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Dr. Joshua A. Lees

*Structural, Analytical, and Molecular Sciences, Medicine
Design, Pfizer, Inc.*

Josh Lees is a Lab Head in Structural Biology and Cryo-EM Lead at Pfizer, where he oversees cryo-electron microscopy efforts supporting drug discovery across a broad portfolio of therapeutic programs. Josh received his Ph.D. in Molecular Biology from Princeton University in 2010 under Fred Hughson, studying vesicle tethering complexes involved in membrane trafficking. During his postdoctoral training at Yale

University with Karin Reinisch and Pietro De Camilli, he used X-ray crystallography and cryo-EM to investigate membrane remodeling by lipid transfer proteins at membrane contact sites and the regulation of multi-subunit lipid kinase complexes. Since joining Pfizer in 2020, Josh's work has applied cryo-EM across a broad range of target classes and therapeutic areas, driving mechanistic understanding of challenging biological targets that have included GPCRs, membrane transporters, and other highly dynamic systems. His group's work integrates structural biology, biophysics, and functional studies to facilitate deep mechanistic understanding of drug targets and enable their therapeutic modulation.



From Structural Insight to Mechanism and Molecular Design in Drug Discovery

Cryo-EM has become a key driver of mechanism-based drug discovery. Its ability to reveal pharmacologically relevant conformational states and unexpected modes of action increasingly enables the rational design of therapeutic molecules, as illustrated by two examples from Pfizer's drug discovery pipeline.

The orphan G protein-coupled receptor GPR61, a constitutively active receptor linked to food intake and body weight regulation, is a potential target for treatment of both obesity and cachexia. Structural elucidation of its active and inactive states revealed a previously unrecognized allosteric mechanism of G protein-competitive inverse agonism at an induced intracellular pocket. These insights provided a structural framework for understanding structure-activity relationships, identifying opportunities for optimization, and guided the development of potent, selective, and brain penetrant inverse agonists.

The solute carrier protein SLC6A19 mediates neutral amino acid absorption and reabsorption in the intestine and kidney, respectively, and has emerged as a target for the treatment of disorders characterized by aberrant amino acid homeostasis. Its essential binding partner, ACE2, also serves as the cellular receptor for SARS-CoV-2, which created a unique opportunity to leverage knowledge gained during development of Pfizer's COVID-19 vaccine. Structural elucidation of SLC6A19 in complex with publicly available inhibitors uncovered a novel allosteric substrate-competitive mechanism of inhibition and revealed how partially overlapping binding modes could be exploited to guide design. Structure-guided optimization of these interactions yielded a highly potent inhibitor series. Together, these examples illustrate how structure-driven mechanistic insight directly informs therapeutic design to accelerate drug discovery.