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HORIZONS



## SEMINAR SERIES 2024

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### Dr. Basil Greber

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Dr. Basil Greber obtained his BSc and MSc in Biology from ETH Zurich, Switzerland, where he also joined the laboratory of Prof. Nenad Ban for his doctoral thesis work. At that time, the development of high-resolution cryogenic electron microscopy (cryo-EM) transformed structural biology. Dr. Greber applied these new methods to ribosomal complexes, resulting in several unexpected discoveries, including a built-in architectural tRNA in the mammalian mitochondrial ribosome and a new structural probing mechanism for the ribosomal tunnel during eukaryotic ribosome assembly. Dr. Greber was awarded the Scaringe Award of the RNA Society for these studies.



In 2015, Dr. Greber moved to the laboratory of Prof. Eva Nogales at the University of California, Berkeley as a postdoctoral fellow. At Berkeley, he determined the complete structure of human transcription factor TFIID, a multifunctional protein complex that is critical both for transcription initiation and DNA repair throughout eukaryotes. In 2020, he joined the Institute of Cancer Research in London as a group leader to perform structural and functional studies of DNA repair complexes. In addition to this biological research programme, he still maintains an interest in probing the boundaries of cryo-EM and its application to difficult targets.

### **High-resolution structures of the human CDK-activating kinase bound to inhibitors: Harnessing the power of cryo-EM for discovery of cancer therapeutics**

The human CDK-activating kinase (CAK) is a trimeric protein complex that acts as a master regulator of cell division and has been identified as a promising target for cancer therapy. Structural data are of great importance for the rational, structure-based design of next-generation therapeutics. Harnessing the power of cryo-electron microscopy (cryo-EM) for this task requires the development of workflows that enable structures of small, asymmetric complexes such as the human CAK to be determined at high resolution and with high throughput. To address these challenges, we initially determined structures of the human CAK bound to nucleotide analogues and inhibitors at up to 2.5 Å resolution. These results provided important insights into the molecular details of the assembly, activation, and inhibition of the human CAK. Recent work has now achieved the routine 2 Å-structure determination for the 85 kDa catalytic module of the human CAK bound to inhibitors, which provides us with new insights into CDK inhibitor selectivity.