SYMPOSIUM ON BIOINFORMATICS AND INTELLECTUAL PROPERTY LAW

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MOLECULES VS. INFORMATION: SHOULD PATENTS PROTECT BOTH?

PROFESSOR COHEN:

This panel is "Molecules vs. Information: Should Patents Protect Both?" I think you know that from your program, so I will tell you about the speakers, who I am delighted to introduce. We have with us Rebecca Eisenberg who comes from the University of Michigan Law School. You probably all know her writing, so she self-introduces through her work. But I will say just that she teaches in patents, copyrights and trademarks. She is also on the Working Group of what we call ELSI – the Ethical, Legal and Social Implications of the Human Genome Project, funded and sponsored by the Department of Energy and National Institutes of Health, and that is a very exciting thing to do. Dr. Andrew Marks will follow Professor Eisenberg. He comes to us as Chief Patent Counsel of Vertex Pharmaceuticals, which is a very, very happening place. So I am excited to hear him this morning, as I am sure you will be. Our third speaker is our very own Professor George Annas, of whom we have permanent custody, since he is both here at the Boston University School of Law and also at the School of Public Health. The last time I counted, he was the author of four books, but he can correct me if I left anything off the list. And he has also recently been the chair of the ABA Committee on Medical Communication, Science and Technology. So I want to welcome all three of our speakers here. They will also take your questions after they finish speaking.

PROFESSOR EISENBERG:

Thank you very much, Jane, for that lovely introduction. This particular presentation grew out of a persistent question that people have been distracting me with for years whenever I talk about anything related to biotechnology patents, and that is: How can you patent DNA sequences? I get this question from everyone. I get this question from lawyers, scientists, business people,

congressional staffers, reporters, social acquaintances. The question has basically been pretty annoying to me, partly because it is generally quite tangential and prior to what I am trying to talk about, and it feels like a distraction.

It feels like I cannot budge my audience from square one, and this is particularly frustrating to me because patenting DNA is not, by any means, a new practice. It has been going on for years, and it was not initially controversial at all. By the time it became controversial, I was really quite ready to take it for granted and move on to the next set of questions. Gene patenting began with little fanfare and little controversy in contrast to other expansions of the patent system that have been very controversial right away. There was lots of public policy about the allowance of patents on microorganisms, for example, and on animals, computer software, business methods. The issuance of patents in each of these areas promptly provoked a great deal of opposition, media commentary, congressional hearings, proposals for moratoria, etc. In recent years, we have been seeing similar kinds of attention focused on the practice of patenting DNA sequences, but nothing like that happened when people first started patenting genes in the early days of the biotechnology industry, some twenty years ago. And so the practice was really quite well established before it provoked any significant public controversy.

The first significant controversy over patenting DNA sequences, which is easy for me to mark because it corresponds to my invitations to speak at various events, was the controversy in the early 1990s over patent applications filed by NIH on the first few thousand gene fragments or expressed sequence tags (ESTs) coming out of the laboratory of Dr. J. Craig Venter when he was still at NIH. And so it was really sort of the dawn of this high throughput DNA sequencing that you start to see controversy focused on the patenting of genes. And I think that is significant.

More recently, we have been hearing lots of stories about patenting of genes in media coverage of the race between the publicly-funded Human Genome Project and Celera. By this point, though, questions about how can you patent DNA seemed sort of quaint and out-of-touch. Nonetheless, the fact that I kept getting this question, over and over again, from different people in different walks of life made quite an impression on me over time. It suggests, even though I was really sick of it and did not want to think about it and did not want to focus on it, that at some level, the patenting of DNA sequences violates some powerful popular intuitions about the proper boundaries of the patent system. And that was, perhaps, worth thinking about.

So why was the patenting of genes so uncontroversial at first? And why has it become so controversial in recent years, in the past decade or so? Well, I think in the early days, patenting genes looked like patenting drugs. Now it looks more like patenting scientific information. We have a clear story – although some people like to contest it, it is about as clear a case for patent protection that you are going to find – about why we want to issue patents on drugs. It is a lot less clear why we might want to issue patents on scientific information. The first generation of DNA sequence patents was directed

toward genes encoding particular proteins of interest: insulin and erythropoietin, a growth hormone. The patents typically claimed isolated and purified DNA sequences encoding the proteins of interest, a recombinant vector that included the DNA sequence, a transformed host cell that included the vector. These claims all covered tangible materials that were used to make pharmaceutical products. A patent on the recombinant starting materials gave its owner an effective commercial monopoly on the recombinant proteins encoded by the DNA sequences. And so the effect was really similar to a patent on a drug, even though the thing that was patented was the recombinant materials used in production of the protein rather than the end product, itself.

The Patent Trademark Office (PTO) and the courts treated these patents the same way that they treated patents on new chemical compounds. The analogy may never have been perfect, but it worked, in the sense that it provided commercially effective patent protection that motivated investments in the development of new products. That mattered because the biopharmaceutical industry is one in which the patent system does real work. That is not so in every industry. I do not believe that the patent system is magic or that it should extend to everything under the sun that is produced by man. In some industries, firms report that patents are not really all that important to their investment decisions, that other things are more important in determining the profitability of innovations such as being first-to-market, that patents are something that they just view as trading currency to get other patent holders to leave you alone, etc.

That is not what you hear in the pharmaceutical industry. There is a lot of empirical evidence that this is a field in which patents really do matter, at least to the people who are making decisions about investments in research and development. Why? Well, the standard account from the pharmaceutical industry is that new drugs cost a fortune to develop. There are many costly failures for each successful product. If generic firms could step in and compete and drive down profits on the successful products without having to incur all the development costs on the full range of successful and unsuccessful candidates, they would drive the research firms out of business. And, so, early biotechnology firms saw themselves as developers of therapeutic protein products. They thought they were basically high-tech pharmaceutical firms, and they, too, wanted patents that would prevent free riders from destroying their profits.

And so patents on genes were their ticket. They promised to provide that protection. They allowed the firms to raise capital, to get pharmaceutical companies to collaborate with them. Some biotechnology firms are still following this model, looking to identify new therapeutic proteins and bring them to market, either on their own or with pharmaceutical firm partners. But the biotechnology industry and the genomics industry have become much more diverse in their research and business strategies, and the role of DNA sequences in these strategies has also become a lot more complex. Some of the DNA sequences that are coming out of recent sequencing efforts, undoubtedly, will encode therapeutic proteins. But that is not what most of it is doing. Most

of the DNA sequence information that is being identified today will have its primary value as an information resource for future research. Some of that research may ultimately lead to the development of products that are far removed from the genomic information that helped researchers on the path to discovery, and it is not obvious how to use patents on genes to capture the value that genomic information contributes to these discoveries.

Different perspectives of different participants in biopharmaceutical research lead to different outlooks on the role of patents. The pharmaceutical industry is generally a big supporter of the patent system. It is sort of like the National Rifle Association of the patent system, and it worried that any slight incursion on anyone's patent rights would be the first step down that slippery slope towards compulsory licensing of all drug patents and that that would be the end of the party. But the industry is not so sure about some of these genomics patents. You do not see those in the industry out there lobbying against these patents, but what you do see them doing is actually investing in research to put genomic information into the public domain, which is interesting, before the genomics firms can claim it as their intellectual property. We saw this is in the early '90s with the Merck Genome Initiative in response to private sector EST sequencing. More recently, we have seen it with the SNP Consortium,[1] trying to get the information out there, in the public domain, before the genomics firms patent it.

I think this is an important reality check on the impact of the patent system. It does not just give out wealth and create value. It also takes wealth away. Usually, though, the wealth that is taken away by patents comes from disaggregated consumers of end products. The argument for patents is that otherwise, consumers would never have had the benefit of that product. And that is a powerful argument. Sometimes, it is true; sometimes, it is not. Usually, though, the consumers are not well enough organized to dispute the claim. In the biopharmaceutical industry, the wealth that is taken away by patents sometimes comes out of the pockets of disorganized consumers. That is the effect, for example, of patents on drugs, although a lot of those consumers are getting better organized, and the prospect of Medicare drug coverage particularly threatens to aggregate the interests of some of these consumers by consolidating them into a single, powerful player which could significantly alter the market for drugs.

If you set drug patents to one side, however, and focus on patents on the many discoveries that are made on the road to drug development, discoveries that are primarily valuable as inputs into future research, the wealth that these patents promise their owners has to come out of the pockets of future innovators. And some of these future innovators are quite savvy and quite well organized, and their pockets are closely guarded. Some of these upstream inventions or pre-end-product inventions are feeding into a course of cumulative innovation, and the trade-off that is presented by offering patent

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[1] *See* SNP CONSORTIUM LTD., *at* http://snp.cshl.org (last visited Jan. 15, 2002).

protection for these inventions is not as simple as how to balance the consumers interest in low prices for existing products versus incentives for further innovation. When talking about these pre-market innovations, both the buyers and sellers are involved in the process of innovation, and the trade-off is between promoting or rewarding early-stage innovation versus promoting or rewarding end-product development.

From the perspective of the pharmaceutical industry, the biotechnology companies and universities that hold patents on all of these inputs to future research in product development look like so many tax collectors diluting their anticipated profits on potential new products. These end-product developers are well organized politically. They have a clear business model and a clear story about the role of patents in that business model. The biotechnology industry is also organized, but less clear on their business models and on the role of patents in those business models. They patent what they can, and they hope that some of those patents will some day help them make a profit, maybe by allowing them to capture a share of the profits on future drugs. So one set of issues raised by patenting DNA sequences is the problem of how to allocate intellectual property claims and, therefore, how to allocate pay-offs along the complex course of cumulative innovation in biomedical research.

Now I, myself, am passionately interested in this set of issues, but I do not think it explains why, for example, friends of my parents ask me, over and over again, how can you patent DNA? I think the widespread puzzlement with the patentability of DNA has less to do with the interests involved in this issue that is of paramount concern to me than it has to do with a couple of other intuitions about the proper boundaries of the patent system. The first of these intuitions, and the easiest one to address with a standard lesson in patent law, is the intuition that one cannot patent products of Nature. The products-of-Nature intuition was perhaps most famously expressed by Justice Douglas of the U.S. Supreme Court, fifty years ago, in the case of *Funk Brothers Seed Company vs. Kalo Inoculant*.[2] There, the Court held invalid a patent claim on a mixed culture of naturally occurring microorganisms that enable plants to fix nitrogen from the environment. Justice Douglas wrote:

> Patents cannot issue for the discovery of the phenomena of Nature. The qualities of these bacteria, like the heat of the sun, electricity or the qualities of metals, are part of the storehouse of knowledge of all men. They are manifestations of laws of Nature, free to all men and reserved exclusively to none. He who discovers a hitherto, unknown phenomenon of Nature has no claim to a monopoly of it which the law recognizes. If there is to be invention from such a discovery, it must come from the application of the law of Nature to a new and useful end.[3]

Now, the standard patent lawyer's response to this products-of-Nature intuition is to treat it as a technical claims drafting problem. The prohibition

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[2] 333 U.S. 127 (1948).

[3] *See id.* at 130.

against patenting products of Nature only prevents patenting of DNA sequences in naturally occurring forms that involve no human intervention for derivation. You cannot get a patent on a DNA sequence that would be infringed, in other words, by someone who goes off to live in a state of Nature on Walden Pond, whose DNA goes on doing its own thing as it has been doing for generations for his ancestors in Nature. But you can get a patent on DNA sequences in forms that only exist through the intervention of modern human technology. So you see, patents issue on isolated and purified DNA sequences that are separate from the chromosomes in which they reside in Nature or on DNA sequences that have been created by splicing with recombinant vectors or introduction by other recombinant means and do not exist on Walden Pond.

All of this is consistent with the long-standing practice. Even prior to the advent of biotechnology and genomics, patents issued on isolated and purified products that exist in Nature only in an impure state when, through human intervention, such products have been made available in a form that meets some human purpose, as with purified adrenaline. There is an old case involving purified adrenaline, purified Vitamin B12. I think this is actually a very satisfying response. This is not simply a patent lawyer's trick. It actually responds to the intuition that patents should only issue for human inventions. You do not want to allow patents to issue that take away from the public things that they were previously using, such as the DNA that resides in our cells, but it is quite another matter to allow patents to issue on new human interventions that serve human purposes. So if you want to mind your own business on Walden Pond, fine. You should not have to worry about patent infringement liability. On the other hand, if you want to get shots of recombinant insulin, well, then maybe, in fairness, you ought to pay a premium to the inventors who made these technological interventions possible.

There is a second intuition about why DNA sequences should not be patentable that is harder to respond to, however. That is the intuition that you cannot patent information, as such, that the subject matter of patents is limited to material products and processes and does not extend to knowledge and information about the world. This intuition is also reflected in traditional patent doctrine, although it is getting harder to find it. Arguably, it is implicit in the statutory categories of patent-eligible subject matter, which extends to any new and useful process, machine, manufacture or composition of matter, all of which seem to relate to human interventions in the physical world. The same intuition, I think, is reflected in previously apparent judicial rules about what you cannot patent that seem to be vanishing from view in more recent cases. Still, there are a lot of old cases saying you cannot patent mathematical algorithms, that you cannot patent printed matter, business methods, or mental steps. In a series of decisions that have opened up the patent system to protection of computer-implemented inventions, however, the courts have minimized the importance of these limitations on what may be patented, if not entirely discredited them.

At the least, you can still find the intuition in the older opinions, and it lingers on even in some of these more recent opinions in the form of

continuing emphasis on tangibility as a requirement for patent eligibility. The Federal Circuit still uses that word "tangibility," over and over again, even when they are referring to things like electricity. But the meaning of the term seems to have shifted, even as the articulation stays the same. A "tangible" now seems to mean "useful," rather than something material. The intuition that you cannot patent information, I think, is also implicit in standard accounts of the patent bargain in which inventors receive patents in exchange for full disclosure of information about their inventions, and the information becomes freely available as soon as the patent issues, or eighteen months after filing in some cases. The patent gives the inventor a right to exclude others from using tangible embodiments of the invention but it does not prevent use of the underlying information. In fact, patent law disables the inventor from excluding others from access to the underlying information by requiring its free disclosure with no restrictions.

Finally, I think this cannot-patent-information intuition is consistent with the picture of the world, maybe a quaint picture of the world, in which patents are for applied technology, not for basic science. In this picture of the world, which also finds expression in judicial decisions from an earlier era, you could do a Lexis search on $E = mc^2$. If you want to find it, you will pull up some interesting dicta that says that you cannot get a patent on a fundamental scientific breakthrough that tells us how the world works, but you can patent a specific technological application that is enabled by that breakthrough. So you can get a patent on a nuclear reactor, for example but not on the insight that $E = mc^2$.

Now what does all of this have to do with DNA sequences? In patenting DNA sequences? Well, I used to think not much. My standard answer, in accordance with the decisions of the courts and the practice of the PTO, was that DNA sequences are molecules, not information. So the intuition that you cannot patent information, whether or not it was true, was beside the point. A patent on a DNA sequence gives you the right to exclude others from making, using, selling or importing the patented molecule, not the information about the structure of that molecule or the information about the structure of the proteins that is encoded in that molecule. But, wait! You know, of course, the truth is that DNA sequences are both molecules *and* information. They are informational molecules, and it is not clear where to put these informational molecules in a taxonomy that distinguishes tangible embodiments from intangible information. One can think of DNA as a tangible storage medium for information, for information about the structure of proteins. Cells read the information stored in DNA to make the proteins that they use to survive in their environment and to re-produce, and people can read the information stored in DNA not only to learn how to make proteins, but to figure out what cells are doing with the information or to learn about the history of evolution or to try to answer any number of other scientific questions.

Advances in genomics are yielding a deluge of DNA sequence information that has far out-paced the identification of biological functions associated with these sequences, as we were hearing earlier this morning. As more and more

DNA sequences are identified, the informational value of the sequences – by which I mean the value of simply knowing what the sequence is – is becoming more significant relative to the material value of having access to a molecule that embodies that information. That is, the value of making and using the DNA molecule as a template for protein production. That shift in perceptions of where the value lies is leading to new intellectual property strategies for appropriating that value. The patent system has not come close to digesting this shift. I think forward-looking patent lawyers are digesting this shift, but the patent office has not really grappled with it yet. So far as I know, and I heard confirmation of this morning, the patents that have issued so far on DNA sequences have all been directed to tangible molecules, constructs, cells, and organisms that incorporate these tangible molecules. There is always informational value to knowing what the sequence was, and this part of the value of the discovery in the traditional DNA sequence patent on molecules simply spills over to the public domain through publication of the patent disclosure. You might not be able to make or use the tangible molecule, once the gene is patented, but you could learn and know its sequence without infringing the patent.

In the early days, when you were talking about patenting the insulin gene or the erythropoietin gene, the informational value was, or at least seemed, trivial in comparison to the commercial value of the tangible DNA molecule as a template for protein production. Typically, the patent claimants already knew a lot about the proteins encoded by the cloned DNA sequences, such as insulin, before they went to the trouble of identifying and claiming the sequences themselves. The primary value of having the DNA sequence in this earlier era was not knowing the sequence but being able to use the tangible molecule as the guts of a recombinant production facility. People are still filing patent claims that follow this model, although often with far less idea of what it is that the protein encoded by the DNA sequence does and whether there is any market for it as a therapeutic product. But many DNA sequences that are being identified today do not, or probably do not, encode therapeutic proteins like insulin or erythropoietin that are going to be sold as end products for use in patients. Some of them may encode proteins that cells make and use but that do not correspond to any obvious pharmaceutical products for delivery to patients. They may encode receptors that serve as drug targets or they may encode proteins whose function is not understood. Or they may play some regulatory role in the cell that does not involve translation into protein but that is still important to understand in the course of unraveling a disease pathway. Or they may be simply junk DNA, with no apparent function at all within the cell that might, nonetheless, be the site of polymorphisms, some of these SNPS that we have been hearing about, that make them useful for possible diagnostic purposes.

Many DNA sequences being identified today come from organisms that diverged from the path of human evolution at some remote point in time, unlikely to encode human therapeutic proteins. They are still interesting and valuable discoveries, even commercially interesting and valuable discoveries.

Sometimes, these DNA sequences, or portions of them, may be immediately valuable as tangible molecules. For example, the DNA vaccine against infection by a pathogen or a diagnostic test that detects the presence of the pathogen's DNA could be an immediately commercially useful, tangible DNA sequence. Some sequences, or parts thereof may encode human therapeutic proteins, and we certainly want to identify which parts of the DNA sequences encode those proteins. Those parts of the sequence will plainly be valuable as tangible molecules, but not all of them are going to be of that sort, and it will take a lot of time to make those determinations.

When an organism's genome is first sequenced, you may not be able to pick out the nuggets of tangible material value. The most important value of knowing the complete DNA sequences of organisms that are coming out of the machines these days is that it gives you a lot of information to analyze. Analyzing the information might allow you to tell, or at least guess, something about the functions of portions of the genome by comparing it to sequences from other organisms that you know more about. You might be able to learn more by taking this information back to the laboratory, altering the sequence, deleting the sequence, creating some sort of a knock-out or something of that sort and seeing what happens in the laboratory. You go back and forth between examining the information in human readable form on your computer and then getting the cells to query the information in cell readable form in the wet lab. In other words, knowing the DNA sequence of an organism gives you an information base that facilitates future discoveries; and that is often, at least initially, more significant than the tangible value of having access to the gene.

Well, what sort of intellectual property protection is appropriate for this sort of discovery? It is not clear that patent claims on tangible molecules are the way to go, as a matter of strategy. From the perspective of someone that identifies the DNA sequence and does not yet know what to do with it, patent claims on tangible molecules are problematic for a variety of reasons. First of all, you might not know what to claim. Initially, you will not know which portions of the sequence are likely to be valuable or likely to encode important products. You can guess, maybe, but you might guess wrong. You might try to cover all possibilities with broad claim language such as "I claim any portion of the DNA sequence disclosed above, at least x-number of base pairs in length" or something like that. But you could easily claim too much, thereby invalidating your claim by running into prior art, or too little, failing to preserve a claim that covers portions of the sequence that ultimately matter. So one problem is not knowing what or how much to claim.

Second, there may be doctrinal obstacles to getting patent protection through the discovery of DNA sequences when you do not know the function. You might have difficulty establishing a patentable utility for your sequence if you do not yet know what it does. Third, if the sequence is similar to previously-disclosed sequences with a known function, that might help you with your utility problem, but then you might have a prior art problem that makes your invention, at least, prima facie obvious. Fourth, and I think most important, a patent on the tangible molecule may offer inadequate protection for the

informational value of the sequence, which may be its most significant value. Once the patent issues, the information about the DNA sequence becomes freely available to the public, and a patent on the molecule will give you no right to stop someone else from reading and using the information.

So what is the alternative? Well, one strategy is to restrict access to databases of DNA sequence information. This is the predominant business model, really, for DNA sequence databases. The strategy works for Human Genome Sciences, Incyte, Celera, and undoubtedly, many others. These firms sequence DNA, create a database, and offer licensed access to those databases under the terms of subscription agreements. This has brought in a lot of money and has motivated a lot of investment in sequencing. It has also been successful in making DNA sequence information available to a lot of researchers working in large pharmaceutical firms. But it depends on secrecy. It forecloses access by users who do not have a lot of money, and it is subject to a loss of exclusivity through duplication of effort by competitors.

A new strategy that is working its way through the system tries to use patents to capture the informational value of DNA sequences, that is, to claim the sequence stored in a computer-readable medium. The first place I saw this strategy was in a published application under the Patent Cooperation Treaty filed by the Human Genome Sciences entitled, "Nucleotide Sequence of the *Haemophilus influenza*, RD Genome," fragments thereof and uses thereof, which we were hearing about earlier this morning. *Haemophilus influenza* is a bacterium that causes ear infections, and it was one of the first organisms for which the entire genome was completely sequenced.

The owners of the sequencing faced this problem of, "What do we claim?" The patent application sets forth the complete nucleotide sequence of the organism, identified as Sequence ID Number One. It goes on for seventy pages of nothing but the letters, A, T, C, and G, and it then concludes, as they all do, with a series of claims. Claim number one reads: "Computer-readable medium. Having recorded thereon, the nucleotide sequence depicted in Sequence ID Number One, a representative fragment thereof or a nucleotide sequence, at least 99.9 percent identical to the nucleotide sequence depicted in Sequence ID Number One." Now this is only a patent application, not an issued patent. This is item number one on the Human Genome Sciences' wish list, basically, for claim language pertaining to the *Haemophilus influenza* genome. It remains to be seen whether they are going to get this claim in the U.S. or anywhere else. But let me tell you, it is not obvious why not.

In a series of decisions that I mentioned earlier, the Federal Circuit has swept away previously apparent limitations on computer-implemented inventions, arguably opening the door to patent claims on information stored in computer-readable medium. The PTO issued 1996 guidelines on the patentability of computer-implemented inventions. These guidelines looked quite expansive when they first came out. At this point, they look more restrictive than the decisions of the Federal Circuit. These old PTO guidelines exclude from protection descriptive material that is not functionally related to the computer-readable storage medium but is merely carried by the medium.

The example that the PTO gives, which they drew from the dissenting opinion in one of these Federal Circuit cases, was music stored in a compact disk. They wanted to make it clear that one could not obtain protection – even though one may patent computer software – for the computer-implemented methods. That is, one cannot get a patent on music stored in a compact disk. Arguably, that is exactly what a DNA sequence for an organism stored in a computer-readable medium is: data, basically, stored in a computer-readable medium. I do not want to open up the whole can of worms of these recent decisions on the patentability of computer-implemented inventions, but I think it is entirely possible that if the PTO invokes their own guidelines and rejects these claims, the Federal Circuit could reverse on appeal. But it is not at all clear.

So how should we think about this? Is this an appropriate subject matter for a patent claim? What good is it? What harm can it do? Well, I do not think it is an appropriate subject matter for a patent claim. I believe that patent claims to DNA sequences stored in computer-readable medium represent a fundamental departure from the traditional patent bargain of exclusionary rights to tangible inventions in exchange for free disclosure of information and should not be allowed. And I begin from the premise that computer-readable medium is the only practical way to perceive and analyze large volumes of DNA sequence information, even something as relatively simple as the genome of *haemophilus influenza*.

Now, admittedly, there are these seventy pages of A's, T's, C's, and G's and a human could read through those. Maybe with scanning technology, even that hard copy is computer-readable medium, but we could tighten up the claim to be sure that we only cover electronic storage medium if that distinction matters. Reading through seventy typed pages of letters is theoretically possible, but it is mind-numbing and relatively unilluminating. As we were hearing earlier in the day, what you want is to be able to pull together and analyze and compare to other sequences, and you really want the information in your computer to do so. The claim to the sequence in computer-readable medium, in effect, gives the patent holder the right to restrict the ability of others to use the information in a computer-readable medium and thus precludes others from perceiving and analyzing the sequence information itself.

This is distinguishable, I think, fundamentally different, from old-fashioned DNA sequence patents that claim only molecules. You can read those old-fashioned patents, learn what the DNA sequence is, type or scan it into your computer, search for similarities to other sequences in databases, all without infringing. By contrast, this HGS claim would allow HGS to capture much, if not all, of the informational value of the discovery, not just its tangible value. This is certainly a departure from the traditional bargain of trading free disclosure of information for exclusionary rights, intangible embodiments. Is it necessarily bad? We have been hearing earlier in the day that information is becoming increasingly important in research, increasingly important commercially, and an increasingly important focus of technology. Maybe the

traditional bargain of free disclosure of information in exchange for exclusionary rights that were limited to tangible molecules does not make sense in this new environment, where the value of the information is large relative to the value of the tangible embodiment.

Perhaps patents that do not allow the inventor to capture the value of the information will motivate investment in DNA sequencing. I think this is a logical possibility, though I am skeptical of this possibility as an empirical matter, given all of the dollars that are going into the DNA sequencing in the public and private sectors and with certainly nothing approaching clarity on the patentability of the information. But it is at least a logical possibility.

A more plausible speculation, I think, in light of the threat to capital investment is that inventors will forego the patent bargain, if they are stuck with the traditional terms of that bargain, and choose instead to exploit their discoveries through restricted access to proprietary databases. So rather than seeing patents, we would be seeing trade secrets.

Once the terms of the bargain are changed to allow patent applicants to capture the informational value, as well as the tangible value, however, it is not clear to me why the public should prefer that DNA sequencers choose patents over secrecy and restricted access. If the patent filings do not involve disclosure of information that others are free to use, the public might be better off withholding patents. This at least, leaves open the possibility that others will make the same invention available either freely or at competitive prices as the information becomes available from multiple sources.

As an empirical matter, in fact, we are seeing a lot of free disclosure of unpatented DNA sequence information into the public domain, much of it coming from the private sector. Some of these private sector benefactors of the public domain are explicitly trying to create prior art that will defeat the patent claims of others. And the willingness of private funds to spend their money that way suggests that there may be a quite high cost to broad exclusionary rights in this area. I prefer the traditional bargain, though, as it ensures that patenting enriches the information base, even as it slows down commercial imitation. This balances the interests of the inventor in recovering the value of his investment against the interest of the larger public in avoiding impediments to future research.

More generally, though, I worry that we may need some kind of intellectual property protection for data. I am really agnostic on that question, but if we do have this need, I worry that patents are the wrong form for that protection to take. They are a very dangerous form of intellectual property rights for information because there are so few safety valves built in to the patent system that constrain the rights of patent holders relative to other models that are out there. For example, unlike copyright law, patent law has no fair use defense. Maureen O'Rourke is here somewhere and has suggested that maybe it should but does not. Patent law has no real research exemption. Patent law has no defense for reverse engineering or for independent creation. Dennis Karjala was saying earlier that none of the proposals for database protection would preclude independent creation. Well, the patent *would* preclude independent

creation of the same information. The most important safety valve that is built into a patent is the disclosure requirement that permits unlicensed use of information about the invention as distinguished from the tangible invention itself.

However, if patents issue in a form that covers the only practical means of perceiving and absorbing and using the information, then the claim itself is effectively defeating that safety valve. In fact, it may be that these claims will simply prove too much. The PTO, itself, maintains a Web site of all issued patents. If they were to issue these patents and put them up on their Web site, would they be infringing by posting the DNA sequence information in computer-readable medium? It is hard to imagine that they would get themselves into that Catch-22. It may be that we have arrived at a point in our information economy where we need some form of intellectual property right that is directed to information itself. It may be that we can no longer afford to assume that investments in the creation of information products will be forthcoming based on an intellectual property system limiting exclusionary rights to tangible things and allowing the value of the information itself to spill over to the general public. If we are at that point, then I think we need to look beyond the patent system for a suitable model. The patent system was designed to meet the needs of a brick-and-mortar world, and it would be foolish to assume that such a system can meet all the needs of the information economy simply by expanding the range of patent-eligible subject matter.

Thank you. (*applause*)

DR. ANDREW MARKS:

Hello. I am Andrew Marks, chief patent counsel at Vertex Pharmaceuticals, which is just on the other side of the river. I have to say that I actually agree with Professor Eisenberg on what I believe was one of her conclusions that information, per se, should not be patentable. That is probably where our agreement is going to end unfortunately. In my ten minutes or maybe a little more, I want to talk about two different issues. First, I want to talk about some patent claims that may, in fact, pass muster under the software guidelines and under the patent statute, as they are without a stretch. For all intents and purposes, they will cover information. I also want to talk a little bit about Professor Eisenberg's contention that the information that comes out of genomics may be more important than the tangible matter.

Starting with the claims that I have handed out, there is a claim which begins "A machine-readable data storage medium . . . ." It represents a claim that Vertex initially filed in the patent office and around the world. The subject matter is not that important, and it is not really that relevant, but the bottom line is just that we solved the crystal structure of calcineurin. What we determined is, essentially, the shape of the binding pocket, which is important for drug design because any drug that you want to develop that would inhibit calcineurin would have to fit into the binding pocket. Thus, it is important to understand what the shape of the binding pocket is, which in this case was

essentially defined by about two dozen amino acids in the protein that interacted to form the pocket when the protein folded. What we were attempting to do was, in fact, claim and protect that information. We were the first in this attempt. This application was filed in mid-'95.

We thought that if we put this information on a disk and ran it through a program on a computer that would convert it into a three-dimensional graphic display, then we could look at the shape of the pocket and model interactions of that shape with other molecules, trying to fit them into the pocket. This would essentially give us an idea of compounds that might ultimately be inhibitors of calcineurin. In attempting to make these claims, we ran into the software guidelines. I was accustomed to filing claims and having them examined by the Chemical Group in the Patent Office, but this one went to the Computer Group, which was helpful and not helpful in some ways because I do not think they understood the invention. They understood, however, that data on a disk was not patentable. Ultimately, after a lot of back-and-forth with the Patent Office, we ended up with a claim that begins "a computer for producing," which is the second claim, and that is in an issued U.S. patent. It is essentially the same, for all intents and purposes, as the original claim, as it covers the same matter. It really just says, "Look, I had this computer. It is programmed with information on the shape, essentially the crystal coordinates of the amino acids, that form the pocket, and when you connect that to a program which converts that to a three-dimensional shape, you actually can see it on a screen."

That is the bottom line. This claim was suggested, to some extent, by the patent examiner. Once it was written in this form, there was absolutely no problem with it. I do not know if Professor Eisenberg's ever seen this sort of intermediate type claim, but the point is that Human Genome Sciences could probably convert their data-on-a-disk claim to the same idea where you just program the sequence into a computer. What are you going to do with that? What do people do with the information? Well, I think Professor Eisenberg is right. One of the things that you do in drug discovery is you basically look at a sequence and you try and find homologous sequences of known function, and you do that through computer searches.

Thus, the claim could read something like, "A computer programmed with DNA sequence information and further programmed with a search engine that searches a database and pulls out proteins homologous to the DNA sequence information, thereby predicting the function of the protein the DNA encodes." The important thing is that this claim, because of the way it is written – and, again, maybe it is just a patent attorney trick – is a claim that, I think, passes muster on all the requirements of patentability. It is an item of manufacture, a computer. Yes, it passes the software bar of non-functional descriptive matter because, in fact, it is not descriptive matter at all. It is actually a physical thing. It is a computer. I hope Professor Eisenberg will say a word or two about her opinions on whether this claim creates the same problems that a data-on-a-disk claim might create.

A further point is that in the real world of drug discovery, ultimately, people

are going to have to use the physical gene or encoded protein. You cannot develop a drug without that. So my point is that patents that Professor Eisenberg agrees are patentable, which cover the physical gene isolated or the encoded protein isolated, cause just as much potential problem in terms of obstructing development of drugs as the information patents.

Allow me, for those of you who are not familiar with the drug discovery field, to quickly give you an idea of how a company like Vertex would use genomic information. Vertex is not a genomic company; we do not do gene mining. That is not our business. Our business is developing drugs to targets. What we believe is the great value of sequencing the genome is that specific drug targets that act in disease pathways will be isolated and identified. In turn, we will be able to create much more specific drugs to target those proteins, in particular, while reducing the side effects of the drugs. In earlier drug development, the problem was that you had a drug that bound to the target, but it also bound to a couple of other proteins and that caused some bad effects. That was problematic. If the bad effects were too serious, the drug never got to the market. I believe that the sequencing of the genome and identification of all the genes in the genome is going to allow the development of much more specific drugs that have fewer and less serious side effects. These drugs will hit targets specifically and, therefore, only inhibit the desired pathway and produce the desired effect.

From the Human Genome Project, which was conducted both in private and public sector, we have just a whole string of A's, C's, G's and T's. A lot of it is garbage. By "garbage" I mean non-coding sequences. The rest – and it turns out to be a much smaller portion than anyone ever thought – actually codes for proteins. What companies like Celera and Incyte do – and I know this is really important because we have a contractual agreement with Incyte and are negotiating one with Celera – is provide information that is not in the public domain and the tools to determine which parts of the sequence are garbage and which are the important coding regions. Once one has identified the coding regions of a sequence, these companies also have the tools to provide some idea of the coded protein's function. What we have done is compare new sequences to known sequences, and based on homology, for example, hypothesize that the new sequence encodes a kinase because it has eighty percent homology to a known kinase sequence, and it has certain key, or signature, features that are really important. That is really the value-added that these companies provide.

I should say as an aside that that information probably has a very limited lifetime in terms of its commercial value because, ultimately, the entire sequence of the genome will be in the public domain. And, ultimately, academics or those who want to put information in the public domain are going to put the tools in the public domain, if they are not there already, to do the same thing that these companies with databases provide for a fee. Celera and Incyte charge multimillion dollars per year to access their databases. More importantly, what they do is try to attach a downstream royalty to any ultimate drugs that are developed because they know that in five years no one is going

to need the database anymore. In ten or twenty years, however, when specific drugs are developed based on genes found in the database, they are going to have their hooks into that for a couple of percentage points. That is their business model, and that is how they hope to make money down the road.

At Vertex, for example, we are very interested in kinases, so we mine the inside database and ask it to spit out all the kinase-like sequences, and then we try to look at kinases that seem interesting and try and figure out what they do. We do that using knock-out mouse technology, proteomics, cell culture, other animal models. Ultimately, the goal is to find a new protein. I know the family to which it belongs from comparisons against the database – it is a kinase – and now, based on these other technologies, I know why it is important. I might know that it plays a role in cancer, for example, and if I can inhibit this kinase, then maybe I have a cancer drug. All that is done without ever making the protein. Now, how do you make the drug?

Well, there are two ways to make the drug, really, and they both end up using the physical material. One way is to solve its crystal structure. It is necessary to make the physical protein material to make the crystals and solve the structure and look at the shape of the binding pocket. Drugs may then be designed to fit in the binding pocket. Some of this can be accomplished on a computer. Ultimately, a computer, even with the most advanced filtering systems and algorithms – and I think Vertex probably has some of the most advanced ones for doing this molecular-modeling – will have an accuracy rate only on the order of thirty to fifty percent in terms of suggesting actual compounds that show efficacy in even simple assays. Of course, there is also the problem that these drugs must also get into the body without breaking down before hitting their targets and have a significant lifetime in the body so that so that they will have their intended effects over period of time. All of these points are necessary in developing a drug to successfully treat a disease. Even after molecular-modeling, ultimately, you create the protein and you screen compounds in physical assays to make these determinations.

The other way of making a drug is to make a lot of the protein for screening. Most drug companies have huge libraries of compounds that they may have purchased or isolated from natural sources. With these compounds they conduct what is called high throughput screening. In this process, a company presents hundreds of thousands of compounds to the target in some assay to figure out if, in fact, the compounds inhibit the target or not. In either case, the physical protein is utilized. The point is that, while in the past, patents on genes and proteins represented proteins that were therapeutic themselves and were the ultimate product, now with the Human Genome Project and all this gene sequencing, the majority of patents on physical genes and proteins are going to represent simply tools that are used in drug development.

The problem, of course, is that the drug that is ultimately produced may not infringe the protein patents when the drug is some small organic molecule and you never have to use the protein again, once you develop the drug. The real problem is not necessarily the distinction between informational patents – whether they should be allowed or not or whether those computer patents

should be allowed or not – the real problem is that even with the patents that we all agree are patentable, that have been patentable for years and years and years – patents on isolated proteins and genes – provide as much of a roadblock in terms of drug development as any of the other types of patents. The patent owners who own those patents want something. They do not just want an up front fee for the two or three years of use in target screening. They want the same thing the database companies want: hooks into the ultimate profit. They want, a couple of percentage points on the ultimate drug that is developed under the "but for" theory. These companies assert that "but for" the isolated protein and the patent on it, which were used in early development, you would never have gotten to the drug.

That is really the problem everyone in the pharmaceutical industry is facing these days. The real question, one which has never been answered and a lot of companies are afraid to ask before the courts, is whether what are termed "reach-through royalties" are valid or not. Where we stand now without any decision or any legislation to the contrary, it is very clear that such royalties are valid. Licensors may certainly reach through and get a percentage point, if they want. The dilemma for drug companies, however, is that it is not just the target patent holder that wants its hooks in your royalties. The company that holds the patent on the assay that you use also wants a cut, as does the company that holds a patent on some other tool that you use, each of which you need to develop the drug but which you never infringe when you sell the drug. Ultimately, these stacking royalties could get to a point where they are so onerous to a drug company that it is not worth it for the drug company to develop the drug given the cut taken from their sales.

That is really what I see as the issue. While I respect Professor Eisenberg's analysis, I think, that to some extent it does not address the real problem. We should recognize the critical issue of informational patents, that there are ways to overcome them on legal grounds, such as asserting potential unpatentability as improper subject matter. We also need to understand that patents on physical genes and proteins, themselves, are probably just as much a problem in terms of roadblocks in the real world as the informational patents.

Thank you. (*applause*)

PROFESSOR GEORGE ANNAS:

Usually, I would feel bad being the only thing that stands between you and lunch, but lunch today doesn't look all that appetizing, does it? I don't think it is patentable either.

If I heard the last two speakers correctly, I certainly agreed with Professor Eisenberg's analysis. You may know, ten years ago, my colleague obstetrician/geneticist Dr. Sherman Elias and I put together the first Ethical, Legal and Social Policy Issues (ELSI)-sponsored external workshop for the Human Genome Project. We tried to identify all the major ethical and legal issues involved in mapping and sequencing the human genome, and we felt quite comfortable with respect to all the areas we covered except one. The

exception was intellectual property, an area, I am happy to say, I knew almost nothing about. So we asked lots of people who we should invite to cover that area, and everybody had the same answer. It was Professor Eisenberg, and I was delighted that she decided to participate in our workshop and tell us what none of us had any idea that we knew or did not know about this.[4]

If I heard her right today, she said we should not patent the information contained in the human genome, as information, even bioinformation, should not be patentable material. Then I heard Andrew Marks saying that, actually, in terms of inhibiting research, there are exactly the same problems with patenting genes and the proteins as there are with patenting information. It seems to me a reasonable response to his presentation is that you could either agree with Andrew that we should patent both or, agree with what all these people who keep asking Rebecca, "How can you patent DNA?" seem to be saying, and not permit the patenting of either one.

What I want to talk about is why people continue to ask Professor Eisenberg the question, "How can you patent DNA?" I will try to answer the question not in technical patent attorney talk, which I don't know much of, but from what might be called an "ethical" viewpoint, fully understanding that there is no ethics gene, and if there was there would not likely be much of a rush to patent it, since money is valued a lot more in our society than ethics. In any event, I will try to address the genetic patenting issue from the point of view of ordinary citizens around the world who say things like, "Gee, I do not think you should be able to patent DNA," and why we have an embryonic movement now. Well, maybe it doesn't qualify as a movement yet. You may know, for example, that in Ralph Nader's ill-fated run for President as the Green Party's candidate, the line he got the loudest applause for was, "Our genes are not for sale." Of course sales and patenting are not the same thing, but "Our genes are not for patenting" just doesn't have the same ring to it.

Obviously, patenting has become a public issue again because of the publication of two almost complete human genome sequences. One sequence was prepared by the public Human Genome Project, which published their product in *Nature* (because although *Nature* is a British publication, it has rules that require all authors to post their data on the Internet so that it is available to all researchers). The other sequence was prepared by the privately financed corporation, Celera, and they published their study in the U.S. journal *Science* and plan to keep their data proprietary.

There are two reasons why most of the public thinks that DNA should not be patented: the nature of the subject matter, and social justice. Let's look at the subject matter first. There are a number of ways in which this concern is expressed. One is that using genetic materials as commercial products is "playing God." This is part of a larger belief that genomes are a central part of nature, and that human beings did not invent nature (and so shouldn't be able

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[4] GENE MAPPING: USING LAW AND ETHICS AS GUIDES (Annas, G.J. & Elias, S. eds., Oxford University Press 1992).

to patent it); and secondly, humans should not be able to commodify everything in nature and exercise this typed of dominion over nature. This can be derived from actual religious beliefs, from an environmental perspective, or simply from free-floating anxiety that humans are getting too much control over nature, and this risks us losing both reverence for nature and perspective on our own place in nature.

This may sound a little "soft" to tough intellectual property lawyers, but much of this anti-patenting, anti-commodification language came out of the U.S. human genome project itself. For example, the head of the project, Francis Collins (and others) often referred to the human genome as the "book of life." And in announcing the completion of the draft human genome, President Clinton said we are learning the "language of God, the language in which God made Man." Seen in these terms, the human genome project becomes a religious quest, and religious quests are not properly the subject of patents. This was the specific conclusion reached by a group of religious leaders in 1995 who argued that we just should not patent genes at all (and when they talk about genes, it is not clear if they are talking about gene sequences, cDNA, tags, or any of these things).

Europe continues to debate the extent of patenting in genomics. Under European patent laws, there is a doctrine called *ordre public* that provides grounds for refusal of a patent application if it is thought that issuance of such patent is against the public order.[5] I have talked to many people in Europe, and they assure me, no one in Europe has a firm idea what this actually means. What they do know, for sure, however, is that no one in the patent office should be able to decide what this means because technical patent language is not what this exception is all about. Rather, it has its foundations in human dignity, a concept that has been much more at home in Europe than here in the U.S. There is also a new proposal in Europe to set up an ethics committee to advise the patent office on what the doctrine means, and whether it is immoral or against the "public order" to issue specific patents. In the United States, we do not have patents on human organs; but we do have a federal statute that prohibits the purchase and sale of human organs for transplant, even if they can save a life. This is because of the nature of the subject matter: we simply do not think that vital organs should be the subject of commerce so that the rich can literally live off the bodies of the poor. On the other hand, we do permit the sale of sperm and eggs. We have even seen publicity stunts in the form of a Web site to auction off the eggs of supermodels to couples looking for an egg "donor." Although auctions have not materialized, it is common for fertility clinics to pay women $5,000 for one cycle of eggs. While commerce does flourish in human eggs, there is a developing backlash against it as well.

The underlying reason, I think, for most of the anxiety about the purchase

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[5] *See generally* PHILIP W. GRUBB, PATENTS FOR CHEMICALS, PHARMACEUTICALS AND BIOTECHNOLOGY: FUNDAMENTAL OF GLOBAL LAW, PRACTICE AND STRATEGY (Clarendon Press 1999).

and sale of human parts is the fear that we will wind up commodifying life. Its not that we are going to actually sell babies (we still have the Thirteenth Amendment to prohibit that), but we can commodify and monetorize their characteristics as eggs and sperm (or DNA sequences) that could produce babies with X, Y, and Z characteristics. In selling eggs, sperm (or certain DNA sequences) we are, by implication, saying that each of your baby's characteristics that we could so influence would have a price. In this way, we could put a price on life; or at least be able to compare the monetary "value" of one child versus another, based on their physical characteristics. So people who simply don't want to go down the road toward commodification of the human body resist both sales and patenting in the hope of preventing that journey.

The second major reason large numbers of the public oppose gene patenting is based on social justice: gene patenting is likely to exploit people and to do so in particularly vicious fashion. The John Moore case,[6] with which you are all very familiar, is a perfect example. Commentators have described it in various ways, but basically, the California Supreme Court held that everyone could own your cells except you. That conclusion simply can't be right; and the court seems to have reached it simply because it thought their decision was needed to protect the nascent biotechnology industry. I don't think the decision can withstand scrutiny, and although industry rightly loves it, cannot survive indefinitely. The court's ruling seems wrong to almost everyone. This is because either the rule should be everyone can own their own cells, including the person him or herself, or nobody should be able to own human cells. It cannot be that only biotech companies can own and patent a person's cells. John Moore will tell you that they patented his cell line (derived from his diseased spleen, and labeled the "Mo line") and when he found out about it he knew what it felt like to be a slave. But that is not the point. The point is that Moore had no say in whether his cell line would be patented. He was deceived and when he found out about it, he was told he was out of the loop and would get no royalties or any other recognition. He gets nothing, and that just seems to be wrong. Of course, this is not necessarily an argument against patenting as it is an argument for fair patenting.

A closer example of exploitation of human genetic material is the Human Genome Diversity Project's idea of going around the world and collecting DNA from the so-called "vanishing tribes" so that their DNA could be used for good scientific reasons to discover the origins of human beings and the evolution of DNA or, more practically in the real world, to find targets that you can use to develop drugs. Not only were people from other countries not being told what was going on, but obviously they were not going to share in any of the benefits. Their DNA was seen as much more valuable than the people

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[6] Moore v. Regents of University of California, 271 Cal. Rptr. 146 (1990); *see also* GEORGE J. ANNAS, STANDARD OF CARE: THE LAW OF AMERICAN BIOETHICS 167-177 (Oxford University Press 1993).

were themselves. So without benefit to the "vanishing tribes" themselves, the project was based on pure exploitation.[7] The indigenous peoples around the world have now organized, based largely in reaction to this proposal, and have taken a strong position against any patenting of DNA, any sales of blood to be used for DNA analysis, and any exploitation of their natural resources without their full participation.

In the United States, as you probably know, there is a recent lawsuit by the Canavan's Foundation against Miami Children's Hospital, which, with the help of the Canavan's Foundation was able to collect DNA from many families afflicted with Canavan's disease around the country before turning around, unbeknownst to the families, and patenting the Canavan's gene. That they patented the gene should not be surprising, but they now claim exclusive control over the test to screen for the Canavan's gene has outraged the families that did so much to help the researchers find this gene in the first place. That the Canavan's Foundation is completely out in the cold again seems to be wrong. It is consistent with patent law, and no one is challenging the patent. It just seems to be exploitative and ethically wrong, and that is what makes people feel that this is not right.

Finally, related to a growing anti-patenting movement (or at least one that has exceptions for public health emergencies) is globalization and the belief that large multinational corporations (not just pharmaceutical companies, but especially such companies) are taking actions without consideration of equity or social justice. There is no accountability. There is no democracy, no transparency, to use the protestor's slogan. In a world where inequalities are getting almost unbearable for us, we still seem quite able to bear it. But there are a few promising signs. Just today, UN Secretary General Kofi Annan announced that he wants a $10 billion fund started immediately to be used to help pay for AIDS drugs (and malaria and tuberculosis as well) for the poor in sub-Saharan Africa. Although that area of the world is experiencing the worst pandemic since the black plague in the 1300s, and although the pharmaceutical industry sells almost no drugs to this region, the industry has refused to permit either compulsory licensing or parallel importing (strategies permitted by the World Trade Organization rules) to help address this crisis. Their claim is that they must protect their intellectual property. This again just seems wrong to many people. Drugs can be priced extremely high on the basis of patent, and so high that most of the people in the world who need them cannot afford them.

Even in the United States, of course, the drug companies have been perfectly happy to say to most of the people over the age of sixty-five who need our drugs and cannot afford them, it's not our problem. The pharmaceutical industry does not even want the government to purchase

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[7] *E.g.*, NATIONAL RESEARCH COUNCIL, EVALUATING HUMAN GENETIC DIVERSITY 55-68 (National Academy Press 1997); GEORGE J. ANNAS, SOME CHOICE: LAW, MEDICINE & THE MARKET 145-48 (Oxford University Press 1998).

needed drugs for our seniors (for fear it will ultimately lead to lower prices, even price fixing by the government). To most people, that just seems outrageous. I understand the worry about "pricing" in the long run, but this is not a sustainable position. The public just cannot see it. They cannot understand why, if your goal is to develop a drug to help sick people, why you would exclude sick people who need it from getting the drug even to the point, as Rebecca and I were talking about this morning, of suing Nelson Mandela, so that South Africa could not acquire AIDS drugs at a price they could afford.

So there are two basic reasons, neither of which has much to do with technical patent law, that people oppose the patenting of genes and gene sequences: they don't believe human genes should be patented because they are an intimate part of human life, and they believe that patenting genes will inevitably involve exploitation and social injustice. You may not be persuaded, but I think you will agree that there is more to patenting genes than can be found in the U.S. patent laws.

Thank you. (*applause*)

QUESTION & ANSWER SESSION

Q: *AUDIENCE*:

Professor Eisenberg, *State Street Bank*[8] is a case about business methods, and I am sitting here thinking, what is the difference between a bioinformatics company and somebody who has a business method? If the patents may, in fact, involve analogous kind of things. Is there an interaction between the State Street Bank case and the whole subject of bioinformatics protection?

A: *PROFESSOR EISENBERG*:

Well, I think *State Street Bank* is not simply about business methods. It is really of a piece with this whole series of cases about the patenting of computer-implemented inventions of various sorts. There is language in there that would be very helpful to somebody who is trying to patent a bioinformatics algorithm. Certainly, *State Street Bank* is one of the cases that you would look to in seeking to support these patents.

Q: *PROFESSOR MEURER*:

I wonder if you could comment in response to Andrew's remarks.

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[8] *See* State Street Bank & Trust v. Signature Financial Servs., 149 F.3d 1368 (Fed. Cir. 1998).

A: *PROFESSOR EISENBERG*:

Actually, I have a question for Andrew, which is, what did this patent do for you, the patent claim that you finally were allowed? Do you want these claims? You were suggesting to me earlier that you would be happy to see a lot of this stuff not patented. Do you feel like you are pursuing these claims just because it looks like this is patentable and you do not want to be the only chumps out there who are not getting patents on everything that you can because you need to survive and you want to make sure that you have something to trade? I assume ultimately you care quite differently about the patents that you hope to get on the drugs that you develop than you care about these kind of roadblocks, what you described as roadblock patents. Do you see the patents that you are getting as essentially roadblocks?

A: *DR. MARKS*:

We see them, essentially, as the same roadblocks as the proteins patents. You said it right. If everyone else is doing it, we have to do it because at least it gives us something to trade ultimately.

A: *PROFESSOR EISENBERG*:

That is pretty interesting to me because that is the way that the automobile industry talks about patents. That is not the way that the biotech industry or the pharmaceutical industry has talked about patents.

A: *DR. MARKS*:

The problem is simply this. As a pharmaceutical company – and Vertex is more of a pharmaceutical company than a biotech company – we need to understand that, ultimately, someone is going to hold a patent on every important drug target. In order to deal with that, in order to develop drugs, we are going to need some other sort of protection in that area. These claims, actually, come out of a case where we not only protected the data, but we protected methods of using the data to design drugs with claims on their crystals themselves. What is important is the next step. Once someone has a patent that protects the protein, what else is available along that tool line that might be useful? The next thing is the crystal information, and so, it is our great hope that in those areas in which we are first with the crystal information, we can cross-license the patents that cover the targets themselves because both parties would really need them in a portfolio to design drugs for that target.

Q: *PROFESSOR EISENBERG*:

So this is a little planning for future events or are you actually trading these

kinds of licenses currently?

A: *DR. MARKS*:

We have not actually traded them per se yet, but it is the plan.

Q: *AUDIENCE:*

So Andrew, where are you going to make money?

A: *DR. MARKS*:

We are not going to make money from these patents. We are going to make money from drugs and selling them.

Q: *AUDIENCE*:

I am someone else who works in industry. We have traded claims like that. What we had, without going into the details that I cannot disclose, was a claim very similar to this, which was crystal structure for a particular target. We went to enter into a license agreement with the person who had the protein sequence, and we had to argue with them because they could do a lot of follow-on research with the crystal structure to which they did not have access. We did not expect them to give us access to the protein for free, but having the patent on the crystal structure certainly gave us a little bit more negotiation power at the table.

Q: *AUDIENCE (PROFESSOR KARJALA)*:

I would like to hear comments about the role of obviousness in this analysis. For example, if you have got a standard computer and a standard computer program that will throw three-dimensional representations onto the screen, and the only thing you are doing is inputting a specific sequence, I do not see how that differs from somebody giving me a piece of moon rock and a standard chemical spectrometer for me to test this unknown material. I do so and say, "Oh, boy, it has got all these things that are on the moon in it," and now I put all that together. I analyze the moon rock and get a patent on the composition and on the information in the moon rock. I should think it is fairly obvious to use that kind of a device for a piece of moon rock, and it seems to me it is clearly obvious to use a computer and the kind of computer program you are talking about to analyze those sequences that you have.

A: *DR. MARKS*:

Well, I think the answer really is that the patentability of the computer claim really was based on the crystal information. The computer itself is just a way of claiming the crystal information. I always thought when I started doing

biotech patents and a lot of protein patents – and I came out of science thirteen or fourteen years ago – that ultimately, what would happen is that everything would become obvious because there would be so many known probes out there that discoveries of proteins and genes would be eliminated as obvious. In fact, some discoveries are obvious. What the Federal Circuit said was just because the method of making a DNA sequence is obvious, does not mean the DNA itself is obvious. That is the same issue here. Just because it is obvious how to get the crystal structure and get the crystal coordinates does not mean the crystal coordinates themselves are obvious.

Q: *AUDIENCE (PROFESSOR KARJALA)*:

Is not it possible that the Federal Circuit is wrong on this?

A: *DR. MARKS*:

I thought they were wrong, but we have to play by the rules they set up. I think they are wrong. I think that whole line of decisions is ridiculous.

A: *PROFESSOR EISENBERG*:

I think they are clearly wrong. (*laughter*) It puts pressure on all these other points of patent doctrine to step in and fill in the void left by this absent, non-obviousness standard.

A: *DR. MARKS*:

The one point I should make is that many of the judges there, or at least some of the more important judges that are sitting on the Federal Circuit, come out of the pharmaceutical industry. There is a desire to essentially pigeonhole DNA sequence and amino acid sequence information into the chemical arts. The problem is, they are not the same. You know, methods of making chemicals are not sufficient enough. We have no idea what the chemical structure is going to look like, but if I know how to sequence a piece of DNA and getting a DNA, I know exactly what the protein is going to look like. I know exactly what it is. Thus, they are not analogous but they have basically been pushed into a situation where they are considered analogous and you get what I think is ridiculous law, nonsensical law.

Q: *AUDIENCE*:

This is a historical question and perhaps Professor Eisenberg has some answers to it. I have always been curious about the relationship between the Chakrabarty case and the DNA sequence patenting. It seems that at the time the Patent Office had a backlog of gene patents, and they were debating the Chakrabarty case to complete it. Yet it does seem that they are quite different,

the patenting of a living organism, which was appealed all the way to the Supreme Court, which found that life forms themselves are, in fact, patentable where engineered by man. Yet genes are not life forms. What am I missing? Is there a relationship between the Chakrabarty case and the patenting of genomic material? If so, what is it? If not, why was there such a backlog, and why did the PTO begin to then process that information?

A: *PROFESSOR EISENBERG*:

I am going to answer that at a couple of different levels. First of all, the narrow answer to your question is, no, there is no relationship. The narrow question before the Court in *Diamond vs. Chakrabarty* was simply: Is something that is living, *ipso facto*, ineligible for patent protection? And the answer to that question was no. The fact that something is living does not remove it from the category of patent-eligible subject matter. A strong current in the opinion was broadly receptive to patenting "anything under the sun that is made by man." That, combined with another decision that had been said to be considered alongside *Diamond vs. Chakrabarty* but was settled before it got before the Supreme Court, involved the patenting of an isolated micro-organism that existed in Nature in an impure state. The CCPA, the Court of Customs and Patent Appeals, predecessor to the Federal Circuit, held that the isolated microorganism as well as the genetically engineered microorganism, were both patentable. The Supreme Court never addressed that second question. The second question might have been more relevant to the patentability of isolated DNA sequences, but it never came before the Supreme Court. Everyone began behaving as if the issue were now completely settled, and I think a lot of things happened at the same time to contribute to that. *Diamond vs. Chakrabarty* was decided the same year as the initial public offering of Genentech stock. I think all of the signals were looking good that the patent system was going to be there for the biotechnology industry.

Q: *AUDIENCE:*

This is mostly random because I just want to get some of the real world perspective on this. It may be slightly off-topic. I have heard different things about how much *Festo*[9] is going to impact the nature of biotech in firms that are patenting. Some people say they had heart attacks when they first read the opinion. Do you have a sense of what the effect will be?

A: *DR. MARKS*:

My gut feeling is that people are making too big a deal out of this. When I

[9] *See* Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki, Ltd., 234 F.3d 558 (Fed. Cir. 2000), *cert. granted*, 121 S. Ct. 2519 (June 18, 2001).

write a patent, it has so many layers in it that if I peel off the two broadest layers, I still have my protection that I am looking for and I have not at all given up. The space between the layers is really what we are talking about here because that is the doctrine of equivalents area. The space is so narrow as to not mean anything. The other thing is that in the chemical arts or in the drug arena, changing a methyl group to an ethyl group can have a huge effect. There is no doctrine of equivalents available for that sort of change. So I do not think the doctrine of equivalents has ever really played as an important a role in the drug industry as people thought it did. Now, there may be other industries that are much different. I think what *Festo* will do is force people to write patents more carefully. It will certainly encourage people to use the multiple layer structure for claims so that there is not a big gap which they were hoping to cover by doctrine of equivalents between the first layer and the second layer if we lose the first layer. Still, at every meeting I go to, people are all up in arms about it. I just do not think it is a big concern. Quite frankly, I think anyone who was relying on the doctrine of equivalents for protection made a mistake in drafting the patent claims. My gut feeling is that if the doctrine of equivalents never existed, it would not amount to that big a deal, at least not to our industry.

Q: *AUDIENCE (SCOTT BROWN)*:

Scott Brown from Millennium Pharmaceuticals. I think as a practical matter, as we are prosecuting DNA claims, it is getting more and more difficult to do anything other than claim the sequence itself. Why? There is so much information out there. Take a look at the publication of all the human genome sequence. It is harder to find a stretch of DNA gene where there is not, at least, one EST forming area, which means you lose all kinds of things that practitioners need to broaden DNA claims. I think the reason *Festo* is being overblown, and that people think the sky is falling, is the reality of prosecution is that when we have gene cases, we are going to have a hard time getting much more than full length sequence claims given the vast amount of information already out there.

A: *DR. MARKS*:

I just want to make one point. One of the ways potentially around gene patents and protein patents as tools in the drug development area that we are exploring is the use of hybrid proteins. We, in fact, have a patent that at least discloses this idea. These hybrid proteins basically look like one protein but have an active site that looks like another protein. With such hybrids, the protein that you use is not covered by the guy who has the patent on the protein whose active site the hybrid mimics because the full protein has a different overall structure. Other than the active site, the rest of this type of protein does not look anything like the patented version. That is one potential area to explore in terms of getting around patent protection. I think there will be a lot

more of that. The problem, of course, with that is you could lose accuracy by using such a hybrid protein screen versus using the actual protein product. Perhaps this is a means to get to a certain point before using whole animals which would not be infringing the isolated gene claims anyway.

Q: *AUDIENCE (SCOTT BROWN)*:

Or endogenous cell forms.

A: *DR. MARKS*:

Right. In other words, you might get past the isolated protein patent, using a modified hybrid version of isolated protein. That is just one idea. We are looking to get around patents.

Q: *AUDIENCE (SCOTT BROWN)*:

As are we. (*laughter*) (*applause*)