

Invention in Dermatology: A Review

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ABSTRACT

Dermatologists are among the most inventive physicians, trained in the multiple disciplines of medical dermatology, surgical dermatology, and dermatopathology. Many of the advances in dermatology practice have been derived from inventive colleagues who identify opportunities for improvement in practice, develop viable prototypes to address these practice opportunities, and persevere through the hard work of developing new technologies to advance the practice of dermatology. In this article, we will review the basic elements of invention, patents, and the range of outcomes associated with the pursuit of invention. Examples of innovative dermatologic technologies and approaches will be reviewed. Opportunities abound for dermatologists to contribute to the advancement of medical care through invention in our specialty.

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INTRODUCTION

Over the course of many decades, the field of dermatology has advanced significantly due to the inventive spirit of many colleagues within our specialty and of allied specialties. With unique training that encompasses all areas of medicine, including medical approaches, surgical interventions, and dermatopathological analysis, dermatologists have a unique perspective on human disease that affords them powerful opportunities for invention. We will review the basics of invention and patent law, intellectual property protection, and review examples of inventive advances in dermatology in the hopes of inspiring the next generation of dermatologists to contribute to the field through invention and innovation.

What is an Invention?

According to U.S. patent law, an invention is a new, useful process, machine, or improvement that did not exist previously and that is recognized as the product of some unique intuition or genius, as distinguished from ordinary mechanical skill or craftsmanship.[1] In practical terms, inventions are a novel solution to a practice gap in medicine that adds to the available technologic approaches to cure or ameliorate dermatologic disease.

Biomedical inventions can be broadly divided into four major categories: (1) Pharmaceutical; (2) Diagnostic and Prognostic Assays; (3) Medical Devices; and (4) Health Care Information Technology. There are unique opportunities within each of these sectors of invention to positively impact human dermatologic disease.

What is a Patent?

A patent is a contract with a national government, which has been provided for within the United States Constitution since 1790.[1] Within a patent, the inventor discloses how to make and/or utilize an invention. In return for the disclosure of the details of an invention, the government confers a time-limited right to exclude others from making, using, selling or importing an identical or similar invention. According to the United States Patent and Trademark Office, there are three types of patents: utility patents, design patents, and plant patents. A patent cannot be obtained based on an idea or suggestion but needs a complete description of the actual invention for which the patent is sought.[1]

Patents encourage the development, public disclosure, and commercialization of new inventions so that society may benefit widely from the dissemination of new technologies. A period of protection is granted to allow an inventor to recover the material and opportunity costs associated with the development of an invention without facing immediate competition from others who have not invested similarly in the development of the respective technology. In the United States, patent protection is generally enforceable for 20 years from the date of patent application, a time during which the invention may be developed and commercialized under the protection of patent law.

Whereas a patent provides the ability to prevent others from practicing the art claimed in a patent, a patent in and of itself does not have inherent value. It is through the commercialization of a technology protected by a patent that the value of an invention is realized. Commercialization is a process through which an invention is fully developed, produced, validated, and introduced into the market for utilization.

Medical Patent History

The first United States medical patent was for the composition of bilious pills, granted to Samuel Lee on April 30, 1796.[2]

Throughout the early 20th century, there was minimal effort to patent medical inventions at academic medical centers, with many universities actively discouraging patenting activity. In the 1970s, the U.S. Government continued to own the rights to intellectual property from research that was supported by U.S. governmental grants. Without a proactive approach to commercialization of this technology, commercialization of inventions developed at US universities was not robust. In the 1980s, the United States Government owned approximately 28,000 patents, only 5% of which were licensed, raising concerns of loss of United States technologic prowess.[3]

In 1980, Senators Birch Bayh and Robert Dole led the bipartisan approval of The Patent and Trademark Law Amendments Act of 1980 (the Bayh-Dole Act) which was amended further in 1984. Under the Bayh-Dole Act, universities were granted the right to retain title to inventions developed with support of federal funds with the stipulation that inventors must share in the income received from the invention and that income must be used to perpetuate the education and research missions of the universities. It is estimated that the Bayh-Dole Act has contributed to the development of 4,000 new companies, 153 new FDA approved technologies including 93 small molecule drugs, 36 biologics, 15 vaccines, 8 in vivo diagnostics, and 1 over-the-counter drug being utilized around the world.[4] Between 1996 and 2010, university and nonprofit institution patent licensing produced an $836 billion impact on U.S. gross industry output, $388 billion on U.S. Gross Domestic Product, and supported 3 million jobs.[5] Some credit the Bayh-Dole act for the creation of the biotechnology industry.

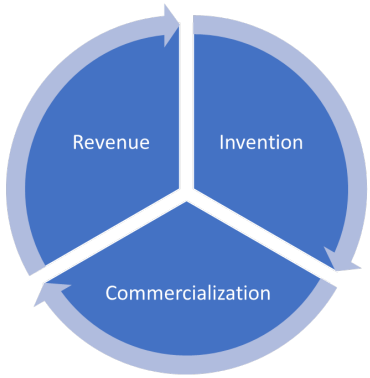
Why Invent?

Biomedical inventors invent for many reasons, including seeing to improve the health and wellbeing of patients and our society, to help patients manage their diseases, and to provide superior technologies for healthcare providers to diagnose and treat illnesses. Medical inventors find the pursuit of new technology intellectually stimulating and challenging, lowering the risk of professional burnout. Successful inventions also return revenue both to inventors and their universities to support further invention, education, and research, resulting in a virtuous cycle of invention that perpetuates further invention (Figure 1).

How to Invent

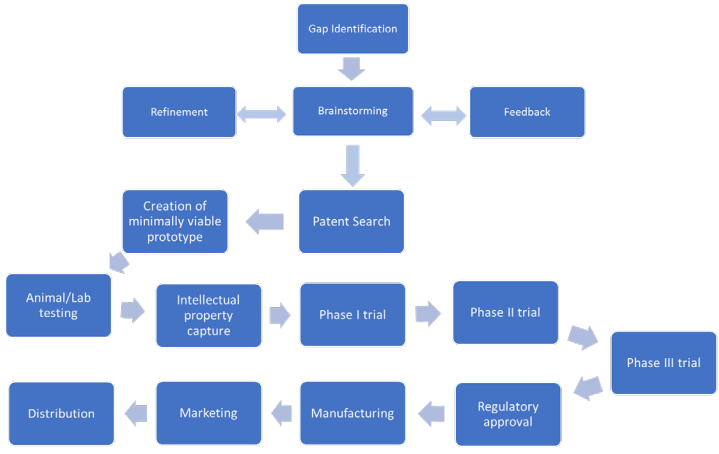
The genesis of an invention often arises through the identification of a "gap" or opportunity within existing medical technology. These practice gaps represent suboptimal approaches with opportunity for improvement. Practice gaps that are large and associated with common disorders represent the most fertile opportunities for successful invention given the realities associated with advancing inventions from the conceptual phase to market.

FIGURE 1. Successful inventions produce revenue for both the institution and inventor. This allows for a self-perpetuating cycle of increased funding for future innovations, commercialization and revenue.



Following identification of practice gaps, the next stage of inventing often involves brainstorming to develop numerous potential solutions that address the issues inherent in the practice gaps. Refinement of the brainstorming ideas through critical evaluation and iterative refinement provides both challenge and excitement to inventors. Early in the lifecycle of an invention, it is important to obtain critical feedback from multiple perspectives and stakeholders to validate or refute the basic hypothesis and approach of the invention. This critical feedback can be facilitated through the completion of a "Business Model Canvas," an organizational tool and methodology to gain critical insights into potential developmental barriers and solutions that an invention will face (Figure 2).[6,7]

FIGURE 2. The invention process begins with the identification of a practice gap, brainstorming solutions and then refining potential solutions through self-analysis and stakeholder feedback. This is followed by a thorough patent search, creation of a prototype and subsequent lab testing. The intellectual property should then be captured through a disclosure to the appropriate institution and submission to the U.S. Patent Office. Lastly, the invention should be tested through clinical trials and if successful, gain regulatory approval from the FDA.



Evaluation of the current state of "prior art" through the search of patent databases is necessary to determine whether the proposed invention is truly new and "non-obvious," requirements for obtaining a patent. If no prior art exists and the invention is truly novel, then a patent application is filed to capture related intellectual property. Finalization and receipt of a patent takes many years and is associated with substantial costs, ranging from $25,000 to $100,000 depending on the jurisdictions in which the patent is sought. With a patent application filed, further development of the invention technology is conducted, often in partnership with colleagues from other disciplines or from industry, including engineers, technology development managers, regulatory advisors, legal advisors, and stakeholders. Commercialization of medical technologies is a long and arduous process requiring passage through minimally-viable prototyping; animal- or laboratory-based studies; phase 1, phase 2, and phase 3 human studies; manufacturing; marketing; and distribution.

The time frames for invention commercialization can range from 1 to 5 years for health care information technology and up to 1 to 2 decades for pharmaceuticals, devices, and diagnostic or prognostic tests. Depending on the technology, a device may be cleared by the FDA for marketing in America through one of five routes: 1) Exemption from premarket submission for Class I devices, 2) the 510(k) process for Class II devices, 3) Premarket Approval (PMA) for Class III devices, 4) "De Novo" approval, and 5) Humanitarian Device Exemption (HDE).[8] Funding for the development of technologies through the various phases is technology dependent but can range from hundreds of thousands to hundreds of millions of dollars. It is currently estimated that the cost to develop a new prescription drug that gains FDA approval is approximately $2.6 billion.[9]

Advice for Inventors

The following advice to potential dermatologic inventors has been shared from one of Mayo Clinic's most experienced inventors, Richard Ehman, MD, as well as from the technology development managers, licensing managers, and business development managers at Mayo Clinic Ventures.

1. Choose an uncrowded field or area of opportunity.
2. Be aware of new technologies in other fields that may represent opportunities to translate technology into your field.
3. Focus on clinically-relevant problems.
4. Target common problems with large-market opportunities.
5. Cultivate your imagination and intuition through the engagement of mentors, colleagues, and students.
6. Engage with multidisciplinary colleagues to access different perspectives.
7. Recognize and learn from failures.
8. Invention takes a lot of time and effort, so focus on the best ideas and let bad ideas go.
9. Be persistent if you have an idea that has unrecognized value.
10. When confronting stalled ideas, consider putting them aside and coming back with fresh eyes later.
11. Always seek to translate ideas for the benefit of patients in hospital and clinic settings.

Inventions and Inventors in Dermatology

Pharmaceuticals

At one time or another, all of the medications used by dermatologists have been invented by colleagues within or outside our specialty. We owe great appreciation to these inventive colleagues as their technologies provide the basis for effective dermatologic therapy.

It is interesting to consider the many dermatologic therapies that have been repurposed from other specialties including methotrexate and cyclosporine, which were originally used for rheumatoid arthritis. Topical nitrogen mustard was originally a chemical warfare agent and was adapted successfully for the topical treatment of cutaneous T-cell lymphoma. Calcipotriol ointment was developed after it was observed that a patient treated with vitamin D for osteoporosis experienced significant improvement in psoriasis.[10] Likewise, the utilization of beta blockers for the treatment of infantile hemangiomas followed an observation of unanticipated regression of hemangioma in a patient treated with beta blockers for hypertension.[11] Botulinum toxin was originally used to treat blepharospasm with the observation that surrounding periocular musculature seemed to relax, resulting in reduction of overlying wrinkled skin.[12]

The invention of cortisone, one of the most commonly used classes of medications in Dermatology, dates back to the mid-20th century when the compound was identified by Drs. Kendall, Mason, and Hench at Mayo Clinic, awarded of the Nobel Prize in 1950.[13] Reichstein, Wintersteiner, and Pfiffner had previously isolated the compound of cortisone but had not recognized its biologic significance. The researchers at Mayo Clinic did not pursue patent protection for cortisone, which was first produced commercially by Merck.

The development of new medications can take many years. An example of the extended time frame for development of new pharmaceuticals is the story of vismodegib, with scientific research dating back to the 1960s when cyclopamine was identified as a responsible compound for one-eyed lambs resulting from the consumption of corn lilies by the mother.[14] In 1995, the Nobel Prize in Physiology/Medicine was awarded for the identification of genes including Hedgehog that control embryonic development.[15] In 1998, Genentech conducted a search of compounds that inhibit the Hedgehog pathway, and in 2004, Genentech identified vismodegib and conducted preclinical research in collaboration with Curis. An investigational new drug application for vismodegib (GDZ-0449) was filed with the U.S. Food and Drug Administration. After a multi-phased development process, the FDA approved vismodegib for the treatment of adults with metastatic basal cell carcinoma or with locally advanced basal cell carcinoma that has recurred following surgery, and who are not candidates for surgery, and who are not candidates for radiation in January 2012, twenty-four years after Genentech initiated their search for compounds that inhibit the Hedgehog pathway.[16] Inventing new therapies takes significant time and resources.

Medical Devices

In the arena of medical devices, dermatologists have been very inventive and productive. The history of phototherapy dates back 3,500 years when plant extracts and seeds were combined with sunlight to treat "leukoderma".[17] Modern phototherapy was initiated in 1903 when Niels Finsen received the Nobel Prize for Chemical Rays Lamp Therapy of Tuberculosis.[18] In 1974, Drs. Parrish, Fitzpatrick, Tanenbaum, and Pathak published their experience with photochemotherapy of psoriasis with oral methoxsalen and long-wave ultraviolet light in the New England Journal of Medicine.[19]

The development of lasers has been fruitful ground for dermatologists, as well. In 1959, the laser was invented by physicist T. H. Maiman with the development of the flashlamp pumped ruby crystal laser.[20] Laser therapy was brought into clinical practice by Dr. Leon Goldman with the use of continuous-wave ruby laser followed by the introduction of argon, carbon dioxide, and neodynium-YAG laser. In 1983, the seminal therapy of selective photothermolysis was advanced by Drs. Rox Anderson and John Parrish.[21] In 2003, Anderson and Manstein developed the concept of fractional thermolysis, a new concept for cutaneous remodeling using non-continuous application of energy to cause controlled thermal injury.[22]

Health Care Information Technology

In health care information technology, the development of the Melanoma Outcome Calculator by the Laboratory for Qualitative Medicine at Massachusetts General Hospital allowed rapid access to patient-specific melanoma prognostic information based on SEER database.[23]

The invention of the Contact Allergen Replacement Database by James Yiannias, M.D., from Mayo Clinic in Arizona turned on its head the usual questions associated with avoidance of contact allergens. Prior to the development of the Contact Allergen Replacement Database, physicians would share information with patients, advising what to avoid. In a clever twist, Dr. Yiannias developed a database which catalogued all ingredients within common commercial topical products allowing patients to receive answers to the more important question: "What can I use safely?"

Diagnostic and Prognostic Assays

Developments within the field of dermatopathology have allowed more precise refinement of disease prognosis and outcomes for patients based on skin biopsies including the iconic contribution of Alexander Breslow, M.D., in the paper "Thickness, Cross-Sectional Areas and Depth of Invasion in the Prognosis of Cutaneous Melanoma".[24]

Recently, molecular based testing and analysis of melanocytic lesions and melanoma have become significant fields of interest. Emerging technologies include DermTech's Adhesive Pigmented Lesion Assay, Myriad's myPath Melanoma test, and Castle's DecisionDx-Melanoma gene expression profile test designed to identify high risk Stage I and II melanoma patients based on biologic information from tumor tissue.

The Future of Invention in Dermatology

Opportunities abound for invention in the future within the field of Dermatology. From digital health solutions to molecular diagnostics, precision and individualized medicine, regenerative medicine, and effective behavioral medicine interventions, dermatologists have many practice gaps that can be filled with innovative and creative solutions. Participating in the "virtuous cycle of invention" allows dermatologists to maximize their positive impact on society while engaging in a stimulating and challenging career endeavor.

REFERENCES

1. [No author listed.] United States Patent and Trademark Office. General information concerning patents. (October 2015). Retrieved from https://www.uspto.gov/patents-getting-started/general-information-concerning-patents#heading-2
2. [No author listed.] "First American Medicine Patent- Today in History: April 30." ConnecticutHistory.org, Connecticut Humanities, connecticuthistory.org/first-american-medicine-patent-today-in-history-april-30/.
3. U.S. Government Accounting Office (GAO) Report to Congressional Committees. May 7, 1998. "Technology Transfer, Administration of the Bayh-Dole Act by Research Universities"
4. The Bayh-Dole Act: It's Working. Association of University Technology Managers website. https://www.autm.net/AUTMMain/media/Advocacy/Documents/BayhDoleTalkingPointsFINAL.pdf. Accessed April 4th, 2018.
5. Fischer S. BIO Study Quantifies Economic Contribution of University & Non-Profit Inventions. Biotechnology Innovation Organization website. https://www.bio.org/media/press-release/bio-study-quantifies-economic-contribution-university-non-profit-inventions. June 21, 2012. Accessed April

4th, 2018.
6. Osterwalder A. *The Business Model Ontology - A Proposition In A Design Science Approach.* (PhD thesis). University of Lausanne; 2004
7. Osterwalder A. Yves Pigneur. Business Model Generation: A Handbook for Visionaries, Game Changers, and Challengers. 1st ed. John Wiley and Sons; 2010.
8. Step 3: Pathway to Approval. U.S. Food and Drug Administration website. https://www.fda.gov/ForPatients/Approvals/Devices/ucm405381.htm. February 9, 2018. Accessed April 4, 2018.
9. DiMasi, J, Grabowski, H, Hansen, R. Innovation in the pharmaceutical industry: New estimates of R&D costs. *J Health Econ.* 2016;47:20-33.
10. Morimoto S, Kumahara Y. A patient with psoriasis cured by 1 alpha-hydroxyvitamin D3. *Med J Osaka Univ.* 1985;35(3-4):51-4. PubMed PMID: 4069059.
11. Leaute-Labreze C, Dumas de la Roque E, Hubiche T, et al. Propranolol for severe hemangiomas of infancy. *N Engl J Med.* 2008;358(24):2649-51.
12. [No author listed.] "The Real History Behind the Birth of Botox". [online] Reader's. Available at: http://www.readersdigest.ca/health/beauty/birth-botox/view-all
13. [No author listed.] "The Nobel Prize in Physiology or Medicine 1950". Nobelprize.org. Nobel Media AB 2014. Web. 8 Dec 2017. http://www.nobelprize.org/nobel_prizes/medicine/laureates/1950/
14. Binns, W, James, LF, Shupe, JL. Toxicosis of veratrum californicum in ewes and its relationship to a congenital deformity in lambs. *Ann N Y Acad Sci,* 1964;111: 571–576. doi:10.1111/j.1749-6632.1964.tb53124.x
15. [No author listed]. "The Nobel Prize in Physiology or Medicine 1995". Nobelprize.org. Nobel Media AB 2014. Web. 8 Dec 2017. http://www.nobelprize.org/nobel_prizes/medicine/laureates/1995/
16. Axelson M, Liu K, Jiang X, He K, Wang J, Zhao H, Kufrin D, Palmby T, Dong Z, Russell AM, Miksinski S, Keegan P, Pazdur R. U.S. Food and Drug Administration approval: vismodegib for recurrent, locally advanced, or metastatic basal cell carcinoma. *Clin Cancer Res.* 2013;19(9):2289-93. doi: 10.1158/1078-0432.CCR-12-1956. Epub 2013 Mar 20. PubMed PMID: 23515405.
17. Hönigsmann H. History of phototherapy in dermatology. Photochem Photobiol Sci. 2013 Jan;12(1):16-21. doi: 10.1039/c2pp25120e. PubMed PMID: 22739720.
18. [No author listed.] "The Nobel Prize in Physiology or Medicine 1903". Nobelprize.org. Nobel Media AB 2014. Web. 8 Dec 2017. http://www.nobelprize.org/nobel_prizes/medicine/laureates/1903/
19. Parrish JA, Fitzpatrick TB, Tanenbaum L, Pathak MA. Photochemotherapy of psoriasis with oral methoxsalen and long-wave ultraviolet light. *N Engl J Med.* 1974;291:1207-1211
20. Maiman TH. Stimulated optical radiation in ruby. *Nature.* 1960187, 493-94.
21. Anderson RR, Parrish JA. Selective photothermolysis: precise microsurgery by selective absorption of pulsed radiation. *Science.* 1983;220:524-527
22. Manstein D, Herron GS, Sink RK, Tanner H, Anderson RR. Fractional photothermolysis: a new concept for cutaneous remodeling using microscopic patterns of thermal injury. *Lasers Surg Med.* 2004;34:426-38
23. Soong S-J, Ding S, Coit, et al. Predicting survival outcome of 116 localized melanoma: An electronic prediction tool based on the 117 AJCC melanoma database. *Ann Surg Oncol.* (in press).
24. Breslow A. Thickness, cross-sectional areas and depth of invasion in the eh prognosis of cutaneous melanoma. *Ann Surg.* 1970;172:902-908

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