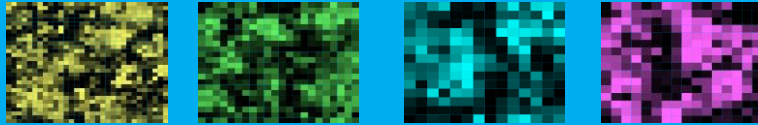


Expression2Kinases- Inferring Pathways from Differentially Expressed Genes



Network Analysis in Systems Biology

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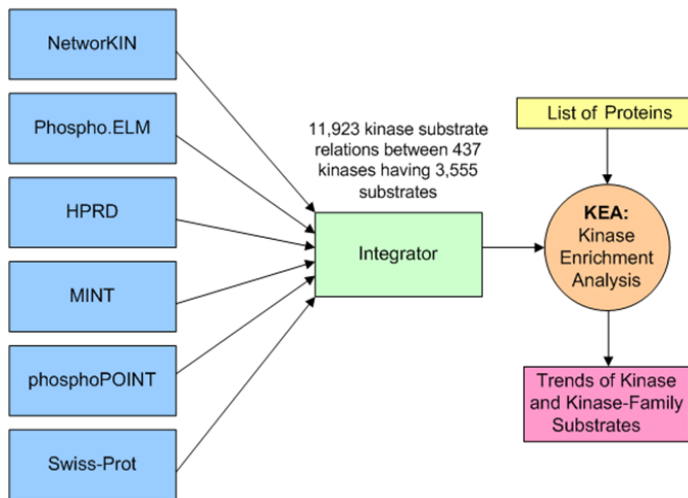
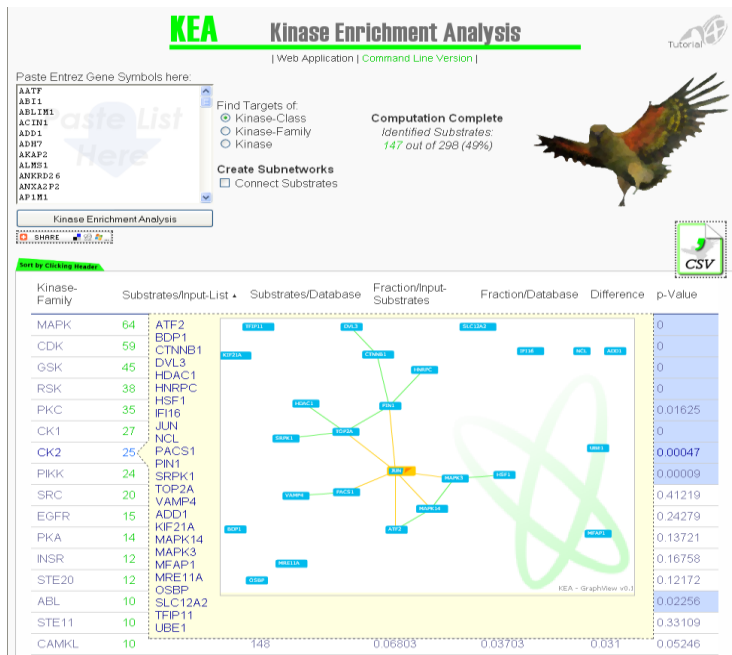


What is a Cell Signaling Pathway?

“It may be necessary not to think of the pathways as sharply and precisely delineated from the broader cellular network, but rather to keep in mind that a pathway representation may always be a **warm, fuzzy, cloud**: that is to say, warm since the answer is close but not necessarily exact; fuzzy, since the membership of components in a pathway is graded; and a cloud, since the boundaries are not sharply defined.”

Kleensang et al. ALTEX. 2013 In press

KEA: Enrichment Analysis for Kinase-Substrate Interactions from Literature



BIOINFORMATICS APPLICATION

Systems biology

KEA: kinase enrichment analysis

Alexander Lachmann and Avi Ma'ayan*

Department of Pharmacology and Systems Therapeutics, Systems Institute, Mount Sinai School of Medicine, 1425 Madison Avenue,

Received on November 8, 2008; revised on December 19, 2008; accepted on Jan

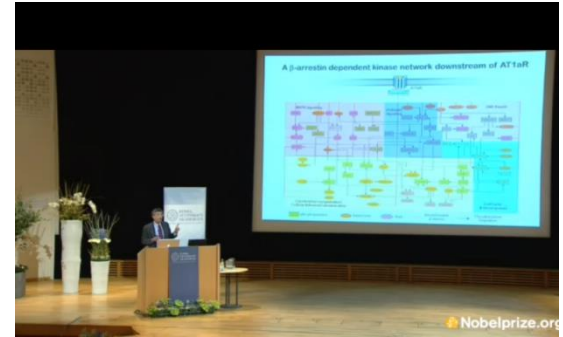
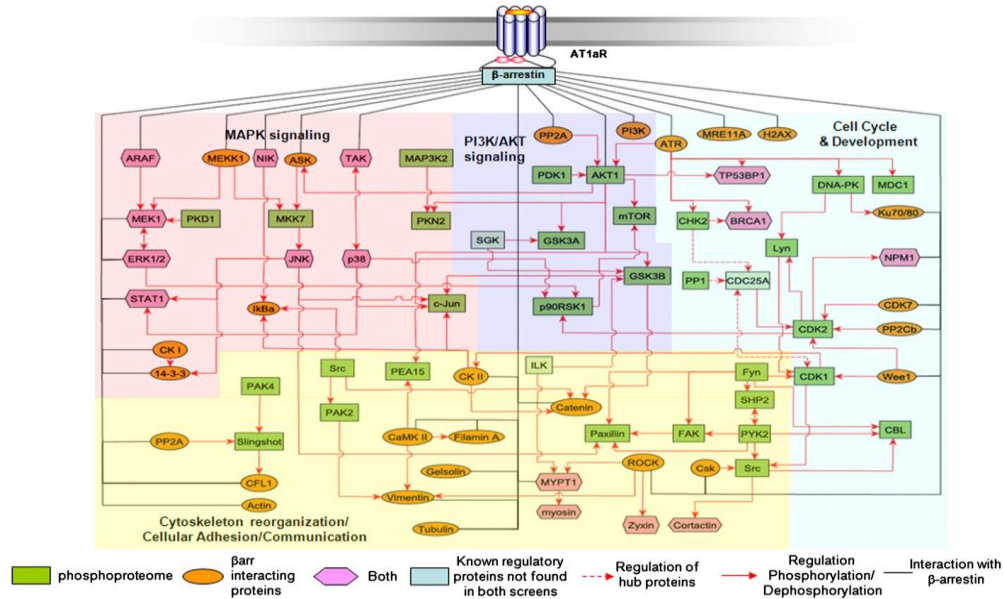
Advance Access publication January 28, 2009

Associate Editor: Burkhard Rost

<http://amp.pharm.mssm.edu/lib/kea.jsp>

Lachmann and Ma'ayan. *Bioinformatics* **11**, 87 (2009)

KEA and G2N were used to construct a network downstream of AT1aR based on SILAC Phosphoproteomics and IP-MS Data



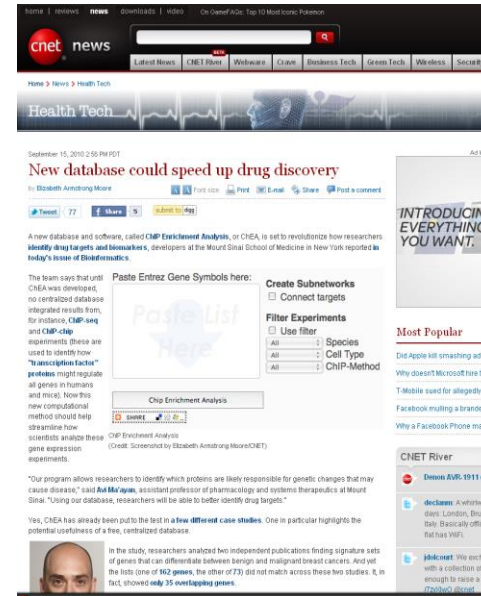
Xiao K, et al. Global phosphorylation analysis of {beta}-arrestin-mediated signaling downstream of a seven transmembrane receptor (7TMR). *Proceedings of the National Academy of Sciences*, **107**, 15299-304 (2010)

ChEA: ChIP-X experiments of TFs in mammalian cells can be integrated to be used to infer transcriptional regulations of changes in gene expression

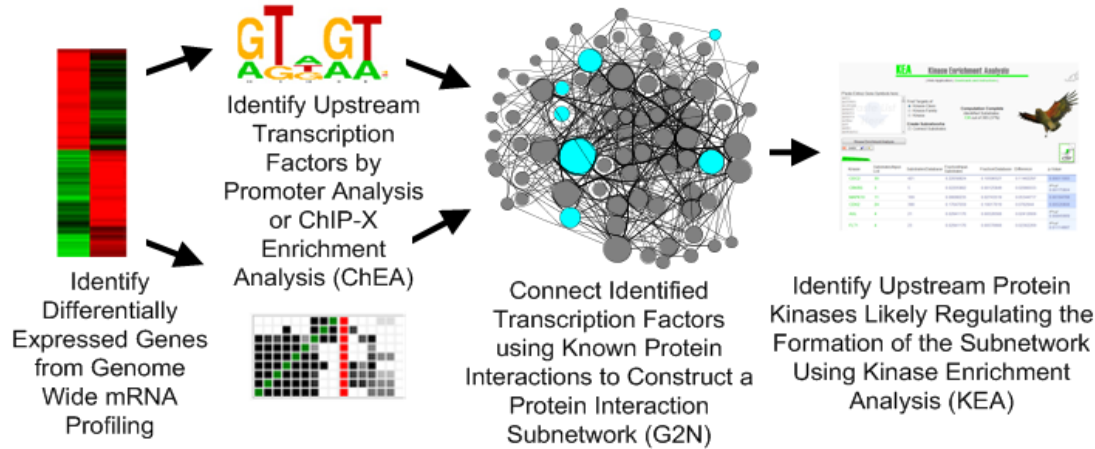
- ▶ 202 unique transcription factors
- ▶ 226 publications
- ▶ 46,988 genes
- ▶ Average targets per transcription factor $\approx 1,300$
- ▶ Total interactions 468,076

Lachmann A, Xu H, Krishnan J, Berger SI, Mazloom AR, Ma'ayan A. ChEA: transcription factor regulation inferred from integrating genome-wide ChIP-X experiments. *Bioinformatics* (2010) 26(19): 2438-2444

<http://amp.pharm.mssm.edu/lib/chea.jsp>



Expression2Kinases: Identifying Upstream Pathways from Gene



www.maayanlab.net/X2K

Chen et al. **Expression2Kinases: mRNA Profiling Linked to Multiple Upstream Regulatory Layers.** *Bioinformatics.* (2012) 28 (1): 105-111

Lachmann et al. **ChEA: transcription factor regulation inferred from integrating genome-wide ChIP-X experiments.** *Bioinformatics* 26(19):2438-44 (2010)

Berger et al. **Genes2Networks: connecting lists of gene symbols using mammalian protein interactions databases.** *BMC Bioinformatics* 8:372 (2007)

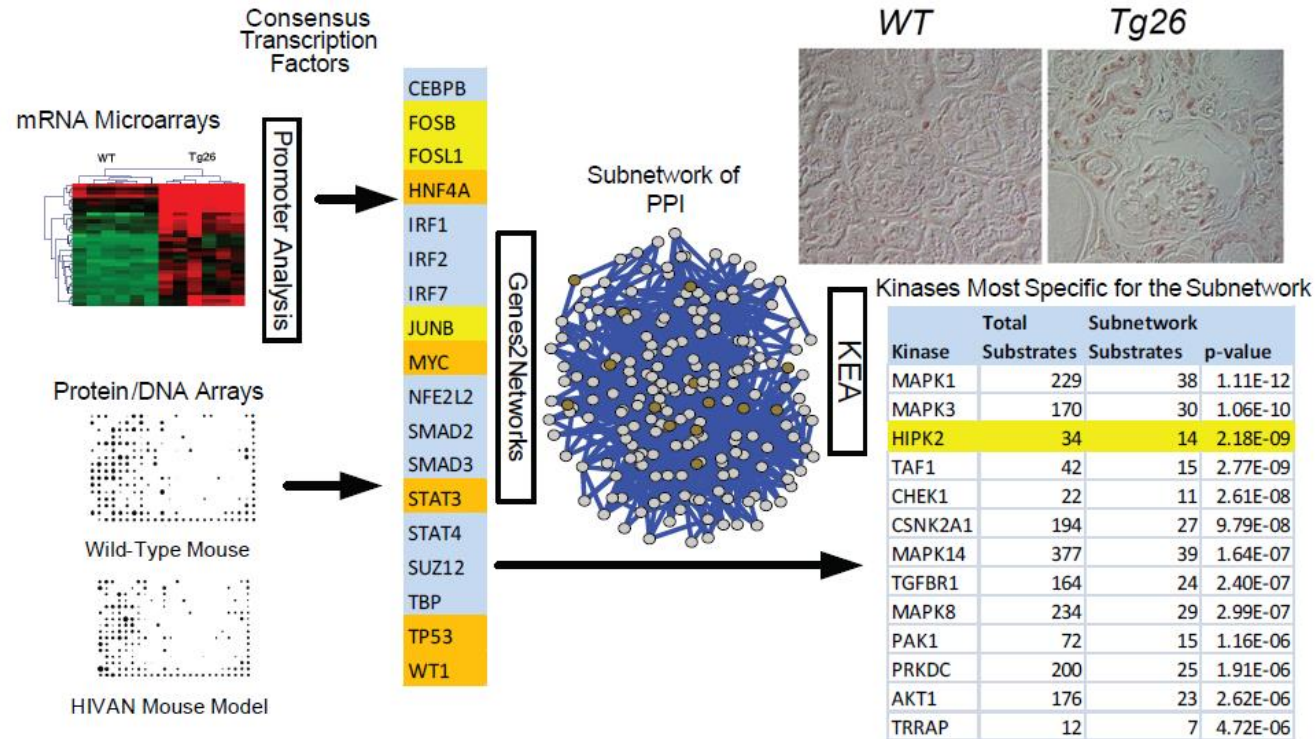
Lachmann et al. **KEA: kinase enrichment analysis.** *Bioinformatics* 25(5):684-6 (2009)

<http://amp.pharm.mssm.edu/lib/chea.jsp>

<http://actin.pharm.mssm.edu/genes2networks>

<http://amp.pharm.mssm.edu/lib/kea.jsp>

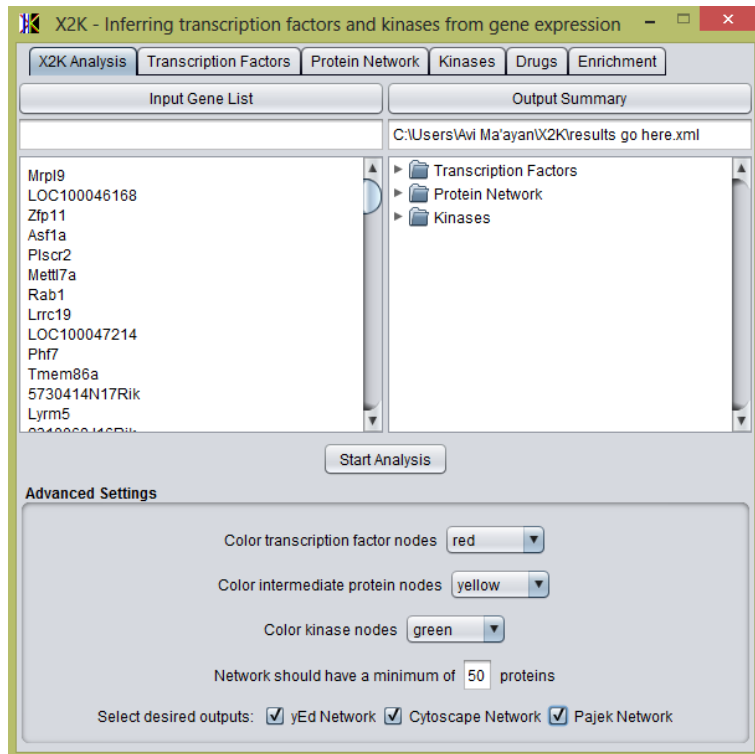
Identifying HIPK2 as a Critical Kinase Driving Kidney Fibrosis



Collaboration with Cijiang He, MSSM

Nature Medicine **18**, 580 (2012)

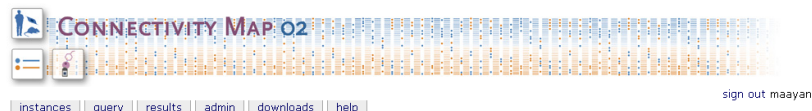
Expression2Kinases Desktop Application



<http://www.maayanlab.net/X2K>

**Does Expression2Kinases really work...
or did we get lucky?**

CMAP: The Connectivity Map Database



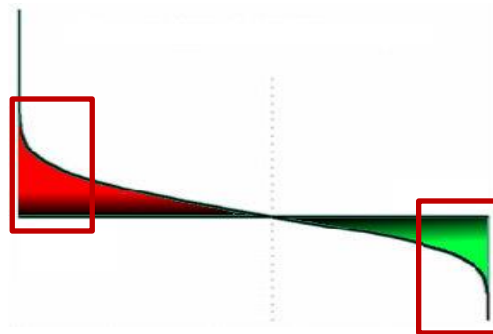
instances

total instances: 6100, export: Excel

search:

found 3 instances

batch ▲▼	cmap name	dose ▲▼	cell ▲▼	instance_id ▲▼	perturb scan	vehicle scan	array name
1057	0297417-0002B	10 µM	MCF7	6902	5500024035736031208614.E08	5500024035736031208614.E07	HT_HG-U133A
1055	0297417-0002B	10 µM	MCF7	6900	5500024035736031208614.D11	5500024035736031208614.D07	HT_HG-U133A
1054	0297417-0002B	10 µM	PC3	6895	5500024035736031208614.D05	5500024035736031208614.D01	HT_HG-U133A




- Drug perturbations are followed by a microarray after 6 hours
- ~6000 perturbations, ~1300 drugs
- Four cell types: MCF7, PC3, SKMEL5 or HL60

Lamb et al. Science 313, 1929 (2006)

DrugBank: Database With Information About Drug Targets

DRUGBANK
Open Data Drug & Drug Target Database



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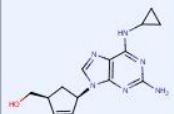
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[Approved](#) [Nutraceutical](#) [Withdrawn](#) [Illicit](#) [Experimental](#)

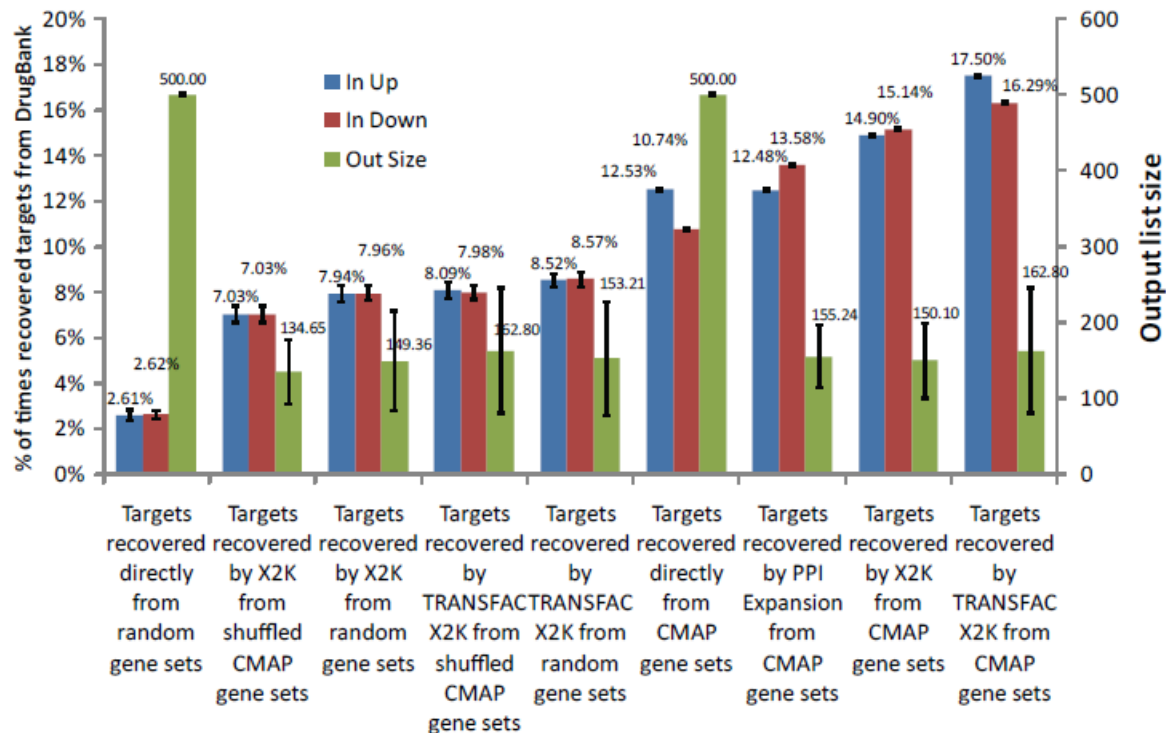
Displaying drugs 1 - 25 of 1541 in total

1 2 3 4 5 ... [Next >](#) [Last >>](#)

DrugBank ID	Name	Weight	Structure	Categories	Therapeutic Indication
	CAS Number	Formula			
DB01048	Abacavir 136470-78-5	286.3323 C ₁₄ H ₁₈ N ₆ O		Anti-HIV Agents / Nucleoside and Nucleotide Reverse Transcriptase Inhibitors / Reverse Transcriptase Inhibitors	For the treatment of HIV-1 infection, in combination with other antiretroviral agents.

<http://www.drugbank.ca>

Validation of Expression2Kinases with Data from CMAP



Further Reading and Resources

Chen et al. **Expression2Kinases: mRNA Profiling Linked to Multiple Upstream Regulatory Layers.** *Bioinformatics*.

(2012) 28 (1): 105-111

Lachmann et al. **KEA: kinase enrichment analysis.** *Bioinformatics* 25(5):684-6 (2009)

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databases. *BMC Bioinformatics* 8:372 (2007)

Lachmann et al. **ChEA: transcription factor regulation inferred from integrating genome-wide ChIP-X**

experiments. *Bioinformatics* 26(19):2438-44 (2010)

Jin Y, Ratnam K, Chuang PY, Fan Y, Zhong Y, Dai Y, Mazloom AR, Chen EY, D'Agati V, Xiong H, Ross MJ, Chen N, Ma'ayan A, He JC. **A systems approach identifies HIPK2 as a key regulator of kidney fibrosis.** *Nat Med.* 2012 Mar 11;18(4):580-8

Rabinowitz KM, Y Wang, E Chen, Z Hovhannisyan, MC Berin, S Dahan, D Chaussabel, A Ma'ayan, L Mayer.

Transforming-growth-factor beta signaling controls the activity of human intestinal CD8+ T suppressor cells.

Gastroenterology 2013 Mar;144(3):601-612

<http://www.maayanlab.net/X2K/>