A new strategy for genetics & pharmacogenomics (GpGx)

Robert M. Plenge, MD, PhD
Vice President
Head of Genetics & Pharmacogenomics

September 2014

EDDS Leadership Team

EDDS will deliver a pipeline of meaningful therapies by nurturing a culture of innovation and collaboration between Clinical and Discovery sciences.

Rupert Vessey
EDDS

Therapeutic Areas

Mark Erion
Cardio-metabolics

Darryle Schoepp
Neuro-science

Deborah Law
Immunology, IMR, Oncology

Daria Hazuda
Infectious Diseases & Vaccines

Functions

Robert Plenge
Genetics & Pharmaco-genomics

John Hunter
Pharma-cology

Chris Hill
Discovery Chemistry

Gary Herman
Early Stage Development

MERCK
Be well

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).

@rplenge

Robert Plenge

Our Shared Goals

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

P. Goldman

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

Disc*PGx*

E. Gustafson

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

Clin*PGx*

B. Blanchard

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

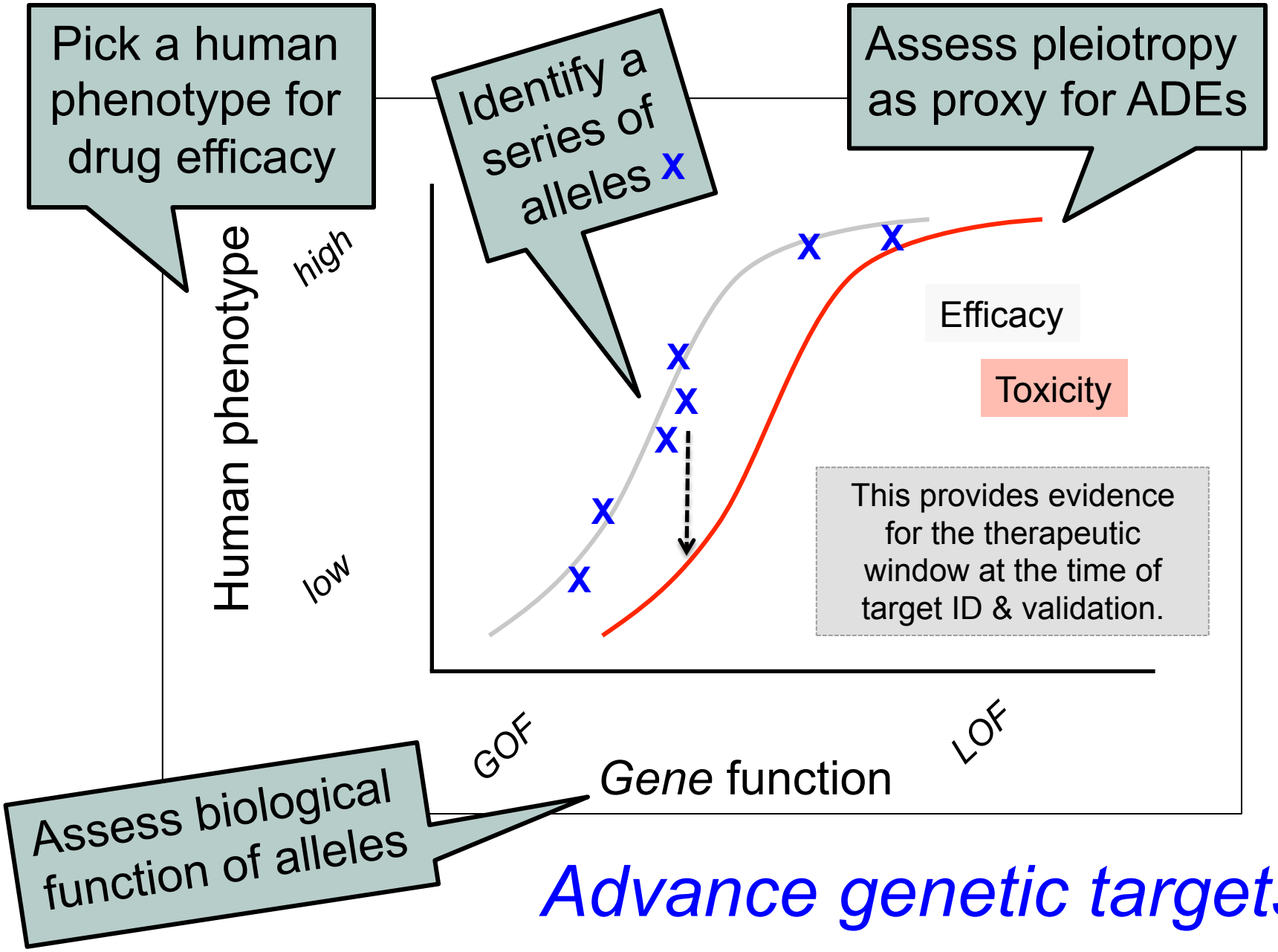
TIDVAL → Lead Optimization → First-in-human Trials → Phase II-III Clinical Trials

Genetics

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



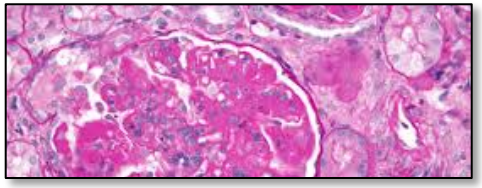
Advance genetic targets!

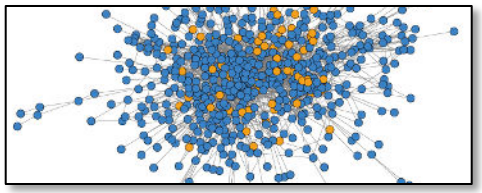
Computational Systems Biology (CSB)

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





unmet clinical need

↓

human data

↓

biological pathways

↓

Human genetics, longitudinal clinical data, therapeutic perturbations

Gene expression, protein-protein interactions, model organisms, etc.

- **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 <u>actionable</u> for drug discovery

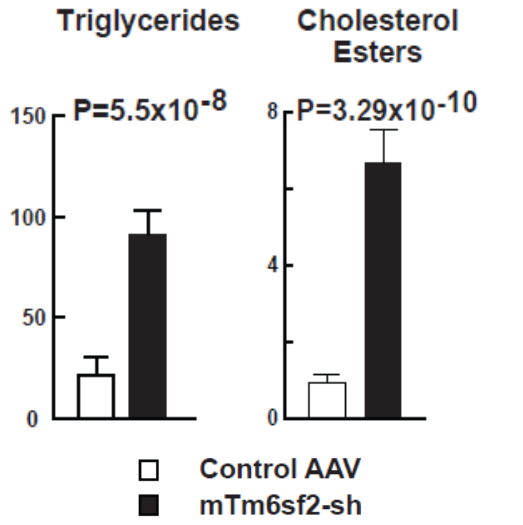
Target and Pathway Biology (T&PB)

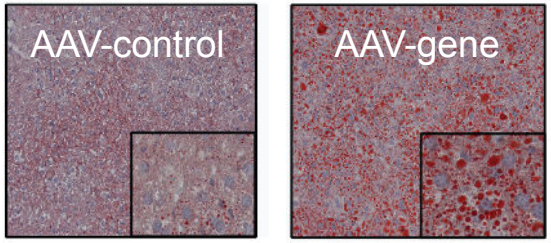
Mission: To provide early functional validation of novel drug targets coming from genetics and disease pathway exploration

High Level Objectives

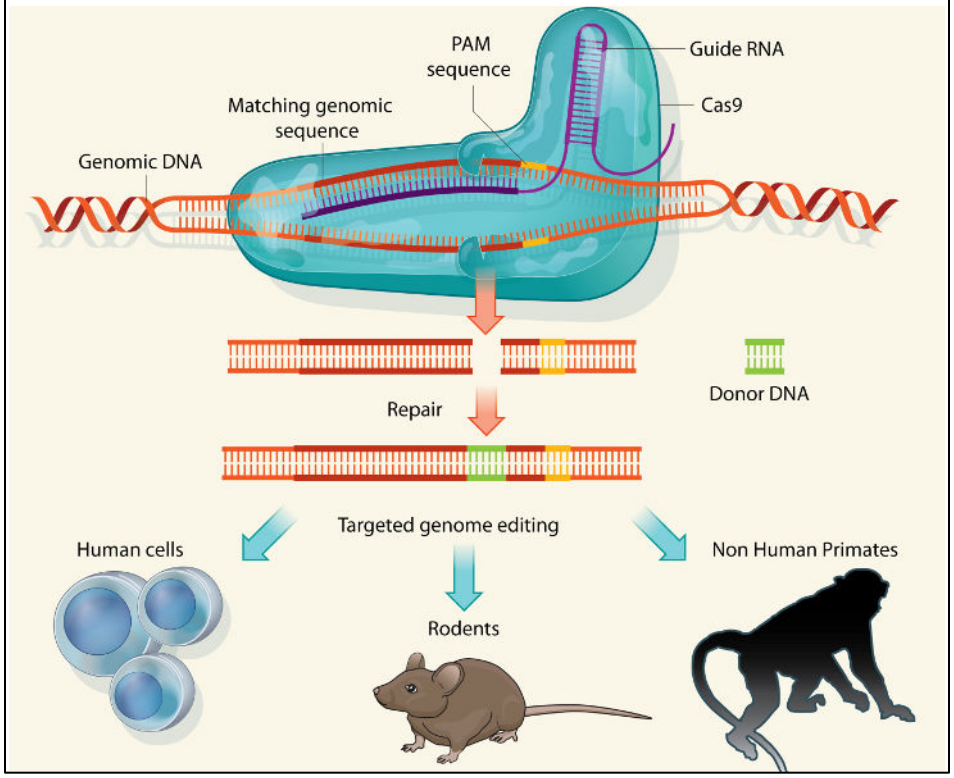
Advance knowledge of biology relevant to targets identified through genetics	Collaborate with disease areas to probe pathways anchored in human genetics	Build new capabilities and models that provide competitive advantage in understanding targets and pathways	Leverage unique capabilities to reach Go/No-Go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

AAV for functional validation of genes, mutations and pathways

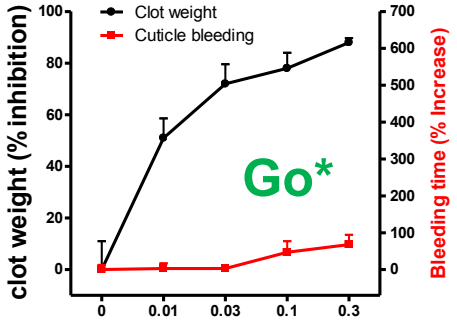




Develop and deploy genome editing technologies (e.g., CRISPR, GEMs)



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



Discovery Pharmacogenomics (DiscPGx)

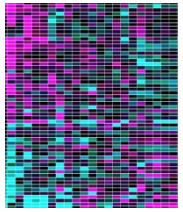
Mission: To use advanced genomics technologies to understand MOA, generate genomic biomarkers, and add long-term value to MRL pipeline projects

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 stream-line bio-processing	Develop genomic biomarkers for the pipeline	Conduct bioinformatic analyses for the pipeline

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

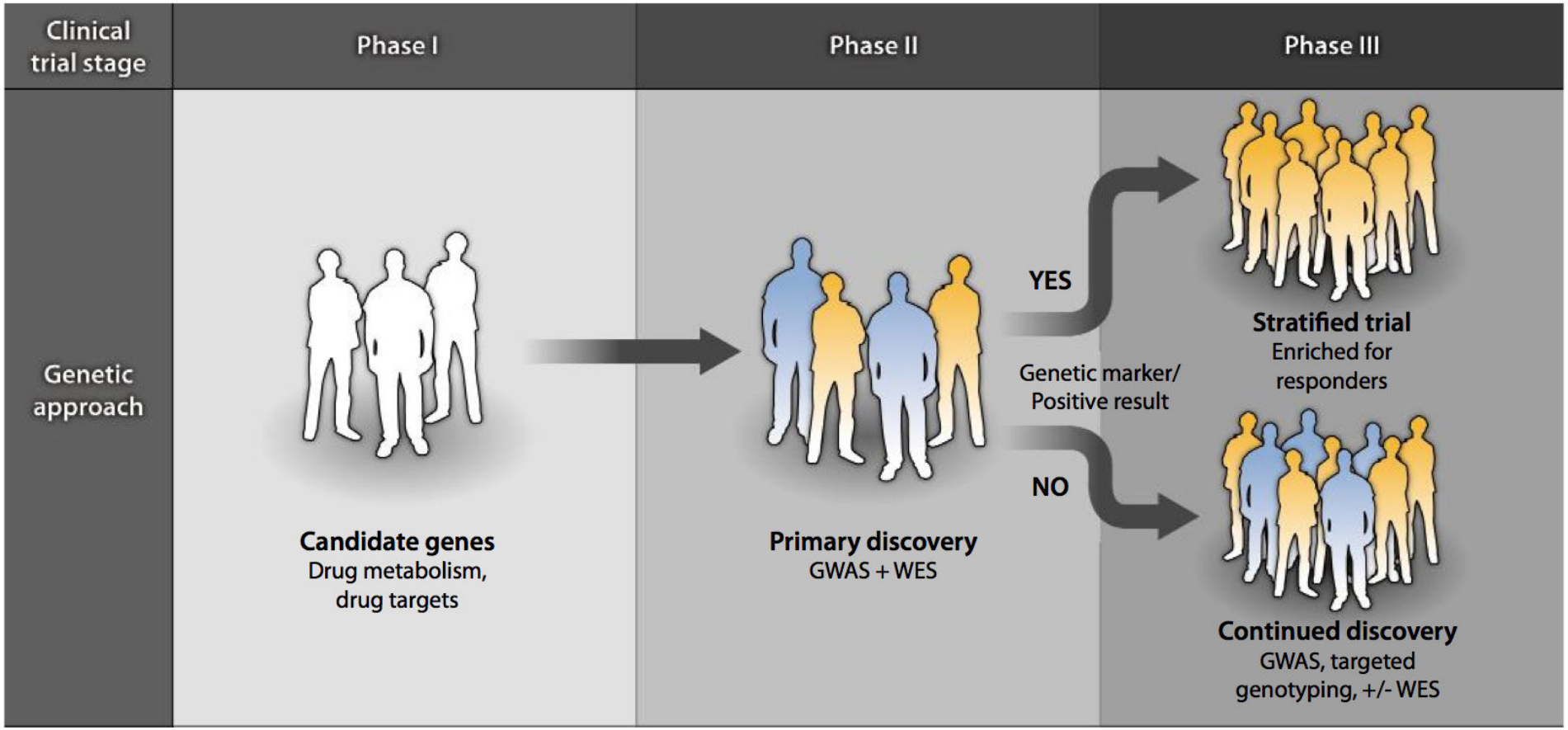
- Bioinformatics
- Bioprocessing
- VZV

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)



Hypotheses			
	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

Simple yet comprehensive approach to pharmacogenetics