A Momentous Time for Humankind

Human ingenuity is marvelous. It boils down to an impeccable and often ethereal balance among its constituent elements, including knowledge, curiosity, creativity, and action. When the magnitude of each element expands in harmony, human ingenuity becomes transformative. It translates to power—the kind that transforms the world!

This book is a testament to that power. Whether you are holding it in your hands or scrolling through pages on a touchscreen, you and I are able to communicate through this medium because, once upon a time, human ingenuity led to the creation of one of the most significant and consequential inventions of all time: the printing press.

Johannes Gutenberg, a German goldsmith who lived in the early to mid-fifteenth century, is generally credited with inventing the printing press circa 1436.\(^1\) Gutenberg did not invent books. In fact, he did not even invent printing. Long before the Renaissance, woodblock printing had already been customary during the seventh and eighth centuries in China, Korea, and Japan.\(^2\) And the metal, movable-type system of printing, which originated in Korea, had been used since the eleventh century.\(^3\) Gutenberg’s contribution rested on his ability to concoct a novel mechanical contraption to mediate ink transfer between the movable type and paper. He used prior knowledge to adapt screw mechanisms found in antecedent inventions—namely, the wine, papermaker, and linen presses of the time—as the basis to create the mechanical, movable-type printing press.\(^4\) But he did not stop there. When he realized that the conventional water-based ink was not durable for printing purposes, he developed oil-based ink, which, as it turned out, bonded more effectively with the types.\(^5\)

The amalgam of knowledge, curiosity, creativity, and action aimed at speeding up the printing process, which culminated in the ingenious design of the first movable-type printing press, fundamentally transformed the world. By the end of the fifteenth century, Gutenberg’s invention had spread all over Europe. For the first time in history, books could be produced en masse and at a low cost relative to other printing methods. Indeed, more than twenty million books had been printed by the year 1500.\(^6\)
The printing press ushered in a new revolution in mass communication and dissemination of information that contributed to the rise of public literacy and the end of the Dark Ages. Although the Gutenberg printing press did not jumpstart the Renaissance, it undoubtedly fueled its swift progression.

Nicolaus Copernicus, the revered Renaissance mathematician and astronomer, as well as other scientists and scholars of the time benefited directly from the printing press. Copernicus, for instance, profited greatly from the printing of various astronomical tables that began to appear in the late fifteenth century—including the Alfonsine Tables, which date back to the year 1252. Astronomical tables contained data to calculate ecliptic longitudes—as well as the position of celestial bodies, including the Sun, Moon, and other planets—that were useful in maritime navigation during the fifteenth and sixteenth centuries when Spain, Portugal, England, France, and other wealthy nations ventured out to sea in search of new lands. Copernicus built upon data from these tables in his groundbreaking book *De Revolutionibus Orbium Coelestium* (*On the Revolutions of the Heavenly Spheres*), which set off the scientific revolution. The book conceptualized his elegant and controversial theory of heliocentrism, which postulated that the Sun—not the Earth—was at the center of the Universe, and that Earth and other known planets actually revolved around the Sun.

![The Gutenberg printing press, circa 1440](https://www.cambridge.org/978-1-108-47570-9-Figure1.1)
As time went on, printing became more widespread. Cambridge University Press, the oldest publishing house in the world and publisher of this book, was established in 1534. Other publishers soon followed. With the advent of an increased flow of information, however, literature that contradicted religious teachings was subject to bans by the Roman Catholic Church. In 1559, the Church published the *Index Librorum Prohibitorum* (Index of Prohibited Books), comprising a list of condemned works. According to legislation of the Catholic Church, no person could read any book on the list unless explicitly granted permission to do so. Copernicus’s book eventually became part of that list.

The aforementioned history surrounding the invention of the printing press is not unique, at least insofar as it represents the fate of a powerful, revolutionary, technological agent that induces a tectonic shift in culture and society. Transformative technologies seem to share a common modus operandi. Nearly six centuries after the printing press, for example, the Internet brought about another modern era of information reminiscent of centuries past.
This book is about a new truly remarkable transformative technology: genome editing. The volume aims to explore interdisciplinary inquiries of science, law, technology, ethics, philosophy, and policy. In so doing, it seeks to demonstrate how modern genome-editing technologies are unique disruptors that open infinite opportunities to venture into areas completely unknown to humans. These new disruptors possess the power to push humanity past knowledge and information boundaries—as was once the case for the printing press, the Internet, and other transformative technologies. But the stakes are higher now. This emerging breed of genome-editing disruptors goes much further into virgin territory than any of its predecessors, propelled by the fact that genome editing holds the power to not only transform the world we live in, but change humanity and every living organism from within.

1 A NEW REVOLUTION

For the first time in the nearly two hundred millennia since *Homo sapiens* first appeared on Earth, humankind has procured the power to rewrite nature’s book of life. Following key scientific developments at the dawn of the twenty-first century, we have—for better or worse—reached the Rubicon of precise genetic manipulation, which until now has existed only in science fiction.

Leading this revolution is the most significant technological breakthrough of our generation. It concerns the discovery of an atomic, programmable, macromolecular machine comprising a pair of precision scalpels that shear DNA molecules known colloquially as “CRISPR,” an acronym that refers to the system of *Clustered, Regularly Interspaced, Short, Palindromic Repeats* and CRISPR-associated (Cas) proteins, which has now been repurposed for genome editing. Only on rare occasions does a technology with such far-reaching implications appear, while holding the power to forever change the world and humankind. Those familiar with this emerging genome-editing technology understand its colossal power and potential to become a global transformative agent, on par with—and arguably surpassing the impact of—the discovery of electricity, or the development of gunpowder, the printing press, the atomic bomb, and the Internet.

A Antecedent Disruptors

More than eight decades ago, for instance, scientific inquiry conceptualized nuclear fission as a theoretical explanation for the recondite empirical evidence that $^{239}$U, an isotope of uranium produced by the neutronic irradiation of $^{238}$U, could have its nucleus split into highly radioactive fragments. That theory was ultimately supported by experimental observations showing the enormous release of ionization energy resulting from nuclear fragmentation, thereby confirming a decades-old relationship between mass and energy—$E = mc^2$—first formulated by Albert Einstein. With remarkable speed, the newfangled knowledge covertly served as the basis for the Manhattan Project, the research program that ultimately developed the atomic bomb through nuclear fission.
The genesis of modern computing too had its principles neatly packaged in a seminal paper authored by the mathematician Alan Turing. The revolutionary notion that a machine could imitate computations performed by humans spawned the first “Turing-complete,” programmable, general-purpose, Electronic Numerical Integrator and Computer (ENIAC). Unpredictably, the technology evolved into personal computers and smartphones, and enabled the ensuing development of the Internet. Other fundamental discoveries over the past few centuries—in mathematics, physics, chemistry, and biology—have facilitated our ability to harness the power of natural phenomena in space travel, wireless communications, medicine, and a myriad of other applications.

The advent of the atomic bomb and the Internet have transformed the world in both positive and negative ways. For example, some argue that the development of the atomic bomb changed the world for the better because it brought an end to the bloodiest conflict the world has ever witnessed. Others decry the nuclear bomb as an instrument that led to utter destruction in the Japanese cities of Hiroshima and Nagasaki, nearly a half-million deaths, and political instability for decades after World War II. Computers and the Internet too have changed how humans communicate, access information, shop, and even perceive reality. At the same time, the
technology has enabled an entire slew of new cybercrimes and other internet-based antisocial behaviors.\footnote{24} Genome editing is no different in this sense. Its impact has become well-nigh indisputable in the last few years. This book explores the disruptive nature of the technology, as well as its potential benefits and perils.

B Who Owns CRISPR?—A Bitter Fight

The ability to manipulate genomes at will harbingers a new era in world history with far-reaching implications for the future of every living organism. Since the debut of CRISPR–Cas9 as a genome-editing tool in 2012, laboratories around the world have adopted CRISPR systems with unparalleled speed. Roughly $17,000$\footnote{25} scientific publications to date feature theory, empirical observations, and description of applications related to genome editing in organisms spanning nearly every biological kingdom from bacteria and fungi, to plants, animals, and now even humans.\footnote{26} Stratospheric expectations for CRISPR systems have already attracted more than $1$ billion in venture capital\footnote{27} in a brief period of time. In 2016, Editas Medicine, Inc., a pioneer CRISPR-based company, became the first to file the requisite paperwork for an initial public offering with the Securities and Exchange Commission (SEC).\footnote{28} Within months, CRISPR Therapeutics AG also filed for an initial public offering.\footnote{29} And
other companies specializing in a wide variety of genome-editing technologies have since debuted, including Intellia Therapeutics, Horizon Discovery, Caribou Biosciences, Synthego, GenEdit, Beam Therapeutics, Precision Biosciences, LogicBio, Locus Biosciences, Inscripta, and many others.

To date, the genome-editing revolution has largely encompassed the province of scientific discovery. In the last few years, however, scientific progress through research and development, as well as an increased demand for technology commercialization—thanks in large part to procurement of intellectual property rights—have summoned the law to become an active and prominent participant. A high-stakes, intellectual property dispute over rights to the first patents related to CRISPR systems ended—at least for now—when the United States Court of Appeals for the Federal Circuit decided Regents of the University of California v. Broad Institute, Inc in 2018.

The case was a highly publicized legal dispute between the University of California, Berkeley, the University of Vienna, and Emmanuelle Charpentier (collectively the “University of California”) on one side, and the Broad Institute of the Massachusetts Institute of Technology (MIT) and Harvard University (collectively the “Broad Institute”) on the opposite side. In early 2016, the US Patent and Trademark Office (USPTO) Patent Trial and Appeal Board (PTAB) declared an interference proceeding, which is a type of patent legal contest under the old, first-to-invent patent system that existed before the enactment of the America Invents Act. An interference is typically declared to determine priority between parties that claim a common invention. In the context of the CRISPR dispute, therefore, declaring an interference would concern the determination of priority for the first CRISPR patents—namely, whether the Broad Institute or the University of California were first to invent CRISPR–Cas9 under United States patent law.

The PTAB, however, did not rule on the issue of priority and found instead that there was no interference-in-fact between the University of California’s patent application and the Broad Institute’s patent claims in twelve issued patents and one pending patent application. The University of California appealed that decision to the Federal Circuit, which ultimately ruled in favor of the Broad Institute and concluded that substantial evidence supported the PTAB’s findings that (1) the parties’ claims were not drawn to the same patentable subject matter—in other words, that the claims were directed to different inventions—and (2) the University of California’s claims did not render the Broad Institute’s claims obvious.

Notably, the litigation did not lead to a decision that any of the parties’ claims were unpatentable, and the Federal Circuit abstained from ruling on the validity of either set of claims. But the bitter fight continues. The PTAB has redeclared an interference proceeding, which will likely set the stage for an award of priority to either party and the resolution of other patentability issues unless the parties settle their dispute out of court.

The battle for patent rights has not been confined to the United States. Early in 2020, the European Patent Office (EPO) Board of Appeal upheld an earlier revocation
of a foundational CRISPR–Cas9 patent that had been granted to the Broad Institute on grounds that the issued European patent lacked novelty in view of prior art. And in a separate proceeding, the EPO Opposition Division announced that another European patent on CRISPR–Cas9 granted to the University of California, the University of Vienna, and Emmanuelle Charpentier survived a patentability challenge and required only minor amendments.

Litigation in these cases has been contentious and with good reason. The companies and interested parties battling over the technology seek dominance in an emerging industry with a multibillion-dollar valuation. As is evident from the litigation history, however, the legal disputes exclusively concern the fight for foundational intellectual property rights over CRISPR–Cas systems. The law has been largely absent outside the intellectual property realm.

II THE GROWING GAP BETWEEN LAW AND SCIENCE

Despite the recent and constant stream of breakthroughs in the field of genome editing and CRISPR’s renown in science, discussions about the technology in the legal and policy realms continue to lag behind the pace of scientific progress. In the absence of on-point law, the scientific community has attempted to reach some consensus to preempt antagonistic regulation and prescribe subjective standards of use. However, significant and complex political, societal, and legal issues concerning this emerging technology are beginning to surface. A considerable bulk of current laws and regulations are not well equipped to address many of those issues, which must be examined within the framework of law and policy, rather than science. Undoubtedly, scientific progress has come at an astounding pace, but uncertainty about how the law will treat this emerging technology looms in the horizon.

A Corrosive Insularism and the Pursuit of Knowledge

Many members of the legal community, including jurists, legal scholars, and practitioners, have either largely ignored this field or kept a distance from it, presumably due, in part, to the challenges that complex scientific principles often pose to nonscientists in the legal and legislative arenas. A concurring opinion penned by the late Justice Antonin Scalia, in Association for Molecular Pathology v. Myriad Genetics, Inc. (Myriad), notoriously illustrated the degree of scientific antipathy among some members of the legal community.

In Myriad, a unanimous US Supreme Court ruled that a naturally occurring DNA segment—such as a gene—constitutes a product of nature that cannot be patented merely because it has been isolated by a researcher. All Justices endorsed this principle in unison. Scalia, nevertheless, found it imperative to qualify his vote by issuing a short, one-paragraph concurrence, which included the following statement:
A Momentous Time for Humankind

I join the judgment of the Court . . . except Part I-A and some portions of the rest of the opinion going into fine details of molecular biology. I am unable to affirm those details on my own knowledge or even my own belief. 43

Exercising great candor, Scalia thus conceded his lack of knowledge of relevant scientific details in the case before him. At the same time, he disturbingly remarked he did not even believe in scientific facts that have been well established for decades. Indeed, the text Scalia quibbled about concerned scientific facts that every student in the fifth grade—and possibly even earlier in today’s primary-education curricula—becomes acquainted with. Genes are made up of DNA. DNA forms a double helix. Mutations are changes in a DNA sequence. Genes encode genetic information to make proteins. And so on. Scalia’s demurral of uncontroversial facts found in every fifth-grade biology textbook is puzzling to many in the scientific community. His statement manifests scientific apathy at best, and utter disbelief at worst.

To some extent, Scalia’s admission is commendable. A person in a position of great power should not be afraid to admit knowledge gaps. After all, no human holds absolute knowledge in any area. Conversely, it is worrisome that a powerful person may be called to decide pivotal questions with broad societal implications when that person makes no effort whatsoever to close self-perceived knowledge gaps. Expressing disbelief in science is not sufficient. Those with power to delineate the contours of what constitutes the rule of law ought to educate themselves about matters before them.

To better perform the functions associated with the judicial branch, judges “need[] to develop an informed—although necessarily approximate—understanding of the state of [the] relevant scientific art.”44 Myriad was true to this aphorism for the role of science in the judiciary. The Supreme Court’s effort to preface its decision with relevant scientific facts should be commended. And despite some minor inaccuracies related to protein synthesis,45 RNA processing,46 and DNA noncoding regions,47 which we will discuss in greater detail in Chapter 2, the Court more or less accurately described the science—certainly enough to competently rule on the merits.

Scalia’s brand of scientific aversion has corrosive effects. It ultimately hinders the sort of interdisciplinary dialogue and insight required to fully understand and address significant problems in an increasingly interconnected world.48 To be fair, scientific aversion among members of the judiciary is not a new phenomenon. But, as retired Judge Richard Posner put it, “it [is] increasingly concerning, because of the extraordinary rate of scientific and other technological advances that figure increasingly in litigation.”49

In the near future, law and policy makers will be confronted with many questions related to genome editing and CRISPR, and the legal community must proactively take steps to familiarize itself with this new technology. Given the rapid expansion of CRISPR-based applications, the gap between science and the law is becoming increasingly problematic.
As a testament to this growing problem, Judge David Neuberger, former President of the UK Supreme Court, published a commentary in the journal *Nature* calling attention to the scientific community and arguing that scientific primers would be “hugely beneficial” for the legal community. Such primers, he contended, would save money and time, help assess the reliability of expert witnesses, and increase the proportion of cases that are settled without trial. Specifically, he singled out genetic engineering as an area in which a primer would be useful to jurists given that legal controversies in the field are likely to proliferate and recur.

In the absence of on-point law, some in the scientific community have campaigned, in arguably self-serving ways, for a consensus to preempt antagonistic regulation and prescribe subjective standards of use under the misguided auspices of a priori scientific empiricism. This must give us pause. Einstein memorably remarked, “[T]he man of science is a poor philosopher.” Most scientists—by training—are unfamiliar with intricate legal principles, constitutional doctrine, regulatory processes, and policy making; likewise, most lawyers are oblivious to scientific theory, physicochemical laws, and cellular and macromolecular processes. Given these vastly different realms of knowledge, it is understandable that many scientists and lawyers often pursue insularism by academic discipline. Surely, there is comfort in academic seclusion, but isolation is often dangerous to learning and the pursuit of knowledge. “People do not learn very much when they are surrounded only by the likes of themselves.” Interdisciplinary colloquy, therefore, is the most sensible approach to bridge the current chasm between science and the law surrounding this momentous technology.

A blueprint for genome-editing science and the law is sorely overdue. This timely monograph addresses the urgent and fundamental need to close critical knowledge gaps among the fields of law, science, and policy relating to emerging genome-editing technologies. To that end, the research presented herein employs both descriptive and normative interdisciplinary tools to foster an understanding of genome editing and propose a legal framework for its use.

**B A Jurisprudence of Scientific Empiricism to Bridge the Gap between Law and Science**

Broadly speaking, the book challenges conventional views regarding the false dichotomy frequently associated with mutually exclusive normative roles for science and law—the proximate cause driving laissez-faire attitudes of deference to elude questions of “law in science and science in law.” It proposes a normative structural legal framework, namely, a jurisprudence of scientific empiricism that is broadly adaptable to addressing questions of science in law. The scientific empiricism referred to in this book specifically concerns the natural sciences—for example, physics, chemistry, biology, and other disciplines of the life and physical sciences—and not the social sciences—such as sociology, psychology, economics, political