EpiTET Therapeutics

Inflammation & Immunology Breakthrough:

Molecular glues for the selective elimination of pathogenic macrophages

Yingqun Huang, MD, PhD | Blavatnik Application ‘24-25

Blavatnik Accelerator Awardee

Team of ***Industry Veterans*** and ***Key Opinion Leaders***

Yingqun Huang, MD, PhD
Scientific Co-founder

Professor, OB/GYN,
Yale School of Medicine

Brooks Leitner, MD, PhD
Advisor, Co-founder

Yale MD/PhD
Cell & Molecular Phys.

Erika Smith, MBA
CEO

>30 Years Life Sciences BD
3 Successful Exits as Investors

George Maynard, PhD
CSO

>30 Years Med Chem Experience
Led Dev Candidates through Phase II

Hugh Taylor, MD
Advisor, Clinical Strategy

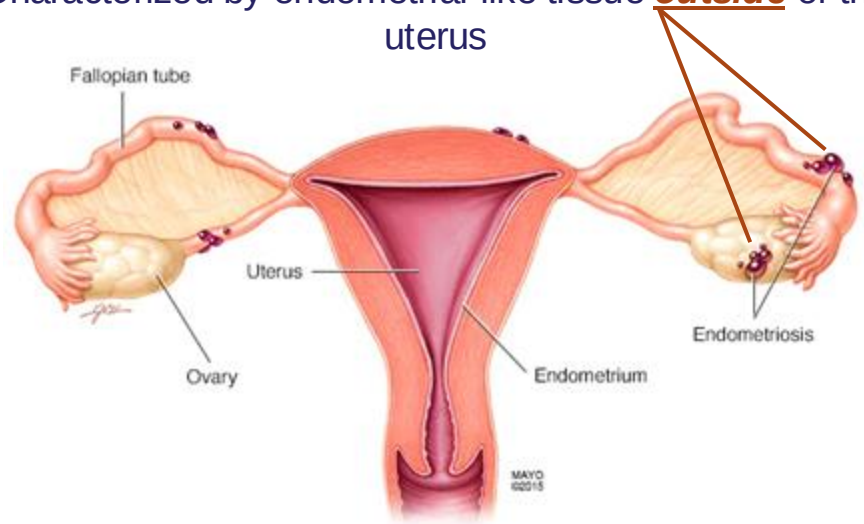
Chair, OB/GYN & Reprod.
Sciences
Yale New Haven Hospital

With Yale Ventures support from: **Hong Peng, PhD, MBA (Business Development)** and **Robert Williams, PhD (Blavatnik Fellow)**

Endometriosis: a ***chronic inflammatory disease*** with ***no cure***

Unmet need for a disease-modifying drug ***targeting the underlying cause*** of disease rather than treating symptoms. Pathogenic Macrophages drive pain and fibrotic lesions.

Characterized by endometrial-like tissue ***outside*** of the uterus



Affects 1 in 10 women

190M reproductive-aged women worldwide

Debilitating symptoms

Severe chronic pain (80%) and infertility (50%)

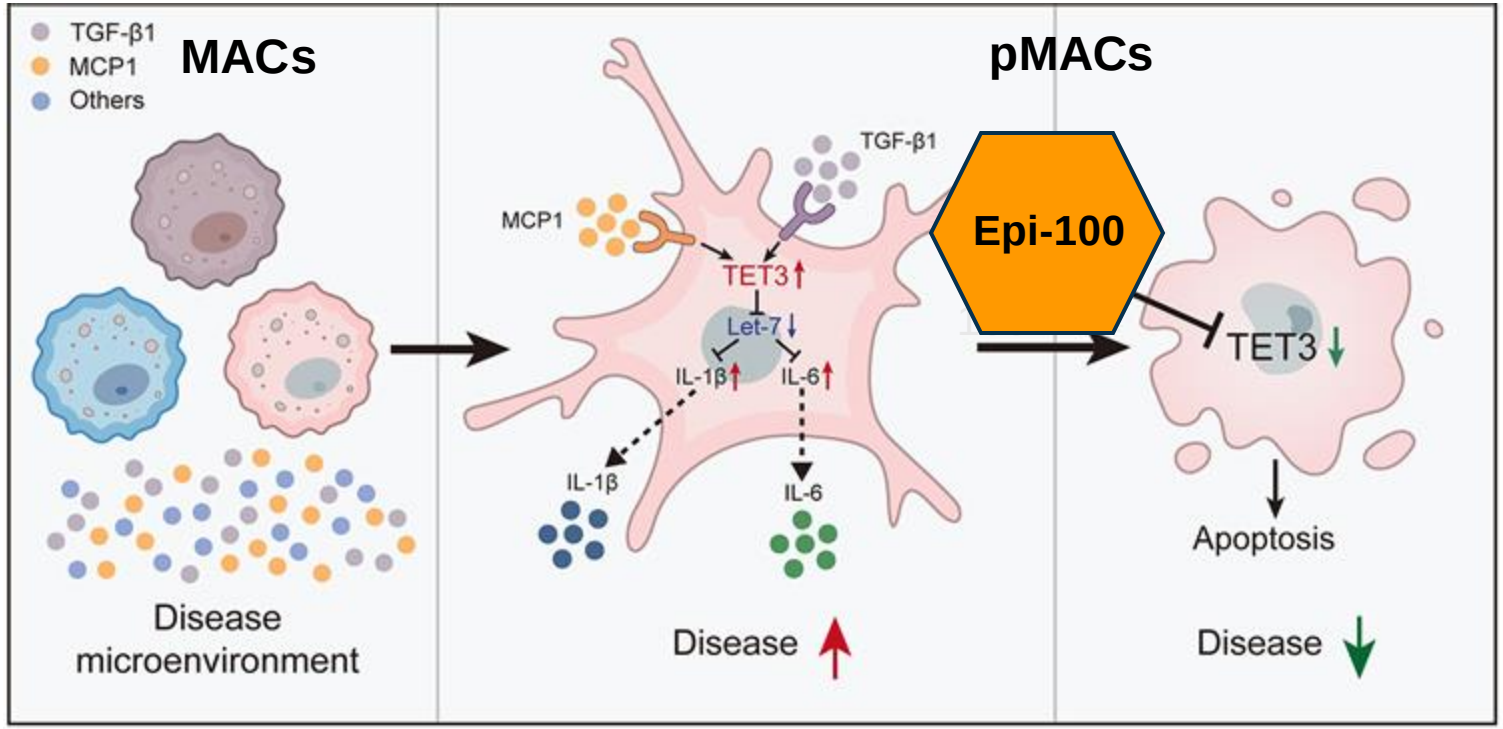
Inadequate standard of care

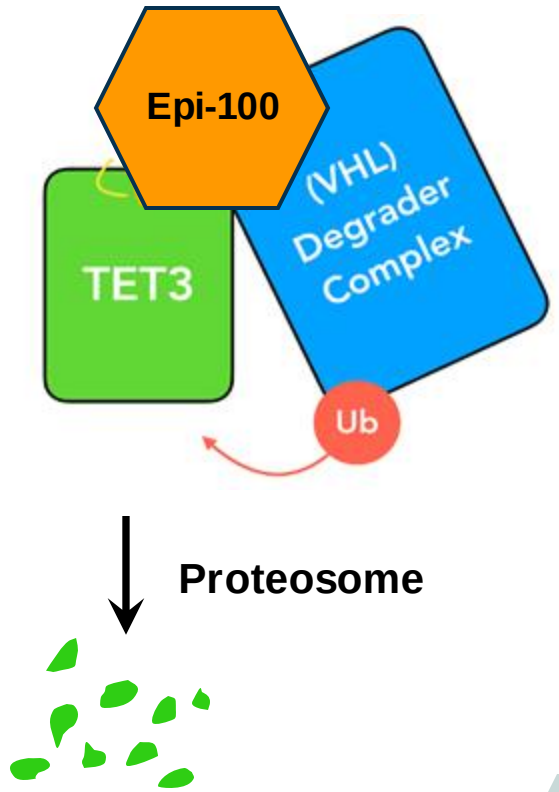
- Ovarian hormone suppression
- Surgical removal: high recurrence rate
- Non-steroidal anti-inflammatories: kidney damage and organ failure

TET3 overexpression is a *major root cause* of pathogenic macrophages (pMACs) ***driving chronic inflammation***

Targeting the epigenetic regulator TET3 in pMACs can eliminate the chronic inflammation and ***reverse disease progression***

Our lead compound, ***Epi-100***, is a ***TET3 degrader*** that selectively eliminates pMACs in the disease state





Lv et al**, *Journal of Clinical Investigation*, 2024, Press release, Commentary, article in *The Scientist***

Lead molecule Epi-100 is a TET3-specific molecular glue with ***excellent drug-like properties***

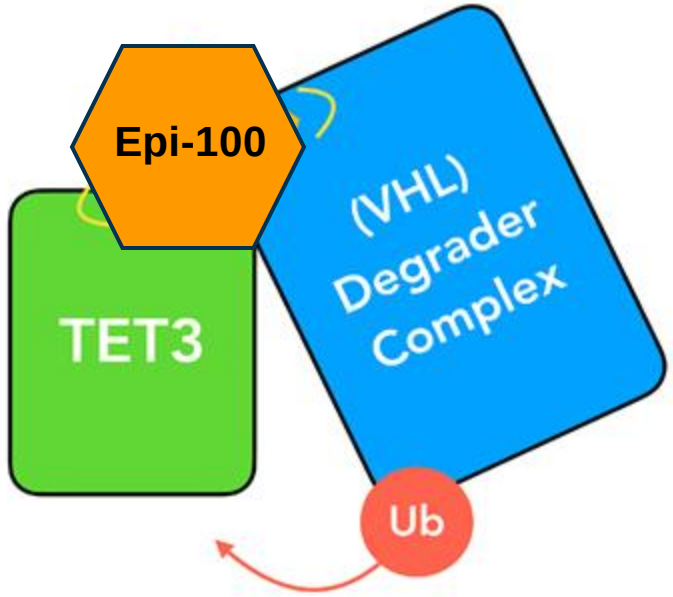
Confirmed by Huang lab to induce VHL-dependent TET3 degradation

Excellent drug-like properties
Rule of 5 compliant
10nM potency

Passed Safety and Specificity Screens
Passed 44 safety targets (w/hERG), 97 kinases, CYP panel
50-fold higher affinity to TET3 vs TET2

Strong Pipeline of Follow-On Compounds
For SAR and Optimization

Strong IP Position
Composition of Matter: Granted, Nov 2022
Methods PCT for Treatment of Disease: Filed Nov 2023



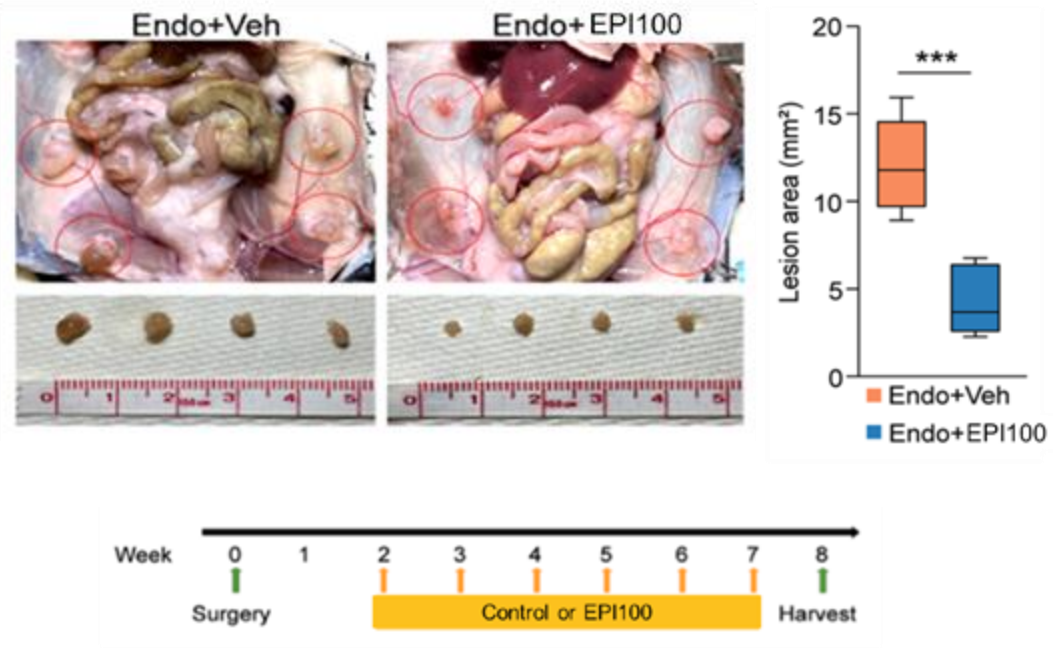
Epi-100 Target Profile:
Oral, twice a week,
to specifically eliminate pMacs

Lv et al**, *Journal of Clinical Investigation*, 2024, Press release, Commentary, article in *The Scientist***

Epi-100 is effective *in vivo* with ***no discernible side effects***

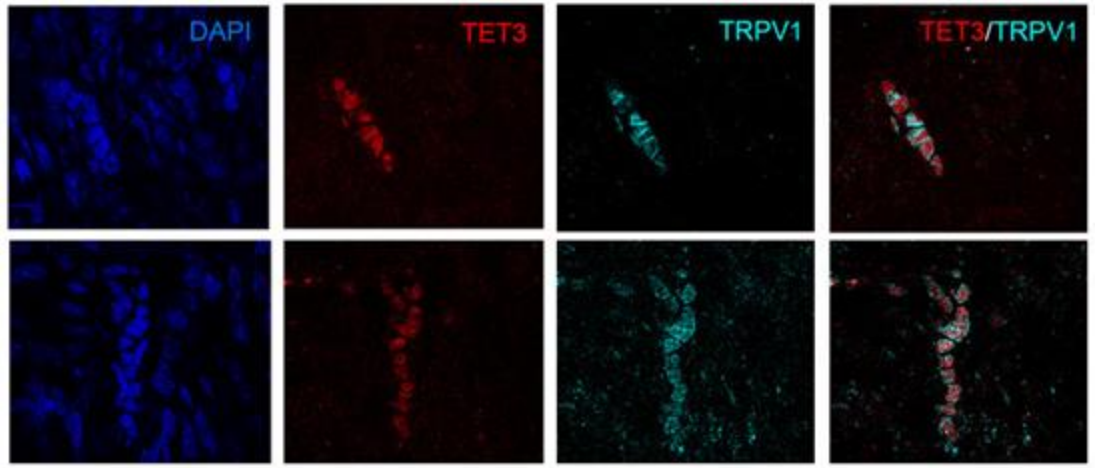
The syngeneic implantation model of endometriosis is ***the most translationally-relevant*** mouse model with ***intact immune system and ovaries***

Epi-100 reduces lesion size by 70%



Epi-100 is likely to decrease pain

pMACs express nociceptive pain-stimulating factors and form complexes with TRPV-1 pain-sensing nerve endings in human endometriosis lesions



*Ongoing preclinical testing to address the relationship to pain as a clinical translational endpoint

Lv et al**, *Journal of Clinical Investigation*, 2024, Press release, Commentary, article in *The Scientist***

>$5 Billion* Initial Market Opportunity

EpiTET's Advantage: non-hormonal treatment addressing the underlying cause of disease without impacting fertility; strong opportunity to ultimately become first-line therapy

6.5 Million
US Women aged 15-44yr with Endometriosis

First Line
- Oral Contraceptive Pills (OCPs)
- Progestins
- NSAIDs

3.1 Million
OCPs Ineffective (33%)
Intolerable Side Effects (15%)

Second Line
- GnRH Agonists
  Myfembree- Pfizer/Myovant
- GnRH Antagonists
  Orilissa- Abbvie/Neurocrine
- Abdominal Surgery

2.2 Million
GnRHs and Surgery Effective for NMPP (30%)

Severe Unmet Need
For non-hormonal anti-inflammatory treatments

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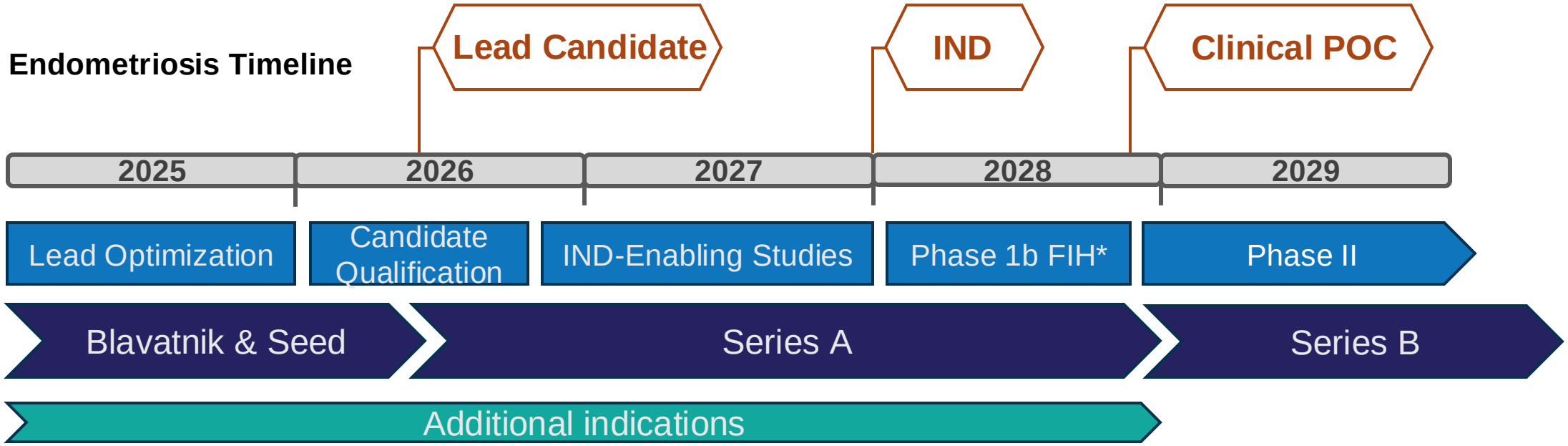
*$1,200 per month for Elagolix (GnRH Antagonist) Drugs.com

GnRH: Gonadotrophin-releasing hormone

EpiTET's Efficient Path to Clinical Validation



Additional indications with in vivo preclinical validation

- Metabolic – MASH
- Oncology – Tumor associated macrophages

Emerging

- Additional Immunology/Inflammation – Undisclosed

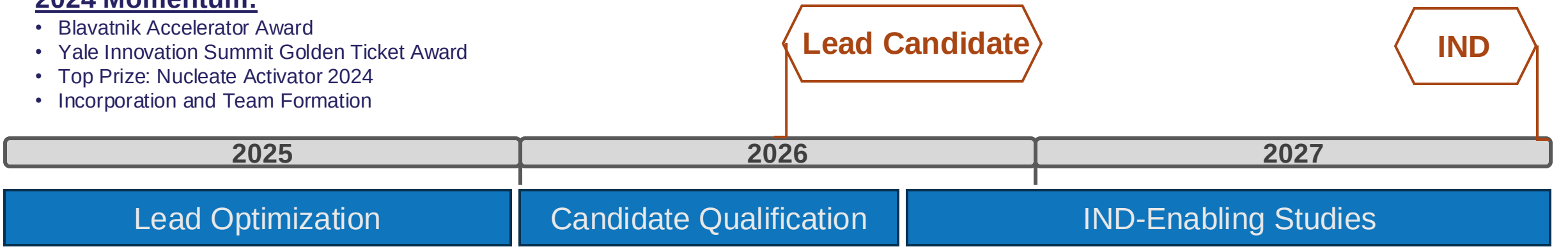
*Potential Translational Biomarkers Identified

Blavatnik Funding to a Key Inflection Point

Full Award will continue our momentum towards a clinical candidate + additional leads enabling a Series A round of $25M

2024 Momentum:

- Blavatnik Accelerator Award
- Yale Innovation Summit Golden Ticket Award
- Top Prize: Nucleate Activator 2024
- Incorporation and Team Formation



$360K Blavatnik Full Award & Raise Seed

Series A $25M

Aim 1: Lead Optimization: $273K

Structure-activity relationship and Strengthening of IP position

- Ternary binding evaluation
- In vitro ADME
- In vivo evaluation of + 2-3 cpds *translational biomarker/endpoint

Milestone: Candidates with optimized potency and ADME

Aim 2: Candidate Qualification/De-risking: $87K

- Candidate Scale up
- Pharmacokinetics
- Non-GLP Rat Toxicology

Milestone: Confirm lead candidate for development and novel composition of matter IP

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Appendix

Molecular Glues are Sticking

Recent transactions are large and interest is continuing to grow

$xM Series A
Q3 2023

Preclinical

Licensors and details of deal

$1.2B Exclusive License
Q1 2024

Preclinical

Takeda signed exclusive license to develop molecular glues for various indications

$2.2B Development Agreement
Q4 2024

Phase 1

Novartis $150M upfront, $2.1 in milestones

$1.45B Research Collaboration
Q4 2024

Preclinical

Biogen partnership for discovery and development of CNS molecular glues

$xB Cash Acquisition
Q4 2023

Clinical

Licensors and details of deal

Positive Safety Profile

Passed Well Established Pharma Battery of Safety and Selectivity Screen*

Passed 44 safety targets (w/hERG), 97 kinases, CYP panel

50-fold higher affinity to TET3 vs TET2

TET3 Myeloid Specific Knockout (murine)

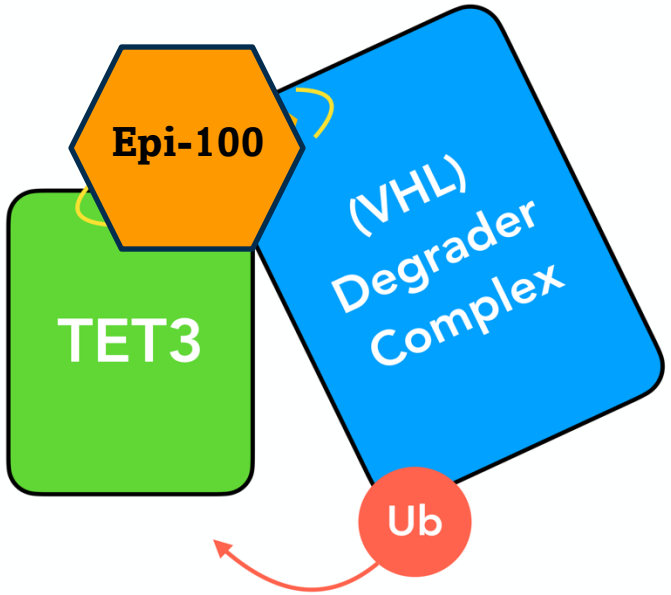
No impact to viability and fertility

No impact on body weight and body composition

No impact on glucose metabolism

Epi-100 In-Vivo Safety Data

No liver toxicity based on serum ALT, AST and bilirubin



Epi-100:
Oral, twice a week,
to specifically eliminate pMacs

Lv et al, ***Journal of Clinical Investigation*, 2024**

Opportunities Beyond Endometriosis

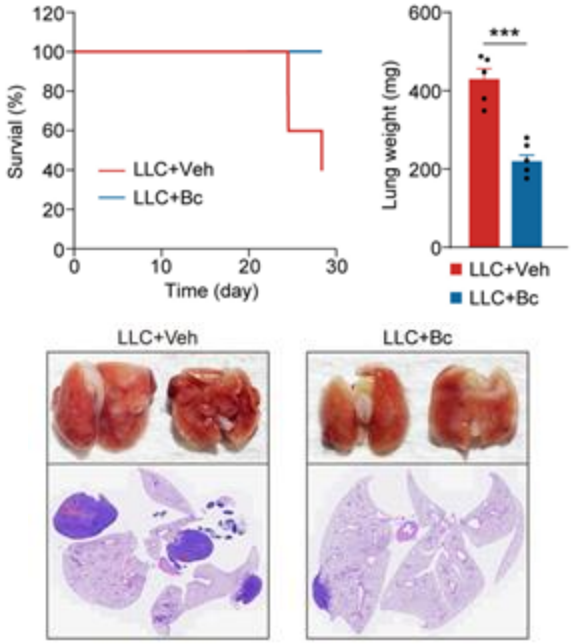
TET3/VHL is upregulated in multiple pMAC-driven chronic inflammatory diseases

Oncology

Tumor-associated macrophages

- ✓ **Target validation** (genetic/seqRNA)
- ✓ **Genetic KO model validation**
- ✓ ***in vivo* efficacy confirmed**

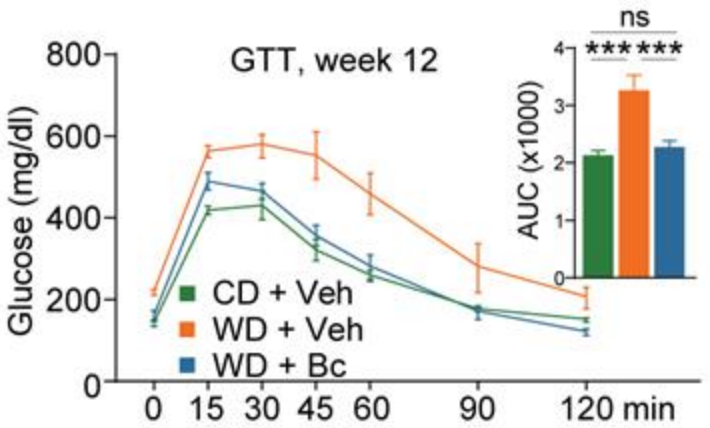
Lewis Lung carcinoma (LLC)



Metabolic/MASH

- ✓ **Target validation** (genetic/seqRNA)
- ✓ **Genetic KO model validation**
- ✓ ***in vivo* efficacy confirmed**

Western diet model



Inflammation/Immunology

Undisclosed

- ✓ **Target validation** (genetic/seqRNA)
- ✓ ***in vivo* efficacy in planning**

Undisclosed

EPI100 Lead Characterization Data

Kinetic Solubility	PBS, pH 7.4	>200	µM
Thermodynamic Solubility	PBS, pH 7.4	31	µg/mL
Permeability, MDCK MDR1	MDCK MDR1, P_{app} A->B	39.8	10^{-6} cm/s
	MDCK MDR1, P_{app} B->A	48.3	10^{-6} cm/s
Chemical Stability	pH 7.4, 120 min	97	% remaining
	pH 4.0, 120 min	92	% remaining
	pH 1.0, 120 min	97	% remaining
GSH Reactivity	90 min	<1	% disappearance
Blood Stability	Human, 120 min	93	% remaining
	Rat, 120 min	94	% remaining
Plasma Stability	Human, 120 min	96	% remaining
	Rat, 120 min	94	% remaining
Plasma Protein Binding	Human	94	%
	Rat	88.9	%
Liver Microsomes	Human, $t_{1/2}$	>120	min
	Rat, $t_{1/2}$	13	min
Hepatocytes	Human, $t_{1/2}$	369	min
	Rat, $t_{1/2}$	21.8	min
Reactive Metabolite	GSH, HLM, 60 min	No peak	Detection by MS
CYP Inhibition	IC_{50}, CYPs 1A2,2C9, 2C19, 2D6	>30	µM
	IC_{50}, CYP3A4	>10	µM
CYP3A4 Induction	PXR reporter, 1 µM	6	% Rifampicin
	PXR reporter, 10 µM	8	% Rifampicin

Rat Pharmacokinetics of EPI100

Route of Administration	**IV**	**PO**
Dose (mg/kg)	**1**	**10**
$t_{1/2}$ (h)	0.3 ± 0.1	4.8 ± 2.7
C_{max} (ng/mL)	688 ± 130	547 ± 240
T_{max} (h)	-	0.25 ± 0
AUC_{0-t} (ng·h/mL)	225 ± 44	1017 ± 234
$AUC_{0-\infty}$ (ng·h/mL)	232 ± 42	1067 ± 213
Cl_{Plasma} (mL/min/kg)	73 ± 13	-
V_{ss} (L/Kg)	1.7 ± 0.3	-
F (%)	-	**46**
Ovary to Plasma ratio @ 1 & 3 h	**2.0 & 1.2**	

High selectivity – No significant binding to 44 safety screen targets (including hERG) and 97 kinases at 10 µM test concentration.

EPI100 lead profiling data indicates low risk for development

Clinical Study Success and Opportunity in Endometriosis

ADDRESSING UNDERLYING CAUSE: Our approach selectively targets underlying cause of disease (pathogenic macrophages).

KEY OPINION LEADERS: Dr. Hugh Taylor expertise for endometriosis drug approval

ENDPOINTS: In-Vivo data confirms reduction of both lesion size and co-expression of TET3 with pain receptors.

COMPETITION (2nd Line):

- Surgical removal of lesions $2,500 to $7,500 with 50% repeat within 5 years
- MYFEMBREE/Orilissa - Blackbox warning, limited to 24 months, ~$1,200 list price/month

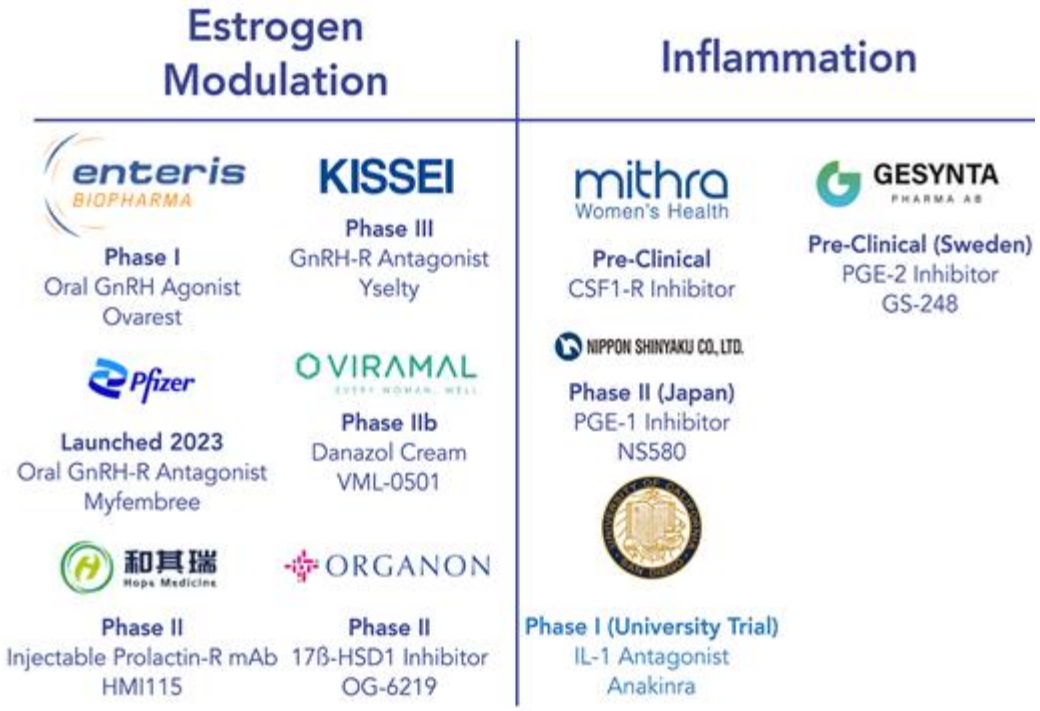
Key Questions to be addressed with Blavatnik Funding for Derisking for Investors/Partners (Total=$360,000)

Activity	Cost
Synthesis of New Compounds (2 chemists/6 mos)	$88,000
Ternary Binding Evaluation of new compounds (100 in dose-response)	$25,000
ADME Testing of new compounds (10 compounds)	$10,000
In Vivo Testing (2 Compounds) for Translation Endpoint*	$150,000
Lead Candidate Scale Up and Testing (Prepare tox lot, Gentox, rat non-GLP tox, PK)	$87,000

Endometriosis Competitive Landscape

Fertility Inhibition (Black Box Warnings)

General anti-inflammatories



Depletes only pMACs

EpiTET Therapeutics

Preclinical efficacy in endometriosis
Oral, twice a week,
Specifically eliminates pMac