No. 2021-1969

IN THE

United States Court of Appeals

FOR THE FEDERAL CIRCUIT

UNIVERSITY OF MASSACHUSETTS, CARMEL LABORATORIES, LLC,

Plaintiffs-Appellants,

v.

L'ORÉAL S.A., L'ORÉAL USA, INC.,

Defendants-Appellees.

On Appeal from the United States District Court
for the District of Delaware
No. 1:17-cv-868, Hon. Colm F. Connolly

SECOND CORRECTED NONCONFIDENTIAL OPENING BRIEF OF APPELLANTS UNIVERSITY OF MASSACHUSETTS AND CARMEL LABORATORIES, LLC

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UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF INTEREST

Case Number 2021-1969

Short Case Caption University of Massachusetts v. L'Oreal S.A.

Filing Party/Entity Appellants University of Massachusetts and Carmel Laboratories, LLC

Instructions: Complete each section of the form. In answering items 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance. **Please enter only one item per box; attach additional pages as needed and check the relevant box**. Counsel must immediately file an amended Certificate of Interest if information changes. Fed. Cir. R. 47.4(b).

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Date: 10/11/2021

Signature: /s/ Jeffrey A. Lamken

Name: Jeffrey A. Lamken

1. Represented Entities. Fed. Cir. R. 47.4(a)(1).	**2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2).	**3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3).
Provide the full names of all entities represented by undersigned counsel in this case.	Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities. ☑ None/Not Applicable	Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities. ☐ None/Not Applicable
University of Massachusetts	None	Not applicable
Carmel Laboratories LLC	None	Teresian Carmelites, Inc.

☐ Additional pages attached

4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

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6. Organizational Victims and Bankruptcy Cases. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

☑ None/Not Applicable ☐ Additional pages attached

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This brief redacts materials that Defendants-Appellees designated as confidential under the protective order entered by the district court. The material omitted includes studies L'Oréal performed to assess the effectiveness of skincare products, internal descriptions of L'Oréal products, and documents relating to a French company's contacts with the United States and the subject matter of the suit. The redacted material appears on pages 13, 16-19, and 62-63.

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STATEMENT OF RELATED CASES

In accordance with Federal Circuit Rule 47.5, Plaintiffs-Appellants University of Massachusetts and Carmel Laboratories, LLC state that:

(a) there have been no other appeals in this case; and

(b) there are no other cases pending in this or any other court that will directly affect or be directly affected by this Court's decision in No. 2021-1969.

PRELIMINARY STATEMENT

For decades, L'Oréal has made billions promising to "enhance" customers' skin. The patents-in-suit—U.S. Patent Nos. 6,423,327 ("the '327 Patent") and 6,645,513 ("the '513 Patent")—claim treatments with an active ingredient that, when employed in accordance with the claims, do just that. Directing application of an "amount effective to enhance the condition of the skin," the patents identify and claim specific numerical concentrations of adenosine that are scientifically proven to be "effective." The patents also define what it means to "enhance" skin condition. "As used herein," the patents explain, "'enhancement of skin condition' means a ***noticeable decrease in the amount*** of wrinkling, roughness, dryness, laxity, sallowness, or pigmentary mottling in skin." And the patents explain techniques, well known in the art, for identifying such decreases in the amount of the listed conditions.

Recognizing the effectiveness of the claimed treatments, L'Oréal tried to patent them itself. But L'Oréal's application was initially rejected as obvious in view of the '327 Patent, which L'Oréal's application invoked to show adenosine's capacity to "improve skin condition." Eventually, L'Oréal abandoned its application. Having failed to secure a patent for itself, L'Oréal infringed the '327 and '513 Patents on a massive scale. Called to account for that infringement, L'Oréal attacked those patents as "indefinite." L'Oréal argued—and the district court held—that the

phrase "amount effective to enhance the condition of the skin" fails to provide reasonable notice of the content of the claims.

That conclusion cannot be reconciled with the patents or the law of this Circuit. The patents disclose and claim the "amounts" of adenosine—specific recited concentrations—that are "effective to enhance" skin condition. As the district court recognized, the patents also provide an explicit definition of "enhancement of skin condition"—a "***noticeable decrease in the amount*** of" specified conditions. That definition is clear: A "decrease" means a lowering or reduction. "Noticeable" means observable. The patents even disclose "well known" techniques for measuring and identifying noticeable decreases, from visual observation to the construction of physical molds that are subjected to computerized scanning and comparison. None of that is disputed.

The district court held the claims indefinite nonetheless, focusing on the specifications' disclosure that methods "well known in the art" for measuring reduction in the listed conditions "can include subjective evaluations." Without considering evidence of how skilled artisans would understand that language, the district court jumped to the conclusion that artisans would have to "guess about the opinions held by doctors, patients, and undefined others" to understand the patents' scope.

That ruling cannot be sustained. It divorces the phrase "amount effective to enhance the condition of the skin" from the patents' fundamental insight: They re-

cite and claim the ***specific adenosine concentrations*** to be applied to dermal cells that constitute the "amount effective to enhance" skin condition. Those amounts are definite—the patents set them forth as molar concentrations (10^{-3} to 10^{-7} M and 10^{-4} to 10^{-7} M). The patents recite evidence showing that those concentrations, when used according to the claims, are effective to enhance skin. Skilled artisans reading those disclosures would understand, with "reasonable certainty," the "amount effective to enhance the condition of the skin."

The district court's "subjective evaluations" theory was unsupported regardless. Skilled artisans could easily determine the therapeutically effective range. "[W]ell known in the art," any necessary evaluations do not turn on value judgments—judgments that are "in the eyes of the beholder." The patents simply disclose methods known to skilled artisans for identifying factual changes—movement in the amount of wrinkling, etc., from more to less—through observation. In dermatological and related arts, observation of the skin is an accepted, if not mandatory, part of evaluation. The district court's rejection of such observation defies the Supreme Court's instruction to construe patents "'having regard to their subject matter.'" *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 910 (2014). The district court's standard would effectively prohibit inventors from relying on well-accepted techniques in their fields.

Summary judgment here was improper unless every reasonable juror would be compelled to find that L'Oréal proved the claims indefinite by clear-and-convincing evidence. L'Oréal made no such showing. The district court ignored intrinsic and extrinsic evidence, including L'Oréal's own materials, that forecloses that burden from being met.

JURISDICTIONAL STATEMENT

The district court had jurisdiction under 28 U.S.C. §§ 1331 and 1338(a). On May 17, 2019, the district court dismissed L'Oréal S.A. for lack of personal jurisdiction, Appx00019-00022. On May 14, 2021, the district court entered final judgment of invalidity, Appx00017-00018, based on its April 20, 2021 opinion, Appx00001-00015, and order, Appx00016. On May 14, 2021, the University of Massachusetts and Carmel Laboratories, LLC timely filed a notice of appeal. Appx22542-22544. This Court has jurisdiction under 28 U.S.C. § 1295(a)(1).

STATEMENT OF THE ISSUES

1. Whether every reasonable juror would be compelled to find, by clear-and-convincing evidence, that the phrase "amount effective to enhance the condition of the skin" is indefinite under 35 U.S.C. § 112(b), despite explicit disclosure of the claimed quantities that are "effective," an express definition of "enhancement" (an observable "decrease in the amount of" specified conditions), and extensive evidence that skilled artisans would reasonably understand those terms.

2. Whether the district court had personal jurisdiction, or should have granted jurisdictional discovery, when a foreign defendant developed infringing products, unsuccessfully sought to patent its infringing formulation in the United States, and then entered "intracompany agreements" with a U.S. subsidiary to sell infringing products the foreign defendant developed.

STATEMENT OF THE CASE

I. TECHNOLOGICAL BACKGROUND

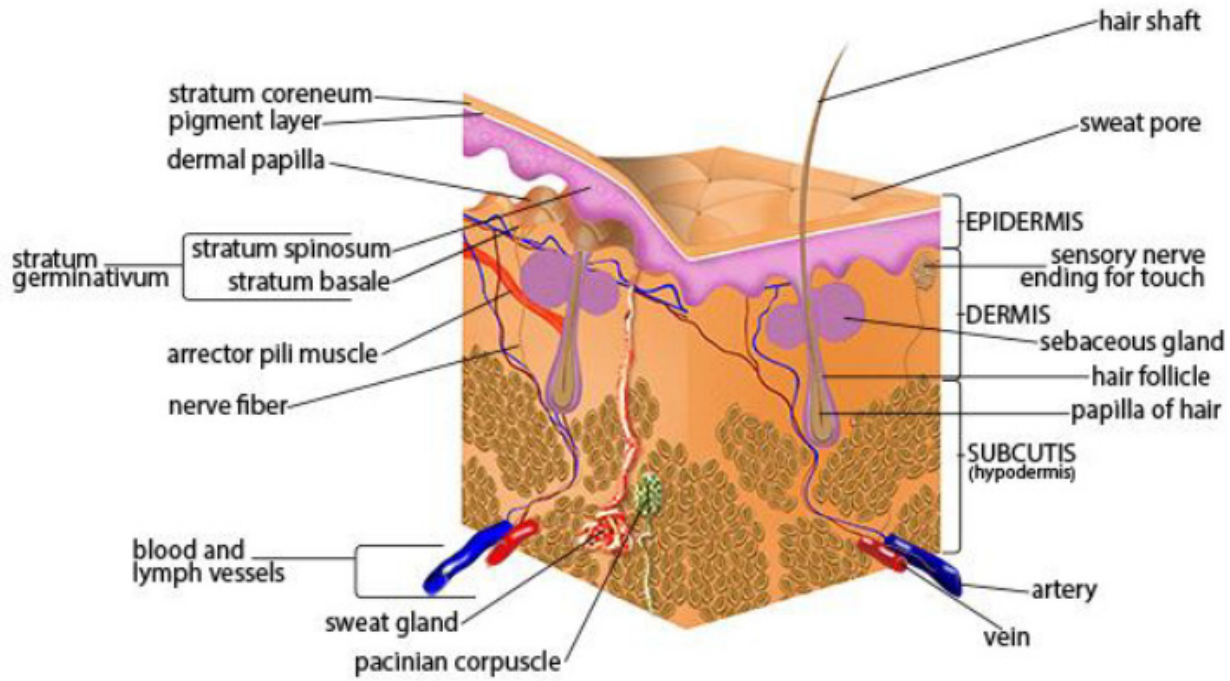
This case involves a leap forward in dermatology and cell biology—a technology clinically proven to reduce wrinkling and other specified skin conditions. Appx02655. Skincare products can treat skin two ways: They can prevent or reverse environmental damage to the epidermis, or address structural changes below that surface layer. In the late 20th century, artisans began considering adenosine (formerly a heart treatment) for skincare, but they focused on the epidermis. The art taught away from addressing lower layers of skin based on various concerns. The inventors, scientists at the University of Massachusetts Medical School, disproved those fears and discovered adenosine's revolutionary capacity to "improve skin condition" by treating skin's lower layers. Appx00266.

A. Skin and Skincare Products

Every year, consumers spend billions on products that "seek to tone down signs of ageing in the skin." Appx00265; *see* Appx01073-01074. Wrinkles, in particular, are consistently among the top cosmetic concerns. Appx12457.

Skin, however, is a complex organ. Some skin problems are caused when the epidermis is harmed by "[e]xogenous" factors, such as "UV-light and chemical irritants." Appx02710; Appx01074. Many skincare products thus focus on "protecting the skin from further damage, nourishing it, [and] stimulating renewal of" the epidermis. Appx01074.

But changes to skin layers beneath the epidermis are also a "major culprit in wrinkle formation." Appx01074.



Appx02870. The epidermis is supported by the dermis, a thicker layer of connective tissue that contains fibroblasts (which secrete collagen and strengthen skin) and elas-

tin (which provides elasticity). Appx02805; Appx00067(1:19-34).[1] As the epidermis sheds cells, new cells from the dermis rise to replace them. Appx00067(1:21-23). With age, however, the dermis produces fewer new cells, and cell function decreases. Appx00067(1:26-34). Those changes degrade the elastin network and reduce fibroblast collagen production, diminishing the skin's ability to "resist gravitational effects." Appx01074; Appx02710; Appx12457. Topical skincare products can have difficulty addressing those subsurface changes, but can use "penetration enhancers" to direct a portion of active ingredients to skin's dermal layer. Appx17370; Appx00069(5:12-16); Appx02877.

B. Limited Use of Adenosine in Skincare Before the Patents-in-Suit

Adenosine is a naturally occurring compound that regulates many physiological processes. Appx02963. In 1997—the patents' priority date—adenosine was indicated primarily for intravenous injection as a heart treatment. *Id.*; Appx19175.

The art that did indicate adenosine for skincare focused on treating the skin's outermost layer, the epidermis. Appx19175-19177. One reference explained that including cyclic adenosine monophosphate ("c-AMP") in "topical compositions" could "temporarily soothe and soften skin," identifying the epidermis as the "area to be treated." Appx14302. A German patent ("DE107") taught that adenosine could

[1] The '327 and '513 Patents share similar specifications and claims. For brevity, this brief cites to the '327 Patent where similar content appears in both.

improve skin's appearance by "enhancing cell proliferation" in the epidermis and relieving "symptoms of exogenous [*i.e.*, external] aging of the skin." Appx02720; *see* Appx02710; Appx14305-14306. And one article, "Hartzshtark," noted that c-AMP decreased indentation in "forehead skin," but "could only speculate on its possible role," noting that it might relate to "β_2 receptors . . . in the epidermis." Appx02918; Appx18105; *see* Appx18115 (describing prior art focused on benefits to "keratinocytes, which are epidermal cells").

The prior art did not teach the use of adenosine to combat what turns out to be a "major culprit in wrinkle formation"—changes in the dermal layer. Appx01074.[2] To the contrary, it taught away from applying "adenosine analogs" to dermal cells. U.S. Patent No. 5,371,089 recommended use of "kinetin," not adenosine, on dermal fibroblasts. Appx19179. It cautioned that, when "fibroblast cells are contacted with adenosine analogs," they "exhibit decreased growth rate and a change in morphology . . . characteristic of cytotoxic response," or "cell death." *Id.* The art thus taught that adenosine harmed dermal cells, and would not be expected to improve their function. Appx19180. And the "cell proliferation" recited in other art, such as DE107, Appx02710, Appx02720, Appx02727, created risks of "scarring, discoloration, and

[2] Hartzshtark "speculate[d]" that c-AMP might "stimulate[ ] the fibroblasts," a type of dermal cell, "to synthesize hyaluronic acid." Appx02918; Appx16445. But it is diminution in collagen and elastin that causes wrinkles. Appx01074.

. . . skin anomalies associated with hyperplasia." Appx02722, Appx02727. Thus, before the invention here, the only known "site of action" for adenosine was the epidermis. Appx18116.

C. Doctors Dobson and Ethier Discover the Use of Adenosine To Fight the "Major Culprit"

Dr. James G. Dobson, Jr., is a renowned cardiovascular physiologist and former Chair of the Department of Physiology at the University of Massachusetts Medical School. Appx00230. Dr. Dobson first began researching adenosine in the mid-1960s. *Id.* In the late 1990s, he and his colleague, Dr. Michael Ethier, discovered that application of certain concentrations of adenosine to dermal cells could reverse structural changes that cause wrinkles and other age-related skin conditions without causing cell proliferation. *Id.*; Appx00070(7:61-62, 8:21-22), Appx00071(9:5-22).

The inventors experimented with treating skin fibroblasts using specific adenosine concentrations and observed the effects on cell size, ability to synthesize DNA, and protein (including collagen) production. Appx00070(7:61-62, 8:21-22), Appx00071(9:5-23). They found that, when tested, adenosine concentrations within specific ranges produced statistically significant improvements in all three metrics. Appx00070(7:61-62, 8:21-22, 8:52-57), Appx00071(9:5-23); *see* Appx02883. The inventors' tests showed such striking results that "objective technicians along with the subjective patients had never seen . . . more healthy appearance of the skin." Appx14371(211:2-9).

When a topical composition is applied to the skin's surface, only a portion (if any) of its active ingredients penetrates to the dermal layer. Appx02877. For topical compositions with adenosine, the inventors determined that "a variety of methods known to those of ordinary skill in the art" could be used to accelerate "penetration of the adenosine into skin tissue" to reach the dermal layer. Appx00069(5:11-16). The inventors also identified alternative methods of administering adenosine to dermal cells, including a "transdermal patch" and other "oral, subdermal, intradermal, or intravenous" methods. Appx00069(5:18-26).

D. The '327 and '513 Patents

The inventors were awarded the '327 Patent on July 23, 2002, and the '513 Patent on November 11, 2003. Appx00064; Appx00073. Both have a priority date of October 26, 1997. *Id.*

The '327 Patent advances one independent claim:

> A method for enhancing the condition of unbroken skin of a mammal by reducing one or more of wrinkling, roughness, dryness, or laxity of the skin, without increasing dermal cell proliferation, the method comprising topically applying to the skin a composition comprising a concentration of adenosine in an amount effective to enhance the condition of the skin without increasing dermal cell proliferation, wherein the adenosine concentration applied to the dermal cells is 10^{-4} M to 10^{-7} M.

Appx00071(10:17-26). Claim 1 of the '513 Patent is identical, except that the "adenosine concentration applied to the dermal cells" expanded to "10^{-3} M to 10^{-7} M." Appx00081(10:17-26).[3]

The patents define skin-condition enhancement: "As used herein, 'enhancement of skin condition' means a noticeable decrease in the amount of wrinkling, roughness, dryness, laxity, sallowness, or pigmentary mottling in skin." Appx00067(2:35-37). The specifications state that "an amount that enhances skin condition" means a "therapeutically effective amount," Appx00067(2:38-40)—"preferably" a molar concentration of "10^{-3} M to 10^{-7} M," and most preferably "10^{-4} M." Appx00067 (2:14-16). The independent claims make application of those "effective" amounts to the dermal layer an express limitation, requiring a concentration of "10^{-4} M to 10^{-7} M" in the '327 Patent (Appx00071(10:17-26)) or "10^{-3} M to 10^{-7} M" in the '513 Patent (Appx00081(10:17-26)). Those concentrations re-

[3] The claims include the phrase "reducing one or more of wrinkling, roughness, dryness, or laxity of the skin," even though the specification defines "enhancement of skin condition" to have that meaning. Appx00067(2:35-37). That was a product of prosecution history. The PTO initially requested "correction and clarification" of the phrase "method of enhancing," which it deemed "vague because it is not clear as to enhance from what and to achieve what effect." Appx14587. In response, the inventors explained that "this phrase is not vague, because it is defined in the specification." Appx02686. In "the interests of moving this application towards allowance, and not for any reason related to patentability," the inventors also agreed to supplement the claim language. *Id.* The PTO accepted that response. Appx02693-02699, Appx02726.

flected the inventors' studies, which demonstrated that concentrations of adenosine ranging from 10^{-4} M to 10^{-7} M have profound effects on skin's structure when administered to dermal cells. Appx00066; Appx00070-00071(7:59-9:50).

The patents-in-suit explain that "[m]ethods of measuring improvements in skin condition" were "well known in the art." Appx00069(5:44-55). The specifications identify "skin topography measurements" as one such method. Appx00069(5:52-53). To take a "skin topography measurement," skilled artisans make "silicone rubber replicas" that "capture fine lines and wrinkles" on a "small area of skin." Appx00069(5:54-58). "[C]omputerized digital-image processing" is then used to measure the "area of deviation of skin surface features above and below an average central line," as well as "the difference between the maximum and minimum heights." Appx00069(5:58-67). When "skin treated with adenosine or an adenosine analog [is] compared to untreated skin," a "statistically significant decline" in topography measurements indicates "enhancement of skin condition." Appx00069(6:1-4); Appx14315. The specifications explain that measurement methods "well known in the art" also "can include subjective evaluations by the patient or a second party, e.g., a treating physician." Appx00069(5:48-52). Literature cited in the patents showed that such evaluations were not only scientifically accepted, but also produced results that, when subjected to statistical analyses, were consistent with objective methods. *See* Elise A. Olsen et al., *Tretinoin Emollient*

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Cream: A New Therapy for Photodamaged Skin, 26 J. AM. ACAD. DERMATOL. 215, 215-24 (1992), *cited* Appx00069(5:49-50).

Plaintiffs University of Massachusetts and Carmel Laboratories, LLC (collectively "UMass") are, respectively, the assignee and exclusive licensee of the '327 and '513 Patents. Carmel Laboratories is affiliated with the Teresian Carmelites, a charitable religious community of which Dr. Dobson was a member. Appx00230-00231. Carmel Laboratories licensed the patents-in-suit from the University to develop adenosine-based skincare products. Appx00232-00233.

II. L'ORÉAL INFRINGES AFTER UNSUCCESSFULLY ATTEMPTING TO PATENT THE SAME INVENTION

Defendant L'Oréal S.A. is a "leading producer and marketer of personal care products," including "skin care" products, which it distributes "worldwide" under "thousands of well-known brands." Appx00552. Headquartered in France, L'Oréal S.A. is L'Oréal USA's parent company. *Id.* L'Oréal S.A. description of intracompany agreement. Appx03949; Appx11647(138:22-139:4), Appx11649(145:13-146:10); Appx12138.

A. L'Oréal Attempts To Obtain a Patent Covering the Same Invention as the Patents-in-Suit

In 2001, researchers at L'Oréal S.A. began exploring use of adenosine in L'Oréal cosmetic products. *In vitro* testing showed that applying adenosine to dermal cell equivalents had positive effects at concentrations of "10 μM," *i.e.*,

10^{-5} M. Appx00267-00268; Appx04276-04277. In September 2003, L'Oréal S.A. launched "Vichy Myokine," a product containing adenosine, in Europe and Canada, but not the United States. Appx11940.

In late 2003, L'Oréal S.A. scientist Jean-Baptiste Galey applied for a U.S. patent covering a method for "relaxing the skin with adenosine." Appx00263. Dr. Galey identified "L'Oréal, Paris (FR)" as the application's assignee. Appx00263. The application cited the '327 Patent as evidence that adenosine would "improve skin condition and in particular combat lines, skin laxity, skin dryness and pigmentary blemishes." Appx00266. While the '327 Patent disclosed that adenosine increases dermal cell size and protein synthesis, Dr. Galey asserted that adenosine also had a "relaxing effect" on "contractile" dermal cells. *Id.* Dr. Galey sought to patent a method of using adenosine for "softening lines and/or relaxing the skin." *Id.*

The PTO initially rejected Dr. Galey's application, holding that the '327 Patent rendered it obvious. Appx00275-00287; Appx11940. The '327 Patent already disclosed using adenosine to enhance "the condition of skin in a mammal by reducing (softening) wrinkles, roughness, dryness, or laxity of the skin." Appx00278. Consequently, skilled artisans "would have been motivated to use the method of Dobson et al. to treat wrinkles or enhance skin or relax facial features with a composition comprising adenosine." Appx00280. The PTO rejected Dr. Galey's

attempts to distinguish the methods and concentrations of adenosine in the '327 Patent. Appx00281. Dr. Galey and L'Oréal later abandoned their application. Appx11940.

B. L'Oréal's Infringement Spree

Around the time Dr. Galey submitted his patent application in 2003, L'Oréal contacted Dr. Dobson about "collaboration and patent sharing relative to" the patents-in-suit. Appx11941. Dr. Dobson declined. *Id.* L'Oréal S.A. then marketed skin-enhancement products containing adenosine throughout Europe and Canada. *Id.*

L'Oréal USA first marketed such products in the United States in February 2009, over five years after L'Oréal S.A. released similar products overseas. Appx11940-11941. L'Oréal came to introduce approximately 150 products containing adenosine in the United States under brands such as L'Oréal Paris, Lancôme, Maybelline, Biotherm, Decléor, Garnier, Giorgio Armani, IT Cosmetics, Kiehl's, La Roche Posay, SkinCeuticals, Vichy, and Yves Saint Laurent. Appx12141-12148.[4]

L'Oréal advertises that those products cause noticeable decreases in wrinkling, roughness, dryness, laxity, sallowness, and discoloration. For example, it

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[4] L'Oréal's infringing products preempted Carmel Laboratories' efforts. Appx00230-00232. Carmel initially enjoyed a successful release of its adenosine product, Easeamine. Appx00231. But efforts to expand Easeamine in 2010 coincided with L'Oréal's release of infringing products. Appx00231-00233.

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touts that Kiehl's "Line-Reducing Eye-Brightening Concentrate" is "noted to diminish the appearance" of "wrinkles and fine lines" around the eyes. Appx15178. Lancôme advertises that its "Génifique Yeux" is "proven to reduce the appearance of fine lines, wrinkles, dark circles and dehydration." Appx15444. Kiehl's describes its "Powerful Wrinkle Reducing Cream" as a "visibly reparative treatment" that "helps strengthen skin's elasticity, an important factor to reduce the appearance of wrinkles." Appx15436. Kiehl's "Super Multi-Corrective Cream" with adenosine "addresses many visible signs of aging including loss of bounce and youthful contours, prominent lines and wrinkles, texture imperfections, and lackluster complexion." Appx15440. Garnier's "Miracle Anti-Fatigue Eye Gel Cream" promises that, "over time," "[d]ark circles appear less visible, eye area is tightened and looks younger." Appx15442.

L'Oréal supports such claims with "subjective evaluations." For example, the representations about Kiehl's "Line-Reducing Eye-Brightening Concentrate" rely on a "[c]linical study" conducted over "[redacted] weeks on study description," in which "results from the dermatologist assessments at the different evaluation times" showed description of study finding [redacted]. Appx15176-15178. Another study considered "clinical grading scores" and patient self-assessment questionnaires, finding both metrics demonstrated visibly improved wrinkles, firmness, and smoothness. Appx15518-15536.

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When UMass analyzed L'Oréal's adenosine products, it found they infringed the patents-in-suit. Using *in vitro* Franz cell-diffusion tests—the gold standard for evaluating skin penetration, Appx15340; Appx14241—UMass determined that 130 L'Oréal products applied adenosine to dermal cells in the concentrations claimed in the '327 and '513 Patents, Appx14246-Appx14249; Appx15340-15342, *i.e.*, "10^{-3} M to 10^{-7} M," Appx00081(10:17-26); Appx00071(10:17-26). Between 2011 and October 2018, those products had gross sales of dollar amount. Appx12066-12134. When Carmel Laboratories contacted L'Oréal about its infringement, a L'Oréal ***S.A.*** representative responded, Appx01160-01170, and came to the United States for a meeting.

III. PROCEEDINGS BELOW

On June 30, 2017, UMass filed this infringement action against L'Oréal S.A. and L'Oréal USA, Inc. Appx00049-00062. Because L'Oréal infringed after contacting Dr. Dobson to seek a patent-sharing arrangement, and after L'Oréal's own patent application was initially rejected as obvious over the '327 Patent, UMass's amended complaint alleged willful infringement. Appx00232, Appx00239.

A. The District Court Dismisses L'Oréal S.A. for Lack of Personal Jurisdiction

On October 16, 2017, L'Oréal S.A. (the French parent) moved to dismiss for lack of personal jurisdiction, Appx00521-00522, relying on a declaration from Roy Rabinowitz, a Senior Vice President of Finance for L'Oréal USA, Appx00551-

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00554.[5] Mr. Rabinowitz asserted that, although L'Oréal USA executes "written intracompany agreements" with L'Oréal S.A. to "engage in the sale of goods or services," it "operates independently from its parent." Appx00553. L'Oréal S.A., he asserted, "does not directly develop, sell, market, or advertise to consumers in Delaware any of the products at issue in this action." *Id.*

The evidence showed, however, that L'Oréal S.A. acts as the "nerve centre" for the broader L'Oréal Group, including L'Oréal USA and all other L'Oréal S.A. subsidiaries. Appx00692. L'Oréal USA, moreover, serves as the L'Oréal Group's "agent in the United States." Appx00693. Despite L'Oréal's assertions that L'Oréal S.A. "does not directly develop" any of the accused products "to consumers in Delaware" [*sic*], L'Oréal S.A. credits its French researchers with developing its earliest products containing adenosine, Appx01090-01092, which were later introduced in the United States.

Discovery eventually revealed that, under the "written intracompany agreements" to which Mr. Rabinowitz alluded, Appx00553, L'Oréal S.A. [redacted] description of intracompany agreement [redacted] Appx03949; Appx11647(138:22-139:4), Appx11649(145:13-146:10); Appx12138. Formulations for many of

[5] L'Oréal USA also unsuccessfully moved to dismiss for failure to state a claim. Appx00351-00353, Appx00022.

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L'Oréal USA's products, particularly brands like Lancôme, were product description. Appx03765-03772; Appx03241-03272. L'Oréal's official ingredient lists for those products reflect that the formulations are product description Appx03075; Appx03144-03156. Description of intracompany agreement, Appx03942-03943, Appx03951-03952, Description of intra-company agreement, Appx03950.

On November 13, 2018, the magistrate judge issued a report recommending that L'Oréal S.A. be dismissed for lack of personal jurisdiction. Appx00023-00048. The magistrate ruled that the record did not show that "L'Oréal S.A. introduced the Accused Products into the stream of commerce." Appx00041. Citing the Rabinowitz declaration, the magistrate concluded that L'Oréal USA was not L'Oréal S.A.'s agent with respect to the infringement. Appx00044. Although the broader L'Oréal Group identified L'Oréal USA as its agent, the magistrate ruled L'Oréal USA could act as an agent for some purposes, but not others. Appx00045.

The magistrate refused jurisdictional discovery. Appx00046-00047. The magistrate acknowledged that jurisdictional discovery is warranted unless a plaintiff's claim is "clearly frivolous," but asserted that UMass had failed to allege "with reasonable particularity facts showing that L'Oréal S.A. might be subject to

personal jurisdiction." *Id.* Over objection, the district court adopted the magistrate's recommendation. Appx00019-00022.

B. L'Oréal Unsuccessfully Seeks *Inter Partes* Review

L'Oréal USA petitioned for *inter partes* review to challenge the validity of the patents-in-suit. Appx02798-02837. The PTAB refused to initiate review. Appx-02816, Appx02836. L'Oréal USA had urged that both patents should be construed to require the "concentration of adenosine ***in the composition*** that is ***topically applied***" to fall within the ranges recited in claim 1 (*i.e.*, that the adenosine concentration ***in the topical composition*** be 10^{-3} M to 10^{-7} M). Appx02805 (some emphasis added); *see* Appx02825.[6] The PTAB rejected that reading as foreclosed by claim 1's clear text.

Claim 1, the PTAB explained, clearly states that the recited concentration of adenosine is "applied to the dermal cells." Appx02806, Appx02832. The patents' specifications, moreover, "expressly contemplate[d] that adenosine will penetrate the skin" and reach dermal cells. Appx02808, Appx02828. The PTAB rejected L'Oréal USA's argument that construing claim 1 consistent with its plain terms—as referring to the concentration applied to "dermal cells"—would render it anticipated or obvious. Appx02812-02815, Appx02833-02836. None of the cited prior art

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[6] L'Oréal pursued this reading because the adenosine in its topical compositions exceeds 10^{-3} M.

provided "evidence reflecting the concentration of adenosine applied to the dermal cells." Appx02813-02815; Appx02833-02836.

C. The District Court's Decision

1. At claim construction, the district court likewise rejected L'Oréal's view that—while the claims recite the adenosine concentration "applied to ***the dermal cells***"—the claims should be construed to specify the concentration "applied ***to the skin*** containing the dermal cells." Appx03673, Appx03700 (emphasis added). Finding the claim language "plain and . . . unambiguous," the court ruled that the recited concentration refers to the adenosine applied to dermal cells, not the skin's outer layer. Appx03719-03720; *see* Appx03739. The concentration "applied to the dermal cells," the court explained, is the concentration "effective to enhance the condition of the skin." Appx03720(57:12-20). In both patents, the court observed, the concentration applied to dermal cells "is referring back" to the therapeutically effective amount expressly recited as a claim limitation. Appx03720(57:14-20). The written description, moreover, "makes it clear that there is a penetration of the concentration from the epiderm[is] through the skin to reach the dermal cells." Appx03721(58:8-10). The adenosine concentration that reaches the dermal cells and enhances skin condition thus is the portion of the topical composition that penetrates through to the dermis.

2. In April 2021—two months before the scheduled jury trial, *see* Appx22589, and after the parties had fully submitted pretrial materials—the district court granted L'Oréal USA summary judgment on invalidity. Appx00001-00015. The court ruled that the phrase "amount that is effective to enhance the condition of the skin" was indefinite. Appx0009-00015; Appx00016.

a. The court did not disagree that the claims specify the amounts to be applied to dermal cells—specifically "10^{-4} M to 10^{-7} M" (in the '327 Patent) or "10^{-3} M to 10^{-7} M" (in the '513 Patent). Nor did the district court deny that, at claim construction, it had interpreted the adenosine concentration "applied to the dermal cells" to "refer[] back to the concentration" that is "effective to enhance the condition of the skin." Appx03720(57:14-20). For indefiniteness, however, the district court distinguished the adenosine concentration "applied to the dermal cells" from the "amount effective to enhance" skin condition. Appx00007-00010. The amount effective to enhance skin condition, the court declared, "does not mean 'a concentration of the recited amount of adenosine.'" Appx00010. It based that conclusion not on intrinsic or extrinsic evidence, but instead a pages-long quotation from UMass's claim-construction brief. Appx00008-00009. That passage explained only that the adenosine "applied to the dermal cells" would be some portion of the amount "topically applied to the skin." *Id.*

The district court did not address the evidence—in the specifications of both the '327 and '513 Patents, Appx00070-00071(7:59-9:50)—that the claimed adenosine concentrations are amounts effective to enhance skin condition under the patents' definition, *i.e.*, to "noticeabl[y] decrease . . . the amount of wrinkling, roughness, dryness, laxity, sallowness, or pigmentary mottling in skin," Appx00067(2:35-37). Even L'Oréal's expert, Dr. Kasting, acknowledged that the patents recited evidence that skilled artisans would understand as showing that the claimed amounts of adenosine are therapeutically effective to enhance skin. Appx02883 (citing Appx00069-00071(6:14-9:50)). Nor did the district court identify evidence that products within the patents' scope are not effective to enhance skin condition as that phrase is defined in the patent.

b. Having denied the import of the patents' specified concentration ranges, the district court conducted a *sua sponte* inquiry into the potential meaning of "amount that is 'effective to enhance the condition of the skin.'" Appx00010. The court conceded that the patents provided an express definition: They "define 'enhancement of skin condition' to mean 'a noticeable decrease in the amount of wrinkling'" and other listed physical skin conditions. Appx00011-00012 (quoting Appx00067(2:35-37), Appx00069(5:44-48)). The district court admitted that "[m]ethods of measuring improvements in skin condition are well known in the art." Appx00012 (quoting Appx00069(5:48-52) (alteration in original)). As the patents

explained, "[o]bjective methods can include skin topography measurements," which involve creating silicone-rubber replicas of small skin areas and "analyz[ing]" them "using computerized digital image processing to provide an objective measurement" of surface variations. Appx00069(5:52-60). "A statistically significant decline" in measurements "compared to untreated skin indicates an enhancement of skin condition." Appx00069(6:1-4).

The district court, however, focused on the patents' disclosure that the "[m]ethods of measuring improvements in skin condition" that are "well known in the art . . . can include subjective evaluations by the patient or a second party, e.g., a treating physician." Appx00012 (quoting Appx00069(5:48-52)). It interpreted "subjective evaluations" to include "purely subjective evaluations of one or more persons." Appx00012. "Accordingly, even if I were to construe the skin enhancement limitation as the term is defined in the written descriptions," the court declared, "the asserted claims would be indefinite." Appx00012-00013. In the court's view, because the claims tolerated "subjective evaluations" that were "well known in the art," skilled artisans identifying effective amounts "would have to guess about the opinions held by doctors, patients, and undefined others with respect to the qualities and desirability of skin conditions." Appx00014.[7]

[7] The district court viewed the inventor, Dr. Dobson, as having conceded that subjective evaluations are permissible, citing his testimony that—when experimenting

Having found that describing assessments as "subjective" renders the claims indefinite, the court did not address how skilled artisans would understand the claims or the art. UMass's expert, Dr. Michniak-Kohn, explained that skilled artisans would understand the patents' definition of enhancement "to mean improvement of the skin on one or more desired metrics, as assessed by well-established standards for determining skin improvement." Appx14314. She identified exemplary methods known in the art, as well as "publications and other patents" explaining them. *Id.* And she cited "[c]omparative studies" that showed "correlation between assessments performed using different metrics." *Id.* Finally, she noted that, notwithstanding the existence of multiple evaluation scales, L'Oréal "frequently makes claims about its products' ability to enhance" skin condition. Appx14315; *see* pp. 15-16, *supra*. By contrast, L'Oréal expert Dr. Kasting cited articles asserting that, because subjective "evaluation scales varied between investigators, it was difficult to relate different studies to each other," and their "degree of inter-observer agreement and repeatability was not high." Appx14179-14180.

The district court never mentioned the dispute between Dr. Kasting and Dr. Michniak-Kohn. It noted only that Dr. Michniak-Kohn did not deny that a "subjec-

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with adenosine on his own skin—he observed "a diminution of fine lines and wrinkles" such that the effective amount would "have satisfied the patent claims." Appx00013.

tive assessment may be used to determine whether the condition of the skin has been enhanced." Appx00013-00014. According to the district court, the specifications' mention of subjective methods that are "well known in the art" itself was sufficient to warrant summary judgment. Appx00012-00014.[8]

SUMMARY OF ARGUMENT

II. A. The Patent Act requires claims to provide skilled artisans such certainty about the invention's scope as is reasonable in view of the art and the invention. The phrase "amount effective to enhance the condition of the skin" provides adequate certainty for multiple, independent reasons.

B. First, the claims recite the adenosine concentrations that, when applied to dermal cells, constitute an "amount effective to enhance the condition of the skin"—*i.e.*, amounts that noticeably decrease wrinkles and other listed conditions. In particular, the claims' "wherein" clause specifies the numerical ranges of adenosine—10^{-3} to 10^{-7} M and 10^{-4} to 10^{-7} M. That leaves no uncertainty. The specifications, moreover, define those concentrations as "therapeutically effective

[8] L'Oréal USA separately moved for summary judgment on the theory that the term "adenosine concentration applied to the dermal cells" was indefinite. Appx11746-11747. The parties' experts disputed how skilled artisans would interpret that term. Dr. Michniak-Kohn cited specific methods for measuring "dermal penetration" that were "widely used," identifying contemporaneous sources that explained those methods. Appx15038-15039. The district court ultimately denied that motion (along with all other pending motions) as moot. Appx00017.

amount[s]." And the specifications recite evidence that skilled artisans would understand as showing that those concentrations are therapeutically effective. The patents clearly inform skilled artisans of the specific adenosine concentrations that, when applied to the dermal cells, fall within the claims.

The district court's distinction between an "enhancement limitation" and the "recited concentration" of adenosine misreads the claims. The patents simply make clear that topical compositions may include (comprise) more than the recited amount of adenosine to ensure that the claimed concentrations reach the dermal cells. The district court accepted that interpretation at claim construction.

C. Second, apart from the recited concentrations, the patents define "enhancement of skin condition" to mean a "noticeable decrease" in "the amount of wrinkling, roughness, dryness, laxity, sallowness, or pigmentary mottling in skin." That definition is clear. A "decrease" in amount means a reduction. And "noticeable" means observable "by the normal human eye," providing "an objective baseline through which to interpret the claims." *Sonix Tech. Co. v. Publications Int'l, Ltd.*, 844 F.3d 1370, 1378 (Fed. Cir. 2017). Skilled artisans thus can determine the amounts that, when applied to dermal cells, are therapeutically effective to produce those effects. L'Oréal has done so: It advertises its products as decreasing the listed conditions. The specifications disclose methods "well known in the art" for measuring changes in listed conditions.

The district court held the claims indefinite because the patents acknowledge that methods "well known in the art" for measuring wrinkles and other conditions "can include subjective evaluations." But such "subjective evaluations" do not involve the type of "value judgment" that runs afoul of § 112(b). *Sonix*, 844 F.3d at 1378. Beauty may be in the eye of the beholder, but amounts are not. Here, the claims recite concentrations effective to "decrease . . . the amount" of specified skin conditions. The decrease in amount is observable. That is why visual inspections are well accepted in cosmetic dermatology (and other fields). The district court's criticism of "subjective evaluations" "well known in the art" would require the patents to meet a standard higher than the art they practice. That is not the law, as the Supreme Court and this Court have repeatedly emphasized.

D. Summary judgment, moreover, would be appropriate only if every reasonable juror would be compelled to find L'Oréal proved indefiniteness by clear-and-convincing evidence. A wealth of evidence, including L'Oréal's own advertisements, precludes L'Oréal from meeting that demanding burden. UMass's expert explained how skilled artisans would understand the amounts of adenosine "effective to enhance the condition of the skin." L'Oréal advertises its adenosine compositions as effective to "diminish the appearance" of "wrinkles and fine lines," basing its representations on "subjective evaluations." That proof demonstrated that skilled artisans—indeed, L'Oréal itself—would know with reasonable certainty the

adenosine concentrations "effective to enhance the condition of the skin" under the patents' definition. The district court did not and could not rule that every reasonable juror would be compelled to find the opposite by clear-and-convincing evidence.

III. The district court erred by dismissing L'Oréal S.A. for lack of personal jurisdiction. UMass's pre-discovery evidence showed that L'Oréal S.A. developed products containing adenosine with knowledge of the patents-in-suit, sought to patent them in the United States, and entered agreements with a U.S. subsidiary it controlled to manufacture and sell infringing products in the United States. Such purposeful direction of infringing products renders the exercise of personal jurisdiction reasonable and fair. At a minimum, UMass was entitled to jurisdictional discovery. And merits discovery UMass ultimately did obtain established personal jurisdiction over L'Oréal S.A.

ARGUMENT

I. STANDARD OF REVIEW

Under Third Circuit precedent, decisions granting summary judgment are reviewed "de novo, applying the same standard as the district court." *SRI Int'l, Inc. v. Cisco Sys., Inc.*, 930 F.3d 1295, 1306 (Fed. Cir. 2019). Summary judgment is appropriate only when, viewing "the facts and evidence . . . in the light most favorable to the nonmoving party," "'there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law.'" *Razak v. Uber Techs.,*

Inc., 951 F.3d 137, 144 (3d Cir. 2020). District courts thus cannot resolve genuine factual disputes against the non-moving party on summary judgment. *Rosen v. Bezner*, 996 F.2d 1527, 1530 n.2 (3d Cir. 1993).

Indefiniteness determinations about "governing legal standards and . . . intrinsic evidence" are reviewed de novo, *BASF Corp. v. Johnson Matthey Inc.*, 875 F.3d 1360, 1365 (Fed. Cir. 2017), including "conclusions relating to the meaning of the intrinsic evidence, and whether it conveys claim meaning with reasonable certainty," *Sonix*, 844 F.3d at 1376. While factual findings about extrinsic evidence are ordinarily reviewed for clear error, *BASF*, 875 F.3d at 1365, district courts may not resolve genuine factual disputes on summary judgment, *Rosen*, 996 F.2d at 1530 n.2.

A district court's conclusion on personal jurisdiction is a question of law subject to review without deference. *LSI Indus. Inc. v. Hubbell Lighting, Inc.*, 232 F.3d 1369, 1371 (Fed. Cir. 2000). A denial of jurisdictional discovery is reviewed "for abuse of discretion, applying the law of the regional circuit." *Autogenomics Inc. v. Oxford Gene Tech. Ltd.*, 566 F.3d 1012, 1021-22 (Fed. Cir. 2009).

II. THE PHRASE "AMOUNT EFFECTIVE TO ENHANCE THE CONDITION OF THE SKIN" IS NOT INDEFINITE

Because L'Oréal must prove indefiniteness by "clear and convincing evidence," *BASF Corp. v. Johnson Matthey Inc.*, 875 F.3d 1360, 1365 (Fed. Cir. 2017); *Biosig Instruments, Inc. v. Nautilus, Inc.*, 783 F.3d 1374, 1377 (Fed. Cir. 2015), its burden on summary judgment is particularly "heavy," *Tillotson, Ltd. v. Walbro*

Corp., 831 F.2d 1033, 1036 (Fed. Cir. 1987). It must "submit such clear and convincing evidence of facts underlying invalidity that no reasonable jury could find" L'Oréal failed to meet that clear-and-convincing burden. *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1340 (Fed. Cir. 2010); *see Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1353 (Fed. Cir. 2003) (showing so compelling "that no reasonable jury could have failed to conclude that [defendant's invalidity] case had been established by clear and convincing evidence"). When the patent examiner has considered the "basis for the validity challenge during patent prosecution," that already "heavy" burden "becomes particularly heavy." *Impax Labs., Inc. v. Aventis Pharms., Inc.*, 545 F.3d 1312, 1314 (Fed. Cir. 2008). L'Oréal did not come close to meeting that burden here.

A. The Patent Act Requires Only Such Definiteness as Is Reasonable Given the Relevant Art and Invention

Under the Patent Act, the claims must "particularly point[] out and distinctly claim[] the subject matter which the inventor . . . regards as the invention." 35 U.S.C. § 112(b). That requirement "entails a 'delicate balance.'" *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 909 (2014) (quoting *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 731 (2002)). A "patent must be precise enough to afford clear notice of what is claimed." *Id.* But the "inherent limitations of language" make some "modicum of uncertainty" the "'price of ensuring the appropriate incentives for innovation.'" *Id.* (quoting *Festo*, 535 U.S. at 732). As a

result, the "certainty which the law requires in patents is not greater than is reasonable, having regard to their subject-matter." *Id.* at 910 (quoting *Minerals Separation, Ltd. v. Hyde*, 242 U.S. 261, 270 (1916)).

Because that analysis adopts the perspective of "those of skill in the art," *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1371 (Fed. Cir. 2014), no "technical measure" is required, *One-E-Way, Inc. v. Int'l Trade Comm'n*, 859 F.3d 1059, 1066 (Fed. Cir. 2017). To the contrary, claim "'language employing terms of degree'" has "'long been found definite where it provided enough certainty to one of skill in the art when read in the context of the invention.'" *Sonix Tech. Co. v. Publications Int'l, Ltd.*, 844 F.3d 1370, 1377 (Fed. Cir. 2017). "Expressions quite as indefinite as 'high' and 'substantial'" are "sufficient." *Eibel Process Co. v. Minn. & Ont. Paper Co.*, 261 U.S. 45, 66 (1923); *see Sonix*, 844 F.3d at 1376 ("visually negligible"); *Exmark Mfg. Co. Inc. v. Briggs & Stratton Power Prods. Grp., LLC*, 879 F.3d 1332, 1346-47 (Fed. Cir. 2018) ("elongated and substantially straight").

The claims of the '327 and '513 Patents, which require an "amount effective to enhance the condition of the skin," easily meet those requirements. "'[E]ffective amount'" is a "common and generally acceptable term" and "is not ambiguous or indefinite" if skilled artisans can "determine the specific amounts without undue experimentation." *Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373,

1383-84 (Fed. Cir. 2003); *see Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 334 F.3d 1274, 1277-78 (Fed. Cir. 2003). No undue experimentation would be required here.

First, the claims set forth numerical adenosine concentrations as express limitations. Those concentrations *are* the "amount effective to enhance the condition of the skin." That straightforward reading of the claims provides numerical measures that clearly inform skilled artisans of the claimed invention's scope.

Second, skilled artisans can identify the effective amount of adenosine to enhance skin regardless. "[E]nhancement of skin condition" means a "noticeable decrease in the amount of wrinkling, roughness, dryness, laxity, sallowness, or pigmentary mottling in skin." Appx00067(2:35-37). That, too, is definite: A "decrease" means a lessening in amount. Even if "[b]eauty . . . is 'in the eyes of the beholder,'" Appx00011, ***amount*** is not. A decrease in amount is an observable phenomenon, not a value judgment. The patents-in-suit identify methods "well known in the art" that permit skilled artisans to measure such decreases with reasonable certainty. Appx00069(5:48-6:13).

Even if that intrinsic evidence did not settle the matter, expert testimony and other extrinsic evidence precluded summary judgment. The district court did not even consider that evidence.

B. The Patents Specify an Exact Concentration of Adenosine Proven To Enhance Skin

1. *The Recited Adenosine Concentrations Are Amounts Effective To Enhance Skin*

The phrase "amount effective to enhance the condition of the skin" is not indefinite, as skilled artisans would understand the claims themselves to specify that "amount" in clear, numerical terms. Claim 1 recites a "composition comprising a concentration of adenosine in an amount effective to enhance the condition of the skin without increasing dermal cell proliferation, ***wherein the adenosine concentration applied to the dermal cells is***" either "***10^{-4} M to 10^{-7} M***" (for the '327 Patent, Appx00071(10:22-26) (emphasis added)), or "***10^{-3} M to 10^{-7} M***" (for the '513 Patent, Appx00081(10:22-26) (emphasis added)). Those are the amounts the inventors disclosed and proved to be "effective to enhance the condition of the skin" when applied to the dermal cells. Appx00071(10:23-24). Because the claims themselves recite the specific numerical "concentration" of adenosine that is effective to enhance the skin—"10^{-4} M to 10^{-7} M" for the '327 Patent and "10^{-3} M to 10^{-7} M" for the '513 Patent—they are as definite as definite could be.

The specifications confirm that conclusion. Both patents identify the "therapeutically effective amount of adenosine" as "preferably 10^{-3} M to 10^{-7} M"—a range that includes the amounts recited in claim 1—and "most preferably" "10^{-4} M." Appx00067(2:14-17). They explain that "'therapeutically effective amount' of

adenosine" "means an amount that enhances skin condition." Appx00067(2:38-40). And both patents recite experimental evidence ***proving*** that application of those "therapeutically effective" amounts to dermal cells increases their size and improves DNA and protein synthesis, thereby enhancing skin condition. Appx00070-00071(7:49-9:50). The "amount" of adenosine "effective to enhance the condition of the skin" is thus the recited numerical concentration range.

Even L'Oréal's expert, Dr. Kasting, recognized the connection between the recited concentrations and the amount effective to enhance skin condition. He agreed that skilled artisans would understand the "experimental work" the patents set forth "to disclose that certain alleged benefits could be obtained" when "adenosine at concentrations of 10^{-4} or 10^{-6} M" is applied to dermal cells. Appx02883 (citing Appx00069-00071(6:14-9:50)); *see* Appx02884; Appx00076. Skilled artisans thus have no need to speculate about whether compositions that apply the recited adenosine concentrations to dermal cells contain "an amount" of adenosine "effective to enhance the condition of the skin." The claim limitations, the patents' definitions, and the disclosed experimental evidence provide all necessary information.

Indeed, the effectiveness of applying adenosine to dermal cells in those concentrations is the essence of the invention. The inventors "discovered that adenosine stimulates DNA synthesis, increases protein synthesis, and increases cell size" when

applied to dermal cells in specified amounts. Appx00067(1:37-39). "Based on this discovery, the invention provides methods and compositions for enhancing the condition of skin." Appx00067(1:39-41). The patents claim a method of "topically applying to the skin a composition comprising a concentration of adenosine in an amount effective to enhance the condition of the skin," "***wherein*** the adenosine concentration applied to the dermal cells" falls within the ranges set forth in the claims—10^{-4} to 10^{-7} and 10^{-3} to 10^{-7} M—and disclosed as "therapeutically effective" amounts. Appx00071(10:25-26) (emphasis added); *see* Appx00081(10:25-26); *see also* Appx00067.

As a result, this case is controlled by *Griffin v. Bertina*, 285 F.3d 1029, 1033-34 (Fed. Cir. 2002). In *Griffin*, the Court addressed the significance of "wherein" clauses in the context of a method for measuring thrombosis risk. After specifying manipulative steps, the claim recited "wherein the presence of said point mutation in said test nucleic acid indicates an increased risk for thrombosis." *Id.* at 1031. The Court held that "wherein" clause "relate[s] back to and clarif[ies] what is required by the [claims]." *Id.* at 1033-34. That was particularly clear because the correlation between the point mutation and diagnosing increased thrombosis risk was "the essence of th[e] invention." *Id.* at 1033.

The same considerations compel the same result here. Here, the "wherein" clause gives "meaning" to the prior "amount effective to enhance" limitation, speci-

fying the concentrations that are effective to enhance skin condition. Here, as in *Griffin*, it thereby "relate[s] back to and clarif[ies] what is required by" the limitations that precede it. 285 F.3d at 1033-34. Here, as in *Griffin*, it sets forth the "essence of th[e] invention"—the amounts that, when applied to dermal cells, result in the desired enhancements. The district court initially recognized as much. At claim construction, it agreed that the "wherein clause is defining . . . the concentration as it is applied to the dermal cells, and it ***is referring back to the concentration that is in an amount effective to enhance the condition of the skin***." Appx03720(57:14-19) (emphasis added). Claim 1 is thus definite: The recited "adenosine concentration applied to the dermal cells" in claim 1 ***is*** the "amount effective to enhance the condition of the skin." *See* Appx00070-00071(7:59-9:50); Appx00066.

Extrinsic evidence supports that construction. Experts from both sides understood "from the specification" that compositions that apply the recited adenosine concentration to the dermal cells "are effective" to improve skin condition, decreasing the amount of wrinkles and other listed conditions. *Compare* Appx13517 *with* Appx14296. Indeed, when L'Oréal conducted *in vitro* testing for its anticipation arguments in this litigation, it analyzed ***only*** whether the recited adenosine concentrations penetrated to dermal cells, without examining whether they also

enhanced skin condition within the claims' meaning. Appx13654-13657.[9] L'Oréal declined to conduct such testing because the answer was obvious, as the evidence disclosed in the patents make clear.

2. *The District Court Based Its Interpretation on a Misreading of UMass's Claim-Construction Briefing*

The district court reached the opposite result by reading the so-called "skin enhancement limitation" to be "distinct from and independent of the recited concentration range limitation." Appx00007. Thus, in the district court's view, claim 1 identifies ***two*** separate adenosine concentrations—one that enhances the skin, and one that is the specified concentration applied to dermal cells. That interpretation divorces the claims from the inventors' insight—that the application of specified concentrations to dermal cells produces the desired effects. It cannot be reconciled with the "fundamental" rule that "claims are to be construed in the light of the specification[ ] and . . . read with a view to ascertaining the invention." *United States v. Adams*, 383 U.S. 39, 49 (1966).

The district court identified no intrinsic or extrinsic evidence that would support its reading. Instead, it relied almost entirely on a pages-long quotation from UMass's claim-construction briefing. Appx00008-00009. The district court misread that passage as distinguishing between an adenosine concentration "effective to

[9] L'Oréal never produced any infringement testing.

enhance the condition of the skin" and the adenosine concentration that reaches the dermal cells. *Id.* But UMass was drawing an entirely different distinction. It was distinguishing the "composition" that is applied "topically" to skin from the adenosine concentration that reaches the dermal cells (and actually enhances skin condition). Appx00008-00009 (quoting Appx02615-02617). As described above (pp. 20-21, 34-38), the claims specify the concentration applied "to the dermal cells." UMass explained that the "***composition***" applied to the skin's outer layer, the epidermis, could contain additional adenosine beyond the recited concentration, "because not all adenosine will necessarily penetrate to the dermal layer." Appx00008-00009. Far from distinguishing between two separate adenosine concentrations, UMass's briefing underscored that the patent recited "one numerical concentration of adenosine," namely "the adenosine concentration . . . applied to the dermal cells," which is effective to reduce the specified skin conditions. Appx-00008-00010.

The distinction between the amount of adenosine in the topical "composition," and the recited concentration that must be applied to dermal cells deeper in the skin to satisfy the claims, does not render the recited "amount effective to enhance the condition of the skin" indefinite. It merely reflects the point of measurement the inventors selected. The "amount effective to enhance the condition of the skin" is an amount within the specified range—10^{-3} M to 10^{-7} M—that reaches, and is applied

to, dermal cells. The amount of adenosine in the "composition" can be different for the reasons UMass explained at claim construction. Appx00008-00009. As skilled artisans would understand, the amount of adenosine in the "composition" is likely more than the amount that will reach the dermal cells because some adenosine will not penetrate that deeply. Thus, more adenosine in the topical composition may be necessary if the methods used to accelerate "penetration of the adenosine into skin tissue," to reach the dermal layer, are less effective; by contrast, a lesser amount in the "composition" may be sufficient if more effective accelerators are used. Appx-00069(5:13-16).

Consistent with that, claim 1 covers a "composition ***comprising*** a concentration of adenosine in an amount effective to enhance the condition of the skin." Appx00071(10:22-26) (emphasis added). "In the patent claim context the term 'comprising' is well understood to mean 'including but not limited to.'" *CIAS, Inc. v. All. Gaming Corp.*, 504 F.3d 1356, 1360 (Fed. Cir. 2007) (collecting cases); *see* Patent & Trademark Office, MANUAL OF PATENT EXAMINING PROC. §2111.03(I) (9th ed. 2020). The topical composition thus must include ***at least*** the specified concentration of adenosine that is "effective to enhance the condition of the skin" when applied to dermal cells. But that concentration can be just one component of a broader "composition" that also includes additional adenosine to ensure that the

recited concentration actually reaches, and thus "is applied to," dermal cells under the skin's outer layers, as the claims require.

Intrinsic and extrinsic evidence confirms that reading. The specifications teach that, "[f]or topical application, the penetration of the adenosine into skin tissue may be enhanced by a variety of methods known to those of ordinary skill in the art." Appx00069(5:13-16). The specifications' acknowledgement that the "penetration of the adenosine" "may be enhanced" by "methods known to" skilled artisans necessarily recognizes that some adenosine in the composition will not penetrate to dermal cells. *Id.* L'Oréal's expert agreed, declaring that adenosine in a topical composition penetrates to the dermis only partially, at a rate that depends on a "number of factors." Appx02884(¶30 & n.6). It was thus undisputed that the topical composition would contain additional adenosine beyond the numerical concentration that reaches the dermal cells and enhances skin condition.[10] Consistent with that, the claims require a composition that includes—that comprises—at least the recited effective amounts.

The district court's summary judgment opinion acknowledged that "UMass was right" on this very point: "The composition that is applied to the skin 'need not

[10] Skilled artisans would understand *in vitro* testing as an "accepted method[] for predicting the transdermal penetration of drugs, chemicals, and cosmetics." Appx14310-14311.

be limited to only the recited adenosine concentration." Appx00009.[11] But it then failed to apply that same reasoning when determining whether the phrase "amount effective to enhance the condition of the skin" was indefinite. The district court ignored its own recognition at claim construction that the "concentration . . . applied to the dermal cells"—claimed in the patents as 10^{-3} M to 10^{-7} M—"is referring back to the concentration that is in an amount effective to enhance the condition of the skin." Appx03720(57:13-19). The claims thus provide unmistakable, numerical notice. *A fortiori* they provide the degree of certainty that "'is reasonable, having regard to their subject-matter.'" *Nautilus*, 572 U.S. at 910.

C. The Disputed Limitation Is Not Indefinite Even Apart from the Claimed and Recited Numerical Concentrations

Even apart from the recited numerical concentrations, the patents provide "reasonable certainty" about claim scope. As explained above, "effective amount" limitations are commonplace in the art. *See* pp. 32-33, *supra*. L'Oréal itself employs them.[12] Here, skilled artisans can apply the patents' express and practical definition of "enhancement of skin condition" to understand the "effective amount" of

[11] No evidence suggested that including additional adenosine in the composition might prevent skin enhancement.

[12] *See* U.S. Patent No. 8,951,775 ("effective amount"); U.S. Patent No. 6,916,464 ("SPF-enhancing effective amount").

adenosine. The district court cited no evidence to the contrary, much less evidence that every reasonable juror would be compelled to accept as clear and convincing.

1. *The District Court Improperly Deemed the Patents' Express Definition of Skin Enhancement Indefinite*

Perhaps no patent-law principle is more familiar than the rule that inventors may act as their own lexicographers. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005); *Cont'l Cirs. LLC v. Intel Corp.*, 915 F.3d 788, 796 (Fed. Cir.), *cert. denied,* 140 S. Ct. 648 (2019). Where the specification reveals "a special definition given to a claim term by the patentee," the "inventor's lexicography governs." *Phillips*, 415 F.3d at 1316.

Here, the '327 and '513 Patents state that "enhancement of skin condition" "***means*** a noticeable ***decrease in the amount*** of wrinkling, roughness, dryness, laxity, sallowness, or pigmentary mottling in skin." Appx00067(2:35-37) (emphasis added). The district court acknowledged that definition. Appx00011-00012. And the PTO considered and accepted it during patent prosecution. *See* Appx02701-02703, Appx02708, Appx02726; *Impax*, 545 F.3d at 1314.

That definition amply provides the reasonable notice that, given the nature of the art, the law requires. The term "noticeable decrease" is comprehensible to skilled artisans and laypeople alike. In ordinary understanding, a "decrease" means a ***reduction in amount***—here, in the amount of specifically listed conditions. While not necessary, dictionaries confirm that ordinary meaning. *See, e.g.*, WEBSTER'S THIRD

NEW INTERNATIONAL DICTIONARY 588 (2002) (defining "decrease" as "to grow less esp. gradually"). Noticeable "involves what can be seen by the normal human eye," thus providing "an objective baseline through which to interpret the claims." *Sonix*, 844 F.3d at 1378 (upholding "visually negligible" as definite). Claim 1 is thus unlike patents that include phrases like "aesthetically pleasing" or "unobtrusive manner," which require a "value judgment" or turn on "matters of taste or preference." *See id.* (distinguishing *Interval Licensing*, 766 F.3d 1364, and *Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342 (Fed. Cir. 2005)). Even if "[b]eauty . . . is 'in the eyes of the beholder,'" Appx00011, ***amount*** is not. And a "decrease in the amount"—a movement from more to less—is an observable phenomenon. It is not indefinite.

That definition satisfies § 112(b) given the nature of the art. *See BASF*, 875 F.3d at 1366 ("[A]n inventor need not explain every detail because a patent is read by those of skill in the art."). The claims require application of an effective amount of adenosine to enhance skin condition, *i.e.*, to decrease the amount of wrinkles and other listed conditions. If, under any set of circumstances within the patent, the quantity will produce the desired result, it is "effective." *Geneva*, 349 F.3d at 1384; *see Abbott*, 334 F.3d at 1277-78. Here, skilled artisans would have no difficulty determining the effective amounts of adenosine (even apart from their express disclosure in the specification and claims, *see* pp. 34-38, *supra*). L'Oréal has done

so: It identifies its adenosine products as noticeably reducing wrinkles, etc. *See* pp. 15-16, *supra*. L'Oréal also identified effective amounts. Appx04276-04277. And the '327 and '513 Patents identify methods "well known in the art" for measuring "wrinkling, roughness, dryness, laxity, sallowness, or pigmentary mottling." Appx00069(5:46-49). The patents explain that skilled artisans can use "skin topography measurements," which employ "silicone rubber replicas" of untreated and treated skin; those are subjected to "computerized digital-image processing" to measure "fine lines and wrinkles" and assess whether changes are statistically significant. Appx00069(5:52-6:1). They specify the statistically significant variances that indicate a noticeable decrease. *See* p. 12, *supra*. That precision surpasses anything §112(b) might require. *Biosig*, 783 F.3d at 1382. Neither the district court nor L'Oréal has contended otherwise.

The district court, however, seized on the patents' acknowledgement that measurement methods "well known in the art . . . ***can include*** subjective evaluations by the patient or a second party, e.g., a treating physician." Appx00012-00013 (quoting Appx00069(5:48-52)) (emphasis added). That language describes the art, not the patents. It recounts the art's recognition that a treatment can so reduce listed defects that more sophisticated measurements are not required; the decrease in amount is apparent to the eye. *See* Appx14371(211:2-9) (noting "objective technicians along with the subjective patients had never seen . . . more healthy

appearance of the skin"); Appx15178. This invention, after all, arises in dermatological arts, where visual observation of skin is a recognized diagnostic method, as references cited below made clear. *See* Gary L. Grove & Mary Jo Grove, *Effects of Topical Retinoids on Photoaged Skin as Measured by Optical Profilometry*, 39 PHARMACOLOGY 360, 366-67 (1990) (finding "excellent agreement between . . . clinical rating schemes" and skin topography measurements, and "suggesting that optical profilometry is less sensitive than the well-trained eye in evaluating very fine lines"), *cited* Appx14314 n.164. A visit to a dermatologist who does not visually inspect the skin would be a surprising experience.

Such evaluations may be "subjective" insofar as they rely on human perception, Appx00069(5:44-55), but that is not the kind of subjectivity that renders patents indefinite, *see Sonix*, 844 F.3d at 1378 (holding that a "user's perception" provides an "objective baseline through which to interpret the claims"). The "well known" "subjective evaluations" described in the patents neither require "value judgment" nor turn on "tastes or opinions"; they are about amount. *Id.* They identify one way of observing a decrease, while specifying others as well. The literature cited in the patents and known to skilled artisans established that those "well known" evaluation methods produce results consistent with objective methods. Elise A. Olsen *et al.*, *Tretinoin Emollient Cream: A New Therapy for Photodamaged Skin*, 26 J. AM. ACAD. DERMATOL. 215, 215-24 (1992), *cited* Appx00069(5:49-50); *see also* Gary

L. Grove et al., *Optical Profilometry: An Objective Method for Quantification of Facial Wrinkles*, 21 J. AM. ACAD. DERMATOL. 631, 631-37 (1989), *cited* Appx-00069(5:53-54); Appx14314.

The district court cited no evidence for its assertion that the "determination of whether the skin enhancement condition is satisfied can be made by ***purely subjective*** evaluations of one or more persons." Appx00012 (emphasis added). Nothing in the patents supports that conclusion. *See* pp. 12-13, 45, *supra*. The patents permit "subjective evaluations" that are "well known in the art," Appx00069(5:48-52), not all conceivable "subjective evaluations," much less "purely subjective evaluations." No evidence suggested that "purely subjective evaluations of one or more persons," Appx00012, were methods "well known in the art."

To the extent the district court meant to criticize "subjective evaluations" that ***were*** "well known in the art"—the only subjective evaluations the patents permit—that was error. Courts must evaluate indefiniteness with "regard to the [patent's] subject-matter." *Nautilus*, 572 U.S. at 899. Methods "well known in the art" provide "reasonable certainty" to skilled artisans. *See Presidio Components, Inc. v. Am. Tech. Ceramics Corp.*, 875 F.3d 1369, 1377 (Fed. Cir. 2017). The district court's approach, if accepted, would require patents to meet a higher standard than the art they practice. That is not the law. *Nautilus*, 572 U.S. at 899. Radiologists interpreting x-ray films, physicians listening to heartbeats with stethoscopes, and derma-

tologists examining skin may all in some sense conduct "subjective evaluations" insofar as they apply and interpret what their senses tell them to evaluate the patient's condition. But their methods are well established in their arts because they apply accepted criteria recognized by skilled artisans. The patents' disclosed methods for identifying a decrease in the amount of specified conditions—well accepted in the art—are no less definite.

The decision in *BASF*, 875 F.3d 1360, underscores the district court's error. There, the district court ruled that a claim reciting two "material composition[s]" that were "effective to catalyze" specified chemical reactions, *id.* at 1362, was indefinite because it did not "recite a minimum level of function needed to meet this 'effective' limitation nor a particular measurement method to determine whether a composition is 'effective' enough," *id.* at 1366. This Court reversed, holding that a "mere observation of information not 'recited' does not answer the question whether a person of ordinary skill in the art would *need* to be given the level and measurement information to understand, with reasonable certainty," whether the limitation is satisfied. *Id.*; *see Tinnus Enters., LLC v. Telebrands Corp.*, 733 F. App'x 1011, 1021 (Fed. Cir. 2018) ("substantially filled" definite because artisan could observe "if the balloon detaches upon shaking"); *Sonix*, 844 F.3d at 1376.

Here, the '327 and '513 Patents provide more certainty and guidance than the patent in *BASF*. They note methods "well known in the art" for determining whether

an amount of adenosine is "effective to enhance" skin condition. Appx00069(5:44-54). They provide a clear-as-water definition to apply: There must be a noticeable decrease in amount of a listed condition. As in *BASF*, the district court failed to ask "whether a person of ordinary skill in the art would ***need*** to be given" additional information to provide the requisite notice. *BASF*, 875 F.3d at 1366. Instead, seizing on the disclosure that methods "well known in the art . . . can include subjective evaluations," Appx00069(5:49-51), the court jumped to the conclusion that "[a]rtisans of ordinary skill" determining the effective amount "would have to guess about the opinions held by doctors, patients, and undefined others," Appx00014. That leap was unjustified. *BASF*, 875 F.3d at 1366. If anything, the fact that the "***art***" accepts "subjective evaluations" demonstrates that skilled artisans deem such evaluations to provide "reasonable certainty." *See* pp. 46-48, *supra*.

2. *The Supreme Court and This Court Have Upheld Broader Terms of Degree as Providing Reasonable Certainty*

The district court's decision cannot be reconciled with Supreme Court precedent and decisions of this Court, which repeatedly uphold "terms of degree" that provide substantially more latitude for disagreement than the term the district court deemed indefinite here. Those decisions emphasize the need for inquiry into "the context of the invention" to ascertain the level of certainty terms provide to "one of skill in the art." *Sonix*, 844 F.3d at 1377. The district court erred by applying its own view rather than the perspective of skilled artisans.

In *Eibel Process*, the Supreme Court upheld a patent on a machine for printing newspapers even though it required the top of the machine to be located at a "substantial elevation." 261 U.S. at 50-51. The possibility of disagreement over what elevation might qualify as "substantial" did not render the claim so dependent "on the unpredictable vagaries of any one person's opinion" as to render it indefinite. Appx00011 (quoting *Intellectual Ventures I LLC v. T-Mobile USA, Inc.*, 902 F.3d 1372, 1381 (Fed. Cir. 2018)). Instead, the Supreme Court concluded that skilled artisans "had no difficulty . . . determining what was the substantial pitch needed," as demonstrated by the "immediate and successful use of" the patented device. *Eibel Process*, 261 U.S. at 65-66. Even before *Eibel Process*, cases repeatedly recognized "[e]xpressions quite as indefinite as 'high' and 'substantial'" as "sufficient." *Id.* at 66.

Like the infringers in *Eibel Process*, L'Oréal had "no difficulty . . . determining" how to use adenosine to enhance skin condition. 261 U.S. at 65-66. It readily understood that the '327 Patent applies adenosine to dermal cells to "improve skin condition." Appx00266. It sought to patent its own adenosine composition designed to "soften[] lines," Appx00263, *i.e.*, "decrease wrinkles," Appx00269. It put the invention to "immediate and successful use*," Eibel Process*, 261 U.S. at 66, releasing 130 infringing products in the United States, Appx14246-12249, repeatedly representing that they "diminish the appearance" of "wrinkles and fine

lines," Appx15178, and "address[] many visible signs of aging," Appx15440. L'Oréal faces no real uncertainty. It knows that the adenosine concentrations recited in claim 1 cause a "noticeable decrease" in "the amount of wrinkling, roughness, dryness, laxity, sallowness, or pigmentary mottling in skin." Appx00067(2:35-37). It markets infringing products for that exact effect.

Since *Eibel Process*, this Court has repeatedly upheld terms of degree with far more leeway. Following remand in *Nautilus*, this Court found the phrase "spaced relationship" definite because, in context, skilled artisans would understand that it could "be neither infinitesimally small nor greater than the width of a user's hands." *Biosig*, 783 F.3d at 1382. In *Guangdong Alison Hi-Tech Co. v. ITC*, 936 F.3d 1353 (Fed. Cir. 2019), this Court found the term "lofty . . . batting" sufficiently definite, despite two disclosed "methods of measuring loftiness," because the challenging party had "not provided any evidence . . . that the different methods . . . lead to different results." *Id.* at 1363; *see Sonix*, 844 F.3d at 1376 ("visually negligible"); *Exmark Mfg.*, 879 F.3d at 1346-47 ("elongated and substantially straight").

The patents' recitation of a "noticeable decrease" here is far more definite than terms such as "spaced," "lofty," "visually negligible," or "substantially straight." There is nothing indefinite about "decrease" or "noticeable": A noticeable decrease is something skilled artisans can easily identify using accepted methods. *See* pp. 44-46, *supra*. The reliability of such assessments is why the art recognizes the tech-

niques the patents disclose. *See* pp. 46-48, *supra*. They can readily be used to identify the "effective amount" of adenosine, even apart from the patents' express disclosure of the relevant concentrations.[13]

D. Material Disputes of Fact Preclude Summary Judgment Regardless

The extrinsic evidence, like the patents' intrinsic guidance, precluded summary judgment. As the movant, L'Oréal bears a heavy burden: It must "submit such clear and convincing evidence of facts underlying invalidity that ***no reasonable jury*** could" find that L'Oréal failed to meet its clear-and-convincing burden. *TriMed*, 608 F.3d at 1340 (emphasis added); *see Boehringer*, 320 F.3d at 1353; pp. 30-31, *supra.* Here, a reasonable juror could easily reject L'Oréal's supposed indefiniteness evidence as less than clear and convincing. UMass's experts and L'Oréal's own conduct contradict L'Oréal's position.

The district court erred at the outset by asking and answering the wrong question. Rather than put L'Oréal to its "heavy" burden of clear-and-convincing proof, *Tillotson*, 831 F.2d at 1036, the district court suggested that summary judgment is

[13] The district court may have been of the mistaken view that there is no infringement unless, in every use, the enhancement is actually observed. The claims' limitations, however, call for application of an "amount" that is therapeutically "effective." It does not demand proof of a successful course of treatment in each and every use. Physicians administer the therapeutically effective amount of other treatments, such as vaccines, with the expectation that the amount produces an immune response, even if occasionally it does not.

appropriate if it believed that claim 1's "plain and ordinary meaning" and the "patents' written descriptions" were, in light of intrinsic evidence, "indefinite." Appx00014; *see* Appx00009. That was error: Extrinsic evidence can show definiteness. *See Guangdong*, 936 F.3d at 1360; *BASF*, 875 F.3d at 1366. Yet the district court failed to consider "extrinsic evidence" regarding "the field of the invention" and "what a person of ordinary skill in the art would understand." *Phillips*, 415 F.3d at 1319; *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1584 (Fed. Cir. 1996).

Here, that evidence demonstrated that L'Oréal understood the very terms it now assails as indefinite. L'Oréal sells 130 infringing products, advertising their ability to "diminish the appearance" (*i.e.*, cause a "noticeable decrease in the amount") of "wrinkles and fine lines." Appx15176-15178, *see* p. 15-17, *supra*. L'Oréal supports its advertisements by invoking, among other methods, "dermatologist assessments," Appx15176-15178, and patient self-assessment questionnaires regarding wrinkles, firmness, and smoothness, Appx15518-15536. L'Oréal itself thus uses putatively "subjective evaluations" to identify "noticeable decrease[s] in the amount of wrinkling" or other skin conditions. Appx00067(2:35-37).

L'Oréal's advertisements and studies powerfully evidence definiteness. In *DDR Holdings, LLC v. Hotels.com, L.P.*, 773 F.3d 1245 (Fed. Cir. 2014), this Court held "look and feel" definite because the defendant's "own advertisements" showed that it "understood" the term's "established meaning." *Id.* at 1260-61. So too here.

L'Oréal asserts indefiniteness when its own advertisements show that it substantiates visible reduction of wrinkles and other conditions—"enhancement of skin condition"—using the "subjective evaluations" it now assails. Dr. Kasting, L'Oréal's expert, thus never disputed that the accused products contain adenosine amounts that ***do*** enhance skin condition within the meaning of the claims; he urged that adenosine has "been known and demonstrated for quite a long time" to have those effects. Appx13511. That history disproves the district court's unexplained fear that skilled artisans would "have to guess" about the claims' scope. Appx00014. At the very least, it precludes any determination that every reasonable juror would have been ***compelled*** to find indefiniteness by clear-and-convincing evidence. *TriMed*, 608 F.3d at 1340.

Moreover, UMass expert Dr. Michniak-Kohn explained that "in 1997-1998 a skilled artisan would have understood" the specifications' definition of enhancement and description of measurement methods "to mean improvement of the skin on one or more desired metrics, as assessed by well-established standards for determining skin improvement." Appx14314. She identified exemplary measurement methods together with "[n]umerous publications and other patents" contemporaneously describing them. Appx14314 & n.166; Olsen et al., *supra*, at 215-24, *cited* Appx00069(5:49-50). She explained that "[c]omparative studies have shown correlation between assessments performed using different metrics." Appx14314 &

n.165; *see* Grove *et al.*, *supra*, at 631-37, *cited* Appx00069(5:53-54). Such testimony established that the measurement methods described in the patents were well understood and would not be expected to "lead to different results." *Guangdong*, 936 F.3d at 1360.

The district court never made any findings regarding Dr. Michniak-Kohn's testimony or her disagreements with L'Oréal's Dr. Kasting. *See Sonix*, 844 F.3d at 1376. The district court suggested it could "grant summary judgment based on indefiniteness even when the parties present conflicting expert testimony about whether an artisan of ordinary skill would be able to understand disputed claim terms." Appx00005. That defies established law. Rule 56(a) precludes district courts from resolving fact disputes on summary judgment where the issue—such as indefiniteness—is ordinarily one for the jury. *Rosen v. Bezner*, 996 F.2d 1527, 1530 n.2 (3d Cir. 1993). None of the district court's citations, Appx00006, supports its contrary view.[14]

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[14] *Halliburton Energy Services, Inc. v. M-I LLC*, 514 F.3d 1244 (Fed. Cir. 2008), states only that proof of indefiniteness requires "an exacting standard because claim construction often poses a difficult task over which 'expert witnesses, trial courts, and even the judges of this court may disagree.'" *Id.* at 1249-50. And the district court in *Capital Security Systems, Inc. v. NCR Corp.*, 725 F. App'x 952 (Fed. Cir. 2018), rejected expert testimony because it was "unsupported" and "conclusory." *Id.* at 956; *see Telemac Cellular Corp. v. Topp Telecom, Inc.*, 247 F.3d 1316, 1329 (Fed. Cir. 2001) ("Broad conclusory statements offered by . . . experts are not evidence."). Finally, in *HIP, Inc. v. Hormel Foods Corp.*, No. 18 Civ. 615 (CFC), 2019 WL 2579266 (D. Del. June 24, 2019), *aff'd*, 796 F. App'x 748 (Fed. Cir. 2020),

The district court's analysis is, in any event, unconvincing—and certainly insufficient to show that no reasonable juror could reject L'Oréal's position as less than clear and convincing. The district court cited testimony of inventor Dr. Dobson that "subject[ive] assessment of a diminution of fine lines . . . does satisfy or qualify as enhancing the condition of the skin." Appx00013 (quoting Appx14346(135:11-18)). That testimony concerned a specific "in vivo experiment[] regarding the use of compositions containing adenosine" that Dr. Dobson performed on his "own skin." Appx14346(134:14-18). Dr. Dobson's testimony says nothing different than the patents, which acknowledge that "subjective evaluations" based on visual observation were "well known in the art." Appx00069(5:44-54).

The district court asserted that UMass's Dr. Michniak-Kohn never disputed "that a subjective assessment may be used" when evaluating decreases in amount of listed conditions. Appx00013-00014. But definiteness does not fail merely because putatively subjective evaluations are permitted. Definiteness turns on whether the patents provide a degree of certainty that is "reasonable" in view of the art. *Nautilus*, 572 U.S. at 910; *BASF*, 875 F.3d at 1366. Here, they do: Even apart from the specifications' disclosure of the effective concentrations, skilled artisans can determine adenosine amounts effective to produce a "noticeable decrease" in the

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the parties had stipulated that the district court could weigh the testimony of their experts. *Id.* at *2.

amount of a listed condition—an observable change from more to less. Dr. Michniak-Kohn showed unequivocally that the identified methods allow such determinations. Appx14314-14315.[15]

The district court's contrary view reflects the same error of law that pervades its opinion—it rests on the mistaken view that ***any*** allowance of "subjective evaluations" renders patents indefinite. *See* pp. 45-47, *supra*. That was error. *BASF*, 875 F.3d at 1366; *Sonix*, 844 F.3d at 1376. Had the district court asked the right question, it would have had to consider and credit evidence showing that "subjective

[15] Nor would other record evidence compel every reasonable juror to find indefiniteness by clear-and-convincing evidence. Dr. Kasting criticized subjective "evaluation scales." Appx14179-14180. But Dr. Michniak-Kohn disputed that testimony, Appx14314, and Dr. Kasting never identified even one example where methods "well known in the art" produced conflicting outcomes—much less did so for a composition containing the recited concentration of adenosine. *See Guangdong*, 936 F.3d at 1363. L'Oréal invoked Dr. Dobson's testimony that it was "a possibility" that an unspecified "formulation can show an improvement in wrinkling in one test but no improvement . . . in [an]other." Appx14362(171:6-11). But such an abstract "possibility" would hardly compel a reasonable juror to find indefiniteness by clear-and-convincing evidence. *TriMed*, 608 F.3d at 1340. That testimony was wholly divorced from, and has no bearing on, whether such results were possible with respect to the recited adenosine concentrations. L'Oréal surely has not proved outcomes conflict ***so often*** that every reasonable juror would have to conclude that it deprives skilled artisans of adequate notice of ***effective amounts***. The "certainty which the law requires in patents is not greater than is reasonable." *Nautilus*, 572 U.S. at 899. Proof which "excludes the possibility of a doubt" is not required to show "reasonable certainty." *Biosig*, 783 F.3d at 1380 n.2 (quoting *Hetzel v. Balt. & Ohio R.R. Co.*, 169 U.S. 26, 38 (1898)).

evaluations," "well known in the art," can provide skilled artisans reasonable certainty regarding effective amounts.

III. THE COURT HAS PERSONAL JURISDICTION OVER L'ORÉAL S.A.

The district court also erred by dismissing L'Oréal S.A. for lack of personal jurisdiction. The parties agreed that the district court would have jurisdiction so long as its exercise comports with due process. Appx01245; *see Synthes (U.S.A.) v. G.M. Dos Reis Jr. Ind. Com. De Equip. Medico*, 563 F.3d 1285, 1293-94 (Fed. Cir. 2009). Jurisdiction thus depends on whether (1) the defendant purposefully directed activities at residents of the forum; (2) the claim arises out of or relates to those activities; and (3) assertion of personal jurisdiction is reasonable and fair. *Akro Corp. v. Luker*, 45 F.3d 1541, 1545-46 (Fed. Cir. 1995). The inquiry focuses on a foreign "defendant's contacts with the entire United States, as opposed to the state in which the district court sits." *Synthes*, 563 F.3d at 1295.

A. This Court's Precedents Support Jurisdiction

This Court's precedents demonstrate that L'Oréal S.A. had sufficient contacts to establish personal jurisdiction. This Court has ruled that foreign defendants have sufficient contacts where they transported samples of their products to the United States or developed and licensed their products to U.S. subsidiaries. *See Synthes*, 563 F.3d at 1298; *Nuance Commc'ns, Inc. v. Abbyy Software House*, 626 F.3d 1222, 1230 (Fed. Cir. 2010); *Genetic Veterinary Sciences, Inc. v. LABOKLIN GmbH &*

Co., 933 F.3d 1302, 1310-11 (Fed. Cir. 2019). In *Nuance*, for example, this Court found personal jurisdiction where the domestic and foreign companies operated under a consolidated management team, and the domestic company had a nonexclusive license to sell its foreign affiliates' allegedly infringing software. 626 F.3d at 1230, 1232. The foreign company had directed activities to the United States because company leadership had focused on the U.S. market and exported the allegedly infringing products here. *Id.* at 1231. The plaintiff's patent infringement claims arose out of those purposefully directed activities. *Id.* at 1233. And jurisdiction was fair because the companies shared common "counsel" and a "consolidated Global Management Team," alleviating "any possible burden." *Id.* at 1234. Having developed the infringing products and licensed them to an American affiliate for U.S. distribution, the foreign company was properly subject to U.S. jurisdiction. *Id.* at 1232-33.

The same is true here. Before discovery, the evidence showed that L'Oréal S.A. acted as the L'Oréal Group's "strong 'nerve centre' based in France," Appx00692, with its "Executive Committee" directing "the activities of L'Oréal all over the world," Appx00624. L'Oréal USA was the L'Oréal Group's "agent in the United States," Appx00693; *see* Appx01040, adapting "global strategy to . . . [U.S.] markets," Appx01044. L'Oréal S.A.'s French researchers developed the products containing adenosine. Appx00263-00269; Appx01073-01077. That research ap-

peared on L'Oréal USA's website touting the infringing technology. Appx01070; Appx01073-01077. L'Oréal S.A. entered into "written intracompany agreements" with L'Oréal USA, Appx00553, to sell those infringing products in the United States, Appx01090-01092. UMass's claims arise from those U.S. sales. *Nuance*, 626 F.3d at 1233. Subjecting L'Oréal S.A. to the foreseeable consequence of litigating alongside another member of the L'Oréal Group, with the same counsel, Appx22550-22553, is neither unreasonable nor unfair, *Nuance*, 626 F.3d at 1234.

Here, moreover, L'Oréal S.A. has ***additional*** contacts not present in *Nuance*. It "purposefully availed itself of the laws of the United States," seeking "a property interest from a U.S. agency," *see Touchcom, Inc. v. Bereskin & Parr*, 574 F.3d 1403, 1416 (Fed. Cir. 2009)—a patent on the very compositions now alleged to infringe, Appx00263-00269. Further, when Carmel Laboratories inquired whether the U.S. products infringed, it was L'Oréal ***S.A.*** that responded. Appx01160-01170. Just like its agreement with the U.S. affiliate to sell the products here, those L'Oréal S.A. "negotiation efforts" are "activities purposefully directed at" the forum. *Trimble Inc. v. PerDiemCo LLC*, 997 F.3d 1147, 1155 (Fed. Cir. 2021); *see Genetic Veterinary*, 933 F.3d at 1310-11. Indeed, that engagement was consistent with L'Oréal S.A.'s broader history of managing U.S. patents. Appx00300-00334; Appx01098-01155.

B. The District Court at Least Should Have Permitted Jurisdictional Discovery

At a minimum, the district court abused its discretion by denying UMass jurisdictional discovery. Jurisdictional discovery should be allowed unless the claim is "clearly frivolous." *Mass. Sch. of Law at Andover, Inc. v. Am. Bar Ass'n*, 107 F.3d 1026, 1042 (3d Cir. 1997). It is "particularly appropriate where a defendant is a corporation." *Rocke v. Pebble Beach Co.*, 541 F. App'x 208, 212 (3d Cir. 2013). "'A plaintiff who is a total stranger to a corporation should not be required, unless he has been undiligent, to try such an issue on affidavits without the benefit of full discovery.'" *Compagnie Des Bauxites de Guinee v. L'Union Atlantique S.A. d'Assurances*, 723 F.2d 357, 362 (3d Cir. 1983).

Here, assertion of jurisdiction was not "clearly frivolous." UMass offered publicly available evidence of L'Oréal S.A.'s involvement in developing the infringing products, selling them in the United States, and responding to infringement allegations. *See* pp. 59-60, *supra*; Appx00566-00569; Appx01253-01255. Neither the district court nor the magistrate judge explained why it was not "possible," in light of UMass's evidence, that L'Oréal S.A. had the "requisite 'contacts.'" *Toys "R" US, Inc. v. Step Two, S.A.*, 318 F.3d 446, 456 (3d Cir. 2003). And neither identified any additional evidence that UMass, as a "total stranger" to L'Oréal S.A., could have reasonably been expected to provide. *Compagnie Des Bauxites*, 723 F.2d at 362. Instead, the magistrate forced UMass to "try" the jurisdictional issue "on

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affidavits," precisely what the Third Circuit prohibits. *Compare id.*, *with* Appx00044-00047 (finding Rabinowitz Declaration "refutes plaintiffs' allegation").

Later ***merits*** discovery confirms that jurisdictional discovery would have established sufficient contacts. The Rabinowitz Declaration—on which the district court relied, Appx00041, Appx00044-00047—alluded to "written intracompany agreements." Description of intracompany agreement . Appx03949; Appx11647(138:22-139:4), Appx11649(145:13-146:10); Appx12138. Agreement includes infringing products that product development information Appx03075; Appx03144-03157. Description of intracompany agreement . Appx03942-03943, Appx03951-03952. L'Oréal S.A. thus controls the technology.[16] Description of intracompany agreement and division of responsibility under it After infringement was discovered, a representative of L'Oréal S.A. came to the United States to meet with Carmel Laboratories. Description of contract rights and reap the resulting profits.

[16] After dismissal of L'Oréal S.A., L'Oréal USA disputed willful infringement by insisting that ***only L'Oréal S.A.*** had analyzed application of the patents-in-suit to the accused products.

MATERIAL REDACTED

That evidence undermines the magistrate's assertion that L'Oréal S.A. had no "role in the design, manufacture, marketing, or sale of the Accused Products," Appx00042, which rested critically on L'Oréal's sworn averment that the French parent did "not directly develop, sell, market, or advertise" the infringing products, Appx00553. But the evidence showed that description of United States contacts [redacted]; and specifically United States contact. *See* pp. 18-19, *supra*. The evidence also shows that "L'Oréal S.A. introduced the Accused Products into the stream of commerce," precisely what the magistrate judge and district court believed would establish personal jurisdiction. Appx00041; *Nuance*, 626 F.3d at 1230; *Genetic Veterinary*, 933 F.3d at 1310-11.

That record evidence is likely the tip of the iceberg. While appellate courts ordinarily do not "consider facts that were not presented to the district court" at the time of decision, subsequent developments in the same case can be considered—particularly where the appellant lacked access to the relevant materials earlier. *Rothenberg v. Sec. Mgmt. Co.*, 667 F.2d 958, 961 n.8 (11th Cir. 1982); *see Werner v. Werner*, 267 F.3d 288, 294-97 (3d Cir. 2001) (vacating dismissal and remanding for consideration of document subsequently produced in state case); *Landy v. FDIC*,

486 F.2d 139, 151 (3d Cir. 1973).[17] Whether viewed through the lens of "judicial notice," *Werner*, 267 F.3d at 295-96, or common sense, the merits-discovery evidence contradicting the Rabinowitz affidavit—and showing forum-directed licensing activities—underscores the importance of jurisdictional discovery. At the very least, the Court should vacate the dismissal and remand to the district court for reconsideration. *Werner*, 267 F.3d at 297; *Landy*, 486 F.2d at 151.

CONCLUSION

The district court's judgment should be reversed.

October 11, 2021

Respectfully submitted,

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[17] Courts sometimes have ***expanded*** the record where (unlike here) it does not include the relevant documents. *See, e.g.*, *Miller v. Benson*, 51 F.3d 166, 168 (8th Cir. 1995).

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNIVERSITY OF MASSACHUSETTS and CARMEL LABORATORIES, LLC Plaintiffs, v. L'ORÉAL USA, INC. Defendant.	Civil Action No.17-0868-CFC-SRF

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MEMORANDUM OPINION

April 20, 2021
Wilmington, Delaware

COLM F. CONNOLLY
UNITED STATES DISTRICT JUDGE

Plaintiffs University of Massachusetts and Carmel Laboratories, LLC (collectively, UMass) have sued Defendant L'Oréal USA, Inc. for infringement of U.S. Patent Numbers 6,423,327 (the #327 patent) and 6,645,513 (the #513 patent). Pending before me is L'Oréal's Motion for Summary Judgment of Indefiniteness of the Skin Enhancement Claim Limitation (D.I. 278). L'Oréal argues that claims 1, 3, 5, 6, 7, and 9 of the asserted patents are invalid for indefiniteness. D.I. 278 at 1.

I. BACKGROUND

The asserted patents teach methods to treat skin using the organic compound adenosine. Each patent has a single independent claim—claim 1 in each patent. For purposes of the pending motion, the patents' independent claims and written descriptions are identical. In each patent, claim 1 recites:

> [a] method for enhancing the condition of unbroken skin of a mammal by reducing one or more of wrinkling, roughness, dryness, or laxity of the skin, without increasing dermal cell proliferation, the method comprising topically applying to the skin a composition comprising a concentration of adenosine in an amount effective to enhance the condition of the skin without increasing dermal cell proliferation, wherein the adenosine concentration applied to the dermal cells is [a recited concentration range].

The two claim 1s differ only with respect to the recited concentration range. In claim 1 of the #327 patent, the recited range of adenosine "applied to the dermal cells" is "10^{-4} M to 10^{-7} M." In claim 1 of the #513 patent, the recited range is "10^{-3} M to 10^{-7} M."

In their jointly filed claim construction chart, the parties identified the recited concentration range limitation (that is, "wherein the adenosine concentration applied to the dermal cells is [within the recited ranges]") as the only claim term that required construction. D.I. 77 at 2. The parties outlined their respective positions with respect to the recited concentration range limitation in an 82-page joint brief. UMass argued that the limitation should be given its plain and ordinary meaning. L'Oréal argued that the limitation should be construed to mean "wherein the adenosine concentration applied to the skin containing the dermal cells is [within the recited ranges]." D.I. 77 at 2.

The parties' claim construction dispute turned on the meaning of "applied to the dermal cells." L'Oréal argued that those words require the concentration of adenosine to be measured when the adenosine is topically applied to the surface (i.e., epidermal layer) of the skin. UMass argued that the concentration of adenosine is measured at the dermal cells underneath the surface of the skin when the adenosine is absorbed and reaches the dermal cells. I agreed with UMass and concluded that, based on the claim language and intrinsic evidence, the plain and

ordinary meaning of the limitation required the concentration to be measured when the adenosine reached the dermal cells under the surface of the skin.

II. LEGAL STANDARDS

A. Indefiniteness

Section 112(b) of the Patent Act requires that the claims of a patent "particularly point[ ] out and distinctly claim[ ] the subject matter which the inventor . . . regards as the invention." 35 U.S.C. § 112(b) (previously § 112 ¶ 2). To satisfy this requirement, a claim must be "sufficiently 'definite.'" *Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1348 (Fed. Cir. 2002). "The primary purpose of the definiteness requirement is to ensure that the claims are written in such a way that they give notice to the public of the extent of the legal protection afforded by the patent, so that interested members of the public, *e.g.*, competitors of the patent owner, can determine whether or not they infringe." *Oakley, Inc. v. Sunglass Hut Int'l*, 316 F.3d 1331, 1340 (Fed. Cir. 2003). "[A] patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014). "[A] patent does not satisfy the definiteness requirement of § 112 merely because 'a court can ascribe some meaning to a patent's claims.'" *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1371 (Fed.

Cir. 2014) (quoting *Nautilus*, 572 U.S. at 911). To comply with § 112, a patent "must provide objective boundaries for those of skill in the art." *Id.* Thus, "[t]he scope of claim language cannot depend solely on the unrestrained, subjective opinion of a particular individual." *Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1350 (Fed. Cir. 2005), *abrogated on other grounds by Nautilus*, 572 U.S. at 901.

"Indefiniteness is a matter of claim construction, and the same principles that generally govern claim construction are applicable to determining whether allegedly indefinite claim language is subject to construction." *Praxair, Inc. v. ATMI, Inc.*, 543 F.3d 1306, 1319 (Fed. Cir. 2008), *abrogated on other grounds by Nautilus*, 572 U.S. at 901. Courts construe claims "as written, not as the patentees wish they had written [them]." *Chef Am. Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1374 (Fed. Cir. 2004).

B. Summary Judgment

A court must grant summary judgment "if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). Federal Circuit decisions, however, appear to confirm that I may grant summary judgment based on indefiniteness even when the parties present conflicting expert testimony about whether an artisan of ordinary skill would be able to understand disputed claim terms. *See, e.g.*,

Halliburton Energy Servs., Inc. v. M-I LLC, 514 F.3d 1244, 1249–50 (Fed. Cir. 2008) (affirming grant of summary judgment of indefiniteness based on intrinsic evidence and noting in dictum that conflicting expert testimony does not preclude a finding of indefiniteness); *Capital Sec. Sys., Inc. v. NCR Corp.*, 725 F. App'x 952, 958–59 (Fed. Cir. 2018) (affirming district court's decision granting summary judgment of indefiniteness despite expert testimony that an artisan of ordinary skill would understand the disputed claim term with reasonable certainty); *HIP, Inc. v. Hormel Foods Corp.*, 796 F. App'x 748 (Fed. Cir. 2020) (summarily affirming district court's decision granting summary judgment of indefiniteness despite expert testimony that an artisan of ordinary skill would understand the disputed claim term with reasonable certainty).

III. DISCUSSION

L'Oréal argues that the patents' skin enhancement limitation—that is, the requirement that the composition applied to the skin contain "a concentration of adenosine in an amount effective to enhance the condition of the skin"—is indefinite and renders the patents invalid as a matter of law.

The determination of definiteness begins with "a construction of the claims according to the familiar canons of claim construction." *Oakley*, 316 F.3d at 1340. UMass argues that the skin enhancement limitation should be construed to mean the concentration ranges recited in the "wherein" clause of the asserted claims. *See*

D.I. 315 at 3 (arguing that "'a concentration of adenosine in an amount effective to enhance the condition of skin' does not—as L'Oréal argues—refer to skin that is 'in fact' enhanced, . . . but 'refer[s] back to' the ***concentration***, which is adenosine of 'ten to the negative 4M to ten to the negative 7M' for '327 claim 1" (alterations and emphasis in original) (citation omitted)); D.I. 315 at 4 (arguing that "[t]he concentration's 'effective' amount is plainly '10^{-4} M to 10^{-7} M[]' in the [#]327 [patent]"); D.I. 315 at 7 (arguing that "the language 'a concentration of adenosine in an amount effective to enhance the condition of the skin' means . . . a concentration of the recited amount of adenosine"). According to UMass, I "ordered this construction months ago"—i.e., at the claim construction hearing. D.I. 315 at 7.

Truth be told, the parties did not dispute or present for my consideration at the claim construction hearing the skin enhancement limitation and I did not construe the term. UMass now seeks to collapse the skin enhancement limitation into the recited concentration range limitation. But the plain and unambiguous language of the asserted claims makes clear that the skin enhancement limitation is distinct from and independent of the recited concentration range limitation. The skin enhancement limitation requires that the concentration of the adenosine composition that is "*topically appl[ied] to the skin*" be "in an amount effective to enhance the condition of the skin." The recited concentration range limitation

requires that the concentration of the adenosine that reaches and is "*applied to the dermal cells*" be in the recited ranges (i.e., 10^{-4} M to 10^{-7} M in the case of the #327 patent and 10^{-3} M to 10^{-7} M in the case of #513 patent).

UMass itself expressly noted the distinction between the two limitations in its claim construction briefing. In UMass's words:

> [T]he claim language twice refers to a "concentration" of adenosine and contrasts the different skin structures the concentration may be "applied" to: a "composition comprising a concentration of adenosine" is "topically applied to the skin," and "the adenosine concentration" is "applied to the dermal cells" in a specific numerical range.
>
> "In the patent claim context the term 'comprising' is well understood to mean 'including but not limited to.'" *CIAS, Inc. v. All. Gaming Corp.*, 504 F.3d 1356, 1360 (Fed. Cir. 2007) (discussing cases). Because the "composition" includes, but is not limited to, the recited adenosine concentration, it may also include other ingredients, such as more adenosine that is not ultimately "applied to the dermal cells." *See* Kasting Dec. ¶ 17 (App'x A0251) (opining that only a portion of a topically applied composition "permeates to a particular layer within the skin"). **The claims disclose a numerical range for only the adenosine that is "applied to the dermal cells," and not the amount of adenosine that is in the "composition" itself, except to say that the composition includes, but is not limited to, the amount of adenosine in the concentration that is "applied to the dermal cells."** The claims are directed to what amount of adenosine will be applied to, and thus affect, the dermal cells.
>
> Had the inventors intended the "composition comprising a concentration of adenosine" to include the identical amount of adenosine as what is "applied to the dermal

> cells," they easily could have said so. They did not, instead carefully contrasting "the skin" and "the dermal cells," requiring the recited numerical concentration of adenosine to be "applied to the dermal cells." . . .
>
> According to Defendant, because the claim language provides only one numerical range of adenosine (the "concentration"), but recites that the concentration will be "applied" to "the skin" (as part of the "composition") as well as "the dermal cells" (a layer of the skin), the claims equate the skin and the dermal cells. Defendant's argument defies logic. The claims disclose one numerical concentration of adenosine, which is "applied to the dermal cells." **The composition applied "to the skin" need not be limited to only the recited adenosine concentration.** Indeed, as Defendant recognizes, it often will not contain the same amount because not all adenosine will necessarily penetrate to the dermal layer. *See* Kasting Dec. ¶ 17 (App'x A0251). Instead, the concentration applied "to the skin" includes the amount of adenosine that penetrates to the dermal cells, as well as other ingredients, such as more adenosine, that may not penetrate to the dermal cells. And the claim then specifies the range of the concentration "applied to the dermal cells."

D.I. 97 at 57–59 (bold emphases added).

UMass's claim construction briefing was spot on. The asserted claims do "carefully contrast[] 'the skin' and 'the dermal cells,'" and they do "require[e] the recited numerical concentration of adenosine to be 'applied to the dermal cells,'" not the surface of the skin. UMass was right: The composition that is applied to the skin "need not be limited to only the recited adenosine concentration."

Precisely for that reason, the skin enhancement limitation does not mean "a concentration of the recited amount of adenosine."

How, then, should the skin enhancement limitation be construed? (Although L'Oréal challenges UMass's proposed construction of the skin enhancement limitation, it does not offer an alternative construction.) The limitation requires that the composition applied to the skin have a concentration in an amount that is "*effective* to enhance the condition of the skin." Thus, the adenosine concentration applied to the skin must be in an amount sufficient to achieve the intended result of skin enhancement. *Cf. Abbott Lab'ys v. Baxter Pharm. Prods., Inc.*, 334 F.3d 1274, 1277 (Fed. Cir. 2003) (noting that "effective amount" has a customary usage meaning an "amount sufficient" for the intended result).

The claims do not define what constitutes "enhance[ment] [of] the condition of the skin"; nor do they describe how an artisan of ordinary skill is to ascertain whether a "topical[] appl[ication] to the skin [of] a composition comprising a concentration of adenosine" enhances the condition of the skin. There is a "heavy presumption that a claim term carries its ordinary and customary meaning," *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002), and neither side suggests that an artisan of ordinary skill would have a different understanding of "enhancing the condition of the skin" than a lay person would. When "the ordinary meaning of claim language as understood by a person of skill in the art

may be readily apparent even to lay judges, . . . claim construction . . . involves little more than the application of the widely accepted meaning of commonly understood words." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314 (Fed. Cir. 2005) (en banc). The commonly accepted meaning of the phrase "enhancing the condition of the skin"—i.e., improving or making better the quality or desirability of the skin—is clearly indefinite. Indeed, the determination of whether a person's skin is enhanced provides a paradigmatic example of indefiniteness. Beauty, after all, is "in the eyes of the beholder." The assessment of whether a person's skin has been improved is "purely subjective" and "depends on the unpredictable vagaries of any one person's opinion." *Intellectual Ventures*, 902 F.3d at 1381 (internal quotation marks, alterations, and citations omitted).

There is, however, a good argument to be made that the skin enhancement limitation should not be given its plain and ordinary meaning but instead the definition provided in the patents' shared written descriptions. When the written description "reveal[s] a special definition given to a claim term by the patentee that differs from the meaning [the term] would otherwise possess," "the inventor's lexicography governs." *Phillips*, 415 F.3d at 1316. In this case, the patents' written descriptions define "enhancement of skin condition" to mean "a noticeable

decrease in the amount of wrinkling, roughness, dryness, laxity, sallowness, or pigmentary mottling in skin." #327 patent at 2:35–37, *see also id.* at 5:44–48.[1]

The claims do not define or suggest what constitutes a "noticeable decrease" in "one or more of wrinkling, roughness, dryness, or laxity of the skin sallowness, or pigmentary mottling in skin." Nor do they describe how an artisan of ordinary skill would ascertain whether an application of the adenosine resulted in such a noticeable decrease. But here again, the written descriptions are informative. They provide that

> [m]ethods of measuring improvements in skin condition are well known in the art (see, e.g., Olsen et al., J. Amer. Acad. Dermatol. 26:215–24, 1992), and can include subjective evaluations by the patient or a second party, e.g., a treating physician.

#327 patent at 5:48–52. Thus, the written descriptions expressly confirm that the determination of whether the skin enhancement condition is satisfied can be made by purely subjective evaluations of one or more persons.[2] Accordingly, even if I

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[1] Because the written descriptions of the patents are identical in all material respects, I will follow the parties' lead and provide written description citations only for the #327 patent.

[2] I have also considered the patents' prosecution histories and specifically those portions of the histories cited by UMass at pages 5 and 6 of its brief in opposition to L'Oréal's motion. The prosecution histories neither clarify the scope of the skin enhancement limitation nor contradict the written descriptions' express confirmation that determining whether the skin enhancement condition is satisfied can be made by purely subjective evaluations. But even if they had, the written descriptions' express confirmation would nevertheless control. *See Phillips v.*

were to construe the skin enhancement limitation as the term is defined in the written descriptions, the asserted claims would be indefinite.

UMass has effectively conceded that the skin enhancement condition is purely subjective. Its corporate designee, Dr. James Dobson, who is a named inventor of the asserted patents, testified at his deposition that a subjective assessment may be used to determine whether the adenosine has enhanced the condition of the skin within the meaning of the claims:

> **Q.** The fact that you used adenosine on your own skin and observed that there was a decrease in elasticity and a diminution of fine lines and wrinkles, would that have satisfied the patent claims in the [#]327 and [#]513 patent?
> . . .
> **A.** Assuming so, yes.
>
> **Q.** Okay. And the point being is that a subject[ive] assessment of a diminution of fine lines and wrinkles or decrease in elasticity does satisfy or qualify as enhancing the condition of the skin, as you've defined it in the patent; correct? . . .
>
> **A.** Yes.

D.I. 286-1, Ex. 17 at 135:4–18. Perhaps because of this explicit testimony, UMass's expert, Dr. Bozena Michniak-Kohn, did not dispute in her expert reports

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AWH Corp., 415 F.3d 1303, 1317 (Fed. Cir. 2005) (en banc) (noting that "because the prosecution history represents an ongoing negotiation between the [Patent & Trademark Office] and the applicant, rather than the final product of that negotiation, it often lacks the clarity of the specification and thus is less useful for claim construction purposes").

that a subjective assessment may be used to determine whether the condition of the skin has been enhanced as required by the asserted claims.[3]

In sum, whether I give the skin enhancement limitation its plain and ordinary meaning or the definition set forth in the asserted patents' written descriptions, the term is indefinite. *See Vivid Techs., Inc. v. Am. Science & Eng'g, Inc.*, 200 F.3d 795, 803, (Fed. Cir. 1999) ("[O]nly those terms need be construed that are in controversy, *and only to the extent necessary to resolve the controversy.*" (emphasis added)). Artisans of ordinary skill seeking to avoid infringement of the asserted claims would have to guess about the opinions held by doctors, patients, and undefined others with respect to the qualities and desirability of skin conditions. The claims thus lack the requisite objective boundaries required by § 112. *See Datamize*, 417 F.3d 1342, 1352–53 (Fed. Cir. 2005) ("Simply put, the definition of 'aesthetically pleasing' cannot depend on an undefined standard. . . . [Nor can it] depend on the defined views of unnamed persons, even if they are experts, specialists, or academics.").

[3] In its responsive concise statement of facts submitted in support of its opposition to L'Oréal's motion, UMass disputed L'Oréal's statement that Dr. Michniak-Kohn "has not disputed that a subjective assessment may be used to determine whether the condition of the skin has been enhanced." D.I. 319 at 3. UMass cited paragraph of 186 of Dr. Michniak-Kohn's rebuttal report in support of its position. Paragraph 186, however, says nothing about subjective evaluations.

IV. CONCLUSION

For the reasons discussed above, the skin enhancement limitation, when viewed in light of the specifications and prosecution histories, fails to "inform those skilled in the art about the scope of the invention with reasonable certainty." *Nautilus*, 572 U.S. at 910. The independent claims of the asserted patents are therefore invalid for indefiniteness. As UMass did not argue that the patents' dependent claims provide clarity regarding the scope of the skin enhancement limitation that is lacking in the independent claims, those dependent claims are also invalid for indefiniteness.

The Court will issue an Order consistent with this Memorandum Opinion.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNIVERSITY OF MASSACHUSETTS and CARMEL LABORATORIES, LLC Plaintiffs, v. L'ORÉAL USA, INC. Defendant.	Civil Action No.17-0868-CFC-SRF

ORDER

At Wilmington this Twentieth day of April in 2021:

For the reasons set forth in the Memorandum Opinion issued this day, **IT IS HEREBY ORDERED** that L'Oréal's Motion for Summary Judgment of Indefiniteness of the Skin Enhancement Claim Limitation (D.I. 278) is **GRANTED** and that claims 1, 3, 5, 6, 7, and 9 of U.S. Patent Nos. 6,423,327 and 6,645,513 are **INVALID**.

UNITED STATES DISTRICT JUDGE

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNIVERSITY OF MASSACHUSETTS and CARMEL LABORATORIES, LLC, Plaintiffs, v. L'ORÉAL USA, INC., Defendant.	C.A. No. 17-cv-868-CFC-SRF

~~[PROPOSED]~~ FINAL JUDGMENT

NOW THEREFORE, IT IS HEREBY ORDERED, ADJUDGED, AND DECREED that:

1. For the reasons stated in the Court's April 20, 2021 opinion (D.I. 410), final judgment of invalidity of claims 1, 3, 5, 6, 7, and 9 of U.S. Patent Nos. 6,423,327 and 6,645,513 is entered in favor of Defendant L'Oréal USA, Inc. and against Plaintiffs University of Massachusetts and Carmel Laboratories, LLC.[1]

2. All pending motions are denied as moot. (*See* May 5, 2021 Oral Order; April 26, 2021 Status Teleconference Tr.)

[1] The April 20 opinion addressed independent claim 1 and dependent claims 3, 5, 6, 7, and 9 of the asserted patents, finding them invalid for indefiniteness. The parties agree that the Court's opinion renders dependent claims 2, 4, 8, and 10 also invalid for indefiniteness.

3. Any motion for attorney fees and/or costs, including any bill of costs under Fed. R. Civ. P. 54(d) and/or D. Del. LR 54.1 or motion pursuant to 35 U.S.C. § 285, Fed. R. Civ. P. 54(d)(2), or D. Del. LR 54.3, shall be considered timely if filed and served (1) within 30 days after final disposition of any appeal or (2) within 30 days after the expiration of the time for filing a notice of appeal under Fed. R. App. P. 3 and 4.

This is a final, appealable judgment.

Dated: May 14, 2021

Judge Colm F. Connolly

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL and CARMEL LABORATORIES, LLC,	:	
Plaintiffs,	:	
v.	:	Civil Action No. 17-868-CFC
L'ORÉAL S.A. and L'ORÉAL USA, INC.,	:	
Defendants.	:	

MEMORANDUM ORDER

In this patent case, Defendant L'Oréal USA, Inc. ("L'Oréal USA") filed a motion to dismiss pursuant to Federal Rule of Civil Procedure 12(b)(6). D.I. 15. Defendant L'Oréal S.A. ("L'Oréal S.A.") filed a motion to dismiss pursuant to Rule 12(b)(6) and Rule 12(b)(2). D.I. 23. Both motions were referred to a Magistrate Judge who recommended in a Report and Recommendation (D.I. 31) that the court (1) deny the motions insofar as they sought dismissal pursuant to Rule 12(b)(6), and (2) grant L'Oréal S.A's motion insofar as it sought dismissal pursuant to Rule 12(b)(2) for lack of personal jurisdiction over L'Oréal S.A.

Plaintiffs object to the Magistrate Judge's recommendation that the court "grant L'Oréal S.A.'s Rule 12(b)(2) motion to dismiss[,]" D.I. 31 at 1, to the extent the recommendation was based on the Magistrate Judge's decision to "discredit[ ] Plaintiffs' argument that L'Oréal U.S.A. is L'Oréal S.A.'s United States agent for the purpose of designing and developing the accused [infringing] products[,]" D.I. 32 at 1. I review de novo the findings to which Plaintiffs object.

Personal jurisdiction analysis for patent claims is governed by Federal Circuit law. *Elecs. For Imaging, Inc. v. Coyle*, 340 F.3d 1344, 1348 (Fed. Cir. 2003). Whether to grant jurisdictional discovery, however, is a question governed by regional circuit law. *See Autogenomics, Inc. v. Oxford Gene Tech. Ltd.*, 566 F.3d 1012, 1021–22 (Fed. Cir. 2009) ("We review the district court's denial of [jurisdictional] discovery, an issue not unique to patent law, for abuse of discretion, applying the law of the regional circuit." (citations omitted)).

Under Federal Circuit law, in deciding whether personal jurisdiction exists, "a district court must accept the uncontroverted allegations in the plaintiff's complaint as true and resolve any factual conflicts in [any] affidavits [submitted by the parties] in the plaintiff's favor." *Coyle*, 340 F.3d at 1349. When a motion to dismiss for lack of personal jurisdiction is decided on the basis of affidavits and other written materials in the absence of an evidentiary hearing, the plaintiff need only make a *prima facie* showing that a defendant is subject to the court's

jurisdiction. *Id.* To establish jurisdiction under an agency theory, Plaintiffs "must show that [L'Oréal S.A.] exercises control over the activities of" L'Oréal USA. *Celgard, LLC v. SK Innovation Co., Ltd.*, 792 F.3d 1373, 1379 (Fed. Cir. 2015).

Under Third Circuit law, "courts are to assist the plaintiff by allowing jurisdictional discovery unless the plaintiff's claim is 'clearly frivolous.'" *Toys "R" Us, Inc. v. Step Two, S.A.*, 318 F.3d 446, 456 (3d Cir. 2003) (citation omitted). If a plaintiff presents factual allegations that suggest with "reasonable particularity" the possible existence of personal jurisdiction over a defendant, then "the plaintiff's right to conduct jurisdictional discovery should be sustained." *Id.*

Plaintiffs argue that the Magistrate Judge "brushed [ ] aside" what Plaintiffs describe as "substantial evidence that L'Oréal S.A. develops and sells the Accused Products in the United States, and in Delaware, by designing and developing the infringing Accused Products, which [L'Oréal USA] then manufactures and distributes here." D.I. 32 at 3–4. But the Magistrate Judge expressly addressed and thoughtfully considered the evidence proffered by Plaintiffs, *see* D.I. 31 at 21–24; and, having reviewed the proffered evidence myself, I agree with the Magistrate Judge that the evidence in question, even when viewed most favorably for Plaintiffs, does not constitute *prima facia* evidence, let alone substantial evidence, that L'Oréal S.A. exercised control over L'Oréal USA's manufacture and/or distribution of the Accused Products in the United States.

I also agree with the Magistrate Judge's conclusion that Plaintiffs have failed to suggest with reasonable particularity that this Court may have personal jurisdiction over L'Oréal S.A. *See* D.I. 31 at 24. "A plaintiff may not [ ] undertake a fishing expedition based only upon bare allegations, under the guise of jurisdictional discovery." *Eurofins Pharma US Holdings v. BioAlliance Pharma SA*, 623 F.3d 147, 157 (3d Cir. 2010) (citation omitted).

Accordingly, Plaintiffs' objection (D.I. 32) is OVERRULED; and, there being no other objections to the Report and Recommendation, the Report and Recommendation (D.I. 31) is ADOPTED. Defendant L'Oréal USA, Inc.'s motion to dismiss (D.I. 15) is DENIED. Defendant L'Oréal S.A.'S motion to dismiss (D.I. 23) is GRANTED.

IT IS SO ORDERED.

COLM F. CONNOLLY
UNITED STATES DISTRICT JUDGE

May 17, 2019

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL and CARMEL LABORATORIES, LLC,	)	
Plaintiffs,	)	
v.	)	Civil Action No. 17-868-CFC-SRF
L'ORÉAL S.A. and L'ORÉAL USA, INC.,	)	
Defendants.	)	

REPORT AND RECOMMENDATION

I. INTRODUCTION

Presently before the court in this patent infringement action are the following motions: (1) the motion to dismiss the complaint pursuant to Rule 12(b)(6) of the Federal Rules of Civil Procedure, filed by defendant L'Oréal USA, Inc. ("L'Oréal USA") (D.I. 15); and (2) the motion to dismiss the complaint pursuant to Rules 12(b)(2) and 12(b)(6), filed by defendant L'Oréal S.A. (together with L'Oréal USA, "L'Oréal" or "defendants") (D.I. 23). For the following reasons, I recommend that the court deny the Rule 12(b)(6) motions to dismiss of L'Oréal USA and L'Oréal S.A., and grant L'Oréal S.A.'s Rule 12(b)(2) motion to dismiss.

II. BACKGROUND

A. Patents-In-Suit

On July 23, 2002, the United States Patent and Trademark Office issued United States Patent No. 6,423,327 ("the '327 patent"), entitled "Treatment of Skin with Adenosine or Adenosine Analog." The '327 patent was filed on September 28, 2000 and is a continuation of Application No. 09/179,006, which was filed on October 26, 1998 and is now abandoned. The patent lists as inventors James G. Dobson, Jr. and Michael F. Ethier ("inventors"), and identifies

University of Massachusetts as the assignee. Carmel Laboratories, LLC ("Carmel Labs") is the exclusive licensee of the '327 patent. (D.I. 13 at ¶ 36) The '327 patent describes methods for improving the condition of unbroken, mammalian skin by applying adenosine "in an amount effective to enhance the condition of the skin without increasing dermal cell proliferation, wherein the adenosine concentration applied to the dermal cells is 10^{-4} M to 10^{-7} M." ('327 patent, col. 10:18-26)

United States Patent No. 6,645,513 ("the '513 patent") (together with the '327 patent, the "patents-in-suit") was filed on June 28, 2002 and issued on November 11, 2003. The '513 patent is a continuation of the '327 patent. The '513 and '327 patents share the same title, abstract, inventors, specification, assignee, and exclusive licensee.

Claims 1 and 9 of the '513 and '327 patents ("the asserted claims") are also identical except for the claimed concentrations of adenosine applied to the dermal cells. Specifically, the '327 patent claims an adenosine concentration of 10^{-4} M to 10^{-7} M, ('327 patent, col. 10:25-26), and the '513 patent claims a concentration of 10^{-3} M to 10^{-7} M, ('513 patent, col. 10:25-26).

B. Parties

University of Massachusetts Medical School is a public institution of higher education in Massachusetts. (D.I. 13 at ¶ 1). University of Massachusetts is identified as the assignee of the patents-in-suit. ('327 patent, Assignee; '513 patent, Assignee)

Carmel Labs (together with University of Massachusetts Medical School, "plaintiffs") is a for-profit Massachusetts limited liability company founded and wholly-owned by Teresian Carmelites, Inc. ("Teresian Carmelites"). (D.I. 13 at ¶ 3) Teresian Carmelites is a Massachusetts non-profit religious organization dedicated to prayer and service to the poor and marginalized. (*Id.* at ¶¶ 2, 14) Carmel Labs' profits financially sustain Teresian Carmelites and fund its

charitable endeavors. (*Id.* at ¶ 15) Carmel Labs is purportedly the exclusive licensee of the patents-in-suit for all cosmetic applications, and has been since 2008. (*Id.* at ¶ 15) Using the patented adenosine technology, Carmel Labs developed "Easeamine," an anti-aging face cream that it released for sale in 2009. (*Id.* at ¶ 16)

L'Oréal USA is a wholly-owned subsidiary of L'Oréal S.A., a French corporation headquartered in France. (*Id.* at ¶¶ 5, 7) L'Oréal USA is Delaware corporation with its principal place of business in New York, New York. (*Id.* at ¶ 6) L'Oréal USA develops and manufactures hair care, skin care, cosmetics, and fragrances distributed globally. (*Id.* at ¶ 18) Plaintiffs accuse eighteen L'Oréal brands of selling infringing products, including but not limited to the following brands with products containing adenosine: Biotherm; The Body Shop; Carita; Decleor; Garnier; Giorgio Armani; Helena Rubinstein; IT Cosmetics; Kiehl's; L'Oréal Paris; La Roche-Posay; Lancôme; Maybelline; Roger&Gallet; Sanoflore; Shu Uemura; Vichy; and Yves Saint Laurent (the "Unnamed Accused Products"). (*Id.* at ¶ 31) However, the only product identified by name in the First Amended Complaint is L'Oréal Paris' RevitaLift Triple Power Deep-Acting Moisturizer (together with the Unnamed Accused Products, the "Accused Products"). (*Id.* at ¶ 34)

C. Facts

Dr. James G. Dobson, Jr., the former Chairman of the Department of Physiology at University of Massachusetts Medical School, and his colleague, Dr. Michael Ethier, discovered that topical application of adenosine to dermal cells in specified concentrations can enhance the condition of the skin without increasing dermal cell proliferation. (*Id.* at ¶ 10) Their discoveries are embodied in the '327 and '513 patents. (*Id.* at ¶ 11) Drs. Dobson and Ethier assigned their intellectual property rights to University of Massachusetts. (*Id.* at ¶ 4)

Teresian Carmelites learned of the adenosine technology Drs. Dobson and Ethier developed through its relationship with Dr. Dobson, and negotiated a license for the technology. (*Id.* at ¶ 15) Since 2008, Carmel Labs has been the exclusive licensee of the patents-in-suit for all cosmetic applications. (*Id.*) After securing a license to the patents-in-suit, Carmel Labs used the patented adenosine technology to develop an anti-aging face cream called "Easeamine," which was released for sale in 2009. (*Id.* at ¶¶ 15-16)

L'Oréal has cited to the '327 and '513 patents in several of its own issued patents and at least one now-abandoned application. (*Id.* at ¶¶ 20-22, Exs. 7-10) In fall of 2003, an agent of L'Oréal contacted Dr. Dobson to discuss the patents-in-suit, but failed to obtain a license. (*Id.* at ¶ 23) Following this conversation, L'Oréal began creating, marketing, and selling the Accused Products. (*Id.* at ¶ 24) On October 15, 2010, L'Oréal publicly announced the upcoming launch of its new Youth Code line of skin care containing adenosine. (*Id.* at ¶ 25; Ex. 5) In March 2015, the president of Teresian Carmelites and Carmel Labs sent a letter to L'Oréal's CEO stating his belief that L'Oréal's products infringe the patents-in-suit, and affirming that Carmel Labs is the exclusive licensee of the patents-in-suit. (*Id.* at ¶ 30)

D. Procedural History

On June 30, 2017, University of Massachusetts Medical School and Carmel Labs filed the present action against L'Oréal U.S.A and L'Oréal S.A., asserting causes of action for the alleged infringement of the '327 and '513 patents. (D.I. 1) On August 4, 2017, L'Oréal U.S.A filed its motion to dismiss plaintiffs' complaint, pursuant to Rules 8(a)(2) and 12(b)(6). (D.I. 7) Plaintiffs subsequently filed their First Amended Complaint ("FAC") on August 18, 2017. (D.I. 13) In response, L'Oréal USA filed its motion to dismiss the FAC on August 23, 2017, alleging that the causes of action failed to state a claim under Rule 12(b)(6). (D.I. 15) L'Oréal S.A.

followed suit on October 16, 2017, filing a motion to dismiss for lack of personal jurisdiction and failure to state a claim upon which relief can be granted. (D.I. 23)

III. LEGAL STANDARDS

A. Failure to State a Claim

Rule 12(b)(6) permits a party to move to dismiss a complaint for failure to state a claim upon which relief can be granted. Fed. R. Civ. P. 12(b)(6). When considering a Rule 12(b)(6) motion to dismiss, the court must accept as true all factual allegations in the complaint and view them in the light most favorable to the plaintiff. *Umland v. Planco Fin. Servs.*, 542 F.3d 59, 64 (3d Cir. 2008).

To state a claim upon which relief can be granted pursuant to Rule 12(b)(6), a complaint must contain a "short and plain statement of the claim showing that the pleader is entitled to relief." Fed. R. Civ. P. 8(a)(2). Although detailed factual allegations are not required, the complaint must set forth sufficient factual matter, accepted as true, to "state a claim to relief that is plausible on its face." *Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 570 (2007); *see also Ashcroft v. Iqbal*, 556 U.S. 662, 663 (2009). A claim is facially plausible when the factual allegations allow the court to draw the reasonable inference that the defendant is liable for the misconduct alleged. *Iqbal*, 556 U.S. at 663; *Twombly*, 550 U.S. at 555-56.

When determining whether dismissal is appropriate, the court must take three steps.[1] *See Santiago v. Warminster Twp.*, 629 F.3d 121, 130 (3d Cir. 2010). First, the court must identify the elements of the claim. *Iqbal*, 556 U.S. at 675. Second, the court must identify and reject

[1] Although *Iqbal* describes the analysis as a "two-pronged approach," the Supreme Court observed that it is often necessary to "begin by taking note of the elements a plaintiff must plead to state a claim." 556 U.S. at 675, 679. For this reason, the Third Circuit has adopted a three-pronged approach. *See Santiago v. Warminster Twp.*, 629 F.3d 121, 130 n.7 (3d Cir. 2010); *Malleus v. George*, 641 F.3d 560, 563 (3d Cir. 2011).

conclusory allegations. *Id.* at 678. Third, the court should assume the veracity of the well-pleaded factual allegations identified under the first prong of the analysis, and determine whether they are sufficiently alleged to state a claim for relief. *Id.*; *see also Malleus v. George*, 641 F.3d 560, 563 (3d Cir. 2011). The third prong presents a context-specific inquiry that "draw[s] on [the court's] experience and common sense." *Id.* at 663-64; *see also Fowler v. UPMC Shadyside*, 578 F.3d 203, 210 (3d Cir. 2009). As the Supreme Court instructed in *Iqbal*, "where the well-pleaded facts do not permit the court to infer more than the mere possibility of misconduct, the complaint has alleged - but it has not 'show[n]' - 'that the pleader is entitled to relief.'" *Iqbal*, 556 U.S. at 679 (quoting Fed. R. Civ. P. 8(a)(2)).

The court's determination is not whether the non-moving party "will ultimately prevail," but whether that party is "entitled to offer evidence to support the claims." *United States ex rel. Wilkins v. United Health Grp., Inc.*, 659 F.3d 295, 302 (3d Cir. 2011). This "does not impose a probability requirement at the pleading stage," but instead "simply calls for enough facts to raise a reasonable expectation that discovery will reveal evidence of [the necessary element]." *Phillips*, 515 F.3d at 234 (quoting *Twombly*, 550 U.S. at 556). The court's analysis is a context-specific task requiring the court "to draw on its judicial experience and common sense." *Iqbal*, 556 U.S. at 663-64.

B. Personal Jurisdiction

Rule 12(b)(2) directs the court to dismiss a case when the court lacks personal jurisdiction over the defendant. Fed. R. Civ. P. 12(b)(2). When reviewing a motion to dismiss pursuant to Rule 12(b)(2), a court must accept as true all allegations of jurisdictional fact made by the plaintiff and resolve all factual disputes in the plaintiff's favor. *Traynor v. Liu*, 495 F. Supp. 2d 444, 448 (D. Del. 2007). Once a jurisdictional defense has been raised, the plaintiff

bears the burden of establishing, with reasonable particularity, that sufficient minimum contacts have occurred between the defendant and the forum to support jurisdiction. *See Provident Nat'l Bank v. Cal. Fed. Sav. & Loan Ass'n*, 819 F.2d 434, 437 (3d Cir. 1987). To meet this burden, the plaintiff must produce "sworn affidavits or other competent evidence," since a Rule 12(b)(2) motion "requires resolution of factual issues outside the pleadings." *Time Share Vacation Club v. Atlantic Resorts, Ltd.*, 735 F.2d 61, 67 n.9 (3d Cir. 1984).

To establish personal jurisdiction, a plaintiff must demonstrate facts sufficient to satisfy both a statutory and a constitutional requirement. With respect to the statutory analysis, the court analyzes the long-arm statute of the state in which the court is located. *See IMO Indus., Inc. v. Kiekert AG*, 155 F.3d 254, 259 (3d Cir. 1998). Next, the court must determine whether exercising jurisdiction over the moving defendant in this state comports with the due process clause of the United States Constitution. *See id.*; *Autogenomics, Inc. v. Oxford Gene Tech. Ltd.*, 566 F.3d 1012, 1016 (Fed. Cir. 2009) (noting that the court must apply the law of the Federal Circuit to the constitutional inquiry in patent cases).

Pursuant to the relevant portions of Delaware's long-arm statute, 10 *Del. C.* § 3104(c)(1)-(4), a court may exercise personal jurisdiction over a defendant when the defendant or its agent:

> (1) Transacts any business or performs any character of work or service in the State;
> (2) Contracts to supply services or things in this State;
> (3) Causes tortious injury in the State by an act or omission in this State;
> (4) Causes tortious injury in the State or outside of the State by an act or omission outside the State if the person regularly does or solicits business, engages in any other persistent course of conduct in the State or derives substantial revenue from services, or things used or consumed in the State.

10 *Del. C.* § 3104(c)(1)-(4). With the exception of subsection (c)(4), the long-arm statute requires a showing of specific jurisdiction. *See Shoemaker v. McConnell*, 556 F. Supp. 2d 351, 354-55 (D. Del. 2008). Subsection (c)(4) confers general jurisdiction, which requires a great

number of contacts, but allows the exercise of personal jurisdiction even when the claim is unrelated to the forum contacts. *See Applied Biosystems, Inc. v. Cruachem, Ltd.*, 772 F. Supp. 1458, 1466 (D. Del. 1991).

If a defendant is found to be within the reach of the long-arm statute, the court then must analyze whether the exercise of personal jurisdiction comports with due process by determining whether the plaintiff has demonstrated that the defendant "purposefully avail[ed] itself of the privilege of conducting activities within the forum State," so that it should "reasonably anticipate being haled into court there." *World-Wide Volkswagen Corp. v. Woodson*, 444 U.S. 286, 297 (1980) (citations omitted). For the court to exercise specific personal jurisdiction consistent with due process, a plaintiff's cause of action must have arisen from the defendant's activities in the forum state. *See Burger King Corp. v. Rudzewicz*, 471 U.S. 462, 472 (1985). The court may exercise general personal jurisdiction consistent with due process if the plaintiff's cause of action is unrelated to the defendant's activities in the forum state, so long as the defendant has "continuous and systematic contacts with the forum state." *Applied Biosystems, Inc.*, 772 F. Supp. at 1458.

IV. DISCUSSION

A. Failure to State a Claim

1. Direct infringement

Pursuant to 35 U.S.C. § 271(a), a patent is directly infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States . . . during the term of the patent." Amendments to the Federal Rules of Civil Procedure, which took effect on December 1, 2015, abrogated Rule 84 and the Appendix of Forms, including Form 18. Under the new rules, allegations of direct infringement are subject to the pleading standards

established by *Twombly* and *Iqbal*, requiring plaintiffs to demonstrate a plausible claim for relief. *See Mayne Pharma Int'l PTY Ltd. v. Merck & Co., Inc.*, C.A. No. 15-438-LPS-CJB, 2015 WL 7833206, at *2 n.1 (D. Del. Dec. 3, 2015). "Direct infringement requires a party to perform each and every step or element of a claimed method or product." *Exergen Corp. v. Wal-Mart Stores, Inc.*, 575 F.3d 1312, 1320 (Fed. Cir. 2009) (internal quotation marks omitted).

Plaintiffs accuse eighteen L'Oréal brands of selling infringing products because they sell "products containing adenosine." (D.I. 13 at ¶ 31) The FAC alleges:

> On information and belief, Defendants' Accused Adenosine Products include, but are not limited to, the following brands with products containing adenosine: Biotherm; The Body Shop; Carita; Decleor; Garnier; Giorgio Armani; Helena Rubinstein; IT Cosmetics; Kiehl's; L'Oréal Paris; La Roche-Posay; Lancôme; Maybelline; Roger&Gallet; Sanoflore; Shu Uemura; Vichy; and Yves Saint Laurent.

(*Id.*) The only product the FAC identifies by name is L'Oréal Paris' RevitaLift Triple Power Deep-Acting Moisturizer. (*Id.* at ¶ 34) L'Oréal contends that the FAC fails to properly plead direct infringement because plaintiffs "indiscriminately target eighteen brands without providing plausible patent infringement allegations for any products made by those brands[.]" (D.I. 16 at 9)

With respect to the Unnamed Accused Products, plaintiffs have properly pled direct infringement. To properly allege direct infringement under *Twombly* and *Iqbal*, plaintiffs must "plead facts sufficient to place [L'Oréal] on notice as to what [it] must defend." *McZeal v. Sprint Nextel Corp.*, 501 F.3d 1354, 1357 (Fed. Cir. 2007). L'Oréal is on notice that products containing adenosine made by the eighteen brands specified in the FAC are accused of infringement. From the FAC, L'Oréal should easily be able to ascertain the identity of the Accused Products. More specific product identification will occur at the appropriate time under

the relevant provisions of the scheduling order once such an order is entered after resolution of the pending motions, but such specifics are not required at this stage. The FAC contains sufficient detail to withstand a motion to dismiss. *See, e.g.*, *E.digital Corp. v. Micron Tech., Inc.*, 2014 WL 12488496, at *4 (S.D. Cal. May 29, 2014) (denying motion to dismiss where the complaint identified accused products by specific characteristics and brand names); *see also Connective Licensing, LLC v. Iceland Health, Inc.*, 2014 WL 11706456, at *3 (S.D. Fla. Feb. 10, 2014) (specific identification of accused products not necessary); *see also Anza Tech., Inc. v. ARRIS Group, Inc.*, 2017 WL 1843280, at *3 (S.D. Cal. May 5, 2017) (same; post-Form 18 abrogation).

The FAC also sufficiently pleads direct infringement with respect to L'Oréal Paris' RevitaLift Triple Power Deep-Acting Moisturizer. The FAC alleges:

> On information and belief, use of one or more of the Accused Adenosine Products constitutes direct infringement of claim 1 of the '327 patent, as such use involves "a method for enhancing the condition of unbroken skin of a mammal by reducing one or more of wrinkling, roughness, dryness, or laxity of the skin, without increasing dermal cell proliferation, the method comprising topically applying to the skin a composition comprising a concentration of adenosine in an amount effective to enhance the condition of the skin without increasing dermal cell proliferation, wherein the adenosine concentration applied to the dermal cells is 10^{-4} M to 10^{-7}."

(D.I. 13 at ¶ 38 (quoting '327 patent, col. 10:18-26)) The FAC further alleges, and L'Oréal does not dispute, that RevitaLift Triple Power Deep-Acting Moisturizer is an adenosine-containing, topical composition used to reduce wrinkles. (D.I. 13, Exs. 11-12) Taking the allegations in the FAC as true, the court can reasonably infer that the use of RevitaLift Triple Power Deep-Acting Moisturizer meets each of the limitations of the asserted claims.

L'Oréal contends that plaintiffs have failed to state a claim for direct infringement of the patents-in-suit because the FAC "does not provide an element-by-element infringement analysis." (D.I. 16 at 4) However, an element-by-element infringement analysis is required to prove direct infringement—not plead it. *See Crypto Research, LLC v. Assa Abloy, Inc.*, 236 F. Supp. 3d 671, 686 (E.D.N.Y. 2017) (declining to require that plaintiff plead every element of the allegedly infringed claims to withstand a motion to dismiss); *Niazi v. Pressure Prods. Med. Supplies, Inc.*, No. 16-cv-670-jdp, 2017 WL 108114, at *1 (W.D. Wis. Jan 11, 2017) ("This court will not require plaintiffs to plead direct infringement element-by-element[.]"). Though L'Oréal repeatedly references the requirements for proving direct infringement in its briefs, there is no requirement that plaintiffs "prove [their] case at the pleading stage." *In re Bill of Lading Transmission & Processing Sys. Patent Litig.*, 681 F.3d 1323, 1339 (Fed. Cir. 2012). To withstand a motion to dismiss, plaintiffs need only present "'enough facts to raise a reasonable expectation that discovery will reveal' that [L'Oréal] is liable for the misconduct alleged." *Id.* at 1341 (quoting *Twombly*, 550 U.S. at 556).

L'Oréal also argues that the FAC is deficient because plaintiffs fail to plausibly assert that the adenosine concentration applied to the dermal cells is 10^{-4} M to 10^{-7} M in the case of the '327 patent and 10^{-3} M to 10^{-7} M in the case of the '513 patent. (D.I. 22 at 4) L'Oréal asserts that "the only documents included or cited in Plaintiffs' FAC contain examples of adenosine concentrations that fall outside the claimed range" and within the range plaintiffs surrendered during prosecution of the '327 patent. (D.I. 16 at 10) Plaintiffs contend that L'Oréal's argument is inapposite because L'Oréal has misconstrued the meaning of "applied to the dermal cells" to mean the concentration of adenosine in a product, not "the concentration that is ultimately applied to the dermal cells" as plaintiffs argue is the correct construction of the phrase. (*Id.* at 6-

7 (emphasis original)) Because plaintiffs' argument is not contradicted by the pleadings or documents incorporated by reference when viewed in the light most favorable to plaintiffs, the FAC plausibly establishes that L'Oréal Paris' RevitaLift Triple Power Deep-Acting Moisturizer practices the claimed concentration.[2] (D.I. 9, Ex. C at 448; D.I. 13, Ex. 3 at ¶ 0068; D.I. 13, Ex. 6 at 5; D.I. 13, Ex. 8 at 6:55-7:27)

L'Oréal also faults the FAC for not referencing testing or any ingredient analysis conducted on the Accused Products. (D.I. 16 at 5; D.I. 9, Ex. A at 2) Contrary to L'Oréal's position, plaintiffs are not required to reveal privileged work product to support their factual allegations at this stage. *See DermaFocus LLC v. Ulthera, Inc.*, 201 F. Supp. 3d 465, 469 (D. Del. 2016) ("Absent specific guidance from the Federal Circuit directing the court to front-load the litigation process by requiring a detailed complaint in every instance, the court declines to do so.") Accordingly, I recommend that the court deny L'Oréal USA and L'Oréal S.A.'s Rule 12(b)(6) motions to dismiss plaintiffs' causes of action for direct infringement of the '327 and '513 patents.

2. Induced infringement

To state a claim for induced infringement, a plaintiff must allege facts showing that: (1) the plaintiff's patent is directly infringed, (2) the defendant induced that infringement by "aid[ing] and abett[ing] another's direct infringement of the patent," *Rodime PLC v. Seagate*

[2] To the extent the parties dispute the meaning of "applied to the dermal cells," this dispute is appropriately reserved for claim construction. *See Novartis Pharma. Corp. v. Actavis, Inc.*, 2012 WL 6212619, at *7 (D. Del. Dec. 5, 2012) ("[I]f a court is required to construe the meaning of claim terms and perform an infringement analysis in order to resolve a motion to dismiss . . . , the motion should be denied, because this type of analysis is inappropriate at the pleading stage."). When affording the broadest possible meaning to the disputed term and drawing all reasonable factual inferences in plaintiffs' favor at this stage, the court finds that plaintiffs have presented a plausible argument as to why dismissal on this ground is inappropriate.

Tech., Inc., 174 F.3d 1294, 1306 (Fed. Cir. 1999), and (3) the defendant possessed the specific intent to encourage the third party to infringe, *see Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1363 (Fed. Cir. 2003).

I recommend that the court deny defendants' motions to dismiss with respect to the causes of action for induced infringement because the FAC adequately pleads direct infringement, knowledge, and intent. First, the FAC states that the acts of L'Oréal's customers, who are end-users of the Accused Products, constitute direct infringement. (D.I. 13 at ¶ 40) The FAC also pleads the requisite knowledge element. "This court has held that a complaint sufficiently pleads a defendant's actual knowledge . . . when a plaintiff alleges that a defendant previously filed papers with the PTO identifying the patents as prior art." *MONEC Holding AG v. Motorola Mobility, Inc.*, 897 F. Supp. 2d 225, 229-30 (D. Del. 2012). Taking plaintiffs' allegations in the FAC as true, it is plausible to infer that L'Oréal knew of the patents-in-suit because L'Oréal referenced the '327 patent and the application that issued as the '513 patent in a provisional patent application in 2002. (D.I. 13 at ¶¶ 20-21) It is also plausible to infer that L'Oréal knew that selling the Accused Products constituted patent infringement because a L'Oréal agent contacted co-inventor Dr. Dobson in fall of 2003 to discuss the patents-in-suit and obtain a license to the patented technology.[3] (D.I. 13 at ¶ 23)

[3] Plaintiffs also contend that a notice letter sent in March 2015 to L'Oréal's CEO is sufficient to show that L'Oréal knew its acts induced infringement. (D.I. 19 at 9) The court declines to consider this letter, however, because its contents are not quoted or specifically referenced in the FAC or attached thereto. *See Trans Video Elecs., Ltd. V. Netflix, Inc.*, No. 12-1743-LPS-CJB, 2014 WL 900929, at *3 (D. Del. Mar. 4, 2014), *adopted by* 2014 WL 1268680 (D. Del. Mar. 26, 2014) (declining to consider on a motion to dismiss a notice letter plaintiff purportedly sent to defendant where the letter and its contents were not quoted or clearly referenced in the complaint or attached thereto).

The FAC also plausibly pleads that L'Oréal intended to induce its customers to infringe the patents-in-suit by identifying the advertising and instructional materials provided with L'Oréal Paris' RevitaLift Triple Power Deep-Acting Moisturizer that teach customers to practice the methods claimed in the patents-in-suit. (D.I. 13 at ¶¶ 30, 34) Federal Circuit precedent establishes that, at the pleading stage, facts comparable to those alleged in the FAC are sufficient to give rise to a reasonable inference of an intention to induce customers to use a patented method. *See In re Bill of Lading*, 681 F.3d at 1341-42 (concluding that advertisements encouraging infringing uses of an accused product give rise to a reasonable inference of an intention to induce customers to use the patented method); *see also DermaFocus LLC*, 201 F. Supp. 3d at 471 (holding that the plaintiff sufficiently pleaded knowledge of alleged infringing use by the defendant, which provided instructions, promotional and educational materials to its customers). Consequently, I recommend that the court deny L'Oréal USA and L'Oréal S.A.'s Rule 12(b)(6) motions to dismiss plaintiffs' causes of action for induced infringement of the '327 and '513 patents.

3. Contributory infringement

"Contributory infringement imposes liability on one who embodies in a non-staple device the heart of a patented process and supplies the device to others to complete the process and appropriate the benefit of the patented invention." *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1327 (Fed. Cir. 2009). "To state a claim for contributory infringement, an infringer must sell, offer to sell or import into the United States a component of an infringing product 'knowing [the component] to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial non infringing use." 35 U.S.C. § 271(c); *see Lucent Techs. v. Gateway, Inc.*, 580 F.3d 1301, 1320

(Fed. Cir. 2009). As with induced infringement, a claim for contributory infringement must contain allegations of the requisite knowledge of the patent-in-suit at the time of infringement. *Mallinckrodt, Inc. v. E-Z-Em Inc.*, 670 F. Supp. 2d 349, 355 (D. Del. 2009); *see also Global-Tech Appliances, Inc. v. SEB S.A.*, 131 S. Ct. 2060, 2068 (2011). The requisite knowledge for contributory infringement is the same as the knowledge for induced infringement. *Nexeon Ltd. v. Eaglepicher Techs., LLC*, No. 15-955-RGA-MPT, 2016 WL 4045474, at *4 (D. Del. July 26, 2016), *adopted by* 2016 WL 6093471 (D. Del. Oct. 18, 2016). In addition, the patentee bears the burden of proving that the accused products are a material part of the patented invention, and that they have no substantial non-infringing uses. *See Golden Blount, Inc. v. Robert H. Peterson Co.*, 438 F.3d 1354, 1363 (Fed. Cir. 2006); *Nexeon Ltd.*, 2016 WL 4045474, at *4.

I recommend that the court deny defendants' motions to dismiss with respect to the causes of action for contributory infringement. As explained in § IV.A.2, *supra*, plaintiffs have shown direct infringement and that L'Oréal had the requisite knowledge of the patents-in-suit. *See Nexeon Ltd.*, 2016 WL 4045474, at *4 ("the knowledge for inducement is the same for contributory infringement"). The FAC also adequately pleads that the Accused Products are a material part of the patented inventions: the "use of the Accused Adenosine Products is a material and substantial part of the invention claimed by the '327 patent." (D.I. 13 at ¶ 43); *see Courtesy Prods., L.L.C. v. Hamilton Beach Brands, Inc.*, 73 F. Supp. 3d 435, 440-41 (D. Del. 2014) (finding that the complaint sufficiently pled that the accused products were a material part of the patented invention where the complaint alleged that the defendant made, sold, or offered to sell components "which [defendant] [knew] constitute[d] a material part of the invention[.]").

Plaintiffs also adequately plead that the Accused Products have no known substantial non-infringing use. (D.I. 13 at ¶ 43) "The Federal Circuit has ruled that affirmatively pleading

the absence of substantial non-infringing uses renders the claim plausible if the pleadings do not undermine that allegation." *Merck Sharp & Dohme Corp. v. Teva Pharma. USA, Inc.*, No. 14-874-SLR-SRF, 2015 WL 4036951, at *7 (D. Del. Jul. 1, 2015) (citing *In re Bill of Lading,* 681 F.3d at 1339). Because the pleadings do not undermine plaintiffs' allegation in the present case, the FAC adequately pleads that the Accused Products have no substantial non-infringing use. Accordingly, I recommend that the court deny L'Oréal USA and L'Oréal S.A.'s Rule 12(b)(6) motions to dismiss plaintiffs' causes of action for contributory infringement of the '327 and '513 patents.

4. Willful infringement

Pursuant to § 284 of the Patent Act, once infringement has been established, the court "may increase the damages up to three times the amount found or assessed." 35 U.S.C. § 284. To state a claim for willful infringement, a patent owner must allege facts showing that the defendant had knowledge of the asserted patent. *See WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1341 (Fed. Cir. 2016). "A patent infringer's subjective willfulness, whether intentional or knowing, may warrant enhanced damages, without regard to whether his infringement was objectively reckless." *Halo Elecs., Inc. v. Pulse Elecs., Inc.*, 136 S. Ct. 1923, 1926 (2016). At the pleading stage, generalized allegations of willfulness, even without a specific showing of egregiousness, are sufficient to withstand a motion to dismiss. *See Shire Viropharma Inc. v. CSL Behring LLC*, No. 17-414, 2018 WL 326406, at *3 (D. Del. Jan. 8, 2018).

I recommend that the court deny defendants' motions to dismiss with respect to the causes of action for willful infringement because the FAC adequately pleads knowledge and willfulness. Plaintiffs allege that L'Oréal knew of the patents-in-suit because L'Oréal referenced the '327 patent and the application that issued as the '513 patent in a provisional patent

application in 2002. (D.I. 13 at ¶¶ 20-21) Plaintiffs further assert that L'Oréal knew that selling the Accused Products constituted patent infringement because a L'Oréal agent contacted co-inventor Dr. Dobson in fall of 2003 to discuss the patents-in-suit and obtain a license to the patented technology. (*Id.* at ¶ 23) Taking plaintiffs' allegations in the FAC as true, it is plausible to infer that by continuing to use and sell the Accused Products after learning of and requesting a license to the patents-in-suit, L'Oréal intentionally or knowingly infringed the patents-in-suit. *Bio-Rad Labs Inc. v. Termo Fisher Sci. Inc.*, 267 F. Supp. 3d 499, 501 (D. Del. 2017) (finding willful infringement to be sufficiently alleged where the facts allowed the court to plausibly infer that the defendant intentionally or knowingly infringed the patent-in-suit). Accordingly, I recommend that the court deny L'Oréal USA and L'Oréal S.A.'s Rule 12(b)(6) motions to dismiss plaintiffs' causes of action for willful infringement of the '327 and '513 patents.

B. Personal Jurisdiction

Plaintiffs do not allege that L'Oréal S.A. is "at home" in Delaware for purposes of establishing general jurisdiction. As such, whether the court has personal jurisdiction over L'Oréal S.A. turns on whether the court has specific jurisdiction over L'Oréal S.A. Rule 4 of the Federal Rules of Civil Procedure governs the court's analysis. *See Synthes (U.S.A.) v. G.M. Dos Reis Jr. Ind. Com. De Equip. Medico*, 563 F.2d 1285, 1293 (Fed. Cir. 2009). Plaintiffs contend that the court's exercise of personal jurisdiction over L'Oréal S.A. is proper under Rules 4(k)(1) and 4(k)(2) because L'Oréal S.A. has "extensive contacts with the relevant forums, both through its admitted agent L'Oréal USA and otherwise." (D.I. 27 at 2) However, for the following reasons, the court finds that plaintiffs fail to present sufficient evidence to meet their burden of

showing that L'Oréal S.A. has the minimum contacts required by the Due Process Clause that would make an exercise of personal jurisdiction proper.

1. Rule 4(k)(1)

Plaintiffs contend that L'Oréal S.A. is subject to the court's jurisdiction pursuant to Federal Rule of Civil Procedure Rule 4(k)(1), which provides that service of process establishes personal jurisdiction over a defendant "who is subject to the jurisdiction of a court of general jurisdiction in the state where the district court is located." Fed. R. Civ. P. 4(k)(1)(A). An inquiry into whether the exercise of personal jurisdiction over a defendant is proper pursuant to Rule 4(k)(1) requires the court to decide whether: (1) the forum state's long-arm statute permits service of process on defendant; and (2) the exercise of personal jurisdiction comports with the Due Process Clause of the Constitution. *Touchcom, Inc. v. Bereskin & Parr*, 574 F.3d 1403, 1411 (Fed. Cir. 2009). Because "[t]he Delaware long-arm statute . . . has been construed broadly to confer jurisdiction to the maximum extent possible under the Due Process Clause . . . the focus of [this] inquiry [will] rest[ ] on the constitutional component." *Nespresso USA, Inc. v. Ethical Coffee Co. SA*, 263 F. Supp. 3d 498, 502 (D. Del. 2017) (internal citation and quotation marks omitted).

Plaintiffs contend that the court's exercise of personal jurisdiction over L'Oréal S.A. comports with constitutional due process requirements under the stream of commerce and agency theories.[4] However, the record reflects that L'Oréal S.A. does not have sufficient

[4] Plaintiffs also argue that personal jurisdiction over L'Oréal S.A. is proper under the dual jurisdiction analysis. (D.I. 27 at 15) "[T]he dual jurisdiction analysis requires a showing of both: (1) an intent to serve the Delaware market; and (2) that this intent results in the introduction of the product into the market and that plaintiffs cause of action arises from injuries caused by that product." *Belden Techs., Inc. v. LS Corp.*, 829 F. Supp. 2d 260, 267 (D. Del. 2010) (citing *Power Integrations, Inc. v. BCD Semiconductor Corp.*, 547 F. Supp. 2d 365, 371-72 (D. Del. 2008)). Plaintiffs' theory fails, however, because the record suggests that L'Oréal

minimum contacts with the forum to support jurisdiction under either of the theories presented by plaintiffs. Accordingly, the court lacks personal jurisdiction over L'Oréal S.A. under Rule 4(k)(1).

(a) Stream of commerce theory

Under the stream of commerce theory, a foreign defendant can be subjected to a forum state's jurisdiction if it "'purposefully avails itself of the privilege of conducting activities within the forum State, thus invoking the benefits and protections of its laws.'" *Nespresso USA, Inc.*, 263 F. Supp. 3d at 503-04 (quoting *Hanson v. Denckla*, 357 U.S. 235, 253 (1958)). Plaintiffs argue that personal jurisdiction is appropriate under this theory because L'Oréal S.A. intends for its products to be sold in the United States through its subsidiary L'Oréal USA. (D.I. 27 at 15) L'Oréal S.A. does not dispute that the Accused Products are sold in Delaware and throughout the United States, but contends that it is not responsible for introducing the Accused Products, which are made and sold by L'Oréal USA in the United States, into the stream of commerce. (D.I. 29 at 5)

The record before the court does not support plaintiffs' argument that L'Oréal S.A. introduced the Accused Products into the stream of commerce. *See id.* Rather, the record suggests that L'Oréal USA introduced the Accused Products into the stream of commerce. (D.I. 25 at ¶ 4) (stating that L'Oréal USA "manufactures and distributes its own products[.]") L'Oréal S.A.'s corporate structure is not sufficient to establish personal jurisdiction under the stream of commerce theory because "mere ownership of a subsidiary does not justify the

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USA—not L'Oréal S.A.—intended to serve the Delaware market and introduced the Accused Products into Delaware. *See* § IV.B.1.a, *infra*; *see also Belden Techs., Inc.*, 829 F. Supp. 2d at 268 (finding that plaintiff's dual jurisdiction theory failed as to the foreign defendant because the evidence showed that the American defendant introduced the accused products into the Delaware market, not the foreign defendant).

imposition of liability on the parent." *Nespresso USA, Inc.*, 263 F. Supp. 3d at 504 (internal quotation marks and citation omitted). Instead, plaintiffs must present evidence showing that the parent company is responsible for introducing the Accused Products into the U.S. or Delaware markets. *See id.* (holding that a plaintiff must show that the defendant parent corporation is "responsible for introducing the [accused products] into the stream of commerce, and not simply that a subsidiary within the United States introduced the [accused products]."). Similar to the circumstances presented in *Nespresso*, the record before the court does not indicate that L'Oréal S.A. had a role in the design, manufacture, marketing, or sale of the Accused Products. (D.I. 13 at ¶ 32-33)

Plaintiffs allege that L'Oréal S.A. is responsible for introducing the Accused Products into the United States market because it spearheads L'Oréal Group, and L'Oréal Group researchers developed the adenosine-containing skincare products sold in the United States. (D.I. 27 at 7) However, plaintiffs do not specifically tie the development or sale of the Accused Products to L'Oréal S.A. As such, plaintiffs cannot show that L'Oréal S.A. "placed—or otherwise influenced the placement of—the [accused products] into either the United States market generally or the Delaware market specifically." *Nespresso USA, Inc.*, 263 F. Supp. 3d at 504. Accordingly, plaintiffs' stream of commerce theory fails.

Plaintiffs also contend that, by owning United States patents and suing to enforce its patents in this and other United States courts, L'Oréal S.A. has purposefully availed itself of the privilege of conducting activities in the forum state. (D.I. 27 at 10) However, the court has repeatedly held that "ownership of a United States patent, without more, cannot support the assertion of personal jurisdiction over a foreign patentee in any state." *Nespresso USA, Inc.*, 263

F. Supp. 3d at 504 (internal quotation marks and citation omitted). As such, plaintiffs cannot prevail on their stream of commerce theory.

(b) Agency theory

Plaintiffs contend that L'Oréal S.A. is subject to the court's jurisdiction under the agency theory as well. (D.I. 27 at 2) Under this theory, a subsidiary corporation's specific jurisdictional acts are imputed to its parent corporation to satisfy the jurisdictional requirements "where the subsidiary acts on the parent's behalf or at the parent's direction." *Cephalon, Inc. v. Watson Pharm., Inc.*, 629 F. Supp. 2d. 338, 348 (D. Del. 2009) (internal quotation marks and citation omitted). The existence of an agency relationship depends on "the degree of control [ ] the parent exercises over the subsidiary." *Applied Biosystems, Inc.*, 772 F. Supp. at 1463. To determine whether the parent has the requisite control over the subsidiary to establish an agency relationship, a court will consider the following factors: "the extent of overlap of officers and directors, methods of financing, the division of responsibility for day-to-day management, and the process by which each corporation obtains its business." *Id.*

Plaintiffs fail to establish personal jurisdiction over L'Oréal S.A. under the agency theory. Plaintiffs contend that L'Oréal S.A. and its subsidiaries act as a "unified entity" because "L'Oréal Group [(the overarching entity consisting of L'Oréal S.A. and its subsidiaries)] discloses the financial results of the entire Group in a consolidated . . . report, which includes L'Oréal USA's financial results." (D.I. 27 at 5) However, "filings [by a parent corporation] presenting the assets, liabilities, and financial earnings of its subsidiaries as one indistinguishable whole do not prove agency." *Nespresso USA, Inc.*, 263 F. Supp. 3d at 505 (internal quotation marks and citation omitted).

Plaintiffs also argue that L'Oréal S.A. and L'Oréal USA "operate as a single entity, particularly for the purposes of designing, manufacturing, and selling the Accused Adenosine Products in the United States." (D.I. 27 at 4) As support, plaintiffs again point to L'Oréal Group's 2016 Annual Financial Report, which recognizes L'Oréal S.A. as the entity responsible for the entire group's strategic, scientific, industrial, and marketing coordination. (*Id.* at 5; *see* D.I. 28, Ex. 6 at 37) Plaintiffs also point to a three-day business trip to New York by L'Oréal Group's Board of Directors in June 2016 to review L'Oréal USA's strategy and L'Oréal Group's business development opportunities in the United States. (D.I. 27 at 5; *see* D.I. 28, Ex. 6 at 64) However, these arguments fail to establish that L'Oréal S.A. had control over L'Oréal USA's day-to-day management and matters of patent infringement. *See Nespresso USA, Inc.*, 263 F. Supp. 3d at 505.

Evidence presented by L'Oréal S.A. refutes plaintiffs' allegation that L'Oréal S.A. and L'Oréal USA operate as a single entity. Specifically, "L'Oréal USA maintains separate licensing and distribution contracts, manufactures and distributes its own products, has its own board of directors, issues separate financial statements, files separate tax returns, and maintains its own workforce from L'Oréal S.A." (D.I. 25 at ¶¶ 3-4) Moreover, L'Oréal USA's marketing, advertising, customer relations, and "Research and Innovation" departments are separate from L'Oréal S.A. (*Id.* at ¶ 4) While L'Oréal USA admits that it "receives overall strategic guidance from L'Oréal S.A.," it still "operates independently from its parent." (*Id.*) L'Oréal S.A.'s overall strategic guidance is not sufficient evidence of agency, as it does not establish that L'Oréal S.A. controlled L'Oréal USA regarding matters of patent infringement. *See Nespresso USA, Inc.*, 263 F. Supp. 3d at 505. Because plaintiffs' allegation that L'Oréal S.A. and L'Oréal

USA operate as a single entity controlled by L'Oréal S.A. is not supported by the record, plaintiffs' agency theory fails.

Plaintiffs also argue that an agency relationship exists because L'Oréal Group once referred to L'Oréal USA (formerly known as "Cosmair") as "an agent in the United States." (D.I. 27 at 6; *see* D.I. 28, Ex. 6 at 13) However, this fact is not dispositive, as "[o]ne may be an agent for some business purposes and not others so that the fact that one may be an agent for one purpose does not make him or her an agent for every purpose." *Daimler AG v. Bauman*, 134 S. Ct. 746, 759 (2014). On its own, this statement by L'Oréal Group does not establish that L'Oréal Group controlled L'Oréal USA regarding matters of patent infringement related to this case.

Plaintiffs further argue that jurisdiction is proper over L'Oréal S.A. because L'Oréal Paris' RevitaLift Triple Power Deep-Acting Moisturizer is a L'Oréal Group brand, not a L'Oréal USA brand. (D.I. 27 at 6-7) L'Oréal S.A. maintains that this is not the case. (D.I. 24 at 3) Plaintiffs present a number of Internet documents that purportedly show that L'Oréal Group—not L'Oréal USA—is responsible for creating and selling L'Oréal Paris products. (D.I. 27 at 7; *see* D.I. 28, Ex. 4 at 7; D.I. 28, Ex. 9 at 3; D.I. 28, Ex. 10 at 6; D.I. 28, Ex. 4 at 27; D.I. 28, Ex. 6 at 185, 238-240, 244; D.I. 28, Ex. 11) However, plaintiffs' own evidence contradicts the point they attempt to prove because the Internet document entitled "L'Oréal USA Facts and Figures" explicitly lists L'Oréal Paris as a L'Oréal USA brand. (D.I. 28, Ex. 7 at 1-2 ("L'Oréal USA's brands are: . . . L'Oréal Paris . . .")) Because the present record indicates that L'Oréal Paris is a L'Oréal USA brand and, as previously explained, L'Oréal USA is not an agent of L'Oréal S.A. such that its actions can be imputed to L'Oréal S.A., personal jurisdiction over L'Oréal S.A.

cannot be predicated on the sale of L'Oréal Paris products. For these reasons, plaintiffs have failed to establish personal jurisdiction over L'Oréal S.A. under Rule 4(k)(1).

2. Rule 4(k)(2)

Plaintiffs also contend that Federal Rule of Civil Procedure 4(k)(2) gives the court personal jurisdiction over L'Oréal S.A. (D.I. 27 at 8) Rule 4(k)(2) "contemplates a defendant's contacts with the entire United States, as opposed to the state in which the district court sits." *Synthes (U.S.A.)*, 563 F.3d at 1295. Similar to the Rule 4(k)(1) analysis, personal jurisdiction under Rule 4(k)(2) must comport with constitutional due process requirements. *See Nespresso USA, Inc.*, 263 F. Supp. 3d at 506. As previously discussed in § IV.B.1, *supra*, plaintiffs have failed to demonstrate that L'Oréal S.A. has sufficient minimum contacts under either the stream of commerce or agency theories. Because plaintiffs have not demonstrated L'Oréal S.A.'s minimum contacts have not been established, personal jurisdiction does not comport with constitutional due process requirements, and cannot be predicated on Rule 4(k)(2). *See id.*

3. Jurisdictional Discovery

Plaintiffs have also failed to present sufficient factual allegations to justify jurisdictional discovery. Generally, "courts are to assist the plaintiff by allowing jurisdictional discovery unless the plaintiff's claim is 'clearly frivolous.'" *Toys "R" Us, Inc. v. Step Two, S.A.*, 318 F.3d 446, 456 (3d Cir.2003) (quoting *Mass. Sch. of Law at Andover, Inc. v. Am. Bar Ass'n*, 107 F.3d 1026, 1042 (3d Cir.1997). "A plaintiff may not, however, undertake a fishing expedition based only upon bare allegations, under the guise of jurisdictional discovery." *Eurofins Pharma U.S. Holdings v. BioAlliance Pharma SA*, 623 F.3d 147, 157 (3d Cir. 2010) (citing *Belden Techs., Inc. v. LS Corp.*, 626 F. Supp. 2d 448, 459 (D. Del. 2009)). Thus, in order to justify jurisdictional discovery, the plaintiff must present "factual allegations that suggest 'with reasonable

particularity' the possible existence of the requisite 'contacts between [the defendant] and the forum state.'" *Toys "R" Us*, 318 F.3d at 456 (quoting *Mellon Bank (East) PSFS, Nat'l Ass'n v. Farino,* 960 F.2d 1217, 1223 (3d Cir.1992)).

In the present case, plaintiffs' factual allegations are insufficient to warrant jurisdictional discovery. Plaintiffs assert that jurisdiction over L'Oréal S.A. is proper under the stream of commerce and agency theories and based on L'Oréal S.A.'s own contacts with the forum. As previously mentioned, *see* § IV.B.1, *supra*, plaintiffs' arguments that jurisdiction over L'Oréal S.A. is proper are contradicted by plaintiffs' own proffered evidence. (D.I. 28, Ex. 7). Plaintiffs' allegations fail to assert with reasonable particularity facts showing that L'Oréal S.A. might be subject to personal jurisdiction under Rule 4(k)(1) or (2). Therefore, I recommend that the court deny plaintiffs' request for jurisdictional discovery.

V. CONCLUSION

For the foregoing reasons, I recommend that the court: (1) deny L'Oréal USA's Rule 12(b)(6) motion to dismiss (D.I. 15); (2) deny L'Oréal S.A.'s Rule 12(b)(6) motion to dismiss (D.I. 23); and (3) grant L'Oréal S.A.'s Rule 12(b)(2) motion to dismiss (D.I. 23).

This Report and Recommendation is filed pursuant to 28 U.S.C. § 636(b)(1)(B), Fed. R. Civ. P. 72(b)(1), and D. Del. LR 72.1. The parties may serve and file specific written objections within fourteen (14) days after being served with a copy of this Report and Recommendation. Fed. R. Civ. P. 72(b)(2). The objections and responses to the objections are limited to ten (10) pages each. The failure of a party to object to legal conclusions may result in the loss of the right to de novo review in the District Court. *See Sincavage v. Barnhart,* 171 F. App'x 924, 925 n.1 (3d Cir. 2006); *Henderson v. Carlson*, 812 F.2d 874, 878-79 (3d Cir. 1987).

The parties are directed to the court's Standing Order for Objections Filed Under Fed. R. Civ. P. 72, dated October 9, 2013, a copy of which is available on the court's website, http://www.ded.uscourts.gov.

Dated: November 13, 2018

Sherry R. Fallon
United States Magistrate Judge

US006423327B1

(12) **United States Patent**
Dobson, Jr. et al.

(10) **Patent No.: US 6,423,327 B1**
(45) **Date of Patent: Jul. 23, 2002**

(54) **TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG**

(75) Inventors: **James G. Dobson, Jr.**, Auburn; **Michael F. Ethier**, Grafton, both of MA (US)

(73) Assignee: **University of Massachusetts**, Boston, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/672,348**

(22) Filed: **Sep. 28, 2000**

Related U.S. Application Data

(63) Continuation of application No. 09/179,006, filed on Oct. 26, 1998, now abandoned.

(51) **Int. Cl.**[7] **A61K 7/00**

(52) **U.S. Cl.** **424/401**; 424/447; 424/448; 424/449; 514/46

(58) **Field of Search** 424/407, 447, 424/448, 449; 514/46

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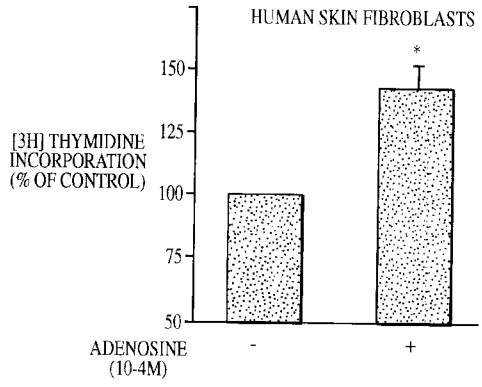
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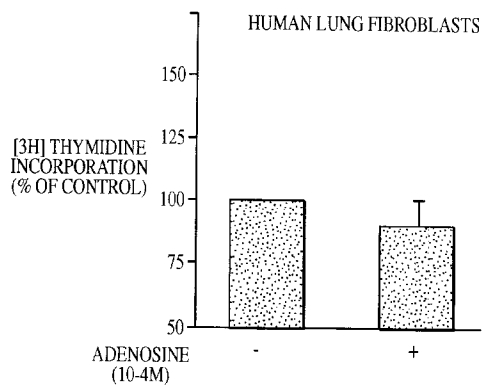
Primary Examiner—Thurman K. Page
Assistant Examiner—Lakshmi Channavajjala
(74) *Attorney, Agent, or Firm*—Fish & Richardson P.C.

(57) **ABSTRACT**

Methods for enhancing the condition of non-diseased skin by application of compositions containing adenosine or an adenosine analog are disclosed. Also disclosed are methods for increasing DNA synthesis or protein synthesis in dermal cells, and methods for increasing dermal cell size, by application of compositions containing adenosine.

10 Claims, 2 Drawing Sheets





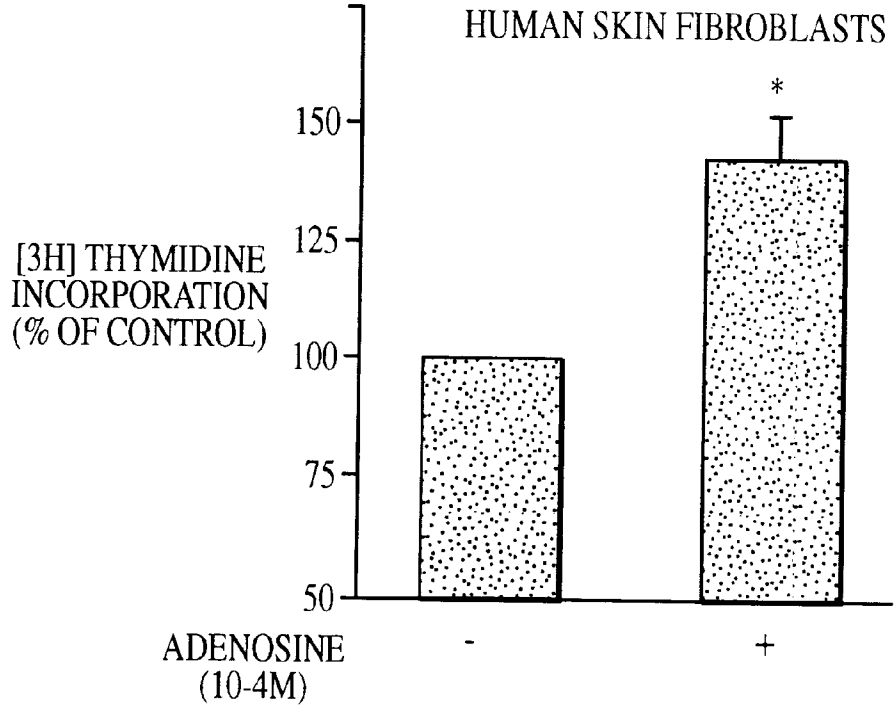

HUMAN SKIN FIBROBLASTS
[3H] THYMIDINE INCORPORATION (% OF CONTROL)
150
125
100
75
50
*
ADENOSINE (10-4M)
-
+

FIG. 1A

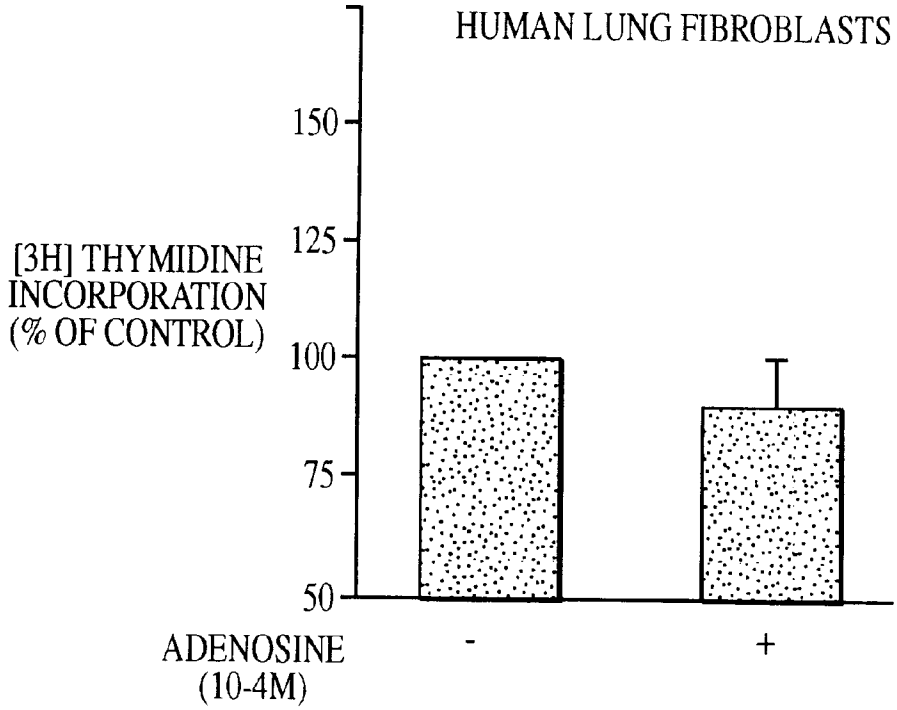

HUMAN LUNG FIBROBLASTS
[3H] THYMIDINE INCORPORATION (% OF CONTROL)
150
125
100
75
50
ADENOSINE (10-4M)
-
+

FIG. 1B

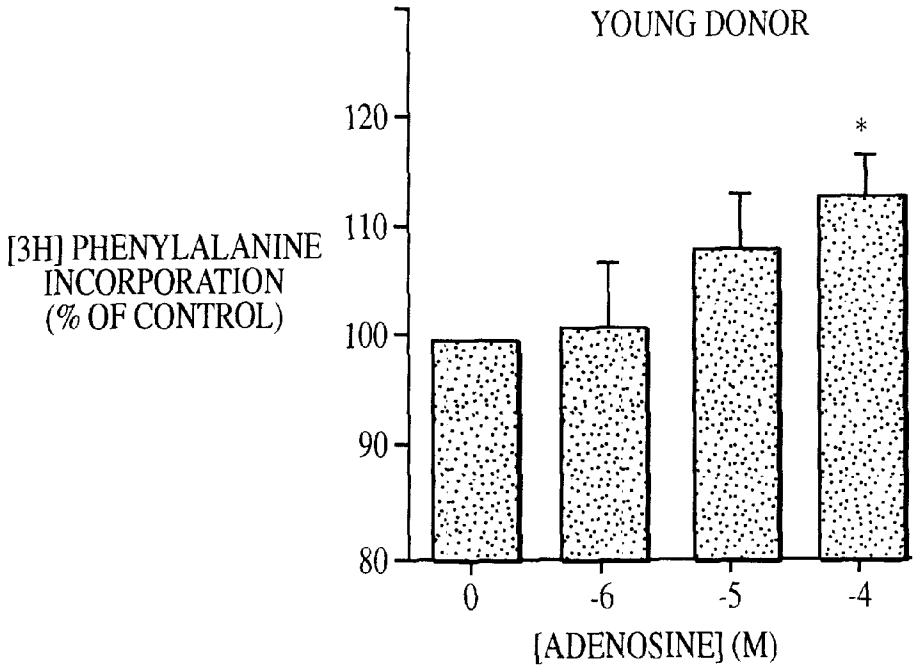

YOUNG DONOR
[3H] PHENYLALANINE INCORPORATION (% OF CONTROL)
120
110
100
90
80
*
0
-6
-5
-4
[ADENOSINE] (M)

FIG. 2A

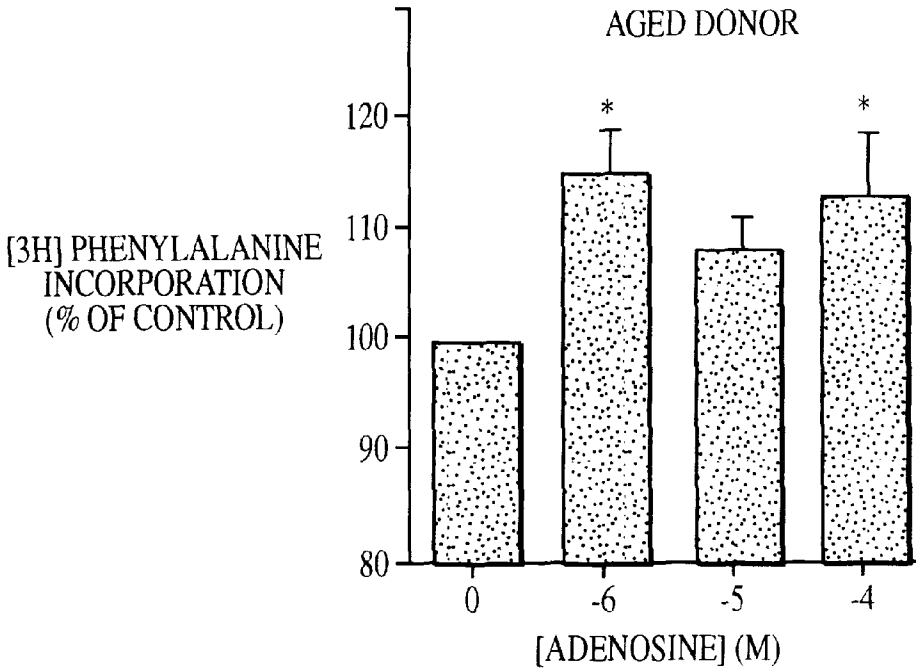

AGED DONOR
[3H] PHENYLALANINE INCORPORATION (% OF CONTROL)
120
110
100
90
80
*
*
0
-6
-5
-4
[ADENOSINE] (M)

FIG. 2B

TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

This application is a continuation of application Ser. No. 09/179,006, filed Oct. 26, 1998, now abandoned.

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

Work on this invention was supported by funds from the United States government (Public Health Service Grants HL-22828 and AG-11491). The government therefore has certain rights in this invention.

FIELD OF THE INVENTION

This invention relates to dermatology and cell biology.

BACKGROUND OF THE INVENTION

Skin includes a surface layer, known as the epidermis, and a deeper connective tissue layer, known as the dermis. The epidermis undergoes continuous turnover as the outermost cells are exfoliated and replaced by cells that arise from inner dermal layers. The dermis is composed of a variety of cell types, including fibroblasts.

Skin thickness begins to decline in humans after the age of 20 as the dermis becomes thinner and the number of skin fibroblasts declines. As skin ages, or is exposed to UV light and other environmental insults, changes in the underlying dermis can lead to the functional and morphological changes associated with damaged skin. Decreases in the abundance and function of products of the fibroblasts, which include collagen and proteoglycans, are believed to play major roles in wrinkled and damaged skin.

SUMMARY OF THE INVENTION

We have discovered that adenosine stimulates DNA synthesis, increases protein synthesis, and increases cell size in cultures of human skin fibroblasts. Based on this discovery, the invention provides methods and compositions for enhancing the condition of skin.

In general, the invention provides a method for enhancing the condition of non-diseased skin of a mammal, e.g., a human. The method includes topically applying a therapeutically effective amount of a composition including adenosine or an adenosine analog to non-diseased skin of the mammal.

The invention also provides a method for promoting healing of broken, non-diseased skin in a mammal by topically administering a composition including a therapeutically effective amount of adenosine or an adenosine analog to the mammal.

Also included in the invention is a method for increasing DNA synthesis in a dermal cell of non-diseased skin of a mammal. The method includes topically administering a therapeutically effective amount of adenosine or an adenosine analog to a region of non-diseased skin of the mammal containing dermal cell. The adenosine is added so that it does not cause proliferation of the dermal cell.

The invention also features a method of increasing protein synthesis in a dermal cell of non-diseased skin of a mammal. The method includes topically administering a composition including a therapeutically effective amount of adenosine or an adenosine analog to a region of skin of the mammal containing the dermal cell. The adenosine or adenosine analog does not cause proliferation of the dermal cell.

Also provided in the invention is a method of increasing cell size in a dermal cell in non-diseased skin of a mammal, e.g., a human. The method includes topically administering a composition including a therapeutically effective amount of adenosine to a region of skin of the mammal containing the dermal cell, wherein addition of the adenosine does not cause proliferation of the dermal cell, wherein addition of the adenosine does not cause proliferation of the dermal cell.

The invention also includes a method for enhancing skin condition in a mammal, e.g., a human. The method includes providing fibroblasts from the mammal ex vivo, culturing the fibroblasts in the presence of adenosine, and reintroducing the fibroblasts into the mammal.

The therapeutically effective amount of adenosine used in the above-described methods is preferably 10^{-3} M to 10^{-7} M, more preferably 10^{-3} M to 10^{-6} M, and most preferably about 10^{-4} M.

The composition used in the above-described methods can include a second agent in addition to adenosine. The second agent can be, e.g. an agent that promotes binding of adenosine or an adenosine analog to an adenosine receptor, an angiogenic factor such as vascular endothelial cell growth factor (VEGF), basic fibroblast growth factor (BFGF), an agent that itself enhances skin condition, such as tretoinin or another known conditioning agent such as an emollient, a humectant, or an occlusive agent.

In preferred embodiments of the invention, the adenosine or an adenosine analog does not promote skin cell proliferation.

The invention also provides a composition including about 10^{-3} M to about 10^{-7} M adenosine and a therapeutically effective amount of an angiogenesis factor. In some embodiments, the composition of the adenosine is about 10^{-4} M.

As. used herein, "enhancement of skin condition" means a noticeable decrease in the amount of wrinkling, roughness, dryness, laxity, sallowness, or pigmentary mottling in skin.

As used herein, a "therapeutically effective amount" of adenosine or an adenosine analog means an amount that enhances skin condition when applied to skin.

As used herein, "non-diseased skin" means skin free of any proliferative disorder observable by visual inspection.

The present invention advantageously allows for enhancement of skin condition. This results in skin that shows a less wrinkled, rough, or dry complexion. For example, the invention provides for enhancing the condition of skin damaged due to exposure to the sun or skin whose condition has deteriorated due to normal aging.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Other features and advantages of this invention will be apparent from the following description of-the preferred embodiments thereof, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. **1A** and **1B** are histograms showing the effect of adenosine on [^{3}H]thymidine incorporation in cultures of

normal human skin (FIG. 1A) and lung fibroblasts (FIG. 1B). After incubation in serum-free medium for 24 hours, cells were exposed to 10^{-4} M adenosine for 18 hours. Medium was replaced with serum-free medium without adenosine, and [^{3}H]thymidine was added. Results are expressed as percent [^{3}H]thymidine incorporation compared to control cultures without adenosine and are means±SEM for 4–5 experiments. "*" denotes value was significantly different from control value without adenosine.

FIGS. 2A and 2B are histograms showing concentration responses of adenosine-stimulated protein synthesis in human skin fibroblasts from a young (FIG. 2A) and aged (FIG. 2B) donor. Cells were grown to 75% confluence. Medium was then replaced with serum-free medium with or without adenosine. After 48 hours, [^{3}H]phenylalanine incorporation was determined as described. Results are expressed as % [^{3}H]phenylalanine incorporation compared to control cultures without adenosine and are means±SEM for 6–25 experiments. "*" denotes value was significantly different from control value without adenosine.

DETAILED DESCRIPTION

The invention is suitable for treating skin of a mammal, e.g., a human, for which promotion of fibroblast-associated dermal functions is desired. For example, promotion of fibroblast-associated functions is desirable in enhancing the condition of aged skin, which is associated with a decrease in dermal cell function and is characterized by increased dryness or roughness, or both. The method can also be used on subjects having otherwise damaged skin, e.g., wrinkled skin and skin with a non-proliferative disorder. The method can may further be used prophylactically on a subject to minimize deterioration of skin condition associated with aging or environmental factors, such as photodamage.

Adenosine and suitable adenosine analogs are suitable for use in enhancing skin condition. Adenosine analogs such as adenosine agonists, adenosine receptor agonists, and compounds that increase intracellular or extracellular adenosine levels are suitable for use in the invention.

Agonists of adenosine include 2'-deoxyadenosine; 2', 3'-isopropoylidene adenosine; toyocamycin; 1-methyladenosine; N-6-methyladenosine; adenosine N-oxide; 6-methylmercaptopurine riboside; 6-chloropurine riboside, 5'adenosine monophosphate, 5'-adenosine diphosphate, or 5'-adenosine triphosphate. Adenosine receptor agonists include phenylisopropyl-adenosine ("PIA"), 1-Methylisoguanosine, ENBA (S(-), N^6-Cyclohexyladenosine (CHA), N^6-Cyclopentyladenosine (CPA), 2-Chloro-N6-cyclopentyladenosine, 2-chloroadenosine, and adenosine amine congener (ADAC), all of which are agonists for the adenosine A_1 receptor. Other receptor agonists include 2-p-(2-carboxy-ethyl) phenethyl-amino-5'-N-ethylcarboxamido-adenosine (CGS-21680), N-ethylcarboxamido-adenosine (NECA) and napthyl-substituted aralkoxyadenosine (SHA-082), 5' (N-Cyclopropyl)-carboxamidoadenosine, DPMA (PD 129, 944), Metrifudil, which are agonists for the adenosine A_2 receptor. Other adenosine receptor agonists include those which preferentially bind the A_1 receptor relative to the A_2 receptor, such as 2-Chloroadenosine, N_6-Phenyladenosine, and N^6-Phenylethyladenosine; and those which preferentially bind the A_2 receptor relative to the A_1 receptor, such as 2-Phenylaminoadenosine and MECA.

Also suitable for use are compounds that increase intracellular adenosine concentration by inhibiting the cellular uptake of adenosine or the breakdown of adenosine. One pathway of adenosine metabolism is the conversion of adenosine to inosine by adenosine deaminase. An example of an adenosine deaminase inhibitor is erythro-9-(2-hydroxy-3-nonyl) adenine ("EHNA"). Adenosine kinase inhibitors can also be used. Adenosine kinase converts adenosine to adenosine monophosphate by adenosine kinase. An example of an adenosine kinase inhibitor is iodotubercidin. Other suitable compounds include those that inhibit the dipyridamole-sensitive nucleoside transporter, which exports adenosine from the cytoplasm, and agents that promote the activity of a 5'-nucleotidase, e.g., the ATP-activated 5'-nucleotidase, which forms adenosine. Compounds that increase tissue adenosine and ATP levels include acadesine (AICA-riboside), which is described in Gruber et al., Circulation 80:1400–1411 (1989).

Adenosine can be also be administered with a second compound. The second compound can enhance the action of adenosine or the adenosine analog, e.g., by enhancing binding of adenosine or an adenosine analog to an adenosine receptor. An example of such a compound is PD 81, 728, which is described in Kollias-Baker et al. J. Pharmacol. Exp. Ther. 281:761–68. Alternatively, the second agent can itself act to enhance skin condition. Examples of these types of agents include tretinoin, a recognized skin conditioning agent (see, e.g., Olsen et al., J. Amer. Acad. Dermatol. 37:217–26, 1997), an angiogenic factor such as vascular endothelial cell growth factor (VEGF) or basic fibroblast growth factor (BFGF), or a conditioning agent.

The second compound can also be a conditioning agent such as an emollient, humectant, or occlusive agent. Numerous examples of particular conditioning agents are provided in the CTFA Cosmetic Ingredient Handbook (Cosmetic Toiletries and Fragrances Association, Washington, D.D., 1988). Emollients help to maintain the soft, smooth, and pliable appearance of skin and function by remaining on the skin surface or in the stratum corneum to act as lubricants, to reduce flaking, and to improve the skin's appearance. Examples of emollients include acetyl trioctyl citrate, cetyl alcohol, butyl myristate, cetyl alcohol, and mineral oil.

Humectants act to increase the water content of the top layers of the skin. Humectants include, e.g., acetamide MEA, fructose, and xylitol. Occlusive agents inhibit the evaporation of water from skin, thereby increasing the water contend of the skin. Acetylated castor oil, mineral oil, and lauryl stearate are examples of occlusive agents.

A subject can be treated by applying adenosine or an adenosine analog in a pharmaceutical composition in an effective amount and for a period of time sufficient to improve the condition of the skin.

The pharmaceutical composition may be formulated using conventional methods to prepare pharmaceutically useful compositions. Such compositions preferably include at least one pharmaceutically acceptable carrier, such as those described in Remington's Pharmaceutical Sciences (E. W. Martin). In addition, the compositions preferably include a pharmaceutically acceptable buffer, preferably phosphate buffered saline, together with a pharmaceutically acceptable compound for adjusting isotonic pressure, such as, for example, sodium chloride, mannitol, or sorbitol.

Adenosine or an adenosine agonist can also be provided in carriers and adjuvants such as ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances, such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen

phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances and polyethylene glycol. Adjuvants for topical or gel base forms of adenosine or adenosine analogs may, for example, be selected from the group consisting of sodium carboxymethylcellulose, polyacrylates, polyoxythylene-polyoxypropylene-block polymers, polyethylene glycol and wood wax alcohols. For all administrations, conventional depot forms may be used.

The adenosine or adenosine analog-containing compositions may be in any pharmaceutically acceptable dosage form. They are preferably applied by topical routes to exert local therapeutic effects. For topical application, the penetration of the adenosine into skin tissue may be enhanced by a variety of methods known to those of ordinary skill in the art. For example, adenosine may be applied directly and mechanically rubbed into the skin. Alternatively, adenosine or adenosine analogs may be incorporated into a transdermal patch that is applied to the skin. Preferably, the penetration resulting from these methods is enhanced with a chemical transdermal delivery agent such as dimethyl sulfoxide (DMSO) or the nonionic surfactant, n-decylmethyl sulfoxide (NDMS), as described in Choi et al., Pharmaceutical Res., 7(11):1099, 1990.

Other modes of administration include, e.g., oral, subdermal, intradermal, or intravenous. When oral administration is used, it is critical that the adenosine or adenosine analog be delivered to that it is not degraded prior to exiting the digestive system.

The most effective mode of administration and dosage regimen of adenosine or the adenosine analog will depend upon the skin condition, previous therapy, the subject's health status, response to the adenosine, the judgment of the treating physician and the mode in which the adenosine is applied. For example, dosages for a therapeutically effective amount for topical application would be in the range of 100 ng to 10 mg per treated surface area per day. The adenosine may be administered to the patient at one time or over a series of treatments. When adenosine or the adenosine analog is administered in conjunction with a second agent, they can be administered either concurrently or sequentially, and can be administered in the same mode or a different mode, e.g., topical or oral.

Adenosine or an adenosine analog enhances skin condition when there is a noticeable decrease in noticeable decrease in the amount of wrinkling, roughness, dryness, laxity, sallowness, or pigmentary mottling of the treated skin. Methods of measuring improvements in skin condition are well known in the art (see, e.g., Olsen et al., J. Amer. Acad. Dermatol. 26:215–24, 1992), and can include subjective evaluations by the patient or a second party, e.g., a treating physician. Objective methods can include skin topography measurements, such as those described in Grove et al., J. Amer. Acad. Dermatol. 21:631–37 (1989). In skin topography measurements, silicone rubber replicas are made of a small area of skin, e.g., a 1 cm diameter circular area. The silicone rubber replicas capture fine lines and wrinkles on the skin. These specimens are then analyzed using computerized digital image processing to provide an objective measurement of the skin's topography. Skin topography measurements generated following digital-image processing can be measured using the values R_a and R_z as described in Olsen et al., J. Amer. Acad. Dermatol. 37:217–26, 1997, where R_a represents the area of deviation of skin surface features above and below an average central line, and R_z represents the difference between the maximum and minimum heights in five equal segments of the skin surface profile. A statistically significant decline (e.g., $P<0.05$) in R_a and R_z values in skin treated with adenosine or an adenosine analog compared to untreated skin indicates an enhancement of skin condition.

Fibroblasts treated with adenosine or adenosine analogs can also be incorporated into a matrix and implanted in the body, e.g., as part of a skin graft. In addition, fibroblasts can be genetically engineered ex vivo to increase the amount of intracellular adenosine levels and then re-introduced into a human patient. (See, for example, Anderson et al. U.S. Pat. No. 5,399,349; and Mulligan & Wilson, U.S. Pat. No. 5,460,959, each of which is incorporated by reference herein in its entirety).

Experimental Information

Cell Culture

Human skin fibroblasts and human lung fibroblasts were supplied by the N.I.A. Aging Culture Repository Center (Camden, N.J.). For skin fibroblasts, primary cultures had been initiated from explants obtained from a 3 mm punch biopsy of the mesial aspect of the upper left arm. Human lung fibroblasts (IMR-90) were established from a 16-week normal female fetus. All cells displayed a normal diploid karyotype and all cells tested negative for bacteria, fungi and mycoplasma contamination.

Cells were grown in Eagle's minimal essential medium (MEM) supplemented with 10% fetal bovine serum (FBS), 100 U/ml penicillin and 100 mg/ml streptomycin in a 37° C., 5% CO_2/95% air environment. After reaching confluence, cells were subcultivated with 0.25% trypsin in MEM with no added Ca^{2+} or Mg^{2+}.

Incorporation of [^{3}H]Thymidine

As an index of DNA synthesis incorporation of [^{3}H] thymidine was measured as described in Ethier et al., Am. J. Physiol. 272:H1470–79 (1997). Confluent monolayers of human skin fibroblasts in MEM plus 10% FBS were seeded into 16 mm diameter culture wells (24-well plates) at a density of 1×10^4 cells/cm^2. Cells were grown at 37° C. under standard culture conditions (5% CO_2–95% air) until they were approximately 75% confluent. Medium was then removed and the cells were made "serum-free" by incubation in MEM with no FBS for 24 hours. Adenosine or vehicle (MEM) was added for an additional 18 hours. This medium was then replaced with fresh MEM, and the cells were pulsed with lmCi/ml [^{3}H] thymidine (6.7 Ci/mmol). After a 2 hour incubation period, the medium was discarded and the cells were rinsed twice with cold (4° C.) Hank's balanced salt solution (HBSS) and incubated for 5 minutes with 0.5 ml cold 10% (w/v) trichloroacetic acid (TCA). The wells were then rinsed with 8% TCA and the TCA-insoluble material was solubilized with 0.5 ml of a solution of 0.2M NaOH and 0.2% sodium decyl sulfate (SDS). The radioactivity of this fraction was determined by standard liquid scintillation spectrometric techniques.

Incorporation of [^{3}H] thymidine was expressed as counts per minute (cpm) of ^{3}H per culture. Data in each experiment was derived from 4 identically treated wells. Since the cpm/well exhibited variation between experiments, data representing combined experiments are expressed herein as a percent of their respective mean control value.

Incorporation of [^{3}H]phenylalanine

Incorporation of [^{3}H]phenylalanine was measured as an index of protein synthesis. Human skin fibroblasts were seeded into 24-well culture plates in MEM containing 10% FBS. When cells had grown to approximately 75% confluence the culture medium was replaced with serum-free MEM with or without adenosine. After 48 hours, 2 μCi/ml

[^{3}H]phenylalanine was added to the cultures. Unlabeled phenylalanine (0.36 mM) was also added to equalize concentrations of intracellular and extracellular phenylalanine. After 8 hours, medium was removed and the cells were washed twice with cold (4° C.) HBSS and incubated for 20 minutes in cold 10% (w/v) TCA. Cells were then incubated 5 minutes in 95% ethanol (4° C.) and the TCA-insoluble material was solubilized with a solution of 0.2M NaOH and 0.2% SDS. The radioactivity of this fraction was determined by standard liquid scintillation spectrometric techniques.

Incorporation of [^{3}H] phenylalanine was expressed as cpm of ^{3}H per culture well and data in each experiment were derived from six identically treated wells. Since the cpm/well exhibited variation between experiments, data representing combined experiments are expressed as a percent of their respective mean control value.

Determination of Cell Size

Human fibroblasts in MEM 10% FBS were seeded into 25 cm^2 culture flasks at a density of 1×10^4 cells/cm^2. When the cells had grown to approximately 80% confluence the culture medium was removed and the cells were incubated in serum-free MEM for 24 hours. Adenosine or vehicle (MEM) was added for 18 hours and cells were then washed twice with cold (4° C.) HBSS. Cells were removed with 0.25% trypsin in calcium-and magnesium-free MEM and diluted in cold (4° C.) HBSS for measurement of relative cell size with a fluorescence-activated cell sorter (FACS; Becton Dickinson Vantage). Cell size was determined by forward light scatter on a minimum of 1×10^4 cells per experiment.

Experimental Materials

MEM, FBS, penicillin, streptomycin, trypsin, and HBSS were obtained from GIBCO (Grand Island, N.Y.), [^{3}H] thymidine (6.7 Ci/mmol) and phenylalanine, L-ring-2,3,4, 5,6-^{3}H] (92 Ci/mmol) were obtained from Dupont NEN (Boston, Mass.). Adenosine was from Boehringer Mannheim, SDS was from National Diagnostics, (Highland Park, N.J.) and TCA and ethanol were obtained from Fisher Scientific (Pittsburgh, PA).

Data Analysis

Analysis of variance (ANOVA) was used to determine statistical differences between means. The Dunett's test was applied for multiple comparisons as described in Zar, J.H., Biostatistical Analysis. Englewood Cliffs, N.J., Prentice Hall, Inc. pp. 150–153, 1984. In addition, the Wilcoxon test was employed to verify differences between values expressed as a percentage. Differences were considered statistically different when $P<0.05$.

DNA Synthesis

Exposure to 10–4M adenosine increased [^{3}H]thymidine incorporation by 43±9% in five studies on cultures of human fibroblasts (AG607720B) made quiescent by serum removal. These results are summarized in FIG. **1**A. In contrast, adenosine (10^{-4}M) had no effect on [^{3}H] thymidine incorporation in cultures of human lung fibroblasts (IMR-90) (FIG. **1**B). Concentrations of adenosine ranging from 10-7 M to 10^{-3} M also failed to stimulate [^{3}H]thymidine incorporation in IMR-90 lung fibroblasts (data not shown).

The effect of adenosine on DNA synthesis was additionally determined on skin fibroblast cultures from six different human donors. Adenosine (10^{-4}M) stimulated DNA synthesis in all three cultures derived from young human donors (Table 1). Values shown are means±SEM, where n is number of experiments. Exposure to adenosine and determination of [^{3}H] thymidine incorporation were as described above. The asterisk denotes a value significantly different from the corresponding control (100%).

TABLE 1

Effect of adenosine on [^{3}H] thymidine incorporation into cultured human skin fibroblasts derived from young donors

Cell Strain	Adenosine (10^{-4}M)	Donor Age	Donor Sex	[^{3}H] thymidine incorporation (% of control)	n
AG07720B	–	24	F	100	24
	+			124 ± 7*	24
AG07306A	–	28	F	100	6
	+			193 ± 20*	6
AG09605	–	30	M	100	12
	+			133 ± 15*	12

Peak stimulation of [^{3}H] thymidine incorporation (93±20%, n=6) was achieved in human skin fibroblast cultures derived from a 28 year old female (AG07306A).

Adenosine (10^{-4}M) stimulated DNA synthesis in 2 of 3 cultures derived from aged human donors (Table 2). As in Table 1, values are means±SEM, and n is the number of experiments performed. The asterisk denotes a measurement significantly different from the corresponding control (100%). Adenosine exposure increased [^{3}H] thymidine incorporation by 53±31% and 54±22% in human skin fibroblast cultures derived from a 70 year-old male and a 84 year-old male, respectively. Adenosine had no effect on cultures derived from a 67-year old female.

TABLE 2

Effect of adenosine on [^{3}H] thymidine incorporation into cultured human skin fibroblasts derived from aged donors

Cell Strain	Adenosine (10^{-4}M)	Donor Age	Donor Sex	[^{3}H] thymidine incorporation (% of control)	n
AG11728	–	67	F	100	6
	+			91 ± 6	6
AG12949	–	70	M	100	11
	+			150 + 31*	11
AG11730	–	84	M	100	10
	+			154 ± 22*	10

Protein Synthesis

The effect of adenosine on protein synthesis was determined by measuring [^{3}H]phenylalanine incorporation into cultures of human fibroblasts from a young and aged donor. Cultures made quiescent by serum removal were exposed to adenosine (10^{-6}M to 10^{-4}M) for 48 hours and then pulsed with phenylalanine. In skin fibroblast cultures derived from a 28-year old female (AG073060A) and an 84-year old male (AG11730), adenosine(10^{-4}M) increased protein synthesis by 13±4% (n=25) and 13±6% (n=17), respectively (FIG. **2**).

Cell Size

The effect of adenosine on cell size was determined on human skin fibroblasts from young and aged donors by measuring forward light scatter in a FACS analyzer. Cultures made quiescent by serum removal were exposed to adenosine for 18 hours, removed by trypsinization, and diluted in 4° C. HBSS. A minimum of 1×10^4 cells were measured for each experiment. The results are shown in Table 2. Values are mean +SEM for relative cell size determined by forward light scatter (FLS) in a fluorescence-activated cell sorter, and

n=number of cells measured. The asterisk denotes the measurement is significantly different from corresponding control.

In skin fibroblast cultures from a 28 year old female (AG073060A) adenosine (10^{-4}M) significantly increased cell size by 1.8 and 2.2% in two of three experiments (Table 3).

The effect of adenosine on cell size was also measured on skin fibroblasts from an aged donor. The results are shown in Table IV. Values are mean±SEM for relative cell size determined by forward light scatter (FLS) in a fluorescence-activated cell sorter, where n is the number of cells measured. An asterisk indicates a value significantly different from corresponding control.

In cultures derived from an 84-year old male (AG11730), adenosine (10^{-4}M) significantly increased cell size by 2.7–4.9% in 3 of 3 experiments (Table 4).

TABLE 3

Effect of adenosine on cell size in cultured human skin fibroblasts derived from young donors

Experiment Number	Adenosine (10^{-4}M)	Relative Size (FLS)	% increase	n
1	–	524 ± 0.55	—	1.5×10^4
	+	526 ± 0.55	0.4	1.5×10^4
2	–	319 ± 1.24	—	1.0×10^4
	+	326 ± 1.16*	2.2*	1.0×10^4
3	–	342 ± 0.94	—	1.0×10^4
	+	348 ± 0.95*	1.8*	1.0×10^4

TABLE 4

Effect of adenosine on cell size in cultured human skin fibroblasts derived from aged donors

Experiment Number	Adenosine (10^{-4}M)	Relative Size (FLS)	% increase	n
1	–	333 ± 0.79	—	1.0×10^4
	+	342 ± 0.75*	2.7*	1.0×10^4
2	–	323 ± 1.01	—	1.0×10^4
	+	337 ± 0.96*	4.3*	1.0×10^4
3	–	306 ± 0.81	—	1.0×10^4
	+	321 ± 0.81*	4.9*	1.0×10^4

Other Embodiments

While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention. For example, while the invention has been described using adenosine and adenosine agonists, other compounds structurally similar to adenosine can also be used, e.g., purine-containing compounds and compounds having a ribosyl moiety. Other aspects, advantages, and modifications of the invention are within the scope of the following claims.

We claim:

1. A method for enhancing the condition of unbroken skin of a mammal by reducing one or more of wrinkling, roughness, dryness, or laxity of the skin, without increasing dermal cell proliferation, the method comprising topically applying to the skin a composition comprising a concentration of adenosine in an amount effective to enhance the condition of the skin without increasing dermal cell proliferation, wherein the adenosine concentration applied to the dermal cells is 10^{-4} M to 10^{-7} M.

2. The method of claim **1**, wherein the composition further comprises an angiogenic factor.

3. The method of claim **1**, wherein the adenosine concentration is 10^{-4} M to 10^{-6} M.

4. The method of claim **1**, wherein the adenosine concentration is about 10^{-4} M.

5. The method of claim **1**, wherein the composition further comprises a conditioning agent.

6. The method of claim **5**, wherein the conditioning agent is a humectant, an emollient, or an occlusive agent.

7. The method of claim **1**, wherein the mammal is a human.

8. The method of claim **1**, wherein the skin comprises a skin graft.

9. The method of claim **1**, wherein the composition further comprises a transdermal delivery agent.

10. The method of claim **1**, wherein the composition is in a transdermal patch and the composition is topically applied by contacting the patch to the skin.

* * * * *

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(12) **United States Patent**
Dobson, Jr. et al.

(10) **Patent No.: US 6,645,513 B2**
(45) **Date of Patent: *Nov. 11, 2003**

(54) **TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(22) Filed: **Jun. 28, 2002**

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Related U.S. Application Data

(63) Continuation of application No. 09/672,348, filed on Sep. 28, 2000, now Pat. No. 6,423,327, which is a continuation of application No. 09/179,006, filed on Oct. 26, 1998, now abandoned.

(51) **Int. Cl.**[7] **A61K 7/00**; A61K 31/7076

(52) **U.S. Cl.** **424/401**; 424/447; 424/448; 424/449; 514/46

(58) **Field of Search** 424/401, 447, 424/448, 449; 514/46

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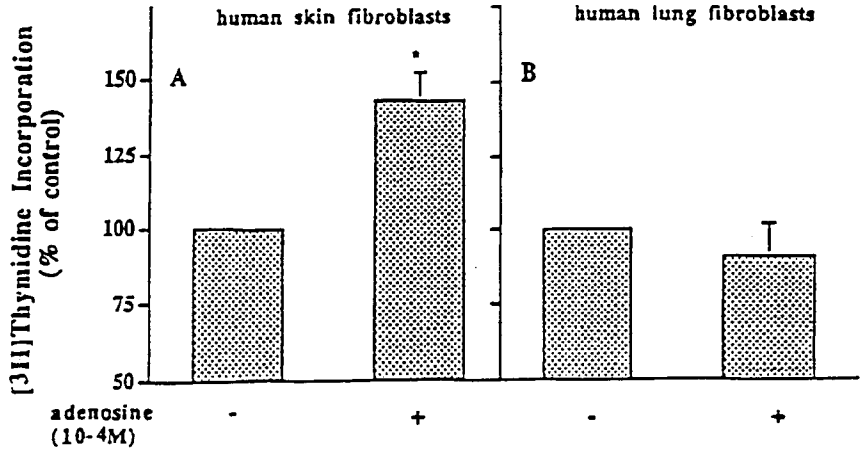
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(57) **ABSTRACT**

Methods for enhancing the condition of non-diseased skin by application of compositions containing adenosine or an adenosine analog are disclosed. Also disclosed are methods for increasing DNA synthesis or protein synthesis in dermal cells, and methods for increasing dermal cell size, by application of compositions containing adenosine.

10 Claims, 2 Drawing Sheets



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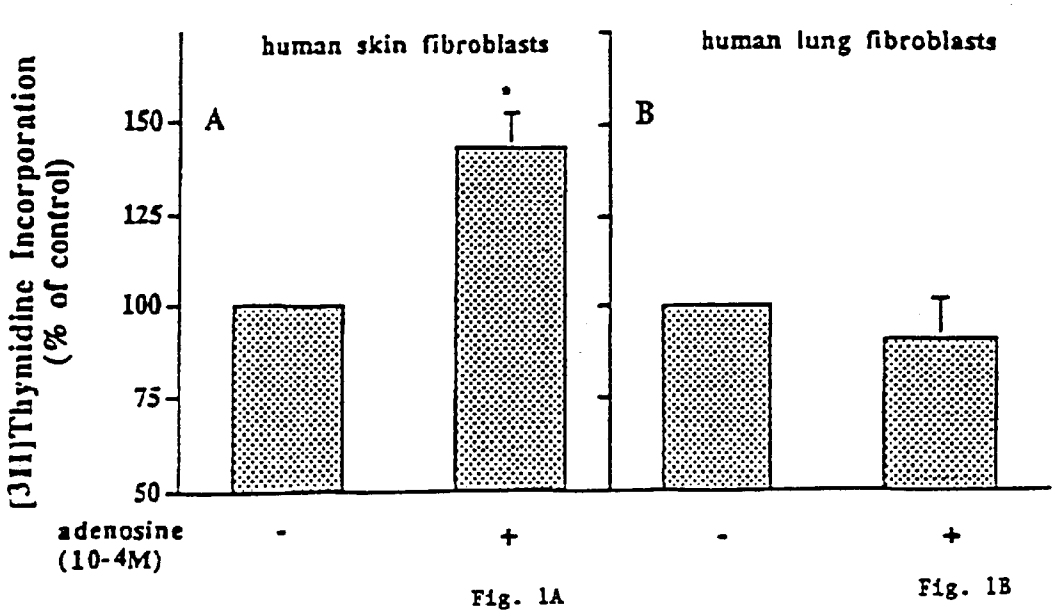

human skin fibroblasts
human lung fibroblasts
A
B
[3H]Thymidine Incorporation
(% of control)
150
125
100
75
50
adenosine
(10-4M)
-
+
-
+

Fig. 1A Fig. 1B

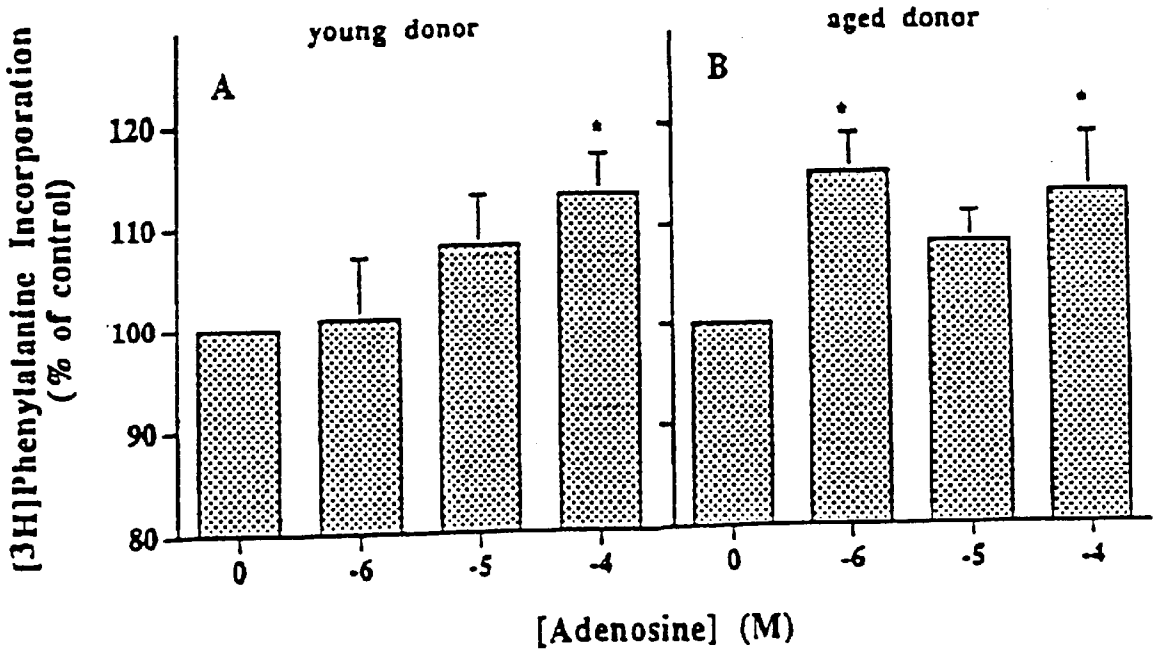

young donor
aged donor
A
B
[3H]Phenylalanine Incorporation (% of control)
120
110
100
90
80
0
-6
-5
-4
0
-6
-5
-4
[Adenosine] (M)

Fig. 2A

Fig. 2B

TREATMENT OF SKIN WITH ADENOSINE OR ADENOSINE ANALOG

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 09/672,348, filed on Sep. 28, 2000, now U.S. Pat. No. 6,423,327, which is a continuation of U.S. patent application Ser. No. 09/179,006, filed on Oct. 26, 1998, now abandoned, which are incorporated herein by reference in their entirety.

STATEMENT AS TO FERDERALLY SPONSORED RESEARCH

Work on this invention was supported by funds from the United States government (Public Health Service Grants HL-22828 and AG-11491). The government therefore has certain rights in this invention.

FIELD OF THE INVENTION

This invention relates to dermatology and cell biology.

BACKGROUND OF THE INVENTION

Skin includes a surface layer, known as the epidermis, and a deeper connective tissue layer, known as the dermis. The epidermis undergoes continuous turnover as the outermost cells are exfoliated and replaced by cells that arise from inner dermal layers. The dermis is composed of a variety of cell types, including fibroblasts.

Skin thickness begins to decline in humans after the age of 20 as the dermis becomes thinner and the number of skin fibroblasts declines. As skin ages, or is exposed to UV light and other environmental insults, changes in the underlying dermis can lead to the functional and morphological changes associated with damaged skin. Decreases in the abundance and function of products of the fibroblasts, which include collagen and proteoglycans, are believed to play major roles in wrinkled and damaged skin.

SUMMARY OF THE INVENTION

We have discovered that adenosine stimulates DNA synthesis, increases protein synthesis, and increases cell size in cultures of human skin fibroblasts. Based on this discovery, the invention provides methods and compositions for enhancing the condition of skin.

In general, the invention provides a method for enhancing the condition of non-diseased skin of a mammal, e.g., a human. The method includes topically applying a therapeutically effective amount of a composition including adenosine or an adenosine analog to non-diseased skin of the mammal.

The invention also provides a method for promoting healing of broken, non-diseased skin in a mammal by topically administering a composition including a therapeutically effective amount of adenosine or an adenosine analog to the mammal.

Also included in the invention is a method for increasing DNA synthesis in a dermal cell of non-diseased skin of a mammal. The method includes topically administering a therapeutically effective amount of adenosine or an adenosine analog to a region of non-diseased skin of the mammal containing dermal cell. The adenosine is added so that it does not cause proliferation of the dermal cell.

The invention also features a method of increasing protein synthesis in a dermal cell of non-diseased skin of a mammal.

The method includes topically administering a composition including a therapeutically effective amount of adenosine or an adenosine analog to a region of skin of the mammal containing the dermal cell. The adenosine or adenosine analog does not cause proliferation of the dermal cell.

Also provided in the invention is a method of increasing cell size in a dermal cell in non-diseased skin of a mammal, e.g., a human. The method includes topically administering a composition including a therapeutically effective amount of adenosine to a region of skin of the mammal containing the dermal cell, wherein addition of the adenosine does not cause proliferation of the dermal cell, wherein addition of the adenosine does not cause proliferation of the dermal cell.

The invention also includes a method for enhancing skin condition in a mammal, e.g., a human. The method includes providing fibroblasts from the mammal ex vivo, culturing the fibroblasts in the presence of adenosine, and reintroducing the fibroblasts into the mammal.

The therapeutically effective amount of adenosine used in the above-described methods is preferably 10^{-3} M to 10^{-7} M, more preferably 10^{-4} M to 10^{-6} M, and most preferably about 10^{-4} M.

The composition used in the above-described methods can include a second agent in addition to adenosine. The second agent can be, e.g. an agent that promotes binding of adenosine or an adenosine analog to an adenosine receptor, an angiogenic factor such as vascular endothelial cell growth factor (VEGF), basic fibroblast growth factor (BFGF), an agent that itself enhances skin condition, such as tretoinin or another known conditioning agent such as an emollient, a humectant, or an occlusive agent.

In preferred embodiments of the invention, the adenosine or an adenosine analog does not promote skin cell proliferation.

The invention also provides a composition including about 10^{-3} M to about 10^{-7} M adenosine and a therapeutically effective amount of an angiogenesis factor. In some embodiments, the composition of the adenosine is about 10^{-4} M.

As used herein, "enhancement of skin condition" means a noticeable decrease in the amount of wrinkling, roughness, dryness, laxity, sallowness, or pigmentary mottling in skin.

As used herein, a "therapeutically effective amount" of adenosine or an adenosine analog means an amount that enhances skin condition when applied to skin.

As used herein, "non-diseased skin" means skin free of any proliferative disorder observable by visual inspection.

The present invention advantageously allows for enhancement of skin condition. This results in skin that shows a less wrinkled, rough, or dry complexion. For example, the invention provides for enhancing the condition of skin damaged due to exposure to the sun or skin whose condition has deteriorated due to normal aging.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Other features and advantages of this invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. **1**A and **1**B are histograms showing the effect of adenosine on [^{3}H]thymidine incorporation in cultures of normal human skin (FIG. **1**A) and lung fibroblasts (FIG. **1**B). After incubation in serum-free medium for 24 hours, cells were exposed to 10^{-4} M adenosine for 18 hours. Medium was replaced with serum-free medium without adenosine, and [^{3}H]thymidine was added. Results are expressed as percent [^{3}H]thymidine incorporation compared to control cultures without adenosine and are means ±SEM for 4–5 experiments. "*" denotes value was significantly different from control value without adenosine.

FIGS. **2**A and **2**B are histograms showing concentration responses of adenosine-stimulated protein synthesis in human skin fibroblasts from a young (FIG. **2**A) and aged (FIG. **2**B) donor. Cells were grown to 75% confluence. Medium was then replaced with serum-free medium with or without adenosine. After 48 hours, [^{3}H]phenylalanine incorporation was determined as described. Results are expressed as %[^{3}H]phenylalanine incorporation compared to control cultures without adenosine and are means ±SEM for 6–25 experiments. "*" denotes value was significantly different from control value without adenosine.

DETAILED DESCRIPTION

The invention is suitable for treating skin of a mammal, e.g., a human, for which promotion of fibroblast-associated dermal functions is desired. For example, promotion of fibroblast-associated functions is desirable in enhancing the condition of aged skin, which is associated with a decrease in dermal cell function and is characterized by increased dryness or roughness, or both. The method can also be used on subjects having otherwise damaged skin, e.g., wrinkled skin and skin with a non-proliferative disorder. The method can may further be used prophylactically on a subject to minimize deterioration of skin condition associated with aging or environmental factors, such as photodamage.

Adenosine and suitable adenosine analogs are suitable for use in enhancing skin condition. Adenosine analogs such as adenosine agonists, adenosine receptor agonists, and compounds that increase intracellular or extracellular adenosine levels are suitable for use in the invention.

Agonists of adenosine include 2'-deoxyadenosine; 2',3'-isopropoylidene adenosine; toyocamycin; 1-methyladenosine; N-6-methyladenosine; adenosine N-oxide; 6-methylmercaptopurine riboside; 6-chloropurine riboside, 5'-adenosine monophosphate, 5'-adenosine diphosphate, or 5'-adenosine triphosphate. Adenosine receptor agonists include phenylisopropyl-adenosine ("PIA"), 1-Methylisoguanosine, ENBA (S(-), N^6-Cyclohexyladenosine (CHA), N^6-Cyclopentyladenosine (CPA), 2-Chloro-N_6-cyclopentyladenosine, 2-chloroadenosine, and adenosine amine congener (ADAC), all of which are agonists for the adenosine A_1 receptor. Other receptor agonists include 2-p-(2-carboxy-ethyl) phenethyl-amino-5'-N-ethylcarboxamido-adenosine (CGS-21680), N-ethylcarboxamido-adenosine (NECA) and napthyl-substituted aralkoxyadenosine (SHA-082), 5'(N-Cyclopropyl)-carboxamidoadenosine, DPMA (PD 129, 944), Metrifudil, which are agonists for the adenosine A_2 receptor. Other adenosine receptor agonists include those which preferentially bind the A_1 receptor relative to the A_2 receptor, such as 2-Chloroadenosine, N^6-Phenyladenosine, and N^6-Phenylethyladenosine; and those which preferentially bind the A_2 receptor relative to the A_1 receptor, such as 2-Phenylaminoadenosine and MECA.

Also suitable for use are compounds that increase intracellular adenosine concentration by inhibiting the cellular uptake of adenosine or the breakdown of adenosine. One pathway of adenosine metabolism is the conversion of adenosine to inosine by adenosine deaminase. An example of an adenosine deaminase inhibitor is erythro-9-(2-hydroxy-3-nonyl) adenine ("EHNA"). Adenosine kinase inhibitors can also be used. Adenosine kinase converts adenosine to adenosine monophosphate by adenosine kinase. An example of an adenosine kinase inhibitor is iodotubercidin. Other suitable compounds include those that inhibit the dipyridamole-sensitive nucleoside transporter, which exports adenosine from the cytoplasm, and agents that promote the activity of a 5'-nucleotidase, e.g., the ATP-activated 5'-nucleotidase, which forms adenosine. Compounds that increase tissue adenosine and ATP levels include acadesine (AICA-riboside), which is described in Gruber et al., Circulation 80:1400–1411 (1989).

Adenosine can be also be administered with a second compound. The second compound can enhance the action of adenosine or the adenosine analog, e.g., by enhancing binding of adenosine or an adenosine analog to an adenosine receptor. An example of such a compound is PD 81,728, which is described in Kollias-Baker et al. J. Pharmacol. Exp. Ther. 281:761–68. Alternatively, the second agent can itself act to enhance skin condition. Examples of these types of agents include tretinoin, a recognized skin conditioning agent (see, e.g., Olsen et al., J. Amer. Acad. Dermatol. 37:217–26, 1997), an angiogenic factor such as vascular endothelial cell growth factor (VEGF) or basic fibroblast growth factor (BFGF), or a conditioning agent.

The second compound can also be a conditioning agent such as an emollient, humectant, or occlusive agent. Numerous examples of particular conditioning agents are provided in the CTFA Cosmetic Ingredient Handbook (Cosmetic Toiletries and Fragrances Association, Washington, D. D., 1988). Emollients help to maintain the soft, smooth, and pliable appearance of skin and function by remaining on the skin surface or in the stratum corneum to act as lubricants, to reduce flaking, and to improve the skin's appearance. Examples of emollients include acetyl trioctyl citrate, cetyl alcohol, butyl myristate, cetyl alcohol, and mineral oil.

Humectants act to increase the water content of the top layers of the skin. Humectants include, e.g., acetamide MEA, fructose, and xylitol. Occlusive agents inhibit the evaporation of water from skin, thereby increasing the water contend of the skin. Acetylated castor oil, mineral oil, and lauryl stearate are examples of occlusive agents.

A subject can be treated by applying adenosine or an adenosine analog in a pharmaceutical composition in an effective amount and for a period of time sufficient to improve the condition of the skin.

The pharmaceutical composition may be formulated using conventional methods to prepare pharmaceutically useful compositions. Such compositions preferably include at least one pharmaceutically acceptable carrier, such as those described in Remington's Pharmaceutical Sciences (E. W. Martin). In addition, the compositions preferably include a pharmaceutically acceptable buffer, preferably phosphate buffered saline, together with a pharmaceutically acceptable compound for adjusting isotonic pressure, such as, for example, sodium chloride, mannitol, or sorbitol.

Adenosine or an adenosine agonist can also be provided in carriers and adjuvants such as ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances, such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances and polyethylene glycol. Adjuvants for topical or gel base forms of adenosine or adenosine analogs may, for example, be selected from the group consisting of sodium carboxymethylcellulose, polyacrylates, polyoxythylene-polyoxypropylene-block polymers, polyethylene glycol and wood wax alcohols. For all administrations, conventional depot forms may be used.

The adenosine or adenosine analog-containing compositions may be in any pharmaceutically acceptable dosage form. They are preferably applied by topical routes to exert local therapeutic effects. For topical application, the penetration of the adenosine into skin tissue may be enhanced by a variety of methods known to those of ordinary skill in the art. For example, adenosine may be applied directly and mechanically rubbed into the skin. Alternatively, adenosine or adenosine analogs may be incorporated into a transdermal patch that is applied to the skin. Preferably, the penetration resulting from these methods is enhanced with a chemical transdermal delivery agent such as dimethyl sulfoxide (DMSO) or the nonionic surfactant, n-decylmethyl sulfoxide (NDMS), as described in Choi et al., Pharmaceutical Res., 7(11):1099, 1990.

Other modes of administration include, e.g., oral, subdermal, intradermal, or intravenous. When oral administration is used, it is critical that the adenosine or adenosine analog be delivered to that it is not degraded prior to exiting the digestive system.

The most effective mode of administration and dosage regimen of adenosine or the adenosine analog will depend upon the skin condition, previous therapy, the subject's health status, response to the adenosine, the judgment of the treating physician and the mode in which the adenosine is applied. For example, dosages for a therapeutically effective amount for topical application would be in the range of 100 ng to 10 mg per treated surface area per day. The adenosine may be administered to the patient at one time or over a series of treatments. When adenosine or the adenosine analog is administered in conjunction with a second agent, they can be administered either concurrently or sequentially, and can be administered in the same mode or a different mode, e.g., topical or oral.

Adenosine or an adenosine analog enhances skin condition when there is a noticeable decrease in noticeable decrease in the amount of wrinkling, roughness, dryness, laxity, sallowness, or pigmentary mottling of the treated skin. Methods of measuring improvements in skin condition are well known in the art (see, e.g., Olsen et al., J. Amer. Acad. Dermatol. 26:215–24, 1992), and can include subjective evaluations by the patient or a second party, e.g., a treating physician. Objective methods can include skin topography measurements, such as those described in Grove et al., J. Amer. Acad. Dermatol. 21:631–37 (1989). In skin topography measurements, silicone rubber replicas are made of a small area of skin, e.g., a 1 cm diameter circular area. The silicone rubber replicas capture fine lines and wrinkles on the skin. These specimens are then analyzed using computerized digital image processing to provide an objective measurement of the skin's topography. Skin topography

measurements generated following digital-image processing can be measured using the values R_a and R_z as described in Olsen et al., J. Amer. Acad. Dermatol. 37:217–26, 1997, where R_a represents the area of deviation of skin surface features above and below an average central line, and R_z represents the difference between the maximum and minimum heights in five equal segments of the skin surface profile. A statistically significant decline (e.g., $P<0.05$) in R_a and R_z values in skin treated with adenosine or an adenosine analog compared to untreated skin indicates an enhancement of skin condition.

Fibroblasts treated with adenosine or adenosine analogs can also be incorporated into a matrix and implanted in the body, e.g., as part of a skin graft. In addition, fibroblasts can be genetically engineered ex vivo to increase the amount of intracellular adenosine levels and then re-introduced into a human patient. (See, for example, Anderson et al. U.S. Pat. No. 5,399,349; and Mulligan & Wilson, U.S. Pat. No. 5,460,959, each of which is incorporated by reference herein in its entirety).

Experimental Information

Cell Culture

Human skin fibroblasts and human lung fibroblasts were supplied by the N.I.A. Aging Culture Repository Center (Camden, N.J.). For skin fibroblasts, primary cultures had been initiated from explants obtained from a 3 mm punch biopsy of the mesial aspect of the upper left arm. Human lung fibroblasts (IMR-90) were established from a 16-week normal female fetus. All cells displayed a normal diploid karyotype and all cells tested negative for bacteria, fungi and mycoplasma contamination.

Cells were grown in Eagle's minimal essential medium (MEM) supplemented with 10% fetal bovine serum (FBS), 100 U/ml penicillin and 100 mg/ml streptomycin in a 37° C., 5% CO_2/95% air environment. After reaching confluence, cells were subcultivated with 0.25% trypsin in MEM with no added Ca^2+ or Mg^{2+}.

Incorporation of [^{3}H]Thymidine

As an index of DNA synthesis incorporation of [^{3}H] thymidine was measured as described in Ethier et al., Am. J. Physiol. 272:H1470–79 (1997). Confluent monolayers of human skin fibroblasts in MEM plus 10% FBS were seeded into 16 mm diameter culture wells (24-well plates) at a density of 1×10^4 cells/cm^2. Cells were grown at 37° C. under standard culture conditions (5% CO_2-95% air) until they were approximately 75% confluent. Medium was then removed and the cells were made "serum-free" by incubation in MEM with no FBS for 24 hours. Adenosine or vehicle (MEM) was added for an additional 18 hours. This medium was then replaced with fresh MEM, and the cells were pulsed with 1 mCi/ml [^{3}H] thymidine (6.7 Ci/mmol). After a 2 hour incubation period, the medium was discarded and the cells were rinsed twice with cold (4° C.) Hank's balanced salt solution (HBSS) and incubated for 5 minutes with 0.5 ml cold 10% (w/v) trichloroacetic acid (TCA). The wells were then rinsed with 8% TCA and the TCA-insoluble material was solubilized with 0.5 ml of a solution of 0.2M NaOH and 0.2% sodium decyl sulfate (SDS). The radioactivity of this fraction was determined by standard liquid scintillation spectrometric techniques.

Incorporation of [^{3}H] thymidine was expressed as counts per minute (cpm) of ^{3}H per culture. Data in each experiment was derived from 4 identically treated wells. Since the cpm/well exhibited variation between experiments, data representing combined experiments are expressed herein as a percent of their respective mean control value.

Incorporation of [^{3}H]Phenylalanine

Incorporation of [^{3}H]phenylalanine was measured as an index of protein synthesis. Human skin fibroblasts were seeded into 24-well culture plates in MEM containing 10% FBS. When cells had grown to approximately 75% confluence the culture medium was replaced with serum-free MEM with or without adenosine. After 48 hours, 2 μCi/ml [^{3}H]phenylalanine was added to the cultures. Unlabeled phenylalanine (0.36 mM) was also added to equalize concentrations of intracellular and extracellular phenylalanine. After 8 hours, medium was removed and the cells were washed twice with cold (4° C.) HBSS and incubated for 20 minutes in cold 10% (w/v) TCA. Cells were then incubated 5 minutes in 95% ethanol (4° C.) and the TCA-insoluble material was solubilized with a solution of 0.2M NaOH and 0.2% SDS. The radioactivity of this fraction was determined by standard liquid scintillation spectrometric techniques.

Incorporation of [^{3}H] phenylalanine was expressed as cpm of ^{3}H per culture well and data in each experiment were derived from six identically treated wells. Since the cpm/well exhibited variation between experiments, data representing combined experiments are expressed as a percent of their respective mean control value.

Determination of Cell Size

Human fibroblasts in MEM 10% FBS were seeded into 25 cm^2 culture flasks at a density of 1×10^4 cells/cm^2. When the cells had grown to approximately 80% confluence the culture medium was removed and the cells were incubated in serum-free MEM for 24 hours. Adenosine or vehicle (MEM) was added for 18 hours and cells were then washed twice with cold (4° C.) HBSS. Cells were removed with 0.25% trypsin in calcium-and magnesium-free MEM and diluted in cold (4° C.) HBSS for measurement of relative cell size with a fluorescence-activated cell sorter (FACS; Becton Dickinson Vantage). Cell size was determined by forward light scatter on a minimum of 1×10^4 cells per experiment.

Experimental Materials

MEM, FBS, penicillin, streptomycin, trypsin, and HBSS were obtained from GIBCO (Grand Island, N.Y.), [^{3}H] thymidine (6.7 Ci/mmol) and phenylalanine, L-ring-2,3,4,5,6-^{3}H] (92 Ci/mmol) were obtained from Dupont NEN (Boston, Mass.). Adenosine was from Boehringer Mannheim, SDS was from National Diagnostics, (Highland Park, N.J.) and TCA and ethanol were obtained from Fisher Scientific (Pittsburgh, Pa.).

Data Analysis

Analysis of variance (ANOVA) was used to determine statistical differences between means. The Dunett's test was applied for multiple comparisons as described in Zar, J. H., Biostatistical Analysis. Englewood Cliffs, N.J., Prentice Hall, Inc. pp. 150–153, 1984. In addition, the Wilcoxon test was employed to verify differences between values expressed as a percentage. Differences were considered statistically different when $P<0.05$.

DNA Synthesis

Exposure to 10^{-4}M adenosine increased [^{3}H]thymidine incorporation by 43±9% in five studies on cultures of human fibroblasts (AG607720B) made quiescent by serum removal. These results are summarized in FIG. **1**A. In contrast, adenosine (10^{-4}M) had no effect on [^{3}H]thymidine incorporation in cultures of human lung fibroblasts (IMR-90) (FIG. **1**B). Concentrations of adenosine ranging from 10-7 M to 10^{-3}M also failed to stimulate [^{3}H]thymidine incorporation in IMR-90 lung fibroblasts (data not shown).

The effect of adenosine on DNA synthesis was additionally determined on skin fibroblast cultures from six different human donors. Adenosine (10^{-4}M) stimulated DNA synthesis in all three cultures derived from young human donors (Table 1). Values shown are means ±SEM, where n is number of experiments. Exposure to adenosine and determination of [^{3}H] thymidine incorporation were as described above. The asterisk denotes a value significantly different from the corresponding control (100%).

TABLE 1

Effect of adenosine on [^{3}H] thymidine incorporation into cultured human skin fibroblasts derived from young donors

Cell Strain	Adenosine (10^{-4} M)	Donor Age	Donor Sex	[^{3}H] thymidine incorporation (% of control)	n
AG07720B	–	24	F	100	24
	+			124 ± 7*	24
AG07306A	–	28	F	100	6
	+			193 ± 20*	6
AG09605	–	30	M	100	12
	+			133 ± 15	12

Peak stimulation of [^{3}H]thymidine incorporation (93±20%, n=6) was achieved in human skin fibroblast cultures derived from a 28 year old female (AG07306A).

Adenosine (10^{-4}M) stimulated DNA synthesis in 2 of 3 cultures derived from aged human donors (Table 2). As in Table 1, values are means ±SEM, and n is the number of experiments performed. The asterisk denotes a measurement significantly different from the corresponding control (100%). Adenosine exposure increased [^{3}H]thymidine incorporation by 53±31% and 54±22% in human skin fibroblast cultures derived from a 70 year-old male and a 84 year-old male, respectively. Adenosine had no effect on cultures derived from a 67-year old female.

TABLE 2

Effect of adenosine on [^{3}H] thymidine incorporation into cultured human skin fibroblasts derived from aged donors

Cell Strain	Adenosine (10^{-4} M)	Donor Age	Donor Sex	[^{3}H] thymidine incorporation (% of control)	n
AG11728	–	67	F	100	6
	+			91 ± 6	6
AG12949	–	70	M	100	11
	+			150 ± 31*	11
AG11730	–	84	M	100	10
	+			154 ± 22*	10

Protein Synthesis

The effect of adenosine on protein synthesis was determined by measuring [^{3}H]phenylalanine incorporation into cultures of human fibroblasts from a young and aged donor. Cultures made quiescent by serum removal were exposed to adenosine (10^{-6}M to 10^{-4}M) for 48 hours and then pulsed with phenylalanine. In skin fibroblast cultures derived from a 28-year old female (AG073060A) and an 84-year old male (AG11730), adenosine (10^{-4}M) increased protein synthesis by 13±4% (n=25) and 13±6% (n=17), respectively (FIG. **2**)

Cell Size

The effect of adenosine on cell size was determined on human skin fibroblasts from young and aged donors by measuring forward light scatter in a FACS analyzer. Cultures made quiescent by serum removal were exposed to adenosine for 18 hours, removed by trypsinization, and diluted in

4° C. HBSS. A minimum of 1×10^4 cells were measured for each experiment. The results are shown in Table 2. Values are mean ±SEM for relative cell size determined by forward light scatter (FLS) in a fluorescence-activated cell sorter, and n=number of cells measured. The asterisk denotes the measurement is significantly different from corresponding control.

In skin fibroblast cultures from a 28 year old female (AG073060A) adenosine (10^{-4}M) significantly increased cell size by 1.8 and 2.2% in two of three experiments (Table 3).

The effect of adenosine on cell size was also measured on skin fibroblasts from an aged donor. The results are shown in Table IV. Values are mean ±SEM for relative cell size determined by forward light scatter (FLS) in a fluorescence-activated cell sorter, where n is the number of cells measured. An asterisk indicates a value significantly different from corresponding control.

In cultures derived from an 84-year old male (AG11730), adenosine (10^{-4}M) significantly increased cell size by 2.7–4.9% in 3 of 3 experiments (Table 4).

TABLE 3

Effect of adenosine on cell size in cultured human skin fibroblasts derived from young donors

Experiment Number	Adenosine (10^{-4} M)	Relative Size (FLS)	% increase	n
1	–	524 ± 0.55	—	1.5×10^4
	+	526 ± 0.55	0.4	1.5×10^4
2	–	319 ± 1.24	—	1.0×10^4
	+	326 ± 1.16*	2.2*	1.0×10^4
3	–	342 ± 0.94	—	1.0×10^4
	+	348 ± 0.95*	1.8*	1.0×10^4

TABLE 4

Effect of adenosine on cell size in cultured human skin fibroblasts derived from aged donors

Experiment Number	Adenosine (10^{-4} M)	Relative Size (FLS)	% increase	n
1	–	333 ± 0.79	—	1.0×10^4
	+	342 ± 0.75*	2.7*	1.0×10^4
2	–	323 ± 1.01	–	1.0×10^4
	+	337 ± 0.96*	4.3*	1.0×10^4
3	–	306 ± 0.81	–	1.0×10^4
	+	321 ± 0.81*	4.9*	1.0×10^4

Other Embodiments

While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention. For example, while the invention has been described using adenosine and adenosine agonists, other compounds structurally similar to adenosine can also be used, e.g., purine-containing compounds and compounds having a ribosyl moiety. Other aspects, advantages, and modifications of the invention are within the scope of the following claims.

We claim:

1. A method for enhancing the condition of unbroken skin of a mammal by reducing one or more of wrinkling, roughness, dryness, or laxity of the skin, without increasing dermal cell proliferation, the method comprising topically applying to the skin a composition comprising a concentration of adenosine in an amount effective to enhance the condition of the skin without increasing dermal cell proliferation, wherein the adenosine concentration applied to the dermal cells is 10^{-3} M to 10^{-7} M.

2. The method of claim **1**, wherein the composition further comprises an angiogenic factor.

3. The method of claim **1**, wherein the adenosine concentration is 10^{-1} M to 10^{-6} M.

4. The method of claim **1**, wherein the adenosine concentration is about 10^{-3} M.

5. The method of claim **1**, wherein the composition further comprises a conditioning agent.

6. The method of claim **5**, wherein the conditioning agent is a humectant, an emollient, or an occlusive agent.

7. The method of claim **6**, wherein the mammal is a human.

8. The method of claim **1**, wherein the skin comprises a skin graft.

9. The method of claim **1**, wherein the composition further comprises a transdermal delivery agent.

10. The method of claim **1**, wherein the composition is in a transdermal patch and the composition is topically applied by contacting the patch to the skin.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,645,513 B2
APPLICATION NO. : 10/184810
DATED : November 11, 2003
INVENTOR(S) : James G. Dobson, Jr.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 10, claim 3, line 2:

Delete "10^{-1}" and insert --10^{-3}--

Signed and Sealed this

Twenty-second Day of June, 2010

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

FORM 31. Certificate of Confidential Material **Form 31**
July 2020

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

CERTIFICATE OF CONFIDENTIAL MATERIAL

Case Number: 2021-1969

Short Case Caption: University of Massachusetts v. L'Oreal S.A.

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Date: 10/11/2021

Signature: /s/ Jeffrey A. Lamken

Name: Jeffrey A. Lamken

FORM 19. Certificate of Compliance with Type-Volume Limitations **Form 19**
July 2020

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATIONS

Case Number: 2021-1969

Short Case Caption: University of Massachusetts v. L'Oreal S.A.

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The foregoing filing complies with the relevant type-volume limitation of the Federal Rules of Appellate Procedure and Federal Circuit Rules because it meets one of the following:

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Date: 10/11/2021

Signature: /s/ Jeffrey A. Lamken

Name: Jeffrey A. Lamken