Data Mining for Drug Repurposing

Lon Cardon

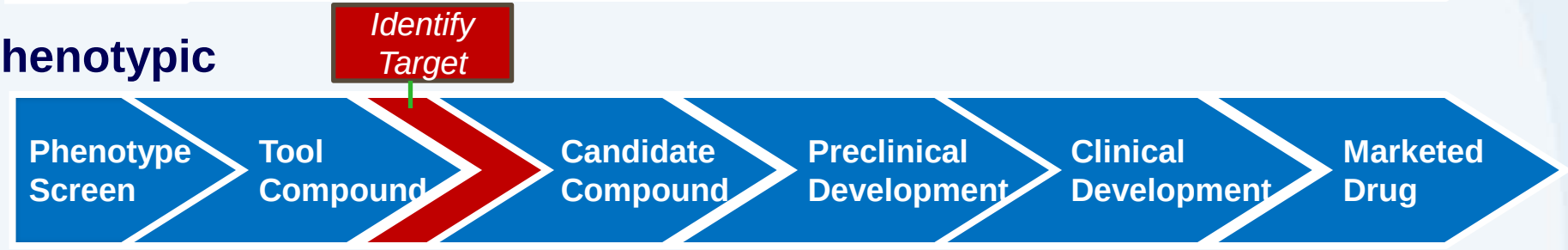
Alternative Discovery and Development

GlaxoSmithKline

Drug Discovery Modalities

Target-based

Phenotypic



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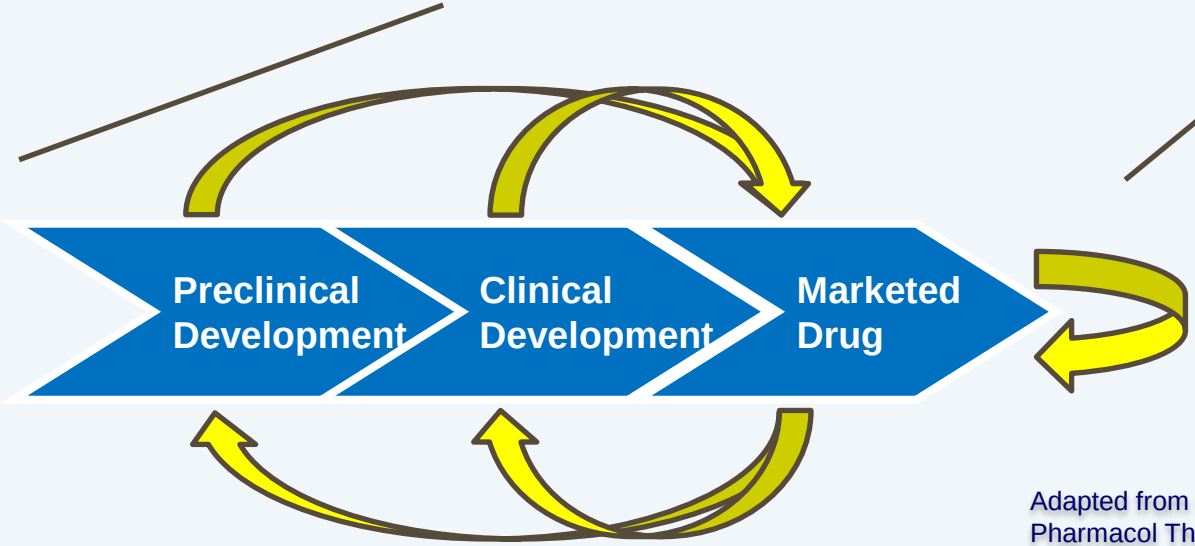
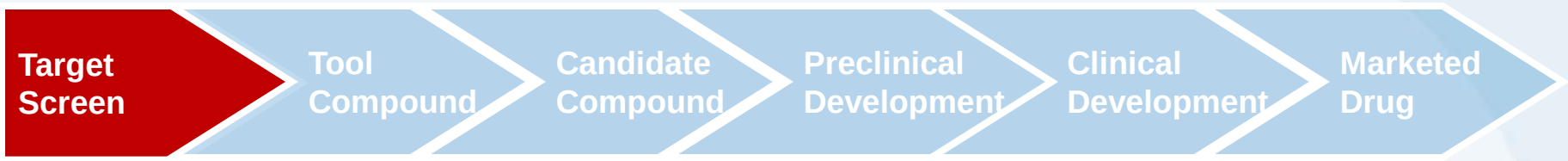


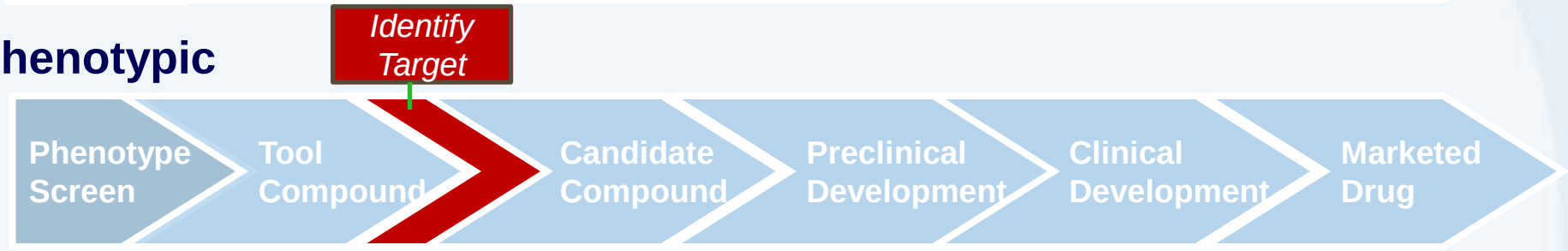
Adapted from Hurle et al..(2013) Clin Pharmacol Ther.

Drug Discovery Modalities

Target-based



Phenotypic



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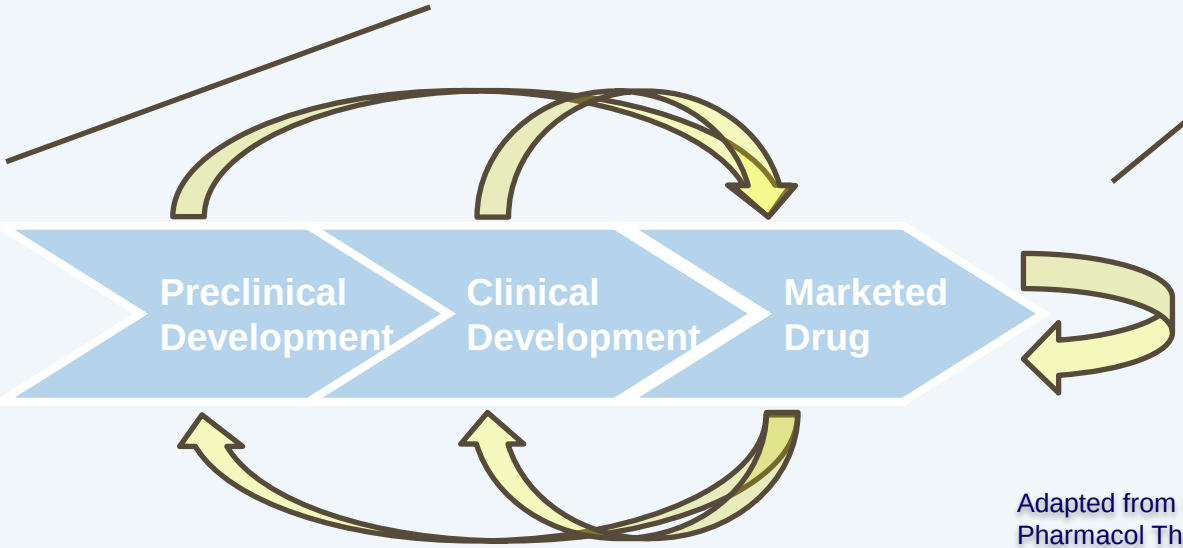

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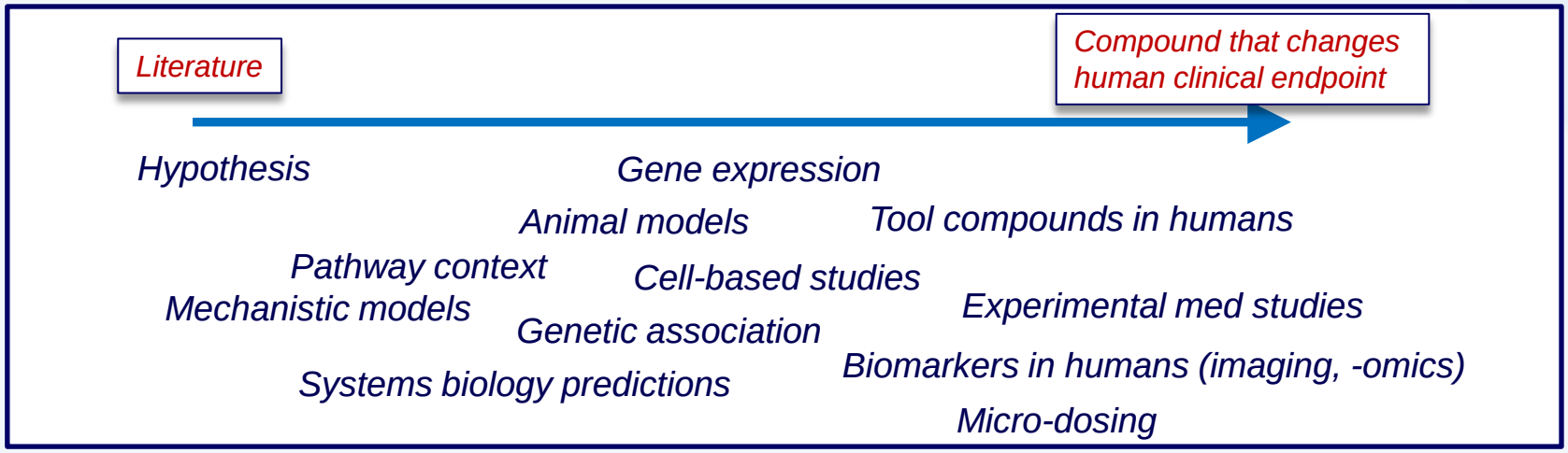
Selection & Validation of Drug Targets

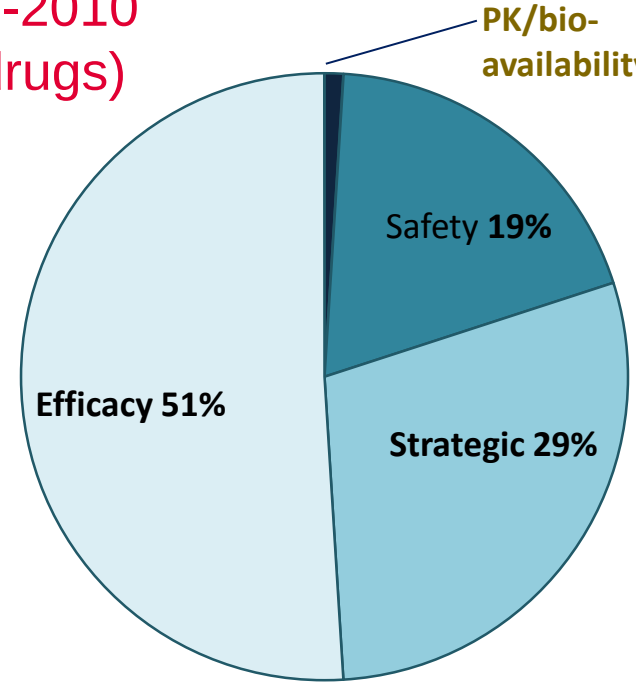


- ✓ Known mechanism
- ✓ Animal models
- ✓ Unmet need
- ✓ Previous success
- ✓ …

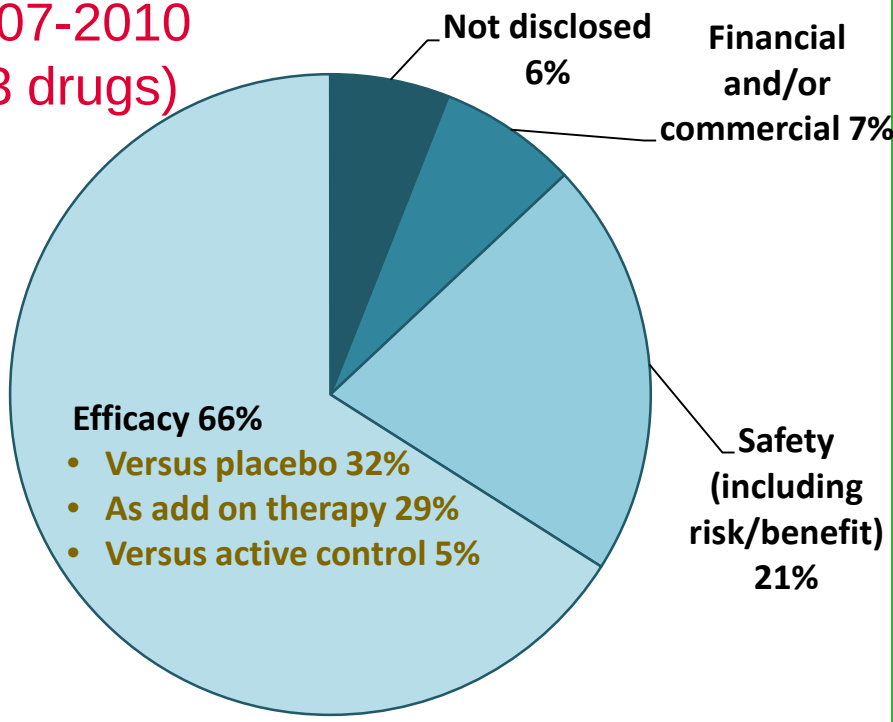
- ✓ Evidence in humans
- ✓ …
- ✓ Genetically validated
- ✓ …

Most drugs fail because they don't work

Phase II Failures: 2008-2010 (87 drugs)



Phase III/Submission Failures: 2007-2010 (83 drugs)



*Industry data from Nature Reviews Drug Discovery **10**, 2011*

Drug (re-)positioning: How much opportunity?

Targets selected vary in level of evidence, yielding

…many targets with weak empirical link to indication

→Many opportunities

Large investment required for drug discovery, yielding

…extensive evaluation before terminating programs

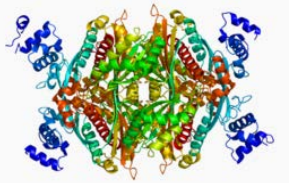
→Few opportunities

Drug (re-)positioning: Target is key

collaboration
models

genetics

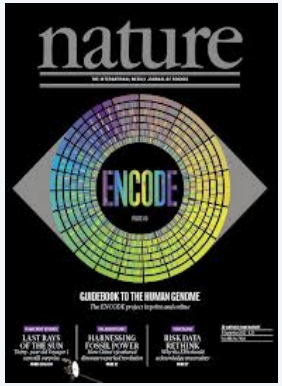
Drug



Target

electronic
health
records

human
validation

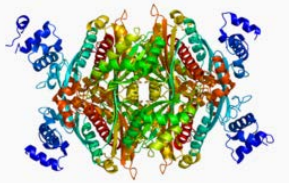


Drug (re-)positioning

collaboration
models

genetics

Drug



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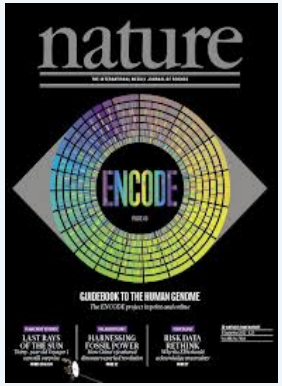
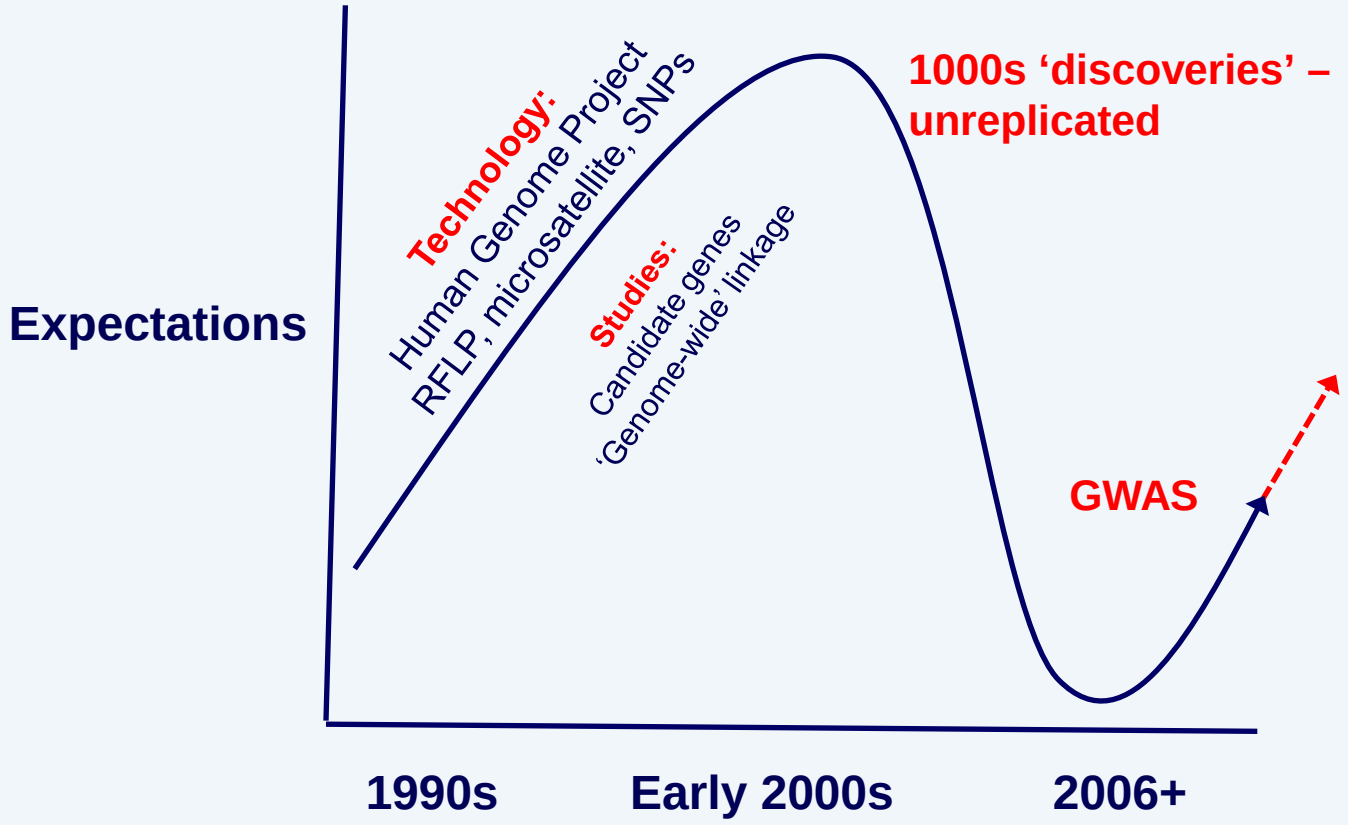
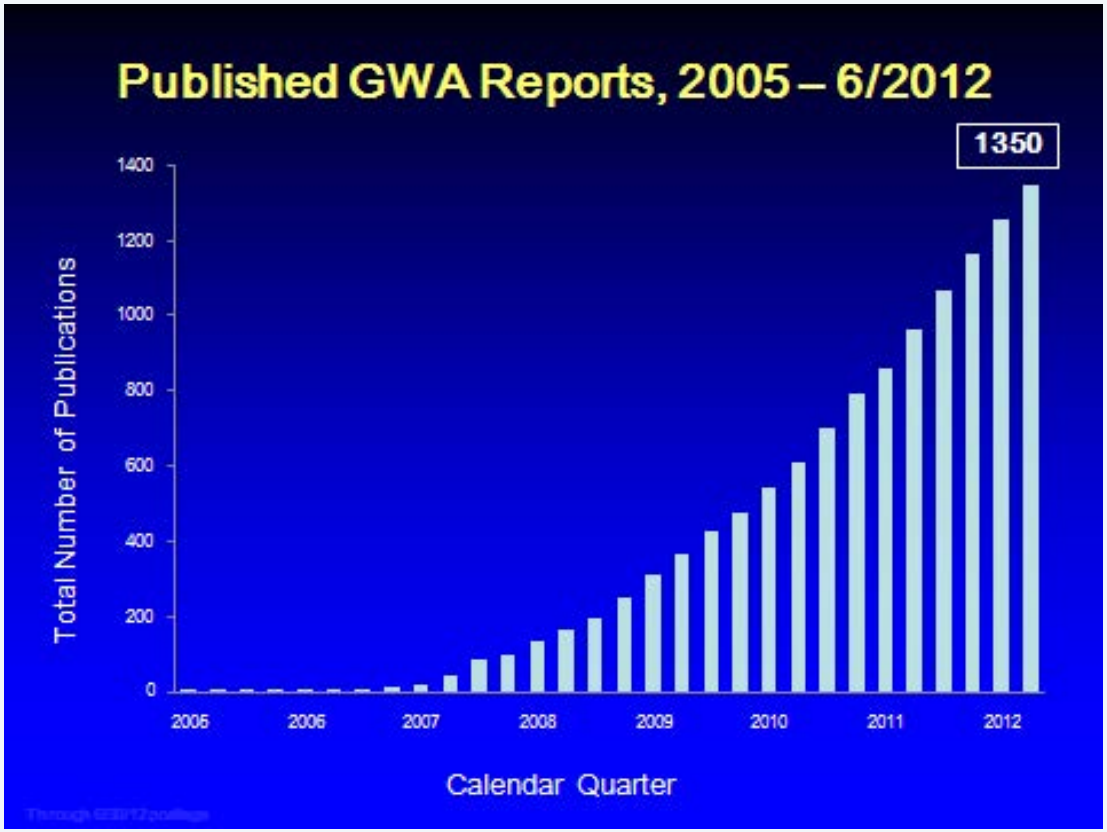


Human Genetics



GWAS Data



NHGRI (National Human Genome Research Institute) GWAS catalog: http://www.genome.gov/gwastudies/
Hindorff *et al.* PNAS, 2009

Feb 2013: 1,505 publications and 8,348 SNPs

Repositioning with GWAS

Genome Wide Association Studies (GWAS)*

Industry pipeline

155 GWAS genes targeted by drugs/biologics actively pursued by the industry (2.5X expected)

GWAS trait similar to drug indication?

No

Potential drug repositioning opportunities (92 genes)

Yes

Increased confidence in the indication (63 genes) (ex., PPARG)

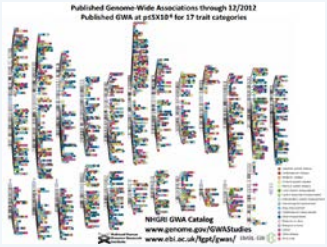
Sanseau, Agarwal *et al.* Nat. Biotech. 30, 2012

Table 1 Selected examples of matches between GWAS trait and drug indication[a]

Drug name or class	Most advanced development phase (for the indication)	Gene	Drug indication	GWAS trait	GWAS reference
Statins	Launched	HMGCR	Hypercholesterolemia	LDL Cholesterol	1
Ustekinumab	Approved	IL12B	Psoriasis	Psoriasis	13
Ustekinumab	Phase 2	IL12B	Crohn's disease	Crohn's disease	2
Anti-IL2 receptor mAb	Phase 2	IL2RA	Ulcerative colitis	Crohn's disease	2
AMG -785/ CDP-7851	Phase 2	SOST	Bone regeneration/ osteoporosis	Bone mineral density	14
Znt8 agonists	Preclinical	SLC30A8	Type 2 diabetes	Type 2 diabetes	15

[a]Examples are ranked from most advanced drug (launched) to less advanced (preclinical). The associated gene between each GWAS and the drug is shown. The drug indication and the phase of development for each drug are derived from the Pharmaprojects database. In each example the GWAS trait is identical (rows 1, 2, 3 and 6) or closely related (rows 4 and 5) to the drug indication. For the full list, see **Supplementary Table 3**. In many cases, more drugs for the gene are listed in the database at different phases. The GWAS references are from the catalog of GWAS data (http://www.genome.gov/gwasstudies).

Repositioning with GWAS



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Sanseau, Agarwal *et al.* Nat. Biotech. 30, 2012

Drug Repositioning Opportunities?

Table 2 Selected examples of mismatch between GWAS trait and drug indication[a]

Drug name	Most advanced development phase (for the indication)	Gene	Current drug indication	GWAS trait (new potential drug indication)	GWAS references
Denosumab/AMG-162	Launched/registered	TNFSF11	Osteoporosis/bone cancer	Crohn's disease	2
RPI-78M	Phase 3	IL27	Adrenoleukodystrophy	Crohn's disease/inflammatory bowel disease	2,16
Nepicastat	Phase 2	DBH	Cocaine addiction/post-traumatic stress disorder	Smoking cessation	7
Biib-033	Phase 1	LINGO-1	Multiple sclerosis	Essential tremor	4,5
AMG-557	Phase 1	ICOSLG	Systemic lupus erythematosus	Crohn's disease/celiac disease/ulcerative colitis	17–19
Cwp-231	Preclinical	TCF4	Cancer	Fuchs's corneal dystrophy	20

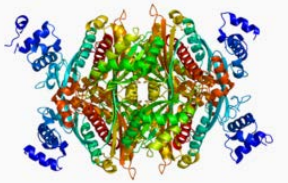
[a]Examples are ranked from most advanced drug (launched) to less advanced (preclinical). The associated gene between each GWAS and the drug is shown. The drug indication and the phase of development for each drug are derived from the Pharmaprojects database. For the full list, see **Supplementary Table 4**. In many cases, more drugs for the gene are listed in the database at different phases. The GWAS references are from the catalog of GWAS data (http://www.genome.gov/gwasstudies).

Drug (re-)positioning

collaboration
models

genetics

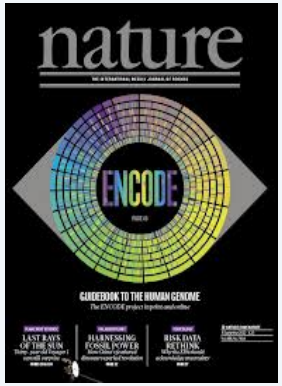
Drug



Target

electronic
health
records

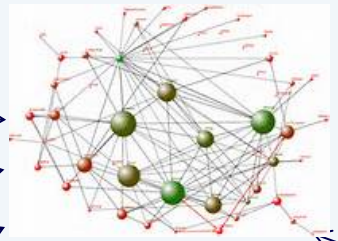
human
validation



Leveraging data to influence drug discovery decisions

- Genetics
- Computational biology
- Statistics
- Molecular/cellular/pathway biology
- Chemistry
- Pharmacology
- Safety Assessment

- Analyse
- Integrate
- Interpret



Animal model data

'omics data summaries

Disease Connectivity mapping

Pathway analysis

GWAS + other human genetic data

Functional genomics (e.g. ENCODE)

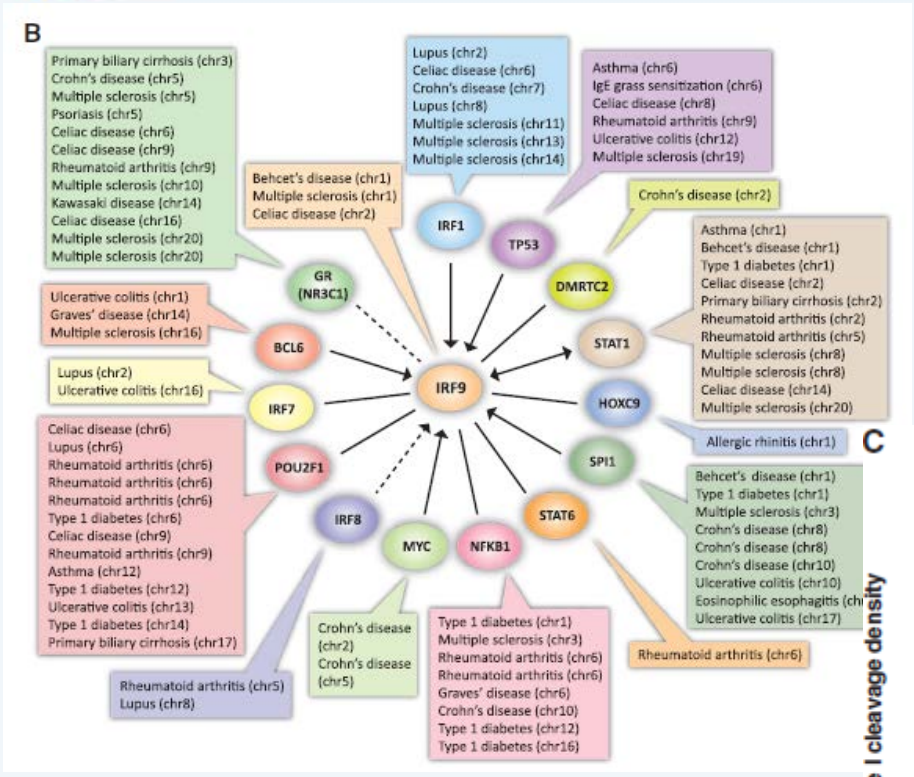
Systems Pharmacology

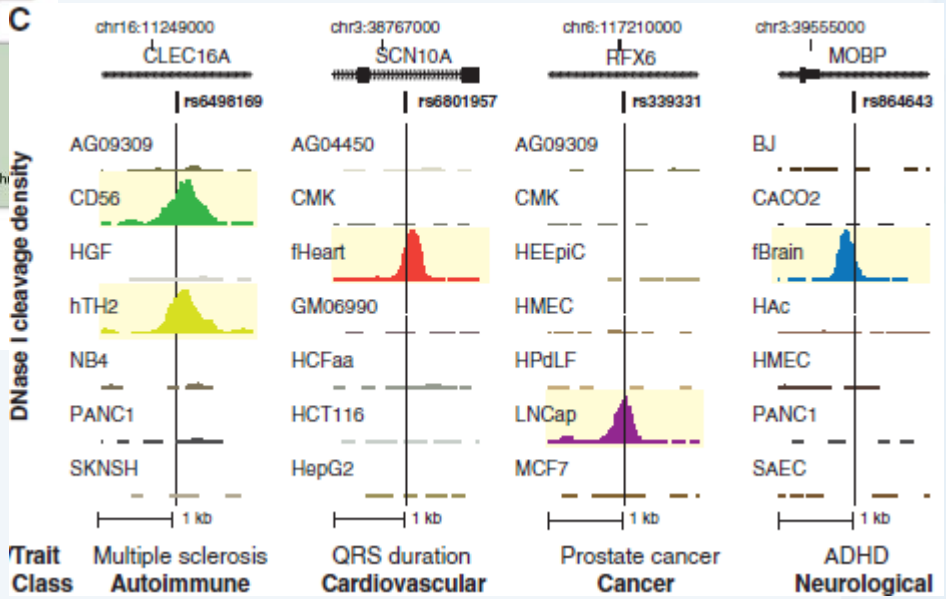
Tractability

Selectivity

External/Internal data & Partnership

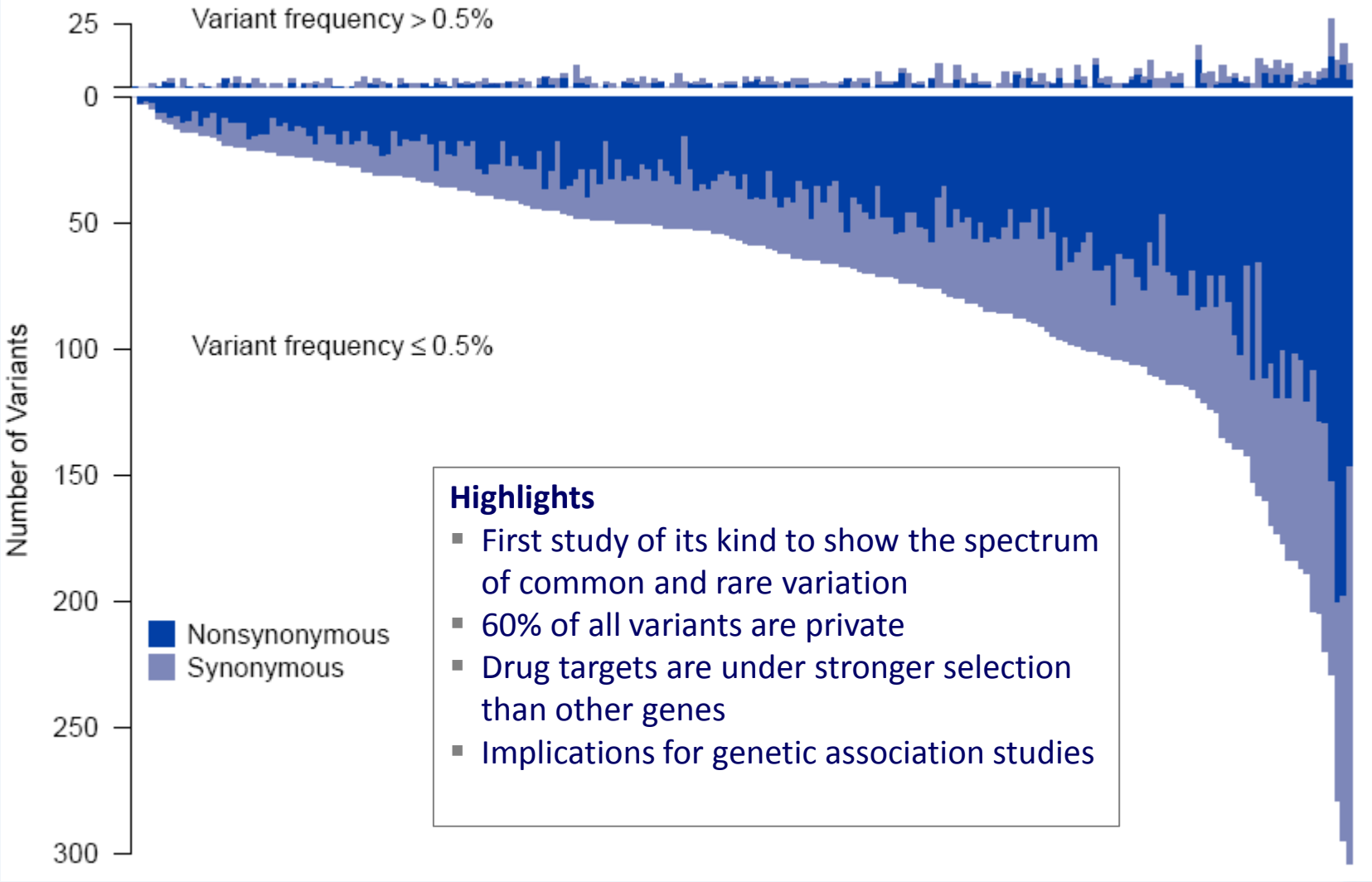
ENCODE: Early, but with potential





Maurano et al. (2012) Science

Deep sequencing of drug targets



Highlights

- First study of its kind to show the spectrum of common and rare variation
- 60% of all variants are private
- Drug targets are under stronger selection than other genes
- Implications for genetic association studies

Nelson et al. Science 2012

Drug (re-)positioning

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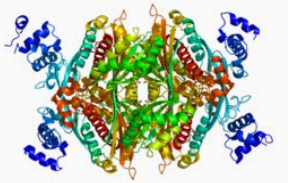
genetics

Drug



Target

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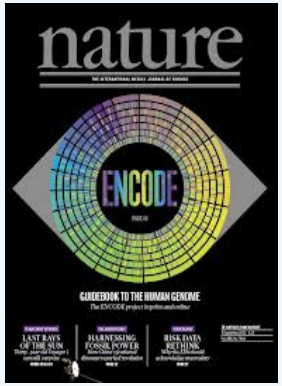
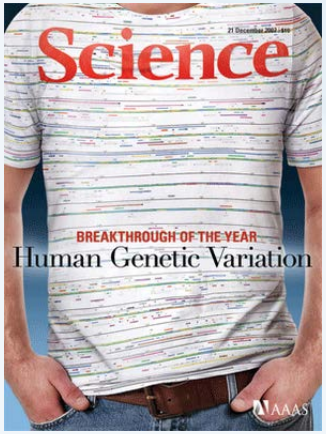


Electronic health records and biological information

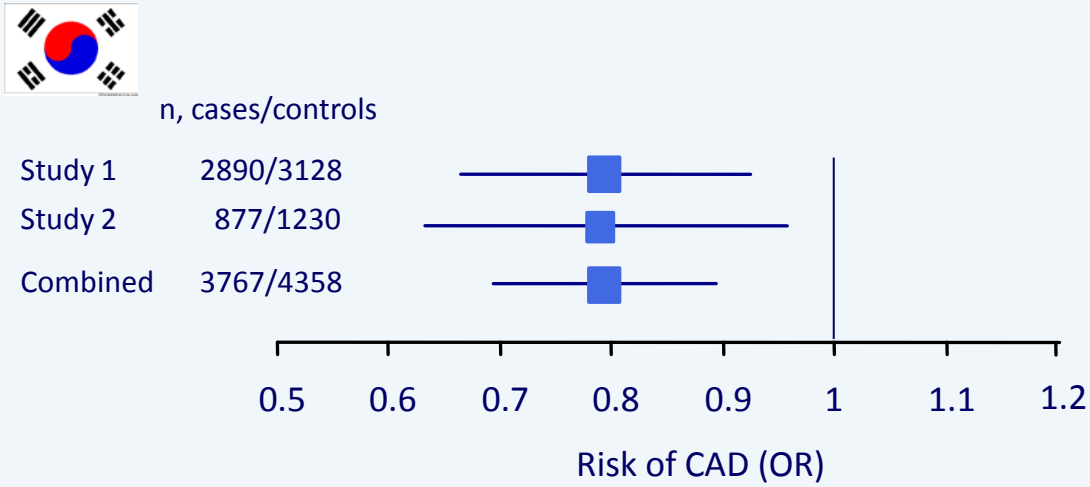


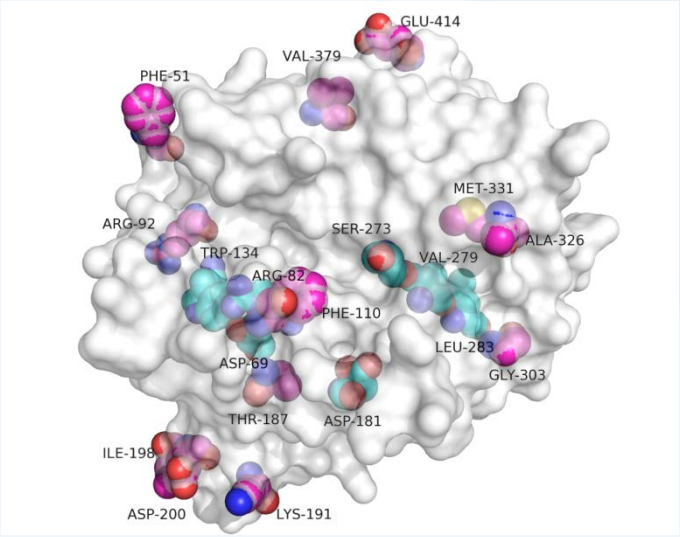
- X-disease effects of variants for repurposing (PheWAS)
- Causality assessment (Mendelian randomization)
- Expand disease knowledge in ‘real world’

- Drug response
- Adverse reactions
- Targeted trial recruitment
- Pilot genetic translation

Target → Preclinical → Clinical → Launch

PLA2G7 – Human "Knock-Out" for CAD





PLA2G7 null allele (V279F) protects against CAD

→ Support for darapladib pharmacology (MOA)
→ Null variant carriers excluded from Asian studies

Jang , PLoS One 2011

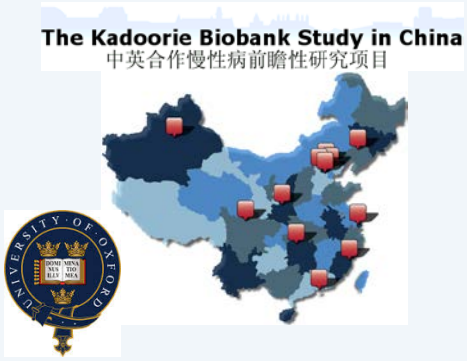
Deep sequencing of _PLA2G7_ in Europeans identifies rare LOF variants

→ New tools to understand target
→ Confidence that LOF variants are not common in Europeans

Song, Pharmacogenomics J 2012

Kadoorie Study: Opportunities for safety prediction & repurposing

- Kadoorie -> 500K subject electronic health record (EHR)-linked biobank study
- PLA2G7 V279F frequency = 4-9% in China
- Provides 'in silico' model of long-term exposure

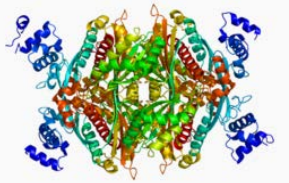


Drug (re-)positioning

collaboration
models

genetics

Drug



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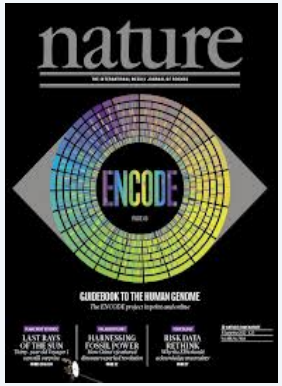


Models of collaboration

- Drug discovery is not the exclusive domain of industry or academia
  - Innovative Medicines Initiative
  - Severe Adverse Events Consortium
  - NCATS
  - …
- Real progress will require re-thinking of established practice
  - Intellectual property
  - Data sharing
  - Transparency
- Need models that play to strengths of all groups

Academia/Industry collaboration requires multiple models

Discovery Partnerships with Academia (DPAc)

1 to 1: to maximize complementary capabilities

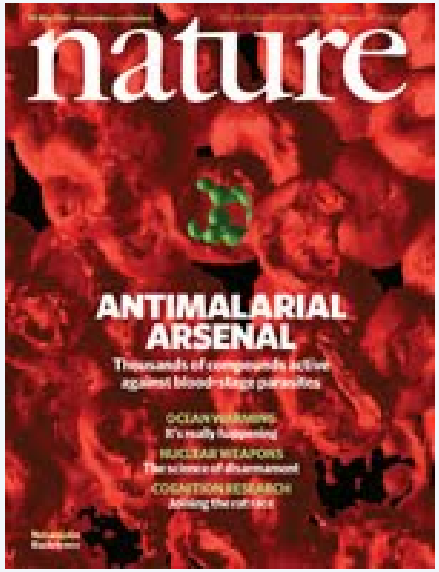
Avalon Ventures

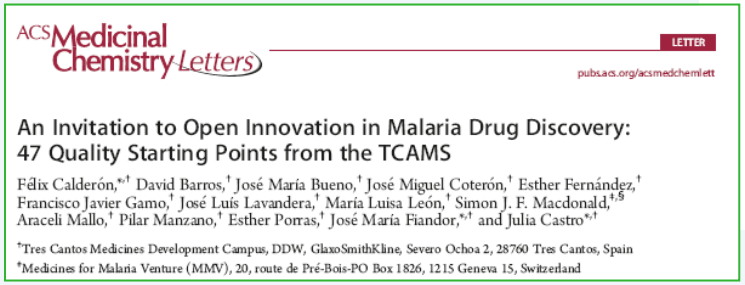
3-way: academia + biotech + pharma

Discovery Fast Track

Open access to high throughput screening

Data sharing/data transparency

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LETTER

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An Invitation to Open Innovation in Malaria Drug Discovery: 47 Quality Starting Points from the TCAMS

Félix Calderón,*,† David Barros,† José María Bueno,† José Miguel Coterón,† Esther Fernández,† Francisco Javier Gamo,† José Luis Lavandera,† María Luisa León,† Simon J. F. Macdonald,‡,§ Araceli Mallo,† Pilar Manzano,† Esther Porras,† José María Fiandor,*,† and Julia Castro*,†

†Tres Cantos Medicines Development Campus, DDW, GlaxoSmithKline, Severo Ochoa 2, 28760 Tres Cantos, Spain
‡Medicines for Malaria Venture (MMV), 20, route de Pré-Bois-PO Box 1826, 1215 Geneva 15, Switzerland

Conclusions

- Drug repositioning is neither straightforward nor guaranteed
- Better understanding of the drug target and mechanism is key for both initial and subsequent applications
- Emergent data in human genetics and increased availability of human samples are attractive drug (re-)positioning
- Pathways to success are collaborative

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