Structural Kinomics – Structural Genomics of the Human Kinome

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1 Structural Kinomics

We describe bioinformatics tools and databases that facilitate global analysis of public and proprietary sequence/structure data on all human kinases (the "kinome" [1]). Kinator™ is a program that rapidly analyzes kinase sequences, while our database, RoKI™, stores a wealth of kinase-specific information for easy retrieval and mining. Alignator™ performs structure alignments of public and proprietary structures, highlights functionally important residues, and identifies residues that interact with natural ligands or inhibitors. These tools simplify selectivity analysis for kinome-based drug discovery.

2 RoKI™

The Repository of Kinase Information (RoKI™) is an intuitive web-based navigation system for rapid searching and browsing of information related to the sequence and structure of all known human kinases; it also serves as an interface to a comprehensive LIMS (Laboratory Information Management System), tracking experimental methods and results regarding cloning, protein purification, mass spectrometric analysis, biochemical assays, (co-)crystallization, and structure determination.

RoKI can be accessed via keyword search (using gene names/descriptions, HUGO aliases, LocusLink IDs, PDB IDs, or LIMS identifiers) or browsing (both textual and graphical). A detailed analysis page is available for each kinase, including literature references, RefSeq data, Pfam domain identification, related 3D protein structures, and annotation of key residues, secondary structure elements, and subdomains. These annotations are mapped onto the 3D structure in a web-based molecular graphics viewer, automatically identifying the activation loop, catalytic residues, hinge region, bound ligands, etc.

Experimental data (using user-selected criteria such as cloning success, purification yields, crystal quality, number of structures, biochemical assay data) can be mapped onto the kinome tree, providing an instant snapshot of the latest results for every kinase. Kinase similarity can be compared graphically by choosing a sequence identity threshold (e.g., 90%, 70%, 50%); all kinases that share at least that level of similarity are linked together on the kinome tree.

3 Kinator™

Our program, Kinator™, identifies important structural and functional residues within kinase sequence(s). Kinator uses a Hidden Markov Model (HMM) to identify the catalytic domain and to

pinpoint critical residues. The program automatically distinguishes serine/threonine and tyrosine kinases and highlights the P-loop, ATP-binding site, catalytic loop, activation loop, hinge region, and gatekeeper residue, as well as the 12 subdomains defined by Hanks & Hunter [2]. It also labels all secondary structure elements according to their canonical nomenclature (e.g., "helix C"). It is simple to determine whether a kinase has a large insertion, unusual termini, or has variant residues that are likely to affect the function.

Kinator can be used to perform comparisons of certain residues or regions within all kinases. For example, using these tools it is easy to tabulate the length of all activation loops, determine the identity of all gatekeeper residues, or calculate the sequence identity between a target and the ATP-binding site residues of all other kinases. Furthermore, our interactive web-based structure alignment program, Alignator™, is able to superimpose multiple structures and highlight residues of functional interest.

Figure 1 shows some of the views available from RoKI, Kinator, and Alignator.

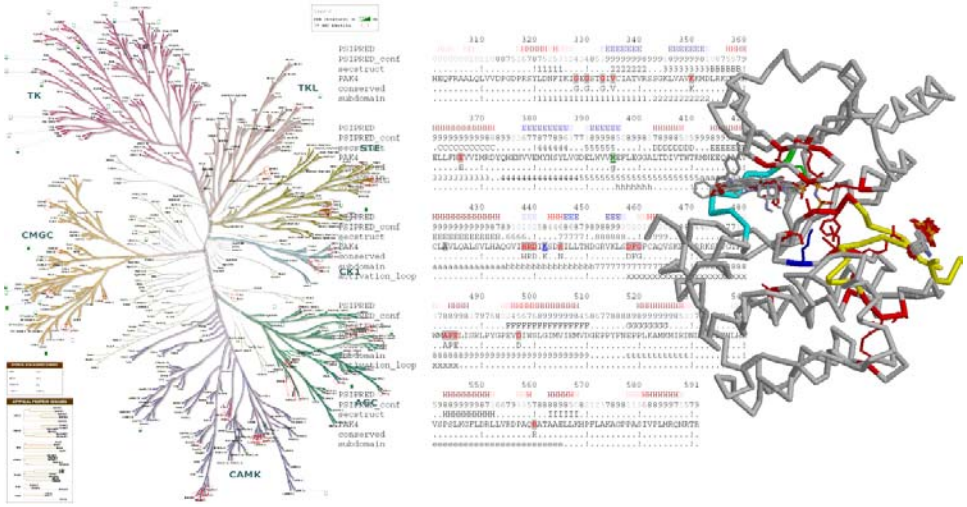

Figure 1: PDB structures (green squares) mapped onto the kinome tree [1] with 90% identity halos (red ovals) using RoKI™ (left), kinase sequence annotation using Kinator™ (middle), and Alignator output of ~30 co-complex structures with Kinator-based color-coding (right).

References

[1] Manning, G., et al 2002. The protein kinase complement of the human genome. *Science* 298:1912-1934.

[2] Hanks, S.K. and Hunter, T. 1995. Protein kinases 6. The eukaryotic protein kinase superfamily: kinase (catalytic) domain structure and classification. *Faseb J* 9:576-596.

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