KU THE UNIVERSITY OF KANSAS

Drug Discovery: Alternative Approaches to Lead Generation

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Main Message

The Aim of a Drug Discovery Program is to …

Discover Drugs.

A word from the wise…

“Reports that say that something hasn't happened are always interesting to me, because 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 Rumsfeld

CNS Pharmacology Rankings in Comparison to Other Subdisciplines

- Known/Knowns: Low
- Known/Unknowns: High
- Unknown/Unknowns: Very High

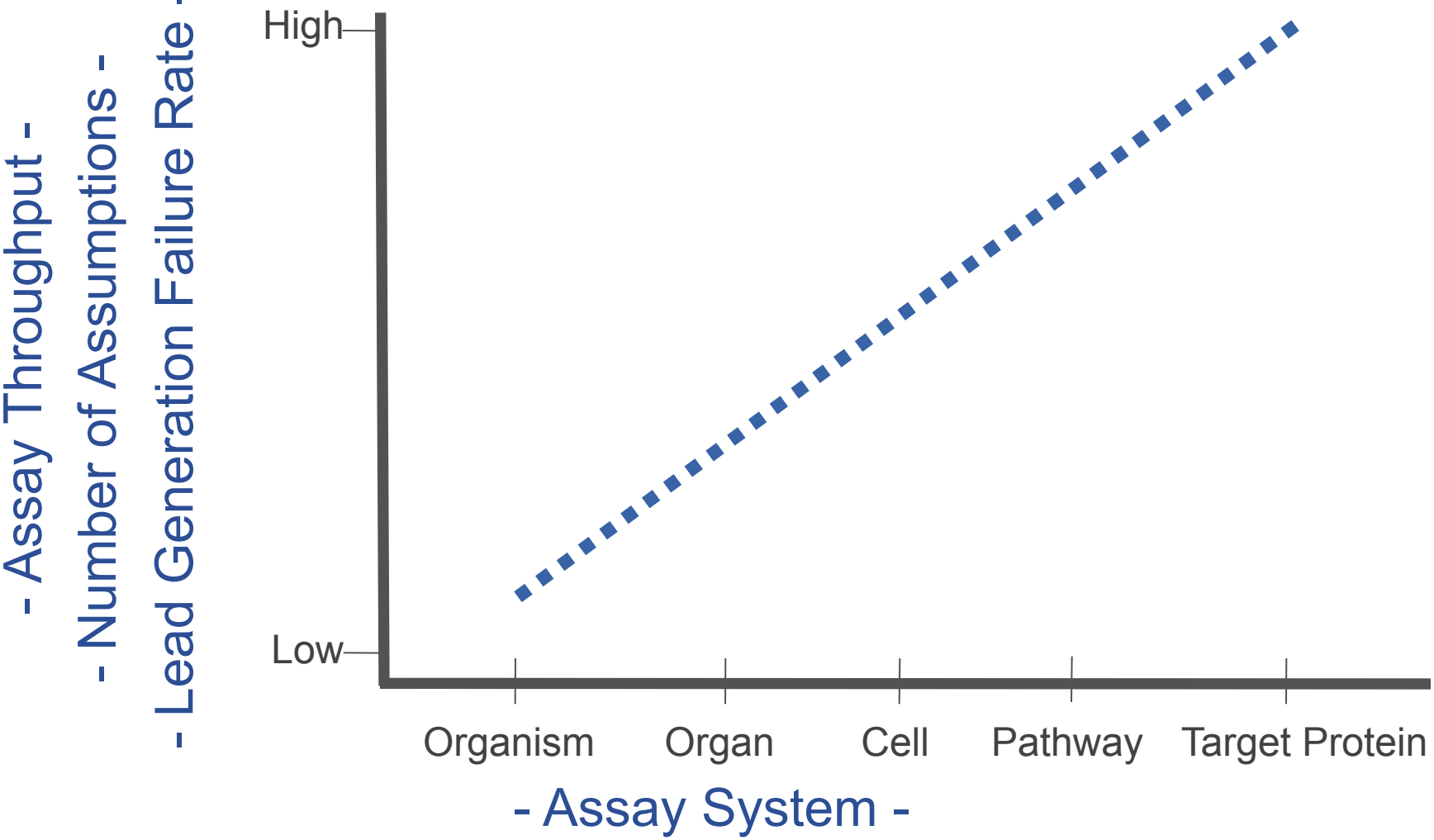
Drug Discovery by Therapeutic Area+

Disease Area	Target-based Screening	Phenotypic Screening
Infectious diseases	**3**	**7**
Immune	1	0
Cancer	5	3
CNS	**1**	**7**
Metabolic	3	2
Cardiovascular	2	3
Gastrointestinal	1	1
Others	1	3
Rare diseases	0	2
Total	17	28

+ First-in-class small molecules approved by FDA 1999 - 2008

* Adapted from Swinney, D.C. and Anthony, J., *Nature Reviews-Drug Discovery*, 10: 507-519, 2011

Relationship between Assay Systems and Drug Discovery



History of Drug Discovery

Paleo Era
199,840 years
Empirical
Observation

Modern Era
160 years
Empirical Observation
and Hypothesis Driven

Paleo Pharmaceuticals

- Low Throughput -

- Salicylates
- Opioids
- Cardiac Glycosides
- Gold Salts
- Hallucinogens
- Curare
- Ergot Alkaloids

Evolution of Research Strategies

Paleo Era

Efficacy/Safety

Modern Era

- Physiology Period

Efficacy/Safety → Organ Systems Analysis

- Biochemical Period

Efficacy/Safety ↔ Cellular Analysis ↔ Organ System

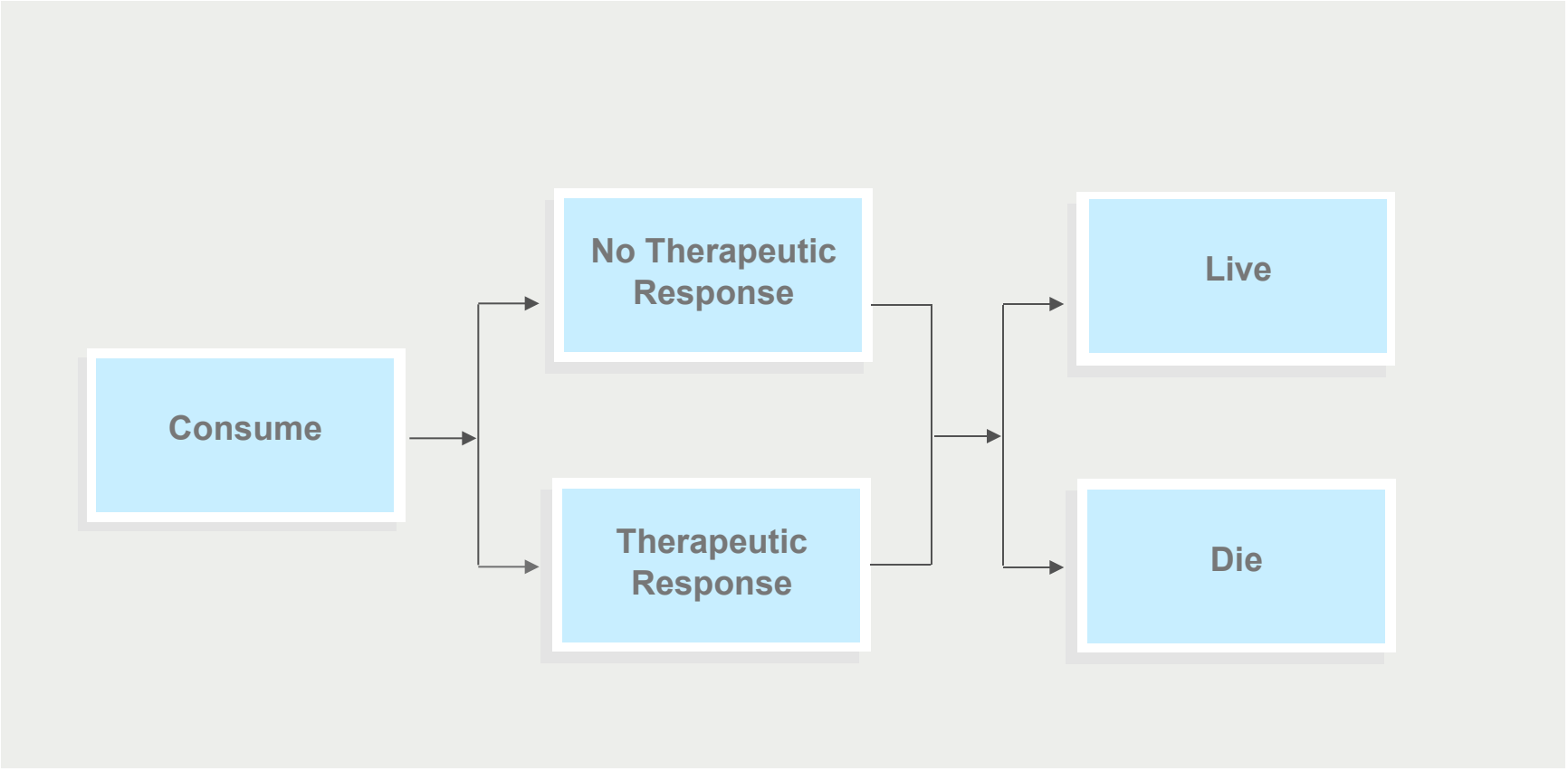
- Molecular Period

Target Analysis → Cellular Analysis → Organ System → Efficacy/Safety

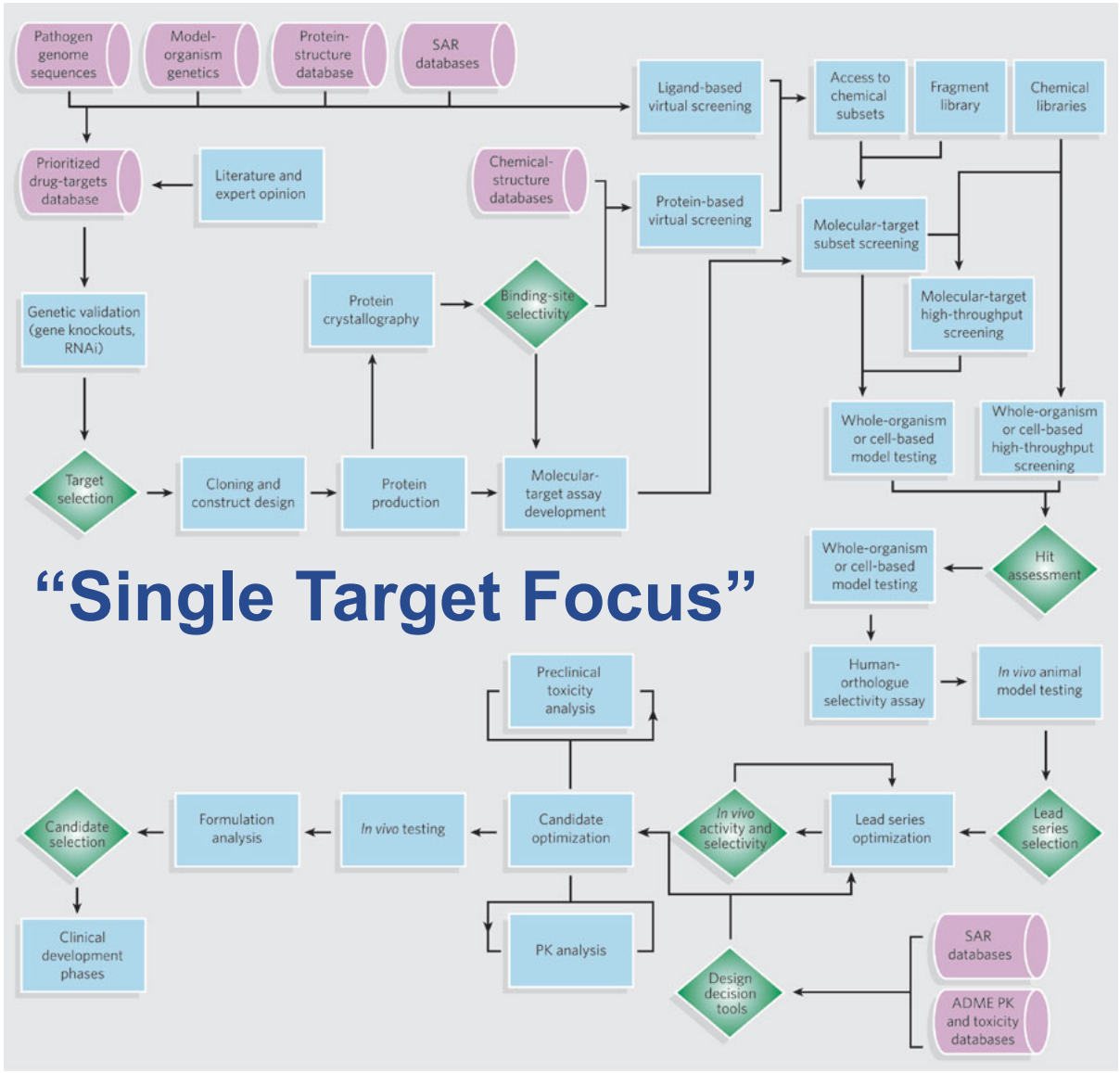
(Ligand Discovery)

targephilia \tär-gə-fil-yə\ *n* (2013) : Obsession with, and excessive focus on, sites of drug action

Paleo Drug Discovery Flowchart



Modern Drug Discovery Flowchart

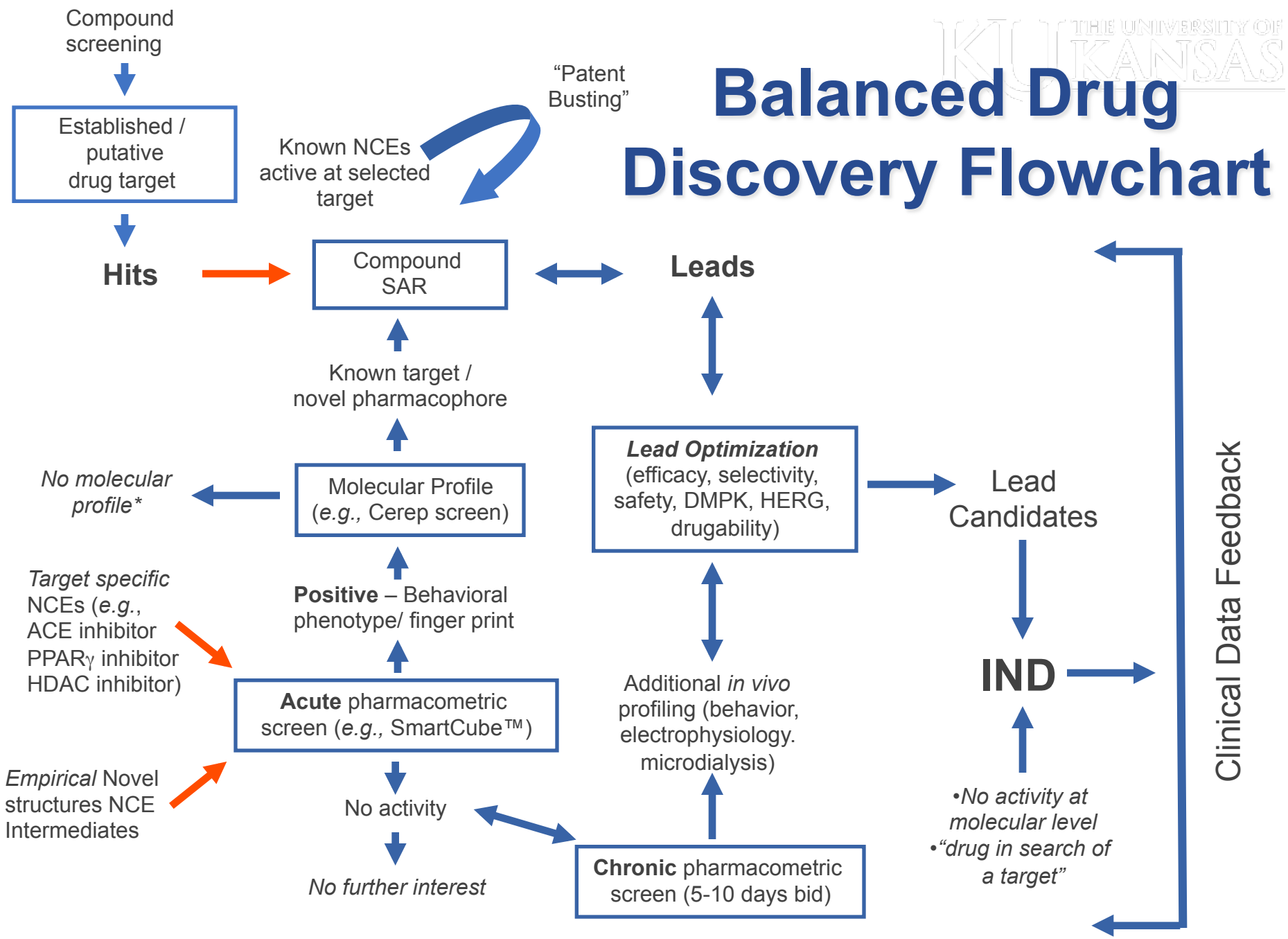


Hopkins, A.L. et al., *Nature* 449:166-169, 2007

Some CNS Agents Launched with Unknown or Uncertain Mechanism of Action

- Opioids
- General Anesthetics
- Barbiturates
- Benzodiazepines
- Phenothiazines
- Tricyclic Antidepressants
- Lithium
- Valproate
- Modafinil

Balanced Drug Discovery Flowchart



Drug Discovery Principles

- An NCE is what it is, not what you want it to be
- Knowledge of MOA is essential for optimizing a therapeutic class, but not for drug discovery

Back to the Future

- Increase emphasis on defining basic biology of CNS function in intact animals
- Increase emphasis on *in vivo* testing of NCEs from all therapeutic classes as possible CNS drug candidates – empirical observation
- Identify sites of action of CNS drugs already known to be therapeutically useful
- Increase training of scientists capable of executing and interpreting experiments in intact organisms

Adapted from Gary Larson