RECOMBINANT DNA

EDITED BY

A.G. WALTON

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Proceedings of the Third Cleveland Symposium on Macromolecules,
Cleveland, Ohio, 22 – 26 June 1981

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PREFACE

The Third Cleveland Symposium on Macromolecules was held under the auspices of Case Western Reserve University at the Somerset Inn in Shaker Heights from June 22 to 26, 1981. The subject of the conference, recombinant DNA, was one which was chosen because of its timely interest. At the onset of planning in April 1980, there appeared to be few conferences planned specifically on this subject, but as time progressed a growing number of meetings on genetic engineering were quickly assembled and held. We are particularly grateful therefore that so many companies chose to support the Cleveland Symposium financially in face of extensive competition.

In contradistinction to most other meetings on genetic engineering, the Cleveland Symposium was not directed to the investment community or corporate management. Nor was it directed toward a narrow area of genetic engineering, but rather to a broad spectrum of science and to young scientists. In fact, over 300 were in attendance at some exceptional presentations. The authors were asked to present their papers at the time of the conference so that rapid publication would result. Some authors were unable to comply but fortunately Verbatim Productions of New York were able to reconstruct the missing papers from the transcribed word and many thanks are due to them for their fine cooperation.

The themes of the conference were interwoven in terms of the philosophy and science of rDNA and in the latter area varied applications in fundamental medical sciences, agriculture and ecology were discussed. This volume contains the papers of invited speakers only. The shorter contributions which were often from non-U.S. authors are available in transcription from Verbatim Productions, 1780 Broadway, New York 10019.

We would like to thank the participants from more than twelve countries around the world for providing a most stimulating environment for the Symposium.

Alan Walton
July 1981

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MOLECULAR GENETICS IN ACADEMIA AND INDUSTRY

David A. Jackson
Genex Corporation

ABSTRACT

During the past five years, 40 to 50 companies have been founded in the United States whose intention is to do business in the general area of applied molecular genetics. The total number of employees in these companies is already in excess of 1000. A substantial fraction of the employees of these companies have Ph.D.'s in some aspect of microbiology, biochemistry, genetics, or biochemical engineering, and many more have bachelors or masters degrees in these fields. These companies have raised in excess of $400,000,000 in capital to support their efforts. In addition, many of the country's largest chemical, pharmaceutical, food processing, and oil companies have made substantial internal financial and personnel commitments in applied molecular genetics.

These facts have had consequences which are unique in the biological sciences, and which are viewed by many as being mixed blessings. Among the real or anticipated consequences have been:

1. A greatly expanded job market for molecular biologists.
2. A sudden increase in the perceived respectability of working in industry and in the salaries of those who do.
3. A perceived decrease in the traditionally free exchange of information among academic laboratories.
4. A shift in emphasis in academic laboratories to research problems which have a commercial application.
5. A substantially heightened interest on the part of universities and of individual faculty members in developing mechanisms for participating financially in this burgeoning industry.

Several of the problems raised by these consequences will be discussed and possible solutions proposed.

INTRODUCTION

The organizers of the conference have asked me to talk about the commercial aspects of molecular genetics from the perspective of someone who grew up with the field in an academic setting, but who now has a full-time association with a company in the group that has come to be known as genetic engineering companies. In thinking about what to say in such a talk -- there is not, after all, the normal multiplicity of charts, graphs, and tables of data on this subject which are the normal accoutrements of presentations at scientific meetings -- I decided that a bit of personal history might be informative. In large part, this is because there is a great deal of interest in genetic engineering companies by academic molecular biologists these days. Graduate students and post-doctoral fellows see the explosion in the commercial job market for molecular biologists, microbiologists, biochemical engineers, etc. as providing job possibilities in what as recently as three years ago was fairly bleak job market. Many of the genetic engineering companies and the genetic engineering divisions of established pharmaceutical and chemical companies are doing research that is at the forefront of the field. The salaries being paid in these companies are extremely attractive relative to those in many academic institutions. These facts have helped considerably to remove the stigma traditionally attached in this field to working for industry.

Established investigators in academic departments are also interested in associations with this new industry as consultants, as full-time employees, or as principals in new ventures. In addition, even those faculty members who have no interest in any direct association with the genetic engineering industry have become interested in it as a possible alternative source of funding. In an era in which the base of federal support for basic research in the biomedical sciences has been shrinking in constant dollars, alternative sources of funding are badly needed. There is thus a considerable reservoir of curiosity in academia about genetic engineering companies without, perhaps, an equivalent fund of knowledge.

A PERSONAL HISTORY

I do not pretend that my experience, which has been a gradual evolution over a period of four years from a full-time tenured university faculty position to a full-time industrial position, is any sort of general model. However, recounting parts of it will serve to illustrate one person's transition from fairly substantial naivite about the commercial world to a position of some comprehension of significant differences between it and the academic world.

When the president of Genex Corporation, Leslie Glick, called me in the spring of 1977 to ask me whether I thought molecular genetics had advanced to the point that it could be applied to a variety of commercial problems, I had had no intention of ever joining a company. Indeed, a summer spent working in the research department of a large pharmaceutical company some years before had persuaded me I would probably not be happy working in industry as I then perceived it. Nonetheless, having been one of the developers of recombinant DNA methodology in the early 1970's, I had given some thought to ways in which it could be applied in a variety of areas besides basic research, and had several ideas in mind when Glick called. The concept that Glick proposed was intriguing enough that I agreed to serve as a consultant and de facto chief scientist during the initial stages of the company's growth.

This stage involved a number of activities, some familiar and some not so familiar. One of the first was generating and presenting proposals to prospective clients, a process not so different from writing grant applications. But in this case a major effort had to be made to educate the clients about microbiology, genetics, and recombinant DNA methodology, so that they had some basis for understanding why we were excited about its potential and why we felt they should be also. This stage also involved making presentations to potential investors, a process seemingly rather like a site visit by a granting agency but in reality rather different. Most potential investors have little expertise available to them to make a detailed evaluation either of the science being proposed or the scientific capabilities of the people doing the proposing. On the other hand, most potential investors have considerable experience running a business; they feel quite secure in their ability to evaluate individuals in terms of their managerial potential and the business plan proposed for the new company. It is thus critical to understand that the criteria on which one is most likely to be evaluated by potential investors are in fact quite different from those which would be used by a granting agency or one's professional colleagues. This is true in spite of the fact that in a high technology new venture, scientific expertise and the ability to recognize and attract outstanding scientists are as essential to success as business acumen.

But it is also very important to recognize that, in spite of the fact that the new venture will be highly dependent on scientific expertise, such expertise is by no means sufficient to assure success. It is equally important that the new venture have in leadership positions individuals who have previous business experience and a clear record of accomplishment in a commercial enterprise.

The greatest difference between a new company such as Genex and an academic department are not in areas that might at first be expected. Although the research done at companies like Genex is ultimately directed towards producing a product -- which may be a bacterial strain or an enzyme or a chemical that one puts in 50 pound bags and sells -- the research is quite similar to what is being done in most academic laboratories. This is of course because the application of molecular genetics to problems of commercial importance involves in its initial stages doing quite sophisticated molecular genetics. Similarly, although company employees have no formal teaching responsibilities, the kind of interaction that goes on with graduate students and post-doctoral fellows in university laboratories is very similar to interactions with research assistants and associates in a company.

The differences between a company such as Genex and a university department are primarily due to the exceedingly rapid growth of the company. Most of the major genetic engineering companies have, like Genex, gone from several tens of employees to several hundreds of employees in a span of two or three years. This rate of growth means that the company must simultaneously conduct its business and develop essentially the entire infrastructure for the company. This infrastructure is already in place and is largely taken for granted in a university department. Its components include financial control and accounting departments, personnel policies, evaluation and promotion and salary policies and procedures, a major planning capability to integrate the personnel, space, equipment, and business demands, a marketing department and many others. It is the nature of fast growing companies that there are never enough people to do everything which needs to be done, and so sooner or later the scientists have a significant involvement in developing various components of the infrastructure. This involvement has both positive and negative aspects. The negative aspect is that it detracts from doing the science. The positive aspects are that it is a very interesting learning experience and that hopefully an infrastructure is generated which is really responsive to the needs of the people it supports.

Genex's initial strategy in starting business operations was similar to that of a number of other genetic engineering companies: rely on conducting research by contractural arrangement with a number of academic laboratores while gradually acquiring the capital resources to construct and staff its own corporate laboratories. During 1977 and early 1978, Genex sought to develop such relationships with scientists at several major academic institutions. In each case, we were readily able to come to agreement with the scientists to perform research under contract to Genex. In each case, the research was of substantial benefit to similar or complementary research programs already being conducted in the scientists' laboratories, and in each case the financial arrangements were such as to benefit both the scientists' research programs and the universities' overhead budget. Nonetheless, to our considerable surprise, the university administrations were unenthusiastic about such arrangements and indeed effectively vetoed them in each case, in spite of protests from their own faculty members. Perhaps the fact that such arrangements were relatively new in the biological sciences in 1977 and 1978 contributed to the atmosphere of suspicion and distrust that we encountered. Or perhaps the university administrations had not recognized as clearly as the individual scientists the intellectual and financial benefits of interaction with the newly developing genetic engineering industry. Whatever the reasons, I doubt that the reaction would be the same today.

Genex's initial inability to subcontract research to academic laboratories fortunately had few adverse consequences for the company, and may in fact have been a blessing in disguise. The lack of adverse consequences stemmed from the fact that Genex was quickly successful in raising a substantial amount of capital, initially from a venture capital firm and subsequently from a major chemical and forest products company. Because of this early success in raising capital, Genex was able to undertake a major laboratory development program and to begin hiring a substantial number of scientists on a much faster schedule than the company had initially thought would be possible. This made it possible to begin operations without subcontracting with academic laboratories. The disguised blessing aspect of our failure to develop contractual research arrangements with universities is that Genex has been spared many of the difficulties and hard feelings encountered by several other genetic engineering companies over ownership of proprietary rights, research materials, and ideas generated in the course of company-sponsored research in university labs. I should note at this point that Genex has had and continues to have highly satisfactory consulting relationships and research collaborations with a number of academic scientists.

As Genex continued to expand, I became more and more impressed with the possibilities for doing innovative and intellectually stimulating science in an organization quite different from a basic research department in a major university. Also, in common with a number of my colleagues who had also been doing basic research in molecular biology for a number of years, I had been hoping to find a way of applying some of my scientific skills in ways that would have a beneficial and relatively rapid impact on society. The new applied molecular genetics industry looked like a good place to satisfy this aim. Finally, it had been clear to me for some time that, in general, the opportunities available for professional job satisfaction and enjoyment in university basic research departments were going to diminish rather than increase, reversing a trend that had attracted many people to biomedical research in the previous twenty-five years. Taking all these factors into account, it was relatively easy to decide in 1980 to resign from my faculty position and join a genetic engineering company, a decision I would not have even contemplated seriously three years previously.

INTERACTION BETWEEN INDUSTRY AND ACADEMIA

Potential problems

Most discussions of the rapidly evolving relationship between academic biomedical research departments and the biotechnology industry start with a litany of real or potential problems: excessive secrecy in industry, inhibition of free flow of information among academic researchers, recruitment of the best young scientists into industry, diversion of research effort from basic research, potential conflicts of interest for faculty members who are also principals in a company, etc. While these problems deserve serious attention, it is important to recognize that there are many more beneficial consequences of interaction between academia and industry in molecular biology than there are problems. I will return below to what some of these beneficial consequences are. Before doing so, however, one particular problem deserves additional comment.

Secrecy. A significant threat to continued rapid development in the field of basic and applied molecular genetics is secrecy. The problem of secrecy exists within both the commercial and academic sectors. The detrimental consequences of secrecy are obvious to all. Science breaks new ground by building on its past, by integrating information and concepts from many sources and synthesizing new ideas from them. To the extent that the past is hidden from the scientific community, whether deliberately or inadvertently, progress is slowed. Imagine, for instance, how different molecular biology would be today if Maxam and Gilbert and Sanger and his colleagues had kept secret for two years their methodologies for rapid sequencing of DNA.

The entry of profit-making companies into the field of molecular genetics has coincided with an increase in secrecy in the field, and the companies have often been blamed for this. However, the fundamental problem is not that companies have entered the field, destroying an openness which existed only as an ideal in any case, but that there is a widespread belief that many of the new facts, concepts, and technical developments coming out of research in molecular genetics can be translated into a large number of dollars very rapidly. Whether or not this is true, it is the existence of the perception that it is true that is the root cause of secrecy. If someone perceives that a large benefit can accrue to him as a result of his ideas, and if he runs a substantial risk of someone else reaping the benefit if they learn about the idea, he is likely to be careful about disclosing the idea until its potential to reward him has been protected. These basic motivations of human nature have operated no less among molecular biologists than among all other groups in our society in the past. There has always been a reluctance to disclose fully new ideas or findings at a preliminary stage of development, i.e. before their originator has established his link to them by publication. Today's situation differs in several respects, though the differences are generally more quantitative than qualitative ones. A major difference is that the stakes are perceived to be much higher. Rather than the difference between a 7% raise and a 10% raise, differences of hundreds of thousands of dollars are widely thought to to be at stake. Another difference is that secrecy has been actively and, in my view, excessively encouraged by companies that have entered the field. And a third factor is that both the academic scientists and the companies tend to have delusions of grandeur about the economic worth of specific ideas or bacterial strains or DNA molecules. The combination of these factors has meant that there is a strong tendency to treat any new development as having huge economic potential, and therefore to be secret about it until that potential has been protected, generally by filing for a patent. Such behavior runs the risk of killing the very goose that is supposed to lay all the golden eggs. If the great potential perceived for biotechnology is to be realized, it is essential to maintain the vitality of molecular biology and the rapidity with which it can develop both in academia and industry. And exchange of information is an essential ingredient in the vitality of science.

I have no magic prescription for how to solve the secrecy problem. However, I do have some suggestions for a common view of the relationship between academia and industry which, if accepted by the parties involved, will lead to an atmosphere where freedom of information flow is valued by all. First, the genetic engineering industry needs to recall very clearly where its roots are and will continue to be: that is, in university research departments. It is the most direct form of self-interest for this industry to insure the health of these academic departments. These departments will continue to develop the majority of new ideas and techniques. They will also be the training ground for the future employees of this industry. To the extent that excessive secrecy represents a threat to the health of the scientific enterprise in academia, industry must simply accept a larger degree of openness than it has historically found comfortable.

Second, both industry and academia should recognize more clearly that in a field which moves as rapidly as does molecular biology, there are relatively few ideas or microbial strains or techniques which will confer significant economic advantage for an extended period of time. The economic race is most likely to be won by those who can work most rapidly and effectively, rather than by those who are the most secret. If this notion is correct, it has two consequences. The first is that it is better to be good than to be secret. And the second is that it is easier to be good if one minimizes secrecy and maximizes information exchange.

Third, it seems to me important for those of us in the genetic engineering field, whether in academia or industry, not to take ourselves too seriously. It is easy to become overly impressed with one's own press clippings, particularly when the consistent message is that one is engaged in a world-shaking enterprise. While it is certainly true that applied molecular genetics and other forms of biotechnology have enormous economic potential during the next several decades, it is important to realize that not all of the projections one reads in Time magazine or the Wall Street Journal, to say nothing of the National Enquirer, are the result of serious, informed analysis. A more balanced view might lessen the tendency to classify everything top secret. It is as important today not to accept uncritically everything one reads about the potential of applied molecular genetics as it was five years ago when one read about the supposedly catastrophic hazards associated with the field.

Fourth, it is in the interests of both academia and industry to push for a speed-up and streamlining of the process by which patents are granted. The patent system is designed to deal with the adverse societal consequences of secrecy, which have been recognized for hundreds of years, by granting a time-limited right to exclude others from practicing an invention. In exchange for this limited monopoly, there must be full disclosure about the nature of the invention and how to practice it, so that others may use it as a stepping stone for further advances. The current long delays associated with the patent examination process, caused in part by inadequate staffing of relevant disciplines in the Patent and Trademark Office, tend to reinforce any inclination to secrecy.

Beneficial Interactions

In spite of the potential problems associated with the rapid growth of the genetic engineering industry, there is much more cause for optimism than despair. Many new and beneficial interactions between the companies in this industry and the academic research world from which they arose have begun to evolve. A positive interaction of major proportions is the expansion of job opportunities for young biochemists, microbiologists, and the like who are just finishing their training in academic departments. This expansion of job opportunities in the commercial sector fortuitously occurred at just the time that a serious oversupply of Ph. D.'s trained in the biological sciences was developing. In contrast to the situation a few years ago, there is now a definite seller's market for individuals trained in many subspecialties of molecular biology, microbiology, and biochemistry.

Another area of interaction between academia and industry which is expanding is provision by industry of financial support for research and training in academic departments. At the present time, provision of substantial amounts of relatively unrestricted support is still being done primarily by large, established chemical and pharmaceutical companies. These companies, which have substantial current revenues and profits, are in a position to finance major commitments. The newer genetic engineering companies, none of which are generating significant profits at the present time, are still not in a position to undertake substantial, relatively unrestricted financial commitments to academic departments. However, I would hope and expect that as these companies develop significant levels of revenues and profits from their operations, support of university based research and training programs will increase. Many of the individuals associated with the genetic engineering companies recognize that the industry cannot survive and prosper without a healthy academic research establishment. At the present time, genetic engineering companies are providing support for fellowships, seminar programs and lectureships, scientific meetings and travel, and for cooperative university-industry programs.

One such cooperative program which may serve as a model for others is the Applied Molecular Genetics program recently announced by the University of Maryland's Baltimore County campus. This program is designed to provide a year of intensive, hands-on training in modern techniques of molecular biology, with special emphasis on nucleic acid biochemistry and molecular genetics. The program was developed by UMBC with the active participation and support of two local genetic engineering companies, Genex and Bethesda Research Laboratories. Staff members of both companies will serve as adjunct faculty members in the program. The companies will also provide support in terms of specialized supplies, equipment, and techniques. In addition, the companies have committed financial support for seminar speakers in areas relevent to the program and to scholarships for several students. The present program will be for college seniors or graduates with a strong background in microbiology and biochemistry, and will award a certificate on completion. However, a master's level program is actively being planned. This program would allow expansion into related areas of biotechnology such as biochemical engineering and hybridoma-monoclonal antibody technology. An important component of the master's degree program would be the opportunity for the students to do internships at Genex or BRL.

A third area in which interaction between academia and industry is proving beneficial is in straightforward scientific collaborations. Opportunities for mutually beneficial, joint efforts on a research problem can only increase as the genetic engineering industry expands and its technology becomes more sophisticated. Such collaborations need not involve any proprietary interests. Indeed, there is no reason for many of them to be any different from collaborations between two academic researchers.

In addition to the individual sorts of interactions just described, there is a growing opportunity for academia and industry to benefit mutually from joint action on a much broader scale. I previously alluded to one such area in suggesting that joint efforts to press for increased speed and efficiency in handling patent applications would be to everyone's benefit. Another such area for broad scale cooperation is in the support of specialized national facilities. A specific example is the widely recognized need for a national computer network via which both universities and companies could access and manipulate nucleic acid sequence data. Such a network would have to include a substantial component which would receive, process, and archive in computer compatible form the flood of sequence data which is now being generated. Dr. Margaret Dayhoff, Director of the National Biomedical Research Council at Georgetown University, and her colleagues, have been collecting and archiving such data for the past several years. Dr. Dayhoff has reported that for most of 1980, the amount of DNA sequence information published increased at a compounded rate of 15% per month.

The National Institutes of Health are currently considering proposals to establish a national DNA sequence computer network, which would include associated archive and software support. However, there is some question as to whether federal funding sources will be adequate for the level of support needed. If a university-industry consortium could be developed from those who would utilize such a facility, the financial burden for any single member of providing financial support to supplement the federal funding would not be large.

CONCLUSION

The opportunities for mutually beneficial interactions between academic departments and the developing biotechnology industry are broad and exciting. As in any situation of rapid growth, there will be growing pains. But with foresight and an open-minded, realistic evaluation of the situation by all parties, the problems should not be serious. A truly exciting possibility is that by