GESELLSCHAFT DEUTSCHER CHEMIKER

KOLLOQUIUM

Sommersemester 2022

Titel

Kinetics of Kinase inhibitor binding and development of highly selective Cyclophilin Inhibitors

Vortragender

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Abstract

The duration of drug binding to a receptor protein is in many cases a better predictor for drug efficacy than the affinity of the drug. Consequently, drug residence time is a potential optimization parameter in drug development. From the perspective of the protein, this also predicts that mutations in a receptor could cause drug resistance by reducing drug residence time. We performed an in-cell screen of imatinib binding against a library of Abl kinase mutants derived from patients with imatinib-resistant chronic myeloid leukemia. We identified several kinetic mutants, one of which binds imatinib with wild-type affinity but dissociates considerably faster from the mutant kinase. Using NMR and molecular dynamics, we found that this mutation increases the conformational dynamics of the mutant protein, linking conformational dynamics of the protein to drug dissociation. The results underline the importance of drug dissociation kinetics for drug efficacy and propose a kinetic resistance mechanism that may be targetable by altering drug treatment schedules.
In a related study, we use unbiased drug binding simulations in a generalizable computational protocol to predict allosteric ligand binding sites. Using Src kinase as a model system we demonstrate the proof of concept, identify a new allosteric inhibitor of Src and confirm a novel allosteric regulatory site on Src.
Finally, I will present a vignette on our efforts to develop highly selective inhibitors of the prolyl isomerase Cyclophilin D. The high sequence and structural conservation of cyclophylins complicates the development of specific inhibitors. In two lines of research, we provided the structural basis for the development of specific inhibitors through the determination of close to 1000 X-ray crystal structures.

Ort

Chemie, HS1 – Campus Nord, Otto-Hahn-Straße 6
Anfahrt: http://gdch.chemie.uni-dortmund.de

Zeit

Dienstag, 05.07.2022, 17:15 Uhr

Meet the Prof. für Studierende im Anschluss an den Vortrag in C2-02-326

gez. Professor Dr. Daniel Rauh
Gesellschaft Deutscher Chemiker
Ortsverband Dortmund