OMICS Group Conferences
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International Conference on
Genetic Syndromes & Gene Therapy

November 19-21, 2012 Hilton San Antonio Airport, USA

# Use of random and targeted genome editing of the RP disease gene *Cngb1* to study and rescue rod photoreceptor structure and function

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The *Cngb1* locus encodes the rod photoreceptor (PR) cGMP-gated cation channel β-subunit and two soluble glutamic acid rich proteins, GARP1 and GARP2. The GARP proteins are generated by alternative splicing towards the 5'-end of the gene. Defects in the α- or β-subunit genes are a cause of retinitis pigmentosa (RP), a heterogeneous hereditary blinding disorder. A recent study has shown that the channel could be a promising new target for RP disease intervention. Knockout of all three proteins in rods leads to disorganized rod outer segment (ROS) structure and an attenuated photoresponse. Transgenic mice expressing a truncated β-subunit missing most of the GARP 5' region exhibit significant rescue of ROS structure and function. When the transgene is placed on a β-subunit knockout background that retains soluble GARP expression, near complete recovery is observed. To further understand the role of GARPs in ROS we have used zinc finger nuclease genome editing technology to selectively remove a GARP2 unique exon from the mouse genome. Two knockout alleles were established in mice, one that removes the entire exon and one that removes only the 3'-UT region that may be a hypomorph expressing lower levels of GARP2. Recent studies on PR GARP-containing proteins have established that the β-subunit and soluble GARPs are required for both normal structure and function. We are now analyzing the mechanism of action of the GARP proteins and moving towards developing treatments for RP that directly involves *Cngb1* mutation or indirectly in related disorders that exhibit elevated cGMP in ROS.

## Biography

Pittler completed his Ph.D. at age 30 from Michigan State University and postdoctoral studies at Baylor College of Medicine. He is a Professor of Vision Sciences, Ophthalmology, and Biochemistry and Molecular Genetics and Director of the UAB Vision Science Core Facilities. He has published more than 50 papers in journals such as Cell, PNAS, Nature Genetics, JBC, JCB, JCS and others and serves on the editorial board of Molecular Vision, Open Ophthalmology, Eye and Brain, and Cell Health and Cytoskeleton. He was the 1995 international Association for Research in Vision and Ophthalmology Cogan Awardee recognizing outstanding vision scientists.

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