

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

WUHAN HEALTHGEN BIOTECHNOLOGY CORP.,
Petitioners

v.

VENTRIA BIOSCIENCE INC.,
Patent Owner

Case No. IPR2022-00712
Patent No. 10,618,951

PETITION FOR *INTER PARTES* REVIEW

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Glossary

Notation	Meaning
AIA	America Invents Act
FDA	U.S. Food and Drug Administration
IPR	<i>Inter partes</i> review
<i>Bold/italicized text</i>	Emphasis added unless otherwise indicated
POSA	Person of ordinary skill in the art
USPTO or Office	U.S. Patent and Trademark Office
'951 patent	U.S. Patent No. 10,618,951
rHSA	Recombinant human serum albumin
pHSA	Human serum albumin derived from blood plasma
rhLF	Recombinant human lactoferrin
Limulus assay	Limulus amoebocyte lysate assay for endotoxins

I. Introduction

Petitioner Wuhan Healthgen Biotechnology Corp. respectfully requests *inter partes* review of claims 1-9 and 11-13 of U.S. Patent No. 10,618,951 (“’951 patent”) (EX1001) assigned to Ventria Bioscience Inc. (“Ventria” or “Patent Owner”).

The ’951 patent concerns cell culture media compositions comprising, e.g., recombinant human serum albumin (“rHSA”) and recombinant transferrin-related proteins such as lactoferrin (“rhLF”). Recombinant proteins are expressed in hosts that would not naturally produce them. Such recombinant proteins provide advantages over animal-sourced proteins in cell culture media, as they curtail the risk of animal-associated pathogens.

Long before the ’951 patent, recombinant proteins were known to serve the same general functions as their natural counterparts in promoting the survival and/or proliferation of cells in culture. Indeed, years before the ’951 patent, Ventria filed a patent application (Deeter) disclosing the use of rHSA (Cellastim™) and rhLF (Lacromin™) in cell culture. These recombinant proteins are no different from those disclosed in the ’951 patent. In fact, the ’951 patent copied nearly verbatim Deeter’s processes for producing rHSA and rhLF in transgenic rice.

The dependent claims of the ’951 patent further recite limitations concerning heat shock proteins (Hsps) inherently present in rHSA produced using Deeter’s transgenic rice. The ’951 patent asserts that the presence of these Hsps renders the

rHSA disclosed therein superior to other albumins in cell culture, but the evidence establishes that the superior growth-promoting activity attributed to heat shock proteins in the '951 patent was also observed for the prior art rHSA of Deeter.

As the proteins of the '951 patent were not themselves new, the sole independent claim is directed to the *purity* of rHSA in the composition, reciting “less than 1 EU endotoxin/mg albumin” and “less than 2% aggregated albumin.”

During prosecution, Ventria relied on *only* the endotoxin limitation to distinguish the rHSA of Deeter, representing that Deeter’s rHSA contained higher levels of endotoxins. Having lower levels of endotoxins, however, does not transform what was done before into a patentable invention, as albumin and rHSA having less than required “1 EU endotoxin” were well-known in the art. Notably, the '951 patent does not claim any method for purifying rHSA—all that is required is a composition comprising less than 1 EU endotoxin/mg albumin.

Indeed, Tanaka and Van Urk provide extensive guidance on preparing plasma-derived albumin (pHSA) and rHSA free of endotoxins and having at most 1% aggregated albumin. Van Urk specifically discloses that its process is suitable for purifying rHSA produced in transgenic plants, i.e., the rHSA of Deeter. Purifying Deeter’s rHSA following the guidance of either Tanaka or Van Urk would have been well within the ordinary level of skill in the art.

The prosecution history does not provide a basis for denying institution, as Tanaka, Van Urk, and Meng were not of record and are not cumulative over the art cited during prosecution. *Infra*, § XVI.

Nor does the status of any related proceeding favor denial of institution, as this petition challenges several claims not at issue in any other proceeding, presenting distinct issues from the handful of claims litigated at the U.S. International Trade Commission (ITC). *Infra*, § XV.

As detailed below, there is a reasonable likelihood that Petitioner will establish that the challenged claims are unpatentable. Petitioner respectfully requests that the Board institute IPR and cancel claims 1-9 and 11–13 of the '951 patent.

II. Grounds for Standing

Petitioner certifies that the '915 patent is available for IPR and that Petitioner is not barred or estopped from requesting IPR review on the grounds presented herein. *Infra*, § XIII.B.

III. Identification of Challenge

Petitioner challenges claims 1-9 and 11–13 of the '951 patent and requests that these claims be found unpatentable under 35 U.S.C. § 103 in view of the following publications, which all qualify as prior art under pre-AIA 35 U.S.C. § 102(a) or (b), § 103.

Ground	References	Basis	Claim(s)
1	Deeter and Tanaka	35 U.S.C. § 103	1-8, 11-13
2	Deeter, Tanaka, and Meng	35 U.S.C. § 103	9
3	Deeter and Van Urk	35 U.S.C. § 103	1-8, 11-13
4	Deeter, Van Urk, and Meng	35 U.S.C. § 103	9

IV. The '951 Patent

The '951 patent concerns cell culture media containing combinations of proteins. EX1001, abstract. As the patent explains, the use of animal-derived proteins in cell culture raises safety and ethical concerns, prompting efforts to develop alternative sources for such proteins. *Id.*, 2:54-56. The '951 patent thus describes preparing rhLF, rHSA, and recombinant transferrin in transgenic rice, purifying them, and using them in cell culture media. *Id.*, 62:59-75:22, 83:4-96:45.

The '951 patent further explains that rice heat shock protein 70 (Hsp70) family members were “found to occur” in the rHSA of Cellastim™. *Id.*, 78:48, 79:9, 79:35. As acknowledged in the specification, standard techniques such as filtration, ion exchange chromatography, and hydrophobic interaction chromatography do not separate Hsp70 from rHSA. *Id.*, 50:39-51:6.

A. Challenged Claims

The '951 patent's sole independent claim recites:

A cell culture media supplement or complete media composition
for improving the growth of a cell in cell culture comprising:

a recombinant mammalian albumin wherein said albumin is

i) produced in a transgenic plant;

ii) has less than 1 EU endotoxin/mg albumin; and

iii) less than 2% aggregated albumin.

The dependent claims require that the composition further comprise at least 0.01% wt/wt of a heat shock protein (claim 2), rice heat shock protein (claim 3), Hsp70 family members (claims 4-6), rhLF (claim 7), recombinant transferrin (claim 8), a ratio of transferrin to albumin of 1:50 to 1:5000 (claim 9), rHSA (claim 11), production in a transgenic grain (claim 12), and production in transgenic rice (claim 13).

B. Priority Date

The '951 patent claims priority to application no. 12/708/462 (filed February 18, 2010) and provisional application no. 61/154,204 (filed February 20, 2009). The '951 patent is not entitled to rely on the 2009 filing date, as the provisional application does not mention "endotoxin" or "aggregated albumin," much less disclose any recombinant mammalian albumin containing "less than 1 EU endotoxin/mg albumin" and "less than 2% aggregated albumin," as required by all claims of the '951 patent. EX1061, 2-76.

V. Background and Asserted Prior Art

A. Recombinant Proteins in Cell Culture Media

Prior to the '951 patent, recombinant proteins had been commercialized and marketed as cell culture media supplements. EX1002, ¶¶ 15-24. For example:

- In 2006, Recombumin (rHSA expressed in yeast) was approved for use in growth media used to produce a new measles, mumps, rubella vaccine. EX1014, 8. Recombumin was reported to be “equivalent to the native human serum albumin in primary, secondary and tertiary structure as well in binding capacity.” *Id.*
- By 2007, Cellastim™ (rHSA) was reported to be biochemically and biophysically “identical” to pHSA, while outperforming pHSA in cell culture media. EX1018, 2, 3.
- In 2008, Grosvenor reported the activity of rHSA and recombinant transferrin in cell culture media, noting that the recombinantly expressed proteins showed equivalence to their natural counterparts. EX1059, 5-6.
- In 2008, Huang detailed the use of Lacromin™ (rhLF) in cell culture media, noting that rhLF produced in transgenic rice “provides a consistent, non-animal source of lactoferrin and is likely to find broad applications in cell culture to promote cell growth and production.” EX1058, 7.

These same publications reflect a concern over the use of animal-derived proteins in cell culture media, rendering recombinant analogues attractive

replacements. *E.g.*, EX1002, ¶¶ 15-27; EX1058, 1; EX1059, 6-7; EX1014, 1; EX1018, 2.

Transgenic rice was known to be an attractive expression system for recombinant human proteins, including rHSA. EX1002, ¶¶ 25-27. Transgenic rice was reported to be superior to other transgenic plants because it does not produce any toxic secondary metabolites and provides rHSA in high yield. EX1023, 10.

B. Endotoxins

Endotoxins were well known to be common contaminants exhibiting cytotoxic effects. The presence of endotoxins in cell culture media supplements was a concern, as cell culture media was commonly used in the production of biological drug products, and if present, complicate purification of downstream products produced in cell culture media. EX1002, ¶¶ 28-31; EX1052, 1, 4; EX1027, 1:49–52; EX1028, 7; EX1029, 3.

Researchers thus reported removing endotoxin from proteins such that they would include at most low levels of endotoxin, *e.g.*, 1 EU endotoxin per mg protein. EX1002, ¶ 28; EX1025, 20-21; EX1026, 10; EX1047, 2; EX1050, 4).

Commercially available chromatography resins had been widely used to remove endotoxins from proteins, including albumin and rHSA. EX1002, ¶¶ 30-34, 253. As Demmer explains, endotoxins have a negative charge in most solutions, making ion exchange chromatography “the most common depyrogenation method

for proteins.” EX1026, 10. Using a buffer pH lower than the isoelectric point of the protein, the endotoxins will bind to an anion exchange chromatography column, and the protein will pass through. *Id.*, 10-11.

As another example, Aida discloses a simple process for removing endotoxin from bovine serum albumin (BSA). EX1060, 1. Aida explains that endotoxins may be removed by treating proteins with a detergent such as Triton X-114. *Id.*, 3. Aida reported that the purified BSA had no detectable endotoxin. *Id.*, 3 (Table 1), 4. Aida explains that a “major advantage of the procedure was that it appeared not to harm the proteins.” *Id.*, 5. Aida suggests this process for removal of endotoxin from recombinant products and albumin. *Id.*

Prior to 2009, rHSA products containing low levels of endotoxin were commercially available, including rHSA having less than 1% aggregated albumin. EX1002, ¶ 34; EX1017, 9; EX1016, 2; EX1014, 8.

C. Heat Shock Proteins (Hsps)

By 2009, certain Hsps were known to associate with recombinant proteins. *See* EX1002, ¶¶ 35-38; EX1031, 4; EX1049, 1. As Dr. Clark explains, Hsps were known to exist in all host cells and serve as “chaperones” that bind to newly translated proteins and help such proteins adopt the same three-dimensional structure as their native counterparts. EX1002, ¶ 35; EX1031, 4; EX1032, 1, 2; EX1033, 1. These chaperones proteins were reported to bind recombinant proteins due to their

chaperone functionality. EX1031, 4; *see also* EX1041, 8 (noting that albumin itself is a “sticky” molecule).

It was also known that rHSA and Hsp70 proteins have similar isoelectric points (pI) and molecular weights, making them difficult to separate. EX1002, ¶ 36. For example, rHSA has an isoelectric point of about 5.3, while the isoelectric point of rice Hsp70 proteins is around 5. EX1034, 4 (Fig. 1); EX1003, [0117] (Table 3). In addition, the molecular weights of rHSA and Hsp70 were known to be ~67 kDa and 70 kDa, respectively. EX1002, ¶ 37; EX1003, Table 3 (page 30).

D. Asserted Prior Art

1. Deeter

Deeter (WO 2007/002762) is assigned to Patent Owner (Ventria) and identifies a set of inventors that overlaps with those on the face of the '951 patent. EX1003 (page 1). Deeter, however, published on January 4, 2007—years before the '951 patent was filed. *Id.* Deeter discloses the use of recombinant proteins produced by transgenic rice in cell culture media. EX1002, ¶¶ 39-48; EX1003, [0009].

Deeter explains that cell culture media components derived from animals “have several undesirable features,” including the risk of contamination. EX1003, [0006]- [0007]. Deeter thus reports that “there is a need to produce components for incorporation into cell culture media that is not derived from, or produced by, animal sources, yet still retain their functional value for cell cultures.” *Id.*, [0008].

Deeter discloses the “production and use of recombinant proteins produced by plant cells as components of cell culture media” (*id.*, [0002]), where such recombinant proteins provide “the same or improved growth and productivity of cells as compared to the use of media containing animal-derived components” (*id.*, [0009]).

Deeter details the production of rHSA and rhLF from transgenic. EX1003, [0100]-[0105]. Deeter’s production system provides a very high yield of rHSA (up to 8.5 grams rHSA/kg flour) and rhLF (about 3 grams rhLF/kg flour). EX1003, [0105], [0109]; EX1002, ¶ 42.

Deeter further describes purifying rHSA and rhLF. EX1003, [0106]-[0110], [0116]. The biochemical and biophysical properties of the Deeter’s rHSA were “equivalent” to pHSA. EX1003, [0117].

Deeter also discloses the activity of rHSA and rhLF in cell culture media. EX1002, ¶¶ 44-48. For example, Deeter reports that “cells grown in media with rHSA supplementation grew equivalently or better than cells grown in media with plasma derived HSA. EX1003, [0118]. According to Deeter, these results indicate that rHSA from rice was “functionally equivalent” or “better than” pHSA in enhancing hybridoma cell growth in reduced-serum media.” EX1003, [0118]; *see also id.*, [0120], Figs. 23, 24.

Similarly, Deeter reports promoting cell growth with cell culture media supplemented with rhLF. EX1003, [0111]-[0115], Table 2, Figs. 20-22. For example, Deeter compares hybridoma growth and monoclonal antibody (IgG) production in un-supplemented cell culture media (control), media supplemented with transferrin (TF), media supplemented with recombinant human lactoferrin (rhLF), and media supplemented with 5% fetal bovine serum (FBS). *Id.*, Table 2 (page 30). Deeter reports that transferrin and rhLF substantially increased the number of cells relative to the control media at all concentrations tested, and when added at concentrations below 100 µg/ml, transferrin and rhLF also substantially increased the amount of monoclonal antibody produced. *Id.* Deeter concludes that rhLF “can be used to replace animal-derived transferrin in cell culture media for hybridoma cell growth.” *Id.*, [0113].

2. Tanaka

Tanaka published in 1998 and provides a simplified method for purifying albumin to remove pyrogens (e.g., endotoxin) and aggregated albumin. EX1053; EX1002, ¶¶ 49-61.

Tanaka’s purification process involves (1) anion exchange chromatography (DEAE-Sepharose), (2) fatty acid removal, (3) gel filtration on Sephacryl S-200 HR, and (4) viral inactivation. EX1053, 2-4. Tanaka explains that the disclosed method

is more time- and cost-efficient than prior methods for purifying albumin from serum. *Id.*, 5.

After purifying albumin using the steps outlined above, Tanaka determined that the albumin was 99.0% to 99.3% monomeric albumin and 0.7% to 1.0% dimeric, with no larger aggregates detected. *Id.*, 4.

Tanaka further discloses that the albumin is free of endotoxins. EX1002, ¶¶ 60-61. For example, Tanaka explains that the disclosed process provides “a high quality, *pyrogen-free* product.” EX1053, 5. As Dr. Clark explains, a product that is pyrogen-free contains no endotoxins. EX1002, ¶ 61.

3. Van Urk

Van Urk (WO 2000/44772) published on August 3, 2000 and provides processes for preparing highly purified albumin, including rHSA produced in a transgenic plant. EX1004, 1:3-9. Van Urk notes that “the albumin may be obtained from a transgenic plant, such as tobacco, potato or corn (maize).” EX1004, 22:27–28.

According to Van Urk, the rHSA of the invention contains no detectable endotoxin, as determined by the sensitive Limulus amoebocyte lysate assay. EX1002, ¶ 65; EX1004, 72-73. Van Urk further discloses that its rHSA was non-pyrogenic, meaning free of pyrogenic agents including endotoxins. EX1004, 63.

Van Urk also discloses that its rHSA contains less than 1% aggregated albumin. EX1002, ¶ 66. For example, Van Urk discloses that in its rHSA, “[t]here may be up to 1% dimeric albumin but no larger polymers or aggregates are detectable.” EX1004, 65; *id.*, 71-72. Van Urk reports that as formulated, its rHSA was “found to contain less than 0.1% polymeric albumin,” such that “the formulation as described herein has no detrimental effect on the polymer/aggregate content of the purified albumin.” EX1004, 71.

4. Meng

Meng (EP 2,177,602) was filed on November 1, 2008 and discloses serum-free cell culture media for stem cell culture comprising transferrin and serum albumin (among other components). EX1054, 5:17-21; EX1002, ¶¶ 68-72. Meng discloses that the serum albumin may be rHSA. *E.g.*, EX1054, 4:28-30, 5:22-27.

Meng discloses that the rHSA preferably “be sufficiently purified to the extent to be used as a drug (injection solution).” EX1054, [0024]. As explained by the Japan Patent Office, it would have been understood that “albumin used in the injectable drug does not contain endotoxin or aggregated albumin.” EX1055, 2.

Meng further discloses that in its cell culture media, the concentration of transferrin is 0.1 mg/L to 10 mg/L, while the concentration of albumin is “not less than 0.1 g/L,” which is 100 mg/L. EX1054, [0022]-[0023]. Thus, Meng teaches that the ratio of transferrin to rHSA should be at least 1:10 to 1:1000. EX1002, ¶ 71.

Meng specifically discloses stem cell culture media comprising, among other components, 5.5 mg/L transferrin and 2.5 g/L rHSA (2,500 mg/L rHSA), i.e., a weight ratio of 1 transferrin to 455 rHSA. EX1054, 13:11-24; EX1002, ¶ 72.

VI. Level of Ordinary Skill in the Art

Petitioner submits that a POSA would have had a Ph.D. in chemistry, biochemistry, or chemical engineering, with at least two years of experience involving production and/or purification of proteins such as a rHSA and/or experience with compositions suitable for use in cell culture media. This level of skill would be the same whether the patent was afforded a priority date based on the provisional application (filed February 20, 2009) or the non-provisional (filed February 18, 2010).

VII. Claim Construction

Healthgen and Ventria agreed to the following claim interpretations in a related proceeding:

Parties' Agreed Upon Claim Construction Proposals in Litigation		
Term	Claim(s)	Parties' Proposed Construction
"A cell culture media supplement or complete media composition <i>[[for improving the growth of a cell in cell culture]]</i> "	1	the preamble term "[a] cell culture media supplement or complete media composition" is limiting; preamble is otherwise not limiting "cell culture media supplement" is "a combination of one or multiple cell culture media components, with or without other ingredients, for addition to cell culture media"

Parties' Agreed Upon Claim Construction Proposals in Litigation		
Term	Claim(s)	Parties' Proposed Construction
"aggregated albumin"	1	Non-monomeric albumin (e.g., albumin dimers)
"less than 2% aggregated albumin"	1	less than 2% non-monomeric albumin by weight
"recombinant albumin comprises at least 0.01% wt/wt of a heat shock protein"	2	Plain and ordinary meaning
"heat shock protein"	2, 3	a naturally occurring or synthetic form of a member of the heat shock protein super family that retains anti-apoptotic activity

EX1036, 5-6. These interpretations have been applied herein.

The parties also disputed the meaning of two claim terms, and the parties' proposals and the Court's adopted constructions are below.

Parties' Disputed Claim Construction Proposals and Adopted Constructions			
Term (claim)	Ventria's Proposed Construction	Healthgen's Proposed Construction	Construction adopted in litigation
"recombinant mammalian albumin" (claim 1)	Mammalian albumin having a molecular weight between 66-69 kDa that is exogenous (i.e., heterologous or foreign) to the transgenic plant and retains the biological or therapeutically beneficial activity of its corresponding native mammalian albumin	recombinant albumin (i.e., albumin heterologous or foreign to the transgenic plant producing it) which has the amino acid sequence of a native mammalian albumin or which is a variant, derivative, fusion protein, or fragment of native mammalian albumin (provided the fragment retains the biological or therapeutically beneficial activity of the native mammalian albumin)	recombinant albumin (i.e., albumin heterologous or foreign to the transgenic plant producing it) which has the amino acid sequence of a native mammalian albumin or which is a variant, derivative, fusion protein, or fragment of native mammalian albumin (provided the fragment retains the biological or therapeutically beneficial activity of the native mammalian albumin)
"produced in a transgenic plant" (claim 1)	The recombinant albumin has been expressed within a plant cell that has been engineered to stably express recombinant albumin	expressed within a host plant cell	expressed within a host plant cell into which a recombinant or heterologous nucleic acid molecule has been introduced

EX1065, 16-17, 24. Regardless of which interpretations are applied, the prior art discloses these claim limitations. EX1002, ¶ 90. Indeed, the prior art rHSA of Deeter is identical to the "recombinant mammalian albumin" of the '951 patent,

and it was also produced by the same “transgenic plant.” *Id.* As such, any proposed constructions capturing the purported invention were also disclosed by Deeter. *Id.*

Claims 7 and 8 of the ’951 patent recite “transferrin related protein.” The specification defines this term as “transferrin family proteins including transferrin, lactoferrin, melanotransferrin, and ovotransfer[r]in.” EX1001, 39:54-56. Consistent with blackletter claim construction law, this definition controls. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (*en banc*).

Claim 9 of the ’951 patent recites a range of ratios of transferrin to recombinant albumin, specifically, 1:50 to 1:5000. The specification describes a cell culture media supplement comprising “a ratio (wt/wt) of transferrin related protein to albumin of about 1 to 5000 to about 1 to 0.5.” *E.g.*, EX1001, 5:1-2. A POSA would have understood that in the context of the ’951 patent, the claimed ratios reflect the weight ratio of transferrin to recombinant albumin. EX1002, ¶¶ 92-93.

All other terms have been afforded their plain and ordinary meaning as they would have been understood in the context of the ’951 patent.

VIII. Ground 1: Claims 1-8 and 11-13 of the ’951 Patent Would Have Been Obvious over Deeter in view of Tanaka

A. Claim 1

All the challenged claims ultimately depend from claim 1, which recites:

A cell culture media supplement or complete media composition
[[*for improving the growth of a cell in cell culture*]] comprising:

- a recombinant mammalian albumin wherein said albumin is
- i) produced in a transgenic plant;
 - ii) has less than 1 EU endotoxin/mg albumin; and
 - iii) less than 2% aggregated albumin.

As noted above, the parties agreed that the phrase “for improving the growth of a cell in cell culture” is non-limiting, and thus this phrase is shown in bracketed italics. EX1036, 5.

Claim 1 would have been obvious over Deeter (EX1003) and Tanaka (EX1053), which collectively taught a cell culture media supplement comprising rHSA produced in a transgenic plant having less than 1 EU endotoxin per mg albumin and less than 2% aggregated albumin. EX1002, ¶¶ 101-12.

1. “A cell culture media supplement or complete media composition”

Deeter discloses “cell culture media supplement,” e.g. “a combination of one or multiple cell culture media components ... for addition to cell culture media.” EX1003, [0068]. For example, Deeter disclosed using rHSA in cell culture media and determined that it is functionally equivalent to plasma-derived HSA. EX1003, [0118]–[0120]. A POSA would have understood that Deeter’s rHSA, when purified using the guidance of Tanaka, would continue to be a cell culture media component. EX1002, ¶ 103.

2. “a recombinant mammalian albumin”

Deeter discloses rHSA, which is a recombinant mammalian (human) albumin. For example, Deeter’s rHSA is foreign to the transgenic rice producing it and has the amino acid sequence of a native HSA. *See* EX1003, [0103], Table 3 (page 30); EX1018, 5 (disclosing in 2007 that the amino acid sequence of Cellastim™ was identical to native HSA); EX1002, ¶¶ 104-06.

3. “wherein said albumin is produced in a transgenic plant”

Deeter discloses rHSA produced in a transgenic plant, specifically, transgenic rice. EX1003, [0103]-[0105]. Deeter’s process for producing rHSA is substantively identical to the ’951 patent’s process for producing rHSA. EX1002, ¶¶ 107-108 (Fig. 7); *compare* EX1003, [0103]-[0105]) to EX1001, 64:9-37).

4. “has less than 1 EU endotoxin/mg albumin”

Deeter’s rHSA, when purified using the guidance of Tanaka, would have been reasonably expected to contain less than 1 EU endotoxin/mg albumin, as recited in claim 1 of the ’951 patent. EX1002, ¶¶ 109-10, 176-91. Indeed, Tanaka’s purification process provides albumin that is “pyrogen-free,” which a POSA would have understood means free of pyrogens including endotoxins. EX1053, 5; EX1002, ¶ 110. Thus, when purified using the guidance of Tanaka, Deeter’s rHSA would have been reasonably expected to contain less than 1 EU endotoxin/mg albumin. *Infra*, § VII.M.

5. “less than 2% aggregated albumin”

When purified using the guidance of Tanaka, Deeter’s rHSA would have reasonably been expected to contain less than 2% aggregated albumin. EX1002, ¶¶ 111-12, 176-91. Tanaka’s purification process provides 99.0-99.3% monomeric albumin, i.e., less than 0.7-1.0% aggregated albumin. EX1053, 4. Thus, Deeter’s rHSA when purified using the guidance of Tanaka would have been reasonably expected contain less than 2% aggregated albumin. *Infra*, § VII.M.

B. Claim 2

As Dr. Clark explains, Deeter’s rHSA necessarily contained “at least 0.01% wt/wt of a heat shock protein,” and a POSA would have reasonably expected that purifying Deeter’s rHSA using the guidance of Tanaka would retain heat shock proteins at levels well above 0.01% wt/wt. EX1002, ¶¶ 113-41; *infra*, § VII.N.

1. Deeter’s rHSA Necessarily Contained More than 0.01% wt/wt of a heat shock protein

Deeter’s rHSA, marketed as Cellastim™, would necessarily have contained substantially more than 0.01% wt/wt of a heat shock protein, as it would have contained rice Hsp70 proteins at levels comparable to those present in the rHSA of the ’951 patent. EX1002, ¶¶ 114-33; *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) (the prior art need not recognize an inherent property); *see also Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999); *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1330

(Fed. Cir. 2020); *Acorda Therapeutics, Inc. v. Roxane Laboratories, Inc.*, 903 F.3d 1310, 1335-36 (Fed. Cir. 2018) (affirming finding of inherency where patentee cited no support for the assumption that inherent properties would differ between the prior art and the claim).

For comparison, the rHSA of the '951 patent contained more than twenty times the minimal level of 0.01% wt/wt Hsps recited in claim 2, including three rice Hsp70 proteins that were “found to occur in recombinant albumin in Cellastim.” EX1001, 78:47-51, 79:8-11, 79:34-35; EX1002, ¶ 116.¹ While the '951 patent is not prior art, its disclosures may be used to establish inherency. *See Hospira*, 946 F.3d at 1329; *Monsanto Tech. LLC v. E.I. DuPont de Nemours & Co.*, 878 F.3d 1336, 1345 (Fed. Cir. 2018).

As Dr. Clark explains, these same rice Hsp70 proteins would also be present in Deeter's rHSA at substantially above 0.01% wt/wt. EX1002, ¶ 117.

¹ A POSA would read the claims of the '951 patent as requiring at least 0.01% wt/wt total heat shock protein. However, even if the claims are interpreted as requiring 0.01% wt/wt of a single heat shock protein, the rHSA of Deeter meets this limitation. Indeed, the amounts of the individual Hsp70 family members in the '951 patent are 7, 9, and 6 times the lower limit of claim 2 (0.07%, 0.09%, and 0.06% by weight). EX1002, ¶ 116.

First, Deeter's rHSA and the rHSA of the '951 patent were produced using the same process in the same transgenic host (rice). EX1002, ¶ 118. In fact, the only difference between the Cellastim/rHSA of the '951 patent and Deeter is the level of endotoxin. EX1002, ¶ 119; EX1042, 693-94 (representing that Deeter's rHSA contained more than 1 EU endotoxin/mg albumin). Notably, during prosecution of the '951 patent, the Examiner rejected the pending claims as inherently anticipated by Deeter, arguing that Deeter's Cellastim would "inherently lack any endotoxin" and that heat shock proteins "would be inherent to the recombinant human serum albumin produced by Deeter et al." EX1042, 560-61. In response, Ventria asserted that Deeter's Cellastim would not have inherently contained less than 1 EU endotoxin—while remaining silent on the heat shock proteins, which the Examiner noted were necessarily present. EX1042, 652, 693-94.

Compared to the rHSA of Deeter, the rHSA of the '951 patent was further purified to remove endotoxins using additional steps in a process the specification refers to as a "new process" (although notably none of the purportedly "new" process steps are claimed). *E.g.*, EX1001, 71:57, 72:1-2, 73:40; EX1002, ¶¶ 115-26. As Dr. Clark explains, if anything, the additional purification steps would have reduced the level of Hsp70 proteins in the rHSA of the '951 patent relative to Deeter. *Id.* The flow chart below compares these "new" purification process described in the '951 patent to the process in Deeter.

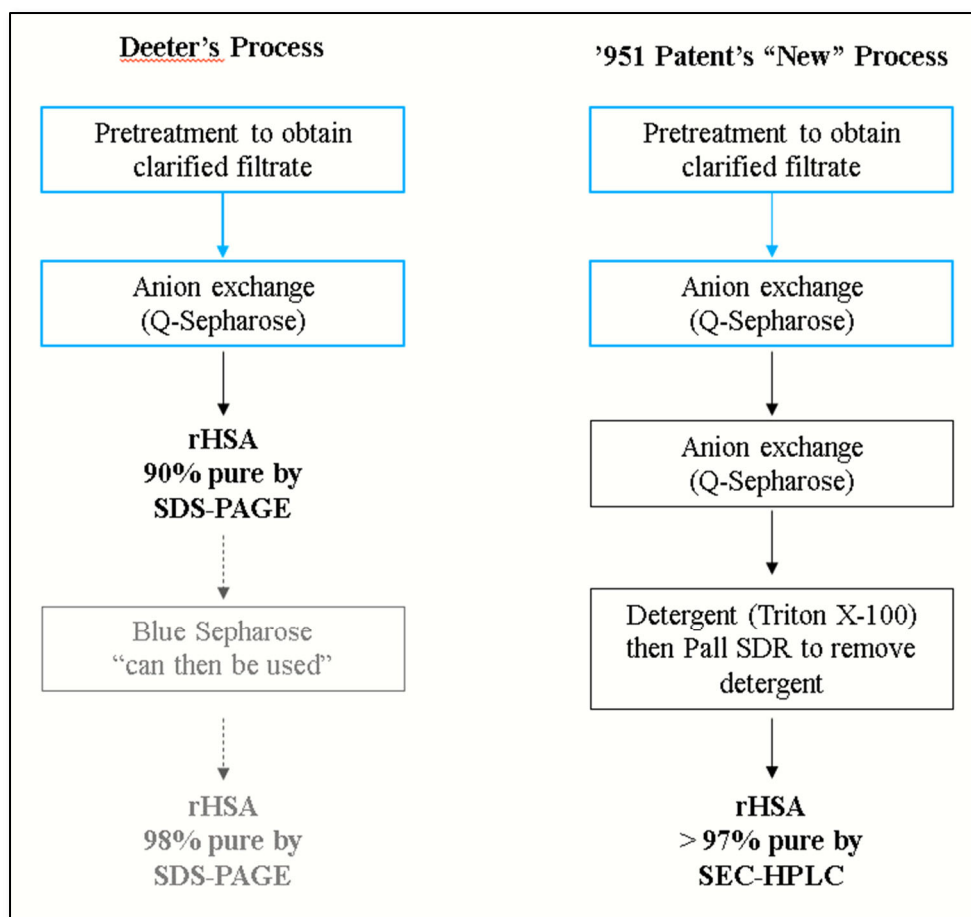


Figure 1. Deeter's purification process (EX1003, [0116]-[0117]) and the "new" process of the '951 patent (68:47-69:22); EX1002, Fig. 8 (page 49).

As shown in Figure 1, Deeter and the '951 patent both purify rHSA using Q-Sepharose. EX1002, ¶ 122. Deeter prophetically suggests further purifying rHSA using Blue Sepharose (EX1003, [0116]), while the '951 patent further employs a detergent wash (Triton X-100) and hydrophobic chromatography to remove the detergent (EX1001, 68:47-69:22). Because the purification process was more rigorous in the '951 patent, a POSA would have expected the rHSA prepared using

the “new” process to contain even less heat shock protein than what was present in Deeter’s rHSA. EX1002, ¶¶ 123.

To be sure, the additional steps in the ’951 patent would not have *increased* the level of rice Hsp70 in rHSA relative to Deeter’s rHSA. For example, the use of Triton X detergent, followed by detergent removal, would not have increased the level of rice Hsp70 proteins in the rHSA of Cellastim. EX1002, ¶ 125. As Dr. Clark explains, this detergent treatment would have been to assist in the removal of endotoxins bound to proteins such as rHSA. EX1002, ¶ 125; EX1060, 1-3 (describing removal of endotoxin from albumin using Triton X-114). If anything, the added detergent wash and subsequent detergent removal may have reduced the level of Hsp70 proteins bound to albumin, which indicates that, if anything, the rHSA of the ’951 patent contained less heat shock protein than Deeter’s rHSA. EX1002, ¶ 125.

By contrast, none of the purification steps in Deeter would have removed Hsp70 proteins to below the very low threshold of 0.01% wt/wt. EX1002, ¶¶ 126-30. For example, Deeter’s Q-Sepharose would not have removed heat shock proteins from its rHSA. *Id.*, ¶ 128. As noted above, the ’951 patent also uses Q-Sepharose and reports that it provides rHSA “enriched” in Hsps, as recited below:

Due to the similar electronegativity of albumin and hsp70, anion exchange chromatography is the preferred method to prepare albumin enriched in Hsps. For example, both albumin and Hsp70

bind to anion exchange columns with resins consisting of either quaternary amine [e.g., Q Sepharose] or diethylaminoethyl Examples of such resins are General Electric (GE) Q Sepharose and GE DEAE Sepharose.

EX1001, 50:39-48. As Dr. Clark explains, Q-Sepharose separates proteins based on net charge and thus would not have separated rHSA from Hsp70 (with isoelectric points of 5.3 and about 5, respectively). EX1002, ¶ 128.

Deeter also discloses that its rHSA was “concentrated and desalted via ultrafiltration prior to freeze drying.” EX1003, [0116]. Ultrafiltration separates molecules based on size, and accordingly, these processing steps would not have removed Hsp70 from rHSA, as rHSA and Hsp70 are approximately the same size. EX1002, ¶ 129. Notably, the '951 patent discloses multiple ultrafiltration and diafiltration steps, and still obtained rHSA comprising three Hsp70 proteins at levels of 0.07%, 0.09%, and 0.06%, totaling 0.22% wt/wt of Hsp. EX1001, 78:47-51, 79:8-11, 79:34-35; EX1002, ¶ 129.

Deeter also proposes to use Blue Sepharose to further purify its rHSA, although the prophetic disclosure indicates that Deeter did not, in fact, perform that step. EX1003, [0116] (“Blue Sepharose (GE Healthcare) *can then be used* to increase the purity from 90% to approximately 98% based on scanning analysis of SDS-PAGE gels.”). But as Dr. Clark explains, even if that step had been used, Blue Sepharose would not function to remove heat shock proteins from rHSA. EX1002,

¶ 126; EX1038, 173; EX1037, 199. In fact, the '951 patent recommends using Blue Sepharose as a suitable ion exchange chromatography resin, e.g., a resin that enhances co-purification of Hsp70 with rHSA. EX1002, ¶ 127; EX1001, 50:39-55, 67:37-42. Thus, even if rHSA was purified using Blue Sepharose (a step Deeter did not perform), the process would still fail to remove rice Hsp70 proteins from rHSA. EX1002, ¶ 127.

As a result, Deeter's rHSA necessarily contained more than 0.01% wt/wt of a heat shock protein, e.g., around 0.22% wt/wt rice Hsp70 proteins. EX1002, ¶ 131.

Notably, both the USPTO and the Japan Patent Office (JPO) agree that Deeter's rHSA inherently contained heat shock proteins. EX1002, ¶¶ 132-22; EX1042, 560-61; EX1055, 2. For example, the JPO rejected the claims of the Japanese counterpart to the '951 patent over Deeter, noting that in Deeter's rHSA, "heat shock proteins are included in the same degree as the present invention, and the kinds thereof are not different from each other." EX1055, 2. The JPO further reasoned that "the heat shock proteins are derived from the genes inherent in rice," and the purification steps of Deeter would not have removed them from rHSA. *Id.*

2. The Activity of Deeter's rHSA Confirms that It Contained More than 0.01% wt/wt Heat Shock Protein

The activity of Deeter's rHSA in cell culture media confirms the presence of rice Hsp70 proteins at levels comparable to the rHSA of the '951 patent. EX1002, ¶¶ 134-39. Hsp70 proteins were known to promote cell viability, such that their

presence would be beneficial in cell culture media. EX1002, ¶ 134; EX1032, 10; EX1051. Although the '951 patent states that the co-purified rice Hsp70 proteins in the “new” rHSA contribute to improved cell viability compared to “old” rHSA (EX1001, 73:44-59), there are no data in the '951 patent to support that claim. EX1002, ¶ 134. Indeed, the data show the opposite.

In particular, the data demonstrate that “Deeter et al.-produced” rHSA performed just as well as the rHSA of the '951 patent at low concentrations.² EX1002, ¶¶ 135-37; EX1042, 693. Comparative data are presented below.

Table 1. Viable cell density (10⁵ cells/ml) representative of “old”/“Deeter et al. produced” rHSA and the “new” rHSA of the '951 patent					
Neg Control	pHSA	“old” rHSA	'951 “new” rHSA	'951 “new” rHSA	'951 “new” rHSA
1 mg/ml				0.5 mg/ml	2 mg/ml
~ 3	~6	14-17.5	~ 14.5	11.1-18.4	14.4-17.5
EX1001, Fig. 10A.	EX1001, Fig. 10A.	EX1001, Table E3.	EX1001, Fig. 10A.	EX1001, Table E4.	EX1001, Table E4.

² Ventria represented during prosecution of the '951 patent that the data in Table E3 of the '951 patent reflect the activity of “Deeter et al.-produced albumin.” EX1024, 2; *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1569 (Fed. Cir. 1988) (admissions during prosecution are binding on the patentee for determinations of anticipation and obviousness).

As shown in Table 1, data representative of Deeter's "old" rHSA show that it performed just as well as the "new" rHSA of the '951 patent in improving cell viability at 1 mg/ml and was far superior to pHSA and untreated (negative control) media.³ EX1001, Fig. 10A (page 20), Tables E3, E4 (col. 73). Because Hsp70 proteins contribute to cell viability, these data support the conclusion that Deeter's rHSA contained about the same level of rice Hsp70 proteins as the "new" rHSA of the '951 patent. EX1002, ¶ 137.

For completeness, it is noted that at higher concentrations (5 or 10 mg/ml), the "new" rHSA resulted in greater cell viabilities versus the "old" rHSA. EX1001, 73:1-40 (Tables E3 and E4). As Dr. Clark explains, however, the different activity at high concentrations of rHSA is attributable to the endotoxins in the "old" rHSA—not the amount of the heat shock proteins. EX1002, ¶ 138, Fig. 9.

Indeed, the '951 patent shows that removing Hsp70 from rHSA decreases cell viability, e.g., from about 13.5×10^5 to 10×10^5 viable cells (0.5 mg/ml). EX1001, Fig. 12. "Accordingly, the comparable activity of Deeter's rHSA and the rHSA prepared in the '951 patent, and the fact that they were prepared using the same recombinant

³ Table E4 of the '951 patent does not contain data for "new" rHSA at 1 mg/ml.

This table thus includes the data for "new" rHSA at 1 mg/ml from Figure 10A and at 0.5 and 2 mg/ml from Table E4.

production system, confirms that Deeter's rHSA contained rice Hsp70 proteins at levels comparable to those disclosed in the '951 patent." EX1002, ¶ 139. "This explains why both Deeter's rHSA and the rHSA of the '951 patent provide comparable cell growth and viability at low concentrations (e.g., 1 mg/ml)." *Id.*

Indeed, the presence of Hsp70 proteins in rHSA produced in transgenic rice appears to have been no more than a *discovery* of an inherent property of Cellastim/Deeter's rHSA. EX1002, ¶ 140. For example, in U.S. Patent No. 8,609,416 (which similarly claims compositions comprising rHSA and heat shock proteins), Ventria stated that the claimed compositions were based on "the *discovery* that heat shock proteins co-purified, or co-mixed in solution with recombinant cell culture component proteins, result in the formation of protein complexes which are capable of significantly enhancing the cell culturing properties of the recombinant cell culture component proteins." EX1066, 3:11–16. This echoes the language in the '951 patent, which repeatedly states that Hsp70 family members were "found to occur" in Cellastim. EX1001, 78:47-50, 79:34-36, 79:7-11.

C. Claim 3

Claim 3 of the '951 patent depends from claim 2 and requires that the heat shock protein "is a rice heat shock protein." EX1001, claim 3. Deeter's rHSA necessarily contains rice Hsp70 proteins, and a POSA would have reasonably been

expected these proteins to remain at levels above 0.01% wt/wt after purification following the guidance of Tanaka. EX1002, ¶¶ 142-43.

D. Claim 4

Claim 4 of the '951 patent depends from claim 2 and further requires that the heat shock protein is selected from the group consisting of “Rice HSP70 genes, and rice endosperm luminal binding proteins.” EX1001, claim 4.

Claim 4 encompasses the rice Hsps “found to occur” in Cellastim at 0.07%, 0.09%, and 0.06% wt/wt. EX1002, ¶¶ 144-46; EX1001, 78:47-50, 79:34-36, 79:7-11. As discussed for claim 2, these Hsp70 proteins would necessarily have been present in Deeter’s Cellastim and would have reasonably been expected to remain at levels above 0.01% wt/wt after purification following the guidance of Tanaka. EX1002, ¶¶ 144-46.

E. Claim 5

Claim 5 depends from claim 2 and further requires that the heat shock protein be selected from the group consisting of Rice (gb1ACJ54890.11), EEC69073/OsI_37938, and AAB63469. Again, these are the rice Hsp70 family members “found to occur” in Cellastim. EX1001, 78:47-50, 79:34-36, 79:7-11. These heat shock proteins would have been necessarily present in Deeter’s Cellastim and would have reasonably been expected to remain at levels above 0.01% wt/wt after purification following the guidance of Tanaka. EX1002, ¶ 147.

F. Claim 6

Claim 5 depends from claim 2 and requires that “said supplement comprises at least 0.04% wt/wt HSP70.” EX1001, claim 6. The ’951 patent acknowledges that the three heat shock proteins “found to occur” in Cellastim are “Hsp70 proteins,” each of which was present at above 0.04% wt/wt. EX1001, 75:46-48 (referring to “three Hsp70 proteins”), 78:47-50, 79:34-36, 79:7-11. These rice Hsp70 proteins would have been necessarily present in Deeter’s Cellastim and would have reasonably been expected to remain at levels above 0.04% wt/wt after purification following the guidance of Tanaka. EX1002, ¶¶ 148-50.

G. Claim 7

Claim 7 depends from claim 2 and further requires that the composition comprise “a recombinant transferrin related protein, wherein said transferrin related protein is lactoferrin.” EX1001, claim 7. Deeter in combination with Tanaka satisfy the limitations of claim 2, as discussed above, and further render obvious claim 7.

A POSA would have been motivated to include rhLF in the cell culture media composition of claim 2, as taught by the combination of Deeter and Tanaka. EX1002, ¶¶ 151-59. For example, Deeter describes preparing both rHSA and rhLF in transgenic rice for use as cell culture media supplements (EX1003, [0100]-[0105]) and specifically suggests combining more than one recombinant protein in cell culture media. EX1003, [0081] (describing embodiments of the invention as cell

culture media “comprising *at least* one plant-produced heterologous protein as a cell culture component.”). Deeter also discloses combining rHSA with transferrin, a common component of cell culture media. EX1003, [0118], [0119].

Given the risk of contamination associated with animal-derived cell culture media components, a POSA would have been motivated to replace Deeter’s transferrin with a recombinant transferrin-related protein. EX1002, ¶ 156. In this regard, Deeter discloses that rhLF “can replace animal-derived transferrin” in cell culture media. EX1002, ¶ 156; EX1003, [0114]-[0115].

In view of Deeter’s teachings, it would have been a routine matter for a POSA to replace transferrin with rhLF in cell culture media comprising rHSA. EX1002, ¶¶ 157-58. A POSA would have been motivated to make this modification to achieve the benefits of plant-derived recombinant proteins over animal-derived proteins and would have had a reasonable expectation of success in doing so in view of the results in Deeter. EX1002, ¶ 158. As such, claim 7 would have been obvious over Deeter in view of Tanaka.

H. Claim 8

Claim 8 depends from claim 2 and further requires “a recombinant transferrin related protein, wherein said transferrin related protein is transferrin.” Deeter in combination with Tanaka satisfy the limitations of claim 2, as discussed above. In

addition, a POSA would have been motivated to combine recombinant transferrin with the cell culture media supplement of claim 2. EX1002, ¶¶ 160-64.

For example, Deeter discloses that rHSA promoted the growth of cells in culture in combination with a base medium supplemented with transferrin. EX1003, [0118]. Deeter also discloses that components of cell culture media such as transferrin are extracted from animal sources “have several undesirable features,” including the risk of contamination with pathogens. EX1003, [0006].

In view of the well-established disadvantages of animal-sourced proteins such as transferrin, a POSA would have been motivated to replace transferrin with recombinant human transferrin. EX1002, ¶ 163.

A POSA would have had a reasonable expectation of success in making this simple substitution, as recombinant human transferrin was commercially available by 2008. *See* EX1059, 4; EX1002, ¶ 164.

I. Claim 11

Claim 11 depends from claim 1 and requires that the albumin “is recombinant human serum albumin.” Deeter’s rHSA purified following the guidance of Tanaka is recombinant human serum albumin satisfying the requirements of claim 1. EX1002, ¶ 165.

J. Claim 12

Claim 12 depends from claim 1 and requires that the transgenic plant is a transgenic grain. Deeter's rHSA is produced in transgenic rice, which is a grain. I thus conclude that Deeter in view of Tanaka renders claim 12 obvious for the reasons stated above for claim 1. EX1002, ¶ 166.

K. Claim 13

Claim 13 depends from claim 21 and requires that the transgenic grain is transgenic rice. Deeter's rHSA is produced in transgenic rice, which is a grain. EX1002, ¶ 167. Deeter in view of Tanaka renders claim 13 obvious for the reasons stated above for claim 1.

L. Motivation to Combine

Deeter discloses a cell culture media composition comprising rHSA produced in a transgenic plant. EX1003, [0103]-[0105], [0116]-[0121]; EX1002, ¶¶ 100-08, 168-74. A POSA would have considered Deeter's rHSA a beneficial alternative to native albumin, as it alleviated the risks associated with animal or human pathogens and was produced in very high yield. EX1002, ¶¶ 169-70. As Deeter explains, given the concerns about the safety of animal-derived cell culture media components, regulators encouraged "replacing animal components with recombinant proteins in vaccine production and other applications of cell culture techniques." EX1003, [0007].

While Deeter's rHSA would have been recognized as a beneficial alternative to traditional, animal-sourced albumin, it contained undesirable levels of endotoxin, which would have been readily detected and known to a skilled artisan. EX1002, ¶¶ 171-72; EX1030; EX1026, 292; EX1027, 1:49–52; EX1028, 261; EX1029, 3. Indeed, as acknowledged by Ventria during prosecution of the '951 patent, "[t]he average endotoxin level in Deeter et al.-produced albumin was **44.97 EU/mg**." EX1042, 693–94 (emphasis in original); EX1042, 693 (identifying Deeter et al. as WO 2007/002762).

As Dr. Clark explains, a POSA would have sought to reduce the endotoxin level in Deeter's rHSA and would have looked to Tanaka for guidance, as Tanaka discloses a simplified process for purifying pHSA to provide albumin free of endotoxins. EX1002, ¶ 173; EX1053, 5; *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 419–420 (2007).

A POSA would have understood that Tanaka's guidance could be beneficially applied to purify Deeter's rHSA. EX1002, ¶ 174. With Deeter's rHSA in-hand, a POSA would have been motivated to use the guidance of Tanaka to further purify the product using DEAE-Sepharose chromatography, fatty acid removal, Sephacryl S-200 HR gel permeation, and viral inactivation. *Id.*

Tanaka's process further provides albumin beneficially containing 99.0–99.3% monomeric albumin, e.g., less than 1% aggregated albumin. EX1002, ¶ 175.

Tanaka explains that its purification process is both time- and cost-effective. EX1053, 5. These added benefits would have further motivated a POSA to use to guidance of Tanaka to remove endotoxins from Deeter's rHSA. EX1002, ¶ 175.

M. A POSA Would Have Reasonably Expected Deeter's rHSA When Purified Following the Guidance of Tanaka Would Have the Low Endotoxin and Albumin Aggregate Levels of Tanaka's pHSA

A POSA would have reasonably expected to reduce the endotoxins in Deeter's rHSA to below "1 EU endotoxin/mg albumin," as recited in claim 1, by following the guidance of Tanaka. EX1002, ¶¶ 176-91; *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364, 1367–68 (Fed. Cir. 2007) (a relevant artisan's expectation of success "need only be reasonable, not absolute").

For example, a POSA would have reasonably expected that when purified using the guidance of Tanaka, Deeter's rHSA would be "pyrogen-free," i.e., free of pyrogens including endotoxin. EX1002, ¶ 177. Such a product would contain well below 1 EU endotoxin per mg albumin. *Id.*

A POSA's reasonable expectation of success would have been bolstered by Matejtschuk. EX1002, ¶ 185. Matejtschuk reported that DEAE-Sepharose chromatography "consistently lowered" endotoxin levels in pHSA. EX1005, 6. As Matejtschuk explains, on the DEAE-Sepharose column, impurities such as endotoxin are bound and removed (they stick to the column), while the albumin flows through. *Id.* A schematic of this process is included below for reference.

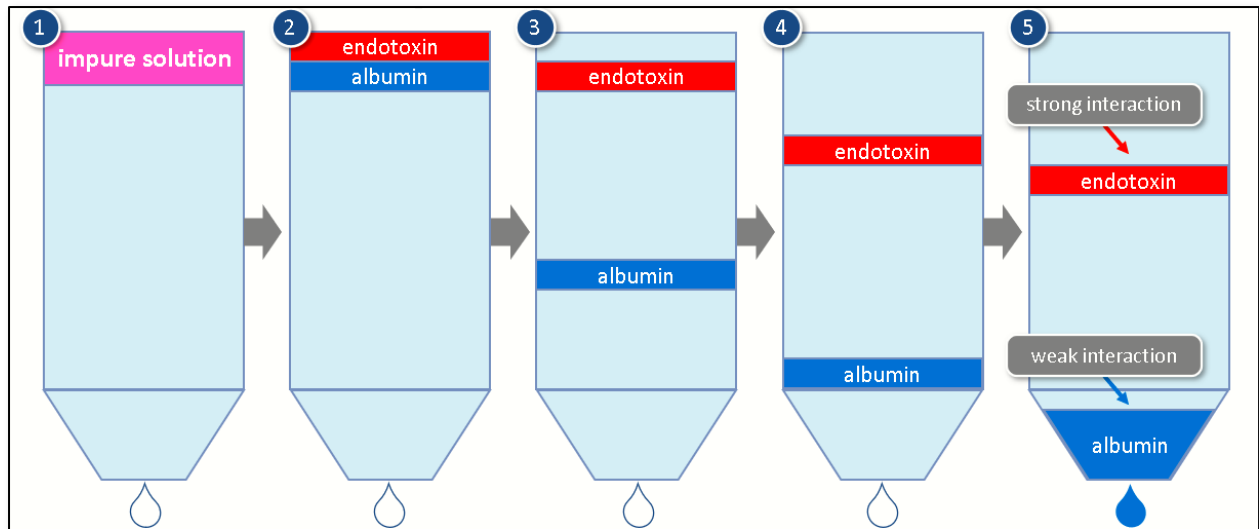


Figure 2. Schematic of Matejtschuk's Removal of Endotoxin from Albumin on a DEAE-Sepharose Column. EX1002, Fig. 9 (page 71).

This type of separation would have been expected using the conditions of Tanaka, which eluted albumin at a pH of 4.5, i.e., a pH above the isoelectric point of endotoxins (generally reported to be around 2) and below that of Deeter's rHSA (pI 5.3). EX1002, ¶ 186; EX1003, Table 3 (page 31).

Notably, the '951 patent also acknowledges that techniques for purifying pHSA (the albumin of Tanaka) were expected to be suitable for purifying the albumin of the invention produced in a transgenic plant. EX1001, 50:1-12; EX1002, ¶¶ 178-81. For example, the patent states:

A search of patents, published patent applications, and related publications will provide those skilled in the art reading this disclosure with *significant possible methods for preparing and purifying albumin*. For example, U.S. Pat. Nos. 4,075,197;

4,086,222; 4,093,612; 4,097,473; 4,136,094; 4,228,154;
5,250,662; 5,656,729; 5,677,424; 5,710,253; 5,728,553;
5,994,507; 6,001,974; 6,638,740; 6,617,133 and 7,423,124
disclose various processes for purifying albumin. In one aspect,
*the albumin for use in the present invention is purified using
any of these art recognized processes listed above*, and then
mixed in aqueous solution with a heat shock protein.

EX1001, 50:1-12 (emphases added).

In the passage above, U.S. Patent 5,250,662 (“Chang”), provides a method for purifying pHSA by anion exchange resins such as DEAE-Sephadex. EX1062 (Chang), 10:18-11:2. As Chang explains: “Contaminants with a PI below the pH of the first aqueous solution, i.e., below the 4.5 to 4.7 pH of the solution, will have a negative charge and will bind to the positively-charged resin during agitation.” EX1062 (Chang), 6:65-68.

Similarly, U.S. Patent 4,228,154 (“Fisher”), also listed in the passage above, describes a process for purifying pHSA to have sufficient purity for “therapeutic administration.” EX1063 (Fisher), 5:6-14. Fisher discloses that by using ion exchange chromatography, the pH may be adjusted to remove contaminants with isoelectric points below and above that of pHSA. *Id.*, 2:23-36, 3:38-67.

In short, Tanaka, Matejtschuk, Chang, and Fisher all reported that anion exchange chromatography on a DEAE-Sepharose column with an appropriate pH

would bind contaminants with low isoelectric points (e.g., endotoxins) while eluting pHSA. EX1002, ¶ 181.

As Dr. Clark explains, a POSA would have considered the removal of endotoxin from rHSA a routine purification step and would have had several techniques at their disposal to do so. EX1002, ¶ 182.

For example, a POSA would have reasonably expected to achieve the successful results in Tanaka using rHSA, as the separation of rHSA from endotoxin does not depend on the source of the albumin. EX1002, ¶ 183. In other words, the process for removing endotoxin does not depend on whether the albumin is produced in a human as disclosed in Tanaka or transgenic rice as disclosed by Deeter. *Id.*

As a matter of science, a POSA would have reasonably expected that albumin, including rHSA, would behave similarly on chromatography columns—regardless of the source or expression system used to produce the rHSA. EX1002, ¶ 184. A POSA would further have reasonably expected that endotoxin would behave similarly on the same chromatography columns. *Id.* Indeed, endotoxin is not produced by the transgenic host—it is a ubiquitous contaminant produced by gram-negative bacteria such as *E. coli* (not rice or yeast). *Id.* A POSA would thus have reasonably expected the same types of chromatography that separated endotoxin from pHSA (Tanaka) would also work for rHSA produced in transgenic rice (Deeter). *Id.*

Moreover, chromatography techniques were well-established and routine in the art, a thus a person skilled in the art would have recognized that minor variations could have been made to the processes disclosed in Tanaka to optimize working conditions for rHSA purification. EX1002, ¶¶ 187-91; *Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1341-42 (Fed. Cir. 2020) (finding an “optimal temperature range” used during chromatography “would have been nothing more than routine optimization”); *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018); *see also Pfizer*, 480 F.3d at 1334–36 (finding routine substitution to achieve optimal manufacturing characteristics).

As Dr. Clark explains, if more endotoxin was present in Deeter’s rHSA compared to the pHSA of Tanaka, a POSA would have understood that the rHSA could simply be run through either a fresh column or a larger column until the level of endotoxin was lowered to desired levels. EX1002, ¶ 188. Indeed, Matejtschuk reported that DEAE-Sepharose “consistently lowered” the amount of endotoxin in albumin solutions. EX1005, 6. A POSA would have understood that the levels of endotoxin could thus be reduced by sequential applications on a fresh chromatography column (one with a fresh resin that did not already have endotoxins bound to it from prior applications). EX1002, ¶ 188. In fact, the Q-Sepharose chromatography of Deeter would have reasonably been expected to remove endotoxins from rHSA, if performed under appropriate conditions, e.g., using an

appropriate pH and suitable loading conditions, including the option for running the solution through a fresh column again to further reduce the level of endotoxin. EX1002, ¶ 189.

In the unlikely event that anion exchange chromatography did not reduce the level of endotoxins to the desired level when performed under appropriate conditions, it would have been well within the general knowledge and skill of a POSA to use the simple modification reported by Aida to remove additional endotoxins. EX1002, ¶ 190; EX1060, 1, 4, 5 (reporting that Triton X-114 “aids in the dissociation of endotoxin from the protein”; that the detergent can be readily removed using chromatography; and that the process does not harm the proteins).

Researchers in the field often targeted levels of 1 EU endotoxin per mg protein as a minimum requirement, and a POSA would have reasonably expected to achieve even lower levels of endotoxin using the guidance of Tanaka. EX1002, ¶ 191.

A POSA would have further expected that when purified using the guidance of Tanaka, Deeter’s rHSA would contain less than 2% aggregated albumin, as Tanaka’s process provided at least 99% monomeric albumin in fifteen separate lots of albumin. EX1053, 4 (Table 1); EX1002, ¶ 192.

N. A POSA Would Have Reasonably Expected Deeter's rHSA When Purified by the Guidance of Tanaka Would Contain "at least 0.01% wt/wt of a heat shock protein"

A POSA would have expected that Deeter's rHSA when purified using the guidance of Tanaka would retain heat shock proteins at levels well above 0.01% wt/wt, as none of the purification steps in Tanaka would have been expected to substantially reduce the levels of heat shock proteins in Deeter's rHSA. EX1002, ¶¶ 193-99.

First, as Dr. Clark explains, Tanaka's DEAE-Sepharose would not have been expected to reduce the level of heat shock proteins. DEAE-Sepharose is an anion exchange resin, meaning it separates molecules based on their isoelectric points. EX1002, ¶ 194. Given the similar isoelectric points of Deeter's rHSA (5.3) and rice Hsp70 (about 5), a POSA would not have expected DEAE-Sepharose would separate heat shock proteins from albumin, particularly at the pH of 4.5 employed by Tanaka. EX1002, ¶ 194; EX1003, [0117] (Table 3); EX1034, 4 (Fig. 1); EX1053, 3, 4.

Next, Tanaka discloses heating albumin at 55 °C for 3 hours to release the fatty acids from rHSA. EX1053, 3. A POSA would not have expected that this step would remove heat shock proteins. EX1002, ¶ 195. Indeed, heat shock proteins "were originally identified as proteins whose expression is induced by heat stress." EX1032 (Sharma), 1. As Sharma explains, "Hsps, primarily of the Hsp70 family, bind partially exposed hydrophobic surfaces, to prevent non-productive interactions

that would lead to aggregation, and to promote protein refolding.” *Id.* A POSA would thus not expect that this step to remove heat shock proteins, which, if anything, may become more tightly bound to albumin under conditions of stress. EX1002, ¶ 195.

Tanaka further purifies albumin by gel filtration chromatography, i.e., size-exclusion chromatography. EX1002, ¶ 196; EX1053, 2, 3. Tanaka’s resin was marketed for the separation of peptides and globular proteins with molecular weights ranging from about 5 kDa to about 150 kDa. E1067, 51. This technique would not have been expected to separate Deeter’s rHSA from rice Hsp70 proteins, which have comparable sizes to rHSA. EX1002, ¶ 196; EX1003, Table 1 (reporting rHSA molecular weight of 66.8-67.9 kDa); EX1035, 209 (explaining Hsps are categorized by their molecular weights, e.g., Hsp70 I indicates approximate molecular weight of 70 kDa).

Finally, Tanaka reports formulating albumin with sodium caprylate (0.16 mmol/g protein) to stabilize the product, then performing viral inactivation via pasteurization at 60 °C for 10 hours. EX1053, 4, 5. Heat shock proteins necessarily remain during this process, as the solution is merely heated and no components are removed from the albumin solution. EX1002, ¶ 197; EX1056, § 640.81(e) (describing viral inactivation of albumin samples).

Moreover, Hsp70 proteins are sticky by nature, and thus researchers developed a specialized type technique for their removal, ATP Agarose affinity

chromatography. EX1002, ¶¶ 38, 198; EX1039, 96; EX1040, 68–69; EX1041, 598; EX1032, 2; EX1031, 4. Neither Deeter nor Tanaka employed a step using an ATP Agarose affinity resin to remove heat shock proteins from albumin, further supporting the conclusion that rice Hsp70 proteins would have remained bound to Deeter’s rHSA following purification. EX1003, [0116]; EX1053; EX1002, ¶ 198.

Thus, as explained by Dr. Clark, a POSA would have reasonably expected that Deeter’s rHSA, purified using the guidance of Tanaka, would continue to comprise “at least 0.01% wt/wt of a heat shock protein,” including at least 0.04% wt/wt Hsp70, as required by claims 2-6 of the ’951 patent.

IX. Ground 2: Claim 9 of the ’951 Patent Would Have Been Obvious over Deeter in view of Tanaka and Meng

Meng discloses ratios of transferrin to recombinant albumin that both overlap and fall within the claimed ratio of 1:50 to 1:5000, as recited in claim 9 of the ’951 patent, rendering claim 9 presumptively obvious. EX1002, ¶¶ 200-07; *Almirall, LLC v. Amneal Pharmaceuticals LLC*, --F.4d--, 2022 WL 760555, *5 (Fed. Cir. Mar. 14, 2022).

For example, Meng teaches that the ratio of the concentrations of transferrin to rHSA should be at least 1:10 to 1:1000, which overlaps with the range of claim 9. EX1002, ¶¶ 202-03. EX1054, [0022]-[0023]. Meng additionally discloses stem cell

culture media comprising a ratio of 1 transferrin to 455 rHSA, which is within the broad range of claim 9.⁴ EX1054, 13:11-24.

A POSA would have been motivated to use the advantageous ratio of transferrin to rHSA disclosed in Meng in the composition of Deeter and Tanaka. EX1002, ¶ 206. A POSA would have had a reasonable expectation of success in doing so, as Meng's cell culture media promoted stem cell growth. EX1002, ¶ 207.

X. Ground 3: Claims 1-8 and 11-13 of the '951 Patent Would Have Been Obvious over Deeter in view of Van Urk

A. Claim 1

Claim 1 would have been obvious over Deeter and Van Urk, which collectively taught cell culture media comprising rHSA produced in a transgenic plant having less than 1 EU endotoxin per mg albumin and less than 2% aggregated albumin. EX1002, ¶¶ 208-20.

1. "A cell culture media supplement or complete media composition"

Deeter discloses "cell culture media supplement," e.g., "a combination of one or multiple cell culture media components ... for addition to cell culture media." EX1003, [0068]. For example, Deeter discloses using rHSA in cell culture media

⁴ As Dr. Clark explains, even if claim 9 were interpreted to refer to the ratio of molecules of transferrin to molecules of rHSA, the ratio of Meng would still be within the broad range of claim 9. EX1002, ¶ 205 n.8.

and determined that it is functionally equivalent to plasma-derived HSA. EX1003, [0118]–[0120]. Van Urk similarly teaches that rHSA may be used “in cell culture.” EX1004, 23:26-24:4 (disclosing that the “albumin of the present invention” may be used “in cell culture”); *id.*, 1:8-9 (disclosing that the term “albumin” refers to HSA and/or rHSA). Van Urk also acknowledges that albumin and rHSA are “used to supplement media used for growing higher eukaryotic cells.” EX1004, 1:13-15.

A POSA would have reasonably expected that Deeter’s rHSA when purified using the guidance of Van Urk would continue to be a cell culture media component, as removing endotoxins from Deeter’s rHSA would have been expected to improve (or at a minimum not reduce) the effectiveness of Deeter’s rHSA in cell culture given the toxic nature of endotoxins. EX1002, ¶ 211.

2. “a recombinant mammalian albumin”

Deeter discloses rHSA, which is a recombinant mammalian albumin. EX1002, ¶¶ 212-13; EX1003 (Table 3), [0103], [0117]; *see also* EX1018, 5 (disclosing in 2007 that the amino acid sequence of Cellastim™ was identical to native HSA). A POSA would have understood that Deeter’s rHSA when purified using the guidance of Van Urk would continue to be a recombinant mammalian albumin. EX1002, ¶ 214.

3. “wherein said albumin is produced in a transgenic plant”

Deeter discloses rHSA produced in a transgenic plant, specifically, transgenic rice. EX1003, [0103]-[0105]; EX1002, ¶¶ 215-16. Van Urk discloses processes for purifying rHSA, including rHSA produced in transgenic plants. EX1004, 1:3-9. For example, Van Urk discloses that its rHSA “may be obtained from a transgenic plant, such as tobacco, potato, or corn (maize).” EX1004, 22:25-27.

4. “has less than 1 EU endotoxin/mg albumin”

Deeter’s rHSA, as purified using the guidance of Van Urk, would have reasonably been expected to contain less than 1 EU endotoxin/mg albumin, as recited in claim 1 of the ’951 patent. EX1002, ¶¶ 217-18, 247-53.

For example, Van Urk’s discloses processes to prepare rHSA having no detectable endotoxin, as determined by the sensitive Limulus amoebocyte lysate assay by kinetic turbidimetric measurement at 340 nm (LAL 5000E). EX1004, 74-75; EX1030, 5 (discussing sensitivity of LAL assays); *see also* EX1004, 63 (disclosing the product is “non-pyrogenic.” i.e., free of pyrogens including endotoxins). Thus, Deeter’s rHSA, as purified using the guidance of Van Urk, would have been reasonably expected to contain less than 1 EU endotoxin/mg albumin. EX1002, ¶ 218.

5. “less than 2% aggregated albumin”

Deeter’s rHSA as purified using the guidance of Van Urk would have reasonably been expected to contain less than 2% aggregated albumin, as recited in

claim 1 of the '951 patent. EX1002, ¶¶ 219-20, 247-54. Indeed, Van Urk's purification process provides rHSA containing up to 1% albumin dimers, with no larger polymers or aggregates detectable. EX1002, ¶ 220; EX1004, 65, 71-72. Thus, Deeter's rHSA as purified using the guidance of Van Urk would have reasonably been expected to contain less than 2% aggregated albumin.

B. Claim 2

Claim 2 depends from claim 1 and requires that the recombinant albumin comprises "at least 0.01% wt/wt of a heat shock protein." As discussed in Section VII.B, Deeter's rHSA necessarily contained substantially more than 0.01% wt/wt of a rice Hsp70 protein. EX1002, ¶¶ 113-41. A POSA would have reasonably expected that when purified using the guidance of Van Urk, Deeter's rHSA would retain rice Hsp70 proteins at levels well above 0.01% wt/wt. EX1002, ¶¶ 255-62; *infra*, § X.N. Deeter in combination with Van Urk thus renders obvious claim 2 of the '951 patent.

C. Claim 3

Claim 3 of the '951 patent depends from claim 2 and requires that the heat shock protein "is a rice heat shock protein." EX1001, claim 3. The heat shock proteins naturally present in Deeter's rHSA are rice heat shock proteins. EX1002, ¶ 226. Claim 3 is thus obvious for the same reasons as claim 2.

D. Claim 4

Claim 4 of the '951 patent depends from claim 2 and further requires that the heat shock protein is selected from the group consisting of "Rice HSP70 genes, and

rice endosperm luminal binding proteins.” EX1001, claim 4. These are the rice Hsp70 family members “found to occur” in Cellastim. EX1001, 78:40-44, 78:47-50, 79:34-36, 79:7-11. These Hsp70 family members would necessarily have been present in Deeter’s Cellastim and would have reasonably been expected to remain at levels above 0.01% wt/wt after purification following the guidance of Van Urk. EX1002, ¶¶ 227-28; *Infra*, § X.N.

E. Claim 5

Claim 5 depends from claim 2 and further requires that the heat shock protein be selected from the group consisting of Rice (gb1ACJ54890.11), EEC69073/OsI_3 7938, and AAB63469. These are the same Hsp70 family members “found to occur” in Cellastim. EX1002, ¶ 229; EX1001, 78:47-50, 79:34-36, 79:7-11. These heat shock proteins would have been necessarily present in Deeter’s Cellastim and would have reasonably been expected to remain at levels above 0.01% wt/wt after purification following the guidance of Van Urk. *Infra*, § X.N.

F. Claim 6

Claim 5 depends from claim 2 and requires that “said supplement comprises at least 0.04% wt/wt HSP70.” The three heat shock proteins “found to occur” in Cellastim are “Hsp70 proteins.” EX1002, ¶ 230; EX1001, 75:46-48, 78:47-50, 79:34-36, 79:7-11. Hsp70 proteins were necessarily present in Deeter’s Cellastim

and would have reasonably been expected to remain at levels above 0.04% wt/wt after purification following the guidance of Van Urk. EX1002, ¶ 231; *infra*, § X.N.

G. Claim 7

Claim 7 would have been obvious over Deeter in view of Van Urk. EX1002, ¶¶ 232-35. Claim 7 depends from claim 2 and further requires that the composition comprise “a recombinant transferrin related protein, wherein said transferrin related protein is lactoferrin.” EX1001, claim 7. Deeter in combination with Van Urk satisfy the limitations of claim 2, as discussed above. In addition, a POSA would have been motivated to replace the animal-derived transferrin in Deeter’s cell culture media with rhLF. EX1002, ¶¶ 152-58, 233-35.

For example, Deeter discloses that rHSA promoted the growth of cells in culture when used in DMEM base medium supplemented with transferrin, among other components. EX1003, [0118]. In view of the well-established disadvantages of animal-sourced proteins such as transferrin, a POSA would have been motivated to replace transferrin with a recombinant protein. EX1002, ¶¶ 156-57; EX1003, [0006]. Deeter specifically teaches that rhLF can replace animal-derived transferrin in cell culture media. EX1003, [0113]-[0114], Table 2 (page 30).

A POSA would have considered the replacement of animal-derived transferrin (used by Deeter in combination with rHSA) with rhLF a routine and advantageous modification. EX1002, ¶¶ 158, 234. A POSA would have had a reasonable

expectation of success in making this simple substitution in view of Deeter's disclosures and the commercial availability of rhLF 2008. *See* EX1058, 2, 4, 7.

H. Claim 8

Claim 8 would have been obvious over Deeter in view of Van Urk. EX1002, ¶¶ 236-40. Claim 8 depends from claim 2 and further requires "a recombinant transferrin related protein, wherein said transferrin related protein is transferrin." EX1001, claim 8. Deeter in combination with Van Urk satisfy the limitations of claim 2, as discussed above. As discussed for claim 7, a POSA would have been motivated to replace the animal-derived transferrin of Deeter with a recombinant protein in view of the well-known risks associated with animal derived cell culture media components. EX1002, ¶ 239; *e.g.*, EX1003, [0006].

A POSA would have considered recombinant transferrin a natural replacement for animal-derived transferrin. EX1002, ¶ 239. A POSA would have had a reasonable expectation of success in making this simple substitution, as recombinant human transferrin was commercially available by 2008. *See* EX1059, 4.

I. Claim 11

Claim 11 depends from claim 1 and requires that the albumin "is recombinant human serum albumin." Deeter's rHSA, as purified following the guidance of Van Urk, is recombinant human serum albumin satisfying the requirements of claim 1. EX1002, ¶ 241.

J. Claim 12

Claim 12 depends from claim 1 and requires that the recombinant mammalian albumin is produced in a transgenic grain. EX1001, claim 12. Deeter's rHSA is produced in transgenic rice, which is a grain. EX1002, ¶ 242. Deeter in view of Van Urk renders claim 12 obvious for the reasons stated above for claim 1.

K. Claim 13

Claim 13 depends from claim 1 and requires that the transgenic grain is transgenic rice. EX1001, claim 13. Deeter's rHSA is produced in transgenic rice. EX1002, ¶ 243. Deeter in view of Van Urk renders claim 13 obvious for the reasons stated above for claim 1.

L. Motivation to Combine

Deeter discloses producing rHSA in transgenic rice at high yield, thereby providing an advantageous and effective cell culture media supplement that avoids the safety risks associated with animal-derived albumin. EX1002, ¶¶ 168-72, 244-45. Deeter's rHSA, however, had an undesirably high level of endotoxin, which would have been detected by and known to a POSA. EX1002, ¶ 244.

Accordingly, a POSA would have been motivated to reduce the endotoxin level in Deeter's rHSA and would have naturally looked to Van Urk for guidance, as Van Urk details a process for purifying rHSA, including rHSA produced in transgenic plants, to achieve a product with no detectable endotoxins. EX1002, ¶ 245; EX1004, 1:3-9, page 73.

Van Urk's process further provides rHSA beneficially containing up to 1% aggregated albumin. EX1002, ¶¶ 66, 220, 246; EX1004, 65, 71-72. This added benefit would have further motivated a POSA to use to guidance of Van Urk to remove endotoxins from Deeter's rHSA.

M. A POSA Would Have Reasonably Expected Deeter's rHSA When Purified Following the Guidance of Van Urk Would Have the Low Endotoxin and Albumin Aggregate Levels of Van Urk's Albumin

Deeter's rHSA when purified using the guidance of Van Urk would have been reasonably expected to contain less than 1 EU endotoxin/mg albumin and less than 2% aggregated albumin. EX1002, ¶¶ 247-254.

First, Van Urk specifically taught that its process applies to purifying rHSA produced in transgenic plants, which alone would have provided a skilled artisan with a reasonable expectation of success in achieving the endotoxin and aggregated albumin levels disclosed by Van Urk. EX1004, 1:3-9; EX1002, ¶ 247.

This reasonable expectation of success would have been bolstered by Matejtschuk, which teaches removing endotoxin from pHSA using a DEAE-Sepharose chromatography column, a purification step also disclosed in Van Urk. EX1002, ¶ 252; EX1005, 6; EX1004, 48, 50, 54.

A POSA would have reasonably expected that techniques to purify rHSA produced in transgenic yeast (the preferred embodiment of Van Urk) would also work to purify rHSA produced in transgenic rice (the rHSA of Deeter). EX1002,

¶¶ 248-51; *supra*, § VIII.N. Indeed, albumin preparations from human plasma, yeast, and rice all exhibit similar isoelectric properties and would have behaved similarly on anion exchange columns. EX1002, ¶ 184. Similarly, endotoxin is not produced by the transgenic host. *Id.* A POSA would thus have reasonably expected the same types of chromatography that separated endotoxin from rHSA produced in yeast (Van Urk's preferred source) would also work for rHSA produced in transgenic rice (Deeter). *Id.*

Moreover, chromatography techniques were well-established and routine in the art, a thus a person skilled in the art would have recognized that minor variations could have been made to the processes disclosed in Van Urk to optimize working conditions for rHSA purification. EX1002, ¶¶ 188-91, 250-53. A POSA would have expected to achieve rHSA containing less than 1 EU endotoxin /mg albumin following the guidance of Van Urk. EX1002, ¶¶ 247-53.

For example, if more endotoxin was present in Deeter's rHSA compared to the rHSA of Van Urk, a person skilled in the art would have understood that the rHSA sample could simply be run through either a fresh column or a larger column until the level of endotoxin was lowered to desired levels. EX1002, ¶ 188.

The '951 patent also acknowledges that techniques for purifying albumin rHSA produced in transgenic yeast (the preferred rHSA of Van Urk) also work to

purify the albumin of the invention produced in a transgenic plant. Patent, 50:1-12.

For example, the patent states:

A search of patents, published patent applications, and related publications will provide those skilled in the art reading this disclosure with *significant possible methods for preparing and purifying albumin*. For example, U.S. Pat. Nos. 4,075,197; 4,086,222; 4,093,612; 4,097,473; 4,136,094; 4,228,154; 5,250,662; 5,656,729; 5,677,424; 5,710,253; 5,728,553; 5,994,507; 6,001,974; **6,638,740**; 6,617,133 and 7,423,124 disclose various processes for purifying albumin. In one aspect, *the albumin for use in the present invention is purified using any of these art recognized processes listed above*, and then mixed in aqueous solution with a heat shock protein.

EX1001, 50:1-12 (emphases added).

Notably, U.S. Patent No. 6,638,740 (Goodey)—cited in the '951 patent passage above—describes processes for purifying albumin, as exemplified by the purification of rHSA produced in yeast, to achieve albumin with no detectable endotoxin and about 0.1% aggregated albumin. EX1046, Abstract, 3:55–62,6:8–16:34; EX1002, ¶ 249. As such, the '951 patent admits that processes exemplified in rHSA produced in yeast would also be expected to work for rHSA produced in a transgenic plant.

A POSA would have further expected Deeter's rHSA when purified using the guidance of Van Urk would contain less than 2% aggregated albumin, as Van Urk

discloses processes that provide about 99% monomeric albumin. EX1004, 65; EX1002, ¶¶ 247-51, 253-54.

N. A POSA Would Have Reasonably Expected that Deeter's rHSA When Purified by the Guidance of Van Urk Would Contained the Recited Heat Shock Proteins

A POSA would have reasonably expected that when purified following the guidance of Van Urk, Deeter's rHSA would have retained at least 0.01% wt/wt of a rice Hsp70 protein, e.g., at least 0.04% Hsp70, as required by claims 2-6. EX1002, ¶¶ 255-62.

As Dr. Clark explains, the purification steps of Van Urk would not have been reasonably expected to remove the rice Hsp70 proteins necessarily present in Deeter's rHSA. *Id.* Van Urk's purification process includes (1) ion exchange chromatography, (2) chromatography using a DBA resin (Delta Blue Agarose, also called "Delta Blue" matrix), (3) chromatography using an aminophenylboronate ("PBA") resin, and (4) filtration (specifically, ultrafiltration and diafiltration). EX1004, 45-55.

First, the ion exchange chromatography would not have been expected to remove rice Hsp70 proteins. EX1002, ¶ 257. A POSA would have known that rHSA and rice Hsp70 proteins carry about the same net charge, such that ion exchange chromatography (which separates proteins based on charge) would not have effectively removed them. EX1003, 30, Table 3; EX1034, 4 (Fig. 1); EX1035, 209.

Similarly, blue-dye-containing columns (e.g., Blue Sepharose and DBA) were reported to function as ionic exchange columns. EX1002, ¶ 258; EX1037, 199; EX1038, 173. As such, DBA would not have been expected to separate rHSA from Hsp70 proteins, as they would have about the same net charge in solution. EX1002, ¶ 258.

Next, Van Urk's PBA column would not have been expected to separate heat shock proteins from rHSA. EX1002, ¶ 259. As Dr. Clark explains, PBA columns were designed to bind molecules with two adjacent hydroxy groups (diols). *Id.*; EX1043, 55; EX1044. As such, a PBA column would bind molecules such as carbohydrates and glycoproteins (proteins with a carbohydrate modification), but not albumin or Hsp70 proteins in their unglycosylated form (which are proteins, not carbohydrates). EX1002, ¶ 259. This is consistent with the teachings of Van Urk, which reports that the PBA column removes glycoconjugates, not heat shock proteins. EX1004, 44, 52.

Finally, Van Urk's filtration steps would not have been reasonably expected to remove Hsp70 proteins from rHSA. EX1002, ¶ 260. Van Urk disclosed various ultrafiltration and diafiltration steps using membranes that separate out species smaller than 10,000 kDa or 30,000 kDa. EX1004, 51, 53. These steps would not have removed any heat shock proteins larger than 10 kDa or 30 kDa, e.g., rice Hsp70 proteins. EX1002, ¶ 260.

The expectation that Van Urk's purification process would not remove heat shock proteins would have been bolstered by their "sticky" nature. EX1002, ¶ 261. Hsp70 in particular tends to bind "somewhat non-specifically to hydrophobic peptides," which allows Hsp70 to act on a broad range of substrates, e.g., rHSA. EX1032, 1; EX1041, 598, 604. For example, Hsp70 prevents protein aggregation and promotes protein refolding. EX1032, 1. As Sharma explains, "Hsp70 is important for helping proteins adopt and maintain native conformations from the time they are synthesized until they are eventually degraded." EX1032, 6. Heat shock proteins such as Hsp70 would have thus been expected to remain bound to rHSA after the routine purification steps employed by Van Urk.

Given their "sticky" nature, Hsp70 proteins were generally isolated using columns containing ATP Agarose affinity chromatography resin, a resin that specifically binds to heat shock proteins. EX1002, ¶ 262; EX1039, 9; EX1040, 2-3; EX1041, 2. Neither Deeter nor Van Urk describe using ATP Agarose affinity chromatography resin to purify rHSA. Accordingly, the general knowledge about difficulties with removing heat shock proteins would have reinforced the expectation that Van Urk's process would not have removed heat shock proteins from Deeter's rHSA.

XI. Ground 4: Claim 9 of the '951 Patent Would Have Been over Deeter in view of Van Urk and Meng

Deeter in view of Van Urk and Meng render claim 9 obvious. EX1002, ¶¶ 263-67. Claim 9 depends from claim 8 and further requires that the “ratio of said transferrin to said recombinant albumin is 1:50 to 1:5000.” Claim 8 would have been obvious based on the combination of Deeter and Van Urk, as discussed above.

Meng discloses that stem cell culture media should comprise a ratio of transferrin to rHSA of at least 1:10 to 1:1000, which overlaps with the range of ratios in claim 9. EX1002, ¶ 265; EX1054, [0022]-[0023]. Meng also discloses stem cell culture media in which the ratio of transferrin to rHSA is 1:455, which is within the range of claim 9. EX1002, ¶ 265; EX1054, 13:11-24. As Dr. Clark explains, even if claim 9 were interpreted to refer to the ratio of molecules of transferrin to molecules of rHSA, the ratio of Meng would still be within the broad range of claim 9. EX1002, ¶ 205 n.8.

A POSA would have been motivated to use the ratio of transferrin to rHSA in Meng, as Meng’s cell culture media promoted stem cell growth. EX1002, ¶ 266. A POSA would have reasonably expected that this ratio would also work for recombinant transferrin, as the recombinant protein would have been expected to behave similarly to its natural analog. *Id.*

XII. Secondary Considerations of Nonobviousness

Petitioner is not aware of any objective evidence of nonobviousness having the requisite nexus to any purportedly novel features of the challenged claims. *See Merck & CIE v. Gnosis S.P.A.*, 808 F.3d 829, 837 (Fed. Cir. 2015).

For example, the claims do not provide any unexpected results. Indeed, cell culture media supplements comprising rHSA containing less than 1 EU endotoxin/mg albumin were already known, and methods for removing endotoxin from pHSA and rHSA were widely reported, including treatment with the detergent of the type disclosed in the '951 patent. EX1060; EX1002, ¶¶ 28-34, 176-92, 247-54, 273.

Second, the purportedly superior activity of the rHSA of the '951 patent is a myth. EX1002, ¶¶ 134-40. As Dr. Clark explains, the old/less purified rHSA performed just as well at low concentrations (at which endotoxins were less problematic), and the fact that removing endotoxins improved activity at higher concentrations is exactly what a POSA would expect. *Id.*

Third, while the patent asserts that combinations of rHSA with other proteins provided “surprising” results (EX1001, 31:37-44, 92:64-67, 94:35-38), combinations of rHSA with transferrin-related proteins, including recombinant transferrin, were already known and were expected to provide advantageous results in cell culture media. EX1002, ¶¶ 274-76; EX1013, 27:19-21; EX1010, 29:14-20,

Fig. 1 (page 34); EX1045, 2; EX1003, [0118]-[0120]; EX1006. Moreover, the discovery of purportedly new properties does not impart patentability to known compositions. *Tyco Healthcare Group LP v. Mutual Pharmaceutical Co.*, 642 F.3d 1370, (Fed. Cir. 2011).

Fourth, while those in the field were interested in non-animal sourced proteins in cell culture media, such supplements were already commercially available. EX1002, ¶¶ 19-27; *supra*, § V.A. As such, the production of recombinant proteins in transgenic rice did not satisfy any long-felt *unmet* need. The production of rHSA and rhLF in transgenic rice—in high yield and suitable for commercialization—was established prior to the '951 patent. EX1002, ¶¶ 19-27.

Fourth, to the extent that Ventria argues that products covered by the claims are a commercial success, the evidence will establish that argument is meritless, as the majority of Ventria's products do not practice any claim of the '951 patent.

Finally, Petitioner is aware of no evidence establishing failed attempts by others, copying, or praise of the claimed compositions or products embodying them.

XIII. Mandatory Notices Under 37 C.F.R. § 42.8

A. Real Parties-in-Interest

Petitioner Wuhan Healthgen Biotechnology Corp. of Wuhan, China is the real party-in-interest.

B. Related Matters

Healthgen is currently involved in the following federal cases alleging infringement of the '951 patent:

- *Ventria Bioscience Inc. v. Wuhan Healthgen Biotechnology Corp.* DKS-5-21-cv-04008 (D. Kan.) (complaint filed Feb. 5, 2021) (“Kansas Litigation”). This district court action was stayed pursuant to 28 U.S.C. § 1659 on March 4, 2021.
- *Certain Plant-Derived Recombinant Human Serum Albumins (“rHSA”) and Products Containing Same*, U.S.I.T.C. Inv. No. 337-TA-1238 (instituted Jan. 15, 2021) (“ITC Investigation”).

In the Kansas Litigation, although Healthgen signed a waiver of service of the complaint (EX1068), Healthgen’s signed waiver sheet has not been filed with the district court and thus does not start the clock under 35 U.S.C. § 315(b). *See Macauto U.S.A. v. Bos GmbH &KG*, IPR2012-00004, Paper No. 18 at 16 (Pat. Tr. & App. Bd. Jan. 24, 2013) (“As Patent Owner has not demonstrated that a service waiver (EX 2004) or other proof of service was ever filed, we conclude that it has not established a service date under the statute.”); *The Brinkman Corp. v. A&J Mfg., LLC*, IPR2015-00056, Paper No. 10 at 6-7 (Pat. Tr. & App. Bd. Mar. 15, 2015) (“Petitioner waived service of the complaint, and Patent Owner filed Petitioner’s waiver of service with the district court on Oct. 21, 2013. This is the date that

Petitioner is deemed to have been served.”) (citing Fed. R. Civ. P. 4(d)(4), which states “these rules apply as if a summons and complaint had been served *at the time of filing the waiver*.”). If signing but not filing such a waiver is deemed sufficient, which would be contrary to earlier decisions, this petition is not time-barred as it is not being filed more than one year since March 17, 2021.

With respect to the ITC investigation, as the Board has repeatedly concluded, “[a]n administrative complaint, such as an ITC action, does not constitute a complaint under 35 U.S.C. § 315(b).” *Arm Ltd. v. Advanced Micro Devices, Inc.*, IPR2018-01149, 2018 WL 6584641, *2 (Pat. Tr. & App. Bd. Dec. 12, 2018); *see also Robert Bosch Tool Corporation v. SD3, LLC*, IPR2016-01751, 2017 WL 1096609, *6 (Pat. Tr. & App. Bd. Mar. 22, 2017) (“We decline to interpret § 315(b) as including ITC complaints.”).

C. Lead and Backup Counsel

Lead Counsel	Backup Counsel
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D. Service Information

Please send all correspondence to lead and backup counsel at the address shown above. Petitioners consent to service by e-mail sent to the following e-mail addresses:

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XIV. Payment of Fees

The required fees are submitted herewith in accordance with 37 C.F.R. §§ 42.103(a) and 42.15(a). If any additional fees are due during this proceeding, the Office is authorized to charge Deposit Account No. 06-0916.

XV. Trial Should Be Instituted

The Board should institute review. The related matters identified in § XIII.B do not warrant discretionary denial under §314(a). See *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 at 5-6 (Pat. Tr. & App. Bd. Mar. 20, 2020) (precedential).

The first *Fintiv* factor favors institution. The Kansas Litigation was stayed on March 4, 2021, and shall remain stayed until the Commission determination

becomes final. *See* 28 U.S.C. § 1659. The Commission’s determination is currently due August 8, 2022, and that will not be final until all appeals have expired (*In re Princo*, 478 F.3d 1345, 1355 (Fed. Cir. 2007)), which can take over a year. The stay in the Kansas Litigation favors institution, as Petitioner will not be able to obtain a binding judgment of invalidity of any claim of the ’951 patent in district court until well after the Board’s Final Written Decision would issue. While the ITC Investigation was not stayed, the ITC does not have the authority to invalidate any claim of the ’951 patent.

The second *Fintiv* factor also favors institution. The target date for completing the ITC Investigation is August 8, 2022. Although this date is before the Board would issue a final written decision (around September 2023), the ITC does not have the authority to invalidate the claims of the ’951 patent. *Tex. Instruments, Inc. v. Cypress Semiconductor Corp.*, 90 F.3d 1558, 1569 (Fed. Cir. 1996). Thus, the Board has the most efficient venue to make a binding determination on the invalidity of claims 1-9 and 11-13 of ’951 patent.

The third *Fintiv* factor also favors institution. While the parties invested considerable resources litigating the ITC Investigation, that investigation was terminated as to claims 2 and 3 of the ’951 patent on the eve of trial—at Patent Owner’s request. Healthgen is challenging both these claims in this petition. Thus, the issues before the PTAB are not commensurate with the issues before the ITC and

if this IPR is not instituted, the parties will need to expend considerable additional resources in district court to resolve their dispute as to the '951 patent.

The fourth *Fintiv* factor also favors institution. This petition challenges claims 1-9 and 11-13 of the '951 patent (12 claims), while only claims 1 and 11-13 (four claims) are at issue in the ITC Investigation. The eight additional claims challenged here present distinct issues concerning heat shock proteins (claims 2-6) and recombinant transferrin-related proteins (claims 7-9) that will not be addressed at the ITC. While it is unclear which claims will be asserted in district court, Patent Owner asserts infringement of “at least” claims 1-3 and 11-13 in its complaint. Kansas Litigation, Complaint, ¶ 27 (Feb. 5, 2021).

Under the fifth *Fintiv* factor, all parties to this proceeding are included in the related proceedings, and as such “this factor does not weigh against exercising our discretion to deny.” *Cast Lighting, LLC v. Wangs Alliance Corp.*, PGR2021-00012, Paper 12 at 36 (Pat. Tr. & App. Bd. June 7, 2021).

The sixth *Fintiv* factor favors institution, as the merits of the case are strong. Patent Owner’s own prior publication (Deeter) discloses nearly all claim elements except recited endotoxin level, but rHSA comprising no detectable endotoxin were already well-known in the art. And the ITC lacks authority to invalidate even the small subset of claims at issue in that proceeding. *See Wirtgen Am., Inc. v.*

Caterpillar Paving Prods. Inc., IPR2018-01201, Paper 13 at 12 (Pat. Tr. & App. Bd. Jan. 8, 2019).

On the whole, five *Fintiv* factors favor institution, and the remaining factor (same parties) does not warrant discretionary denial here. Patent Owner respectfully requests the Board institute this IPR.

XVI. Non-Institution under § 325(d) Would Be Improper

This IPR should be instituted under the *Advanced Bionics* test for §325(d) discretion because the evidence identified in this Petition was neither before the Office nor fully considered during prosecution. *See Advanced Bionics, LLC v. MED-EL Elektromedizinische Gerate GmbH*, IPR2019-01469, Paper 6, at 6–11 (Pat. Tr. & App. Bd. Feb. 13, 2020) (precedential).

None of the secondary references relied on in this Petition—Tanaka, Van Urk, or Meng—were before the USPTO during examination of the '951 patent. *See* EX1001, 1-2 (identifying art of record). Accordingly, each ground presented in this Petition alone is sufficient to find the first prong of the *Advanced Bionics* test not satisfied. *See Thorne Research, Inc. v. Tr. of Dartmouth Coll.*, IPR2021-00491, Paper 18, at 8–9 (Pat. Tr. & App. Bd. Aug. 12, 2021) (using a reference that discloses new or additional subject matter may prevent the Board from finding the art to be substantially the same).

Moreover, Tanaka, Van Urk, and Meng are not cumulative over the art cited during prosecution. While the Examiner did rely partially on Deeter (the primary reference in each ground here) during prosecution, the Examiner incorrectly found that “the compositions of Deeter et al. are *incapable* of achieving the claimed less than 1 EU endotoxin/mg albumin.” EX1042, 716-17. But the Examiner did not have the benefit of publications detailing the removal of endotoxin from albumin (Tanaka) providing processes for purifying rHSA produced in a transgenic plant such as maize (a grain) to provide a product free of endotoxins (Van Urk). In addition, the Examiner did not have benefit of any expert declaration, like the declaration of Petitioner’s expert Dr. Clark (EX1002), which explains the teachings of the prior art, what a POSA would have understood from the asserted references, and how a POSA would readily combine those teachings as of Ventria’s earliest filing date.

Accordingly, any argument for non-institution under § 325(d) is misplaced.

XVII. Conclusion

Healthgen respectfully requests that the Board grant this Petition for IPR, institute trial, and find all challenged claims unpatentable.

Respectfully Submitted

Date: March 17, 2022

By: /Maximilienne Giannelli /
Maximilienne Giannelli (Reg. No. 57,286)

*Lead Counsel for Petitioner Wuhan
Healthgen Biotechnology Corp.*

CERTIFICATE OF COMPLIANCE WITH WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that this Petition complies with the type-volume limits of 37 C.F.R. § 42.24(a)(1)(i), because it contains 13,898 words, according to the word-processing system used to prepare this Petition, excluding the words in the Table of Contents, Table of Authorities, Mandatory Notices, Certification Under § 42.24(d), and Certificate of Service, as set forth in 37 C.F.R. § 42.24(a)(1).

Respectfully Submitted

Date: March 17, 2022

By: /Maximilienne Giannelli /
Maximilienne Giannelli (Reg. No. 57,286)

*Lead Counsel for Petitioner Wuhan
Healthgen Biotechnology Corp.*

CERTIFICATE OF SERVICE

The undersigned certifies that, in accordance with 37 C.F.R. § 42.6(e) and 37 C.F.R. § 42.105, **Petition for *Inter Partes* Review; Petitioner's, Wuhan Healthgen Biotechnology Corp., Power of Attorney; Petitioner's, Wuhan Healthgen Biotechnology Corp., Exhibit List, and the associated Healthgen Exhibits 1001-1069 (other than exhibit nos. that were not used, 1008, 1009, and 1057) are being served via FedEx on the 17th day of March 2022**, the same day as the filing of the above-identified documents in the United States Patent and Trademark Office/Patent Trial and Appeal Board, upon the Patent Owner by serving the correspondence address of record with the USPTO as follows:

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and electronic courtesy copies upon counsel of record for the Patent Owner in the litigation pending before the U.S.I.T.C. Inv. No. 337-TA-1238 (instituted Jan. 15, 2021), *Certain Plant-Derived Recombinant Human Serum Albumins ("rHSA") and Products Containing Same*:

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