UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FLUIDIGM CORP.,
Petitioner,

v.

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIV.,

Patent Owner.

Case IPR2017-00014
Patent 7,695,926

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 7,695,926 UNDER TO 35 U.S.C. §§ 311 *ET SEQ.* AND 37 C.F.R. § 42.100 *ET SEQ.*

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Exhibit 1005	PCT Application No. WO 99/44067 to Darzynkiewicz, et. al., entitled "Flow Cytometric Detection of Conformations of pRB in Single Cells", publication date of Sept. 2, 1999 ("Darzynkiewicz")
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Exhibit 1007	[intentionally not used]
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Exhibit 1009	Morgan, M., *et al*., Cell-cycle–dependent activation of mitogen-activated protein kinase kinase (MEK-1/2) in myeloid leukemia cell lines and induction of growth inhibition and apoptosis by inhibitors of RAS signaling, *Blood*, Vol. 97, No. 6, pp. 1823-1834, March 15, 2001 ("Morgan")
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I. Introduction

The Real Party in Interest, Fluidigm Corp. (hereinafter "Petitioner") hereby respectfully requests *Inter Partes* Review pursuant to 35 U.S.C. §§ 311 *et seq.* and 37 C.F.R. §§ 42.100 *et seq*., of claims 1-9 and 11-12 of U.S. Patent No. 7,695,926 ("the '926 patent") filed January, 18, 2007 to Perez *et al. See* Exhibit 1001.

On its face, the '926 patent acknowledges that each limitation recited in claims 1-9 and 11-12 utilizes well-known techniques and commercially available reagents. This includes activation state-specific antibodies specific for selected proteins (Ex. 1001 at 29:7-28), antibody conjugation procedures and kits (*id*. at 26:33-36), and distinguishable labels (*id*. at 20:60-24-15). That all of these techniques and technologies were well known prior to the time of the invention is further confirmed by the declaration of Dr. Tom Huxford. Ex. 1002 at ¶¶14-35 (describing the state of technology at the time of the invention).

Thus, the '926 patent does not purport to have invented any new antibody, protein, antibody-protein conjugation technique, or antibody labeling technique. Rather, at best, the '926 patent purports to be the first to use these well-known techniques and commercially available reagents to "provide[] methods and compositions for simultaneously detecting the activation state of a plurality of proteins in single cells using flow cytometry." Ex. 1001 at Abstract.[1]

[1] Petitioner notes that none of "detecting," "simultaneously," or "flow cytometry"

However, Shen discloses using activation state specific antibodies as capture molecules to determine the activation state of multiple different proteins at the same time. Ex. 1016 at 53:12-17 ("the capture molecules are specific for 2 or more phosphorylated proteins"). In addition, Darzynkiewicz and Fleisher provide explicit teachings to apply their methodology to the detection of the activation state of a plurality of proteins using different labeled antibodies:

> *Present multiparametric flow cytometric techniques permit more than two antibodies to be discriminably detected in a single assay*. …these further antibodies may, for example, be used to report, concurrently with the phosphorylation status of pRB, the concurrent levels of other proteins that participate in the regulation of the cell cycle.

Ex. 1005 at 12:50-59 (emphasis added).[2]

> This technique should find applications in the study of multiple phosphorylation-dependent pathways such as those involving other Jak–STAT combinations, IkB, and MAP kinases…This approach should be valuable in studying any activation pathway for which antibody reagents exist that discriminate between a native and an activation modified protein

Ex. 1004 at 429. By the time of the '926 patent, one of skill in the art would have been knowledgeable about the numerous commercially available activation state-

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are recited or required in any claim of the '926 patent.

[2] All emphasis herein added by Petitioner unless otherwise noted.

specific antibodies (as admitted to be known in the '926 patent) that could be used to detect a plurality of activatable proteins of interest using the methods of Darzynkiewicz and Fleisher. Ex. 1002 at ¶23; Ex. 1001 at 29:7-28.

Therefore, the prior art anticipates and/or renders obvious claims 1-9 and 11-12 of the '926 patent. Accordingly, Petitioner respectfully requests that claims 1-9 and 11-12 of the '926 patent be canceled based on the grounds of unpatentability set forth below. 35 U.S.C. § 314(a).

II. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8(a)(1)

Petitioner satisfies each requirement for *Inter Partes* Review of the '926 patent pursuant to 37 C.F.R. § 42.8(a)(1).

A. Real Party In Interest Under 37 C.F.R. § 42.8(b)(1)

The Real Party in Interest is Fluidigm Corp., 7000 Shoreline Court, Suite 100, South San Francisco, CA 94080.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

Petitioner is not aware of judicial or administrative proceeding involving the '926 patent.

C. Lead and Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3)

Petitioner is represented by the following counsel:

Lead Counsel	Backup Counsel
James P. Murphy (Reg. No. 55,474) Polsinelli PC 1000 Louisiana Street Fifty-Third Floor Houston, Texas 77002 Telephone: 713.374.1631 jpmurphy@polsinelli.com	Margaux A. Savee (Reg. No. 62,940) Polsinelli LLP Three Embarcadero Center Suite 1350 San Francisco, California 94111 Telephone: 415.248.2100 msavee@polsinelli.com

Pursuant to 37 C.F.R. § 42.10(b), a Power of Attorney has been filed with this Petition.

D. Service Information Under 37 C.F.R. § 42.8(b)(4)

Service information for lead and back-up counsel is as follows:

James P. Murphy
Polsinelli PC
1000 Louisiana Street, Fifty-Third Floor
Houston, Texas 77002

Petitioner also consents to service by e-mail at the above e-mail addresses provided for lead and back-up counsel.

III. GROUNDS FOR STANDING UNDER 37 C.F.R. § 42.104(a)

Petitioner certifies that the '926 patent is available for *inter partes* review. Petitioner is not barred or estopped from requesting an *inter partes* review of the '926 patent claims on the grounds identified in this Petition. 37 C.F.R. § 42.104(a).

IV. IDENTIFICATION OF GROUNDS FOR WHICH REVIEW IS REQUESTED UNDER 37 C.F.R. § 42.104(b)(1)

Petitioner asserts that claims 1-9 and 11-12 of the '926 patent are unpatentable based on the following grounds:

Ground 1: Claims 1-5 and 11-12 are anticipated under 35 U.S.C. § 102 by Shen;

Ground 2: Claims 1-9 are rendered obvious under 35 U.S.C. § 103 by Fleisher;

Ground 3: Claims 1-9 are rendered obvious under 35 U.S.C. § 103 by Darzynkiewicz in view of Yen;

While some of the above grounds cover the same claims the technical teachings between the different grounds are not cumulative.

Shen expressly discloses detection of two activatable proteins using state-specific antibodies on a solid substrate. Fleisher discloses using flow cytometry to detect activated STAT-1 using an activation state specific antibody along with teaching to use the disclosed methodology to detect the activation state of other intracellular proteins including Jak, NFκB, or MAPK. Darzynkiewicz in view of Yen teach a flow cytometric method to concurrently detect the activation state of proteins that regulate the cell cycle such as RB, ERK 1/2 and MEK 1/2.

Thus, the different grounds either anticipate or render obvious the claims, but they do so based on different non-cumulative teachings.

V. HOW THE CHALLENGED CLAIMS ARE TO BE CONSTRUED UNDER 37 C.F.R. § 42.104(b)(3)

In an *inter partes* review, claim terms are to be given their broadest reasonable construction consistent with the specification. 37 C.F.R. § 42.100(b). Here, the specification of the '926 patent defines certain terms used in the claims as follows:

A. Protein

The '926 patent states "[a]s used herein, the terms 'protein' and 'polypeptide' may be used interchangeably and mean at least two covalently attached amino acids, which includes proteins, polypeptides, oligopeptides and peptides." Ex. 1001 at 15:36-42. In addition, claim 2 provides specific examples of "protein[s]" that are within the scope of claim 1. *Id.* at 51:34-56.

Therefore, the broadest reasonable construction of "protein" in light of the '926 patent should be "at least two covalently attached amino acids, which includes proteins, polypeptides, oligopeptides and peptides." *id*.; *see also* Ex. 1002 at ¶¶45-51.

B. Activation state-specific antibody

The '926 patent states "[a]s used herein, the term 'activation state-specific antibody' or "activation state antibody' or grammatical equivalents thereof, refer to an antibody that specifically binds to a corresponding and specific antigen." Ex. 1001 at 26:55-59. Therefore, the broadest reasonable construction of "activation

state-specific antibody" in light of the '926 patent is "an antibody that specifically binds to a corresponding and specific antigen." *See* Ex. 1002 at ¶¶52-53. In addition, claim 5 provides specific examples of "activation state-specific antibod[ies]" that are within the scope of claim 1. *Id.* at 52:22-4.

Petitioner notes that the definition provided in the '926 patent for "activation state-specific antibody" would encompass virtually any antibody, as all antibodies bind to a specific antigen. Thus, if the Board determines the above construction is too broad despite what is expressly stated in the specification, then the broadest reasonable construction of "activation state-specific antibody" in light of the '926 patent is "an antibody that specifically binds to a corresponding and specific isoform of an activatable protein." Ex. 1002 at ¶¶54-55.

VI. OVERVIEW OF THE '926 PATENT

A. Summary of the disclosure of the claimed subject matter

The '926 patent states the "invention provides methods and compositions for simultaneously detecting the activation state of a plurality of proteins in single cells using flow cytometry." Ex. 1001 at Abstract. However, the claims do not require any detection, let alone simultaneous detection using flow cytometry.

While many embodiments relate to determining the presence of activated isoforms of a multiplicity of receptor elements, the '926 patent also notes that the methods are not limited to receptor elements but applies generally to activatable

protein kinases and their substrates. *Id*. at 29:29-43. ("[a]dditional means for determining kinase activation are provided by the present invention. Substrates that are specifically recognized by protein kinases and phosphorylated thereby are known. Antibodies that specifically bind to such phosphorylated substrates but do not bind to such non-phosphorylated substrates (phospho-substrate antibodies) may be used to determine the presence of activated kinase in a sample.")

An "activation state-specific antibody" binds to a corresponding and specific antigen, which is preferably a specific isoform of an activatable protein. *Id*. at 26:55-59. The '926 patent admits that activation state-specific antibodies were well known and commercially available prior to the time of the invention. *Id*. at 29:7-28 ("many such antibodies have been produced which specifically bind to phosphorylated, activated isoforms") and 27:18-30 ("A variety of recognition structure are well known in the art and can be made using methods known in the art" to bind "activation state-specific antibodies" to a target structure on a protein.)

In preferred embodiments, the activated isoform is a form having a particular biological, biochemical, or physical property that is not possessed by at least one other isoform. *Id*. at 28:22-26. Examples of such properties include "enzymatic activity (e.g., kinase activity…)". *Id*. at 28:27-33. In preferred embodiments, the activated isoform is distinguishable from a non-activated

isoform due to a difference in epitopes or moieties between the two isoforms. *Id*. at 28:55-64.

The '926 patent acknowledges and admits that activation state-specific antibodies to detect kinases were known in the art and commercially available for purchase. *Id*. at 29:7-28. ("Many antibodies, many of which are commercially available….have been produced which specifically bind to the phosphorylated isoform [sic] of a protein but do not specifically bind to a non- phosphorylated isoform of a protein.") Prior to the '926 patent, these antibodies have been used "for the study of signal transducing proteins." *Id*. at 29:13-15; Ex. 1002 at ¶40.

To provide detectability, an antibody may be distinguishably labeled, such as with different fluorescent, enzymes and radioisotopes labels. Ex. 1001 at 20:60-24-15. As acknowledged by the '926 patent, the use of distinguishable labels was well known in the art and numerous distinguishable labels that were commercially available before the '926 patent can be used in the present invention. *Id*. at 21:17-24:15; Ex. 1002 at ¶41.

In a preferred embodiment a flow cytometer is used to detect fluorescence. Ex. 1001 at 32:19-29. The "detecting, sorting or isolating steps of the methods of the invention can entail fluorescence-activated cell sorting (FACS) techniques…[a] variety of FACS systems are known in the art and can be used in the methods of

the invention." *Id*. at 32:19-29. In a preferred embodiment, a commercially available Becton Dickinson "FACSVantage^{TM}" cell sorter is used. *Id*. at 32:30-34.

Finally, the 926 patent mentions "the present invention provides kits….these kits comprise two or more activation-state specific antibodies as described herein in [sic] container and, optionally, instructions." *Id*. at 3:25-40.

In summary, the claimed invention purports to provide a kit with well-known state-specific antibodies that bind to well-known activatable proteins which can be detected using well-known labels by using commercially available detection devices. Ex. 1002 at ¶44; *see also id*. at ¶¶14-35 (describing the state of technology at the time of the invention).

B. Exemplary claim

The '926 patent has a single independent claim, reproduced below. Petitioner has emphasized the limitation that the Applicant relied on for allowance, as will be discussed more fully in Section VI(C) below.

> 1. A kit comprising a first activation-state specific antibody and a second activation-state specific antibody and instructions for use of the antibodies, wherein at least one of the antibodies is specific for a phosphorylation site, *wherein said first activation state-specific antibody binds to an activation form of a first protein within the MAPK (mitogen activated protein kinase), AKT (homolog of V-akt murine thymoma viral oncogene), NFkB (nuclear factor kappa B), PKC (protein kinase C), STAT (signal transducers and activators of*

transcription) or WNT (Win gless/Int) signaling pathways, and said second activation state-specific antibody binds to an activation form of a second protein within the MAPK, AKT, NFkB, PKC, STAT or WNT signaling pathways, and wherein said first and second proteins are different proteins.

Ex. 1001 at 51:20-33 (emphasis added to show limitation added as reason for allowance as discussed below).

C. Reason for Allowance

During the prosecution of the application that became the '926 patent, the Examiner rejected pending claims 14-23 and 26-27[3] as obvious over U.S. Pat. Appl. Publication 2002/0177179A1 (which issued as U.S. Patent No. 6,806,056) to Glickman *et. al.*[4] in light of the antibodies admitted to be known in the prior art and commercially available from Cell Signaling Technologies. Ex. 1015 at 5-6. Claim 24 was rejected as obvious in view of Glickman over U.S. Patent No. 6,972,198 to Craig *et al.* and claim 25 was rejected as obvious in view of Glickman over U.S. Patent No. 7,102,005 to Singh *et al*. *Id*. at 6-8.

[3] Claims 14 and 17-27 later issued as claims 1-12 in the '294 patent.

[4] Glickman's publication was prior art to the '926 patent since the Examiner determined that the claims of the '926 patent were not supported by the earliest provisional applications due to the lack of support for a "kit" in those applications. Thus, the earliest priority date of the claims of the '926 patent is July 10, 2002.

Applicant apparently overcame the rejections by amending then pending claim 16 into then pending claim 14 which limited the claims to proteins within the MAPK, AKT, NFκB, PKC, STAT or WNT signaling pathways. *Id.* at 21.

D. Petition is not cumulative to the arguments and evidence relied on in the prosecution history

The instant Petition relies on Darzynkiewicz[5], which had a family member cited on the face of the '926 patent. However, the Examiner never considered or discussed if Darzynkiewicz in view of Yen renders obvious the claims of the '926 patent. In addition, the Petition also relies on the teachings of Shen. Fleisher and the declaration of Dr. Huxford, none of which were considered when examining the patentability of claims during the prosecution of the application that led to the '926 patent. Therefore, the Board should not exercise its discretion under 35 U.S.C. § 325(d) to deny any ground in the Petition.

VII. OVERVIEW OF THE PRIOR ART

1. Summary of Shen

Shen discloses:

> Kits of the invention are designed to detect protein modification in a biologically active sample of proteins. The kits comprise a solid

[5] Petitioner relies on a PCT publication due to its availability as prior art under pre-AIA 35 U.S.C. § 102(b) while a U.S. Patent to Darzynkiewicz is cited on the face of the '926 patent. The disclosure of each appears substantially the same.

> support of 2 or more capture molecules immobilized on the solid support, each of which can specifically bind a target protein that is capable of a subject protein modification; …and instructions for use of the kit.

Ex. 1016 at 50:21-28; Ex. 1002 at ¶64. Shen further discloses that, "[t]he capture molecules on the solid support can be antibodies" and "[t]he subject protein modification on the solid support can be a phosphorylation." Ex. 1016 at 51:13-15; Ex. 1002 at ¶65.

In addition, Shen provides a list of specific proteins who phosphorylation/activation state can be detected using his assay, which includes many of the exact same activateable proteins and signaling pathways recited in the claims of the '926 patent. Ex. 1016 at 52:19-32 (assay detects "phosphorylation of any of p44/42 MAP Kinase (Thr202/Tyr204) and MEK1/2 (Ser217/221)… Akt (Ser473)… ikB…."); Ex. 1002 at ¶66. Finally, to the extent relevant, Shen discloses that his array allows "the protein modification status [e.g., activation state] (or profile) of a plurality of target proteins can be assessed simultaneously." Ex. 1016 at 4:29-32.

2. Summary of Fleisher

Fleisher teaches a method of using an activation state-specific antibody for STAT-1 to detect and analyze the activation state of STAT-1 protein in peripheral blood mononuclear cells. Ex. 1004 at 425. Fleisher also teaches the benefits of

using flow cytometry to analyze the active isoforms of other intracellular signaling proteins to obtain an understanding of a fuller range of cellular signaling pathways:

> *This approach should allow for the evaluation of different intracellular signaling pathways using a combination of monoclonal reagents that are specific for* native and *activation modified proteins*. Application of this form of testing should prove valuable in screening for signaling defects in selected patients with recurrent infections. In addition, this technique should permit dissection of a full range of cellular signaling pathways at the protein level.

Ex. 1004 at 425. Indeed, Fleisher identifies his teachings apply generally to the evaluation of activatable proteins in signaling pathways so long as there is an activation state-specific antibody for that protein:

> General application of this technique in the evaluation of intracellular signaling proteins requires combinations of monoclonal antibodies that are specific for native and activation modified proteins. It has the potential of being applicable in any setting where immunoblotting has been useful to dissect intracellular signaling pathways.

Ex. 1004 at 425; *see also id*. at 429 ("This approach should be valuable in studying any activation pathway for which antibody reagents exist that discriminate between a native and an activation modified protein."). In fact, Fleisher expressly teaches some other activatable proteins other than STAT-1 that are of interest for further study:

> *This technique should find applications in the study of multiple phosphorylation-dependent pathways such as those involving other Jak–STAT combinations, IkB, and MAP kinases.* This approach has distinct advantages in terms of sensitivity, speed, and technical simplicity compared to immunoblotting. In addition, *multiple phenotypes can be assayed within the same sample based on the cellular discrimination inherent to flow cytometry*.

Ex. 1004 at 429.

In sum, Fleisher teaches a method of using flow cytometry to analyze activated intracellular proteins using an activation state specific antibody. The only technical restriction to using his technique is the existence of an antibody that discriminates between the native and active state of the protein of interest. Ex. 1002 at ¶79. At the time of the invention, one of ordinary skill in the art was aware of activation state specific antibodies for many proteins, including STAT-1 and various MAP kinases, which could be assayed together using the teachings of Fleisher. Ex. 1002 at ¶83.

3. Summary of Darzynkiewicz

Darzynkiewicz discloses "methods and reagents that permit the concurrent and discriminable detection of discrete functional conformations of proteins in a single cell." Ex. 1005 at 7:2-6. In addition, Darzynkiewicz uses fluorescently labeled state-specific antibodies to detect the phosphorylation state of proteins in a single cell with the use of a flow cytometer. *Id*. at 8:21-29; 27:22-34. Thus

Darzynkiewicz is trying to solve the exact same problem of the '926 patent, namely using state-specific antibodies to permit the concurrent detection of discrete protein isoforms via flow cytometry.

To perform this method, Darzynkiewicz first teaches contacting a cell with a "first" and "second" antibodies where the two antibodies are specific for different conformations of the same protein. *Id*. at 9:12-19. In addition, a "third" antibody can be used which is "specific for a second protein and distinguishable from each of said first and second antibodies, and then detecting the concurrent binding of each of said antibodies to said cell." *Id*. at 10:8-16. As his primary example, Darzynkiewicz discloses the first protein being activated retinoblastoma (pRB) and the second protein is chosen from a cyclin, cyclin dependent kinase, or a cyclin dependent kinase inhibitor. *Id*. at 9:20-20 and 10:13-16.

Antibodies are labeled to enable multiparametric detection using a flow cytometer, such as using distinguishable fluorescent labels. *Id*. at 22:13-17 and 22:17-23:21. As noted by Darzynkiewicz, "multiparametric flow cytometric techniques permit more than two antibodies to be discriminable detected in a single assay. *Id*. at 27:22-24. Moreover, "further antibodies may, for example, be used to report, concurrently with the phosphorylation status of pRB, the concurrent levels of other proteins that participate in the regulation of the cell cycle. *Id*. at 22:28-34 and 28:13-15.

4. Summary of Yen

Yen is directed to studying the effects of activation of proteins in the MAPK pathway on cell differentiation and cell cycle arrest associated with hypophosphorylation of the retinoblastoma (RB) tumor suppressor protein. Ex. 1005 at 3163 ("G_0 growth arrest and RB tumor suppressor protein phosphorylation…, *also depended on ERK2 activation by MEK*."); *Id*. at 3165 ("The antibody used to detect activated ERK1 and ERK2 (V6671 rabbit polyclonal antibody; Promega, Inc., Madison, WI)").

Therefore, Yen teaches a method of using activation state-specific antibodies to detect the activation state for ERK 1/2 and to analyze those findings in connection with the detection of other proteins in the MAPK signaling pathway in correlation with the detection of retinoblastoma protein. *Id*. at 3163.

VIII. HOW THE CONSTRUED CLAIMS ARE UNPATENTABLE UNDER 37 C.F.R. § 42.104(b)(4)

A. Level of Skill in the Art

In view of the subject matter of the '926 patent, a person of ordinary skill in the art ("POSITA") as of July 10, 2001 or July 10, 2002 was typically a person who had a Ph.D. in the areas of chemistry, biochemistry, cell biology or molecular biology including five or more years of experience in dealing with antibodies, protein labeling, protein interaction, and protein detection. Ex. 1002 at ¶¶12-13. Whether the time of the invention is July 10, 2001 or July 10, 2002 depends on the

priority date of the '926 patent, see discussion in Section II(B)(1) below, but Dr. Huxford's opinions would not change regardless of which date is used as the time of the invention.

Dr. Huxford is well versed in the technology of the '926 patent and was personally working on analysis of protein activation in at least the July, 10 2001 to July, 10 2002 time frame. Ex. 1002 at ¶¶2-7; Ex. 1003. Thus, Dr. Huxford is qualified to provide his opinion on the level of skill and the knowledge of one of skill in the art at the time of the invention.

B. Claims 1-5 and 11-12 are anticipated 35 U.S.C. § 102 by Shen

As discussed above, during prosecution the only limitation found not to be taught by the prior art are activatable proteins within specific signaling pathways. However, this limitation and all other limitations of claims 1-5 and 11-12 are anticipated in light of the disclosure of Shen of simultaneously analyzing the activation form of multiple different proteins using activation state-specific antibodies. Ex. 1002 at ¶73.

1. Shen is Prior Art under either 35 U.S.C. § 102(a) or (b)

Shen published on April 19, 2001, which is before the '926 patent's earliest possible priority date of July 10, 2001, qualifying Shen as prior art at least under pre-AIA 35 U.S.C. § 102(a).

In addition, Shen qualifies as prior art under pre-AIA 35 U.S.C. § 102(b) because the claims of the '926 patent are only entitled to a priority date of July 10, 2002, which is more than one year after Shen was published. As found by the Examiner in prosecution, the earlier filed provisional applications do not provide any disclosure to support a claim reciting providing a kit with the claimed antibodies or any equivalent disclosure. Ex. 1015 at 3-4; *See* Ex. 1017 and 1018.

In fact, the only mention of "kits" at all is to "protein-protein/protein-dye crosslinking kits from Molecular Probes (Eugene, Oregon)." *See e.g.,* Ex. 1017 at pg. 14, lines 28-29. Further, the claims of the '926 patent cannot claim priority to the provisional applications even if a kit would have been obvious in light of the disclosure of the provisional applications. *Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co*., 598 F.3d 1336, 1352 (Fed. Cir. 2010) ("[A] description that merely renders the invention obvious does not satisfy the requirement" of 35 U.S.C. § 112).

Thus, there is no written description in the provisional applications that supports the claims of the '926 patent under 35 U.S.C. § 112. Thus, the earliest claim of priority for the claims of the '926 patent is July 10, 2002.

Claim 1

a. **1. A kit comprising a first activation-state specific antibody and a second activation-state specific antibody and instructions for use of the antibodies,**

Shen discloses:

> *Kits of the invention* are designed to detect protein modification in a biologically active sample of proteins. The kits comprise a solid support of *2 or more capture molecules* immobilized on the solid support, each of which can specifically bind a target protein that is capable of a subject protein modification; …*and instructions for use of the kit*.

Ex. 1016 at 50:21-28; Ex. 1002 at ¶64. Shen further discloses that, "[t]he capture molecules on the solid support can be antibodies" and "[t]he subject protein modification on the solid support can be a phosphorylation." Ex. 1016 at 51:13-15; Ex. 1002 at ¶65; *see also* Ex. 1016 at 19:24-27 ("the protein modification status (or profile) of a plurality of target proteins can be assessed simultaneously by contacting the plurality of target proteins with…a plurality of immobilized capture molecules, simultaneously").

Therefore, Shen discloses a kit with instructions on how to use two or more antibody capture molecules [e.g., first and second antibodies] which specifically bind to target proteins that have been modified by activation through phosphorylation.

b. wherein at least one of the antibodies is specific for a phosphorylation site, and

Shen discloses that "[t]he subject protein modification on the solid support can be a phosphorylation and the phosphorylation can comprises [sic] tyrosine,

serine or threonine phosphorylation." Ex. 1016 at 51:13-15; *id*. at 47:25-26 ("Their activation requires the phosphorylation of a threonine and a tyrosine residue located in a Thr-X-Tyr motif (where x is any amino acid)"); *see also id*. at 23:10-12 ("Antibodies that can be used to detect these modifications include an antibody specific to a phosphorylated residue of a protein.").

In one embodiment, Shen discloses "A protein array may comprise immobilized capture molecules on a solid support capable of specifically binding certain proteins, wherein *the capture molecules [e.g., antibodies] are specific for 2 or more phosphorylated proteins selected from the group consisting of p44/42 MAP Kinase, MEK1/2*, …"*Id*. at 53:12-17; *see also id*. at 52:19-32 ("the capture molecules are specific for 2 or more of proteins consisting of mitogenic pathway group comprising phosphorylation of any of p44/42 MAP Kinase (Thr202/Tyr204) and MEK1/2 (Ser217/221).") The parenthetical listed after the protein is the specific phosphorylation site on the protein that the capture molecule is specific for. Ex. 1002 at ¶67.

c. wherein said first activation state-specific antibody binds to an activation form of a first protein within the MAPK (mitogen activated protein kinase), AKT (homolog of V-akt murine thymoma viral oncogene), NFkB (nuclear factor kappa B), PKC (protein kinase C), STAT (signal transducers and activators of transcription) or WNT (Win gless/Int) signaling pathways,and

Shen discloses "[a] protein array may comprise immobilized capture molecules on a solid support capable of specifically binding certain proteins, wherein *the capture molecules [e.g., antibodies] are specific for 2 or more phosphorylated proteins selected from the group consisting of p44/42 MAP Kinase, MEK1/2*, *…Akt…*" Ex. 1016 at 53:12-17; *see also id*. at 52:19-32.

P44/42 MAP Kinase[6], MEK 1/2, and Akt are proteins in the MAPK, MAPK, and AKT signaling pathways respectively that are activated via phosphorylation. Ex. 1002 at ¶69. Thus, Shen discloses two or more capture molecules (e.g., first and second activation state specific antibodies) specific to a phosphorylated form (e.g., activation form) of proteins in the MAPK and AKT pathways.

For example, Shen discloses a first activation state specific antibody can be a capture molecule that is specific for an isoform of p44/42 MAP Kinase that has been phosphorylated at Thr202/Tyr204.

[6] P44/42 Map Kinase is an alternative name for ERK 1/2. Ex. 1002 at ¶24.

d. said second activation state-specific antibody binds to an activation form of a second protein within the MAPK, AKT, NFkB, PKC, STAT or WNT signaling pathways, and

As just discussed, Shen discloses "[a] protein array may comprise immobilized capture molecules on a solid support capable of specifically binding certain proteins, wherein *the capture molecules [e.g., antibodies] are specific for 2 or more phosphorylated proteins selected from the group consisting of p44/42 MAP Kinase, MEK1/2*, *…Akt…*" Ex. 1016 at 53:12-17; *see also id*. at 52:19-32 ("phosphorylation of any of Akt (Ser473)").

P44/42 MAP Kinase, MEK 1/2, and Akt are proteins in the MAPK, MAPK, and AKT signaling pathways respectively that are activated via phosphorylation. Ex. 100e at ¶69. Thus, Shen discloses two or more capture molecules (e.g., first and second activation state specific antibodies) specific to a phosphorylated form (e.g., activation form) of proteins in the MAPK and AKT pathways.

For example, Shen discloses a second activation state specific antibody can be a capture molecule that is specific for an isoform of AKT that has been phosphorylated at Ser473. *id*.

e. wherein said first and second proteins are different proteins.

Shen discloses "[a] protein array may comprise immobilized capture molecules on a solid support capable of specifically binding certain proteins,

wherein the capture molecules [e.g., antibodies] are specific for 2 or more phosphorylated proteins selected from the group consisting of p44/42 MAP Kinase, MEK1/2, …Akt…" Ex. 1016 at 53:12-17; *see also id*. at 52:19-32.

Thus, Shen discloses using two or more antibodies to detect two different proteins, such as phosphorylated P44/42 Map Kinase and phosphorylated AKT. Ex. 1002 at ¶70.

Claim 2

2. The kit of claim 1, wherein said first and second protein are independently selected from the group consisting of: AKT,…, MAPK, p44/42 MAP Kinase, …, MEK[]1/2…, NF-kB, ….

Claim 1 is anticipated as discussed above. Shen discloses "[a] protein array may comprise immobilized capture molecules on a solid support capable of specifically binding certain proteins, wherein the capture molecules [e.g., antibodies] are specific for 2 or more phosphorylated proteins selected from the group consisting of p44/42 MAP Kinase, MEK1/2, …Akt…" Ex. 1016 at 53:12-17; *see also id*. at 52:19-32.

Thus, Shen discloses using two or more antibodies to detect two different proteins, such as phosphorylated P44/42 Map Kinase and phosphorylated AKT. Ex. 1002 at ¶70.

Claim 3

3. The kit of claim 1, wherein said first activation state-specific antibody binds to a phosphorylation form of a first protein and said second activation state-specific antibody binds to a phosphorylation form of a second protein.

Claim 1 is anticipated as discussed above. Shen discloses "[a] protein array may comprise immobilized capture molecules on a solid support capable of specifically binding certain proteins, wherein the capture molecules [e.g., antibodies] are specific for 2 or more *phosphorylated* proteins selected from the group consisting of p44/42 MAP Kinase, MEK1/2, …Akt…" Ex. 1016 at 53:12-17; *see also id*. at 52:19-32.

Thus, Shen discloses using two or more antibodies to detect two different phosphorylated proteins, such as phosphorylated P44/42 Map Kinase and phosphorylated AKT. Ex. 1002 at ¶70.

Claim 4

4. The kit of claim 3, wherein said first activation state-specific antibody binds to a phosphorylation form of a first protein within the MAPK, AKT, NFkB, PKC or WNT signaling pathways and said second activation state-specific antibody binds to a phosphorylation form of a second protein within the MAPK, AKT, NFkB, PKC or WNT signaling pathways.

Claim 3 is anticipated as discussed above. Shen discloses "the capture molecules [e.g., antibodies] are specific for 2 or more of proteins consisting of mitogenic pathway group comprising phosphorylation of any of p44/42 MAP

Kinase (Thr202/Tyr204) and MEK1/2 (Ser217/221)…a cell survival pathway group comprising phosphorylation of Akt (Ser473)…NFkB signal pathway comprising phosphorylation of ikB….” in addition to numerous other phosphorylated proteins. Ex. 1016 at 52:19-32.

Thus, Shen discloses using two or more antibodies to detect two different proteins, such as phosphorylated P44/42 Map Kinase and phosphorylated AKT. Ex. 1002 at ¶70. P44/42 Map Kinase is in the MAPK signaling pathway and AKT is in the AKT signaling pathway. Ex. 1002 at ¶¶69-70.

Claim 5

5. The kit of claim 4, wherein said phosphorylation state-specific antibodies are independently selected from the group consisting of: anti-phospho-AKT Ser473, anti-phospho-p44/42 MAP kinase (Thr202/Tyr204),…,anti-phospho-MEK1/2 (Ser217/221), …

Claim 4 is anticipated as discussed above. One of ordinary skill in the art understands the claim term “anti-phospho-AKT Ser473” refers to an antibody that is specific for a form of AKT that phosphorylates at Ser473 (Serine 473). Ex. 1002 at ¶68. Likewise, anti-phospho-p44/42 MAP kinase (Thr202/Tyr204) and anti-phospho-MEK1/2 (Ser217/221) refer respectively to antibodies specific for a form of MAP Kinase that phosphorylates at Thr202/Tyr204 and forms of MEK1/2 that phosphorylates at Ser217/221. Ex. 1002 at ¶68. As discussed above, Shen

discloses selecting phosphorylation specific antibodies specific to these binding sites. Ex. 1016 at 52:19-32.

Thus, Shen discloses the antibodies can be independently selected from the claimed group.

Claim 11

11. The kit of claim 1, wherein said first and second activation state-specific antibodies are immobilized in a solid surface.

Claim 1 is anticipated as discussed above. Shen discloses "the kits comprise a solid support of *2 or more capture molecules immobilized on the solid support*, each of which can specifically bind a target protein that is capable of a subject protein modification." Ex. 1016 at 50:21-28; *id*. at 51:13-15. ("[t]he capture molecules on the solid support can be antibodies"); *id*. at 40:7-10 ("The antibody array used in the kit can be produced on any suitable solid surface").

Therefore, Shen discloses the first and second phosphorylation specific antibodies are immobilized on "any suitable solid surface." Ex. 1002 at ¶¶71-72.

Claim 12

12. The kit of claim 11, wherein said surface is selected from the group consisting of a plate, chip, membrane and bead.

Claim 11 is anticipated as discussed above. Shen also discloses "[t]he solid surfaces may be in the form of tubes, *beads*, discs, *silicon chips*, *microplates*, polyvinylidene difluoride (PVDF) *membrane*, nitrocellulose membrane, nylon

membrane, other porous membrane, non-porous membrane, …" Ex. 1016 at 40:12-16.

Therefore, Shen discloses the solid surface can be selected from any of a plate, chip membrane or bead. Ex. 1002 at ¶¶71-72**.**

C. Claims 1-9 are rendered obvious under 35 U.S.C. § 103 by Fleisher

As discussed above, during prosecution, the only limitation found not to be taught by the prior art are activatable proteins within specific signaling pathways. However, this limitation and all other limitations of claims 1-9 would have been obvious to one of skill in light of Fleisher's teachings of analyzing proteins in the STAT, NFkB, and MAPK signaling pathways.

Although Fleisher does not expressly use a state-specific antibody for a second protein, this is because the specific examples provided in Fleisher were only attempting to determine the ratio of the activated state of STAT-1 to the native state of STAT-1. Ex 1002 at ¶¶74 and 77. Yet, Fleisher identifies his teachings apply generally to the evaluation of other activatable intracellular signaling proteins where activation state-specific antibodies exists. Ex. 1004 at 425; Ex. 1002 at ¶74. In addition, Fleisher teaches certain other activatable proteins of interest for further study:

> This technique should find applications in the study of multiple phosphorylation-dependent pathways such as those involving other Jak–STAT combinations, IkB, and MAP kinases.

Ex. 1004 at 429; Ex. 1002 at ¶74.

Therefore, it would have been obvious at the time of the invention to use Fleisher's method to analyze multiple proteins where antibodies specific to the activated state of those proteins were known at the time of the invention. Ex. 1002 at ¶¶15-17, 79-81 and 93; *see also* Ex. 1001 at 29:7-28.

Claim 1

a. 1. A kit comprising a first activation-state specific antibody and a second activation-state specific antibody and instructions for use of the antibodies,

While Fleisher does not expressly disclose a kit, it would have been obvious to one of ordinary skill in the art to provide a kit comprising the state-specific antibodies and proteins discussed below. Ex. 1002 at ¶85. A kit would beneficial in assisting practitioners who only occasionally need to perform an assay and to increase the reliability and ease of performing the assay. *Id*.

Fleisher teaches one of skill in the art a method of detecting the activation state of multiple different activatable proteins in a single cell. Ex. 1004 at 425 and 429; Ex. 1002 at ¶¶80-81. In particular, Fleisher provides the example of detecting the activation state of STAT-1 and expressly teaches one of skill in the art to detect

the activation state of "other Jak–STAT combinations, IκB, and MAP kinases." *Id*.; Ex. 1002 at ¶74.

Finally, "instructions" on the use of antibodies constitutes printed matter that should not be given patentable weight to distinguish the claims over the prior art. *In re Ngai*, 367 F.3d 1336, 1337–38 (Fed. Cir. 2004) ("A kit for normalizing and amplifying an RNA population, said kit comprising instructions describing the method of claim 1" found to claim printed matter). In the event providing "instructions" is limiting, it would have been obvious to provide instructions with the kit to provide a detailed protocol for the use of the antibodies. Ex. 1002 at ¶85.

b. wherein at least one of the antibodies is specific for a phosphorylation site, and

In light of Fleisher's teachings that his "technique should find application in the study of multiple phosphorylation-dependent pathways" and his express teaching to apply his technique to "MAP kinases," it would have been obvious to one of skill in the art to apply teachings of Fleisher to use antibodies to detect activated STAT-1 as well as detect ERK1/2 and MEK1/2, which are MAP kinases. Ex. 1002 at ¶¶80 and 82.The only requirement to do so is the existence of an antibody specific to the activated form of the proteins of interest. Ex. 1004 at 429; Ex. 1002 at ¶79. So long as an antibody was available that was specific to an activated protein of interest, it would only require routine optimization to apply the

teachings of Fleisher to detect the activation state of a protein using that antibody. Ex. 1002 at ¶79.

Fleisher expressly discloses an antibody specific to a STAT-1 phosphorylation site. Ex. 1004 at 425. One of skill in the art at the time of the invention would have been aware that antibodies specific to the phosphorylation sites of ERK1/2 and MEK 1/2 were commercially available, such as anti-phospho-p44/42 MAP kinase (Thr202/ Tyr204) and anti-phospho-MEK1/2 (Ser217/221). Ex. 1002 at ¶¶22-24, 81 and 83; *see also* Ex. 1001 at 29:7-28; Ex. 1008 at 5107-5108; Ex. 1010 at 39436. [7]

One of skill in the art would have used these antibodies in Fleisher to gain a better understanding of the MAPK signaling pathway. Ex. 1002 at ¶82.

c. wherein said first activation state-specific antibody binds to an activation form of a first protein within the MAPK (mitogen activated protein kinase), AKT (homolog of V-akt

[7] Cited references not named in a ground of rejection are cited for the purpose of showing the background knowledge of a person of ordinary skill in the art at the time of the invention and to corroborate the testimony of Dr. Huxford. *See Randall Mfg. v. Rea*, 733 F.3d 1355, 1362 (Fed. Cir. 2013); *see also*, *Edmund Optics Inc. v. Semrock Inc*., IPR2014-00599, Paper No. 72 at 37 (Sept. 16, 2015) (background knowledge "may be evidenced through secondary references").

murine thymoma viral oncogene), NFkB (nuclear factor kappa B), PKC (protein kinase C), STAT (signal transducers and activators of transcription) or WNT (Win gless/Int) signaling pathways,and

As discussed above, Fleisher expressly teaches a first distinguishable labeled antibody can be "rabbit anti-human phosphorylated STAT-1" which is specific for the activated isoform of STAT-1, which is in the STAT signaling pathway. Ex. 1004 at 426; Ex. 1002 at ¶¶76, 78 and 91. Alternatively, it would have been obvious in light of Fleisher's teachings to use his technique on MAP kinases to use anti-phospho-p44/42 MAPK (Thr202/Tyr204) as the first antibody, which is specific for activated ERK1/2, which is in the MAPK signaling pathway. Ex. 1002 at ¶¶82-85; Ex. 1004 at 429.

d. said second activation state-specific antibody binds to an activation form of a second protein within the MAPK, AKT, NFkB, PKC, STAT or WNT signaling pathways, and

While Fleisher does not expressly teach a second activation-state specific antibody, it would have been obvious to one of skill in the art to use a second activation-state specific antibody in light of Fleisher's statement to use his technique to "permit dissection of a full range of cellular signaling pathways" which would require investigation into the sequential activation of multiple

proteins in a signaling path and not just the investigation of a single activated protein. Ex. 1002 at ¶80; Ex. 1004 at 425 and 429.

In addition, Fleisher notes his technique is "applicable in any settings where immunoblotting has already been useful to dissect intracellular signaling pathways." Ex. 1004 at 425. One of skill in the art at the time of the invention was aware of numerous immunoblot assays that detected multiple different intracellular signaling proteins at the same time. Ex. 1002 at ¶81; *see also* Ex. 1006 at 3165; Ex. 1008 at 5107-5108; Ex. 1009 at 1823-1824; Ex. 1010 at 39436.

There, it would have been obvious in light of Fleisher's teachings to use his technique on MAP kinases to use anti-phospho-MEK1/2 (Ser217/221) as the second antibody, which is specific for activated MEK1/2, which is in the MAPK signaling pathway. Ex. 1002 at ¶¶82-85; Ex. 1004 at 429.

e. wherein said first and second proteins are different proteins.

As discussed above, it would have been obvious in light of the teachings of Fleisher for the first activatable protein to be a protein within the group of STAT-1 Jak, NkB, or MAPK and the second protein to be a different protein within the group of STAT-1 Jak, NkB, or MAPK. Ex. 1004 at 425 and 429; Ex. 1002 at ¶¶82-85. For example, if the first protein is STAT-1 or ERK 1/2 then the second protein can be MEK 1/2. *Id*.

Claim 2

2. The kit of claim 1, wherein said first and second protein are independently selected from the group consisting of:…MEK[]1/2…, ERK []1/2 … STAT1, ...

Claim 1 is rendered obvious as discussed above. Fleisher teaches analyzing the activated form of the STAT-1 protein. Ex. 1004 at 425. In addition, it would have been obvious to one of skill in the art to use Fleisher's method to also analyze the activated forms of ERK1/2 and MEK1/2. Ex. 1002 at ¶¶85-87. Thus, Fleisher teaches the first and second protein can be independently selected from the group STAT1, ERK 1/2, or MEK 1/2

Claim 3

3. The kit of claim 1, wherein said first activation state-specific antibody binds to a phosphorylation form of a first protein and said second activation state-specific antibody binds to a phosphorylation form of a second protein.

Claim 1 is rendered obvious as discussed above. Fleisher teaches analyzing the activated form of the STAT-1 protein. Ex. 1004 at 425. In addition, it would have been obvious to one of skill in the art to use Fleisher's method to use antibodies specific to the activated forms of ERK1/2 and MEK1/2. Ex. 1002 at ¶¶85-87. All of these proteins activate due to phosphorylation. Ex. 1002 at ¶¶76 and 88.

Claim 4

4. The kit of claim 3, wherein said first activation state-specific antibody binds to a phosphorylation form of a first protein within the MAPK, AKT, NFkB, PKC or WNT signaling pathways and said second activation state-specific antibody binds to a phosphorylation form of a second protein within the MAPK, AKT, NFkB, PKC or WNT signaling pathways.

Claim 3 is obvious as discussed above. It would have been obvious to one of skill in the art to use Fleisher's method to also analyze the activated forms of ERK1/2 and MEK1/2 which are both in the MAPK signaling pathway. Ex. 1002 at ¶¶85-87. Both of these proteins activate due to phosphorylation. Ex. 1002 at ¶88.

Claim 5

5. The kit of claim 4, wherein said phosphorylation state-specific antibodies are independently selected from the group consisting of:…, anti-phospho-p44/42 MAP kinase (Thr202/Tyr204),…, anti-phospho-MEK1/2 (Ser217/221),…

Claim 4 is obvious as discussed above. It would have been obvious to one of skill in the art to use Fleisher's method to also analyze the phosphorylated form of ERK1/2 using anti-phospho-p44/42 MAP kinase (Thr202/ Tyr204) and to analyzing the phosphorylated form of MEK1/2 using anti-phospho-MEK1/2 (Ser217/221). Ex. 1002 at ¶¶86-88.

Claim 6

6. The kit of claim 1, wherein said first and second activation state-specific antibodies are uniquely labeled.

Claims 1 is obvious as discussed above. A specific example taught in Fleisher focuses on contacting the cells with a labeled antibody to detect the active state of the STAT-1 protein (Ex. 1004 at 425); however, Fleisher identifies his teachings apply generally to the evaluation of other activatable proteins as discussed above. Ex. 1004 at 425 and 429.

One of skill in the art would understand anti-phospho-p44/42 and anti-phospho-MEK 1/2 could be distinguishably labeled using well known fluorescent labels, such as FITC (fluorescein isothiocyanate) and PE (phycoerythrin) that could both be detected with a single argon laser. Ex. 1002 at ¶107; Ex. 1004 at 426. In addition, multi-parametric flow cytometers were well-known at the time of the invention that could simultaneously distinguish between these fluorescent labels. Ex. 1002 at ¶¶32-34, and 104-105; *see also* Ex. 1005 at 27:22-24; Ex. 1011 at 79 and 83.

Claim 7

7. The kit of claim 6, wherein said first and second activation state-specific antibodies are independently labeled with a label selected from the group consisting of a fluorescent label, FRET (fluorescence resonance energy transfer) label and etag.

Claims 6 is obvious as discussed above. Fleisher teaches using a fluorescent label, such as FITC, and a Becton Dickinson FACS device to detect and sort the cells containing the activated proteins of interest. Ex. 1004 at 426; Ex. 1002 at ¶89

and 91. At the time of the invention, multicolor FACS devices were well known to concurrently analyze and sort based on the detection of multiple fluorescent signals. Ex. 1002 at ¶¶32-33 and 90; *see also* Ex. 1001 at 32:19-29 ("A variety of FACS systems are known in the art and can be used in the methods of the invention").

In addition to fluorescent labels taught by Fleisher, FRET labels were well-known to those of ordinary skill in the art at the time of the invention and it would have been obvious to use a FRET label for Fleisher's fluorescent labels. Ex 1002 at ¶¶27-30. In particular, one of skill in the art would have looked to tandem labels as a type of FRET label that would provide an added benefit in the method of Fleisher. *Id*. at ¶90. Examples of tandem labels include Cy5PE and Cy7PE. *Id*.

It would have been obvious to one of skill in the art to use a distinguishable label with the method of Fleisher to detect a second protein. A well-known laser at the time of the invention that could excite FITC, as disclosed in Fleisher, was an argon laser which could also excite the fluorescent label PE and the FRET labels Cy5PE and CY7PE. Ex. 1002 at ¶90; *see also* Ex. 1011 at 83; Ex. 1012 at 168-69.

Therefore, based on the teachings of Fleisher, it would have been obvious to one of skill in the art at the time of the invention to use a flow cytometer to simultaneously detect signals from anti-phospho-p44/42 MAPK labeled with either a fluorescent label (FITC) or a FRET label (Cy5PE) and anti-phospho-MEK1/2

labeled with a either fluorescent label (PE) or a FRET label (Cy7PE) and sort cells based on the detection of those signals. Ex. 1002 at ¶92.

Claim 8

8. The kit of claim 6, wherein said first and second activation state-specific antibodies are labeled with a fluorescent label.

Claims 6 is obvious as discussed above. Fleisher teaches using a fluorescent label, such as FITC, and a Becton Dickinson FACS device to detect and sort the cells containing the activated proteins of interest. Ex. 1004 at 426; Ex. 1002 at ¶89. At the time of the invention, multicolor FACS devices were well known to concurrently analyze and sort based on the detection of multiple fluorescent signals. Ex. 1002 at ¶90; *see also* Ex. 1001 at 37:16-24 ("A variety of FACS systems are known in the art and can be used in the methods of the invention").

It would have been obvious to one of skill in the art to use a second fluorescent label with the method of Fleisher to detect a second protein. A well-known and readily available laser at the time of the invention was an argon laser that could simultaneously excite FITC and PE. Ex. 1002 at ¶89. Simultaneous detection and sorting based on detecting excited FITC and PE only required routine filters. *id*.

Therefore, it would have been obvious to one of skill in the art at the time of the invention to include phospho-p44/42 MAPK (Thr202/Tyr204) that has been

fluorescently labeled with FITC and anti-phospho-MEK1/2 (Ser217/221) that has been fluorescently labeled with PE. Ex. 1002 at ¶¶89, 91 and 92.

Claim 9

9. The kit of claim 6, wherein said first and second activation state-specific antibodies are labeled with a FRET label.

Claims 6 is obvious as discussed above. Fleisher teaches using fluorescent labels to sort by FACS, but does not expressly teach FRET labels. However, FRET labels were well-known to those of ordinary skill in the art at the time of the invention and it would have been obvious to use a FRET label for Fleisher's fluorescent labels. Ex 1002 at ¶¶27-30. In particular, one of skill in the art would have looked to tandem labels as a type of FRET label that would provide an added benefit in the method of Fleisher. *Id*. at ¶90. Examples of tandem labels include Cy5PE and Cy7PE. *Id*.

One of skill in the art would use a tandem label since it would broaden the selection of compatible dyes for flow cytometry and enable up to four different colors to be detected using only a single argon laser. Ex. 1002 at ¶90; *see also* Ex. 1011 at 83 and Ex. 1012 at 168-69. In addition, tandem labels could be used to shift the emission wavelength further above the wavelength cellular autofluorescence to reduce background noise. Ex. 1002 at ¶90.

Therefore, based on the teachings of Fleisher it would have been obvious to one of skill in the art at the time of the invention to include anti-phospho-p44/42

MAPK labeled with FRET label Cy5PE and anti-phospho-MEK1/2 labeled with FRET label Cy7PE and sort cells based on the detection of those signals. Ex. 1002 at ¶¶91-92.

D. Claims 1-9 are rendered obvious under 35 U.S.C. § 103 by Darzynkiewicz in view of Yen

As discussed above, during prosecution, the only limitation found not to be taught by the prior art are activatable proteins within specific signaling pathways. However, this limitation and all other limitations of claims 1-9 would have been obvious to one of skill in the art in light of Darzynkiewicz's teachings of using an activation state-specific antibody to detect activated retinoblastoma protein concurrently with other proteins and Yen's teaching of concurrently detecting proteins in the MAPK pathway, including activated ERK 1/2 and retinoblastoma protein.

1. Reason to Combine the Teachings of Darzynkiewicz in view of Yen

Darzynkiewicz states the "third" antibody is "specific for a second protein" but is silent if it is specific for an activated isoform of a second protein. Ex 1005 at 10:8-16. However, the method of Darzynkiewicz is not limited to measuring the correlation of activated pRB with the presence of another protein. Rather, the disclosed method is generally applicable to measuring the concurrent correlation of two different proteins. Ex. 1005 at 10:8-16. One of skill in the art reading

Darzynkiewicz would understand the teaching of using distinguishable antibodies generally would include the use of activation state-specific antibodies. Ex. 1002 at ¶¶16-17. There is no change in the approach needed to use and detect a state-specific antibody compared to using and detecting a non-state-specific antibody. Ex. 1002 at ¶17.

Consistent with Darzynkiewicz's statement to analyze other proteins that participate in the regulation of the cell cycle, Yen teaches an assay that concurrently detects retinoblastoma protein (RB) in conjunction with activated ERK 1/2 to analyze the effect of these proteins on cell cycle regulation. Ex. 1006 at 3163. Yen also discussed the effect other MAPK proteins have on cell cycle regulation including MEK, RAS and RAF. *See e.g.,* Ex. 1005 at 3163. Yen teaches using activation state-specific antibodies that target the phosphorylated Thr^{183} and Tyr^{185} sites on active ERK proteins used in the cell cycle regulation of the HL-60 cell line, which is the same cell line used in Darzynkiewicz. Ex. 1005 at 11:12-18 and 24:47-65; Ex. 1006 at 3163; Ex. 1002 at ¶97. Both Darzynkiewicz and Yen induce the HL-60 cells with retinoic acid, which further indicates to one of skill in the art the complementary nature of the teachings of Darzynkiewicz and Yen. Ex. 1005 at 11:12-18; *see also* Ex. 1006 at 3163 and 3165; Ex. 1002 at ¶97.

Finally, Darzynkiewicz teaches that multiparametric flow cytometric techniques to concurrently detect two or more antibodies, including state-specific

antibodies, was known in the art and provided a reason to apply his method to proteins other than retinoblastoma:

> Present multiparametric flow cytometric techniques permit more than two antibodies to be discriminably detected in a single assay…In the methods of the present invention, these further antibodies may, *for example, be used to report, concurrently with the phosphorylation status of pRB, the concurrent levels of other proteins that participate in the regulation of the cell cycle*.

Ex. 1005 at 27:22-24; *see also id.* at 23:23-34; Ex. 1002 at ¶95.

Therefore, in light of the teachings of Darzynkiewicz and Yen, one of skill in the art would have been motivated to analyze the effects of cell cycle regulation by concurrently analyzing the activated state of retinoblastoma protein, ERK 1/2, MEK 1/2, or RAS using the multiparametric flow cytometric method of Darzynkiewicz. Ex. 1002 at ¶¶96 and 108.

Claim 1

a. 1. A kit comprising a first activation-state specific antibody and a second activation-state specific antibody and instructions for use of the antibodies,

Darzynkiewicz teaches "any one clinical laboratory may have only sporadic need to perform the assay, and there is thus a need for compositions and kits that permit the assay readily to be performed on an as-needed basis. Thus, in another

aspect, the present invention provides reagents and kits that permit the assay readily to be performed on an as-needed basis." Ex. 1005 at 39:28-40:2.

Darzynkiewicz teaches a method of detecting two different proteins in a single cell. Ex. 1005 at 10:13-16; Ex. 1002 at ¶94. While Darzynkiewicz uses retinoblastoma protein as its primary example to explain his method of detecting an activatable protein, the method of Darzynkiewicz can be used to detect the activation state of other activatable proteins. Ex. 1002 at ¶95; Ex. 1005 at 23:23-34 and 27:22-24.

In the same HL-60 cell line cited in Darzynkiewicz, Yen teaches detection of retinoblastoma protein in addition to the detection of activated ERK1/2. Ex. 1002 at ¶¶96-97; Ex. 1005 at 11:12-18 and 24:47-65; Ex. 1006 at 3163. This cell line also contains other proteins in the MAPK signaling pathway that help regulate the cell cycle, including MEK 1/2 and Ras. Ex. 1002 at ¶¶96-97; Ex. 1006 at 3163. As discussed above, one of skill in the art reading both Darzynkiewicz and Yen would be motivated to detect the activation state of two or more of these activatable proteins in order to better understand the correlation of the activation of these proteins as they regulate the cell cycle. Ex. 1002 at ¶96.

Finally, "instructions" on the use of antibodies constitutes printed matter that should not be given patentable weight to distinguish the claims over the prior art. *In re Ngai*, 367 F.3d at 1337–38. In the event providing "instructions" is limiting,

it would have been obvious to provide instructions with the kit to assist practitioners that "only sporadically need to perform the assay" and to provide detailed protocols for use of the antibodies. Ex. 1005 at 18:16-19; Ex. 1002 at ¶100.

b. wherein at least one of the antibodies is specific for a phosphorylation site, and

Darzynkiewicz only expressly discloses one state-specific antibody, pRB^{P-} mAb, which detects the underphosphorylated state of retinoblastoma susceptibility gene protein (abbreviated pRB in Darzynkiewicz). Ex. 1005 at 3:2-26; Ex. 1002 at ¶98. However, as discussed above, Darzynkiewicz teaches his method can be used to investigate other proteins that participate in the regulation of the cell cycle. One of skill in the art understands Darzynkiewicz's method can employ other state-specific antibodies to detect other cell cycle regulation proteins of interest. Ex. 1002 at ¶96.

Yen teaches an assay that, like Darzynkiewicz, analyzes the effect of intracellular signaling proteins on cell cycle regulation. In particular, Yen teaches measuring the level of activated ERK2. To perform these measurements, Yen conjugates an activation state-specific antibody, V6671 rabbit polyclonal antibody, to activated ERK 1/2. Ex. 1006 at 3165; Ex. 1002 at ¶98. This antibody binds to phosphorylated Thr183 and Tyr185 sites of active ERK2 proteins. *Id*. Moreover,

Yen teaches other proteins in the MAPK pathway effect cell cycle regulation including MEK and Ras. Ex. 1006 at 3163.

Therefore, it would have been obvious to one of skill in the art to use a second distinguishably labeled state-specific antibody in the method of Darzynkiewicz based on the teachings of Darzynkiewicz and Yen. For example, one of skill in the art could contact the cells with the activation state-specific antibody pRB^{P-} mAb taught by Darzynkiewicz and an activation state-specific V6671 rabbit polyclonal antibody for ERK 2 taught by Yen. Ex. 1002 at ¶98.

In addition, one of skill in the art would also understand that the teachings of Darzynkiewicz and Yen are not limited to these antibodies. It would have been obvious to use state-specific antibodies that were well known at the time of the invention which correspond to cell cycle regulation proteins in the MAPK pathway, such as anti-phospho-p44/42 MAPK (Thr202/Tyr204) to detect activated ERK 1/2 and anti-phospho-MEK1/2 (Ser217/221) to detect activated MEK1/2. Ex. 1002 at ¶¶22-24 and 99; *see also* Ex. 1008 at 5107-5108; Ex. 1010 at 39436.

At the time of the invention, utilizing appropriate activation state-specific antibodies within the methods of Darzynkiewicz would only require routine application of standard laboratory techniques. Ex. 1002 at ¶¶83 and 99**.**

c. wherein said first activation state-specific antibody binds to an activation form of a first protein within the MAPK (mitogen activated protein kinase), AKT (homolog of V-akt

murine thymoma viral oncogene), NFkB (nuclear factor kappa B), PKC (protein kinase C), STAT (signal transducers and activators of transcription) or WNT (Win gless/Int) signaling pathways,and

As discussed above, it would have been obvious in light of the teachings of Darzynkiewicz in view of Yen to use either anti-phospho-p44/42 MAPK (Thr202/Tyr204) to detect activated ERK 1/2 in the MAPK signaling pathway or to use anti-phospho-MEK1/2 (Ser217/221) to detect activated MEK1/2 which is also in the MAPK signaling pathway. Ex. 1002 at ¶¶22-24, 99 and 103.

d. said second activation state-specific antibody binds to an activation form of a second protein within the MAPK, AKT, NFkB, PKC, STAT or WNT signaling pathways, and

As discussed above, the method of Darzynkiewicz is not limited to the specific example of using pRB^{P-} mAb to detect unphosphorylated pRB, but as stated in Darzynkiewicz is applicable to measure the "concurrent levels of other proteins that participate in the regulation of the cell cycle." Ex. 1005 at 10:13-16; and 27:22-24 Ex. 1002 at ¶¶96-97.

As taught by Yen, another activation specific antibody is V6671 rabbit polyclonal antibody to detect activated ERK2. Ex. 1006 at 3165; Ex. 1002 at ¶98. In addition, Yen teaches that other proteins of interest that regulate the cell cycle in connection with RB include ERK, MEK and Ras. Ex. 1006 at 1363; Ex. 1002 at

¶¶96-97. For example, anti-phospho-p44/42 MAPK (Thr202/Tyr204) to detect activated ERK 1/2 and anti-phospho-MEK1/2 (Ser217/221) to detect activated MEK1/2 were commercially available by the time of the invention and could be used in the method of Darzynkiewicz. Ex. 1002 at ¶¶22-24 and 99; *see also* Ex. 1008 at 5107-5108; Ex. 1010 at 39436. Thus, it would have been obvious to one of skill in the art for either of these activation state-specific antibodies to be the claimed second antibody. Ex. 1002 at ¶99.

For example, if anti-phospho-p44/42 MAPK (Thr202/Tyr204) is the first activation state-specific antibody to detect activated ERK 1/2 then anti-phospho-MEK1/2 (Ser217/221) can be the second activation state-specific antibody to detect activated MEK1/2. Ex. 1002 at ¶100.

e. wherein said first and second proteins are different proteins.

As discussed above it would have been obvious in light of the teachings of Darzynkiewicz in view of Yen for the first activatable protein to be ERK 1/2 and for the second activatable protein to be MEK 1/2, which are different proteins. Ex. 1002 at ¶100.

Claim 2

2. The kit of claim 1, wherein said first and second protein are independently selected from the group consisting of:…, MAPK, …, RAS…,

Raf…, MEK[]1/2…, ERK[8] []1/2 …, NF-kB, … STAT1, STAT2, STAT3, STAT5 and STAT6.

Claim 1 is rendered obvious as discussed above. Darzynkiewicz in view of Yen teaches the first activatable protein can be ERK 1/2, and the second protein can be MEK 1/2. Ex. 1005 at 3163 and 3165; Ex 1002 at ¶¶86-87. Therefore, it would have been obvious to independently select ERK 1/2 and MEK 1/2 in light of the teachings of Darzynkiewicz in view of Yen. Ex 1002 at ¶¶86-87.

Claim 3

3. The kit of claim 1, wherein said first activation state-specific antibody binds to a phosphorylation form of a first protein and said second activation state-specific antibody binds to a phosphorylation form of a second protein.

Claim 1 is rendered obvious as discussed above. Darzynkiewicz in view of Yen teaches it would have been obvious to one of skill in the art to use activation state-specific antibodies to analyze the activated forms of ERK1/2 and MEK1/2.

[8] Claim 2 describes the acronym for ERK as Elk-related tyrosine kinase. One of ordinary skill in the art understands this description of ERK and the extracellular signal regulated kinase description for ERK are alternatives known in the art that are referring to the exact same ERK protein. Ex. 1002 at ¶86.

Ex. 1002 at ¶¶101-102. Both of these proteins activate due to phosphorylation. Ex. 1002 at ¶¶98 and 103.

Claim 4

4. The kit of claim 3, wherein said first activation state-specific antibody binds to a phosphorylation form of a first protein within the MAPK, AKT, NFkB, PKC or WNT signaling pathways and said second activation state-specific antibody binds to a phosphorylation form of a second protein within the MAPK, AKT, NFkB, PKC or WNT signaling pathways.

Claim 3 is obvious as discussed above. It would have been obvious to one of skill in the art to use Darzynkiewicz's method to use activation state-specific antibodies to analyze the activated forms of ERK1/2 and MEK1/2 which are both in the MAPK signaling pathway. Ex. 1002 at ¶¶101-103. Both of these proteins activate due to phosphorylation. Ex. 1002 at ¶¶98 and 103.

Claim 5

5. The kit of claim 4, wherein said phosphorylation state-specific antibodies are independently selected from the group consisting of:…, anti-phospho-p44/42 MAP kinase (Thr202/Tyr204),… anti-phospho-MEK1/2 (Ser217/221),…

Claim 4 is obvious as discussed above. It would have been obvious to one of skill in the art to use Darzynkiewicz's method to also analyze the phosphorylated

form of ERK1/2 using anti-phospho-p44/42 MAPK (Thr202/Tyr204) and to analyze the phosphorylated form of MEK1/2 using anti-phospho-MEK1/2 (Ser217/221). Ex. 1002 at ¶¶101-103.

Claim 6

6. The kit of claim 1, wherein said first and second activation state-specific antibodies are uniquely labeled.

Claims 1 is obvious as discussed above. Darzynkiewicz teaches contacting these cells with the proteins of interest with labeled antibodies. Ex. 1005 at 11:61-67 ("Next, the cells are labeled with antibodies conjugated to flow cytometrically detectable fluorophores."). The labels "are mutually distinguishable" and as "is well known in the art, there are a number of two-fluorophore combinations that permit concurrent and discriminable detection." *Id*. at 12:1-9; *see also id.* at 12:10-49 and 19:9-14 (giving examples of particular fluorophores that can be used in Darzynkiewicz's invention, including FITC and PE-CY5 available under the brand name CYCHROME®); *see also* Ex. 1001 at 31:9-53 (the '926 patent also cites to fluorescein and PECY5 as preferred fluorophores).

At the time of the invention, utilizing appropriate activation state-specific antibodies with the distinguishable labels and methods of Darzynkiewicz would only require routine application of standard laboratory techniques. Ex. 1002 at ¶¶99 and 104.

Claim 7

7. The kit of claim 6, wherein said first and second activation state-specific antibodies are independently labeled with a label selected from the group consisting of a fluorescent label, FRET (fluorescence resonance energy transfer) label and etag.

Claims 6 is obvious as discussed above. Darzynkiewicz teaches using a "flow cytometer/cell sorter" using "an argon laser (emission at 488nm)" to detect fluorescent labels such as FITC and PE attached to antibodies. Ex. 1005 at 44:25-29; Ex. 1002 at ¶104. In addition, one of skill in the art understood that multi-parametric flow cytometers were well-known at the time of the invention that could distinguish between different types of fluorescent labels concurrently, including detecting both FITC and PE using a single laser. Ex. 1002 at ¶¶104-105; *see also* Ex. 1005 at 27:22-24 and Ex. 1011 at 79 and 83.

In addition, Darzynkiewicz teaches using fluorescent labels to sort by FACS, and teaches some of his labels are "tandem" labels. Ex. 1005 at 8:29-33 and 26:9-24 (PE-CY5 "tandem resonance energy transfer fluorophore" and Per-CP-Cy5.5). One of skill in the art understands these tandem labels taught by Darzynkiewicz are examples of FRET labels that were known to be compatible with flow cytometry. Ex. 1002 at ¶¶104-105; *see also* Ex. 1012 at 168. Two tandem fluorophores known to be excitable by an argon laser and used in flow cytometry for multiparametric

analysis include PE-CY5 and PE-CY7. Ex. 1002 at ¶¶104 and 106; *see also* Ex. 1011 at 79 and 83.

Therefore, it would have been obvious to one of skill in the art at the time of the invention to use Darzynkiewicz's argon laser "flow cytometer/cell sorter" with anti-phospho-p44/42 MAPK labeled with either a fluorescent label (FITC) or a FRET label (Cy5PE) and anti-phospho-MEK1/2 labeled with either a fluorescent label (PE) or a FRET label (Cy7PE), and sort cells based on the detection of those signals. Ex. 1002 at ¶107. Using any combination of the above labels (FITC, PE, Cy5PE, and Cy7PE) could be accomplished using Darzynkiewicz's argon laser. Ex. 1002 at ¶106; see also Ex. 1011 at ¶¶79 and 83.

Claim 8

8. The kit of claim 6, wherein said first and second activation state-specific antibodies are labeled with a fluorescent label.

Claims 6 is obvious as discussed above. Darzynkiewicz teaches using a "flow cytometer/cell sorter," which is a fluorescent activated cell sorter (FACs), using "an argon laser (emission at 488nm)," to detect fluorescent labels such as FITC and PE attached to antibodies. Ex. 1005 at 44:25-29; Ex. 1002 at ¶104. At the time of the invention, multicolor FACS devices were well known to concurrently analyze and sort based on the detection of multiple fluorescent signals. Ex. 1002 at ¶104.

It would have been obvious to one of skill in the art to use a second fluorescent label with the method of Darzynkiewicz to detect a second protein. The argon laser as disclosed in Darzynkiewicz could excite both FITC and PE simultaneously. Ex. 1002 at ¶¶104-105; *see also* Ex. 1011 at 79 and 83.

Therefore, it would have been obvious to one of skill in the art at the time of the invention to include FITC labeled phospho-p44/42 MAPK (Thr202/Tyr204) and PE labeled anti-phospho-MEK1/2 (Ser217/221). Ex. 1002 at ¶107.

Claim 9

9. The kit of claim 6, wherein said first and second activation state-specific antibodies are labeled with a FRET label.

Claims 6 is obvious as discussed above. Darzynkiewicz teaches using fluorescent labels to sort by FACS, and teaches some of his labels are "tandem" labels. Ex. 1005 at 8:29-33 and 26:9-24 (PE-CY5 "tandem resonance energy transfer fluorophore" and Per-CP-Cy5.5). One of skill in the art understands these tandem labels taught by Darzynkiewicz are examples of FRET labels that were known to be compatible with flow cytometry. Ex. 1002 at ¶¶105-106; *see also* Ex. 1012 at 168. Two tandem fluorophores known to be excitable by an argon laser and used in flow cytometry for multiparametric analysis include PE-CY5 and PE-CY7. Ex. 1002 at ¶¶105-106; *see also* Ex. 1011 at 79 and 83.

Therefore, based on the teachings of Darzynkiewicz in view of Yen, it would have been obvious to one of skill in the art at the time of the invention to

use Cy5PE labeled anti-phospho-p44/42 MAPK and Cy7PE labeled anti-phospho-MEK1/2 and to sort cells based on the detection of those signals. Ex. 1002 at ¶¶106-107.

IX. CONCLUSION

In view of the foregoing, claims 1-9 and 11-12 of the '926 patent are not patentable over the prior art documents cited herein. The prior art documents teach the subject matter of the '926 patent in a manner establishing a reasonable likelihood that the Petitioner will prevail with respect to at least one of the claims challenged in this Petition as required by 35 U.S.C. § 314(a). Accordingly, Petitioner respectfully requests that Trial be instituted and claims 1-9 and 11-12 of the '926 patent be canceled.

October 4, 2016

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

I, the undersigned, certify that the above IPR Petition complies with the applicable type-volume limitations of 37 C.F.R. § 42.24(a)(i). Exclusive of the portions exempted by 37 C.F.R. §42.24(a), this IPR Petition, including footnotes, contains 11,525 words, as counted by the word count function of Microsoft Word. This is less than the limit of 14,000 words as specified by 37 C.F.R. §42.24(a)(i).

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CERTIFICATE OF SERVICE UNDER 37 C.F.R. § 42.6 (e)(4)

The undersigned hereby certifies that a copy of the **PETITION FOR INTER PARTES REVIEW**, all accompanying exhibits, and the **POWER OF ATTORNEY** has been served via Federal Express to the patent owner on October 4, 2016, upon the following: Bozicevic, Field & Francis LLP, 1900 University Avenue, Suite 200, East Palo Alto, CA 94303.

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