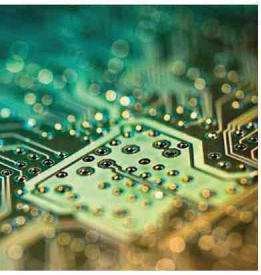



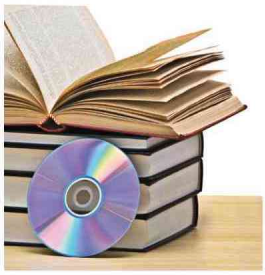

Forty Years Since *Diamond v. Chakrabarty:* Legal Underpinnings and its Impact on the Biotechnology Industry and Society

Matthew Jordan, Neil Davey, Maheshkumar P. Joshi, & Raj Davé

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This article is dedicated to Dr. Ananda Chakrabarty, a pioneer in the biotechnology world, who passed away on July 10, 2020.

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I. Introduction: The *Diamond v. Chakrabarty* (1980) Supreme Court Decision

In 1972, Ananda Chakrabarty—a genetic engineer at General Electric—filed a patent application for genetically modified bacteria capable of breaking down crude oil. Dr. Chakrabarty introduced genetic fragments into the *Pseudomonas* bacterium, altering the bacteria to decompose hydrocarbon components of crude oil. Dr. Chakrabarty intended the bacteria to assist in cleaning up oil spills. The engineered bacteria were especially suited for bioremediation given their resistance to adverse environments and safety as a non-pathogen.

The examiner rejected the application under Section 101 of the Patent Act, which covers patentable subject matter, because living things were not patentable.[1] The Board of Patent Appeals and Interferences (now known as the Patent Trial and Appeal Board) affirmed the examiner's decision,[2] however, the U.S. Court of Customs and Patent Appeals (now part of the U.S. Court of Appeals for the Federal Circuit) sided with Dr. Chakrabarty.[3] The Court of Customs, in an opinion by Judge Giles Rich, reasoned that only naturally occurring articles, not all living things, were ineligible for patenting. Importantly, the court said, "the fact that microorganisms are alive is a distinction without legal significance" for purposes of the patent law.[4] Then, U.S. Patent and Trademark Office (USPTO) Commissioner Sidney Diamond appealed the case to the Supreme Court.

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The Supreme Court of the United States held that Dr. Chakrabarty's invention consisted of patentable subject matter.[5] Section 101 states: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."[6] The Court ruled in a landmark 5-4 decision that Dr. Chakrabarty's invention was a patentable, manmade, "composition of matter" or "manufacture."[7] Chief Justice Warren Burger famously quoted a Senate Report that was part of the legislative history for the Patent Act of 1952: patentable subject matter included "anything under the sun that is made by man."[8]

This decision had immense implications for biotechnology. It resulted in patents for genetically modified seeds, DNA amplification technology, and monoclonal antibody therapy. The rise of biotechnology has impacted many technological fields and society as a whole. The Supreme Court's distinction between manmade and naturally occurring phenomena was clarified in *Mayo v. Prometheus*[9] and *AMP v. Myriad*.[10] The Court found that naturally occurring biological relationships and isolated DNA sequences were not eligible for patenting.

II. Analysis of the Decision Through Interviews

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Judge Rader gave an incredible perspective on the legal implications surrounding the case, as well as recent Supreme Court decisions in the realm of biotechnology. In Judge Rader's opinion, the majority's ruling in *Chakrabarty* "gave a very expansive reading to Section 101 of 35 U.S.C. and encompasses any inventive activity that occurs at the hand of man."[11] From his perspective, Chief Justice Burger's opinion could not have been broader. Judge Rader suggested that the line between a naturally occurring product and one imbued with human ingenuity is that:

> No one invents something that already exists; that is natural phenomenon. The key component of patentable material that I used to use is the phraseology of isolate or purify. If you extract a component and isolate that from its natural environment or purify it, it is patent eligible. This has been somewhat undercut by the *Myriad* decision, which in more recent years has said, just isolating and purifying may not be enough. You are going to have to do something more to show you have a truly inventive concept.[12]

Recently *Myriad* held that purified DNA is naturally occurring and therefore not patent eligible. In Judge Rader's eyes, this is at odds with Chief Justice Burger's vision that any natural product with some human intervention is patentable. Judge Rader noted that "a truly inventive concept"[13] is incredibly subjective and difficult to define. He stated:

> So, as the *Myriad* case showed, it is not enough to just isolate and purify. You have to do something more. There have been a lot of cases trying to define what that something more is. It's quite controversial. I frankly find the whole area to be troubling. I think the rule that made the most sense was the rule in effect after the *Chakrabarty* decision, which is that if you have the human intervention that has removed the substance from its natural environment, through isolation or purification, that would be enough. But in today's jurisprudence, you have to have something beyond that. And what that something is varies from case to case.[14]

Responding to concerns about creating detrimental technologies or engaging in catastrophic research, Judge Rader noted:

> The Supreme Court very quickly pointed out that the Patent Act doesn't stop certain development at all. It has no restrictive capacity on what researchers may wish to pursue, and it is just an incentive that gives additional protection and indeed exclusive rights to those who apply for and receive patent protection. But the Supreme Court made it clear. Even if there was no patent protection, people could continue to study new life forms.[15]

Our interview with Dr. Chakrabarty was focused on the criticisms that arose in response to the decision, fear of manipulation and commercialization of life. Dr. Chakrabarty noted that some opposed the patent due to concerns about "creating monsters and making human cloning possible."[16] However, the decision spurred numerous inventions that have been incredibly beneficial to mankind, including "medicines such as insulin could be made in large quantities and pieces of DNA could be patented for therapeutic purposes."[17] In response to Chief Justice Burger's adoption of the Senate Report's statement about anything under the sun made by man being patentable, Dr. Chakrabarty recalled: "I approve of all types of research, as long as they can cure a disease or improve the nutritional value of food. Research should not be used to create specific types of human beings, that is God's job. It should not be used to destroy life."[18]

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III. Impact on the Biotechnology Industry: Case Studies

Forty years ago, *Chakrabarty* opened the floodgates for the biotech industry by adopting the Senate Report's statement that "anything under the sun that is made by man" is patentable.[19] Regarding the impact of the decision, Judge Rader noted that it "had a profound and far-reaching effect. It laid the foundations for our biotechnological industries."[20] The following three case studies highlight the decisions importance in the creating the modern biotech industry.

A. Genetically Modified Seeds

Genetically engineered crops are agricultural plants whose DNA has been modified to resist disease, pests, or chemical treatments such as herbicides, and increase their nutrient profile. Genetically engineered crops differ from traditional breeding methods because genetically modified organisms (GMOs) contain DNA from organisms besides the native plant. These traits are not natural to the native species, and so the plants and their alterations are considered manmade organisms patentable under *Chakrabarty*.

In 1990 and 1993, Dr. Dilip Shah *et al.* of the Monsanto Company filed U.S. patent numbers 4,940,835A and 5,188,642A describing the technique for genetically altering plant seeds. Monsanto's goal was to confer resistance to glyphosate-containing herbicides, specifically Monsanto's Roundup herbicide line. The invention was a technique for cloning EPSPS enzymes.[21] A plasmid containing a chloroplast transit peptide transports the enzyme from the cytoplasm to the chloroplast of the cell, bestowing glyphosate resistance upon the plant and its progeny.[22]

This breakthrough allowed Monsanto to develop and commercialize its genetically modified seeds, Roundup Ready.[23] Herbicide-resistant soybeans enabled farmers to spray glyphosate-weed killer without harming their crops. By the late 2000s, Roundup Ready dominated American soybean production, occupying 90% of nation's output.[24] By 2009, Monsanto's success expanded outside of the U.S. with its Roundup Ready seeds distributed across 20 million acres of cotton in India, 35 million acres of soybeans in Brazil, and 43 million acres of soybeans in Argentina.[25]

Patenting these seeds was a critical step for innovative agri-tech companies like Monsanto. In 2017, Monsanto earned $10.4 billion in yearly sales of genetically engineered seeds.[26] A 2014 meta-analysis study concluded that genetically engineered crops reduce chemical pesticide use by 37%, increase crop yields by 22%, and increase farmer profits by 68%.[27] The product has provided significant benefits to society in terms of farmer's wages, food yield, and the market economy.[28]

Chakrabarty created the necessary incentives and protection for researchers to create the genetically engineered crops that feed the world today.

B. Polymerase Chain Reaction (PCR)

Polymerase chain reaction (PCR) is a technique to rapidly magnify a sequence of DNA. PCR is used extensively in laboratory research, medical diagnostics, evolutionary biology, and forensics.

In 1987 and 1990, Dr. Kary Mullis *et al.* of the Cetus Corporation filed U.S. patent numbers 4,683,195A, 4,683,202A, and 4,965,188A that covered the technique for amplifying a sequence of DNA. This method utilizes molar excess of two oligonucleotide primers to target DNA regions. These DNA regions serve as templates for large-scale DNA synthesis. Heat resistant Taq polymerase is then driven through thermal cycles to perform temperature dependent reactions such as DNA melting and DNA replications.[29]

The applications for DNA sequencing technology are immense. PCR is the primary component of genetic fingerprinting, a forensic technique that identifies an

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individual by comparing their DNA to previous samples or a database. Genetic fingerprinting has been invaluable to forensic analysis and the accurate incarceration of criminals.[30] In, 1987, DNA evidence proved pivotal in the rape conviction of Tommy Lee Andrews,[31] and in 1992, PCR technology helped exonerate Glendale Woodall who was accused of multiple sexual assaults in 1987.[32]

PCR is also an excellent technology for rapidly detecting pathogens such as HIV-1 (Human Immunodeficiency Virus Type 1),[33] HBV (Hepatitis B Virus),[34] and HCV (Human Cytomegalovirus).[35] It is useful tool to diagnosis bacterial infections. Commercial PCR assays have been developed for *M. tuberculosis*, *C. Trachomatis*, *N. gonorrheae*, *Microbacterium avium complex*.[36] Finally, PCR can search for genetic mutations[37] and determine tissue type prior to organ transplantation.

In 1992, the Cetus Corporation sold the rights to PCR technology for $300 million to Hoffmann-La Roche,[38] while Dr. Kary Mullis, the inventor, received a $10,000 bonus and the Nobel Prize in Chemistry in 1993.[39] This technique for efficient DNA sequencing was ground-breaking both for the Cetus Corporation and society as a whole.

As with genetically modified seeds, *Chakrabarty* created the necessary incentives and protection for researchers to invest in new DNA purification procedures. These procedures enabled the creation of the polymerase chain reaction that is widely used in medical diagnostics and forensic science.

C. Monoclonal Antibody Therapy

Antibodies are Y-shaped proteins that function as a part of the immune system to identify and attach to pathogens. They serve as a signal for other cells in the immune system, such as T cells,[40] to attack the indicated pathogen. Antibodies contain a fragment antigen binding region at the tip of the Y-shaped protein that serves as a lock for a specific key, or epitope, located on an antigen. This small region—the hypervariable region—is extremely diverse and allows for the natural, or modified, production of various distinct antigen-binding sites.[41] Monoclonal antibodies are antibodies produced from identical B cells, which are clones of a unique parent cell.[42]

Monoclonal antibody-based treatments are some of the most successful therapeutic strategies against cancer and inflammatory diseases. This therapy focuses on activating an immune response. Monoclonal antibodies are deployed to target a specific protein or cell and stimulate the patient's immune system to kill those malignant cells.[43] Monoclonal antibodies are designed with a variety of mechanisms—flagging harmful cells for T cells to attack, inducing apoptosis in target cells, modulating signal pathways—to prevent blood supply to cancerous tumors, inhibit immune system inhibitors, or deliver targeted radiation or chemotherapy.[44] These drugs are effective against a variety of cancers due to their recognition of cancer cell-specific antigens which prompt an immune response.[45]

In 1992, 1995, and 2004, Genentech filed U.S. patent numbers 6,407,213B1, 6,054,297A, and 7,575,893B2 that covered the technology and methods to produce a new class of monoclonal antibody drugs, angiogenesis inhibitors.[46] Commercially known as Avastin,[47] the product is a recombinant, humanized, monoclonal antibody that disrupts angiogenesis[48] by inhibiting VEGF-A.[49] Mechanically, this antibody binds to VEGF-A and obstructs the interaction of its receptors, Flt-1 and KDR, on the surface of endothelial cell. This obstruction prevents proliferation and angiogenesis controlled by Flt-1 and KDR interaction.[50] In multiple clinical studies, Avastin has been shown to increase the overall survival and progression free survival time for numerous cancers including metastatic colorectal cancer,[51] non-squamous non-small cell lung cancer,[52] glioblastoma multiforme,[53] renal-cell carcinoma, and epithelial ovarian cancer.[54]

PCR is used extensively in laboratory research, medical diagnostics, evolutionary biology, and forensics.

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In 2019, the World Health Organization added bevacizumab (Avastin) to its list of essential medications.[55] In 2017, Avastin global revenues alone totaled $7.1 billion for Hoffmann-La Roche.[56] Overall, the size of the global monoclonal antibody therapeutics industry was estimated at $95.5 billion in 2017.

The ability to patent "anything under the sun made by man" propelled the development of several life-altering monoclonal antibody therapies such as Humira for rheumatoid arthritis ($18.4 billion in 2017 sales); Rituxan for lymphoma and leukemia ($9.2 billion in 2017 sales); and Herceptin for breast cancer ($7.4 billion in 2017 sales).[57] This would not have been possible without the incentives and intellectual-property protections that *Chakrabarty* established for these man-made biologic systems.

IV. Broader Implications for Society

As Judge Rader noted, *Chakrabarty* had a far-reaching impact on American society:

> The key here was to look at it as an international event, because at the same time as this research was being done in the United States, there was similar kinds of research being done in Europe and Asia. But Europe encountered the European Patent Convention, which required a care to protect public morality. And that gave rise to many suits that questioned research in the biotechnological areas. Things such as the potential harm to animals. These different kinds of challenges to the patent applications would delay them and make them very expensive. . . . With that additional expense to European biotechnological research and the protection of that research, the U.S., having quickly transcended that problem, gained advantage in the biotech industry. They could quickly acquire patents on their inventive activities. And it tended to act as an incentive to shift resources out of Asia and Europe into the United States, where it was easier to protect them and obtain the patent rights that were applied for.[58]

In his view, this Supreme Court ruling allowed America to take the lead in biotechnological innovation, which is reflected today by the industry's market size and number of patents in the United States.

Never has there been a greater focus on biotechnology than during the search for a COVID-19 vaccine. United States firms, such as Pfizer and Moderna, are leaders in a diverse field of biotech companies. The U.S. biotechnology industry boasts multiple biotech firms that have more than $10 billion in revenue, including AbbVie, Genentech, Amgen, and Gilead. According to an industry report in 2019, U.S. biotechnology generated $113.4 billion and close to 3,000 companies were listed as biotechnology firms.[59]

Biotechnology companies around the world are focusing on the application of biotechnology to fight COVID-19. For instance, one of two leading candidates for the vaccine is ChAdOx1 nCoV-19, produced by a collaboration between Oxford University, Vaccitech, and AstraZeneca.[60] Similarly, a Beijing-based biotech company Sinovac is conducting stage 2 trials with 1,000 plus volunteers.[61]

In fact, the worldwide biotechnology industry revenue came close to $300 billion in 2019 with approximately 56% of revenue derived from human health technology and the remaining revenue comprised of agricultural tech (about 20%), industrial tech (10%), and animal health (about 8%).[62] More than 11,000 companies are listed as biotechnology firms or research centers.[63] According to a report by IBIS, countries across the world take biotechnology as a strategic industry and incentivize its growth. For instance, countries such as Spain and Denmark have reported more than 10% of their public sector R&D expenditures on biotechnology, and 22% in the case of South Korea.[64]

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Dr. Gary Pisano, in the Harvard Business Review, argues that the rise of the biotechnology industry brought about critical changes in the evolution of science and industry. He suggests that:

> Before the emergence of biotech, science and business largely operated in separate spheres. Conducting research to expand basic scientific knowledge was the province of universities, government laboratories, and nonprofit institutes. Commercializing basic science—using it to develop products and services, thus capturing its value—was the domain of for-profit companies. Historically, a handful of companies, including AT&T (the parent of Bell Labs), IBM, Xerox (the parent of the Palo Alto Research Center), and GE, did some remarkable research, but they were the exception. By and large, businesses did not engage in basic science, and scientific institutions did not try to do business.[65]

Dr. Pisano's argument is that the biotech industry emerged as a science-based industry that required a great deal of collaboration between "for-profit" businesses and "not-for-profit" scientific institutions (mainly research universities).[66] One current example is Oxford University's collaboration with AstraZeneca for the discovery of a vaccine for COVID-19.

An additional factor that aided the growth of the biotech industry, besides strong industry-university relations, was U.S. government policy, specifically the provision of intellectual property (IP) protection. However, IP protection was virtually non-existent in the initial stages of the biotechnology revolution and that actually becomes an interesting conjunction when examining the rise of biotechnology worldwide.[67]

Incorporating academic scientists into the industry, along with changes in U.S. rules and regulations in the 1980s—including the Stevenson-Wydler Technology Innovation Act (involving tech transfer from the government to the private sector), the Bayh-Dole Act (making uniform across government agencies the default of title in federal funding recipients such as universities), and *Chakrabarty*—were catalysts for the biotechnology industry.

In a report on the development of biotechnology, Dr. Terry Bradford stated: "Without *Diamond v. Chakrabarty*, commercial biotechnology based on recombinant DNA technologies would not exist today."[68] Dr. Bradford further suggested that the Supreme Court decision in favor of Dr. Chakrabarty was in parallel with the scientific discovery of recombinant DNA cloning and gene splicing by Drs. Stanley Cohen and Herbert Boyer.[69] After the decision in *Chakrabarty*, the USPTO granted 114 pending applications relating to manmade organic materials.[70] This subsequent flood of biotech patents supports Dr. Bradford's argument that Dr. Chakrabarty's case was instrumental in creating the biotechnology industry we know it today.

Additionally, the rise of new financing vehicles through venture capital (VC) funds fueled the rapid growth of the industry. For instance, from 1978 until 2004, VC funds invested close to $40 billion in U.S. biotech-related ventures.[71] Emphasizing the role that Dr. Chakrabarty's case played in the rise of biotechnology firms, Kevin Howe stated:

> Neither Stanford University nor Genentech would be first to present the question of ownership of living material to the United States Supreme Court. That distinction belonged to an India-born biochemist employed by the environmental division of General Electric in its New York research lab. Ananda Chakrabarty was educated in Calcutta and developed the concepts for his work at the University of Illinois, Urbana. He joined General Electric in 1971 and began doing groundbreaking research in the science of cleaning up oil spills, resulting in a patent application that included a claim for a new form of bacteria that Chakrabarty had created in the laboratory.[72]

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When examining the rise of biotechnology in the United States, as compared to other countries, researchers have focused on the key elements that are needed for the rapid growth of an industry. Dr. Yu Shan Su and Ling Chung Hung synthesized these key elements into five factors, namely, strong science and industry base, funding availability, local entrepreneurial mindset, social networks, and social capital—trust among a variety of civic organizations in the society.[73]

For researchers and analysts, the origins and evolution of an industry are typically assumed to be, and are treated as, diffused with multiple possible sources. However, in a few instances, there are well-documented trigger points. For instance, Dr. Maheshkumar Joshi and his colleagues have examined the rise and subsequent reshaping of the U.S. telecom industry originating from Regional Operating Bell Companies (RBOCs) based on Judge Harold Greene's decision in the case by the Federal Trade Commission against AT&T.[74] This was the antitrust lawsuit that broke up AT&T's vertical market monopoly concerning the U.S. telecommunications industry.

Similarly, the *Chakrabarty* case can be seen as the trigger point for the biotechnology industry in the United States and around the world. Such trigger points help us appreciate the journey the industry has taken as well as the trajectory it may take in the future.

V. Conclusion

Diamond v. Chakrabarty revolutionized the biotechnology industry in the United States by incentivizing the advancement of inventions that are beneficial to human life. However, as noted by Judge Randall Rader: "This whole patent eligibility question—which was so clear and well-defined, was practically implementable and understandable, and gave life to our whole biotech industry after *Chakrabarty*—now has had a heavy cloud cast over it in recent jurisprudence such as *Myriad*."[75]

When asked if our legislature should take action to clear up the confusion, Judge Rader stated: "If the statute was the written law that was being interpreted by the Supreme Court, we wouldn't need legislative change. But the sad truth is that the Supreme Court has created a whole overlay of doctrine that makes the statute almost irrelevant. And now we don't look at whether there's a process, a machine, an article of manufacture, or a composition of matter. Instead, we look at whether there's something more beyond the conventional and the routine and the well-known. We argue over what is something and what is more, and what is an inventive concept. And so in that state of confusion, yes, we're probably going to need legislation."[76]

Within the dire context of the COVID-19 pandemic and other countries racing past the United States in biotechnology, it is crucial for Congress to clarify what currently qualifies as patentable subject matter.

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