


National Project Factsheet (*maximum 1 page per project*)

	FULL TITLE:
ACRONYM	QuantPro
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SUMMARY	<p>Understanding signal transduction networks is one of the big challenges in modern Biology. In spite of the abundance of protein interaction data information on physiologically meaningful interactomes is limited. There is even less information on how mutations alter discrete protein networks. Proteomic as well as genomic experimental techniques, each with their own inherent experimental errors, have evolved to address this, yet additional functional as well as structural criteria must be considered to delineate a trustworthy protein interaction network from experimental data. Combining and integrating several layers of information gathering from biochemistry, in silico network analysis as well as structural biology we have developed an analytical workflow to distinguish between direct and indirect interactions, and more importantly to determine the quality of a set of interactions possible to act on a specific target protein with respect to a possible simultaneous compatibility or competitive nature.</p> <p>The biological system we have chosen for our study is the light receptive physically highly compartmentalized organellar structure in mammalian rod photoreceptors called photoreceptor outer segment, which is the light sensitive cellular structure in mammalian eyes. This cellular structure is maintained through directed protein transport from the inner segment of the cell to the outer segment. Defining protein interactions mainly by tandem affinity purification (<i>Gloeckner et al., Proteomics 2007</i>) we have analysed the interactome of lebercilin, which is genetically linked to a severe form of blindness, Leber's congenital amaurosis (LCA). The interactome links this protein to the transport of vesicular cargo to the outer segment along ciliary structures (<i>Den Hollander et al., Nature Genetics 2007</i>). Members of this interactome represent candidate genes for LCA and other ciliopathies. Our findings emphasize the emerging role of disrupted ciliary processes in the molecular pathogenesis of this blinding disease. Further on, we have systematically analysed protein composition and interactions in the outer segment. Rhodopsin functions as light receptor in rods and was the first structurally resolved mammalian GPCR. By combining</p>

	<p>biochemical separation, affinity based isolation and mass spectrometry we were able to identify 72 different proteins associated with rhodopsin. This primary dataset was filtered against the human interactome deposited in the MINT database. The resulting network was then merged with own experimental interaction data to further qualify a virtual interaction network containing 150 nodes and 395 edges. In parallel we decomposed the 70 proteins into their functional domains using pfam or smart. We then screened the 3id structure database for domain-domain interactions to identify mutually exclusive or mutually compatible interactions in between all possible interactions allowing us to define ternary complex formation as well as to model the composition of macromolecular assemblies and its dynamic dissection into mutually exclusive complexes. Finally information regarding protein localization was added. The resulting network does not only offer an unprecedented view of signal transduction induced by this GPCR but also suggests important new functions, as well as displaying temporally regulated biological phenomena such as vesicle transport, cytoskeletal dynamics and dynamics in protein interactions regulating light adaptation.</p>
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PROJECT WEB-SITE	<p>http://www.fz-juelich.de/ptj/quantpro www.interaction-proteome.org</p>