Dermatology Innovation Forum

an Advancing Innovation in Dermatology conference

Michael D. Howell, PhD

DIF Entrepreneur Bootcamp
Orlando, Florida
March 6, 2025
9:30 – 11:00AM

MOUNTAINEER BIOSCIENCES

Scientific and Career Journey

PhD
Card Carrying
Immunologist

Spesolimab/SPEVIGO
Rizankizumab/SKYRIZI

Ruxolitinib/OPZELURA
Ruxolitinib/JAKAFI
Povorcitinib
Parsaclisib

Co-Founder/CEO
AhR Modulators

Chief Scientific Officer
Tibulizumab
Torudokimab
Crebankitug

Assistant Professor
Th2 and Epithelial Biology

Tralokinumab/ADBRY
Tezepelumab/TEZSPIRE
Tozorakimab
Brodalumab/SILIQ
MEDI9314

Chief Scientific Officer
Novel Dx Approaches

Board of Directors
SAB

Scientific Advisor
OR-101
OR-102

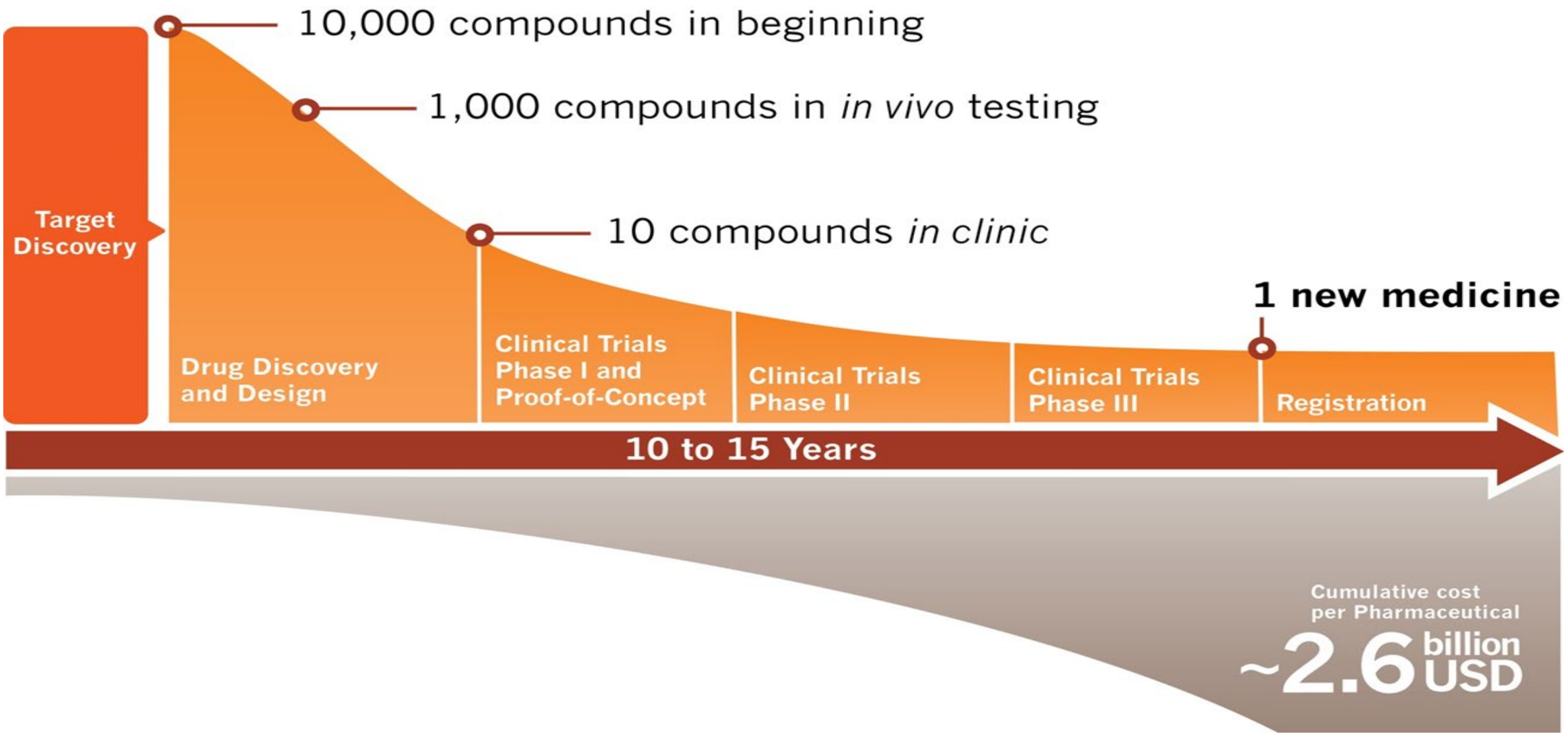
Strategic/Scientific Advisor

- Investment Firms,
- Venture Capital Groups,
- Biotech Startup
- Pharma

Career has encompassed the research and development of more than seven FDA-approved therapies

“Medicine is not only a science; it is also an art. It does not consist of compounding pills and plasters; it deals with the very processes of life, which must be understood before they may be guided.” - Paracelsus

Drug Development is Long, Expensive, and Risky



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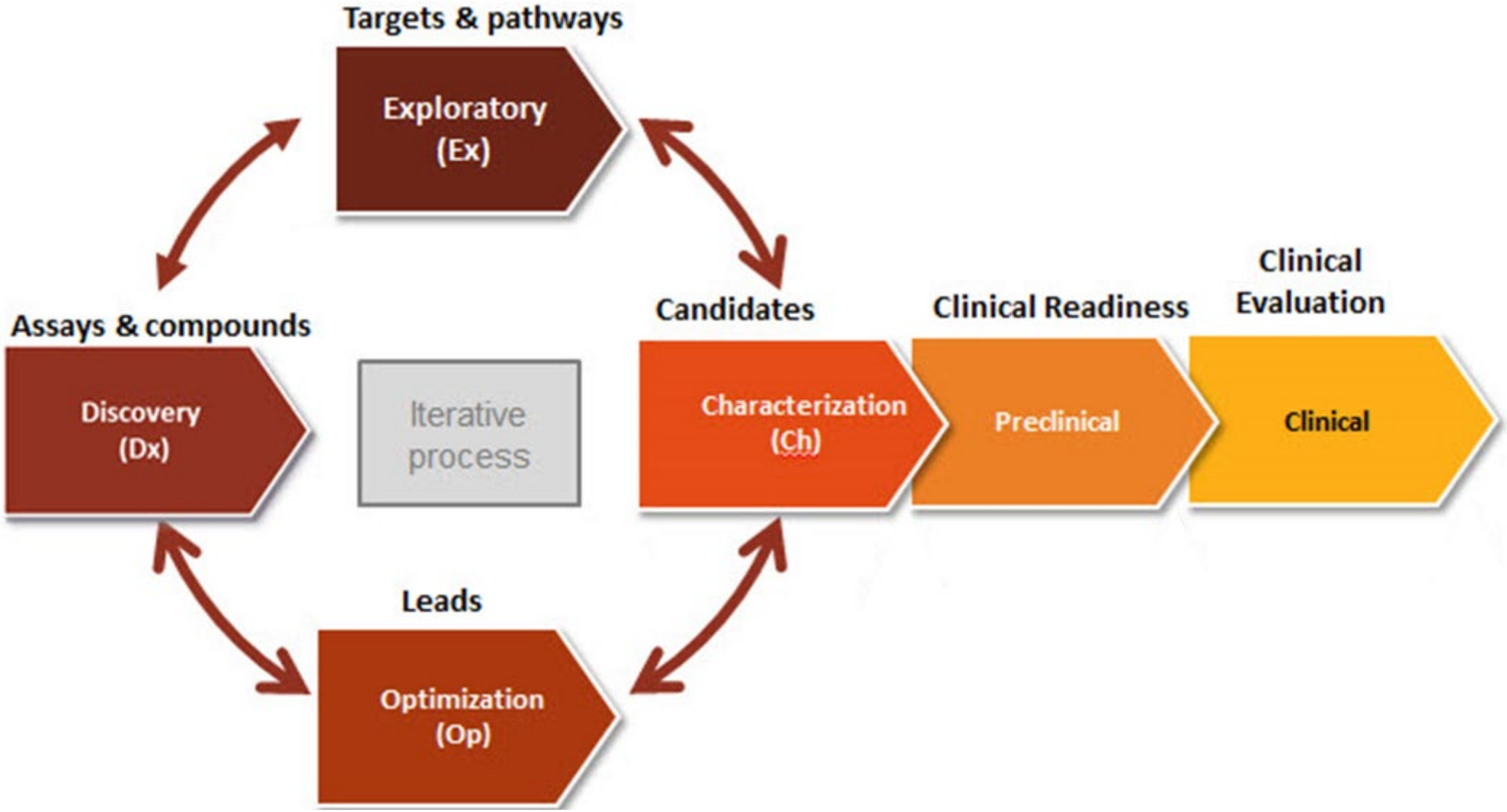
Drug Development is an Iterative Process



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Key Questions to Ask/Address During Development

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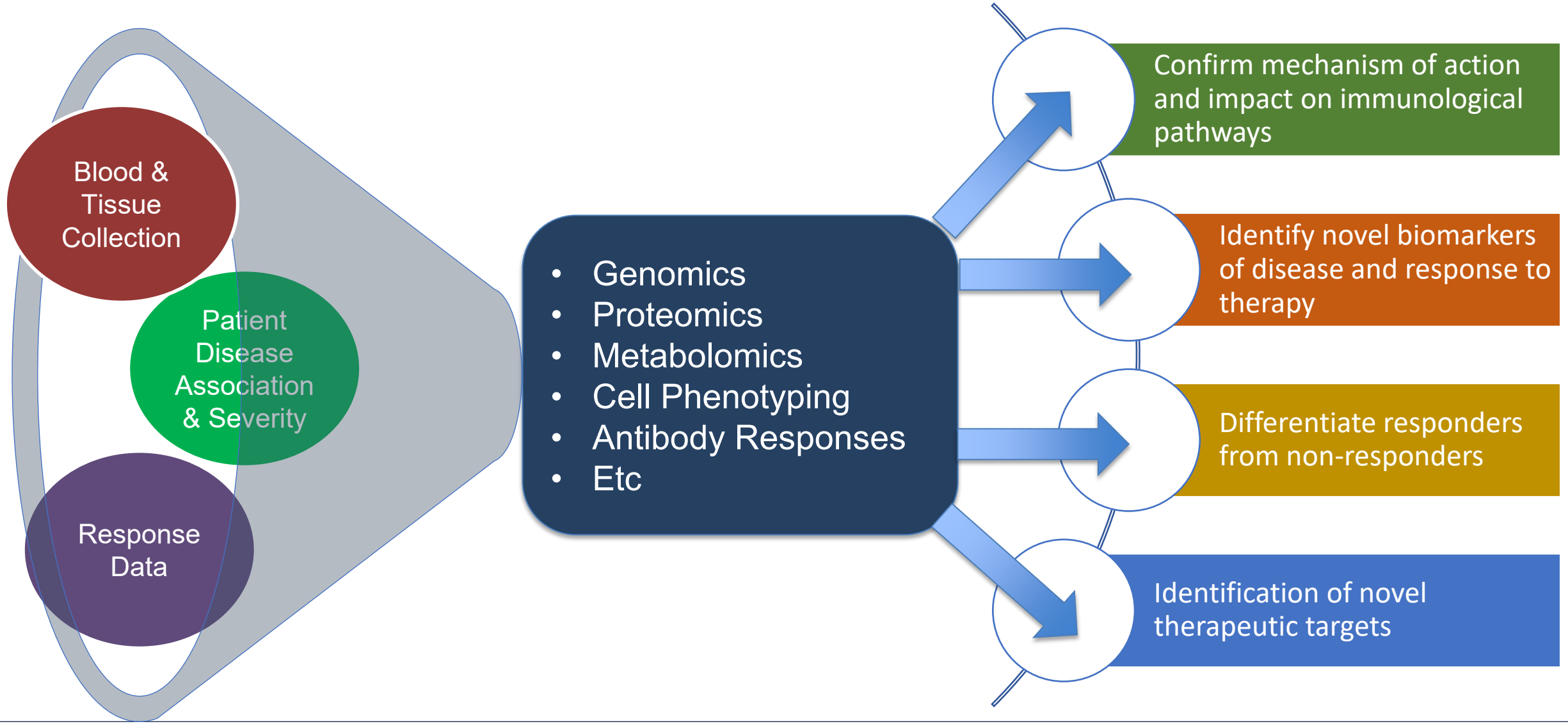
Target Identification and Validation



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Derisking Dermatology Development

In Vitro

Cellular activity

3D *in vitro* cultures

Cellular proliferation & function

Off-target safety screening

In Vivo

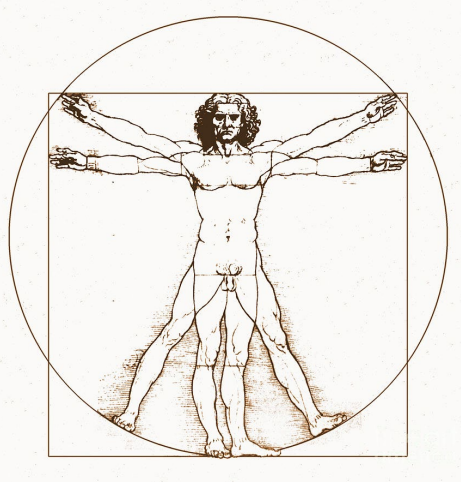
Pharmacokinetics

Pharmacodynamics / target occupancy

Mechanistic models

Disease models

Ex Vivo



Complex 3D *in vitro* co-cultures

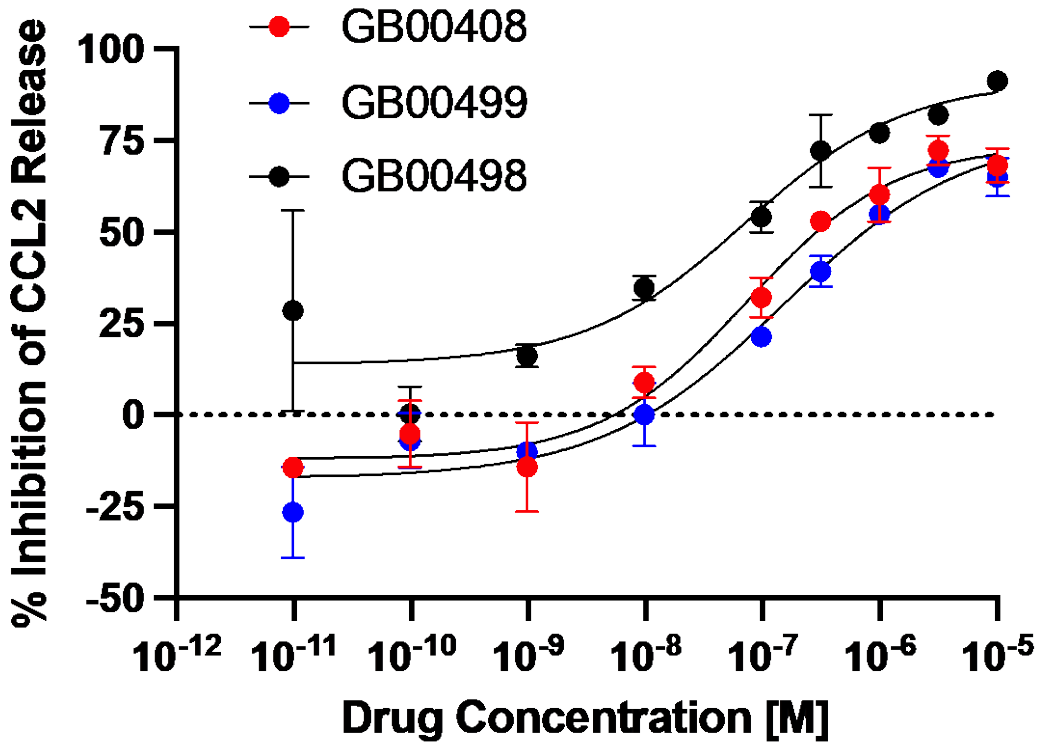
Translational Models

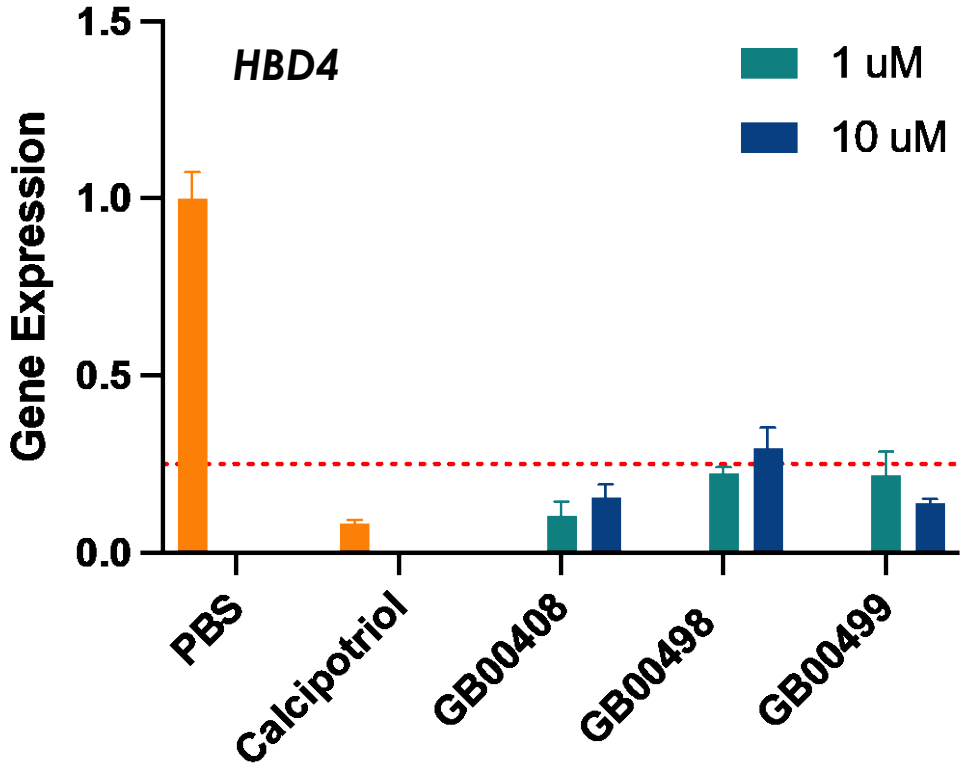
Proteomic / genomic profiling

Cytokine / chemokine biomarkers

Keep it Simple (KISs) with Keratinocytes

- Screen or counter screen drug candidates for their cellular activity in defined pathways
- Benchmark drug candidates against competitors in defined assays
- Characterize immunomodulatory of drug candidates in unstimulated cells to understand on-target and off-target effects





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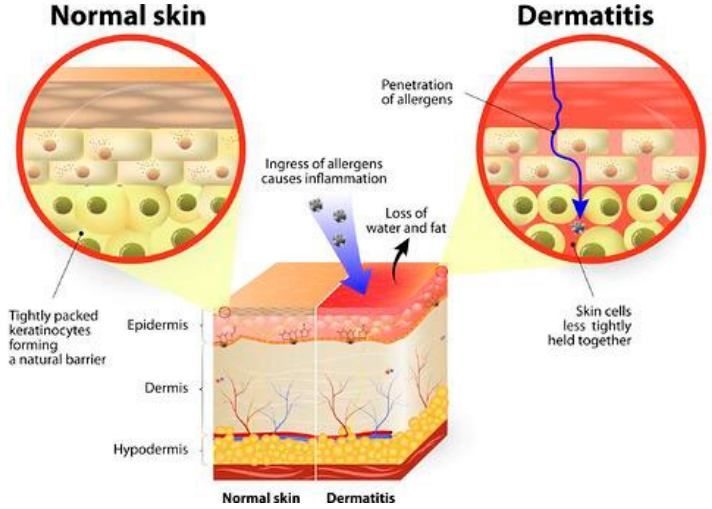
Integrated *In Vitro, In Vivo, and Translational Readouts*

Th2

Th2 Stimulated Ex Vivo Skin Explant
- CCL17/TARC (Th2 driven inflammation)
- CCL26/Eotaxin-3 (Eosinophil recruitment)
- Filaggrin (Barrier deficiency)

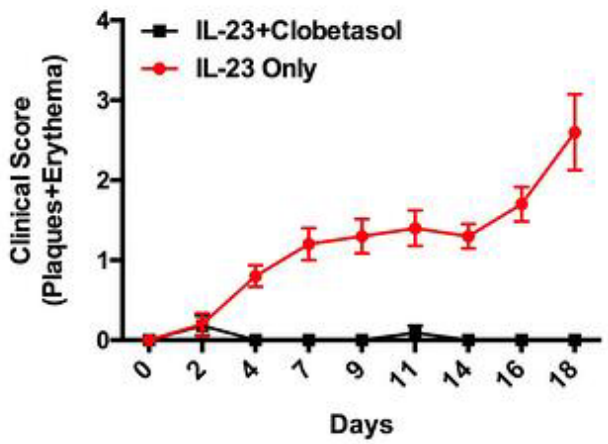
FITC Induced Atopic Dermatitis Murine Model
- Barrier and inflammatory genes
- Eosinophils (CCL26/Eotaxin-3)z

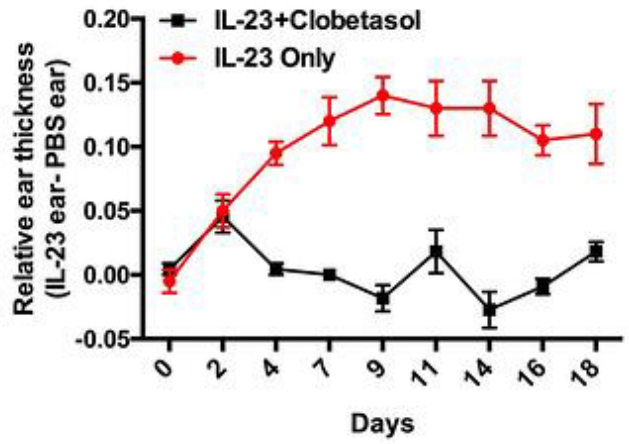


Th17

Th17 Stimulated Ex Vivo Skin Explant
- IL-17A (Disease pathogenesis)
- IL-22 (Acanthosis/epidermal thickening)
- CCL20/MIP3a (Th17 cell recruitment)

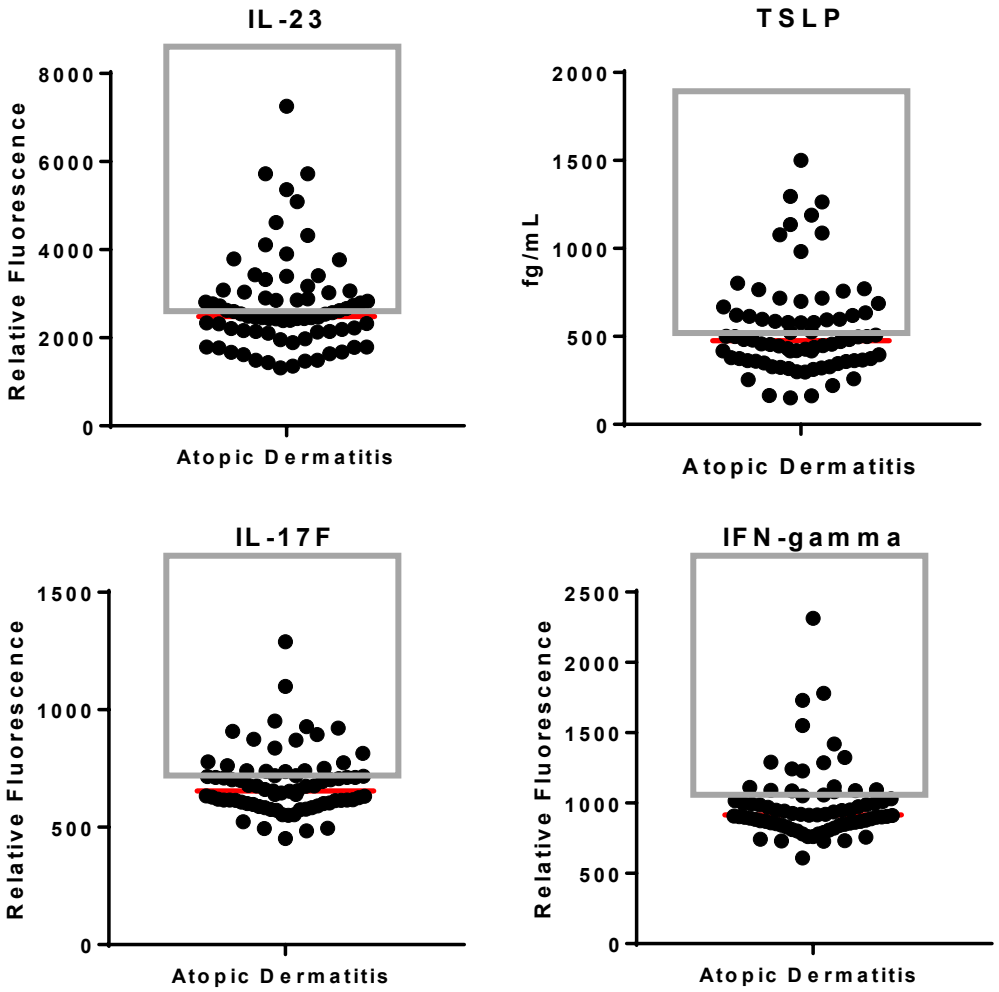
IL-23 Induced Psoriasis Murine Model
- Skin severity scores & ear swelling
- Cytokine Expression (IL-17, IL-22)





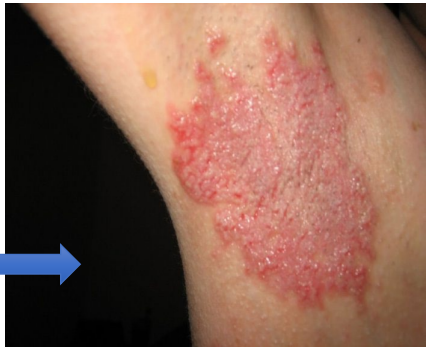
Understanding the Target Population

Do these represent distinct populations of AD patients or is there significant overlap?



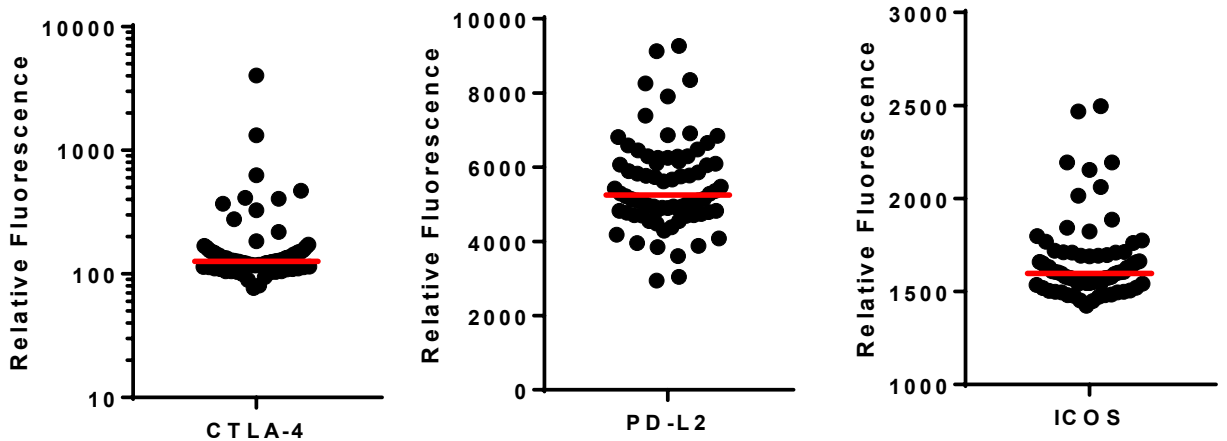
39 healthy control subjects with no history of skin disease

76 patients with moderate to severe (>12% BSA) AD



Emerging Role for Checkpoint Inhibitors in AD?

- No positive correlation between secreted ligands suggests distinct activation pathways in patients



Leonard *et al.* JACI

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Additional Studies Needed to Support Drug Development

AMES
- Bacterial reverse mutation test performed with *Salmonella typhimurium*
- Reveals whether the compound is causing direct mutations to the DNA

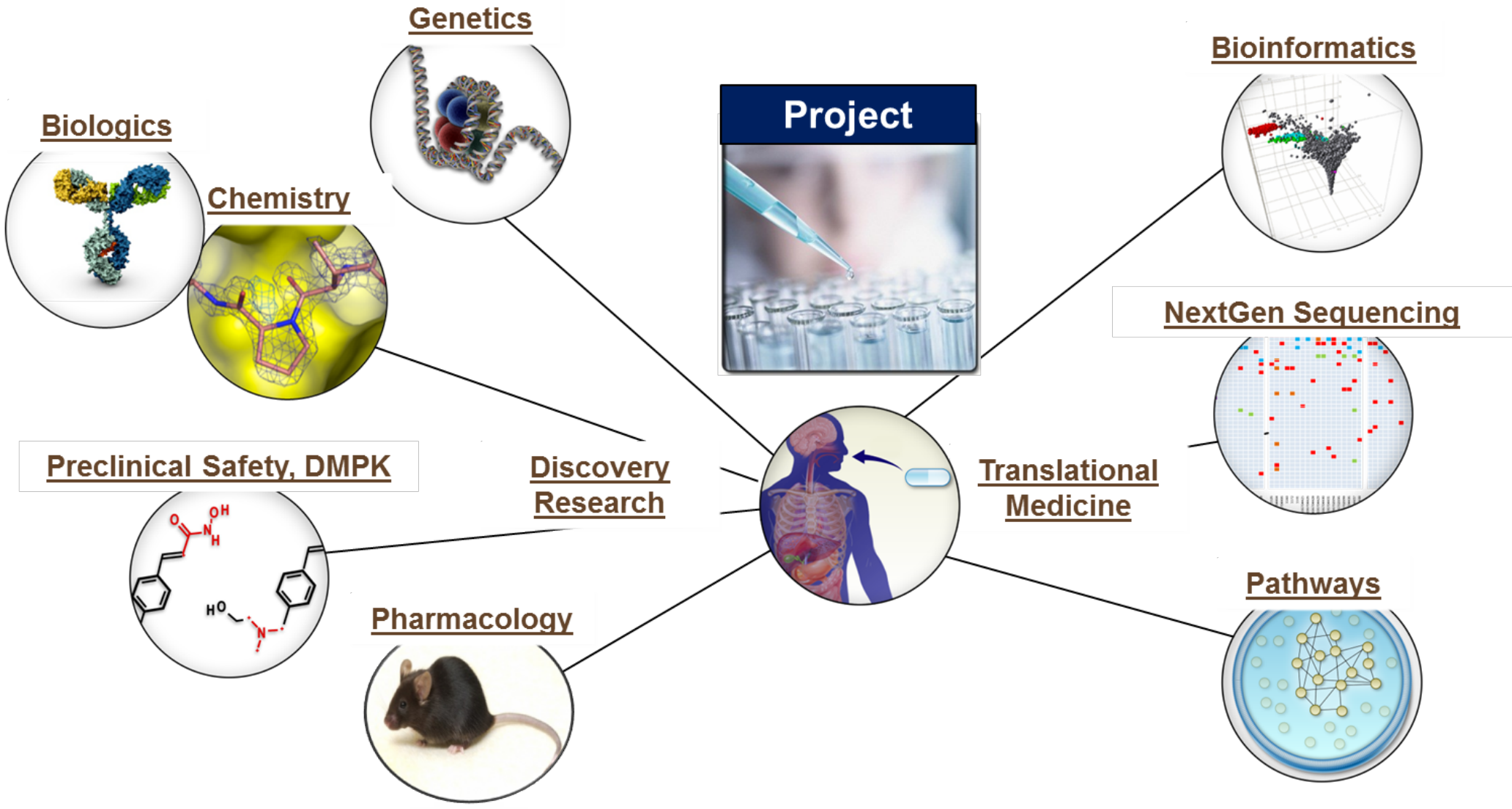
***In vitro* Micronucleus Test**
- Cell division assay using ChoK1 cell line
- Reveals whether the compound causes abnormalities in chromosome distribution (aneugenity) or even chromosome breaks (clastogenity) during cell division.

Pharmacokinetic
- Define active drug concentration & PK profiles
- Characterize over range of dosages, including expected clinical and toxicology dosages (1x-10x efficacious dosages)
- Single & Repeat-dose PK (3-7 days)

Safety Pharmacology
- Detect adverse effects (hazard identification)
- Investigate the mechanism of effect (risk assessment)
- Mitigation strategies (risk management)
- Calculate a projected safety margin

Toxicology
- Maximum tolerated dose
- Repeated dose range finding study
- 14-28 day GLP studies in 2 different species

Drug Development Requires Cross-Functional Collaboration



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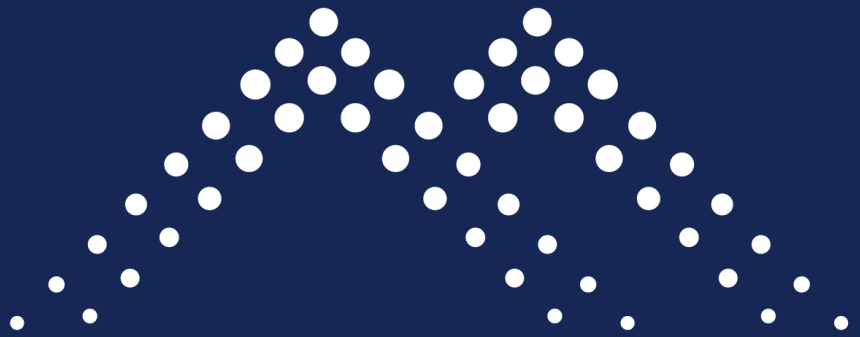

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March 6, 2025
Orlando, FL

Entrepreneur Bootcamp

Unlock the Future of Dermatology Product Development

Vijendra NALAMOTHU, Ph.D.
Founder & CEO
ApoStrata, LLC

Formulation of Dermatological Drugs

- **Topics covered:**
  - **Skin Biology**
  - **Product Development**
  - **Analytical R&D**
  - ***In Vitro* Testing**

- **What you will learn:**
  - Begin with end in mind®
  - Understanding your product
  - Why systematic development matters?
  - Using the skin data properly
  - Pitfalls of analytical data / impurities
  - Other means of verifying product: Skin Biology/IVPT
  - How will you use this data to go to clinic?

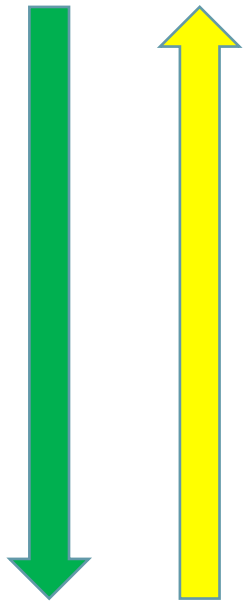
Begin with the end in mind®

- Next stage gate: tox / clinical / commercial
- Type of dosage form / dossier
- In vitro skin PoC or animal / disease models or straight to FIM / PoC
- Clinical de-risking and reduce CMC surprises
- Irritation / approved ingredients / vehicle effect, permeation, scale-up, QbD, stability, phase-specific validations
- Launch-ready products

Product Development: end-to end approach

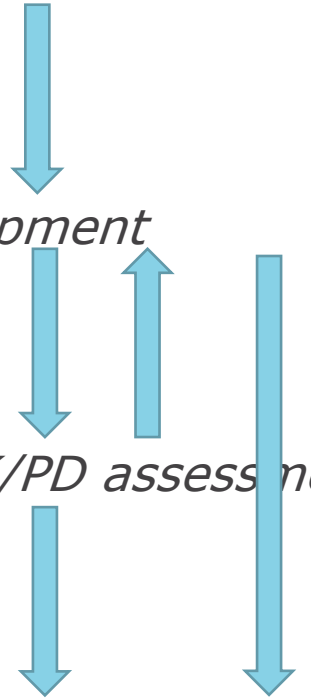
Decide the Commercial Pathway, regulatory strategy and work backwards-

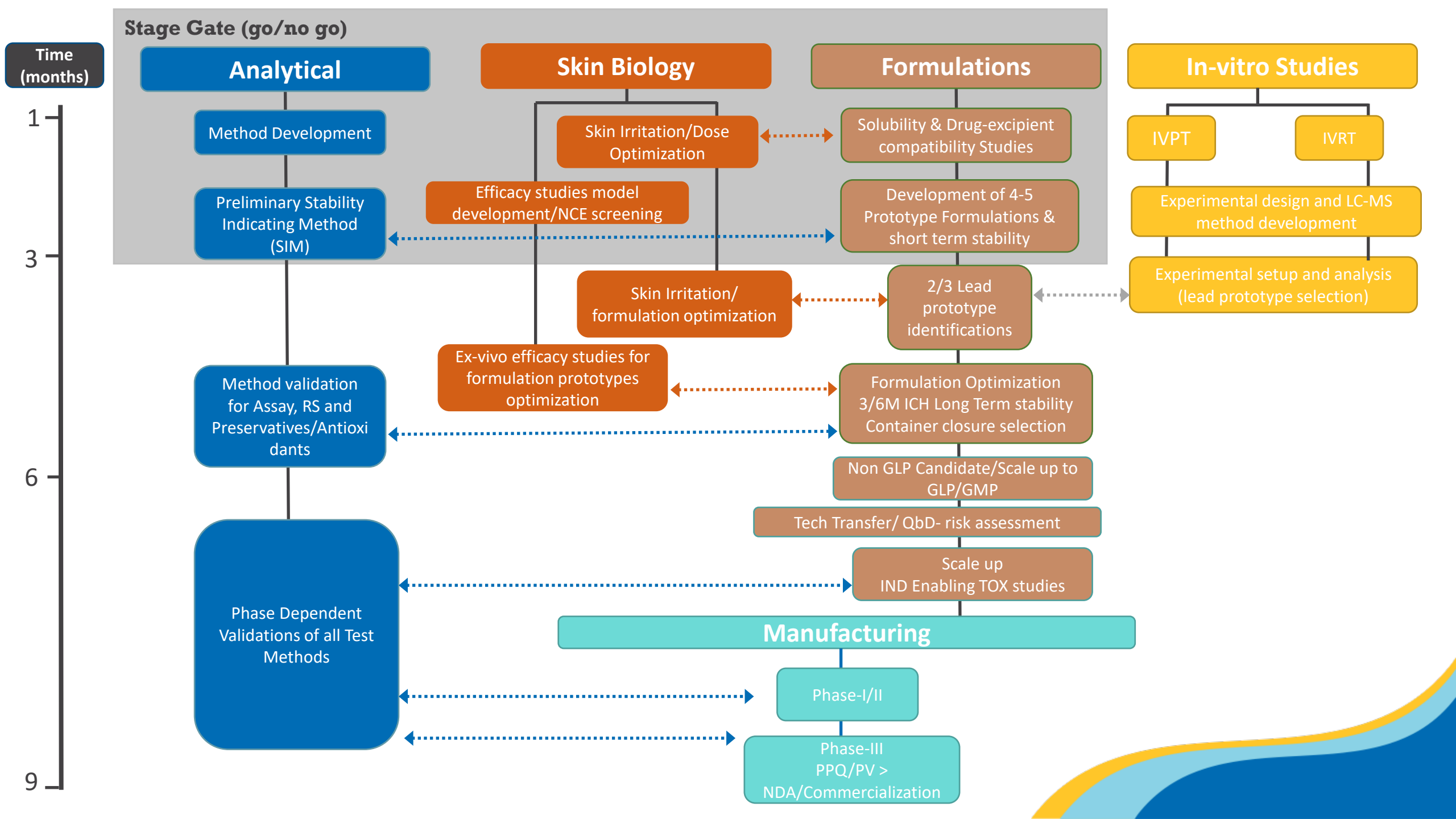
- Launch Plan
- Commercial Manufacturing / Process Validation / Supply Chain activity
- PDUFA / Registration /filing
- Clinical Trial Materials - Phase I/II/III
- Clinical De-Risking / Scale-up / PoC Formulations (FIM)
- R&D Formulations / Tox Safety assessment
- R&D Prototypes / In-Vitro / In-Vivo evaluations
- Idea / Proof-of-Concept / IP



Product Development Snapshot

- Skin Biology
  - *Early Candidate Selection / Molecule Assessment*
- Early Formulation Development
  - *Concurrent Analytical Method Development*
- Skin Permeation (PoC)
  - *Other Proofs-of-Concept such as PK/PD assessment, target engagement*
- Formulation Optimization
  - *Mfg. process Development / Scale Up – Tox Supplies / Clinical Trial Materials*
  - *QbD / Risk Assessment / IVRT*

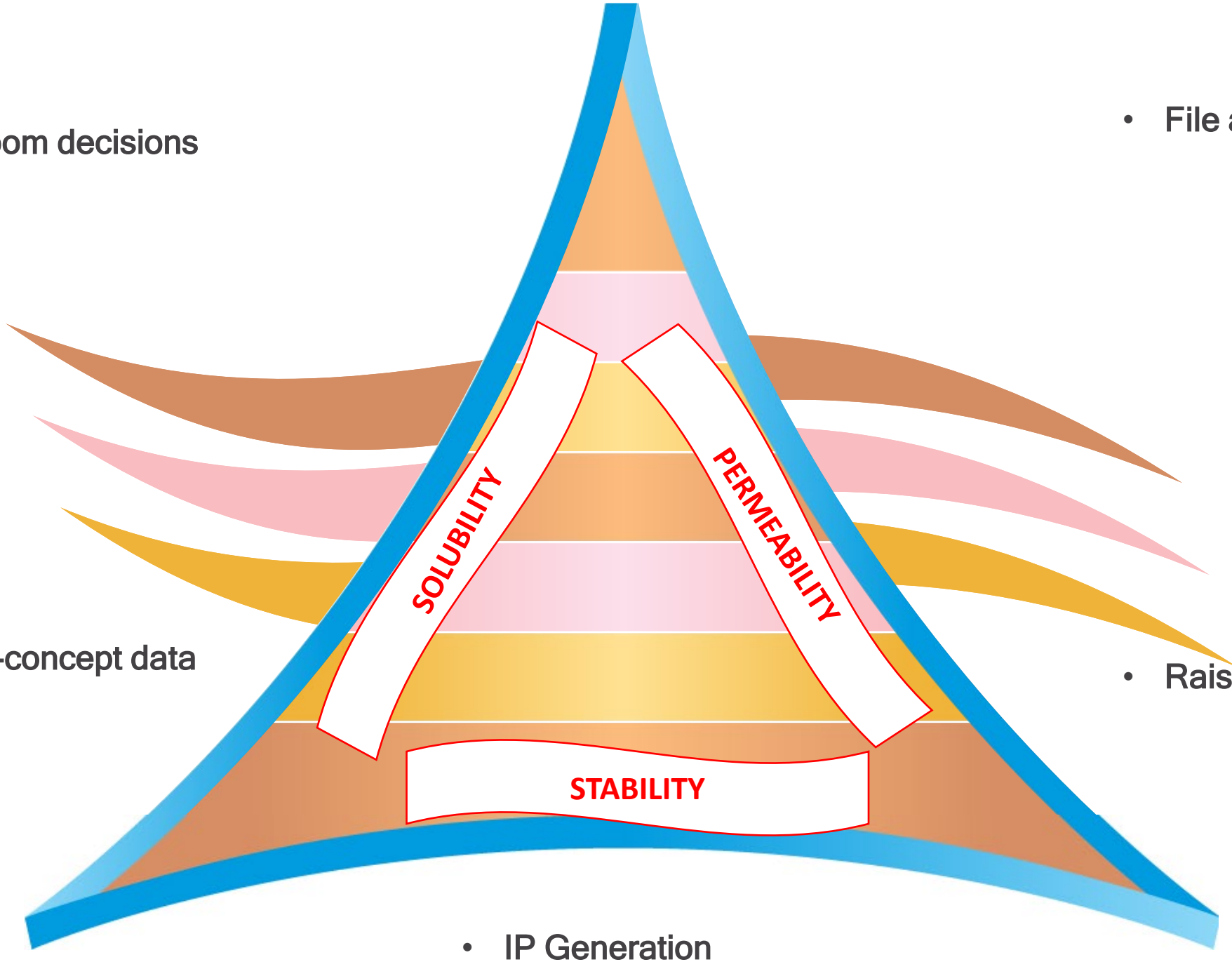



Stage Gate (go/no go)
Time (months)
1
3
6
9
Analytical
Skin Biology
Formulations
In-vitro Studies
Method Development
Skin Irritation/Dose Optimization
Solubility & Drug-excipient compatibility Studies
IVPT
IVRT
Preliminary Stability Indicating Method (SIM)
Efficacy studies model development/NCE screening
Development of 4-5 Prototype Formulations & short term stability
Experimental design and LC-MS method development
Skin Irritation/ formulation optimization
2/3 Lead prototype identifications
Experimental setup and analysis (lead prototype selection)
Ex-vivo efficacy studies for formulation prototypes optimization
Method validation for Assay, RS and Preservatives/Antioxidants
Formulation Optimization 3/6M ICH Long Term stability Container closure selection
Non GLP Candidate/Scale up to GLP/GMP
Tech Transfer/ QbD- risk assessment
Phase Dependent Validations of all Test Methods
Scale up IND Enabling TOX studies
Manufacturing
Phase-I/II
Phase-III PPQ/PV > NDA/Commercialization

Who is your client?

- We all want to win
- Formulate a product for positive pre-clinical and/or clinical outcomes that will:
  - Win Investor's Confidence
  - Win Internal Management's Approval
  - Win Regulatory approval & commercial success
- Design your product development strategy based on the Target Product Profile (TPP)
  - Early Candidates
  - Late-Stage Formulations
  - Me-too brands or differentiated formulations
  - Me-too generics or brand equivalents
- Develop a strategy early on for effective clinical end points and successful manufacturing scale-up

- Board room decisions
- File an IND/CTA



- Proof-of-concept data
- Raise funds
- IP Generation

An ideal Approach

- **Stages of formulation**
  - Basic (early) Formulation
  - Pre-clinical Formulation
  - Clinical Formulation
  - Commercial Formulations
- **Type of formulation**
  - Disease specific
  - Delivery kinetics
  - Unmet needs
- **Type of Dossier**
  - NDA - 505(b)(1)
  - 505(b)(2)
  - ANDA
    - Q1/Q2/Q3

- Acne formulations are different from Psoriasis
- Anti-fungal delivery is different than Basal Cell Carcinoma
- Wide-surface area coverage of a psoriasis formulation may dictate a type of formulation when compared to a small FTU application of Actinic Keratosis

- Delivery to Stratum Corneum vs. Dermis dictates the selection of right formulation
- Need for a drug to stay in dermis vs. transdermal delivery into systemic circulation drives the choice of excipients
- Targeted delivery for pharmacological action
- Peptide / protein delivery also has its own choice of formulation components

- Clinical Unmet Needs
- Commercial Unmet Needs
- Technical Unmet Needs

Target Product Profile (TPP)

- Talk to your clinical group and/or marketing-sales organization very early on
- Based on early / concept formulations first
- How much levy do you have ‘changing’ the formulation later
  - How much can you change *i.e.,* just preservatives or ..?
  - When or how late can you change *i.e.,* Phase I/II changes?
- Is it a dynamic TPP or etched in stone? Early clinical/late stage/ changing market scenario
- Ask for definitive ‘not acceptables’
- Who drives it? Early feedback vs. Last minute changes
- Setup a minimum acceptable criterion *vs.* ideal acceptable profile
- Focus on core formulation and achieve it first

Case Studies

- 2 People and a Molecule
- University Tech Transfer
  - Early formulations *vs*. Final Formulations?
  - How much to rely on skin permeation data
  - Formulation stability data: just enough or IND-ready?
- US Development *vs.* Ex-US PoC
- FIM – CTA – IND
  - Is it PoC or powering for future clinical trials
  - Safety / tox formulations?
- Global Large-Pharma Development
  - Dosage form / packaging finalized?
  - Manufacturing process optimized?