



**Charles River Laboratories, Inc.
Petitioner,
v.
Seikagaku Corporation
Patent Owner.**

**Case No. PGR2025-00023
U.S. Patent No. 11,959,109
Seikagaku EX2115**

**Seikagaku Trial Demonstratives
June 9, 2026**

Petitioner Has Failed to Demonstrate Unpatentability

I. The Challenged Claims are Entitled to a Dec. 10, 2013 Priority Date

II. Ground 1: Petitioner Fails to Show Invalidity for Lack of Written Description

III. Ground 2: Petitioner Fails to Show Invalidity for Lack of Enablement

IV. Ground 3: Petitioner Fails to Show Anticipation By the '629 Publication

The '109 Patent



US011959109B2

(12) United States Patent Mizumura et al.

(10) Patent No.: US 11,959,109 B2
(45) Date of Patent: *Apr. 16, 2024

- (54) RECOMBINANT FACTOR C AND METHOD FOR PRODUCING THE SAME, AND METHOD FOR MEASURING ENDOTOXIN
- (71) Applicant: SEIKAGAKU CORPORATION, Tokyo (JP)
- (72) Inventors: Hikaru Mizumura, Tokyo (JP); Toshio Oda, Tokyo (JP); Shun-ichiro Kawabata, Fukuoka (JP)
- (73) Assignee: SEIKAGAKU CORPORATION, Tokyo (JP)
- (*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.
- This patent is subject to a terminal disclaimer.

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Primary Examiner—David Steadman
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(57) ABSTRACT

A horseshoe crab Factor C protein having activity of Factor C, wherein the horseshoe crab is selected from *Tachypleus tridentatus*, *Limulus polyphemus*, and *Carcinoscorpius rotundicauda*, and wherein the horseshoe crab Factor C protein is produced through being recombinantly expressed from a Chinese Hamster Ovary (CHO) DG44 cell or HEK cell.

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10 Claims, 10 Drawing Sheets
Specification includes a Sequence Listing.

(21) Appl. No.: 18/346,420

(22) Filed: Jul. 3, 2023

(65) Prior Publication Data

US 2023/0357742 A1 Nov. 9, 2023

Related U.S. Application Data

(63) Continuation of application No. 17/554,128, filed on Dec. 17, 2021, which is a continuation of application No. 16/399,386, filed on Apr. 30, 2019, now Pat. No. 11,236,318, which is a continuation of application No. 15/983,725, filed on May 18, 2018, now Pat. No. 10,982,202, which is a continuation of application No. 14/650,767, filed as application No. PCT/JP2013/083082 on Dec. 10, 2013, now Pat. No. 10,144,923.

Claim 1 is a Method of Production Claim

What is claimed is:

1. A method for producing an endotoxin assay agent comprising a horseshoe crab Factor C, a horseshoe crab Factor B, and a horseshoe crab Pro-clotting enzyme, the method comprising:

expressing the horseshoe crab Factor C in a Chinese Hamster Ovary cell or a Human Embryonic Kidney cell as a host cell, secreting the horseshoe crab Factor C into an extracellular culture supernatant, and recovering the horseshoe crab Factor C in the culture supernatant, wherein the recovered horseshoe Factor C has activity of Factor C, and wherein the horseshoe crab Factor C is a *Tachypleus tridentatus* Factor C or a *Limulus polyphemus* Factor C,

expressing the horseshoe crab Factor B having activity of Factor B in a mammalian cell as a host cell,

expressing the horseshoe crab Pro-clotting enzyme in a mammalian cell as a host cell, and

producing an endotoxin assay agent comprising the horseshoe crab Factor C, the horseshoe crab Factor B, and the horseshoe crab Pro-clotting enzyme,

wherein the host cell for expressing the horseshoe crab Factor C, the host cell for expressing the horseshoe crab Factor B, and the host cell for expressing the horseshoe crab Pro-clotting enzyme may be the same or different.

Claim 1 requires:

1

Secreted *Lp* or *Tt* Factor C having Factor C activity

2

Factor B having Factor B activity

3

Pro-clotting enzyme having PCE activity

4

Expressed in same or different mammalian cell

5

Combined into an endotoxin assay agent

**The claim is for a method of producing
an endotoxin assay agent**

Dependent Claims Add Requirements

2. The method according to claim 1, wherein the mammalian cell expressing the Factor B is a Chinese Hamster Ovary cell or a Human Embryonic Kidney cell.

3. The method according to claim 1, wherein the mammalian cell expressing the Pro-clotting enzyme is a Chinese Hamster Ovary cell or a Human Embryonic Kidney cell.

4. The method according to claim 1, wherein the horseshoe crab for the Factor B and/or the horseshoe crab for the Pro-clotting enzyme is selected from the group consisting of *Tachypleus tridentatus* and *Limulus polyphemus*.

5. The method according to claim 1, wherein the horseshoe crab Factor C contains (α -2,3)-linked terminal sialic acid in a greater amount, as compared with a corresponding Factor C protein recombinantly expressed using Sf9 as a host cell.

6. The method according to claim 1, wherein the horseshoe crab Factor C has a molecular weight of 115 kDa to 130 kDa, as measured through SDS-PAGE under a nonreducing condition.

7. The method according to claim 1, further comprising filtering the culture supernatant comprising the horseshoe crab Factor C.

8. The method according to claim 1, wherein the endotoxin assay agent is formulated as a solid, a liquid, or a gel.

9. The method according to claim 1, wherein the horseshoe crab Factor C, the horseshoe crab Factor B, and the horseshoe crab Pro-clotting enzyme are separately expressed in individually established host cells.

Dependent claims 2-9



Claims 2-4

crab species and host cell selections



Claims 5-7

additional Factor C properties and recovery method



Claims 8-9

assay agent formulation, separate expression

Written Description

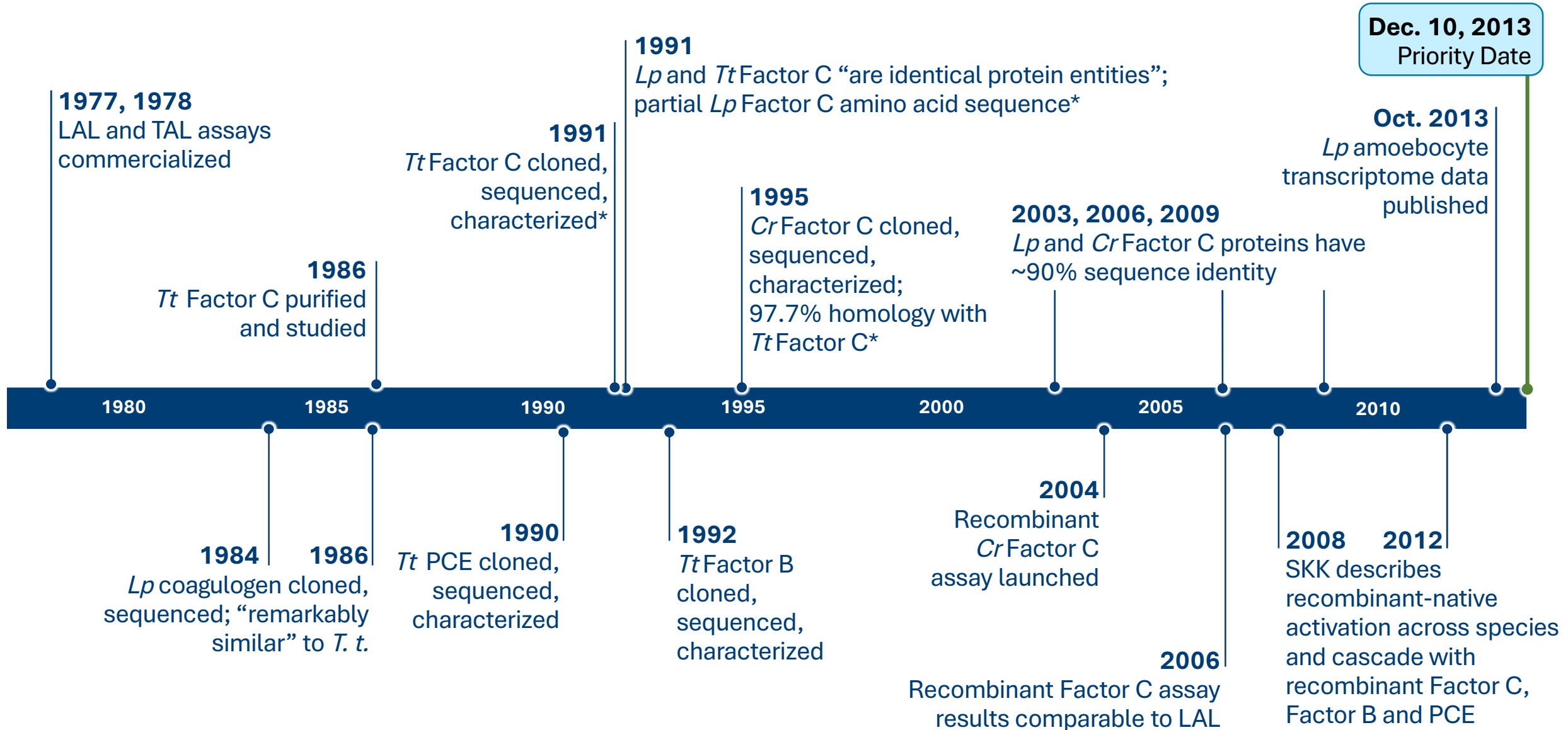
I.

The Challenged Claims are Entitled to a Dec. 10, 2013 Priority Date

Ia.

The '767 Application Provides Written Description Support

Undisputed the Proteins Were Well-Known and Well-Characterized



The Claimed Method Uses a Small, Well-Known Genus of Proteins

Teva

Ajinomoto

Background knowledge and routine techniques can supply representative species for a well-known genus



Claims here use:

A genus of proteins that is small, well-known and identified in the specification

Not persuasive:

Case law involving an unknown or unexplored genus
(*Rochester, Boston Scientific, Carnegie Mellon*)

Petitioner's attempts to distinguish *Teva*

The Genus of Claim 1 is Thirty-Two Combinations

3,456

Petitioner's artificial number

- counts non-recited variables
- unsupported host-cell and recovery distinctions

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32

proper claim scope

- ten distinct proteins
- as few as ten expression vectors needed

Board

“We are not persuaded, at least on the present record, that the purported 3,456 possible combinations are persuasive of a lack of written description or enablement.”

Petitioner Argues: No Representative Species/Example

Petitioner:

T. tridentatus sequences and insect cell examples “**cannot be...** representative species of the genus of assay agents of claim 1, no matter what its size”

Examples Need Not Use Members of the Genus



Examples outside the genus can support written description

Teva

Murine antibodies support humanized antibody claims

Falkner

Herpesvirus examples support poxvirus vaccine claims

BASF

***Arabidopsis* examples support canola cell claims**

Small, Well-Known, Structurally and Functionally Similar Proteins

Claim 1	Crab Species	Factor C	Factor B	PCE	Claim 4
	<i>L. polyphemus</i>				
	<i>T. tridentatus</i>	✓	✓	✓	
	<i>T. gigas</i>				
	<i>C. rotundicauda</i>				

Small, well-known genus of proteins

Known / expected high sequence similarity, known functional similarity

Robust, cross-species function

Petitioner Attempts to Dismiss the Evidence

Petitioner:

“a POSA would not simply extrapolate” or predict successful protein expression

Patent Owner:

specification teaches extrapolation and evidence supports successful expression

The Weight of the Evidence Supports Patent Owner

Petitioner evidence



Dr. Jain

Cannot predict success for Factor B or PCE – must do experiment

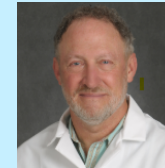
Only 23 references considered

Outdated, overly general or inapplicable art

VS

Patent Owner evidence

'767 application teaches extrapolation



Petitioner's EP Expert Prof. Frohman

Would extrapolate and predict (Limulus Factor C)



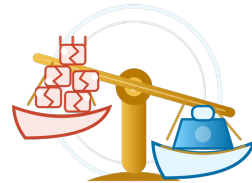
Prof. Schaefer

Would extrapolate and predict

100 references considered

Similarities support extrapolation and predicted success

No reason to expect or evidence of difficulties with Factor B and PCE



The *T. tridentatus* proteins and examples are representative

Petitioner's Arguments Are Legally Unsupported

Petitioner argues no written description because:

No example / no actual reduction to practice

No sequences



Not required

Not required

**Written description concerns *constructive* possession
shown in the specification**

Petitioner Argues Lack of Examples and Actual Possession

The inventors “did not describe and were *not in possession of any single claimed example*”

The inventors “*did not possess even a single example*”

“the lack of any *actual example*... proves no written description as a matter of law”



Written description can be satisfied without examples or actual reduction to practice.

Falkner

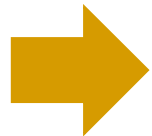
"examples are not necessary"

The written-description standard may be met even when the specification does not include working examples.

BASF

"actual reduction to practice is not a requirement"

Delay in actual production does not negate constructive possession at the time of filing



Petitioner demands more than what the law requires.

Petitioner's Misplaced Emphasis on Sequences

“the gene and sequence information ... was ***not yet known or disclosed***”

“the coding sequences ... do not appear in the '767 Application and ***had not been published*** by December 10, 2013”

“the coding information for these proteins from these species of horseshoe crabs ***was unknown*** by 2013”

Federal Circuit: Sequence Recitation Not Required



The specification need **not** recite known or easily determined sequences to show possession

Ariad / Capon

No nucleotide-by-nucleotide recitation rule

No heightened written description requirement to recite entire genus nucleotide-by-nucleotide

Falkner

Accessible literature can supply sequence information

Where literature sources provide genes and sequences, written description does not require recitation or incorporation of every sequence.

Teva

Inventors possessed sequences of disclosed or accessible antibodies

Where murine antibodies were accessible and determining sequences necessary to humanize antibodies was routine, inventors possessed those sequences.

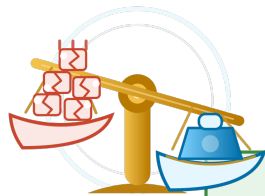
Petitioner Argued to EPO Routine to Obtain Sequences

Petitioner to EPO:

“[T]he skilled person **merely had to carry out the teaching of... [the ‘767 Application]... using standard techniques to arrive at the claimed” *Limulus* Factor C sequences.**

“[I]t is a matter of routine practice for a person skilled in the art to determine the sequence of a known protein.”

“Therefore, all the skilled person needed to derive the claimed sequences was a standard kit to carry out a **common general knowledge technique**, which had been around since 1988.”



Petitioner’s arguments are not credible

The Claims Are Entitled to a 2013 Priority Date

The '767 application:



Identifies the horseshoe crab species and the proteins used



Teaches mammalian expression of Factor C and extrapolation to Factor B, PCE



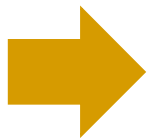
Discloses a fully recombinant endotoxin assay agent



Discloses expression in the same or different mammalian host cell



Provides representative species; structure-function correlation known in the art



The '767 Application provides written description support for the Challenged Claims

I.

The Challenged Claims are Entitled to a Dec. 10, 2013 Priority Date

Ib.

The '767 Application Enables the Full Scope of the Challenged Claims

Amgen is Different

Petitioner invokes *Amgen*, but *Teva* explains why these claims are different.

Amgen

- claimed the genus of proteins itself by function
- required making broad antibody genus
- unpredictable functional scope

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Challenged Claims

- method of using well-known proteins
- proteins expressly identified in specification
- functions were known and robust

The Challenged Claims do not require trial-and-error discovery of an unknown genus

Teva's Framing Controls: Extra Credit, Not a Research Assignment

Teva

Humanization work *"more akin to extra credit than a necessary research assignment"* where specification teaches all antibodies will work

Petitioner: Too Challenging

Ascertain sequences,
design and express proteins in every
mammalian system, and
confirm functionality



Patent Owner: Routine Techniques

Specification teaches how to make and use
functional proteins

Routine techniques are not a research assignment

Petitioner's Reply Arguments Are Limited and Unconvincing

Prior Art Failures

**Failure to express
Factor C in COS-1**



**PO answer: inventors
solved this problem**

Unpredictability

**Protein function
unpredictable**



**PO answer: function
known and robust**

Inadequate Guidance

**Instructions for
Factor B / PCE
unscientific boilerplate**



**PO answer: evidence
confirms adequacy**

Petitioner: No Substantive Rebuttal

No Response From Petitioner

Breadth

Claims are broad
(3,456 combinations)



PO answer: claims
require only ten vectors
to practice

Level of Skill

Level of skill high



PO answer: level of skill
and level of routine
experimentation high

Struggles

Struggles to sequence
Limulus genes



PO answer: many
Limulus sequences
known in the art

Petitioner: No Response

Petitioner's Inconsistent Positions on PCT '498

Petitioner in Opposition

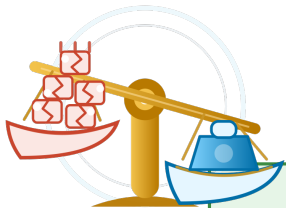
Criticizes PCT '498 ¶ 12 as
“very generic”
“entirely unsupported”
“factually incorrect”

vs

Petitioner in PGR

Relies on PCT '498 ¶ 12 as
proof of struggles and
unpredictability

No attempt to explain or reconcile

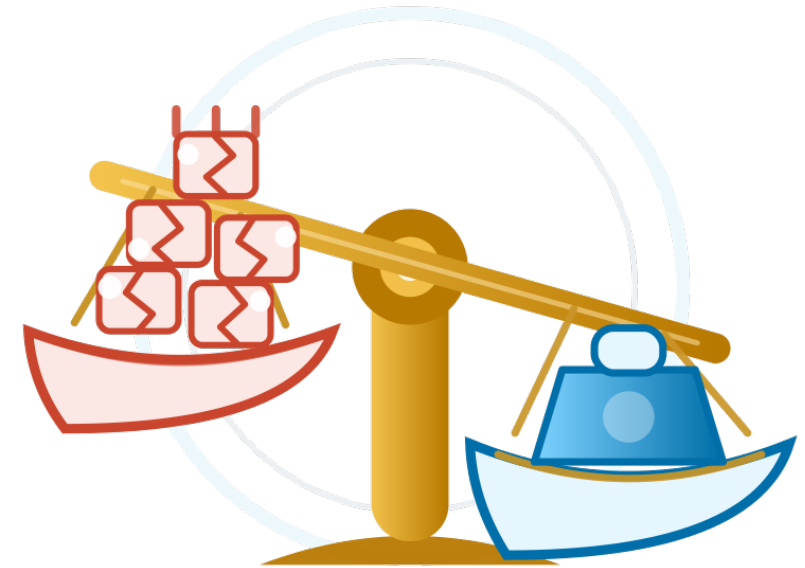


Petitioner's inconsistency and gamesmanship undermine its credibility

Petitioner's Evidence Falls Short of Its Burden

Petitioner's Evidence Deserves Little Weight

- ✗ No explanation of Opposition arguments or evidence
- ✗ Imported limitations into claim 1
- ✗ Limited literature review
- ✗ Relied on outdated / irrelevant support for unpredictability
- ✗ No evidence of difficulties or inadequacy of routine techniques
- ✗ Did not defend genus size calculation



Patent Owner's Evidence Outweighs Petitioner's

Petitioner evidence



Dr. Jain

Nearly impossible to obtain sequences

VS

Patent Owner evidence

Unrebutted Schaefer testimony

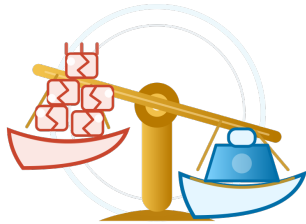
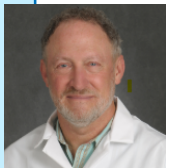
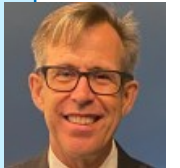
'767 application disclosures

High levels of skill, knowledge, routine experimentation in the art

Opposition arguments + Frohman testimony

Jain: lacking experience, can only speculate on how to obtain sequences

Jain: making vectors and expressing proteins not undue once sequences known



Only routine experimentation required

Confirmed by the '629 publication and McClymont thesis

Petitioner Has Failed to Demonstrate Unpatentability on Any Ground

II.

Ground 1: Petitioner Fails to Show Invalidity for Lack of Written Description

III.

Ground 2: Petitioner Fails to Show Invalidity for Lack of Enablement

IV.

Ground 3: the '629 Publication is Not Prior Art

The Petition Should Be Denied



Priority supported

The challenged claims are entitled to Dec. 10, 2013.



'629 publication is not prior art

The publication cannot support Ground 3.



Ground 3 fails

Grounds 1-2 fail

Petitioner offered no evidence concerning lack of written description or enablement as of July 3, 2023 filing date.



Thank You