August 2025

SEED THERAPEUTICS

A TPD 2.0 Company

Transforming Undruggable Targets into Therapeutics

Forward-looking Statements

This presentation contains forward-looking statements about SEED Therapeutics, Inc., and/or its Affiliates. Forward-looking statements are based on management's beliefs and assumptions and on information currently available to our management.

Such statements are subject to known and unknown risks, uncertainties, and other factors that may cause our or our industry's actual results, levels of activity, performance, or achievements to be materially different from those anticipated by such statements. In some cases, you can identify forward-looking statements by terminology such as "may," "will," "should," "expects," "plans," "anticipates," "believes," "estimates," "predicts," "potential," "intends," or "continue," or the negative of these terms or other comparable terminology. Forward-looking statements contained in this presentation include, but are not limited to, (i) statements regarding the timing of anticipated clinical trials for our product candidates and our research and development programs; (ii) the timing of receipt of clinical data for our product candidates; (iii) our expectations regarding the potential safety, efficacy, or clinical utility of our product candidates; (iv) the size of patient populations targeted by our product candidates and market adoption of our product candidates by physicians and patients; and (v) the timing or likelihood of regulatory filings and approvals.

Except as required by law, we assume no obligation to update these forward-looking statements publicly, or to update the reasons why actual results could differ materially from those anticipated in the forward-looking statements, even if new information becomes available in the future.

Company Highlights

SEED is a leading Targeted Protein Degradation (TPD) 2.0 company focusing on developing novel "Molecular Glues" (MG) for breakthrough therapeutics

TPD Potential	• Focusing on Molecular Glues (MG) to **address 80% of disease-causing proteins considered "undruggable"** by traditional methods.
World-class Founding Team	• Co-Founders are **scientific leaders on TPD** E3 ligase structures and ubiquitin biology, including the Nobel Prize Winner Dr. Hershko. • **Target-centric**: Differentiation in using novel E3 ligases among 640 E3s for protein of interest.
Technology Platform	• Proprietary RITE3 platform featured in 2 Nature review articles in 2024; • **RITE3 platform** with investment and R&D collaboration from **Lilly and Eisai,** with **potential value** exceeding **$2.3 billion**.
Robust Pipeline	• **9 programs (6 internal; 3 partnered)** across multiple indications, involving **6 novel E3s**. • **RBM39 degrader (oncology)**: presentation at **AACR 2025**; **IND submission in mid-2025;** and clinical data in 2H 2026. • **Tau degrader (neurodegeneration):** current cell activity, in vivo efficacy 2H 2025.
Finance Optionality	• Runway to the end of 2026; • Potential exits from IPO, partnership, and additional financing.

Experienced Team with Successful Track Record

Founders

Nobel Prize winner, Pioneers in TPD

Management Team

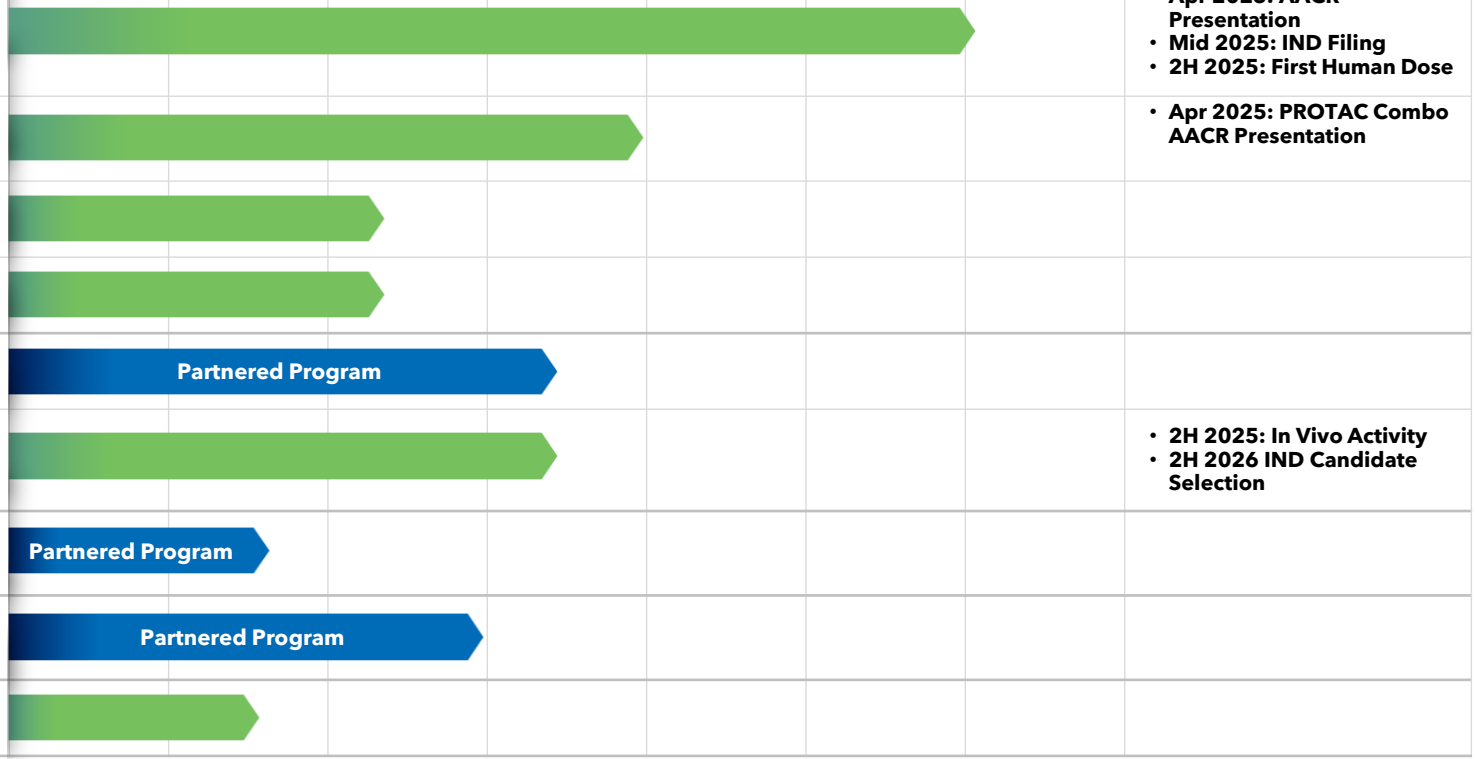
40 IND and 12 NDA experience

Board Members

Experienced business and legal expert and independent board member from Eli Lilly and Eisai

Pipeline Targeting Key Undruggable Proteins Across Human Disease

Indication	Target Protein	Milestones
Oncology	RBM39	• **Apr 2025: AACR Presentation** • **Mid 2025: IND Filing** • **2H 2025: First Human Dose**
	KRAS-G12D	• **Apr 2025: PROTAC Combo AACR Presentation**
	Target Beta	
	FEN1	
Neurodegeneration	Target Alpha*	
	Tau	• **2H 2025: In Vivo Activity** • **2H 2026 IND Candidate Selection**
	Target Delta*	
Immunology	Target Gamma*	
Antiviral	HBx	



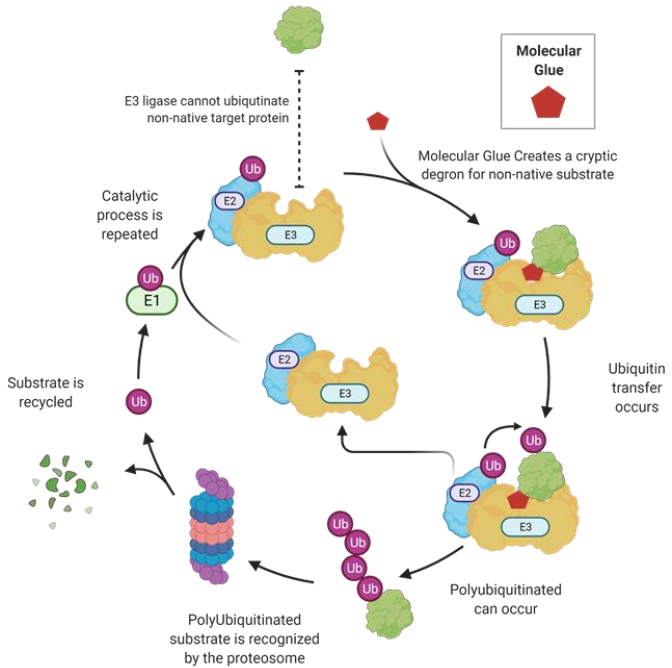
SEED owns 100% on all programs except for three partnered programs (labeled with *)

Global Pharma Partnerships: Validating SEED's Leadership in TPD Space

- Research collaboration with **Eli Lilly** on TPD with multiple targets.
- **$10 million upfront**, and a **$10 million** equity investment in series A-2.
- Eligible to receive up to **$780 million** in potential milestones, and **tiered royalties** of sales.

- Series A-3 financing: first close of $24 million from investors led by **Eisai** in August 2024.
- SEED-Eisai Collaboration: SEED receive upfront and milestone payments of up to **$1.5 billion** plus **tiered royalties** upon Eisai's exercise of their exclusive rights under the strategic research collaboration.

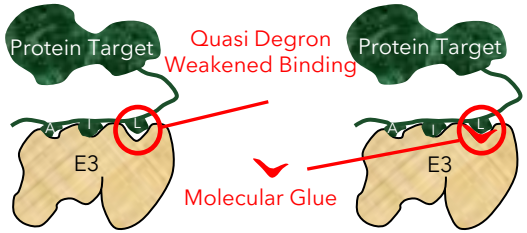
Targeted Protein Degradation (TPD) for Disease Proteins That are Undruggable



- **E3 Ligase Expertise**: > 600 E3 ligases in human E3ome, with only 2 structural classes, solved by SEED Co-founders;
- **Target-Centric Approach**: Capable of selecting the right E3 ligase for each disease-causing protein;
- **Ubiquitin Biology Expertise:** Select targeted clinical indication based on ubiquitin biology, pioneered by SEED co-founders;
- **Published & Recognized**: Featured in *Nature Biotechnology* and *Nature Reviews Drug Discovery* in 2024.

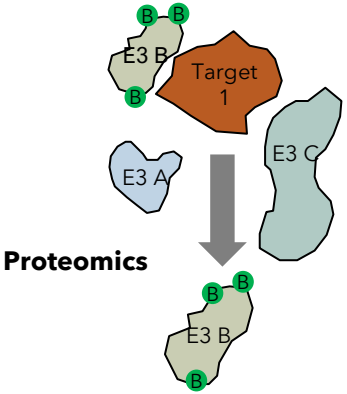
Multi-dimensional Platform RITE3™ to Select E3 for Protein Target*

Quasi-Interface Analyses



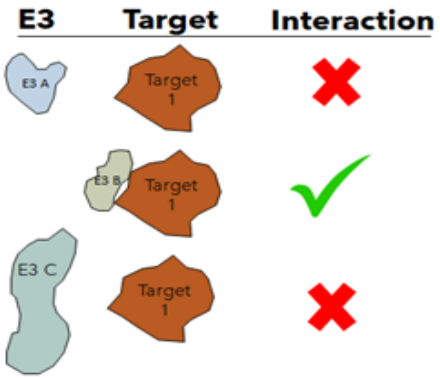
Computational and structural biology

LumID: identify the right E3 near POI in live cell



Cell biology: real-time monitoring of target-E3 interactions

Basal Affinity Validation



Biophysics: distinguishing productive vs. non-specific interactions

Novel E3 Selection for Disease Protein of Interest

↓ High-throughput screening (E3/POI) + Optimization

Molecular Glue

*Two Nature Review Papers: Garber, *Nature Biotechnology* 42(4):546-550 (2024); Mullard, *Nature Reviews Drug Discovery* 23 (11):799-802 (2024)

Lead Oncology Asset:
Oral Novel RBM39 Degrader

IND Submitted in mid-2025

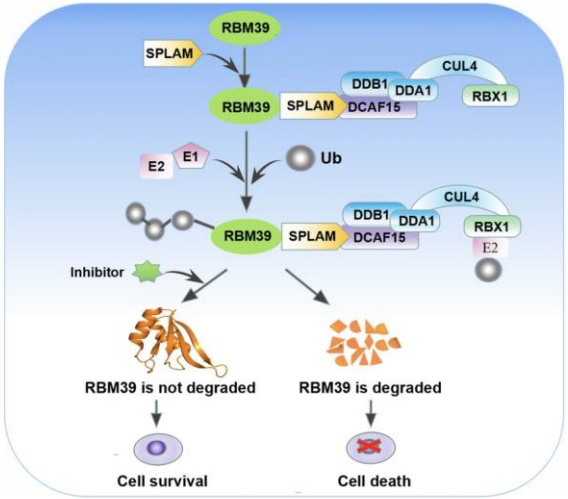
RBM39 Degrader: RNA Splicing for Multiple Cancers

The Problem

Cancer cells rely on precise RNA splicing to maintain oncogene expression and survival

Most spliceosome components are **non-enzymatic and undruggable**

Aberrant splicing is linked to **drug resistance, tumor progression, and immune evasion**

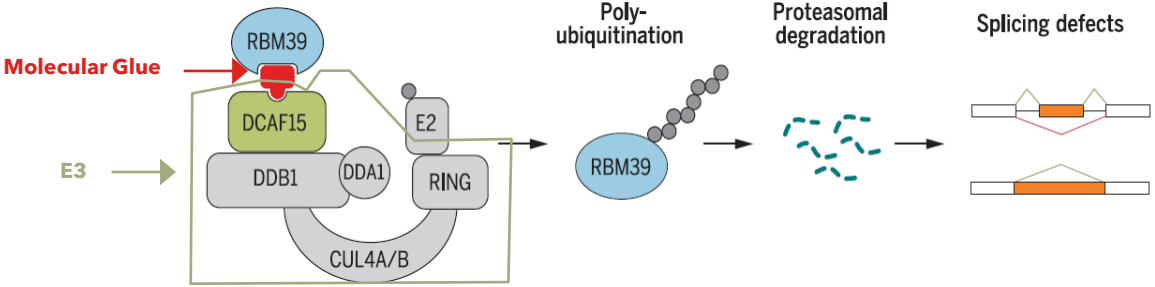


The Solution

RBM39 is a **core splicing factor** essential in a subset of cancers

Targeted degradation via **molecular glues** induces lethal mis-splicing in sensitive tumors

Offers **synthetic lethality** and tumor selectivity with **limited impact on normal cells**



Han et al., *Science*, 2017

RBM39 Degradation Addresses Core Unmet Needs Across Multiple Tumors

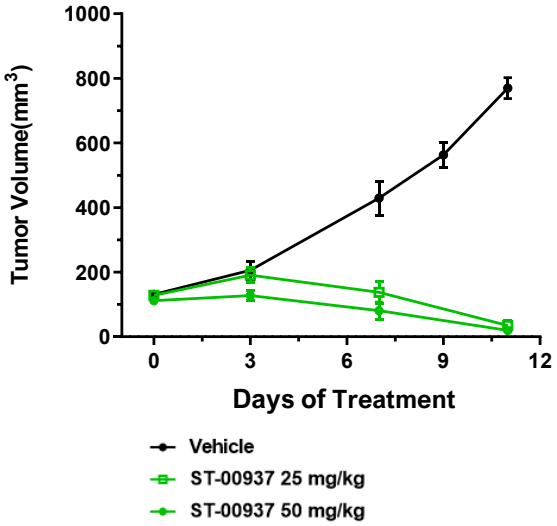
Unmet Need	Ewing's Sarcoma	Neuroblastoma	Hepatocellular Carcinoma	Colorectal Cancer	Prostate Cancer	RBM39 Degrader Impact
No effective targeted therapies	🔴 High	🔴 High	🟠 Medium	🔴 High	🟠 Medium	✅ Transcriptional targeting independent of drivers
Therapy resistance and relapse	🔴 High	🔴 High	🔴 High	🔴 High	🔴 High	✅ New mechanism, orthogonal to existing therapies
Lack of predictive biomarkers	🟠 Medium	🔴 High	🔴 High	🔴 High	🔴 High	✅ RBM39 expression and splicing signatures as markers
Late-stage diagnosis	🟢 Low	🟠 Medium	🔴 High	🔴 High	🔴 High	✅ Activity in advanced and metastatic settings
High toxicity of standard treatment	🔴 High	🔴 High	🟠 Medium	🟠 Medium	🟠 Medium	✅ Potential for lower-toxicity regimens
Lack of innovation	🔴 High	🔴 High	🟠 Medium	🟠 Medium	🟠 Medium	✅ First-in-class degrader targeting spliceosome

RBM39 degradation offers a novel, biomarker-driven, cross-indication strategy that addresses both therapeutic resistance and the lack of transcription-targeted options in hard-to-treat cancers.

Rational Indication Selection for SEED's RBM39 Degrader

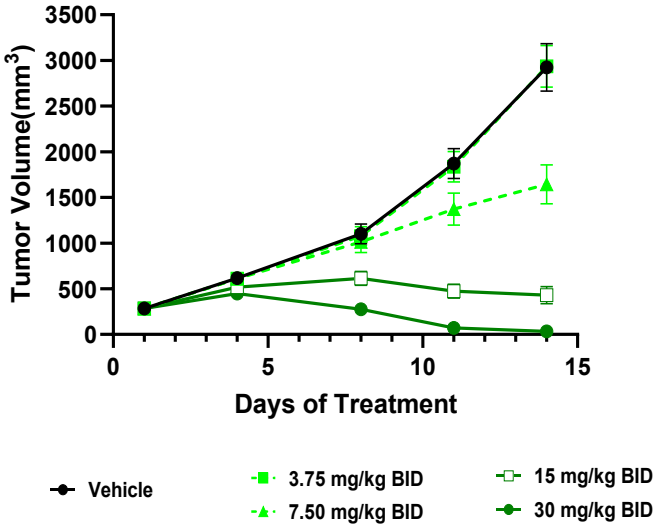
Can Target Multiple Cancers Based on Its MoA

Complete Tumor Regression in Colon Cancer Model



Complete Tumor Regression in Ewing Sarcoma

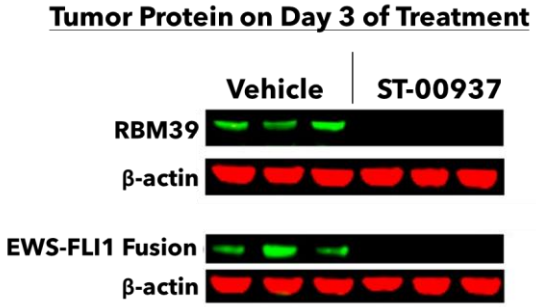
- Rare Pediatric and Orphan Cancer designation by FDA, presentation at AACR



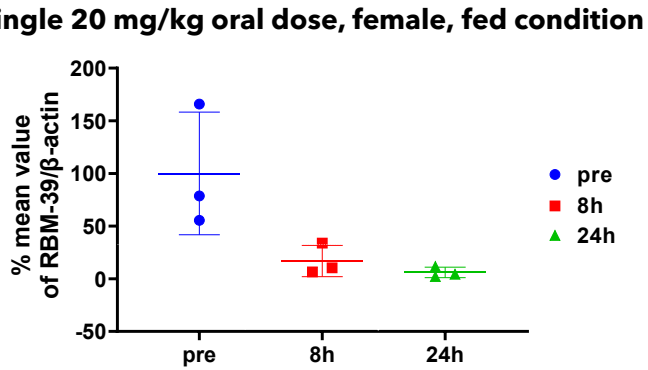
Induce RBM39 Degradation in Tumors and PBMCs in blood After Oral Dosing

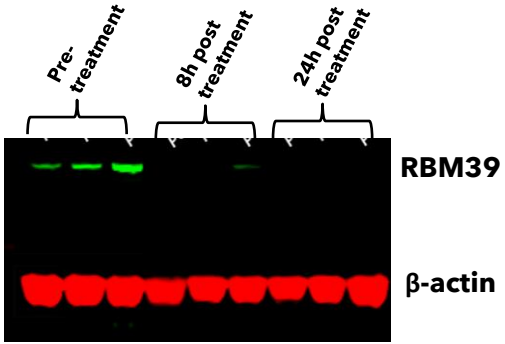
Target Engagement Assay for Phase 1 to Achieve Rapid RP2D Dose

Mice Tumor Model



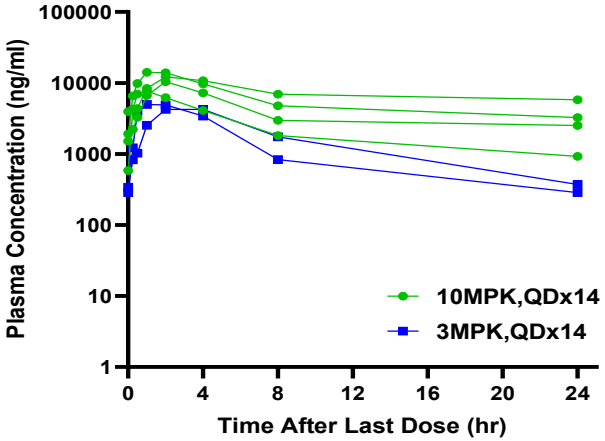
Normal Cynomolgus Monkey





NHP: Non-human Primate
PBMCs: Peripheral Blood Mononuclear Cells

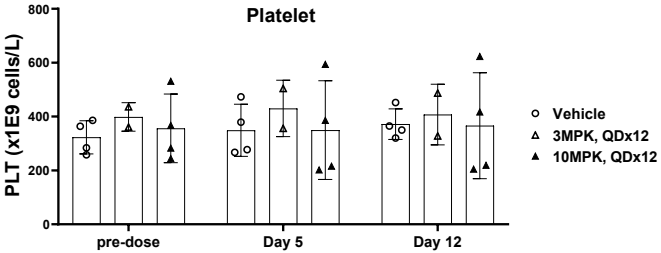
RBM39 Degrader **Safety Dose at >10 Times Plasma PK** for Anticancer Activities

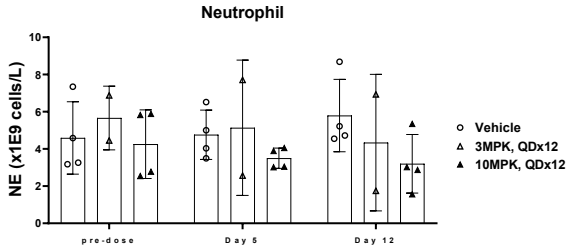


Mean Plasma PK Parameters

Dose	C_{min} (ng/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}24hr}$ (h*ng/mL)
3MPK	321	4615	37902
10MPK	2560	11093	116813

Good Hematological Safety





**Platelet and neutrophil related dose-limiting toxicities reported for prior RBM39 degraders in patients

ST-01156: Clinical Development Plan - "Precision Medicine" Approach

2H'25 to 2H'26

Phase 1
Safety + Preliminary Efficacy

All comer solid tumors, enriched for "MoA Targeted" Indications:

- ✓ Orphan indications;
- ✓ Large cancer indications including Liver, Prostate and Colorectal Cancers
- ✓ Target engagement in blood
- ✓ US leading cancer centers

2H'26 to 1H'28

Phase 1b / Phase 2
Expansion Cohort

- Potential to enroll pediatric patients for orphan indications
- Expansion on large indications with preliminary efficacy in Phase 1

Market Potential: >$7 B potential peak sale with orphan and large cancer indications

ST-01156: Oral RBM39 Degrader Advancing to Clinical Trials in 2025

Focus on MoA-based Indications; Potential to Accelerate Clinical Development

MoA understanding and preclinical screening on patient-derived models is being used by SEED for **rationale clinical indication selection**

Orphan and large cancer indications to be enriched for "MoA targeted" indications in the first clinical trials to accelerate progress to NDA for responsive cancer types

Nonclinical PK/PD and Tox/TK established and set to inform dose escalation to speed progress to dosing regimens with a therapeutic window

Experienced innovative oncology drug development team with investigators from **leading institutions** with patients of all targeted cancer types.

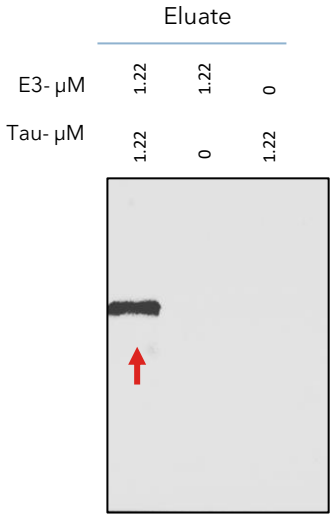
Oral Tau Degrader

Achieved Cell Activity to Decrease Tau level in Neuron Cells

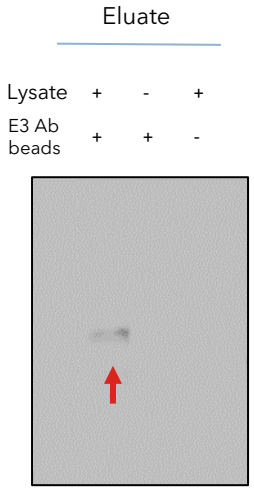
Identified Novel E3 to Degrade Tau Protein for Alzheimer's Disease

- **Well-positioned for success**: we selected a novel E3 ligase which is highly expressed in neuron, and identified the specific lysine residues of Tau being ubiquitinated using SEED's RITE3 platform

Novel E3 Recombinant protein and Tau Binding - Western Blot (In Vitro)

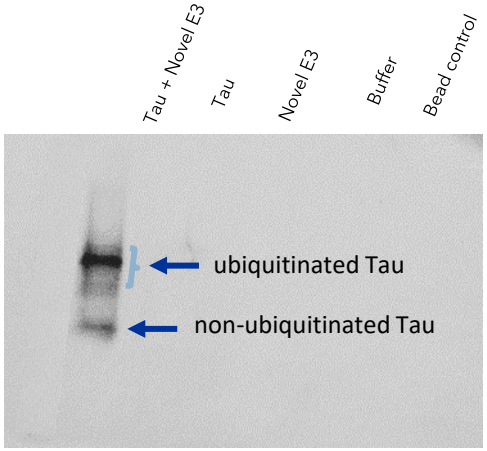


Novel E3 and Tau Binding in Endogenous Human Cell - Western Blot



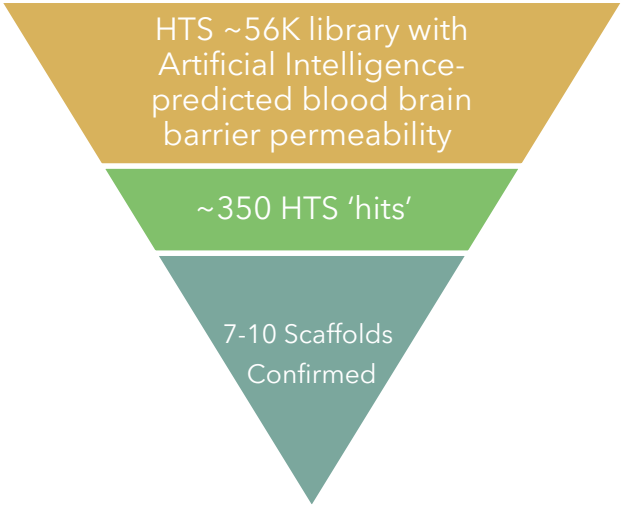
Note: Red arrow pointing to Tau pulled down along with novel E3 ligase

Novel E3 Ubiquitination of Tau



Immunoprecipitated ubiquitin, followed by Immunoblotting for Tau

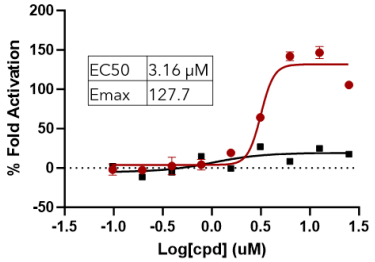
HTS Hits: Increase Binding & Poly-ubiquitination and Reduce Tau level in Neuron cells



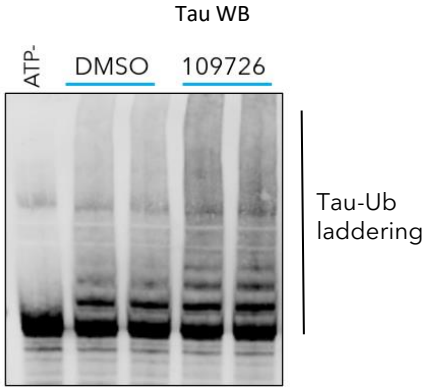
STX-109726 (example)

- ✓ Increase binding and poly-ubiquitination;
- ✓ Reduce Total Tau Levels in a Human Neuronal Cell Line, not affecting cell viability

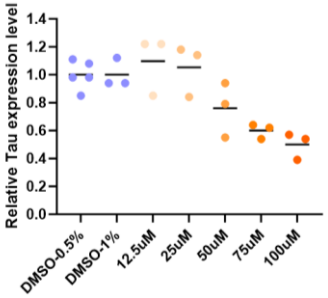
Increase binding between Tau/E3 (TR-FRET Assay)



Increase Tau Poly-Ubiquitination



Reduce Tau Protein Level in Neuron Cells (ELISA Assay)



Key Catalysts and Highly Experienced Team

Key Catalysts and Financing to Support RBM39 and Pipeline Growth

Strengthening RITE3™ Platform
Advancing Internal and R&D Pipelines with Lilly and Eisai

2H 2025 Catalysts:

- ST-01156 IND submitted mid-2025
- Tau degrader in vivo efficacy

2H 2026 Catalysts:

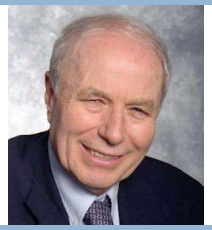
- Phase I data for RBM39: Safety and efficacy
- Tau degrader: IND candidate expected

Financing:

- SEED raised $40 million in equity + $13 million in collaboration upfront and milestone since inception Nov. 2020;
- Series A-3 part 1 of $24 million closed ; runway to end of 2026;
- Part 2 potentially be rolled into large fundraising after our value inflection point IND is open in 2H 2025.

World Class Founding and Leadership Team

Avram Hershko MD, PhD[+]



"**Godfather" of TPD**; **2004 Nobel Laureate;** Advisor to Millennium on developing **Velcade**

Ning Zheng, PhD[+]

Howard Hughes Professor, University of Washington; World's foremost **thought leader on E3 and MG**

Michele Pagano, MD [+]

Howard Hughes Professor, NYU Medical School; Global **thought leader on TPD biology and application**

Lan Huang, PhD [+] * (Chairman & CEO)

E3 structural expert; Serial biotech entrepreneur with **20+ years** of drug development experience, including NDA-ready assets

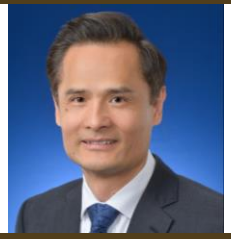
Bill Desmarais, PhD (CFO & CBO)

20+ years in finance, business development, and strategic operations; Ex leadership role at Alchemab, TScan, Momenta and Lilly

James Tonra, PhD* (President & CSO)

20+ years of drug discovery experience that led to **5 NDAs**; Ex leadership role in Regeneron, Millennium, ImClone, Kadmon, and BYSI

Linus Lin, PhD*

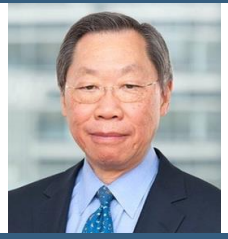


AVP of Molecular Discovery Capabilities at Lilly Global; Ex leadership role in Lilly Chorus, Lilly China R&D Center, WuXi AppTec, and Merck

Yoshiharu Mizui, PhD*

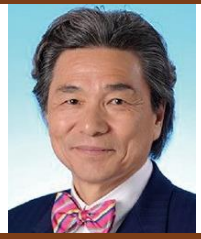
Founder and President of Eisai Innovations, Inc.; former Global Business Development and Strategy Head in Eisai's Oncology Business Group

Jackson Tai*



Retired board member for Lilly, HSBC Holdings, Mastercard; **Former DBS Bank CEO**, former J.P. Morgan & Co. investment banker; **Expert in finance and risk**

Ko-Yung Tung, JD*



Former Eisai director, World Bank general counsel, and lecturer at Harvard and Yale Law School; **Expert in law and international business**

[+]SEED Co-Founder and Scientific Advisory Board Member
*Board Member

Company Highlights

SEED is a leading Targeted Protein Degradation (TPD) 2.0 company focusing on developing novel "Molecular Glues" (MG) for breakthrough therapeutics

TPD Potential	• Focusing on Molecular Glues (MG) to **address 80% of disease-causing proteins considered "undruggable"** by traditional methods.
World-class Founding Team	• Co-Founders are **scientific leaders on TPD** E3 ligase structures and ubiquitin biology, including the Nobel Prize Winner Dr. Hershko. • **Target-centric**: Differentiation in using novel E3 ligases among 640 E3s for protein of interest.
Technology Platform	• Proprietary RITE3 platform featured in 2 Nature review articles in 2024; • **RITE3 platform** with investment and R&D collaboration from **Lilly and Eisai,** with **potential value** exceeding **$2.3 billion**.
Robust Pipeline	• **9 programs (6 internal; 3 partnered)** across multiple indications, involving **6 novel E3s**. • **RBM39 degrader (oncology)**: presentation at **AACR 2025**; **IND submission in mid-2025;** and clinical data in 2H 2026. • **Tau degrader (neurodegeneration):** current cell activity, in vivo efficacy 2H 2025.
Finance Optionality	• Runway to the end of 2026; • Potential exits from IPO, partnership, and additional financing.

Thank You

Lan Huang, PhD
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Lan.Huang@seedtherapeutics.com

James R. Tonra, PhD
President and CSO
James.Tonra@seedtherapeutics.com

Bill Desmarais, PhD, MBA
CFO and CBO
Bill.Desmarais@seedtherapeutics.com

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Appendix

Business Overview

Proprietary RITE3™ Platform

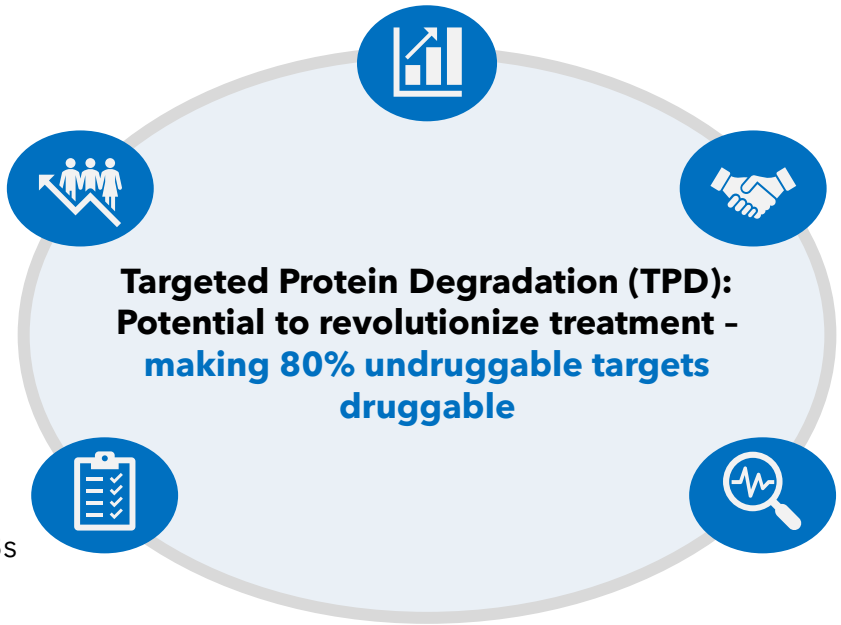
Integrates novel E3 ligases and multi-dimensional approaches to discover novel molecular glues.

Worldclass Leadership

Co-founded by Nobel Laureate, TPD pioneers; experienced team
✓ 40 IND, 12 NDA

Strategic Collaborations

Eli Lilly and Eisai investment and R&D collaboration with potential value >$2.3 B
✓ First companies worked on RBM39.



Robust Pipeline

9 programs across multiple indications, involving 6 novel E3s
✓ Lead oncology asset RBM39 IND filing in Q2/Q3 2025.

Strong Financial Position

Raised $40 Million + $13 Million R&D upfront and milestone since Nov 2020; Runway to end of 2026.

RBM39: Validated Oncology Target

SEED's differentiated RBM39 degrader
- Optimized for drug-like properties with precise target engagement;
- Limited Competition in Clinic: Recursion Pharmaceuticals in Phase 1

Now

Publications validating new cancer indications for RBM39 degraders in preclinical setting

2021 - 2023

Aryl sulfonamide class first reported as RBM39 degraders

2017

Target for development but mechanism unknown
- Eisai developed cytotoxic agents, such as E7820
- IV drugs weekly dosing insufficient to maintain required low levels of RBM39

1993 - 2001

A Rational Strategy for Molecular Glue Discovery

(Unliganded)

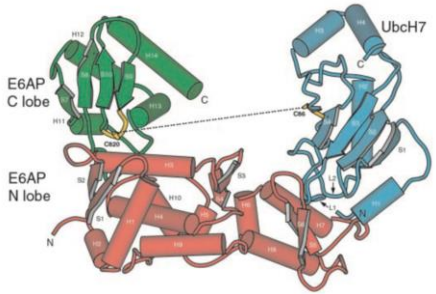
neoSubstrate

Genetically Validated Target

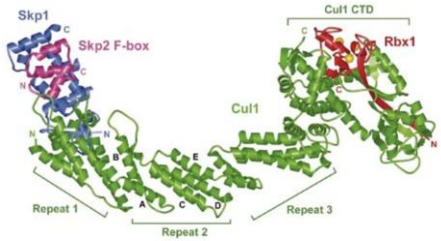
600 E3 ligases in human E3ome with only 2 structure classes solved by SEED Co-founders

Tissue distribution
Subcellular localization
Abundance & capacity
Druggability (glue-ability)
Biological function

Basal affinity



HECT E3 ligase
Huang L et al. Science 286: 1321-1326 (1999)



RING Finger E3 (CRL)
Zheng N et al. Nature 416: 703-709 (2002)

A Rational Strategy for Molecular Glue Discovery

600 E3 ligases in human E3ome
with only 2 structure classes
solved by SEED Co-founders

(Unligandable)

Genetically
Validated Target

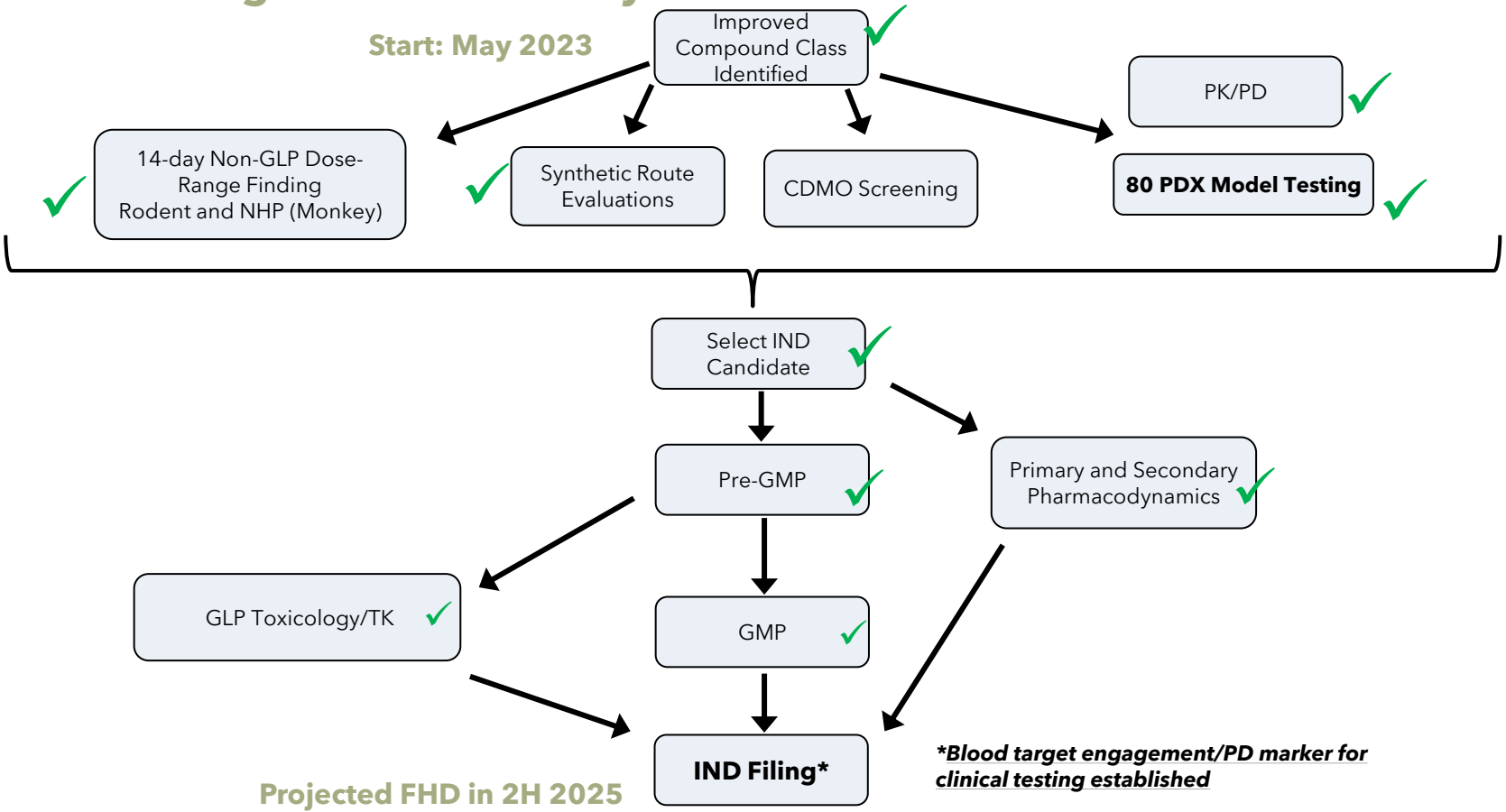
neoSubstrate

Tissue distribution
Subcellular localization
Abundance & capacity
Druggability (glue-ability)
Biological function

Basal affinity

IND-Enabling Efforts Underway

Start: May 2023

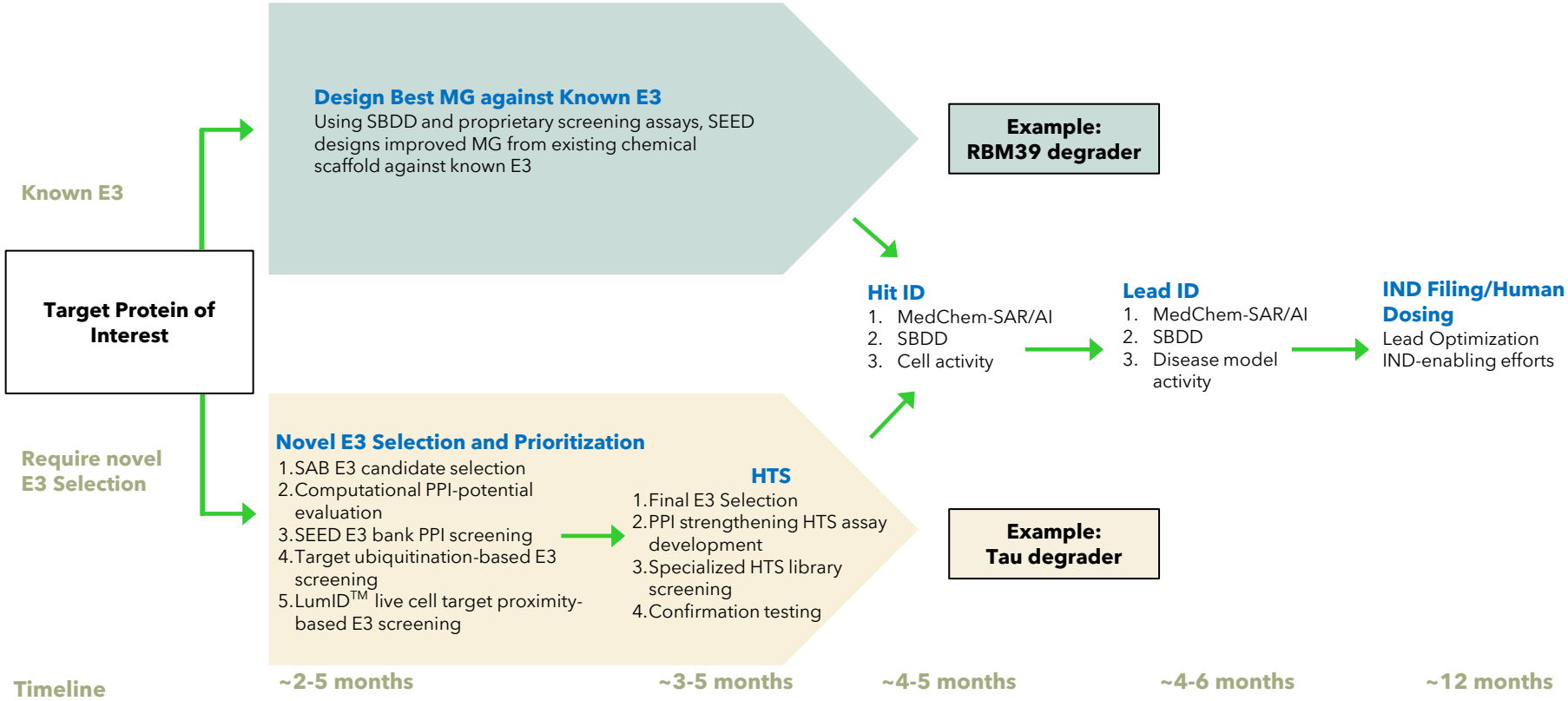


Projected FHD in 2H 2025

Blood target engagement/PD marker for clinical testing established

Strategic Partnership

Powerful Two-Pronged Approach Tackling Both Novel and Known E3s



SBDD: Structured-based Drug Design; SAR: Structure Activity Relationship; PPI: Protein-Protein Interactions; HTS: High Throughput Screening

Controlled Protein Degradation: Reprogramming Ubiquitin Ligases with New Small Molecule Modalities to Target Un-ligandable Proteins

PROTAC

TPD 1.0
- Arvinus agent in Phase 3 for breast cancer

Molecular Glue

TPD 2.0
– SEED's Focus

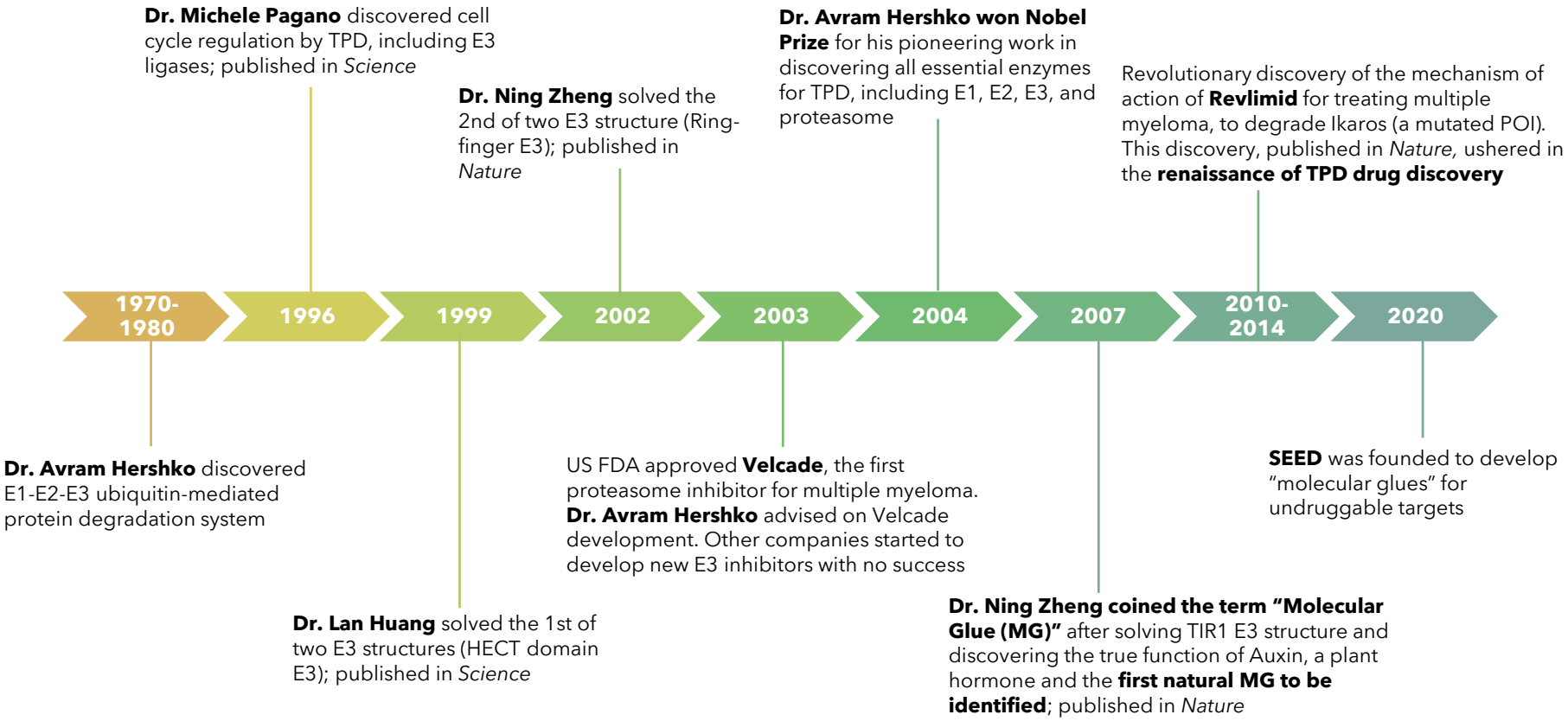
LIMITATIONS:

- × Bi-functional molecule
- × >500 Da (may limit cell availability)
- × High affinity on both ends (ligandable pockets required)
- × Mostly limited to two UBLs

ADVANTAGES:

- ✓ Involves a single non-chimeric small molecule
- ✓ Small enough to be drug-like compounds
- ✓ Does not need high affinity on either sides (ligandable pockets not required)
- ✓ Many UBLs can be used (Substrate-centric)

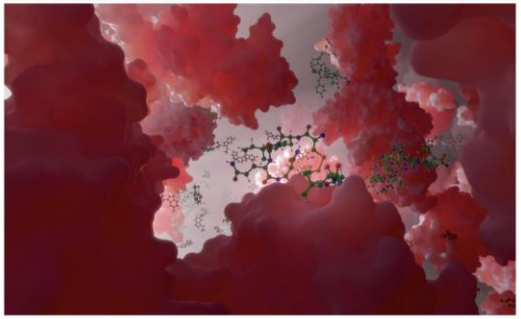
SEED Co-Founders Played Pivotal Roles in the Advancement of TPD Field



“Nature Biotechnology” Review on “The Glue Degraders” (3/6/2024)

News feature

https://doi.org/10.1038/s41587-024-02164-9



THE GLUE DEGRADERS

Companies are hoping to discover small molecules that remove undruggable proteins. It won't be easy. **By Ken Garber**

In December 2023, two days after the US Food and Drug Administration approved separate gene editing and gene therapy treatments for sickle cell disease, Novartis biochemist Pamela Ting made a plenary presentation at the American Society of Hematology annual meeting[1]. She described a phenotypic screen that yielded hits causing a surge of fetal hemoglobin, the same protein that the recently approved gene editing therapy is engineered to produce. But unlike that treatment, which is priced at $2.2 million, Novartis's compounds are small-molecule protein degraders, molecular 'glues' that would be much cheaper to produce and administer. Animal studies were positive. "We are currently conducting the experiments necessary to translate these findings to a human clinical trial," Ting said at the meeting. The Novartis work is the latest sign that molecular glue degraders, which hijack the cell's disposal machinery to remove disease-related proteins, have arrived.

Much of pharma is invested, directly or through partnerships. In 2019 Bristol Myers Squibb spent $74 billion to acquire Celgene and its portfolio of molecular glue degraders. More than two dozen biotech companies are now seeking these drugs (Table 1). "We're very active in this space and see tremendous potential in molecular glues," says Ryan Potts, head of the induced proximity platform at Amgen.

Yet the field faces some serious obstacles. Prospective screening for molecular glue degraders is a major undertaking (Fig. 1). It's often done in cells, unlike standard biochemical assays with recombinant proteins, adding time and expense, and involves extensive follow-up work to validate hits and understand mechanism of action. And those hits are rare because it is hard to drug protein–protein interactions. With hit rates low, small-molecule libraries must be sizable. And the field does not yet know what chemical features molecular glues have in common, making it difficult to select these libraries. Biological information on the more than 600 E3 ligases – the enzymes that molecular glues recruit to degrade a drug's target – is scant, except for a handful of these proteins. For all these reasons, molecular glue discovery remains a high-risk enterprise. "The field needs a success story," says Simon Bailey, head of drug discovery at Plexium.

nature biotechnology

SEED was prominently featured in “Nature Biotechnology” Review.

Table 1 | Selected molecular glue degrader companies discussed

Company	Pharma partners	Discovery approach	Deployed E3 ligases	Lead program
Monte Rosa Therapeutics	Roche	Remodel cereblon to recruit neosubstrates; proximity assays, proteomics	Cereblon	MRT-2359, GSPT1 degrader, phase 1 (cancer)
Plexium	Amgen, AbbVie	Miniaturized, cell-based DNA-encoded library screening; target-centric	Cereblon, DCAF11, others undisclosed	IKZF2 degrader, phase 1 (cancer) December 2023
Seed Therapeutics	Eli Lilly	Target centric; detect basal E3–target interactions; proximity assays	Working with 25–30 E3s, including DCAF15	ST-00937, RBM39 degrader (cancer), IND filing, 2H24
Novartis	Dunad Therapeutics	Phenotypic screens, cereblon binders, others undisclosed	Cereblon, others undisclosed	Wiz degrader (sickle cell anemia), IND-enabling studies
Proxygen	Boehringer Ingelheim, Merck KGaA, Merck & Co.	Broad range, from unbiased phenotypic screens to target-centric	Many; undisclosed	Undisclosed
A-Alpha Bio	Amgen, Bristol Myers Squibb, Kymera Therapeutics	Detect basal E3–target interactions using yeast cell surface display, mutagenesis to interrogate interface	Many; undisclosed	Undisclosed

Others in this space include Ambagon Therapeutics, Astellas Pharma, AstraZeneca, Bayer, Biotheryx, Celgene (Bristol Myers Squibb), ChemPartner, Coho Therapeutics, Degron Therapeutics, Gandeeva Therapeutics, GSK, GluBio Therapeutics, Magnet Biomedicine, Neomorph, Orionis Biosciences, PhoreMost, Pin Therapeutics, Progenra, Proximity Therapeutics, Ranok Therapeutics, Revolution Medicines, Salarius Pharmaceuticals, SK Biopharmaceuticals, SyntheX and Triana Biomedicines. IND, Investigational New Drug.

Sticking without glue

Molecular glue company Seed Therapeutics, like Proxygen, is looking beyond cereblon. It's a majority-owned subsidiary of Beyond-Spring Pharmaceuticals, a drug company co-founded by Lan Huang, who published the first E3–E2 crystal structure[15], and Ning Zheng, who solved the structure of auxin bound to its transport inhibitor response 1 (TIR1) receptor[4].

Seed emphasizes proper E3 selection. The discovery process is lengthy: pick a candidate E3 on the basis of complementarity with the target protein (as predicted by AlphaFold and other computational methods) and cell location of the E3; detect a basal E3–target interaction in a cell system; confirm ability of the E3 to ubiquitinate the target; and perform high-throughput screening for degraders, followed by validation assays and then medicinal

Garber, *Nature Biotechnology* 42(4):546-550 (2024)

“Nature Reviews Drug Discovery” Review on “Protein Degraders Push into Novel Target Space” (10/14/2024)

News & analysis

News https://doi.org/10.1038/d41573-024-00170-9

Protein degraders push into novel target space

By Asher Mullard

Clinic-ready molecular glues and heterobifunctional PROTAC drugs are taking targeted protein degradation into uncharted territory.

With the rise of targeted protein degraders over the past decade, early adopters promised that these small molecules would be able to unlock previously intractable targets. A first wave of molecular glue and heterobifunctional degraders mostly focused on well-validated targets. A second surge is now pushing into more novel target space.

“We’re on the cusp of a revolution,” says Nell Bence, head of oncology discovery at Bristol Myers Squibb (BMS), which is using both molecular glues and ligand-directed degraders to breakdown novel targets in cancer and other indications.

Traditionally hard-to-drug targets – including transcription factors, GTPases and guanine nucleoside exchange factor (GEFs) – are increasingly within reach, shows the growing degrader pipeline (Table 1).

“We’re on the cusp of a revolution”

This is enabling molecular glue degraders – small molecules that reshape an E3 ligase to make it tag targets with ubiquitin, shunting problem proteins to the cell’s proteasomal recycling system – to expand beyond their oncology origins. BMS is testing a transcription-factor-degrading glue for sickle cell disease, while Monte Rosa has advanced its VAV1-targeted GEF degrader into the clinic for autoimmune diseases.

Heterobifunctional degraders – larger dumbbell-like molecules that bind a target of interest with one end and an E3 ligase with the other – are making headway in novel target space too. Kymera is advancing a first-in-class degrader against the immune-mediating transcription factor STAT6, for example, while both BMS and Arvinas are taking on the oncogenic transcription factor BCL6.

Zoran Rankovic, director of the Centre for Protein Degradation at the Institute of Cancer Research, is buoyed by this progress. Degraders against previously drugged targets could be a boon to patients, he explains, if they can outperform approved inhibitors. But most of the human proteome is still undrugged, and the bigger opportunity for degraders is to push these boundaries.

The field has a way to go, he adds. Glue degrader discovery remains limited as yet mostly to serendipitously identified targets, and heterobifunctional degraders remain constrained by ligandability issues and rational-design limitations. But researchers are making progress across the entirety of the degrader modality.

This is a hype that actually lives up to its promise,” says Rankovic.

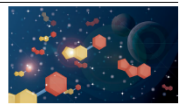
“This is a hype that actually lives up to its promise”

Old glues, new clues

Interest in targeted protein degraders has exploded in the past 10 years, and dozens of companies are now operating in this space. While heterobifunctional drug discovery companies were faster out of the gate, the ranks of the glue degrader biotechs are growing too – fuelled especially by the field’s understanding of how the FDA-approved myeloma drug lenalidomide and related immunomodulatory drugs (IMiDs) bind and reshape the E3 ligase cereblon to ubiquitinate the transcription factors IKZF1 and IKZF3. Other small-molecule glues might be able to reshape cereblon to take on other targets too, researchers quickly realized.

The first programmes to advance into the clinic, however, took on targets that were also degraded by lenalidomide. Celgene, now part of BMS, for example, worked quickly with its lenalidomide analogues to discover and optimize CC-92480, now mezigdomide, to breakdown IKZF1 and IKZF3. That drug is now in phase III development for myeloma. The kinase CK1α was another low-hanging fruit that is degraded by lenalidomide.

A further stepping stone was GSPT1, a GTPase that researchers pulled down during an immunoprecipitation assay of cereblon and a lenalidomide analogue. GSPT1 helps the protein-making machinery to disengage from completed proteins, and its blockade kills cells – especially fast-growing cancerous ones – creating oncology applications for the previously undrugged GTPase target. BMS first advanced its GSPT1 degrader CC-90009 into the clinic in 2016, but has since terminated that glue for undisclosed reasons.



“GSPT1 degradation shuts down global protein translation, and there are a number of adverse events that are likely to be associated with that,” cautions Ian Churcher, a consultant with Janus Drug Discovery and a former degrader developer at both Amphista and GSK. “It’s all about therapeutic index.”

At BMS, that now means using an antibody–glue conjugate to better deliver the degrader to cancer cells. Its BMS-986497, acquired from Orum Therapeutics, consists of a GSPT1-degrading glue tacked on to a CD33-targeted antibody, to home in on malignant B cells.

“To improve both the efficacy and tolerability of GSPT1 degradation, an antibody–conjugate approach would be ideal,” says Bence. “We’re excited to see how this type of approach performs. It’s a really exciting time right now for degrader–antibody conjugates.”

BMS has also moved a glue degrader forward against another transcription factor for sickle cell disease, but as yet has not disclosed its target. “Stay tuned,” says Bence.

A cereblon-based glue degrader that targets the transcription factor WIZ can boost fetal haemoglobin levels in mice and primates, Novartis reported this year, showcasing one way a glue could be useful in sickle cell disease.

Target hopping

Monte Rosa was another early mover against GSPT1, developing MRT-2359. Clinical data as yet shows that this glue has a viable therapeutic index and a tolerable safety profile in patients with MYC-driven solid tumours.

SEED was prominently featured in “Nature Reviews Drug Discovery”.

Table 1 | Degraders move into novel target space

Target	Target properties	Molecule (degrader type)	Company	Indication	Status
Newly prosecuted targets					
GSPT1	GTPase, translation termination factor	BMS-986497 (antibody–glue conjugate); MRT-2359 (glue); CC-90009 (glue)	BMS/Orum; Monte Rosa; BMS	Haematological malignancies; MYC-driven cancer	Phase I; Phase I/II; Discontinued
VAV1	GEF, scaffold protein	MRT-6160 (glue)	Monte Rosa	Autoimmunity	Phase I
Not disclosed	Transcription factor	HbF-activating CELMoD (glue)	BMS	Sickle cell disease	Phase I
WIZ	Transcription factor	NA (glue)	Novartis	Sickle cell disease	Preclinical
BCL6	Transcription factor	ARV-393 (heterobifunctional); BMS-986458 (heterobifunctional)	Arvinas; BMS	B-cell malignancies	Phase I; Phase I
STAT6	Transcription factor	KT-621 (heterobifunctional)	Kymera	Allergic diseases	Phase I in 2024
IKZF2	Transcription factor	Helios CELMoD (glue); PLX-4545; DKY709 (glue)	BMS; Plexium; Novartis	Cancer	Phase I; Phase I; Discontinued
HuR (ELAVL1)	mRNA stability regulator, RBP	NA (glue)	Degron	Cancer	Preclinical
Previously prosecuted targets, without approvals					
IRAK4	Kinase, scaffold protein	KT-474 (heterobifunctional)	Kymera/Sanofi	AD and HS	Phase II
LRRK2	Kinase, scaffold protein	ARV-102 (heterobifunctional)	Arvinas	Parkinson’s disease	Phase I
STAT3	Transcription factor	KT-333 (heterobifunctional)	Kymera	Cancer	Phase I
MDM2	E3 ligase	KT-253 (heterobifunctional)	Kymera	Cancer	Phase I
RBM39	Splicing factor, RBP	NA (glue)	Seed	Cancer	Phase I in 2025
NEK7	Kinase	MRT-8102 (glue); NA (glue)	Monte Rosa; Novartis	Inflammation	Preclinical; Preclinical

Pipeline data from Cortellis database and company websites. AD, atopic dermatitis; CELMoD, cereblon E3 ligase modulatory drug; GEF, guanine nucleotide exchange factors; HS, hidradenitis suppurativa; RBP, RNA-binding protein.

SEED Therapeutics is amongst those who are nevertheless working to let other E3 ligases shine. Its lead programme harnesses the DCAF15 ligase to degrade the splicing factor RBM39. This programme builds on over 25 years of research on aryl sulfonamide small molecules, adds SEED president and CSO James Tonra. In 1999, Eisai reported that its indisulam stalls cell cycle progression in cancer cells – prompting a failed attempt to develop the drug as a chemotherapy candidate. In 2017, researchers reported that this class of drug in fact acts by remodelling DCAF15 to ubiquitinate RBM39, a protein that regulates the splicing of mRNA precursors.

Armed with a better understanding of RBM39 biology, SEED is set to advance an optimized RBM39 degrader into the clinic next year.

“There’s a big opportunity for RBM39 degraders in the clinic for new indications, in everything from neuroblastoma to liver cancer,” says Tonra.

Mullard, *Nature Reviews Drug Discovery* 23(11):799-802 (2024)