CeMMP Centre for Cryo-electron Microscopy of Membrane Proteins

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Dr. Raphael Trenker is a Postdoctoral Fellow in the lab of Dr. Natalia Jura at the University of California San Francisco (UCSF). He obtained his Diploma in Biochemistry from the University of Frankfurt in Germany in 2013 while performing his research on chemokine receptors and ligands in the group of Prof. Hartmut Michel at the Max-Planck-Institute of Biophysics in the Department of Molecular Membrane Biology. Dr. Trenker obtained his PhD in 2018 from the University of Melbourne, Australia, where he worked with Drs. Matthew and Melissa Call in the Structural Biology division at WEHI investigating transmembrane helix-helix interactions in single-span transmembrane receptors using crystallography and deep mutational scanning analysis. He joined Dr. Natalia Jura's lab at UCSF in 2018 where in collaboration with the group of Dr. Kliment Verba he applies cryo-electron microscopy to investigate structural basis for the activation mechanism of human epidermal growth factor receptors (HERs/ERBBs).

Cryo-EM structures of the active HER2/HER3 receptor complex reveal dynamics at the dimerization interface induced by binding of a single ligand

The Human Epidermal Growth Factor Receptor 3 (HER3) and its close homolog, the orphan receptor HER2, are single pass transmembrane receptor tyrosine kinases that form a pro-oncogenic signaling complex upon binding to the HER3 ligand neuregulin-1b (NRG1b). Until recently, there were no structural insights into the HER2/HER3 heterodimer owing to the difficulties in its reconstitution in vitro. We isolated near full-length HER2/HER3/NRG1b heterocomplex and obtained a 2.9 Å cryo-electron microscopy (cryo-EM) reconstruction of the extracellular domain module, which revealed a surprisingly dynamic dimerization interface. Based on additional structures of this heterocomplex in which HER2 harbors its most frequently observed oncogenic mutation, S310F, and of this complex bound to the therapeutic antibody trastuzumab, it will be discussed how oncogenic mutations and therapeutics appear to exploit the intrinsic dynamics of the HER2/HER3 heterodimer. Strategies for receptor complex expression, isolation and cryo-EM sample preparation for imaging on graphene oxide-coated holey carbon grids will be highlighted, as well as current challenges in obtaining cryo-EM maps of full-length receptor tyrosine kinases.