Drug Discovery for Orphan G Protein-Coupled Receptors

INSTITUTION: Omeros Corporation  PI: Gregory A. Demopulos, M.D.

Orphan GPCRs already unlocked by Omeros

The Cellular Redistribution Assay — that finds synthetic compounds that bind orphan GPCRs, unlocking them for drug development. Omeros' revolutionary approach achieves this by modifying the orphan GPCR to reverse its normal trafficking pattern, causing the altered receptor to localize intracellularly. The modified orphan GPCR is then screened against hundreds of thousands of synthetic compounds. When bound by a compound that affects signaling, the receptor localizes to the cell membrane and fluoresces. This change in receptor localization is detected through high-content imaging, allowing for the identification of ligands that functionally interact with the target GPCR. The CRA detects both agonists and antagonists and is unaffected by downstream signaling pathways. Using its CRA, Omeros has unlocked 12 orphan GPCRs and plans to screen all remaining orphan GPCRs within the next 18 months. These are actual images, using Omeros' CRA technology, of a cell line expressing clones of a single modified GPCR. In the presence of a compound that does not functionally interact with the modified GPCR, the unbound GPCR clones are predominantly located intracellularly (left image). In the presence of a compound that does functionally interact with that same GPCR, the bound GPCR clones are predominantly localized to the cell membrane (right image). This interacting compound can now be used for drug development.

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Potential Indication(s)  Orphan GPCR
Squamous cell carcinoma  GPR87
Pancreatic cancer  GPR182
Acute lymphoblastic leukemia  P2Y8/P2RY8
Metabolic and psychotic disorders  GPR27, GPR85, GPR173
Appetite control  GPR101
Cognitive disorders  GPR12
Sleep disorders  OPN4
Movement disorders  GPR139

Using its proprietary CRA, Omeros has begun screening orphan GPCRs against its 320,000-compound library. Omeros has publicly announced that it has identified and confirmed sets of compounds that interact selectively with 10 orphan GPCRs linked to a wide variety of disorders — an unprecedented achievement.

Screening of the remaining orphan GPCRs is expected over the next 18 months. Omeros has already initiated medicinal chemistry efforts, and its strategy is to develop independently a handful of orphan GPCRs that it unlocks while partnering with other pharmaceutical companies to develop and commercialize the remainder of its new GPCR drug targets.

Orphan GPCRs have been linked to a wide variety of medical conditions, including Alzheimer's disease, multiple sclerosis, Parkinson's disease, bipolar disorder, addiction, appetite, sleep disorders, schizophrenia, depression, pain, diabetes, hypertension, hypercholesterolemia, inflammation, asthma, osteoporosis, osteoarthritis, fertility and many types of cancer. Unlocking orphan GPCRs could lead to new therapeutics to treat these and a host of other disorders.

The number of new drug targets that Omeros' GPCR program could introduce within the next year is unprecedented, and the associated value is expected to be substantial. In 2007, annual drug sales per commercial GPCR target averaged $3.5 billion, and many of these drugs were low-cost generics. New drugs targeting unlocked orphan GPCRs would be higher-priced proprietary drugs. To meet the demand for new GPCR drug targets, Omeros expects to create a significant number of additional high-paying life-sciences jobs in the State of Washington.