Crystallography, biophysical and cheminformatics studies for next-generation kinase inhibitor design
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Background: The human genome contains over 500 homologous protein kinases, which control cellular signalling processes. They have become one of the most important target classes for the design of therapeutic inhibitors; many diseases are caused by dysregulation of cellular signalling processes. Most therapeutic inhibitors approved to now are for cancer therapies, but this focus is now broadening. Emerging targets of interest are relevant e.g. for neurodegenerative diseases, inflammation, and other areas. Further protein kinase targets are of non-human origin, with impacts for antibacterial, antifungal, and antiparasitic therapies.

Research into protein kinase inhibitor drugs has been progressing for the past 20-30 years with many high-throughput tools, including synthesis, screening, and structural studies. As a result, an enormous body of relevant data exists, including three dimensional structures, binding strengths and selectivity determinants. Further, many and growing numbers of highly active kinase inhibitors are now coming off patent for the first time, including the first approved protein kinase drugs. This creates a drug discovery environment with unparalleled richness. Protein kinase selectivity determinants are known that can retarget such substances to similar but distinct kinases with relatively minor changes. Due to the complexities of drug-target interactions, and especially in connection with the natural flexibility of protein kinases, inhibitor binding properties can be predicted with only limited success. Taken together, these facts highlight the future of protein kinase inhibitor drug discovery: 1) increased interest in new targets, 2) cheminformatics driven and rapid refuctionalization of known binders to these targets, and 3) ongoing discovery of key selectivity determinants.

Project goals and activities

• (Application writing phase) Evaluation of up-to-date inhibitor and target data to select a protein kinase target area of interest.
• Selection of specific constructs for protein production, based on strategies for successful crystallography, variations to identify key binding interactions, and possible related target interactions (to optimize selectivity profiles, avoid toxicities, and forestall drug resistance)
• Protein production, crystallography and biophysical binding studies, studying mechanisms of ligand binding strengths and kinetics.
• Cheminformatics studies to identify the most promising inhibitor design approaches; modelling and possible synthesis of new compounds

The research environment

• The project is based at the Norwegian Center for Structural Biology (NORSTRUCT), Department of Chemistry, Tromsø, Norway
• NOSTRUCT facilities include state-of-the-art recombinant protein production facilities allowing both prokaryotic and eukaryotic expression with scalable chromatographic purification, and also recently upgraded (2017) systems for automated liquid handling, crystallization, X-ray data collection, and biophysical ligand binding studies (SPR, ITC, MST)
• The Department of Chemistry hosts and encourages collaboration with the Center for Computational and Theoretical Chemistry (Norwegian Center of Excellence) and the Norwegian node for the pan-European research infrastructure Elixir
The strategic research focus of the Department of Chemistry prioritizes therapeutic target/ligand interaction studies with a Drug Discovery and Design technology and networking platform, with ongoing projects in antibiotic, anticancer, and other drug discovery areas.

Tromsø is a center for marine bioprospecting studies, with potential impact for this projects.

The project supervisor (https://www.linkedin.com/in/richard-a-english-77949a88) has extensive experience and a wide ranging publication record beginning with very early protein kinase crystallography efforts (see publications below)

Tromsø is a vibrant and unique city north of the Polar Circle with a large international community, often cited in "top ten" lists of places to experience (northern lights, midnight sun, whale watching, unspoiled nature).

Selected relevant publications (see also http://www.researchgate.net/profile/Richard_Engh/)

- Phosphotransferase and substrate binding mechanism of the cAMP-dependent protein kinase catalytic subunit from porcine heart as deduced from the 2.0 Å structure of the complex with manganese(2+) adenyl imidophosphate and inhibitor peptide PKI(5-24); D.Bossemeyer, R.A.Engh, V.Kinzcl, H.Ponstingl & R.Huber; EMBO Journal (1993) 12; 849-59.