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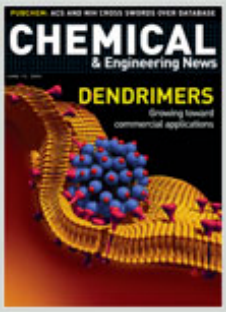

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NIH INITIATIVES TARGET CHEMISTRY

New road-map-related initiatives show agency values role of chemistry in biomedical research

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Chemistry has long played an important role in advancing all areas of science. This point has not been lost on the officials at the National Institutes of Health who included chemistry research in their six-year strategic plan for the agency, known as the Roadmap for Medical Research.

This commitment to chemistry is evidenced by two new road-map-related requests for applications (RFAs) put out by the agency in mid-November. The first deals with the development of pilot-scale chemical diversity libraries for high-throughput screening, and the second deals with the development of new methodologies for natural products chemistry. Both initiatives are part of the Molecular Libraries & Imaging component of the road map and will be administered by the National Institute of General Medical Sciences (NIGMS)--the largest supporter of chemistry-related research at NIH.

DEVELOPERS Graduate student Shiying Shang (left) and postdoctoral fellow Jae-Sang Ryu work on developing diversity-oriented syntheses of libraries in the lab of Tan--work that fits nicely into a new road-map-related initiative.
COURTESY OF MEMORIAL SLOAN-KETTERING CANCER CENTER

"These two RFAs are squarely targeted at the chemistry community," says John M. Schwab, program director for both of the new initiatives at NIGMS. "They really underscore NIH's conviction that chemistry is central to the future of everything in biomedical science," he points out.

Schwab expects the pair of RFAs to result in about 15 to 25 grants the size of traditional researcher-initiative grants (known as R01 grants). The grants are a single-time solicitation with a maximum project length of three years. "This is really tangible proof that the NIH road map is benefiting the chemical community in meaningful ways," he says.

NIGMS Director Jeremy Berg agrees. "These RFAs are opportunities for

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chemists to contribute to the Molecular Libraries Roadmap initiative through individual investigator-level mechanisms," he says. "From the point of view of chemists, these are funding opportunities in areas where there has been considerable interest independent of the road map. From the point of view of NIH, the results of this research will be novel molecules and methods that will be useful in producing compounds for the screening pipeline."

At the start of this pipeline are chemically diverse libraries that will provide novel compounds for screening for biological activity. The development of such library collections is the goal of the pilot-scale libraries for the high-throughput screening initiative.

"What's unique about this initiative is that the end product isn't just knowledge and publications, but it's real, concrete libraries of compounds," Schwab explains. "We are soliciting compounds that will be used to make an NIH collection that is unique and truly valuable."

According to Schwab, the resulting compounds will be placed in the NIH small-molecule collection, which will be part of the NIH Small-Molecule Repository--a facility that is being run under contract by Discovery Partners International. These compounds will then be used for high-throughput screening by NIH's Molecular Library Screening Center Network. The resulting data from the screenings will be available to the public through PubChem--a chemical informatics database that is also part of the road map.

"It is particularly gratifying to see NIH step up and fund natural products identification-related research."

"IN THAT WAY, we can step in and facilitate what pharmaceutical and biotechnology industries are doing," Schwab points out. "We can get in on some of the target discovery, and then pharma and biotech can take it from there, using PubChem in order to identify potentially useful targets or small molecules that can then be developed into useful therapeutics," he notes. And it's this long-term product that is of interest to the pharma and biotech industries. "Pharmaceutical researchers mine synthesized compound libraries and natural sources for potential small-molecule therapies, which are really products of the intersection of biology and chemistry," says Lila Feisee, director of intellectual property at the Biotechnology Industry Organization. "We're pleased to see this component of the road map, emphasizing the chemistry side of drug discovery, get under way."

Another noteworthy aspect of this initiative is that it will be funded using a Biotechnology Resource Grant (P41) mechanism, which, contrary to its designation, is not a center grant mechanism. Instead, Schwab explains, the mechanism allows for support of grants from single investigators or by collaborating teams of investigators.

One interested applicant, Derek S. Tan, says, "This RFA is tremendously important for smaller labs such as mine that are working in diversity-oriented synthesis, since previous funding for this work has been primarily through large center grants and has been difficult to obtain under the conventional R01 mechanism." Tan is an assistant professor at Memorial Sloan-Kettering Cancer Center.

"I expect that these new libraries will be critically important to screening efforts under the Molecular Libraries Roadmap and that they'll have broader implications as well," Tan says. "Many pharmaceutical companies, and hence commercial library suppliers, are focusing on increasingly narrow regions of chemical structure space. On the other hand, academic screening will likely require much more diverse compounds."

In the case of the natural products chemistry initiative, the emphasis is on addressing perceived bottlenecks in product development. "This RFA has really come out of the historical observation that over half of the drugs with novel structures approved in recent years are either natural products or are directly related to natural products," Schwab points out.

"We've cast a pretty broad net in this RFA--looking for everything from isolation and structural elucidation techniques to genetically based techniques," he says. But the goal of this RFA is not simply to isolate new natural products, he notes; it's to encourage the development of tools that will make it easier, more efficient and economical, and less labor intensive to look in natural sources for bioactive molecules.

Facilitating this work is important because pharmaceutical companies are downsizing their natural product programs based on profitability, notes Ben Shen, a professor in the University of Wisconsin, Madison, School of Pharmacy. Shen tells C&EN that he and his colleagues plan to submit several applications for this RFA.

"THIS INITIATIVE sends the strongest message to the scientific community that NIH has a vision of the value of natural products--in spite of the current perception in the pharmaceutical industry--and is committed to developing enabling technologies to exploit these natural product resources," Shen says. "It is also clear from these RFAs that NIH recognizes the critical role and value that small molecules play in probing various biological processes. This should help chemistry compete for resources at NIH."

PRODUCTION NIH is looking for ways to facilitate natural products chemistry--something that researchers like the one seen here can use in the fermentation of natural products for clinical use. COURTESY OF PETER LICARI/KOSAN BIOSCIENCES

"It is particularly gratifying to see NIH step up and fund natural products identification-related research," says John A. Porco Jr., a chemistry professor at Boston University and prospective applicant for both RFAs. "As synthetic organic chemists are also involved in complex target-oriented synthesis, many of these natural products and derivatives will become important projects for further investigation."

And that's something NIGMS's Schwab hopes to see happen for both of these new RFAs. He points out that even after these RFAs close--the deadline for the natural products chemistry RFA is Jan. 24, and the pilot-scale libraries deadline is Feb. 15--there will continue to be opportunities to submit unsolicited applications for NIGMS's regular funding programs.

Whether through these new road-map solicitations or via other

programs, initiatives like these are good for chemistry as a whole. "I think this demonstrates that there is more than one way for us to get really worthwhile chemical science supported," Schwab notes. In fact, he says, these new initiatives may have a "catalytic effect and may open the eyes of a lot of nonchemists to the power of chemistry to address really difficult biological issues."

"These RFAs are good for chemistry because they recognize the central and invaluable role that chemistry plays in developing tools for biomedicine," says Chaitan Khosla, a chemistry professor at Stanford University and prospective applicant for the natural products chemistry initiative. "There is also the possibility that these RFAs will accelerate the chemistry-biology cycle of tool building and evaluation; if so, superior tools will start to emerge on a faster timescale."

Porco agrees, noting that these RFAs "remind us of the critical importance of organic synthesis and allied fields on the overall mission of discovering molecules with important biological properties." He adds that "on a fundamental level, NIH is aware and is placing emphasis on the need for new chemical synthesis methodology to access novel chemical structures, and on the synergy of this work with methodology for natural products isolation and identification."

But some researchers in the chemical community still question the wisdom of the broad road map in diverting precious resources from the pool of investigator-initiated grants. "Projects that are left to the imagination of individual minds are invariably more imaginative than resources-driven research," says Vern L. Schramm, a biochemistry professor at Albert Einstein College of Medicine, New York City.

For example, Schramm explains, "individual investigators may respond to these RFA initiatives with the most clever methods imaginable to make new and diverse chemical libraries, but the product of the research is not a new insight into biomedical function, it is a chemical library. Chemical libraries have been produced by the score in the pharmaceutical industry. The wisdom of following in the footsteps of already-developed technology should be questioned when the resources now available from NIH are so limited that funding for investigator-initiated grants is shrinking rapidly."

NIGMS's Schwab, however, counters that the road map is such a small fraction of the NIH budget that its impact on R01 funding is minimal. And regarding the library synthesis and screening effort, he says, "we will be using some of the same techniques, but we will be asking very different questions, and the entire scientific community will have access to the results of our experiments."

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