Rab7 GTPase as Small Molecule Targets

Published date: June 24, 2014

Technology description

The present technology developed at the University of New Mexico is a pan inhibitor of small molecular weight GTPases with submicromolar activity against the Rab7GTPase measured using in vitro assays, as well as in cell-based assays.
Based on in vitro analyses, the compound behaves like a competitive inhibitor and docking studies show the compound can be accommodated in the nucleotide binding pocket of Rab7. In cell based assays, the compound may mimic the activated state of Rab7 and increases membrane bound Rab7. This can occur by compound binding promoting the transition of the Rab7 GTPase in to the GTP-bound conformation.

Background

Ras and related small molecular weight GTPases function in the regulation of signaling and cell growth, and collectively serve to control cell proliferation, differentiation and apoptosis. The Ras-related GTPases are divided into four subfamilies with the Rab proteins regulation membrane transport, Rho proteins regulating cytoskeletal rearrangements and responses to signaling, Arf/Sar proteins regulating membrane and microtubule dynamics as well as protein transport, and Ran proteins controlling nucleocytoplasmic transport. There are currently no small molecules directed against Rab GTPases. Ras and Ras-related GTPase functions are tightly regulated, and dysregulation is casual in a wide variety of human diseases. Ras mutations resulting in impaired GTP hydrolysis and plasma membrane hyperactivation are linked to many human cancers. To date, inhibition of Ras and Ras-related proteins has relied largely on altering membrane recruitment with various drugs affecting prenylation. Generally, Ras proteins must be farnesylated for proper membrane localization, while Rab and Rho proteins are geranylated. Such strategies lack specificity and are problematic because each of these renylation machineries is required for the proper function of many Ras superfamily members. Rab7 is a regulator of transport from early to late endosomes and as such is critical for growth factor receptor down-regulation, for control of cell fate through autophagy pathways, nutrient uptake, immune cell regulation, to name a few.

Technology Description

The present technology developed at the University of New Mexico is a pan inhibitor of small molecular weight GTPases with submicromolar activity against the Rab7GTPase measured using in vitro assays, as well as in cell-based assays. Based on in vitro analyses, the compound behaves like a competitive inhibitor and docking studies show the compound can be accommodated in the nucleotide binding pocket of Rab7. In cell based assays, the compound may mimic the activated state of Rab7 and increases membrane bound Rab7. This can occur by compound binding promoting the transition of the Rab7 GTPase in to the GTP-bound conformation.

About STC.UNM

As the technology-transfer and economic-development organization for the University of New Mexico, STC.UNM protects and commercializes technologies developed at the University of New Mexico (UNM) by filing patents and copyrights and transferring the technologies to the marketplace. We connect the business communication (companies, entrepreneurs and investors) to these UNM technologies for licensing opportunities and the creation of startup companies. Visit www.stc.unm.edu.

Application area

There are currently no small molecules directed against Rab7 GTPases, a family with over 60 members and functions in regulating diverse membrane transport steps.
Rab7 is a regulator of transport from early to late endosomes and as such is critical for growth factor receptor down-regulation, for control of cell fate through autophagy pathways, nutrient uptake, and immune cell regulation. Thus, a small molecule inhibitor specific for Rab GTPases has general utility for elucidating protein function through protein-protein interaction assays.
The compound is also an ideal lead compound for increasing target specificity through structure activity relationships determinations and for identifying the protein contact sites critical for small molecule binding through crystallography.
Targets all cells simultaneously and enable resulting consequences and phenotypes to be measured within 1 hour or less.

Activates the activity of the haplo insufficient wild-type protein or inactivates the mutant protein, which may act as a dominant negative, and are likely to be promising compounds for treatment of Charcot-Marie-Tooth type 2B disease
Treatment for neuropathies, immune dysfunction, neurodegenerative disorders, cancer, and lipid storage diseases

Institution

The University of New Mexico

Inventors

Angela Wandinger-Ness
Denise Simpson
Jacob Ongudi Agola
Jeffrey Aube
Jennifer Golden
Larry Sklar
Zurab Surviladze
Chad Schroeder

手 机 : 13414935137
邮 箱 : yeyingsheng@zf-ym.com