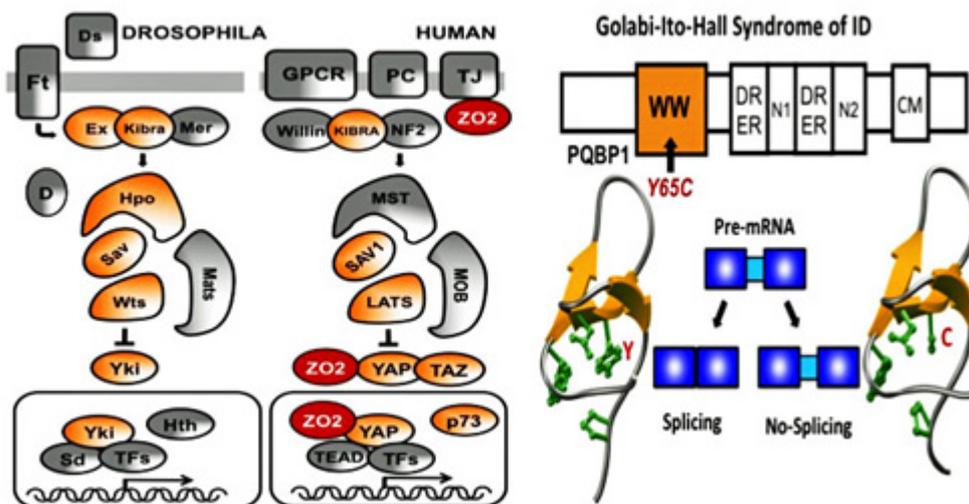


# Research

## Synopsis of Research

Marius Sudol was trained as a molecular oncologist. Among his most significant achievements to date are the identification of a modular protein domain, known as the WW domain, and the characterization of its cognate ligands. In 2004, together with a research team at AxCell-Cytogen company, Marius Sudol reported the first comprehensive protein interaction map for a human modular domain. Today, the WW domain is known to mediate critical signals in tumor suppressor networks including the Hippo signaling pathway. More importantly, syndromes such as the Golabi-Ito-Hall syndrome of intellectual disability and Liddle syndrome of hypertension are caused by loss-of-function point mutations in the WW domain or its cognate ligands.

Over the course of his scientific career spanning more than three decades, Marius Sudol has authored 140 publications (see Google Scholar), including original research articles and invited reviews in refereed journals as well as numerous book chapters. His current work focuses on the role of WW domain-containing proteins in the Hippo tumor suppressor network and Golabi-Ito-Hall syndrome of intellectual disability.



**Figure Legend:** LEFT PANEL is a general scheme of the Hippo pathway in *Drosophila* fly and in human. For details see a review by Harvey and Sudol in *TiBS* (2010, Volume 35, pages 627-633.). The main question that we ask experimentally is: How a tight junction protein, ZO2, which is depicted in red, could act as a shuttle that regulates YAP translocation to the nucleus? Being a *bona fide* structural protein that is integral to the architecture and function of tight junctions, ZO2 has also emerged as a transcriptional co-factor that affects gene expression. Hippo pathway must sense the status of cell-to-cell junctions via ZO2-YAP shuttle. RIGHT PANEL is composite cartoon of a point mutation in the WW domain of brain factor, named PQQBP1, that regulates mRNA splicing. The Y to C amino acid substitution mutation is

a loss of function mutation for the WW domain, which results in intellectual disability (ID) syndrome named as Golabi-Ito-Hall (GIH) syndrome. The GIH syndrome phenocopies a severe form of autism. For more details see a review by Sudol et al., in FEBS Letters, (2012, Volume 586, pages 2795-2799). By deciphering which mRNAs in the brain of GIH patients are changed, compared to normal brains we should get insight into molecular processes that underlie intellectual disability and autism.

#### **-Hippo-YAP Animal Model**

Hippo-YAP tumor suppressor pathway is regulated by multiple WW domain-containing proteins. One such protein is YAP, the major effector of the pathway, whose translocation to the cell nucleus is critical for its activity as a transcriptional co-activator that promotes robust proliferation of cells. We have shown that YAP's PDZ binding motif is required for its translocation from the cytoplasm to the nucleus and that one of the shuttle proteins for YAP is a PDZ domain-containing protein, ZO2. We have generated YAP knock-in mice without the PDZ binding motif. Together with Walter Hunziker and Wanjin Hong, we analyze these mutant mice by genetic crosses with ZO2 knock-out heterozygotes to reveal the most likely signaling connection between Hippo-YAP pathway and cell-to-cell junctional complexes.

#### **-Golabi-Ito-Hall Syndrome Animal Model**

A single point mutation in the WW domain of PQBP1 gene, which encodes a brain-enriched mRNA splicing factor, causes mental retardation that phenocopies severe form of autism. Using cells derived from GIH patients, we have documented that the causative mutation in the PQBP1 gene is a 'loss of function' mutation that compromises the complex of the WW domain with cognate splicing factors. We are in the process of generating an animal model of the GIH syndrome to investigate global changes in mRNA processing in the affected brains.