsically technically linked to the other sequences of the mixture according to the express Original Disclosure.

Claim 1 has also been amended to refer to “a mixture of polypeptides, said mixture comprising species of polypeptides ~~having~~ consisting of the sequences set forth in SEQ ID NO: 4-8”. This amendment also does not add any information going beyond the original disclosure. Moreover, it is well-established that the term “comprising” (and corresponding terms) also provides basis for “consisting of” (see CLBA10, II-E, 1.15, in particular cited decisions T 759/10, T 107/14 and T 1634/13).

Claim 1 has further been amended to remove the term “about”.

Previous claims 17 and 18 have also been removed.

All present amendments to the claims comply with Articles 76(1) and 123(2) EPC.

As requested, the applicant herewith also provides a detailed table of correspondence for all claims in the root application PCT/US2009/001455 (published as WO 2009/111066).

Claim	Basis	
	in original PCT claim no.	in PCT/US2009/001455 (published as WO 2009/111066)
1	1	Page 20, line 17; page 8, lines 24-26; page 39, lines 3-4; page 8, lines 19-20
2	2	
3	3	
4	4	
5	5	

¹ Herein, the term Original Disclosure refers collectively to the root application as filed (PCT/US2009/001455) and the effectively identical disclosures of specifications as filed of the previous and present divisional applications. In divisional applications, the original PCT claims have been incorporated into the description as numbered clauses (starting on page 120).

6	6	
7	7	
8	8	
9	9	
10	10	Page 48, lines 27-29 and page 101, lines 18 and 19
11	11	Page 48, lines 27-29 and page 101, lines 18 and 19
12	12	
13	13	
14	14	
15	15	
16	16	
17		Page 8, lines 19-31
18	19, 20	Page 5, line 28 – page 6, line 2; page 8, lines 19-31; page 10, lines 12-15; page 62, lines 22-31; page 107, lines 4-15

The claims thus comply with Articles 76(1) and 123(2) EPC.

2 Clarity, support and sufficiency (Art. 83, 84 EPC)

The claims comply with Art. 83 and 84 EPC.

2.1 The term “having” has been amended to “consisting of”

The examination report states that SEQ ID NOs: 4-9 are nested sequences, and the term “*having sequences*” (understood to mean “*comprising sequences*”) is considered problematic for defining the sequences.

Without prejudice, claim 1 has been amended and now refers to a “*composition comprising a mixture of polypeptides, said mixture comprising species of polypeptides ~~having~~ consisting of the sequences set forth in [...]*”.

The claims comply with Art. 83 and 84 EPC.

2.2 Support and disclosure for SEQ ID NOs 4-8

The examination report states that there is only technical support and sufficient disclosure for a mixture of SEQ ID NOs: 4-8 on page 111, tables 27, 28. It is requested that the claims be limited to a mixture of all of SEQ ID NOS: 4-8.

Without prejudice, the claims have been amended and now refer to a *“composition comprising a mixture of polypeptides, said mixture comprising species of polypeptides consisting of the sequences set forth in SEQ ID NO: 4-8”*. The claims thus require the presence of all of SEQ ID NOS: 4-8 in the composition.

The claims comply with Art. 83, 84 EPC.

2.3 Composition comprising a mixture of species

The examination report states that it is considered unclear whether the composition comprises one of SEQ ID NOs: 4-9, or all of them, or a subset thereof. The report particularly makes reference to a passage on page 8 in the description that refers to *“a mixture of species that can include one or more of SEQ ID NOs: 4-9 in various abundance”*.

The present amended claims do not recite that language. The pending claims do not refer to a presence of only *“one”* polypeptide; they clearly and unambiguously require that the claimed composition comprises *“a mixture of polypeptides, said mixture comprising species of polypeptides consisting of the sequences set forth in SEQ ID NO: 4-8”*. Regarding the wording on page 8 of the description, we request that any adaptation of the description to bring it into line with the claims be deferred until a set of claims has been agreed upon.

The claims comply with Art. 83 and 84 EPC.

2.4 Product-by-process claims

The claims are allowable product-by-process claims. Product-by-process claims can be granted if the following two criteria are satisfied:

- i. The product as such is novel and inventive, taking into account any structural features of the product that are an inevitable result of the method recited in the claim; and
- ii. It is impossible to define the claimed product other than in terms of a process of manufacture.

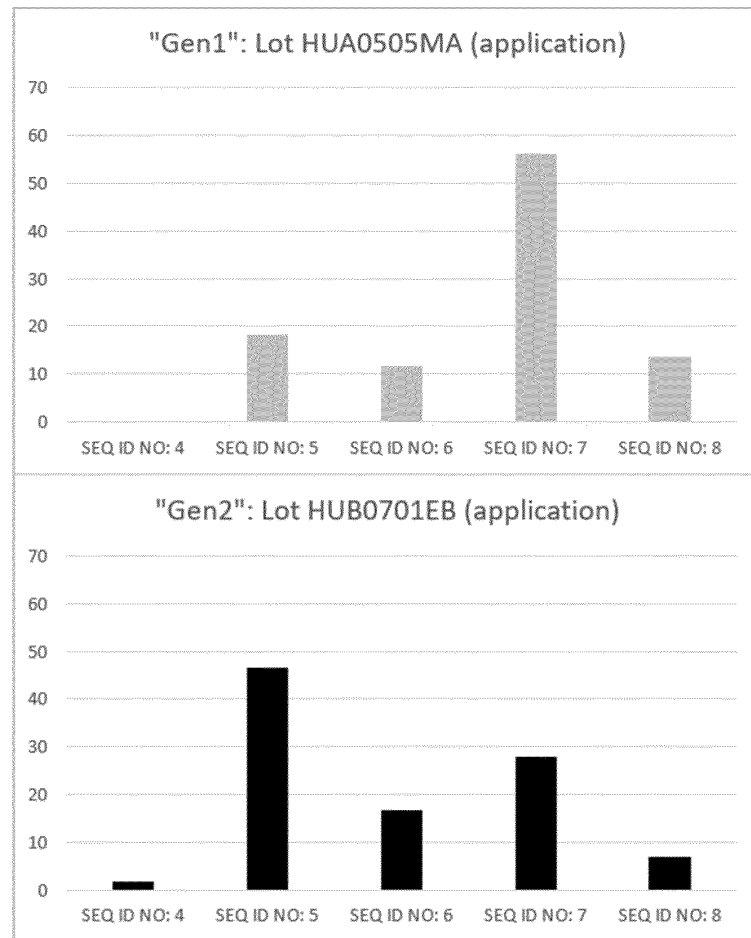
We will explain below that the present claims satisfy these criteria:

2.4.1 The method recited in the claim inevitably results in distinctive structural product/composition features

Cited prior art document D1 shares inventors with the present application, and describes an earlier approach for producing soluble hyaluronidase. The Examples in the application as filed include comparative data showing results obtained both with this earlier generation method (referred to as “Gen1” producing product lots labelled “HUA[...]”) and with the method described in the present claims (referred to as “Gen2” producing lots labelled “HUB[...]”).

The present method differs from that of D1 in the specific method steps recited in the appended claims. Examples of differences include the four specific feeding steps that are carried out in conjunction with adjusting the culture temperature.

The different method results in a different composition. This can be seen, e.g., in the data shown on page 111 of the application as filed, to which the examination report also refers. More specifically, these data show that the relative abundance of SEQ ID NOs: 4-8 within the obtained mixture of species is different. For clarity and illustration, the numerical data of Tables 27 and 28 on page 111 of the application as filed is represented in two following bar graphs:

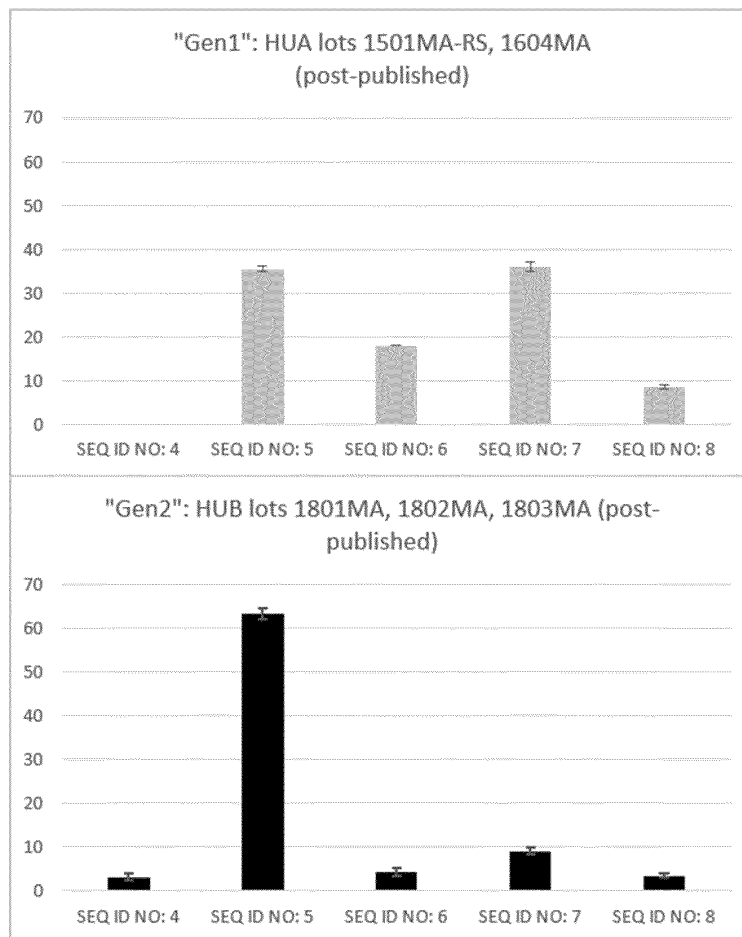


The bar labelled SEQ ID NO: 4 indicates the abundance of the longest polypeptide species consisting of 447 amino acids. SEQ ID NOs 5-8 are successively shortened by one amino acid. SEQ ID NO: 8 thus indicates the abundance of the polypeptide species consisting of 443 amino acids. The data on page 111 of the application as filed thus show that the "Gen1" method predominantly produces shorter polypeptide species, wherein SEQ ID NO: 7 is the most abundant.

In contrast, the "Gen2" method recited in the present claims predominantly produces longer polypeptide species, with SEQ ID NO: 5 as the most abundant. In other words, the method recited in the present claims results in a structurally different product (composition) having a higher abundance of longer polypeptide species.

This shift towards producing a higher abundance of the longer polypeptide species reflects a general trend that is observed when using the production method according to the present application's claims, in comparison to using the production method disclosed in D1.

For the avoidance of doubt, and to confirm this teaching of the application, we herewith also provide further comparative data demonstrating this difference. These post-published data entirely confirm that the same trend is consistently observed throughout batches that were produced using the "Gen1" ("HUA"-Lots) method versus the "Gen2" ("HUB"-Lots) methods. The following graph summarises data obtained in two further "Gen1" "HUA"-lots, as well as three further "Gen2" "HUB"-lots (plotted as average $\pm$ standard deviation):



Thus, post-filing data confirms the trend toward longer sequences that is apparent in the data of page 111 of the application as filed. Specifically, the “Gen1” method predominantly produces shorter polypeptide species, with SEQ ID NO: 7 as the most abundant, whereas the “Gen2” method of the present claims predominantly produces longer polypeptide species, with SEQ ID NO: 5 as the most abundant.

The data in the Original Disclosure therefore show that the process by which the claimed composition is produced confers identifiable and unambiguous technical features on the composition, in particular in terms of the length distribution of species SEQ ID NOs: 4-8.

2.4.2 The product as such is novel and inventive

It is clear from the above discussion that a composition obtainable by the method recited in the present claims differs from that obtainable by the “Gen1” method disclosed in D1, for example, in the abundances of the different species of polypeptides. The claimed product as such is thus novel.

The claimed product as such is also inventive.

D1 is the only cited prior art document and may thus be considered the closest prior art.

Claim 1 of the present application is distinguished from D1 at least by the specific features of the product that are the inevitable result of the process recited in the claim.

For example, as explained above, the data on page 111 show that the relative abundances of the components of the claimed mixture are different – longer, more complete sequences are relatively more abundant. The post-filing data that we also file herewith further confirms this effect on the structure of the composition.

This higher abundance of longer polypeptide species in the composition indicates that the method recited in the present claims reduces cleavage of the product, i.e.,

stabilises the product. This clearly reflects an improvement over compositions resulting from the “Gen 1” method of the prior art.

We also note that this distinct and improved product is obtained only in connection of and by virtue of the method for which an inventive step has already been acknowledged in the patent granted from the root application. We note immediately that a novel product produced by that method must necessarily involve an inventive step for the same reasons as the method that allows the product to be made.

Further, as has been explained in detail and acknowledged by the EPO during prosecution of the parent case EP 3 760 715, the “Gen 2” method is in turn also associated with additional underlying advantages, such as that the harvested cell culture fluid in which the novel mixture of species of polypeptides is obtained has an increased enzymatic activity per volume compared to that obtained in D1 (cf. Examples 4-8 of the present and root applications).

The claimed subject matter thus solves the objective technical problem of providing an improved rHuPH20 composition.

The solution provided in the present claims would not have been obvious in view of D1. D1 provides no motivation or suggestion that would have led the skilled person to the Gen 2 method and thus to a composition obtainable by the process recited in the claims in an obvious manner. The required enabling teaching and experiments are disclosed only in the present application. D1 provides no pointers, e.g., towards using the exact feeding steps or temperature adjustments recited in the pending claims.

Thus, the claimed product, as such, is both novel and inventive over the state of the art.

2.4.3 It is not possible to define the claimed product appropriately other than in terms of a process of manufacture

As explained above, the inventive method of the pending claims reproducibly results in a mixture of species of polypeptides of the sequences SEQ ID NO: 4-8 that clearly differs from the mixture that is obtainable by the method disclosed in D1. This novel

and inventive characteristic of the product according to claim 1 is causally associated with and defined by the process parameters of the recited method.

However, it will also be generally clear to the person skilled in the art of protein expression and purification that a certain degree of batch-to-batch variation will necessarily occur in methods of protein production using cell culture and purification. While the difference between the product and the prior art is entirely clear, and the method recited in the claims consistently results in a product that is novel and inventive as such over the prior art, the percentages at which the individual species occur in the mixture will obviously not always be exactly the same. This is also evident from the graphs of the data shown above.

It would be an undue limitation of the claims to require the claims to recite, e.g., the exact percentages of the components, e.g., as obtained in the specific experimental data of page 111 of the application. The data overall, including the confirmatory post-filing data provided herewith, show that, if the “Gen 2” as recited in present claim 1 method is reproduced, the size distribution of the species in the product will again follow the characteristic novel pattern discussed above, so an entirely equivalent novel and inventive product will be obtained. But the exact values of the percentages at which the individual species occur in the mixture will somewhat differ from those shown on page 111 (see the confirmatory post-filing data above).

Therefore, the polymer composition is characterised by a range of size distribution that results from the process parameters, and the production process is the most suitable and just way to define the product composition. It would be an undue limitation of the claims to require, e.g., the exact percentages of page 111 to be recited. Products obtained by the same inventive method and thus benefiting equally from the inventive disclosure in the present application, but with slightly differing percentages, would be clear equivalents of the specific product composition that is described on page 111.

We note that, for such reasons, product-by-process claims are common in technical areas of complex compositions, such as pharmaceutical compositions having novel and inventive product features that cannot be adequately defined by its components, structure or other parameters (e.g., a higher activity achieved, as in

T 0148/87), as well as compositions comprising mixtures of expressed proteins (e.g., the mixture of antibodies in T 130/90).

The situation in the present case is fully in line with principal requirements for product-by-process claims as established in the case law. For example, in T 205/83 relating to polymers, it was held that *“novelty of a product-by-process claim can be established only if evidence is provided that modification of the process parameters results in other products”* and that *“it is sufficient for this purpose”* to show that *“distinct differences exist in the properties of the products”* (headnote of this decision). As a further example, in T 748/98, novelty of a product-by-process claim was accepted on the grounds that there were *“marked differences between the process steps of claim 1 [and the prior art]”*, which *“necessarily lead to the conclusion that the products of claim 1 are not identical to the products obtainable by wording according to [the prior art]”* (see T 748/98, reason 7).

In line with this established case law, the applicant has provided evidence that modification of the process parameters results in other products, in that the composition is inherently structurally distinct. Moreover, there is no doubt that there are marked differences between the process steps of claim 1 and those disclosed in D1, e.g., in that D1 neither discloses nor teaches culturing steps recited in the present claims, such as feeding steps and temperature adjustments (the novelty and inventive step of the method has already been acknowledged on the patent granted in 2015 from the root application, EP 2 268 805).

The products obtainable by the method according to the present claims are clearly not identical to those obtainable by the method disclosed in D1, and, due to inherent variability of the process, it is also not possible appropriately to define the claimed product other than in terms of its process of manufacture.

The present product-by-process claims thus comply with Art. 83, 84 EPC.

2.5 Claims 17 and 18

The examination report objects to claims 17 and 18, in that these claims allegedly refer to sequence variants of the encoding vector. Without prejudice, claims 17 and 18 have been removed. None of the claims submitted herewith refer to sequence variants. The claims thus also comply with Art. 83, 84 EPC under this aspect.

2.6 Removal of the term “*about*”

The examination report states that the approximate term “*about*” should be deleted in all instances throughout the claims. The claims have been amended accordingly.

In conclusion, the claims comply with Art. 83, 84 EPC.

3 Novelty and inventive step (Art. 54, 56 EPC)

As already discussed in connection with the allowability of product-by-process claims above, the claimed subject matter is novel and inventive.

We have demonstrated above that the product as such is novel and inventive. We have shown that the product obtainable by the method recited in the claims

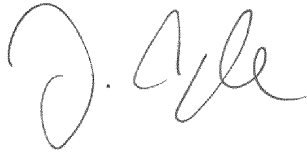
- i. differs as such from products obtainable by the method disclosed in D1, e.g., in its C-terminal microheterogeneity profile; and
- ii. is, as such, a solution to a technical problem which was not obvious in light of the state of the art, namely the provision of an improved composition comprising hyaluronidase.

The claims comply with Art. 54, 56 EPC.

4 Conclusions

The amended claims meet the requirements of the EPC. If the Examining Division considers that any objections remain, we would be pleased to discuss them with the Primary Examiner by telephone. Alternatively, we request that a further communication be issued.

Purely as a precaution, we note that oral proceedings are requested should the Examining Division at any time be considering refusing the application without allowing the Applicant a further opportunity to respond in writing.

A handwritten signature in black ink, appearing to read "J. Ogle". The signature is fluid and cursive, with the first letter "J" being particularly large and stylized.

OGLE, James Matthew, PhD
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Association No. 151

Enc. Amended claims (clean and marked-up copies)