Patent Owner's Oral Argument Presentation

10x Genomics, Inc. v. Bruker Spatial Biology, Inc.
IPR2023-01298

March 12, 2025

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

’689 Patent: Claim 1

1. A method for spatially detecting at least one target analyte in a first location and a second location of a tissue sample comprising:

a) contacting the tissue sample with a plurality of nucleic acid probes, wherein each of the nucleic acid probes comprise a target binding domain that binds to the at least one target analyte, wherein the tissue sample [has been] is treated to facilitate binding of the nucleic acid probes to the target analyte;

b) collecting the nucleic acid probes, or portions thereof, bound to the at least one target analyte in a first location of the tissue sample under conditions that release the nucleic acid probes, or portions thereof, from the first location of the tissue sample;

c) collecting the nucleic acid probes, or portions thereof, bound to the at least one target analyte in a second location of the tissue sample under conditions that release the nucleic acid probes, or portions thereof, from the second location of the tissue sample;

d) performing an extension reaction that incorporates at least one nucleic acid sequence that identifies the first location of the tissue sample into each of the nucleic acid probes, or portions thereof, collected in step (b), thereby forming a first plurality of extension products that comprise the nucleic acid probes, or portions thereof, collected in step (b) and the at least one nucleic acid sequence that identifies the first location of the tissue sample;

e) performing an extension reaction that incorporates at least one nucleic acid sequence that identifies the second location of the tissue sample into each of the nucleic acid probes, or portions thereof, collected in step (c), thereby forming a second plurality extension products that comprise the nucleic acid probes, or portions thereof, collected in step (c) and the at least one nucleic acid sequence that identifies the second location of the tissue sample; and

f) identifying the first plurality of extension products and the second plurality of extension products by sequencing the first plurality of extension products and the second plurality of extension products, thereby spatially detecting the at least one target analyte in the first location of the tissue sample and the second location of the tissue sample.

’689 Patent: Claim 16

16. A method for spatially detecting at least one target analyte in a first location and a second location of a tissue sample comprising:

a) contacting the tissue sample with a first plurality of nucleic acid probes and a second plurality of nucleic acid probes,

wherein each of the nucleic acid probes in the first plurality of nucleic acid probes comprise a target binding domain that binds to the at least one target analyte,

wherein each of the nucleic acid probes in the second plurality of nucleic acid probes comprise a target binding domain that binds to the at least one target analyte,

wherein the tissue sample is treated to facilitate binding of the first plurality of nucleic acid probes and the second plurality of nucleic acid probes to the at least one target analyte;

b) forming ligated probes by ligating each of nucleic acid probes from the first plurality of nucleic acid probes and each of nucleic acid probes from the second plurality of nucleic acid probes that are bound to each of identical molecules from the at least one target analyte;

c) collecting the ligated probes, or portions thereof, bound to each of the identical molecules from the at least one target analyte in a first location of the tissue sample under conditions that release the ligated probes, or portions thereof, from the first location of the tissue sample;

d) collecting the ligated probes, or portions thereof, bound to each of the identical molecules from the at least one target analyte in a second location of the tissue sample under conditions that release the probes, or portions thereof, from the second location of the tissue sample;

e) performing an extension reaction that incorporates at least one nucleic acid sequence that identifies the first location of the tissue sample into each of the ligated probes, or portions thereof, collected in step (c), thereby forming a first plurality of extension products that comprise the ligated probes, or portions thereof, collected in step (c) and the at least one nucleic acid sequence that identifies the first location of the tissue sample;

f) performing an extension reaction that incorporates at least one nucleic acid sequence that identifies the second location of the tissue sample into each of the ligated probes, or portions thereof, collected in step (d), thereby forming a second plurality extension products that comprise the ligated probes, or portions thereof, collected in step (d) and the at least one nucleic acid sequence that identifies the at least second location of the tissue sample; and

g) identifying the first plurality of extension products and the second plurality of extension products by sequencing the first plurality of extension products and the second plurality of extension products, thereby spatially detecting the at least one target analyte in the first location of the tissue sample and the second location of the tissue sample.

’689 Patent, Claim 16; Petition at 6

Petition Grounds

Ground	35 U.S.C. Section (AIA)	Claims	References
1	§ 102	1-8, 11-23, and 26-30	So-456
2	§ 103	1-30	So-456
3	§ 103	9, 10, 24, 25	So-456 and Stahl
4	§ 102	1-30	Chell

Ground 1: The Board Found That Petitioner Did Not Have A Reasonable Likelihood of Prevailing

> In sum, based on the record before us, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing that So-456 anticipates claims 1–8, 11–23, and 26–30. Nevertheless, the Board, in a decision to institute under 35 U.S.C. § 314(b), may not institute review on fewer than all claims challenged in the petition. *SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1355–56 (2018). In addition, if the Board institutes trial, it will institute on all grounds in the petition. *See* 37 C.F.R.

Paper 14 (Institution Decision) at 24-25

Ground 2: The Board Found That Petitioner Did Not Have A Reasonable Likelihood of Prevailing

However, Petitioner's allegations regarding the obviousness of independent claims 1 and 16 do not address the deficiency discussed above with regard to the limitation "collecting the nucleic acid probes." *See* Section II.D.2.a. Specifically, Petitioner does not allege or provide evidence to support that the skilled artisan would have found it obvious based on the teachings of So-456 to collect the cleaved identifier oligonucleotides rather than the genomic amplicons as alleged. In addition, we share Patent Owner's view that Petitioner, on this record, does not sufficiently show a motivation for the ordinarily skilled artisan to have included a spatial barcode in the capture probes of So-456. We suggest the parties further address these issues at trial.

Institution Decision at 31

Ground 3: The Board Found That Petitioner Did Not Have A Reasonable Likelihood of Prevailing

> Challenged claims 9, 10, 24, and 25 depend from independent claims 1 or 16. Petitioner relies on the same allegations it made regarding anticipation and obviousness over So-456 for the disclosure of all limitations of independent claims 1 and 16. Pet. 49. Petitioner does not rely on Stahl to cure the deficiencies for any of the limitations we found lacking in the prior challenges. *See* II.D., II.E. For the same reasons discussed in the prior challenges, on the current record, Petitioner has not shown a reasonable likelihood of success in showing obviousness of claims 9, 10, 24, and 25.

Institution Decision at 32

Ground 4: Board Invited Parties To Discuss Written Description Support Of The Priority Application For The Patent Claims

As described above, all references to "collecting probes" refer only to cleaved off identifier oligonucleotides, not release of entire probes. Thus, for purposes of institution, we find that the 487 application does not provide written description support for the full scope of the claims, and that Chell is prior art. We invite the parties to further develop this issue as well as the issue of whether the 487 application provides written description support for "on-analyte" ligation as recited in the claims during trial. We now turn to the question of whether Chell anticipates the challenged claims.

Institution Decision at 36

Topics For Argument

Chell is not prior art because the ’689 patent claims have priority support
(Ground 4)

So-456 does not anticipate the ’689 patent claims
(Ground 1)

So-456 does not render the ’689 patent claims obvious
(Grounds 2 and 3)

Chell Is Not Prior Art

(10) International Publication Number
WO 2021/133849 A1

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)
(19) World Intellectual Property Organization
International Bureau
(43) International Publication Date
01 July 2021 (01.07.2021)
WIPO | PCT
(10) International Publication Number
WO 2021/133849 A1

(51) International Patent Classification:
C12Q 1/6841 (2018.01)
(21) International Application Number:
PCT/US2020/066720
(22) International Filing Date:
22 December 2020 (22.12.2020)
(25) Filing Language: English
(26) Publication Language: English

na; Södra Fiskartorpsvagen 15 C, 114 33 Stockholm (SE). **BAVA, Felice Alessio**; 6230 Stoneridge Mall Road, Pleasanton, California 94588-3260 (US). **KATIRAEE, Layla**; 6230 Stoneridge Mall Road, Pleasanton, California 94588-3260 (US).

(74) Agent: **KNABEL, Matthew K.** et al.; Fish & Richardson, P.C., P.O. Box 1022, Minneapolis, Minnesota 55440-1022 (US).

(81) Designated States *(unless otherwise indicated, for every*

(DE); **GALLANT, Caroline Julie**; Södra Fiskartorpsvagen

UG, ZM, ZW); Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,

(43) International Publication Date
01 July 2021 (01.07.2021)

International Filing Date:
22 December 2020 (22.12.2020)

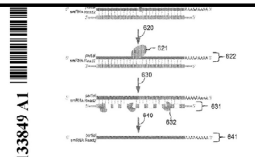


FIG. 6

WO 2021/133849 A1

[Continued on next page]

10x Genomics EX1006

Patent No.: US 11,377,689

(12) **United States Patent**
Beechem et al.
(10) **Patent No.: US 11,377,689 B2**
(45) **Date of Patent: *Jul. 5, 2022**

(54) **CHEMICAL COMPOSITIONS AND USES THEREOF**

(71) Applicant: **NanoString Technologies, Inc.**, Seattle, WA (US)

(72) Inventors: **Joseph M. Beechem**, Eugene, OR (US); **Dae Kim**, Bellevue, WA (US); **Margaret Hoang**, Seattle, WA (US); **Mark Gregory**, Boise, ID (US); **Erin Piazza**, Edmonds, WA (US); **Denise Zhou**, Seattle, WA (US)

(73) Assignee: **NanoString Technologies, Inc.**, Seattle, WA (US)

(58) **Field of Classification Search**
USPC 435/6.1, 6.11, 6.12, 91.1, 91.2, 91.51, 435/283.1, 287.1, 287.2; 436/94, 501;
(Continued)

(56) **References Cited**
U.S. PATENT DOCUMENTS
5,320,814 A 6/1994 Walt et al.
5,543,838 A 8/1996 Hosier et al.
(Continued)
FOREIGN PATENT DOCUMENTS

Continuation of application No. 16/272,487, filed on Feb. 11, 2019, now abandoned.

Related U.S. Application Data
(63) Continuation of application No. 16/272,487, filed on Feb. 11, 2019, now abandoned.
(Continued)

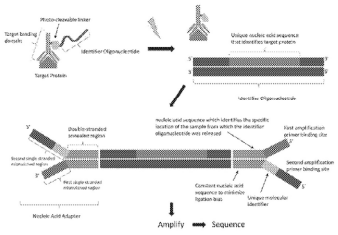
(51) **Int. Cl.**
C12P 19/34 (2006.01)
C12Q 1/6876 (2018.01)
(Continued)

(52) **U.S. Cl.**
CPC ***C12Q 1/6876*** (2013.01); ***C12Q 1/6804*** (2013.01); ***C12Q 1/686*** (2013.01);
(Continued)

(57) **ABSTRACT**

The present invention relates to, among other things, probes, compositions, methods, and kits for simultaneous, multiplexed detection and quantification of protein and/or nucleic acid expression in a user-defined region of a tissue, user-defined cell, and/or user-defined subcellular structure within a cell that are adaptable for use with existing sequencing technologies.

30 Claims, 40 Drawing Sheets
(29 of 40 Drawing Sheet(s) Filed in Color)
Specification includes a Sequence Listing.



Petitioner's Position: The '689 Patent Is Not Entitled To Its Priority Date

> As discussed below, Chell was filed and published before the 689 patent was filed, and is intervening prior art because the 689 patent is not entitled to any of its claimed priority dates.

> The 689 patent claims are not entitled to priority benefit from any of the priority applications because none of those applications provides written description support for the full scope of the claims. EX1002, ¶¶271-293.

Petitioner's Position: Priority Application Does Not Provide Written Description Support For Two Claim Terms

in the specification in two material ways. ***First***, all challenged claims recite "collecting the [] probes, or portions thereof," which on its face encompasses two distinct sets of options—collecting *whole* probes, or portions of probes. However,

Second, as discussed above in Section IX.A–IX.B, claims 16-30 are drawn to a particular arrangement and usage of primary (analyte-binding) probes that is not disclosed in the priority applications. Claims 16-30 require hybridizing pairs of

The 689 patent's priority application neither describes using ligation on the analyte nor binding primary probes to each other. Instead, the priority applications

Topics For Argument

Chell is not prior art because the ’689 patent claims have priority support
(Ground 4)

- The ’487 application describes collecting “whole probes”
- The ’487 application describes “on-analyte” ligation

So-456 does not anticipate the ’689 patent claims
(Ground 1)

So-456 does not render the ’689 patent claims obvious
(Grounds 2 and 3)

Claims Terms At Issue

Claim 1(b) and 1(c):	"collecting the nucleic acid probes, or portions thereof"
Claim 16(c) and (d):	"collecting the ligated probes, or portions thereof"

Petitioner's Position: "Whole Probes" Is Not Described

> The applications never disclose releasing or collecting *whole* probes, nor do they disclose applying forces to release entire probes. The challenged claims are

> The challenged claims encompass collecting *whole* nucleic acid probes or portions thereof, yet the 487 application exclusively describes methods that collect a *portion* (identifier oligonucleotide) of the nucleic acid probes. Pet., 53-55;

Written Description Is From The View Of A POSA



> As the "hallmark" of written description, *see Ariad*, 598 F.3d at 1351, the disclosure must be considered as a whole, as the person of ordinary skill in the art would read it, to determine if it ***reasonably conveys*** possession.

Allergan USA, Inc. v. MSN Lab'ys Priv. Ltd., 111 F.4th 1358, 1375 (Fed. Cir. 2024) (emphasis in original)

Level Of Detail Required To Reasonably Convey Possession Varies



> This inquiry, as we have long held, is a question of fact. Thus, we have recognized that determining whether a patent complies with the written description requirement will necessarily vary depending on the context. Specifically, the level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology.

Ariad Pharms., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1351 (Fed. Cir. 2010) (citations omitted)

Unnecessary To Spell Out Every Detail For Written Description



A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. That is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before. Placed in that context, it is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation.

LizardTech, Inc. v. Earth Res. Mapping, Inc., 424 F.3d 1336, 1345 (Fed. Cir. 2005) (citations omitted)

Written Description Need Not Include Known Information



The purpose of the written description requirement is to assure that the public receives sufficient knowledge of the patented technology, and to demonstrate that the patentee is in possession of the invention claimed. The requirement is applied in the context of the state of knowledge at the time of the invention. The written description "need not include information that is already known and available to the experienced public."

Zoltek Corp. v. United States, 815 F.3d 1302, 1308 (Fed. Cir. 2016) (citations omitted)

Written Description Need Not Include What Is Known In The Prior Art



The law is clear that patent documents need not include subject matter that is known in the field of the invention and is in the prior art, for patents are written for persons experienced in the field of the invention. To hold otherwise would require every patent document to include a technical treatise for the unskilled reader. Although an accommodation to the "common experience" of lay persons may be feasible, it is an unnecessary burden for inventors and has long been rejected as a requirement of patent disclosures.

S3 Inc. v. NVIDIA Corp., 259 F.3d 1364, 1371 (Fed. Cir. 2001) (citations omitted)

The POSA Is Highly Skilled Under Petitioner's Definition

VII. PERSON OF ORDINARY SKILL IN THE ART

A POSA is a hypothetical person who is presumed to be aware of all pertinent art, equipped with conventional wisdom and ordinary creativity. Here, a POSA would have possessed a strong understanding in the use and development of genetics and genomics approaches for detecting or monitoring human diseases, such as spatial detection of a target analyte (*e.g.*, mRNA or DNA) in a tissue, and would typically have a Ph.D. in a relevant field (*e.g.*, molecular biology, genetics, and bioinformatics) with two years of experience. EX1002, ¶¶24-25. *See also* EX1004, 268 (NanoString admitting during prosecution that "the skill level of a [POSA] in the context of the instant application is high, at least that of a PhD in biology, if not higher.").

Petitioner Ignores Disclosure In The ’487 Application For “Whole Probes”

1. **Denaturation is described**
2. Indirect hybridization is described
3. The ’487 application is not limited to probes that are *always* cleaved

Denaturation Is Described To Separate Strands

[00240] An identifier oligonucleotide can be a single-stranded, a double-stranded, or a partially double-stranded nucleic acid molecule. In the aspects in which an identifier oligonucleotide is double-stranded or partially double-stranded, at least one of the two strands can comprise at least two separate nucleic acid molecules which, without being bound by theory, allows for denaturing of the identifier oligonucleotide at lower temperatures.

[00285] Following the cleavage step, regardless of the method used for cleavage, the product of the cleavage reaction may be subjected to denaturing conditions in order to remove the portion(s) of the cleaved strand(s) that are not attached to the solid support. Suitable denaturing conditions will be apparent to the skilled reader with reference to standard molecular biology protocols.

EX1009 ¶¶ 240, 285; EX2006 ¶¶ 94-95; PO's Response at 43-44; PO's Sur-Reply at 3

Both Experts Agree That Denaturation Is Well Known



Dr. David Sherman
Patent Owner's Expert

> acids. In my opinion, a POSA would be well-versed with this concept of denaturation because it is a basic concept in genetics and molecular biology. For



Dr. Paul Spellman
Petitioner's Expert

> **Q.** Would [a skilled artisan in 2018] know whether – would they know how to denature a probe that's attached to a target of interest? Which is what this describes in various ways –
>
> **A.** So as an abstract concept, denaturation is well known to a POSA.

EX2006 ¶ 94; EX2007 at 113:25-114:7;
PO's Response at 43; PO's Sur-Reply at 3

Denaturation Of "Whole Probes" Is Described In The Incorporated Application No. 14/946,386

[0010] Provided herein is a method for sequencing a nucleic acid using a sequencing probe of the present invention. The method comprises steps of: (1) hybridizing at least one sequencing probe, of the present invention, to an target nucleic acid that is immobilized (e.g., at one, two, three, four, five, six, seven, eight, nine, ten or more positions) to a substrate; (2) binding to the first attachment region a first complementary nucleic acid molecule (RNA or DNA) which has a detectable label (e.g., a fluorescent label) or a first complementary nucleic acid molecule of a first reporter complex comprising detectable labels (e.g., fluorescent labels); (3) detecting the detectable label(s), and (4) identifying the position and identity of the first nucleotide in the immobilized target nucleic acid. Optionally, the immobilized target nucleic

[0012] In embodiments, when a plurality of populations (i.e., more than one population) of probes are used, the method further comprises steps of: (10) de-hybridizing each sequencing probe of the first population from the nucleic acid; (11) removing each de-hybridized sequencing probe of the first population; (12) hybridizing at least a second population of sequencing probes of the present invention, where each sequencing probe in the second population de-hybridizes from the immobilized target nucleic acid under about the same conditions and de-hybridizes from the immobilized target nucleic acid under different conditions from the sequencing probes in the first population; (13) binding a

The Incorporated Patent Application's Example Describes Denaturation

Example 1

The Present Invention's Method of Sequencing a Target Nucleic Acid is Rapid

[0174] Below is described the timing for steps in the methods of the present invention and as shown in FIGS. **8** to **12**.

[0175] The present invention requires minimal sample preparation. For example, as shown in FIG. **13**, nucleic acids in a sample can begin to be read after 2 hours or less or preparation time; this is significantly less time required for Ion Torrent (AmpliSeq™) or Illumina (TruSight) sequencing, which, respectively, require about 12 or 9 hours of preparation time.

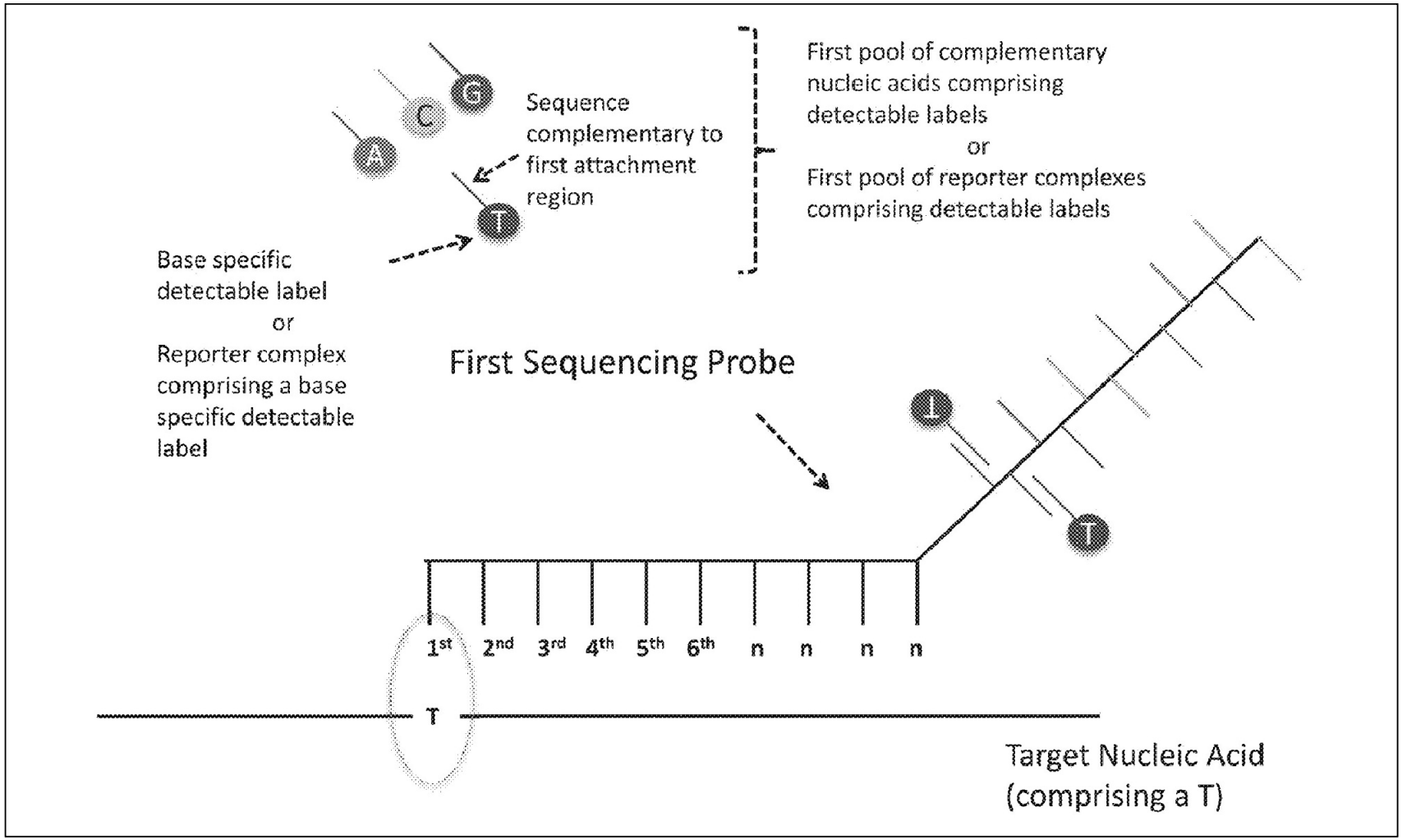
[0176] Calculations for an exemplary run are shown in FIG. **14** and calculations for cycling times are shown in FIG. **15**.

[0177] Binding a population of probes to an immobilized target nucleic acid takes about sixty seconds. This reaction can be accelerated by utilizing multiple copies of the target binding domain on the synthetic backbone. With microfluidic-controlled fluid exchange device, washing away un-bound probes takes about a half a second.

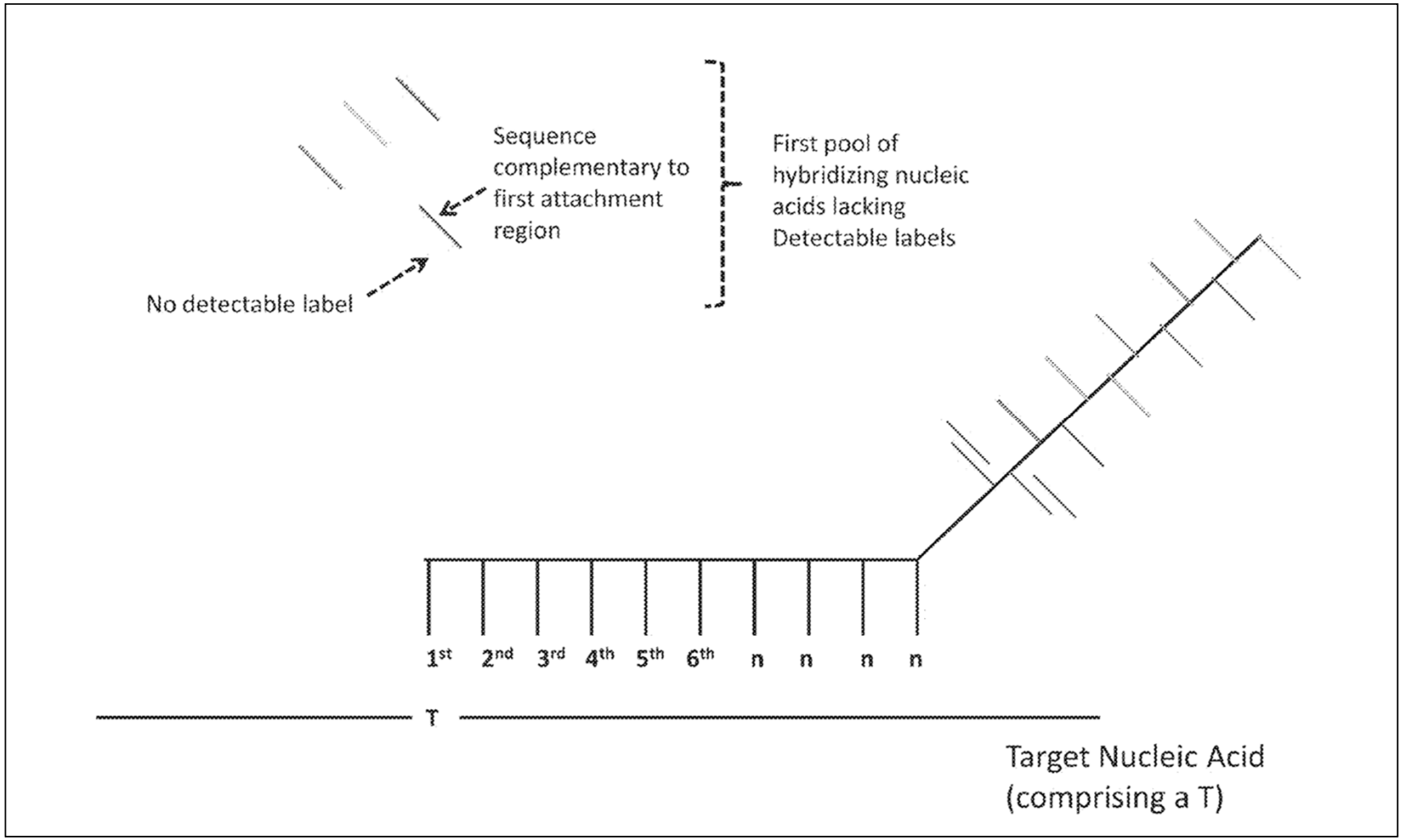
[0183] Probes of the first population are de-hybridized. This takes about sixty seconds.

[0184] The above steps are repeated for second and subsequent populations of probes. If populations of sequencing probes are organized by melting temperature (Tm), each population of probes will require multiple hybridizations to ensure that each base is covered to required depth (this is driven by error rate). Moreover, by analyzing the hybridization reads during a run, it is possible to recognize each individual gene that is being sequenced well before the entire sequence is actually determined. Hence cycling can be repeated until a particular desired error-frequency (or coverage) is met.

The Incorporated Patent Application's Example Describes Denaturation

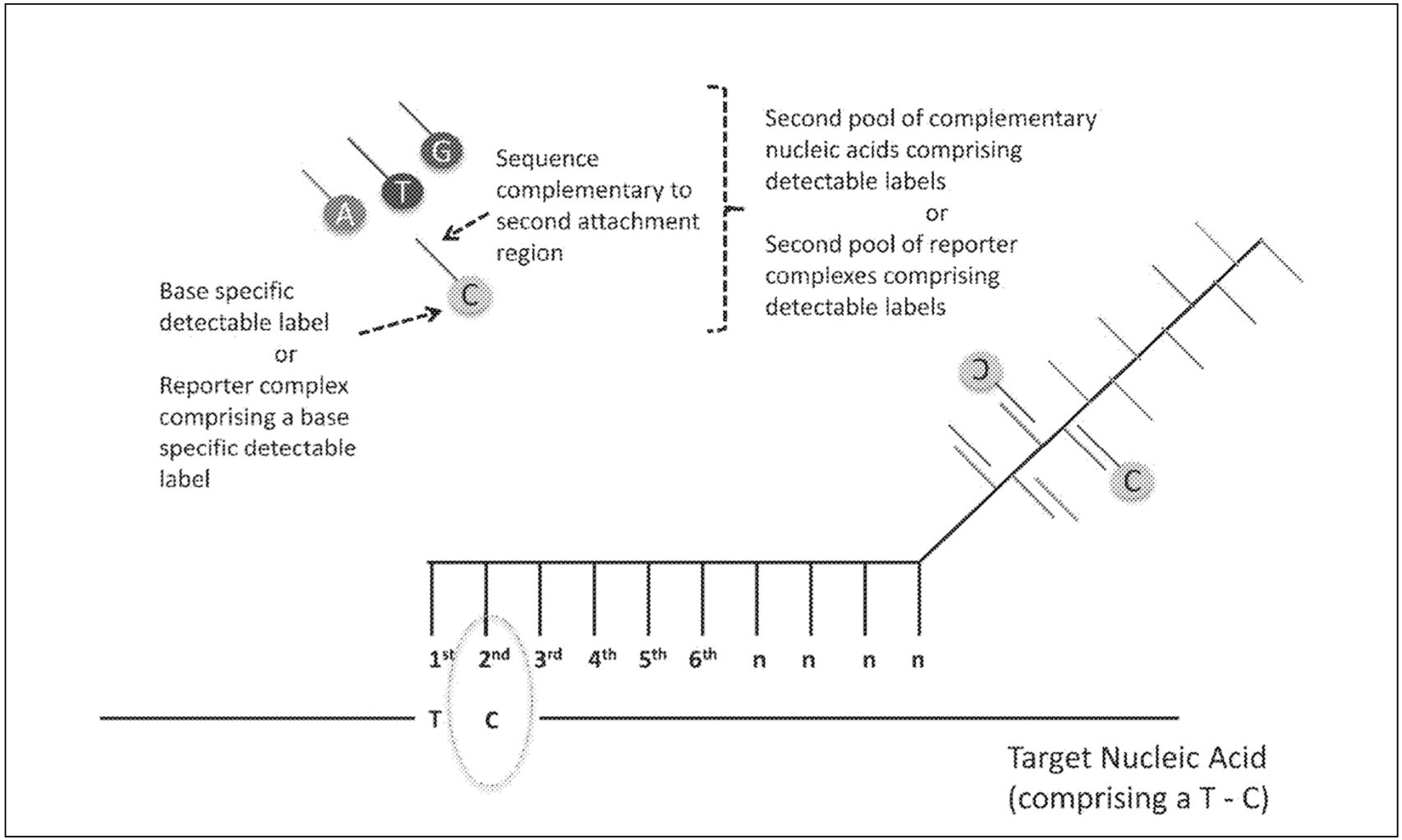


The Incorporated Patent Application's Example Describes Denaturation

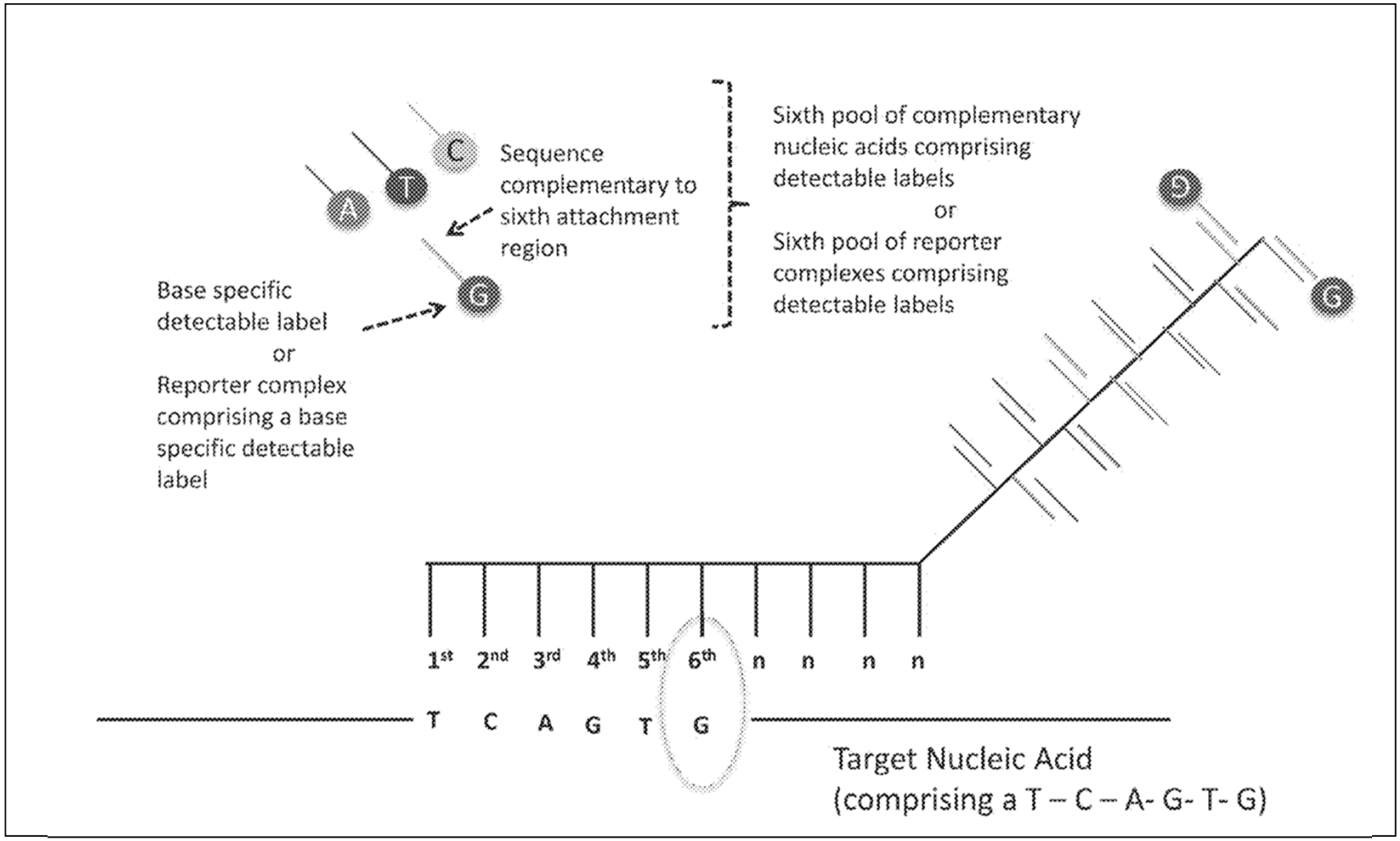


EX2008 Fig. 8B; PO's Response at 44

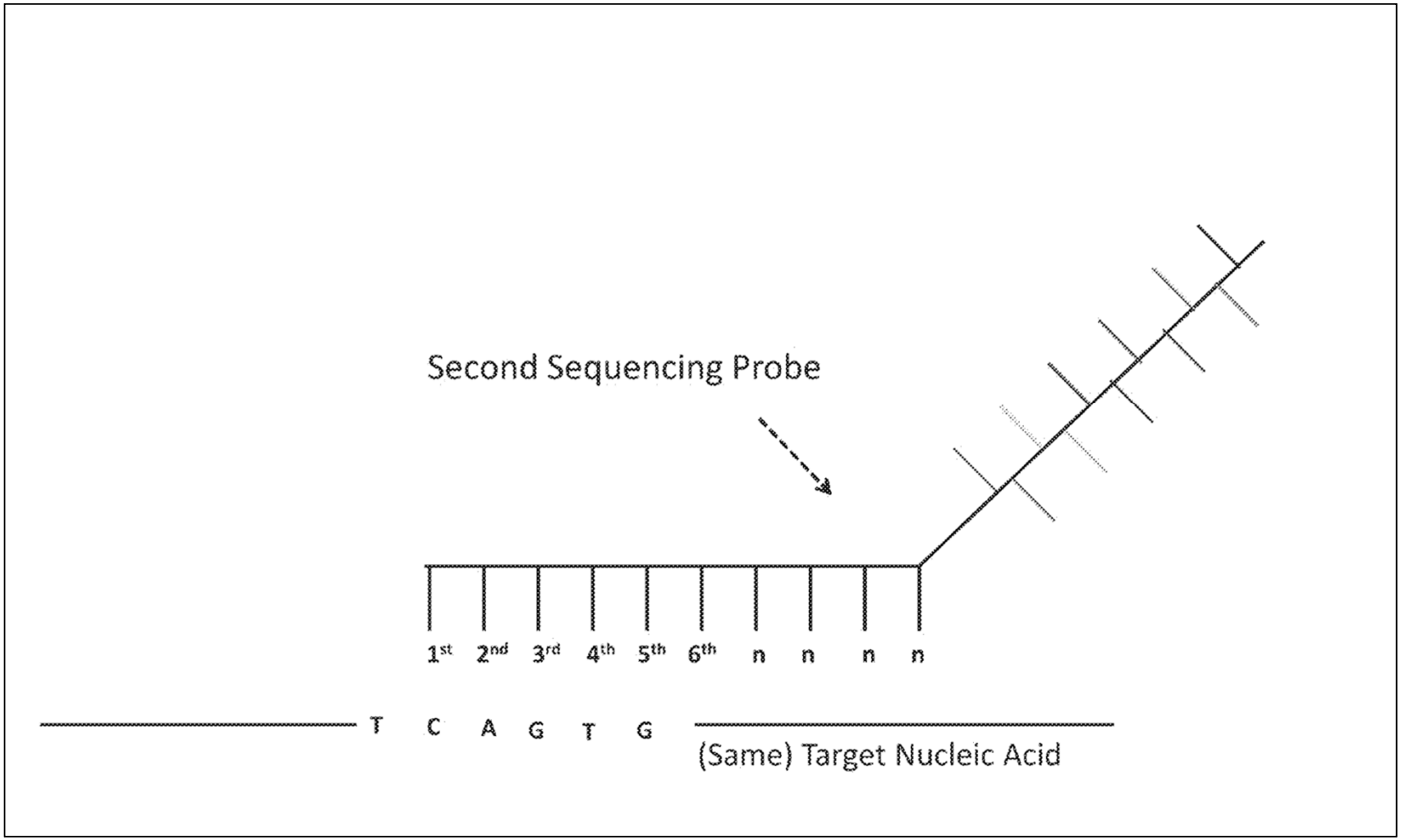
The Incorporated Patent Application's Example Describes Denaturation



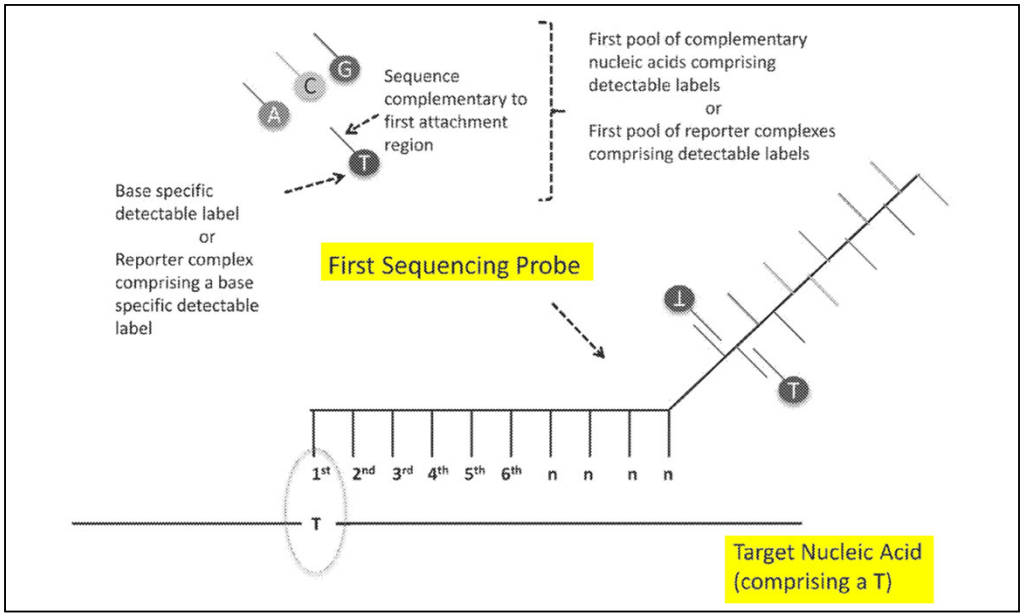
The Incorporated Patent Application's Example Describes Denaturation

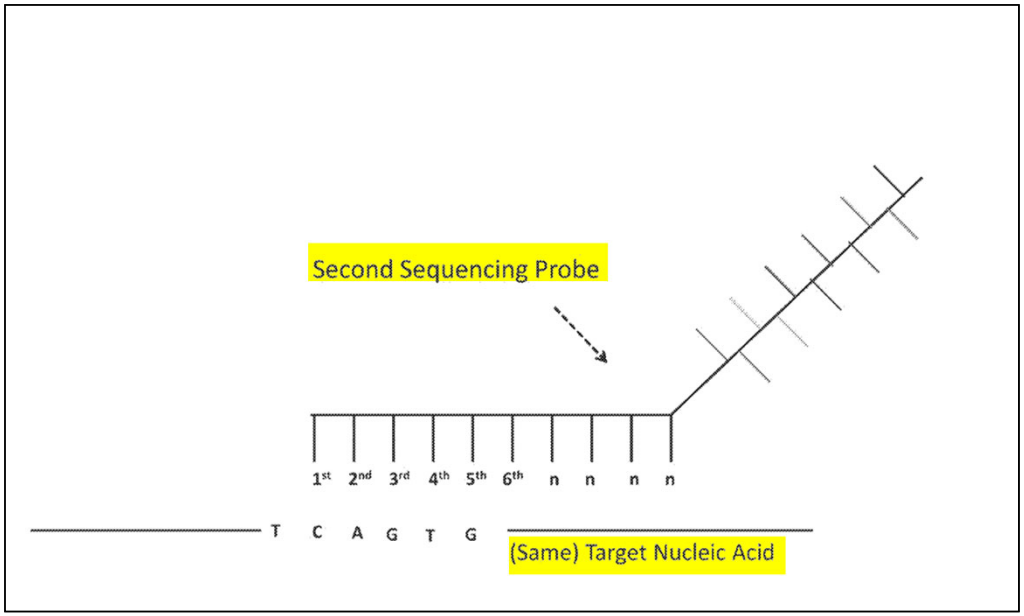


The Incorporated Patent Application's Example Describes Denaturation



The Incorporated Patent Application's Example Describes Denaturation





EX2008 Figs. 8A, 8E; PO's Response at 44

The Incorporated Patent Application Describes Denaturation Conditions

[0086] Probes can be designed to control the likelihood of hybridization and/or de-hybridization and the rates at which these occur. Generally, the lower a probe's Tm, the faster and more likely that the probe will de-hybridize to/from a target nucleic acid. Thus, use of lower Tm probes will decrease the number of probes bound to a target nucleic acid.

[0011] Provided herein is a method for sequencing a nucleic acid using one population of probes of the present invention or a plurality of populations of probes of the present invention. The method comprises steps of: (1) hybridizing a first population of sequencing probes (of the present invention) to a target nucleic acid that is immobilized to a substrate (with each sequencing probe in the first population de-hybridizing from the immobilized target nucleic acid under about the same conditions, e.g., level of chaotropic agent, temperature, salt concentration, pH, and hydrodynamic force); (2)

EX2008 ¶¶ 11, 86; PO's Response at 44

Petitioner's Position: Three Reasons Against The Incorporated Application

1

EX1055, ¶¶97-99, 102. A POSA reading these disclosures thus would have understood that the 386 application's *sequencing probes* and sequencing methods are separate and distinct from the collecting step of the claimed methods. *Id.*

2

thus is not an effective incorporation by reference. Even if the 386 application were incorporated, it is incorporated for disclosure of *sequencing methods*, which occur *after* the collection step. EX1009, ¶¶[00216], [00227]; EX2008, Abstract;

3

publication." 37 C.F.R. §§1.57(c)-(d), (h). The 487 application purports to incorporate a document identified as "US2014946386." "US2014946386" is neither an application serial number nor an application publication number, and thus is not an effective incorporation by reference. Even if the 386 application

1 Petitioner's Argument Against The Term "Sequencing Probe" Is Contrary To Law



Substantial evidence supports a finding that the specification satisfies the written description requirement when "the essence of the original disclosure" conveys the necessary information—"regardless of ***how*** it" conveys such information, and regardless of whether the disclosure's "words [a]re open to different interpretation[s]."

Inphi Corp. v. Netlist, Inc., 805 F.3d 1350, 1354 (Fed. Cir. 2015) (emphasis in original)

1 Petitioner's Argument Against The Term "Sequencing Probe" Is Contrary To The Priority Application's Specification

> **[00259]** Any probe or set of probes described herein may be used in methods and kits of the present disclosure.

EX1009 ¶ 259; PO's Response at 45; PO's Sur-Reply at 4

2 Petitioner's Argument That Denaturing Probes Is Not Incorporated Is Contrary To The Priority App's Specification

[00216] A hybridized product produced in step (4) can be sequenced using an enzyme free method of sequencing. Enzyme-free methods of sequencing have been described in, e.g., US2014946386 and US15/819,151, each of which is incorporated herein by reference in its entirety.

[00227] A hybridized product produced in step (4) can be sequenced using an enzyme free method of sequencing. Enzyme-free methods of sequencing have been described in, e.g., US2014946386 and US15/819,151, each of which is incorporated herein by reference in its entirety.

[0064] Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. The references cited herein are not admitted to be prior art to the claimed invention. In the case of conflict, the present Specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be limiting. Other features and advantages of the disclosure will be apparent from the following detailed description and claim.

 EX1009 ¶¶ 64, 216, 227; PO's Response at 44; PO's Sur-Reply at 5

2 Petitioner's Argument That Denaturing Probes Is Not Incorporated Is Contrary To Law



The '817 application expressly incorporates Severinsky in the following passage:

> This application discloses a number of improvements over and enhancements to the hybrid vehicles disclosed in the inventor's *U.S. Pat. No. 5,343,970 (the "'970 patent") (Severinsky), which is incorporated herein by this reference*. Where differences are not mentioned, it is to be understood that the specifics of the vehicle design shown in the '970 patent are applicable to the vehicles shown herein as well.

The first sentence of this passage is broad and unambiguous. It states that Severinsky "*is*," without qualification, incorporated into the '817 application "by this reference"—i.e., the reference contained in the sentence. The sentence identifies with detailed particularity the specific material subject to incorporation (Severinsky, and not just particular portions thereof) and where that material can be found (U.S. Patent No. 5,343,970). Such language is plainly sufficient to incorporate Severinsky in its entirety. *See Harari*, 656 F.3d at 1335–36 (finding that prior art applications were incorporated in their entirety based on the following "broad and unequivocal language": " 'The disclosures of the two applications are hereby incorporate[d] by reference' "); *Advanced Display*, 212 F.3d at 1282.

Paice LLC v. Ford Motor Co., 881 F.3d 894, 907 (Fed. Cir. 2018)

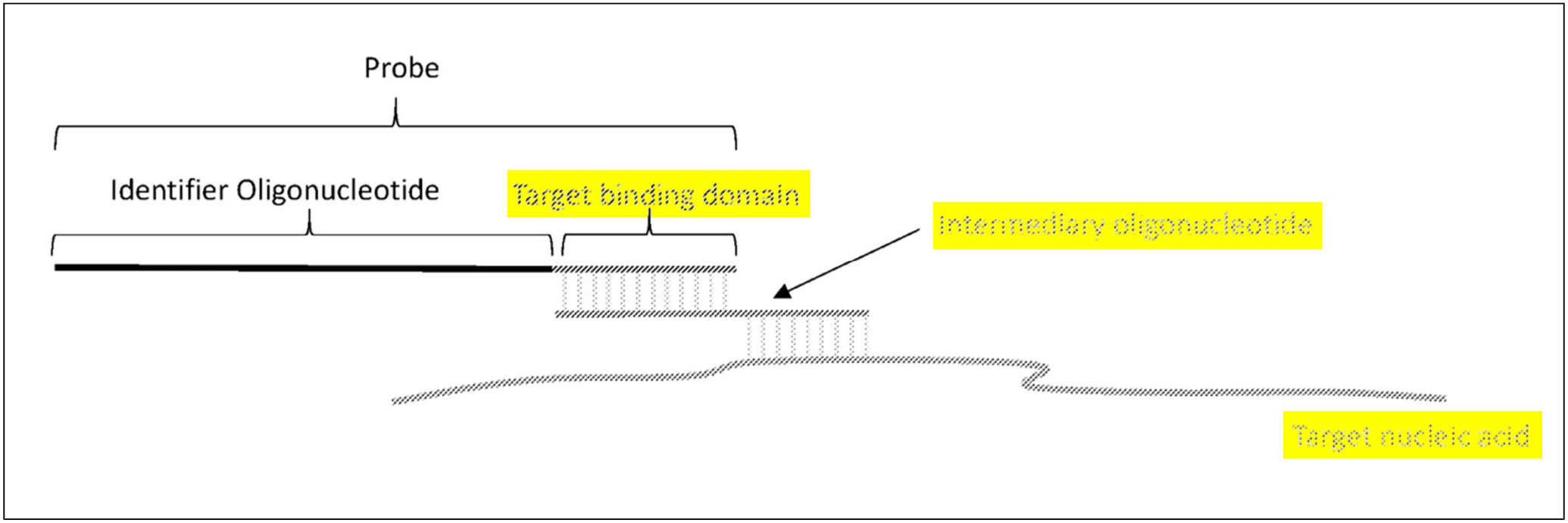
3 Petitioner's Argument Of Ineffective Incorporation Is Not Supported By Facts Or Law

- Petitioner does not deny that the '487 application's reference to "US2014946386" refers to application no. 14/946,386
- Petitioner does not deny that EX2008 is the published application of application no. 14/946,386
- Petitioner does not deny that the '487 application has an obvious typographical error
- Petitioner cites no law that an incorporation is negated by an obvious typographical error

Petitioner Ignores Disclosure In The ’487 Application For “Whole Probes”

1. Denaturation is described
2. **Indirect hybridization is described**
3. The ’487 application is not limited to probes that are *always* cleaved

The ’487 Application Describes Indirect Hybridization



DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

EX1009 Fig. 14; PO’s Response at 46-47; PO’s Sur-Reply at 6

The ’487 Application Describes Intermediary Oligonucleotide Probes

[00233] The target nucleic acid-binding region can directly hybridize to a target nucleic acid present in a sample. Alternatively, the probes of the present disclosure can indirectly hybridize to a target nucleic acid present in a sample (via an intermediary oligonucleotide). Figure 14 illustrates a probe (or composition) of this aspect. The probe includes a target nucleic-acid binding domain which binds to a synthetic oligonucleotide (the intermediary oligonucleotide) that in turn binds to a target nucleic acid in a biological sample. It could be said that the intermediary oligonucleotide is a probe, as defined herein, since it comprises a nucleic acid backbone and is capable of binding a target nucleic acid. In these aspects, a probe’s target nucleic acid-binding region hybridizes to a region of an intermediary oligonucleotide (*i.e.*, a

EX1009 ¶ 233; PO’s Response at 46-47; PO’s Sur-Reply at 6-7

The ’487 Application Describes Probes That Bind Indirectly

[00310] In some aspects of the methods and compositions of the present disclosure, the term target binding domain is used in its broadest sense to refer to a portion of a probe of the present disclosure that binds to, either directly or indirectly, a target analyte located in a sample. A target binding domain can comprise nucleic acid, protein, at least one antibody, an aptamer, or any combination thereof. A target binding domain can comprise DNA, RNA or any combination thereof. A target binding domain can comprise any number of modified nucleotides and/or nucleic acid analogues.

The ’487 Application Describes Cleavable Probes

[00246] A probe of the present disclosure can include a region which permits the release of an identifier oligonucleotide following the application of a suitable force. In one non-limited example, the region is a cleavable motif (*e.g.*, a restriction enzyme site or cleavable linker). The cleavable motif allows release of an identifier oligonucleotide from a bound target nucleic acid or protein and the identifier oligonucleotide can then be collected and detected. The region which permits the release of an identifier oligonucleotide can be positioned between the target-binding domain and the identifier oligonucleotide, allowing for the release of the identifier oligonucleotide from the target binding domain. An identifier oligonucleotide is said to be

EX1009 ¶ 246; PO’s Response at 46-47; PO’s Sur-Reply at 7

The Cleavable Region Of A Probe Is Not Restricted

binding domain. The identifier oligonucleotide can also comprise a first amplification primer binding site, a second amplification primer binding site, or a unique molecular identifier. The identifier oligonucleotide can comprise any combination of these features. Any of these features can also be flanked by regions comprising constant nucleic acid sequences of about 1 nucleotide to about 10 nucleotides.

[00131] In some aspects, the nucleic acid adapter can also comprise a constant nucleic acid sequence to minimize ligation bias caused by differences in sequences of particular identifier oligonucleotides. The constant nucleic acid sequence can comprise a cleavable moiety. The cleavable moiety can be enzymatically cleavable. In a non-limiting example, the enzymatically cleavable moiety can be a USER sequence, wherein the USER sequence comprises the sequence GUGUATUG.

EX1009 ¶ 199, 131; PO's Response at 43; PO's Sur-Reply at 7-8

Petitioner's Expert Agrees That The '487 Application Describes A Cleavable Intermediary Oligonucleotide



Dr. Paul Spellman
Petitioner's Expert

Q. But you do not disagree that Paragraph 233 states, 'It could be said that the intermediary oligonucleotide is a probe as defined herein'?

A. The specification does say that, yes.

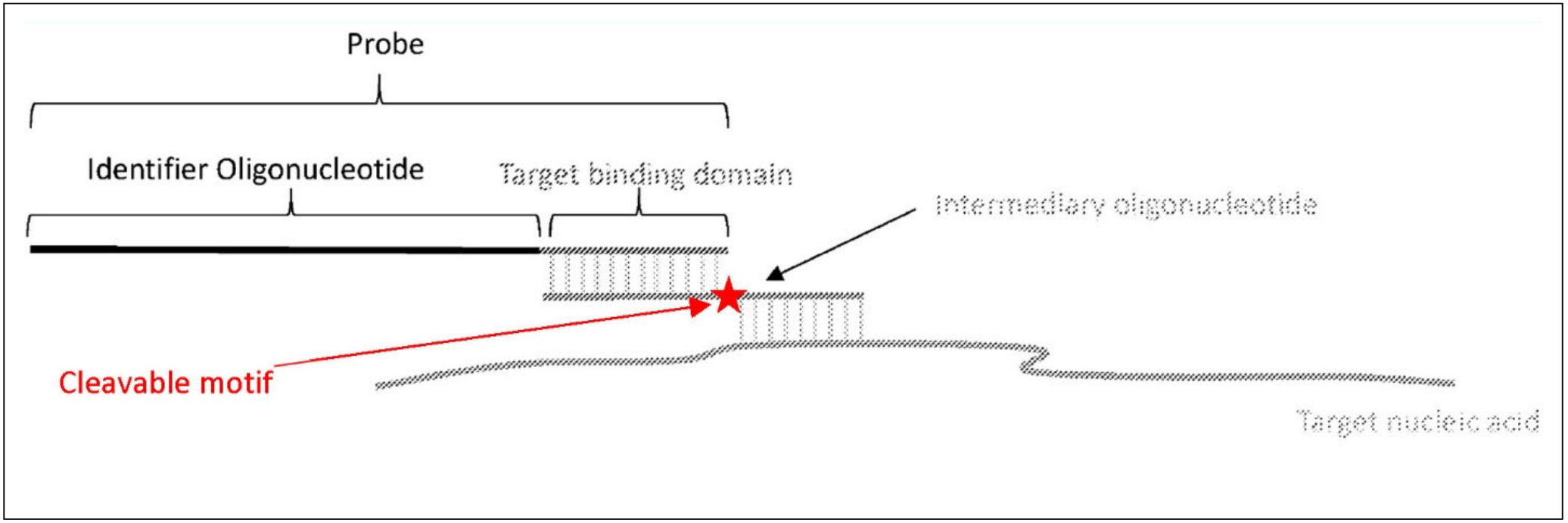
…

Q. Do you agree that the '487 application teaches a probe with a cleavable linker?

A. The '487 teaches a probe with a cleavable linker, yes.

EX2053 at 43:9-13, 96:19-22; PO's Sur-Reply at 7

Cleaving An Intermediary Oligonucleotide Releases A "Whole Probe"



Petitioner's Position: "No Economical Advantage" To A Cleavable Intermediary Oligonucleotide

Moreover, as Dr. Spellman explains, it makes no sense for Molecule B to have a cleavable motif, because doing so renders Molecule A needless. EX1055, ¶¶119-123. The 487 application discloses that indirect hybridization "allows economical and rapid flexibility in an assay design" by including "target (present in the sample)-specific components … in inexpensive and widely-available synthetic DNA oligonucleotides [i.e., Molecule B] rather than the more expensive probes [i.e., Molecule A]." EX1009, ¶[00233]; EX1055, ¶¶119-122. Adding a cleavable motif in Molecule B, as Bruker speculates, would make the indirect hybridization method superfluous with no economical advantage because it would still require custom synthesis of target-specific probes with a cleavable motif. *Id.* Molecule B with a cleavable motif is no different than the standard direct-hybridization probes of the 487 application. EX1055, ¶¶121-122.

Petitioner's Expert Admits To Having No Knowledge Regarding Commercial Cleavable Oligonucleotides



Dr. Paul Spellman
Petitioner's Expert

Q. By 2018 were synthetic oligonucleotides with a cleavable linker commercially available for purchase?

A. I presume so, although I had never ordered them. So I can't actually be certain.

Petitioner's Expert Admits To Having No Knowledge Regarding Commercial Cleavable Oligonucleotides



Dr. Paul Spellman
Petitioner's Expert

Q. Did you have any reason to believe that oligonucleotides with cleavable linkers were not available for purchase in 2018?

A. Photocleavable linkers are a far less common technology. They are not nearly as well utilized as fluorescents or biotin. And I am unsure how readily they were available commercially, at scale, et cetera.

Petitioner's Expert Admits To Having No Knowledge Regarding Commercial Cleavable Oligonucleotides



Dr. Paul Spellman
Petitioner's Expert

Q. Is it your understanding that no vendors sold oligonucleotide with cleavable linkers by 2018?

A. I have no knowledge whether or not they were broadly commercially available to incorporate into traditional oligonucleotides. Photocleavable linkers had been broadly used in the industry, but I don't -- so in many situations. But whether or not they were commercially available as oligonucleotides for sale in pre-made oligonucleotides, I have no knowledge. And I have never utilized them. Nor do I know anyone outside of very specific chemistry projects or the large companies that utilized them in their commercial products who had access to them. But that may be erroneous.

Nowhere Does The '487 Application Explain The Cost Difference Between Synthetic Oligonucleotides And Probes

> Thus, the probe's target binding region is independent of the ultimate target nucleic acid in the sample. This allows economical and rapid flexibility in an assay design, as the target (present in a sample)-specific components of the assay are included in inexpensive and widely-available synthetic DNA oligonucleotides rather than the more expensive probes. Such synthetic oligonucleotides are simply designed by including a region that hybridizes to the target nucleic acid present in a sample and a region that hybridizes to a probe. Therefore, a single set of indirectly-binding probes can be used to detect an infinite variety of target nucleic acids (present in a sample) in different experiments simply by replacing the target-specific (synthetic) oligonucleotide portion of the assay.

The Advantage Described In The '487 Application Is Maintained With A Cleavable Intermediary Oligonucleotide

Thus, the probe's target binding region is independent of the ultimate target nucleic acid in the sample. This allows economical and rapid flexibility in an assay design, as the target (present in a sample)-specific components of the assay are included in inexpensive and widely-available synthetic DNA oligonucleotides rather than the more expensive probes. Such synthetic oligonucleotides are simply designed by including a region that hybridizes to the target nucleic acid present in a sample and a region that hybridizes to a probe. Therefore, a single set of indirectly-binding probes can be used to detect an infinite variety of target nucleic acids (present in a sample) in different experiments simply by replacing the target-specific (synthetic) oligonucleotide portion of the assay.

Petitioner Ignores Disclosure In The ’487 Application For “Whole Probes”

1. Denaturation is described

2. Indirect hybridization is described

3. **The ’487 application is not limited to probes that are *always* cleaved**

Petitioner's Position: "Whole Probes" Are Not Disclosed Because Probes Are Always Cleaved

Bruker also relies upon the 487 application's ¶¶14-15, 18, 131, and 199 to argue that a cleavage site is an optional probe feature. POR, 43; EX2006, ¶93. Again, the methods disclosed in these paragraphs all involve collecting the probe's *released identifier oligonucleotide portion*. EX1055, ¶90; EX1009, ¶¶[0014]-[0017], [00199]-[00203] (disclosing providing a force to release the probes' identifier oligonucleotide portions), [0018], [00131] (disclosing ligating adaptors to the released identifier oligonucleotides). Cleavage of probes is not an optional feature, and collecting whole probes is not part of the described methods in the 487 application. EX1055, ¶¶87-91.

Petitioner's Expert Does Not Admit That A Probe Must Be Cleavable



Dr. Paul Spellman
Petitioner's Expert

Q. So are you prepared to say whether a POSA, in light of the teaching, would find that a cleavable probe is required in the '487 application's methods?

A. As I've said, the Board interpreted the claim "nucleic acid probe" to mean an oligonucleotide comprising a target binding domain that binds to one or more target analytes, and is modified after collection to comprise a location-identifying nucleic acid. The Board's construction does not require a cleavable element, to the best of my ability to understand.

Petitioner Unduly Focuses On Specific Embodiments That Are Non-Limiting

[00107] Following contacting the at least on target analyte with the at least one probe, a two-ended adapter ligation method can further comprise: (2) providing a force to a location of the sample sufficient to release the identifier oligonucleotide. In a non-limiting example, in aspects in which the probe comprises a photo-cleavable linker between the identifier oligonucleotide and the target binding domain, a region-of-interest is excited with light of a sufficient wavelength capable of cleaving the photo-cleavable linker.

EX1009 ¶ 107; PO's Response at 43; PO's Sur-Reply at 2
Similar broad language is used to describe embodiments. *See, e.g.*, EX1009 ¶¶ 127, 145, 159, 184, 200, 211, 221, 317, etc.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Target Binding Region And Identifier Oligonucleotide Have Functional Roles That Do Not Proscribe Overlap

[00158] A short probe hybridization method of the present disclosure can comprise: (1) contacting at least one target analyte in a sample with at least one probe of the present disclosure. The at least one target analyte can be a target protein or a target nucleic acid. In the aspect that the at least one target analyte is a target protein, the probe can comprise a target binding domain that is a target protein-binding region that can specifically bind to a target protein of interest. In the aspect that the at least one target analyte is a target nucleic acid, the probe can comprise a target nucleic acid-binding region that can directly or indirectly hybridize to a target nucleic acid of interest. The probe further comprises an identifier oligonucleotide. The identifier oligonucleotide can comprise a unique nucleic acid sequence which identifies the target analyte bound to the target binding domain.

EX1009 ¶ 158; PO's Response at 45-46; PO's Sur-Reply at 9-10
Similar functional language used throughout. *See, e.g.*, EX1009 ¶¶ 106, 126, 144, 183, 199, etc.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Probe Cleavage Cannot Be Required Because A Negative Purification Of Entire Probes Can Occur After Probe Release

[00252] Background noise, during nucleic acid detection, can be reduced by performing a negative purification of the intact probe molecule. This can be done by conducting an affinity purification of the target binding domain or photo-cleavable linker after collection of eluate from a region of interest. Normally, released signal oligonucleotides will not be pulled out of solution. To assist in the negative purification, a universal purification sequence may be included in a probe, e.g., in the target binding domain.

Topics For Argument

Chell is not prior art because the ’689 patent claims have priority support
(Ground 4)

- The ’487 application describes collecting “whole probes”
- The ’487 application describes “on-analyte” ligation

So-456 does not anticipate the ’689 patent claims
(Ground 1)

So-456 does not render the ’689 patent claims obvious
(Grounds 2 and 3)

Claim Term At Issue

Claim 16(b):	"forming ligated probes by ligating each of nucleic acid probes from the first plurality of nucleic acid probes and each of nucleic acid probes from the second plurality of nucleic acid probes that are bound to each of identical molecules from the at least one target analyte"

Petitioner's Term "On-Analyte Ligation" Describes Known Concepts

"On-Analyte" probes:

Probes that
hybridize to a target analyte

"Ligation" of probes:

Probes that
are ligated together

PO's Response at 48; PO's Sur-Reply at 12

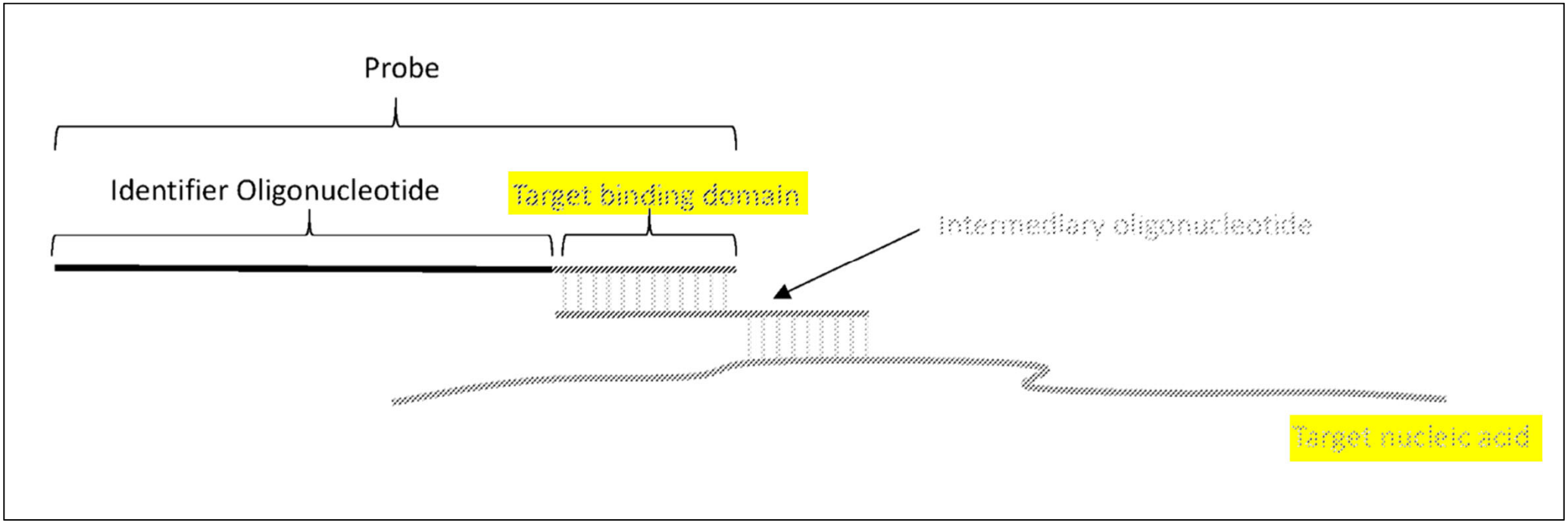
Standard Methods Hybridize Probes "On-Analyte"

BACKGROUND OF THE INVENTION

[0003] Standard immunohistochemical and *in situ* hybridization methods allow for simultaneous detection of, at most, six to ten protein or nucleic acid targets, with three to four targets being typical. There exists a need for probes, compositions, methods, and kits for simultaneous, multiplexed detection and quantification of protein and/or nucleic acid expression in a user-defined region of a tissue, user-defined cell, and/or user-defined subcellular structure within a cell. Furthermore, there is a need for such systems to be adaptable for use with existing sequencing technologies that are already available to a large number of end users.

EX1009 ¶ 3; PO's Response at 53-54; PO's Sur-Reply at 12

Petitioner's Distinction Of "On-Analyte" Vs. "Off-Analyte" Binding Ignores Indirect Hybridization



EX1009 Fig. 14; PO's Response at 52-53; PO's Sur-Reply at 6

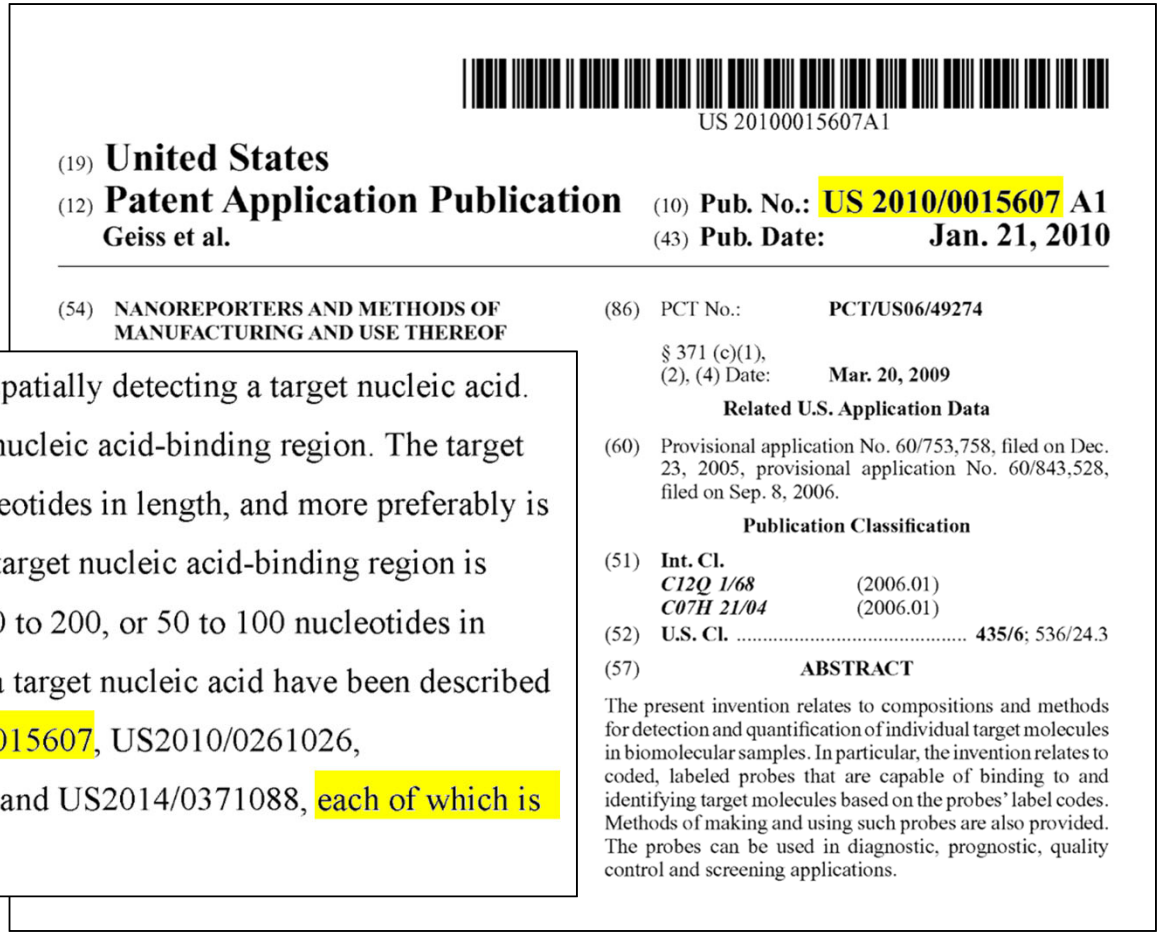
The ’487 Application Does Not Proscribe Ligation Of Probes Prior To Probe Release

- Hybridizing nucleic acid probes and performing nick repair can occur prior to providing a force

[0024] The present disclosure provides a method for spatially detecting at least one target analyte in at least one cell from a tissue sample comprising: (1) contacting at least one target analyte in at least one cell in a tissue sample with at least one probe comprising a target binding domain and an identifier oligonucleotide, wherein the identifier oligonucleotide comprises a unique nucleic acid sequence which identifies the target analyte bound to the target binding domain; (2) providing a force to a location of the tissue sample sufficient to release the identifier oligonucleotide; (3) collecting the released identifier oligonucleotide; (4) hybridizing to the released identifier oligonucleotide a first nucleic acid probe and a second nucleic acid probe, wherein the first nucleic acid probe comprises a nucleic acid complementary to a portion of the identifier oligonucleotide, a nucleic acid sequence which identifies the specific location of the tissue sample from which the identifier oligonucleotide was released and a first amplification primer binding site, and wherein the second nucleic acid probe comprises a nucleic acid complementary to a portion of the identifier oligonucleotide, a nucleic acid sequence comprising a unique molecular identifier and a second amplification primer binding site, and wherein the first the second nucleic acid probes hybridize to the identifier oligonucleotide such that the first and the second nucleic acid probes are adjacent but not overlapping; (5) performing nick repair such that the hybridized first and second nucleic acid probes are ligated together; (6) amplifying the ligation product produced in step (5); and (7) Identifying the released identifier oligonucleotide by sequencing the amplified products produced in step (6), thereby spatially detecting the at least one target analyte in the at least one cell in a tissue sample.

EX1009 ¶ 24; PO’s Response at 54; PO’s Sur-Reply at 15-16

An Incorporated Patent Publication Describes A Probe Pair That Hybridizes To An Analyte



US 20100015607A1

(19) **United States**

(12) **Patent Application Publication**

Geiss et al.

(10) **Pub. No.: US 2010/0015607 A1**

(43) **Pub. Date: Jan. 21, 2010**

(54) **NANOREPORTERS AND METHODS OF MANUFACTURING AND USE THEREOF**

(86) PCT No.: **PCT/US06/49274**

§ 371 (c)(1),
(2), (4) Date: **Mar. 20, 2009**

Related U.S. Application Data

(60) Provisional application No. 60/753,758, filed on Dec. 23, 2005, provisional application No. 60/843,528, filed on Sep. 8, 2006.

Publication Classification

(51) **Int. Cl.**
C12Q 1/68 (2006.01)
C07H 21/04 (2006.01)

(52) **U.S. Cl.** **435/6**; 536/24.3

(57) **ABSTRACT**

The present invention relates to compositions and methods for detection and quantification of individual target molecules in biomolecular samples. In particular, the invention relates to coded, labeled probes that are capable of binding to and identifying target molecules based on the probes' label codes. Methods of making and using such probes are also provided. The probes can be used in diagnostic, prognostic, quality control and screening applications.

[00232] Probes of the present disclosure can be used for spatially detecting a target nucleic acid. In this aspect, the target binding domain can be a target nucleic acid-binding region. The target nucleic acid-binding region is preferably at least 15 nucleotides in length, and more preferably is at least 20 nucleotides in length. In specific aspects, the target nucleic acid-binding region is approximately 10 to 500, 20 to 400, 25, 30 to 300, 35, 40 to 200, or 50 to 100 nucleotides in length. Probes and methods for binding and identifying a target nucleic acid have been described in, *e.g.*, US2003/0013091, US2007/0166708, US2010/0015607, US2010/0261026, US2010/0262374, US2010/0112710, US2010/0047924, and US2014/0371088, each of which is incorporated herein by reference in its entirety.

An Incorporated Patent Publication Describes A Probe Pair That Hybridizes To An Analyte

[0013] In alternative embodiments, the present invention provides a dual nanoreporter, or a "probe pair," comprising two components: a first probe and a second probe. In specific embodiments, the first probe is a complex comprising: (a) a first molecule, or a scaffold, comprising: (i) a first label attachment region to which are attached (directly or indirectly) one or more label monomers that emit light constituting a first signal; (ii) a second label attachment region to which are attached (directly or indirectly) one or more label monomers that emit light constituting a second signal; and (b) a first target-specific sequence attached to the first molecule.

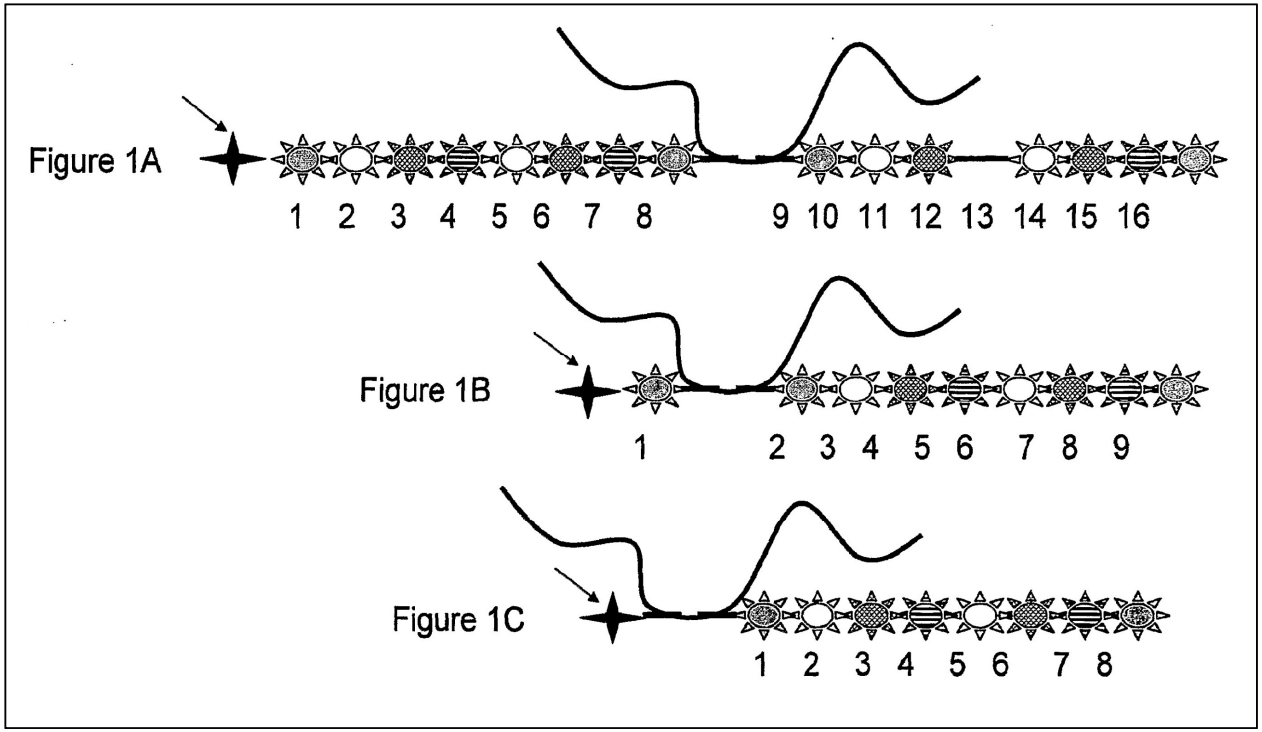
The second probe is a second molecule or a complex comprising a second molecule, said second molecule comprising (i) a second target-specific sequence; (ii) optionally, a third label attachment region to which are attached (directly or indirectly) one or more label monomers that emit light constituting a third signal; and (iii) optionally, an affinity tag attached to said second molecule; wherein the first signal and the second signal are spatially or spectrally distinguishable; wherein the first target-specific sequence and the second target-specific sequence bind to different regions of the same target molecule and wherein when said probe pair is bound to its target molecule, the identity of the first and second signals and their locations relative to each other constitutes at least part of a code that identifies the target molecule.

EX2009 ¶ 13; PO's Response at 51-52; PO' Sur-Reply at 13

An Incorporated Patent Publication Describes A Probe Pair That Hybridizes To An Analyte

4. BRIEF DESCRIPTION OF THE FIGURES

[0071] FIG. 1A-1F: FIG. 1A illustrates a dual nanoreporter with a 16-position nanoreporter code, using two 8-position nanoreporter components. FIG. 1B illustrates a dual nanoreporter with a 9-position nanoreporter code, using one 8-position nanoreporter component and one single-position nanoreporter component. FIG. 1C illustrates a dual nanoreporter with an 8-position nanoreporter code, using one ghost probe and one 8-position nanoreporter component. FIG. 1D illustrates a single nanoreporter with an 8-position nanoreporter code. In FIGS. 1A-1D, the star shape (depicted with an arrow) is illustrative of an affinity tag, which can be used to purify the nanoreporter or immobilize the nanoreporter (or nanoreporter-target molecule complex) for the purpose of imaging. The numbered region in FIG. 1A-1D refer to separate label attachment regions. All except for position 12 of FIG. 1A are labeled with one of four types of label monomers, depicted as grey, white, hatched or stripe "sun" diagrams. Position 12 of FIG. 1A is an unlabeled "dark spot." FIGS. 1E and 1F represent variations on the nanoreporters of FIGS. 1B and 1D, respectively, in which the target molecule to which the nanoreporters are bound comprises biotin moieties (shown as small asterisks), for example biotin-modified nucleotides randomly incorporated into a target nucleic acid. The nanoreporters themselves further optionally comprise an affinity tag (not shown).



EX2009 Figs. 1A-1C, ¶ 71; PO's Response at 51-52; PO' Sur-Reply at 13

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

The ’487 Application Repeatedly Discloses Ligating Two Probes Via A Nick Repair Reaction

[0024] The present disclosure provides a method for spatially detecting at least one target analyte in at least one cell from a tissue sample comprising: (1) contacting at least one target

and the second nucleic acid probes are adjacent but not overlapping; (5) performing nick repair such that the hybridized first and second nucleic acid probes are ligated together; (6) amplifying

Patent Owner's Expert Confirms That Ligating Two Probes Is Well Known



Dr. David Sherman
Patent Owner's Expert

120. Ligation involves little more than adding the proper ligase in the proper conditions, which a POSA would have understood. As such, a POSA would have been able to perform a simple ligation step to ligate a probe pair as claimed.

EX2006 ¶ 120; PO's Response at 54; PO' Sur-Reply at 13

An Incorporated Patent Publication Describes Ligating A Probe Pair Hybridized To A Nucleic Acid

US 20110086774A1

(19) **United States**

(12) **Patent Application Publication**

Dunaway

(10) **Pub. No.: US 2011/0086774 A1**

(43) **Pub. Date: Apr. 14, 2011**

(54) **PROTEIN DETECTION VIA NANOREPORTERS**

filed on Apr. 16, 2010, provisional application No. 61/326,787, filed on Apr. 22, 2010.

[00235] Probes of the present disclosure can be used for detecting a target protein. In this aspect, the target binding domain can be a target protein-binding region. A target protein-binding region

lication Classification

(2006.01)
(2006.01)

..... **506/9**; 506/18

and peptidomimetics. Probes and methods for binding and identifying a target protein have been described, *e.g.*, in US2011/0086774, the contents of which is incorporated herein by reference in its entirety.

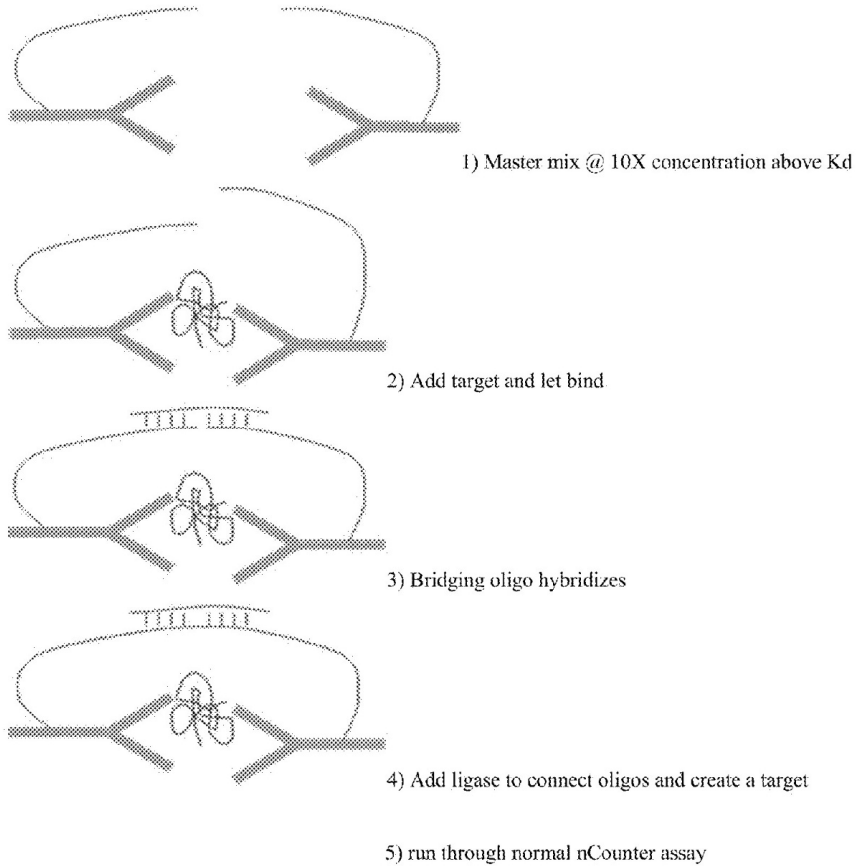
ABSTRACT

ides methods, compositions, kits and tion of proteins. In some embodiments, for multiplexed protein detection.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

EX1009 ¶ 235; PO's Response at 54; PO' Sur-Reply at 14

An Incorporated Patent Publication Describes Ligating A Probe Pair Hybridized To A Nucleic Acid



[0037] FIG. **8**A is a schematic diagram depicting certain embodiments of the invention using proximity ligation. A first and a second oligo are attached to a first and a second antibody, respectively, both antibodies being specific for a target protein. The first and second antibodies bind to the target protein, bringing the first and second oligo to close proximity. A bridging oligo and a ligase are added to the solution to connect the first and second oligo to generate a signal oligo. The signal oligo can then be analyzed by any the methods described herein.

EX2010 Fig. 8A, ¶ 37; PO's Response at 54-55; PO' Sur-Reply at 14

Patent Owner's Expert Confirms A POSA's Understanding

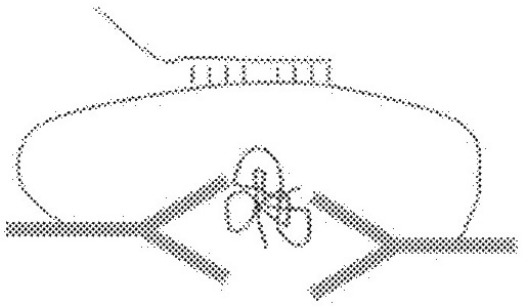


Dr. David Sherman
Patent Owner's Expert

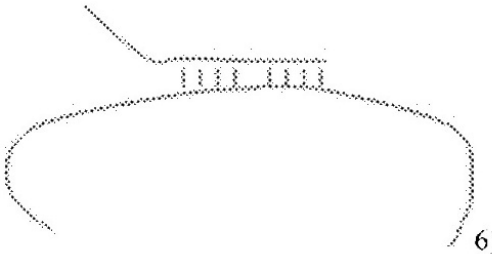
Id. Fig. 8A. In my opinion, a POSA would have understood from this disclosure that two oligonucleotides, as a pair, can jointly be designed to hybridize to a third nucleic acid and, while hybridized, the two oligonucleotides can be ligated together. A POSA would further have understood that this is analogous to a probe pair, such that a probe pair can be designed to hybridize to a nucleic acid, the target analyte. A POSA would have understood that such a design is viable and would have understood the '487 Application to have disclosed this.

EX2006 ¶ 117; PO' Response at 55; PO's Sur-Reply at 14

Petitioner's Position: Patent Owner Omits Disclosure



5) Bridging oligo has a purification tag (sequence or biotin).



6) Release oligo (via disulfide reduction, uracil excision, restriction digest, or proteinase K, etc.)

7) Purify signal oligo via tag (sequence or biotin). Only the ligated oligo will have enough overlap to remain hybridized to signal oligo.

8) Run through normal nCounter assay.

- Name of probe does not affect disclosure
- Release and collection of the ligated oligonucleotide is described
- Possession of ligated probe pair is described

Petitioner's Arguments Contravene *Allergan*



> The issue before us, then, is not whether the inventors had possession of the formulation that is expressly claimed. That question answers itself. Rather, the issue is whether the inventors had possession of a formulation that lacked a component that is ***not*** claimed, or only optional. In the district court's view, they did not. We disagree…
>
> To be sure, the specification does largely focus on more detailed formulations that include a glidant...But that a glidant ***may*** be necessary does not mean that the inventors did not possess a formulation in which it ***was not*** necessary.

Allergan USA, Inc. v. MSN Lab'ys Priv. Ltd., 111 F.4th 1358, 1372, 1374-75 (Fed. Cir. 2024) (emphasis in original)

Petitioner's Arguments Contravene *Allergan*

- Similar to *Allergan*, while the '487 application "does largely focus on" embodiments with "off-analyte ligation," it is ***not necessary*** and the specification supports "on-analyte ligation" from the perspective of a POSA.

- The '487 application does not ***require*** "off-analyte ligation" and ***no function or significance*** is attributed to "off-analyte ligation."

Standard Requires Reasonable Conveyance Of Possession



As the "hallmark" of written description, see Ariad, 598 F.3d at 1351, the disclosure must be considered as a whole, as the person of ordinary skill in the art would read it, to determine if it ***reasonably conveys*** possession.

Allergan USA, Inc. v. MSN Lab'ys Priv. Ltd., 111 F.4th 1358, 1375 (Fed. Cir. 2024) (emphasis in original)

Petitioner's Expert Admits That A POSA Can Practice The Claims



Dr. Paul Spellman
Petitioner's Expert

Q. A skilled artisan would have a strong enough understanding of genomics in the spatial area to implement the method of Claim 1 of the '689 patent at the date of the priority documents?

A. As written, I believe that the claims could likely be practiced.

Q. When you say "likely be practiced," you mean by a skilled artisan?

A. Yes.

Topics For Argument

Chell is not prior art because the ’689 patent claims have priority support
(Ground 4)

So-456 does not anticipate the ’689 patent claims
(Ground 1)

- So-456 does not collect the claimed probes
- So-456 does not treat tissue samples
- So-456 does not disclose the claimed extension
- So-456 does not disclose the claimed ligation

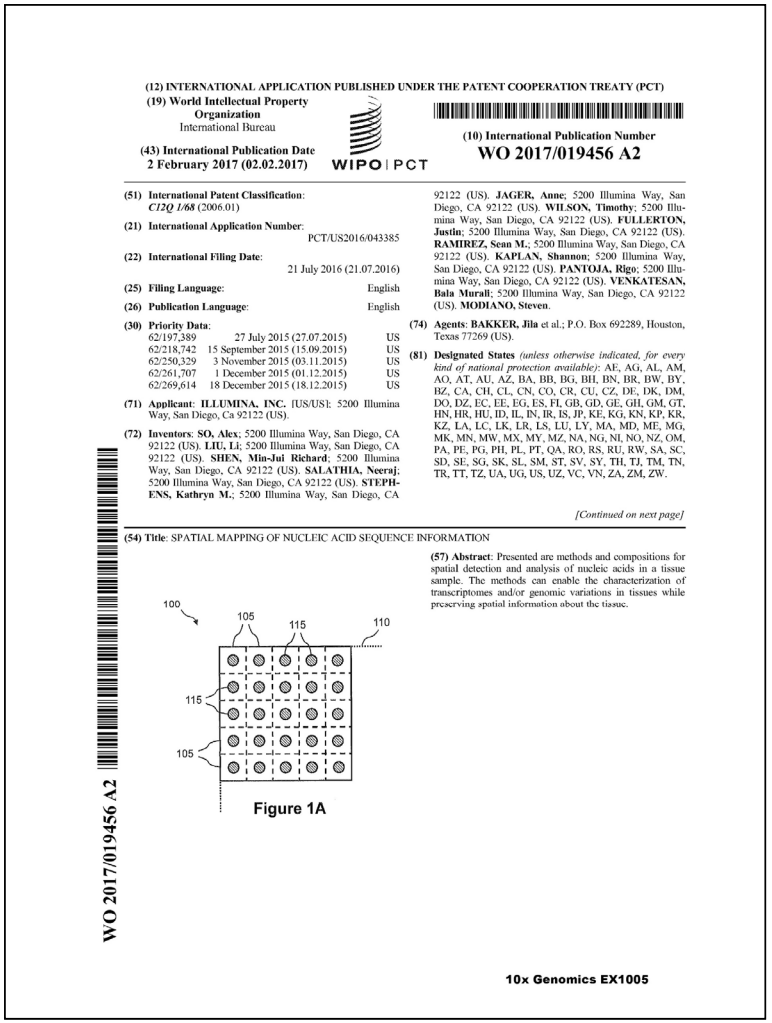
So-456 does not render the ’689 patent claims obvious
(Grounds 2 and 3)

The Board Found That Petitioner Did Not Have A Reasonable Likelihood of Prevailing

> In sum, based on the record before us, we determine that Petitioner has not established a reasonable likelihood that it would prevail in showing that So-456 anticipates claims 1–8, 11–23, and 26–30. Nevertheless, the Board, in a decision to institute under 35 U.S.C. § 314(b), may not institute review on fewer than all claims challenged in the petition. *SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1355–56 (2018). In addition, if the Board institutes trial, it will institute on all grounds in the petition. *See* 37 C.F.R.

Institution Decision at 24-25

Overview of So-456



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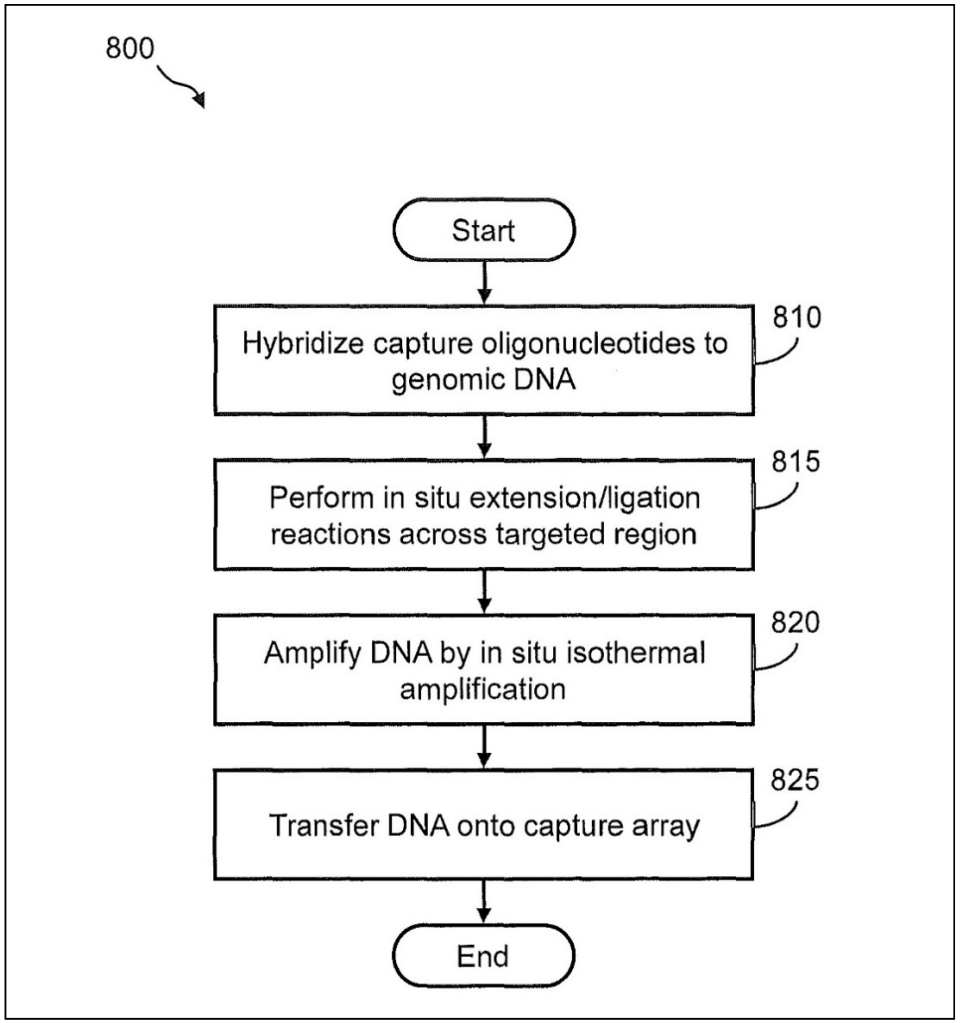
(54) Title: SPATIAL MAPPING OF NUCLEIC ACID SEQUENCE INFORMATION

(57) Abstract: Presented are methods and compositions for spatial detection and analysis of nucleic acids in a tissue sample. The methods can enable the characterization of transcriptomes and/or genomic variations in tissues while preserving spatial information about the tissue.

Figure 1A

WO 2017/019456 A2

10x Genomics EX1005



Claims Require Collecting Probes Bound To Target Analyte

1. A method for spatially detecting at least one target analyte in a first location and a second location of a tissue sample comprising:

b) collecting the nucleic acid probes, or portions thereof, bound to the at least one target analyte in a first location of the tissue sample under conditions that release the nucleic acid probes, or portions thereof, from the first location of the tissue sample;

c) collecting the nucleic acid probes, or portions thereof, bound to the at least one target analyte in a second location of the tissue sample under conditions that release the nucleic acid probes, or portions thereof, from the second location of the tissue sample;

16. A method for spatially detecting at least one target analyte in a first location and a second location of a tissue sample comprising:

c) collecting the ligated probes, or portions thereof, bound to each of the identical molecules from the at least one target analyte in a first location of the tissue sample under conditions that release the ligated probes, or portions thereof, from the first location of the tissue sample;

d) collecting the ligated probes, or portions thereof, bound to each of the identical molecules from the at least one target analyte in a second location of the tissue sample under conditions that release the probes, or portions thereof, from the second location of the tissue sample;

The Board Did Not Find So-456 To Collect Required Probes

> The question then becomes whether So-465, which teaches replication of a probe that was bound and then at least partially released to make genomic amplicons, followed by collection of those genomic amplicons, anticipates collection of probes as recited in claims 1 and 16. On this record, we do not see sufficient evidence that the genomic amplicons disclosed in So-456 that Petitioner identifies as "captured" were ever "bound to the analyte" in part or in whole as required by the claim language, but rather were amplified in situ from the probe or partial probe that was released.

Petition Identified Amplicons That Were Never Bound To A Target Analyte

After ligating the primary probe pairs, So-456's method amplifies the ligated probes (950) "to generate multiple copies … of the targeted region of interest" by "isothermal amplification," generating unbound amplified ligated probes ("amplicons"). EX1005, ¶[00182]; EX1002, ¶¶134-135. The amplified ligated probes (950) free from the target DNA molecules are "transferred from a sample . . . onto a capture array by passive diffusion" and "*captured* onto the capture site 105" of the array. EX1005, ¶¶[00182], [00215]; FIGs. 2, 8, 9; EX1002, ¶¶134-135.

Petition at 20; PO's Response at 16; PO's Sur-Reply at 17

Petition Features Annotated Figure For "Capturing Amplicons"

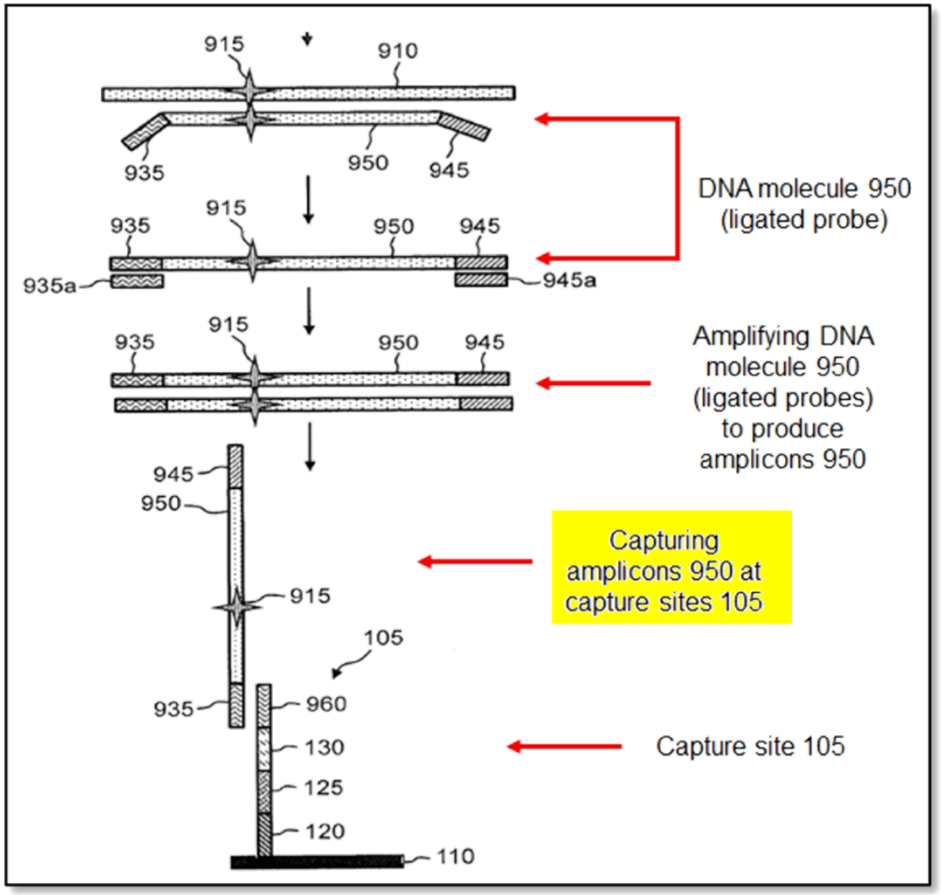


Figure 9

So-456 Confirms That Amplicons Are Collected

[00183] In this example, the tissue sample is contacted with capture probe 115 that is fixed on the surface of capture site 105. Genomic amplicon 950 is captured onto the array by hybridization of universal capture sequence 935 to capture sequence 960. In another example (not shown), the tissue sample is contacted with the array and capture probes 115 are released from capture site 105 into the tissue sample by cleavage of optional cleavable sequence 120.

So-456 Confirms That Amplicons Are Copies

[00121] As used herein, the term "amplicon," when used in reference to a nucleic acid, means the product of copying the nucleic acid, wherein the product has a nucleotide sequence that is the same as or complementary to at least a portion of the nucleotide sequence of the nucleic acid. An amplicon can be produced by any of a variety of amplification methods that use the nucleic acid, or an amplicon thereof, as a template including, for example, polymerase extension, polymerase chain reaction (PCR), rolling circle amplification (RCA), ligation extension, or ligation chain reaction. An amplicon can be a nucleic acid molecule having a single copy of a particular nucleotide sequence (*e.g.* a PCR product) or multiple copies of the nucleotide sequence (*e.g.* a concatameric product of RCA). A first amplicon of a target nucleic acid can be a complementary copy. Subsequent amplicons are copies that are created, after generation of the first amplicon, from the target nucleic acid or from the first amplicon. A subsequent amplicon can have a sequence that is substantially complementary to the target nucleic acid or substantially identical to the target nucleic acid.

Petitioner's Expert Applied So-456's Definitions



Dr. Paul Spellman
Petitioner's Expert

Q. In forming your opinions did you apply the definitions in So-456?

A. Definitions of what?

Q. The definition of terms within So-456.

A. Sorry. Did I -- did I read So-456 in the context of itself?

Q. Correct, in the context of a definition provided for the terms within itself?

A. Yes.

On Reply, Petitioner Presents A New Theory That The "Original" Probes Are Collected

EX1002, ¶69. Next, "950"—i.e., both the original ligated probes released from the target analyte and the amplicons—are captured on the capture probes (Step 825). EX1005, FIG. 9; EX1055, ¶40; EX1002, ¶¶169 ("capturing whole ligated probes (formed by ligating the primary probe pairs)"), 104 (p. 54) ("captured ligated products (950)"), 237 ("amplicons (950) (i.e., ligated probes of the claims)"); EX2007, 117:5-7 ("the 950 that is ligated is amongst the 950s that bind to 960 at the capture oligo…."). Thus, So-456's method captures the original ligated probes that were bound to the target analytes along with the amplicons. EX1055, ¶¶37-41;

Petitioner's Expert Declaration Clearly Identified Amplicons



Dr. Paul Spellman
Petitioner's Expert

134. So-456's method of Figures 8-9 specifies that the DNA molecules (950) formed in the previous step by ligating primary probe pairs (capture oligonucleotides) are "amplified by in situ isothermal amplification to generate multiple copies . . . of the targeted region of interest, *i.e.*, multiple genomic *amplicons.*" (Step 820). EX1005, ¶¶[00182] (emphasis added), [00180], FIGs. 8, 9. The amplicons generated by isothermal amplification are free from (*i.e.*, not bound to) the target nucleic acid molecules.

135. These amplicons (950) (*i.e.*, ligated probes of the claim) are "captured onto the capture site 105" of a spatially barcoded array, such as an array in Figure 1A. EX1005, ¶¶[00182], [00180], [00181], FIGs. 1, 8, 9. The annotated excerpts of Figures 9 and 1A below depict these steps in So-456's method.

Petitioner's Expert Disclaims The Position In His Own Declaration To Support The New Theory



Dr. Paul Spellman
Petitioner's Expert

Q. Are you able to give me a yes or no on whether the capture of the derived copies of 950, the ones generated at Step 820, do those meet the collecting claim step of the '689 patent?

A. I don't believe I comment on that in my clarification [sic].

Q. So you're not able to say one way or the other today. Is that right?

A. I don't believe I comment on that in my declaration, and I'm not prepared to form an opinion about that right now.

The Board Should Disregard Petitioner's New Theory



> It is of the utmost importance that petitioners in the IPR proceedings adhere to the requirement that the initial petition identify with particularity the evidence that supports the grounds for the challenge to each claim…

Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd., 821 F.3d 1359, 1369 (Fed. Cir. 2016)

The Board Should Disregard Petitioner's New Theory



"A reply may only respond to arguments raised in the corresponding opposition, patent owner preliminary response, patent owner response, or decision on institution." This regulation means that an "IPR petitioner may not raise in reply 'an entirely new rationale,'" not "raised in its petition" or "responsive to arguments raised in the patent owner's response brief."…

Yita, as the "master of its complaint," could have "presented its reply argument in its petition but chose not to."

Yita LLC v. MacNeil IP LLC, 69 F.4th 1356, 1365–66, 1367 (Fed. Cir. 2023) (citations omitted)

The Board Should Disregard Petitioner's New Theory



> Once the Board identifies new issues presented for the first time in reply, neither this court nor the Board must parse the reply brief to determine which, if any, parts of that brief are responsive and which are improper.

Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd., 821 F.3d 1359, 1369 (Fed. Cir. 2016)

The Board Found The Petition To Contend That Amplicons Are Captured

> Petitioner alleges that So-456's method discloses amplification of the ligated probes (950) to produce "unbound amplified ligated probes" or "amplicons" (also 950), which are free from the target DNA molecules. Pet. 20. These amplicons are then "captured" on a capture array by passive diffusion where they bind to a capture site, 105, as shown in Figure 1A. *Id.* (citing Ex. 1005 ¶¶ 182, 215; Figures 2, 8, 9; Ex. 1002 ¶¶ 134, 135).

Nonetheless, Petitioner's Expert Confirmed That The Likelihood Of Capturing The Original Probes Is Low



Dr. Paul Spellman
Petitioner's Expert

Q. Can there be more than 10,000 copies created at Step 820?

A. The specification describes at least up to 10,000 and as few as one.

Q. Does the specification provide an upper limit to the number of copies that can be generated?

A. No.

...

Q. To clarify, a million copies is possible. Is that right?

A. It is not precluded.

EX2053 at 51:19-52:4, 52:17-21; PO's Sur-Reply at 20-21

Petitioner's Expert Confirmed That The Likelihood Of Capturing The Original Probes Is Low



Dr. Paul Spellman
Petitioner's Expert

Q. Based on your understanding of So-456, can you provide an estimate on the proportion of probes that hybridize to the captured probes?

A. I have not considered that. The specification describes a -- as few as one cycle of amplification, and as many as 10,000. And I believe it would be, therefore, a function of what worked best for the POSA in that application. But presumably as few as -- it could be a very high fraction, given that they propose a small number of cycles.

Q. When you say a "high fraction," what would that be in percentage?

A. If a POSA were going to implement this, they -- and use a small number of cycles of amplification, it would have to be above 10 percent binding for it to be useful. But again, a POSA would choose that number appropriately.

Petitioner's New Theory Fails To Establish Inherency



A party must, therefore, meet a high standard in order to rely on inherency establish the existence of a claim limitation in the prior art in an obviousness analysis—the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art…

Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.

PAR Pharm., Inc. v. TWI Pharms., Inc., 773 F.3d 1186, 1195–96 (Fed. Cir. 2014)

Topics For Argument

Chell is not prior art because the ’689 patent claims have priority support
(Ground 4)

So-456 does not anticipate the ’689 patent claims
(Ground 1)

- So-456 does not collect the claimed probes
- So-456 does not treat tissue samples
- So-456 does not disclose the claimed extension
- So-456 does not disclose the claimed ligation

So-456 does not render the ’689 patent claims obvious
(Grounds 2 and 3)

Claims Require A Tissue Treatment Step To Facilitate Binding

1. A method for spatially detecting at least one target analyte in a first location and a second location of a tissue sample comprising:

a) contacting the tissue sample with a plurality of nucleic acid probes, wherein each of the nucleic acid probes comprise a target binding domain that binds to the at least one target analyte, wherein the tissue sample [has been] is treated to facilitate binding of the nucleic acid probes to the target analyte;

16. A method for spatially detecting at least one target analyte in a first location and a second location of a tissue sample comprising:

a) contacting the tissue sample with a first plurality of nucleic acid probes and a second plurality of nucleic acid probes,

wherein each of the nucleic acid probes in the first plurality of nucleic acid probes comprise a target binding domain that binds to the at least one target analyte,

wherein each of the nucleic acid probes in the second plurality of nucleic acid probes comprise a target binding domain that binds to the at least one target analyte,

wherein the tissue sample is treated to facilitate binding of the first plurality of nucleic acid probes and the second plurality of nucleic acid probes to the at least one target analyte;

Petitioner's Position: Two Paragraphs Disclose Tissue Treatment

So-456 also teaches treating the tissue sample to facilitate probe binding, as claimed, because So-456 discloses that the "*tissue sample is prepared* for analysis" and that "in situ *biochemistry is performed* on the tissue section to *facilitate subsequent manipulation* of a nucleic acid in the sample." EX1005, ¶¶[00152]-[00153]; EX1002, ¶¶125-127. Further, So-456's Figure 2 depicts performing "in situ biochemistry" on the tissue sample, which facilitates probe binding because Figure 8 depicts "[h]ybridiz[ing] capture oligonucleotides to genomic DNA" (*i.e.*, binding). EX1005, FIGs. 2, 8, 9, ¶¶[00153], [00178], [00182]; EX1002, ¶¶125-127. Thus, So-456's tissue was treated to facilitate probe binding, as claimed. *Id.*

Both Paragraphs Disclose Techniques That Have Nothing To Do With Treating Tissue To Facilitate Probe Binding

[00152] At a step 210, a tissue sample is prepared for analysis. In some embodiments, the tissue sample is a FFPE tissue sample that is sectioned onto a slide. Other examples include fresh tissue, frozen tissue, etc.

[00153] At a step 215, in situ biochemistry is performed on the tissue section to facilitate subsequent manipulation of a nucleic acid in the sample. In some embodiments, an in situ reverse transcription reaction is used to synthesize cDNA from targeted mRNA in the tissue sample. In some embodiments, an in situ amplification reaction can be used to produce multiple genomic DNA amplicons from targeted genes in the tissue sample. In some embodiments, there is no in situ biochemistry step, and synthesis of cDNA is performed after capture or extraction of the RNA from the tissue.

Petitioner's Position: A Treatment Step Is Disclosed Because One Must Occur

Similarly, So-456's ¶[00153] disclosures are not limited to reverse transcription and in situ amplification reactions. EX1055, ¶17. Again, So-456 lists these reactions as non-limiting. EX1005, ¶[00153]; EX1055, ¶17. Moreover, So-456's method *must* treat the tissue sample to facilitate binding of the probes to the target analytes because the probes in Figures 8-9 bind to the target analytes and are processed in the subsequent steps. Pet., 18-19; EX1002, ¶126; EX1055, ¶18; EX1056, 50:22-52:2.

The Law Is Not Whether A POSA Would "At Once Envisage" The Missing Treatment Step



The Board held that anticipation can be found even when a prior art reference fails to disclose a claim element so long as a skilled artisan reading the reference would "at once envisage" the claimed arrangement. The Board's misapplication of *Kennametal* improperly assumed disclosure of a claim element…

Kennametal does not stand for the proposition that a reference missing a limitation can anticipate a claim if a skilled artisan viewing the reference would "at once envisage" the missing limitation. Rather, *Kennametal* addresses whether the disclosure of a limited number of combination possibilities discloses one of the possible combinations…*Kennametal* does not permit the Board to fill in missing limitations simply because a skilled artisan would immediately envision them.

Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd, 851 F.3d 1270, 1274-75 (Fed. Cir. 2017).

Topics For Argument

Chell is not prior art because the ’689 patent claims have priority support
(Ground 4)

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(Ground 1)

- So-456 does not collect the claimed probes
- So-456 does not treat tissue samples
- So-456 does not disclose the claimed extension
- So-456 does not disclose the claimed ligation

So-456 does not render the ’689 patent claims obvious
(Grounds 2 and 3)

Claims Require An Extension That Incorporates A Location-identifying Sequence

1. A method for spatially detecting at least one target analyte in a first location and a second location of a tissue sample comprising:

d) performing an extension reaction that incorporates at least one nucleic acid sequence that identifies the first location of the tissue sample into each of the nucleic acid probes, or portions thereof, collected in step (b), thereby forming a first plurality of extension products that comprise the nucleic acid probes, or portions thereof, collected in step (b) and the at least one nucleic acid sequence that identifies the first location of the tissue sample;

e) performing an extension reaction that incorporates at least one nucleic acid sequence that identifies the second location of the tissue sample into each of the nucleic acid probes, or portions thereof, collected in step (c), thereby forming a second plurality extension products that comprise the nucleic acid probes, or portions thereof, collected in step (c) and the at least one nucleic acid sequence that identifies the second location of the tissue sample; and

16. A method for spatially detecting at least one target analyte in a first location and a second location of a tissue sample comprising:

e) performing an extension reaction that incorporates at least one nucleic acid sequence that identifies the first location of the tissue sample into each of the ligated probes, or portions thereof, collected in step (c), thereby forming a first plurality of extension products that comprise the ligated probes, or portions thereof, collected in step (c) and the at least one nucleic acid sequence that identifies the first location of the tissue sample;

f) performing an extension reaction that incorporates at least one nucleic acid sequence that identifies the second location of the tissue sample into each of the ligated probes, or portions thereof, collected in step (d), thereby forming a second plurality extension products that comprise the ligated probes, or portions thereof, collected in step (d) and the at least one nucleic acid sequence that identifies the at least second location of the tissue sample; and

The Board Did Not Find So-456 To Perform Claimed Extension

After review of the evidence of record, we conclude that, on this record, Petitioner does not show sufficient evidence of inherently bi-directional extension. In particular, we do not find that one of ordinary skill in the art would have read So-456 to disclose an extension reaction replicating the spatial barcode due to the lack of disclosure on this issue. We encourage the parties to further develop this issue at trial.

Inherency Is A High Standard

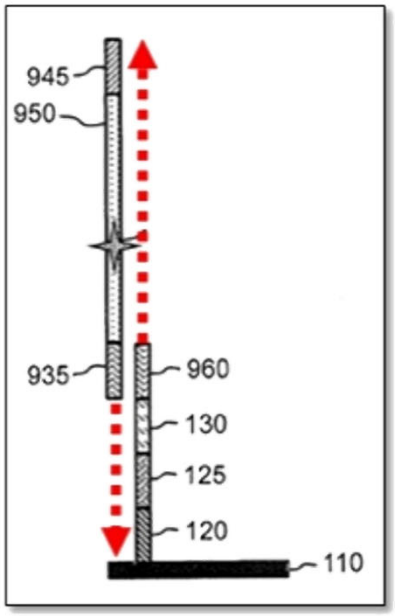


A party must, therefore, meet a high standard in order to rely on inherency establish the existence of a claim limitation in the prior art in an obviousness analysis—the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art…

Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.

PAR Pharm., Inc. v. TWI Pharms., Inc., 773 F.3d 1186, 1195–96 (Fed. Cir. 2014)

Petitioner Identifies Sequence 130 As The Spatial Barcode



EX1002, ¶150; EX1005, FIG. 9. The resulting extension products are DNA molecules comprising the sequences of the captured ligated probe (935, 950, and SBS site 945), the spatial barcode 130, and SBS site 125. EX1005, ¶¶[00141], [00182], FIG. 9; EX1002, ¶151-152.

Petitioner's Expert Confirms He Is Relying On The Downward Reaction To Allegedly Meet The Claim Element



Dr. Paul Spellman
Petitioner's Expert

Q. So to clarify, you are relying only on the reaction as depicted by the downward red arrow to satisfy the claimed extension reaction step in the '689 patent?

A. The requirement under the IPR's board determining that the nucleic acid probes being modified after collection only -- the only – only the 950 downward extension product meets that requirement in Figure 9.

Q. And the reaction depicted by the upward red arrow, just to reiterate, does not meet that criteria. Is that right?

A. That's correct.

So-456 Is Clear That Sequence 130 Is Sequencing Primer SBS3

is contacted with the capture site 105. In this example, capture probe 115 on the capture site 105 comprises a capture region 960 that is complementary to universal capture region 935; SBS primer region 130 is SBS3. DNA amplicons 950 are captured on the capture site 105 by hybridization of universal capture region 935 to capture region 960.

Petitioner's Expert Explains That A POSA Would Recognize An Error In Figure 9 Because Of Different Ones In Figure 6



Dr. Paul Spellman
Petitioner's Expert

Q. So is it your opinion that Segment 130 in Figure 9 has to be a spatial barcode?

A. The last sentence of Paragraph 56 is my conclusion. A POSA would readily know that Segment 130 in Figure 9 and Figure 6's capture probe is a spatial barcode. In Figure 6, a different typographical error has occurred, in which Segment 130 has two different functions that are incompatible with one another. And as a consequence, a POSA would look to all the other figures identified midway through Figures 1B, 1C, 3, 4, 6, 7, et cetera, for clarification as to the function of the sequences, knowing that the purpose is spatial identification, and that a spatial barcode must be present on the products to achieve that.

Petitioner's Argument That A Spatial Barcode Must Exist On The Capture Probe Contravenes Petitioner's Burden



As the Supreme Court has stated, in an IPR "the petitioner's contentions, not the Director's discretion, define the scope of the litigation all the way from institution through to conclusion." The IPR petition, thus, must provide an understandable explanation of the element-by-element specifics of the patentability challenges, including ***the identification of particular portions of prior art on which the petitioner is relying.***

Corephotonics, Ltd. v. Apple Inc., 84 F.4th 990, 1001 (Fed. Cir. 2023) (citation omitted) (emphasis added)

So-456 Depicts Direction Of Arrows Where It Chooses To

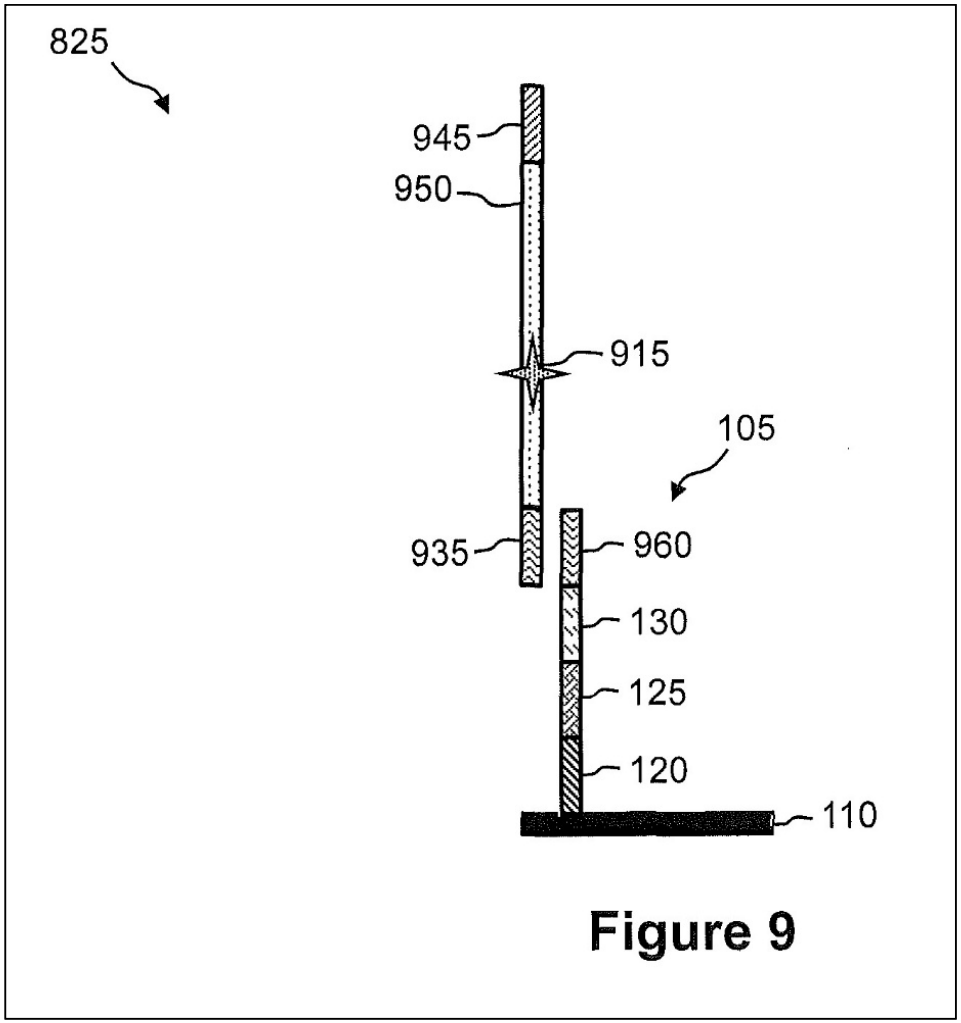


Figure 9

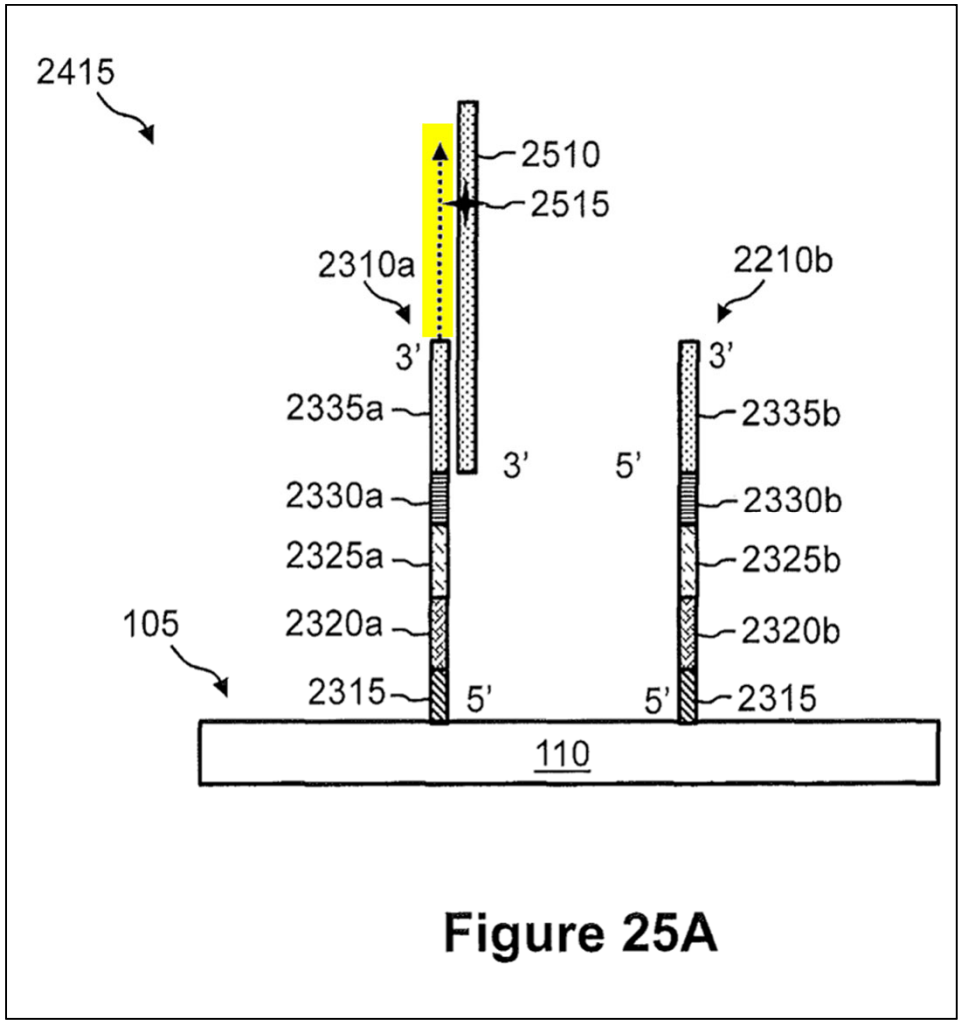


Figure 25A

Petitioner's Expert Confirms That The Upward Extension Product Is Sufficient For So-456's Method



Dr. Paul Spellman
Petitioner's Expert

Q. Is it your opinion that only one of the two strands is sufficient for downstream library generation?

A. When we look at Figure 9, both strands would encode all of the necessary elements to go into the next steps. So both strands would be capable of further manipulation after the cleavage of the 120 sequence releasing the bound -- the product formed by the bound molecule -- sorry, by the covalently attached to the substrate molecule.

Petitioner's Position: Figure 6 Discloses "Bidirectional Extension"

Meanwhile, another example involving the same enzyme (DNA-dependent DNA polymerase) and design as Figure 9 is Figure 6. EX1005, ¶¶[00172]-[00174]; EX1002, ¶149; EX1055, ¶67. And just like Figure 9, Figure 6 does *not* depict a unidirectional extension arrow. EX1005, FIGs. 6, 9; EX1055, ¶67. Rather, So-456 states in Figure 6 that *both* the capture region 660 and capture region 630 "can also function as primers for an extension reaction" (bidirectional extension), and that "[b]oth extension products can be used for downstream library generation." EX1005, ¶[00173]; Pet., 25; EX1002, ¶149; EX1055, ¶¶67-68. Thus, Figure 9's extension reaction proceeds in both directions. Pet., 26; EX1055, ¶¶42-69.

Petitioner's Expert: Figures 6 And 9 Are Related Due To A Similar Capture Region



Dr. Paul Spellman
Petitioner's Expert

Q. Is it stated anywhere in So-456 explicitly that Figure 6 disclosure applies to Figure 9?

A. In Figure -- in Paragraph '142 of So, for example, there is a direct relationship where the capture region that they're labeling 135 is – is used to capture cDNA in Figure 6 and DNA amplicons in Figure 9. So the POSA would understand that they are related.

Q. Are you aware of any other disclosure in So-456 that relates Figure 6 to Figure 9?

A. They are both examples of capturing DNA onto the array with similar structures. And a POSA would look to the entire specification to understand how the system works.

Topics For Argument

Chell is not prior art because the ’689 patent claims have priority support
(Ground 4)

So-456 does not anticipate the ’689 patent claims
(Ground 1)

- So-456 does not collect the claimed probes
- So-456 does not treat tissue samples
- So-456 does not disclose the claimed extension
- So-456 does not disclose the claimed ligation

So-456 does not render the ’689 patent claims obvious
(Grounds 2 and 3)

Claim 16 Requires Ligating Two Probes Together

16. A method for spatially detecting at least one target analyte in a first location and a second location of a tissue sample comprising:

b) forming ligated probes by ligating each of nucleic acid probes from the first plurality of nucleic acid probes and each of nucleic acid probes from the second plurality of nucleic acid probes that are bound to each of identical molecules from the at least one target analyte;

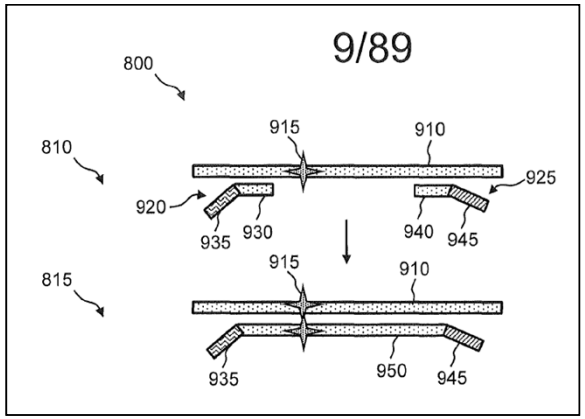
Patent Owner's Expert: So-456's Ligation Is A Large Gap That Captures A Region Of Interest



Dr. David Sherman
Patent Owner's Expert

Q. What's your understanding of how that gap compares to the gap that is potentially in figure -- in column 30 of the '689 application. '689 patent. Sorry.

A. I mean, visually, Figure 9, you can see that it's a large gap. I mean, it's a region that needs to be extended through a evidently large region. These probes aren't adjacent to each other. There's got to be an extension, you know, whereas here, in column 30 of the '689, it states that the nucleic acid probes on the one end are not adjacent and not overlapping, but you can use this gap extension which is then closed with a formal ligation by a ligase enzyme.



EX1056 at 77:21-78:7; PO's Sur-Reply at 27

Topics For Argument

Chell is not prior art because the ’689 patent claims have priority support
(Ground 4)

So-456 does not anticipate the ’689 patent claims
(Ground 1)

So-456 does not render the ’689 patent claims obvious
(Grounds 2 and 3)

Petitioner Is Required To Provide A POSA's Motivation



> [O]bviousness concerns whether a skilled artisan not only ***could have made*** but ***would have been motivated to make*** the combinations or modifications of prior art to arrive at the claimed invention.

Belden Inc. v. Berk-Tek LLC, 805 F.3d 1064, 1073 (Fed. Cir. 2015) (citation omitted)

The Board Did Not Find Obviousness In View Of So-456

However, Petitioner's allegations regarding the obviousness of independent claims 1 and 16 do not address the deficiency discussed above with regard to the limitation "collecting the nucleic acid probes." *See* Section II.D.2.a. Specifically, Petitioner does not allege or provide evidence to support that the skilled artisan would have found it obvious based on the teachings of So-456 to collect the cleaved identifier oligonucleotides rather than the genomic amplicons as alleged. In addition, we share Patent Owner's view that Petitioner, on this record, does not sufficiently show a motivation for the ordinarily skilled artisan to have included a spatial barcode in the capture probes of So-456. We suggest the parties further address these issues at trial.

For Independent Claims 1 And 16, The Petition Only Discusses The Claimed Extension Steps With Any Details

X. GROUND 2: CLAIMS 1-30 WOULD HAVE BEEN OBVIOUS OVER SO-456

To the extent NanoString argues that So-456 does not disclose all the elements of claims 1 and 16, such as the claimed extension steps, claims 1-30 still would have been obvious over So-456 under NanoString's interpretation. EX1002, ¶¶217-254.

A. Claims 1 and 16

The claimed extension steps would have been obvious to a POSA in view of So-456, which teaches including the claimed extension steps in its methods. EX1002, ¶¶218-233. Figure 2—which provides an overall workflow for So-456's

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Petition at 39; PO's Response at 37; PO's Sur-Reply at 28-29

Petition Provides No Motivation Why A POSA Would Modify So-456 To Perform The Downward Extension

Motivation: A POSA would have been motivated to practice So-456's method in Figures 2, 8, and 9 (including the use of extension reaction steps) because the purpose of So-456's methods is to create a sequencing library of sequences that are (i) tagged with spatial barcodes and (ii) include the necessary pair of SBS primer-binding sites for NGS. EX1005, ¶¶[0002], [0089], [0092], [00137], [00141]; EX1002, ¶¶234-236. The use of an extension reaction to extend So-456's capture (and captured) probes was a well-known, obvious, and routine technique for incorporating the spatial barcode (and necessary second sequencing primer) into the resulting extension reaction products to produce the desired finished sequencing library. EX1005, ¶[00173]; EX1002, ¶¶234-236.

Petition at 42; PO's Response at 39; PO's Sur-Reply at 26, 28-29

Petitioner's Expert Confirms That The Upward Extension Product Is Sufficient For So-456's Method



Dr. Paul Spellman
Petitioner's Expert

Q. Is it your opinion that only one of the two strands is sufficient for downstream library generation?

A. When we look at Figure 9, both strands would encode all of the necessary elements to go into the next steps. So both strands would be capable of further manipulation after the cleavage of the 120 sequence releasing the bound -- the product formed by the bound molecule -- sorry, by the covalently attached to the substrate molecule.

Petitioner Provided No Recognized Argument To Establish Motivation For Obviousness



> Here, there was no argument about common sense in the petition or in Dr. Mohazzab's declaration. There was no evidence that there are a finite number of identified, predictable solutions. There is no evidence of a design need or market pressure. In short, this case involves nothing other than an assertion that because two coordinate systems were disclosed in a prior art reference and were therefore "known," that satisfies the motivation to combine analysis. That is an error as a matter of law. It does not suffice to simply be known. A reason for combining must exist.

Virtek Vision Int'l ULC v. Assembly Guidance Sys., Inc., 97 F.4th 882, 887–88 (Fed. Cir. 2024) (citation omitted)

Petitioner's Motion To Exclude

Accordingly, the Board should exclude paragraphs 35-82 and 91-122 of EX2006 because Dr. Sherman's opinions are unsubstantiated, unreliable, and will not help the Board understand the evidence or determine a fact in issue. FRE 702, 703. Neither Dr. Sherman nor Bruker show that Dr. Sherman's opinions are based on sufficient facts or data, as required by FRE 702 and 703 and 37 C.F.R. § 42.65. And Dr. Sherman's technical background is not credible to provide unsupported opinions. "In the end, [the Board is] left with an expert opinion derived from

Patent Owner's Expert Is Imminently Qualified



Dr. David Sherman
Patent Owner's Expert

- **Hans W. Vahlteich Professor of Medicinal Chemistry**
  University of Michigan College of Pharmacy
- **Principal Investigator**
  University of Michigan Natural Products Biosciences Initiative
- **Faculty Lead and co-Founder**
  University of Michigan Natural Products Discovery Core
- **Professor of Microbiology and Immunology**
  University of Michigan Medical School
- **Professor of Chemistry**
  College of Literature, Science, and the Arts, University of Michigan
- **Co-Founder and Co-Managing Partner**
  PharmaForensics Laboratories
- **Microbiology Spectrum Advisory Board**
  American Society for Microbiology Press
- **Member Editorial Board**
  Journal of Biological Chemistry, American Society for Biochemistry and Molecular Biology
- **Associate Editor**
  Engineering Microbiology (Elsevier Press)
- **Authored 300+ peer-reviewed research articles**
- **Co-invented 17 U.S. Patents**
- **Post-doctoral research**
  Yale University
  Massachusetts Institute of Technology
- **Ph.D. in Organic Chemistry**
  Columbia University

Patent Owner's Expert Is Well Above Both Experts' Definition of a POSA



Dr. David Sherman
Patent Owner's Expert

In my opinion, a POSA would have been someone with a Ph.D. in a relevant field, such as molecular biology, genetics, chemistry, biochemistry, organic chemistry, microbiology, or a related discipline, with at least two years of experience in the use and development of approaches for spatial detection of proteins and nucleic acids of interest in a biological sample, including multiplex detection of target analytes in a tissue sample for purposes including as an aid in the diagnosis and treatment of human diseases.



Dr. Paul Spellman
Petitioner's Expert

A POSA, with respect to the 689 patent, would have possessed a strong understanding of genetics and genomics approaches for detecting or monitoring human diseases, such as spatial detection of a target analyte (e.g., mRNA or DNA) in a tissue section. A POSA would typically have a Ph.D. in a relevant field (e.g., molecular biology, genetics, and bioinformatics) with two years of experience in the use and development of genetics and genomics approaches for detecting and monitoring human diseases, such as spatial detection of a target analyte (e.g., mRNA or DNA) in a tissue section.

EX2006 ¶ 23; EX1002 ¶ 24; PO's Opposition to Petitioner's Motion to Exclude at 6

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Patent Owner's Expert Has Direct Experience In Spatial Technologies



Dr. David Sherman
Patent Owner's Expert

Q. Do you have any experience in your research using commercial products for spatial transcriptomics?

A. Yes. For my HIV drug discovery project, yes.

Q. What products -- product or products did you use in that research?

A. We -- at Michigan, we have core laboratories that have both 10x Genomics and NanoString's capabilities, so I have used them both.

Petitioner's Motion Contravenes The Law



> There is…no requirement of a perfect match between the expert's experience and the relevant field.

Consolidated Trial Practice Guide (Nov. 2019) at 34 (citing *SEB S.A. v. Montgomery Ward & Co.*, 594 F.3d 1360, 1373 (Fed. Cir. 2010))

Petitioner's Motion Contravenes The Federal Rules Of Evidence



> Unless the court orders otherwise, an expert may state an opinion — and give the reasons for it — without first testifying to the underlying facts or data. But the expert may be required to disclose those facts or data on cross-examination.

FRE 705

Petitioner's Arguments Go To Weight And Not Admissibility



> At their core, however, Verizon's disagreements are with the conclusions reached by ActiveVideo's expert and the factual assumptions and considerations underlying those conclusions, not his methodology. These disagreements go to the weight to be afforded the testimony and not its admissibility.

ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc., 694 F.3d 1312, 1333 (Fed. Cir. 2012)

Thank You