Engineering Synthetic Ligands for Molecular Imaging

Biology is dynamically driven by non-covalent interactions, predominantly involving proteins. The ability to study biological systems as well as engineer them for benefit – in medical and industrial settings – is dependent upon the ability to control these protein-protein interactions. With regards to personalized medicine, molecular targeting agents for medical imaging and targeted therapy have been limited by suboptimal physiological transport, non-specific retention, and inefficiency of binder evolution related to library design and target fidelity. The seminar will highlight advances in each of these elements with a focus on engineering synthetic binding ligands for molecular imaging. Non-invasive in vivo imaging at the molecular level is a powerful clinical approach for the detection, characterization, and monitoring of disease.

I will discuss an algorithm to efficiently evaluate naturally occurring protein domains for their evolutionary capacity and the resultant development of a small (5 kDa) scaffold capable of efficient evolution of high affinity binding functions. This scaffold, termed Gp2, was engineered to create synthetic ligands for binding various clinical biomarkers including insulin receptor and epidermal growth factor receptor (EGFR) for breast cancer imaging, as well as oligomeric α-synuclein for neuropathological targeting. An evolved Gp2 was site-specifically radio-labeled with 64-Cu to enable molecular positron emission tomography of EGFR with superior performance relative to alternative radio-tracers.

To improve the efficiency of evolving ligands towards clinical biomarkers, we demonstrate strong evolutionary benefit of site-specifically biased amino acid distributions within combinatorial libraries and highlight their relation to natural antibody repertoires. We empower ligand engineering towards biomarkers integrated in cellular membranes via enhanced selection techniques. Lastly, we demonstrate an efficient evolutionary approach to modulate charge density on the surface of protein ligands, while retaining biophysical integrity, to improve physiological targeting.

Tuesday, Nov. 8, 2016
Lecture at 4:00 p.m.
Room 1610, Engineering Hall
Refreshments will be served at 3:45 p.m.