A new strategy for genetics & pharmacogenomics (GpGx)

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Vice President
Head of Genetics & Pharmacogenomics
Leverage human genetic data to find targets that are safe and effective

Discover new pathways using a systems approach anchored in human genetics

Validate novel drug targets and pathways that emerge from human genetics

Apply cutting-edge genomic technologies to understand MOA and generate biomarkers

Apply genetics in clinical trials to ensure that our drugs are safe and effective

Our Shared Goals
- Impact the entire pipeline
- Drive early discovery
- Integrate with EDDS

Robert Plenge

H. Runz
- Genetics

A. Loboda
- CSB

M. Cleary
- T&PB

E. Gustafson
- DiscPGx

B. Blanchard
- ClinPGx

TIDVAL

Lead Optimization

First-in-human Trials

Phase II-III Clinical Trials
Mission: To leverage human genetic data to identify targets that, when perturbed, have an increased probability of being safe and effective in humans.

High Level Objectives

1. Identify single gene targets in key therapeutic areas that impact decisions on new drug discovery programs.
2. Collaborate with CSB, T&PB and disease areas to probe pathways anchored in human genetics.
3. Establish an aspirational model with a comprehensive strategy to guide MRL investment decisions.
4. Support genetic analyses across GpGx and MRL, including ClinPGx.
Pick a human phenotype for drug efficacy

Identify a series of alleles

Assess pleiotropy as proxy for ADEs

Assess biological function of alleles

This provides evidence for the therapeutic window at the time of target ID & validation.

Discover genetic targets
Computational Systems Biology (CSB)

**Mission:** To advance genetics driven target discovery using a systems approach linking genetics with key pathways and disease states

**High Level Objectives**

- **Advance knowledge of biology relevant to targets, pathways and disease mechanisms identified through genetics**
- **Develop a framework to probe pathways and discover targets anchored in human genetics (e.g., phenotypic screens)**
- **Leverage a systems approach to understand MOA and impact decision making throughout drug development pipeline (e.g., IMR, PD1)**
- **Build capabilities (e.g., methods, datasets) that provide a competitive advantage in understanding targets/pathways**
Genotype

Mendelian mutations
GWAs loci
Cancer associated genes

Systems and networks

Perturbations

Phenotypes

Mendelian disorders
Complex traits
Tumors

Make complex systems actionable
Mission: To provide early functional validation of novel drug targets coming from genetics and disease pathway exploration

High Level Objectives

- Advance knowledge of biology relevant to targets identified through genetics
- Collaborate with disease areas to probe pathways anchored in human genetics
- Build new capabilities and models that provide competitive advantage in understanding targets and pathways
- Leverage unique capabilities to reach Go/No-Go decisions on more mature targets
Functional validation of genes, mutations and pathways

<table>
<thead>
<tr>
<th>Triglycerides</th>
<th>Cholesterol Esters</th>
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<tbody>
<tr>
<td>P = 5.5 x 10^{-8}</td>
<td>P = 3.29 x 10^{-10}</td>
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Control AAV  
$mTm6sf2$-sh

AAV-control  
AAV-gene

Develop and deploy emerging genome technologies (e.g., CRISPR)

Build biological packages for genetic targets
**Discovery Pharmacogenomics (DiscPGx)**

**Mission:** To use advanced genomics technologies to understand MOA, generate genomic biomarkers, and add long-term value to MRL pipeline projects

<table>
<thead>
<tr>
<th>High Level Objectives</th>
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<tbody>
<tr>
<td>Conduct preclinical and clinical studies focused on MOA and response biomarkers for PD-1</td>
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<tr>
<td>Utilize preclinical and clinical studies to advance novel targets (e.g., IMRs) in the Merck pipeline</td>
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<tr>
<td>Perform safety genomics to de-risk targets</td>
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<td>Utilize genomics to streamline bio-processing</td>
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<tr>
<td>Develop genomic biomarkers for the pipeline</td>
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<tr>
<td>Conduct bioinformatic analyses for the pipeline</td>
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Traditional methods

Clinical Tissue Sample

Pathology

Genomic technologies

Data generation

GWAS
TcR
DGE

Complex data analysis

Immune Gene Signature

Merck Genetics & Pharmacogenomics (GpGx)
Clinical Pharmacogenomics (ClinPGx)

**Mission:** Create opportunity for Merck to understand and leverage key genetic determinants of patient response to our drugs

**High Level Objectives**

- Develop the infrastructure, execution plan and stakeholder relationships to routinely generate genetic data from patients in ongoing clinical trials
- Conduct scientific analyses of genotype-phenotype data (esp. safety and efficacy) from clinical trials
- Impact clinical development strategy
- Adopt enabling capabilities (e.g., genomic technologies, EMRs, regulatory guidance, patient consenting practices)
Simple yet comprehensive approach to pharmacogenetics

<table>
<thead>
<tr>
<th>Clinical trial stage</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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<tbody>
<tr>
<td>Genetic approach</td>
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<tr>
<td>Candidate genes</td>
<td></td>
<td>Primary discovery</td>
<td>Stratified trial</td>
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<tr>
<td>Drug metabolism, drug targets</td>
<td></td>
<td>GWAS + WES</td>
<td>Enriched for responders</td>
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<tr>
<td>Cost</td>
<td>&lt; $100,000</td>
<td>$100,000 - $600,000</td>
<td>$250,000 - $2,000,000</td>
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<tr>
<td>Number of patients</td>
<td>50-300 patients</td>
<td>300-1,000 patients</td>
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