Translational Neuroscience: It's Importance and Skills required for success

Translational science and the current situation of Neuroscience Drug Discovery/Development.

The Impact on Pharma Neuroscience.

Where we are going and what is needed from Translational science

What Skills might be needed

Neuroscience presents daunting challenges

Scientific challenges	• Biological complexity and un-validated targets • Poor pre-clinical models • Challenge of the blood-brain-barrier • Direct examination of drug exposure and target engagement
Clinical challenges	• Patient recruitment • Patient heterogeneity • Disease is advanced when symptoms appear • Capturing therapeutic effects on clinical scales with high variability
Low productivity	• Long cycle times • High costs • Low probability of success

R&D Cuts Curb Brain-Drug Pipeline

Development of new medicines for brain disorders could be threatened as major drug makers scale back research

Analysis: Neuroscience under threat as Big Pharma backs off

Pharmafile

Drug firms walking away from dementia research

PM By Emily Bourke

Novartis to shut brain research facility

Drug companies give up on Alzheimer's drug research

Is Pharma Running Out of Brainy Ideas?

Recent cutbacks raise concerns about the future of drug development for nervous system disorders

Bapineuzumab Failure Raises More Doubts About Beta Amyloid Approach In Alzheimer's

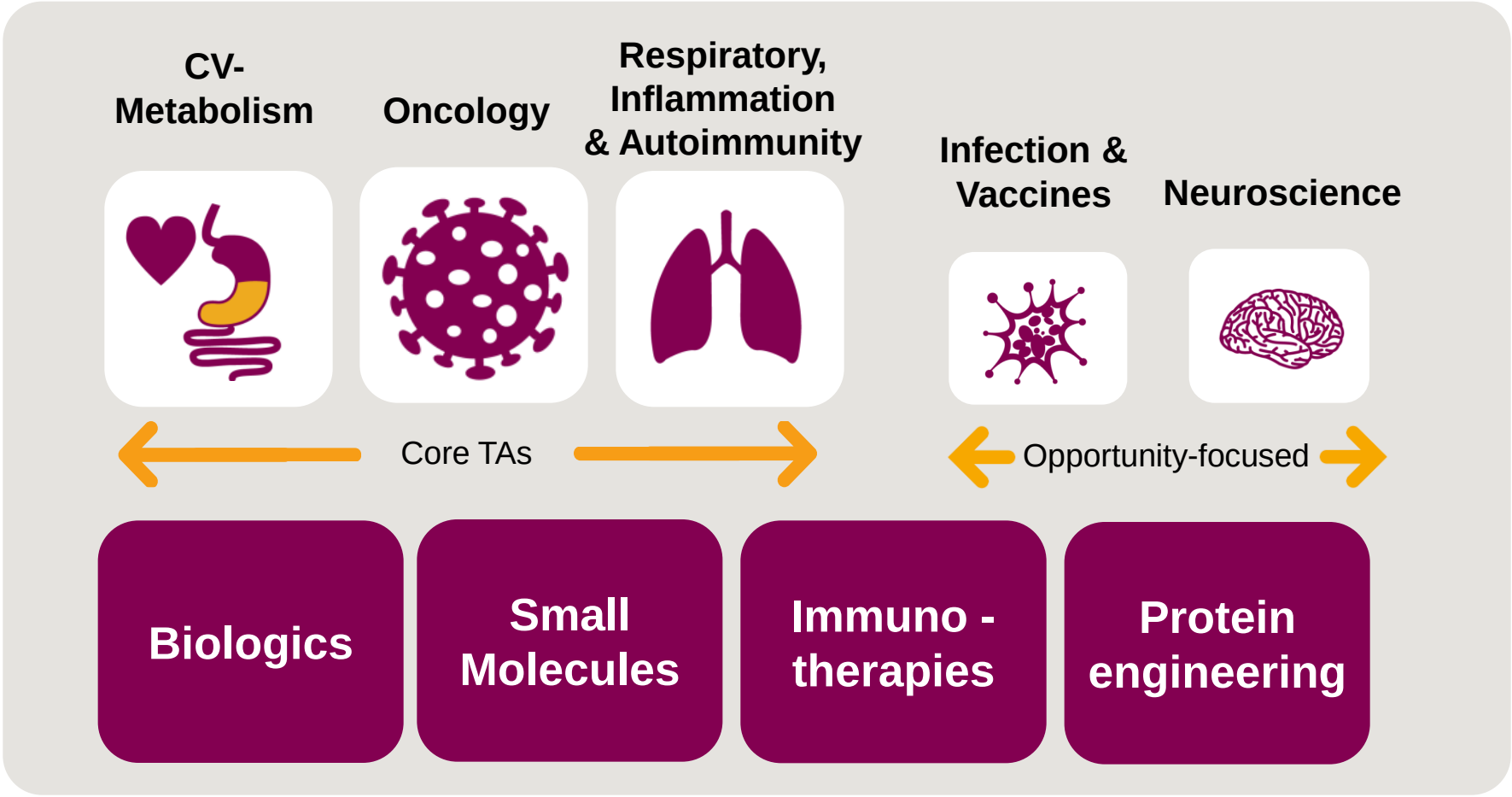
"The Pink Sheet"®

We've had our own problems, despite a proud history, tremendous effort and significant investment…

- 3 large facilities in Sodertalje, Wilmington, Montreal
- More than 700 scientists, Clinicians
- Significant investment (>$5B from 2000 to 2011 in CNS and pain
- Project Failures predominated in Phase II (Efficacy)
- Lack of defined Biomarker in most projects.
- Lack of patient stratification.

EXPENSE + RISK = doubt in financially constrained Pharma

AZ Neuroscience: “Opportunity Focused”



A Clear need to Change our Approach

From…	To…
▪ Large internal teams working on literature targets and follow-on approaches	▪ A small internal team collaborating with academic and biotech partners working on genetically driven innovative targets
▪ Limitations driven by rigid disease strategies	▪ More opportunistic approach to find tractable targets regardless of disease state
▪ Template approaches	▪ Smart discovery and development strategies (Translational focus)
• Focus on larger diseases driven by PYS	▪ Focus on smaller, genetic-based diseases driven by “line of Sight” and ROI.

AstraZeneca

The 5Rs: Creating a ”Line of Sight”

The 5 dimensions

Right target

- Strong link between target and disease
- Differentiating efficacy
- **Available and predictive biomarkers**

Right tissue/ Right exposure

- Adequate bioavailability and tissue exposure
- **Human PK / PD prediction, Target engagement**
- Drug-drug interaction

Right safety

- Clear assessment of safety risks
- Clear understanding of risk-benefit
- **Availability of predictive biomarkers**

Right patients

- Scientific evidence in lead indication
- **Risk / benefit stratification of patient population**
- **PHC strategy including diagnostic / biomarkers**

Right commercial

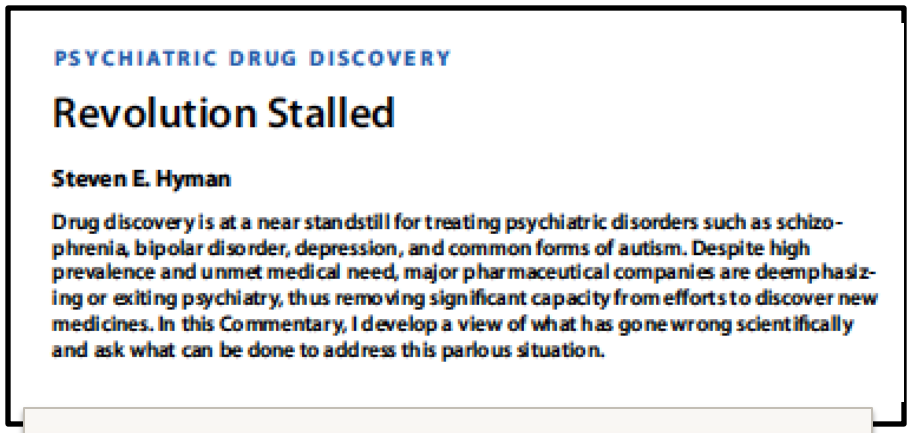
- Differentiated value proposition vs. future standard of care
- Invest to win / priority areas – DTPP / CDTP
- Market access / payer / provider focus
- **Personalised healthcare strategy including diagnostic / biomarkers**

MedImmune

AstraZeneca

Scientific Rationale

The Impact of 21st Century Science on Psychiatry



PSYCHIATRIC DRUG DISCOVERY

Revolution Stalled

Steven E. Hyman

Drug discovery is at a near standstill for treating psychiatric disorders such as schizophrenia, bipolar disorder, depression, and common forms of autism. Despite high prevalence and unmet medical need, major pharmaceutical companies are deemphasizing or exiting psychiatry, thus removing significant capacity from efforts to discover new medicines. In this Commentary, I develop a view of what has gone wrong scientifically and ask what can be done to address this parlous situation.

‘large scale unbiased approaches to data collection and analysis
‘DNA sequencing’

‘Human neurons can be derived from readily obtainable skin fibroblasts or blood cells and these systems are starting to show promise as disease models that should provide amenable to high-throughput biological and chemical interrogation’

“Optogenetics has given neuroscientists the ability to activate or inhibit single cell types and thus selected circuits’
‘studies of structural and functional connectivity’

“identification of biochemical pathways involved in disease pathogenesis’

“issue might be akin to cancer, in which the mutations within cancer cells are proving to be more important to therapy than cell of origin’

The best of times, the worst of times for psychiatric disease

Maria Karayiorgou[1], Jonathan Flint[2], Joseph A Gogos[3], Robert C Malenka[4] & the Genetic and Neural Complexity in Psychiatry 2011 Working Group[5]

As long-awaited advances in psychiatric genetics begin to materialize in force, promising to steer us safely to the best of times in psychiatric disease research, many pharmaceutical companies pull away from the challenge of drug development, threatening to bring us to the worst of times for the field. There is a real danger of missed opportunities and a sense of urgency for defining a clear path forward.

“The best way to determine convergent pathophysiological mechanisms lies in starting with genetic discoveries”

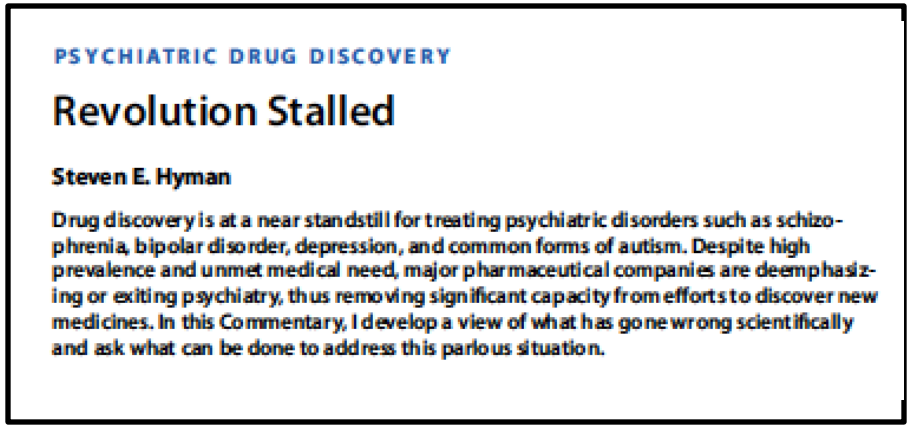
“Elucidating the causal pathway from mutation to behavioral disorder will be challenging, and multi-level analysis will be necessary for testing causal connections among findings at various hierarchical levels of affected networks”

“progress in reprogramming skin cells from patients into functional neurons affords us the opportunity to develop cellular disease models”

“substantially reduce investment risk by concentrating drug development efforts either on smaller, biologically stratified subsets of patients guided by genetic findings, or on specific circuits and synaptic processes.”

Scientific Rationale

The Impact of 21st Century Science on Psychiatry

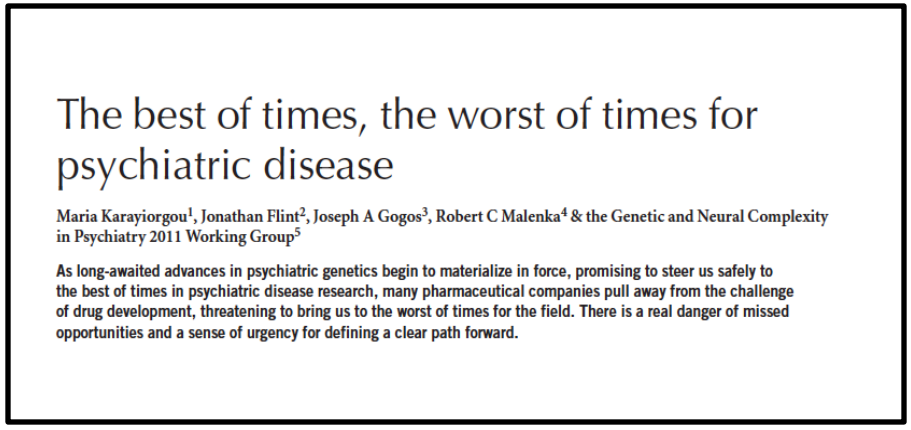


PSYCHIATRIC DRUG DISCOVERY

Revolution Stalled

Steven E. Hyman

Drug discovery is at a near standstill for treating psychiatric disorders such as schizophrenia, bipolar disorder, depression, and common forms of autism. Despite high prevalence and unmet medical need, major pharmaceutical companies are deemphasizing or exiting psychiatry, thus removing significant capacity from efforts to discover new medicines. In this Commentary, I develop a view of what has gone wrong scientifically and ask what can be done to address this parlous situation.



The best of times, the worst of times for psychiatric disease

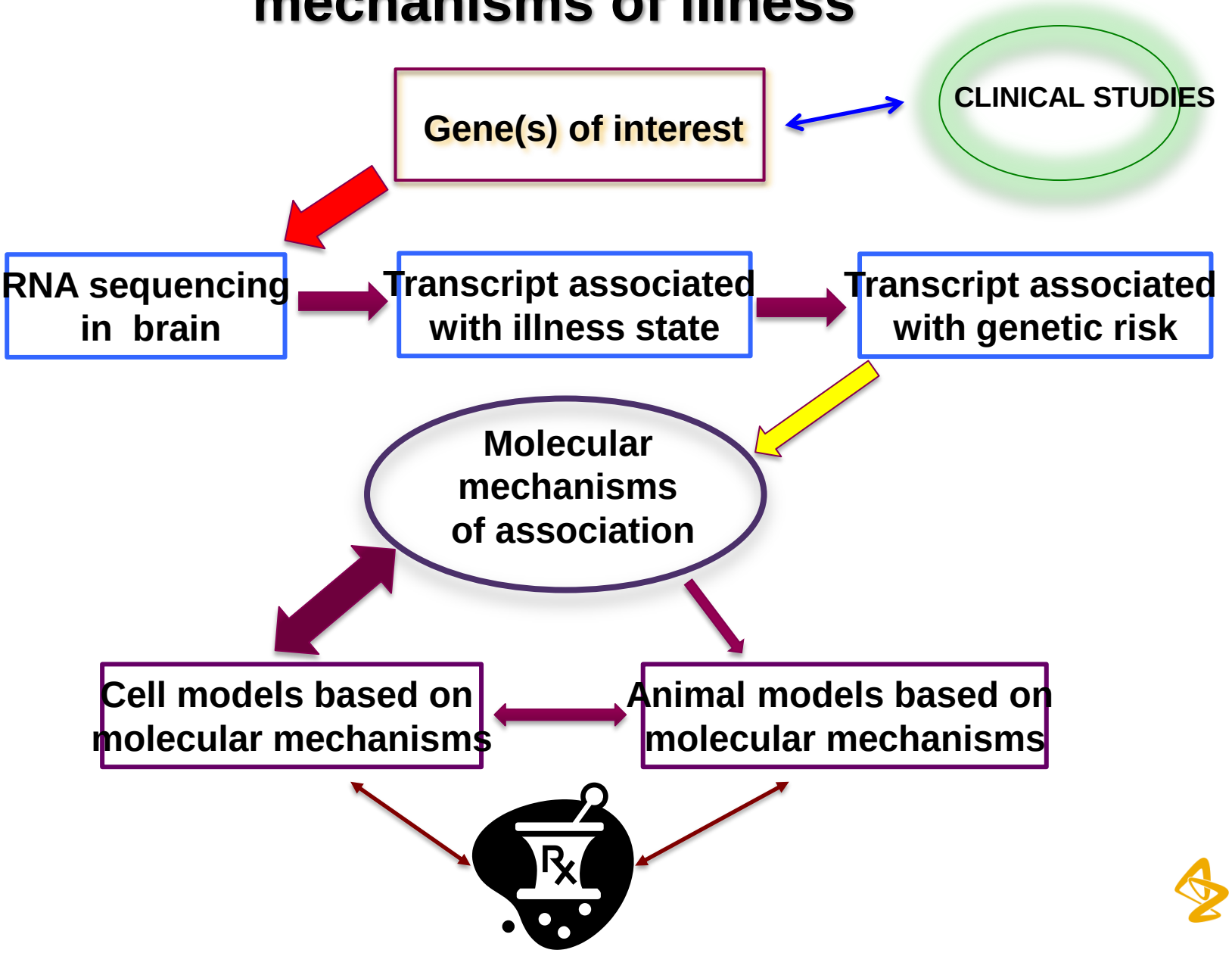
Maria Karayiorgou[1], Jonathan Flint[2], Joseph A Gogos[3], Robert C Malenka[4] & the Genetic and Neural Complexity in Psychiatry 2011 Working Group[5]

As long-awaited advances in psychiatric genetics begin to materialize in force, promising to steer us safely to the best of times in psychiatric disease research, many pharmaceutical companies pull away from the challenge of drug development, threatening to bring us to the worst of times for the field. There is a real danger of missed opportunities and a sense of urgency for defining a clear path forward.

New approaches will be driven by integration of

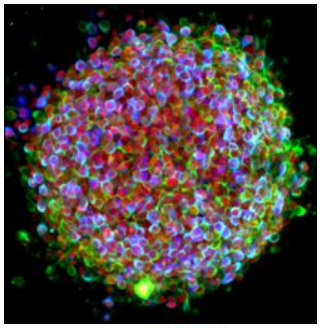
1) Large Multi-Level Data Sets
2) Genetics
3) iPS cells
4) Genetic Endophenotypes
5) Circuits inc optogenetics

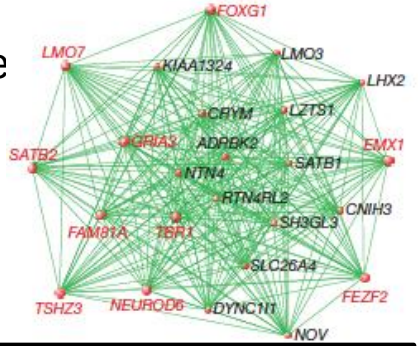
A roadmap for new target discovery based on mechanisms of illness



Essential Role of iPSC Derived Neurons & Glia

- Human iPSC derived neurons can be used to probe mechanisms associated with genetic risk for neuropsychiatric illness and identify novel drug targets by screening directly.
- Critical requirements include
  1. Tissues from clinically & genetically characterized subjects
  2. Robust and validated stem cell capabilities
     - Standardized procedures to generate neural stem cells
     - The ability to validate against brain tissue from the disease state
  3. Quantitative assays and pathway de-convolution
     - Transcriptional assays, informatics and phenotypic measures

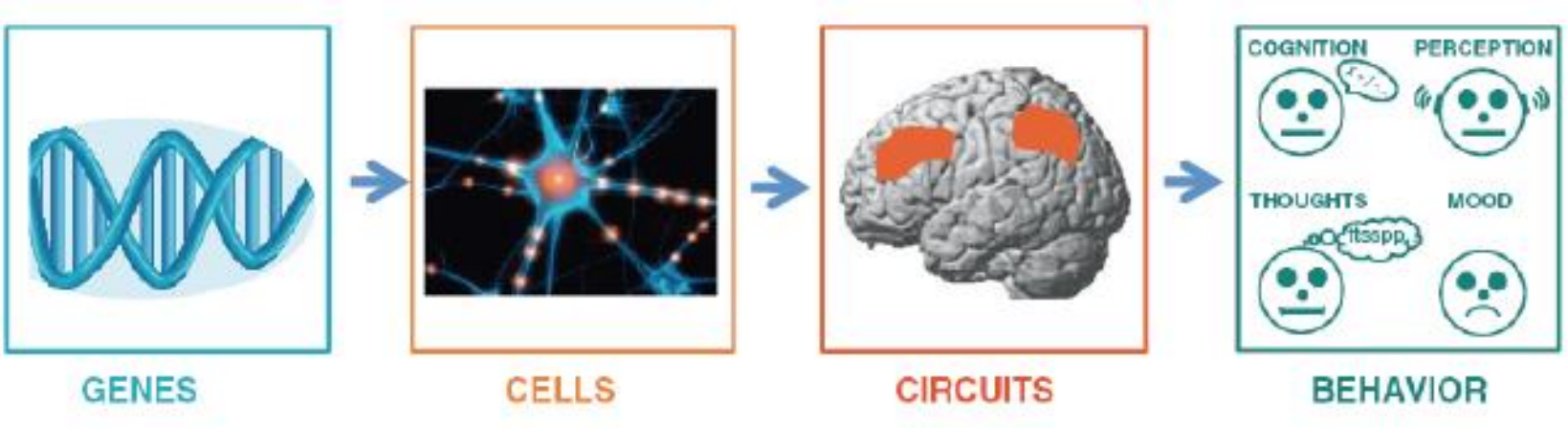




Translating advances in neuropsychiatric genetics into innovative drug discovery and development programs will require close collaboration between leading disease biology expertise and Pharma experience

Summary - partnerships are key

Innovative Treatments for Neuropsychiatric Disorders from Genetics and Neurodevelopmental Mechanisms

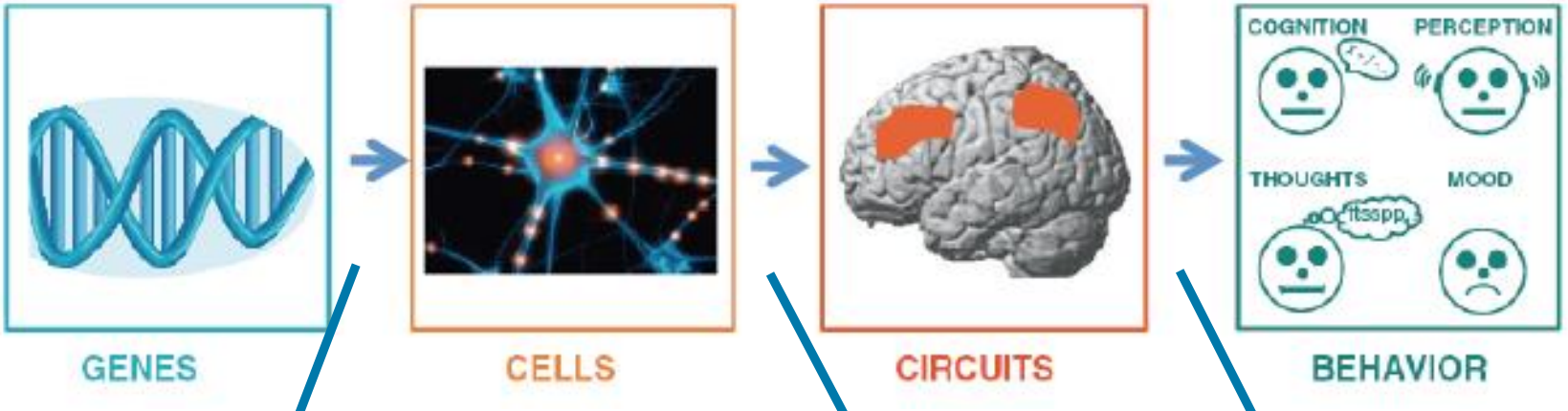


- Breakthroughs in neuropsychiatric genetics implicate genes and pathways involved in neurodevelopment and neuronal plasticity
- Advances in the use of iPS derived neurons provide an *integrated* platform for the discovery of novel targets and mechanisms

➢ Industry/academia collaborations , combining expertise in drug-hunting and discovery platforms with expertise in disease biology, iPS technology and access to patient material to develop innovative treatments of neuropsychiatric disorders

Critical gaps in translational skills

Cross-functional skill sets are essential



- **Neuroscientists with expertise in informatics/statistics**
- **Neurobiologists with expertise in genetic manipulations (eg CRISPR)**

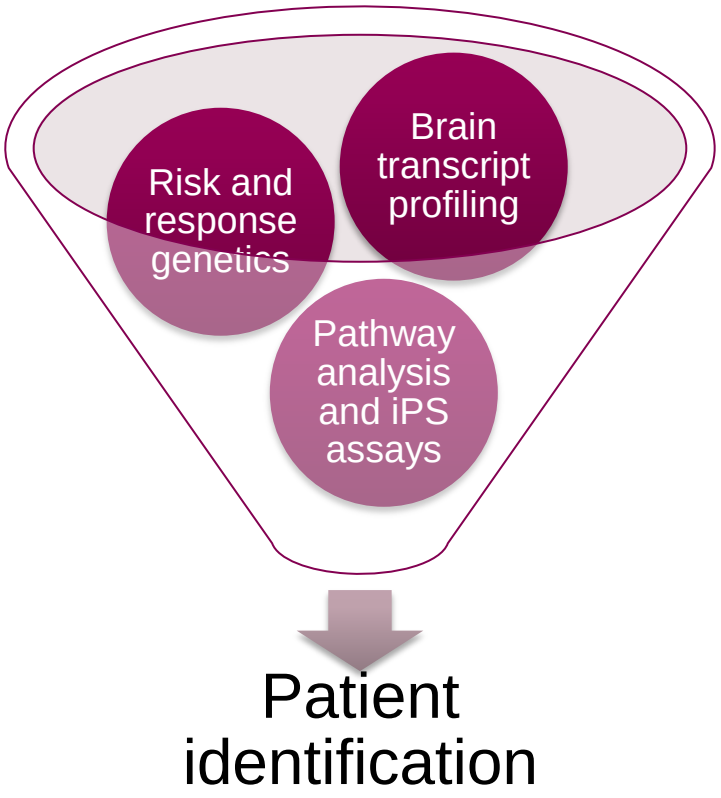
- **Cell biologists with expertise in neuroscience and neurodevelopment**
- **Neurophysiologists with system modeling expertise**

- **Clinicians with expertise in neuroscience and neurodevelopment**
- **Neurophysiologists/neuropsychologists**

Back Translation for Repositioning/Revisiting?

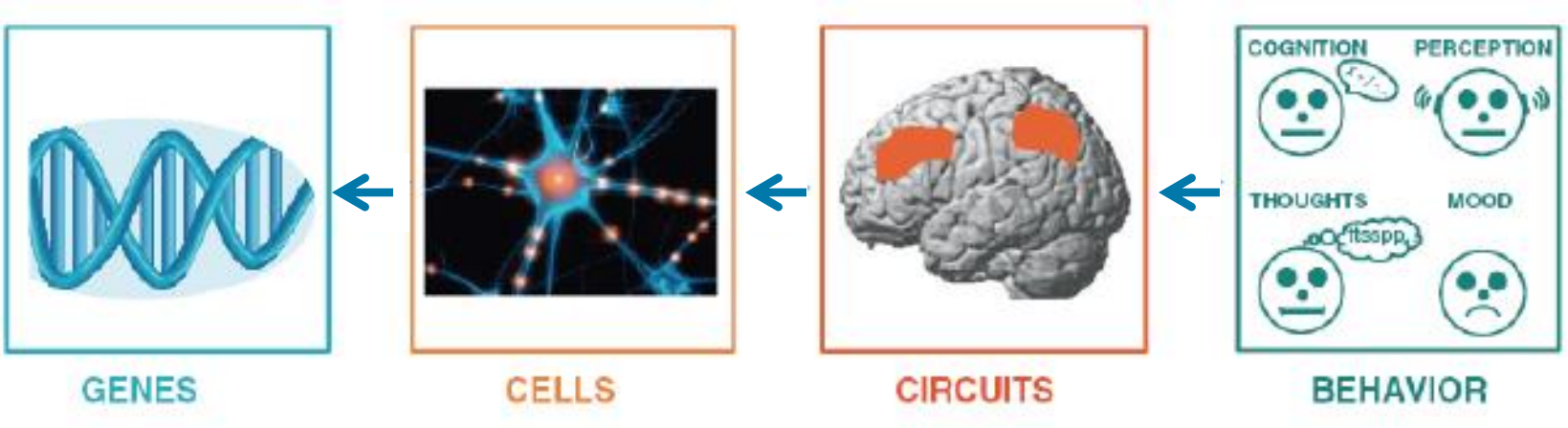
- Several novel targets have shown signals of efficacy in traditional Phase 2 studies in schizophrenia which have not translated into robust effects in pivotal studies
- Analysis of targets, gene, gene expression, genetic variation, etc. may drive identification of relevent patient subgroups
- Boost rationale for a target and contribute to patient selection.

e.g. mGluR2PAM, 5HT2C, PDE10A, GlyT1



Back-translation

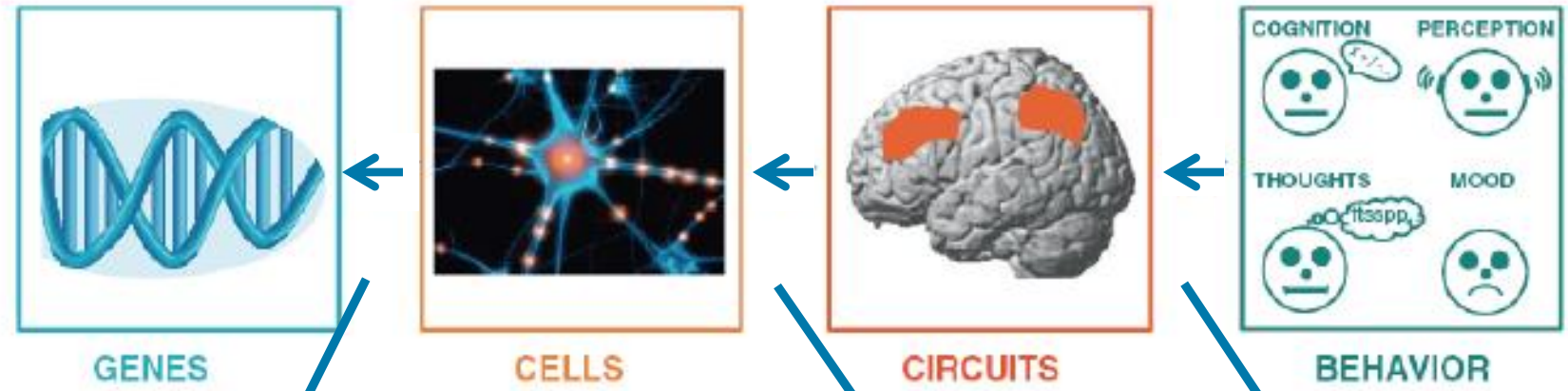
Clinical neuroscientists are essential



- High quality clinical studies
- Novel pharmacology and repositioning tools
- Genetics and patient segmentation
- Objective end-points and biomarkers

Back-translation

Clinical neuroscientists are essential



- High quality diagnostics and patient segmentation
- Response biomarkers

- Clinical neurophysiologists and clinical psychologists
- Functional imaging

- High quality clinical studies
- Novel treatment strategies
- Patient segmentation