

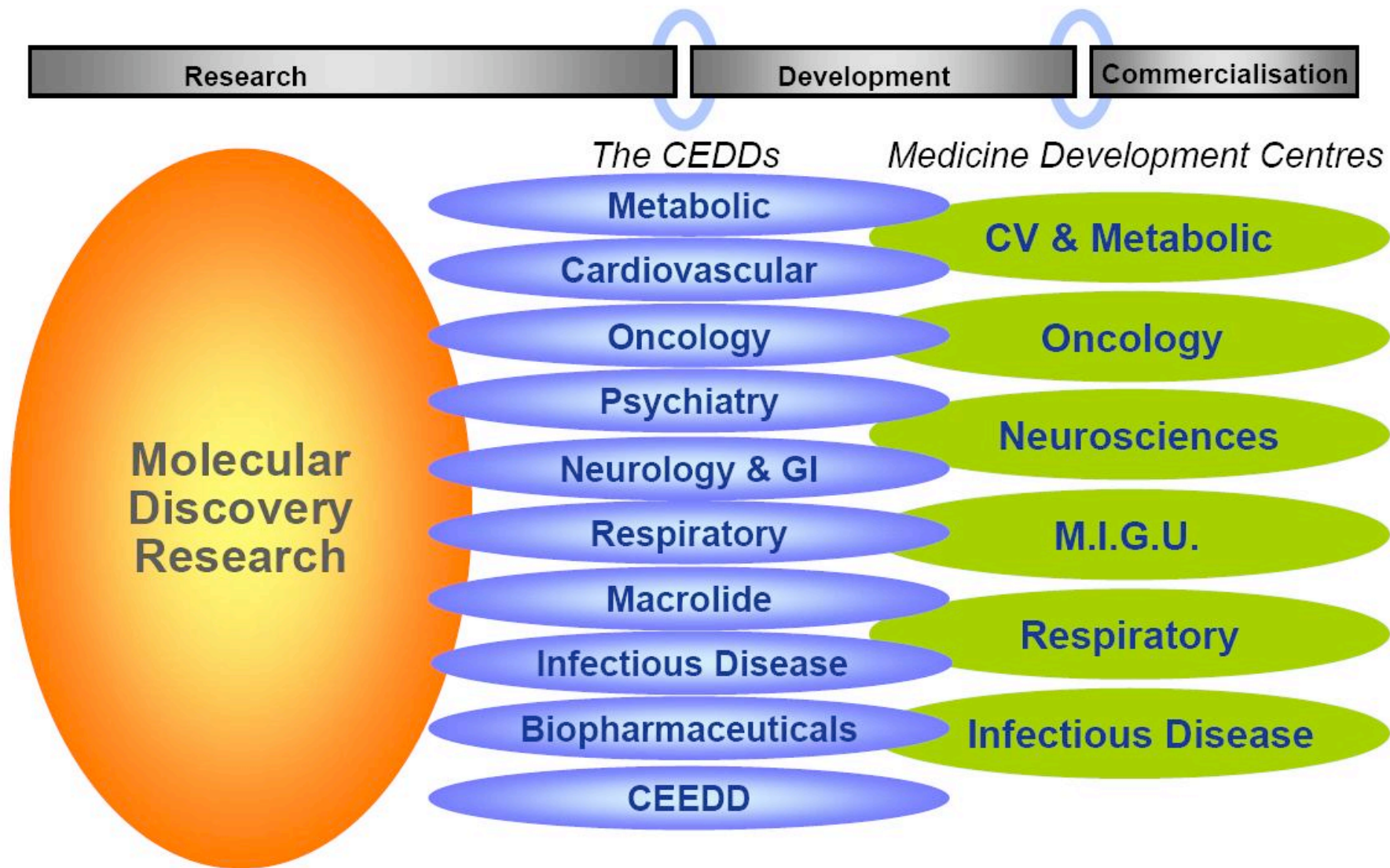
Bioinformatics at GSK: Application to Target Identification and Asset Progression

Chris Larminie

Presentation Summary

- QUICK overview of GSK R&D
- Integrating data
- Network / pathway analysis
- Neuroinformatics and issues pertinent to this field
- Informatics and Industry

R&D's Structure for Innovation & Flexibility



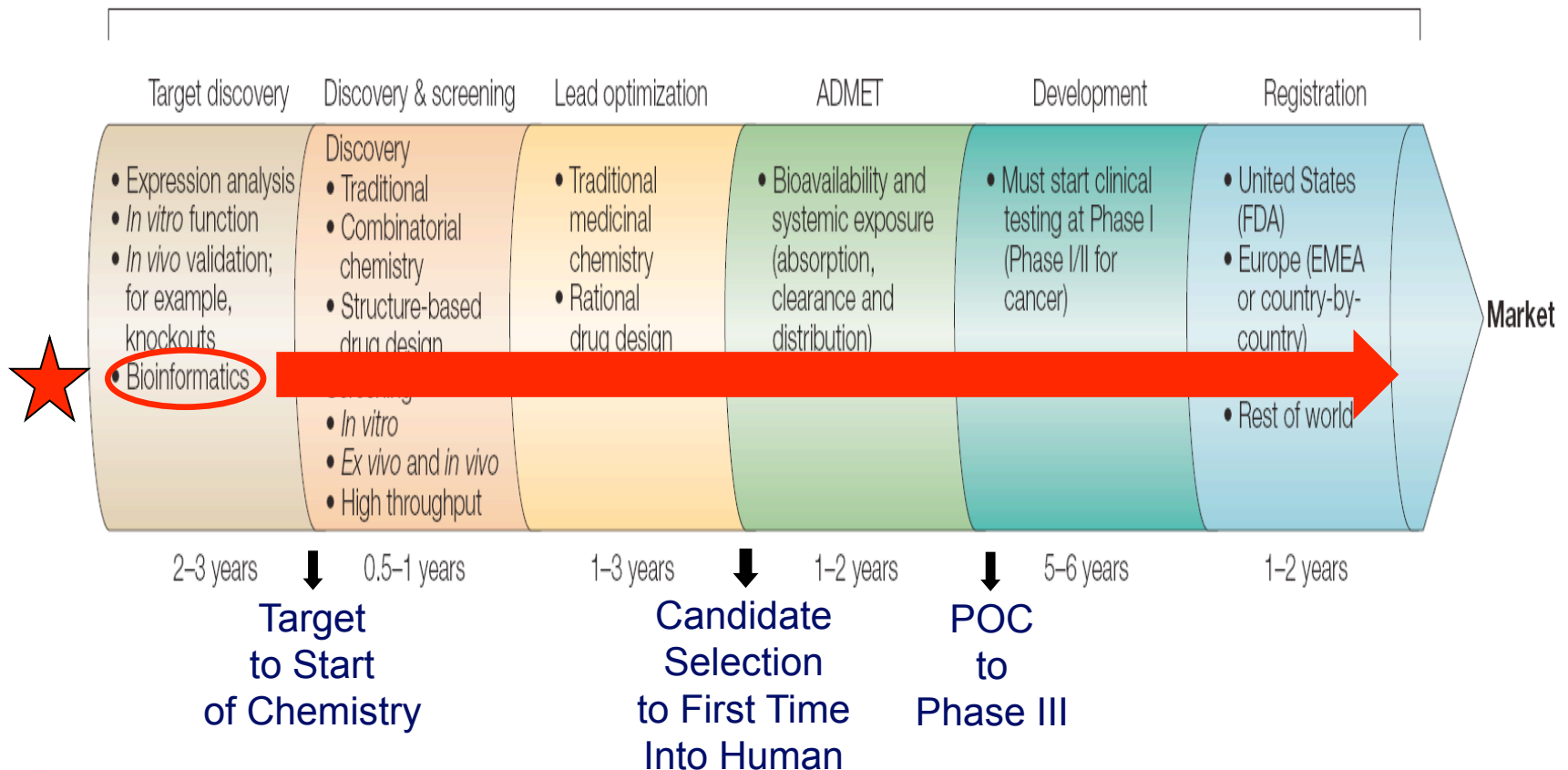
Drug Discovery Pipeline

Developing a new medicine costs over \$800 million

a

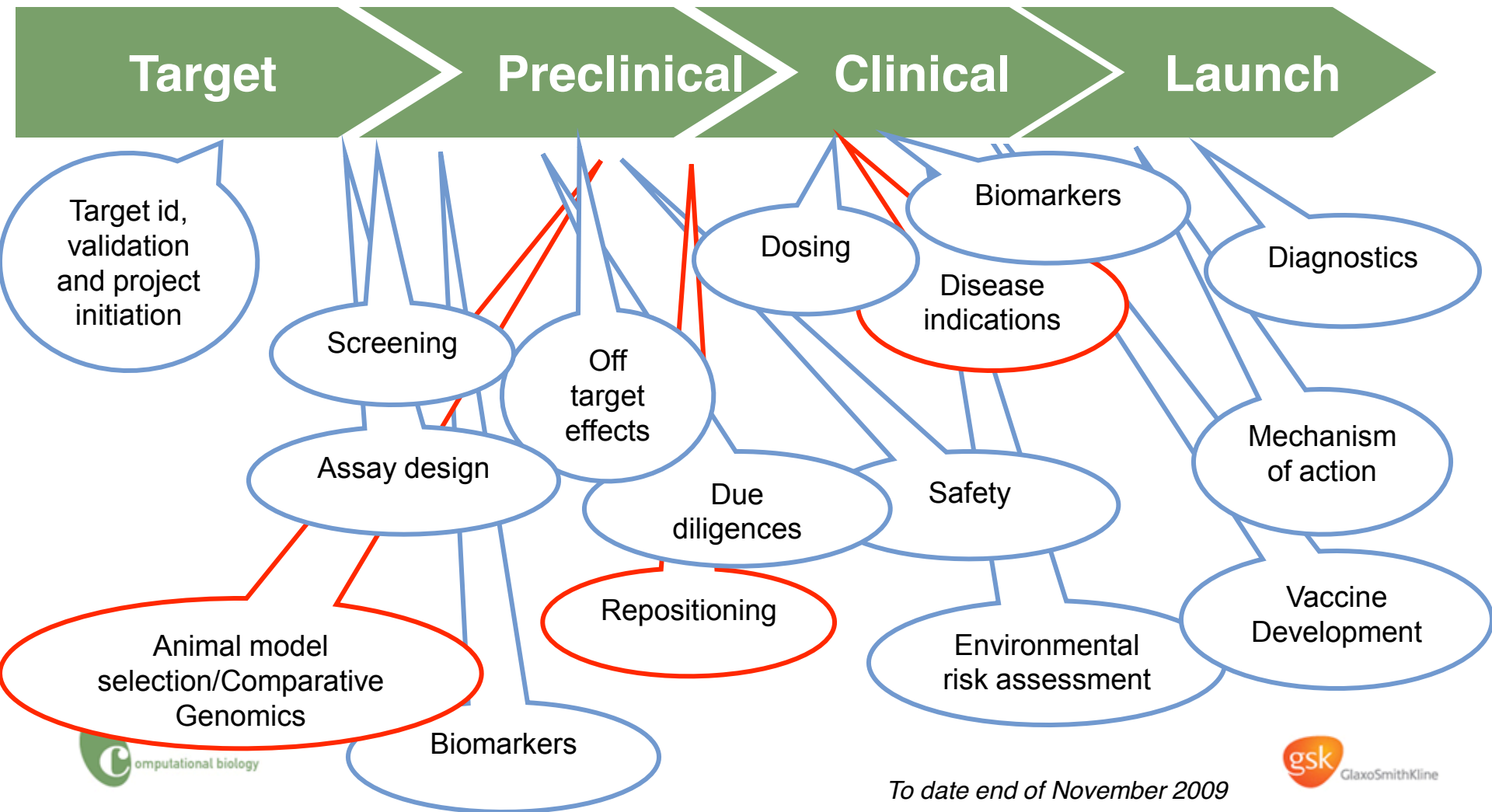
De novo drug discovery and development

- 10–17 year process
- <10% overall probability of success



CB (Computational Biology) and the Drug Discovery Pipeline

- CB is not only supporting early drug discovery: target identification, target validation etc.....



To date end of November 2009

SYSTEMS BIOLOGY: A Driver for Integration

- Progress in systems biology may be seen to rest on (*at least*) a three-way foundation:
 - **Pathways/Networks**: understanding the interactions that comprise biosystems
 - **Ontologies**: the effective representation of biological knowledge in all its richness
 - **Data Integration**: the ability to combine and analyse (*quality*) data from myriad sources

Data Integration: What data is there to integrate

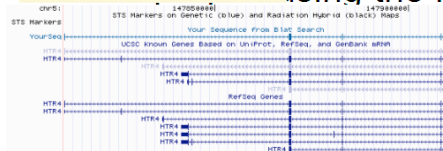
Gene Relevant Annotation

- Names & Aliases
- Putative function
- Representative sequence
 - Genetic context
 - Tracking variants
 - Polymorphisms / splice variants / mutations

Representative Sequence

- Do splice variants exist? Do they have differing functions? Regulated expression? Polymorphisms?

UCSC Genome Bioinformatics using the right cloned



Names & Aliases

Putative Function

FUNCTION
Receptor to interleukin-8, which is a powerful neutrophils chemotactic factor. Binding of IL-8 to the receptor causes activation of neutrophils. This response is mediated via a G-protein that activate a phosphatidylinositol-calcium second messenger system. This receptor binds to IL-8 with a high affinity and to MGSA (GRO) with a low affinity.

OMIM
Online Mendelian Inheritance in Man

GeneRef -- Gene Reference Into Function

1. CXCR-1 and CXCR-2 chemokine receptors of synovial fluid neutrophils may have diverse functions in the course of inflammatory arthritides
2. No association is found for chemokine (C-X-C motif) receptor 1 (CXCR1) single nucleotide polymorphisms in patients with increased susceptibility to bronchiectasis.
3. In CXCR1-expressing cells FAK phosphorylation was adhesion-independent. Overall, several aspects of CXCL8-induced FAK phosphorylation and migration are regulated in a receptor-specific manner.
4. Intrinsic abnormalities concerning IL-8 and its receptor system may be present in eutopic endometrium of women affected by adenomyosis. IL-8 receptors may be involved in pathogenesis and/or pathophysiology of adenomyosis.
5. Gene polymorphisms active in the EGFR pathway may be associated with the sensitivity of colorectal cancer patients to platinum-based chemotherapy.

Data Integration:

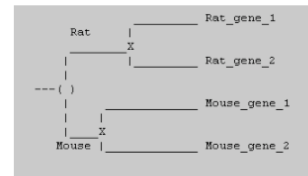
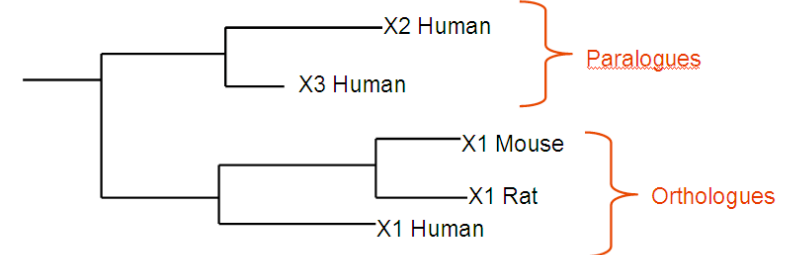
What data is there to integrate?

- Gene Relevant Annotation
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Orthologues

- Model organisms – allow study of the target in an animal to gain useful biological or genetic information relevant to the human gene
 - ◆ Function / disease relevance / toxicity / DMPK
- Best defined by phylogeny and/or synteny, but reciprocal blast often used
- Absence of clear orthologue may indicate organism is not a suitable model

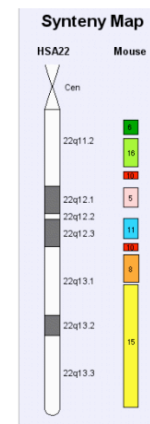
Phylogeny



• A sequence in another species that shares a direct common ancestor with the current sequence. Orthologues are typically the most similar genes between 2 species. For some time after a speciation event this relationship is easily inferred from homology, as the two genes will differ only a little. As evolutionary time passes, the orthology relationship becomes less obvious and eventually becomes ill-defined because of duplication and divergence

• Parologue - A sequence in the same species that shares a direct common ancestor with the query sequence

Synten



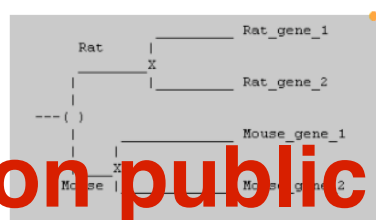
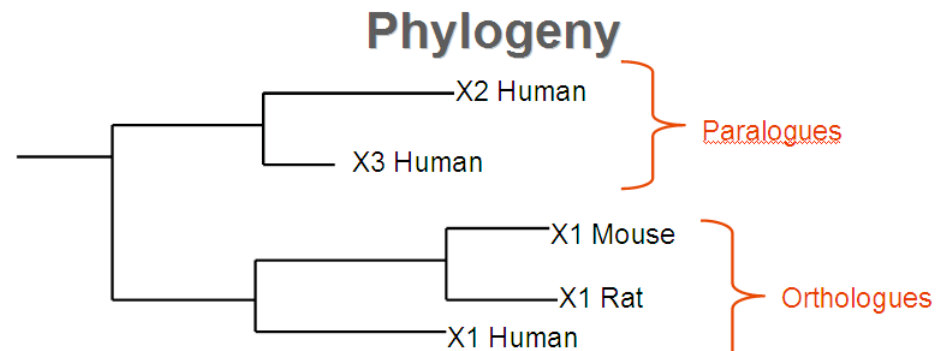
Synten between species means not only that orthologous genes are present but that they are present in the same order on the genome, thus indicating common ancestry

90.2% of the human genome and 93.3% of the mouse genome lie in conserved syntenic segments

It is possible to dismiss homology as arising from similar function, but it is not possible to dismiss synten this way

Data Integration: What data is there to it

- Gene Relevant Annotation
 - Names & Aliases
 - Putative function
 - Representative sequence
 - Genetic context



A sequence in another species that shares a direct common ancestor with the current sequence. Orthologues are typically the most similar genes between 2 species. For some time after a speciation event this relationship is easily inferred from homology, as the two genes will differ only a little. As evolutionary time passes, the orthology relationship becomes less obvious and eventually become un-definable because of duplication and divergence

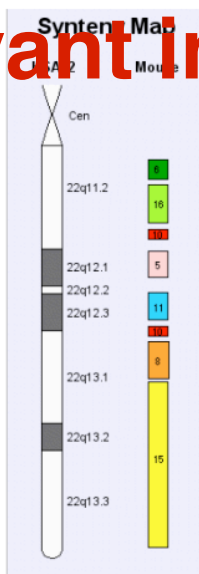
We are reliant on public domain sources but enhance this with GSK relevant information and standards

Synteny

Synteny between species means not only that orthologous genes are present but that they are present in the same order on the genome, thus indicating common ancestry

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A sequence in the same species that shares a common ancestor with the query sequence

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L-8 and its receptor system may be present in eutopic adenomyosis. IL-8 receptors may be involved in gy of adenomyosis.
GFR pathway may be associated with the sensitivity of um-based chemotherapy.

- Ortholog
- Mc in ge ge
- UCS
- STS Markers
- YourSeq
- HTK
- HTK
- Be bu
- At org

Data Integration:

What other data is there to integrate

- Literature
 - key stimulant of interest
- Expression
 - is the gene expressed in tissues relevant to the disease?
 - Genome scale: Microarray technology
 - Focused follow up: TaqMan, ISH, IHC
- Phenotypic data:
 - Genetics
 - ◆ do people with *flaws* in this gene get sick more often?
 - ◆ Polymorphisms (SNPS) – genetic association, linkage analysis
 - Mouse KO/Transgenics
 - ◆ Identifying pathways from genetics
 - RNAi *in-vitro/in-vivo*
- Protein Structure analysis/modelling

Diseases associated with gene and/or query

The following results are from Diseases Medical Subject Heading terms associated with Human primarily 5H4 in Normal mode. Only terms with P-values above 0.05 are listed. If you find the list of MeSH is too large, please run the search with 'Specific' or 'Extremely Specific' Mode. Alternatively, the P-Value threshold can be increased. On the other hand, if too few MeSH are listed, please run the search in a more sensitive Mode, lower the P-Value threshold, or expand the MeSH category. Please click the 'Titles' in the table to retrieve the articles suggesting the association.

Get more results by including more subject headings per article into the analysis especially if you started with significance none

Google the gene and its aliases (full-text 1, WWW 1, full-text 2, WWW 2)

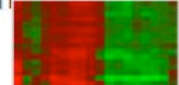
Genes with many aliases have to be split up into multiple queries because Google places a limit of 10 words on every search.

of PubMed articles retrieved that contain gene 5H4 with all its aliases = 719

No.	MeSH	LocusLink	Sequence Description	PubMed citations	Gene	Observed Medline count	Expected Medline count	P-Value
1	Polycystic Disease		E. coli		LDLR			

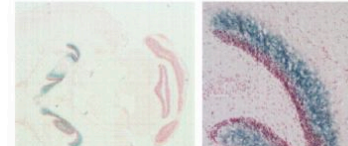
Expression - n

- Microarray -



Expression - protein

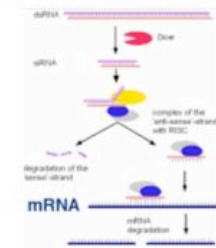
- Immunohistochemistry (IHC)



- Uses antibodies to

Expression - KOs

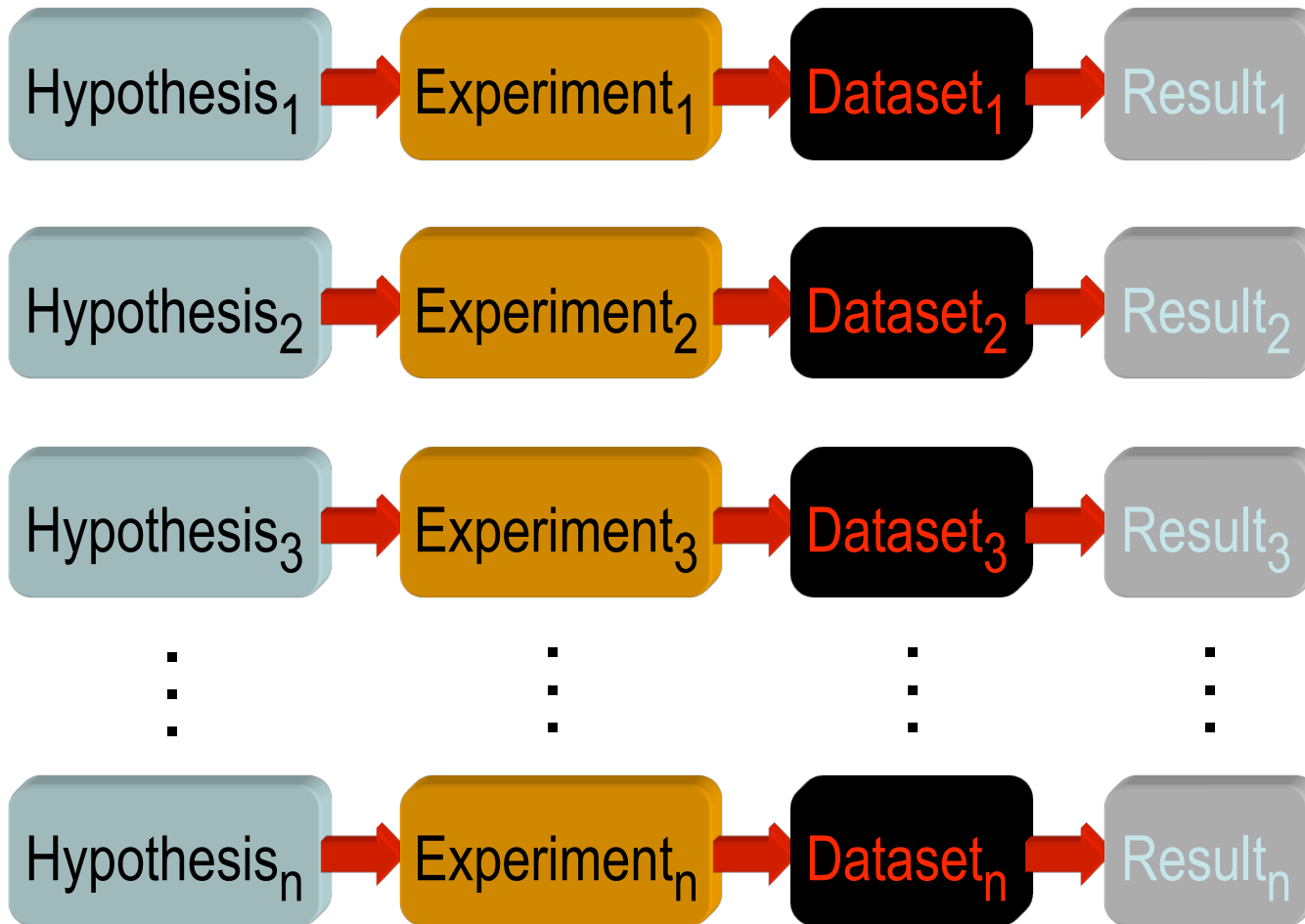
- RNAi
- KO mice



Atherosclerotic lesions in the aorta of an LDLR knockout mouse

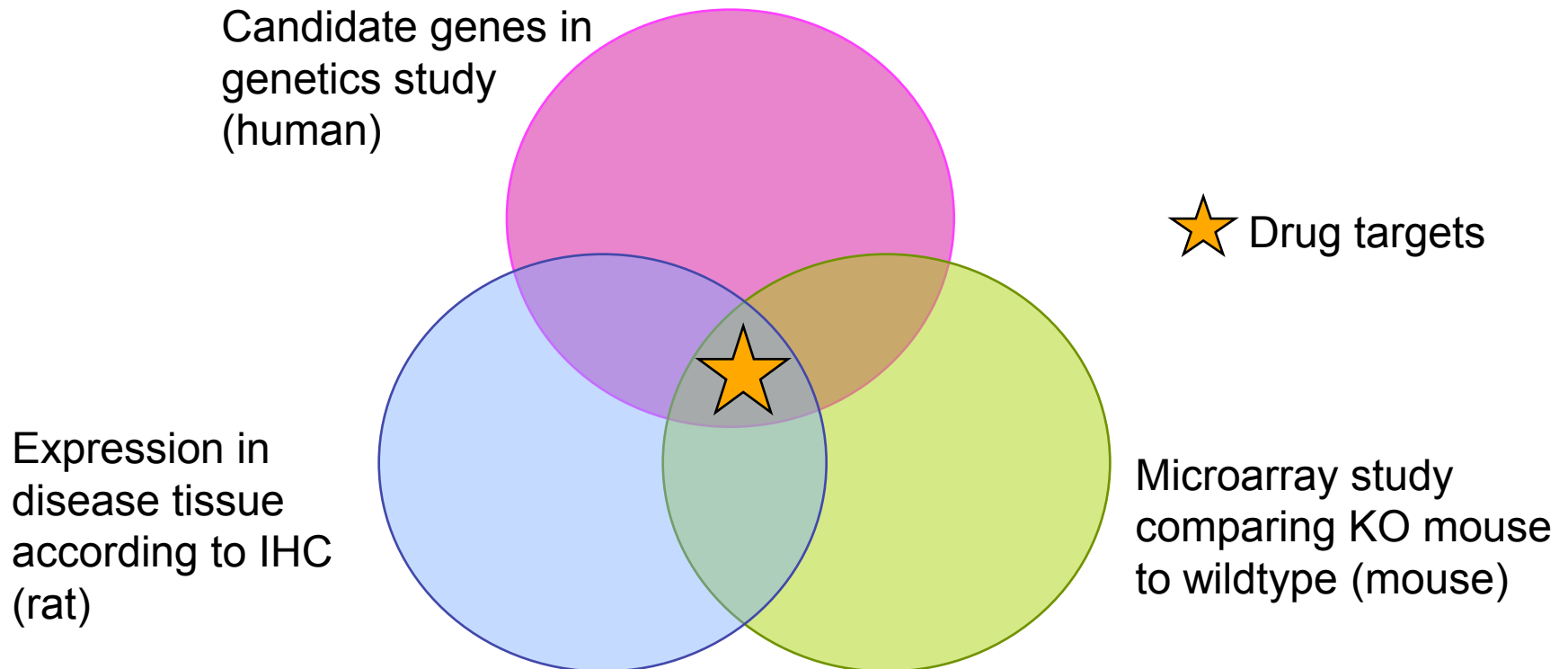


Hypothesis-Driven Research

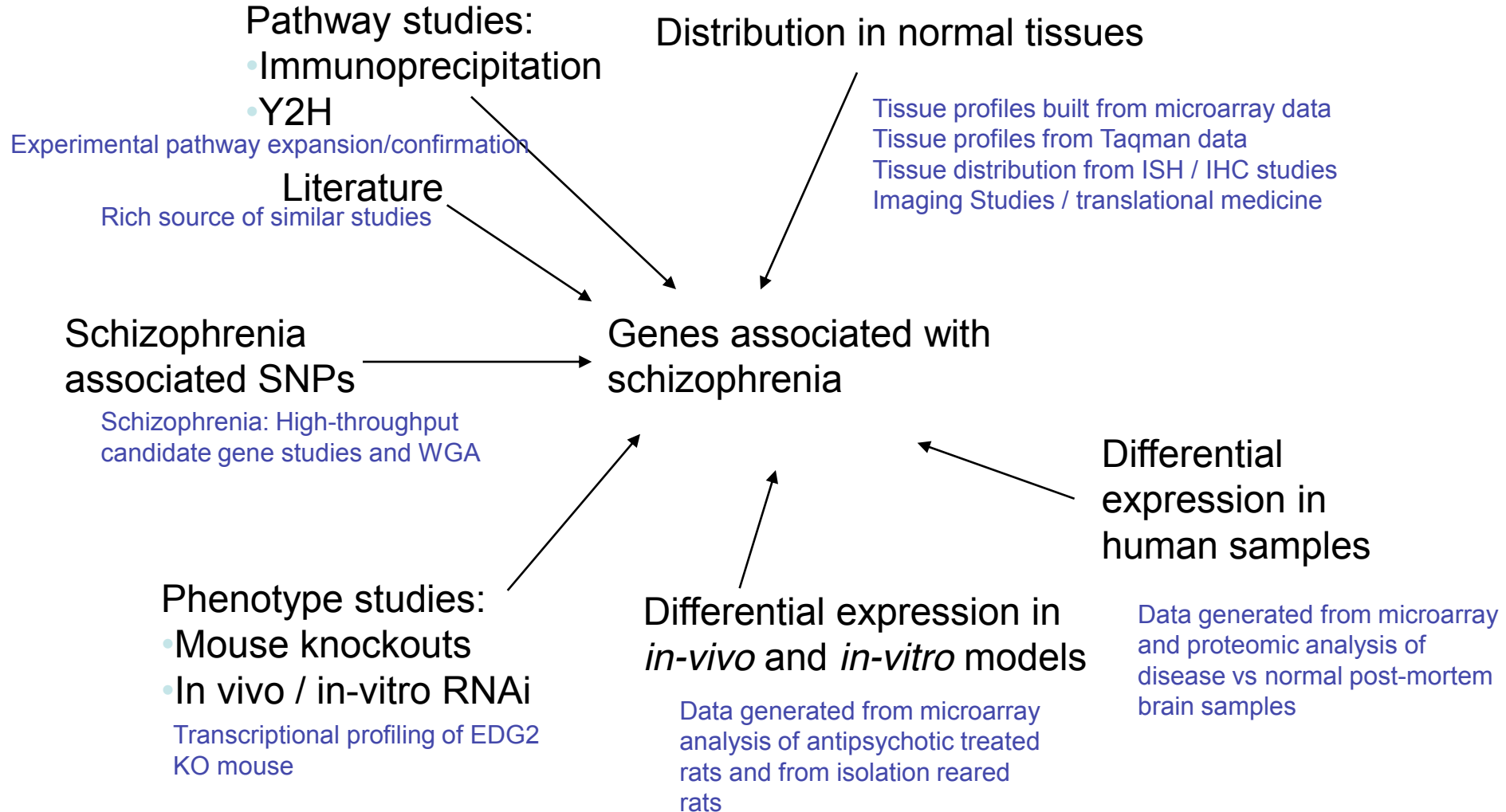


Combining validation data for finding targets – integrating validation data

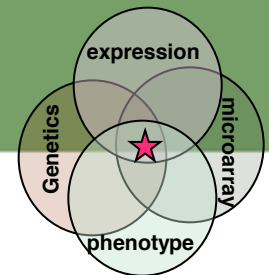
- Data from different sources can be combined to be more powerful than one source alone (reduced risk of false positives)
- Permits prioritisation of targets to progress based on genetic, genomic and tractability data
- Represents a systematic and stringent approach



An example: Schizophrenia



Disease view (PSTUD)



Different lines of evidence to find a drug target for a specific disease:

Gene	Candidate study	Associated loci	Linked to terms in literature	Mechanism	Comments	Expression uarray	Gene expression	Expression - IHC	Pathways - SYZYGY	Expression - IHC	Expression - Vendor provided IHC	Diff expression - VP	Diff expression - IH	Diff expression - Lit	Mouse Transgenics	Expression - RT-PCR	Proteomics
Gene X TIG1434 Portfolio • Status Lead to Candidate Selection • CEDD: PSYC, NG • Primary Disease: Compulsive Disorder	Yes Human AD/HD level 6 phenotype independent	Yes Human AD/HD level 6 phenotype independent	Yes Human AD/HD level 6 phenotype independent	Yes Target AD/HD level 6 phenotype independent	Yes Human AD/HD level 6 phenotype independent	Yes Human AD/HD level 6 phenotype independent	Yes Human AD/HD level 6 phenotype independent	Yes Human AD/HD level 6 phenotype independent	Yes Human AD/HD level 6 phenotype independent	Yes Human AD/HD level 6 phenotype independent	Yes Human AD/HD level 6 phenotype independent	Yes Human AD/HD level 6 phenotype independent	Yes Human AD/HD level 6 phenotype independent	Yes Human AD/HD level 6 phenotype independent	Yes Human AD/HD level 6 phenotype independent	Yes Human AD/HD level 6 phenotype independent	Yes Human AD/HD level 6 phenotype independent

This Approach permits merging of general information with disease-specific/relevant information at gene level

What is required

- Standard sample management/handling
- Standard data generation methods
- Standard QC analysis methods
- Standard significance/reporting cut-offs
- Agreed common standard for cross-reference
 - Gene?
 - Protein?
 - Genomic position?
- Pragmatism!
 - Balance standardisation with the need for the bespoke, avoid needless digression from established protocols
 - Some detail is inevitably lost through standardisation, determine cost-benefit and tactical versus strategic
 - If reasonable, report results from non-standard analyses and annotate as such
- Where one size does not fit all...

Ontologies

- Build standard vocabularies to accommodate these different data
- Effective and standardised representation of biological knowledge to permit mining and

t h e o b o f o u n d r y

The Open Biomedical Ontologies (OBO) Foundry is a collaborative experiment: to produce well-structured vocabularies for shared use across different biological and medical domains. The OBO Foundry introduces a new paradigm for biomedical ontology development by the establishment of gold standard reference ontologies for individual domains of inquiry.

Those involved comprise a group of biological researchers and ontology developers who agree in advance to the adoption of a growing set of principles specifying best practices in ontology development. These principles are designed to foster interoperability of ontologies within the broader OBO framework, and also to ensure a gradual improvement of quality and formal rigor in ontologies, in ways designed to meet the increasing needs of data and information integration in the biomedical domain.

By joining the OBO Foundry, the authors of an ontology commit to its maintenance in light of scientific advance, and to soliciting community feedback for its improvement. They also give an assurance that they will work with other Foundry members to ensure that, for any particular domain, there is community convergence on a single reference ontology. Application ontologies developed for specific purposes can then be referred back to this common reference, which will be updated in light of scientific advance. In this way application ontologies, too, for example the application ontologies developed for purposes of managing clinical trial data, can take advantage of the Foundry methodology.

This site contains ontologies and points to some other efforts within the community. Ideally we see a range of ontologies being designed for biomedical domains. Some of these will be generic and apply across all organisms and others will be more restricted in scope, for example to specific taxonomic groups.

[View the OBO Foundry ontologies in table form](#)

[Browse the index of the OBO Foundry ontologies](#)

generated in one area to another

- Utilise current data/knowledge more effectively
- Improve interpretation of data generated through new initiatives cited above

Ontologies are powerful tools for connecting data

MGI 4.0: Mammalian Phenotype Ontology Annotations Query Results -- Summary - Microsoft Internet Explorer

Address: <http://www.informatics.jax.org/javawi2/service/WZFetch?page=mpAnnotSummary&id=MP:0008658>

mammalian Phenotype Ontology Annotations
Query Results -- Summary

13 genotypes with 13 annotations displayed

Searched Term: decreased interleukin-1 beta secretion

Allelic Composition (Genetic Background)	Annotated Term	Reference
Casp1^{tm1Flv}/Casp1^{tm1Flv} (involves: 129S2/SvPas * C57BL/6)		
Casp1^{tm1Seah}/Casp1⁺ (involves: 129S2/SvPas * C57BL/6)		
Casp1^{tm1Seah}/Casp1^{tm1Seah} (involves: 129S2/SvPas * C57BL/6)		
Casp1^{tm1Seah}/Casp1^{tm1Seah} (NOD.129S2(B6)-Casp1 ^{tm1Seah} /Lt)		
Myd88^{tm1Axi}/Myd88^{tm1Axi} (involves: 129P2/OlaHsd * C57BL/6)		
Nlrp3^{tm1Tas}/Nlrp3^{tm1Tas} (C57BL/6-Nlrp3 ^{tm1Tas})		
P2ry7^{tm1Gsb}/P2ry7^{tm1Gsb} (either: (involves: 129P2/OlaHsd * C57BL/6) or (involves: 129P2/OlaHsd * C57BL/6) or (involves: 129P2/OlaHsd * C57BL/6))		
Pycard^{tm1Flv}/Pycard^{tm1Flv} (involves: 129S5/SvEvBrd * C57BL/6)		
Pycard^{tm1Nnz}/Pycard^{tm1Nnz} (involves: 129S5/SvEvBrd * C57BL/6)		
Pycard^{tm1Tne}/Pycard^{tm1Tne} (involves: 129S4/SvJae * C57BL/6)		
Pycard^{tm1Vmd}/Pycard^{tm1Vmd} (involves: 129S1/Sv * 129X1/Sv) * C57BL/6		
Pycard^{tm1Vmd}/Pycard^{tm1Vmd} (involves: 129S1/Sv * 129X1/Sv) * C57BL/6		
Tlr2^{tm1Kir}/Tlr2^{tm1Kir} (B6.129-Tlr2 ^{tm1Kir})		

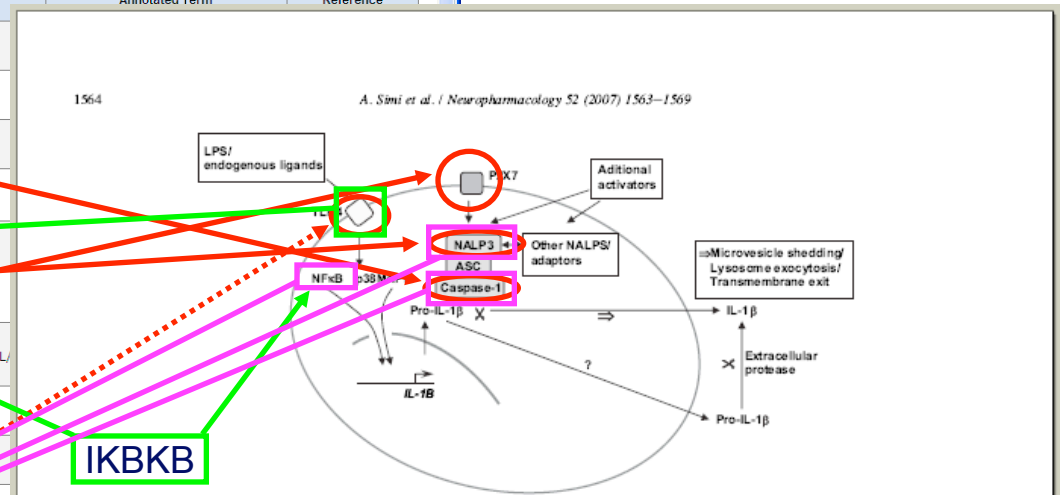


Fig. 1. A schematic diagram summarising the currently known mechanisms involved in the generation and release of bioactive IL-1 β .

factor-1 (HIF-1) can regulate IL-1 β expression in cultured human and mouse astrocytes (Zhang et al., 2006). Downstream of these pathways, transcriptional activation of the IL-1 β gene by NF- κ B, AP-1, CREB, NF-IL-6 and SP-1 transcription factors can also occur (for review see Watkins et al., 1999). Additional mechanisms of control may include mRNA stabilisation through an LPS-responsive 3'-UTR element on the IL-1 β gene (Kern et al., 1997) and a mechanism which may involve the p38 MAPK pathway and its downstream target MAPKAP-K2 (MK2) (Young et al., 1993; Kotlyarov et al., 1999).

Far less information is available on the mechanisms of

Acute necrosis and disruption of the blood-brain-barrier (BBB) during brain injury will result in the release of factors that had previously remained intracellular or peripheral, and thus not present in a healthy brain. Such factors will become present in the interstitial fluid, subject to microglial surveillance and may promote microglial activation. Notably many of these factors such as gangliosides (Jou et al., 2006), small heat-shock proteins (Kakimura et al., 2002) and the extracellular A of fibronectin (Okamura et al., 2001) may be endogenous ligands for TLR4. However, a caveat to studies using recombinant ligands is the possible effects of low levels of endotoxin contamination

RED: Genes with an IL-1 β secretion KO phenotype that relate to the inflammasome

GREEN: Genes with an IL-1 β secretion KO phenotype that link directly to components of inflammasome

Pathway/Network Biology and Drug Discovery

- Pathway identification, extension, inference, modelling *can* help for:
 - Novel targets and biomarkers identification
 - Disease understanding
 - Mechanisms of action (MOA) understanding
 - Potential safety concerns
 - Combination therapies
 - Alternative indications
- Permits collapse of pertinent data around a series of genes linked by a common biological context
- Permits identification of common, known pathways represented in multiple platform datasets
 - Pathways are often more stably represented than their constituent genes
- Permits identification of “novel” disease mechanisms from datasets
- Essential for data driven polypharmacological approaches

Pathway/Network Analysis

- Do we have sufficient data within Neurosciences to power pathway/network based analysis approaches?
 - Advent of platform based approaches to studying neuroscience has dramatically increased data space over recent years
 - Are these data of sufficient quality?
 - Reproducibility/variability
 - Can we gain sufficient access to it?
 - Data storage and structure
 - Data silos/ Data access
 - Data reporting, sharing and distribution
 - Data annotation: can we find it?
 - Semantics of data
- We need to generate more data and improve reporting, description and storage of these data to maximise its benefit
 - Better industry, academic partnering
 - Support ontologies
 - Enforce journal and grant awarding body rules
 - PISTOIA

What data is particularly relevant to Neuroscience?

- **The 1990s: “Decade of the Brain”**
 - Recognition of social and economic burden of brain disease
 - Increasing confidence amongst research community that brain disease is now a tractable problem
- **Are we only now realising the benefits of this?**
 - Broad Institute
 - Allen Brain Atlas
 - Genetic studies
 - Genomic studies
 - (Jackson Lab KO ontologies)
 - Neuroimaging and other translational medicine approaches
 - Better integration between these data / sites

Pathway/Network Informatics

- Pathway Informatics (*and platform data*) require tools to analyze **gene sets** rather than individual genes, in the context of very large databases of **known relationships and interactions**:
 - **Relationship** data compiled into gene ‘buckets’ from multiple sources in multiple ‘universes’
 - *involved in the same pathway, part of the same network, coexpressed, genetically linked, phylogenetically related, ...*
 - *In excess of 1m currently available*
 - **Interaction** data from different sources *binds, regulates, phosphorylates, degrades*
 - *Gene/protein/metabolite/compound*
- And determine if those observations are **significant**

Generating networks

Mechanistic hypothesis

Relevance to disease

Add to database of annotation buckets

In-house interaction data

Literature interaction database

Generate interaction network

Appropriate mechanism based platform studies
In-vivo/invitro

Co-expression / correlation filters
(genelogic / Allen Brain Atlas)

Annotate ← Refine interaction network

Disease relevant/specific data
Whole Genome Scans
Disease/control post-mortem microarray/proteomic studies

Annotate ← Interrogate interaction network

Buckets generated through automated methods far outweigh those derived from manual processes outline above. Source data and assumptions affect quality

Literature

- Our molecular mechanistic understanding of CNS is improving
 - genes” returned (B4):
 - Query: “central nervous system[mh]” OR “central nervous system diseases”[mh]
 - 1997-2006: 1271
 - 1987-1996: 902
 - 1977-1986: 96
 - Gene Ontology annotation reflects this
 - We can improve on this by “hijacking” knowledge of molecular mechanisms and pathways elucidated from other tissues/diseases
 - BUT...

Literature

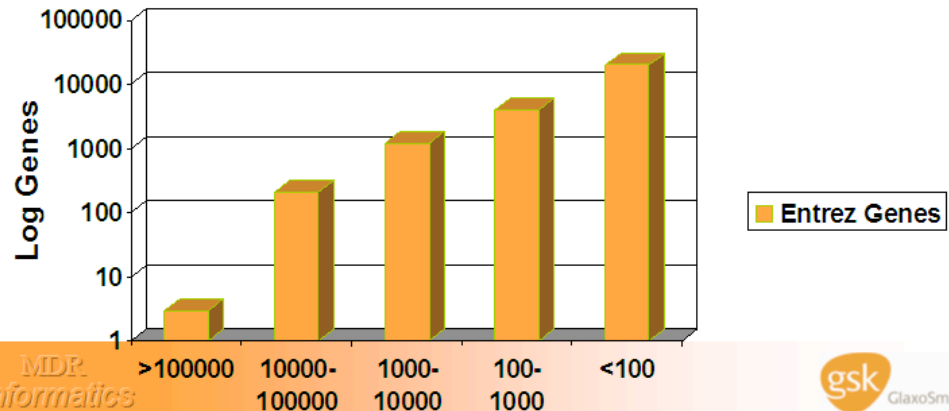
- Using literature knowledge to identify CNS disease mechanisms will bias interpretation of your dataset

- Query: "central nervous system"
- 1997-2006: 12
- 1987-1996: 90
- 1977-1986: 96

- Gene Ontology
- We can improve knowledge of n pathways elucidate tissues/disease
- BUT...

How much do we know from literature? (as of Nov. 1st)

- Take all Human Entrez genes (~25K) along with their Mouse and Rat orthologues
- Enumerate all synonyms for each, remove any synonym that may not only be a gene name (English words, Medical terms)
- Find all PubMed titles and abstracts with mention of any synonym
- Top scorer: **TNF** with 226,606 publications



Building network from literature

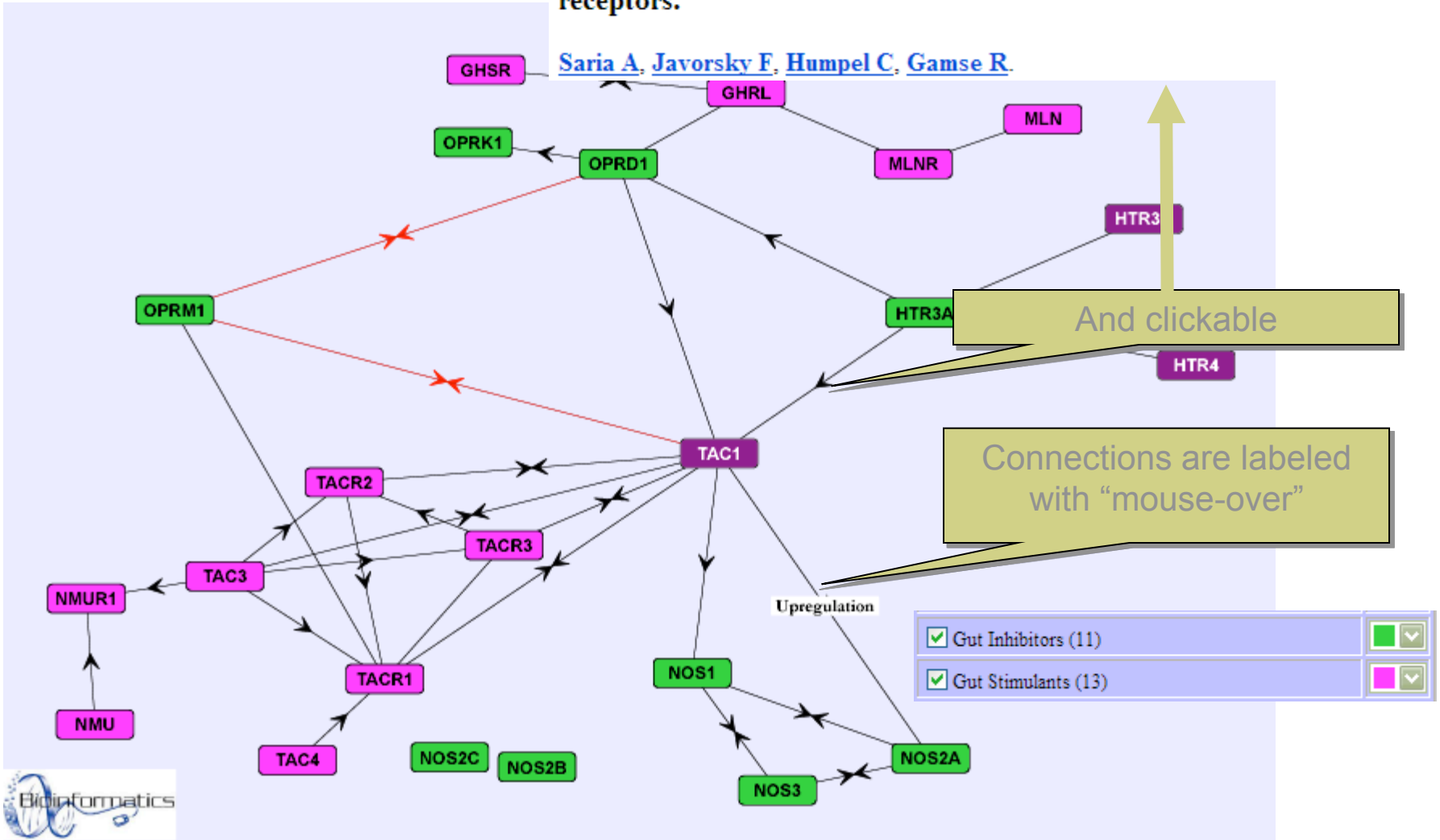
Ann N Y Acad Sci. 1991;632:464-5.

Related Articles,

Endogenous 5-hydroxytryptamine modulates the release of tachykinins and calcitonin gene-related peptide from the rat spinal cord via 5-HT3 receptors.

Saria A, Javorsky E, Humpel C, Gamse R.

Connections between groups



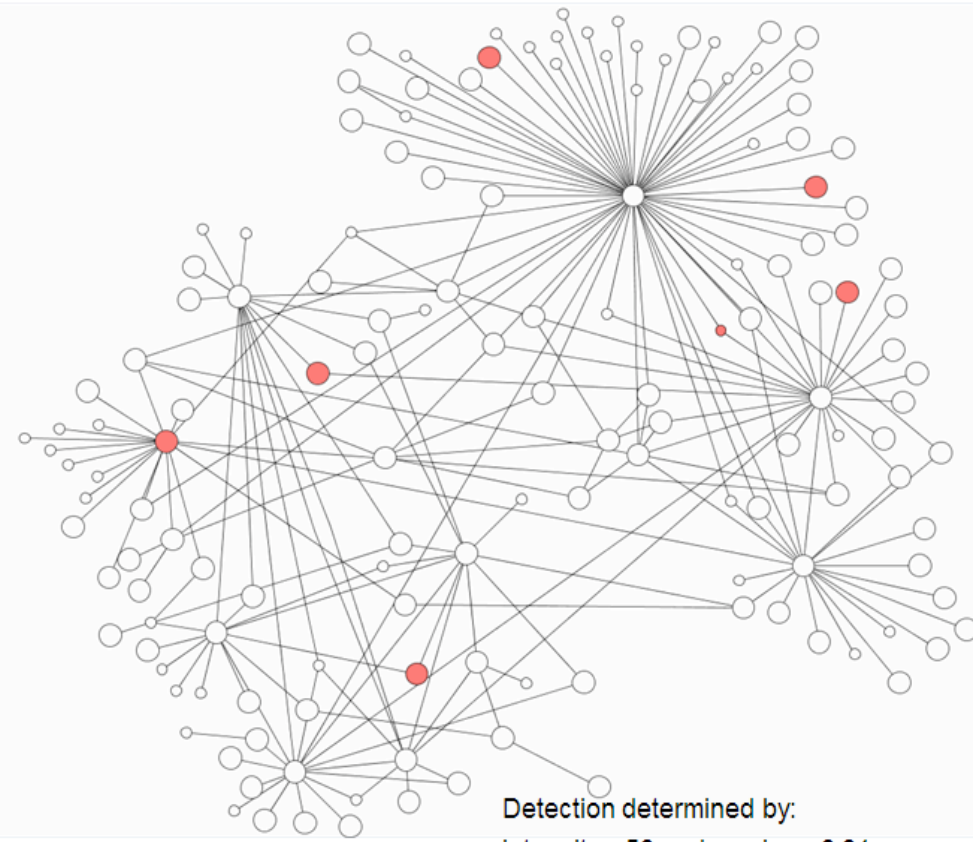
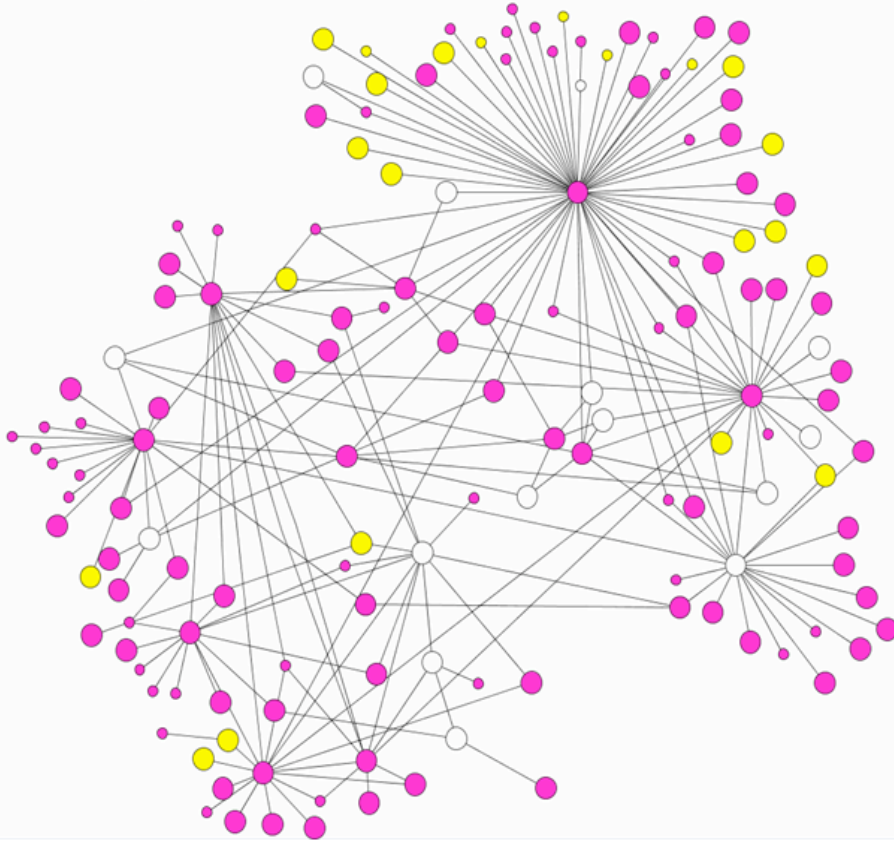
Identification of Pathways from Network

- Overlay specific cell type data to help with comparison of model systems/ cell lines

Monocyte derived Macrophages

Resting:

LPS:





Detection determined by:

Intensity >50 and p value <0.01

Change in regulation determined by:

P value < 0.05 , >1.5 Fold change

 Detected


 Not Detected


 Up-Regulated

Dose Response Effect on Network

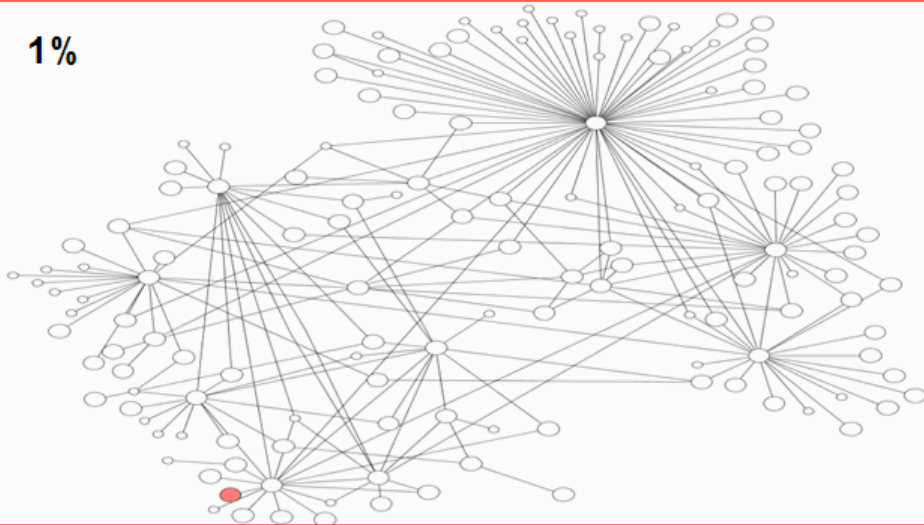
Monocyte derived Macrophages
experiment

- 3 different % of cigarette stimulation
- Changes tracked from resting
 - Pvalue < 0.05, >1.5 Fold change

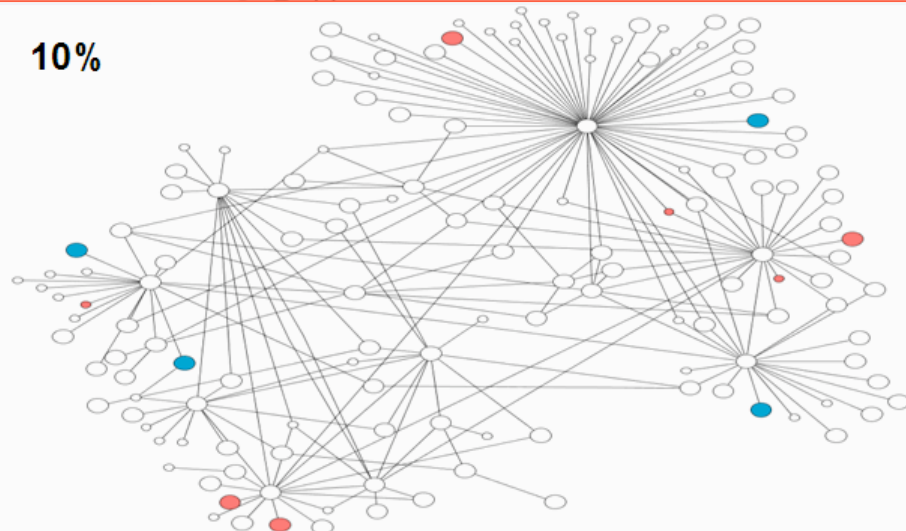
 Up regulated genes

 Down regulated genes

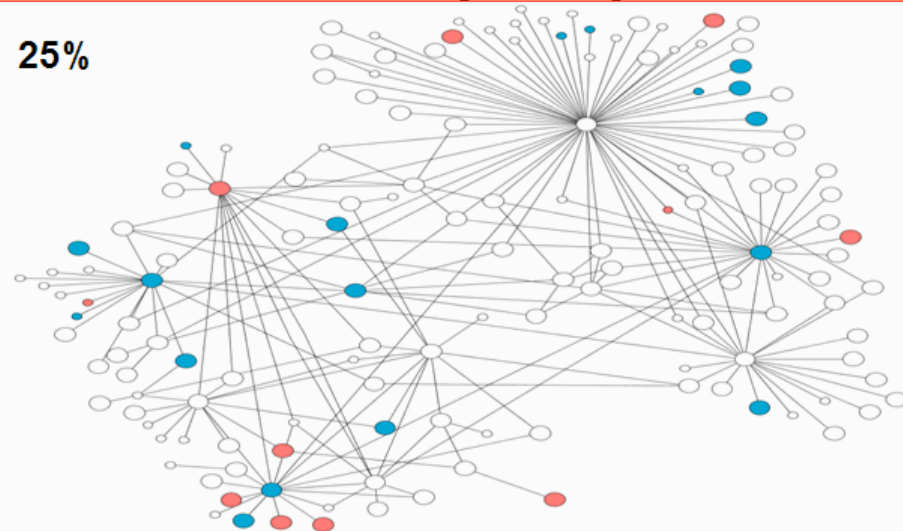
1%



10%



25%

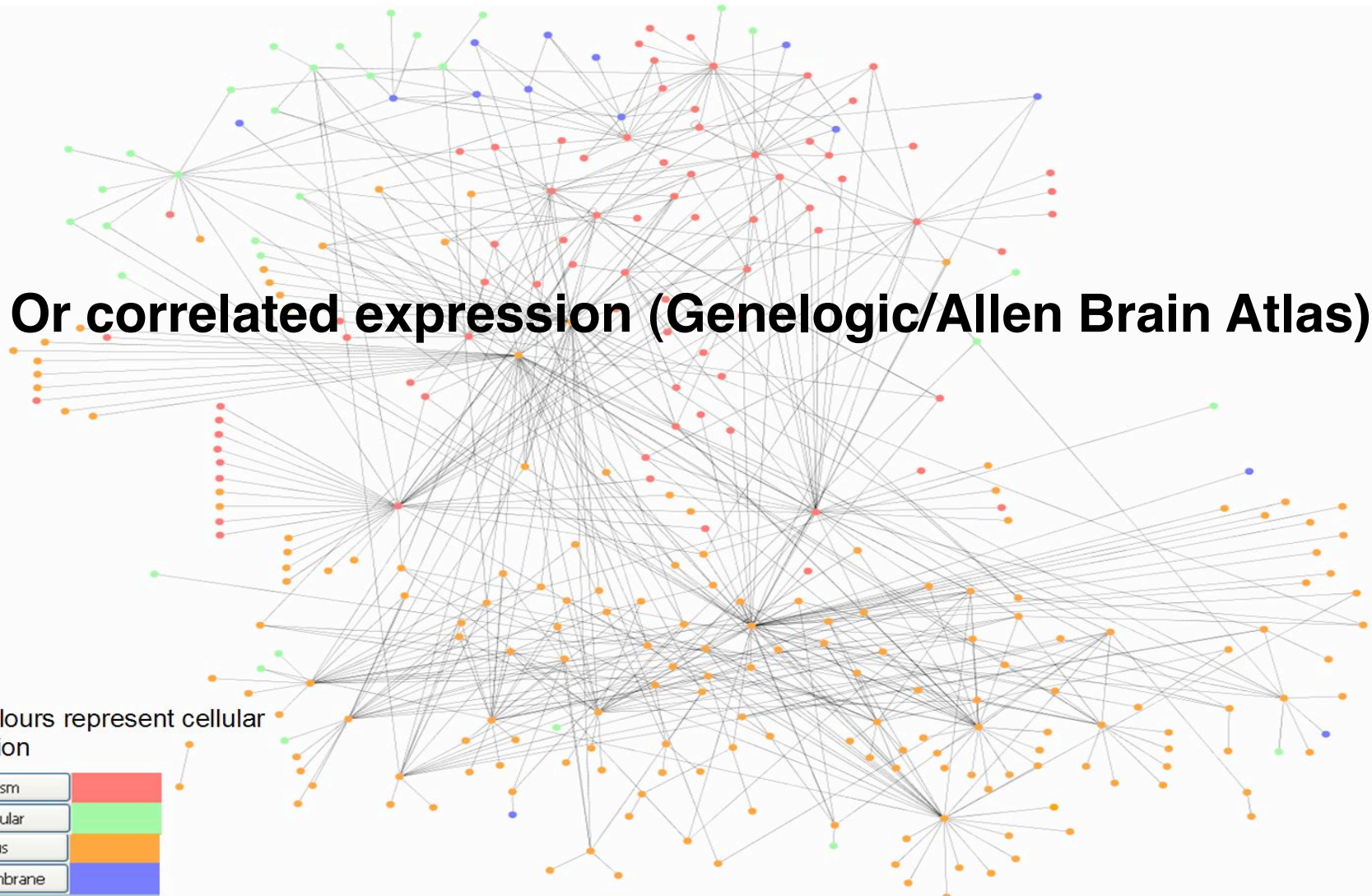


Compartmentalisation can help refine expanded Network

Or correlated expression (Genelogic/Allen Brain Atlas)

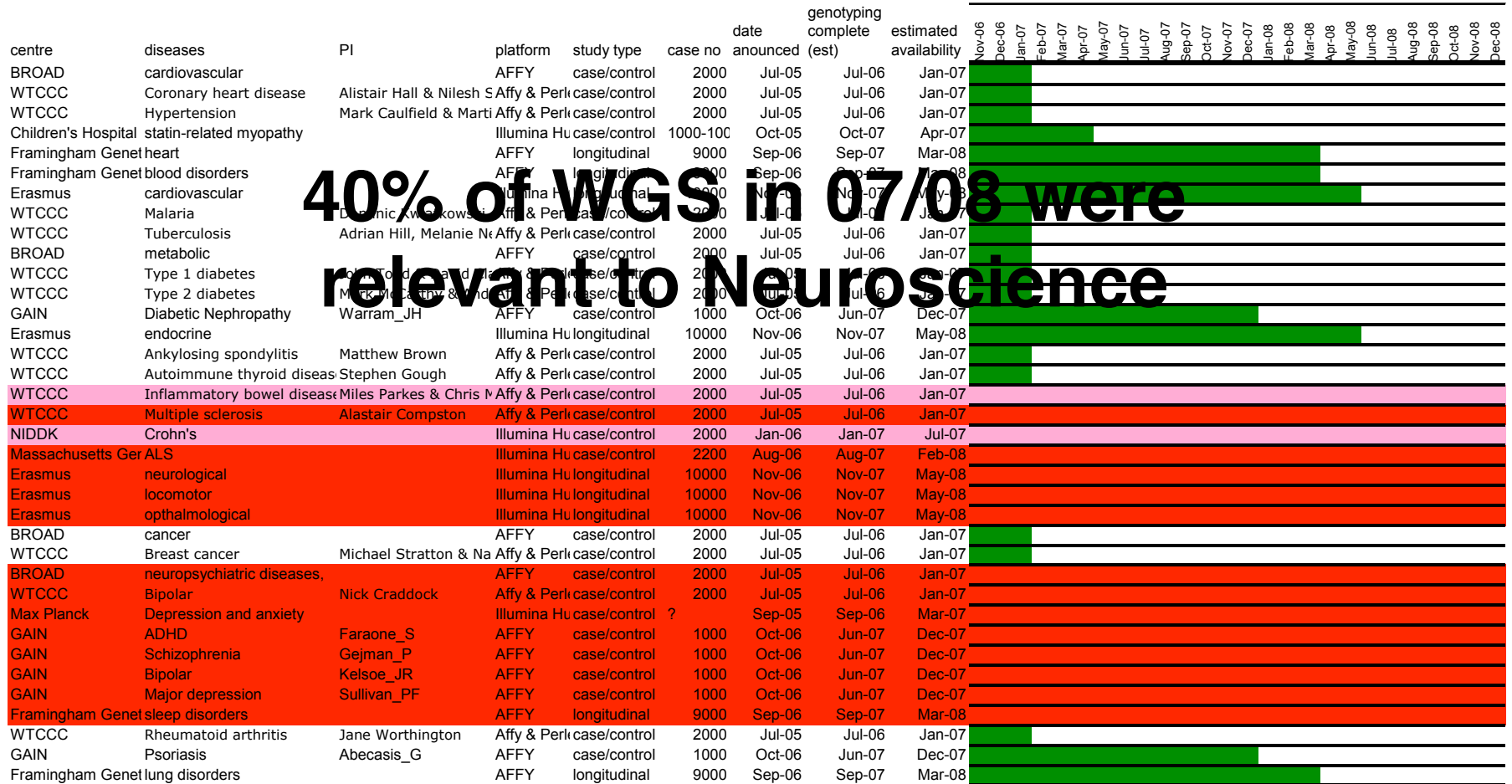
Node colours represent cellular localisation

Cytoplasm	Red
Extracellular	Green
Nucleus	Orange
Plasma Membrane	Blue



Whole Genome Scans

40% of WGS in 07/08 were relevant to Neuroscience



Genetic Analysis

Clinical data acquisition

Sample Management

Sample Tracking

WGS expt

Analysis

Result

Interpretation

Statistical Methods
Development

HapMap:
Linkage disequilibrium

SNP function prediction
And Data integration

Associated SNPs

Associated Loci with
SNP functional effect
predictions and
candidate genes

Associated Gene
Hypothesis

Genetic Analysis

Clinical data acquisition

Sample Management

Sample Tracking

WGS expt

AND THEN THERE IS PATHWAY ANALYSIS: GENETIC ANALYSIS OF COMPLEX DISEASE MUST FACTOR IN MULTIGENE EFFECTS

And Data integration

Linkage disequilibrium

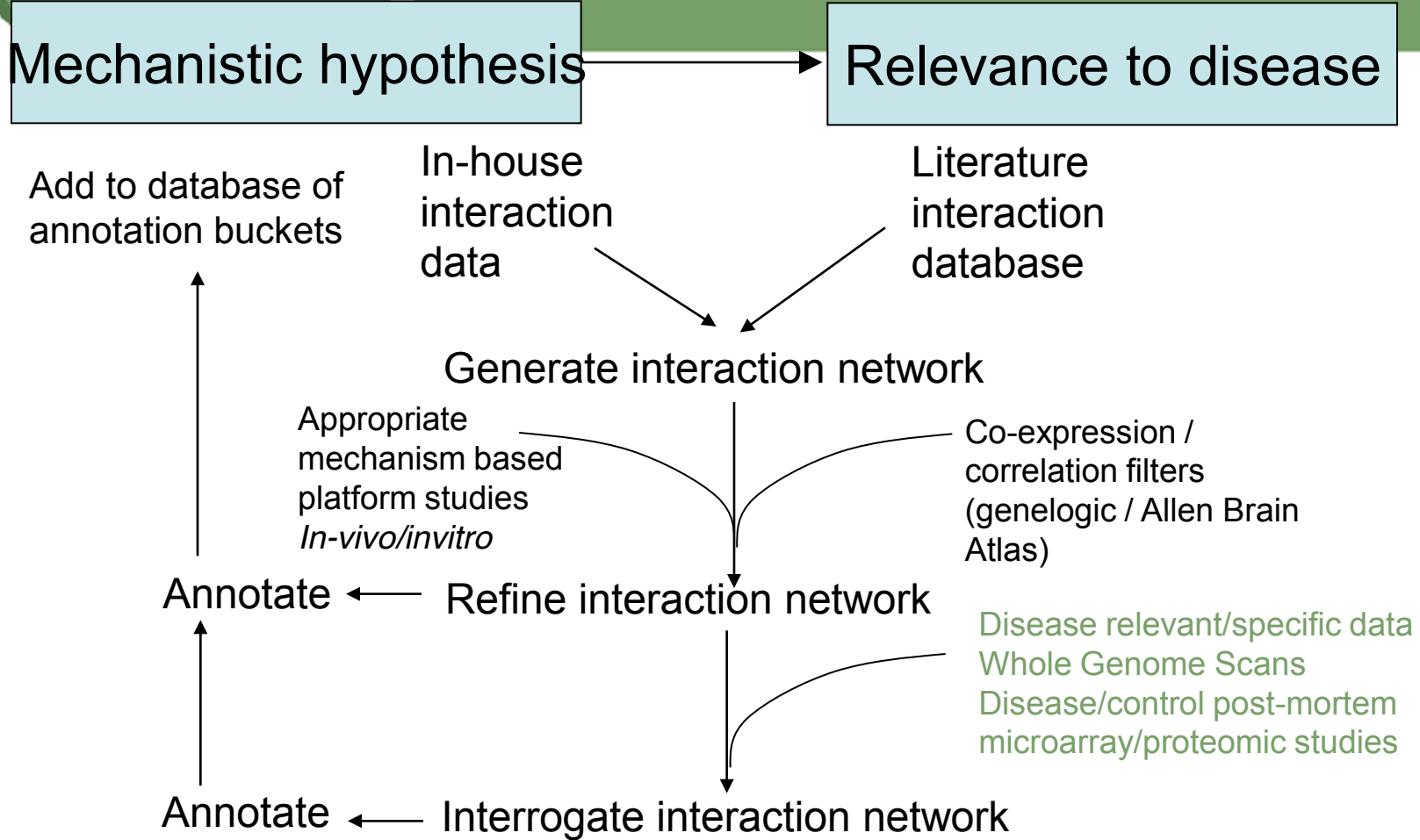
Result

Associated Loci with
SNP functional effect
predictions and
candidate genes

Interpretation

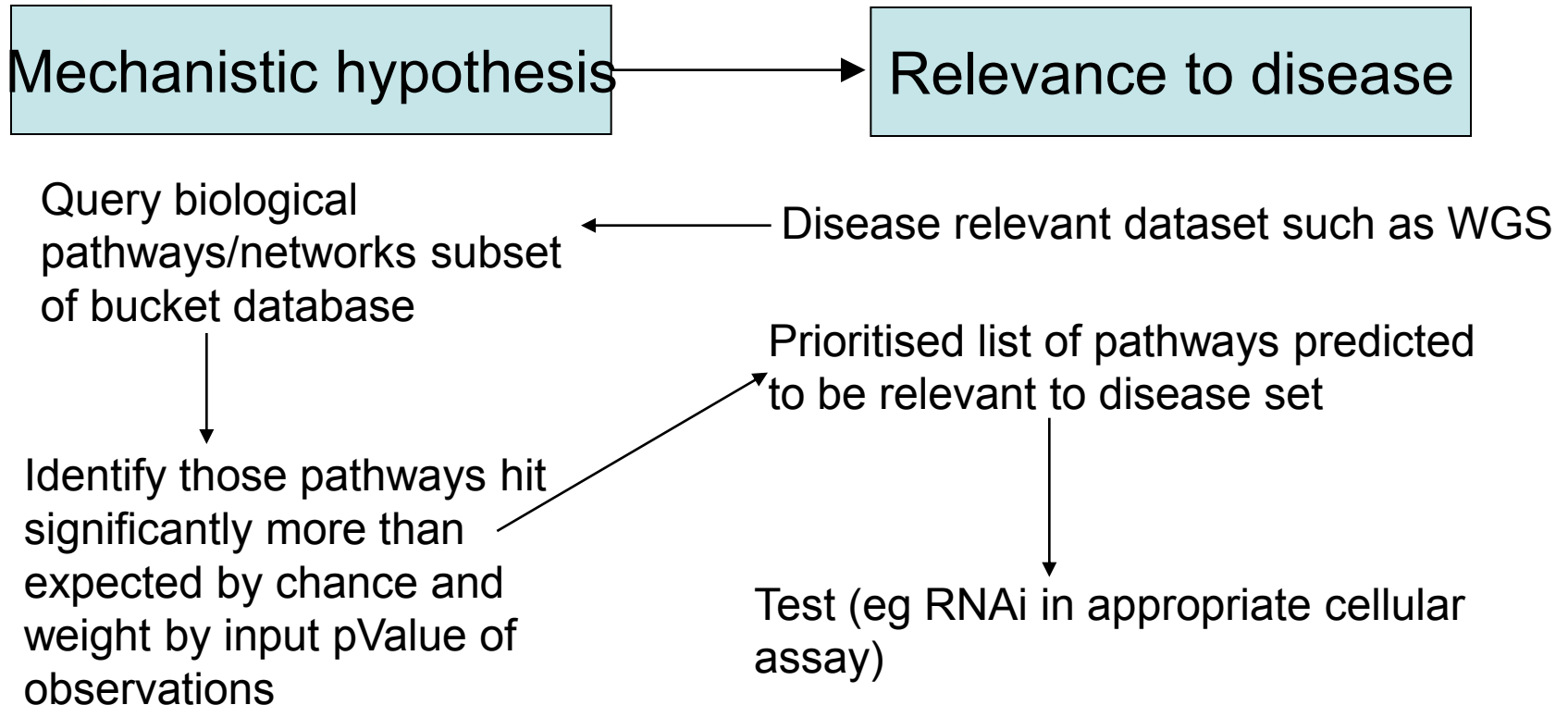
Associated Gene
Hypothesis

Generating networks



Buckets generated through automated methods far outweigh those derived from manual processes outline above. Source data and assumptions affect quality

Identifying significant biological processes within complex disease relevant datasets

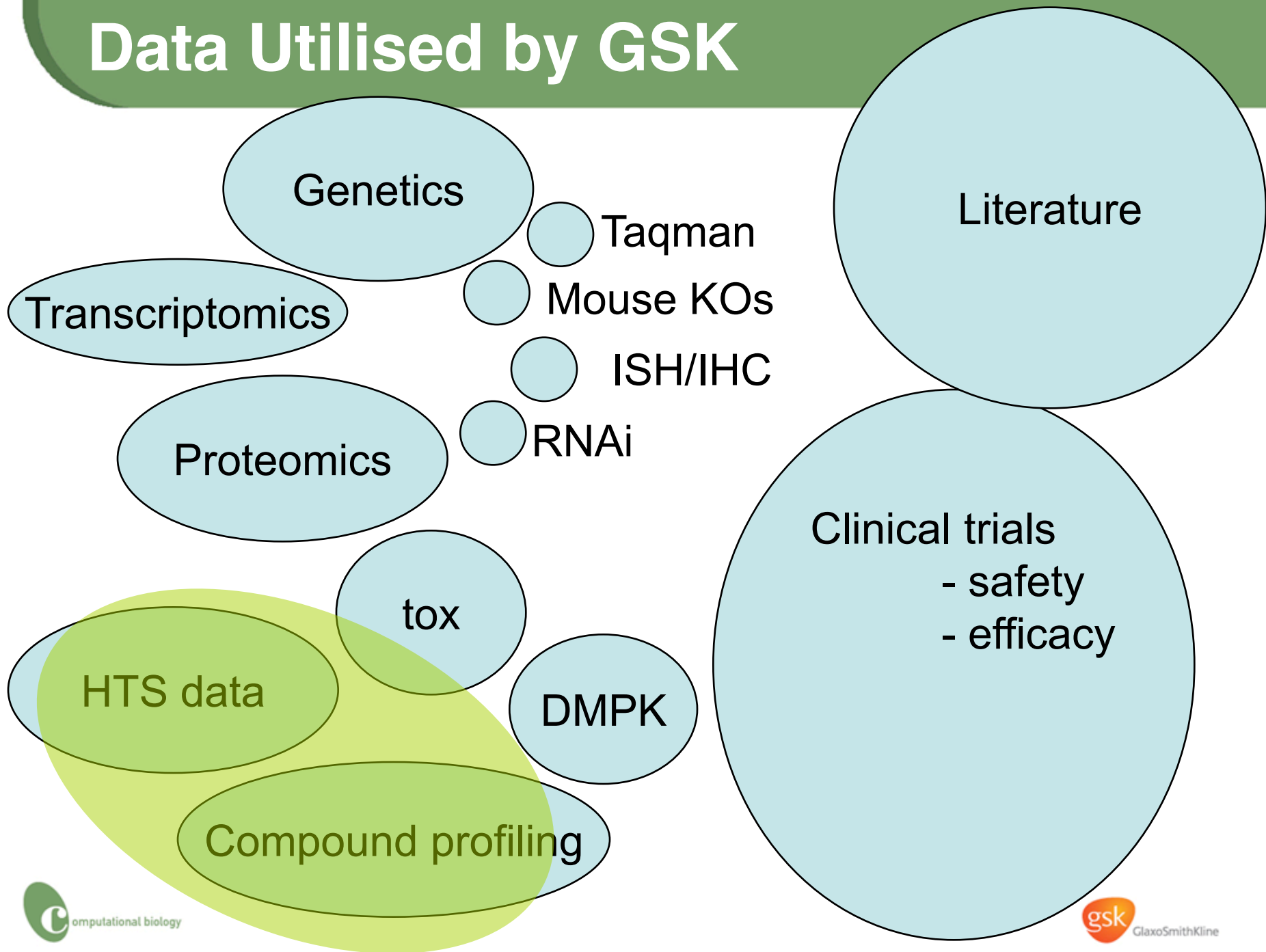


BUT: Which gene(s)?

A pathway may be significant but individual genes may have small component effects, may need to knockout/down >1

Many significant pathways/networks identified, do we test in each?

Data Utilised by GSK



Data Utilised by GSK

INTEGRATION

Genetics

Literature

Transcriptomics

Proteomics

Preclinical trials
- safety
- efficacy

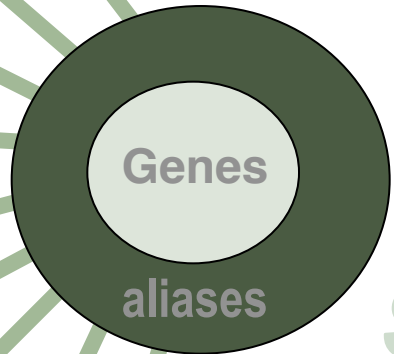
HTS data

DMPK

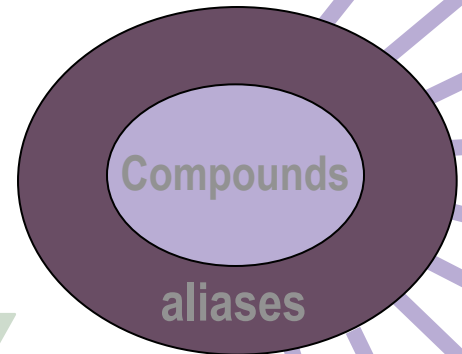
Compound profiling

Compound view

MOLECULAR DISEASE UNDERSTANDING



Potency
Specificity



CLINICAL TRIALS RESULTS

Compound view

MOLECULAR DISEASE UNDERSTANDING

CLINICAL TRIALS RESULTS

Potency

B4 Literature Query
24thFeb06

Compounds (Top 15 CCP > 5.5)

Compounds (Top 15 KATE > 5.5)

Compound	Potency	n	Specificity	# genes	# I	# E	# X
GSK	<5.82	1	-1.89	24	23	1	0
AH2	=5.63	2	-1.84	26	23	3	0
GR4	=5.6	2	-3.87	21	21	0	0

Unknowns (Total=15)

Compound	Potency	Specificity	# genes
BR	8.6	+?	1
GV	8.5	+?	1
BB	8.5	+0.60	2
SK	8.1	+?	1
12	7.5	+?	1
BR	6.5	+?	1
BR	6.3	+?	1
BR	6.3	-0.10	1

Portfolio

- Status: Target to Lead
- CEDD: PSYC
- Primary Disease: Unipolar depression
- HITDIP: Schizo 1st Round Lv6; Unipolar 1st Round

GeneLogic Normal Brain and Peripheral Distribution
8thMar06
Yes Human 100% Brain, 22% Non-brain

GeneLogic
12thMar06
Yes Human thalamus N (U133): Median Intensity = 1776, 217 (Potential)

HITDIP Accredited Data
12thMar06
Yes Human Unipolar Depression Combined HITDIP Level: Accredited locus associated with SNP.

HITDIP Primary Screen
12thMar06
Data is Superseded by Accredited Data
Preliminary data: strong risk of false positives
Maybe Human Unipolar Depression Primary HITDIP Level: 5

HITDIP Primary and Pilot Schizophrenia Screens
Preliminary data: strong risk of false positives
Maybe Human Schizophrenia HITDIP Pilot Screen: 6, p value <=0.05

Methods Find Exp Clin Pharmacol 2005, 27(5): 289
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CCC: 0379-0355
DOI: 10.1358/mf.2005.27.5.908643

Research on adverse drug events. I. Muscarinic M3 receptor binding affinity could predict the risk of antipsychotics to induce type 2 diabetes
Silvestre, J.S., Prous, J.

Lifespan (Expression Level: 0 - negative, 1 - positive)
13thMar06

- Yes Human Brain, Amygdala (Adjacent to nucleus accumbens)
- Yes Human Brain, Amygdala (Neurons)
- Yes Human Brain, Hypothalamus (Neurons)
- Yes Human Brain, Hypothalamus (Neurons)
- Yes Human Brain, Pituitary (Anterior pituitary)
- Yes Human Brain, Pituitary (Posterior pituitary)
- Yes Human Brain, Thalamus (Astrocytes)
- Yes Human Brain, Thalamus (Neurons)
- Yes Human Brain, Substantia nigra (Ependyma)
- Yes Human Brain, Substantia nigra (Neurons): 3
- Yes Human Brain, Substantia nigra (Nonpigmented neurons): 3
- Yes Human Brain, Substantia nigra (Pigmented neurons): 3
- Yes Human Brain, Medulla (Ependyma): 3
- Yes Human Brain, Medulla (Neurons): 3
- Yes Human Brain, Medulla (Neurons in the region of the cuneate nucleus): 3

- ***Application*** of computational methods towards drug discovery
- Looks to public science for methods development
 - Next Gen. Seq.
- More focus in public science on disease and drug discovery
 - ChEMBL
 - PubChem
 - Cheminformatics emerging in public science
- Move towards greater communication and collaboration between public science and industry sectors
 - *Better science applied to drug discovery*