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).
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

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.
Pick a human phenotype for drug efficacy

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

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**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
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
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
AAV for functional validation of genes, mutations and pathways

Triglycerides

P=5.5x10^{-8}

Cholesterol Esters

P=3.29x10^{-10}

Control AAV  mTm6sf2-sh

AAV-control  AAV-gene

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

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

Factor IX LNP (mg/kg, 7 days post bolus IV)

Clot weight (% inhibition)

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

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<thead>
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<th>High Level Objectives</th>
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<tr>
<td>Conduct preclinical and clinical studies focused on MOA and response biomarkers for PD-1</td>
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<td>Utilize preclinical and clinical studies to advance novel targets (e.g., IMRs) in the Merck pipeline</td>
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<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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<td>Develop genomic biomarkers for the pipeline</td>
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<td>Conduct bioinformatic analyses for the pipeline</td>
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Genetics & Pharmacogenomics (GpGx)
**Clinical Pharmacogenomics (ClinPGx)**

**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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### Hypotheses

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<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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<td><strong>Candidate genes</strong>&lt;br&gt;Drug metabolism, drug targets</td>
<td><strong>Primary discovery</strong>&lt;br&gt;GWAS + WES</td>
<td><strong>Stratified trial</strong>&lt;br&gt;Enriched for responders&lt;br&gt;<strong>Continued discovery</strong>&lt;br&gt;GWAS, targeted genotyping, +/- WES</td>
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**Genetic variation explains PK variability**

**A drug-drug interaction is unlikely**

**Genetic variation explains variable efficacy**

**There is a genetic determinant of risk of an adverse event**

**Validation: Phase II GWAS “hit” predicts for response in Phase 3**

**Clinical validation of companion diagnostic**

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**Simple yet comprehensive approach to pharmacogenetics**

Merck Genetics & Pharmacogenomics (GpGx)