Biology and chemical engineering bond

WASHINGTON, D.C.—As is the case in many fields of science, the distinction between biology and biochemical engineering is blurring. What is going on at this biotechnology interface? This question was posed at a recent meeting here entitled "Research Opportunities in Biomolecular Engineering: The Interface Between Chemical Engineering and Biology." The meeting was sponsored by the National Institute of General Medical Sciences (NIGMS, Bethesda, MD), the component of the National Institutes of Health that supports basic, non-disease-targeted research and research training.

Decisively dispelled at the meeting was the notion that chemical engineers serve merely to scale up processes suggested by fundamental biological science. It has become clear instead that chemical engineering and biology can work hand in hand, from "upstream" efforts to elucidate basic mechanisms to "downstream" attempts at devising practical technology.

The key term is "molecular," which characterizes the forefront of research in both chemical engineering and the life sciences. Chemical engineers are trained to apply engineering principles—including physics, thermodynamics, mechanics, kinetics, and transport phenomena, along with an analysis and synthesis approach, quantitative whenever possible—to break down complicated problems into essential components, thereby providing a basis for the rational design of the reintegrated system. At the same time, modern biology typically pursues and identifies underlying molecular mechanisms from a qualitative, descriptive perspective, wherein the identification of a molecular species, along with the conditions governing its presence or absence, provide new insight.

An example is the work of Steve Wiley at the Univesity of Utah in Salt Lake City. Wiley and his coworkers in chemical engineering and molecular biology have shown how advances in understanding receptor trafficking and signaling—functions that are intrinsic to the regulation of such cellular undertakings as proliferation—are emerging from the posing of quantitative questions concerning rates, once the principal molecular species involved have been identified.

Wiley has been exploring the epidermal growth factor (EGF) receptor, with the goal of relating changes in receptor-trafficking properties to changes in the ability of cells to bind and respond to EGF. Potential applications include reducing growth-factor requirements for cell culture, stimulating wound healing, and enhancing transport of growth factors through tissue,.

A critical feature of Wiley's mathematical model is that specific, second-order interactions occur between receptor/ligand complexes and membrane-associated sorting components at the cell surface (governing internalization) and in intracellular endosomes (governing degradation and recycling). This model can predict, for instance, how changes in the affinity of these interactions should alter the numbers of EGF/EGF-receptor complexes on the cell surface. Wiley has exploited site-directed mutations of the EGF receptor transfected into cell lines lacking endogenous EGF receptors to test these predictions. For example, truncation of this receptor at residue 973 dramatically reduces its internalization-rate constant, leading to a loss of receptor down-regulation and its consequent attenuation of mitogenic signaling.

Model predictions, using parameter values determined from independent kinetic experiments, are in quantitative agreement with experimental observations that a fibroblast line transfected with this EGF-receptor truncation mutant proliferates with maximal rate at an EGF concentration an order-of-magnitude lower than for that for cells transfected with the normal receptor. Not only do the cells possessing the internalization-mutant receptor exhibit reduced EGF requirements in culture, they become transformed at high EGF concentrations and demonstrate tumor formation when transplanted into mice.

—Douglas Lauffenburger

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Chemical engineering and biology are cooperating upstream to elucidate basic mechanisms and downstream to devise practical technology.

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out, the experts identified by FDA may just as likely be working as consultants for companies readying their products for regulatory scrutiny. Such overlapping interests can lead to both apparent and real conflicts of interest.

Although experts in the field of biotechnology tend to move fluidly among academic and corporate consulting posts, conflict-of-interest challenges are just as likely to arise in any specialty field where there is a "small community of experts," notes Henry Miller of FDA's Office of Biotechnology. "The issue is a pervasive one, so I don't see that there is a special issue with biotechnology."

To cope with the general issue of conflict of interest among advisory-committee members, FDA has a "waiver" system in place, allowing agency officials to identify potential conflicts and to determine when a committee member's expertise is so useful that it outweighs the threat to his impartiality of judgment. The problem with the system, according to the report, is that "there are no relevant written standards for granting waivers." Thus, IOM encourages FDA officials to work with the Office of the Special Counsel for Ethics within the Department of Health and Human Services to codify the agency's waiver system.

The IOM report also recommends that uniform management guidelines be developed so that unnecessary differences in advisory-committee practices be minimized. Some committees, for instance, take formal votes when making recommendations, while other committees informally reach a consensus. Along these lines, the report also urges FDA to centralize its management of the advisory committees, preferably by appointing an individual in the Commissioner's office to provide agency-wide guidance.

—Jeffrey L. Fox