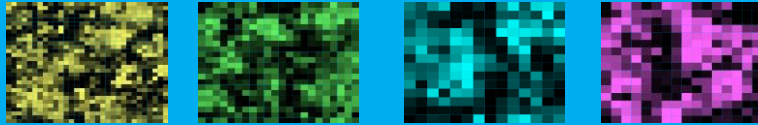# Expression2Kinases- Inferring Pathways from Differentially Expressed Genes

Network Analysis in Systems Biology

Avi Ma'ayan, PhD

Associate Professor

Department of Pharmacology and Systems Therapeutics

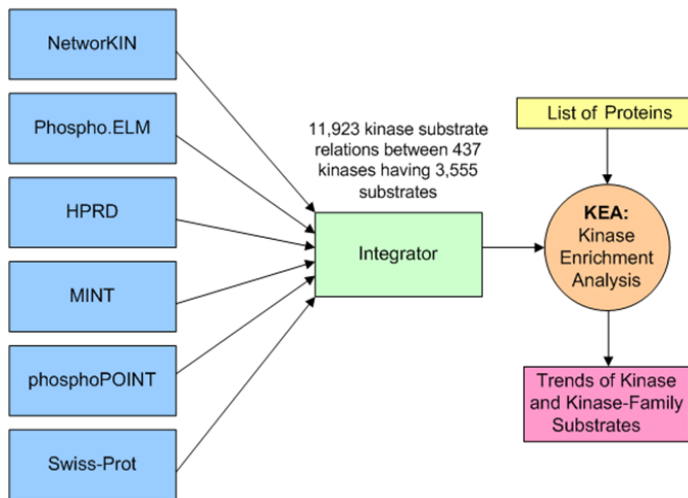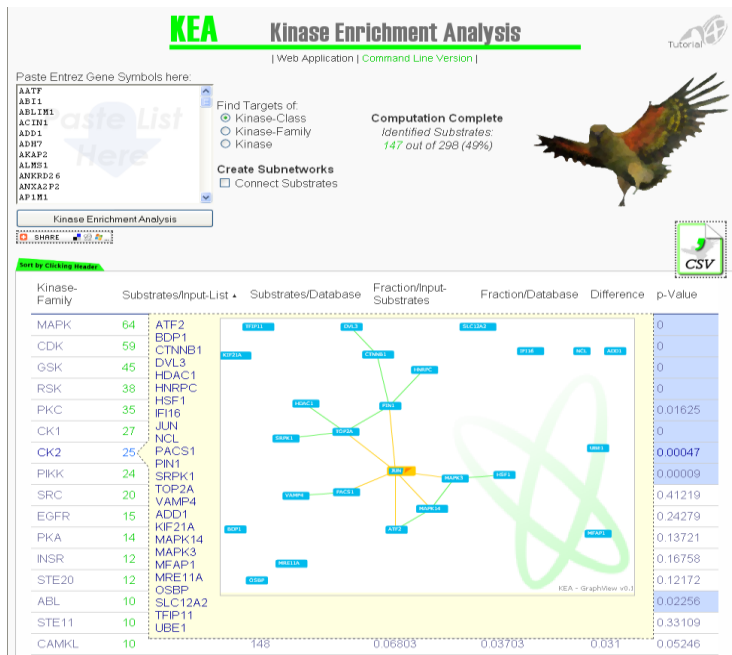Icahn School of Medicine at Mount Sinai, New York, NY 10029

Mount Sinai

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

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 Phosphoprteomics and IP-MS Data
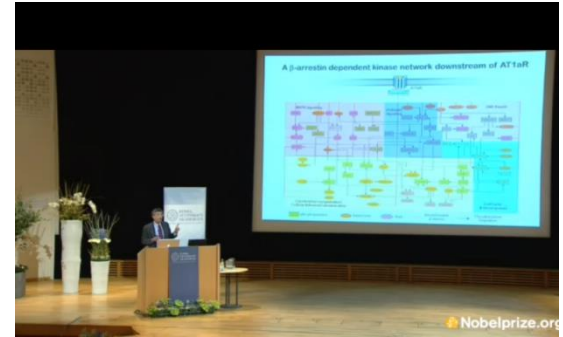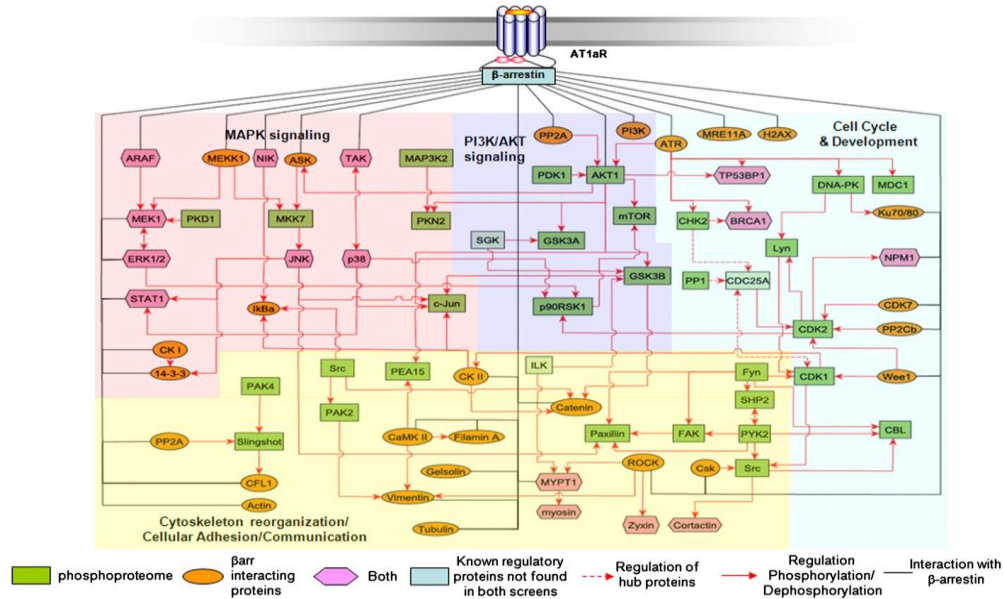

Xiao K, et al. Global phosphorylation analysis of {beta}-arrestin-mediated signaling downstream of a seven transmembrane receptor (7TMR). *Proceedings of the National Academy of Sciences*, **107**, 15299-304 (2010)

ChEA: ChIP-X experiments of TFs in mammalian cells can be integrated to be used to infer transcriptional regulations of changes in gene expression
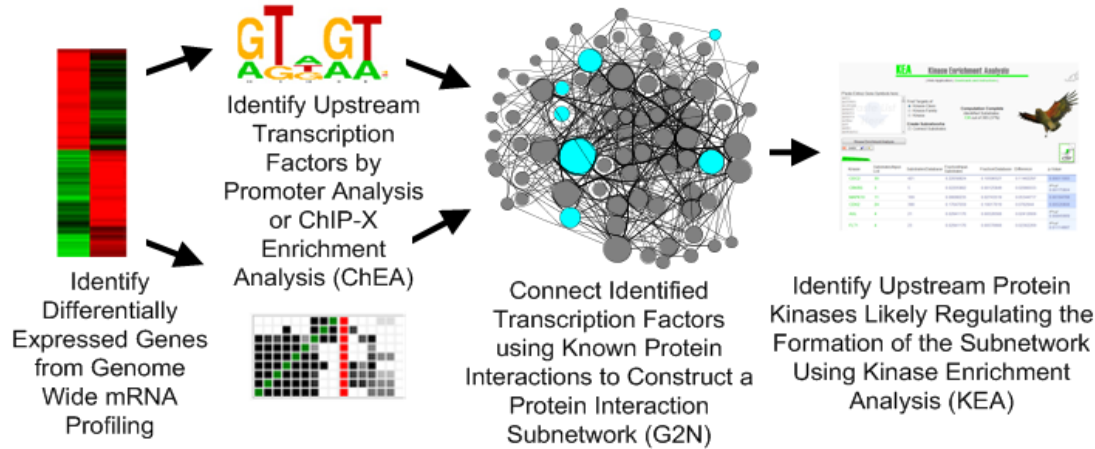
- 202 unique transcription factors
- 226 publications
- 46,988 genes
- Average targets per transcription factor ≈ 1,300
- Total interactions 468,076

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
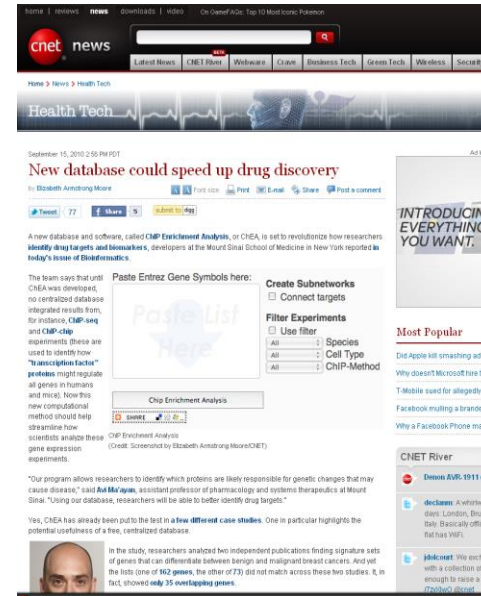
Expression2Kinases: Identifying Upstream Pathways from Gene

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)

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

Berger et al. **Genes2Networks: connecting lists of gene symbols using mammalian protein interactions databases.** *BMC Bioinformatics* 8:372 (2007)
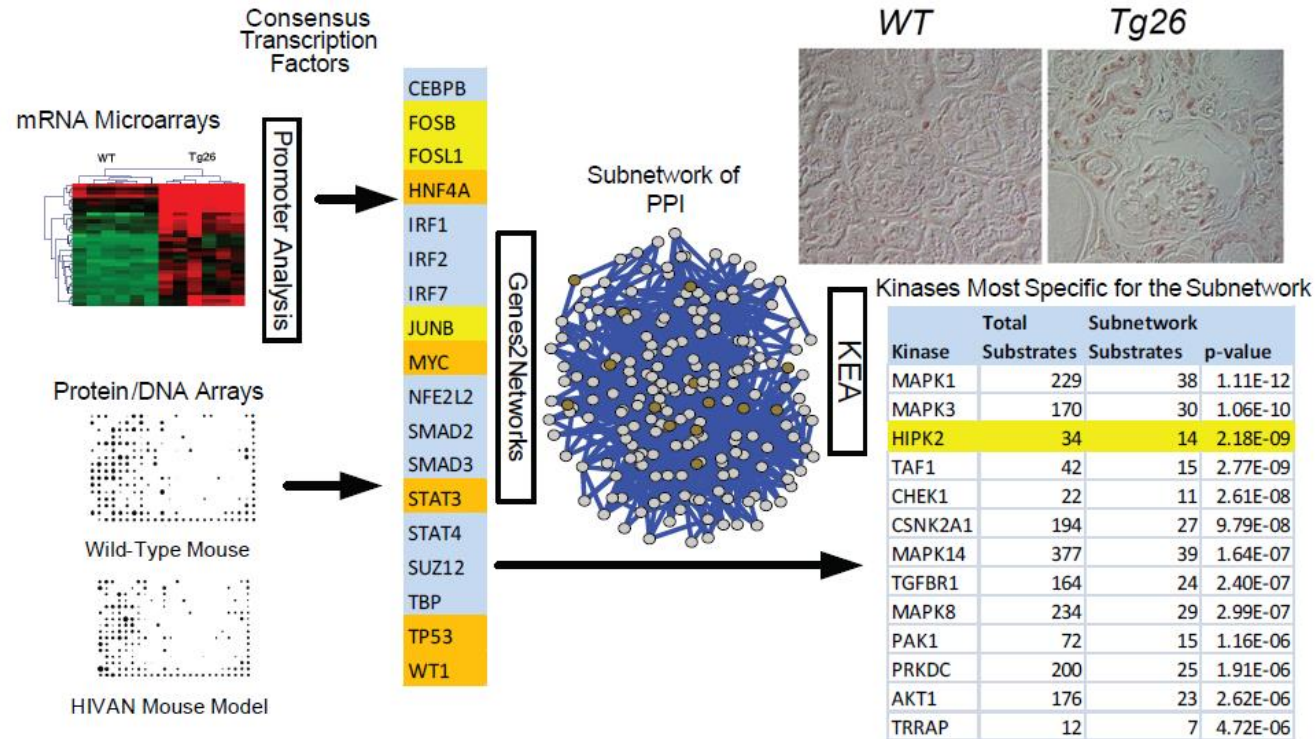
http://actin.pharm.mssm.edu/genes2networks

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

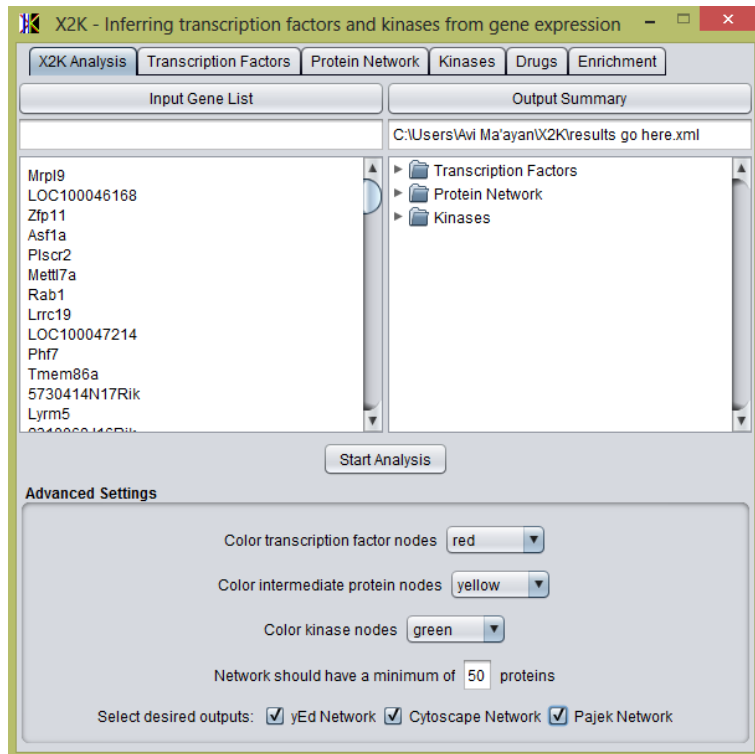http://amp.pharm.mssm.edu/lib/kea.jsp

Identifying HIPK2 as a Critical Kinase Driving Kidney Fibrosis

Collaboration with Cijiang He, MSSM   *Nature Medicine* **18**, 580 (2012)
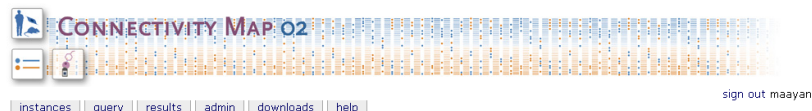
Expression2Kinases Desktop Application

http://www.maayanlab.net/X2K

Does Expression2Kinases really work… or did we get lucky?

CMAP: The Connectivity Map Database

- 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

http://www.drugbank.ca

Validation of Expression2Kinases with Data from CMAP
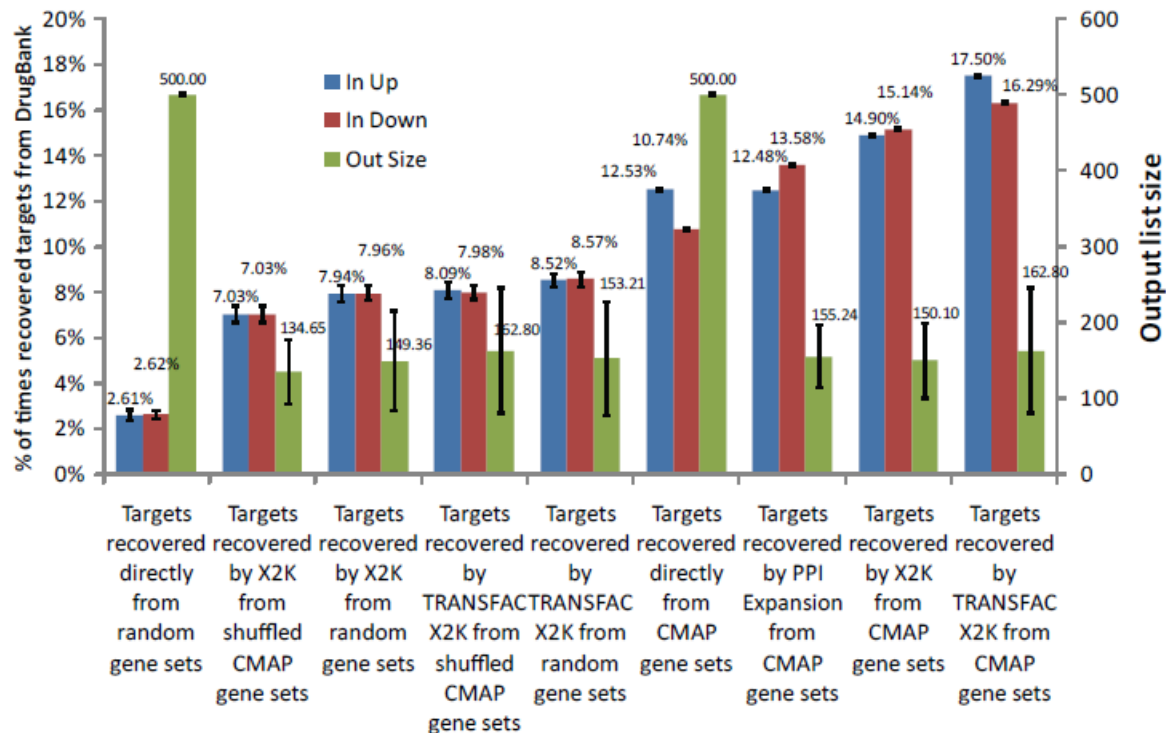
Further Reading and Resources

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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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/