The Gene Patenting Issue:
Urgent Problems in Science Policy and Law

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In many ways, the Human Genome Project (HGP) epitomizes the promise of the biological sciences for the future. The impact on our lives of the vast amount of new knowledge of the living world is just beginning to be realized - it will inevitably transform medicine, agriculture, food manufacture, chemical technology, and many other industries in ways that are difficult to predict. The HGP is also a project that holds within its promise the capacity to raise some significant and difficult issues concerning human genetic information under the law. Among these are the issues you are beginning to grapple with today - questions related to the conditions and constraints under which human genetic information can be patented, the implications for the future of scientific inquiry, the commercialization of scientific advances and of other uses of genetic information by society.

The way to approach the complex of issues most effectively, I think, is to consider what the most desireable outcomes for science and the applications for society are, and then to devise and consider appropriate policies and guidlines that can achieve those outcomes. I wish to leave you with the realization that there are fundamental issues involved and that solutions to these difficult problems are needed urgently.

The Department of Energy (DOE) has sponsored the Human Genome Project (HGP) from its initiation, and DOE and NIH now jointly support this research effort. We consider this historic project of immense potential value to the American people and to the world. We strongly support the expeditious transfer of the benefits of this research and of the associated technologies to the public. For DOE and for 11 other Federal agencies, there exists a real imperative for the rapid and effective public use of the results of biotechnology research, including the HGP and

many other research efforts.

In the HGP the overall approach to elucidating the genetic contents of the genome is first to physically "map" it and then sequence large parts of it, in order to create a knowledge base of unprecedented detail and complexity, so that subsequent research can be more effective and efficient. This process is well underway and is making spectacular progress. Never before has so much genetic information been gained, so many genes been located, identified or characterized. Never before has the technical means to gain information been more promising. No matter how strongly I say it here you will undoubtedly be surprised in the next few years by the sheer rate of information acquisition. This prospect makes it critical that we squarely face the problems of how to deal with the patenting of any genes - but particularly of human genes. Though the problem has been with us for some time, it has never been adequately dealt with.

The NIH Patent Applications:

The recent controversy engendered by the patent applications based on partial cDNA sequences submitted by the NIH has actually provided an important impetus to finally address this problem. It is an impetus we should heed well, and use in order to grapple with the immediate issues, but the broader issues must also be dealt with. I will argue here that the NIH patent applications themselves are certainly not the most critical issues facing us.

I wish to say at the outset that I strongly support the aggressive pursuit of a resolution to the immediate issues raised by these applications. This is clearly important for both the commercial sector and the international scientific research community. While we were not supportive of the point of view represented by the original filing by NIH, we are certainly not against patenting, nor against patenting genes. On the contrary, we are in favor of a wide application of the patent mechanism to protect rights to inventions, and to open up the transfer of knowledge and inventions for the public good. The full mechanism must also include various licensing arrangements, however, which also deserve full and informed consideration.

In a general sense, we of course recognize and support applications of the patent process that fulfill the criteria laid down by the Constitution of the United States that they "promote science and the useful arts". In the specifics, however, lies the difficulty. These are time-honored criteria that focus our attention on some of the most important questions about biotechnology patents: do they promote or inhibit the vigor of science; and, do they promote the development and commercialization of biotechnology; e.g., "the useful arts"?

Turning to the specfic case of the now notorious NIH cDNA patent applications, consider some of their potentially unsettling effects. These include:

a) The sequences of anonymous cDNA fragments, of no known function, cannot reasonably be described as "complete or discreet inventions" - rather they are intermediate research results. For technical reasons, including the incomplete nauture of the sequences, we expect that patent applications like this will likely lead to a tangle of disputes requiring judicial resolution, and delay and dilute the benefits of the research.

c) If a cDNA patent were to be issued (this seems unlikely but by no means foreclosed at the moment), such patents could serve as a basis for claims against later, truly creative and novel inventions that have a clear and specific use, and that are developed independently of the partial sequence. A cDNA patent based on an anonymous fragment could in this way be a strong disincentive to investment and economic exploitation of the results of the HGP.

c) The potential for inhibition of free collaboration and rapid exchange of data, both nationally and internationally, is real. This is not an evident, or necessarily expected effect, but this inhibition has been observed. Inhibition of free exchange would reduce the effectiveness of our research in many areas.

We are also concerned that the logic of the NIH patent applications, if it were applied rigorously as it is, could put all genomic sequences, mapping information, DNA fragments, clones (YAC's, cosmids etc..) into the same category as the cDNA fragments. All "intermediate research results" could serve as the basis for broad, relatively unspecific claims on the fundamental structure of the human genome. In my view, it is <u>this</u> kind of broad, sweeping claim that is clearly the dominant problem, and <u>not</u> the patent applications on anonymous cDNA patent applications themselves.
All this being said, the NIH patent applications really represent only a clarion call, a warning that the system may not be equal to the strains placed on it by modern gene technology. They represent only the beginning of our problems. The most important issues, I would argue, do not concern patentability, but rather concern what claims on genetic sequences can be protected by the patent system, and what constraints on use and availability to society are desireable.

<u>Knowledge of Nature versus Invention:</u>

A central question for your consideration is one that extends well beyond the cDNA patenting

case: where should the line be drawn between entirely appropriate patent protection for useful inventions and unwarranted claims on the ownership of fundamental knowledge of nature? What distinguishes the basic genetic information that is the fundamental currency of biological science from, for example, the spectrum of neon or any other element that is the basic currency of atomic physics. This question must be answered with due consideration for the good of private industry, the long-term vigor of the scientific enterprise, the benefits to the American public, and the benefit of the international community. Other ways of asking the question might be: where is the boundary between fundamental knowledge about ourselves and those useful inventions that patent law properly protects; where should we draw that line between basic research results and a product or process? Central to this issue, in turn, is the closely related question of what rights patents on genes should really protect. This important aspect is touched on in the next section. These are not really new questions, but there are new features here specifically related to genetic information, and there is a new urgency.

Use versus Ownership:

Is genetic information qualitatively different from other natural information? Should our own genes be subject to the same property values implicit in our current "intellectual property" laws? What does it mean for an individual or a company (or a Government agency) to "own" a gene? Given that we can define the rights and claims entailed, should "ownership" rather than a particular utility be the focus of patent rights? These are among the difficult questions that now must be addressed. Given that the function of a specific gene in question is known, the most significant intellectual property question is probably: should a patent on that gene include the right to all possible future uses of that information, the broadest kind of claim, or should the patent claims should be confined to the utilities specified, a quite limited kind of patent. The distinction is fundamental, I think - ownership or uses, broad far-reaching claims or limited well-specified claims.

While practice in the US has been strongly in favor of "ownership", I propose to you that careful consideration must be given to strengthening the important notion, already inherent to a limited extent in US law, of only allowing the patenting of DNA sequence information for specific, anticipated uses, and only for those uses - the only difficulty in this, other than that inherent to a shift of practice, would seem to be in clarifing how specifically the "use" needs to be defined. Though there are, I understand, recognized practical problems with "use patents" versus "structure of matter patents", a sufficient emphasis on utility in patents on genes might deftly accomplish at once several important goals. It could actually resolve the present NIH patent

controversy, guide future policy on problems like that discussed below, and refocus our attention on the real purposes of the patent law.

Patenting the T-cell Receptor Genes?

Now I would like to describe a specific situation that has recently arisen which epitomizes the most difficult questions above, and suggest a possible course of action. This example - one of several possible - could provide a concrete, practical and immediate issue on which to focus an otherwise broad and relatively abstract deliberation. A research group supported by the DOE Human Genome Program has just completed the DNA sequence of the genes determining a major component of the human immune system - the T-cell receptors. About 450,000 base-pairs of sequence of a major site of this information in the human genome (the beta locus) have been obtained. The question is: of the primary sequence information, the known and unknown functions encoded in this information, and potential utilities, what is it that can and should be protected by patents?

Something of the nature of the genetic information in the T-cell receptor genes should be understood before the issue is discussed further. The human immune system depends on a set of cells called T-cells as a fundamental part of the apparatus for the immune response. These cells have proteins on their surfaces that determine the specificity of their immune activity. They have the same enormous repertoire of binding specificities that circulating antibodies have, which is produced by a combinatorial mechanism similar to that used to produce the enormous variety of antibodies. It is illustrative of the importance of the T-cells that it is the destruction of one class of these cells that is the central, lethal effect of the AIDS virus. The T-cell surface proteins, called T-cell receptors, are encoded by several complexes of gene segments located together in the T-cell receptor loci - one of which (the beta locus on chromosome 7) has now been sequenced.

These gene complexes encode key components of the human immune system, and are also, by the same token, implicated as the locations of genetic alterations that may cause, or contribute to, a variety of autoimmune diseases, or suceptabilities to diseases. So far only a genetic marker for multiple sclerosis has been clearly identified in the T-cell receptor locus, but it is likely that markers for rheumatoid arthritis, and a variety of other autoimmune diseases, will also be found in this region. This region is clearly one that holds the key to a number of prevalent, serious human diseases.

Because the function of the T-cell receptors are known the uses that could be described for a patent application on this DNA sequence are many, both for identifying the important sequence variations that are linked to disease states, and for possible therapeutic purposes. The utility would therefore be very much more compelling than that described for the cDNA's in the NIH patent applications. Since the uses and applications associated with the immune loci are much more identifiable and more closely related to the sequence data, the problem is much more acute, concrete and perhaps more difficult. In addition, since the T-cells are a major component of the immune system, anything involving cellular immunity could conceiveably be covered by the broadest of claims.

While I am inclined to think that the genetic structure of the human T-cell receptor loci itself, like most of the human genome, should be viewed as fundamental knowledge of nature, and not as an invention, the issue is complex and difficult and present practice does not seem to make the distinction well. The line has never been definitively drawn between these two types of knowledge, especially in the biotechnology areas. The question is even more poignant in this case in which we are dealing with the genetic structure of the human body, and with genes closely linked to human diseases. The question of "ownership" versus "uses" apears to be a sharp one here. In the face of these difficulties I would like to propose a specific course of action for your consideration.

The researcher leading the T-cell receptor sequencing project, Prof. Leroy Hood, intends, with our full support, to file, within the next few months, a patent application on the DNA sequence of the human T-cell receptor *beta* locus for the specific uses of developing the diagnostic and theraputic tools for dealing with specific autoimmune diseases, as outlined above. At the time of the filing it is intended that all the sequence information will be submitted to GenBank, the sequence database, and thereby released for the scrutiny and use of the international scientific community. In our view, this action - patenting in the strict context of uses to be made of the information, with claims covering only specified utilities rather than broad "ownship" claims - should have several important effects. It will make this important sequence information immediately available to the scientific community for the study of the immune system. It should protect specific rights for the investigator but not block future rights to important, novel inventions yet to be made using this information, and it should stimulate the consideration of some important questions on gene patents.

What is being proposed here would seem to be in sharp contrast to past practice. The recent example of the patenting of the erythropoieten (EPO) gene is illustrative of this contrast. When the structure of the EPO gene and the function of the gene product in stimulating differentiation

of red blood cells was determined, the patent claimed the structure of the gene and all its possible future uses. No matter what might later be discovered about this gene, or invented using it, the patent would establish prior rights to those inventions - virtual "ownership" of the gene. What is intended for the T-cell receptor genes is that only uses directly related to what is now known and can be specified will be claimed. In this sense, "ownership " and "uses" are contrasted.

A very recent discovery can serve to emphasize this point further. The gene in which a mutation leads to "Lou Gehrig's disease" (ALS) has just been identified. It happens that the gene product, superoxide dismutase, has been known for many years - it is an enzyme that supresses free radicals in the cell. The gene has also been known for some time and has been mapped on chromosome 21 for more than 2 years. If the gene had been patented, and therefore "owned" in some sense, there could be no new claims on it by the disocverers for diagnostic or therapeutic purposes related to ALS. If, on the other hand, the gene had been patented only for the uses that could be specified before the recent discovery, the way would be clear for the newly discovered role of the gene to lead to valid patent claims for this unanticipated utility. This latter scenario would seem to be much more in the proper spirit of the patent system.

It is vital that the research use of sequence data and the rights to future inventions using this information be protected. I strongly encourage you to look closely and wisely at the above example of the T-cell receptors, and consider whether the suggested course of action will be useful, and also whether the patent system needs to be changed to permit this to work well. It is clear that this example is an early indicator of an abundance of rapidly approaching problems stemming from the imminent deluge of genetic and sequence information.

Conclusion:

In the final analysis, the vigor and competitiveness of a country's technological economy is driven by the vitality of its scientific research enterprise. The vitality of the US research enterprise has been remarkable and has yielded benefits in a wide spectrum of scientific disciplines. That vigor depends critically on the continued free exchange of information about scientific research data, results, methods, and tools. The quality of both science and application will be negatively affected by anything that inhibits, or even slows, the free exchange of this knowledge.

The purpose of Article 1, Section 8 of the Constitution, "...to promote the Progress of Science and useful Arts," is vague, and has been interpreted in many different ways. Ultimately, it is

the hard job of Government to take the long view and try to see what is best for the future of the scientific enterprise itself and for the vigor of science and technology-based industry. It is also the job of government to bring some clarity to the present chaotic situation with respect to gene patenting. The clear benefit to both of a solid and fair patent system is particularly important to a thriving biotechnology sector. Biotechnology has now presented us with some serious problems that extend the discussion of gene patents to questions of the boundary between fundamental knowledge of nature, including ourselves, and useful inventions, and the question of very nature of property rights for genes. These questions must be addressed. I have presented you with an outline of the central issues and an example that epitomizes the nature of some of the difficulties. I trust that you will wisely consider its implications. The thoughtful deliberations and recommendations of this panel should provide a catalyst for careful formulations of future policy, national and international, that will lead to a stronger and wiser system.

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