Put your thinking caps on

Opportunities abound for chemical biologists to contribute to global initiatives designed to unlock the secrets of the human brain.

The proclamation of the 1990s as the 'Decade of the Brain' by US President George Bush may have been an idea before its time. Though neurobiology progressed apace in the 1990s, the decade that followed was a far more productive period for technological advances and conceptual insights into the workings of the brain. Scientists and governments across the world have taken note and launched several large-scale research initiatives—characterized as Human Genome Project–like opportunities for neuroscience—that indicate that the next decade of brain research may be transformative. Chemical biology, which has already tackled challenges in neuroscience (*Nat. Chem. Biol.* **4**, 215, 2008), will assume a leading role in these initiatives by pioneering new technologies and delivering fundamental mechanistic insights in neurobiology.

The Human Brain Project (HBP; http://www.humanbrainproject.eu/), which is funded by the European Commission and involves 135 institutions in 26 nations, represents an ambitious venture into large-scale neuroscience. The HBP seeks to use information and communications technologies to integrate diverse neuroscience data and build robust models of the brain to enable basic research, advance our understanding of neurological disease and, more broadly, inspire next-generation computing technologies. In 2013, the HBP initiated its 30-month 'ramp-up' period, investing €72 million in building the technology base for the ten-year program.

The Brain Research through Advancing Innovative Neurotechnologies (BRAIN; http://www.nih.gov/science/brain/) initiative has only recently taken shape but represents a bold neuroscience effort in the United States. In April 2013, US President Barack Obama announced the BRAIN initiative and its emphasis on technology development in neuroscience but left the participating US agencies (National Science Foundation (NSF), National Institutes of Health (NIH) and Defense Advanced Research Projects Agency (DARPA)) to work out the details in consultation with the neuroscience community and private sector partners. At the NIH, an advisory committee gathered community feedback and issued an interim report in September 2013 that identified high-priority research areas for the NIH BRAIN initiative (http://www.nih.gov/science/brain/11252013-Interim-Report-Final.pdf). Late in 2013, the NIH committed $40 million for 2014 BRAIN initiative proposals to be distributed across six funding opportunities (http://www.nih.gov/news/health/dec2013/nih-17.htm/) with submission deadlines in the first quarter of 2014.

Taken together, these interdisciplinary research programs, along with other projects that are emerging worldwide, are focusing scientific attention on neurobiology at all levels: from the molecular mechanisms of neurotransmitters, receptors and channels, through the cell biology of neurons, to neuronal circuits and brain and nervous system architectures. Chemical biology is uniquely positioned to contribute new structural and functional insights at all levels. An analysis of the NIH research priorities for the BRAIN initiative reveals an emphasis on new technology development, including tools for identifying and targeting neurons, approaches for mapping and manipulating neural circuits and techniques and reagents for functional brain imaging. These aims provide chemical biologists with an opportunity to showcase their skills in creating new tools, understanding biology *in situ* with mechanistic precision and collaborating productively on interdisciplinary projects that are likely to have broad impacts in science.

Chemical tool development is an established strength of chemical biology, and neuroscience is a frontier that will inspire new inventiveness. Chemical probes—small molecules that specifically and potently modulate the activities of cellular targets—offer significant potential as tools for perturbing and understanding neuronal function and, secondarily, as lead compounds for therapeutic development. Funding agencies should prioritize chemical screening and target identification approaches to facilitate further chemical probe development for neurobiology targets. Beyond chemical probes, chemical biology methods for tagging and manipulating biomolecules within cells—ranging from translational reprogramming with non-natural amino acids to bioorthogonal labeling and photocaging chemistries—mesh well with BRAIN initiative aims to develop techniques for neuron-specific labeling, delivery of biomolecules and reagents to specific neurons and selective control of neuronal activities.

Chemical biology will also contribute to diverse imaging methodologies that are a central focus of current neuroscience initiatives. Optogenetics methods have revolutionized neurobiology in the past decade by permitting light-mediated control and real-time imaging of neuronal processes. Chemical biology know-how, along with experience in translating chemical systems into biological contexts, will be essential for developing the next generation of optogenetic tools. It will also lead to the identification of new molecular dyes, engineered fluorescent proteins and biophysical imaging platforms that will be required to map neuronal circuitry and expand functional brain imaging approaches.

Finally, with its emphasis on understanding the molecular basis of biological systems, chemical biology will also contribute to a deeper mechanistic understanding of neurobiology. For instance, chemical biology is already transforming the study of neuronal signaling. It was apparent at the 2013 Society for Neuroscience meeting that a technique called DREADD (*Proc. Natl. Acad. Sci. USA* **104**, 5163–5168, 2007), which makes use of engineered G protein–coupled receptors that can be selectively regulated in neurons by synthetic small-molecule ligands, has been widely adopted by neuroscientists to probe signaling networks in neurons. Further, continued efforts to elucidate the molecular details of seemingly intractable problems in neurobiology, such as proteostasis and its role in neurodegeneration (see, for example, *Nat. Chem. Biol.* **9**, 586–592, 2013), will dovetail with the broader goals of these large-scale projects, which include applying newfound knowledge of the brain to better understand behavior and treat neurological diseases.

The HBP and BRAIN initiative have set ambitious goals for the next decade of neuroscience, the achievement of which will depend heavily on the success and sustained funding of collaborative, interdisciplinary teams that will identify and develop promising technologies and apply them to the most important scientific questions in neuroscience. Chemical biologists have much to contribute to this frontier area of chemical neurobiology, which merits the attention of the community's substantial brainpower. ■