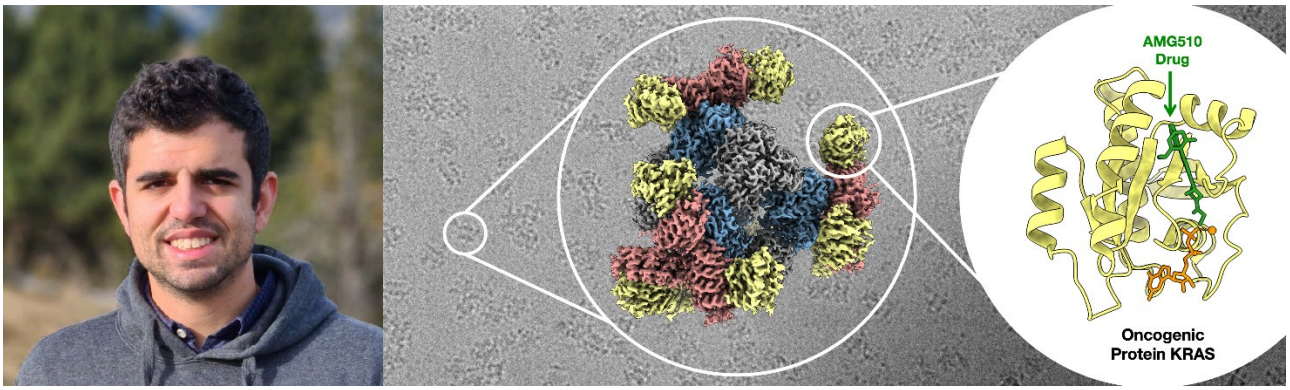
CryoEM Current Practices Webinar

Engineered Protein Cages for Imaging of Small Proteins by Cryo-EM



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Recent technical advances have made cryo-electron microscopy (cryo-EM) an attractive method for atomic structure determination, but problems of low signal-to-noise prevent routine structure determination of proteins smaller than about 50 kDa. We have developed symmetric protein imaging scaffolds to display and solve the structure of small proteins. In earlier work, we demonstrated the design of a novel protein cage scaffold with sufficient rigidity and modularity to reach an imaging resolution of 3.8 Å for a 26 kDa protein. In the present work, we use molecular engineering techniques to further rigidify a new cryo-EM imaging scaffold, enabling 3 Å or better resolution imaging to be achieved, even for very small proteins. We apply this system to the key cancer signaling protein KRAS (19 kDa in size), obtaining four structures of oncogenic mutational variants by cryo-EM. Importantly, a structure for the key G12C mutant bound to an inhibitor drug (AMG510) reveals significant conformational differences compared to prior data in the crystalline state. The findings highlight the promise of cryo-EM scaffolds for advancing the design of drug molecules against small therapeutic protein targets in cancer and other human diseases.

All are welcome to attend. Registration is at no-cost, but sign-up is required:
https://us02web.zoom.us/webinar/register/WN_6Vc1PwERRL6z7S_AtfPgDQ

This webinar series is jointly hosted by the NIH Transformative High Resolution CryoEM Program Service Centers: the National Center for CryoEM Access and Training (NCCAT), the Pacific Northwest Center for CryoEM (PNCC), and the Stanford-SLAC CryoEM Center (S2C2) who provide no-cost access to cryoEM instrumentation and training. In this monthly series, we will highlight cryoEM methods and use the Q&A session after the seminar to stimulate discussion of best practices and interesting challenges that will be helpful to researchers new to the field. Representatives from all three service centers will also be on hand to answer questions about the cryoEM resources available to biomedical researchers and how to access them.