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Heterologous expression of cyclic nucleotide-metabolizing enzymes for drug discovery using *Schizosaccharomyces pombe* and PKA-repressed reporters

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The fission yeast *Schizosaccharomyces pombe* cAMP/PKA pathway is ideal for chemical genetics as it is not essential, thus allowing one to replace either the *S. pombe adenylyl* cyclase (AC) that produces cAMP or the phosphodiesterase (PDE) that hydrolyzes cAMP with genes encoding related proteins from other organisms. Our strain collection includes strains expressing 15 of the 21 mammalian PDE genes, all 10 of the mammalian AC genes, and both wild type and mutationally-activated forms of the human GNAS Gα that stimulates the activity of the mammalian transmembrane ACs. In addition, the *S. pombe fbp1* gene is transcriptionally-repressed by PKA such that an *fbp1-ura4* reporter can be used to detect PDE inhibitors by their ability to confer 5FOA-resistant growth, while *fbp1*-GFP and *fbp1*-luciferase reporters can be used to detect AC and/or GNAS inhibitors that confer increased reporter expression. One advantage of this screening platform is that compounds identified in these screens are cell permeable. In the case of the PDE inhibitors, hit compounds must be highly selective for binding as a promiscuously-binding compound would likely inhibit cell growth. Prior screens for PDE inhibitors have identified PDE4 and PDE7 inhibitors that display anti-inflammatory activity in mammalian cell culture, a PDE4/7 inhibitor that induces apoptosis in CLL cells, a PDE4/8 inhibitor that elevates testosterone production by Leydig cells, and a PDE11 inhibitor that elevates cortisol production by adrenocortical cells. Our most recent HTS has been for inhibitors of GNAS or AC9, as the mutationally-activated is found in McCune-Albright patients, as well as in many patients with pancreatic intraductal papillary mucinous neoplasms and associated adenocarcinomas. Current efforts are underway to profile the activity of these putative AC and GNAS inhibitors.

Speaker Biography

Charles S Hoffman received an SB in Life Sciences from MIT and completed his PhD in Molecular Biology and Microbiology from the Tufts University Sackler School of Graduate Biomedical Sciences. He has conducted his Post-doctoral studies at the Harvard Medical School, Department of Genetics, where he began his studies of glucose/cAMP signaling and transcriptional regulation of the *fbp1* gene in *Schizosaccharomyces pombe*. He has been a faculty member of the Boston College, Biology Department since 1990, and has published more than 60 papers and book chapters. He is an Associate Editor for Current Genetics and *G3 Genes, Genomes, Genetics*, and is a Member of the Luxuriant Flowing Hair Club for Scientists and the Scotch Malt Whisky Society of America.

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