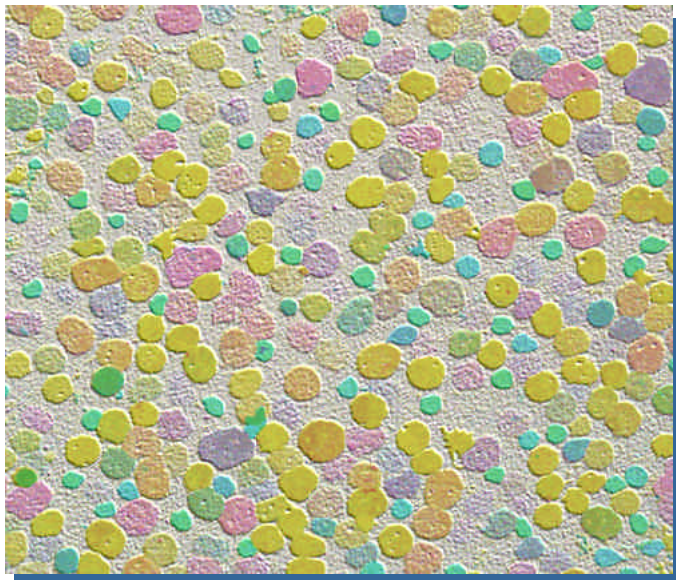




Computational Cellular Metabolic Phenotyping

Computational Metabolic Phenotyping

Each of the thousands of known eukaryotic cell types is a unique entity whose genomic / proteomic profile drives a metabolic phenotype that may be visualized by **signature mapping**: A fusion of molecular probe and computational technologies that captures the differentiation of metabolic phenotypes across cell types, from hepatocytes to neurons. Signature mapping is a novel tool for exploration of mechanisms controlling normal, developing or perturbed metabolic signatures in individual cell types; discovery of new cellular



Molecular signatures in retinal ganglion cells visualized by computationally fusing endogenous gaminobutyrate and glutamate signals with ligand-activated arginine signals.

classes; the associations of physiological properties with signatures; and developing atlases for phenotype screening of disease states

We have developed an immunoglobulin (IgG) library targeting over 30 small metabolic molecules, such as alanine, aspartate, glutamate, glutathione and taurine.

Multiple probes are applied to arrays of ultrathin tissue samples, forming archival N-dimensional databases of cellular signatures that may be computationally explored using N-space clustering and visualization methods. We have applied these methods to the study of retinal organization, the progression of retinal diseases, brain structure and, finally, cellular patterns of metabolic differentiation in all eukaryote species

Functional Cellular Phenotyping

The key functions of most cells involve ion and metabolite fluxes mediated by channels and transporters. We have developed a series of channel/transporter probes that can be combined with signature mapping to yield **functional** metabolic phenotypes, refining cell classification and providing more tools with which to visualize cell function in both health and disease

One of our recent advances is the development of **excitation mapping**. Most neurons decode excitatory synaptic signals with ionotropic glutamate receptors (iGluRs). As hundreds of neuronal types coexist in varied assemblies, expressing multiple subunit forms of iGluRs in unknown mixtures with dynamic receptor modulation, the problem of defining excitatory coding is complex. Neither genomic nor proteomic mapping is sufficient for this task: receptor expression alone does not predict cell pharmacology. We have developed excitation mapping based on the ability of cationic guanidinium analogues to permeate ion channels gated by glutamate, and our ability to track that permeation. This excitation mapping allows assignment of agonist sensitivities to cells; facilitates pharmacologic dissection of entire pathways; permits us to map the development of pathways and can be applied *in vivo*. Finally, excitation mapping will enable the global screening of new receptor-specific ligands. The permeant molecules themselves may have therapeutic roles in excitotoxicity management in the central nervous system and retina. Further developments in this area include computational inhibition mapping and energetics mapping

For more information:

Robert E. Marc • robert.marc@hsc.utah.edu

University of Utah • Moran Eye Center • 75 N Medical Dr. • Salt Lake City, Utah • 84132

Tel: (801) 585-6500 • Fax: (801) 581-3357 • www.moraneyecenter.org/marc