A new strategy for genetics & pharmacogenomics (GpGx)

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Merck Genetics & Pharmacogenomics (GpGx)

Our Shared Goals

• Impact the entire pipeline
• Drive early discovery
• Integrate with EDDS

Robert Plenge

Genetics
H. Runz
Leverage human genetic data to find targets that are safe and effective

CSB
A. Loboda
Discover new pathways using a systems approach anchored in human genetics

T&PB
M. Cleary
Validate novel drug targets and pathways that emerge from human genetics

DiscPGx
E. Gustafson
Apply cutting-edge genomic technologies to understand MOA and generate biomarkers

ClinPGx
B. Blanchard
Apply genetics in clinical trials to ensure that our drugs are safe and effective

TIDVAL
Lead Optimization
First-in-human Trials
Phase II-III Clinical Trials

Merck Genetics & Pharmacogenomics (GpGx)
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:

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

Assess biological function of alleles

Identify a series of alleles

Assess pleiotropy as proxy for ADEs

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

Discover genetic targets
**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**
Make complex systems actionable
**Target and Pathway Biology (T&PB)**

**Mission:** To provide early functional validation of novel drug targets coming from genetics and disease pathway exploration

### High Level Objectives

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<th>Objective</th>
<th>Description</th>
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<td>Advance knowledge of biology relevant to targets identified through genetics</td>
<td>Collaborate with disease areas to probe pathways anchored in human genetics</td>
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<td>Build new capabilities and models that provide competitive advantage in understanding targets and pathways</td>
<td>Leverage unique capabilities to reach Go/No-Go decisions on more mature targets</td>
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Genetics & Pharmacogenomics (GpGx)
Functional validation of genes, mutations and pathways

- Triglycerides: $P = 5.5 \times 10^{-8}$
- Cholesterol Esters: $P = 3.29 \times 10^{-10}$

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

### High Level Objectives

- **Conduct preclinical and clinical studies focused on MOA and response biomarkers for PD-1**
- **Utilize preclinical and clinical studies to advance novel targets (e.g., IMRs) in the Merck pipeline**
- **Perform safety genomics to de-risk targets**
- **Utilize genomics to streamline bio-processing**
- **Develop genomic biomarkers for the pipeline**
- **Conduct bioinformatic analyses for the pipeline**
**Mission:** Create opportunity for Merck to understand and leverage key genetic determinants of patient response to our drugs

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