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CAR T Cells As A Patentable Therapeutic

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CAR T Cells As A Patentable Therapeutic

McKenzie List

A Senior Honors Project Submitted in Partial Fulfillment of
Requirements of the Honors Degree Program

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Abstract

The development of a therapeutic to treat a particular disease is a complicated process that incorporates numerous components such as drug discovery, clinical trials, FDA approval and patentability. In the last two decades, cancer research and development has shifted from identifying small molecule therapeutic agents to focusing research on a novel approach designated as immunotherapy. Today, immunotherapy has progressed from a twentieth century scientific theory into an innovative treatment to cancer. In particular, CAR T cells have demonstrated therapeutic properties for certain types of cancers, but these living cells are not compatible with the traditional therapeutic model. First, the drug development process and the historical path of therapeutics in the FDA is introduced to provide a foundation of knowledge concerning drug discovery. Second, the biological and medicinal elements of CAR T cells are outlined and compared to the traditional small molecule Taxol. The third chapter presents CAR T cell patent trends and relevant historical patent debates that focus on evaluating the patentability of biological subject matter. The fourth chapter discloses current CAR T cell patent debates and the potential implications of CAR T cells on patent law and the pharmaceutical industry. It is established that although CAR T cell therapy does not fit into the traditional therapeutic patentability model, CAR T cell therapy should be patentable based on previous biological subject matter patentability decisions made in the court of law. The patentability of CAR T cells continues to be debated in present-day CAR T cell patent disputes which will have significant effects on future patent law and drug development.

Chapter 1: Introduction To Drug Development And The Path Of Therapeutics In The FDA

Introduction

The path to bringing a drug to market is a complex and lengthy process that requires a multitude of experts in a variety of fields collaborating towards a common goal: improving patients' lives with the production of novel, modern medicines. The goal of therapeutics is to improve and extend the quality of life and possibly even cure diseases that continue to plague our population today. Specifically, therapeutics that treat cancer have had a successful and profound effect on the human population in recent years. The survival rates have increased due to novel discoveries made in the laboratory and maturation of the field of medicinal chemistry. "In the United States, from 1950 to 2009, overall cancer death rates have decreased by 11.4%."¹ Certain treatments have made notable breakthroughs in substantially increasing the five-year survival rates of patients with melanoma, breast, and prostate cancer.¹

Overall, these recent advancements in clinical outcomes for the treatment of cancer have focused on developing new chemotherapeutic agents while simultaneously improving current and older generations of small molecules. A traditional small molecule refers to a compound that has a defined chemical structure with the ability to regulate biological or cellular processes. Typically, small molecules are generated by a designed chemical synthesis that is safe and feasible to manufacture on a large scale. The discoveries of small molecules for the treatment of diseases commenced prior to the establishment of the Food and Drug Administration (FDA) in the early 19th century.¹ For example, the production of Aspirin, acetylsalicylic acid, began in 1899 and remains one of the most frequently used analgesics in the world.²

The sector of pharmaceutical industry that is focused on cancer treatments has become recently captivated by the profoundly innovative approach referred to as immunotherapy. As a

result of researchers and companies collaborating with one another, in conjunction with basic research advancements in the fields of biochemistry and molecular biology, immunotherapy as a viable therapeutic approach has increased. Such collaboration has demonstrated how the pharmaceutical industry can be effective in the translation of preclinical research to the clinic which leads to opportunities to market new drugs to the patient population.

Over the last two decades, both the business landscape and the scientific research environment of the pharmaceutical industry has changed. Commensurately, intellectual property rights and patentability framework have altered to accommodate new innovative therapies.¹ In drug development, when a traditional small molecule is approved by the FDA the drug is protected for the life of the patent from the filing date. These typical small molecules are fixed; once the drug approval is given, standard manufacturing and distribution moves forward into the market. However, CAR T cells as a therapy exhibit therapeutic properties that challenge this traditional notion. CAR T cells are living cells that fluctuate based on a person's genes and the particular disease of interest.³ This is in essence a therapy that represents the personalized medicine approach that healthcare companies are currently expanding their research on.

The idea behind CAR T cells comes from the broader immunotherapy approach in which the immune cells of a patient are collected to treat the patients' specific type of cancer.⁴ The central component of the immune cells are the T cells, which is the fundamental element to enacting an immune response within the body and aids in the destruction of infectious pathogens.⁵ Moreover, CAR T cells involve complex mechanisms of action that require detailed methods of production that typical small molecule manufacturing methods do not necessitate.⁶

It is evident that CAR T cells do not fit into the traditional pharmaceutical model. This paper will not address the costs of pharmaceuticals, the ethical issues surrounding the

pharmaceutical industry, the European Union involvement or the role of international patents in the industry. First, the paper will concentrate on the history of the FDA and the initiatives that have been implemented as a result of the technologic advances in pharmaceuticals. The process for the effective translation of preclinical research to the development of a drug, including the phases of the drug approval process, and mass production are presented. The ‘normal’ path taken by traditional small molecules in drug development is described to highlight how CAR T cells are significantly different, therefore posing challenges and pushing the current patent and legal boundaries. The innovative therapy of CAR T cells will be analyzed to determine the legal and patent ramifications that may arise from the movement of traditional small molecule science into biologics. An argument will be constructed to explain why CAR T cells should be patentable, and this will potentially have significant implications on the role of patent law in drug development.

The Path Of Therapeutics In The FDA

The contemporary drug development path and commensurate regulatory bodies that exist today has not always been the case. Prior to the twentieth century, there were very few, miniscule notions that had to be considered prior to selling a medicine in the U.S. For example, in the nineteenth century there were no regulatory guidelines on addictive substances like cocaine and heroin being added as an ingredient of a drug.¹ Safety issues were not addressed at this time. Thus, the Food and Drug Administration (FDA) began as a way to federally mandate the protection of consumers in correlation with the 1906 Pure Food and Drugs Act.^a The FDA is charged with the regulation of the production of pharmaceutically prescribed drugs and non-prescription drugs that

^a 1906 Pure Food and Drugs Act aimed to rid the medicines being consumed from containing secret ingredients and thus, to a degree regulating the industry.¹

can be purchased over the counter. In this context, the focus is on the FDA mandate to improve the public health by facilitating the process for innovative products proven to be beneficial.⁷

Prior to 1906, no detailed list of ingredients was required to market a drug and no potential side effects were displayed to inform the consumer. It was common for medicines to contain addicting ingredients like cocaine and heroin.¹ The 1906 Pure Food and Drugs Act commenced the regulation of ingredients by not allowing perceived dangerous ingredients to be included as a secret ingredient. One had to properly identify these addictive drugs on the label.¹ If the guidelines were not met, the newly established Bureau of Chemistry acted as inspectors and enforcers of the rules outlined in the 1906 Act.¹ Although these dangerous drugs were not banned in 1906, this step laid the foundation of the FDA. However, the 1906 Act, and thus the FDA, lacked the scientific research and funding to enact any form of requirements on adequately testing the safety of drugs in humans.⁷

This oversight of safety requirements was exhibited in 1937 by the debacle that surrounded the antibiotic termed the Elixir of Sulfanilamide.¹ In summary, a new formulation of the sulfanilamide antibiotic, triggered by societal demands, was met by generating a liquid form of the antibiotic.¹ This new formula included the poisonous solvent diethylene glycol (a component of antifreeze).¹ This liquid antibiotic killed 107 people, many of which were children, as the poisonous compound induced kidney failure.¹ At the time, a simple animal study would have been able to detect such a lethal toxicity. However, animal studies were not a requirement for marketing a drug to the public. The Elixir of Sulfanilamide is just one example of many that exemplified the need for the development of guidelines to test the safety and the efficacy of potential drugs for the market.¹

After the events in 1937, Congress proceeded in 1938 to pass the Food, Drug and Cosmetic Act.¹ The Food, Drug and Cosmetic Act heightened the power of the FDA by providing the ability to enforce new laws.¹ Such laws generated stricter rules in regards to the food and drug production process in the U.S. Further, it created the New Drug Application (NDA) that manufacturers complete for FDA approval; completed today in phase III of clinical trials.¹ This act specifically stated that safety had to be shown through animal studies that must be conducted by the pharmaceutical companies before any regulatory approval to market could be granted. Even though the 1938 act did not contain aspects to prove effectiveness and safety, this act did initiate the major elements that still exist in the process of discovery and development of contemporary drugs.

In the early 1960s, there was another medicinal disaster that was centered around thalidomide, a marketed drug in Europe and Canada for the treatment of morning sickness in pregnant women.⁸ At the time scientists believed that the placenta protected the fetus from absorbing small molecule drugs like thalidomide.¹ However, this belief was disproven as the amount of birth defects reported in those countries steadily increased in mothers who had ingested thalidomide.¹ Thus, the FDA medical officer Frances Kelsey denied the drug application of thalidomide in the United States citing a lack of established safety data and a significant number of personal accounts of birth defects.⁸ By late 1961, thousands of children had been born with various birth defects in countries across the world.⁸ Soon legislators in the United States began a discussion on how to prevent such a disaster from occurring in the U.S.

On October 2nd, 1962 the Kefauver-Harris Amendments for the 1938 Food, Drug and Cosmetic Act were passed by Congress.⁸ The Kefauver-Harris Amendments stipulated that effectiveness of a drug must be proven through controlled clinical studies prior to reaching the

market and that severe side effects must be continuously reported.⁸ The most significant rule of law that resulted from these amendments was that FDA approval must be granted before any drug is marketed in the United States.⁸ The Kefauver-Harris Amendments to the 1938 Act are the foundational guidelines of the FDA approval process today.

Contributing scientific advancements have led to the production of life saving pharmaceuticals. However, the impact of society on the pharmaceutical industry should not be underestimated. There is a critical balance that must be understood between societal need, development of scientific advancements, and pharmaceutical companies staying in business. Societal needs continue to contribute to the next market for a pharmaceutical company to explore; in general, new drugs are produced as a result of a demand, need or public health crisis.¹ Further, pharmaceutical companies have the ability to conduct research on current drugs that may meet a new societal need; treating a new patient population and contributing positively to the pharmaceutical company. In a way, the societal demands aid in the success of drug companies: if a company spends a significant amount of resources investing in a product that addresses a societal need, the company will likely have made an adequate investment.

With the influence of societal needs considered, one can state that in conjunction with the proper governmental regulations that both of these factors, societal and governmental, continue to have a major impact on the development of modern drugs. Today, there are concrete guidelines to prove safety and efficacy prior to FDA approval of a new drug for market. Yet, in recent years the success rate of a drug to market has significantly decreased while the costs of modern drugs have substantially increased. The U.S. pharmaceutical prices have become a major dispute among the public, insurance companies, government and pharmaceutical companies.⁷ In addition, safety concerns are on the rise, society is demanding longer and more comprehensive studies be

conducted for a drug candidate before market approval is granted. As a result of these competing societal and governmental demands that are occurring in the pharmaceutical industry, in 2004 the FDA enacted the Critical Path Initiative.⁷

Critical Path Initiative And Role In Immunotherapy

The Critical Path Initiative's three core objectives include (1) enhancing the drug and medical device development processes, (2) advancing the quality of evidence generated during development and (3) boosting the outcomes of clinical use of such products.⁷ The Critical Path Initiative ideally fosters the collaborations of researchers in both private/public companies and academia to create scientific advancements at a faster rate.⁷ Today, the work flow of drug development involves a multitude of people, companies, and both private and public research institutions. The safety and efficacy of a drug candidate must be proven by researchers completing research and development (R & D) stage. The researchers tasked with completing the R & D are generally located at academic or commercial research institutions. These researchers are typically sponsored either by government funding or by drug companies that are willing to make the multimillion dollar investment for the R & D of a potential drug candidate. Researchers testing the candidate report to the individuals who are funding the development on the progress, or lack thereof in the laboratory or clinical trials. Both researchers and the drug companies work together to complete the necessary steps for FDA approval of a drug candidate, the cost paid for by the sponsoring company.

The Critical Path Initiative has substantially decreased the amount of time it takes for the FDA to approve a drug.⁷ In general, the FDA approval time is relatively small in relation to the overall picture of drug discovery (Figure 1).⁹ In comparison, the length of time it takes to complete basic scientific research to find a target or hit, move into preclinical evaluations, and enter clinical

trials (at least a decade) is a significant amount of time compared to the FDA approval process timeline (Figure 1).⁹ The FDA approval of a drug does not occur until the drug candidate has passed all of the clinical trial phases. The amount of time it takes the FDA to assess and examine a drug depends on the safety, efficacy and complexity of the drug. In general, the government approval of a drug averages between six months to over two years to transpire (Figure 1).⁹

<http://sitn.hms.harvard.edu/flash/2017/make-fda-great-trump-future-drug-approval-process/>

Figure 1. The average number of years for the primary steps of the drug discovery pathway.⁹

Despite improvements in FDA guidelines, criticisms including requirements stifle innovation, standards are too low, and astronomical pharmaceutical prices should be regulated are ongoing. These concerns are difficult to address with a single solution as both the time and cost of developing a drug is at the center of the public's comments and concerns. On average, it takes over twelve years and billions of dollars invested by drug companies for a single safe drug to be marketed to patients.¹ Thus, pharmaceutical companies are looking to invest in drug candidates that are innovative and indicate a high level of market potential to a diverse population.

In the last few years, scientific advancements of medicines, specifically in cancer treatment have moved in the direction of an immunotherapy approach. Immunotherapy has revolutionized the cancer industry and as a result many treatments have shown promising outcomes. However, an immunotherapy approach to cancer does not involve creating a traditional small molecule, the most common type of medicine developed in the industry thus far. Immunotherapy is generating comprehensive treatments that do not fit the traditional small molecule drug development path. Therefore, alterations and changes in the drug development pathway will have to be adopted to suit the novel immunotherapy treatments that are being generated from continuous scientific

advancements. What will these changes look like? Perhaps, additional or more modern core guidelines might be established by the FDA to effectively translate into the clinic. Moreover, as the drug development path continues to evolve, how will this affect the intellectual property laws, specifically in regard to patents? As the cancer pharmaceutical industry moves away from traditional small molecule development and into more immunotherapy treatments, the way in which pharmaceutical companies protect their investments through patenting must adapt.

Patents In Pharmaceutical Industry

The two most important aspects of drug development are frequently overlooked in comparison to a drug candidate progressing through the drug discovery pipeline. These two topics, protection of patents and intellectual property are the key to producing an effective pharmaceutical business.¹ Without an adequate organizational structure and proper patent protection in the pharmaceutical industry, the goals of bringing drugs to market for patient benefit would not be met. The cost to develop a modern drug can be considered astronomical, thus large profit margins are required for companies to take a leap and be self-sustaining when investing in the development of novel therapeutics.¹ A large profit margin must be built into a drug development plan because of the low hit rate and failed target attempts that increases the spending of drug development funds. The protection of intellectual property rights through the use of a patent is what affords the pharmaceutical companies the capital to invest in identifying new drugs as a patent offers a company the market exclusivity for a number of years to gain maximum profit.

“Patents and the protection that they afford are the lifeblood of the pharmaceutical industry.”¹ This quote illustrates the necessity for critical members of the pharmaceutical industry to have a certain level of knowledge regarding the establishment of patents. The purpose of a patent is to spur technological and scientific progress through the safeguarding of intellectual property

rights. Ultimately, this allows for profit to be generated and the likelihood of failure to be worth such the economic risk. Patentability is the exclusive right, permitted by governmental law, to inventors for manufacturing, selling and utilization purposes for a defined number of years.¹⁰ One may assume that simply discovering something or some idea that has never been published before warrants acquiring a patent for such a discovery. However, there are explicit requirements that one is obliged to comply with in order for the United States Patent and Trademark Office (USPTO) to consider an invention or idea to be patentable subject matter.¹

Patentable Subject Matter

A novel idea or invention must first determine the category in which it fits for patentable subject matter.

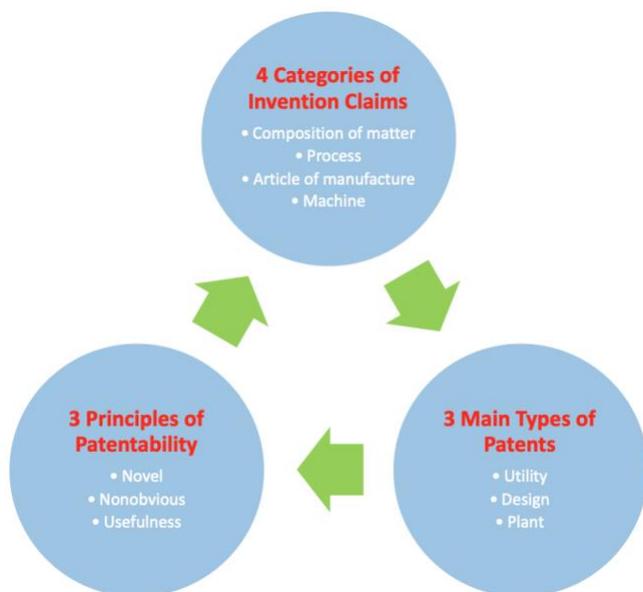


Figure 2. The pathways for patentable subject matter.¹

The four categories of invention claims are: (1) composition of matter, (2) process, (3) article of manufacture and (4) machine (Figure 2).¹¹ The first category, composition of matter is defined as “all compositions of two or more substances and all composite articles, whether they be the results of chemical union, or of mechanical mixture, or whether they be gases, fluids,

powders, or solids” (Figure 2).¹¹ Typical composition of matter claims that are patentable subject matter in the pharmaceutical industry describe small molecules or proteins.¹ A composition of matter invention claim is considered the most highly valued patent claim. This claim supplies a pharmaceutical company full ownership of a compound, no matter the circumstances regarding the use of the compound. Therefore, pharmaceutical companies desire to acquire a composition of matter patent claim, rather than the three other types of patent claims. In general, investors are further inclined to make a larger investment in a drug that has a composition of matter claim that ensures substantial ownership of future profits.⁶ If a small molecule fits the criteria for a composition of matter claim, then the patent details the creation of the small molecule and will note the range of diseases it may treat.

The second category of invention claims is process which is detailed by “an act, or a series of acts of steps” (Figure 2).¹¹ This definition includes a variety of meanings when applied to the pharmaceutical industry. For example, process subject matter is a synthetic procedure that generates a small molecule, or a method utilized to treat a certain disease with a small molecule.¹ Either procedural or method claims are common patentable subject matter in the pharmaceutical industry. Despite that, process claims are not as highly regarded in the pharmaceutical industry, compared to receiving a patent that states a composition of matter claim for a potential therapeutic.

The third category of invention, an article of manufacture that is described as “the production of articles for use from raw or prepared materials by giving to these materials new forms, qualities, properties, or combinations...” (Figure 2).¹¹ An article of manufacture may contain numerous amounts of parts that are fixed in relationship to one another.¹ Invention claims in the pharmaceutical world that fit this description are generally tools like medical devices. For

example, a transdermal patch that is composed of a drug which is then released when the patch comes in contact with the skin is an article of manufacture patent claim.¹

The difference between an article of manufacture and the last category of invention claims, a machine, is that an article of manufacture's parts are static in their interactions while in a machine the parts are usually moving with one and other (Figure 2). A machine is a "concrete thing, consisting of parts, or of a certain device or combination of devices" (Figure 2).¹¹ For instance, a machine in drug discovery is an auto injecting syringe or a pump system that is intended to deliver a drug when a patient's body sends the appropriate signal to the machine.¹

In addition to the four eligible claims of invention that are deemed patentable subject matter, one has to illustrate that an invention corresponds to one of the three broad classifications of patents. The three most common types of patents are utility, design and plant patents (Figure 2).¹ The foremost patent that specifically relates to the pharmaceutical industry is the utility patent. The utility patent is defined as "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof."¹ The composition of matter or process invention claims are classified as a utility patent.

Moreover, the three basic principles that aid in establishing that one's invention can be protected by a patent are novel, nonobvious and usefulness (Figure 2). The invention can only meet the requirement of novelty when it lacks corresponding prior art references. There are no earlier patents, no similar types of publications in the public domain or no inventions like it currently being sold.¹ If an invention is deemed novel as a consequence of an absence of prior art, then one must display the invention is nonobvious. Thus, one must evaluate this statement in relation to one's proposed invention; "if the subject matter of a patent application would be obvious to one of ordinary skill in the art to which the application pertains" then the invention is regarded

as obvious and thereby unpatentable.¹ Lastly, in order for one to patent an invention or idea of any type the novel and nonobvious subject matter must display a level of usefulness. It is not worth obtaining a patent and going through such a process to protect an idea or invention that does not provide any form of ‘utility’ to the world.¹

An obstacle that typically halts the process of being granted a patent is prior art. Prior art is the total body of previous knowledge of any form that is accessible by the public.¹ Prior art searches can be voluntarily conducted by an individual seeking a patent to deem the eligibility of the patent before submitting a patent application. A patent examiner always completes a thorough prior art search of their own once a patent application is received. For example, patent examiners may reject various aspects of the proposed claims in the initial patent application citing a diverse set of prior art as the reason. From there, an attorney amends the claims, balancing specificity to remove the prior art rejections by the patent examiner and keeping the claims as broad as possible to maximize inventor benefit. In the area of pharmaceuticals, if the molecule is known in the prior art then it does not fit into patentable subject matter for the composition of matter.¹ However, the molecule might be valid by the process subject matter depending on the circumstances and if the synthetic route taken to produce the prior art small molecule is different than the prior art process patent.

U.S. Patent Application Timeline

The lifespan of a drug patent, how long the pharmaceutical company retains the exclusive marketing profits, depends on one aspect: when the patent application for the drug is filed. The lifespan of a patented drug is exactly twenty years from the date the patent application is filed with the USPTO.¹ The drug is protected for the life of the patent which begins once the patent application process is set in motion, usually during the early stages of drug development.

A U.S. provisional patent application is frequently filed about twelve months after the initial lead hit when efficacy in cells is demonstrated (Figure 3).¹ Upon filing of the provisional patent application, one has twelve months to file a Patent Cooperation Treaty (PCT)/U.S. Non-Provisional application that includes additional information regarding the current investigation and status of the proposed invention (Figure 3).¹ About eighteen months into this process one is able to publish the most recent Non-Provisional Application (Figure 3).¹ This publication of the patent application ensures that the invention currently proposed is added to the prior art realm of information. At the eighteen to twenty-four month mark, the International Search Authority (ISA) conducts a review of the application, providing a written report that describes whether or not the invention is patentable (Figure 3).¹ After about thirty months the patent reaches its National Phase process which means patent examination and communication between the applicant and a patent examiner commences. The many variables that can impact how swiftly an invention is patented include “nature of the prior art, content/claims of the patent and interactions between patent officer and applicant.”¹ Therefore, at the thirty month mark it is difficult to continue to predict an accurate timeline of when a patent application will be granted.

Blass, B. E. *Basic Principles of Drug Discovery and Development*; Elsevier Inc.: San Diego, 2015; p. 490.

Figure 3. The U.S. Patent Application timeline of critical steps in this process.¹

As stated before, on average it takes twelve years from initial hit identification of a drug to reach the market with plenty of obstacles and chances of failure along that journey.¹ Thus, by the time the novel drug reaches the market, the pharmaceutical company will only have about eight to ten years left on the drug patent. Once the drug patent expires, companies are free to manufacture

generic competitors or variations of that drug at their will. The market exclusivity for the drug company that invested in the novel therapeutic fades away as the patent expires, forcing the pharmaceutical company who developed the drug to compete with generic forms from competitors.

On account of a delay in regulatory approval that can occur in the pharmaceutical industry when attempting to obtain a patent, one may make a request for extending the life of a patent. The maximum amount of time that can be granted for extending the life of a patent is five years.¹ A study examining patent extensions conducted in March of 2008 found that about 70% of issued patents have an extension.¹² Another way one can extend the life of a patent is by applying for a patent that overlaps another invention that is already patented.¹

An example of an overlapping patent in the pharmaceutical industry is a new formulation of a small molecule that already exists.¹ This new formulation for the molecule, i.e. extended release, may decrease the amount of doses a patient needs while increasing the likelihood of patient compliance. The advances made to the previously patented small molecule can be patented, extending the life of the original small molecule with a new formulation. However, overlapping patents are typically more specific and less broad than the original, novel patents. Other common instances of overlapping patents in this field is the establishment of alternative uses of a small molecule, treating a different target disease state with a patented molecule, or implementing a small molecule in a combination therapy.¹ This is exemplified by the drug Sildenafil, known as Viagra, that can treat pulmonary arterial hypertension (high blood pressure that impacts arteries in lungs) and erectile dysfunction.^{13,14}

Given that patents are purposely created to be vague, patents are generally open to differing interpretations. The claim section at the end of a patent is the most important component of a

patent; the aspects that are precisely identified in the claims are the only part of the patent that is protected.¹ The claims section contains both independent and dependent claims that aim to explain and expand on the invention. The claims must prove how the invention or idea is both novel and non-obvious in its method or use.¹ A patent examiner analyzes the claims based on the proposed invention, prior art, the three main principles and the four categories of patentable subject matter. However, even though there are established frameworks that are followed for patents and their claims, disputes in regard to the patentability of certain subject matters continue to be put forward.

Mayo Collaborative Services Verse Prometheus Laboratories, Inc.

The case of *Mayo Collaborative Services v. Prometheus Laboratories, Inc.* in 2012 is a recent example of the deliberation that can unfold between the various courts of government about the fine line of patentable subject matter within the claims of a patent.¹⁵ There were two patents held by Prometheus Laboratories being evaluated as to whether or not the ideas contained in the patent were even patentable. The two patents described the utilization of thiopurine drugs to treat autoimmune diseases which detailed blood metabolite levels, drug dosages and correlations to effectiveness and toxicity.^{6,15} The two patents gave the laboratory company the rights to sell procedural diagnostic tests for the purpose outlined above.

The debate over patentability of these two patents held by Prometheus laboratories was highlighted as a result of an infringement case against Mayo Collaborative Services filed in the Southern District Court of California.¹⁵ Under § 101 of the Patent Act, Mayo Collaborative Services was found to have infringed on Prometheus patents.¹⁵ This spurred the District court to further analyze the specific claims made in the utility patents; the District court deemed the patents invalid under the provision that the claims were not patentable subject matter.¹⁵ The debate on the

claims of these two patents continued into Federal court in which the Federal court ruled to reverse the District court's decision, stating the claims were patentable.¹⁵

The case went to the Supreme Court who reversed the Federal courts' decision, agreeing with the District court that the claims were indeed not patentable subject matter.¹⁵ The Supreme Court stated that the favorable range of blood metabolite levels that denote the appropriate thiopurine dosage were known values and the system of evaluation of blood levels was typical protocol.⁶ Basically, the claims made in the patents displayed an insufficient degree of originality. Thus, the Supreme Court's reasoning detailed that the Prometheus laboratory patents were made up of claims that were attempting to assert descriptions on natural laws or natural phenomena which are unpatentable subject matter under law.

This is one of many cases in the pharmaceutical industry where the various levels of court have differing opinions on patentable and unpatentable subject matter. Thereby, it is essential that both the pharmaceutical industry and intellectual property law, specifically patent rights, continue to adapt to the advancing technology and modernization that is materializing today. The development of therapeutics in the realm of immunotherapy is an area of cancer research that is experiencing an increase in patent disputes and infringement cases.¹⁶ The increase in patent debates has highlighted the need for the patent process to be thoroughly reviewed and for potential changes to be brought to the forefront of discussions.

Effective Translation Of Scientific Research

The process of successfully translating scientific research ideas into novel therapeutics is a challenging feat that involves a multitude of factors that requires a certain level of collaboration between scientific disciplines. The lay observer does not realize how complex and time-consuming it is when researchers attempt to find a missing puzzle piece to solve a medical issue. There is no

one right path to follow nor one wrong path not to follow. Neither path is illuminated, and the only further instruction given may come from an inclination that researchers may have. Instead, scientists have to evaluate numerous factors, predict based on previous drug discoveries and fail multiple times before producing one preliminary compound. Prior to identifying a target or a lead, a team of individuals must analyze the vast amount of biological targets through kinetics, drug disposition, safety, biomarkers, and efficacy.¹⁷

The effective translation of research involves not just one group of scientists focused on a specific target. This translation can only be completed utilizing a multidimensional process that requires the effort of individuals that have a variety of skill sets, including those skilled in intellectual property and patents.¹ In 2011, the cost to hit a target and develop one new drug to bring to market was roughly calculated at 1.75 billion dollars.¹ If the drug makes it to market, the pharmaceutical company that holds the patent for that successful drug will then not only be able to break even, but they will have an incoming profit that can then be utilized to explore the next promising drug target. Patent protection is what provides a pharmaceutical company with the ‘market exclusivity’ which incentivizes a drug company to have a high stakes investment in the potential drug. Pharmaceutical companies are a for profit business as they assist with the medical needs of certain patient populations. Their assistance includes streamlining and providing the necessary resources for the next novel therapeutic to reach the market through the completion of the drug discovery process. The ability to recognize patentable compounds in the early stages of scientific research of a wide spread of targets is crucial to the eventual progress and development of a drug candidate.¹

Basic Research And Drug Discovery Process

There are two main components, drug discovery and drug development that encompass the phases that a drug must succeed in before entering the pharmaceutical market and gaining FDA approval (Figure 4).¹ These steps are what aid in ensuring the identification of a leading drug candidate and an effective drug campaign to market. The drug discovering component is categorized by three main stages that are involved in the establishment of the optimal target: target discovery, lead discovery and lead optimization (Figure 4).¹ The main goal of the drug discovery component and its counterparts is to continuously be able to confirm a concrete scientific link from a biological target to the disease state that is being modeled.

Blass, B. E. *Basic Principles of Drug Discovery and Development*; Elsevier Inc.: San Diego, 2015; p. 8.

Figure 4. The components and stages in the path for drug discovery.¹

However, confirming these necessary links between molecules and disease states or even recognizing a potential drug candidate takes multiple attempts. The success rate for the target discovery stage is 80%, which confirms interaction with the optimal drug target (Figure 5).¹ Furthermore, only about 1 in every 24.3 drug programs will be able to successfully recognize a target, at this stage, that will reach the commercial market (Figure 5).¹ Likewise, the success rate for completing the lead optimization stage of the larger drug discovery component is 85% (Figure 5).¹ In general, during the drug discovery stages teams of researchers will aim to produce a set of similarly related compound structures. The average amount of targets that are screened before identifying a hit molecule is about 100,000 compounds (Figure 5).¹ Thus, the need for more than one possible lead compound is due to the minuscule success rate.

Blass, B. E. *Basic Principles of Drug Discovery and Development*; Elsevier Inc.: San Diego, 2015; p. 7.

Figure 5. The success rates of each stage, the number of programs that move forward through the stages and the amount of compounds screened or clinical studies completed in this drug discovery and development process.¹

It has been reported that there is a success rate of less than 0.001% for a drug candidate to make it to market based on the number of candidates that are proposed or considered in the beginning phases.¹ This likely failure of one specific lead candidate is a result of the difficulties and challenges associated with predicting the exact compound that will measure up in the remaining phases of drug development. Therefore, in order to have the largest probability of success in the next major stage, drug development, one must propose multiple lead series and make a highly informed decision on candidate selection.

The second component, drug development, after the completion of the drug discovery component includes preclinical, proof of concept, full development and launch stages (Figure 4).¹ Typically, at this point in the identification, target progression and validation, one will only move forward with one singular compound that is determined to have the most potential. Keeping in mind that throughout both broad components and their respective individual stages one is constantly endeavoring to optimize seven main properties that should aid in recognizing the ideal drug candidate for success. The variety of properties that must continuously be considered and balanced for the potential drug candidate are active, novel, selective, pharmacokinetics (PK), stable, soluble and safe properties (Figure 6).¹

Blass, B. E. *Basic Principles of Drug Discovery and Development*; Elsevier Inc.: San Diego, 2015; p. 21.

Figure 6. The properties utilized in discerning the most optimal drug candidate.¹

All seven properties must be evaluated with respect to the established lead compound as a failure or oversight of one property has the potential to halt and conclude a drug candidate's journey early. The drug discovery and development components and their subsequent stages endeavor to optimize the majority of these properties mentioned; the optimization of all of these properties suggest that one has identified a compound that has “the best opportunity for success” (Figure 6).¹ The one identified compound and its evaluated properties than travels along a path that involves a diverse set of studies aimed at gathering evidence and confirmation to display to the governing bodies, including the FDA, that such a compound should be brought to market.

Once a single drug candidate has been established it will venture into the progressive phases of clinical trials. At this point one might assume that the path to market is one step closer and that the success rate increases. However, in reference to the success of clinical trials it has been computed that 1 out of every 10 clinical candidates will effectively complete all clinical trials and further, move into the drug market.¹

Clinical Trials

The first preliminary phase involved in clinical trials is the preclinical phase in the drug development stage. The preclinical phase's goal is upon completion of the phase, the submission of an Investigational New Drug (IND) Application.¹ The IND appeals to the regulatory bodies, the FDA in the United States, for the movement of the drug candidate to the study of the human population. It should be noted that one cannot move forward in the drug development stage into

clinical trials phases I through IV until the IND is properly applied for and the request is granted. In order to complete the IND differing animal studies and synthetic protocols must be conducted successfully. Specifically, there are sections of the IND that detail the preclinical data collected: animal pharmacology studies, safety, toxicity, information on chemical manufacturing, and clinical trial protocols featuring how clinical trials will be used in the future to study the compound in humans.¹

To meet the preclinical goal of submitting an IND for the drug candidate, one must explore the synthesis of the active pharmaceutical ingredient (API) on a pharmaceutical grade scale, the possible delivery method of the drug, and the delivery vehicle including the addition of any excipients, lubricants or flavors.^{1,b} In the preclinical phase, researchers may face major hurdles especially in relation to the production of API on a large scale.¹ The synthesis of pharmaceutical grade API requires that kilos of pure good manufacturing process (GMP) of the drug is generated under stricter conditions.^{1,c} For instance, the synthesis of a drug must be carried out with no transition metal catalysts or column chromatography.¹ These restrictions typically mean process chemists have to alter the reagents, solvents and techniques to produce pure GMP of the drug.

Additionally, the optimal form of delivery for the drug must be determined.^d Deciding on the most adequate form of delivery method for the drug candidate is crucial for moving the drug on its path to human studies. The preferable and optimal delivery method of a drug is orally, about 70% of the current drugs on the market.¹ However, patient compliance issues may make the drug candidate unsafe for oral delivery. Other delivery methods for a drug candidate that must also be

^b API is the molecule inside the drug candidate that elicits the biological response.¹

^c GMP is a process that aims to verify that small molecules are generated in line with quality standard practice.¹

^d The reason generating kilos of pure API is difficult can be attributed to the fact that one can no longer use techniques and/or reagents like transition metal catalysts, certain solvents and column chromatography. All of the above are typically utilized in the early stages for the synthesis of the drug candidate by medicinal chemists.

examined in the preclinical phase include subcutaneous (SC), intravenous (IV), intramuscular injection (IM), intranasal and intraperitoneal (IP).¹

Prior to the commencement of clinical trials, there are two main obstacles that must be met. First, the drug compound or molecule is required to show how efficacious it is in the designed animal studies. Efficacious refers to the capacity of the molecule to display sufficient therapeutic effect on the animals.¹ Second, the drug candidate must be tested in two animal studies, one rodent and the other a non-rodent animal. Both of the animal type studies must individually exhibit an appropriate safety window to move forward into human studies.¹ Once efficacy and safety are met by the proposed drug molecule and the preclinical data is detailed in the IND application, one awaits the approval by the regulatory bodies to enter into phase I, that involves the human population.

Clinical trials are categorized into four main phases, excluding the preclinical phase, that contain differing designs for studies that all aim to reach the same goals: the molecule is both safe and efficacious (Figure 7). In other words, the compound is free of toxicity and produces the expected and desired effect.¹ The safety and efficacy of drug candidates can only be accomplished when humans are involved in the studies conducted in the phases. Each phase contains individual objectives that are motivated by the design of the studies that each phase conducts.

Phase I

Phase I explores the safety and tolerability representing the first time the molecule reaches the human population. The overall objective of phase I is to use the data collected to define the safety margins, including the pharmacokinetic profile of the drug candidate.¹ Studies require the use of ‘healthy’ humans, not the population that carries the disease state that the molecule is attempting to target. In a typical phase I trial, the molecule is tested in about 30 to 100 healthy

patients over twelve to eighteen months (Figure 7).¹ As displayed in Figure 7, the number of patients and completion time relative to the other phases is minor.

<https://www.cancer.nsw.gov.au/data-research/clinical-trials/how-do-clinical-trials-progress>

Figure 7. The order, amount of time, and number of humans involved in each phase of clinical trials.¹⁸

There are two types of studies that are evaluated by the small patient population to establish dosing for the next phase if the molecule is proven safe enough to move on. The first type of study, the single ascending dose (SAD), includes a group of people given a dose and monitored for dosage tolerance (Figure 8).¹ If that dose is tolerated, a second group are tested with a higher dose, typically doubled, until it is evident there are adverse side effects with a certain dosage (Figure 8). The SAD study aids in deducing the maximum tolerated dose (MTD) of the molecule in healthy subjects and identifies any dose limited toxicity (DLT) issues that may occur as a result of the potential molecule (Figure 8).¹

Blass, B. E. *Basic Principles of Drug Discovery and Development*; Elsevier Inc.: San Diego, 2015; p. 398.

Figure 8. A SAD study conducted in phase I to determine MTD and DLT.¹

In contrast, a second study termed the multiple ascending dose (MAD) is performed by giving groups of people multiple increasing low doses of the molecule over a certain time period. The MAD study also verifies the MTD, establishes the DLT of the molecule and the side effects that occur with such a dosage.¹ The information obtained from studying this small patient population determines whether or not the safety margins are acceptable enough that the drug

candidate warrants moving forward to further testing. By completing the SAD and MAD studies, researchers have collected more accurate data *in vivo* and discerned the tolerable doses for testing in phases II and III.

Phase II

Phase II studies reveal preliminary data in regards to the safety and efficacy within the desired patient population that the drug candidate is aiming to treat.¹ This is the first time that the molecule will reach its intended population and researchers must solidify that the drug candidate generates the desired biological effect anticipated. Phase II requires approximately 100 to 300 patients with the actual disease that on average takes two years to complete depending on if the disease of interest is a chronic condition (Figure 7).¹ It should be noted that there are strict inclusion and exclusion protocols that must be followed in order to have the highest patient homogeneity possible.¹

In phase II studies, the patient population is split into various groups to either go through a single arm study or a two armed study in which either study can be staged or not staged.^e A simple single arm study is when a group of the patient population are all administered the same initial dose of the candidate molecule (Figure 9).¹

Blass, B. E. *Basic Principles of Drug Discovery and Development*; Elsevier Inc.: San Diego, 2015; p. 400.

Figure 9. A simple and staged single arm study in phase II, a and b respectively.¹

^e A staged study involves an interim analysis that is described by giving a dose of the molecule to half the population than if the outcome is desirable the remaining half of the population is administered that same dosage.¹

In a staged, single arm study the first group of the patient population is administered the molecule then testing is halted and results are analyzed (Figure 9).¹ The interim analysis involves determining if the analyzed results align with the fixed goal of the study. If the goal and results align, the second group of patients receive the compound and if the goal and results do not agree the study is aborted (Figure 9).¹

In contrast, a two armed, randomized study requires a group of people to be separated further into two groups where one half will receive a dose of the molecule and the other half is delivered a placebo (Figure 10).^{1,f} The advantage to performing a two armed study is that now efficacy can be measured from the patient outcomes in the two different groups. The efficacy established in these studies are used to produce the most optimal design of studies to be complete in phase III.¹

Blass, B. E. *Basic Principles of Drug Discovery and Development*; Elsevier Inc.: San Diego, 2015; p. 401.

Figure 10. A two armed, randomized study in phase II.¹

Moreover, a two armed, randomized study can also become a staged study which involves an interim analysis as described for the staged simple armed study (Figure 11). In this instance, the interim analysis is utilized to inspect the results verse the predicted outcomes of the study (Figure 11).¹ This inspection aims to establish if it is safe and beneficial for a new set of the patient population to enter into the current study being investigated.

^f A placebo is a substance that consists of no medicinal or therapeutic effects that act as a control in a study.⁵⁹

Blass, B. E. *Basic Principles of Drug Discovery and Development*; Elsevier Inc.: San Diego, 2015; p. 401.

Figure 11. A two armed, randomized staged study in phase II.¹

From the data collected in the desired patient population that is studied in phase II, researchers must again validate the dose that generates the appropriate therapeutic effect and overall efficacy of the molecule. In addition, studies specifically designed to test the safety of the molecule continues throughout phase II.¹ Data accumulated up to 2011 revealed that only 34% of phase II drug candidates are successful to move on to phase III (Figure 5).¹ This statistic shows how challenging it is for a drug candidate to succeed in phase II as the majority fall short in phase II. Ultimately, the likelihood of a drug candidate progressing through phase I into phase III is 18.36%.¹

Phase III

Phase III continues to investigate the safety and efficacy of the molecule but in the largest disease state patient population to date. Phase III is key in establishing the efficacy of the drug candidate by comparing the molecule to the current, typical standard of care.¹ Numerous clinical trial sites are utilized to test the molecule in a patient population of approximately 1000 to 5000 people over a period of three to five years (Figure 7).¹ Phase III design of studies is critical as this phase must demonstrate at least two, commonly three, well controlled studies that display pointed efficacy of the molecule.

Common types of studies conducted in phase III include randomized parallel and randomized crossover studies.¹ Both studies incorporate the new drug and the standard of care; however there is an advantage to performing a randomized crossover study as each patient will

receive both the standard of care and the new molecule (Figure 12).¹ This unique aspect brings about additional data for proving efficacy as each patient tested in the randomized crossover study becomes their own control. Specifically, in a randomized, crossover study the patients are split into two groups in which each group is randomly assigned either the candidate molecule or the standard of care (Figure 12).¹ After a designated amount of time has passed, the treatments for each group are reversed and the study continues until it has concluded (Figure 12).¹ This particular type of study aids in establishing whether or not the molecule is both safe and efficacious, delivering a more beneficial biological response than the currently marketed standard of care.

Blass, B. E. *Basic Principles of Drug Discovery and Development*; Elsevier Inc.: San Diego, 2015; p. 405.

Figure 12. A randomized, crossover study conducted in phase III trials.¹

Safety of the patients participating in these larger studies in clinical trials continues to be strictly observed in the context of adverse side effects. It can be expected from testing a larger population that some adverse side effects become more noticeable or the severity may differ from studies with a smaller patient population.¹ As a result of the variety of differently designed trials that are conducted in phase III, phase III is considered to take the most amount of time, resources, and money of both the drug discovery and the drug development components.¹

One may make conclusions of how successful phase III is for a drug candidate based on whether or not a New Drug Application (NDA) is submitted to the FDA at the completion of the phase.¹ This application is more comprehensive and detailed in comparison to the IND application as it includes the results, design, side effects and dosing methods of the human and animal studies.¹ Furthermore, the NDA must include the method of manufacturing and proper storage conditions

for the molecule, preparing it for market. The regulatory bodies then carefully review the application to potentially grant regulatory approval which generally includes the rights to begin marketing the official new drug.¹ Although, it is more likely that the FDA will demand further information on certain topics or require more studies to confirm that the safety and efficacy guidelines are adequately met. In most instances, once approval is given based on the NDA, additional clinical trials are necessary to ensure the safety of the new marketed drug in patients, deemed phase IV.

Phase IV

The broad objective of phase IV, frequently termed the post marketing surveillance phase, is to observe the newly marketed drug, including how it functions, and an evaluation of the drug's therapeutic potential.¹ Specifically, what is being monitored in these studies is a potential trend in adverse side effects or the development of long-term side effects that could not be predicted from the three to five year timelines of phase III studies. Basically, both the safety and efficacy of the new drug continues to be recorded in hopes that no safety concerns arise in the market. With the ongoing analysis of safety at the forefront of studies in phase IV, the data collected may also reveal desired information to pharmaceutical companies about competition, new possible areas of market and additional ideas for novel therapeutics.¹ For example, the new molecule may show it has a profound effect on a disease that was not the intentional target which may lead to the completion of further studies and new ways a company can patent or market the drug.

Chapter 2: Biological And Medicinal Chemical Aspects Of CAR T Cells And Traditional Small Molecule

The drug discovery world continues to strive for more innovative approaches for patient care as a result of the various scientific and technological advances. Patient priorities are being met while researchers strive to generate a robust personalized medicine approach to treating individual diseases. One of the areas of science that is experiencing a shift from traditional treatment methods to innovative personalized approach's is immunology. In the past two decades, major breakthroughs in the area of immunology have transpired and impacted cancer research.¹⁹ Such breakthroughs in immunology are possible as the research surrounding the fundamental principles of the traditional immune response to the invasion of infectious cells in the body has advanced.

Traditional Immune Response

The human body is continuously exposed to possible infectious cells and it is the immune system's responsibility to be able to detect and appropriately respond to the threat. The role of the immune system in the human body is to act as the line of defense in opposition to foreign invasions of cells or organisms.²⁰ The immune system consists of various types of cells, proteins, organs and tissues that work together to fight against an attack. The most significant cells in the immune system are the leukocytes, white blood cells that aid in the eradication of infectious cells.²¹ White blood cells flow throughout the organs, tissues and blood vessels of the human body to effectively detect foreign cells.²¹

There are two types of leukocytes, that have a pivotal part in the human immune response: lymphocytes and phagocytes.²² A phagocyte is a cell that consumes unfavorable particles, bacteria or cells that are dying.²² A lymphocyte is a vital cell that offers a level of recognition of previous

infectious invaders and contain an understanding on how to destroy such foreign subjects.²² There are two main types of lymphocytes, B cells and T cells.²¹ The primary functionality of B cells is to generate antibodies and release them to the identified targets (Figure 13).²¹ In contrast, T cells contain a T cell receptor on the surface of the cell that allows a cell to kill the foreign cells that the immune system has recognized (Figure 13).²¹

If an organism with a foreign antigen enters the body, the immune system responds by prompting the B cells to generate antibodies (Figure 13).^{g,h,22} Once an antibody is produced for a distinct antigen, the antibody will remain in the body so that the next time the immune system comes in contact with that antigen, the antibody will counteract the invader antigen by latching onto it.²⁰ Antibody's on their own do not have the ability to destroy the foreign cell, rather they require assistance from the T cells in the body. The T cells operate by attacking the antigens that were previously tagged by the antibodies leading to cell death (Figure 13).²² The various cells described above all aid the body in the development of the appropriate immune response to the invasion of foreign pathogens.

<https://www.dreamstime.com/stock-photography-cell-mediated-immune-response-immunity-t-lymphocytes-do-not-secrete-antibodies-incorporates-activated-macrophages-natural-image39284952>

Figure 13. Illustration of the immune response to an infected cell.²³

A generic example of an immune response is an allergic reaction or the development of allergies to various substances (allergens), deemed allergic disease.²⁴ Allergic disease is one of the

^g An antigen is a molecule that can be bound to antibodies or located on the surface of a cell which can stimulate an immune response.²¹

^h An antibody is a blood protein that is produced in response to an antigen which is then utilized in the immune system to neutralize the foreign antigen.²¹

most common, chronic health conditions that humans frequently experience.²⁴ An allergic reaction occurs when the body comes in contact with numerous allergens from the environment that activate the immune system to send a signal to produce antibodies.²² The allergen that induced the creation of antibodies causes the immune system to overreact. Overreaction of the immune system can affect people in differing ways, most commonly excessive sneezing, swelling, watery eyes, hives, asthma or anaphylactic shock.²² The symptoms that one can experience from an allergic reaction depends on the individual immune system and the amount of allergen the person is subjected to.²⁴

A method of treatment for people suffering from allergic disease to a particular allergen is immunotherapy. Immunotherapy as a treatment for allergies depends on the specific allergen which can teach an individual's immune system on how to become less allergic to the allergen.²⁵ In this context, people utilize immunotherapy for the treatment of allergies as a preventive measure to reduce the potential immune response. Generally, the method of treatment for allergy immunotherapy incorporates the delivery of a steady increase in the allergen dosage.²⁵ The gradual increase in allergen allows the immune system to become less reactive to the allergen. This results in fewer signals for the production of antibodies, generating a smaller number of antibodies and a minimal immune response.²⁵ Overall, it is evident that a properly functioning immune system and its countless cellular components have a critical part in signaling and responding to foreign invaders to ensure the health of the body.

Cancer Growth And Traditional Small Molecule, Taxol

When cancer cells develop in the body, the typical immune response detailed above is not generated. In this case, the body's immune system cannot cure itself by its innate immune response because T cells cannot locate their exact target on the surface of the cancer cell to ultimately kill

the cell.²⁶ Hence, it is important that the development of cancer cells in the body is understood. Cell division is critical for cell growth allowing the body to execute normal functions while also repairing damaged cells when necessary.²⁷ The main distinction between cancer cells and normal cells relates to how cell division occurs. Under normal conditions in the body, cell division occurs in an orderly and controlled manner (Figure 14).²⁷ Cancer cells do not divide in an organized manner nor do they have any control of their growth. Cancer cells abnormally multiply at astronomical rates, which result in the formation of localized tumors as well as the spread of tumors in other parts of the body (Figure 14).²⁷

Hanahan, D.; Weinberg, R. A. Hallmarks of Cancer: The Next Generation. *Cell* **2011**, *144* (5), 646–674.

Figure 14. Depiction of cell division of normal cells verse cancer cells.²⁷

Traditional treatments of cancer include radiation and chemotherapy to terminate any cells in the body that are hastily multiplying.²⁸ As a result of this traditional therapy, the drug molecules in chemotherapy kill not just the intended cancer cells but healthy, living cells too.²⁸ The elimination of healthy cells causes the body's immune system to weaken, producing side effects such as low blood cell counts. Similarly, radiation as a therapy for cancer encompasses the use of highly energized X-rays that kill cancer cells in the specific targeted region.²⁸ Limitations of radiation include not being able to eradicate all of the cancer cells present in the body and, again, the destruction of healthy cells and tissues.²⁸

A traditional small molecule like Taxol can be controlled, synthesized, and easily administered to the patient population because it is a static natural product. Taxol (Paclitaxel) is a natural product that is acquired by a semi-synthetic process from *Taxus baccata* that contains

antitumor activity.²⁹ Paclitaxel, found in a Pacific Yew tree, was discovered as part of a national cancer center screening program in 1960 by Dr. Jonathan L. Hartwell.²⁹ This program was searching for plant extracts that exhibited antineoplastic activity. To this day investigations of paclitaxel in its role as an anticancer agent continue to be conducted.³⁰ Taxol is a prescription chemotherapy medicine for the treatment of a variety of cancers including ovarian, breast, lung and Kaposi's sarcoma; mainly solid tumor cancer types.^{29,30} The active ingredient in Taxol chemotherapy is paclitaxel which is delivered to patients intravenously once every three weeks (Figure 15).^{29,30}

Barbuti, A.; Chen, Z.-S.; Barbuti, A. M.; Chen, Z.-S. Paclitaxel Through the Ages of Anticancer Therapy: Exploring Its Role in Chemoresistance and Radiation Therapy. *Cancers (Basel)*. **2015**, 7 (4), 2360–2371.

Figure 15. The structural formula of paclitaxel.²⁹

Taxol's therapeutic mechanism stems from its ability to interfere with the normal function of microtubules responsible for dividing and replicating cells in the body during cell division.²⁹ Taxol is classified as a "antimicrotubular agent" and hence Taxol's objective is to target tubulins.^{29,30} Antimicrotubular agents cause disorder in the dynamics of microtubules which then triggers mitotic arrest, prohibits cell division and triggers apoptosis (death) of a cancer cell.^{29,30} Paclitaxel is still a major anticancer drug with a long history but "its therapeutic efficacy can be limited by common encumbrances faced by anticancer drugs" which include matters like toxicity and acquired multidrug resistance.^{29,30} Traditional small molecule treatments are generally less specific in their mechanism of action and produce a considerable number of side effects as a result of the death of healthy cells. For this reason, in the last twenty years there has been a major

movement from small molecule research into the development of immunotherapy products that display a higher degree of specificity and tailoring to the individual patient.

Although today there are a large number of traditional therapies that provide adequate benefits, and even possible cures for some types of cancer, there are significant limitations with the rate at which people undergo relapses.¹⁹ A relapse typically occurs when tumor cells or cancer cells evolve in the presence of the drug molecule that is trying to fight them. Basically, the cancer cells in the presence of the drug develop a resistance to the drug mechanism and thereby learn how to avoid being killed by the drug molecule.¹⁹ The main draw of immunotherapy as an approach to the treatment of cancer is that immunotherapy patients may not experience relapse as frequently as patients using traditional medicines; immunotherapy has the potential to eliminate a cancer cell's resistance.¹⁹ Moreover, traditional therapies utilized for the treatment of cancer incorporate a high chance of killing a large amount of healthy tissue and cells that are necessary for the body to use to fight such a disease. The drawbacks of traditional cancer treatments have revealed a need for improvements in the types of treatments offered to patients. Immunotherapy has quickly become an evolving field that is remarkably different than traditional approaches to the treatment of cancer.

Immunotherapy

All immunotherapy approaches have one objective: to manipulate the immune system in a different way. Immunotherapy concentrates on using one's own immune cells and the fundamental mechanisms of the immune system to destroy cancer cells.¹⁹ The promise of immunotherapy for the treatment of cancer has continued to thrive as research into the techniques and mechanisms that cancer cells use to evade the human immune system continue to develop and gain in understanding.¹⁹ Improved understanding of the molecular and cellular mechanisms of the immune

system has led to many pioneering ideas that are presently being developed into cancer therapeutics. Immunotherapy can be a standalone therapy for the treatment of cancer or can be utilized in combination with other, more traditional therapeutics.²⁸ Researchers may want to treat cancer with a type of immunotherapy but also provide an additional drug molecule to aid in the suppression of some side effects that may occur as a result of the immunotherapy. Thus far, the immunotherapy approach that has had the largest amount of scientific research and development invested into the notion of personalized medicine is CAR T cell therapy.

Basics Of CAR T Cells

Chimeric antigen receptor T-cells (CAR T) are a type of therapy that contains living cells that fluctuate based on a person's genes and the particular cancer cells that make up the disease.³ There has been an evolution of CAR T cells since the late 1900s, interest in CAR T cells has risen in the last decade. The first generation CAR T cells were discovered in the late 1980s in Israel by the chemist Zelig Eshhar.³¹ The CARs part of CAR T cells are responsible for the recognition of the target antigen.⁵ The reason T cells are the chosen hosts of the CARs is that T cells are the key to enacting any immune response within the body and aids in the destruction of infectious pathogens.⁵ The goal of CAR T cells is to shift a patient's immune response to fight against the cancer cells by genetically engineering the killer T cells.³²

The synthetic CARs that are planted on the surface of the T cells are "engineered proteins that contain an extracellular antigen-binding domain composed of a single-chain variable fragment (scFv) that is derived from an antibody and intra-cellular signaling domains" (Figure 16).⁵ The reprogrammed T cells that contain CARs typically target antigens that are mainly on the surface of cancer cells (Figure 17).³³ When the CAR binds to the tumor antigen on the surface of the cell, the CAR T cell causes apoptosis (cell death) to occur in the same manner a normal T cell would

undergo apoptosis (Figure 17).³¹ Basically, CAR T cells are genetically modified antigen specific immunotherapies that are generated to express the particular antigen that is affiliated with the diseased cells (Figure 16).³⁴

In first generation CAR T cells, the CARs are composed of three main components (Figure 16). The first component is the extracellular antigen-binding domain that stems from a tumor-specific “monoclonal antibody” scFv (Figure 16).^{i,31} The second component of the CAR is a transmembrane domain that acts as an anchor for the CAR and the T cell (Figure 16).³¹ The third component is the intracellular T cell activation domain, CD3, which has the ability to contain additional costimulatory molecules (Figure 16).^j The transmembrane also aids in connecting the scFv to the T cell which binds to the tumor antigen and to the intracellular domain CD3; this is the part of the CAR that is in charge of the T cell being activated.³¹ As displayed in Figure 16, one may notice that as the generation of CARs progressed, the more costimulatory domains were added to ensure the stimulatory molecule could activate the T cell.³¹

Abate-Daga, D.; Davila, M. L. CAR Models: Next-Generation CAR Modifications for Enhanced T-Cell Function. *Mol. Ther. - Oncolytics* **2016**, *3*, 16014.

Figure 16. The evolution of the design of CARs in CAR T cells.³¹

Referencing Figure 16, in the first generation CAR, there is a singular stimulatory molecule, CD3. The stimulatory molecules’ ability to activate T cells was found to be inadequate,

ⁱ A monoclonal antibody is an antibody that is generated by a cell line that is composed of uniform antibody molecules.³¹

^j Costimulatory molecules are membrane bound or secreted products of cell pathways that are required for conducting signals.⁶⁰ Co-stimulation of molecules during the activation of white blood cells is critical to producing an effective immune response. The costimulatory signal occurs as a result of the interactions of costimulatory molecules located on the membrane of the T cell.⁶⁰

creating issues with weak proliferation and anti-tumor effects. The survival rate of the T cells was small and therefore problematic.³¹ Second generation CARs contain two intracellular costimulatory domains that enhanced the survival rate and increased proliferation of the T cells (Figure 16).³¹ The most progressive CARs to date, the third generation, display three costimulatory domains including CD3, to significantly improve the durability of the T cells and the cytotoxicity (Figure 16).^{k,31} The observed improvement in cytotoxicity of normal cells with the third generation CAR T cell is vital as immunotherapy approaches aim to cause limited harm on the surrounding healthy cells in the body compared to traditional chemotherapy treatment methods.

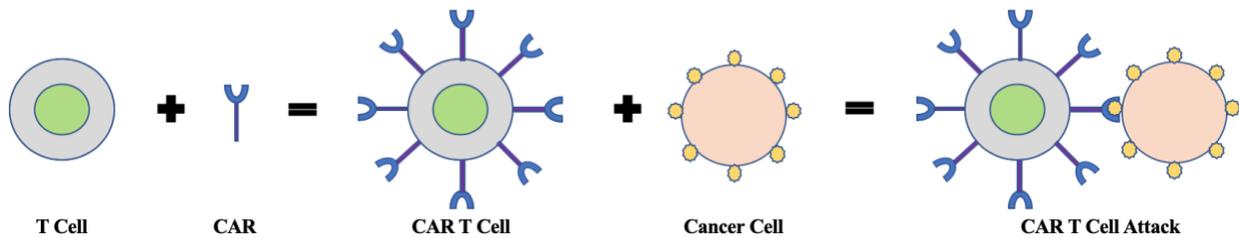


Figure 17. The components of a CAR T cell and a target tumor cell.^{31,35}

A general representation of how T cells are transformed into CAR T cells and the subsequent attack of a CAR T cell to a tumor cell is illustrated in Figure 17. The main elements of the CAR are the tether and the connector that attach to the T cell forming CAR T cells (Figure 17). The tether includes the multiple costimulatory domains that are responsible for sending activation signals to the T cell and the transmembrane domain that aids in securing the CAR to the T cell (Figure 16, 17). The connector part of the CAR is the scFv that is tumor specific and functions as the region for antigen binding (Figure 17). Once the CAR T cell recognizes the particular antigen that is expressed on the surface of the tumor cell, the connector (scFv) of the CAR fuses itself to the tumor antigen to trigger apoptosis (Figure 17).

^k Cytotoxicity is the quality measure of how toxic a therapeutic is to healthy cells.¹

Note that the majority of current clinical data involves first and second generation CARs designed in CAR T cells. The above description of CAR T cells is what has led to the declaration that CAR T cells are a “living drug.”²⁵ This idea of living cells being used as a form of treatment is a new approach for the pharmaceutical industry that is saturated with the traditional development of small molecules.

Development Of A “Living Therapy”

Since CAR T cells are a living drug, there are apparent differences that arise between this therapy and small molecules. For instance, traditional drugs immediately begin to break down as the molecule enters the blood stream. CAR T cells are a living therapy which means that once the cells identify the target antigen on the cancer cells in the blood, the CARs multiple exponentially. As CAR T cells attack cancer cells, the attack subsequently releases molecules termed cytokines. This buildup of cytokine molecules in the body increases the amount of inflammation present, which then enlists more immune cells to join the attack. The additional immune cells and inflammation occur at a rapid pace that can result in an immune flare-up defined as a cytokine storm or cytokine release syndrome (CRS).³⁶ Currently, the symptoms of CRS can be reduced by treating patients with tocilizumab; a rheumatoid arthritis drug meant to dampen prolific inflammation in the body.³⁶

It is evident that researchers should focus on creating new effective generations of CAR T cells which limit the number and severity of side effects. Despite CRS as a side effect associated with CAR T cell therapy, CAR T cells have specifically shown therapeutic benefits to patients who did not respond to conventional methods of treatment or frequently relapse with non-immunotherapy approaches.³³ Therefore, CAR T cells are often their last option to beat the disease and a possible severe side effect becomes a minimal risk worth taking.

CAR T Cells: A Novel Immunotherapy Reaches The Market

Some researchers believe the technology rooted in CAR T cells may contain the potential to cure cancers deemed incurable.³⁷ The ability to reconfigure a body's immune system to battle against cancer cells has produced high expectations leading CAR T cells to be regarded as the "next huge cancer treatment to hit the market."³⁷ CAR T cell expectations depend on the ability to fund the costs associated with the next steps in R & D and the successful completion of such steps by skilled scientists and physicians. Given the expense and the relative infancy of the immunotherapy market, the incentive to invest money into CAR T cells is prompted from the potential rate of business return that can only be assured through patent protection.

In August, 2017 Kymriah by Novartis became the first cell therapy or CAR T cell to be approved by the FDA to treat patients 25 years old and younger for B-cell acute lymphoblastic leukemia (ALL).³⁶ Kymriah's CAR T cell specifically targets antigen CD19 that is on the surface of B cell malignancies.³⁴ Kymriah is a second generation CAR T cell that is composed of extracellular anti-CD19 antibody fragment with two costimulatory intracellular signaling domains (Figure 16).³¹ Patients had previously undergone numerous traditional treatment methods prior to attempting CAR T cell therapy. The clinical study of Kymriah found that after being administered Kymriah, three months later 83% of patients were in complete remission states of ALL.³⁶ This unprecedented clinical study observed CAR T cells could indeed rid a person of their blood cancer.³⁶ The former head of Novartis's cell and gene therapies unit commented on the success of Kymriah in clinical trials stating the results "were like landing on the moon for this field."³⁶

Since Kymriah was approved, the excitement and interest surrounding CAR T cells has only grown. The approval of another CAR T cell therapy Yescarta, funded by Kite Pharma, which generated remission in 72% of adult patients with aggressive B-cell non-Hodgkin lymphoma

quickly followed on October 18th, 2017.^{6,36,37,1} Presently, both Kymriah and Yescarta are the only two FDA approved CAR T cell therapies on the market. The potential of CAR T cell therapy might be measured or assessed through the amount of heavy investments by venture capitalists in biotechnology firms attempting to create the next generation of CAR T cells.

Manufacturing Process Of CAR T Cells

Traditional drugs are synthesized natural products, generated in bulk to meet their market demand: CAR T cells cannot be manufactured in this manner.³⁶ Both Kymriah and Yescarta must be individually manufactured for every patient, taking the idea of “personalized medicine” for cancer care to another level.³⁸ The first step in the manufacturing process occurs at a hospital where a machine is utilized to extract and separate the patients white blood cells, T cells, from the patient’s blood (Figure 18).³⁶ The patient’s extracted cells are then shipped to a designated manufacturing plant to move forward in the regeneration of their T cells. It should be noted that if cells other than T cells are present in the extraction, the non-T cells die during the manufacturing process. The approved CAR T cell production method for reprogramming a T cell involves a viral vector (Figure 18). A viral vector is utilized to transport a gene encoded synthetic CAR in T cells (Figure 18).³³ In simple terms, a vector is implemented to stably insert DNA encoding of CARs into T cells as illustrated in Figure 18.

Park, J. H.; Riviere, I.; Wang, X.; Bernal, Y. J.; Yoo, S.; Purdon, T.; Halton, E.; Quintanilla, H.; Curran, K. J.; Sauter, C. S.; et al. CD19-Targeted 19-28z CAR Modified Autologous T Cells Induce High Rates of Complete Remission and Durable Responses in Adult Patients with Relapsed, Refractory B-Cell ALL. *Blood* **2014**, *124* (21).

Figure 18. A depiction of a viral vector used in the transfection of CAR DNA into T cells.³⁹

¹ Gilead Sciences purchased Kite Pharma for \$11.9 billion weeks prior to FDA approval of Yescarta as a cancer therapy on August 28th, 2017.^{16,36}

In short, the extracted T cells from the patient are reprogrammed to stably express CARs and be able to distinctly target the antigen on the type of cancer cells desired (Figure 19).⁵ The CAR receptors that attach to the T cell generate the encompassing CAR T cell which gives the cell the ability to attach itself to particular antigens or proteins that are on cancerous tumor cells.³³ Once the cells have been engineered and modified appropriately they are considered CAR T cells. These CAR T cells are then multiplied in a bioreactor at the manufacturing facility (Figure 19).³⁶ In preparation for the delivery of the CAR T cells to the specific patient, the patient must first be given chemotherapy before CAR T cells can be added to their system (Figure 19).³⁶ The addition of chemotherapy aids in lowering the white blood cell count which is essential as one cannot substantially increase the T cell count without first diminishing some of the T cells. Basically, the chemotherapy gets rid of enough white blood cells in the body to allow for the delivery of CAR T cells without producing any harmful inflammation affects.

Levine, B. L. Performance-Enhancing Drugs: Design and Production of Redirected Chimeric Antigen Receptor (CAR) T Cells. **2015**.

Figure 19. The main steps in the manufacturing process of CAR T cells.³⁵

The last step of the manufacturing process is the treatment step in which the regenerated CAR T cells are infused back into the patient's blood (Figure 19). Once the CAR T cells enter the blood, they begin to target and identify cancer cells while exponentially multiplying themselves.³⁶ Overall, the main dispute regarding the manufacturing process of CAR T cell therapy is that it involves manipulating living cells of patients to then be delivered back into the specific patient, instead of a simple, reproducible synthesis of a natural product given to a patient by a prescribed dosage. The more steps involved in the manufacturing process of CAR T cells, the higher the

likelihood that some part of the process will fail or deviate from the desired, successful therapeutic outcome. The challenge of this type of personalized medicine is the adaptations and alterations that the differing fields, immunology, oncology and patent protection, may have to make in order for the benefits of this therapy to be delivered to the patients.

Future Endeavors For CAR T cells

At this moment, Kymriah and Yescarta are only approved to treat specific rare blood cancers. The potential to develop various types of CAR T cells that could be used for the treatment of other types of cancers, including those of solid tumors is vast. There are over 240 clinical trials being conducted globally that involve the evaluation of CAR T cells as a cancer therapy (Figure 20).³⁷ A large number of CAR T cell therapies discovered and in various stages of clinical trials involve different signaling domains that influence recognition of tumor cells and CAR T cell functionality.³ In addition, it is likely that as more versions of CAR T cells reach the market, the manufacturing companies of the therapy will be challenged to deliver the product at a lower cost. Today, the cost of this personalized medicine comes at a price: a one time injection of Kymriah CAR T cells costs \$475,000.³⁶

Sadelain, M. CD19 CAR T Cells. *Cell* **2017**, *171* (7), 1471.

Figure 20. The number of clinical trials involving CAR T cells throughout the world.³⁷

Cost is not the only challenge, there are accumulating amounts of reports of patients experiencing severe side effects after treatment with CAR T cell therapy. CAR T cells kill the cancer cells, but also cause systemic inflammation within the body that can result in death.³⁶ In the

clinical trials of Kymriah about 49% of the patients suffered strong cytokine release syndrome (CRS) which was responsible for several deaths.³⁷

As a result of the severe side effects observed, neurotoxicity, and cytokine release syndrome, some biotech companies are shifting focus to designing control systems that can make new versions of CAR T cells safer and more potent. Some researchers have been working on the development of emergency off switches that involve the addition of traditional small molecules to control and tune the T-cell activity in the body when necessary.³⁶ Other groups are focusing on the construction of highly selective sensors on the CAR T cells for better control of the therapy.³⁶ The scientific challenge is to keep the immunotherapy benefits of CAR T cells while simultaneously making the immunotherapy behave like traditional pharmaceuticals in which doses and sensitivity can be controlled and managed by doctors.

Chapter 3: CAR T Cell Patentability And Patent Trends

The scientific research and investment in immunotherapy, specifically CAR T cells, and their potential to treat a variety of cancers continues to flourish in the pharmaceutical industry. The cancer field is projecting that CAR T cells are the next blockbuster therapeutic with sales of genetically engineered CAR T cells estimated to be 10 billion dollars per year by 2021.⁴⁰ As a result of this steady movement of investors and pharmaceutical companies becoming involved in the production and commercialization of CAR T cells, the USPTO is observing a staggering increase in patent applications regarding CAR T cells. This increase in patent filing also suggests that patent protection and the field of intellectual property is a vital part of the advancement in research that is being accomplished in the area of immunotherapy.

When Kymriah and Yescarta became FDA approved this further motivated other pharmaceutical companies to join in on the potentially profitable future that CAR T cell therapy represents.⁴¹ Improved innovation of CAR T cells includes methods for quality control of the cells, manufacturing processes, identification markers, other types of expressions of antigens, dosing and toxicity.⁴⁰ Therefore, it is likely that the CAR T cell field will soon become a crowded and competitive environment that involves a race to the patent office with the next, enhanced CAR T cell technology. It is therefore essential for companies to acquire the most valuable patent claims to protect their investment and become a pharmaceutical success story.⁴⁰

CAR T Cell Patent Trends

The patent landscape in the United States supplies minimal assurance to investors in immunotherapy. Currently immunotherapies are not able to obtain the most desirable form of patent protection to ensure the market exclusivity that is traditionally obtainable for small molecule products.⁴² Patentability requirements state that there are four categories of invention claims, three

main types of patents and three principles of patentability (Figure 2).¹ A typical idea not only must meet these stipulations but also an invention that can be designated as a “living cell” must also demonstrate why it is not a natural phenomenon, therefore unpatentable subject matter.¹ In order to authenticate this argument for a patent, one must incorporate similar or relevant case rulings that provide evidence that the invention consists of patentable subject matter.

In general, under section 101 of 35 U.S.C. subject matter is patentable if it does not fall into the laws of nature and natural phenomena.^{6,m} Natural phenomena subject matter is described as existing in the world without the aid of humans.⁶ However, it is evident that some grey area surrounds patentable subject matter that may or may not be deemed natural phenomena in the realm of biology and pharmaceuticals. In addition, section 101 of 35 U.S.C. demonstrates that the language utilized in the statutory requirements were written for applicability to a broad scope of ideas.⁶ As a result of the extensiveness of patentable subject matter, judicial court decisions have displayed that there are exceptions that are made for certain inventions that do not necessarily completely align with the statutory guidelines. Also, it is evident that issues arise when attempting to join both legal and scientific concepts together in regard to the definition of a law of nature and natural phenomena.⁶ Thus, patentable subject matter that is designated as a law of nature has a history of being highly debated in courts of law.

Funk Bros. Seed Co. Verse Kalo Inoculant Co.

This case is an example of a United States Supreme Court ruling that upheld the requirements of section 101 of 35 U.S.C. by invalidating a patent that contained unpatentable

^m 35 U.S.C. is Title 35 of the United States Code that states the patent law requirements.¹¹ Each section in 35 U.S.C. details all of the components of patent law that are complied with in the United States.¹¹ Specifically, section 101 of 35 U.S.C. describes patentable subject matter stipulations.¹¹

subject matter, a law of nature.⁶ In 1948, Kalo sued for patent infringement against Funk claiming the mixture of bacteria being sold by Funk was similar to the bacteria Kalo was producing according to the claims made in their patent.⁴³ Kalo's invention was the combination of a total of six naturally occurring bacteria to treat the legume plant group.⁶ However, Kalo filing an infringement suit against Funk brought Kalo's bacteria patent to the forefront of deliberations.

The Supreme Court determined the bacteria patent granted to Kalo contained unpatentable subject matter and thus, the patent was invalid. The court stated that the combination of natural bacteria did not add any novel, distinct properties to the bacteria or offer additional usefulness.⁴³ The Supreme Court decided that in conjunction with the meaning of the statute in section 101, this invention was not a novel application of a nature law because none of the properties of bacteria were significantly altered by mixing them.⁴³ Thereby, the infringement case against Funk was dropped and Kalo's bacteria patent was withdrawn.⁴³ This ruling is an example of when section 101 of 35 U.S.C. was utilized to examine a case that questioned the ability to patent a law of nature or natural phenomenon.

Diamond Verse Chakrabarty

Diamond verse Chakrabarty is an example of a different outcome than the *Funk Bros. Seed Co. v. Kalo Inoculant Co.* argument about patentability of a law of nature. In this situation, General Electric filed a patent for Chakrabarty's invention that detailed a bacterium that was genetically engineered to express two different pathways that could dismantle crude oil to be applied in cleaning up oil spills.⁶ The patent application was rejected by the USPTO citing that living things are not patentable subject matter according to section 101 of 35 U.S.C.⁴⁴ The Board of Patent Appeals confirmed the original patent examiner's decision that the bacterium was not patentable.⁴⁴ However, the United States Court of Customs and Patent Appeals disagreed with the patent

rejection stating that a refusal cannot be made on the sole fact that the invention is a living organism.⁴⁴

This case reached the Supreme Court on March 17th, 1980 and a decision rendered on June 16th, 1980.⁴⁴ The Supreme Court determined the living bacterium to be patentable subject matter because the living cell was genetically altered; it was “manufactured” or contained a “composition of matter” aspect that was not a natural phenomenon.⁶ The Supreme Court made the argument that the simple definitions of “an article of manufacture” and “composition of matter” aligned with the genetically modified bacteria presented in the patent.⁶ The bacteria were altered to contain an oil degradation mechanism that without the additional matter, the natural bacteria would not display the desired properties. Thus, it was noted that the genetically engineered bacteria were significantly distinct from natural bacteria.⁶

The debate surrounded the notion that bacteria is a living cell that would typically fit into the category of a natural phenomenon. Diamond, who argued the patent was invalid, cited the 1930 Plant Patent Act which specifically stated that living things did not qualify as patentable subject matter.^{6,44} The court decision revealed that even though under section 101 of 35 U.S.C. living things or natural phenomenon are patent ineligible, certain exceptions may apply provided the court is convinced of a certain level of novel, useful alteration. In reference to this court ruling, it is evident that individual opinions differ in regard to patent eligibility of living things, but that the role of human ‘handiwork’ is crucial in the overall patentability of the invention.

Assoc. For Molecular Pathology Verse Myriad Genetics, Inc.

The case between the Association for Molecular Pathology and Myriad Genetics, Inc. is an instance in which two particular patent claims had two differing outcomes. One claim was considered a law of nature, hence unpatentable subject matter while the other claim was deemed a

manufactured product, therefore, patentable. In this case, Myriad Genetics was granted a patent that consisted of a variety of claims regarding the isolation of two gene sequences, BRCA1 and BRCA2, and the construction of complementary DNA (cDNA) for gene identification markers related to breast and ovarian cancer.⁴⁵

In September of 2012, the Association for Molecular Pathology contested that Myriad Genetics, Inc's claims for the isolation of two gene sequences violates the law of nature rule that states such subject matter is not patentable.⁴⁵ The Association for Molecular Pathology asserted that the isolated genes are found in nature and that they do not offer any new properties that differ from the natural gene form.⁴⁵ The District Court determined that the two isolated genes exist in nature and thus, ruled that none of the claims were patentable.⁴⁶ This debate went onto the Federal Court, which declared that the District Court's ruling on the isolation of DNA was incorrect. Therefore, the Federal Court reversed the major decision of the District Court stating that the isolation of these specific genes was patentable subject matter.⁴⁵

On June 13th, 2013 the United States Supreme Court determined that the isolation of a particular sequence of genes is a law of nature, therefore, unpatentable subject matter.⁴⁵ The court established that the isolation of the two gene sequences was obvious and not novel.⁶ Isolating a particular gene of DNA is not considered a new product. The court made a note that Myriad did not make any type of claim in their patents to the method of pinpointing the location of the isolated gene sequences as such a method is a common process utilized in genetic testing.⁶ The isolated genes determination, BRCA1 and BRCA2, was a new development for its application in an elevated risk of ovarian and breast cancer.⁴⁶ This usefulness was not enough to sway the court that the isolation of these specific genes should be patentable. Moreover, in the same court ruling the Supreme Court stated that the cDNA claim made was patentable subject matter.⁴⁵ The production

of cDNA involves an alteration of the coding of the DNA sequences to become cDNA.⁶ Thereby, the court ruled that cDNA is a synthetic product, not natural occurring DNA or a law of nature.

Patentability Of Antigens And Receptors

CAR T cells are made out of T cells that are a natural part of every human's immune system and thus, are technically not patentable subject matter. However, some may argue that the insertion of a viral DNA vector into the T cells that then express the CARs allows for CAR T cells to be patentable. The addition of the vector into the T cells, results in the genetically modified T cells that aim to express a particular antigen that is on the surface of a specific type of cancer cell. As a result, CAR T cells have different characteristics and varying components than a typical T cell that is generated by the immune system. This slight addition is one of the key elements in displaying to the USPTO that CAR T cells are eligible, patentable subject matter.

Currently, the patentability of CAR T cells, to a certain extent, is apparent as the USPTO has granted distinct CAR T cell patents. However, this does not mean that the patentability of CAR T cells is not being thoroughly questioned. Patent filing, whether that be a patent application under review by the USPTO or a granted patent, of CAR T cells has developed a certain trend that relates to one distinct component of CAR T cells: the ability of CAR T cells to recognize antigens. The CAR T cell patents held by pharmaceutical companies are solely categorized based on the antigen that is being targeted by the T cells. The ability to identify the particular antigen that is expressed by the tumor cells of the disease and have little to no expression in normal cells in the body is a critical part of developing a successful CAR T cell therapy and securing the market exclusivity through a patent.⁴¹ For instance, today the most patented CAR T cell therapy surrounds the CD19 antigen which is supported by research completed on the use of the CD19 antigen in the treatment

of ALL.⁴¹ Today, different antigens are being explored in order for other companies to potentially patent their own CAR T cell that targets other types of cancers or diseases.

Moreover, each treatment of CAR T cells is personalized to each patient, thus it makes the typical notion that one must first be able to determine the actual medicinal product aspect of the drug rather complex. Historically, one must define the product of the drug to aid in developing an acceptable patent application for a composition of matter patent. There are two ways in which it is apparent intellectual property lawyers are attempting to patent CAR T cells. One way is to make claims related to the modified T cell, which is described as a patient's T cell that has been genetically engineered to express the receptor of chimeric antigen receptors.⁴⁷ For instance, manipulating the costimulatory domains of the receptor or the antigen recognition areas of the modified T cell.⁴⁸ In contrast, other patent applications have not claimed the modified T cell, instead they have stated detailed claims about the receptor and the various components of the receptor that is later inserted into the T cells.⁴⁷ For example, if one was to make a claim about the receptor, one would characterize the particular DNA encoding of the receptor or the specific viral vector that it is utilized to place the receptor into the T cell.⁴⁷

Strategy Of Patentability In Personalized Medicine

The two ways of making claim to the actual CAR T cell itself in an attempt to obtain a patent contains its challenges as it is not as definite as patenting a small molecule. Therefore, it can be noted that process claims in patents presenting the methods involved in the production of CAR T cells will be even more significant than composition of matter claims in the realm of personalized medicine approaches to the treatment of cancer. It is likely that as the pharmaceutical industry shifts from a traditional small molecule focus to immunotherapy that process claims in

patents will now be the priority of the industry, taking the place of composition of matter claims in patents.⁴⁸

The personalized medicine approach that encompasses CAR T cell therapy explains why it is so important that companies continue to invest in the manufacturing process of CAR T cells. Typically, small molecules can be manufactured on a large scale at one facility and can then be given to numerous amounts of patients. In comparison, CAR T cells must be processed and manufactured in a laboratory with each individual patient's CAR T cells to insert the appropriate vector that expresses the particular antigen to fight the specific cancer cells in the patient's body. Thus, this personalization of CAR T cell therapy may contribute to some of the patentability issues that have arose in the last couple of years. As research into cancer therapeutics advances away from small molecule production into immunotherapy, the dividing line between medicinal aspects of a drug and patient treatments is no longer clear.⁴⁷ The patent framework the pharmaceutical industry uses to patent and produce claims that are well defined and structured to fit the United States patentability model. CAR T cells make generating claims challenging as one has to figure out a way to potentially make claim to an actual medicinal aspect of CAR T cells that is being administered, to adequately protect CAR T cells that come from individual patients.⁴⁹

Strategy Of Patentability In Manufacturing CAR T Cells

The current manufacturing process that is implemented to generate CAR T cells from a patient's T cells incorporates countless steps from separating a patient's T cells to T cell expansion. This process is typically performed at various laboratories, manufacturing sites and hospitals.⁴⁹ A patient's T cells have the potential to travel across many state or country borders. Therefore, it is crucial that the claims within a patent are properly protected no matter the differing jurisdictions that the CAR T cell moves through and the patent claims are not dependent on dissimilar governing

laws.⁴⁹ It is evident that in the current CAR T cell landscape companies ought to determine a patent strategy that includes who will be conducting each step of the manufacturing process and where each step is completed to effectively protect their investment in CAR T cell technology.⁴⁹

Hence, whether these treatments are patentable will impact the logistics of manufacturing, administration of the drug and generating cost effective products. Kymriah by Novartis was the first pharmaceutical company to construct a manufacturing facility for the production of CAR T cells.⁶ Gilead followed suit after their treatment, Yescarta, was approved by the FDA.³⁶ It has been reported that Gilead's manufacturing facility located in El Segundo, California has a 99% success rate in the manufacturing of Yescarta CARs into a patient's T cells.⁵⁰ The average amount of time a patient's T cell is genetically modified in Gilead's facility is 17 days.⁵⁰ It is essential that pharmaceutical companies continue to have the means to manufacture such products that can impact a patient's life. This can only be accomplished if the appropriate patent strategy is determined for the production and manufacturing of CAR T cell therapy.

In general, methods describing any type of process, especially the detailed and definitive process involved in producing CAR T cells for each individual patient should be patentable subject matter. However, some issues regarding the specific processes that are currently required by the FDA to produce CAR T cells may allow for one single company to reap a substantial reward. Concurrently, other pharmaceutical companies are intending to make breakthroughs by significantly improving or altering the methodical process so that such companies can patent a new process that is novel and nonobvious. Furthermore, as the CAR T landscape continues to expand, it will become increasingly challenging for researchers to prove their CAR T cell is both novel and nonobvious.

Patents 4 Patients

In response to the pharmaceutical industry shifting towards immunotherapy approaches for cancer, the USPTO constructed a program in 2016 termed the Cancer Immunotherapy Pilot Program, or Patents 4 Patients.⁵¹ Patents 4 Patients was created to aid in accelerating the review process of patent applications that relate to the treatment of cancer that specifically utilize the immune system.⁶ In order to meet the criteria for this program, a patent application must be a method patent that incorporates three independent claims and no repeating dependent claims with a maximum of 20 claims proposed.⁶ The program's goal is to cut the amount of time it takes to review immunotherapy patent applications in half.⁵¹ The USPTO aims to issue final decisions on a patent application in one year or less from the filing date.⁵¹ The requirements present challenges to pharmaceutical companies who intend to pursue a patent through this program. Such challenges include the desire to obtain composition of matter claims and that the accelerated review process removes the potential for patent term modifications.⁵¹

Patents 4 Patients progress reports have shown from January 2018 to January 2019 a dramatic increase in patent applications that are fast tracked through this immunotherapy program. By January 2019 the total number of submissions of patent applications through this program had more than doubled the number of submissions recorded in January 2018: increased from 146 to 318 total patent submissions.⁵¹ On the account of the success and popularity of the Patents 4 Patients program it was extended until June 30th, 2020.⁵¹ The USPTO is aware of the strain that cell based therapies have put on patent guidelines and the field of intellectual property. This program is one way that the USPTO displayed that they are willing to work with the pharmaceutical industry to determine the proper framework of patentability for a genetically engineered living cell, in hopes of not delaying progress in immunotherapy.

Given, the number of patent filings are steadily increasing and collaborations and licensing agreements between industry and academia are rising, there are a large amount of infringement cases surrounding patent issues that concern the patentability of CAR T cells.⁴⁷ These patent disputes convey that indeed the decision on whether or not CAR T cells should be patentable has yet to be determined. Furthermore, it is evident that the amount of litigation cases and patent disputes related to CAR T cells will likely intensify in the coming years.

Chapter 4: CAR T Cell Patent Debates, Implications On Patents, And The Pharmaceutical Industry

The history of the USPTO includes many instances in which the notion of patentable subject matter has been contested and debated. Patentability debates and determinations have led to the adoption of soft case rules; meaning declarations from court cases on patentability issues are then utilized in either obtaining or nullifying a future patent. Immunotherapy research in the pharmaceutical industry has grown exponentially in the past decade. However, there is not as much patent case law surrounding immunotherapy in comparison to patent case law that displays the defined, patentable framework of traditional small molecules.

Hence, it is challenging to define the patentability framework that will lead to obtaining a patent for an immunotherapy product, especially CAR T cell therapy, when the field lacks a sizeable amount of subject case law. Thus, it is imperative that the claims within a patent take into account all of the differing components that go into generating an immunotherapy product like CAR T cells. As additional companies proceed with CAR T cell research, it is likely one will observe a steady increase in similarities between patent applications. Consequently, the more similar CAR T cell patent applications are, the higher the probability that the pharmaceutical and legal world will witness future patent challenges related to CAR T cells.

It is a sprint for pharmaceutical companies who are entering or continuing to do research into the development of the most optimal CAR T cell therapy, manufacturing process and delivery method. The more patents a single pharmaceutical company can be issued that relate to CAR T cell therapy, the greater market control a company will retain in the immunotherapy field. Such companies are capable of protecting themselves from legal attacks as they are more likely to commence infringement cases on other companies late in entering the CAR T cell market. The

outcomes and resolutions of past and current patent disputes will continue to impact future patent applications regarding the patentability of CAR T cells. As the patentability of CAR T cells is dependent on the resolutions that are declared by the District, Federal or Supreme Court during patent disputes.

Novartis Verse Juno Therapeutics

A patent dispute between two of the major players in CAR T cell therapy took place from 2013 to 2015.⁵² This dispute was based on a commonality of a specific part of the genetically modified CAR T cell products that each party owns. The common component of the CAR T cell products was the costimulatory signaling domain 4-1BB.⁵² However, the patent fight originally commenced in 2013 between the partners of each pharmaceutical company, St. Jude's Children's Research Hospital (Juno Therapeutics partner) and the University of Pennsylvania (Novartis partner).⁵² The major issue arose when a researcher at St. Jude's patented the costimulatory domain 4-1BB and then set in motion a deal with stipulating conditions to share this domain technology with researchers at Penn.⁵²

By late 2013, neither St. Jude's and Penn researchers were complying with the agreed upon conditions, which led to Juno intervening on St. Jude's behalf to defend the patent that detailed the 4-1BB technology, with Penn backed by Novartis.⁵² Furthermore, in 2014 Juno licensed a CAR T patent from St. Jude's (U.S. Patent No. 8,399,645) while at the same time Novartis licensed a Penn patent (U.S. Patent No. 7,638,325).¹⁶ The Penn patent was determined to have followed from the research collaboration between St. Jude's and Penn that occurred in 2013. As a result of this split in partnership between St. Jude's and Penn, the CAR T cell intellectual property field observed a race to the patent office which led to the Novartis verse Juno patent dispute over the costimulatory domain 4-1BB.

After a lengthy patent dispute between these two major companies in the CAR T cell market, agreement was made that authorized each separate party to proceed onward with their own particular CAR T cell therapy. The settlement agreed upon in mid 2015 detailed that Novartis and its counterpart, the University of Pennsylvania, must make a payment of 12.25 million dollars to Juno Therapeutics and its partner St. Jude's Children's Research Hospital.⁴⁰ In addition, the settlement requires Novartis to submit Juno royalty payments from future sales in the U.S. market of Novartis's CAR T cell therapy.⁴⁰

Today, a number of patent applications related to Novartis's CAR T cell therapy, Kymriah are still under review by the USPTO.⁶ Although Novartis was granted fast track FDA priority approval of Kymriah, there are several applications related to Kymriah CAR T cells that are pending patent agreement. For example, patent application US 2017/0137783 A1 published on May 18th, 2017 initially contained 72 proposed claims including methods for improving the efficacy and expansion of immune cells remains under review.⁵³ The amount of pending patent applications that are concerned with immunotherapy, specifically CAR T cells, indicates that USPTO examiners and attorneys continue to debate the patentability of such subject matter.

Kite Pharma Verse Juno Therapeutics

Kite Pharma is another pharmaceutical company that is now a major part of the CAR T cell landscape as Kite has accumulated a sizeable number of patents related to the development of CAR T cell therapy. Kite states that they have a growing patent portfolio that contains over 200 patents that are associated with T cell therapy and related manufacturing processes.⁵⁴

In August of 2015, Kite filed an inter partes review against a patent held by Juno, U.S. Patent No. 7,446,190 (the 190 Patent), stating that all of the claims made in this patent were

obvious in their nature and thus should not be patentable.^{n,40} The Patent Trial and Appeal Board (PTAB) determined that the claims in the 190 patent were nonobvious and that Kite had not proven the claims to be invalid; thus, the patent was firmly upheld.⁵⁵ As a result, Juno filed a patent infringement case against Kite Pharma on December 19th, 2016 regarding the 190 patent that stated Kite's leading CAR T cell therapy does or will infringe on their 190 patent.⁵⁵ A decision was made on June 13th, 2017 by the District Court of Delaware that declared the infringement case would be dismissed.⁵⁵ Even though the inter partes filing and infringement case was resolved, it is likely that legal disputes between these two parties as well as other companies competing in the CAR T cell therapy landscape will continue to transpire.

Kite Earns Patent For Method To Increase Efficacy Of CAR T

In January 2018, Kite, now Gilead Sciences, was issued a new patent that details a definitive protocol that involves a regimen for priming patients prior to the delivery of CAR T cell therapy. This patent, U.S. Patent No. 9,855,298, granted the rights to Kite on a critical part of the CAR T cell therapy process: “optimal preconditioning regimen.”⁵⁶ The patent states that the efficacy of CAR T cell therapy is increased when two chemotherapy agents, cyclophosphamide and fludarabine, are administered to patients by a particular dosing regimen in conjunction with the delivery of CAR T cells.⁵⁶ Now that Kite has obtained a patent for their research efforts that detail how to best prime a patient for receiving CAR T cells, other pharmaceutical companies may have to reconsider their own strategy concerning the subject of preconditioning methods for CAR T cell therapy.

ⁿ An inter partes review is a course of action that allows one to dispute the validity of a United States patent by questioning the patentability of the claims within the patent.⁶¹

This patent will likely present challenges to other pharmaceutical companies that are generating their own preconditioning method for CAR T cell therapy treatment.⁵⁶ For instance, Kite's patent may hinder other companies from optimizing their regimen for patients undergoing CAR T cell therapy. The industry is competing against one another to determine the most favorable outcomes for their patients being treated with CAR T cell therapy. As a result of this patent that details an optimal preconditioning method for patients undergoing CAR T cell therapy, it is possible that other companies in the process of developing a similar conditioning method may risk infringing on Kite's patent in the near future.⁵⁶

For example, Novartis's CAR T cell, Kymriah, has a method of administration that involves certain doses of both cyclophosphamide and fludarabine before CAR T cells are given to the patient.⁵⁶ The patients are dosed with these chemotherapy agents from a range of two to fourteen days prior to Kymriah infusions.⁵⁶ In comparison, Kite's patent details a very similar methodical dosing per day to that of Novartis' Kymriah recommendations. Kite's patent covers the broad methods for preconditioning patients and administering CAR T cells to the patients. As a result of the broadly scoped patent, Kite's patent has the potential to affect the way other pharmaceutical companies have to administer their experimental or developing CAR T cell therapy.

Yet, because of the similarities between Kite's patent and Novartis' already FDA approved Kymriah CAR T cell therapy, Novartis could consider appealing Kite's patent to the PTAB.⁵⁶ Namely, if a pharmaceutical company or multiple companies can convince the PTAB that each individual company came to the same conclusion separately regarding the optimal preconditioning method for patients receiving CAR T cells, without the influence of Kite's patent, then one could make the argument that Kite's patent is invalid.⁵⁶ Since, if other companies are skilled in the same

art and can put the pieces together to create the same method then that process is deemed obvious and therefore, not eligible to be patented.

Celyad Retains U.S. Patent For CAR T Cell Therapy

On February 10th, 2016 an ex parte was filed by an anonymous party against Celyad's U.S. Patent No. 9,181,527 that specifies a manufacturing process for allogenic CAR T cells.^{o,57} As a result of the ex parte, on March 24th, 2016 the USPTO stated that they would be undergoing a reexamination of claim 1 of patent 527.⁵⁷ A final decision was issued on January 6th, 2017 that declared claim 1 of patent 527 is patentable; therefore, the validity of the patent was upheld and the patent is no longer subject to such forms of appeal.⁵⁷ Thus, Celyad remained the owner of a valid CAR T cell patent, affording the company with the exclusive right to protect and enforce their allogenic T cell product and manufacturing process.^p It is likely that Celyad will have the advantage if allogenic CAR T cells succeed in patients, because allogenic T cells have a greater potential for mass production and standardization of properties compared to current autologous T cells that are specific to an individual.⁴²

The Extent Of Patentability Of CAR T Cells

It is evident from examples of cases and rulings that subject matter eligibility is a highly debated topic that has been going on throughout court history. In recent years, courts have attempted to officially produce a general test to determine patentability that contains two main investigational guidelines that one should utilize when filing a patent application that may present

^o An ex parte is a form of reexamination request which can be submitted by any party to question a patent.¹¹ The party must display that there is a significant enough new question about the patentability of the invention. If the patentability is rightfully questioned, then the USPTO begins a reexamination process of the patent in question.¹¹

^p Allogenic T cells mean that a patient would receive T cell treatment using T cells that are not genetically identical to their own T cells; it is the use of donor T cells.⁶²

exceptions to section 101 of 35 U.S.C.⁶ The first recommendation states that one should analyze all of the claims for connections to ineligible subject matter, for instance natural laws or phenomenon.⁶ The purpose of the second part is to examine the remaining claims for an aspect that proves the concept is inventive.⁶ Overall, one aims to answer the question of whether or not the claims made alter the patentable decision from unpatentable subject matter to patentable because of the innovative aspects that employ a natural law. The central debate surrounding patent eligibility of subject matter regarding scientific ideas is if the claims encompass “significantly more” than a natural law.⁶ This was the case in the ruling of *Association for Molecular Pathology v. Myriad Genetics, Inc.* regarding the concept of cDNA as patentable subject matter.

Considering the modern formal review guidelines for subject matter eligibility above with the rules of the Court’s in numerous examples presented one could argue that a Court may or may not find immunotherapy patent claims to be ineligible subject matter. The general immune response was discussed at length and it is apparent that one could assert that the response of the human body to types of immunotherapy treatments is a natural phenomenon, a known concept.⁶ In addition, the patentability of CAR T cells should not be labeled unpatentable subject matter under the singular notion that T cells are “living cells.”⁶ The *Diamond v. Chakrabarty* case ruling revealed that a genetically modified bacteria, a living organism, is not necessarily equivalent to a natural phenomenon.⁴⁴ Rather, it was a product as the bacteria was genetically modified and no longer simply apart of natural law unpatentable subject matter.⁶ Hence, an argument could be made in conjunction with *Diamond v. Chakrabarty* that CAR T cells should be patentable under section 101 of 35 U.S.C. as “an article of manufacturer” or “composition of matter.”^{6,44}

Furthermore, CAR T cells should meet the second recommendation of the patentable subject matter test because one can prove that CAR T cells consist of enough novel components

to warrant the therapy as nonobvious. CAR T cell therapy is one of the initial method of treatments to incorporate isolation of T cells, insertion of receptors and expansion of a cell therapy product.⁶ All of the elements of CAR T cells mentioned argue that CAR T cells contain further novelty than innate living T cells that are found in the human immune system. However, uncertainty of CAR T cell patentability will continue to exist. This unpredictability of patentable subject matters stems from whether or not companies will be able to consistently argue that specific CAR T cell patent claims demonstrate a notable amount of inventiveness from the living cell natural phenomenon.⁶ It is distinctly possible that the patentability of CAR T cells will continue to be debated and only granted on individual patent cases.⁵⁸ The topic of patentability has continuously fluctuated over the years depending on patent claims, courts, judges and historical exceptions to section 101 of 35 U.S.C.

CAR T cells demonstrate therapeutic properties, but they do not fit into the traditional model of a patentable therapy. Nonetheless, CAR T cell therapy has transformed the cancer treatment market and encouraged advanced research into immunotherapy. Additionally, it is apparent through examples of patent infringement cases that CAR T cells have inspired debate on patentable subject matter in the field of intellectual property and pharmaceuticals that extends beyond this particular therapy. The arrival of CAR T cell therapy as a patentable living drug has quickly impacted the patentability framework governed under section 101 of 35 U.S.C. Additional questions regarding patentability may emerge as there is movement towards further commercialization of the manufacturing process for the genetically modified CARs and T cells. The development of novel therapeutics for the treatment of cancer, CAR T cell therapy, has conveyed that patentable subject matter guidelines may need to be altered to adjust to the technological progress evolving in this growing pharmaceutical industry.

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