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Molecular Imaging

Editorial overview

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Molecular Imaging, the creation and application of new approaches to study molecular-level events in biological systems, is a rapidly growing field that has attracted a broad base of researchers with diverse backgrounds spanning chemistry, physics, biology, medicine, and engineering. Perhaps more so than any other area of current scientific inquiry, Molecular Imaging offers a modern paradigm of how coordinated, collaborative efforts have advanced our understanding of medicine and the life sciences through fundamental inventions in the physical sciences and engineering. A major key to the success of these efforts is that the goals of Molecular Imaging are so readily appreciated by researchers from a disparate landscape of traditional disciplines. Chemists are motivated to directly visualize the location and action of specific molecules within complex living systems. Physicists and engineers embrace the theoretical and practical challenges of pushing imaging modalities to new extremes in order to obtain molecular information in both the spatial and temporal regimes with ever-higher resolution. Biologists and physicians, as the primary end users of Molecular Imaging technologies, are the major driving force for the continued advancement of tools for probing the chemistry of life at its most fundamental level.

This special issue of *Current Opinion in Chemical Biology* dedicated to Molecular Imaging seeks not only to present a cross-sectional overview of recent technological advances in the field, but to highlight specific examples of how novel tools for visualizing real-time events in complex living systems has and continues to enable researchers to gain critical new insights into important and long-standing biological problems. This synergy between technology and application continues to push the boundaries of how we understand the natural world around us and further drives the need for innovation in the development of new Molecular Imaging tools.

Whereas most biochemical measurements are averaged over an ensemble of molecules, fluorescence imaging approaches can enable researchers to interrogate single molecules either in the test tube or in their native biological context. Three contributions in this issue highlight recent developments in the area of single molecule imaging technology and applications. Haw Yang of Princeton University provides an update on recent technological progress in observing single molecules in cells, predicting that single molecule spectroscopy in living cells will be the next frontier in this exciting area of investigation. Bo Huang from the University of California, San Francisco writes a timely introduction to the various super-resolution optical microscopy techniques that have been generating much excitement in the biological imaging community. Staying within the realm of single molecule studies, Stephen Kowalczykowski of the University of California, Davis presents a fantastic illustration of how real-time single molecule imaging can be used to gain mechanistic insight into an important biological problem, detailing recent advances in the understanding of the mechanisms of proteins involved in DNA recombination.

The widespread availability of genes encoding intrinsically fluorescent proteins has been a boon to researchers interested in determining protein localization and dynamics in single cells. Three articles in this issue serve to illustrate just how far fluorescent protein technology has advanced since the first reports of applying *Aequorea* green fluorescent protein (GFP) for imaging applications in the mid-1990s. Vladislav Verkhusha of the Albert Einstein College of Medicine describes a variety of fluorescent proteins that change their fluorescence hue either upon illumination with specific wavelengths of light or with the passage of time. These new classes of tools have enabled a variety of new applications including super-resolution imaging and the determination of protein age. Robert Campbell of the University of Alberta summarizes the various classes of fluorescent protein-based biosensors, and Jin Zhang of the Johns Hopkins University School of Medicine illustrates how these biosensors can be used to reveal some of the most intimate details of cellular signaling networks.

Since long before anyone even had the idea to use *Aequorea* GFP as a tool for imaging, organic and inorganic chemists have been developing and refining synthetic dye-based probes for a wide variety of biologically relevant ions and molecules. In this issue we have three reviews that patently demonstrate the high level of sophistication of the latest generation of fluorescent probes for live cell applications. In separate reviews, Stephen Lippard of the Massachusetts Institute of Technology and Christopher Chang of the University of California, Berkeley describe recent progress in the development and application of probes that can be used to detect reactive nitrogen species and reactive oxygen species. Christopher Cairo at the University of Alberta provides an overview of the use of synthetic fluorophores as probes of biochemical changes that occur at the lipid membrane. These three reviews clearly presage that, for the foreseeable future, there will remain numerous outstanding biochemical problems that can only be addressed using synthetic (as opposed to genetic) tools.

One of the advantages of synthetic dyes relative to GFP variants as probes for fluorescence imaging applications is the fact that there exist numerous synthetic dyes with strong absorbance and bright fluorescence in the so-called near infrared (NIR) window, where tissue absorbance is at a minimum. As described by Robert Strongin at Portland State University, the development of improved NIR fluorophores for deep tissue bioimaging applications continues to be a highly active area of investigation. Ralph Weissleder and Scott Hilderbrand from the Massachusetts General Hospital at Harvard University review recent applications of NIR dyes for *in vivo* imaging, with emphasis on specific challenges that researchers in the area are currently working to overcome. A popular alternative to fluorescence for *in vivo* imaging in small mammals is bioluminescence. Bioluminescence benefits from the fact that excitation light is not required and thus greater sensitivity can be realized. Jennifer Prescher and Christopher Contag of Stanford University provide an overview of bioluminescent imaging technologies and highlight some of the most recent applications.

With the exception of a small number of FDA-approved clinical uses of NIR fluorescence, optical Molecular Imaging modalities are generally confined to the research lab. In contrast, the Molecular Imaging modalities of positron emission tomography (PET) and magnetic resonance imaging (MRI) are well established in the clinic. Included in this issue are three reviews describing current work in developing new methods and probes for exploiting the powerful technologies for addressing detailed biological questions in model animals and even humans. Silvio Aime at the University of Torino provides an overview of the application of hyperpolarization for signal enhancement in MRI, and Ivan Dmochowski from the University of Pennsylvania discusses the use of Xe biosensors that are responsive to specific biochemical activities. Finally, Jacob Hooker of Brookhaven National Lab and Harvard Medical School discusses the role of improved methods for radiosynthesis in facilitating the exponential growth in uses of PET imaging.

We hope that readers of this special issue will grow to appreciate, no matter what the background of the authors or the focus of the article, the common themes that are emerging in the Molecular Imaging field and the new opportunities that await young researchers from many different traditional disciplines. Indeed, Molecular Imaging research has cultivated a set of terms and concepts that constitute a nascent universal language to facilitate the interchange of ideas between a dynamic, growing community of chemists, physicists, engineers, biologists, and physicians. The evolution of this common language can be heard at any of the increasing number of scientific gatherings that feature Molecular Imaging, where one is certain to find researchers who will follow the introduction to their system of biological interest with a detailed discussion of the chemical structure of their favorite imaging probe and the operating principle of their cutting-edge imaging instrumentation. This inclusive, collaborative mindset offers a promising new window into viewing and understanding life at a molecular level and presages a rich future for the field of Molecular Imaging.