INITIATING CROSSDISCIPLINARY RESEARCH

The Neuron-Based Chemical Sensor Project

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CHEMICAL ENGINEERING is essential to the process of bringing new areas like biotechnology, electronic, and other advanced materials to commercial success. The success of this process depends on significant cooperation between chemical engineering and other disciplines. Although there is a large volume of literature on the subject of interdisciplinary and/or crossdisciplinary research [1-3], most of it concerns large projects (as defined in Table 1) and little has been written from a chemical engineering perspective. The rationale behind the levels of funding used in Table 1 is called for. Usually in the initial stages of a project, $30,000 to $70,000 for a single year is only sufficient to generate pilot data and perhaps to provide incentive for the formation of a cross- or an interdisciplinary team. A yearly budget of $70,000 to $150,000 for a period of three to five years provides enough for more than one graduate student to focus on specific aspects relating to the expertise of each co-investigator. Amounts above $150,000 can support large groups with more personnel per discipline involved as well as supporting inter-university research activities where extensive travel may be necessary. The purpose of this paper is to address the problems of initiating and conducting a small university level crossdisciplinary project with a yearly budget at $30,000-$70,000. As an example, specific reference is made to a Washington State University (WSU) project on neuron-based chemical sensors which involved chemical and electrical engineers as well as neuroscientists and an immunologist. The experience gained by this group in putting together a research team from various disciplines could be of value to chemical engineering professionals, particularly for young faculty and graduate students who are considering multi-disciplinary projects.

TABLE 1
Project Size Based on Yearly Budget

Project Size	*Yearly Budget (US $)*
Small	Between $30,000 and $70,000
Medium	Between $70,000 and $150,000
Large	Greater than $150,000

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DISCIPLINE AND CROSSDISCIPLINARITY

What is a discipline? Generally the term 'discipline' refers to a specialized field of knowledge. Swanson [4] has pointed out that disciplines in a university environment develop when both faculty and administration come to recognize reasonably distinct areas of inquiry. It is important to realize that each discipline is usually composed of a set of narrower specializations and that the comprehensiveness of the discipline has at least three properties [5]: 1) a conceptual model shared by individual members that forms the heart of the discipline—an example is the paradigm of transport phenomena, presented in the 1960 textbook by Bird, Stewart, and Lightfoot, which suggests that the proper study of chemical engineering is the molecular phenomena that are fundamental to the understanding of the performance of chemical equipment; 2) a set of phenomena common to the various specializations (*e.g.*, chemical kinetics, thermodynamics, and others); and 3) breadth of the discipline, achieved through overlapping of multiple narrow specializations of different individuals as opposed to being embodied in one scholar. Through this overlap comes cohesiveness, and a common discipline language, or jargon, develops to an extent less possible between disciplines [4].

It should be mentioned that currently there is no agreement among practitioners of multi-disciplinary research on a unifying terminology. However, there is a need for such a consensus. The interchangeable use of the terms interdisciplinary, multidisciplinary, crossdisciplinary, transdisciplinary, and others, when describing research across disciplines, is widespread. Recently, Castri [6] suggested a set of precise definitions for the above terms which is based on the level of cooperation among researchers. These definitions, reproduced in Figure 1 (with minor changes), have minimized the confusion. Multidisciplinary research involves several disciplines, usually at the same hierarchical level, without any demand for cooperation. In most cases interaction occurs only during the final stages of the project through editorial integration of the findings. Crossdisciplinary work is characteristic of projects that are problem-focused, where one discipline interacts with others for what those disciplines can offer toward achieving a solution. The project described in this paper fits into this category. Interdisciplinary research, on the other hand, tends

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to be characterized by the dominance of a common view. This type of cooperation may involve more than one hierarchical level and usually results in new concepts. One example that fits into this category is the work of Barry Richmond, a neurobiologist with the National Institute of Mental Health, and Lance Optican, a biomedical engineer with the National Eye Institute. This interdisciplinary team has come up with a complex mathematical theory (the multiplex filter hypothesis) that challenges scientific orthodoxy by proposing that visual nerves transmit information by multiplexed, encoded signals [7]. This work has the potential of replacing the current way of thinking about the brain. Finally, transdisciplinary efforts involve multilevel interactions that lead to an entire common purpose system. A typical example is the development and deployment of military aircraft [8]. A

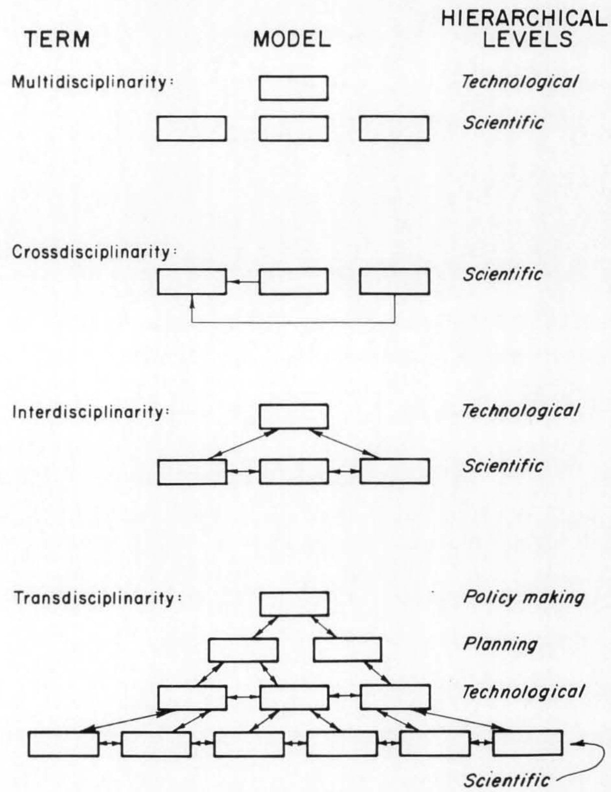

FIGURE 1. Models of increasing cooperation and coordination of research management. (Used by permission from the International Science Policy Foundation.)

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Bernard J. Van Wie received his PhD at the University of Oklahoma in 1982 and did an additional year of postdoctoral work in the area of thermodynamics. Since then he has been an Assistant (now Associate) Professor of Chemical Engineering at Washington State University, where he has established a multidisciplinary effort for the development, monitoring, and control of bioreactors and bioseparation processes.

Rodney S. Skeen received his BS and MS in chemical engineering from Washington State University in 1986 and 1987 respectively. He is currently a PhD student working on the development of neuron-based chemical sensors for long-term continuous monitoring. In the past he has been involved in developing piezoelectric sensors.

William C. Davis received his BA in biology from Chico State College in 1955, an MA in biology from Stanford University, and his PhD in medical microbiology from Stanford University School of Medicine in 1966. He is currently engaged in analysis of the mechanisms governing the immune response to AIDS related viruses in goats and the development of subunit vaccines to protozoan parasites and infectious agents.

Charles D. Barnes received his BS in biology and physics from Montana State University in 1958, his MS in physiology and biophysics from the University of Washington in 1961, and his PhD in physiology from the University of Iowa in 1962. He is currently undertaking a detailed study to delineate the descending modulatory role played by the locus coeruleus of the cat, rat, and mouse on spinal and autonomic motor systems.

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project of this magnitude involves all the levels from scientific to policy-making and demands extensive cross-interactions.

In the next section a specific example of an ongoing crossdisciplinary effort between the authors is presented, from which general principles will be extracted on how to initiate and conduct such research.

NEURON-BASED SENSOR RESEARCH PROJECT

The project rationale is presented below. A detailed description of findings are reported elsewhere [9].

Justification

The major problems in reliably determining *in vitro* or *in vivo* concentrations of antibodies or antigens, and for that matter any hormone, protein, ion, toxin, drug, or hazardous substance, are the lack of fast, reusable, and accurate sensing devices. To date, many solutions have been tried [10-18], yet most are still unsatisfactory. In this project, a new approach to sensing is being investigated in which the long term goals are to develop biochips which will be used to monitor electrical activity of neurons and later, excitable synthetic membranes on exposure to analytes. The proposed sensing devices will allow one to take advantage of the specificity, sensitivity, and speed of response characteristic of neurons.

Neurons are the primary nervous system components for processing and transmitting information. An example of a differentiated neuroblastoma (a tumorous nerve cell), cultured in our laboratory, is shown in Figure 2. Some of the processes (axons) receive, while others send, information. Nerve cell membranes contain receptors for neurotransmitters and other chemical species. Receptor/neurotransmitter binding events may lead to the activation of second messenger compounds within the cell, or to the opening or closing (gating) of specific ion channels (*e.g.*, Na^+, K^+ or Ca^{2+}). The opening of the channels results in ion passage that changes the electrical state of the neuron which in many cases affects neuron electrical properties like action potential (AP) characteristics. For electrically active cells, the channels are voltage sensitive and can be caused to open or close by changing the transmembrane potential through applied current pulses [19].

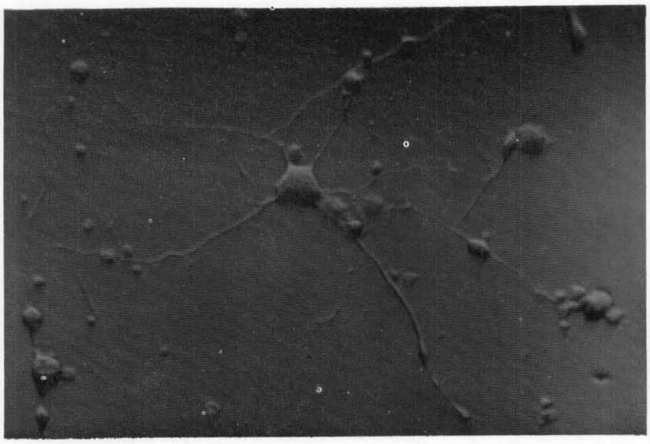

FIGURE 2. Typical morphological appearance of an N-18 neuron, differentiated with 2% serum and aminopterin treatment.

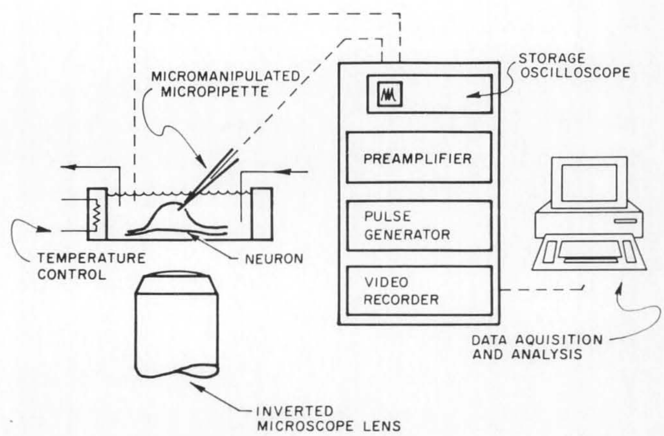

FIGURE 3. Schematic of experimental equipment.

To achieve a solution to the problem outlined above within a reasonable economic timeframe, we assembled a crossdisciplinary team of engineers and biologists. The engineers brought a systems approach to the project, with a clear view of how the final product should be implemented. The biologists brought essential basic information on the general methodology used to study neurons. To demonstrate proof of concept, neurons from a fresh water snail, *Limnea stagnalis*, were used with alcohols as model analytes (methods and results reported are limited to the initial studies).

Methods and Interpretation of Results

A schematic of the exprimental set up is shown in Figure 3. The visceral and right parietal ganglia (a mass of tissue containing nerve cells) were removed from the snail, *Limnea stagnalis*, using the methods of Byerly and Hagiwara [20]. The ganglia were transferred to a continuous flow recording chamber and exposed to varying concentrations of ethanol (0.2-1.0

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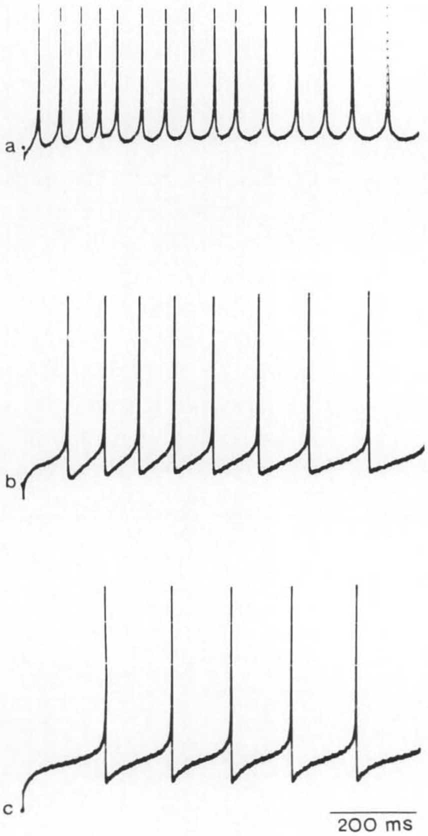

FIGURE 4. Effects of ethanol on the firing frequency in* Limnea *neurons (stimulating current was 0.8* nA*).

M) in saline solutions. Random cells were impaled with glass micro-electrodes and stimulated to produce APs by passage of current through a bridge circuit from the preamplifier. Signals were monitored using the storage oscilloscope and stored for later analysis on the video recorder. Cells selected for analysis were limited to those which regularly induced spike discharges of amplitudes greater than 50 *mV*. Repetitive firing rate was based on the interspike intervals of the first four APs, for cells induced by passage of a 1.0 *S* current pulse with a 0.25 *Hz* repetition rate.

Responses of different neurons were compared by normalizing firing frequency values to the baseline (no alcohol) response at a given current level and plotting the results as a function of concentration. Some cells showed excitatory effects with increasing concentration, as show in Figure 4. The higher the ethanol con-

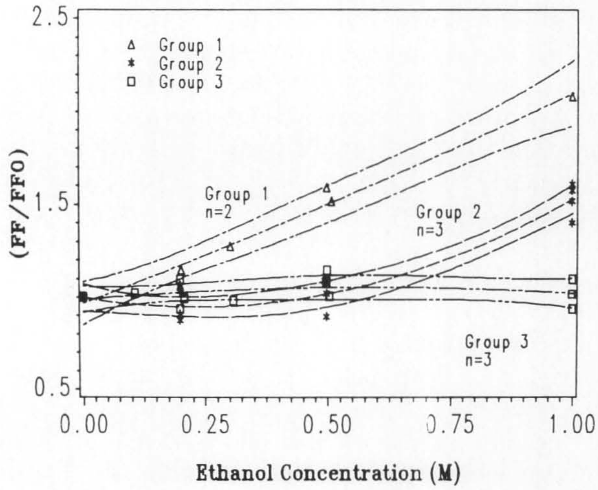

FIGURE 5. Normalized firing frequency (FF/FFO) at 0.7* nA*. Outer lines for each group of cells represent 95% confidence limits on the mean values.

centration, the higher the firing frequency. In Figure 5, plots of normalized firing frequency versus ethanol concentration with 95% confidence interval bands on the mean values, shows three distinct categories. Group 1 with a strong excitatory response, Group 2 with a weaker response, and Group 3 with no response. Linear correlation between analyte concentration and a property of a neuron demonstrates in a preliminary way the feasibility of the sensor concept. More basic and applied work is currently being conducted to demonstrate an expanded scope of applications and to explain the mechanism involved in the sensing process.

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PROJECT FUNDING

Typically an investigator with a problem looks for new methods or solutions from another discipline, or may alternatively have a novel solution in need of a problem. For the neuron biosensor project, one of us

(BVW) recognized that advances in biosensing technology would require the systematic study of biological chemical sensing. The results obtained from such studies would provide the insights needed to design highly sophisticated detection and signal transmission devices that mimic those present in living systems (*e.g.*, the olfactory system). To verify the concept, suitable techniques for studying neuron behavior were needed. Faculty members who traditionally study neurons were needed for a crossdisciplinary team. A group was identified with expertise in spinal cord neurophysiology, having laboratory facilities with intracellular recording equipment similar to that shown in Figure 3. A proposal was put together for preliminary studies with the main intent of obtaining pilot data to demonstrate the concept.

Crossdisciplinary ideas such as the one in this paper depart dramatically from the current knowledge base and contain substantial uncertainties concerning appropriate methods and outcome. Most systems for selecting university research projects for funding tend to favor proposals with logical and systematic extensions of current knowledge. Such proposals are less risky, tend to have easily predictable outcomes, and are relatively easy to defend. Therefore, the new and innovative crossdisciplinary projects may have difficulty surviving the conventional peer review process. At this point one has to identify a funding source that can entertain exploratory research projects. Table 2 contains a non-exhaustive list of such programs known to the authors. Some of the programs are specifically designed for this purpose.

The neuron-based chemical sensor project was first funded as a NSF Expedited Award for Novel Research at a $30,000 level for 1986/87. Additional funds of $94,000 were obtained from the Washington Technology Center (WTC) for the 1987-1989 biennium as well as a $12,400 grant from the WSU College of Engineering. WTC funds are provided on a matching basis to encourage faculty of universities in the State of Washington to obtain extramural resources in research areas of critical importance to the State. Based

TABLE 2
Possible Sources of Support for Risky Proposals

Sponsoring Agency	*Program*	*Contact*	*Comments*
National Science Foundation	Expedited Awards for Novel Research	Engineering Director NSF Washington, DC 20550	• for exploratory research of high but unproven potential for future advances • non-renewable funding up to $30,000 • does not require external review • to be re-evaluated after 1988/89
National Science Foundation	Research Initiation Awards	Engineering Director NSF Washington, DC 20550	• designed to encourage faculty to begin their careers and to make an academic career more attractive • funding up to $60,000 for 24 months • multiple investigator proposals not eligible
National Science Foundation	Presidential Young Investigator Awards	Engineering Director NSF Washington, DC 20550	• provides cooperative research support for the most outstanding and promising young science and engineering faculty • nominations originate from department chairs • minimum of $25,000 and up to $37,000 in matching funds, which comes to a maximum possible total of $100,000/year, for five years
Engineering Foundation	Engineering Research Initiation Grants	Dr. R.E. Emmert, Exec Dir. AIChE, United Eng. Cent. 345 East 47th St. New York, NY 10017	• for initiating research for new full time engineering faculty without research support • support limited to $20,000 • crossdisciplinary projects encouraged
National Institute of Health	Biotech. Research Training	Dr. H. Landsdell Federal Building Room 916 Bethesda, MD 20892	• This program has recently been initiated in response to the enormous growth of the biotechnology industry that has resulted in critical shortages of experts in areas such as biochemical separations and engineering. • support up to $31,500
State Biotechnology and/or Technology Centers	Not applicable	Not applicable	• Several states have set up centers to support local efforts in biotechnology. However, the nature of the centers varies greatly. Each has a different focus and source of support and set of programs. Some are designed to support business and create new companies. A survey of 40 state-supported biotechnology centers in 28 states was conducted by the Biotechnology Information Program of the North Carolina Biotechnology Center in the fall of 1987.
Not For-Profit and For-Profit Corporations	University Exploratory Research (P & G Co.)	Procter and Gamble Co. Miami Valley PO Box 398707 Cincinnati, OH 45238	• focuses on proposals that depart dramatically from current knowledge base that entail substantial uncertainty • support up to $150,000 for three years • not renewable after the three-year period
Local University Grant and and Research Offices	Not applicable	Not applicable	• Most universities have monies that are available internally for limited support. The graduate or grants office puts out announcements for such competitions.

on successful completion of the first phase, a proposal has been submitted to WTC for funding for the next biennium (1989-91). Two additional proposals have also been submitted to NSF: one to the Biotechnology Program to support the present group's effort and another to the Emerging Technology Program for an inter-university program with the University of Washington to support a broader based microsensor effort. If these proposals are funded, our project will advance from a small to a medium sized program as defined in Table 1.

PROPOSAL WRITING

Once the funding source(s) is/are identified, it is important that contact is made with the program director(s) to obtain their input on the suitability of the proposal. The next task is writing the proposal—the following procedure worked well for us. First, a tentative table of contents was generated by the ChE group, clearly identifying the parts of the proposal to be written by each participating discipline. Then the participants were asked to write those sections consistent with their expertise. These were circulated one to two weeks before a meeting was held to merge the sections, and after the meeting, the chemical engineering group had the responsibility of preparing a first draft. We have found that this approach solves two key problems associated with proposal writing in a crossdisciplinary environment. First, any misunderstandings regarding approach, paradigms, or jargon are resolved at the outset. Second, consistent terminology and style of writing are adopted since the integration of the proposal components is entrusted to one individual. After preparation of the first draft, the usual procedures for proposal preparation are followed. These include distribution to each participant to check for logical progression of ideas, appropriateness of experimental design to the problem solution, and clarity of experimental protocols and general editing, followed by a meeting to incorporate the new changes prior to preparation of the final copy.

OBSTACLES TO GETTING THE WORK DONE

Although the literature is replete with do's and don'ts regarding the management of crossdisciplinary projects [21 & 22], there is a paucity of practical suggestions to obviate some of the frequently listed obstacles. In attempting to address this problem, we have limited our discussion to those aspects with which we have had experience.

Language or Jargon

During the proposal writing stages, it is important to remember that credibility must be maintained among reviewers who are aware of the specific disciplines united in the proposal. Therefore, well-known terms and concepts must be used. Because of this, the integration of different language and jargon becomes a problem and it usually surfaces at this point. Some researchers have asserted that jargon should be eliminated [23], but this cannot happen quickly since it takes time to learn another 'discipline language'. However, efforts have to be made to minimize confusion. For newly formed groups frequent discussions, querying of co-workers, and exchange of relevant papers serve as short term solutions. On a long term basis, participating in a relevant course offered by the co-workers in the other disciplines makes a big difference. For example, three of us (BVW, WSK and RSS) attended a course, "Advanced Neurophysiology," offered by CDB. Another useful effort, especially for students and postdoctoral associates, is to spend time in the laboratories of the other investigators, under their supervision. For example, WSK does 50% of his experimental work in the laboratory of WCD. The focus of this effort is to develop monoclonal antibodies to differentiated neuroblastoma membrance antigens and to determine the extent of crossreactivity among several cell lines.

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Skepticism

In the early stages of a small crossdisciplinary project, there is usually some doubt about the future success of the project. This skepticism has been explained by Bella and Williamson [24] to reflect an understanding of the magnitude of the research problem and the potential inappropriateness of the existing methods. Such an attitude of healthy skepticism is essential. Overconfidence usually reflects a shallow understanding of the important questions. It should be pointed out, however, that extreme skepticism can be disruptive.

Openness to the Evolving Nature of Crosdisciplinary Work

It is unlikely that a principle investigator deliberately identifies the intellectual and social components of a research program organizational pattern in advance. The project organization more often evolves into a stable pattern by trial and error. In our case the project began with one chemical engineering faculty member (BVW) and two neurophysiologists (CDB and SJF). After a year of initial experimentation, it was determined that if the neurons were to be successfully used as the primary transducers in biosensors, emphasis needed to include fabrication of microdevices that would contain the neuron and the electrical connections. Therefore, electrical engineers (KC and NSD) with expertise in micromachining and integrated circuits technology were invited to join the team. Furthermore, since sensor development efforts are now directed toward biological molecules of economic significance, such as monoclonal antibodies and antigens, an immunologist (WCD) has joined our team. This demonstrates the evolving nature of crossdisciplinary work and the importance of openness to the need of other expertise, which, if ignored, may result in the demise of the project.

Other Issues

Based on our experience, frequent team meetings (on top of the standard weekly or bi-weekly meetings between students, postdocs, and their direct supervisors) can be time-consuming. Hence, meetings should be pegged to specific project milestones, as opposed to fixed intervals, in order to avoid unproductive discussions. However, some flexibility should be maintained for emergency meetings as needed. In this regard, availability of modern computers attached to high-speed data networks, such as those donated to numerous universities by AT&T through their University Equipment Donation Program, can temper the inconvenience of emergency meetings. For example, when data are being collected or analyzed, questions that arise which require discussion can be dealt with instantly by all investigators across campus via information sharing workstations.

Also, financial management (especially for work done in more than one laboratory) can lead to time delays. Most universities have straightforward accounting procedures to handle this type of problem. In cases where this is not true, a procedure for billing the project account should be put in place immediately. This will save valuable time. For example, our group needed to immunize rabbits to generate polyspecific serum for testing neuron responses when subjected to antibodies. However, the chemical engineers, in whose hands the budget account resided, lacked clearance to handle live animals, and obtaining this clearance would have taken at least one month. To circumvent this problem, rabbits were purchased through the laboratory of WCD and work was performed under his supervision. The chemical engineering group was later billed for those expenses.

Another obstacle that is often mentioned is conflict of paradigms or concepts. This is potentially the case between scientists (whose focus is mainly on understanding the principle mechanism underlying important processes) and engineers (whose emphasis is mainly on applying existing fundamental knowledge to solving practical problems). Under such circumstances, the best solution might be maintaining good communication links through reviewing progress toward the team's long-term objectives.

DISCUSSION

In this paper we have attempted to describe our experience in initiating and conducting a small biotechnological crossdisciplinary project in a university environment. It is wise to put in perspective the relationship between small university crossdisciplinary projects and the American competitiveness in the global marketplace. The history of science and technology teaches us that most significant developments have occurred as a result of approaches that involved crossing disciplines. In fact, chemical engineering as a discipline is one of these developments. Hence, adaptation of technical information from two disciplines, resulting in a major development, is not new. Reasons for the greater current interest in the subject are better expressed by the NSF in their program announcement for Centers for Crossdisciplinary Research in Engineering, otherwise called Engineering Research Centers (ERC), as follows:

> *The need for ERC's arose from the fact that despite America's preeminence in science, our competitive position in the international marketplace has been increasingly eroded. Besides the various economic and managerial factors, part of this competitiveness problem can be attributed to the gradual loss of U.S. industrial prowess in turning research discoveries into high-quality, competitive products. Many practitioners and leaders have come to the realization that while American academic engineering has made great strides in basing modern engineering on advanced scientific knowledge and the latest laboratory and computational tools, it has not placed sufficient emphasis on the design of manufacturing processes and products to keep pace with increasingly sophisticated consumer demands around the world. In addition, crossdisciplinary research focused on technological advancements from an engineering systems perspective is needed to better prepare engineering graduates with the diversity and quality of education needed by U.S. industry.*

The National Research Council study on "Chemical

Engineering Frontiers: Needs and Opportunities," chaired by N. R. Amundson of the University of Houston, identified four major areas of opportunity. One of these is the development of new high technology industries that are driven by scientific breakthroughs, including 1) biotechnology, 2) electronic, photonic, and recording materials and devices, and 3) advanced materials. When one focuses on biotechnology, it is not clear whether we at the university are doing enough to "win the war." For example, of the eighteen Engineering Research Centers currently supported by NSF, only one (at the Massachusetts Institute of Technology) addresses a biotechnological aspect (Process Engineering). It appears the process of creating research groups has to begin with small crossdisciplinary projects similar to the one described in this paper, and then grow through the medium and large size levels to finally attain a level where the participants can successfully compete for an ERC grant. The key ingredients to the formation of small projects are the availability of faculty who are willing to cross disciplines and the availability of funds for novel (yet risky) proposals. We believe that a larger pool of funds targeting such studies, which would not be funded through conventional means, may be one step, among many, that could ensure that America maintains the lead it currently enjoys in areas such as biotechnology.

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