



Centre for Biosystems Science and Engineering

SEMINAR

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MRDG Seminar Hall

Identification of a small molecule modulator of Niemann Pick Type C disease using simple model organisms

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Perlara PBC, is a public benefit company committed to discovering small molecule therapeutics for rare genetic diseases. Our approach consists of the use of simple, whole animal models such as yeast, worm, flies in drug discovery screens. Molecules that pass successfully through our screens are validated in patient cells before advancing into higher animal models of the disease.

Niemann Pick Type C (NPC) caused by defects in the gene NPC-1 is a devastating lysosomal storage disease with high mortality rates. The orthologous nematode gene, ncr-1, was genetically engineered to generate a worm model lacking functional ncr-1 protein. The resulting animal showed slowed development, small brood size and sensitivity to cholesterol deprivation. We capitalized on the growth defect observed in the absence of cholesterol to conduct a discovery screen. 50000 molecules were screened at an initial concentration of 25 μ M to identify candidates that rescued the growth defect. 'Hits' resulting from this screen were validated in a secondary assay on worms as well as on patient-derived cells. Perl101 was identified as a lead candidate for a class of molecules that rescued the NPC phenotype in worms and changed the cellular fingerprint of NPC cells. Furthermore, as an unoptimized screening hit, Perl101 demonstrated high oral bioavailability, blood brain barrier permeability and minimal adverse effects in a mouse tolerability study. Additional studies to probe the mechanism of action of Perl101 and its efficacy in a mouse model of NPC are underway.

About the speaker:

Dr. Iyer received her PhD in Molecular Pharmacology from the University of Pittsburgh and completed her postdoctoral research at the University of Texas at Austin. She has over eight years of experience in model/assay development and drug screening for human disorders. Since 2014, Dr. Iyer has been employed as a senior scientist with Perlara PBC, a drug discovery company in San Francisco committed to finding therapeutics for rare genetic diseases.