

Briefing on the Report of the National Academy of Sciences Committee on Intellectual Property Rights in Genomics and Protein Research and Innovation

David Korn, M.D.

DR. KORN: Good morning, everybody. First of all, let me thank Reed, whom I've known for at least 25 years, and Debra, and the rest of you for asking that I come out to talk to you about this National Academy of Sciences report that was only just recently printed, although it was released in October.

I spent seven years in this room chairing the National Cancer Advisory Board, and I think this is the first time I've been back since the spring of 1991, and the carpet is new, and I think the upholstery on those chairs is new, but not much else has changed. So I'm glad there's continuity in life.

The National Academy was asked to form a committee to do a study by NIH mainly, and mainly by the Genome Institute and the National Institute of General Medical Sciences. I don't know what other NIH funding might have been in this study. In its typical fashion, the Academy, fiercely independent, formed a committee, and the committee is actually shown here. The committee is there, and it was co-chaired by Shirley Tilghman, who is a well-known reproductive biologist and now president of Princeton University, and by Judge Rod McKelvie, who is now in private law practice but for many, many years was a judge in the State of Delaware on what I think is called the Chancery Court, but I'm not positive. Anyway, he adjudicated a vast number of issues in litigation regarding patents and is really quite an authority on patent law.

Ashish Arora is an economist at Carnegie Mellon who studies the economics of scientific innovation, technical innovation. Helen Berman is a protein chemist, biochemist, who runs the International Protein Databank at Rutgers. Joyce Brinton for almost 30 years was in charge of all intellectual property matters at Harvard University. Steve Burley is a former, quite renowned crystallographer, I think at Rockefeller, who is now in a small company. I don't know if it's still a start-up; maybe it is. It's very into proteomics. Todd Dickinson, now senior counsel to General Electric Company for intellectual property matters, served under the Clinton administration as the director of the U.S. Patent and Trademark Office, the PTO, and I guess has spent his entire life in patent law issues and their interpretations. Rochelle Dreyfuss is a professor of law at NYU. Rebecca Eisenberg is a professor of law at the University of Michigan. Both of those ladies are very highly respected academic legal scholars who have written extensively on issues of patent law and patent interpretations and so forth. Charles Hartman was a venture capitalist who died during the course of this committee's work. His company was very involved in biotech start-up companies. Dan Kevles is a very distinguished historian of medical science, a long time at Cal Tech, now a professor of Yale. I am myself. George Milny, who is now in venture capital and start-ups, was for a long, long time the senior V.P. for global research development at Pfizer. Richard Sheller, a former faculty member of mine at Stanford, is now a senior person, maybe V.P. for research, at Genentech. He's a neurobiologist. Rochelle Site is a patent lawyer in private practice in a large firm. Nancy Wexler you all know. Bob Waterston you all know, a very distinguished genomics researcher at the University of Washington. Brian Wright is a professor at U.C. Berkeley whose field is agro-biotech, and he has also been involved in issues relating to biotech R&D and the patent system.

Now, the charge to the committee is here, and I know you have all this stuff, so I'm not going to read it to you. It's in your packet. It was basically to look at how the U.S. patent system is working with regard to technologies in genomics and proteomics, evaluate our systems against those of Europe and Japan, try to get some information on whether the application of patent law

and practice are inhibiting research and innovation. Notice research and innovation. There was nothing in this charge explicitly about the practice of medicine. I did not write the charge.

Let me just say that I agreed to deliver this report straight, and that's what I'm going to do. I was supposed to have been joined by Judge McKelvie, but some time ago he got into an irreconcilable schedule conflict, so he can't be here, and I promised the Academy people I would be faithful to the report. But afterwards we can talk about it.

(Laughter.)

DR. KORN: And then make recommendations to NIH and others.

Now, what did the committee find, in brief? That patenting varies greatly among biotech categories; that patenting seems to have leveled off. That is, there's this spate of application that flooded the patent office beginning in the late '80s and early '90s seems to have been leveling off a bit, sort of like the D.C. housing market, but pendency has increased. That means applications that have not yet been ruled on -- and there is a huge backlog of genomic and proteomic applications sitting in the patent office waiting for a decision to be made. The fourth bullet on here is that U.S. inventors and their signees dominate patents in almost all the categories of interest in genomics and proteomics. So it's more a U.S. problem at the moment than an international problem from that perspective.

The committee found, and I think this is important, that perhaps the chief difference in how the U.S. as compared to Japan and Europe deal with patent issues is in the requirement that we call non-obviousness, that a claim to a patent must be non-obvious, which means that a person skilled in the field would not have thought of it, perhaps, obviously based on his or her knowledge. In Europe and Japan, it's called the inventor's step, and inventor's step implies something creative, invention. In the U.S., some time ago, court rulings changed the patent laws consideration of inventiveness to discovery. Again, we can talk about this later, but there is a big difference between discovering something and inventing something. Other countries respect that difference. Our country, in law, seems not to as much. So the bar is higher in Europe and Japan.

Then another difference that's on here at the bottom, the last bullet, is that other countries, most other countries have a statutory provision for compulsory licensing, which may be relevant to some of the issues that Debra posed to you, and they shield research on patented inventions from infringement liability. In other words, Europe and Japan, the way the U.S. does, sort of, allow research to be done -- and I'll get back to this -- on patented inventions, on and not with, which is a very important legal distinction.

Concerns that were raised to the committee -- and Rebecca Eisenberg is the creator of this concept, an anti-commons, that there are so many patents out there on enabling technologies that marshaling licenses or permission to do something that requires the agreement of 10 or 50 different patent owners could be a great inhibitor of valuable research and development and commercialization of new therapies and so forth. When golden rice was produced, the rice that contains the precursor of Vitamin A, one of the committee members was involved, the one at Berkeley was involved in that work, I think something like 67 patents had to be negotiated to enable the people who were trying to develop golden rice to use the tools and technologies that they needed to get golden rice, and I think that Francis Collins made a very persuasive presentation to the committee at one of its very first meetings, pointing out that for certain kinds of biomedical or biotechnological research that involves sophisticated inputs, like knockout animals or this or that, monoclonal antibodies or whatever, you could also generate a list of 10 or

20 patent owners who technically control one's ability to use these particular steps of a process. So that's what the concerns are about.

The second bullet on here has to do with access, which I think we've already talked about. The patent system in the United States, and to some extent worldwide, in the last 25 years has been moving steadily upstream toward the basic research end of the research discovery product chain. It's not a perfect chain. It isn't uni-directional. We all know that. But the point is that the Supreme Court in 1980 made a ruling on a challenged patent on a genetically engineered bacteria that was able to digest oil, and the inventor thought it would be a useful biological weapon against oil spills, for example. You just toss these bacteria in an oil spill and they start chewing up the globules. The Supreme Court ruled that this was patentable even though it was a living thing, and they also said in their opinion that anything under the sun made by man is patentable, anything, and that really opened up patenting in biotechnology with a full faucet. I mean, before that it was not clear what the boundaries were in biotech and biodiscovery of what you could patent. But that ruling essentially opened the floodgates, and we've been struggling, we being our society and lawyers and courts, ever since to figure out what the limits are on patenting, if there are any limits.

Then the last concern was that there might be an erosion of the norms of open science that would inhibit research and restrictions on sharing research materials. I'm not going to go through all the slides that you have in your packet. I kind of reorganized these last night to make them a little bit easier to digest, but there was a survey commissioned by the committee while it was at work. Walsh and Cohen are both very well known economists who study innovation, and I don't know who Dr. Cho is but he was a member of that team, and they did a quick and dirty survey to ask the questions that are on your handout, really trying to understand whether academic investigators were being inhibited by the application of patent laws and licenses.

What they found -- and again, I've pulled a few slides out of the several that are in your handout -- was that the academics that were sampled -- this was a smaller sample with a 30 percent response rate, so I don't know how generalizable this is. But there was substantial commercial activity reported by the faculty who responded. Nineteen percent have some industry funding. I'm surprised it's that low, to be honest with you. Twenty-two percent had personally been engaged in patenting their own discoveries in the last two years. That's a pretty good chunk of the community. Thirty-five percent of these academic researchers had been involved in such business activities as start-ups and so on. There was a prevalence of those who were doing drug discovery.

Now, this is important. The question was asked: What are the main reasons that you and your team are doing the science that you're doing right now when we're asking you the question? If you look at this, you will see that the most important reasons are the ones that are obvious to all of us who have lived long enough. We may be out of date, but we think these are obvious. They are scientific importance, interest, feasibility, and sufficient funding, because without those things, why would anybody in his or her right mind want to do the hard work of research? But it is nice to see that those still are the motivators of research, in academia at least.

Health benefit. This was not limited to biomedical scientists. So health benefit was only 60 percent, which is not surprising to this group. Then there were the usual other things. But notice that patentability and personal income are way down here. So yes, a few people thought those were important reasons why they chose projects, but it clearly wasn't the prevalent dominator of why people were doing research.

This result -- I mean, I just have to tell you, I think I'm older than anybody in this room, but it really made me feel good because I would have been so distraught if this chart had been inverted and people said, gee, the reason we're doing this is to get patents and make money. So that made me feel good.

Now, similarly, complimentarily, the reasons for not pursuing projects also kind of makes sense. There's no funding available. Research costs money. I'm too busy. It's not feasible. It's not scientifically important. It's not interesting. Again, it's not rocket science. I mean, that's what we would expect a sane person, a mentoring person, to tell you. Some said little social benefit. But again, notice that very few people, a very tiny fraction thought that there were too many patents out there or I wouldn't be able to patent what I did or I wouldn't get income from it. The economics of research did not seem to be predominant motivators of either pursuing or not pursuing projects. I like that. I personally just felt good about that.

Now, 8 percent -- but remember, it's a small sample, thought they needed knowledge or information covered by patents. The key thing here is that most of these academic researchers didn't know from patents, or at least they didn't care about patents. They did what they wanted to do. They didn't say, oh gee, I'd better go call a lawyer and do a patent search and see if I can use this tool or this material or whatever. This is something that even since the Madey decision of 2002 I think it was, or 2000, I don't remember, that we can talk about later but which worries a lot of us. It doesn't seem to have had much impact on how academic research has behaved.

Now, a fifth of them did say they had received "instruction from their institution." I don't know what that means. It might have been a letter from the general counsel's office saying please be aware that there's a patent system in the United States and if you're thinking of using materials, tools, animals, you might want to check on whether or not somebody owns those things and we have to negotiate a license. That figure I think is higher than it would have been a decade ago, but I can't prove that to you.

Several of us joined with the AAAS to do a study of how Madey, the decision, was affecting the major research universities, and you see that only about 14 percent of the institutions said they give instructions. The survey didn't find that even if you got instructions, it didn't change behavior, and anybody that's been a faculty member or the dean of a faculty knows damn well that the faculty don't listen to instructions. They ignore them most of the time, and that's what a faculty member is. It's a person who thinks otherwise.

(Laughter.)

DR. KORN: Now, sharing. This actually now becomes important. About 75 percent of the respondents had requested materials from some other person or institution in the last two years, and 19 percent said they did not receive the last requested input. Input is the way the economist talks about tools. They did not receive it. That's a fifth. A fifth of the requests according to this survey were not granted. These economists think that problem may be increasing. I don't know if that's really relevant or not, but the point of the matter is that for most people -- I'm sorry, let me say it differently. For the people who were requesting inputs, there was some delay of their research in a small percentage, and that seemed to be higher when the request involved pure intellectual property, and I'll explain what that means in a minute.

You see that about 40 percent of these require what's called a material transfer agreement. A material transfer agreement is a legal document, like a contract, that a provider of a research tool, usually the general counsel of the provider's institution, develops that tells the recipient of this

research tool what he or she may or may not do with that tool. Usually they restrict dissemination. That is, if I give you my knockout mouse, I may say you may not disseminate it to anybody else outside your lab group. If somebody else wants it, I will deal with it. It may say that you can do whatever research you want to do with my knockout mouse, but if you develop a commercial product, you've got to come talk to me about what my share of the economic benefits may be from this product. Again, these aren't patents and licenses so much. These are just I have it, you want it, and there has developed this culture of contractualizing the transaction between me and you in handing over my material.

The NIH has been very worried about MTAs for quite a long time, and in 1999 I think Rebecca Eisenberg, a member of this committee, chaired a special panel to the advisory committee to the director of NIH, I think it was then Harold Varmus, and wrote a superb report pointing out that this kind of restriction was very, very threatening to research, very worrisome, and advising that NIH flex its muscles in trying to have grantees, those who get money, behave better. In particular, they proposed a simple one-page agreement for material transfers, a simplified one-page universal agreement and urged NIH to enforce that.

NIH has urged and exhorted, has not really, at least until recently maybe, enforced. Now why is this a problem? Because in 38 percent of these cases, you want reach-through rights. A reach-through right is what I just described. I'm going to give you my mouse, but if you get something really interesting that you can commercialize out of it, I have a right to some portion of your return. That's a reach-through right. Reach-through rights can be extremely irritating, and the more material transfer agreement stuff you have, each with its own research rights, you can be working on a project and owe 200 percent of the benefit to the people that gave you the tools, and that's kind of not very encouraging -- royalties, manuscript review, this sort of thing.

So why do scientists not provide materials? Competition. This is as old as I am. It's older than I am. When you work real hard to get a breakthrough on something, and everybody knows about it right away because we all talk about these things, then everybody wants it, and you haven't even had a chance sort of to digest your meal, and all of a sudden people want to share your dinner. So people often -- and this doesn't have anything to do with patents. This just has to do with personal motivations and stuff. That still remains the major reason why people are reluctant to share some of these tools, which can in fact be very, very hard to (inaudible). They're not trivial.

Anyway, let me skip away from that. So what did the committee conclude? It concluded that it appears that access to patents or information inputs really are a significant burden, information inputs, but the committee agreed that the patent landscape could become much more complex and troublesome over time. There is no evidence right now that patent stacking is causing a lot of concern in academic research, but institutions are aware since Madey that they do not have the kind of immunity from patent infringement charges that they had before Madey. We all grew up believing that patents didn't involve anything we did as academic researchers. We didn't have to worry about it. Madey said we do. Clearly, most people are still not worried about it, but at some point that could change, and patent holders could try to get benefits by asserting their patent rights against universities. There are some anecdotal cases where that has occurred. In the both of them that I know, the university essentially told the claimant to go away, they were too busy to deal with them. I don't know how much longer that's going to work.

There again is this concern that as research becomes very complicated and multidisciplinary and this and that, that needing tools and inputs and reagents and things of that sort could really get to be a problem if everything you need is owned by somebody who really wants to control access to it.

So there was no evidence that this was causing problems in research -- that is, patents -- but there was awareness that it could become a problem. Conjecture. There was concern about these MTAs, which may or may not deal with patents, and there was a lot of committee concern about MTAs being a burden.

So now, after almost a year of deliberation, often extremely tense, with very strong positions that were difficult to bridge, the committee almost miraculously at one meeting decided to agree on some recommendations. None of these came easy. I'll just tell you that. None of these came easy. There were very strong opinions in this committee, as one expected, that the patent law kind of came down to Moses on Mt. Sinai, it's perfect, it's not up to man to tinker with it, and there were other people who thought that the way patent law was applied to genomics and proteomics was troubling. It's sort of like arguing abortion, I guess. You believe in it or you don't believe in it, and it's very hard to convince either side that the other side has any merit.

There was a lot of that kind of almost ideological polarization in this committee, which comes with balancing a committee. You get people on all sides of the issue. So what the committee did agree with was that NIH should continue to encourage the free exchange of research materials and data. It went a little further to say that NIH should monitor the actions of their grantees and contractors with regard to this, and if necessary require, require grantees and contractors to comply with their approved intellectual property and data-sharing plans. When you apply for a grant at NIH now, as part of the application you have to spell out how you are going to share either data or materials that you discover in the course of your research.

NIH really requires things. I mean, sometimes it does, but most of the time it urges things. It gives guidance rather than regulations. So this is actually much stronger language in this recommendation than you might recognize at first reading. The NIH should adopt, adapt and extend the Bermuda Rules, and you know the Bermuda Rules were the basic operating agreement for the human genome sequencing project -- should adapt and extend these rules to structural biology data generated by NIH-funded centers for large-scale structural genomics efforts and so on, and make the data promptly and freely available in a database like the protein database, operated under an NIH grant or contract by the committee member at Rutgers University, which has a huge collection of protein crystal structures that have been freely deposited for anybody to see and make use of. It's almost like the deposition of the human genome sequencing information every 24 hours. It's that kind of spirit of sharing.

The third recommendation was, again, focused on structural biology. So they wanted the European and Japanese patent holders to establish mechanisms to getting structural biology data from published patent applications into the protein database, and so on, and to the extent feasible all researchers, including those in the private sector, should be encouraged to submit their sequence data to GenBank, the DNA Databank of Japan, or the European Molecular Biology Databank. So again, this is urging the community to behave well.

The fourth recommendation, which is dense on that slide, is really endorsing already published guidances of the NIH. It's lending the Academy's strong endorsement to these already existing NIH documents. The first document, which is about six years old, was from the Becky Eisenberg committee study back at the end of the 1900s, and the more recent one was issued from the Genome Institute which has to do with best practices for the licensing of genomic inventions.

Now, the recommendation then goes on to say that NIH should require, again require, not guide, require, that all award recipients adhere to and comply with these guidance documents. That kind of language has never appeared to date. So even though I realize this committee will have some

difficulties with portions of the report, this is very, very strong language if NIH decides to adhere to it -- require adherence, compliance with these sharing documents, and then they urged other non-profit funders and agencies to do similarly.

The fifth recommendation is directed to universities, urging that they retain in any license agreements the authority to disseminate research materials to other research institutions and permit them, the other institutions, to use this patented technology in their non-profit activities. This you would think is ABC, right? The university patents something, which everybody does now. Every intellectual hiccup is patented by everybody looking for the big winner. They ought to retain in their licensing agreements the right to disseminate this material for research. Some universities have not done this, and there are others who have been in the business a long time who routinely do it. So there's a great diversity in the community about that.

This long recommendation basically urges that inter-institutional transfer of research materials use a simple so-called Uniform Biological Material Transfer Agreement, which could be the one-pager that Rebecca Eisenberg's committee crafted in their report. But they urge NIH to adapt such a thing, and they even encourage industry to adopt similar practices. Again, this is urging people to behave well.

Now, this is an important one, and this asks that the patent office should create a regular formal mechanism whereby they can bring leading scientists in relevant emerging fields to the patent office, just like this committee comes periodically, to inform examiners about what's going on in their fields. There really is a concern that the patent office is underfunded and overwhelmed and that the examiners do not recognize what experts in the art know is commonplace, and they regard that as novel and non-obvious and so on and so forth. If the patent office adopted this, there would be a regular advisory committee of top-grade scientists that would meet on a regular schedule to talk about what's happening in their fields.

This is kind of legal jargon, but in general this has to do with this non-obvious standard criterion that I mentioned before is quite weaker in our country than it is in Europe or Japan. It asks that the patent office really think hard about whether a scientist of ordinary skill would have been motivated to make the invention with a reasonable expectation of success -- this is all patent jargon -- at the time the invention was made. In other words, you may try to patent something, but then the question is would I and others of you who are working in the field regard it as obvious. I mean, yes, so what? Anybody could have done that. This is the only way that the committee was able to agree to get at strengthening the non-obvious obviousness criterion. We can talk about that later if you want to.

It urges PIs and their institutions to be familiar with the heightened utility guidelines that Debra mentioned. They are, in fact, much more stringent than existed before those guidelines came out, and avoid seeking patents on hypothetical proteins, random single-nucleotide polymorphisms and haplotypes and things that have only research as opposed to therapeutic, diagnostic or preventive functions. Again, this was as far as the committee was willing to go in urging institutions to refrain from some of their patent-seeking behavior. But if everybody adhered to this, I think we would be better off than we are right now.

This has to do with the research exemption, which the Madey decision has already weakened considerably. It proposes language for a Congressional action -- that is, a legal amendment to the patent law, which is what would be required here -- to permit without worries about infringement certain kinds of research on but not with patented inventions. Again, you can read these things because you've got this slide in your book, but why is "on" versus "with" so important? Because

consider a balance. I mean, there's a circuit court judge downtown I know who loves this analogy. If I own a balance and you have one in your lab, you can take it apart, you can do research on the balance. You can take it apart, you can see how it works, you can try to make a better one. All that stuff is okay, but you can't use it to weigh anything because that's what its intended use is, and I have the right to that use because I own the patent on the balance. So "on," not "with," is central to discussions of the research exemption.

Indeed, there is a document that was handed to me by somebody who either talked to you this morning or sent it in to this committee expressing great unhappiness with this recommendation on behalf of an industry organization, I guess, of small biotechnology and start-up companies. I think that's what the organization is, RUE, or something like that. But in any event, this is a limited research exemption which some people think doesn't really go far enough to do what really needs to be done, but it's the only way to protect the inventors of research tools, because research tools, by definition, are useful in research. I mean, that's what a research tool is. So to allow somebody to use it to do research with it clearly says to the inventor that your research tool has no economic value whatever because anybody who wants to use it is able to use it. They don't have to buy it, they don't have to get permission. So keep in mind the "on" versus "with." It's very important.

So now we get into the meat here. This is simply another direction to NIH to study how universities, government and industry may be engaging in cross-licensing and pooling of patents to enable research to go forward. Number 12 is important. The courts should continue to decline, to prevent and join patent infringement in those extraordinary situations -- there were a lot of hours spent over that one -- extraordinary situations in which the restricted availability of genomic or proteomic inventions threatens the public health or sound medical practice.

This is, from this committee, a major give, whether you think so or not. It is a major give. It gets close to the issue you're concerned about. It doesn't quite get there, but it does say that there are instances where public health needs or sound medical practice would justify infringement. That's what this really says. Much blood was spilled to get this. Of course, extraordinary situations, not just ordinary situations.

Number 13, the last one, has to do with your issue of genomic- or proteomic-based diagnostic tests. The only part of this issue that the committee was able to come to any agreement on was that independent verification of test results ought to be allowed just for sound medical practice. The concern they did resonate to was that a monopoly provider of a test, if there's a monopoly provider of a test, that an individual or a physician or whatever could not get an independent verification if the only place that does the test is the monopoly holder, or the one or two labs that the monopoly holder allows. So this and the preceding were as close to your issue of gene-based diagnostic testing as we could get.

That's the end of my formal report, which is my committee obligation. I am now David Korn. I am just talking about my own personal opinions, okay? I want to be really clear about that.

We struggled very, very hard to get this committee to understand the issues that are exemplified by BRCA. In fact, Debra came to a committee meeting on a cold, miserable day in Princeton, as I remember, and gave a very strong presentation that simply did not move the committee at all. So for people like Bob Waterston and me and Rochelle Dreyfuss, who did come to understand this problem, not at the beginning but as the committee went on really did come to understand this problem very well, tried very hard to push for something that would have been a little bit stronger than this, but the way the committee was constituted, we couldn't. So that is why the

SACGHS Meeting Transcript
March 27-28, 2006

recommendations are what they are. I just will remind you that I think some of them that deal with what NIH should require are very strong, and if NIH really exercised its ability to require on these things, it would help a lot to allow research to go on.

On the public health side of the issue, I think probably the committee's best efforts fall short of what many would have liked to see, but that's the way it is.

Now I am finished and I would be happy to do as the chair wishes.

DR. LEONARD: Thank you, David.

What I'd like to do is anyone with questions for David regarding the NAS report, please feel free to ask questions now, and then I have another presentation that basically walks through what the task force did in reviewing the report and what our recommendations are, and then time for discussion of next steps that SACGHS would like to take.

So if there are any questions for David.