

9<sup>th</sup> International Conference on

# STRUCTURAL BIOLOGY

September 18-20, 2017 Zurich, Switzerland

## Construction of structural mimetics of the thyrotropin receptor intracellular domain

**Stanislav Engel**

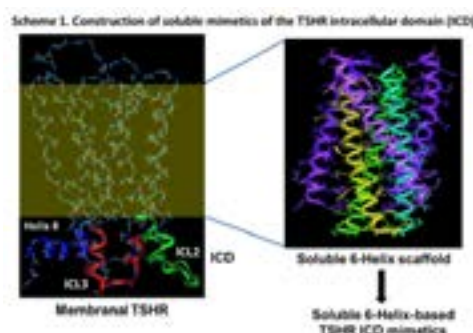
Ben-Gurion University, Israel

**Background:** Dissecting G protein-coupled receptors (GPCR) signaling in terms of the pathways being activated will boost our understanding of the molecular fundamentals of hormone action. The structural determinants governing the selectivity of GPCR/G protein coupling, however, remain obscure. The selectivity of GPCR/G protein recognition appears to be determined by both specific inter-residue interactions and features related to the overall 3D conformation of the ICD. It appears, therefore, that to elucidate the fundamentals of the selectivity of GPCR/G protein recognition, a comprehensive analysis of the structure-activity relationships of multiple GPCR complexes with different G protein isoforms is required. However, enormous technical difficulties associated with the isolation of functional receptors in quantities required for direct structural studies effectively impede progress in the field.

**Methodology:** We constructed the functional mimetics of the intracellular domain (ICD) of a model GPCR - thyrotropin receptor (TSHR), based on a unique scaffold, 6-Helix, an artificial protein that was derived from the elements of the trimer-of-hairpins structure of HIV gp41 and represents a bundle of six  $\alpha$ -helices.

**Findings:** The 6-Helix scaffold, which endowed the substituted TSHR ICD elements with spatial constraints analogous to those, found in native receptors, enabled the reconstitution of a microdomain comprising the intracellular loops ICL-2 and ICL-3, which is capable of binding and activating  $G\alpha$ -(s).

**Conclusion & Significance:** By using a soluble scaffold, which furnishes peptides derived from the GPCR ICD with spatial constraints similar to those, found in native receptors, the reconstitution of a native-like G protein-recognition epitope can be facilitated. The 6-Helix-based mimetics could be used as a platform to study the molecular basis of GPCR/G protein recognition. Such knowledge could lead to the development of novel therapeutic strategies for GPCR-related disorders by targeting the GPCR/G protein interfaces and help counteract cellular dysfunctions *via* focused tuning of GPCR signaling.



**Figure 1:** The three conformational states of the KpCitS dimer. (a) Schematic representation of the KpCitS protomer. Two helical hairpins of the transport domain are highlighted in purple. (b) The homodimeric KpCitS structure in different functional states viewed from the membrane plane (top) and from the periplasm (bottom). Citrate is shown as an orange ball-and-stick model. The black oval is a pseudo 2-fold axis, perpendicular to the membrane.

### Biography

Stanislav Engel PhD, is an Assistant Professor in the Department of Clinical Biochemistry and Pharmacology, Faculty of Health Sciences, The National Institute for Biotechnology, Ben-Gurion University in the Negev, Beer-Sheva, Israel. He got his BSc in Biochemistry, MSc and PhD in Biochemistry and Biotechnology Engineering at the Ben-Gurion University in the Negev. Currently, his researches focus on understanding the structural basis of "protein misfolding" diseases, such as ALS, and structure-based drug discovery.

engels@bgu.ac.il