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Bioengineering programmes rise to meet the challenge of a young science

When biology met engineering, they created a new field for scientists who don't want to be hedged into one discipline.

Scanning the c.v. of someone who is established in bioengineering (BE), you might get the impression of a highly educated individual who could not decide on a major field of study. "If you look at my c.v. I think this shows it well: materials science, mechanical engineering, mathematics," says Mauro Ferrari. After a maths degree in Italy, Ferrari was hired in 1989 by the University of California, Berkeley, as an assistant; he became a tenured professor after getting his graduate degree in mechanical engineering. He entered the faculty ranks with a split appointment between the departments of materials science and engineering and of civil and environmental engineering.

According to Ferrari, however, his work was always on micromechanics and its application to biomedicine. The problem back then, he says, was that the field was young and poorly defined. Berkeley did not have a biomedical engineering (BME) department. Instead, there were graduate groups — Ferrari joined those for BE, applied science and technology and biophysics.

Contrary to what his c.v. might suggest, Ferrari seems to know exactly where he is going and to enjoy the trail he is blazing. Today, he is getting closer to what he says he is supposed to be. In 1999, he moved to the Ohio State University (OSU) — still with a split appointment as a professor of internal

Ferrari: enjoys blazing a trail.

medicine and mechanical engineering, but now directing the OSU Center for Biomedical Engineering. He made the change to be nearer the interface of clinical work — UC Berkeley lacked clinical facilities. It's quite a leap, though, from physical scientist/engineer to clinical investigator. For example, says Ferrari, to get funded by the National Science Foundation, one must demonstrate 'proof of principle' for the technology. To receive funding from the US National Institutes of Health (NIH), one must show some clinical evidence. Currently, the mode of funding from the NIH is not conducive to triggering great advances in technology, he says.

Whither biomedicine?

According to Robert Nerem, director of the Georgia Institute of Technology's Parker H. Petit Institute for Bioengineering and Bioscience, the time has come to bring biology formally into engineering. First physics, then chemistry, were originally integrated into engineering. Biology is following.

Nerem makes an important distinction: biomedical engineering is simply the biggest

application of BE at the moment. "As we move into the twenty-first century, I think that there will be just as many applications outside the medical area where the integration of biology and engineering will be required," he says.

Douglas Lauffenburger, co-director of the Massachusetts Institute of Technology's (MIT's) division of Bioengineering and Environmental Health (BEH), agrees. He cites three reasons: biology is now mechanistic enough at a molecular level to be accessed by quantitative engineering analysis and design methodologies; new technologies built on biological components are becoming increasingly important to society; and complex biological systems require an infusion of systems-integrative engineering for continuing advances in fundamental understanding.

Elaborating on the broader meaning of BE, Lauffenburger sees a persistent confusion over the terminology, in that people use biomedical engineering and bioengineering interchangeably. Biomedical engineering is a field of application, he points out, whereas bioengineering is a new discipline: "We want to train students to apply it broadly to medicine, the environment, to materials and to defence." At the same time, he predicts that bioengineering will soon become the central discipline for major advances in biomedical engineering applications.

Passing the baton?

The Whitaker Foundation has long been a major supporter of biomedical engineering in the US. Peter Katona, president of biomedical engineering at the foundation, is hopeful that the NIH will show long-term commitment to bioengineering. While Whitaker has helped to build the educational infrastructure of biomedical engineering with some \$50 million annually, it now plans to shut its doors in 2006. At the moment, the foundation has about \$400 million, almost half of that already committed, says Katona. The rest will probably be committed in the next three years.

According to Katona, Whitaker research grants are typically intended for faculty members who are early in their careers at universities. The foundation also provides funds to universities to start programmes and departments in BME, which often include equipment, facilities and start-up costs for new staff.

With regard to the NIH, Katona hopes that some permanent arrangement will be found to continue what BECON is doing. This is extremely important, he says, because once Whitaker goes out of business he expects that BME will stand on its own. "NIH's recognition is a very big element of that," he says.

B.H.

Building research support

In 1997, NIH formed BECON, the bioengineering consortium. BECON has been the NIH-wide focal point for bioengineering, bringing visibility to their bioengineering needs and bridging the cultural gap between the BE community.

The NIH now seems eager to pursue BME. According to Dick Swaja, who works directly for Wendy Baldwin, NIH deputy director for extramural research and organizing chair for BECON, it is their overall responsibility "to ensure that the missions of the NIH are being met", while figuring out how BME will fit into NIH's traditional structure.

BECON concentrates its effort in four main

areas: nanotechnology and nano-science; tissue engineering (which includes biomaterials and, more specifically, biomimetics, biosensors, organ-culture systems and tissue regeneration); bioimaging; and bioinformatics and computer simulations, which is only now being used in medical teaching.

According to Swaja, BECON, or something like it, will continue to be the focus of activities at NIH for the near future. There is appropriations language that indicates that an Office of Bioengineering/Bioimaging, reporting to the director of NIH, will assume responsibility and direction of BECON.

In the mid-1990s, Nerem believed that it was enough to integrate BME into the various institutes at NIH. Over the past five years, however, "I've become convinced that unless you are an institute at NIH, you're a second-class citizen — the power really resides with the institute directors". For Swaja, the current environment is one in which there are opportunities for engineers and physical scientists to show what they are capable of doing and to demonstrate that they can work with the biomedical and imaging community to foster this transdisciplinary field.

Unconventionally NIH

BME feeds into a better understanding of cancer, as well as better treatment and diagnosis, says Carol Dahl, one of the National Cancer Institute's (NCI's) two primary representatives to BECON and director of the

Creative fusion of many minds

Working mainly with synthetic biomaterials such as lipids and polymers, as well as functional derivatives that involve carbohydrates and other molecules, James Baker (left) and colleagues at the University of Michigan, Ann Arbor, on the Unconventional Innovations Program, are creating devices that will engineer cells on a nanoscale.

Polymers, for example, can make 'smart delivery' systems for drugs and genes. They target a malignant cell, release the drug or gene and report any effects.

The participation of people from liberal arts and sciences, chemistry, physics, engineering and toxicology is crucial, says Baker, who is head of allergy and immunology in the medical school as well as leading the university's centre for biologic nanotechnology. "All of us have come to this, if I can put it politely, 'ad hoc', training ourselves," he says. "There is a lot of self-selection in this area because people who don't want to interact won't show up." He explains that his team can define something experimentally and then say to the synthesis people: "We see this structure-function relationship, how can we magnify that?" The toxicologist might then say the compound has a bad history *in vivo*, vetoing that line of thinking. "It's remarkable how you can overcome problems or prevent yourselves from going down blind alleys, if you have everyone together."

Baker and his colleagues would like to see a larger institute based on their current centre. "One of the really important things is that you get people who are cross-trained and understand the engineering side, the materials science side and the analytical side, as well as the biology and the toxicology," he says. **B.H.**

Office of Technology and Industrial Relations at the NCI. To capitalize on this opportunity, the NCI has been an active participant in BECON and its initiatives, as well as developing NCI-specific programmes to nurture technology development and BE.

These have been created to smooth the problems technology and BME have encountered in gaining support from what is primarily a hypothesis-driven research focus at the NIH, says Dahl. The Phased

Innovation Award, developed by the NCI, allows people to move rapidly from a feasibility stage to a development stage (see NCI in the 'Institutions' panel on page 466). There is also the Unconventional Innovations Program (UIP), an NCI programme that invests in long-term, high-risk and high-impact areas.

The NCI takes a more active scientific role in the UIP, which announced its first five awards last autumn (see 'Institutions' panel for new announcements). Investigators

Exploring the territory in tissue engineering

A disagreeable side effect of longer lifespans is the failure of one part of the body — the knees, for example — before the body as a whole is ready to surrender. For decades, bovine collagen and other materials have been used for repairs, but it is now possible to use human material to restore damaged or worn-out tissue.

Tissue engineering, which occupies the fertile area between materials science and biology, has its roots in cell biology, immunology, chemistry and bioengineering, but it's not uncommon to see apparently unrelated fields thrown together. Glenn Booma, a director of 'outcomes research' at Genzyme Tissue Repair, in Cambridge, Massachusetts, cites a laser-optics physicist joining a team of physiologists working on a process for solidifying an injected substance by photoactivation.

A working knowledge of more than one branch of science could be very helpful. A postgraduate education is necessary for most research jobs, although a bachelor's degree may suffice in technical support roles. Equally important is an ability to work and communicate with people from other fields, and to keep a global perspective

even when concentrating on the details of a project. In a company environment the ability to shift gears rapidly is also a must. If a project turns out not to work, or if a competitor files a patent, says Booma, "then the company is going to want to rapidly reassign you to something new".

Your fate is out of your hands

Nancy Parenteau, chief scientific officer at Organogenesis, a company making wound-repair products in Canton, Massachusetts, says that the cross-fertilization between disciplines is part of the fun. "You should be able to pick up some of the other specialty's language, appreciate their issues and how they go about doing things." The hardest thing for scientists to come to grips with, she says, is that a project does not depend solely on any individual's work, even if it's an outstanding achievement. "In a way, your fate is no longer in your own hands. That can be difficult to become comfortable with."

Non-scientific factors can impinge on careers in a small company. Booma says that none who saw the seminal paper on cartilage defects in rabbits in 1984 would have dreamed it would take until 1997 to get

approval from the Food and Drug Administration and commercialize their Carticel product. Now, however, investors do know, so even small companies with impressive technology platforms and good intellectual property may be bought up, as his company was in 1994 when, as Biosurface Technology, it joined Genzyme. "Genzyme and Organogenesis have shown that tissue-engineering products are effective and marketable, but now we have to show that they can be profitable," he says.

Those contemplating a career in tissue engineering should also be politically aware. Positive public attitudes translate into public support, whereas a negative impression can mean restrictive legislation, loss of funding and, in extreme cases, physical attacks on labs and personnel. Scientists should engage in discussion and clarify issues. Parenteau deplores the speculation that occasionally appears in the media as being harmful to the field and misleading and frightening to the public. Even preliminary or limited results can be misinterpreted, raising false expectations for many and confusing the few for whom a breakthrough will truly bring help. "The

propose the work and the NCI then negotiates with them and engages them under contract for the next few years. The five most recent contracts amount to nearly \$11.3 million over three years.

James Baker, principal investigator for a group receiving \$4,427,711 at the University of Michigan at Ann Arbor, will use the grant to develop nano-scale devices for detecting and treating cancer. Although there was a lot of input from the NCI, says Baker, "I have to give them their due. They are setting their priorities, but are allowing us to direct towards those priorities in a way that makes the most sense given the specific technology."

One common aspect among the BE and BME groups that *Nature* has spoken to is that they have organized their departments and divisions in ways that are administratively more challenging in order to gain an intellectually richer environment.

At MIT's division of bioengineering and environmental health, most faculty members hold either 'dual' or 'joint' appointments. "We believe that joining the science of biology with engineering is so important that you do not want to do it in an isolated structure that departments often are," says Lauffenburger. Dual appointments are shared equally with the other department in terms of teaching and service duties, as well as hiring, promotion, tenure and salary review. Joint appointments are positions in which these areas are

governed by another department. The departments sharing BEH faculty include chemical, mechanical and electrical engineering, as well as computer science, materials science, biology and chemistry. "Our strategic plan calls for adding another 10 to 12 faculty over the coming five to seven years, from a combination of internal transfers and external hiring," says Lauffenburger.

At the graduate level, BEH offers PhD degrees in bioengineering and toxicology. At the undergraduate level, there are minor bachelor degrees in both biomedical engineering and environmental health, and a mechanical engineering degree is in the planning stages. The goal of the graduate-level programmes is to define these disciplines, whereas the undergraduate programmes will connect traditional disciplines with problems and approaches in biotechnology and human health.

At the Georgia Institute of Technology (GT), a joint biomedical engineering department is being put together with the medical school at nearby Emory University. According to Nerem, the department will have space on both campuses, with two-thirds of faculty appointed through GT and one-third through Emory. Once appointed, they will act as a single department. A new PhD degree is going through the approval process, which will be a BME degree offered jointly by GT and Emory.

Over the next seven or eight years, Nerem

estimates that GT will be hiring some 15 faculty. There are already seven faculty with primary appointments in the department, he says. They did not want simply to move the existing faculty into the new department. "I think it's important that mechanical engineering at GT is still strong in biomedical research," he says. A few of the faculty have moved into this new department, but most will be new faculty.

Generally speaking, Nerem thinks that "some of the best engineering students have an interest in biology and are excited about bioengineering". Getting biology students interested in engineering is not quite so easy, he says. The problem, he explains, is that many people who do biology as an undergraduate shy away from quantitative courses. Too often biology majors do not study calculus or ordinary differential equations.

According to Lauffenburger, bioengineering is in the very early stages of development in terms of both its definition and the identification of career opportunities for its students. "I think that it's a crucial challenge for us to help industry understand what we're trying to accomplish with this education, and how people like this will be useful to hire alongside the chemical, mechanical and electrical engineers they have traditionally hired," he says.

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companies themselves, which have to go out and raise money in order to survive, have a need to play up the bright side and not dwell unduly on the limitations," Booma adds.

New university training programmes and faculty positions and public funding initiatives are good news for hiring trends. In the United States, the National Institute of Standards and Technology's Advanced Technology Program has funded product development in tissue engineering for the past two years with grants of \$2–5 million. Last year the NIH set up a tissue-engineering working group, and may set up an institute. Says Gail Naughton, president of Advanced Tissue Sciences in La Jolla, California, "Tissue engineering used not to fit into any single category, but now the agencies are actually out there soliciting grant proposals. This is making a big difference." She foresees career opportunities at various levels.

With growing institutional support, the outlook for the next 10 to 15 years is rosy. Improvements in technique and understanding will speed up progress. For example, Naughton thinks that the question of embryonic stem cells will be obviated by improvements in separations and culturing.

Parenteau: hybrid vigour adds interest.

"Our growing understanding of how to keep cells functioning outside the body will allow us to manipulate them so that they can become almost any cell type," she predicts, citing recent publications (for example, see Jackson, K. A. *et al. Proc. Natl Acad. Sci. USA* 96, 14482; 1999) showing that human cells collected from bone marrow can be transformed into fat, bone or cartilage cells.

Parenteau worries about speculative media coverage, but agrees that what's true

now for skin products will probably become reality for vascular, neurological, bone, tendon and corneal tissue. The immunological barrier is a major challenge, but inroads are being made. For example, the Boston company Diacrin has worked out how to mask animal cells so that they can be transplanted into humans; a product made from porcine neural cells to treat Parkinson's disease is in phase II trials. A decade ago neural regeneration at trauma sites was thought impossible. Today it is known that, if scarring is kept at bay, neural tissue has a great capacity to regenerate.

The role of genetics will also increase as tissue engineering is combined with gene therapy to enhance the growth of implanted tissue. The discoveries of genomics will affect the field, such as the as-yet unknown signals that differentiate between normal growth and healing. "Especially in a young field the opportunities are broad and abundant. It is exciting to participate in a field that is being born. Few of us get to do that," says Parenteau.

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