A new strategy for genetics & pharmacogenomics (GpGx)

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EDDS Leadership Team

EDDS will deliver a pipeline of meaningful therapies by nurturing a culture of innovation and collaboration between Clinical and Discovery sciences.
Our passion is to use human data via genetics and genomics to influence the entire process of drug development: (1) identification and validation of new targets, (2) biomarkers for target engagement and safety in pre-clinical studies, and (3) biomarkers for efficacy and toxicity in clinical trials (e.g., precision medicine).
Merck Genetics & Pharmacogenomics (GpGx)

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

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

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

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

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

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

B. Blanchard
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

*Stages of Drug Development*
- 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**

- 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.

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

**High Level Objectives**

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

unmet clinical need

human data

biological pathways

Develop a systems approach to link genetics with pathways and clinical phenotypes
Assign targets to genetic pathways and assess differentiation from SOC
Identify new targets for drug discovery programs
Develop cellular and molecular assays to advance pathway-based screens

Make complex pathways actionable for drug discovery

Human genetics, longitudinal clinical data, therapeutic perturbations
Gene expression, protein-protein interactions, model organisms, etc.
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**

- 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

Genetics & Pharmacogenomics (GpGx)
AAV for functional validation of genes, mutations and pathways

- Triglycerides
  - Control AAV: P=5.5x10^-8
  - mTm6sf2-sh: P=3.29x10^-10

- Cholesterol Esters

siRNA to make Go / No-Go decisions on targets in the pipeline

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

Go*
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**

Genetics & Pharmacogenomics (GpGx)
Merck Genetics & Pharmacogenomics (GpGx)

Data generation

Complex data analysis

GWAS
TcR
DGE

Immune Gene Signature

PD-1/IMR
MOA studies
Response BMX

Safety
Organ Tox signatures
Novel assay platforms

Bioinformatics
Bioprocessing
VZV

Merck Genetics & Pharmacogenomics (GpGx)
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)
### Genetic approach

<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>
<td>Candidate genes&lt;br&gt;Drug metabolism, drug targets</td>
<td>Primary discovery&lt;br&gt;GWAS + WES</td>
<td>Stratified trial&lt;br&gt;Enriched for responders&lt;br&gt;&lt;br&gt;Genetic marker/Positive result&lt;br&gt;&lt;br&gt;Continued discovery&lt;br&gt;GWAS, targeted genotyping, +/- WES</td>
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### Hypotheses

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<th>Genetic variation explains PK variability</th>
<th>Genetic variation Explains variable efficacy</th>
<th>Validation: Phase II GWAS “hit” predicts for response in Phase 3 Clinical validation of companion diagnostic</th>
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<tbody>
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<td>A drug-drug interaction is unlikely</td>
<td>There is a genetic determinant of risk of an adverse event</td>
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**Simple yet comprehensive approach to pharmacogenetics**

Merck Genetics & Pharmacogenomics (GpGx)