HelmholtzZentrum münchen
German Research Center for Environmental Health

Scientific Highlight April 2016

☐ co-ordinated with the Director of the Institute / Research Unit

Institute of Diabetes and Regeneration Research

PSP-Element:
G-502300-001

Person to contact for further enquiries:
Heiko Lickert; heiko.lickert@helmholtz-muenchen.de; +49 89 3187 3760

Title of the highlight:
Ciliary transport machinery is a molecular target to inhibit oncogenic Hedgehog pathway activation

Keywords:
Primary cilium, Hedgehog (Hh) pathway, Smoothened (Smo), G protein-coupled receptor associated sorting protein 2 (Gprasp2), Image-based high throughput screening, Hh related developmental defects and cancer, ciliopathies.

Central statement of the highlight in one sentence:
Inhibitory effect of small molecules on a novel heterotrimeric Smo ciliary targeting complex (Smo-Gprasp2-Pifo) block constitutive Hh target activation and tumour growth.

Text of the highlight:
Trafficking of the G protein-coupled receptor (GPCR) Smoothened (Smo) to the primary cilium (PC) is a potential target to inhibit oncogenic Hedgehog (hH) pathway activation in a large number of tumors. One drawback is the appearance of Smo mutations that resist drug treatment, which is a common reason for cancer treatment failure. Thus, identifying the activation and transport mechanisms offers molecular targets to treat over 80 Hh-related cancer forms. In a first publication we describe the identification of Pitchfork (Pifo) and G protein-coupled receptor associated sorting protein 2 (Gprasp2) as part of the Smo ciliary targeting complex necessary for all Hh pathway activation (Jung et al., 2016; PlosOne). Having identified the ciliary targeting complex as molecular target for cancer therapy, we undertook a high content screen with compounds in preclinical or clinical development and identified ten small molecules that prevent oncogenic constitutive active mutant SmoM2 transport into PC for subsequent Hh pathway activation (Jung et al., 2016; Scientific Reports). Eight of the ten small molecules act through direct interference with

the G protein-coupled receptor associated sorting protein 2 (Gprasp2)-SmoM2 ciliary targeting complex, whereas one antagonist of ionotropic receptors prevents intracellular trafficking of Smo to the PC. Together, these findings identify several compounds with the potential to treat drug-resistant SmoM2-driven cancer forms, but also reveal off-target effects of established drugs in the clinics.

Publication:

Novel small molecules targeting ciliary transport of Smoothened and oncogenic Hedgehog pathway activation.
Jung B, Messias AC, Schorpp K, Geerlof A, Schneider G, Saur D, Hadian K, Sattler M, Wanker EE, Hasenöder S, **Lickert H**.
Sci Rep. 2016 Mar 2;6:22540. doi: 10.1038/srep22540. PMID: 26931153

Pitchfork and Gprasp2 Target Smoothened to the Primary Cilium for Hedgehog Pathway Activation.
Jung B, Padula D, Burtscher I, Landerer C, Lutter D, Theis F, Messias AC, Geerlof A, Sattler M, Kremmer E, Boldt K, Ueffing M, **Lickert H**.
PLoS One. 2016 Feb 22;11(2):e0149477. doi: 10.1371/journal.pone.0149477. eCollection 2016. PMID: 26901434

Taking account of the HMGU mission:

Translation, new therapeutic approaches, “drugs from Helmholtz”. We have identified a novel Smo ciliary targeting complex (Smo-Gprasp2-Pifo) that is essential for Hedgehog pathway activation as a molecular target for drug treatment. Furthermore we have performed small molecule screens to identify compounds that pharmacological interference with the Smo ciliary targeting complex to antagonizes constitutive activation of Hh signalling, which occurs in more than 80 Hh related cancer forms, e.g. basal cell carcinoma, medulo-blastoma, glioblastoma etc. Specifically we identified compounds that might be universally applicable to cancers associated with constitutive Hh signalling, but also to cancer forms that became drug resistant due to mutations in Smo that escape common cancer therapy. Novel molecular targets and novel drugs are the first step towards precision and personalized medicine approaches in cancer therapy.

The internal HMGU co-operation partners with whom the highlight was compiled, if appropriate:

Institute of Stem Cell Research
Institute of Structural Biology
Assay Development and Screening Platform
Institute of Computational Biology
Institute of Molecular Immunology
Institute of Diabetes and Adipositas
Department of Protein Science