CCR – IMPROMPTU

Monday, March 10th, 2025, 13:00 PM

Zaritza Petrova

Yale University, USA

Understanding how kinase domain interactions contribute to dimerization and activation of receptor tyrosine kinases

The Epidermal Growth Factor Receptor (EGFR) is a receptor tyrosine kinase (RTK) that mediates signals for cell proliferation, differentiation, migration, and survival. While its activation mechanism has served as a paradigm for RTK activation, EGFR has unique features that make it susceptible to oncogenic mutations, leading to dysregulated activity and cancer, particularly NSCLC. My research focuses on the role of asymmetric kinase dimerization in EGFR activation. Using biochemical and biophysical techniques—including SAXS, HDX-MS, AUC, and steady-state enzyme kinetics—I measure the homo-dimerization affinity of the EGFR kinase domains. I show that while kinase dimerization is weak and transient, it significantly enhances kinase activity. Dimerized EGFR, previously considered a slow kinase, exhibits activity comparable to other tyrosine kinases, whereas both wildtype and mutationally activated monomers are far less active. Consequently, mutations that enhance dimerization can produce a much stronger signaling effect than those acting on monomeric kinases. To further investigate this mechanism, I study a disulfide-linked synthetic dimer and an oncogenic kinase domain duplication (KDD) in which two kinase domains are connected by a disordered linker. Using SAXS and Cryo-EM, I demonstrate that KDD's high oncogenic activity depends on transient, not constitutive, asymmetric kinase dimer formation. These findings highlight the importance of kinase dimerization dynamics in understanding RTK signaling and suggest that this knowledge can also inform EGFR-targeted therapies.

Venue: Lecture Hall B1, Borschkegasse 4a
Time: Monday, March 10th 2025, 13:00 PM
Host: Maria Sibilia

CENTER FOR CANCER RESEARCH
MEDICAL UNIVERSITY OF VIENNA