

Impromptu Seminar

Venue: Medical University Vienna, Center for Physiology and Pharmacology,
Institute of Pharmacology, Waehringenstrasse 13a, 1090 Vienna,
"Leseraum"

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Tuesday 5.12.2017 14:00 s.t.

Host: Harald Sitte

Eduard Stefan

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"Decoding Signaling Circuits: Surveillance of Kinase Conformations & GPCR Interactions"

Eduard Stefan

Scaffolding proteins act as organizing centres for molecular switches such as kinases and GTPases to relay membrane receptor-sensed input signals. First, I will discuss the implementation of a phospho-proteomics approach to identify unanticipated physical connections between kinase and G protein-coupled receptor (GPCR) signalling. We identified that the GPCR Gpr161 is both, a protein kinase A (PKA) substrate and a high-affinity scaffolding protein for PKA holoenzymes. This function of the orphan GPCR is relevant for recruiting cAMP-sensing PKA complexes to the primary cilium where the Gpr161:PKA signalosome antagonizes Hedgehog signalling. Second, I will present a strategy to systematically track kinase conformations and interactions which are controlled by GTPases, cancer mutations, and clinical kinase inhibitors. The full-length RAF kinase is the basis for an extendable cell-based reporter platform which enables non-invasive recordings of (i) open (active) and closed (inactive) RAF conformations and (ii) transformations of binary GTPase:kinase interactions following lead molecule exposure. The in vivo recording of auto-inhibited enzyme conformations and interactions opens new opportunities for engineering biosensors for 'undruggable', novel, or neglected drug targets.