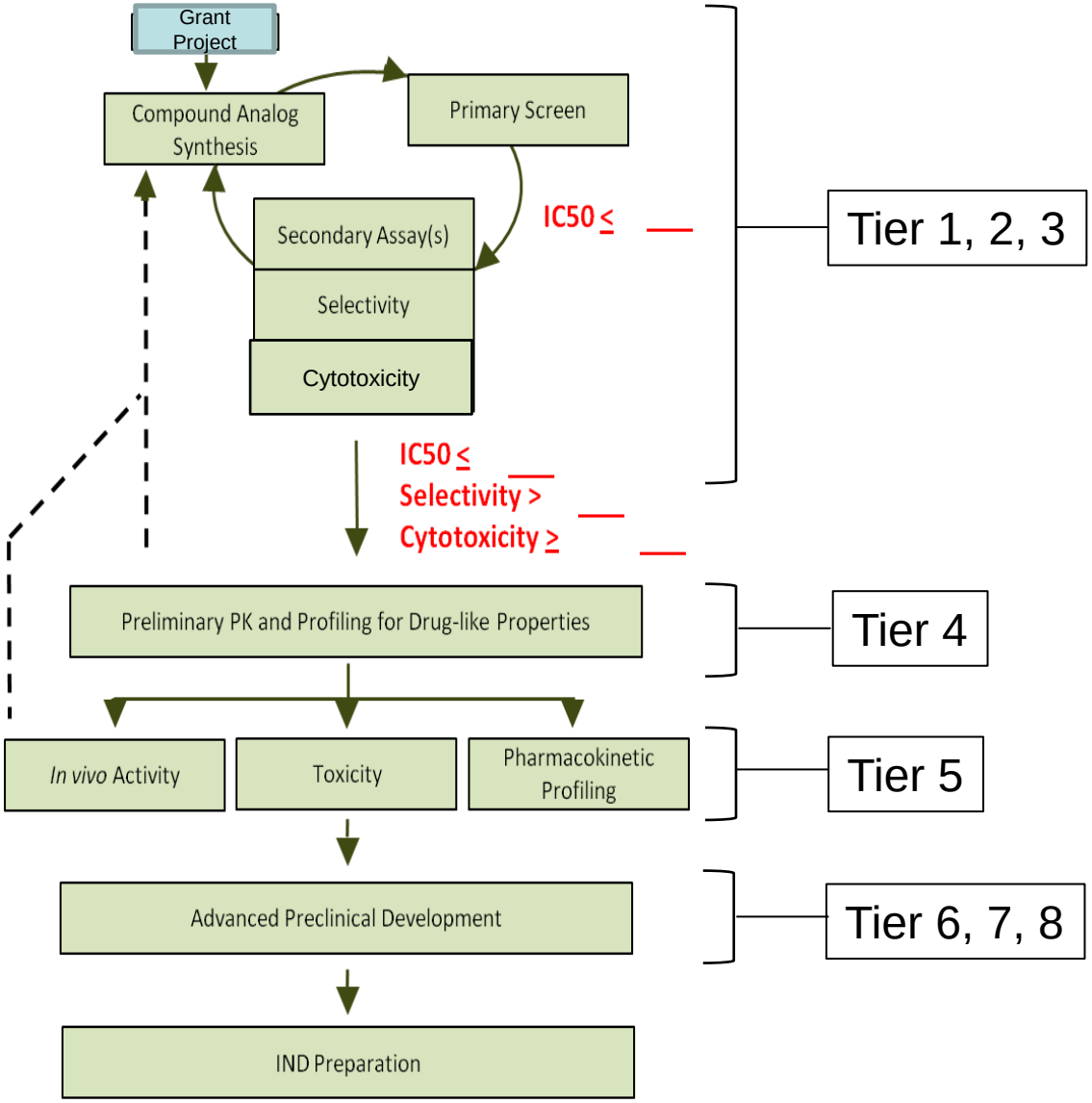
Example Drug Discovery & Development Testing Funnel



Example Drug Discovery & Development Testing Funnel

TIER 1A – Primary Screen

- Chemical purity and identity of active compounds
- Primary bioactivity screen
- Cell viability (When Appropriate)
- Scaffolds/Moiety Chemical liabilities (*for example: Michael acceptor, GSH reactive*)
- Calculated properties:
  - CLogP
  - PSA
  - Molecular Weight
  - rotatable bonds
  - H-bond donors and acceptors
  - permeability
  - pKa
  - Solubility

TIER 1B

- Confirm EC50 determinations for actives compounds in primary screen with fresh compounds from the original stock. Confirm EC50 determinations for the lead (most active) compound in primary screen with a new sample either repurchased, purified and characterized in-house, or independently synthesized in-house.

Compounds with IC50s (EC50s) less than X advance to Tier 2

Example Drug Discovery & Development Testing Funnel

TIER 2A – Activity Confirmation

- Secondary screen

TIER 2B

- Repeat EC_{50} determinations for actives in secondary screen with fresh compounds from the original stock

Compounds with IC50s (EC50s) less than X advance to Tier 3

Example Drug Discovery & Development Testing Funnel

TIER 3 – Drug-like Properties, Specificity

- IC_{50} selectivity in selectivity screen
- CYP450 Inhibition competitive and time-dependent if structural alerts exist (spot check illustrative examples from compound series)
- Measured solubility
- Measured protein binding (spot check illustrative examples from compound series)
- Test of Permeability *in vitro* permeability [indicate assay, e.g., Caco2 or/and PAMPA], (spot check illustrative examples from compound series)
- hERG
- Cytoxicity assays

All compounds with no significant issues (Define Minimum Conditions for Advancement) to advance to Tier 4

Example Drug Discovery & Development Testing Funnel

TIER 4 – Scale-up Synthesis and Preliminary PK

- Scale-up synthesis
- Purity determination: >98% with no single impurity >1%
- Rodent bioavailability and PK (define target delivery route):
  - Tmax
  - Cmax,
  - AUC,
  - Bioavailibility,
  - Vss, CL, T1/2, MRT
  - Brain to Plasma ratios
  - P-glycoprotein transport MDCK-MDR1 and MDCK-mdr1a
  - Plasma Protein Binding (species),
  - Microsomal Stability – rodent and human
- Define/plan Patent Protection Strategy

All compounds with no significant issues (Define Minimum Conditions for Advancement) advance in parallel to Tiers 5A&B

Example Drug Discovery & Development Testing Funnel

TIER 5A – In Vivo Bioactivity

- Animal efficacy
- Validate Biomarker
- Target engagement

TIER 5B – Advanced Drug-like Properties

- Microsomal stability in multiple species
- Chemical Stability
- CYP450 induction
- CYP reaction phenotyping
- Metabolism – human hepatocytes/microsomes
- Metab ID:
  - define major human, rat, dog and non-human primates (NHP) metabolites
- *In vitro* Tox:
  - Ames
  - Chromosome Aberration
  - CNS effects

Advance to Tier 6 if (Define Minimum Conditions for advancement)

Example Drug Discovery & Development Testing Funnel

TIER 6 – Liability Assessment

- Broad Pharmacological Profile and Toxicology
- PK in second species

TIER 7

- Non-GLP exposure studies, single and multiple dose

Advance to late stage pre-clinical development (Define Minimum Conditions for advancement)