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Editorial overview: Molecular imaging for seeing chemistry in biology

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Xing Chen is Professor and Associate Dean of Chemistry at Peking University. He received his Ph.D. in Chemistry from University of California, Berkeley in 2007. After the postdoctoral training at Harvard Medical School, he started his own lab at Peking University in 2010. His lab focuses on developing chemical tools to elucidate the biological function of glycosylation, with an emphasis on *in vivo* labeling, visualization, and profiling of glycosylation dynamics.

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Yanyi Huang received both BS and ScD degrees in Chemistry from Peking University, and then conducted his postdoc research at Caltech and Stanford. In 2006 he returned to Peking University to start his independent career. He is Professor of Materials Science and Engineering, and Analytical Chemistry (by courtesy). His group is working on technology development for integrative biology researches, especially the new methods for genomic sequencing, bioimaging, and microfluidics.

The quest for better understanding of complex biosystems, especially their heterogeneity nature and dynamics, has been pushing researchers to continuously develop new molecular imaging technologies. Albeit *molecular imaging* has evolved to be a very inclusive field, there are two grand challenges from chemical biologists' perspective. First, how to directly see the chemistry (contents, flux, conversions, and dynamics) in living systems? Second, how to integrate the knowledge across multiple scales, from atomic structures to whole bodies, through integrated approaches of imaging? On one hand, a major theme in the field is to develop new probes, both chemically synthetic and genetically encoded, with superior properties including better stability, improved specificity, higher sensitivity, and lower invasiveness. On the other hand, new imaging modalities along with the engineering and instrumentation, always bring new insights to decipher the complex yet robust bioprocesses through new data that never been acquired before. In this issue of *Current Opinion in Chemical Biology*, we present seven reviews that highlight some of the recent efforts from chemists and biologists to address the grand challenges of molecular imaging.

Advancing imaging techniques often relies on the development of fluorescent probes with desired properties. Zheng and Lavis describe the current understanding of the mechanism of fluorophore photobleaching and recent efforts in improving photostability by tailoring fluorescent dyes with precise chemistries. One would expect continuous demands on tailored fluorophores for molecular imaging and synthetic chemistry is one of the key solutions to this challenge.

Tagging fluorescent dyes onto biomacromolecules of interest enables fluorescent imaging on single cells and tissues. Among the biomacromolecules, glycans are a type that is quite challenging to label. Ovryn, Wu and co-workers review recent advances in single-molecule tracking and super-resolution imaging of glycans, protein-specific visualization of glycosylation, and tissue and whole-body imaging of glycans. Most of these advances have been enabled by combining metabolic oligosaccharide engineering, a chemical method for labeling glycans, with the state-of-the-art imaging techniques.

To image small molecules such as metabolites, reactive species, and metals in live cells, a sensing strategy is often employed. Fluorescent probes are designed to have a turn-on fluorescence response upon reacting with the analytes. Along this direction, Chang and co-workers summarize progress on the development of fluorescent probes for detection and visualization of

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formaldehyde (FA), an endogenously produced reactive carbonyl species, in living systems.

Molecular imaging also enables us to obtain chemical and physical properties with high spatial resolution. As an example, genetically encoded protein sensors have been developed to detect and visualize membrane vantages. Zou, Cohen, and co-workers describe recent progress in the design and application of the family of genetically encoded voltage indicators (GEVIs).

One of the major advantages of imaging-based analyses is quantitative. Besides the spatial information of the images, the signal intensity embedded in each pixel of the image may be quantitatively correlated with the chemical contents, and the time-trajectory of such signal may also reveal the kinetics of specific processes. Chiu and co-workers have concisely summarized the recent progress of quantitative fluorescence microscopy, especially the precise copy number assessment of proteins in biological samples.

In addition, Fu provides another piece of review on quantitative chemical imaging that does not dependent on fluorescence. Thanks to the stimulated Raman scattering process, which is both sensitive and quantitative, many chemicals in live cells or animals can be real-time observed *in situ* and without labeling. This new modality also opens new playgrounds for chemists to develop 'minimal labels' such as stable isotopes or single bonds, to overcome many difficulties that conventional bulky probes are facing.

Unlike all the above technologies, which are or will be prevailing in the field, we include a timely introduction to synchrotron based X-ray microscopy contributed by Zhang, Fan, and co-workers. Such unique tool provides an unusual modality for observing the ultrastructure of organelles and molecules at the nanometer scale, with exceptional long penetration depth and specificity of elemental composition.

In summary, the seven reviews collected in this special issue elaborate various facets of the fascinating world of molecular imaging, from probe development, to single-molecule detection, to label-free observation, to emerging imaging modalities. Although such a collection is only a glimpse of this fast evolving field, the accumulation of these developments will eventually enable us to see chemistry in biology.

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