IMPACT OF HUMAN GENETICS ON DRUG R&D

Robert Plenge
Harvard Medical School, Executive Education
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Introduction
- Why human genetics?

Day 1:
- The model
- Picking targets and pathways
- Matching modality and mechanism

Day 2:
- Predictive biomarkers
- Clinical development
- Emerging resources
A disciplined approach to integrating all four components will lead to the following improvements:

- Increased probability of success in phase 2/3 clinical trials
- Increased probability for differentiation from standard of care
What is a biomarker?

- **Pharmacokinetic (PK)** – what the body does to the drug
- **Pharmacodynamic (PD)** – what the drug does to the body

![Diagram](image)

- **Concentration vs. Time**
- **Effect vs. Concentration**
- **Exposure**
- **Response**
Human genetics can help select PD biomarkers and model exposure-response relationship.
The immune system is imbalanced in I&I diseases

- Th17 cell
- CD4+ T cell
- CD8+ T cell
- B cell
- Treg
- Tolerized T cell
- Exhausted T cell

Excessive Killing

Insufficient Resolution
Regulatory T cells (Tregs) are key modulators of immune homeostasis.

**Tregs Employ Multiple Regulatory Mechanisms:**
- IL-2 consumption
- CTLA-4
- IL-10
- TIGIT
- CD39/CD73
- GARP

**IL-2 Controls Treg Expansion and Function**
Regulatory T cells are key regulators of immune homeostasis

*IL2RA* gene codes for CD25 protein, which is the “alpha” receptor...

...and “alpha” receptor is selectively expressed on Tregs.

**IL-2**
Human knockouts of *IL2RA* have severe autoimmunity

**IPEX Syndrome**
- Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked syndrome
- Rare, fatal immune disorder
- Skin, intestinal, endocrine autoimmune disease

- Reduced Treg cell levels and/or function
- Cured by hematopoietic stem cell transplantation
- Loss-of-function mutations in *FOXP3* gene
- Also caused by nonfunctional alleles of *IL2RA*
Common *IL2RA* variants predispose to multiple autoimmune diseases

- Story is complicated, but...protective allele is associated with higher expression on CD4+ memory T cells

*Suggests* that GoF on Tregs increases Treg function and protects from autoimmunity

Partial GoF protects from autoimmunity (GWAS)

Complete LoF leads to absence of Tregs and autoimmunity

Function-phenotype dose-response curve for IL2RA
Therapeutic hypothesis

Agonizing CD25 (alpha subunit of IL2 receptor) will selectively expand Tregs and treat a wide-variety of autoimmune disorders
IL2 “muteins” selectively bind to CD25 (alpha subunit of IL2R)

IL-2

IL-2 mutein

Teffector cell
Immune killing

Treg
Immune resolution

Teffector cell
Immune killing

Treg
Immune resolution
Therapeutic hypothesis

Agonizing CD25 (alpha subunit of IL2 receptor) will selectively expand Tregs and treat a wide-variety of autoimmune disorders

What PD biomarkers should be used to measure exposure-response in Phase 1?
Treg : T effector ratio is a good PD biomarker

IL-2 mutein

Treg : Teff ratio ~5-fold expansion

Treg : Teff ratio

Immune killing

Immune resolution

Koreth et al NEJM (2011)
Therapeutic hypothesis

Agonizing CD25 (alpha subunit of IL2 receptor) will selectively expand Tregs and treat a wide-variety of autoimmune disorders

What PD biomarkers should be used to measure exposure-response in Phase 1?

What indications should be pursued for PoC?
Rare LoF IPEX mutations guide indication selection

Common GoF GWAS variants guide indication selection

$IL2RA$ variant

Psoriasis, inflammatory arthritis, type 1 diabetes, other

Li et al Nat Genet (2015)
Phenome-wide association studies (PheWAS)

- **Data Sources**
  - EHRs, Claims, Questionnaires, etc.
  - Disease-agnostic cohort
  - Genetic data (GWAS, exome sequencing, etc.)

**Process**

1. **Clinical data**
   - Test association of selected SNP with clinical endpoints

2. **Genetic data**
   - SNP
   - Gene function: GOF, LOF
   - Human Phenotype

**Outcomes**

- **Risk**
  - Surrogate for efficacy
  - Surrogate for toxicity

**Graph**

- Efficacy vs. Toxicity
  - GOF vs. LOF
But it doesn’t always work!

Plenge Science Translational Medicine (2016)
Amyloid hypothesis and Alzheimer’s disease: the role of the APP gene and BACE1 in disease initiation

Causal human biology
- APP, PSEN1, PSEN2 mutations cause FAD, increase Aβ cleavage
- APP-A673T variant reduces AD risk, decrease Aβ cleavage
- Naturally occurring antibodies to Aβ oligomers decrease AD risk

Aβ oligomers aggregate to form oligomers and β-amyloid plaques that are toxic to surrounding neurons

Neuron cell death leading to cognitive decline and other symptoms of AD
Therapeutic hypothesis: **BACE-inhibition blocks release of toxic Aβ and reduces AD progression**

1. Protective **APP** mutation reduces BACE1 cleavage in vitro
2. BACE1 inhibitor mimics APP mutation and blocks first step in release of toxic Ab peptides
3. Decrease in Aβ oligomers in brain protect from AD
$A\beta$ peptide levels measured in CSF serve as a quantitative biomarker for target modulation.

Does the drug engage and modulate the target (PD)?

Is there a dose-dependent relationship in human subjects?

Healthy Volunteers

Drug

Low dose
High dose

CSF

Alzheimer’s Patients

Drug

Low dose
High dose

CSF

Kennedy et al STM (2016)
MK-8931 lowers Aβ levels in CSF from healthy volunteers and Alzheimer’s disease patients.
Fig. 7. Simulated steady-state verubecestat dose-response curves and predicted distribution of individual responses. A prospectively planned mechanistic PK/PD model was generated that used data across all time points, CSF PD end points, and studies to develop an integrated characterization of verubecestat effects in humans. (A) The solid and dashed lines represent the median and 90% confidence interval, respectively, of 1000 replicates of the response in a typical AD patient (black line) and a healthy nonelderly adult subject (red line). (B) Simulated distributions of individual CSF Aβ40 and de novo brain Aβ40 production in AD patients (n = 1000 subjects per dose level).
But not every therapy against a genetic target is successful…

Egan et al. NEJM (2018)
Key points about biomarkers and why genetic targets fail

- Essential to have robust PD biomarkers and PK/PD model to predict safety / efficacy
- Ideally, quantitative PK/PD model should be firmly rooted in human genetics
- Even so, not all therapies based on genetic targets will lead to approved drugs
  - Genetics is lifelong, drugs are not
  - Not all genetic phenotypes are good surrogates for drug discovery
  - Modality and molecular mechanism may not be precisely matched
  - Intervention may not sufficiently test therapeutic hypothesis
There are emerging resources to help maximize human genetics for drug discovery and development
Genetics can bridge biomarker with clinical data, establishing a causal link for drug discovery.
Mendelian randomization: *nature’s clinical trial*

- Randomised controlled trial
  - Randomisation into groups
    - Intervention
      - Protein biomarker lower
        - Disease risk lower
    - Control
      - Protein biomarker higher
        - Disease risk higher
Mendelian randomization: *nature’s clinical trial*

**Randomised controlled trial**

- Randomisation into groups

  **Intervention**
  - Protein biomarker lower
  - Disease risk lower

  **Control**
  - Protein biomarker higher
  - Disease risk higher

**Mendelian randomisation**

- Random allocation of alleles

  - Protein increasing allele(s) absent
    - Protein biomarker lower
    - Disease risk lower

  - Protein increasing allele(s) present
    - Protein biomarker higher
    - Disease risk higher
MR example: *PRTN3* and ANCA+ vasculitis

- Tested 3,622 plasma proteins in 3,301 healthy individuals from INTERVAL population cohort
- Identified 1,927 genetic associations with 1,478 proteins
- Example: *PRTN3* GoF allele increases PR3 protein and increases risk of PR3-associated vasculitis
- Therapeutic hypothesis: eliminating PR3 protein or deleting autoantibody secreting B cells may treat vasculitis

Phenome-wide association studies (PheWAS)

- EHRs, Claims, Questionnaires, etc.
- Disease-agnostic cohort
- Clinical data
- Genetic data
- SNP

Test association of selected SNP with clinical endpoints

- risk surrogate for efficacy
- risk surrogate for toxicity

GWAS, exome sequencing, etc.
Population cohorts as unique genetic resource

Kaadorie Biobank
Geisinger
NIH-AMP
INTERVAL
Estonia Precision Medicine Initiative
Finnish Founder Population
Kaiser-Permanente
deCODE genetics
Genomics England
HUNT/NTNU
The Children's Hospital of Philadelphia
Veteran's Administration
23andMe
ancestry
Saudia Arabia Genome Project
Kaadorie Biobank
Singapore Biobank

Ranking (estimates 10/2015):
- Size/quality of genetic data
- Size/quality of phenotypic data
- Connectivity of genetics & phenotypes
- Setup for recalls & Ph1 trials
PheWAS example: *IFIH1*, autoimmunity, asthma

- PheWAS in ~800,000 individuals from four population cohorts
- Tested 25 SNPs for association with 1,683 clinical endpoints
- 10 novel associations discovered
- Example: *IFIH1* LOF allele protects from autoimmunity (known) but increases risk of asthma (novel finding)
- Therapeutic hypothesis: inhibiting *IFIH1* may be effective in some autoimmune diseases but may make asthma worse

Diogo et al *under revision*
Predicted impact of therapeutic inhibition of IFIH1

Beneficial effect for some autoimmune diseases, but increase risk of asthma and UC