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Systasy‘s Drug Discovery Engine

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1 Billion

People live with a mental disorder worldwide

1 out of 4 people

will suffer from a mental disorder at some point in their lives

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These numbers will significantly rise due to modern lifestyle, aging population and the COVID-19 pandemic

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Drug Discovery for Mental Disorders & All Complex Genetic Diseases

Problems

1. Lack of Human Cellular Models
2. Cellular and Genetic Complexity
3. Patient Heterogeneity, Clinical Diagnosis

Solution

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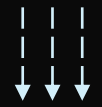
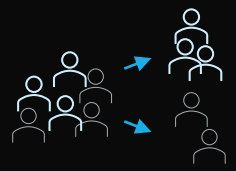
Patient derived cellular models

High translational power of 2/3-dimensional disease models minimizes drug attrition



Pathway-based target identification & compound screening

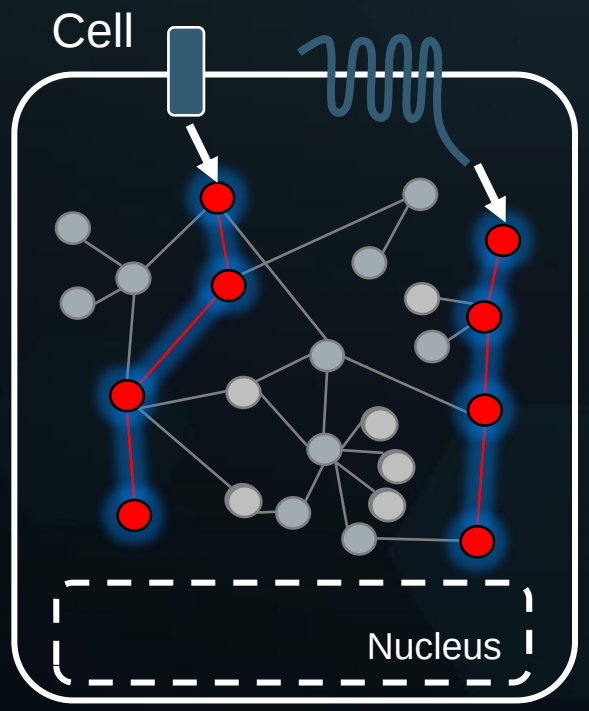
High-content pathway profiling assays enable molecular phenotyping



Deeply stratified patient cohorts

Big data insights enable better patient stratification to improve clinical trial design.

Drugs for Complex Disorders are not easy to find



- Complex Disorders are caused by Multiple Genes.
- A Genetic Variation causes a Dysregulation of Cellular Networks whose Activity converges on Key Signaling Pathways in Patients and leads to Clinical Symptoms.
- Complex Disorders can be classified as Pathway Diseases.

Thus,

➡ Pathways are Our Targets

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Game Changing Approach to Drug Discovery

Novel Approach

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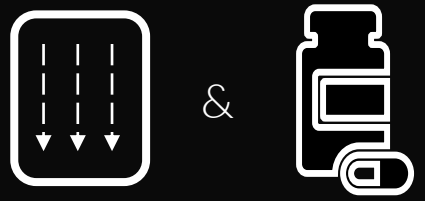
Patient & Pathway Centric
Drug Target Identification & Screening



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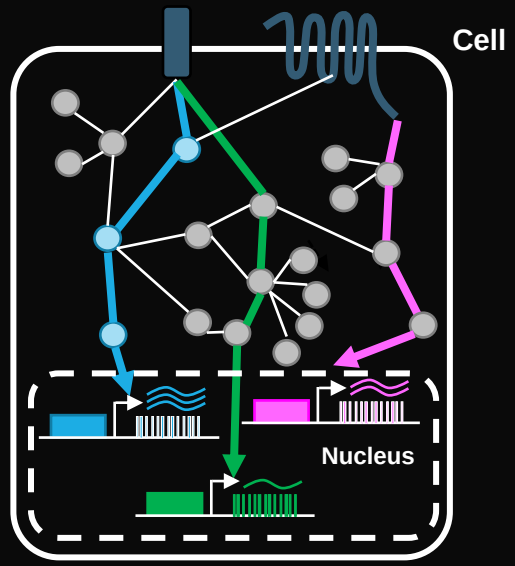
A Drug Development Tool for Complex Genetic Disorders

Targets
(Cell surface)

Signaling
Pathways

Genetic
Biosensors



Barcoded Readouts

Patient Stratification

Systasy‘s technology groups patients with complex diseases according to many signalling pathways activity profiles. These patients have similar molecular alterations in a complex network of molecules. Systasy‘s technology captures this complexity.

Target Identification

The comparison of those grouped patients with healthy subjects allows to identify pathways that are altered through the disease. Analysing these pathways allows to identify new targets that potentially can be manipulated to treat the disease.

Drug Screenings

Systasy‘s technology allows to screen small compund libraries (focused libraries up to 10k molecules) for hits that change diseased pathway activity profiles back to normal

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Molecular Barcodes as Reporters for Cellular Signaling

Genetic Biosensors

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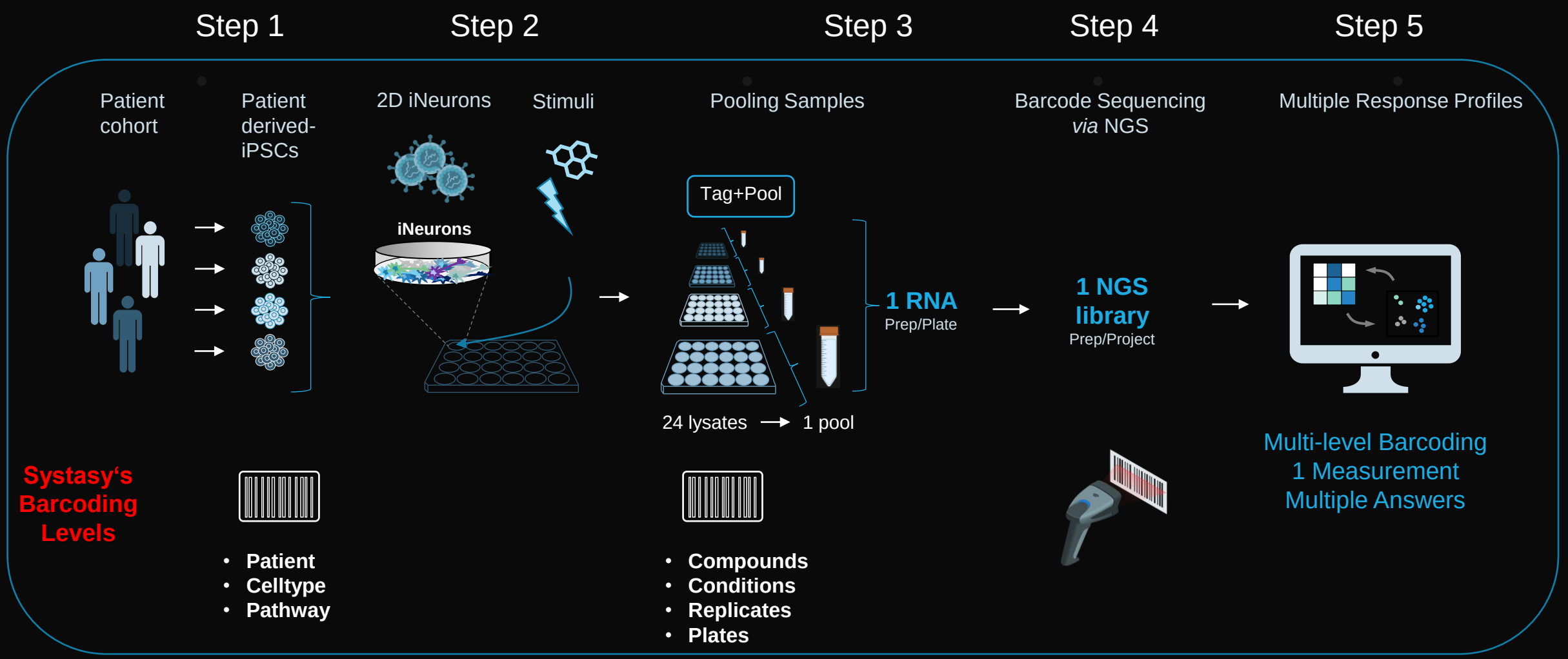
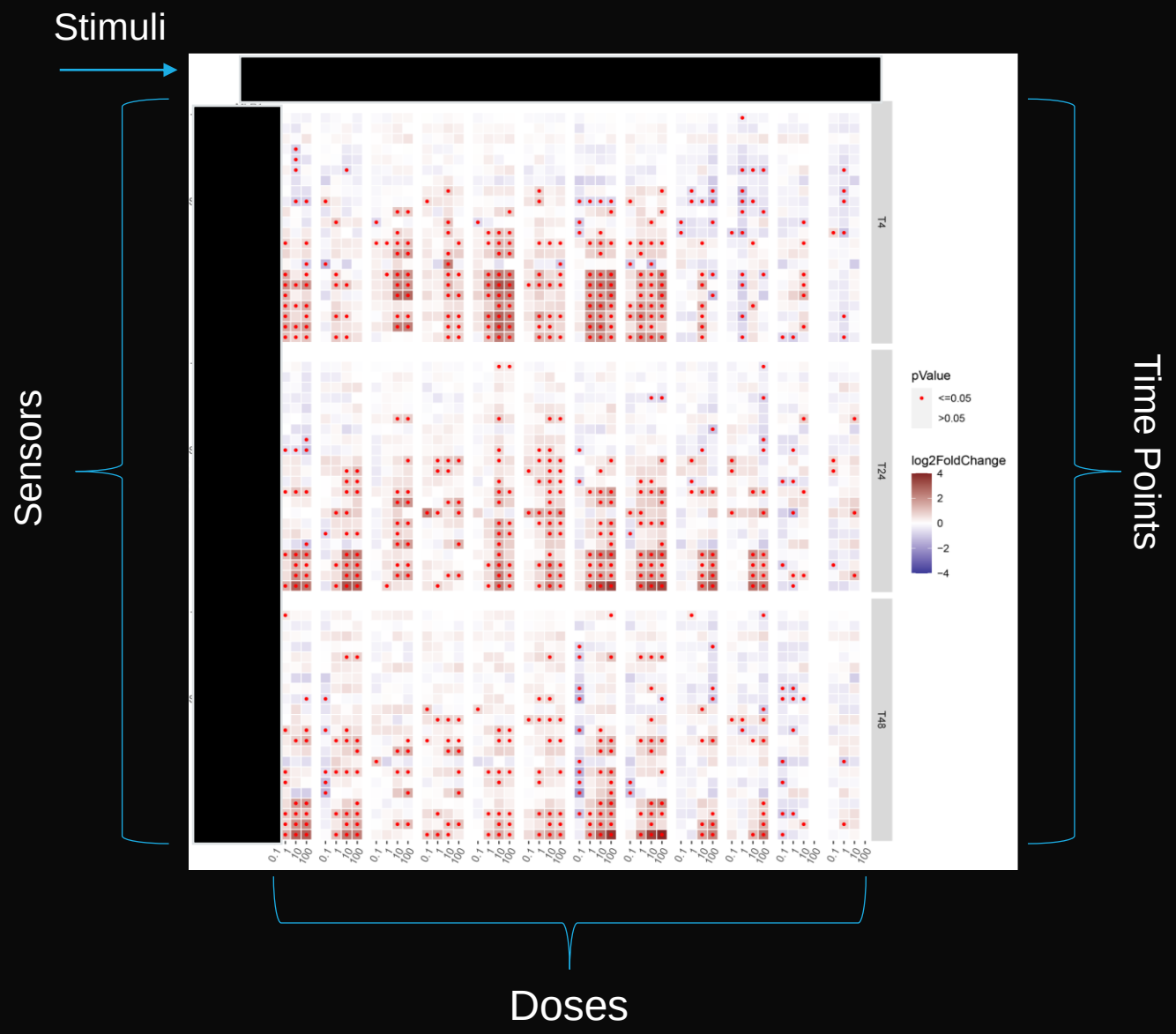
Patient-Centric Pathway Profiling - Workflow



Patient-Centric Pathway Profiling Readout - Example



6 x 96-well plates
22 sensors, **6** stimuli, **4** doses, **3** time points
2 genotypes, **4** replicates

1 Run

→ **12 000 Barcoded Data Points**

Comparison to Conventional Screen
12 000 data points measured in 96-well plates
→ **125** plates of 96-well plates needed

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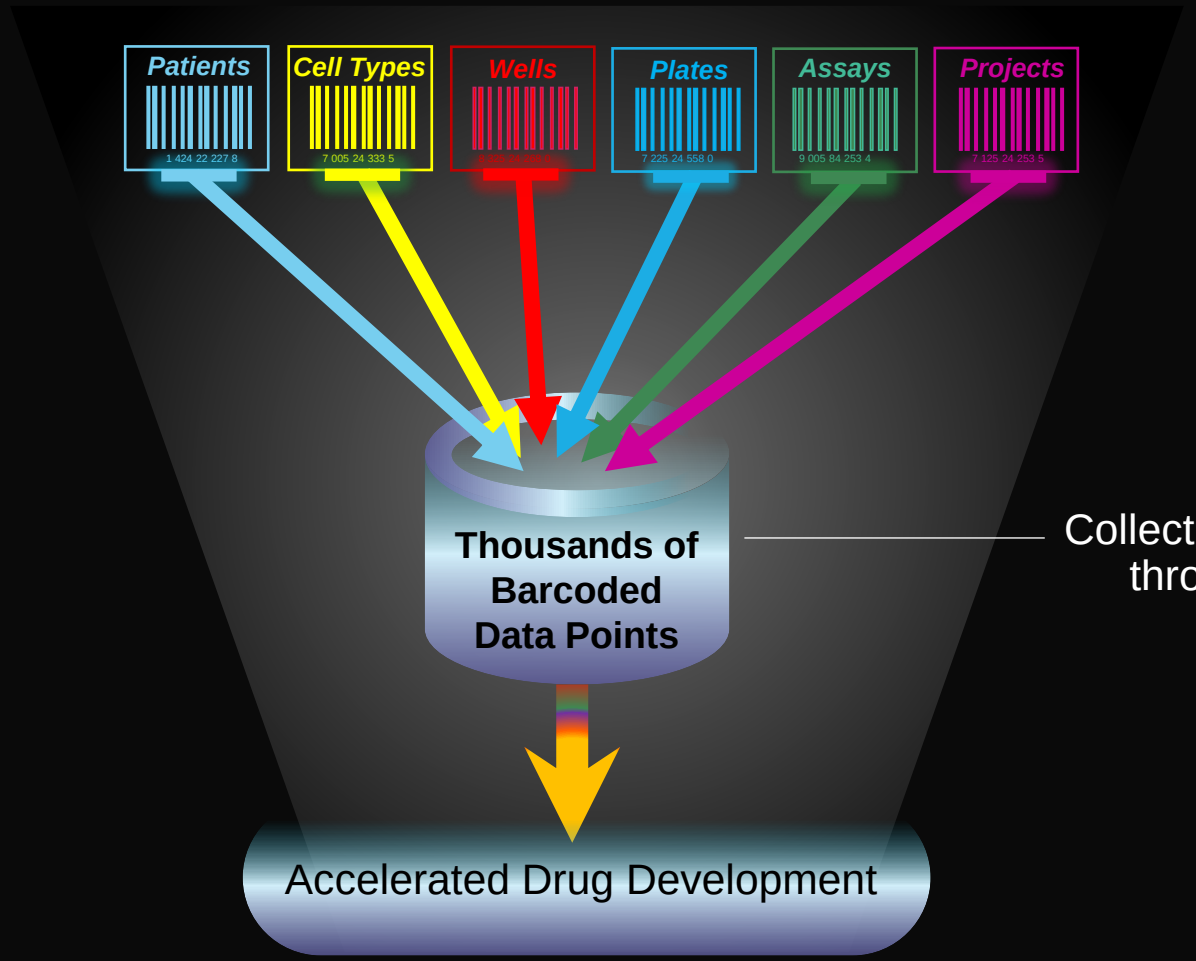
Why is Our Approach Unique?

At Systasy, we are using a multi-level Molecular Barcoding technology to obtain multiple answers in only 1 experiment.

Barcoding Options



Collection of Thousands of Data Points through ONE Single Experiment

We provide **cost-effective** and **highly innovative solutions** to address critical and unmet needs of the pharmaceutical industry

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Our Team

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11	4	3	5	9	7
PhDs/MDs	PhD/MD Students	Bioinformaticians	Lab Technicians	Business Managers	Nationalities

Our Strong Partners

LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN

Max Planck Institute of Psychiatry

DZG DEUTSCHE ZENTREN DER GESUNDHEITSFORSCHUNG

DZNE German Center for Neurodegenerative Diseases within the Helmholtz Association

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Systasy Bioscience GmbH is a Munich-based start up, operating on two sites:

- Headquarter at Balanstr. 6
- Additional laboratories at LMU Psychiatry Hospital where Alois Alzheimer described the Alzheimer‘s disease for the first time in 1906

Systasy Technology Applications

Cross Disorder Technology

Mental disorders
Neurodegeneration
Oncology
Cardiovascular
…

Human Disease Models

Mental disorders
Neurodegeneration
…

Functional Validation of AI Predictions

Schizophrenia cohort

Drug Development

Hit ID I Hit 2 LEAD I Target ID I Mode of Action I Toxicity

Gene & Cell Therapy

Viral Tropism I Viral Viability …

Patient Stratification based on Pathway Profiling

Schizophrenia cohort

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Systasy Core Competences

Access to:
- ✓ Clinical Patient Data
- ✓ Patient Material (iPSC collection)

- ✓ Proprietary Barcoding Technology

- ✓ Human Disease Models
- ✓ Relevant Animal Models

- ✓ Strategic Alliances for AI

Integration of AI & Systasy's Barcode Technology Will Transform the Drug Development Process

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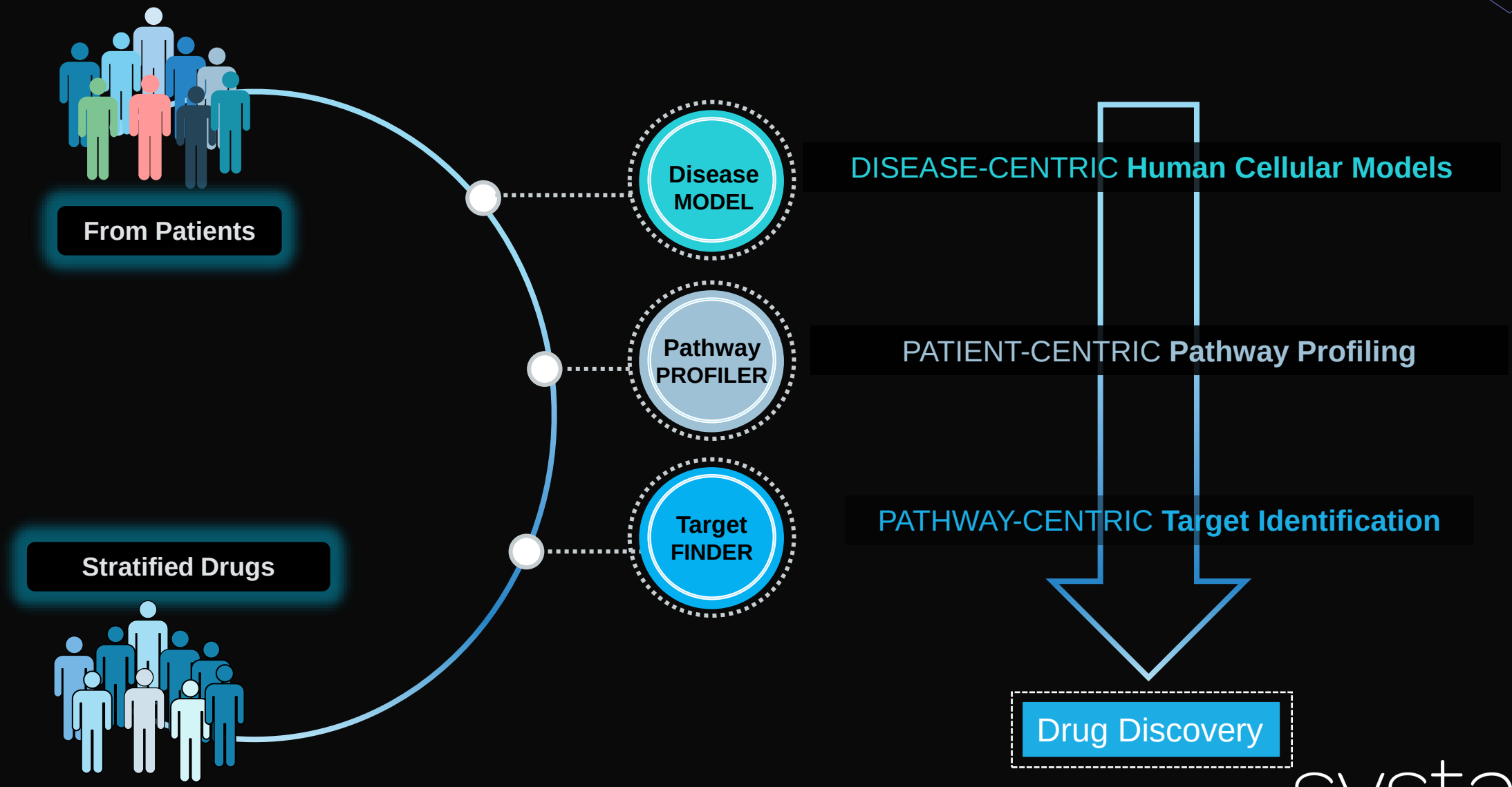
Systasy's Barcoded Toolbox for Drug Discovery



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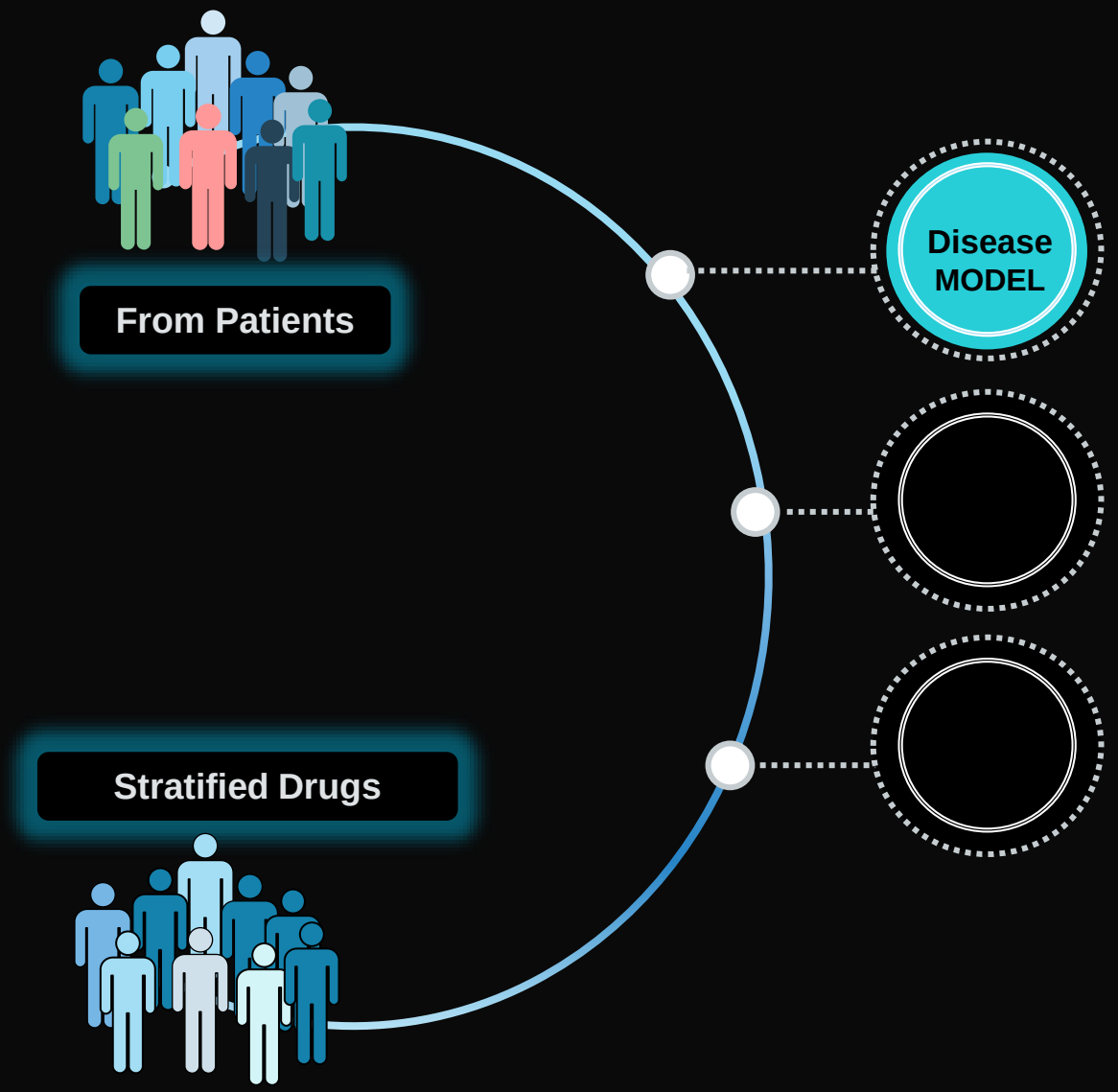
Human Cellular and Humanized Mouse Models



General Applicability

- Principally to any indication / patient cohort

Requirements

- Access to fresh Human blood or frozen PBMCs (Genetic Complex)
- Knowledge of Disease Mechanism (High Penetrance)
- Conversion of Cell Type of Interest (Context)

Challenges

- Disease Model/Readout Characterization
- Adaptation of Genetic Libraries / Protocols

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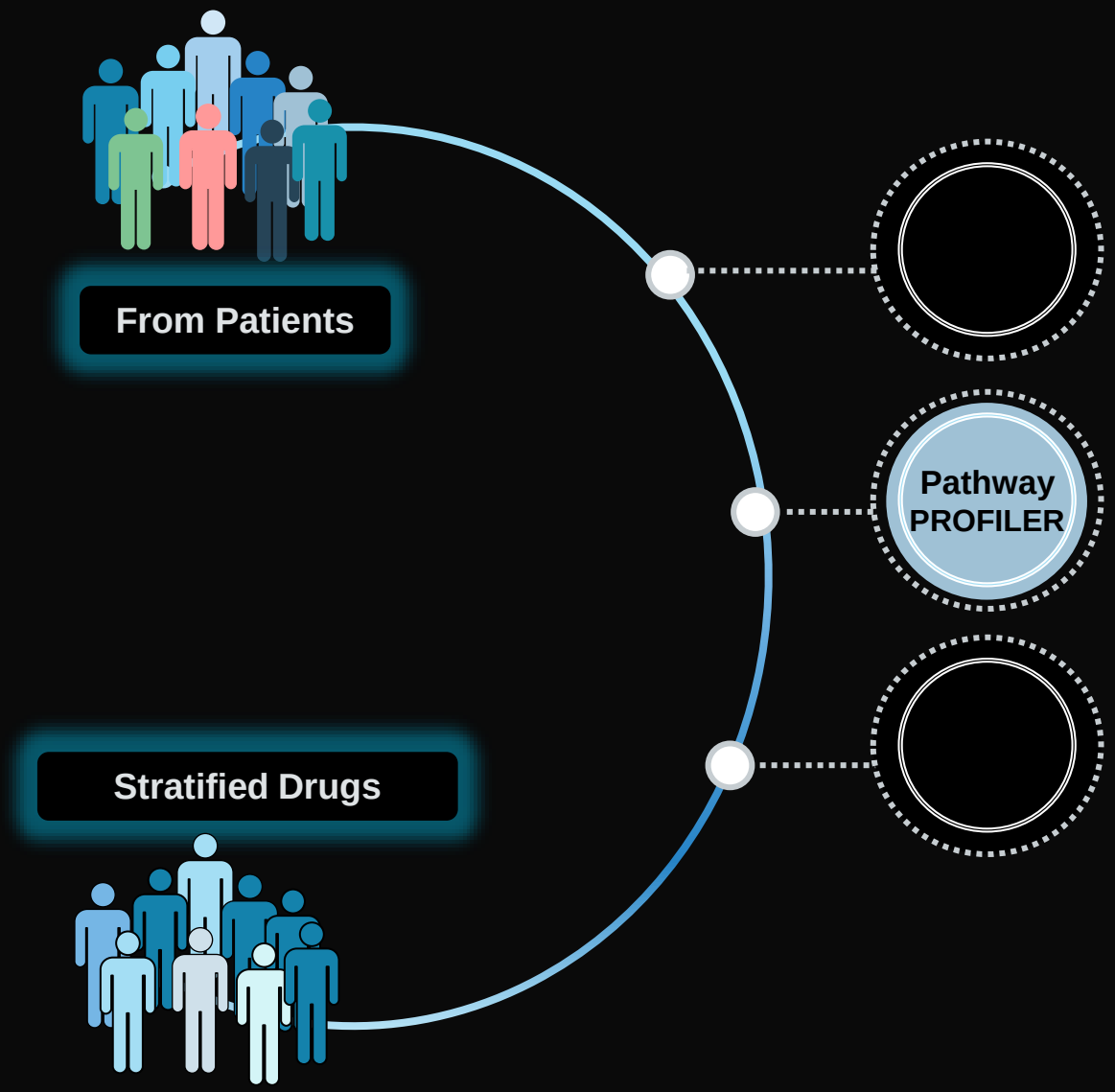
High Content Pathway Identification



General Applicability

- Principally to any genetically amenable cell type/line

2D/3D Primary, Heterologous Models

Requirements

- Corresponding BC library in prefered backbone

AAV, Lenti, PiggyBAC

Challenges

- Definition of Disease Mechanism Relevant Condition
- Adaptation of Sensor Set / New Sensor Development

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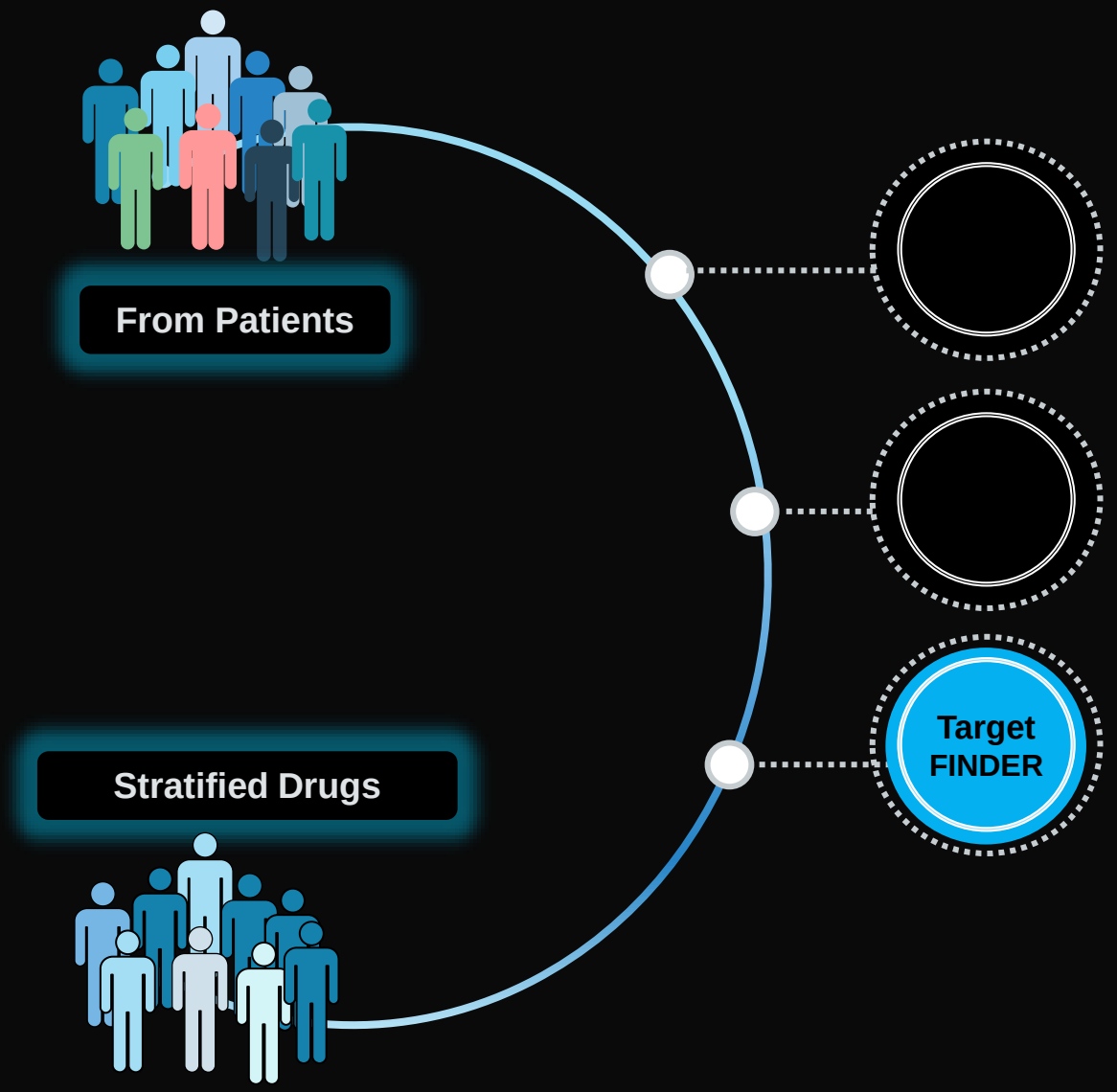
Pathway- Centric Target Identification



General Applicability

- Principally to any genetically amenable cell type/line

  Primary, heterologous

Requirements

- CRISPR/Cas9 expression
- Disease mechanism relevant sensor/condition

Challenges

- Adaptation of screening libraries (size) and conditions

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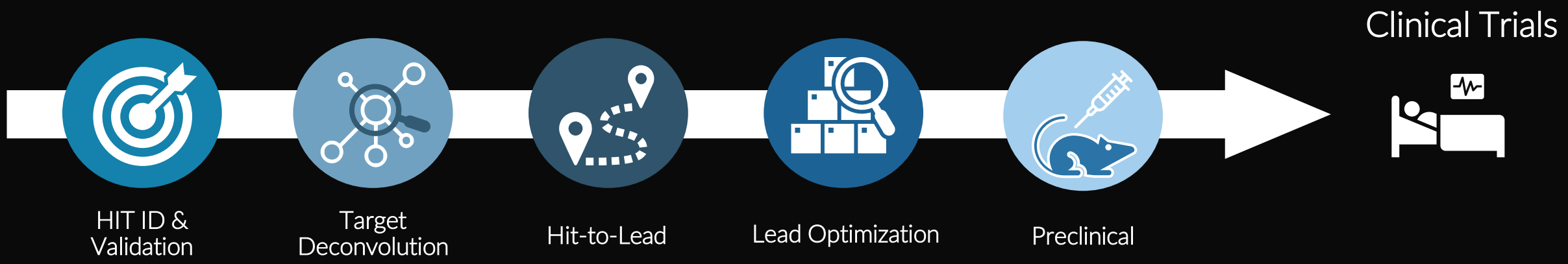
Successful initial drug screenings & Clinical PoC



Projects

1. Phenogenomic profiling of a schizophrenia cohort

2. Target identification in mental disorders

3. Drug repurposing screening for RTK-X in Schizophrenia

4. De novo compound screening campaign for RTK-X kinase inhibitors

5. Phenogenomic screening and compound validation in a mouse model for hyperactivity

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Systasy Publication List Technology

- 2022

- Hausruckinger A, F J Raabe et al. Mislocalization of SHANK3 contributes to synaptic impairment in schizophrenia. Nature, under review.

- F J Raabe et al. Expression of Lineage Transcription Factors Identifies Differences in Transition States of Induced Human Oligodendrocyte Differentiation. Cells 11(2):241.
Expression of Lineage Transcription Factors Identifies Differences in Transition States of Induced Human Oligodendrocyte Differentiation - PubMed (nih.gov)

- 2021

Herholt A et al. Dissecting intercellular and intracellular signaling networks with barcoded genetic tools. Curr Opin Chem Biol. 66:102091.
Dissecting intercellular and intracellular signaling networks with barcoded genetic tools - PubMed (nih.gov)

- 2020

Herholt A et al. Multiparametric Assays for Accelerating Early Drug Discovery. Trends Pharmacol Sci 41(5):318-335.
Multiparametric Assays for Accelerating Early Drug Discovery - PubMed (nih.gov)

- 2019

Wintgens, J.P. et al. Monitoring activities of receptor tyrosine kinases using a universal adapter in genetically encoded split TEV assays. Cell. Mol. Life Sci. 76, 1185–1199.
Monitoring activities of receptor tyrosine kinases using a universal adapter in genetically encoded split TEV assays - PubMed (nih.gov)

- 2018

- Herholt, A. et al. Pathway sensor-based functional genomics screening identifies modulators of neuronal activity. Sci Rep 8, 17597.
Pathway sensor-based functional genomics screening identifies modulators of neuronal activity - PubMed (nih.gov)

- Galinski, S. et al. Multiplexed profiling of GPCR activities by combining split TEV assays and EXT-based barcoded readouts. Sci Rep 8, 8137.
Multiplexed profiling of GPCR activities by combining split TEV assays and EXT-based barcoded readouts - PubMed (nih.gov)

- Raabe, F.J. Studying and modulating schizophrenia-associated dysfunctions of oligodendrocytes with patient-specific cell systems. NPJ Schizophr 4, 23
. Studying and modulating schizophrenia-associated dysfunctions of oligodendrocytes with patient-specific cell systems - PubMed (nih.gov)

- 2017

Wehr, M.C. et al. Spironolactone is an antagonist of NRG1-ERBB4 signaling and schizophrenia-relevant endophenotypes in mice. EMBO Mol Med 9, 1448–1462.
Spironolactone is an antagonist of NRG1-ERBB4 signaling and schizophrenia-relevant endophenotypes in mice - PubMed (nih.gov)

- 2016

Wehr, M.C. et al. Split protein biosensor assays in molecular pharmacological studies. Drug Discov. Today 21, 415–429.
Split protein biosensor assays in molecular pharmacological studies - PubMed (nih.gov)

- 2013

Wehr, M.C. et al. Salt-inducible kinases regulate growth through the Hippo signalling pathway in Drosophila. Nat Cell Biol 15, 61–71.
Salt-inducible kinases regulate growth through the Hippo signalling pathway in Drosophila - PubMed (nih.gov)

- 2011

Djannatian, M.S. et al. Studying G protein-coupled receptor activation using split-tobacco etch virus assays. Analytical Biochemistry 412, 141–152.
Studying G protein-coupled receptor activation using split-tobacco etch virus assays - PubMed (nih.gov)

- 2010

Botvinnik, A. et al. Integrated analysis of receptor activation and downstream signaling with EXTassays. Nat. Methods 7, 74–80.
Integrated analysis of receptor activation and downstream signaling with EXTassays - PubMed (nih.gov)

- 2006

Wehr, M.C. et al. Monitoring regulated protein-protein interactions using split TEV. Nat. Methods 3, 985–993.
Monitoring regulated protein-protein interactions using split TEV - PubMed (nih.gov)

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Systasy Publication List

Neurological & Psychiatric Diseases

- **2021**

Volkmann, P., Stephan, M., et al. PsyCoP - A Platform for Systematic Semi-Automated Behavioral and Cognitive Profiling Reveals Gene and Environment Dependent Impairments of Tcf4 Transgenic Mice Subjected to Social Defeat. Front Behav Neurosci 14, 618180.

PsyCoP - A Platform for Systematic Semi-Automated Behavioral and Cognitive Profiling Reveals Gene and Environment Dependent Impairments of Tcf4 Transgenic Mice Subjected to Social Defeat – PubMed (nih.gov)

- **2020**

Hasan A et al. Add-on spironolactone as antagonist of the NRG1-ERBB4 signaling pathway for the treatment of schizophrenia: Study design and methodology of a multicenter randomized, placebo-controlled trial. Contemp Clin Trials Commun. 17:100537.

Add-on spironolactone as antagonist of the NRG1-ERBB4 signaling pathway for the treatment of schizophrenia: Study design and methodology of a multicenter randomized, placebo-controlled trial - PubMed (nih.gov)

- **2019**

Papiol, S. et al. Polygenic burden associated to oligodendrocyte precursor cells and radial glia influences the hippocampal volume changes induced by aerobic exercise in schizophrenia patients. Transl Psychiatry 9, 284.

Polygenic burden associated to oligodendrocyte precursor cells and radial glia influences the hippocampal volume changes induced by aerobic exercise in schizophrenia patients - PubMed (nih.gov)

Raabe, F.J. et al. Oligodendrocytes as A New Therapeutic Target in Schizophrenia: From Histopathological Findings to Neuron-Oligodendrocyte Interaction. Cells 8, 1496. doi:10.3390/cells8121496.

Oligodendrocytes as A New Therapeutic Target in Schizophrenia: From Histopathological Findings to Neuron-Oligodendrocyte Interaction - PubMed (nih.gov)

Stephan, M. et al. Assessing behavior and cognition in rodents, nonhuman primates, and humans: where are the limits of translation? Dialogues Clin Neurosci *21*, 249–259.

Assessing behavior and cognition in rodents, nonhuman primates, and humans: where are the limits of translation? - PubMed (nih.gov)

- **2017**

Papiol, S., Popovic et al. Polygenic risk has an impact on the structural plasticity of hippocampal subfields during aerobic exercise combined with cognitive remediation in multi-episode schizophrenia. Transl Psychiatry 7, e1159.

Polygenic risk has an impact on the structural plasticity of hippocampal subfields during aerobic exercise combined with cognitive remediation in multi-episode schizophrenia - PubMed (nih.gov)

- **2016**

Brzózka, M.M. et al. Molecular Signatures of Psychosocial Stress and Cognition Are Modulated by Chronic Lithium Treatment. Schizophr Bull *42 Suppl 1*, S22-33.

Molecular Signatures of Psychosocial Stress and Cognition Are Modulated by Chronic Lithium Treatment - PubMed (nih.gov)

- **2015**

Falkai, P. et al. Kraepelin revisited: schizophrenia from degeneration to failed regeneration. Mol. Psychiatry *20*, 671–676.

Kraepelin revisited: schizophrenia from degeneration to failed regeneration - PubMed (nih.gov)

- **2014**

- Agarwal, A. et al. Dysregulated expression of neuregulin-1 by cortical pyramidal neurons disrupts synaptic plasticity. Cell Rep 8, 1130–1145.

Dysregulated expression of neuregulin-1 by cortical pyramidal neurons disrupts synaptic plasticity - PubMed (nih.gov)

- Badowska, D.M. et al Data calibration and reduction allows to visualize behavioural profiles of psychosocial influences in mice towards clinical domains. Eur Arch Psychiatry Clin Neurosci.

Data calibration and reduction allows to visualize behavioural profiles of psychosocial influences in mice towards clinical domains - PubMed (nih.gov)

- Quednow, B.B. et alTranscription factor 4 (TCF4) and schizophrenia: integrating the animal and the human perspective. Cell. Mol. Life Sci. *71*, 2815–2835.

Transcription factor 4 (TCF4) and schizophrenia: integrating the animal and the human perspective - PubMed (nih.gov)

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