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Istituto Europeo di Oncologia

EPIgenetic marks for unbiased, high content functional profiling of clinical KINase inhibitors

Introduction

Protein kinases are among the most important drug targets. More than 500 kinase are implicated in the control of most cellular process and dysregulation of their activity is linked to a large number of diseases, including cancer and inflammatory disorders. It is estimated that Clinical Kinase Inhibitors (CKIs) account for about 30% of the overall drug development efforts in the world.

Medical Need

Most CKIs are intrinsically promiscuous multi-target drugs, therefore able to target multiple kinases. The simultaneous inhibition of multiple kinases and downstream effectors may enhance therapeutic effects but, at the same time, is also expected to increase risk and extent of off-target effects. A major challenge in the development of CKIs is the lack of high-content and unbiased *functional* profiling approaches in current screening platforms. These factors result in a high attrition rate, with 90% of CKIs clinical trials failing, and limited use of each of these drugs despite their potential to target multiple pathways.

Solution

EPIKIN represents an innovative platform integrating experimental, computational and Artificial Intelligence-based approaches for a functional profiling of CKIs' effects in living cells. Such platform is based on high-throughput and genome-wide measurement of the genomic distribution of chromatin modifications upon treatment with CKIs for an unbiased, high-content readout of their functional effects on cell functions. The resulting unbiased high-content data are integrated and analyzed through computational and machine learning approaches. As proof-of-concept data, the EPIKIN workflow enabled the identification of Midostaurin, an inhibitor of the kinase FLT3 used in therapy of leukemias, as a potent inhibitory of the TBK1 kinase, a central regulator of immune responses.

Advantages & Applications

- **Stand-alone platform** providing *ad hoc* experimental and computational pipeline with an **in-depth know-how**
- Epigenome-centered approach providing **unprecedented high-resolution** view of CKIs' functional effects
- Platform employable in the **early clinical pipeline** to guide decision making process
- **Repurposing platform** for approved/failed CKIs identifying new targets and new clinical applications.

Opportunity

IEO (Istituto Europeo di Oncologia) is seeking industrial partners and investors willing to support the development of EPIKIN platform pipeline for an integrated profile of CKIs accelerating their journey from bench to bedside.

Team

Gioacchino Natoli, MD
Principal Investigator at IEO
Established scientist in the field of genomic regulation in inflammation and cancer
Highly Cited Researcher
2 x Advanced ERC grant winner

Sara Polletti, PhD
Senior Scientist at IEO
Technologist with training in biotechnology and expertise in development and implementation of genomics applications

Francesco Gualdrini, PhD
Senior scientist at IEO
Computational scientist with training in biomedicine and in-depth expertise in omics data analysis and machine/deep learning

References: Gualdrini et al. *Molecular Systems Biology* 2024

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