Abstract

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Lead Generation without an X-Ray Crystal Structure: An NMR Method to Probe Protein-Ligand Complexes

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Abstract

X-ray crystallography molecular replacement (MR) is a highly versatile tool for the detailed characterization of lead compound and binding modes in the pharmaceutical industry. The two major limitations of its application to drug research are (i) the availability of a similar protein structure, and (ii) obtaining well-diffracting crystals of the ligand-protein complexes of interest. While nowadays the first point is often not a limitation anymore, obtaining well-diffracting crystals might be difficult. In such situations structure determination of protein-ligand complexes by liquid-state NMR is a good option. Unfortunately, the established standard structure determination protocol is in general time-consuming, and a shortcut using available structural data as in the case of MR in X-ray crystallography is not available.Here, we present NMR2(NMR Molecular Replacement), a MR-like approach in NMR to determine the structures of the binding pockets of ligands at atomic resolution. The calculation of structures of protein-ligand complexes relies on the collection of unassigned semi-quantitative inter-molecular NOE distance restraints and on previously solved structures.[1] The NMR2 method uses a high throughput structure calculation protocol, rather than a docking-scoring simulation. It is fast since it requires only a few days of measuring time and bypasses the time-consuming sequential assignment steps for the protein.We will present multiple NMR2 applications covering several ligand topologies ranging from peptidomimetic to small molecules that bind strongly or weakly to protein receptors. We also report how NMR2 can make use of partially labelled protein using methyl-specific isotope labelling. Our findings demonstrate that NMR2 may open an avenue for the fast and robust determination of the binding pocket structure of ligand-protein complexes at atomic resolution.

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Biography

Julien Orts studied Physics and Biophysics and graduated in 2010 jointly from the Max Planck Institute for Biophysical Chemistry and the European Molecular Biology Laboratory under the guidance of Prof. Carlogmano and Prof. Griesinger. Julien joined the BioNMR laboratory at the ETH Zurich led by Prof. Riek, first as a post-doc and then as a junior group leader. Since 2021 he is an Assistant Professor at the University of Vienna in the Division of Pharmaceutical Chemistry.

His laboratory is focusing on Drug Discovery by advanced NMR methods, including integrated methods for fast protein-ligand complex structure determination, NMR based drug design, protein allostery, and thermodynamics of protein-protein and protein-ligand interactions.

We apply these techniques to therapeutically relevant receptors in-house or in collaborations with pharmaceutical industries.