☐ co-ordinated with the Director of the Institute / Research Unit

Institute/ Research Unit / Clinical Co-operation Group / Junior Research Group:
Description

PSP-Element:
G-505700-001
A-630700-001

Person to contact for further enquiries:
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Title of the Highlight:
Structural and functional protein network analyses predict novel signaling functions for rhodopsin

Keywords:
Rhodopsin, multiscale protein network, systems biology, mass spectrometry, protein complexes, structural modeling

Central statement of the Highlight in one sentence:
Work on modeling the protein network of rhodopsin was selected and highlighted by the Faculty of 1000 (http://f1000.com) and placed in their library of the top 2% of published articles in biology and medicine.

Text of the Highlight:
Understanding complex signal transduction networks is one of the big challenges in modern Biology. Traditionally protein interactions that provide a physical architecture to such networks have been studied by combining biochemical and genetic experiments. Large throughput experiments using different techniques like two hybrid, or pull downs have added a new level of complexity. However in the majority of these studies network dynamics, the simultaneous regulation of several distinct higher order biological outputs by one network, and the fact that many interactions detected for a particular protein are not compatible simultaneously could not be tackled. In consequence, information on networks remains static, often fails to represent physiology and in many cases lead to wrong interpretations.

By integrating proteomic datasets, literature mining, computational analysis, and through structural information a team around Marius Ueffing and Andreas Vogt, PROT, has generated an approach, that tackles some of these problems. Conceptually, this work, that

describes rhodopsin protein network architecture and behaviour presents a general strategy applicable to the analysis of any cellular pathway.

The article, published in Molecular Systems Biology in November 2011, has been selected and highlighted by the Faculty of 1000 (http://f1000.com) a few weeks after its publication and was placed in their library of the top 2% of published articles in biology and medicine.

Rhodopsin, the major visual pigment of the retina belongs to the G-protein-coupled receptor (GPCR) family and is extremely sensitive to light, enabling vision under low-light conditions. This GPCR is tightly packed into stacks of membranes ("discs") in the outer portion of rod photoreceptor cells. Photon-activated rhodopsin translates light into a biochemical signal followed by an electrical cue that is transmitted through the neuronal network of the retina. Mutations in rhodopsin and other proteins in the signal transduction cascade of light cause severe blinding diseases such as retinitis pigmentosa, rod-cone dystrophies, and congenital stationary night blindness.

Identifying protein interactions and their networks is therefore an important step towards improving our understanding of the molecular defects that underlie blinding diseases and may directly lead to identifying new disease-associated genes.

Using proteomic methods the group cataloged the proteins involved in the rod outer segment signaling pathway of mammalian photoreceptors. By applying a new conceptual strategy the group then generated a comprehensive multiscale protein interaction network. Together with the groups of Luis Serrano at the CRG in Barcelona (Spain) and Gianni Cesareni at the University of Rome (Italy) the group combined experimental proteomics data with literature mining and structural information to develop a structural model allowing discrimination between protein interactions that are compatible and those that are mutually exclusive.

Computational analysis was combined with experients to test and validate the models generated. These experiments provided evidence for rhodopsin interactions with small GTPases involved in cytoskeleton assembly/disassembly and dynamics, as well as vesicle and Golgi trafficking. Taken together this work suggests a new functional role for rhodopsin in self-regulating and fine-tuning the structural and functional integrity of photoreceptors.

Publication:

Kiel C*, Vogt A*, Campagna A*, Chatr-aryamontri A, Swiatek-de Lange M, Beer M, Bolz S, Mack AF, Kinkl N, Cesareni G, Serrano L, Ueffing M. Structural and functional protein network analyses predict novel signaling functions for rhodopsin. Molecular Systems Biology. 2011 Nov 22;7:551. doi: 10.1038/msb.2011.83.

Taking account of the HMGU mission:

How does the Highlight described relate to the HMGU mission?
(1-2 sentences)

This study presents a systems biology approach and demonstrates a new conceptual strategy for generating comprehensive multiscale protein networks, applicable for any cellular pathway, by combining experimental data with literature mining and structural information. The identification of protein interactions and their networks is an important step toward improving the understanding of the molecular defects that underlie genetically-inherited and age-related diseases, and may directly lead to the identification of disease-associated genes.

The internal HMGU co-operation partners with whom the Highlight was compiled, if appropriate:

CRG-EMBL System Biology Program, Centre de Regulació Genòmica (CRG) Barcelona, Spain; [4] University of Rome Tor Vergata, Rome, Italy; [5] Institució Catalana de Recerca I Estudis Avançats (ICREA).
Information about institute and PSP-Element.

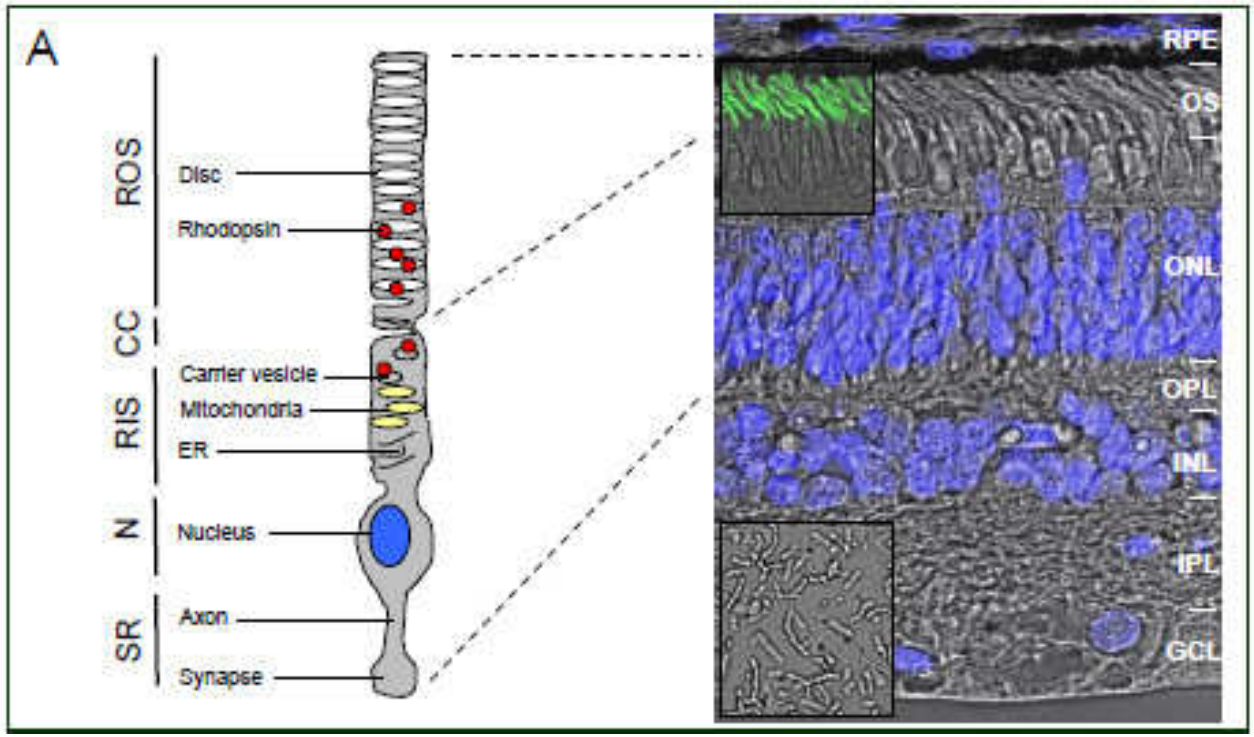

Figure 1 (**A**) Schematic model of a rod photoreceptor cell (left) and its corresponding location within the retina (depicted in the micrograph to the right). Segments labelled in the model are: rod outer segment (ROS) with enclosed stacks of discs membranes containing the visual pigment molecules rhodopsin; connecting cilium (CC); rod inner segment (RIS) containing mitochondria, Golgi, and ER membranes, and vesicles in which opsin molecules are assembled before transported to the outer segment; and the cell body containing the nucleus and a synaptic termini where neurotransmission to second order neurons occurs. The micrograph depicts the vertical porcine retina with its cytoarchitectural organization labeled as: photoreceptor outer segments (OS); the outer nuclear layer (ONL) containing cell bodies of rods and cones; the outer plexiform layer (OPL); the inner nuclear layer (INL); the inner plexiform layer (IPL), and the ganglion cell layer (GCL). Retinal pigment epithelium (RPE) is localized above the photoreceptor cell layer (for details, see http://webvision.med.utah.edu). Retinal cells nuclei were stained with DAPI (magnification 40×). Insets show micrographs of the OS immunolabeled with anti-rhodopsin with second antibody FITC-conjugated (magnification 40×; top inset), and of the OS preparation (magnification 40×; bottom inset).

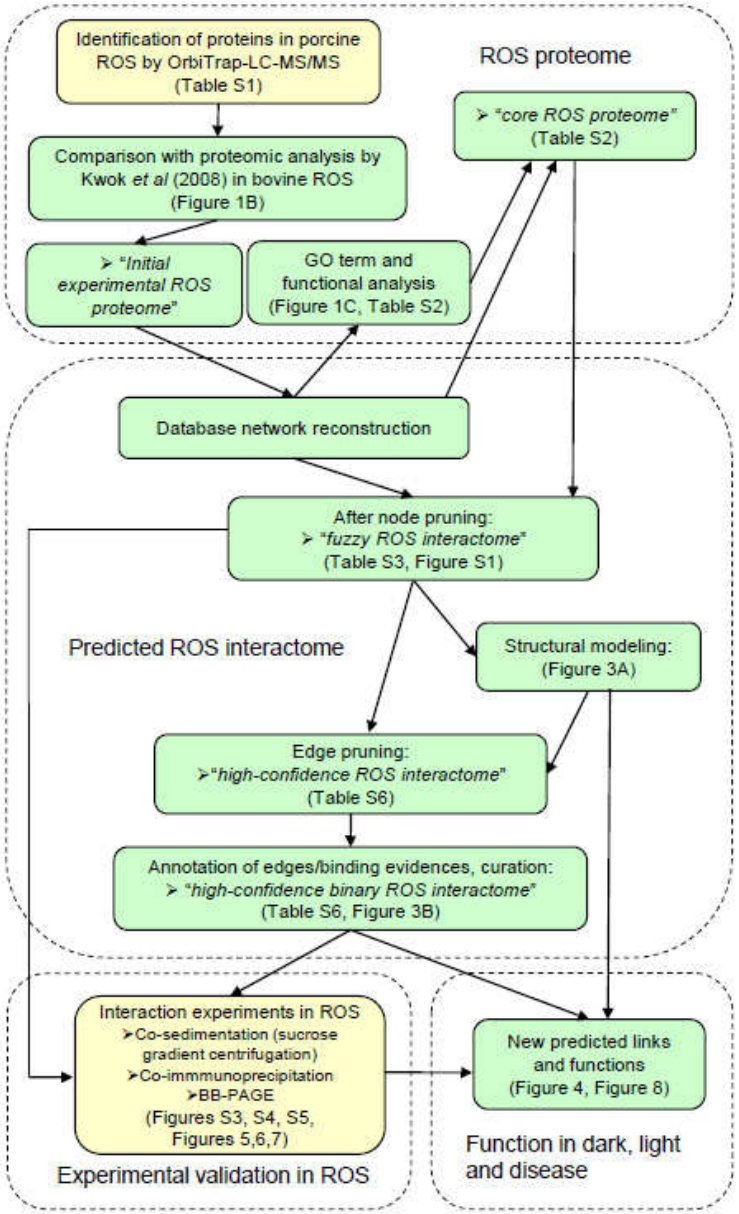

Figure 2 Experimental and computational workflow. The flow charts of experimental (yellow boxes) and bioinformatic (green boxes) methods used in this work are shown. The initial ROS proteome was generated based on the union of proteins identified in bovine ROS in this work and those from a proteomic analysis of porcine ROS (Kwok *et al*, 2008). After filtering, a high-confidence ROS proteome was defined. A static ROS interactome was compiled by literature mining. In addition, new experiments were performed in ROS in this work (co-sedimentation and co-immunoprecipitation). Further, we performed structural analyses and homology modeling, to distinguish between compatible and mutually exclusive interactions. This enabled us to break the network of nodes and edges into functional machines or sub-networks and modules. The comprehensive multiscale network highlights new predicted links and functions. Lastly, disease-associated genes were identified and modeled into available structures.

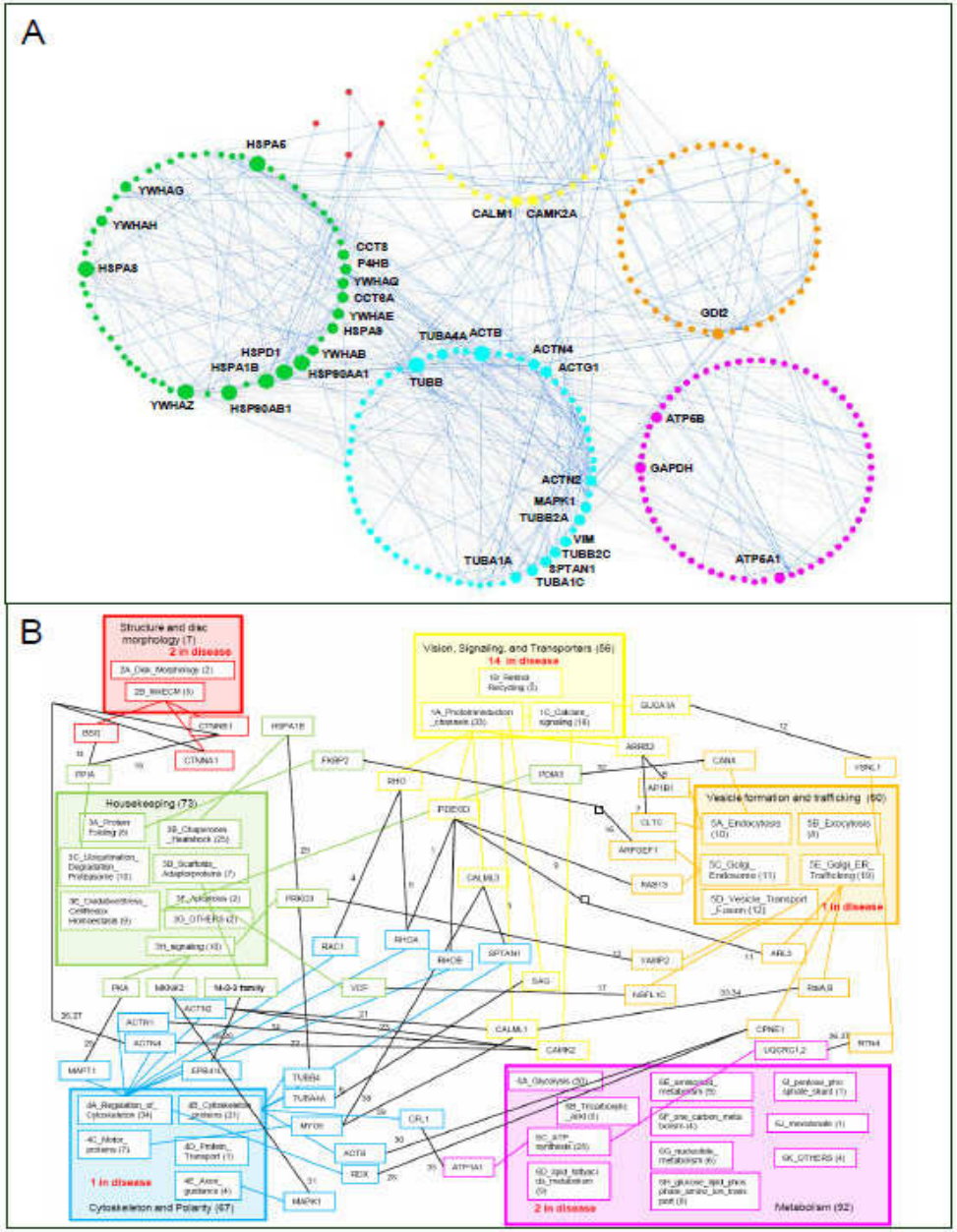

Figure 3 The high-confidence ROS interactome and the high-confidence binary ROS interactome. (**A**) The high-confidence ROS interactome. The 694 higher confidence interactions of the ROS interactome are listed (Supplementary Table S6). The size of the nodes indicates the number of interaction partners for a given protein (of >10 or >20). for Edges with binary evidence are indicated with blue, while edges supported by more than one evidence are indicated in grey. Proteins are colored according to their function. (**B**) The high-confidence binary ROS interactome. Modules and sub-modules are shown, and only the interactions of proteins from two different modules are indicated (see Supplementary Material 2). The number of proteins implicated in diseases in each category is indicated.

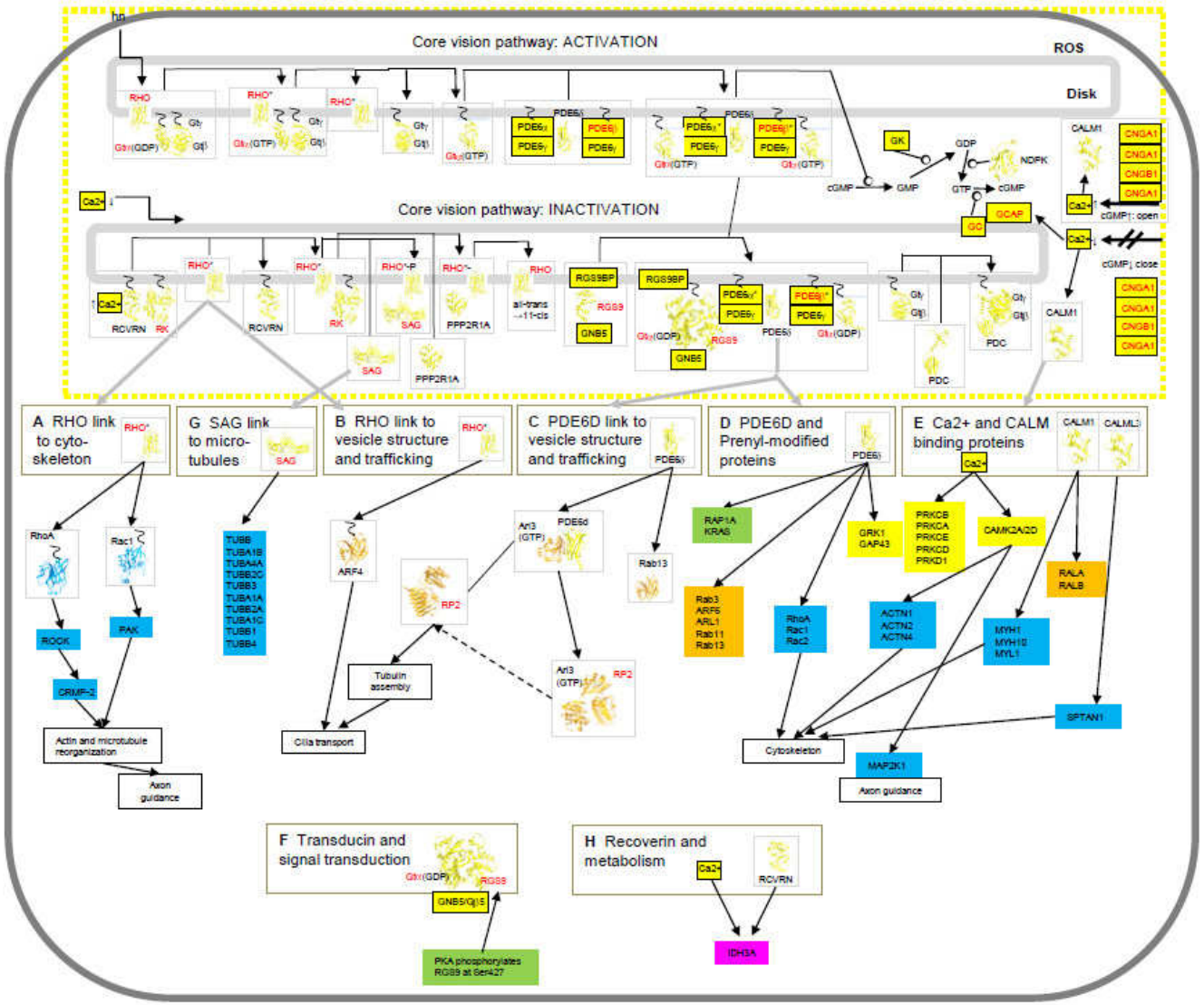

Figure 4 Structural coverage of the core vision pathway and its links to other functional modules. The published core pathway (Dell'Orco *et al*, 2009) was extended using evidence from our high-confidence network. Outputs to different functional cellular processes emanating from the proteins in the pathway are indicated, and structures are displayed if available by ribbon representation (see the main text and Supplementary Material 2). Proteins are colored according to their function.