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IN THE
Supreme Court of the United States

ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,
Petitioners,
v.

MYRIAD GENETICS, INC., *et al.*,
Respondents.

ON WRIT OF CERTIORARI TO THE
UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

BRIEF FOR AMICI CURIAE GENENTECH, INC.; ROCHE MOLECULAR SYSTEMS, INC.; VENTANA MEDICAL SYSTEMS, INC.; ROCHE DIAGNOSTICS OPERATIONS, INC.; ROCHE DIAGNOSTICS CORPORATION; AND HOFFMANN-LA ROCHE INC. IN SUPPORT OF RESPONDENTS

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INTEREST OF AMICI CURIAE[1]

Amici curiae are biotechnology and biopharmaceutical companies with a long history of industry leader-

[1] No counsel for a party authored this brief in whole or in part, and no persons or entities, other than amici or their counsel, made a monetary contribution to the preparation or submission of this brief. Letters consenting to the filing of this brief are on file with the Clerk of the Court.

ship in research and development of therapeutic and diagnostic applications of recombinant DNA technology. Amici rely on patent protection to finance and develop these technologies, which have saved countless lives and which promise even greater future benefits.

Amici are all members of the Roche Group ("Roche"), a corporate family comprising innovative, research-oriented healthcare groups across the globe. Roche is the world's largest biotechnology company. It divides its operations into two core businesses—pharmaceuticals and diagnostics—both of which rely heavily on investment in and use of recombinant DNA technologies. Close cooperation between Roche's pharmaceutical and diagnostic divisions enables the company to tailor treatments to specific patient subpopulations based on the latest scientific understanding of biology and disease at the molecular level. Roche has been at the forefront of the development and commercial application of these technologies since their inception.

Genentech is a leading biotechnology company that uses human genetic information to discover, develop, manufacture, and market human pharmaceuticals for significant unmet medical needs, especially in the areas of oncology, immunology, neuroscience, metabolism, and infectious disease. In the early 1970s, Genentech's founders pioneered the use of recombinant DNA technology to develop products with practical applications. Genentech has an extensive track record in all phases of bringing new disease treatments to patients—from discovery research through clinical development, manufacturing, and commercialization.

Roche Molecular Systems develops, manufactures, and supplies a wide array of innovative medical

diagnostic products, services, tests, platforms, and technologies. Many of these products use the company's Nobel Prize-winning polymerase chain reaction technology to detect genetic material from cancerous cells and infecting pathogens, such as HIV or hepatitis. Because the tests are capable of identifying and characterizing disease earlier and more specifically than tests based on the body's immune response, patients can be treated and monitored with great precision.

Roche Diagnostics offers a broad portfolio of tools that help healthcare providers in the prevention, diagnosis, and management of diseases like HPV, HIV, heart failure, and diabetes, as well as other medical conditions, such as infertility and blood coagulation. These products and services are used by researchers, physicians, patients, hospitals, and laboratories worldwide to help improve people's lives.

Ventana Medical Systems is an innovator in the field of tissue-based diagnostic solutions. The company discovers, develops, and delivers medical diagnostic systems and biopsy-based cancer tests that are shaping the future of healthcare. Ventana is the leading supplier of cancer diagnostic systems to the pathology market, manufacturing over 220 cancer tests with related instruments for four million people afflicted with cancer yearly around the world.

The development of both diagnostic and therapeutic applications of recombinant DNA technologies is capital intensive and time consuming. Success in these fields could not be achieved without the protections and incentives provided by the patent system. Uncertainty regarding the patent eligibility of isolated DNA molecules would jeopardize current and future innovation in

these fields. The question presented in this case is thus of great significance to amici.

SUMMARY OF ARGUMENT

Biotechnology companies use modern DNA technologies to identify, characterize, and treat disease. Through a combination of diagnostic and therapeutic tools, the industry has provided physicians and patients with effective products to detect, monitor, and treat a wide range of debilitating diseases. In many instances, the diagnostic or therapeutic tool is a synthetically created protein or nucleic acid product that is intended to resemble, at least in some respects, natural compositions of the body. Biotechnology companies can only make and justify the enormous investment necessary to develop these types of products if they can be assured that patent protection will allow them a return on their investments.

Petitioner proposes denying patent protection to any isolated "product of nature," a category that he defines exceptionally broadly. Such an expansive rule could threaten the patentability of a vast array of biotechnology products that, although they may contain some analogue of a substance found in nature, are engineered in a lab through complex scientific processes and are manufactured by scientists, not by nature. This Court should proceed with extreme caution and should consider the impact of any potential decision not only on the case before it or fanciful hypotheticals like the patenting of leaves or gold but also on the many groundbreaking innovations in biotechnology that could be affected.

The dangers and difficulties of a broad "product of nature" exception are illustrated by three examples of

technologies from amici's own portfolio: (1) recombinant therapeutic proteins; (2) monoclonal antibodies; and (3) DNA-based diagnostic tests. All of these technologies have or might have analogues in nature, but they are all decidedly the product of human ingenuity and deserving of patent protection. Mindful of the law of unintended consequences, the Court should ensure that its ruling in this case does not imperil the patent protection relied on by innovators for financing and developing these inventions.

ARGUMENT

As the Court observed only last Term, "all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas." *Mayo Collaborative Servs.* v. *Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1293 (2012). That is equally true of discoveries in biotechnology, most of which harness natural principles or build on structures found in nature. The sweeping "product of nature" exception to patent eligibility that petitioner seeks could create tremendous uncertainty for the biotechnology industry if the Court were to adopt it. The purpose of this brief is to educate the Court about the broad range of biotechnology inventions beyond the single invention at issue in this case, the complex questions that could arise if the Court adopts petitioner's position, and the need to ensure that the Court does not sweep too broadly.

I. AMICI AND OTHERS IN THE BIOTECHNOLOGY INDUSTRY HARNESS HUMAN INGENUITY TO DEVELOP PRODUCTS THAT ADDRESS UNMET MEDICAL NEEDS

A. Recombinant Technology That Utilizes Isolated DNA Has A Wide Range Of Therapeutic And Diagnostic Uses

1. Recombinant proteins are synthetic products made in a laboratory through complex techniques that are intended to create a product closely resembling molecules found in nature, including in the human body. Armed with these techniques, biotechnology has played an increasingly important role over the last several decades both in the elucidation of the molecular causes of disease and in the development of new diagnostic methods and better targeted drugs. The modern biotechnology industry emerged in the 1970s and took off after this Court's decision in *Diamond* v. *Chakrabarty*, which held a bacterium to be patent eligible as a "manufacture or composition of matter—a product of human ingenuity 'having a distinctive name, character [and] use.'" 447 U.S. 303, 309-310 (1980). Since then, the industry has created hundreds of new therapies, drug products, and vaccines.

Amici were among the pioneers of the use of recombinant techniques to create products to treat disease. This unique approach uses proteins as therapeutic drugs, rather than the smaller chemicals of traditional pharmaceuticals. One way to create such a protein is to create a cDNA molecule that codes for a particular protein and then use controlled laboratory conditions to produce that protein outside the human body. *See, e.g.*, Holman, *The Impact of Human Gene Patents on Innovation and Access*, 76 UKMC L. Rev. 295, 324-325 (2007). Through this technique, living cells—such

as bacteria or more complex mammalian cells—serve as mini-factories to manufacture the appropriate proteins. Although produced in a lab, the finished proteins closely resemble molecules found in the human body.

The first medicine to be produced in this way was human insulin, which is used to treat diabetes. By developing a technique to produce human insulin in bacterial cells, Genentech replaced the traditional process of extracting insulin from the pancreatic glands of pigs and cows. *See* Roche, *Biotechnology: New Directions in Medicine* 11-13 (3d ed. 2008); National Research Council, *Reaping the Benefits of Genomic and Proteomic Research* 47-48 (2006). Some 200 million diabetics worldwide now benefit from the development and production of human insulin. *See Biotechnology* 12.

Recombinant therapeutic proteins like human insulin have increased dramatically in number and frequency of use in recent years, providing patients with effective products to treat a wide range of debilitating diseases such as cancer, arthritis, and macular degeneration, and are in development for other unmet medical needs, such as Alzheimer's disease.

2. Biotechnology companies also use recombinant technologies to create diagnostic tests to identify patients predisposed to a given disease, to conclusively diagnose disease or differentiate disease subtypes and prognosis, to monitor treatment efficacy, and to ensure the safety of the blood supply. Before these innovations, clinicians were often forced to rely on tests that could take weeks to produce conclusive results. Earlier detection of disease can mean earlier and more effective treatment.

Many of these innovative diagnostic tests are based on Roche's Nobel Prize-winning polymerase chain reac-

tion (PCR) technology. *See Biotechnology* 58-59. PCR is a technique for "produc[ing] enormous numbers of copies of a specified DNA sequence." Watson *et al.*, *Recombinant DNA* 79 (2d ed. 1992) (emphasis omitted). PCR involves repeated cycles of heating and cooling during three key steps. First, double-stranded DNA containing the target DNA sequence is heated until it denatures into single strands. Second, the mixture is cooled to allow "primers" to bind to each of the strands. A primer is a short single-stranded DNA molecule that is synthetically designed to be complementary to "sites that flank the target region, one on each strand." *Id.* at 81 fig.2. The primer marks out the starting points on each strand of the sequence to be copied. Third, the mixture is heated to the point at which the enzyme DNA polymerase begins synthesizing new complementary strands at the primer sites. The result is two double-stranded molecules—each consisting of one strand from the original DNA molecule and one strand synthesized by DNA polymerase—that contain the target region marked out by the primers. After more heating and cooling cycles, two copies become four, then eight, sixteen, and so forth, all synthetically created in the lab.

A more advanced form of PCR, called "real-time PCR," makes use of an additional short single-stranded DNA molecule that is designed to bind at the middle of the target DNA sequence. This "probe" is labeled to generate a signal when it binds, enabling even more specific and sensitive detection of a target sequence.

PCR thus allows scientists to take a specimen of genetic material, even from just one cell, and copy its genetic sequence over and over, generating a test sample with millions of copies. The primers and probes that make this technique possible are synthetically produced isolated DNA molecules.

3. These advances in DNA-based diagnostics and therapeutics are part of biotechnology's nascent personalized medicine revolution. The goal of personalized medicine is "tailor[ing] treatment to individual patients" based on advances in diagnostic testing for genomic variations. FDA, *Advancing Regulatory Science at FDA* 10 (2011); *see also* Personalized Medicine Coalition, *The Case for Personalized Medicine* 2 (3d ed. 2011) ("What is different about medicine today, and the reason the word 'personalized' has been added for emphasis, is that technology has brought us much closer to exquisite precision in disease diagnosis and treatment."). Personalized medicine recognizes that differences in the genome make each of us a unique individual—not only in appearance and behavior, but also in terms of our health risks and response to treatments. These differences offer key insights to help in finding the right treatment for each individual.

Amici are at the forefront of this new field, which bridges both therapeutic and diagnostic applications of recombinant DNA technologies. For example, every drug being developed by amici now has a biomarker program associated with it, meaning that measurable biological indicators are studied to evaluate whether the drug is indicated for a given patient and to monitor the drug's therapeutic efficacy. This type of personalized medicine has become a priority healthcare issue at the highest levels of government. The FDA has increasingly required the use of "companion diagnostic[s]" as a condition of approving therapeutic products. *See* FDA, *Draft Guidance for Industry and Food and Drug Administration Staff—In Vitro Companion Diagnostic Devices* 6-7 (2011). Obtaining FDA approval of such companion diagnostics requires rigorous validation techniques and a substantial investment of resources.

B. Biotechnology Innovation Depends On A Stable Patent System To Fund The Research, Development, And Commercialization Of These New Technologies

Biotechnology companies such as amici invest substantial sums of private capital to make these innovations possible. While advances in scientific knowledge are leading to dramatic improvements in identifying biological targets to fight many diseases, the complexity of research is rising significantly. Bringing a single biotechnology product to market, including basic research, clinical trials, and post-approval testing, now takes up to 12 years and costs on average $1.6 billion. Roche, *Annual Report 2012*, at 25 (2013); Grabowski, *Follow-on Biologics*, 7 Nature Revs. Drug Discovery 479, 482 fig.2 (2008).

This type of private investment depends on a stable patent system that rewards innovation and risk-taking. Biotechnology companies can only make and justify the enormous investment necessary to develop new products if they can be assured that patent protection will allow them a return on their investments. *See, e.g.*, Toneguzzo, *Impact of Gene Patents on the Development of Molecular Diagnostics*, 5 Expert Op. Med. Diagnostics 273, 274 (2011) ("industry has consistently confirmed that the protection that a patent affords is a key consideration for making an investment" in molecular diagnostic development); *id.* ("without a patent investment is not made and technology is not developed"). Patents are critical to reassuring investors that they will earn a reasonable financial return on products that make it to market. *See* Barfield & Calfee, *Biotechnology and the Patent System* 27-28 (2007).

The future of the biotechnology industry "depends on the continued support that patent exclusivity facilitates through the incentive to invent and the incentive to invest in innovation." Sung, *Medical Alert: Alarming Challenges Facing Medical Technology Innovation*, 6 J. Bus. & Tech. L. 35, 58 (2011). Indeed, uncertainty over the patentability of biotechnology products has in the past had dramatic negative effects on the industry. *See* Davies, *Cracking the Genome* 205 (2001) (explaining that after President Bill Clinton and Prime Minister Tony Blair issued a statement implying that human DNA would not receive patent protection, "the markets panicked, sending the technology sector of the U.S. stock market into a tailspin"). Similar uncertainty following this Court's decision in *Mayo* may have contributed to the decrease of 15 percent in investment dollars in the industry in 2012. *See* Press Release, PricewaterhouseCoopers & National Venture Capital Association, *Annual Venture Investment Dollars Decline For First Time In Three Years* (Jan. 18, 2013); *see also* Thomas, Cong. Research Serv., R42815, Mayo v. Prometheus*: Implications for Patents, Biotechnology, and Personalized Medicine* 3 (2012) ("VC firms must carefully weigh the economic value of a company's patent portfolio in determining whether to make an investment, and the security of intellectual property is a key component in this analysis."). The Court should be careful not to upset reliance interests or to create uncertainty that will chill future innovation and potentially cripple this vital industry.

II. Many Therapeutic And Diagnostic Applications Of Biotechnology Resemble Compounds Found In Nature Only Because Human Ingenuity Achieved This Congruence

Petitioner urges the Court to create a general "product of nature" exception broad enough to deny patent protection to many isolated nucleic acids and proteins. But, as the examples below illustrate, petitioner's argument is flawed in multiple respects and could have serious unintended consequences.

First, petitioner's argument underestimates the role of human ingenuity in creating isolated molecules that have new utilities beyond anything that exists in nature. Although many of these molecules are claimed in isolated form to differentiate them from any naturally occurring analogue, it would be a mistake to assume that this means they are simply extracted from nature like gold from a mine. More typically, the isolated form of a molecule is created in a laboratory or a factory. The isolated molecule often becomes useful therapeutically or diagnostically only when it can be synthetically created by humans rather than nature.

Second, the fact that the compositions of matter created through recombinant processes and other techniques resemble naturally occurring analogues does not detract from the inventive nature of these products. In many instances, genetically engineering proteins that are similar to those that the human body might produce is a chief design goal, achievable only at great expense and difficulty. Because these proteins are, by design, similar to what occurs in nature, it is easy to fall into the trap of equating them with natural molecules. But as the examples below illustrate, their very similarity is a product of human ingenuity.

Third, even when there is no known naturally occurring analogue to a molecule at the time of invention and patenting, a broad product of nature exception would create a cloud of uncertainty because there is always a risk that a comparable molecule might later be found to exist in nature. In fact, patent challengers would have a strong incentive to seek out such evidence, much in the way that petitioner has tried to find examples of DNA or cDNA that he claims is "isolated" within the body.

Fourth, it is important not to lose sight of the basic bargain at the heart of the patent system. The full cycle of patent protection moves from the incentive to invent and disclose, through a limited period of market rewards, to the end point of every patent—its expiration and the enrichment of the public domain.

A. Past Therapeutic Breakthroughs Using Recombinant DNA Were Made Possible By The Patent Eligibility Of Isolated DNA

Recombinant techniques and isolated DNA molecules have played a central role in therapeutic advances achieved by amici. These advances are well illustrated by Genentech's path-breaking synthesis in the 1980s of two proteins found in human blood: tissue-type plasminogen activator (t-PA) and Factor VIII. The patent system was integral to fueling the development and commercialization of these lifesaving therapeutics, which have now been used to treat hundreds of thousands of patients. The possibility of patent protection spurred investment in research and development, and the security of a patent encouraged researchers to disclose their discoveries. Yet, because the products Genentech created through recombinant technology resemble proteins found in the human body—and in-

deed are therapeutically useful for that very reason—petitioner's broad rule would have created substantial uncertainty that could have chilled these advances.

1. t-PA is a protein that plays a role in the process of dissolving blood clots, which are helpful in staunching bleeding but which can also clog blood vessels and cause heart attacks and strokes. Blood clots are formed in part by a fibrous protein called fibrin. *See* Colman *et al.*, *Overview of Hemostasis*, *in Hemostasis and Thrombosis* 3, 11-14 (5th ed. 2006). t-PA catalyzes the conversion of another protein (plasminogen) into an enzymatically active form (plasmin) that dissolves the fibrin in a blood clot.

Genentech's interest in synthesizing t-PA was sparked by Belgian chemist Désiré Collen and colleagues, who in 1978 reported a key conceptual insight into the function of the protein: It is much more active in catalyzing the conversion of plasminogen into plasmin when fibrin is present—such as at the site of a blood clot—than when fibrin is not present. *See* Wiman & Collen, *Molecular Mechanism of Physiological Fibrinolysis*, 272 Nature 549, 549-550 (1978). By contrast, prior to Genentech's innovation, the only available therapeutic plasminogen activators were not fibrin specific. *See* Pennica *et al.*, *Cloning and Expression of Human Tissue-Type Plasminogen Activator cDNA in* E. Coli, 301 Nature 214, 214 (1983). When given to patients, the plasminogen activators available at the time caused systemic activation of plasminogen—not merely activation near the blood clot—which was inefficient and risked causing hemorrhaging. *Id.* Although it appeared that t-PA would be a superior treatment to dissolve blood clots in heart attack and stroke victims, at the time there was no way to produce t-PA in therapeutically useful quantities.

Genentech and Collen collaborated on a project to synthesize t-PA. After almost three years of work, the Genentech team successfully mapped and isolated the DNA coding for human t-PA. *See* Pennica *et al.*, 301 Nature at 217 fig.3B. The first step was to isolate the messenger RNA (mRNA) present in a line of melanoma cells known to produce human t-PA in significant quantities. *Id.* at 215. The mRNA thought to express t-PA was identified by sorting mRNA samples according to size, translating size-selected samples into polypeptides, and observing which polypeptides would bind with an antibody specific to t-PA. *Id.* The most promising pool of size-sorted mRNA was then used to prepare a library of cDNA. The team designed a labeled nucleic acid sequence based on the amino acid sequence of a short fragment of the t-PA protein and used the nucleic acid "probe" to search the cDNA library for cDNAs that encoded the t-PA protein fragment. *Id.* at 215-216. The team succeeded in identifying a single promising candidate, a 2,304 base pair cDNA fragment that the team knew could not be the complete code because it did not express the terminal sequence of the t-PA molecule. *Id.* at 216. A second cDNA library was created and successfully probed to identify the remainder of the cDNA that encodes t-PA. *Id.* at 216-219.

Genentech promptly disclosed this discovery in a patent application. *See* U.S. Patent No. 4,766,075 col. 30, ll. 67-68 (claiming the "DNA isolate consisting essentially of a DNA sequence encoding human tissue plasminogen activator"). The patent claims a "DNA isolate," but recombinant t-PA was not isolated in any conventional sense. It was synthetically constructed, over several years and at significant expense, through careful construction and probing of bacterial libraries of

cDNA fragments, then combining portions of the cDNA fragments to create the full cDNA.

2. Genentech's invention of recombinant Factor VIII followed a similar pattern. Factor VIII is a protein that plays an essential role in blood clotting. In the human body, Factor VIII is secreted into the bloodstream by certain cells found in the liver, kidneys, spleen, and lymph nodes. Kaufman *et al.*, *Factor VIII and Hemophilia A*, *in Hemostasis and Thrombosis* 151, 153. The protein is missing or inactive in persons with Hemophilia A, a condition that can be marked by spontaneous and uncontrolled internal bleeding. *See* Wood *et al.*, *Expression of Active Human Factor VIII from Recombinant DNA Clones*, 312 Nature 330, 330-331 (1984). If proper measures are not taken promptly, the bleeding can cause crippling deformities or even death. More than 130,000 people around the world suffer from this type of Factor VIII deficiency. World Federation of Hemophilia, *Annual Global Survey 2011*, at 3 (2012).

In 1981, a team of Genentech scientists began research into producing human Factor VIII through recombinant technology. "[T]he plight of hemophiliacs was the crucial driving force" behind researchers' development of synthetic human Factor VIII. Gitschier, *Remembrances of Factor VIII*, 2 J. Thrombosis & Haemostasis 383, 383 (2004). Prior to Genentech's development of the recombinant method for producing human Factor VIII, hemophiliacs were treated with Factor VIII concentrates, which were purified from human blood plasma. Because Factor VIII occurs naturally in only minute quantities in blood, it was necessary to pool blood plasma from thousands of donors in order to produce the purified Factor VIII. *See id.*; Wood *et al.*, 312 Nature at 331. This method

carried the risk that the treatment would transfer infectious agents such as HIV and hepatitis from the blood of a donor. *See id.*; Kaufman *et al.*, *Synthesis, Processing, and Secretion of Recombinant Human Factor VIII Expressed in Mammalian Cells*, 263 J. Biological Chem. 6352, 6352 (1988).

To address this unmet medical need, Genentech began by isolating and characterizing the region of the human X chromosome containing the complete Factor VIII gene. *See* Gitschier *et al.*, *Characterization of the Human Factor VIII Gene*, 312 Nature 326, 326 (1984). The Factor VIII protein is "four times as big" as t-PA, which made isolating its corresponding genomic DNA and cDNA "extremely difficult." Kleid, *Scientist and Patent Agent at Genentech* 161 (2002) (oral history). The Genentech team started by breaking the large protein into small pieces and then painstakingly determining the amino acid sequence of one of the small protein pieces. *See id.*; Gitschier, 2 J. Thrombosis & Haemostasis at 383-385; *see also Scripps Clinic & Research Found.* v. *Genentech, Inc.*, 666 F. Supp. 1379, 1382 (N.D. Cal. 1987). Based on the amino acid sequence of a short Factor VIII protein fragment, the team designed and constructed a radiolabeled nucleic acid probe, which was used to probe a large library of small pieces of human genomic DNA. A new labeled nucleic acid probe was then designed using sequences from the ends of this genomic DNA, and the library was screened again with the probe to identify "the next sequence downstream" along the Factor VIII sequence. Kleid 161; *see also* Wood *et al.*, 312 Nature at 332. By repeating this process, the Genentech team was able to piece together the entire sequence necessary to express Factor VIII. Kleid 161.

In 1984, Genentech disclosed this information in a patent application. Gitschier, 2 J. Thrombosis & Haemostasis at 387; *see* U.S. Patent No. 5,618,789 col. 41, ll. 1-2 (claiming "[r]ecombinant functional human factor VIII free of viral contaminants that affect humans").

3. t-PA and Factor VIII were not therapeutically useful until they could be manufactured in a laboratory, and they could not be manufactured in a laboratory until Genentech had synthetically constructed the cDNAs needed to express them. That breakthrough permitted the company to express the proteins in mammalian ovary cells. *See* Activase® (alteplase) Prescribing Information 1 (2011); Kleid 162; Gitschier, 2 J. Thrombosis & Haemostasis at 383-385. Once the proteins could be expressed in and harvested from mammalian cells, they were available in sufficient quantities to permit clinical trials and, ultimately, production of commercial therapeutics.

Recombinant t-PA is approved by the FDA to treat heart attacks, strokes, and pulmonary embolisms. *See* Activase® (alteplase) Prescribing Information 1. It is the only thrombolytic drug approved for the treatment of acute ischemic stroke, and it has been used to treat more than 240,000 patients in the United States alone. The public disclosure of Genentech's work on recombinant t-PA has prompted further downstream innovation, including the creation of synthetic variants of t-PA with utilities that are still being explored. *E.g.*, White & Van de Werf, *Thrombolysis for Acute Myocardial Infarction*, 97 Circulation 1632, 1641 (1998).

Genentech's development of a recombinant, virus-free version Factor VIII virtually eliminated the risk of transmitting human viruses when administering this protein. Recombinant Factor VIII has been approved

since 1993 for the treatment of Hemophilia A. *See* Gitschier, 2 J. Thrombosis & Haemostasis at 383. Since then, the therapeutic has been instrumental in saving the lives of thousands of hemophiliacs.

4. Recombinant t-PA and Factor VIII are success stories not only for biotechnology but also for the patent system. The arc from unmet medical need to investment, discovery, disclosure, commercialization, and further innovation is exactly how the patent system is intended to work.

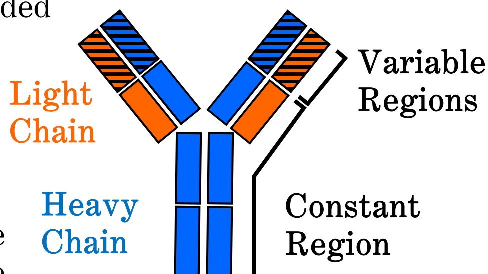
Uncertainty regarding the patent eligibility of the cDNA used to produce recombinant t-PA or Factor VIII or the recombinant proteins themselves could have significantly impeded these advances. The peril is particularly vivid for Factor VIII. It was patent protection for Factor VIII that permitted Genentech to license the rights to production and marketing of the protein in order to make the product available commercially quickly and efficiently. *See* Press Release, Genentech, *Cutter To Receive Factor VIII License from Genentech* (Sept. 11, 1984). Genentech also entered into cross-licensing agreements designed to allow multiple companies to "proceed with independent development of recombinant Factor VIII products, while avoiding potential disputes over competing patent positions." Press Release, Genentech, *Cross-Licensing Agreement Reached on Factor VIII Genetically Engineered Clotting Agent for Hemophiliacs* (Mar. 21, 1989). The limited period of exclusivity that the patent system provided made it economically viable for these companies to disclose their discoveries and to work together to make the products quickly available to patients in need.

B. Therapeutic Monoclonal Antibodies Are A Highly Promising Avenue Of Research That Would Be Imperiled By Petitioner's Broad Rule

Antibodies are another vivid example of the technologies that could be threatened by an overbroad "product of nature" exception. "The market for monoclonal antibodies is the fastest-growing segment of the pharmaceutical industry." Ledford, *Monoclonal Antibodies Come of Age*, 455 Nature 437, 437 (2008). As judged by sales, five of the top ten pharmaceuticals of 2012 were antibodies, treating a range of illnesses like cancer, rheumatoid arthritis, and Crohn's disease. The substantial investment required to investigate and develop novel monoclonal antibodies is currently driven by the patent system and could be imperiled if the patentability of these molecules were thrown into question by petitioner's sweeping rule. Many genetically engineered antibodies are designed to be similar to the antibodies that occur naturally in the human immune system so that the genetically engineered antibodies will not be attacked by the immune system as foreign. But this very design goal creates a risk that a similar antibody might one day be discovered in nature.

1. Antibodies are Y-shaped proteins generated by the body's immune system as a response to exposure to "bacteria, viruses, and other disease-causing organisms." Murphy, *Janeway's Immunobiology* 127 (8th ed. 2011). Antibodies bind to these "pathogens and their products, to facilitate their removal from the body." *Id.* at 136; *see also* Alberts *et al.*, *Molecular Biology of the Cell* 1018 (2d ed. 1989). The molecule or portion of a molecule to which the antibody binds is called an antigen. Murphy 127.

Antibodies consist of paired heavy- and light-weight polypeptide chains; the two heavy chains bind together in the distinctive Y shape, and one light chain is attached to each arm of the Y. Murphy 128-129. The Y-shape is also divided into two different functional regions. The top portions of the heavy and light chains forming each arm of the Y are called the variable regions because their surface varies widely among antibodies. *Id.* at 128. The variable regions contain the parts of the antibody that contact the target protein, or antigen; thus, it is the differences in these variable regions that primarily determine whether an antibody will bind to a given antigen, akin to the way a lock and key fit together. *See id.* at 136 fig.4.8d (models of antibody-antigen binding); Alberts *et al.* 1016-1017 (measurement of antibody-antigen affinity). The remainder of the molecule is called the constant region because it is identical among large groups of antibodies. Murphy 127, 134.



Antibodies, especially at their variable regions, exhibit an enormous diversity in the body. The number of antibodies present in a person at any given time is limited and changes from person to person based on antigen exposure. Murphy 158. But the multiple means by which the body produces a diverse catalogue of antibodies could theoretically give rise to billions of variations. *Id.* at 166. This natural variability has obvious advantages for combatting different antigens, but historically it limited the study or *in vitro* reproduction of any particular antibody. *Id.* at 730. In 1975, it was

shown in Nobel Prize-winning work that identical antibodies of a known antigen specificity could be produced by immunizing a mouse with an antigen to trigger an immune response and then fusing together an immunized mouse spleen cell (responsible for producing the antibody) and a mouse myeloma cell (which produces no antibodies but has the useful property of living indefinitely). Köhler & Milstein, *Continuous Cultures of Fused Cells Secreting Antibody of Predefined Specificity*, 256 Nature 495, 497 (1975); *see also* Murphy 731. The resulting fusion is called a "hybridoma." *Id.* The hybridoma can be cloned in a laboratory, and all of its clones will produce an antibody with the same antigen specificity. Because these antibodies are all produced from clones and are all ultimately derived from the same initial antibody-producing cell, they are called "monoclonal." *Id.*

Monoclonal antibodies "are valuable research and clinical tools because they are so specific." Drlica, *Understanding DNA and Gene Cloning* 210 (4th ed. 2004). "[O]nce cultured, the cells producing the monoclonal antibodies always produce the same antibody; this consistency is not found when animals are used as antibody sources, since their antibody specificities often change over time." *Id.* at 212. This specificity led some to view antibodies as potential "magic bullet[s]" that might be designed to seek out and destroy specific targets, like cancer cells, while causing no other harm to the body. *Recombinant DNA* 460. But the therapeutic utility of monoclonal antibodies produced from mouse hybridomas is limited.[2] "[T]hey are not identical to human an-

[2] Monoclonal antibodies also have non-therapeutic applications. They can be used, for example, in diagnostic tests to determine whether a sample contains a specific protein. *Biotechnology* 59-60; *e.g.*, Summary of Safety and Effectiveness Data: Ventana

tibodies," and when introduced into a human patient they "will eventually be recognized as foreign proteins and will be cleared from the circulation." *Recombinant DNA* 464; *see also* Chan & Carter, *Therapeutic Antibodies for Autoimmunity and Inflammation*, 10 Nature Revs. Immunology 301, 301 (2010).

Some of these problems can be overcome by genetic engineering of the antibody produced from the mouse hybridoma. In the 1980s, scientists developed recombinant techniques to create "chimeric" antibodies combining the variable regions of a mouse monoclonal antibody with the constant regions of a human antibody. *See* Chan & Carter, 10 Nature Revs. Immunology at 301; *Recombinant DNA* 464 & fig.23-8. A later strategy, called "humanization," relied on other techniques, such as combining virtually an entire human antibody with only the highly variable sub-regions *within* the variable region of the mouse monoclonal antibody. *See id.* at 464-465; *see also* Murphy 134-135 (explanation and diagrams of "hypervariable" regions within variable region).

Humanized and chimeric antibodies have both enjoyed significant clinical success. For example, Genentech's cancer therapeutic Herceptin® is a humanized monoclonal antibody. *See* Herceptin® (trastuzumab) Prescribing Information 20 (2010). Herceptin® works by binding to a protein found in large amounts on the surface of a particular type of aggressive breast cancer, blocking signals that make the cancer more aggressive, and signaling the body's immune system to destroy the cancerous cells. In clinical trials, it has been shown to extend overall survival for patients with metastatic

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Medical Systems' PATHWAY™ Her 2, at 1 (2000) (mouse monoclonal antibody for use as companion diagnostic to Herceptin®).

breast cancer and, for early-stage cancer, to decrease significantly the chances of the cancer recurring after surgery. *Id.* at 22-29. More than 1.2 million patients have now benefited from this invention.

Herceptin® is just one illustration of the range of therapeutic successes for chimeric and humanized monoclonal antibodies. *See also, e.g.*, Rituxan® (rituximab) Prescribing Information 20 (2012) (chimeric antibody approved to treat rheumatoid arthritis and non-Hodgkins lymphoma); Chan & Carter, 10 Nature Revs. Immunology at 302 tbl.1 (list of monoclonal antibodies in development or already approved for autoimmunity and inflammation diseases). Nevertheless, both humanized and chimeric antibodies retain elements of mouse proteins and can sometimes be recognized by the human immune system as foreign. *Id.* at 301; *Recombinant DNA* 464.

2. The future of monoclonal antibodies is fully "human" antibodies: antibodies constructed in a laboratory with recombinant DNA technologies to be indistinguishable from antibodies produced by the human immune system.[3] The two leading techniques for producing such antibodies—phage display and transgenic mouse antibody production—could both be imperiled by a broad ruling in this case.

Phage display. The first technique relies on an ingenious modification of bacteriophages. "Bacterio-

[3] "Human" antibodies is a perhaps misleading term used widely in the literature to refer to these genetically engineered proteins. *E.g.*, Chan & Carter, 10 Nature Revs. Immunology at 301. These antibodies are "human" in the sense that they no longer rely on or derive from mouse proteins. As will become clear, they are not "human" in the sense of being found in and taken from human beings. They are a product of laboratory engineering.

phages, commonly called phages, are viruses that infect bacteria." Drlica 108. In phage display, the DNA required to express a fragment of a human antibody is fused to the DNA that encodes the phage's protein coating, which causes the phage to express the antibody fragment on its own surface. Murphy 731-732. So, for example, phages can be made to display the variable region of a human antibody. Because the variable region is what binds to a target antigen, the phage itself now binds to the target antigen.

To locate an antibody that binds to a specific antigen, researchers can engineer entire libraries of phages that express different antibody fragments, expose the libraries to the antigen, and experimentally sort for the phages that bind well to the antigen. In the search for new therapeutic antibodies, researchers initially built phage libraries by cloning DNA molecules coding for antibody variable regions and then randomly recombining those molecules and fusing them into phages. *E.g.*, Murphy 733 fig.A.16; *see also* Hoogenboom *et al.*, *Antibody Phage Display Technology and Its Applications*, 4 Immunotech. 1, 5-6 (1998). Next-generation phage display libraries rely on more elegant methods. Now, scientists are building synthetic libraries, which have "designed diversities introduced with synthetic DNA." Lee *et al.*, *High-Affinity Human Antibodies from Phage-Displayed Synthetic Fab Libraries with a Single Scaffold Framework*, 340 J. Molecular Biology 1073, 1074 (2004). For example, Genentech scientists have successfully built a library consisting of phages displaying an antibody fragment with a single "scaffold" or "framework"—portions of the antibody molecule, chosen for stability, that all the phages in the library express in common—combined with carefully designed sequence variations only in the hypervariable regions

most involved in antigen binding. *See id.* at 1074; *see also* Bostrom & Fuh, *Design and Construction of Synthetic Phage-Displayed Fab Libraries*, *in Antibody Phage Display* 17, 20 (2d ed. 2009) (protocols for choosing framework and generating desired variability). The result of using phage display is a genetically engineered composite antibody sourced from human or human-like DNA, but stitched together in the laboratory. Synthetic phage display libraries are among the most promising current approaches to the search for novel "human" antibodies.

Transgenic mice. An alternative current approach relies on fusing human DNA into the DNA of mice, such that the so-called transgenic mice themselves are capable of producing "human" antibodies. Lonberg, *Fully Human Antibodies From Transgenic Mouse and Phage Display Platforms*, 20 Current Op. Immunology 450, 451 (2008); *see also Recombinant DNA* 255-270 (overview of transgenes). When the mice are immunized with antigens to stimulate an immune response, the variable regions of the antibodies they produce appear to be indistinguishable from the variable regions of antibodies produced by human beings. Lonberg, 20 Current Op. Immunology at 451. The clinical hope is that these antibodies will require less "humanization" than has been required in the past for monoclonal antibodies produced by mouse hybridomas.

3. The current promise of monoclonal antibodies could be imperiled by an overbroad ruling in this case. There is an attenuated sense in which every monoclonal antibody derived from a mouse hybridoma could be characterized as a mere isolated product of nature because it has the same amino acid sequence as the antibody produced by an immunized mouse. This would be a mistake, not the least because the initial immuniza-

tion involved human intervention, not merely natural processes. But this is the type of argument that patent owners could be subject to should the Court adopt a broad version of petitioner's position.

Monoclonal antibodies from phage display or transgenic mice are also not immune from risk. The purpose of these techniques is to isolate DNA molecules that can be used to express fully "human" antibodies—antibodies genetically engineered from the same building blocks used in the human immune system to produce a diverse antibody repertoire. The purpose of genetically engineering antibodies this way is to produce recombinant proteins that will not be attacked as foreign pathogens when introduced into a human patient. But it is at least theoretically possible that an antibody engineered in a laboratory from the same building blocks as used in nature has occurred or may occur at some point in time somewhere in someone's immune system as a result of the body's natural mechanisms for producing an enormous variety of antibodies. Of course, it would be a mistake to regard the genetically engineered antibody as a product of nature merely because a natural analogue might serendipitously occur.[4]

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[4] Petitioner in this very case has relied on ephemeral occurrences of what he claims is "isolation" of genomic DNA—like fragments in maternal plasma (Br. 10 & n.2)—as a reason to find the patents in suit to be drawn to ineligible naturally occurring substances. If petitioner's broad rule prevails, future parties will have a similar incentive to search for or speculate about fleeting natural analogues to a patented synthetic molecule. The fact that any such analogues were unknown or undiscovered at the time of the invention might not be a defense because unlike other doctrines, such as novelty and obviousness, 35 U.S.C. §§ 102, 103, the issue of patentable subject matter under § 101 is not expressly tied to information available before the patent is filed.

But a broad product of nature exception would invite such arguments.

C. Isolated DNA Molecules Are Used In Diagnostic Applications That Would Also Be Jeopardized By A Broad Ruling

DNA-based diagnostic tests are a third example of the innovations potentially at risk if petitioner's broad rule were adopted. Patent eligibility, and the incentive for disclosure that it creates, is especially important for these technologies because the process of obtaining FDA approval for their use as *in vitro* diagnostic devices, 21 U.S.C. § 321(h), is expensive. *See* Ernst & Young, *Beyond Borders: Global Biotechnology Report 2008*, at 70 (2008) (roundtable discussion). Tests developed by laboratories for exclusively "in-house" use are subject to far less stringent regulation than FDA-approved *in vitro* devices.[5] If the key DNA molecule used as a primer or probe for diagnosis cannot be protected by a patent, there will be significant financial pressure to maintain that information as a trade secret and to forgo seeking FDA approval.

1. Amici's tests for the Hepatitis C virus provide a clear example of patent protection paving the way for disclosure, investment in clinical trials, and FDA approval. These tests rely on isolated DNA molecules to serve as the primer for PCR to amplify a portion of the genetic material of Hepatitis C in a sample, if the virus

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[5] Laboratory-developed tests have traditionally not been regulated by the FDA and are instead regulated only indirectly by the Centers for Medicare and Medicaid Services under the provisions of the Clinical Laboratory Improvement Amendments of 1988 (CLIA), Pub. L. No. 100-578, 102 Stat. 2903. CLIA does not require laboratories to establish the clinical validity of the tests.

is present in the sample. *See, e.g.*, COBAS® AmpliScreen HCV Test, version 2.0 Package Insert 1-2 (2007); *see also supra* p. 8 (explaining use of primers for PCR). Isolated DNA molecules also serve as the probes to determine whether the PCR-amplified sample in fact contains the genetic material of the Hepatitis C virus.

After their invention by amici, the isolated DNA molecules used as probes and primers for this diagnostic testing were disclosed in a patent application along with their specific nucleotide sequences. *See* U.S. Patent No. 5,527,669 col. 47, ll. 35-63 (probe claims); *id.* col. 49, ll. 21-45 (primer claims). Those sequences were selected by the inventors so that the probes and primers would hybridize with specific portions of the genetic material of Hepatitis C that are well conserved in various iterations of the virus. *See id.* cols. 9-10. Once the sequence was identified, the primers and probes themselves could be produced by several methods, including direct chemical synthesis. *Id.* col. 6, ll. 44-57. Before these inventions, PCR-based screening for Hepatitis C relied on less accurate probes and primers that had to be applied in multiple steps, introducing sources of possible contamination or error into the diagnostic process. *Id.* cols. 2-3.

Now, after clinical testing, the FDA has approved amici's commercial applications of these patented inventions for both diagnosing Hepatitis C in individual patients and screening donated blood for the virus. *See* COBAS® AmpliScreen Package Insert 15; Summary of Safety and Effectiveness Data: COBAS Amplicor™ HCV Test, v2.0, at 14-19 (2001).

Patent protection for the isolated DNA molecules used as primers or probes has not preempted further diagnostic innovation; several other competitors have

been spurred to invent and commercialize other probes and primers to diagnose the virus. *See* Ghany *et al.*, *Diagnosis, Management, and Treatment of Hepatitis C*, 49 Hepatology 1335, 1337-1338 (2009) (listing FDA-approved assays). There are multiple ways to approach the problem, and the patent system has encouraged rather than impeded these advances.

2. Patent-protected DNA molecules also play an important role in the development and clinical validation of companion diagnostic tests. For example, Genentech's Herceptin® therapeutic is indicated only for a particular type of breast cancer characterized by an abundance of receptors for human epidermal growth factor-2 (HER-2). This type of cancer can be identified by DNA-based diagnostic testing for the gene that expresses the HER-2 protein. Ross *et al.*, *The HER-2 Receptor and Breast Cancer*, 14 Oncologist 320, 321-322 (2009). The first such test to receive pre-market approval from the FDA relies on exposing a tissue sample to a fluorescent DNA probe synthetically constructed to hybridize with a stretch of the gene expressing HER-2. *See* Summary of Safety and Effectiveness Data: Oncor® INFORM™ HER-2/neu Gene Detection System 1-2 (1997) (subsequently acquired by Ventana Medical Systems). If the probe indicates that the gene is amplified and thus that HER-2 is overexpressed, the sample likely contains "HER-2 positive" cancer, for which Herceptin® is indicated.

The isolated DNA molecule used for this diagnostic probing was itself disclosed in a patent application. *See* U.S. Patent No. 5,985,553 col. 35, ll. 10-31. As with Hepatitis C diagnostic probes and primers, the patenting of this invention has not impeded further diagnostic innovation by competitors. There are now nine other FDA-approved companion diagnostic tests for Her-

ceptin®, including several other DNA-based *in situ* hybridization tests. *See* FDA, *In Vitro Companion Diagnostic Devices*, http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm (updated Nov. 21, 2012). Physicians and patients now have their choice of several clinically validated tests, spurred by the patenting and public disclosure of the first test.

3. A broad ruling that isolated DNA is not a patent-eligible composition of matter would chill this sort of diagnostic innovation and disclosure. If FDA approval is not required for these diagnostic devices, and if there is no commercial incentive to disclose the probe or primer in a patent application, companies are much more likely to opt to keep these probes and primers as undisclosed trade secrets. The result would be less knowledge in the public domain, not more.

* * *

Amici do not mean to say that there are no distinctions between the inventions just described and the patent claims at issue in this case. But as these examples illustrate, the line between natural and man-made compositions of matter is fluid.

The examples also show that when someone invents an isolated compound with some analogue in nature, it is often inaccurate to say that the compound was isolated *from* nature because, in fact, it was synthesized in a lab. Indeed, the very point is that the compound typically cannot be put to practical use as it exists in nature, and the creation of a human-made, isolated form of the compound opens up a range of new uses. A ruling for petitioner would, at best, create significant uncertainty in the biotechnology industry and,

at worst, would sweep far beyond anything the Court may have intended.

CONCLUSION

For the foregoing reasons, this Court should affirm the judgment of the Federal Circuit.

Respectfully submitted.

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