Patenting a New Form of Taxol Fermentation

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Abstract:

Taxol, also known as pacilitaxel, is a widely used chemotherapy drug typically extracted from the Yew tree. Mere extraction, however, does not yield sustainable returns because too-frequent extraction involves destroying the Yew tree source. Demand for Taxol has outstripped supply, and scientists have turned to developing Taxol in plant cells followed by industrial fermentation. The Duke University International Genetically Engineered Machine Project looks to go a step further, by generating Taxol in bacteria cell cultures instead of plant cell cultures. In order to use this invention to boost the market supply of Taxol, the IGEM team will eventually need a corporate or non-profit partner, and this partner will only be incentivized to participate if the IGEM team can offer exclusive licensing. Thus, the success of IGEM's new genetically engineered bacteria largely hinges on its patentability with the United States Patent and Trademark Office. This report walks through the relevant patent requirements, analyzes the case law, and comes to the conclusion that IGEM's new genetically engineered bacteria meets the conditions for successful patentability.

Introduction:

Prior research has already shown Taxol to be an effective chemical in combatting cancer. As explained by a professor at the University of Massachusetts-Amherst, the compound "binds to micro-tubules, which are important in cell division, and prevents the cancer cells from dividing properly.[1]"

However, just because a product is useful does not mean supply has kept pace with rising demand. Taxol is primarily obtained by extracting it from Yew trees, which naturally

[1] Creekmore, B. C. (2005, August 15). Research focuses on increasing supply of anti-cancer drug. Retrieved October 15, 2016, from https://www.umass.edu/newsoffice/article/research-focuses-increasing-supply-anti-cancer-drug

synthesize the product. Given the solvents and treatment necessary to do so, however, this approach also destroys the very same Yew trees in the process. As such, extraction is unlikely to achieve demand-supply equilibrium in the market. Researchers have since pivoted to modifying plant cell cultures to produce Taxol and other significant precursors found along the metabolic pathway[2]. These plant cell cultures are in turn used in industrial processes designed to produce Taxol on a substantial scale. Even this, however, is not the most efficient solution to the current shortage—the plant cell's complex infrastructure and subsequent energy needs have prevented the cell's resources from being fully directed towards Taxol production. Low product yield is typically the result.[3]

The 2016 Duke University International Genetically Engineered Machine team's goal is to produce Taxol more efficiently, by using bacteria cell cultures rather than plant cells. The process of optimizing bacteria to produce a product for later industrial fermentation has already been demonstrated, but its application to Taxol has not. The IGEM team has worked on characterizing five enzymes involved in the natural process of Taxol production, and then merging them into one strain by genetically engineering the DNA of the bacteria culture. At the end of this process, the bacteria culture produces Taxol, with less energy expenditure than was required in plant cells and subsequently higher yield.

But a more efficient process is meaningless if the means to boost market supply are not available, which requires cooperation with a biopharmaceutical company. The Duke IGEM project does not on its own have the resources to mass produce Taxol through

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[2] Exposito, O., Bonfill, M., Moyano, E., Onrubia, M., Mirjalili, M., Cusido, R., & Palazon, J. (2009). Biotechnological Production of Taxol and Related Taxoids: Current State and Prospects. *Anti-Cancer Agents in Medicinal Chemistry ACAMC*, *9*(1), 109-121. doi:10.2174/187152009787047761

[3] Wilson, S. A., & Roberts, S. C. (2011). Recent advances towards development and commercialization of plant cell culture processes for the synthesis of biomolecules. *Plant Biotechnology Journal, 10*(3), 249-268. doi:10.1111/j.1467-7652.2011.00664.x

industrial fermentation, so licensing the new bacteria cell culture to a pharmaceutical manufacturer is the logical next step.

> "A company that owns rights in a patent, know-how, or other IP asset, but cannot or does not want to be involved in the manufacturing of products, could benefit from licensing out of such IP assets by relying on the better manufacturing capacity, wider distribution outlets, greater local knowledge and management expertise of another company (the licensee)[4]"

Details of such a licensing agreement would need to be worked out in individual contract negotiations. For example, the manufacturer might require more research by IGEM at the front-end before agreeing to commercialize the product[5]. Before any negotiation can take place, however, the manufacturer needs reassurance the venture will be profitable. These industries are not in the business of charity. Acquiring a patent on the new genetically engineered bacteria will provide the necessary financial incentive.[6]

The remainder of this report will outline the fundamentals of patent law and requirements to getting a patent approved by the United States Patent and Trademark Office. It will explain out the main roadblocks towards getting approved, but will ultimately provide a case for a successful patent prosecution.

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[4] LICENSING OF INTELLECTUAL PROPERTY ASSETS; ADVANTAGES AND DISADVANTAGES. (n.d.). Retrieved October 15, 2016.

[5] LICENSING OF INTELLECTUAL PROPERTY ASSETS; ADVANTAGES AND DISADVANTAGES. (n.d.). Retrieved October 15, 2016.

[6] The alternative would be keeping the new bacteria a trade secret. Protecting a trade secret requires that reasonable efforts be taken to keep the secret isolated. Given the competitive nature of the IGEM project, this does not seem a viable option for the group.

Fundamentals of Patent Law:

Patent protection gives the right-holder what is known as a "negative right" to prohibit others from making, using, selling, offering to sell, or importing from elsewhere the patented invention[7]. Because the grant of a patent removes the application of new knowledge from the public domain for 20 years from the date of filing, the criteria for patentability are strict. There are four key patent criteria—novelty, utility, nonobviousness, and disclosure[8].

Each of the four criteria is equally important, but some are harder to prove than others. Disclosure is the simplest. It requires that when filing for the patent, the right-seeker disclose an explanation of the product in the "best mode" possible, such that another person "reasonably skilled" in the field would be able to recreate the product. While the simplest to fulfill, disclosure is typically the most frightening for the right-seeker, because the law asks that the invention be explained to the public *before* the patent right has officially been granted. Careful discussion with the potential licensee and lawyers will be crucial in this stage to minimize risk. Next, the utility requirement asks that the potential usefulness of the product be proven. With the IGEM team's documentation of the enhanced efficiency of Taxol production, the utility requirement will not pose a significant obstacle.

Novelty and non-obviousness are the strictest, and hardest to meet, criteria for patentability. The novelty requirement essentially asks whether the invention is "new" compared to prior inventions in the field that existed *more than a year prior* to the date of

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[7] Ghosh, S., Gruner, R., J., & Reis, R. (2007). *Intellectual property: Private rights, the public interest, and the regulation of creative activity*. St. Paul, MN: Thomson/West.

[8] Ghosh, S., Gruner, R., J., & Reis, R. (2007). *Intellectual property: Private rights, the public interest, and the regulation of creative activity*. St. Paul, MN: Thomson/West.

filing the patent application. The America Invents Act of 2011 sets out specific tests for novelty[9]:

- The product cannot have been patented before.
- The product cannot have been described in a printed publication *more than a year prior to the date of filing the application*.
- The product cannot be in the public domain *more than a year prior to the date of filing the application.*
- The product cannot have been sold *more than a year prior to the date of filing the application.*

Lastly, the nonobviousness criteria asks whether "an ordinary person with skill" in the designated field could have come up with the same invention by virtue of his expertise, or whether the invention needed a "creative leap."

The specific application of the utility, novelty and nonobviousness requirements will be explained in the "analysis" portion of this report. Before diving into that territory, however, a brief history of Taxol's relationship to intellectual property law is instructive.

Taxol, Historically:

For several years, the pharmaceutical giant Bristol-Myers Squibb had exclusive rights to market Taxol. Taxol was first discovered in 1962, after researchers from the United States Department of Agriculture and the National Cancer Institute extracted the compound from the *Taxus brevifolia* Yew tree[10]. The initial extract was not pure Taxol, but within two years researchers at Research Triangle Park isolated the Taxol in pure form. In

[9] Leahy-Smith America Invents Act, H.R. 1249—1 § H.R. 1249 (2011).
[10] Taxol® (NSC 125973). National Cancer Institute (n.d.). Retrieved October 15, 2016

1977, the National Cancer Institute granted a professor at Yeshiva University a grant to study the compound's functions, and Dr. Susan Horwitz eventually discovered its potential in preventing the division of cancer cells[11]. The NCI ran clinical trials to prove the compound's efficacy, and upon doing so began looking to get a pharmaceutical company involved. In 1991, a "cooperative research and development agreement" was awarded to Bristol-Myers Squibb, along with an exclusive right to market the drug for five years[12].

The exclusive right to market the drug was legally problematic for several reasons. First and foremost, it superseded patent law. As mentioned before, patent law provides the patent holder "negative rights" to prevent others from using the invention. But a core principle of patent law is that "the laws of nature, physical phenomena, and abstract ideas" cannot be patented[13]. The Plant Patent Act of 1930 also gives inventors the ability to patent plants, but only to the extent they are "*new varieties* of many asexually produced plants."[14] In essence, the principles mentioned above and the Plant Patent Act reinforce a more general idea—that inventions are patentable, discoveries are not. Extracting a naturally occurring Taxol compound from a tree is a discovery, not an invention, and simply isolating the compound does not change that it already existed in nature[15][16]. In 2013, the Supreme Court more concretely noted a "natural product" exception to patentable subject matter,

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[11] Taxol® (NSC 125973). National Cancer Institute (n.d.). Retrieved October 15, 2016

[12] American Chemical Society National Historic Chemical Landmarks. Discovery of Camptothecin and Taxol

[13] Levy, R. C. (1995). *The inventor's desktop companion: The guide to successfully marketing and protecting your ideas*. Detroit: Visible Ink.

[14] Transgenic Crops: An Introduction and Resource Guide. (n.d.). Retrieved October 15, 2016, from http://cls.casa.colostate.edu/transgeniccrops/patent.html

[15] Hirshfeld, A. (2014). *2014 Procedure For Subject Matter Eligibility Analysis Of Claims Reciting Or Involving Laws Of NaturelNatural Principles, Natural Phenomena, And/Or Natural Products* (United States, Patent and Trademark Office).

[16] Apply the PTO's guidance after the Association of Molecular Pathology v. Myriad Genetics Supreme Court decision to plants, noting that "merely isolating a nucleic acid changes its structure but that change does not create a marked difference in structure between the isolated nucleic acid and its naturally occuring counterpart."

and that mere isolation does not constitute a "marked difference" allowing for patentability[17]. In essence, the NCI granted Bristol-Myers Squibb an exclusive right to something that was not eligible for a patent in the first place[18].

The initial NCI agreement with Bristol-Myers Squibb included a fair pricing agreement, but monopoly prices indicate the company got around such requirements. When it entered the market, a single dose was $1,800 and full treatment was between $10,000 and $20,000[19]. In 2002, a lawsuit alleged that Bristol-Myers Squibb was extending its monopoly by misusing and acquiring patents in ways it was not entitled to (by failing to inform the PTO about prior Taxol research in the public domain) in conjunction with another company American BioScience. The two companies allegedly did this, the complaint alleged, to prevent generic competitors from entering the market and dramatically weakening their market share[20]. A related Federal Trade Commission complaint explains the alleged patent fraud in considerable detail[21]:

> "Among other things, BMS: paid a would-be generic competitor millions of dollars to abandon its patent challenge and agree to withhold competition until patent expiry; misled the United States Food and Drug Administration about the scope, validity, and enforceability of its patents and abused FDA regulations to block generic entry; breached its duty of candor and food faith before the Patent and Trademark Office."

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[17] The Myriad Genetics case in question involved DNA, and legal experts are divided on its application to other types of material. See Lowe, D. (2014). Can You Patent A Natural Product? Prepare For a Different Answer. Retrieved October 15, 2016 vs. Mellmann, D., & Smith, M. B. (2014, June 4). Patentable claim types after Myriad. Retrieved October 15, 2016

[18] In a 1991 congressional hearing, BMS admitted that Taxol was not patentable. In the matter of Bristol-Myers Squibb (Before Federal Trade Commission: Complaint).

[19] Brody, H. (2007). *Hooked: Ethics, the medical profession, and the pharmaceutical industry*. Lanham: Rowman & Littlefield.

[20] Peterson, M., & Walsh, M. (2002, June 5). States Accuse Bristol-Myers of Fraud on Taxol. *The New York Times*. Retrieved October 15, 2016.

[21] In the matter of Bristol-Myers Squibb (Before Federal Trade Commission: Complaint)

Eventually, an FTC proposed order barred Bristol-Myers Squibb from "seeking to enforce, or collect royalties on, any Taxol patent if the infringement claim involves the use of Taxol.[22]" Bristol eventually backed off, perhaps due to the FTC pressure. At the end of the legal disputes, generic Taxol became accessible on the market and several companies have entered that market, including IVAX Pharmaceuticals[23].

The core lessons to be taken away from this protracted legal dispute are that Taxol is not patent-protected, and generic Taxol is available on the market. However, methods of producing Taxol are still patent-eligible. The IGEM team should still look to file the genetically modified bacteria with the patent office, in the hopes of later licensing to a pharmaceutical company.

Patentability of the IGEM Product:

This section of the report will walk through each of the three (excluding disclosure, which is done with a lawyer's expertise at the time of the filing) requirements for patentability.

Meeting the utility requirement will not be hard for the IGEM team. The most applicable case in terms of utility for the process of generating a chemical compound is Brenner v. Manson, decided by the Supreme Court in 1966[24]. Andrew Manson had filed a patent for a process to develop a steroid, but was unable to specifically prove what the

[22] In the matter of Bristol-Myers Squibb, Federal Trade Commission, Analysis To Aid Public Comment, March 2003

[23] Garber, K. "Battle Over Generic Taxol Concludes, But Controversy Continues." *CancerSpectrum Knowledge Environment* 94.5 (2002): 324-26. Web.

[24] Brenner, Commissioner of Patents v. Manson, 383 U.S. 519

value of the steroid would actually be. Manson argued instead, that there is utility solely in creating the compound regardless of the compound's utility, and that the steroid was related to other compounds that had demonstrable utility. In order to ensure that a "patent is not a hunting license," the Supreme Court rejected both claims. It held that "specific utility"—of the compound and of the process—is necessary for patentability. The effectiveness of Taxol has already been proven in theory and practice, so what the IGEM team has to show is that creating a single enzyme stream within bacterial DNA is actually a more efficient production process than other methods. This should not pose a substantial obstacle.

Before addressing novelty and nonobviousness, there is some important case law on the fundamental patentability of bacteria that must be considered. In *Funk Bros. Seed Corporation v. Kalo Inoculant Corporation* in 1948, the Supreme Court held that merely aggregating several types of bacteria into one culture is "hardly more than packaging of the inoculants" and not patentable because it is essentially a natural phenomenon:

> "The combination of species produces no new bacteria, no change in the six species of bacteria, and no enlargement of the range of their utility. Each species has the same effect it always had. The bacteria perform in their natural way[25]."

Reading into this case, there are some requirements laid out for generating patentable bacteria:

- The bacteria must be new OR
- The bacteria species must be changed OR
- The range of utility must be enlarged

[25] Funk Brothers Seed Corporation v. Kalo Inoculant Corporation. 333 U.S. 127

The bacteria produced by the IGEM team will likely pass this test, because it is being *genetically* modified to produce a strain of five enzymes the bacteria did not naturally produce before. The Supreme Court's decision in *Diamond v. Chakrabarty* confirms this intuition. In *Diamond*, the patent-seeker had genetically modified bacteria to break down crude oil, by incorporating multiple plasmids—each of which broke down a component of crude oil—into one bacterium. The Supreme Court decided the new bacteria were patentable, because it was a "non-naturally occurring manufacture or composition of matter.[26]" Instead of deciding that animate objects are simply non-patentable, the Supreme Court decided that animate objects are patentable as long as that they perform functions that they could not have done in nature absent human intervention. Incorporating five enzymes into the DNA of a new bacterium—allowing it to generate Taxol, something the bacterium had not done before—falls in line with *Diamond's* holding[27]. IGEM's genetically engineered bacteria are fundamentally patentable, pending decisions on novelty and nonobviousness.

Novelty is a tougher rung, but one that can still be met by genetically engineered bacteria. As mentioned before, there are four ways novelty can be precluded as specified by the America Invents Act:

- The product cannot have been patented before.
- The product cannot have been described in a printed publication *more than a year prior to the date of filing the application*.

[26] Sidney A. Diamond, Commissioner of Patents and Trademarks, v. Ananda M. Chakrabarty. 447 U.S. 303

[27] The 2013 Association of Molecular Pathology v. Myriad Genetics case, while dealing with the patentability of portions of DNA, also supports this contention. That case held that complementary DNA (cDNA) that spliced introns from the normal DNA sequence was non-naturally occuring and thus patentable.

- The product cannot be in the public domain *more than a year prior to the date of filing the application.*
- The product cannot have been sold *more than a year prior to the date of filing the application.*

The last requirement will not be a consideration here, as the product IGEM would claim in the patent is the genetically modified bacterium, not Taxol itself.

With regards to the printed publication and public domain requirements, there is an immediate irony that needs to be addressed. In *In re Hall*—considered by the United States Court of Appeals For The Federal Circuit in 1986—the court held that a doctoral thesis published in a library more than a year prior to filing, even when filed by the patent-seeker, was a violation of the novelty requirement[28]. In other words, if the IGEM team were to publish the contents of the genetically modified bacteria *more than a year prior to* filing a patent, patentability might be barred. There is a statutory exception, however, indicating that you will not be barred if you file *within one year of making the printed publication or otherwise disclosing it publically*[29]. Once IGEM presents its work, the clock is ticking.

A cursory search of the Patent and Trademark Office database did not find anything that would bar IGEM's invention, in terms of prior patents. An internet search also did not yield evidence that the bacteria engineered by IGEM is already in the public domain.

Non-obviousness is the hardest requirement for the IGEM team to fulfill. This requirement asks whether or not another person with reasonable skill in the field could have generated the bacteria, or if it required a "creative leap" on the part of the inventors.

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[28] **In Re** Leo M. **Hall**, 781 F.2d 897

[29] Leahy-Smith America Invents Act, H.R. 1249—1 § H.R. 1249 (2011)

Several factors weigh against a successful finding of nonobviousness. First, the process of genetically modifying bacteria to create new products is old science. Secondly, there are other labs in the country also working to use bacteria in producing Taxol. In 2010, for example, "U.S. and Singaporean researchers engineered strains of E. Coli that produce two precursors of the cancer drug Taxol.[30]" The Massachusetts Institute of Technology was also doing something similar in 2010[31]. This does not make it impossible for IGEM to fulfill the nonobviousness requirement—especially because the cited examples involve precursors, whereas IGEM is using the bacteria to produce Taxol itself. The team's lawyers would need to argue to the PTO that the unique choice of enzymes to include in the bacteria to produce the final Taxol product was a "creative leap," not obtained by other researchers despite tinkering with similar technology.

Ultimately, the utility, novelty and nonobviousness requirements can all be met with regards to the specific genetically modified bacteria. The process of making that bacteria would likely not be patentable due to nonobviousness requirement, but the bacterium itself could be. The exclusive right to produce a bacterium that makes Taxol production more efficient could be of immense value to a pharmaceutical licensee.

Next Steps:

Through correspondence with Eric Wagner, an attorney in Duke University's Office of Licensing and Ventures, it is clear that the group itself does not have the rights to the product. Rather, because Levine Science Research Laboratory facilities were used in conjunction with a faculty mentor, Duke University owns anything created from the work.

[30] Hass, M. (2010, October 14). Paclitaxel plants routes in bacteria. Retrieved October 15, 2016, from http://www.nature.com/scibx/journal/v3/n40/full/scibx.2010.1199.html

[31] Trafton, A. (2010, October 1). Getting bacteria to do a plant's job. Retrieved October 15, 2016, from http://news.mit.edu/2010/cancer-drug-taxol

Any filing for patentability and subsequent licensing would have to be done in conjunction with Duke University, which could be a benefit given the University's institutional resources. If IGEM plans on patenting this bacteria, the next step should be meeting with the Office of Licensing and Ventures, informing them of the product and negotiating with them what licenses and royalties should ensue.

Conclusion:

The Duke University IGEM team has created a new genetically modified bacteria that produces Taxol more efficiently than past fermentation efforts using plant cells. In order to expand the market supply of Taxol, licensing this bacteria to a pharmaceutical company is almost essential, as is acquiring the patent to do so. Specifically, the most-logical patent would be on the genetically modified bacteria itself, which provides a stronger case for meeting the patent requirements than other possibilities such as the process or Taxol.

IGEM has to work with the University to license out the product to either a pharmaceutical company or a non-profit. There is a trade-off: the former would be able to fund more production in bulk, but the latter would likely have a more distributive interest (and less prone to price-gouging). Either way, the patent is the surest way to guarantee active interest by another party.

Should the patent be denied, the invention still has value. The best course of action in that instance would be academic publication and dissemination of the work to various non-profits and academic circles. Without patent rights, the group would be hard-pressed to receive further funding, but by expanding the store of knowledge other pharmaceutical professionals could work to supplement IGEM's work. Eventually, this could lead to an

increase in Taxol supply, just divorced from the initial IGEM work compared to if a patent was acquired.

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