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.

2. Hilf R & Dutzler R. Structure of a potentially open state of a proton-activated pentameric ligand-gated channel. *Nature* **457**, 115-118 (2009)
X-ray structure of GLIC, which provides the first structural insight at high resolution into a 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

4. Hohl M, Briand C, Grütter MG, Seeger MA. Crystal structure of a heterodimeric ABC transporter in its inward-facing conformation. *Nat Struct Mol Biol.* **19**, 395-402 (2012).
Crystal structure of a bacterial heterodimeric ABC exporter at a very high resolution. This ABC transporter depicts an inward-facing conformation with the nucleotide binding domains (NBDs) interacting via an interface involving highly conserved structural motifs which provide a functional link between the two asymmetric ATP hydrolysis sites.

5. Lizak C, Gerber S, Numao S, Aebi M, Locher KP. X-ray structure of a bacterial oligosaccharyltransferase. *Nature* **474**, 350-355 (2011).
The first crystal structure of an oligosaccharyltransferase. These proteins catalyse protein N-glycosylation, an essential cellular process. The study not only revealed the architecture of this protein and the molecular basis of substrate recognition, but also suggested the mechanism of glycan transfer.

6. Liang Y, Fotiadis D, Filipek S, Saperstein DA, Palczewski K, Engel A. Organization of the G protein-coupled receptors rhodopsin and opsin in native membranes. *J Biol Chem.* **278**, 21655-62 (2003).
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*.

7. Sennhauser G, Amstutz P, Briand C, Storchenegger O, Grütter MG. Drug export pathway of multidrug exporter AcrB revealed by DARPin inhibitors. *PLoS Biol.* **5**, 106-113 (2007).
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.

8. Zheng L, Kostrewa D, Bernèche S, Winkler FK, Li XD. The mechanism of ammonia transport based on the crystal structure of AmtB of Escherichia coli. *Proc Natl Acad USA* **101**, 17090-17095 (2004).
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.

9. Richmond TJ, Davey CA. The structure of DNA in the nucleosome core. *Nature* **423**, 145-50 (2003).
Crystal structure of the first level of hierarchical DNA packaging.

10. Schalch T, Duda S, Sargent DF, Richmond TJ. X-ray structure of a tetranucleosome and its implications for the chromatin fibre. *Nature* **436**, 138-41 (2005).
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.

11. Yamada K, Frouws TD, Angst B, Fitzgerald DJ, DeLuca C, Schimmele K, Sargent DF, Richmond TJ. Structure and mechanism of the chromatin remodelling factor ISW1a. *Nature* **472**, 448-53 (2011).
This study shows how a chromatin remodelling factor could set the spacing between two adjacent nucleosomes acting as a 'protein ruler'.

12. Oberstrass FC, Auweter SD, Erat M, Hargous Y, Henning A, Wenter P, Reymond L, Amir-Ahmady B, Pitsch S, Black D and Allain FH-T. Structure of PTB Bound to RNA: Specific Binding and Implications for Splicing Regulation *Science* **309**, 2054-2057 (2005).
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.

13. Stefl R, Oberstrass FC, Hood JL, Jourdan M, Zimmermann M, Skrisovska L, Maris C, Peng L, Hofr C, Emeson RB, Allain FH-T. The solution structure of the ADAR2 dsRBM-RNA complex reveals a sequence-specific readout of the minor groove. *Cell* **143**, 225-237 (2010).
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.

14. Rabl J, Leibundgut M, Ataide SF, Haag A, Ban N. Crystal structure of the eukaryotic 40S ribosomal subunit in complex with initiation factor 1. *Science* **331**, 730-6 (2011).
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.

15. Klinge S, Voigts-Hoffmann F, Leibundgut M, Arpagaus S, Ban N. Crystal structure of the eukaryotic 60S ribosomal subunit in complex with initiation factor 6. *Science* **334**, 941-8 (2011).
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.

16. Ataide SF, Schmitz N, Shen K, Ke A, Shan SO, Doudna JA, Ban N. The crystal structure of the signal recognition particle in complex with its receptor. *Science* **331**, 881-6 (2011).
This crystal structure together with the biochemical data provide mechanistic insights into the function of this ribosomal complex.

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.

18. Vetsch M, Puorger C, Spirig T, Grauschopf U, Weber-Ban EU, Glockshuber, R. Pilus chaperones represent a novel type of protein folding catalyst. *Nature* **431**, 329-332 (2004).
This study describes the identification of bacterial pilus assembly chaperones as a previously unknown class of protein folding catalysts and demonstrates that pilus chaperones act as kinetic assembly traps that prevent premature, intracellular assembly of pilus subunits prior to subunit translocation through the outer bacterial membrane.

19. Nishiyama M, Ishikawa T, Rechsteiner H, Glockshuber R. (2008) Reconstitution of pilus assembly reveals a new type of bacterial outer membrane catalyst. *Science* **320***,* 376-379.
This paper describes the first example of a protein-catalysed assembly of a supramolecular protein complex, the reconstitution of the entire *E. coli* type I pilus assembly system *in vitro* form purified components, the identification of the membrane protein FimD as assembly catalyst, and the quantitative kinetic description of all individual assembly reactions.

20. Fiaux J, Bertelsen EB, Horwich AL, Wüthrich K. NMR analysis of a 900K GroEL GroES complex. *Nature* **418**, 207-11 (2002).
This study establishes the utility of solution NMR techniques for the exploration of structure, dynamics and interactions in large macromolecular complexes.

21. Wüthrich K. NMR studies of structure and function of biological macromolecules (Nobel lecture). *Angew Chem Int Ed Engl*. **42**, 3340-63 (2003).
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".

22. Borgia M, Borgia A, Best RB, Steward A, Nettels D, Wunderlich B, Schuler B, Clarke J. Single-molecule fluorescence reveals sequence-specific misfolding in multidomain proteins. *Nature* **474**, 662-665 (2011).
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.

23. Binz HK, Amstutz P, Kohl A, Stumpp MT, Briand C, Forrer P, Grütter MG, and Plückthun A. High-affinity binders selected from designed ankyrin repeat protein libraries. *Nat. Biotechnol*. **22**, 575-582 (2004).
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.

24. Sarkar CA, Dodevski I, Kenig M, Dudli S, Mohr A, Hermans E, Plückthun A. Directed evolution of a G protein-coupled receptor for expression, stability, and binding selectivity. *Proc. Natl. Acad. Sci. U.S.A*. **105**, 14808-14813 (2008).
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.

25. Schmid N, Allison JR, Dolenc J, Eichenberger AP, Kunz AP, van Gunsteren WF. Biomolecular structure refinement using the GROMOS simulation software. *J Biomol NMR* **51**, 265-81 (2011)
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.

26. Mueller M, Grauschopf U, Maier T, Glockshuber R, Ban N. The structure of a cytolytic alpha-helical toxin pore reveals its assembly mechanism. *Nature* **459,** 726-30 (2009).
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.