

Neurochem

An Overview of Drug Discovery for Neurological Disease

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Drug Discovery for Neurological Disease

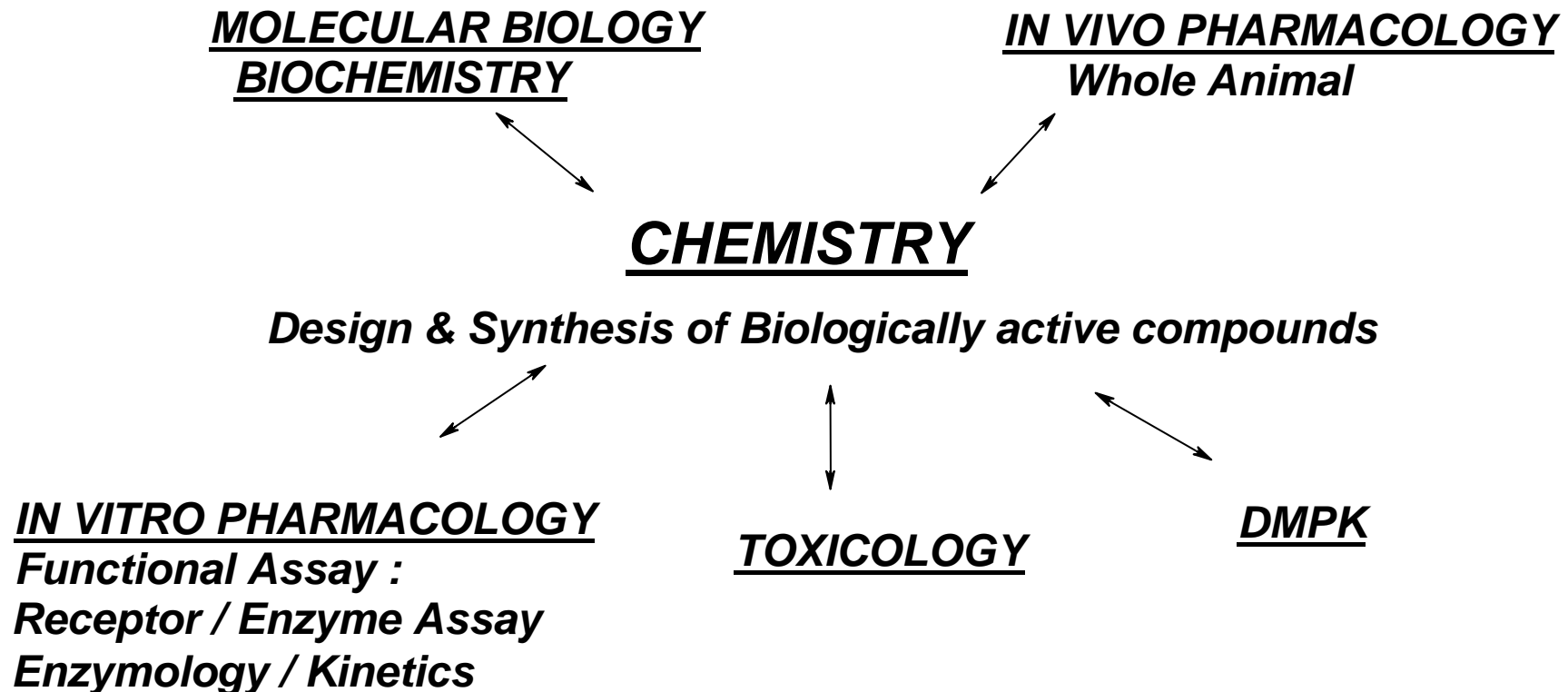
- ***As we know,
There are known knowns.
There are things we know we know.***
- ***We also know
There are known unknowns.
That is to say
We know there are some things we do not know.***
- ***But there are also unknown unknowns,
The ones we don't know
We don't know.***



***Donald H. Rumsfeld
Former US Secretary of Defense
Feb. 12, 2002, Department of Defense news briefing***

Challenges - Discovery

- Extremely multi-disciplinary endeavor requiring coordination of large number of diverse technical capabilities



Challenges - Discovery

- Extremely multi-disciplinary endeavor requiring coordination of large number of diverse technical capabilities
- Clarity of target with which therapeutic compound interacts directly
- MOA validation
- Requirement for validated predictive screening flow
- Compound availability as starting points, structural diversity, series druggability
- Preclinical PoC – generally weak models of neurodegeneration
 - Animal model is not a human – it's a PD readout
 - Variability in pathophysiology (reproducibility often an issue)
 - Translation of preclinical model effects to humans
- Acute vs. chronic effects
 - Safety issues more critical than many other disease areas
 - Unexpected safety issues when modulating targets of unknown/multiple function(s)

Challenges - Development

- Translation from *in vitro* → *in vivo* → clinical effects
- Variability of disease
 - unclear/variable pathogenesis
 - pharmacogenomic impacts
 - multifactorial and interdependent genetic/environmental/experiential risk factors
- Diagnostic criteria for early intervention
- Surrogate markers for efficacy, dosing guidance
- Drug delivery to the CNS
 - e.g. blood-brain barrier penetration, central vs. peripheral homeostasis
- Extremely challenging clinical trials
 - Long term studies and soft outcome measures
- Regulatory environment is developing

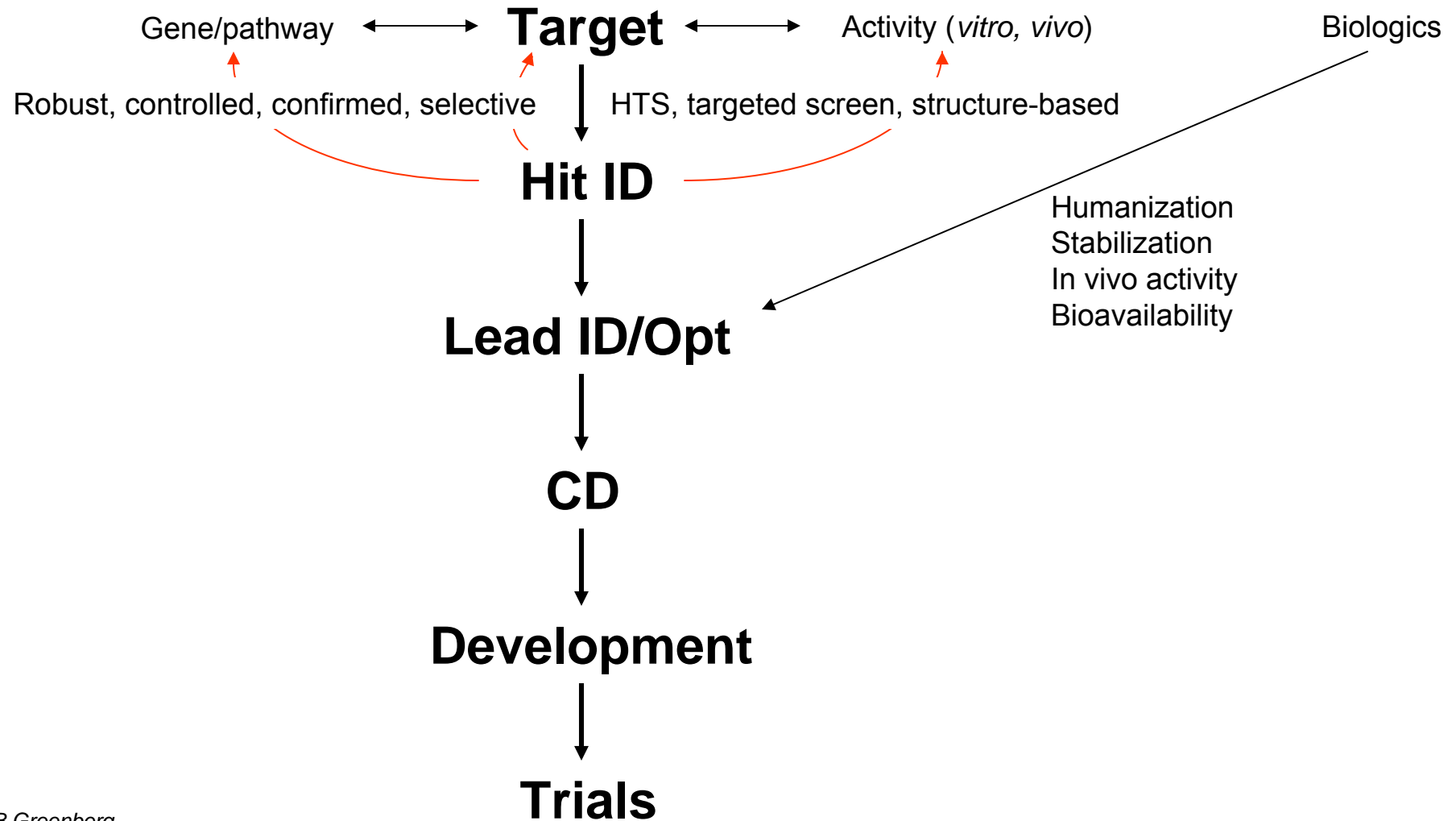
Most common reasons for failure

- Unacceptable DMPK profile *in vivo*
- Toxicity
 - Structure-based
 - Mechanism-based: target-related or pleiotropic effects
- Lack of clinical efficacy; failure to obtain clinical PoP
 - PoP = intended pharmacologic effect that results in measurable change in biomarker as physiological or biochemical effect
 - particularly difficult with soft outcome measures

Definitions

- Hit
 - An **active**: A compound that is active in a screening assay
 - Confirmed structure and purity
 - Natural product extracts \neq hits. They are actives.
 - Activity and selectivity in follow-up screens
 - Rational dose-response relationship relative to target
 - Preliminary SAR
- Lead
 - A structural **hit** series that demonstrates acceptable affinity, desired activity and SAR indicating that it has potential to be further optimized

Drug discovery process



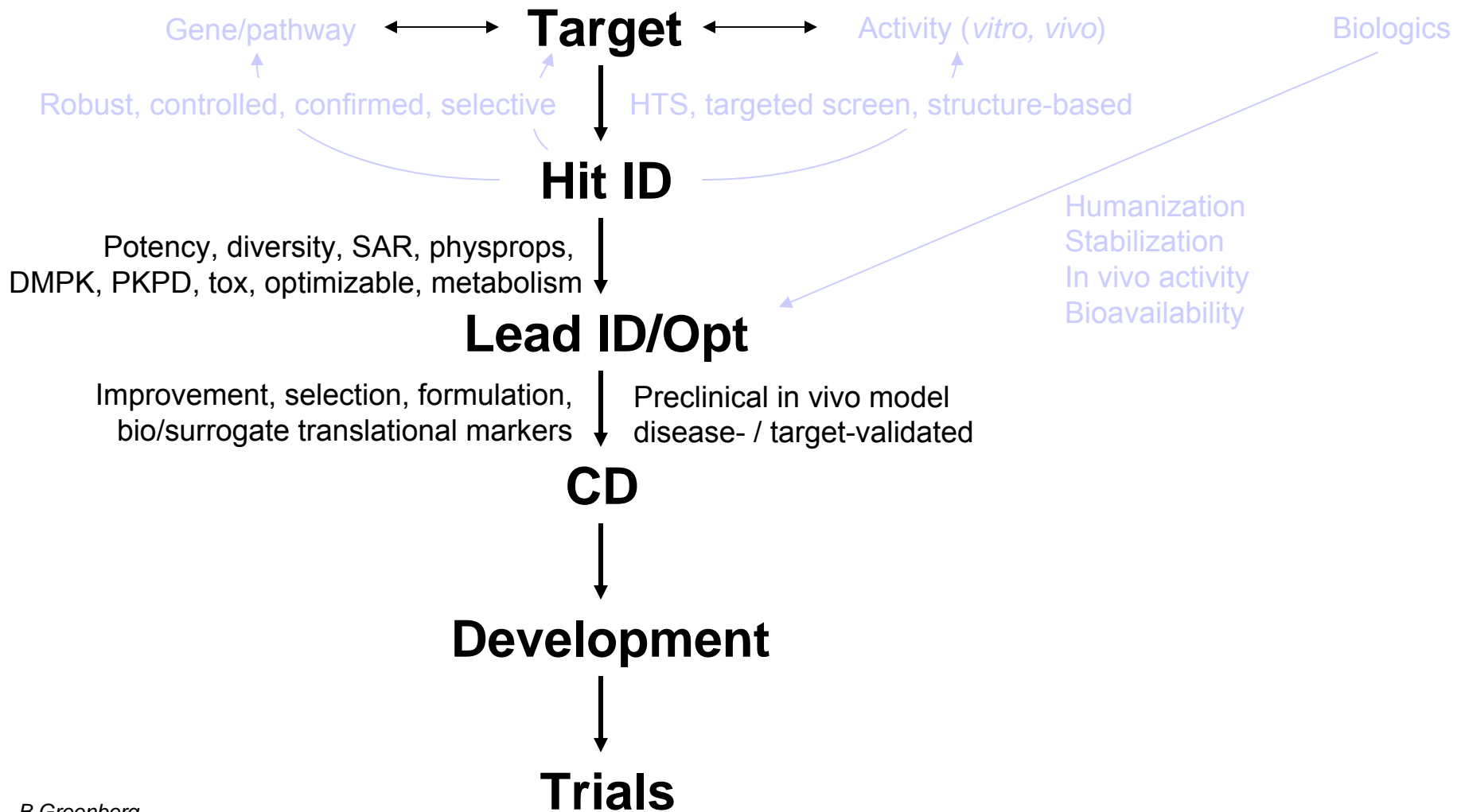
Target identification and validation

- A validated target = Biological entity that can be manipulated to generate a desired disease-relevant profile
- May emerge from gene/pathway analysis, known disease-related target, activity of selected compound(s) in biochemical assays in cells and/or *in vivo*
- Assayable biochemically, *in vivo* and/or in cells
- Validated with respect to disease
- Knowledge of pathways important
 - May imply additional targets for investigation
 - May explain/predict side-effect profiles and challenges that should be proactively addressed

Hit identification

- Screening – HTS vs. targeted screening? Structure-based design?
- Validated robust assay scheme for establishing SAR, including secondary cross-predictive screens, in turn predictive of *in vivo* activity. Cross-validation = key.
 - linear dose- & time-related activities
 - availability of authentic positive and negative controls
 - good dynamic range
- Active hit structures confirmed by resynthesis and rescreening
- Active hit structures ranked using predictive physicochemical and DMPK attributes, suitable for chemical modification/optimization. Are they druggable?
- Selectivity in appropriate secondary screens (substrate, target)
- Potency at agreeable cutoff
- Structural diversity among multiple series → lead identification phase

Drug discovery process



Lead identification

- Establishment of rational SAR. No lead stands alone.
- Structural diversity among multiple lead series to reduce risk
- Appropriate physicochemical properties for lead series
- Appropriate DMPK parameters
 - metabolic stability, clearance, permeability, Cyp inhibition, plasma protein binding
- Determination if selected chemical series are improvable with respect to potency, selectivity and DMPK attributes / parallel SAR considerations throughout
- Acceptable cytotoxicity profile
- PKPD evaluation in appropriate target model to establish *in vitro/in vivo* correlations
 - confirms *in vivo* activity and helps to validate biological target

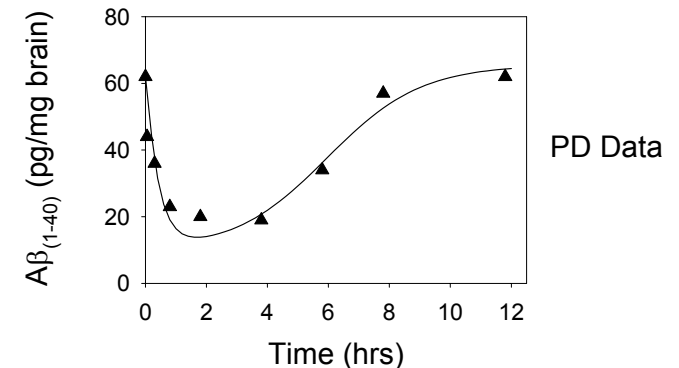
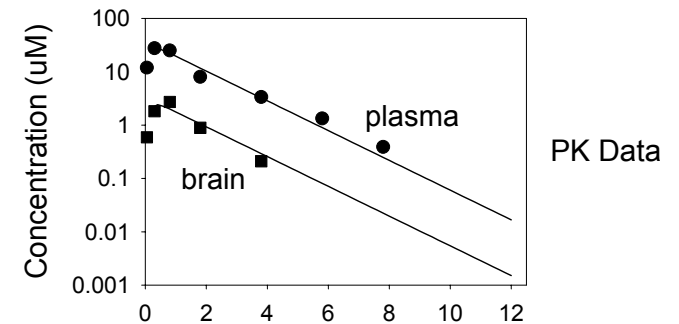
PK-PD

Example: γ -secretase inhibitor

- PK: relationship between dose of a drug and changing concentrations of drug in body or tissue
- PD: relationship between drug concentration at the site of action and the effect that is elicited

“**Pharmacokinetics** is what the body does to the drug. **Pharmacodynamics** is what the drug does to the body”

Lewis B. Sheiner, 1981

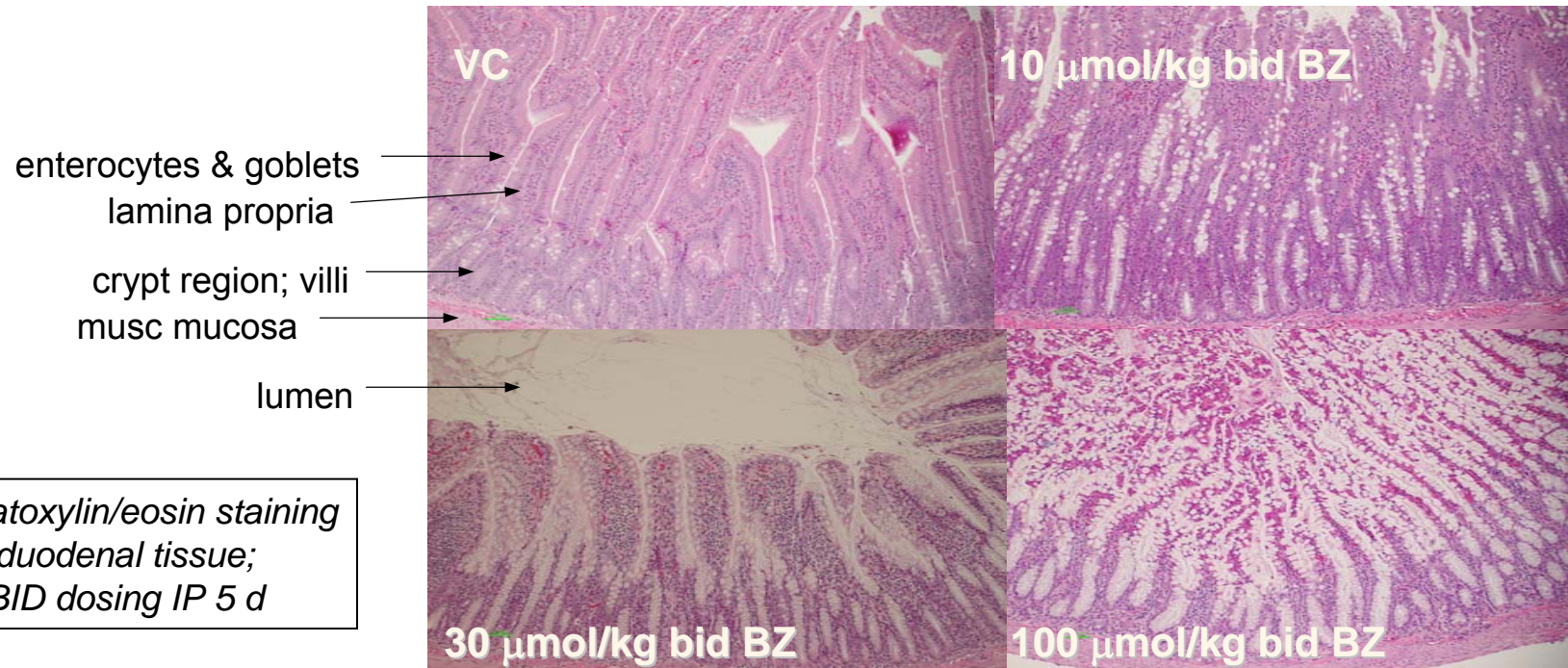


Lead optimization

- **Def: The synthetic modification of leads to fulfill all physicochemical, stereoelectronic, pharmacokinetic and toxicological properties required for clinical usefulness.**
- Elaboration of selected lead series for optimization
 - e.g. parallel synthesis, derivatization, “scaffold-hopping”, etc.
- Highly iterative process optimizing all features to balance attributes and risks
 - Physicochemical properties, DMPK parameters, removal of metabolic attack sites, potency, selectivity optimization for intended dosage
- Establishment of full PKPD/ADME in appropriate animal model (brain exposure)
- Safety pharmacology profile. Structure- or mechanism-based liabilities?
 - Acceptable acute in vivo toxicity profile
 - Interspecific differences in activity, PK profile, plasma protein binding, bioavailability in order to support multi-species tox studies and dosing to man
- Selection of a small number of compounds for final preclinical selection/development

Mechanism-based toxicity, an unknown unknown

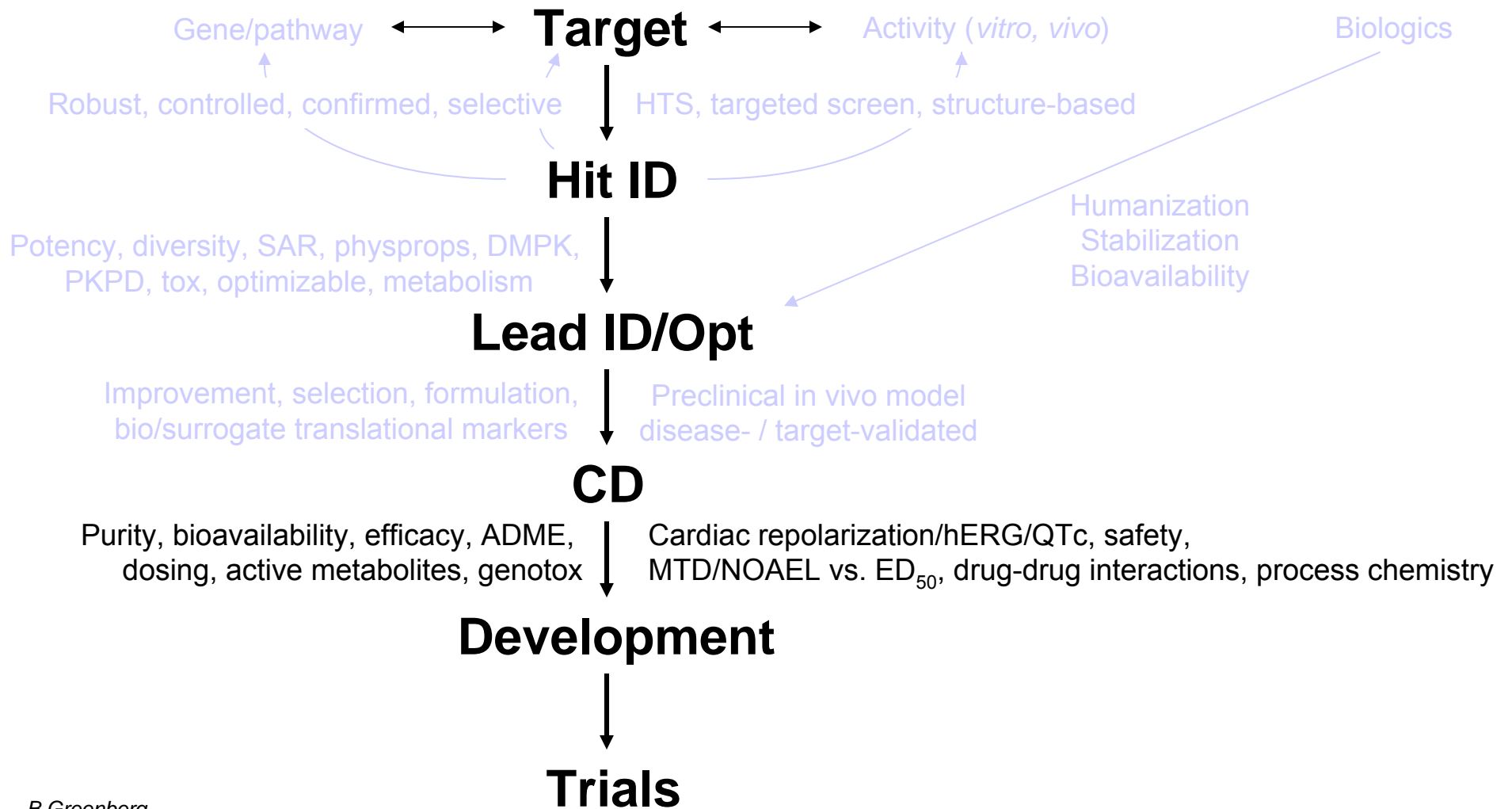
Ex: γ -Secretase inhibitor-mediated goblet cell metaplasia in rat GI



- VC: normal architecture, cellular stoichiometry, differentiation pattern
- Lo dose: normal architecture except for increased goblet cell # relative to surrounding enterocytes
- Mid dose: increased goblet cell #, stunted villi, luminal mucous evident
- Hi dose: completely disrupted architecture, marked increase in goblet cell #, luminal mucous, villi stunting, apoptotic & necrotic cell death. Animals unable to absorb nutrients & water, severe dehydration and electrolyte imbalance
- Crypt & glandular epithelial cell apoptosis – days 1-5
- Goblet cell metaplasia – days 2-5
- Crypt & glandular epithelial cell regeneration – days 4-5

Milano et al. (2004)
Toxicol. Sci. 82:341-358.

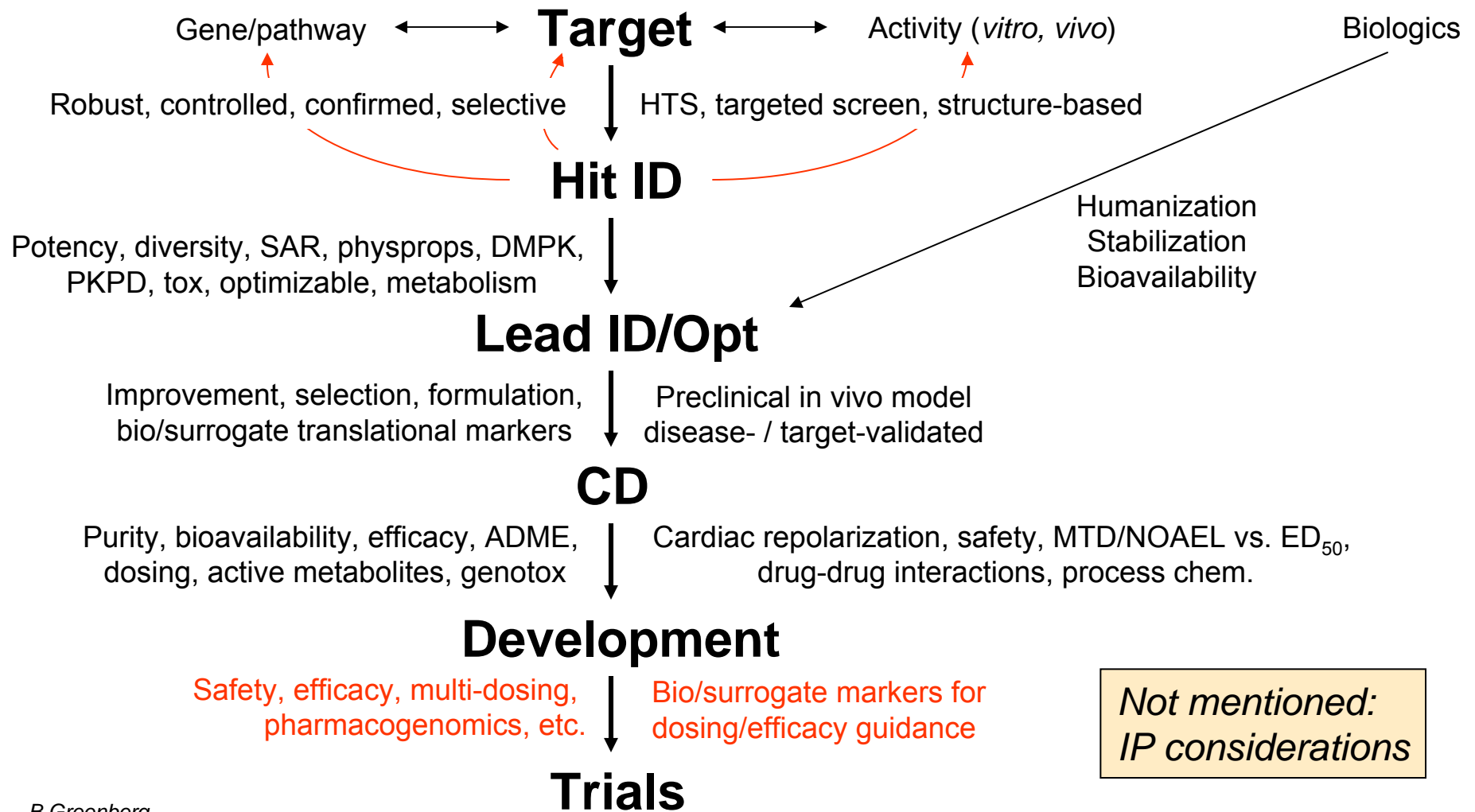
Drug discovery process



CD criteria

- Acceptable physicochemical properties, *in vivo* potency/efficacy in disease model, metabolic profile, defined ADME and PK/PD for intended exposure to maintain effective drug concentrations/therapeutic window throughout dosing interval
- Metabolites identified, active metabolite effects understood
- Acceptable MTD/NOAEL relative to *in vivo* ED₅₀
- Acceptable genotox, cardiac repolarization/hERG/QT interval and overall safety profile for CD and metabolites in two or more relevant species, short and long-term
- Relevant biomarkers/surrogate markers available to guide dosing and efficacy
- Likelihood of drug-drug interactions understood and acceptable
- Formulations suitable for *in vivo* dosing of selected compounds compatible with required exposure for efficacy and toxicity
- Process chemistry sufficient to support GLP studies/early clinical evaluation
- ***Risk assessment based on balance of all factors***

Drug discovery process



Drug Discovery for Neurological Disease

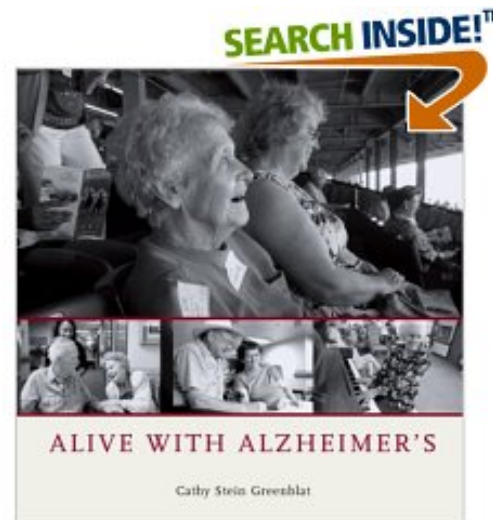
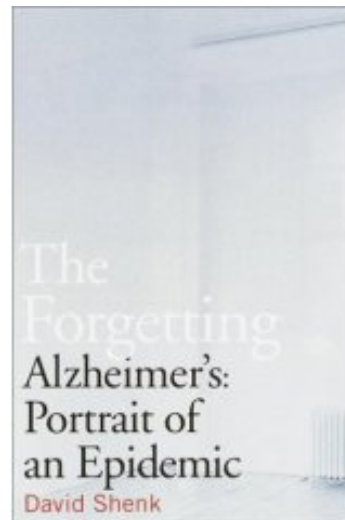
Alternative strategies

Serendipity

In-licensing

Take-home

- *In vivo* studies are not the same as biochemical *in vitro* assays.
- Drug discovery depends on academic science, but it is a distinct discipline. Both together are necessary and complimentary. Both are intellectually stimulating. They optimally exist together as an iterative partnership.
- “Discovering a new drug is one of the hardest and most frustrating things known to mankind.” (*particularly for CNS disease*)
 - The rewards of success cannot be overstated.



Criteria for drug-like compound

PHYSICOCHEMICAL PROPERTIES :

- Stable compound
- Non-hygroscopic
- Soluble material
- Preferably without chiral center
- Stable metabolites

LIPINSKY RULES (rule of 5)

Molecular weight : < 500

clog P : < 5

Number of hydrogen bond donor : < 5 (NH + OH)

Number of hydrogen bond acceptor : < 10 (N + O)

C.A. Lipinski, J. Pharmacol. Toxicol. Methods, 2000, 44, 235

Prediction of poor oral absorption
and solubility (2 or more are exceeded)

Number of rotatable bond : < 10

PSA (Polar surface area) : < 140 A

D. Veber (GSK) : J. Med. Chem. 2002, 45, 2615