UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY

Innovation @ UMB: Exploring Therapeutic Product Development

Academic / Industry Partnerships

Jeff Hasday (SOM), Paul Shapiro (SOP) and Ritu Lal (GEn1E Lifesciences)

Feb. 14, 2024

GEN1E LIFESCIENCES

www.gen1e.com

Outline:

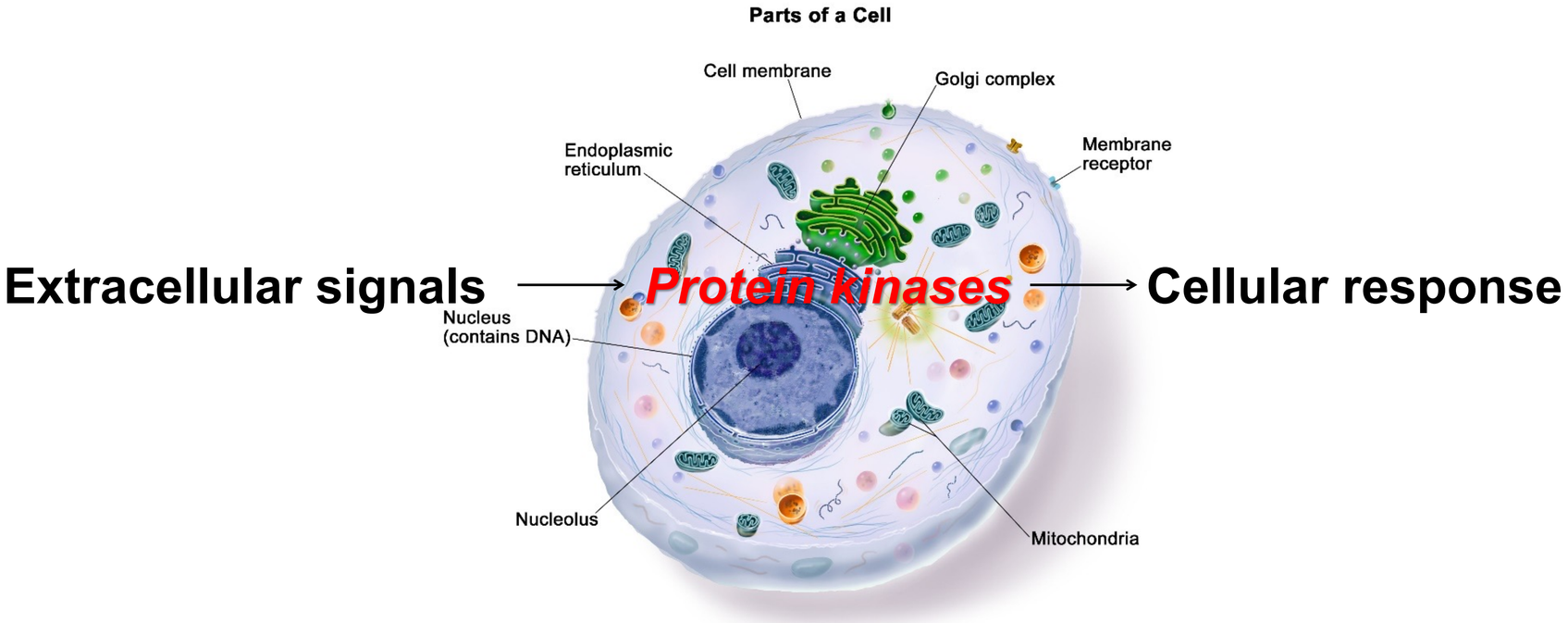
1. Proteins kinase overview: drug targets in disease

2. Modulators of kinase functions in disease

3. Industry partnerships

4. Advancement to clinical trials

Overview: Protein Kinase Function



Reversible Phosphorylation

Enzyme + Substrate ⟷ [Enzyme-Substrate] ⟷ Enzyme + Product ⟶ Response

E + S [E-S]+ATP E + $P_{(+phosphate)}$

Cell image from: https://nci-media.cancer.gov/pdq/media/images/761780.jpg

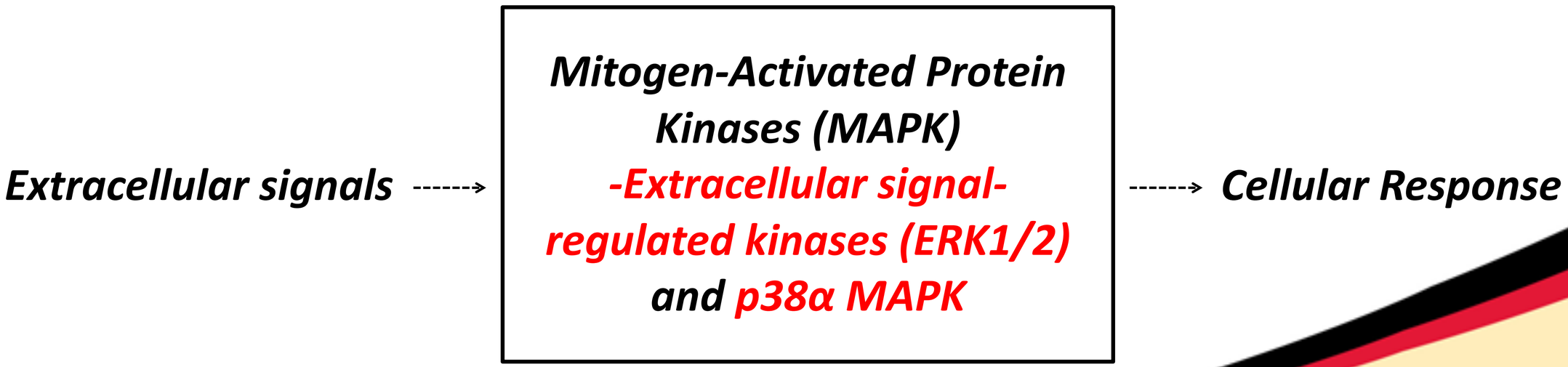
Protein Kinases and Disease

***Activating mutations or constitutive activation in:**

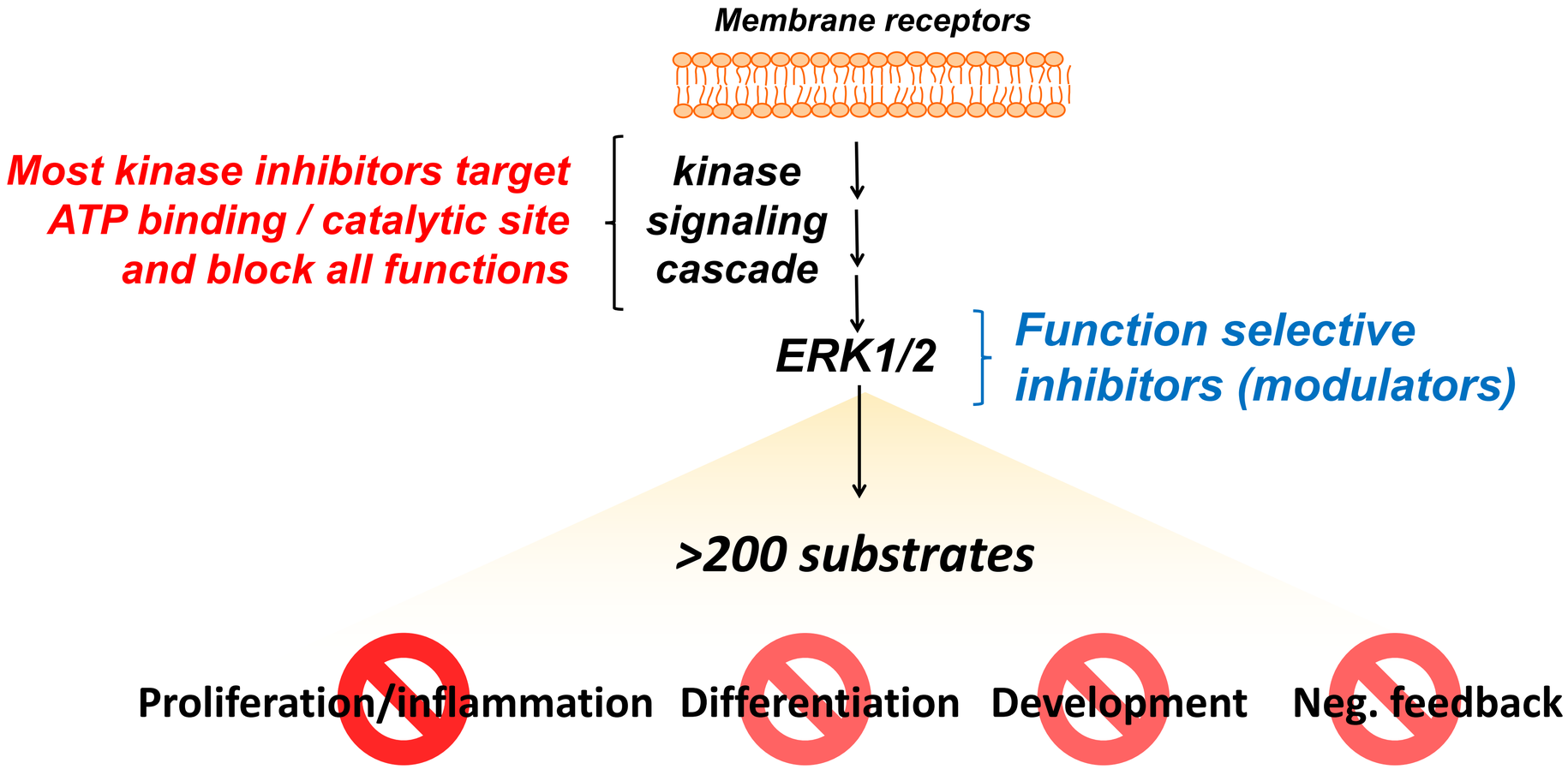
Proliferative disorders (cancer)

Inflammatory disorders (ARDS, asthma)

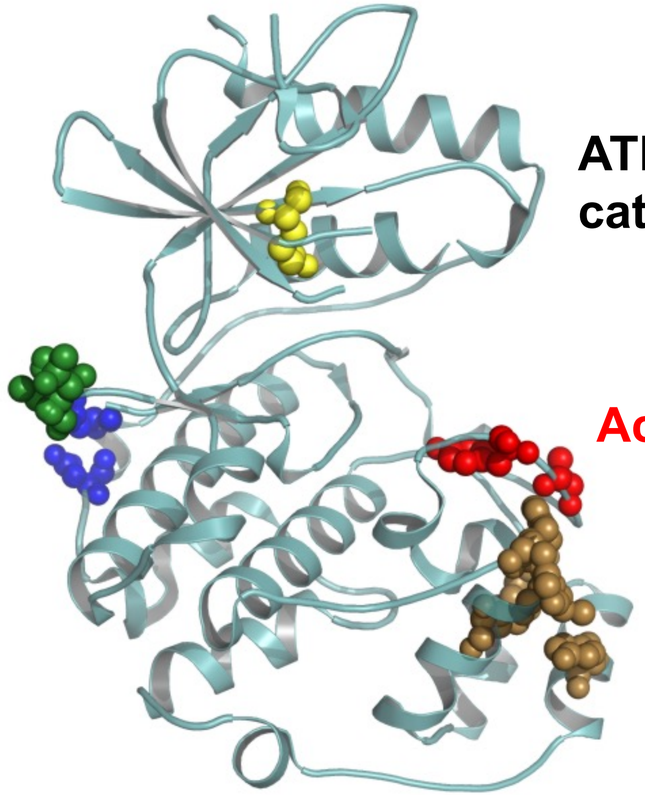
Neurodegenerative, developmental, and other disorders



ERK1/2 Signaling, Substrates, and Functions



The Idea: Modulating MAPK Functions



ATP binding / catalytic site

Current small molecule inhibitors

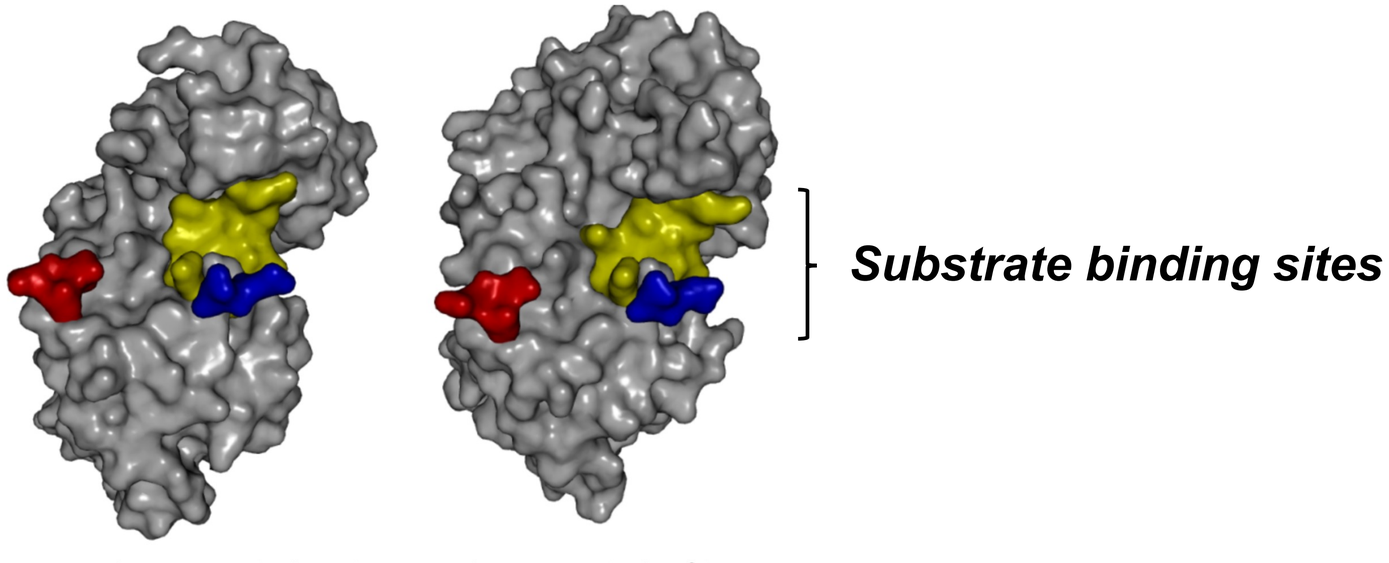
substrate binding site

Activation loop

substrate binding site

ERK2

p38α and p38β are 75% Identical But Have Differences



p38α (MAPK14) p38β (MAPK11)

Pro-inflammatory Functions

Cytoprotective Functions

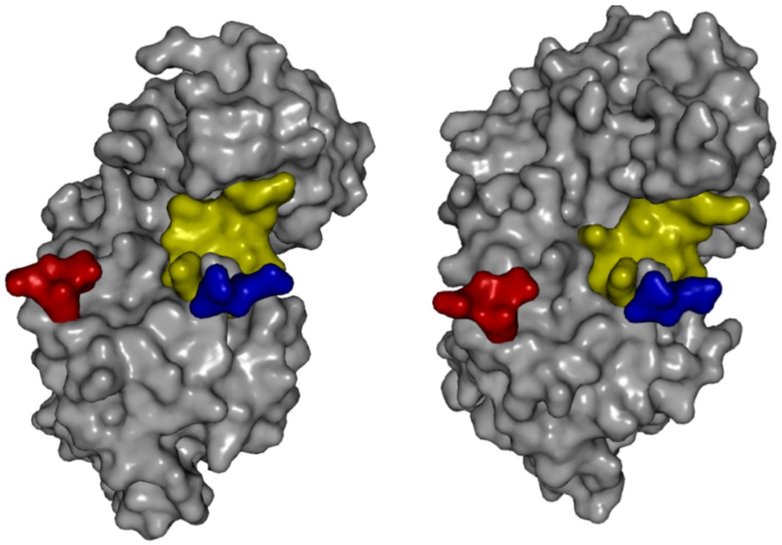
CADD Screening of p38α MAP Kinase Selective Compounds

Maybridge Screening Collection:
low MW compounds tested for best fit in p38α-targeted pocket (electrostatic /VdW interactions) using DOCK
(50,000 selected)

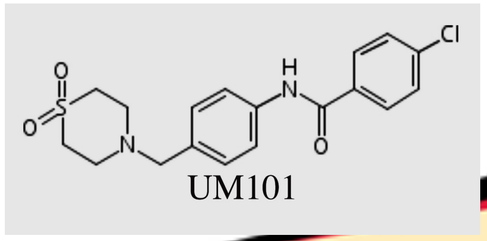
Second screen allowing additional ligand relaxation during docking
(1000 selected)

Chemical diversity and drug-like characteristics
(150 selected)

20 compounds obtained for screening

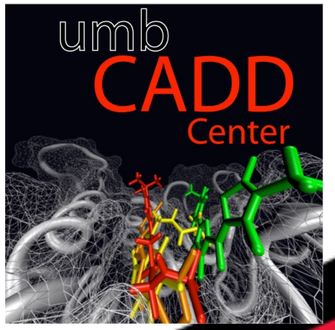


MAPK14 (p38α) MAPK11 (p38β)



UM101

Alex MacKerell, PhD, Director
UMB CADD Center



Developing an Industry Partnership

- Intellectual property (IP) and patent protection (UMB)
- IP licensed to GEn1E Lifesciences

GEN1E LIFESCIENCES

www.gen1e.com

Ritu Lal, PhD, MS
CEO & Co-Founder

Acknowledgments

*UMB Institute for Clinical and Translational Research

*Center for Maryland Advanced Ventures Life Sciences Fund

*National Institutes of Health (HL168723 and AI126492)

Happy Valentine’s!

Outline of my talk

- My background, journey and experience
- Meeting UMB, genesis of GEn1E and excellent collaboration 🙂
- Use of AI and what's next for GEn1E

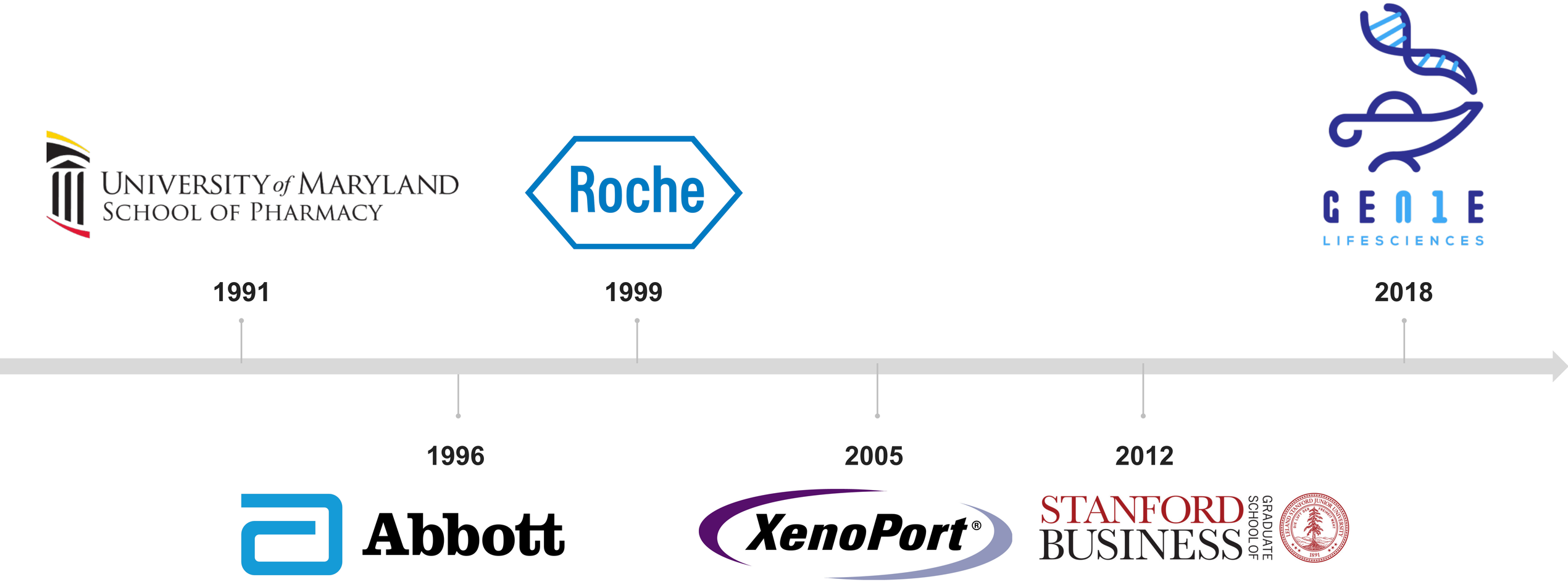
A proud alum of

UNIVERSITY of MARYLAND BALTIMORE

UNIVERSITY of MARYLAND SCHOOL OF PHARMACY

- Ph.D. Pharmaceutical Sciences, University of Maryland, 1996
- Dissertation: Modeling Placebo Effects for Pain drugs + Effect of Fampridine in Multiple Sclerosis

Timeline


UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY
Roche
GENIE
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1991
1999
2018
1996
2005
2012
Abbott
XenoPort®
STANFORD
BUSINESS
GRADUATE
SCHOOL OF

Roche and p38 kinase inhibitors

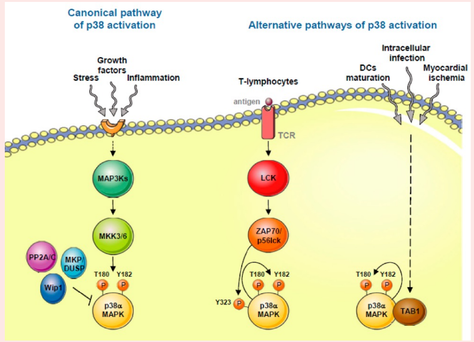
Palo Alto, CA

Early 2000's

- Medicines for Emphysema, HIV, Hepatitis C, Rheumatoid Arthritis and Osteoporosis
- Led p38 kinase inhibitor clinical team – failed for safety or lack of efficacy. Entire Pharma industry had similar fate

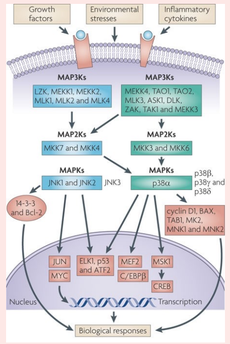
GEn1E's compounds are NOT p38 & NOT MK2 inhibitors

p38 inhibitors



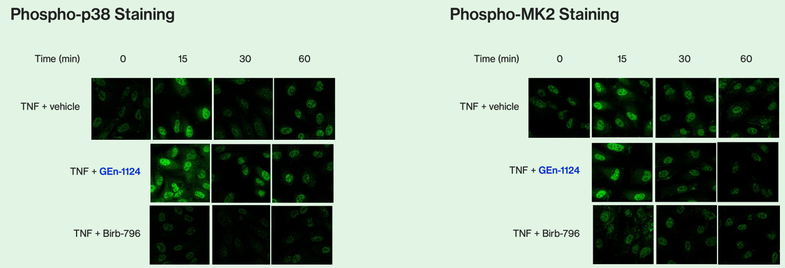
Causes Toxicity &
causes Tachyphylaxis

MK2 inhibitors



Solves Tachyphylaxis but
causes Liver Toxicity & Infection

Dual Signal Modulators



- p38α is activated and kept in the nucleus **AVOIDS Tachyphylaxis**
- MK2 is not inhibited but degrades in cytoplasm **AVOIDS Toxicity**

GEN1E LIFESCIENCES

Becoming a Pharmapreneur

- Holistic view of the entire industry
- Entrepreneurship
- Embrace change
- Experiential learning
- Be comfortable being uncomfortable!

The birth of GEn1E Lifesciences

- Solving the drug development and approval problem
- The search for technology and working with the right Team
- Serendipity - back to UMB and back to p38 from my time at Roche. This time with a novel mechanism making them super selective

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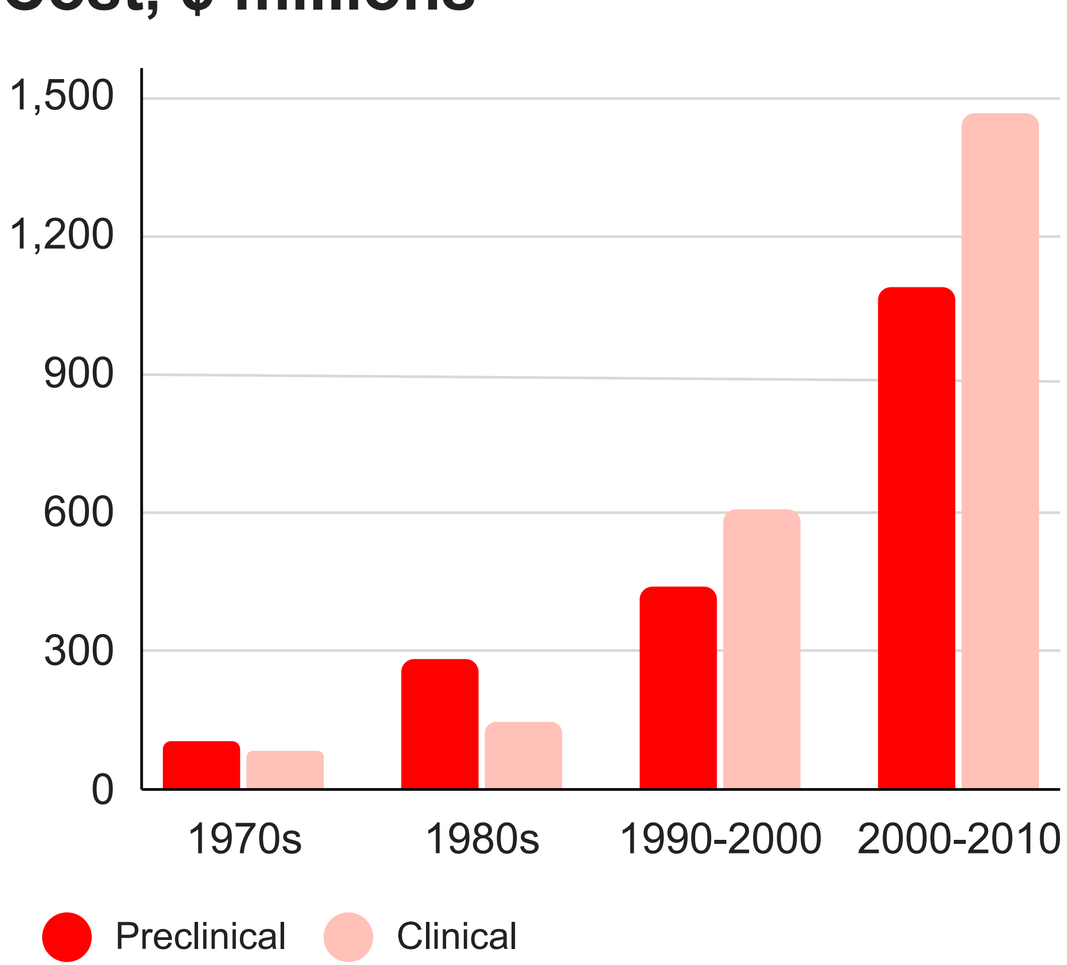
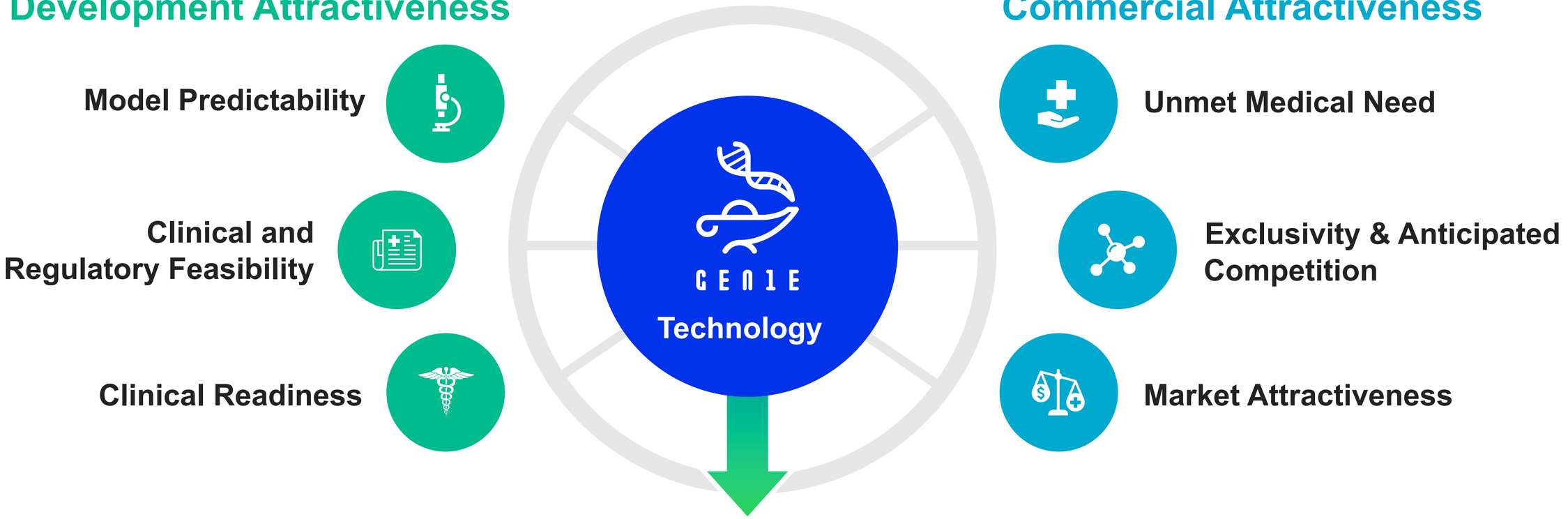
The Drug Development Problem

- **>$1B to bring a single drug to market**
- **15 years from preclinical to NDA approval**
- **1% of preclinical phase therapies reach FDA approval**



* Tufts Center for the Study of Drug Development

GEn1E's solution to be 10x cheaper, 2x faster and 2x more likely to get to market



AI/ML
FDA Incentives (Orphan)
Quick POC Studies and FDA approval

Wonderful collaboration with UMB inventors and the Office of Tech Transfer

+ Alex MacKerell
+ Steve Fletcher
+ Mohan
+ others

+ others

Accelerating with right partners

Y Combinator

StartX

BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT AUTHORITY
BARDA

vituity®

Consistent support from Strategic Angels + Investors

Dr. Francois Nader

Board Member: Moderna, Benevolent AI, Acceleron

Thomas Ebeling

Ex-CEO, Novartis Pharma

George Bickerstaff

Ex-CFO, Novartis Pharma

vituity®
At the heart of better care.

CLEAR VENTURES

Y Combinator

StartX

khosla ventures

SV LC
SV LATAM CAPITAL

GENIE
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A Clinical Stage, Phase 2 Company

Accelerating 1st-in-class Precision Therapies for inflammatory and rare diseases with unprecedented efficiencies

How GEn1E's story is *different*?

- **Unique biology** of Dual Signal Modulators with a validated MOA
- **Unprecedented efficiency** to accelerate drug development using our AI platform
- **Precision approach using AI** for heterogeneous diseases with no approved therapies and devastating health economics
- **Team** with a track record of developing novel drugs. CEO has 3 FDA approvals in US and in Japan

What we are NOT

NOT an AI company for just drug discovery

NOT an AI company with same spend and long timelines of a bio company

NOT a p38 or MK2 kinase inhibitor

Early discovery to Phase 2 in ~2.5 years & seed capital

- **FDA approved Phase 2** study enrolling ARDS patients

Mount Sinai · KU Medical Center, The University of Kansas · Singing River Health System · Houston Methodist, Leading Medicine

- Received **FDA Fast Track** designation
- Partnership with BARDA DRIVe and Vituity
- Completed Phase 1 SAD/MAD study in 48 humans
- **Pre-IND to FDA for 2nd indication**

IV for Acute

Additionally

- **Oral Chronic Package** is progressing rapidly
- 2nd target **ERK** is optimized
- Patent portfolio is robust and expanding

Oral for Chronic

Lead program: ARDS

- No FDA approved treatments
- 40% mortality rate
- Total Cost to US Society: $25 Billion

Confalonieri, et al.. 2017. European Respiratory Review 26 (144): 160116. 2. Bice, et al. 2013. Seminars in Respiratory and Critical Care Medicine 34 (4): 529–36.

Preclinical and Clinical Data Favorable for Lead Compound

- Good preclinical data in multiple ARDS models
- ICH Toxicology studies completed, Highest feasible doses in the studies were No Observed Adverse Effect Levels (NOAEL)
- Clinical Phase 1 study in 48 humans completed- good safety/tolerability, PK and PD
- Reviewed by US FDA (Fast Track), actively enrolling Phase 2 ARDS clinical trials

Favorable results from Phase 1 SAD/MAD study in contrast to old p38 kinase inhibitors

Side Effects	Old gen p38s[1]	GEn-1124
Secondary Infections (requiring antibiotic treatment)	Yes	No
Elevated ALT/AST (liver enzymes)	Yes	No
Elevated Creatine Kinase	Yes	No
Severe Rash	Yes	No
Severe Dizziness	Yes	No
Unpredictable Human PK/PD	Yes	No

1. Cohen SB,. Arthritis Rheum.60(2):335-44 (2009) 2. Damjanov Arthritis Rheum. 60, 1232–1241 (2009) 3. MacNee Thorax 68, 738–745 (2013)

Pipeline developed efficiently with multiple targets

Area	Disease	Discovery	Lead Optimization	Pre-clinical Development	IND Enabled	Phase 1	Phase 2	Phase 3
Asset 1 is IV for Acute Inflammatory diseases								
Respiratory	ARDS (w/ BARDA)							
PiP								
Asset 2 is Oral for Chronic immunology diseases								
	Rare & Non-Rare							
Asset 3 for Onco-immunology								
Oncology	Glioblastoma/Melanoma							
Respiratory	Asthma							

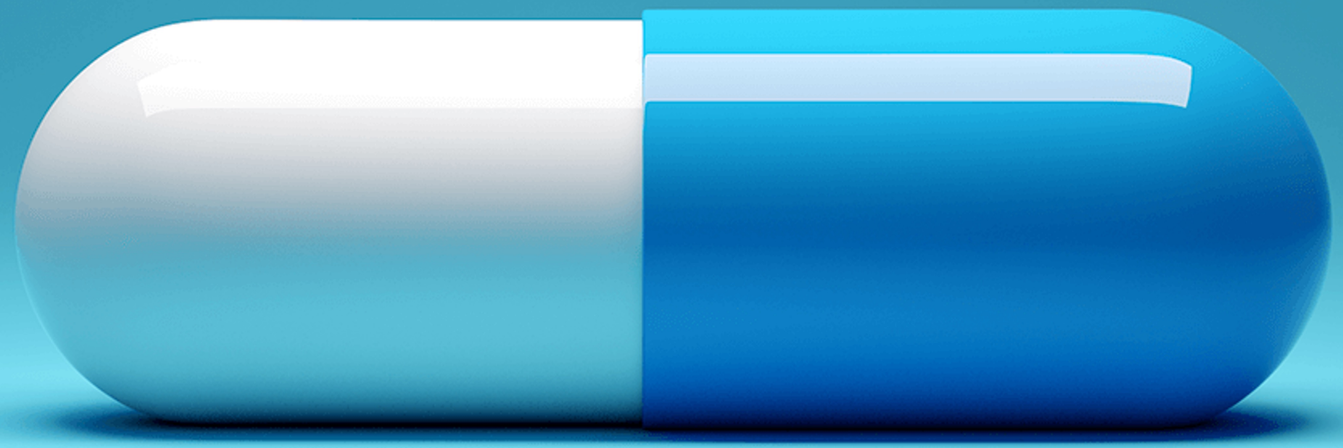
BARDA partnership

Second Asset

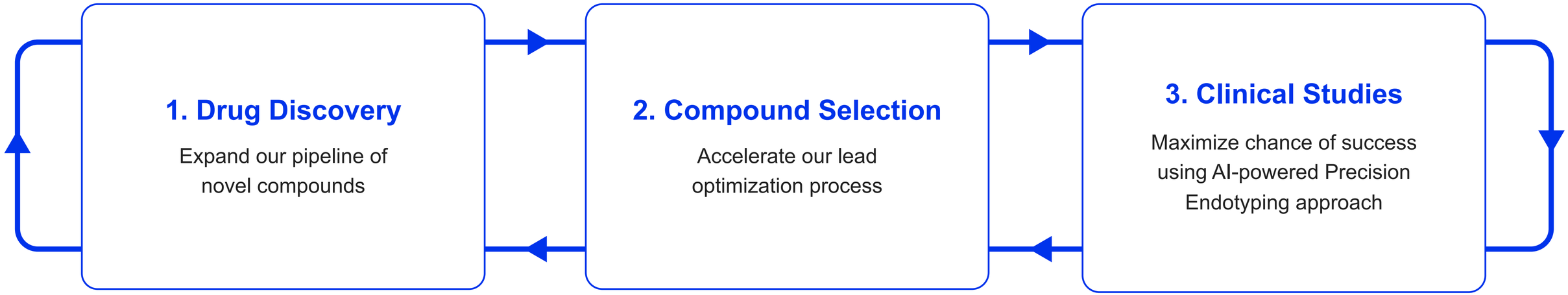
Oral medicine for Chronic diseases

Our second compound:

- Shows NO Tachyphylaxis
- Has 80%+ oral bioavailability in monkey
- Is progressing rapidly with plan to conduct Phase 1 human study in 2024



GEn1E's AI Platform (RIDGE™) is by GEn1E, for GEn1E. It spans end-to-end and uses proprietary data generated by us



In-house Data Generation and In-house Data Curation

Lab Data

Safety

Toxicology

PK/PD

Clinical Trial Data

Our Phase 1 data

NIH data sets

Disease & Gene Data

Genomics

Proteomics

Pathways Data

Pubmed

Medline

Molecular Functional Data

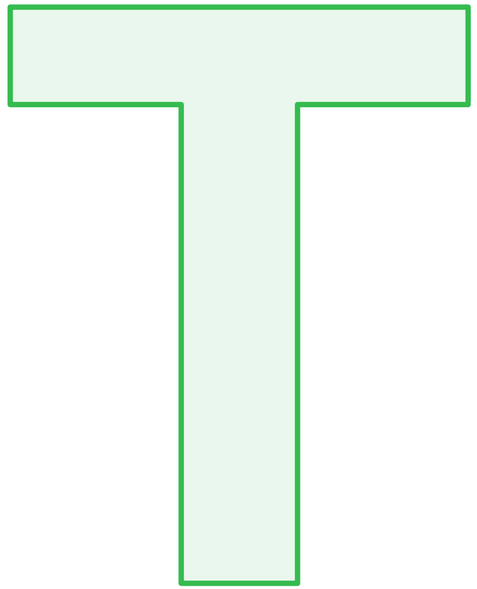
Our AI-powered Precision Endotyping model has been built to increase our probability of success

1. **Stratify** general patient populations
2. **Subtype** underlying disease mechanisms
3. **Identify** patients who would benefit most from our novel drug

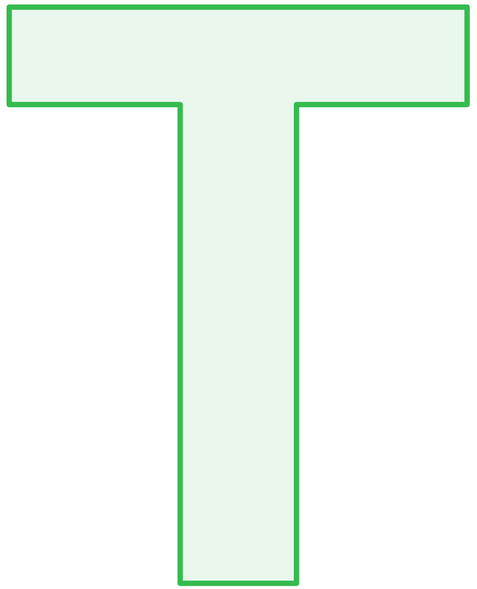
Source: Wildi, K., Livingstone, S., Palmieri, C. et al. The discovery of biological subphenotypes in ARDS: a novel approach to targeted medicine?. j intensive care 9, 14 (2021). https://doi.org/10.1186/s40560-021-00528-w

Trifecta of 3Ts to boost the fourth T

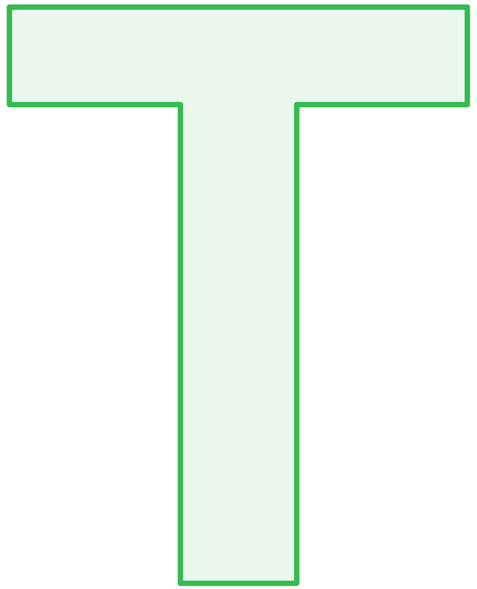
Target



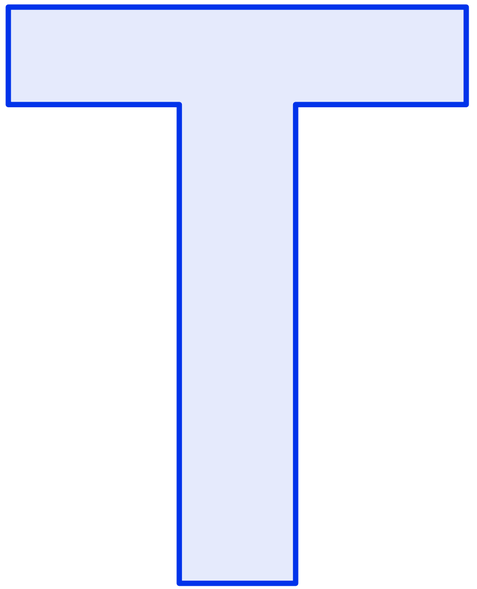
Technology



Team



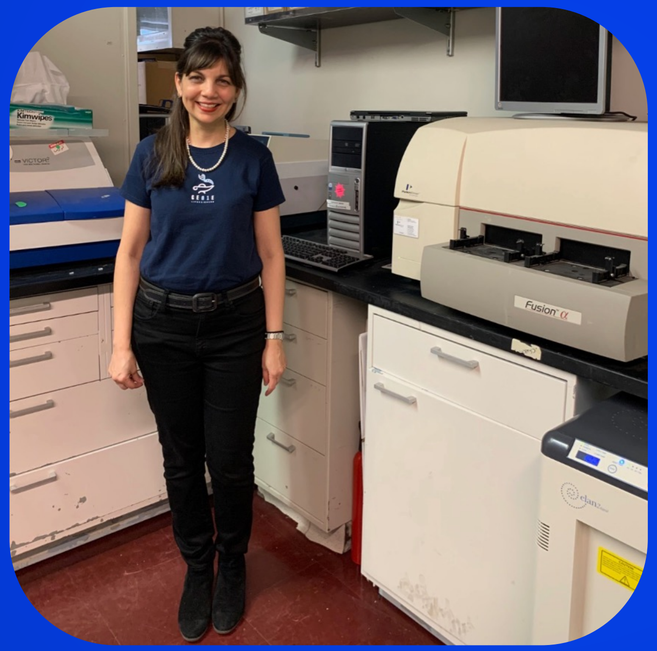
Time to Market



TLDR

GEn1E's unprecedented efficiency enables development of Novel Precision Therapies for devastating inflammatory & rare diseases

Palo Alto Office



Mountain View Lab

- Accelerated lead from early discovery to Phase 2 in ~2.5 years & seed capital
- Multiple novel 1st-in-Class Dual Signal Modulators for Chronic/Oral + IV
- Fast Track from FDA + Enrolling patients for Phase 2 + Plan to bring 2 more indications to IND Enabling stage
- BARDA for ARDS study + Vituity (3,000+ Physician Network)

Stay in touch!

Dr. Ritu Lal

ritu@gen1elifesci.com

Phil Knight

Founder of Nike
(Stanford GSB, 1962)