DRAFT
NJR:sh
5/14/76

C O N F I D E N T I A L

PLEASE NOTE:
THIS DOCUMENT IS NOT
TO BE REPRODUCED OR
CIRCULATED.

TO: File S74-43, Recombinant DNA Process

FROM: Niels Reimers

SUBJECT: Licensing Plan

I. Background

A. The Technology and the Threat

In 1973, researchers at Stanford University and the University of California reported the construction in a test tube of biologically functional DNA molecules that combined genetic information from two different sources. They dubbed the composite molecules DNA "chimeras" because they were conceptually similar to the mythological chimera, a creature with the head of a lion, the body of a goat, and the tail of a serpent and were the molecular counterparts of hybrid plant chimeras produced by agricultural grafting. A DNA chimera can replicate itself and express genetic information of both parent plasmids.

The method has potential for creating a wide variety of novel genetic combinations in microorganisms. The method has thus been termed "genetic engineering." Genetic engineering also makes it possible to construct bacterial cells that can be grown easily and inexpensively to synthesize a variety of biologically produced substances such as protein and polypeptides (including insulin), amino acids, vitamins, antimicrobial drugs, etc.

Genetic engineering also has the potential of producing novel biological combinations that, if accidentally released, may

present varying degrees of potential risk from innocuous to cataclysmic. This potential for bio-hazard is resulting in self policing by the worldwide scientific community and Federal "guidelines." The science and safety aspects of genetic engineering are discussed in more detail in the following selected attachments:

1. Asilomar Conference on Recombinant DNA Molecules, by P. Berg et al, Science, 6 June 1975.
2. The Manipulation of Genes, by S. N. Cohen, Scientific American, July 1975.
3. The Frankenstein Patent: And GE Created Life, and It was Hungry, Rolling Stone, 1 January 1976.
4. The Genetic Engineers Still Await Guidelines, New York Times, 15 February 1976.
5. Genetic Engineering Will Fight Disease, San Francisco Chronicle, 15 April 1976.

B. Rights in Invention

Upon investigation, it was determined inventors, for purposes of the patent, would be Dr. Stanley Cohen of Stanford and Dr. Herbert Boyer of the University of California. It was also determined that the research which led to the invention was accomplished with support of the American Cancer Society, the Department of Health, Education & Welfare, and the National Science Foundation. Agreement was reached with the research

sponsors and the University of California to allow Stanford to undertake a program of licensing the genetic engineering technology to industry and to share equally net royalties with the University of California.

II. Objectives

The objectives of the universities are to develop and implement a licensing program which (a) will be consistent with the public service ideals of universities, (b) will provide the appropriate incentives to industry to bring the potential of the genetic engineering technology forward to public use and benefit, in an adequate and timely manner, and (c) will minimize the potential for controversy because of the biohazards issue.

III. Market

Genetic Engineering is a landmark technical achievement in the field of molecular biochemistry, and can form the basis for a broad number of commercial applications of enormous potential. The largest industrial markets include enzymology (fermentation) and industrial microbiology. The following are a list of general categories of composition which could form the basis for field of use licensing. These categories also have the potential for being broken down into

subcategories:

1. Protein and polypeptides, particularly small polypeptide hormones such as parathyroid hormone and growth hormone. Other hormones such as the gonadotropins (FSH, luteinizing hormone, and cohorionogonadatropin and glycoproteins). Certain hormones such as thyroxin and triiotothyrinine are iodine-containing amino acids and might be best covered under amino acids. Insulin, ACTH, and somatostatin should probably be considered as separate examples.

2. Amino acids.

3. Vitamins, such as Vitamin B-12 and other members of the B vitamin complex. In addition to the water soluble vitamins, the fat soluble vitamins might represent a separate category.

4. Antimicrobial drugs (this involves putting genes for current antimicrobial agents into bacteria that will produce a higher antibiotic yield and also the design of new antimicrobial drugs that are insensitive to inactivation by "resistance" enzymes.)

5. Other chemotherapeutic agents, such as antitumor drugs, interferon, etc. Many of these are biologically synthesized agents.

6. Human enzymes such as fibrinolysin and urokinase. Also heparin, antihemophilia protein, etc.

7. Immunological agents, such as immunoglobulins.

8. Nitrogen fixation genes to new hosts.

9. Diagnostic reagents for diseases like thalacemia, etc.

10. Energy-producing gene combinations into more readily grown bacteria (photosynthesis, hydrogen production, etc.).

We are also aware of ongoing programs of research and development, not now using genetic engineering, for specific commercial applications as discussed below:

1. Antibiotics, Hormones and Animal Care Products

Industrial micro-organisms rather than synthetic methods are used to produce most antibiotics and animal care products. The principal advantage for using microbes lies in their efficient production, which results in significant cost savings. The large multi-national pharmaceutical companies such as Pfizer, Merck, Upjohn, Lilly and American Cyanamid would be target companies already doing extensive research and development in this area.

In addition, the production of hormones for medical research and treatment purposes is extremely limited because of inefficient extractive methods. If the recombinant DNA process is shown to be adaptable for hormone production, then Syntex might be the ideal target company.

2. Industrial Enzymes

The second largest commercial field lies in the production of industrial enzymes. Again, microbes are used as

the principal means for production. The Japanese companies, which are the world's largest producers of amino acids and other industrial enzymes, would be the ideal target companies. Specific companies include Ajinomoto, Takeda Chemical, and Hayashibara.

3. Environmental Applications; Single Cell Protein

The large oil companies are doing extensive research to develop better microbes, which are used to clean up chemical waste material. As a by-product of this research, British Petroleum and American Oil are actively developing the single-cell protein. Also, GE has developed a microbe which digests oil. An attachment, "The Frankenstein Patent--And G.E. Created Life, and It Was Hungry" describes this work and its potential.

4. Nitrogen-Fixation Microbes

Dow and DuPont are doing extensive work in the development of bacteria with nitrogen-fixation properties for grain crops. However, extensive research is necessary for understanding the fundamental mechanism of the nitrogen-fixation property as well as genetic research before successful commercial development would emerge.

5. Yeast, Cheese, Liquor Production

The bread, cheese and liquor industries depend upon natural fermentation as a key step in their production of goods.

However, it is certainly not clear how extensive their research is in molecular biochemistry. It is most likely government funding for industrial research in this area would be necessary for application of the process to emerge.

IV. Hazards

A. The Biological Hazard

As observed earlier, certain chimeras could be developed which could be accidentally disseminated to bacterial populations in humans and other species with dangerous consequences. The scientific community has been very concerned with the possibility that potentially hazardous experiments might be performed. Largely through the leadership of Professor Paul Berg of Stanford, eminent scientists from around the world were brought together in Asilomar in February of 1975 to review the progress in this field of research and to formulate guidelines for continued research in this area in order to eliminate or reduce potential for (a) the creation of, and (b) the escape of, any hazardous organisms.

Attachment 4 from the New York Times tells of the current status of the guidelines. The last paragraph of that article bears repeating: "Even if the N.I.H. adopts strict guidelines, it is hard to see how they will apply--except perhaps morally--to such other government areas as the Defense Department, or to private research. The greatest need for regulation may really lie elsewhere: outside of N.I.H., outside the biomedical community, and outside of any regulatory procedure yet devised."

It is reasonable to consider that licensing by Stanford of the Genetic Engineering process will be of some value in inhibiting commercial research into hazardous areas. That is, a company would not be prudent to conduct an extensive research program into developing a product if it could not be assured of obtaining proprietary rights in order to market that product. Stanford, in its role as licensor of proprietary rights, cannot, however, by a license agreement, legislate morality, nor prevent a licensee from conducting research in an area of potential hazard, nor prevent an accident by a licensee in releasing a biologically hazardous substance.

It does appear reasonable, however, to seek from licensees, prior to issuing a license, an expression of their understanding of the potential hazards involved and their agreement to take appropriate precautions to conform with both law, good sense, and common ethics.

B. The Public Relations Hazard

It is unlikely that licensing by Stanford and the University of California will have any practical effect whatsoever in inhibiting a scientist from conducting research which might result in an "Andromeda Strain" being unleashed upon the world. However, if that occurs, regardless of whether the licensing by the universities had anything to do with either (a) the development of the microbe or (b) its accidental release, the fact that the universities can

be perceived to be profiting from genetic engineering may cause the universities to be tarred with the same brush as the researcher or organization which develops the Andromeda Strain. It is also apparent that, even if a dangerous organism is not developed, the potential will still exist, and "bad press" is possible.

In a certain sense, "patents" are an unknown to members of the molecular biology scientific community. One scientist has argued that because it is such a basic process, it should be left in the "public and scientific community domain and not be patented." The important role of patents in bringing scientific achievements to public use and benefit is not generally known. Often, patents are considered "secret," whereas the primary intent of the patent system, which was established during the industrial revolution, is to provide to an inventor the incentive to freely disclose his technology to all rather than relying on secrecy, in return for receiving the patent "grant". The "grant" gives the inventor proprietary rights in his technology for a limited period of time. It is analogous to a copyright to prevent plagiarism of an author's works. The specific scientists most directly involved, Drs. Boyer and Cohen, have expressed concern that licensing not adversely reflect upon their scientific reputation. Dr. Paul Berg of Stanford has also expressed concern of the possible misperception of his role in the initial moratorium while Stanford was at the same time filing a patent.

Notwithstanding this potential for bad press, it is clear that licensing of the proprietary rights can serve not only to enhance early utilization of the beneficial aspects of genetic engineering for public use and benefit but also has the potential for royalty income for educational and research purposes with the potential for producing yet other landmark scientific achievements for the public in a self-regenerative fashion.