Chemical Probes: A Route for Exploration of Under-Studied Protein Kinases as Novel Drug Targets.

Gileadi, O.[1, 2], Counago, R.[1], Ruela-de-Sousa, R.R.[1], Godoi, P.H.C.[1], Reis, M.B.C.[1], Gileadi, C.[1,2], Salmazo, A.[1], Verza, N.C.[1] Massirer, K.B.[1], Arruda, P.[1]

[1]Structural Genomics Consortium, Universidade Estadual de Campinas (UNICAMP), Campinas, Brazil; [2]Structural Genomics Consortium, University of Oxford, Oxford, UK.

INTRODUCTION: Protein kinases are key signalling proteins regulating development, cell growth, physiology, cell-cell communication and responses to the environment. The human genome encodes ~520 protein kinases, yet most research has focussed on 10% of this family. Furthermore, the ~30 approved drugs targeting protein kinases are mostly directed at cancer. One of the reasons for the narrow focus of academia and industry is the lack of high-quality, readily accessible reagents to study the therapeutic potential of novel kinases. The SGC is a public-private partnership that aims to promote the discovery of new medicines by providing open-access knowledge and reagents to elucidate the roles of under-studied human proteins.
OBJECTIVES: The SGC-UNICAMP aims to develop potent and selective inhibitors of human protein kinases, to be distributed to the community without restrictions. By applying strict quality criteria (K_I < 50 nM; 50x selectivity against most other kinases; and activity on intact cells with EC_{50} < 1 μM), researchers can directly investigate the consequences of selective pharmacological inhibition of the target kinases on physiology and disease processes.
MATERIALS AND METHODS: To perform medicinal chemistry in a quick and efficient manner, we have built an industrial-like process of cloning, protein production, compound screening, protein crystallography, and cell-based assays that provide quick feedback to the medicinal chemists to allow compound optimization.
RESULTS AND DISCUSSION In the year since starting operations, we have purified 30 protein kinases (to be expanded to 130 in the next year), implemented in-house screening assays based on 3 different technologies; solved the crystal structures of several protein kinases in complex with inhibitors; and demonstrated cellular activity of one inhibitor series.
CONCLUSIONS: With a wide in-house panel of purified protein kinases and assays, we are well-poised to identify and exploit new hits for chemistry-driven target discovery.

Keywords: *Protein kinase, medicinal chemistry, target discovery, small-molecule inhibitors*
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