Tyrosine Kinase Screening Library

Protein kinases belong to a complex group of enzymes that arose in the early stages of evolution and, along with protein phosphatases, are involved in phosphorylation and dephosphorylation of proteins. Separate groups of proteins: serine/threonine specific-, Mg^{2+}/Mn^{2+}dependent-, tyrosine and dual specific kinases are unique in structure and functions and typical for representatives of individual kingdoms [1].

Numerous studies have shown that tyrosine kinases (TKs) are important mediators of signaling cascades, determining key scenarios in diverse biological processes, such as growth, differentiation, metabolism, and apoptosis in response to external and internal stimuli [2]. Tyrosine kinases are attractive biological targets for cancer therapy, as their abnormal signaling has often been linked with tumor development and growth. They are a group of around 90 enzymes capable of phosphorylating the amino acid tyrosine on another protein that leads to conformational changes and, typically, to activation of that protein (Fig. 1) [3].

Life Chemicals has designed a new Tyrosine Kinase Screening Library of about **5,700** drug-like screening compounds offered for high throughput screening (HTS).

Initially, about 150,000 reference compounds with known TKs blocking activity were obtained from ChEMBL, CHEBI, and DrugBank databases. The compounds have been filtered to retain only those possessing moderate and high activity against TKs that has narrowed down the reference set to 48,064 compounds. At the next step, a similarity search of the Life Chemicals HTS Compound Collection has been done against the reference set employing 2D molecular fingerprints with similarity metrics (Tanimoto > 0.85). Compounds obtained by this search were filtered by the Lipinski's Rule of Five to include only drug-like ones. In addition, PAINS compounds, as well as those with "bad" and reactive groups, have been removed from the Library (Ro5 compliance is indicated).

The selected potential tyrosine kinase inhibitors are predicted to possess activity against the following targets:

ALK tyrosine kinase receptor	Tyrosine-protein kinase ITK/TSK
Discoidin domain-containing receptor 2 (Tissues remodeling TK)	Tyrosine-protein kinase JAK1
Dual specificity protein kinase TTK	Tyrosine-protein kinase JAK2
Dual specificity tyrosine-phosphorylation-regulated kinase 1A	Tyrosine-protein kinase JAK3
Dual-specificity tyrosine-phosphorylation regulated kinase 1A	Tyrosine-protein kinase LCK
Dual-specificity tyrosine-phosphorylation regulated kinase 3	Tyrosine-protein kinase Lyn
Ephrin type-A receptor 2 (Receptor TK)	Tyrosine-protein kinase receptor FLT3
Ephrin type-A receptor 4 (Receptor TK)	Tyrosine-protein kinase receptor RET
Ephrin type-B receptor 3 (Receptor TK)	Tyrosine-protein kinase receptor TYRO3
Ephrin type-B receptor 4 (Receptor TK)	Tyrosine-protein kinase receptor UFO
Epidermal growth factor receptor erbB1 (Receptor TK)	Tyrosine-protein kinase SRC
Epithelial discoidin domain-containing receptor 1 (Receptor TK)	Tyrosine-protein kinase SYK
Fibroblast growth factor receptor 1 (Receptor TK)	Tyrosine-protein kinase TIE-2
Hepatocyte growth factor receptor (Receptor TK)	Tyrosine-protein kinase TXK
Vascular endothelial growth factor receptor 1 (Receptor TK)	Tyrosine-protein kinase YES
Macrophage-stimulating protein receptor (Receptor TK)	Tyrosine-protein kinase ZAP-70
Maternal embryonic leucine zipper kinase (non-membrane TK activity)	Leukocyte tyrosine kinase receptor
Nerve growth factor receptor Trk-A (Receptor TK)	Protein tyrosine kinase 2 beta
Neurotrophic tyrosine kinase receptor type 2	Tyrosine kinase non-receptor protein 2
NT-3 growth factor receptor (Receptor TK) (Receptor TK)	Tyrosine-protein kinase ABL
Vascular endothelial growth factor receptor 2	Tyrosine-protein kinase BTK
Proto-oncogene tyrosine-protein kinase MER	Tyrosine-protein kinase CSK
Receptor protein-tyrosine kinase erbB-2	Tyrosine-protein kinase FER
Stem cell growth factor receptor (Receptor TK)	Tyrosine-protein kinase FES
Interferon-induced, double-stranded RNA-activated protein kinase (non-membrane spanning protein tyrosine kinase activity)	Tyrosine-protein kinase FYN
	Tyrosine-protein kinase TYK2

References:

1. Roskoski R Jr. A historical overview of protein kinases and their targeted small molecule inhibitors // Pharmacol Res. 2015; 100:1-23.
2. Yamaoka T, Kusumoto S, Ando K, Ohba M, Ohmori T. Receptor Tyrosine Kinase-Targeted Cancer Therapy // Int J Mol Sci. 2018;19(11).
3. Roskoski R Jr. Src protein-tyrosine kinase structure, mechanism, and small molecule inhibitors // Pharmacol Res. 2015;94:9-25.

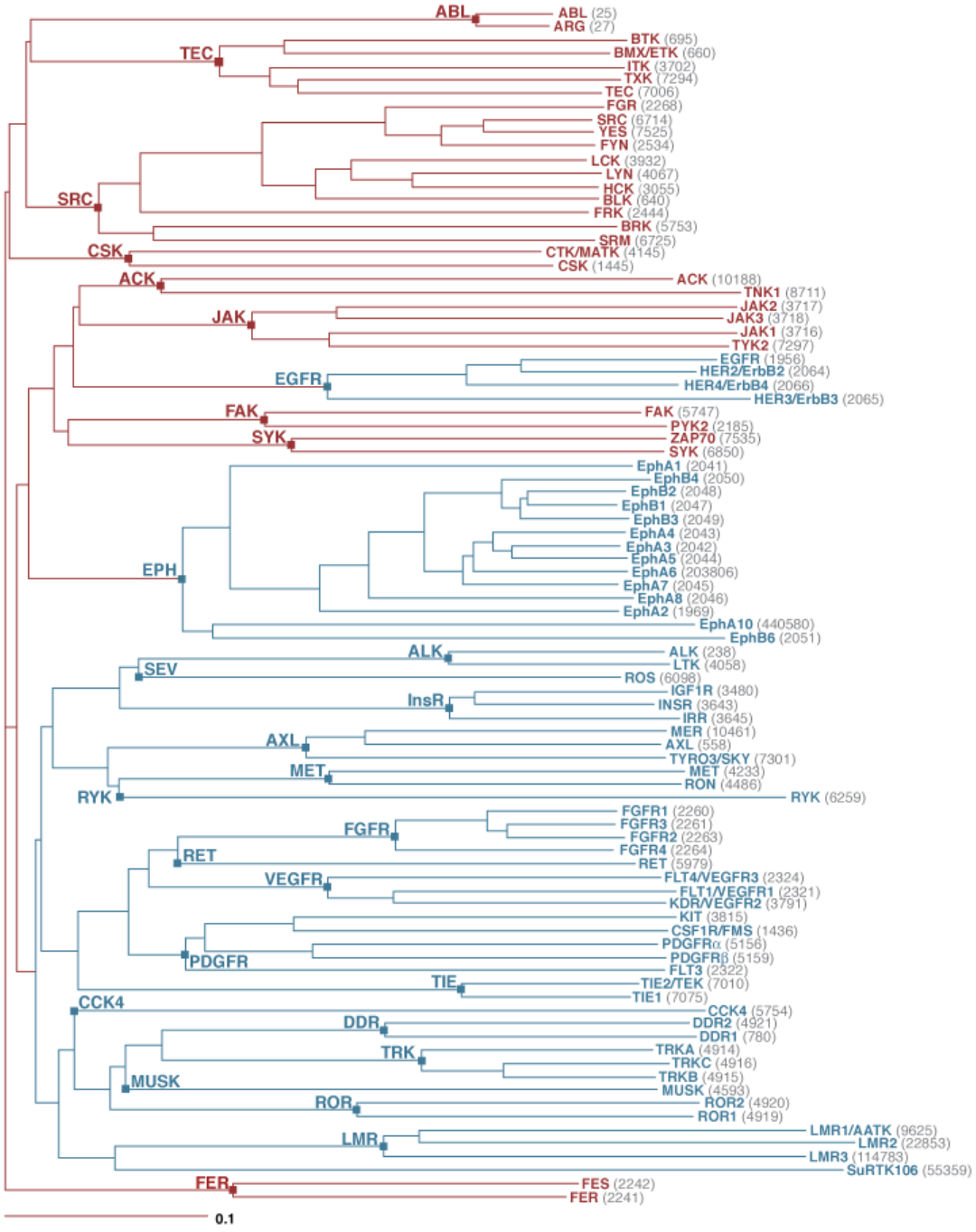

Figure 1. Histogram of tyrosine kinase family: receptor tyrosine kinases are in red, non-receptor tyrosine kinases are in blue. Image source: Cell Signaling Technology website.