Annex 1  Most important publications of NCCR Structural Biology (Year 1-Year 11, in order of appearance in Chapter 3.1)

1. Hilf R & Dutzler R. X-ray structure of ELIC, a member of an important family of neurotransmitter receptors. *Nature* **452**, 375-379 (2008). The structure has provided the first view of this ion channel family at high resolution and shows a non-conducting conformation of the channel.


3. Dawson RJP, Locher KP. Structure of a bacterial multidrug ABC transporter. *Nature* **443**, 180-185 (2006). The first structure of an ABC exporter. These proteins are relevant in multidrug extrusion and (glyco-)lipid flipping. The study revealed the architecture of these proteins and suggested a drug extrusion mechanism that exploits the binding and hydrolysis of cellular ATP. Five papers (including three in Science) were retracted after this work was published, which underscores the importance of this paper. [http://xray0.princeton.edu/~phil/Facility/Guides/ABCtransporter.html](http://xray0.princeton.edu/~phil/Facility/Guides/ABCtransporter.html)


High resolution atomic force microscopy on native mouse retina disc membranes revealed rows of rhodopsin dimers. Since rhodopsin is a member of the GPCR family, this has significant implications for the understanding of GPCR organisation *in situ*.

This is the first report of the selection and co-crystallisation of a DARPin with a membrane protein, which demonstrates the potential of DARPins not only as inhibitors but also as tools for the structural investigation of integral membrane proteins. This paper describes the crystal structure of AcrB at the highest resolution obtained so far.

Crystal structure of the bacterial ammonium transporter AmtB. The trimeric structure lined by hydrophobic residues suggests that the transported species is the neutral ammonia molecule rather than the charged ammonium ion.

Crystal structure of the first level of hierarchical DNA packaging.

This study describes the structure of a tetranucleosome and models its stacking. The models suggest that the interfaces between nucleosomes along a single helix start are polymorphic.

This study shows how a chromatin remodelling factor could set the spacing between two adjacent nucleosomes acting as a 'protein ruler'.
Studies on the alternative splicing repressor PTB revealed how it recognises RNA by solving the structures of all four RNA recognition motifs of the protein in complex with RNA.

The second most frequent RNA binding module, the double-stranded RNA binding motif dsRBM, recognises RNA in a sequence specific manner. This is an unexpected result as dsRBMs were considered to be non-specific RNA binding domains.

The structure reveals the fold of the entire 18S ribosomal RNA and of all ribosomal proteins of the 40S subunit, and defines the interactions with the initiation factor eIF1. It provides insights into the eukaryotic-specific aspects of protein synthesis, including the function of eIF1 as well as signaling and regulation mediated by the ribosomal proteins RACK1 and rpS6e.

The T. thermophila 60S subunit was solved in complex with the eukaryotic initiation factor 6 (eIF6) and co-crystallised with the antibiotic cycloheximide, a eukaryotic-specific inhibitor of protein synthesis. The 60S large subunit structure contains 3 rRNA molecules and 42 proteins of which 6 are eukaryotic-specific. These 6 proteins are not homologous to the structures of known ribosomal proteins and thus the range of known ribosomal protein folds has been broadened.

17. Maier T, Leibundgut M, Ban N. The crystal structure of a mammalian fatty acid synthase. *Science* **321**, 1315-22 (2008). This study provides the first mechanistic insights into substrate shuttling and delivery in such megasynthases, with direct implications for our understanding of polyketide synthases and non-ribosomal peptide synthases.


Nobel citation: The Nobel Prize in Chemistry 2002 was awarded "for the development of methods for identification and structure analyses of biological macromolecules" with one half to Kurt Wüthrich "for his development of nuclear magnetic resonance spectroscopy for determining the three-dimensional structure of biological macromolecules in solution".


Single-molecule spectroscopy of the misfolding of IG-like domains shows that the interactions that lead to misfolding are highly specific. This specificity appears to be the reason that sequence similarity in multidomain proteins is avoided in evolution. Similar interactions may be involved in neurodegenerative diseases, such as Alzheimer's or Parkinson's.


This is the first paper detailing the DARPin technology, it has been cited 218 times to date. There are many potential applications: in vivo targeting reagents, intracellular sensors, crystallisation chaperone. A spin off biotechnology company was founded to exploit the clinical applications of this technology, Molecular Partners AG.


This paper laid the foundation of the directed evolution of membrane proteins for stability and expression. It was the first time that a Darwinian evolution has been applied to such a problem.
The refinement methods and analysis techniques implemented in the GROMOS software for biomolecular simulation are presented. It allows structure refinement combining different types of experimental data with different types of restraining functions, while using a variety of methods to enhance conformational searching and sampling and the thermodynamically calibrated GROMOS force field for biomolecular simulation.

This paper describes the first structure of a bacterial α-helical pore forming toxin. The structure of the pore complex of the E. coli toxin ClyA suggests a mechanism for the membrane-induced conformational transition from the soluble, monomeric ClyA protein to the assembly competent protomer, and reveals one of the largest conformational changes in a protein observed so far.