

Computational Medicine and Bioinformatics at the University of Michigan

Gilbert S. Omenn, MD, PhD

Director, Center for Computational Medicine and Bioinformatics

Components:

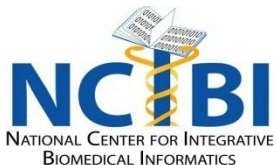
Bioinformatics Graduate Program

Collaborative Computing & Data Unit

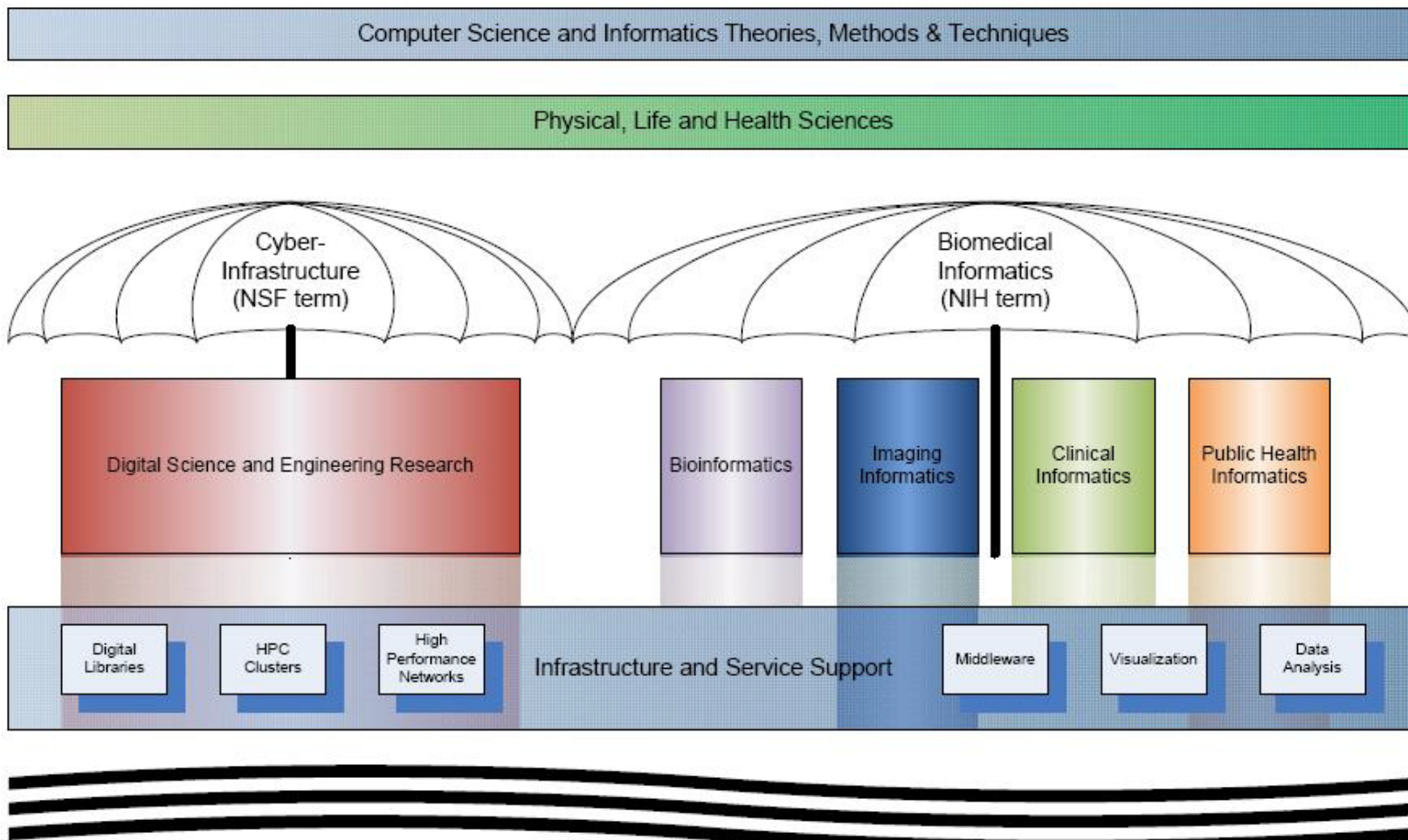
Interdisciplinary Research, led by NCIBI

Peking Union Medical College

23 March, 2010



Scope of Biomedical Informatics and Cyberinfrastructure



NCIBI: National Center for Integrative Biomedical Informatics

An NIH NCBC Resource to Enhance Basic and Translational Research

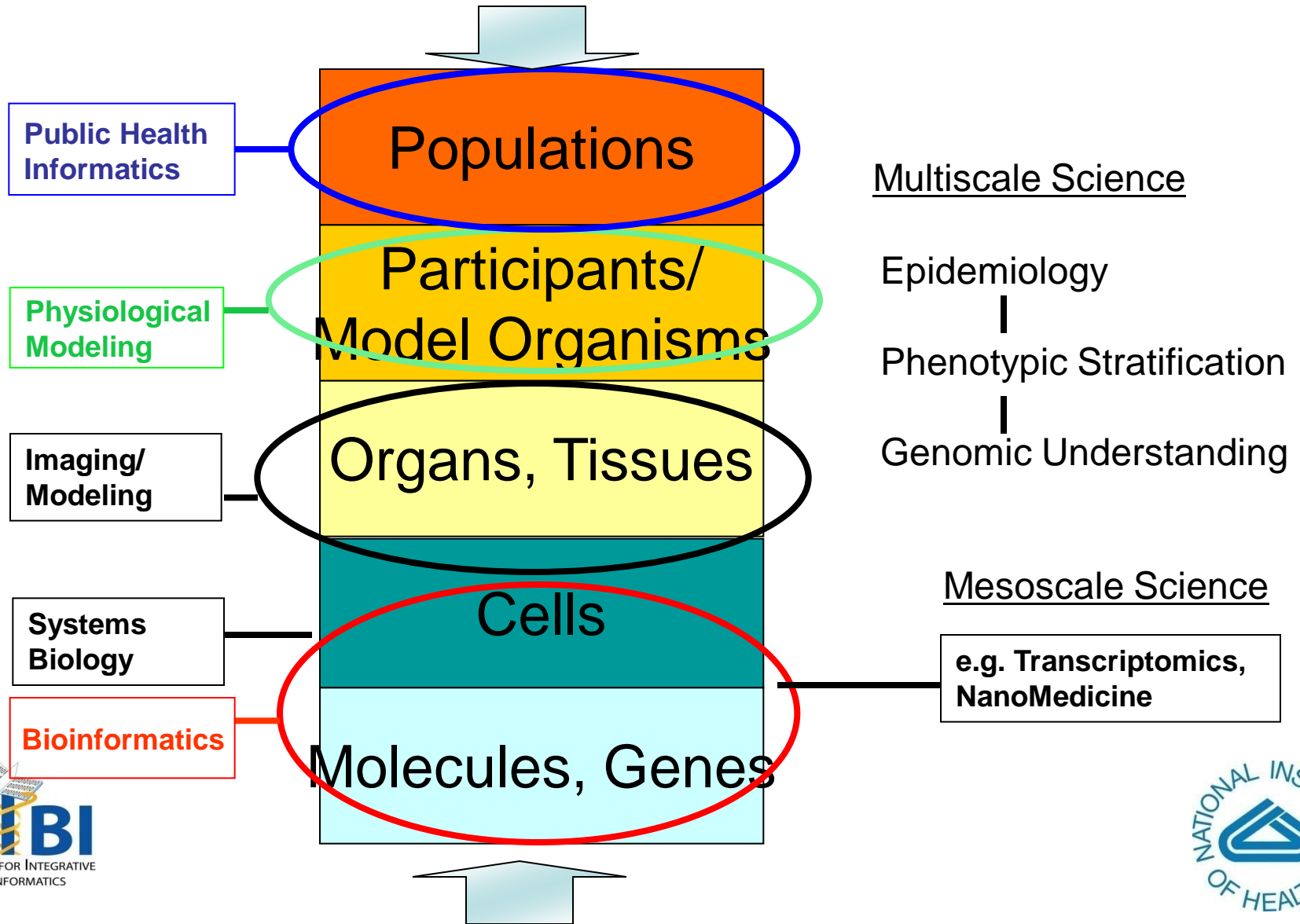
<http://NCIBI.org>, Brian Athey, PI

**Center for Computational Medicine and Biology
University of Michigan**

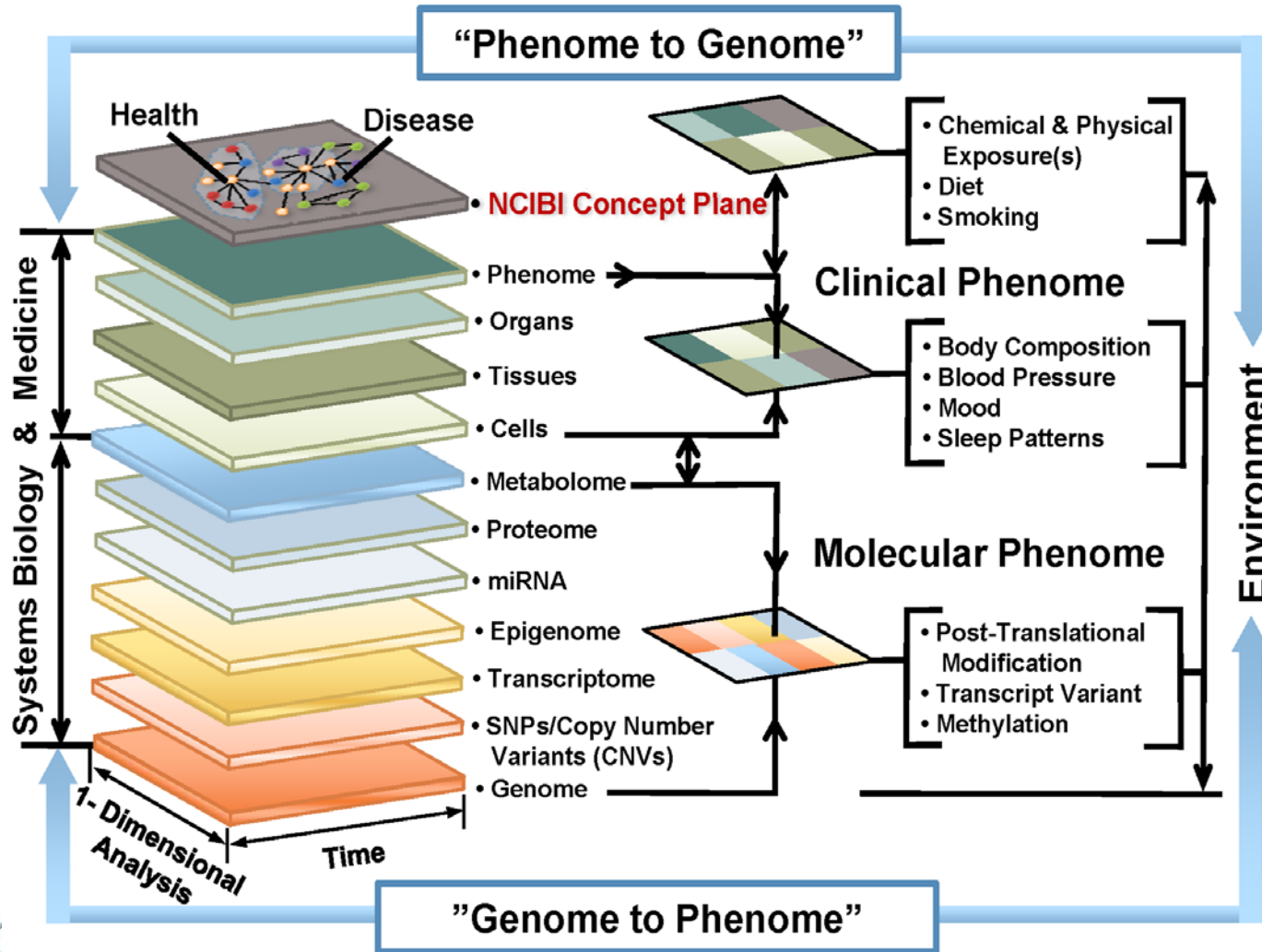
NIGMS/NIDA U54-DA-021519



Integrative Informatics Enables Synthesis of Knowledge at Multiple Levels



Integrating High-Throughput Measurements with the Phenotype is Key



Integrated Tools that Track the Levels

Gene2MeSH – Gene Annotation with MeSH Terms

Search Gene2MeSH

Search for: Gene Symbol | MeSH Term | Limit Search by: Organism | All Organisms

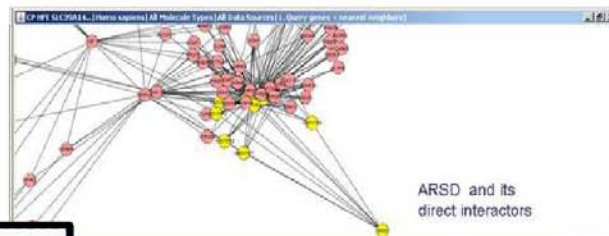
Gene2MeSH Search

History: bipolar disorder

745 genes found matching MeSH heading "bipolar disorder"

Case Symbol	MeSH Heading	LastID	Index's Year	MeSH Qualifier
ADDC	Cerebral Disorders	N40	1.2v-2002	genetics
MAJ	Major Depressive Disorder	N40	1.4v-2007	genetics

Gene2MeSH



NCIBI

Upload Dataset

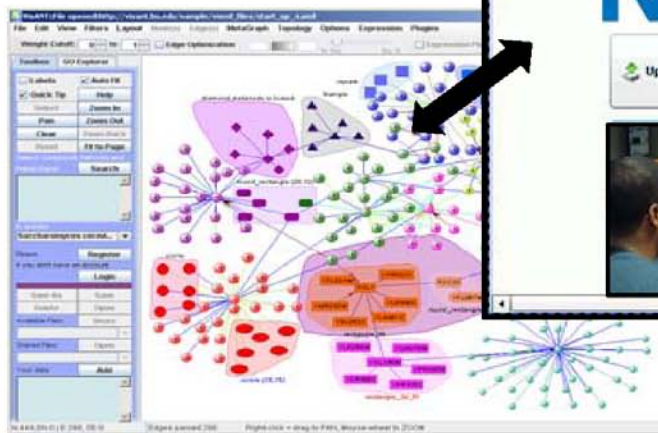
selected datasets

process

PubIO (Local)

Enzyme ID	Description	Pubmed	Pubmed
EC:3.1.1.1	aroyl esterase activity (EC:3.1.1.1)	aroyl esterase activity (EC:3.1.1.1)	Arroyl esterase activity (EC:3.1.1.1)
EC:3.1.1.2	glucuronosyltransferase 2 family, polypeptide 1 (EC:3.1.1.2)	glucuronosyltransferase 2 family, polypeptide 1 (EC:3.1.1.2)	glucuronosyltransferase 2 family, polypeptide 1 (EC:3.1.1.2)
EC:3.1.1.3	glucuronosyltransferase 1 family, polypeptide 1 (EC:3.1.1.3)	glucuronosyltransferase 1 family, polypeptide 1 (EC:3.1.1.3)	glucuronosyltransferase 1 family, polypeptide 1 (EC:3.1.1.3)
EC:3.1.1.4	glucuronosyltransferase 1 family, polypeptide 2 (EC:3.1.1.4)	glucuronosyltransferase 1 family, polypeptide 2 (EC:3.1.1.4)	glucuronosyltransferase 1 family, polypeptide 2 (EC:3.1.1.4)
EC:3.1.1.5	glucuronosyltransferase 1 family, polypeptide 3 (EC:3.1.1.5)	glucuronosyltransferase 1 family, polypeptide 3 (EC:3.1.1.5)	glucuronosyltransferase 1 family, polypeptide 3 (EC:3.1.1.5)
EC:3.1.1.6	glucuronosyltransferase 1 family, polypeptide 4 (EC:3.1.1.6)	glucuronosyltransferase 1 family, polypeptide 4 (EC:3.1.1.6)	glucuronosyltransferase 1 family, polypeptide 4 (EC:3.1.1.6)
EC:3.1.1.7	glucuronosyltransferase 1 family, polypeptide 5 (EC:3.1.1.7)	glucuronosyltransferase 1 family, polypeptide 5 (EC:3.1.1.7)	glucuronosyltransferase 1 family, polypeptide 5 (EC:3.1.1.7)
EC:3.1.1.8	glucuronosyltransferase 1 family, polypeptide 6 (EC:3.1.1.8)	glucuronosyltransferase 1 family, polypeptide 6 (EC:3.1.1.8)	glucuronosyltransferase 1 family, polypeptide 6 (EC:3.1.1.8)
EC:3.1.1.9	glucuronosyltransferase 1 family, polypeptide 7 (EC:3.1.1.9)	glucuronosyltransferase 1 family, polypeptide 7 (EC:3.1.1.9)	glucuronosyltransferase 1 family, polypeptide 7 (EC:3.1.1.9)
EC:3.1.1.10	glucuronosyltransferase 1 family, polypeptide 8 (EC:3.1.1.10)	glucuronosyltransferase 1 family, polypeptide 8 (EC:3.1.1.10)	glucuronosyltransferase 1 family, polypeptide 8 (EC:3.1.1.10)
EC:3.1.1.11	glucuronosyltransferase 1 family, polypeptide 9 (EC:3.1.1.11)	glucuronosyltransferase 1 family, polypeptide 9 (EC:3.1.1.11)	glucuronosyltransferase 1 family, polypeptide 9 (EC:3.1.1.11)
EC:3.1.1.12	glucuronosyltransferase 1 family, polypeptide 10 (EC:3.1.1.12)	glucuronosyltransferase 1 family, polypeptide 10 (EC:3.1.1.12)	glucuronosyltransferase 1 family, polypeptide 10 (EC:3.1.1.12)
EC:3.1.1.13	glucuronosyltransferase 1 family, polypeptide 11 (EC:3.1.1.13)	glucuronosyltransferase 1 family, polypeptide 11 (EC:3.1.1.13)	glucuronosyltransferase 1 family, polypeptide 11 (EC:3.1.1.13)
EC:3.1.1.14	glucuronosyltransferase 1 family, polypeptide 12 (EC:3.1.1.14)	glucuronosyltransferase 1 family, polypeptide 12 (EC:3.1.1.14)	glucuronosyltransferase 1 family, polypeptide 12 (EC:3.1.1.14)
EC:3.1.1.15	glucuronosyltransferase 1 family, polypeptide 13 (EC:3.1.1.15)	glucuronosyltransferase 1 family, polypeptide 13 (EC:3.1.1.15)	glucuronosyltransferase 1 family, polypeptide 13 (EC:3.1.1.15)
EC:3.1.1.16	glucuronosyltransferase 1 family, polypeptide 14 (EC:3.1.1.16)	glucuronosyltransferase 1 family, polypeptide 14 (EC:3.1.1.16)	glucuronosyltransferase 1 family, polypeptide 14 (EC:3.1.1.16)
EC:3.1.1.17	glucuronosyltransferase 1 family, polypeptide 15 (EC:3.1.1.17)	glucuronosyltransferase 1 family, polypeptide 15 (EC:3.1.1.17)	glucuronosyltransferase 1 family, polypeptide 15 (EC:3.1.1.17)
EC:3.1.1.18	glucuronosyltransferase 1 family, polypeptide 16 (EC:3.1.1.18)	glucuronosyltransferase 1 family, polypeptide 16 (EC:3.1.1.18)	glucuronosyltransferase 1 family, polypeptide 16 (EC:3.1.1.18)
EC:3.1.1.19	glucuronosyltransferase 1 family, polypeptide 17 (EC:3.1.1.19)	glucuronosyltransferase 1 family, polypeptide 17 (EC:3.1.1.19)	glucuronosyltransferase 1 family, polypeptide 17 (EC:3.1.1.19)
EC:3.1.1.20	glucuronosyltransferase 1 family, polypeptide 18 (EC:3.1.1.20)	glucuronosyltransferase 1 family, polypeptide 18 (EC:3.1.1.20)	glucuronosyltransferase 1 family, polypeptide 18 (EC:3.1.1.20)
EC:3.1.1.21	glucuronosyltransferase 1 family, polypeptide 19 (EC:3.1.1.21)	glucuronosyltransferase 1 family, polypeptide 19 (EC:3.1.1.21)	glucuronosyltransferase 1 family, polypeptide 19 (EC:3.1.1.21)
EC:3.1.1.22	glucuronosyltransferase 1 family, polypeptide 20 (EC:3.1.1.22)	glucuronosyltransferase 1 family, polypeptide 20 (EC:3.1.1.22)	glucuronosyltransferase 1 family, polypeptide 20 (EC:3.1.1.22)

MiMI-Cytoscape



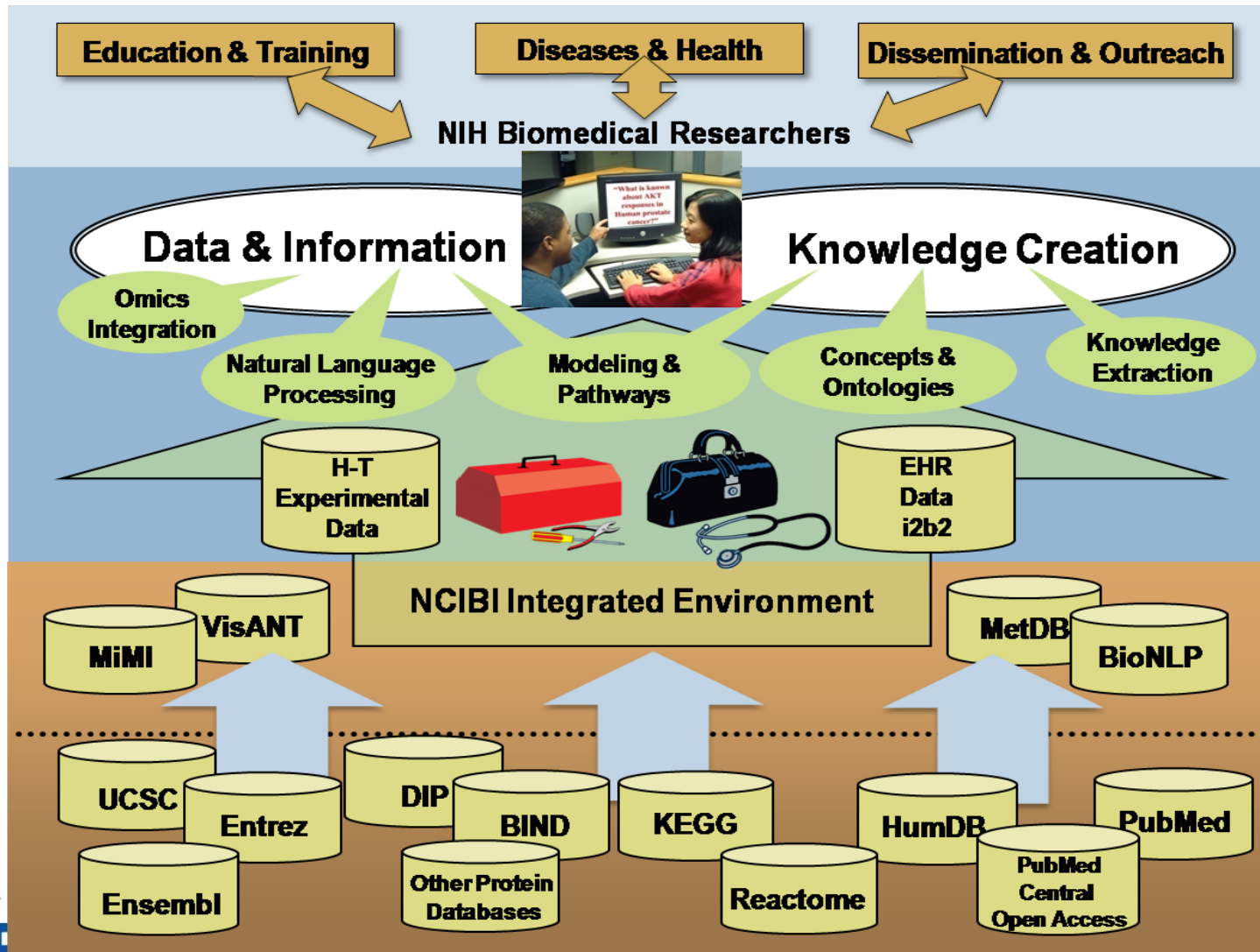
VisANT

Fatty Liver Steatosis

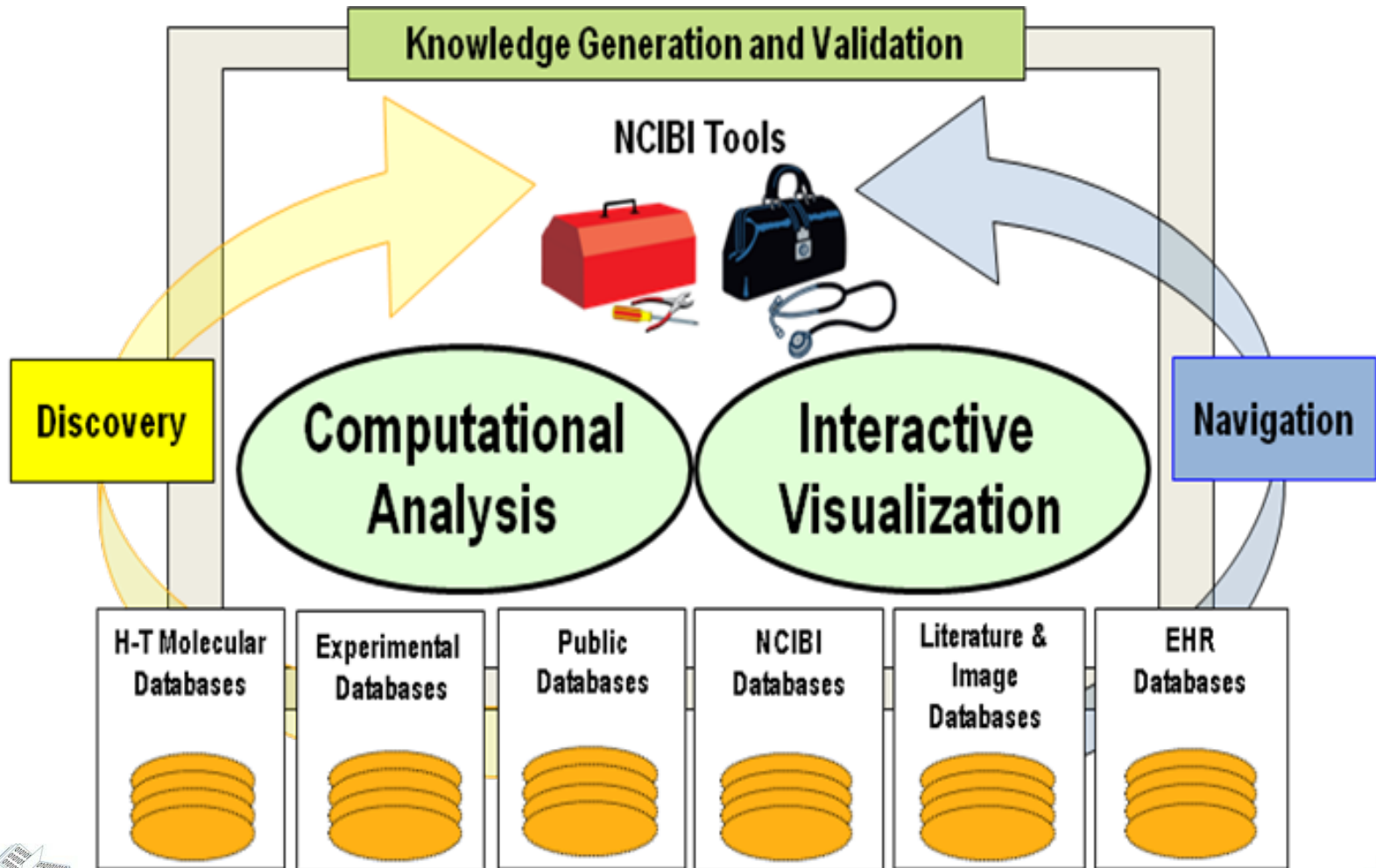
PubAnatomy



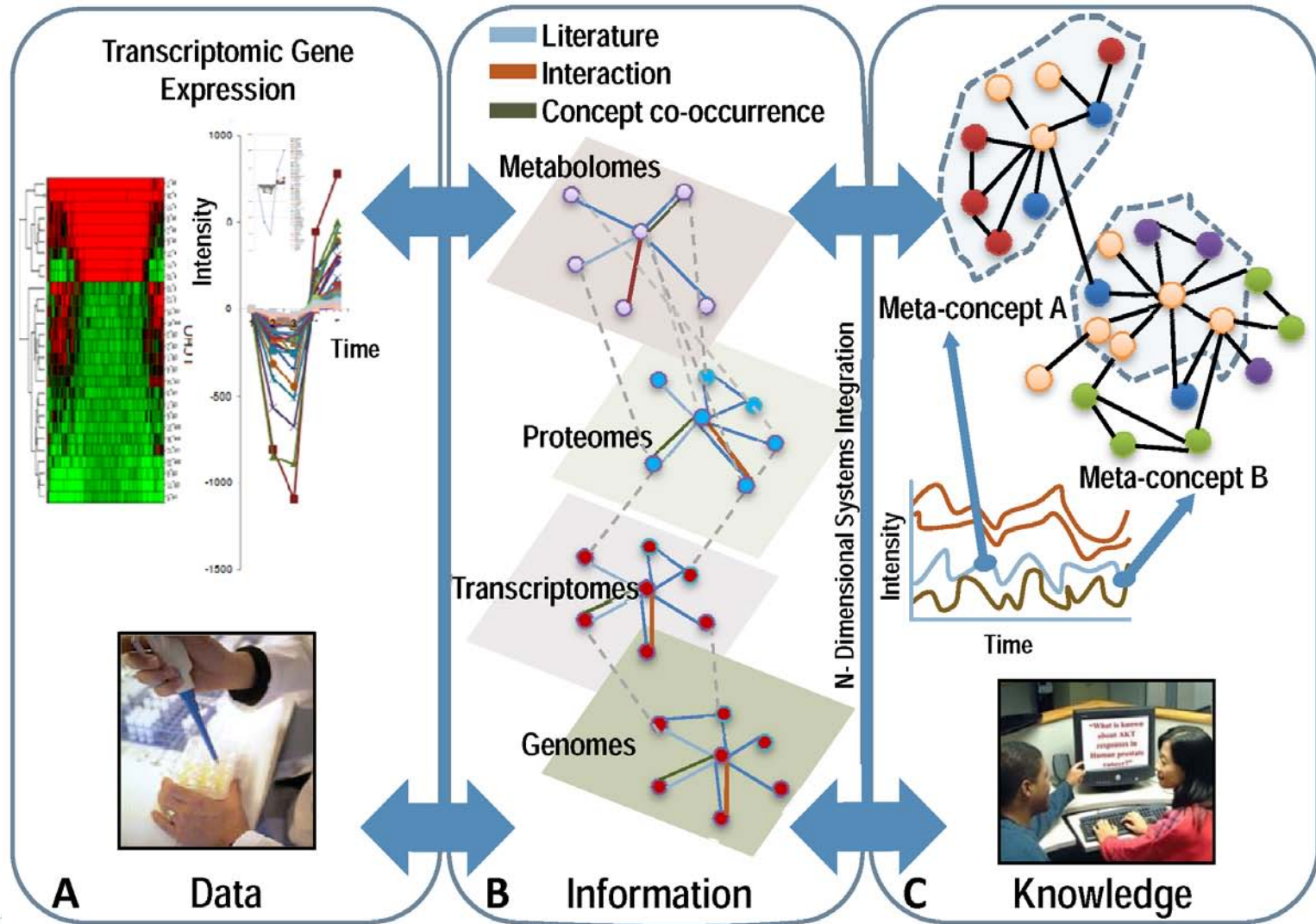
Overview of the NIH National Center for Integrative Biomedical Informatics (NCIBI)



NCIBI Computational Science Core Abstract View



Theme: From Data to Knowledge



NCIBI Senior Leadership Team



H.V. "Jag" Jagadish, Ph.D.
*Senior Scientific Director
Core 1 Director*



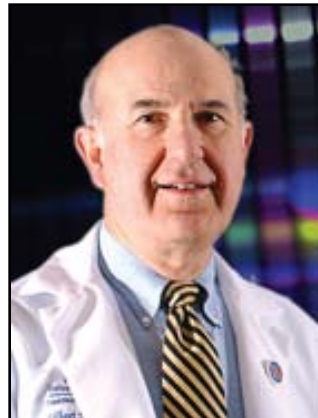
Brian D. Athey, Ph.D.
*PI and Core 2, Core 7 Chair
Senior Scientific Director*



Barbara Mirel, PhD.
Cores 5 & 6 Co-Director



James D. Cavalcoli, Ph.D.
NCIBI Project Manager

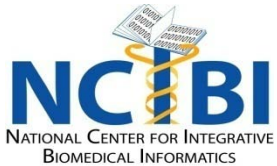


Gilbert S. Omenn M.D., Ph.D.
*Senior Scientific Director
Core 3 Director*



Matthias Kretzler, M.D.
Core 3, Diabetes complications

NCIBI Collaborative National Partners





NIH Roadmap

National Centers for Biomedical Computing

Home

NCBC Summary

Tools and Applications

Ontology Working Group

DBP Interactions

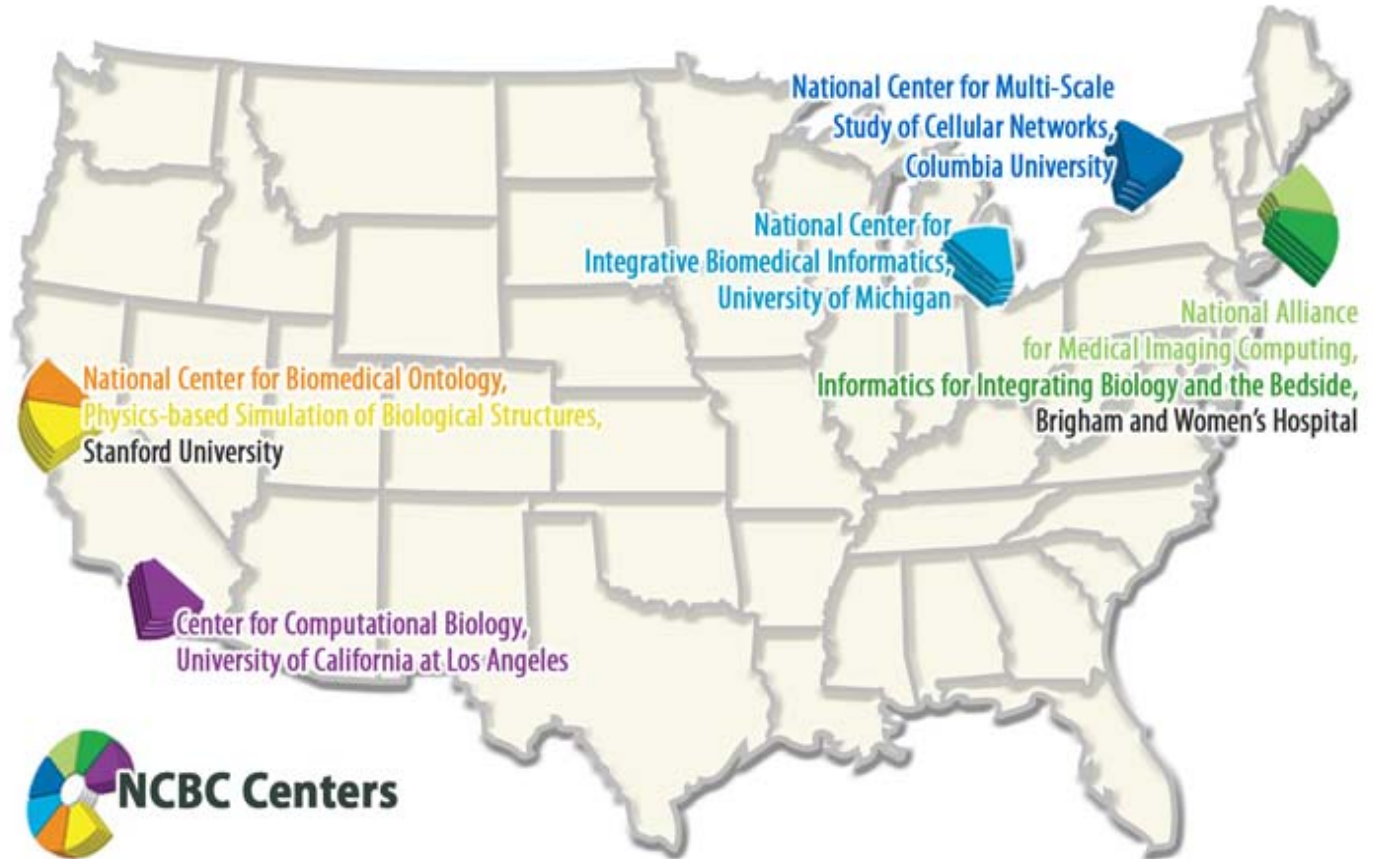
SDIWG



i2b2



simbios



<http://www.ncbcs.org>



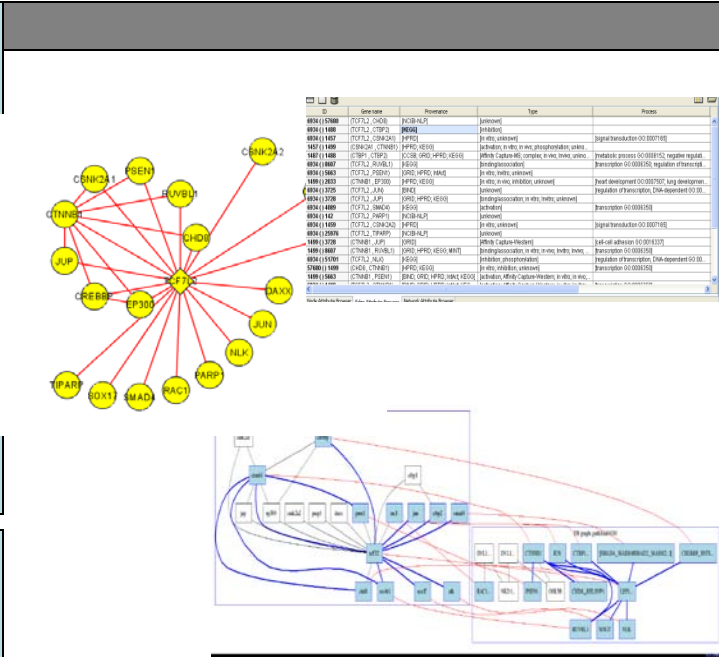
**Concept or
 Keyword**

**Browsing
 Discovery**

**Validation
 Expansion**

Gene List

- MiSearch**
- Gene2Mesh**
- GIN**
- BioSearch2D**



**MiMI
 Cytoscape**

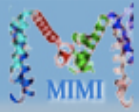
SAGA/TALE

ConceptGen

NLP Data

Experimental

MiMI Data



MICHIGAN MOLECULAR INTERACTIONS



Free Text Search

Gene List Search

Query Interactions

Browse Database

About MiMI

Help

[Download as PSI-MI](#)



Gene Details



Molecule Details for Gene Entry TGFB1 (GeneId: 7040) - [show/hide](#)



Protein Interactions (64 gene interactions found) - [show/hide](#)



Literature on gene TGFB1 (1203 publications found) - [show/hide](#)



Pathways (8 pathways found) - [show/hide](#)

View TGFB1 With Other NCIBI Tools

Gene2MeSH

Cytoscape

Netbrowser

GIN

MiSearch



National Institutes of Health grant #U54DA021519.
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www.ncibi.org - For support and questions email: mimi-help@umich.edu



NCIBI ConceptGen NetBrowser

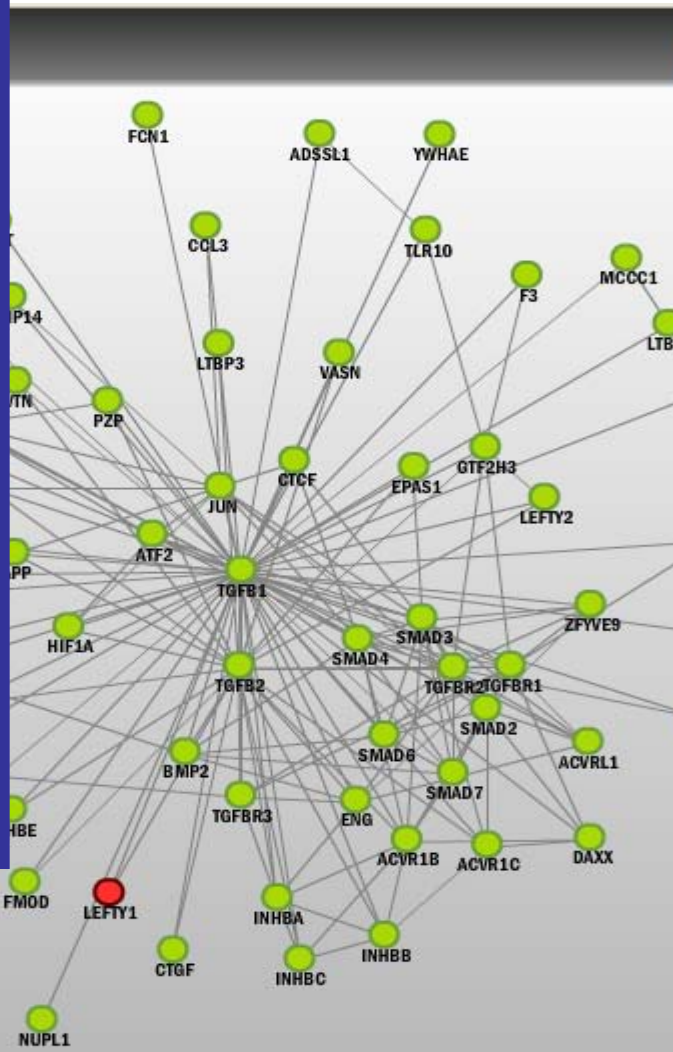
Gene Annotation Remove | Expand X

LEFTY1
left-right determination factor 1

Gene ID: 10637
Gene Type: protein-coding
Organism: Homo sapiens
Chromosome: 1
Map Location: 1q42.1
Locus Tag:
Alias: LEFTY1, LEFTB, LEFTYB
Alias Type: synonym
Kegg Pathway: hsa:10637
Gene Complex: KEGG:path:hsa04350:69

GO Term	Category
extracellular region	Component
extracellular space	Component
cytokine activity	Function
growth factor activity	Function

Path Name	Description
path:hsa04350	TGF-beta signaling pathway

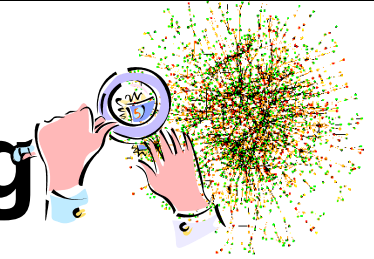


Grant #U54DA021519
University of Michigan

Close Gene List

Gene Id	Symbol
91	ACVR1B
94	ACVRL1
351	APP
633	BGN
650	BMP2
651	BMP3
1280	COL2A1
1386	ATF2
1490	CTGF
1616	DAXX
1634	DCN
1805	DPT
2022	ENG

SAGA and TALE: Effective and Efficient Graph Matching



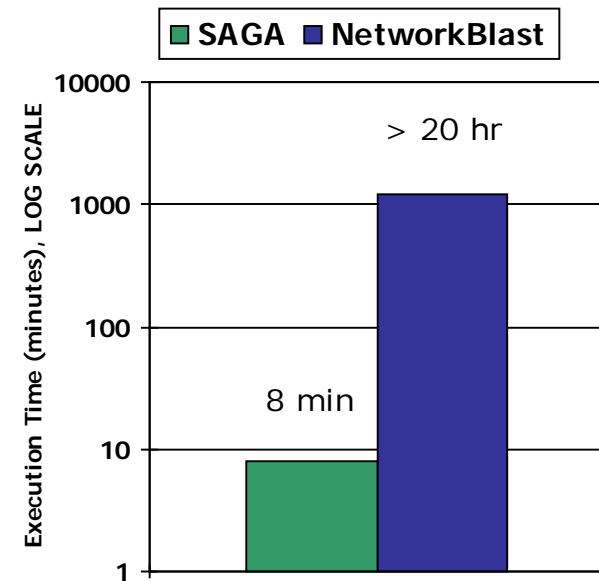
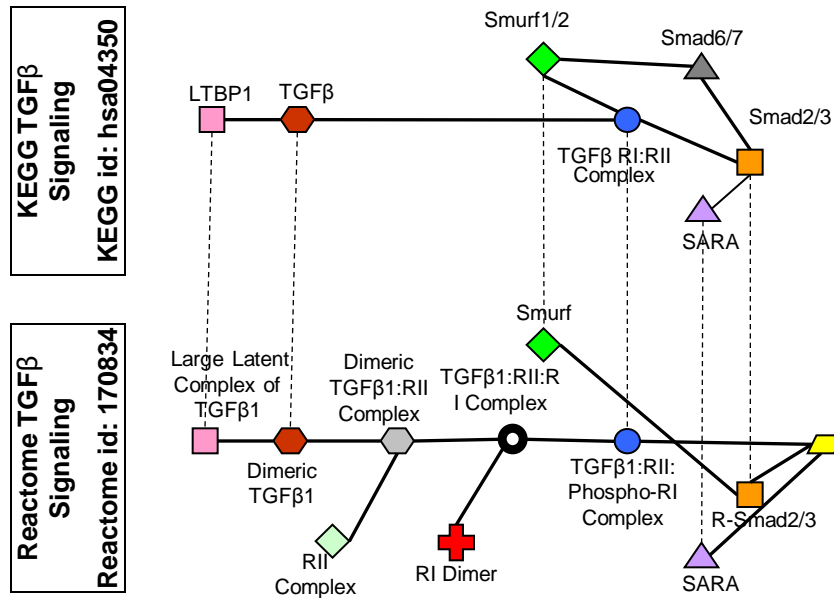
- Graph databases are large and growing rapidly in size. e.g. KEGG has grown by ~1000x since 1999.
- Data is noisy or incomplete (or both)
- Need “approximate” graph matching
 - SAGA: when the query graph is small (< 100 nodes)
 - TALE: when the query graph is large (1000s of nodes)
- Shown to be:
 - More **effective** - able to find results other tools miss
 - Orders of magnitude **faster** than existing tools
- Publications:

- SAGA: Tian et al. Bioinformatics'07

- TALE: Tian and Patel, IEEE Data Engineering'08

SAGA Example: Integrating Different Pathways Databases

KEGG Database vs. Reactome Database



Potential: Integrate graphs from different sources.

Orders of magnitude faster than existing tools

Match No.	Match Graph Name (#Nodes, #Edges)	Graph Dis
Match #1	path:hsa04330 (17,16) [Notch signaling pathway]	29.00
Match #2	path:hsa04310 (59,70) [Wnt signaling pathway]	36.00

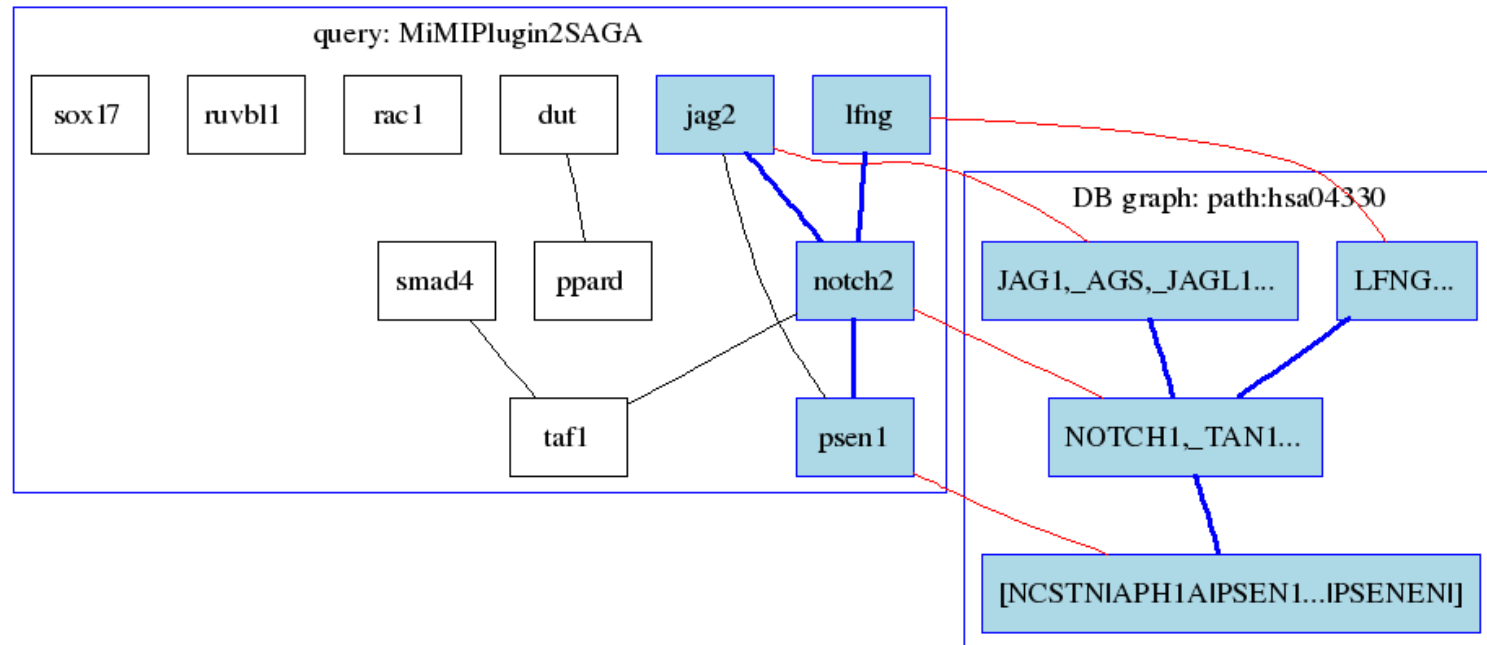
Details of the Matches:

[\[Go Back to Matches Overview\]](#)

Match #1: path:hsa04330 (17 nodes, 16 edges) [Notch signaling pathway]

Graph Distance 29.00 (4 out of 11 nodes match)

[\[Link to KEGG Picture\]](#) (with the matching nodes highlighted)



Gene2Mesh: Automated Literature-Based Genome Annotation Using MeSH

- GO
 - Linked to genes and genomes
 - Only describes normal physiology
- OMIM
 - Heritable disorders
 - Hard to search
- MeSH
 - Broad coverage of biomedical concepts
 - Need links to genes
- Statistical association
 - All of PubMed
 - All MeSH terms
 - All papers referring to genes
- Fisher's exact test
 - Significant associations
 - Informative ranking
- <http://gene2mesh.ncibi.org>

Mesh and the OMIM MorbidMap

Genes associated with “prostatic neoplasms”

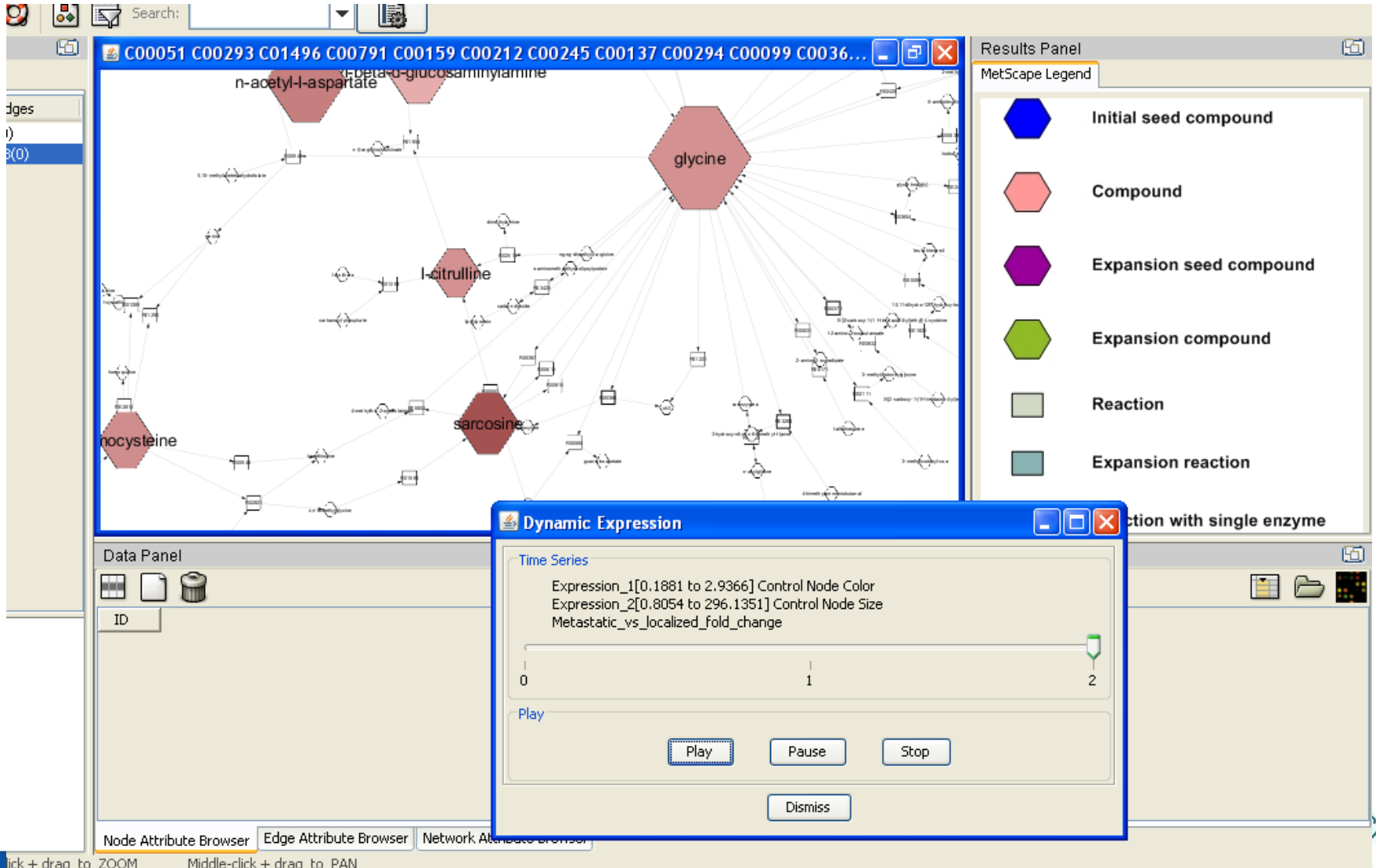
<u>Symbol</u>	<u>Description</u>	<u>OMIM</u>
AR	androgen receptor	Prostate Cancer
RNASEL	ribonuclease L	Prostate Cancer, Hpc1 ;Prca1
ELAC2	elaC homolog 2 (E. coli)	Prostate Cancer
PTEN	phosphatase and tensin homolog	Prostate Cancer
CD82	CD82 molecule	Prostate Cancer
PCA3	prostate cancer antigen 3	Prostate Cancer Antigen 3; Pca3
MSR1	macrophage scavenger receptor 1	Prostate Cancer
KLF6	Kruppel-like factor 6	Prostate Cancer
TMEM16G	transmembrane protein 16G	Prostate Cancer-Associated Protein 5;

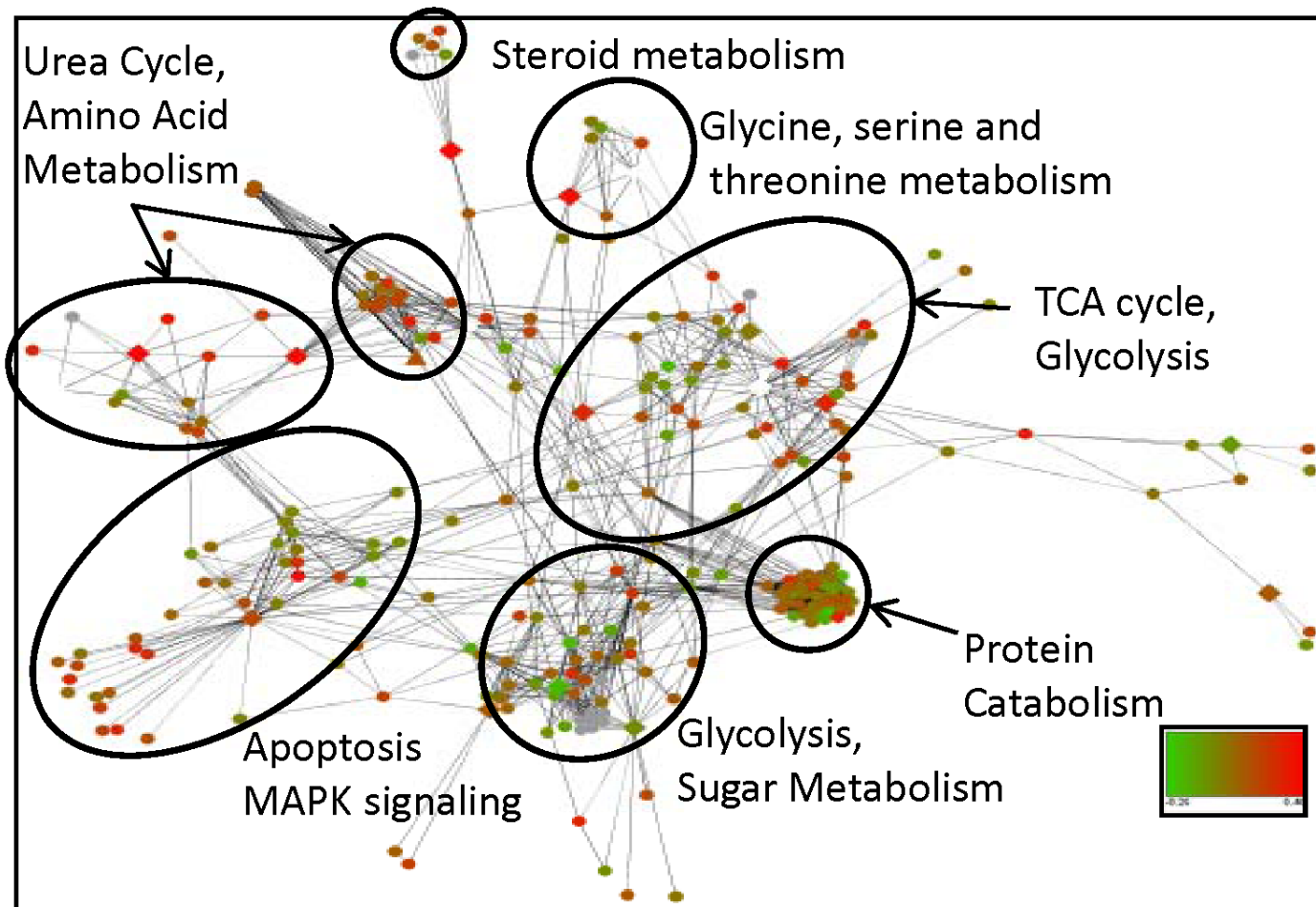
74 Additional prostate cancer associated genes identified using MeSH analysis
KLK3 (PSA), NKX3, FOLH1 (PSMA1), AMACR, ACPP, SRD5A2, TMPRSS2...

11 Genes in OMIM, not found by MeSH analysis

BRCA2 and CHEK2 missed threshold, 9 genes with minimal literature or not enriched

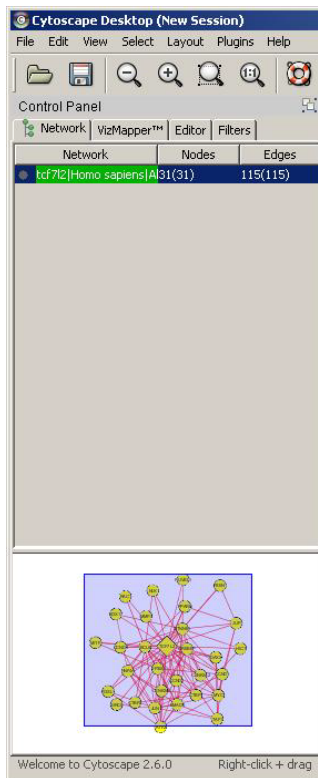
New NCIBI Tool--Metscape





MetScape visualization of liver mRNA levels (nodes) whose expression pattern correlates positively (red) or negatively (green) with liver glutamine levels

Visualization tools: MiMI Plugin for Cytoscape Integrated with BioNLP and SAGA



Result for the Query

Total Execution Time

Number of Matches

Matches Overview

Match No.

[Match #1](#)

[Match #2](#)

[Match #3](#)

[Match #4](#)

[Match #5](#)

[Match #6](#)

[Match #7](#)

[Match #8](#)

[Match #9](#)

47 Set

SORT (SINGLE CLICK)

PubmedID Section

[9880534](#) ABSTRACT

[9916915](#) ABSTRACT [TCF7L2](#) [HNF4A](#)

[9916915](#) ABSTRACT [TCF7L2](#) [HNF4A](#)

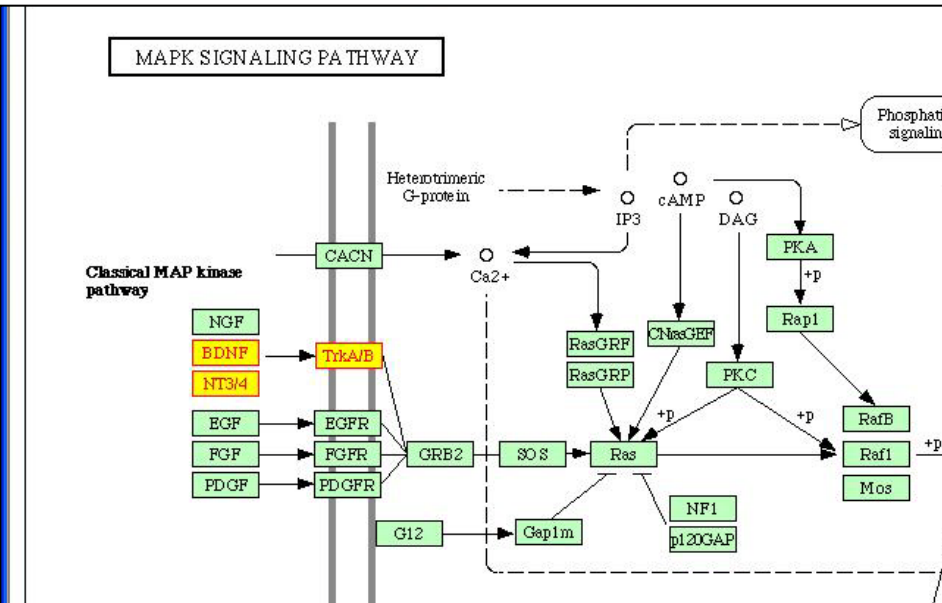
[10485457](#) ABSTRACT [TCF7L2](#) [HNF4A](#)

[10597289](#) ABSTRACT [TCF7L2](#) [HNF4A](#)

Data Panel

ID	Category
3728	JU
2033	ER
4286	MI
5663	PS
1457	CS
8607	RR

Node Attribute



- [path.mmu04010 \(123,166\) \[MAPK signaling pathway\]](#)
- [path.rno04010 \(112,149\) \[MAPK signaling pathway\]](#)
- [path.rno04010 \(112,149\) \[MAPK signaling pathway\]](#)
- [path.ptr04010 \(99,120\) \[MAPK signaling pathway\]](#)

Tcf-4 is a member of the Tcf/Lef family of transcription factors that interact functionally with beta-catenin to mediate Wnt signaling in vertebrates.

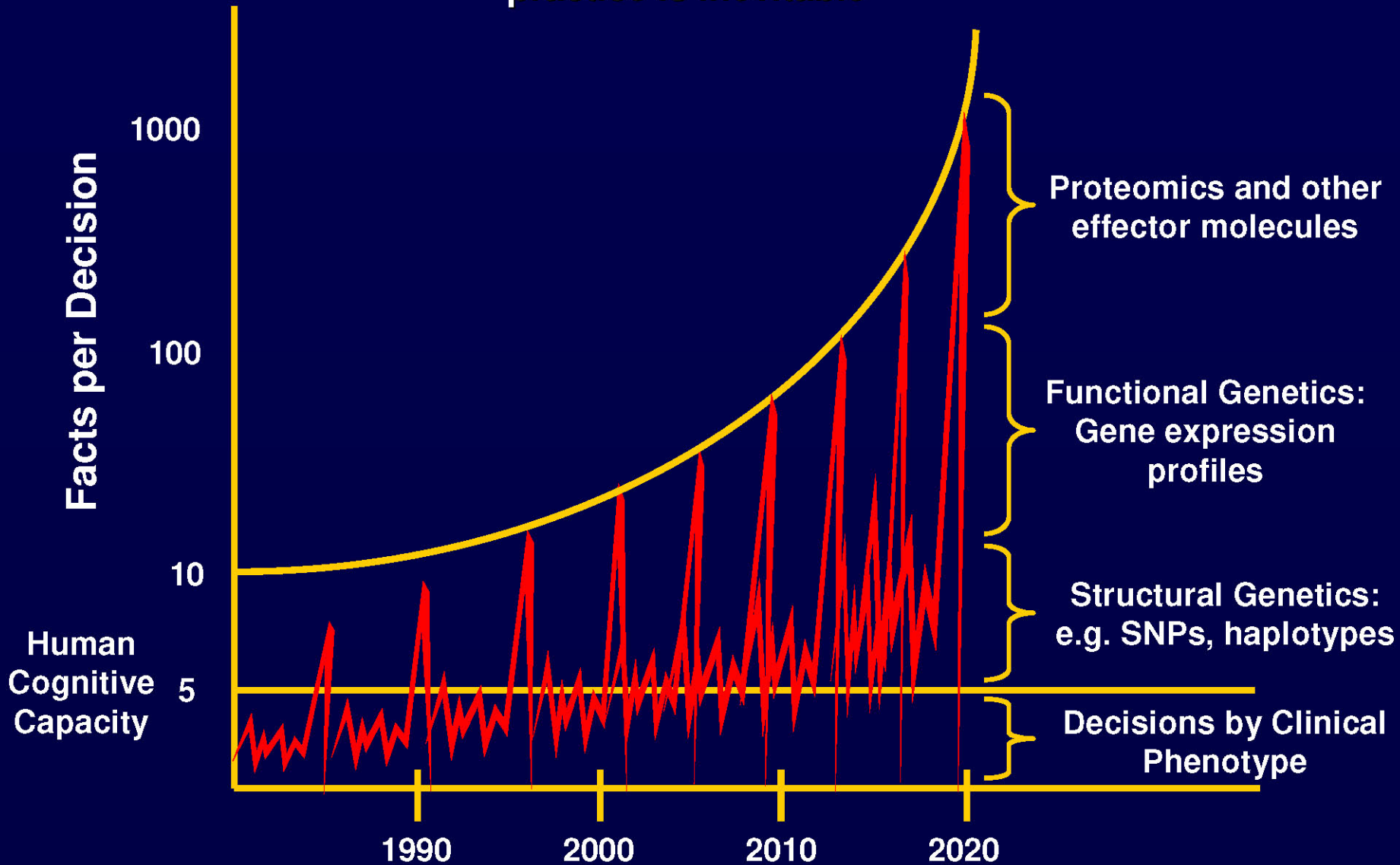
To gain further insight into the role of Tcf-4 in development and carcinogenesis we have generated several mouse monoclonal antibodies, one of which is specific for Tcf-4 and another of which recognizes both Tcf-3 and Tcf-4.

TCF-4 codes for a transcription factor that is a crucial member of the adenomatous polyposis coil (APC)/beta-catenin/T-cell factor (TCF) pathway.

We recently showed in a large series of MSI-H colorectal tumors that approximately 40% of them exhibited frameshift mutations in an (A)⁹ tract within the coding region of the TCF-4 gene, a crucial member of the APC/beta-catenin/TCF pathway.

Inhibition of beta-catenin/Tcf transcription by expression of the dominant-negative mutant of Tcf-4

The demise of expert-based practice is inevitable

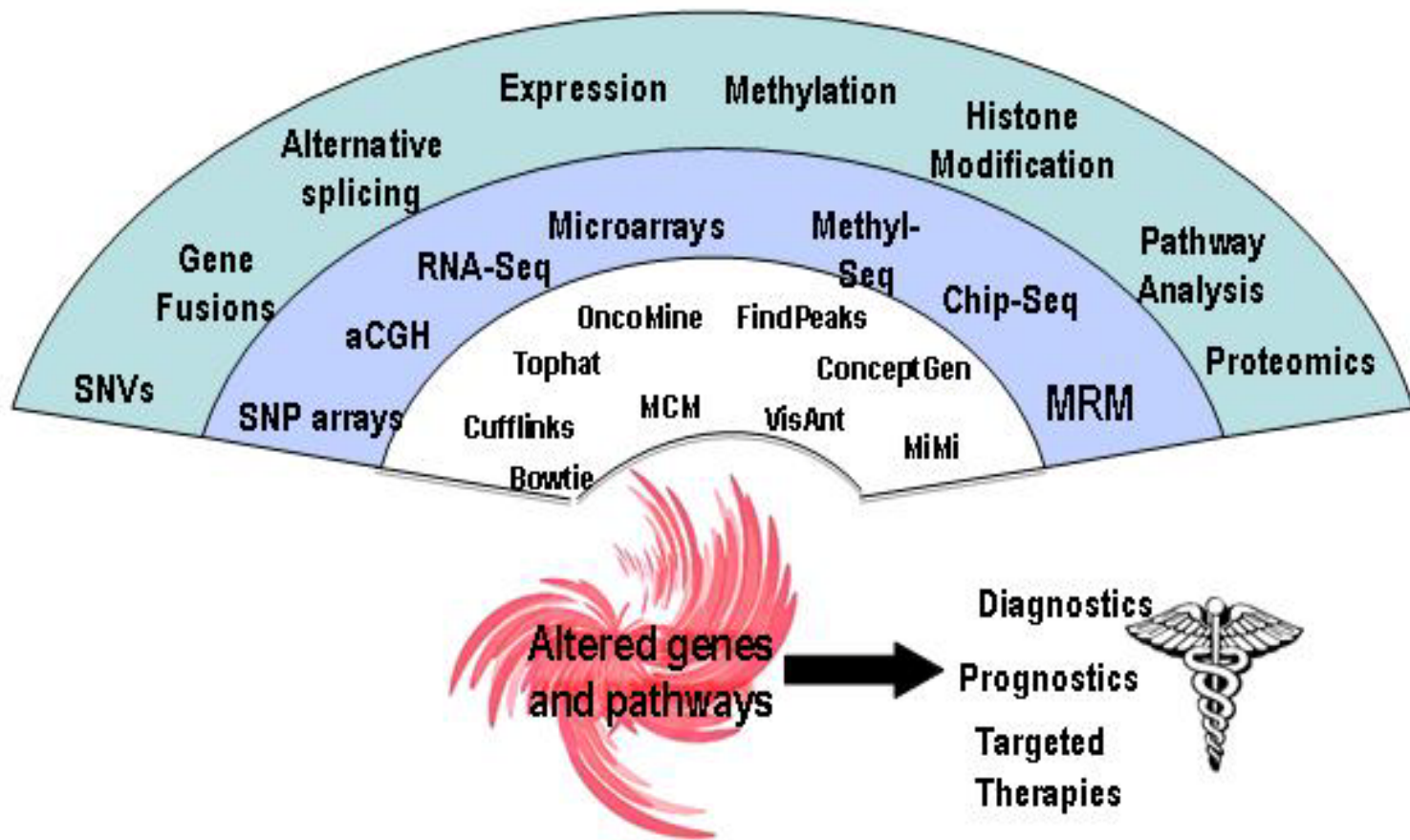


NCIBI Driving Biological Problems (DBPs) Y1-Y5

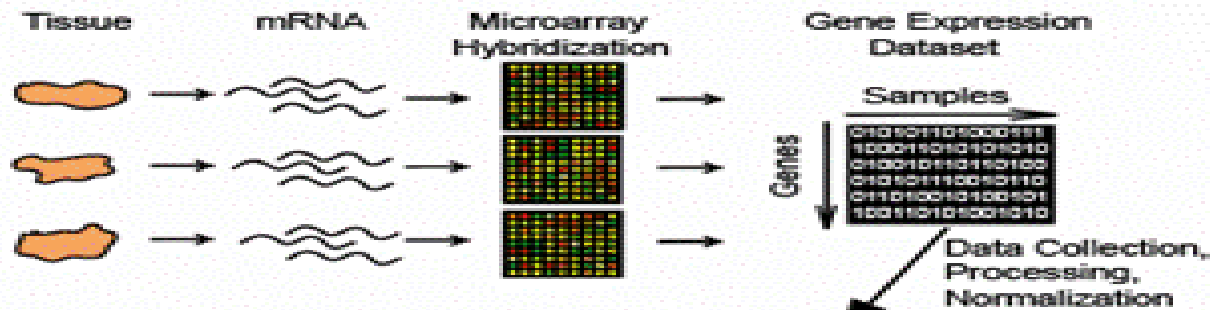
Year 1	Year 2	Year 3	Year 4	Year 5
Prostate Cancer Progression		Gene Fusions In Cancers		
Type 1 Diabetes Complications Neuropathy		Type 1 Diabetes Complications Nephropathy		
Type 2 Diabetes Genetic Heterogeneity		Type 2 Diabetes Metabolomics		
Bipolar Susceptibility Genetics		Bipolar Disease Co-Morbidities With Drug Abuse		

Gil Omenn MD, PhD, Senior Scientific Director

Prostate Cancer Progression DBP *Integration Strategy*

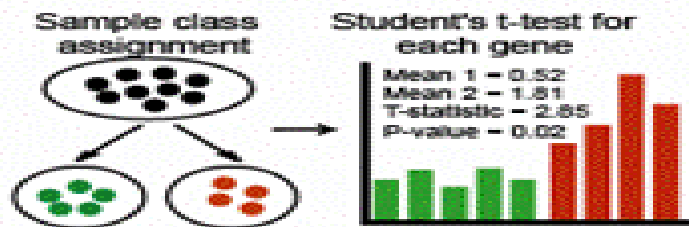


Cancer gene expression profiling with DNA microarrays

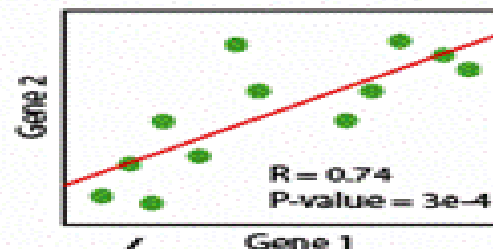


ONCOMINE Microarray Database
90 independent datasets, 15 cancer types
7,292 microarray experiments
79,098,564 gene expression measurements

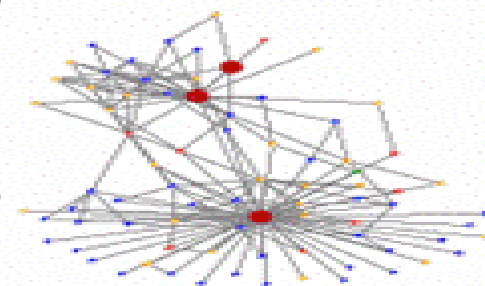
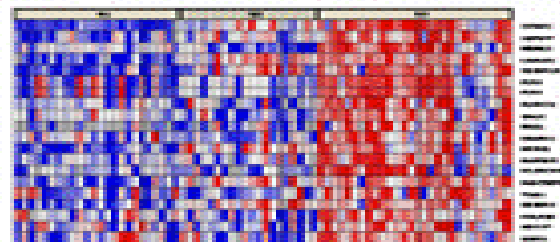
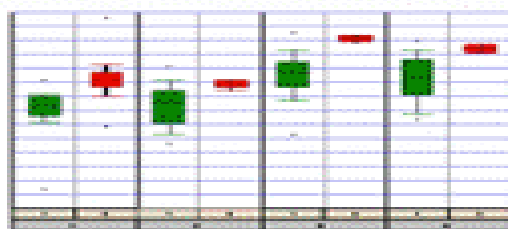
Differential Expression Analysis (380 to date)



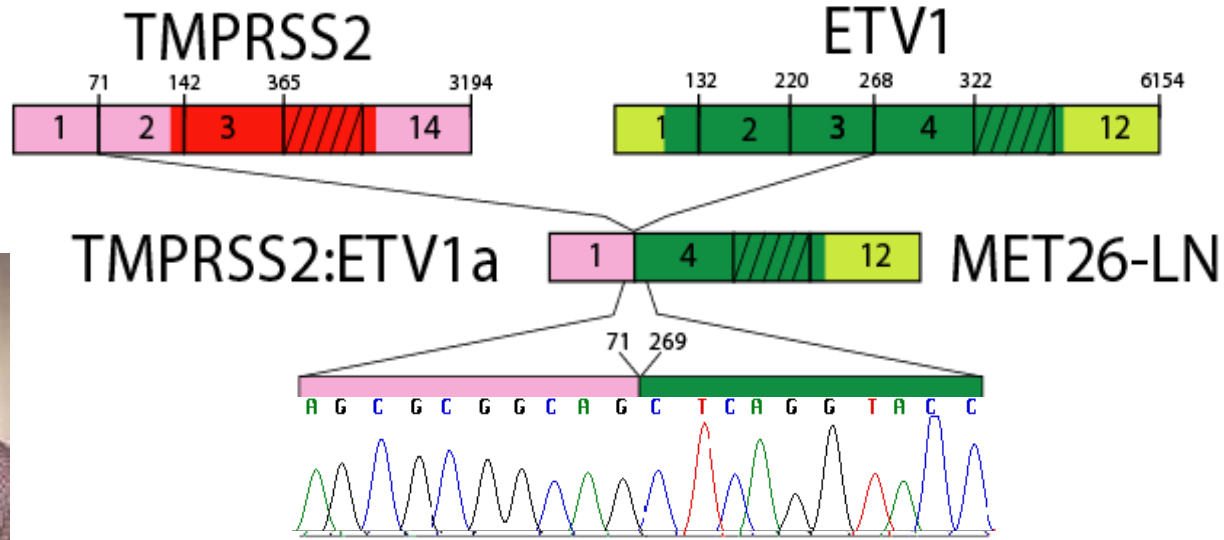
Correlation Analysis



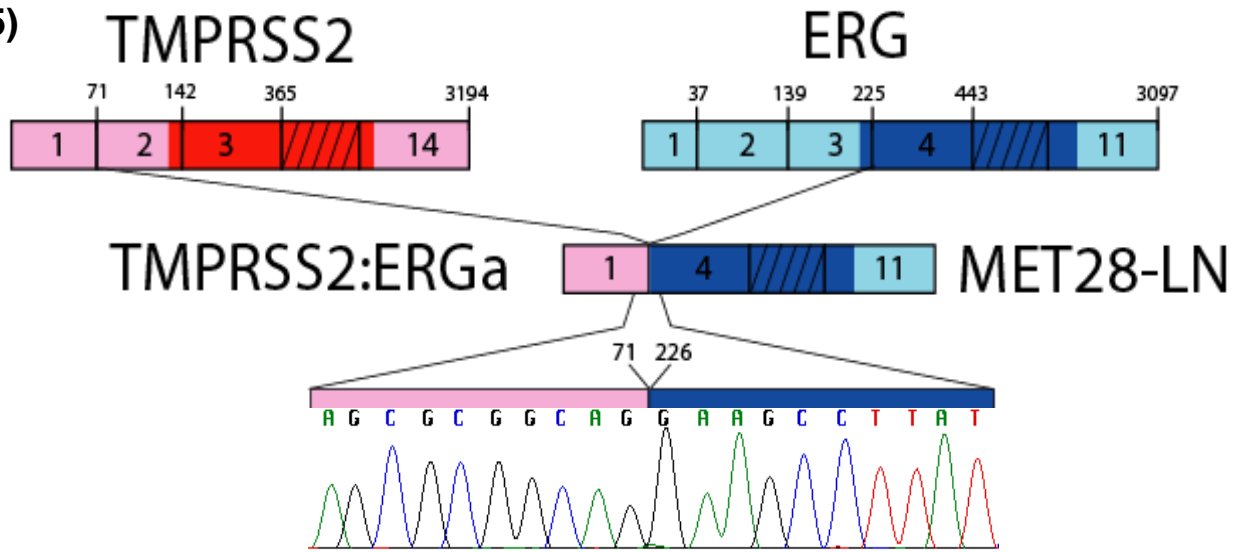
Data-mining at www.oncomine.org



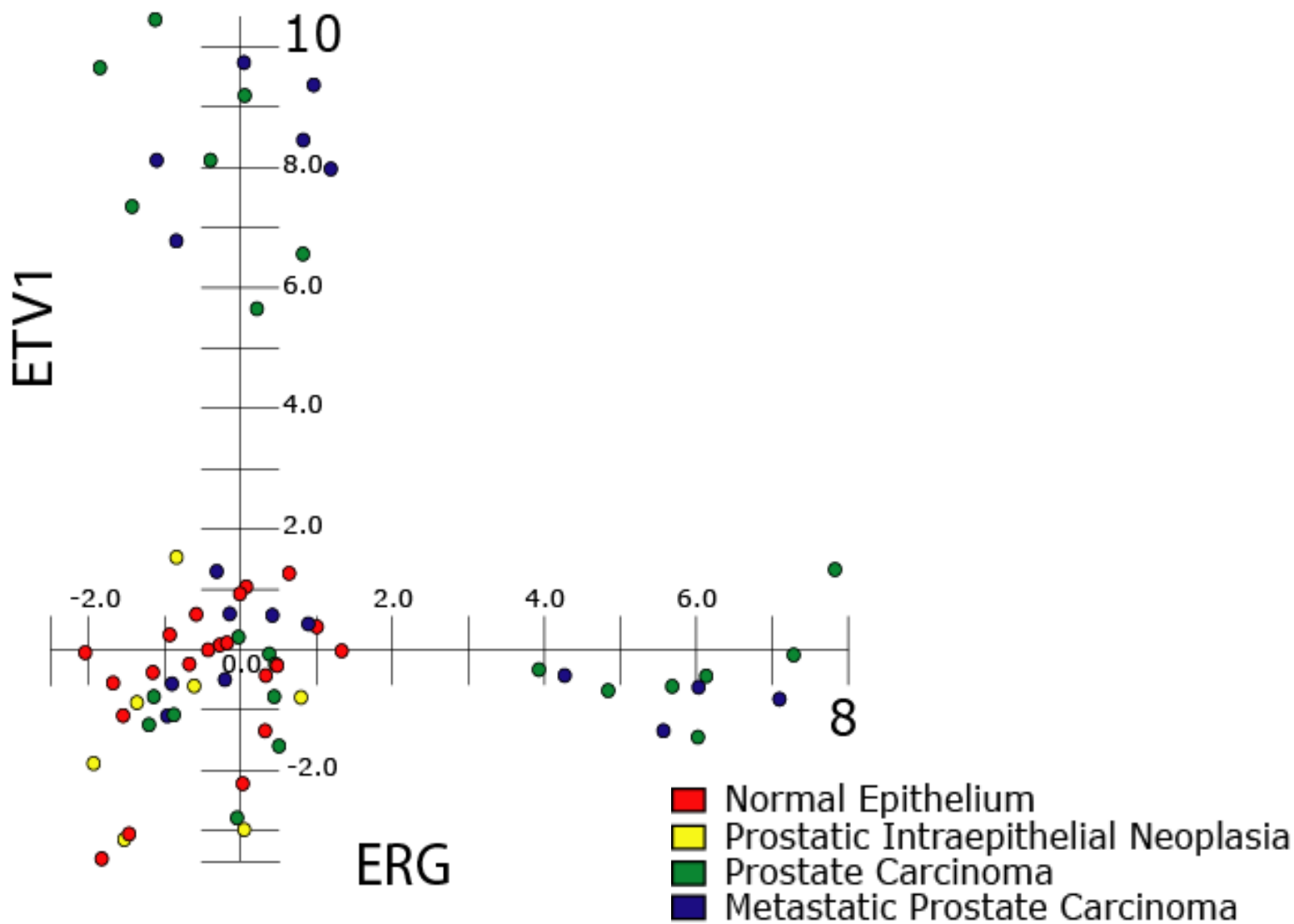
Fusions of TMPRSS2 to the ETS Family of Transcription Factors



Scott Tomlins et al
Science (2005)

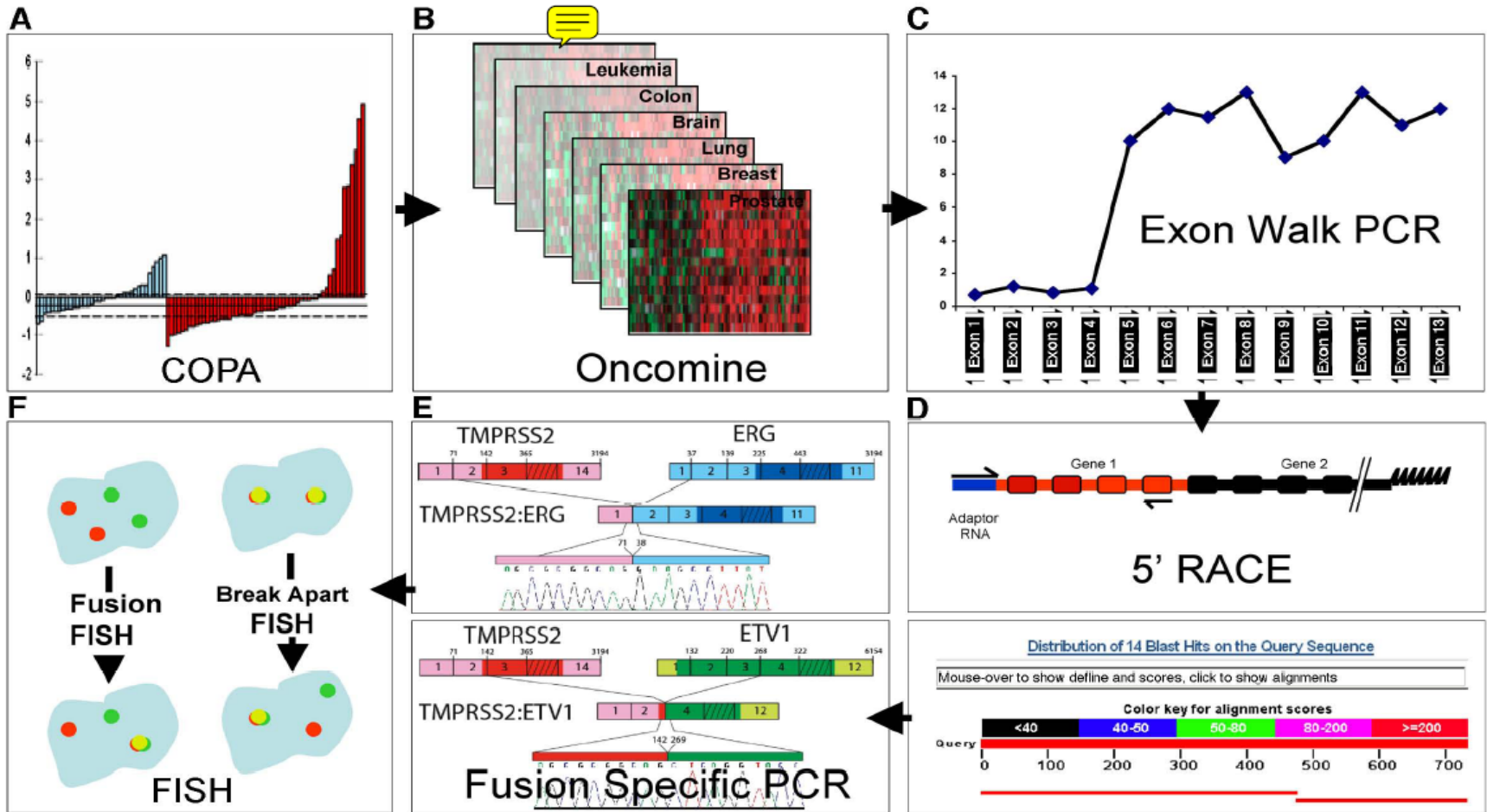


Exclusive Outlier Expression of ETV1 and ERG

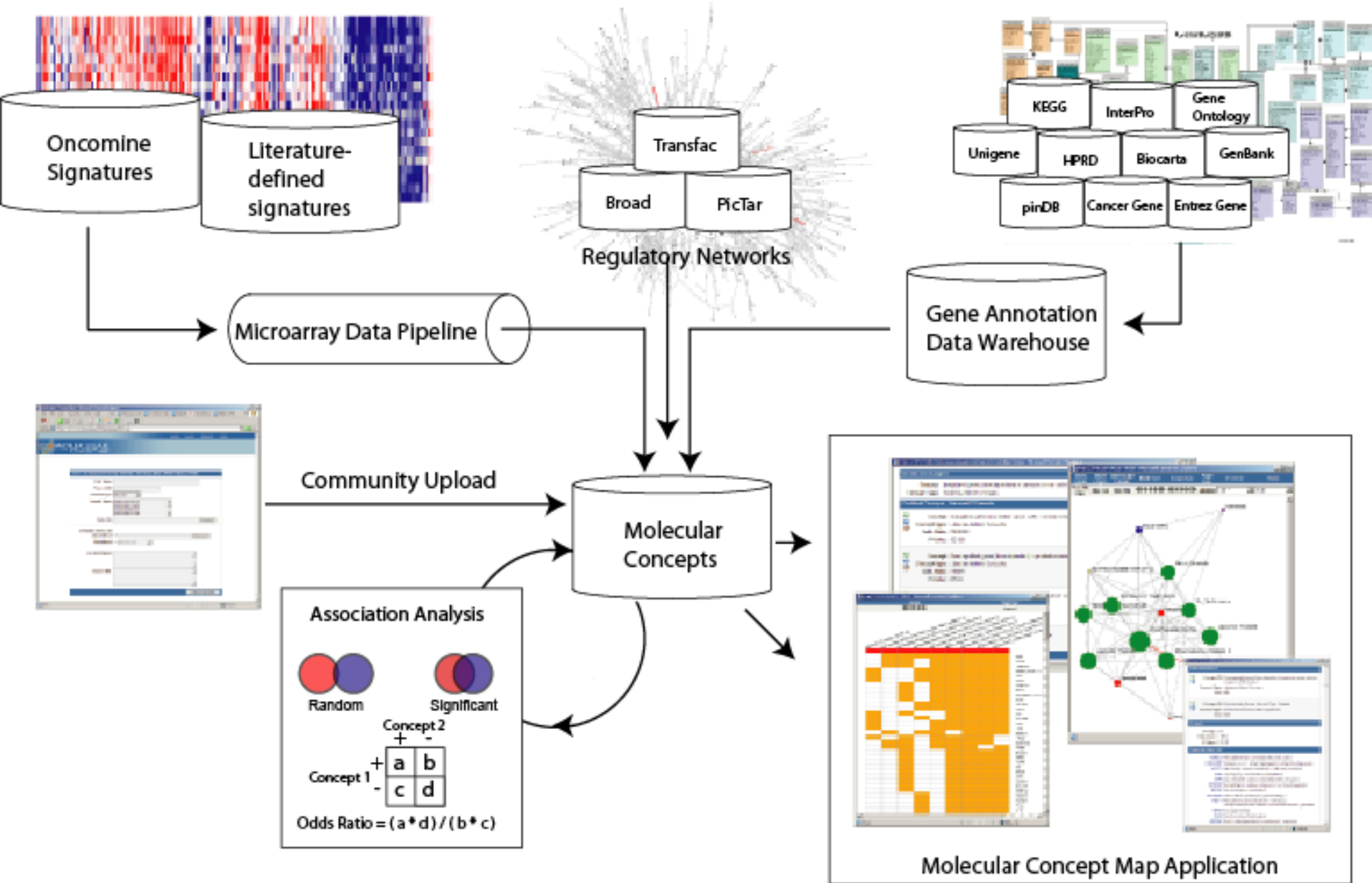




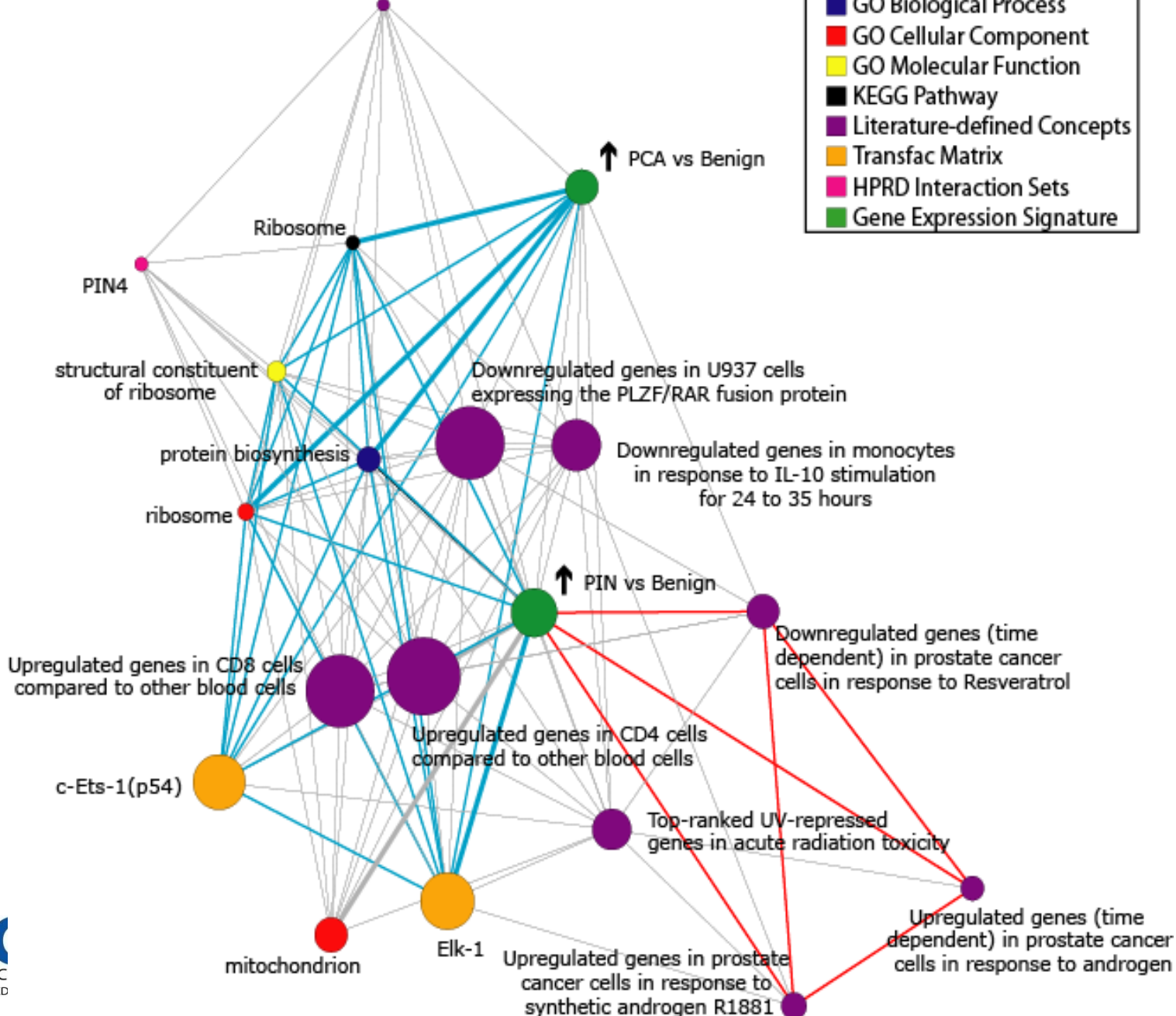
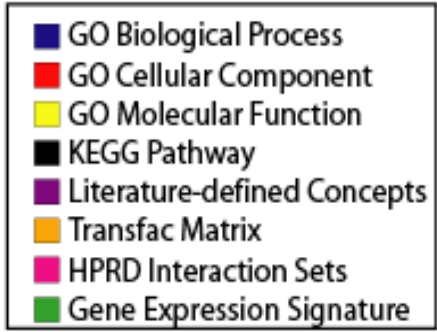
A Bioinformatics Approach Leads to Discovery of Gene Fusions in Prostate Cancer



The Molecular Concept Map Project



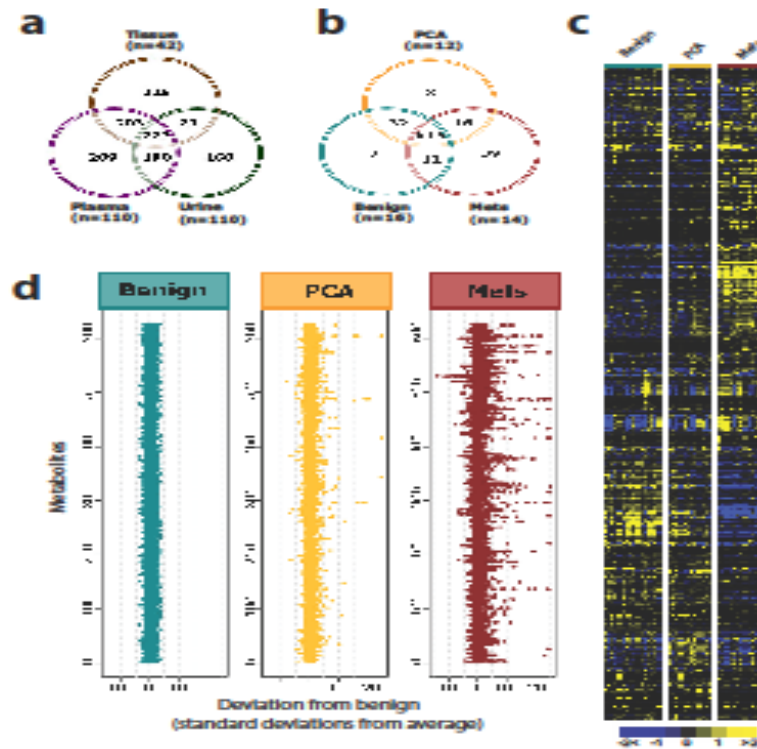
Downregulated genes by IFN-alpha in basal cell carcinoma



Metabolomic and Bioinformatic Analysis of Prostate Cancers

Sreekumar et al, Nature 2009

Figure 1



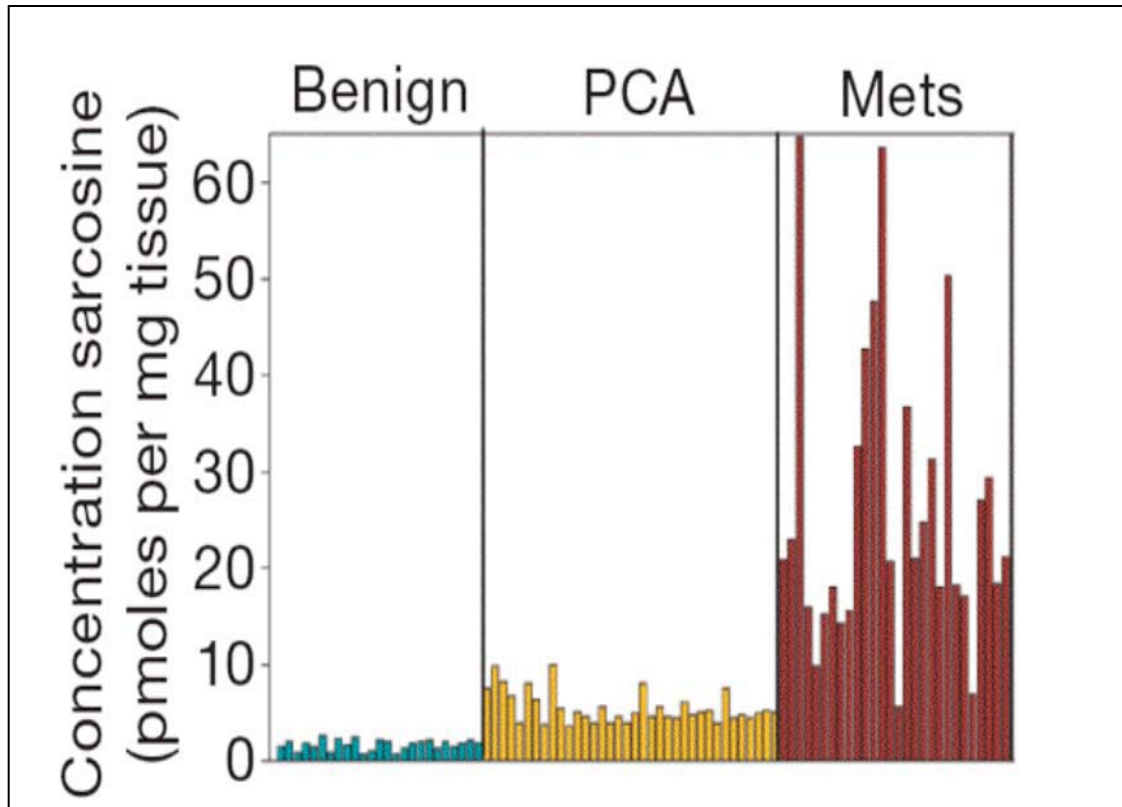


Figure Sarcosine concentration is greatly increased in metastatic prostate cancers, compared with localized tumors or benign tissue.

Biomarker Discovery from Tumor Tissues and Plasma: Strategies

1. Start with microarray or next-gen sequencing evidence for carcinogenic pathway mechanisms in tumor and track corresponding protein biomarker candidates to the plasma; e.g., TMPRSS2/ETS fusion and sarcosine in prostate cancers.
2. Identify alternative splice isoforms of biologically meaningful proteins in cancers and in plasma of humans and mouse models.
3. Perform targeted proteomics with SRM/MRM to identify and quantitate these candidates.
4. Detect auto-antibodies in plasma as a biological amplification of tumor protein signals, confirm in tumor tissue.

A New Class of Biomarker Candidates, from Alternative Splicing

Generates protein diversity without increasing genome size

Most genes produce alternative transcript isoforms

Alternative Splice Isoforms

- Contribute to diseases, especially cancers**
- Potentially useful as biomarkers for cancer**

Greatly improved MS/MS instrumentation enables confident identification of peptides from proteins coded by mRNA transcript sequences expressed at quite low levels.

Summary of Total Number of Alternative Splice Variants Identified

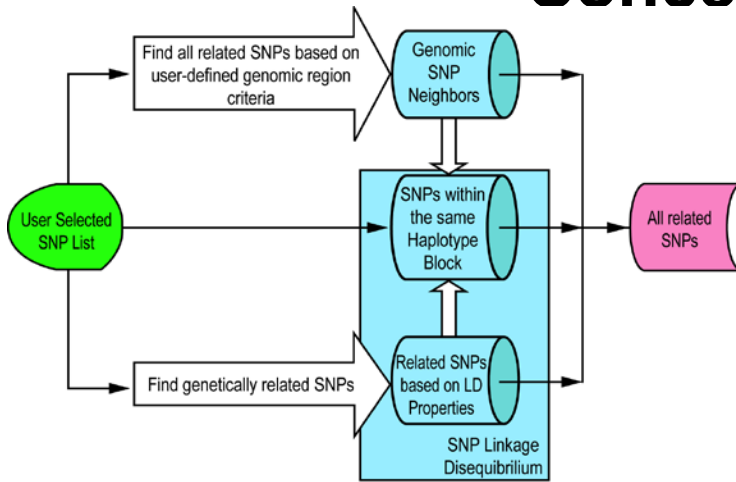
	Breast		Colon		Pancreatic	
Distinct proteins	Known	Novel	Known	Novel	Known	Novel
	540	68	461	28	328	92

Type 2 Diabetes: Genetic and Phenotypic Heterogeneity

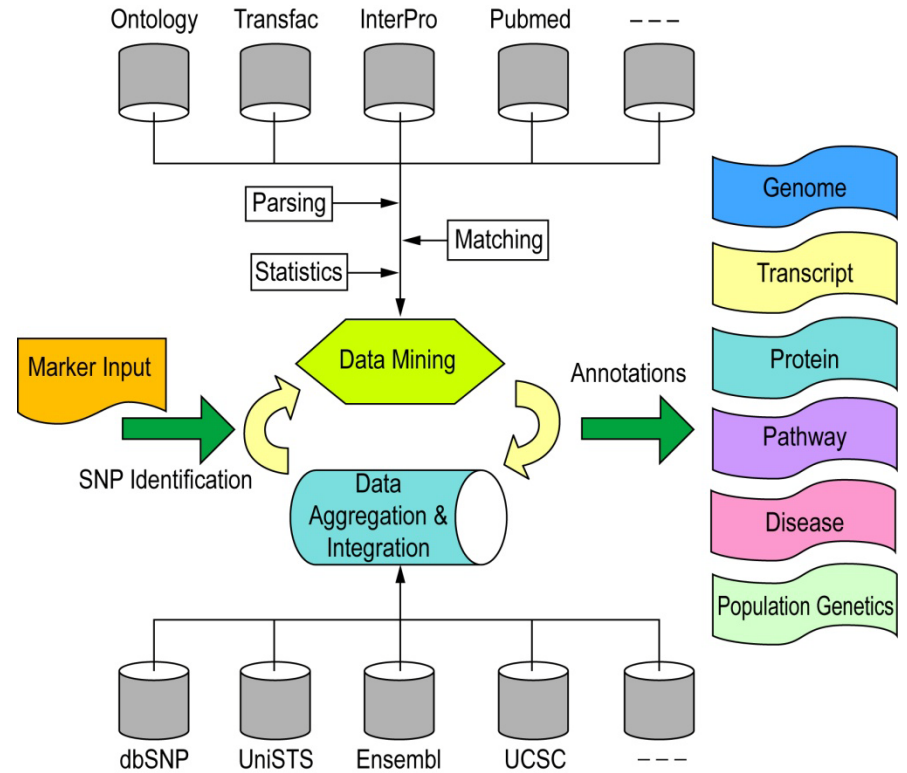
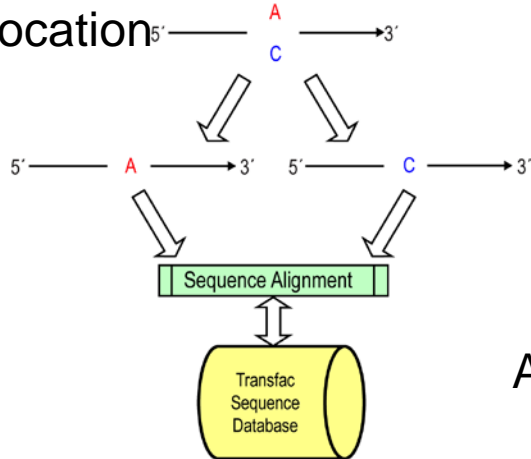
- Exploit ongoing FUSION study datasets
- Implement SNP analysis workflow for whole genome association study (GWAS)
 - For each SNP (and then haplotype), screen databases to identify: coding/noncoding, effect on protein, evolutionary conservation, splice variant, transcriptional regulation, microRNA binding, CpG island, DNase hypersensitivity, disease associations (adding epigenomic marks)
 - Devise algorithms with much higher throughput

NCIBI Innovations in SNP Analysis and Genome

Concept Annotation



Determining all related SNPs by genomic location

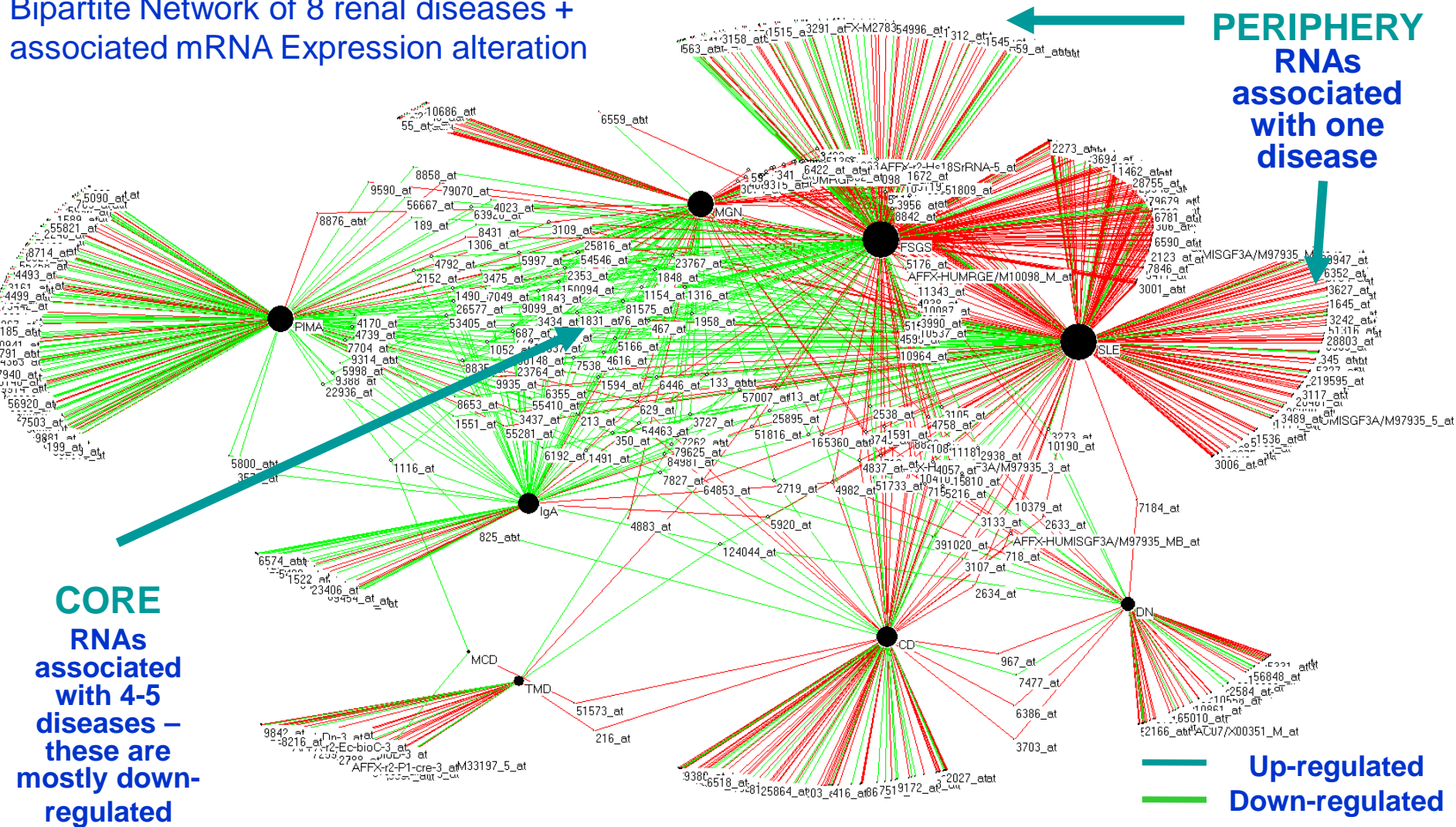


Annotating SNPs: Datasources and workflow

Mapping SNP variation to transcription factor binding sites

Global Molecular Network View of Kidney Diseases

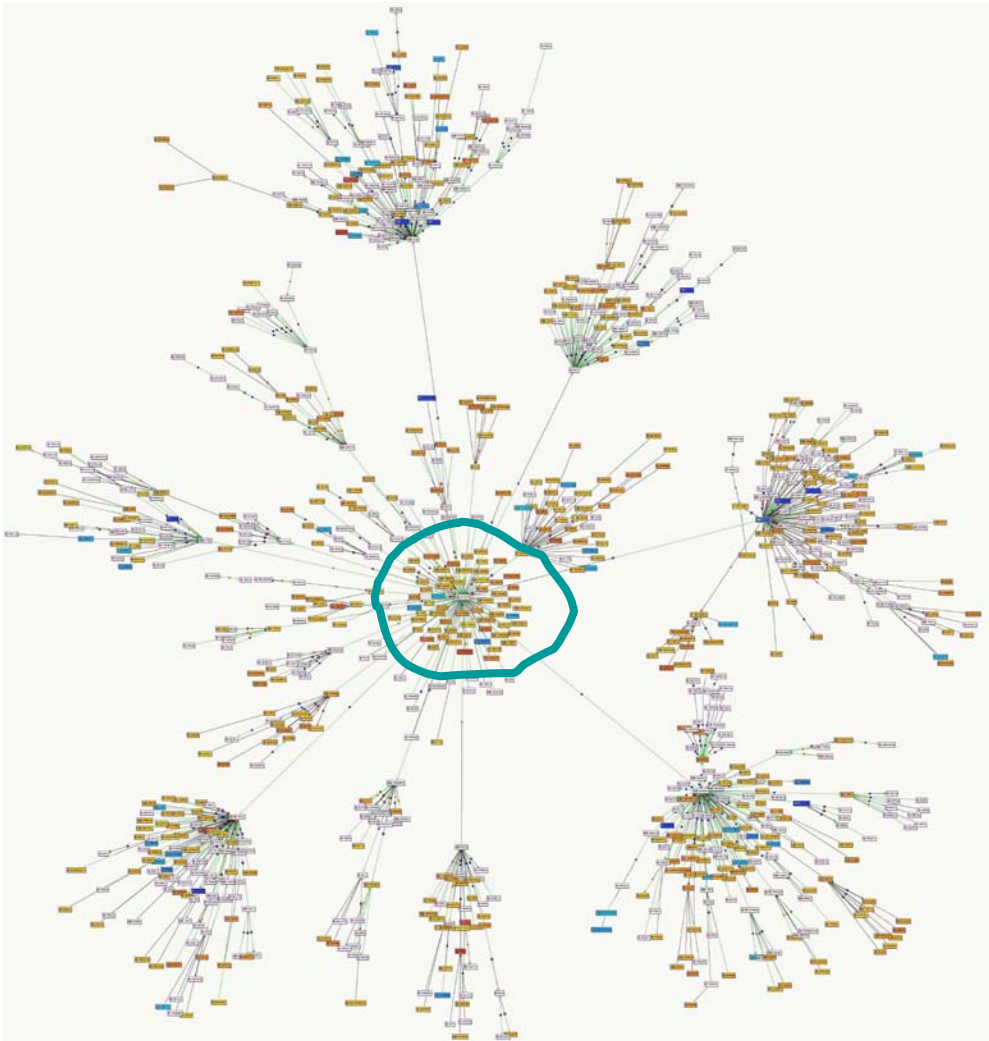
Bipartite Network of 8 renal diseases + associated mRNA Expression alteration

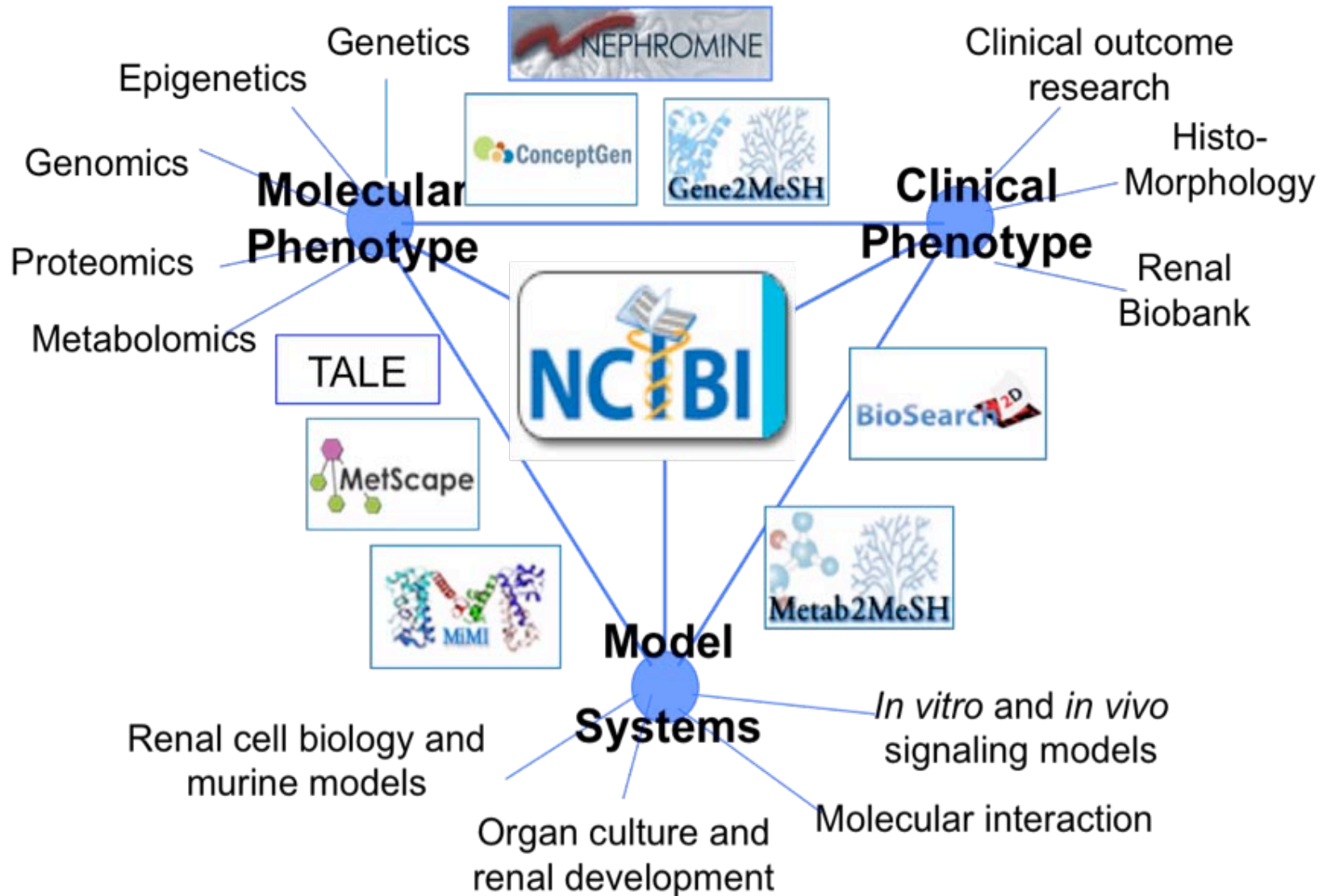


Defining Cross-species Conserved Networks of Early Diabetic Glomerulopathy

- 24 early DN glomerular biopsies (NIDDK trial “Renoprotection in Early Diabetic Nephropathy in Pima Indians, OH95-DK-N037) versus 24 living donor transplants.

- Nodes: differentially regulated mRNA
 - Blue nodes are repressed;
 - Orange nodes induced genes;
 - White: non-regulated transcription factors
- Black edges: co-citation of mRNAs
- Green edges: respective transcription factor binding sites in promoter regions of regulated mRNAs
- Stat1 dependent genes are induced and form a key node in the network, consistent with JAK/STAT pathway activation in human DN.





New NCIBI NIDA Genetics Consortium Pilot Project

“Genetic Predisposition to Co-Morbidity of Bipolar Disorder and Substance Abuse in African-American Women”



Dr. Sharon Lewis
Langston University



Dr. Tonya Gerald
NC Central
University



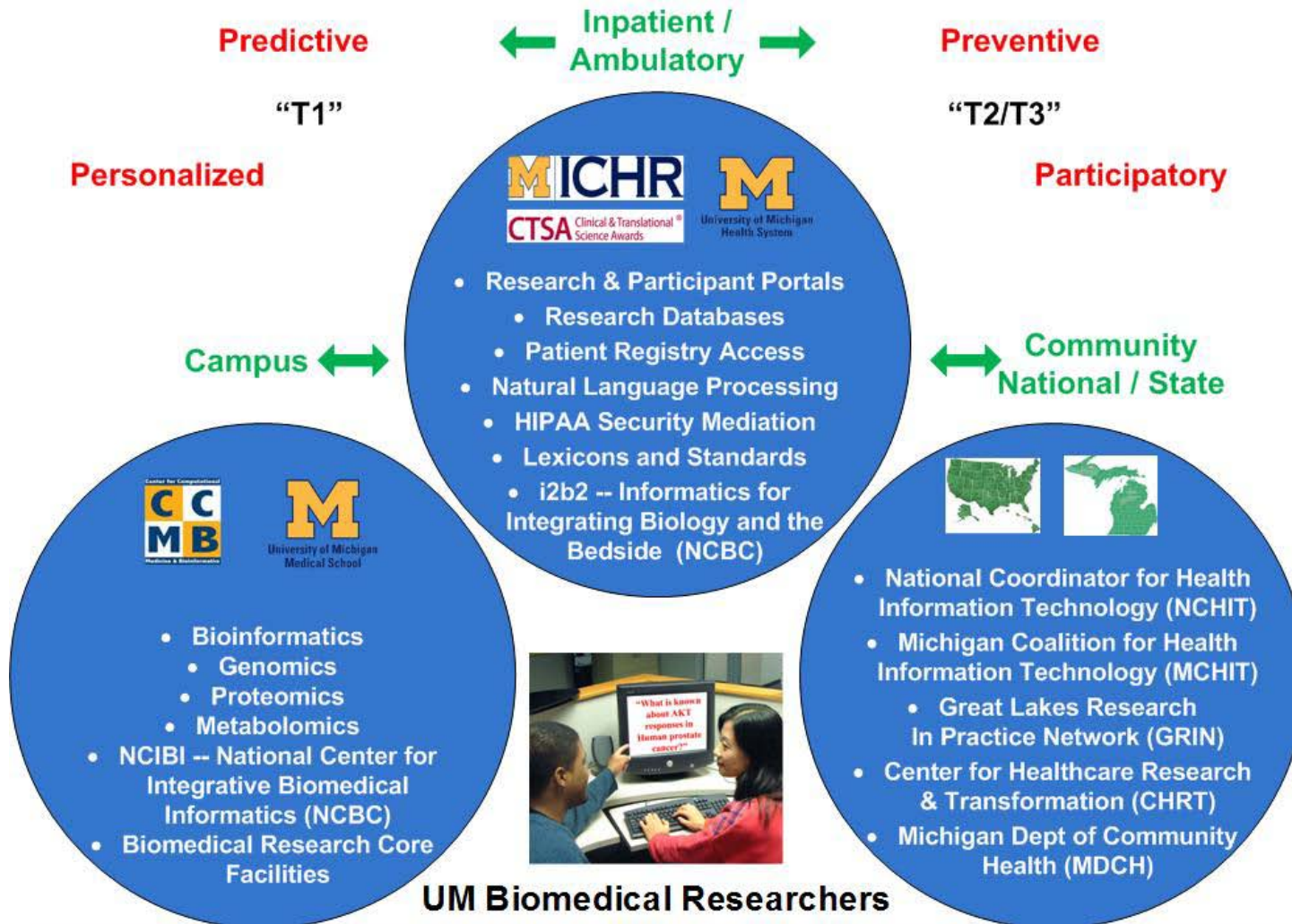
Dr. Raphael D. Isokpehi
Jackson State
University



Dr. Wellington K. Ayensu
Jackson State University

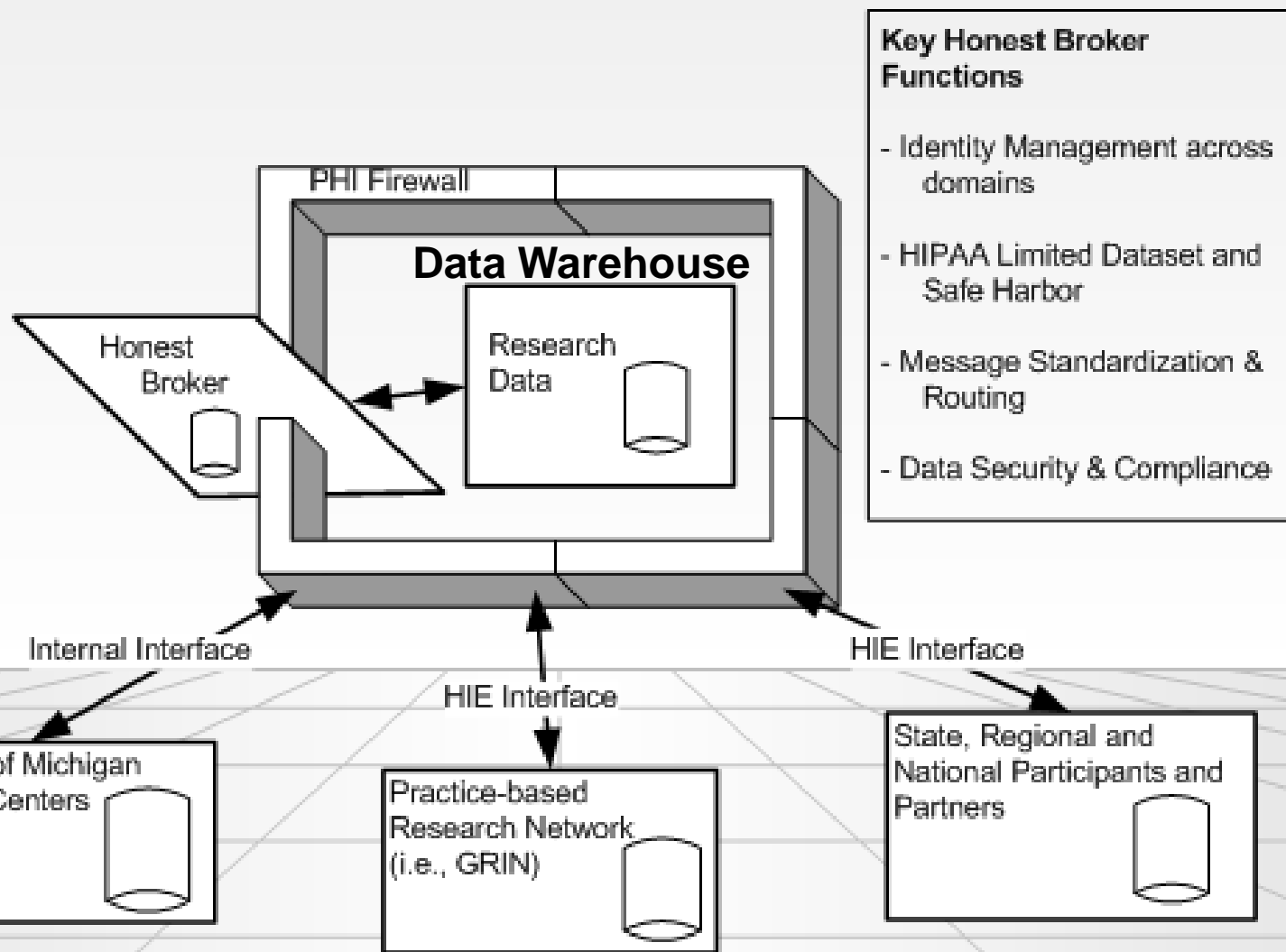
The Scope of Biomedical Informatics

Striving Toward Desired Future P4 Medicine

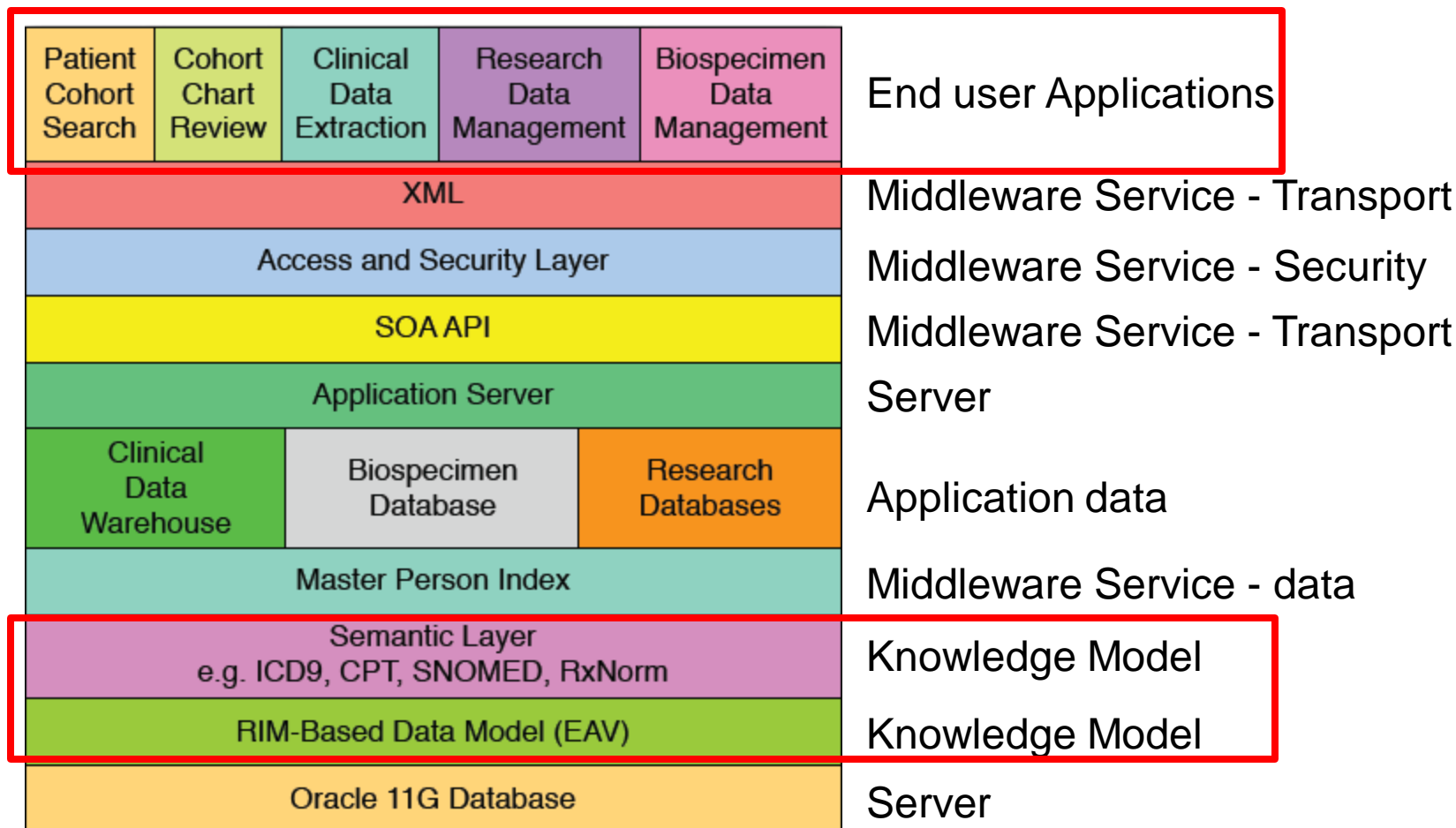


Federated Data Warehouse (Basic Research, Clinical and Outcomes Data)
Spans – Genotype, Phenotype, Populations, and Comparative Effectiveness

Honest Broker: Critical Component to Implement into our Production IT Fabric



Necessary Details

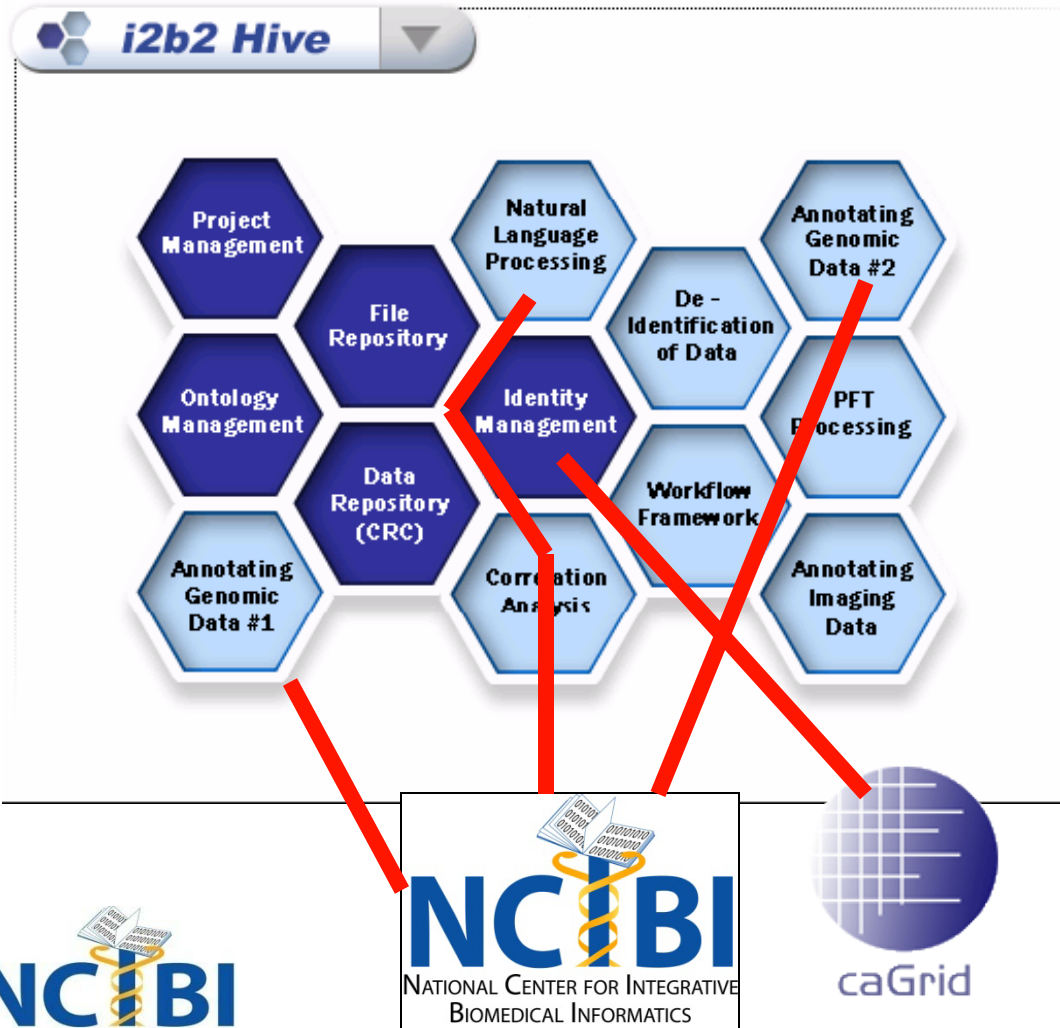


Stanford STRIDE Architecture Stack

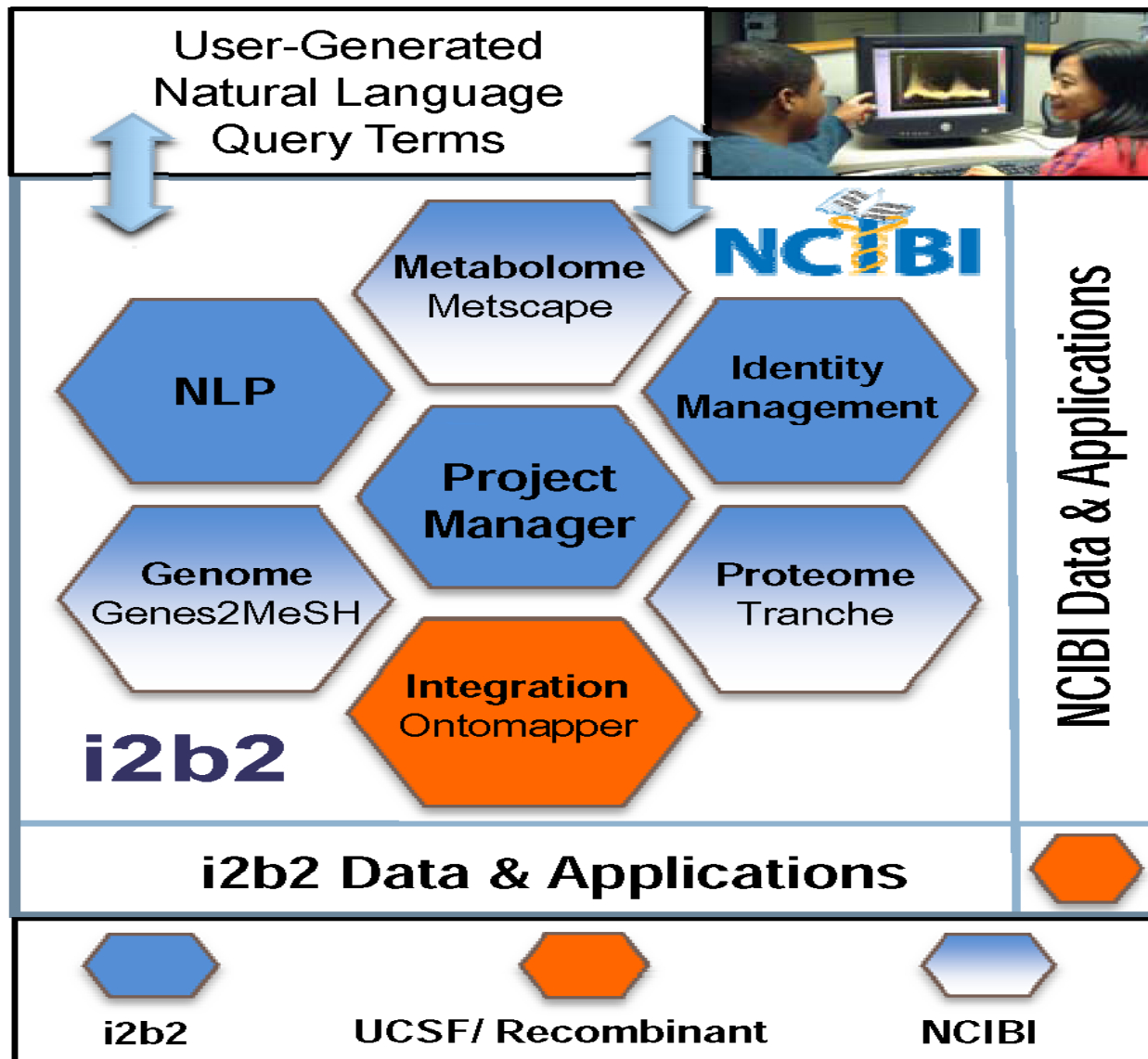
adapted from H. J. Lowe, AMIA 2009 Symposium Proceedings, p 391.

Our “Next-Gen” i2b2 Hive Vision

In cooperation with Harvard University

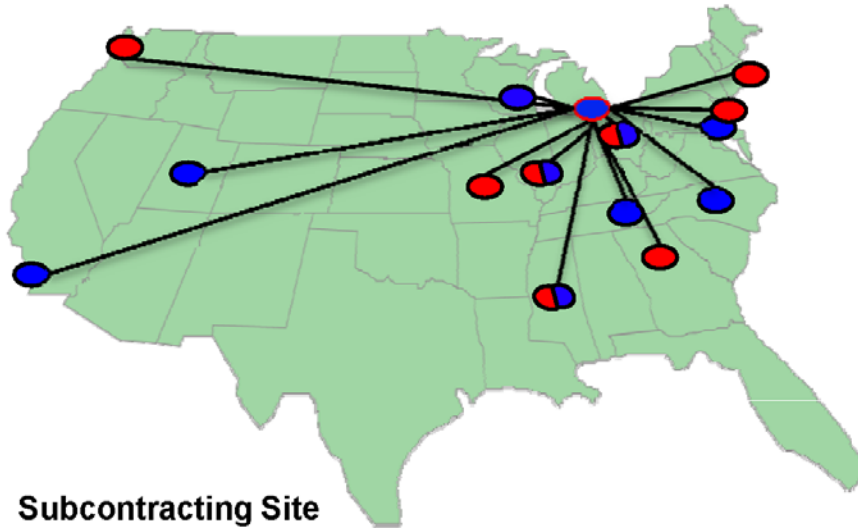


- The i2b2 Hive is centered around two concepts –
- Services applications are “wrapped” into functional units, with functionality exposed as messages that travel to and from the cells of the hive
- Persistent data storage managed by the Clinical Research Chart



National NCIBI/CTSA Partner Network Emerging

● NCIBI (University of Michigan, Ann Arbor, MI)



Collaborator Site

- Albert Einstein Medical School, Yeshiva University, NYC
- Duke University, Durham, NC
- Institute of Systems Biology (ISB), Seattle, WA
- Jackson State University, RTRN DTCC
- Johns Hopkins University Medical School, Baltimore, MD
- Mt. Sinai School of Medicine, NYC
- National Center for Supercomputing Applications (NCSA)
- Oak Ridge National Laboratory (ORNL)
- Ohio State University Medical Center, Columbus, OH
- Ohio Supercomputing Center (OSC)
- Rockefeller University, NYC
- University of California, San Diego
- University of Utah
- University of Wisconsin, Madison, WI
- Washington University in St. Louis, MO

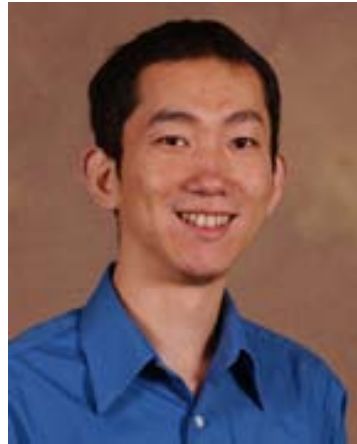
Subcontracting Site

- Boston University, Boston, MA
- Emory University, Atlanta, GA
- University of Illinois, Urbana-Champaign, IL
- Institute of Systems Biology (ISB), Seattle, WA
- Princeton University, Princeton, NJ
- Jackson State University, Jackson, MS

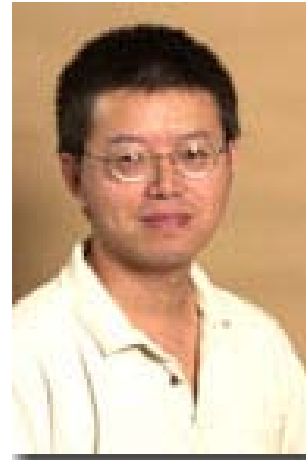
NCIBI Training the Next Generation of Informaticians



Junior Faculty Actively Engaged in NCIBI *Enhanced Paths to Promotion and Tenure*



Steve Qin, Ph.D.
Biostatistics



Fan Meng, Ph.D.
Psychiatry



James D. Cavalcoli, Ph.D.
**Computational Medicine
& Bioinformatics**



Jignesh Patel, Ph.D.
Computer Science



Peter Woolf, Ph.D.
Chemical Engineering



Drago Radev, Ph.D.
Information Science

First Annual RCMI/NCIBI Translational Bioinformatics Summer Institute July 29 - 30th, 2009

