EDDIT

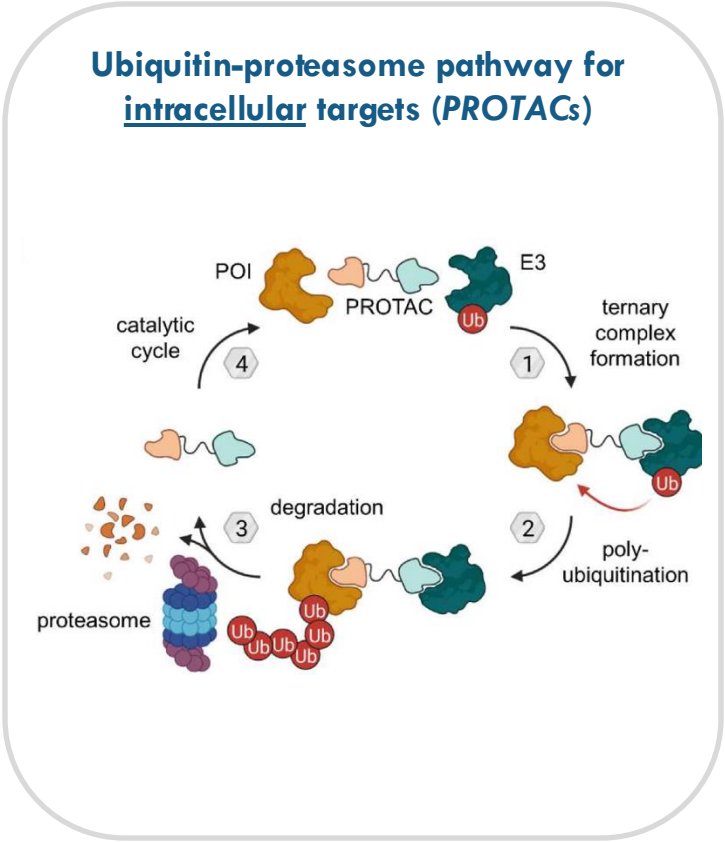
Early Drug Discovery for Targeted Protein Degradation

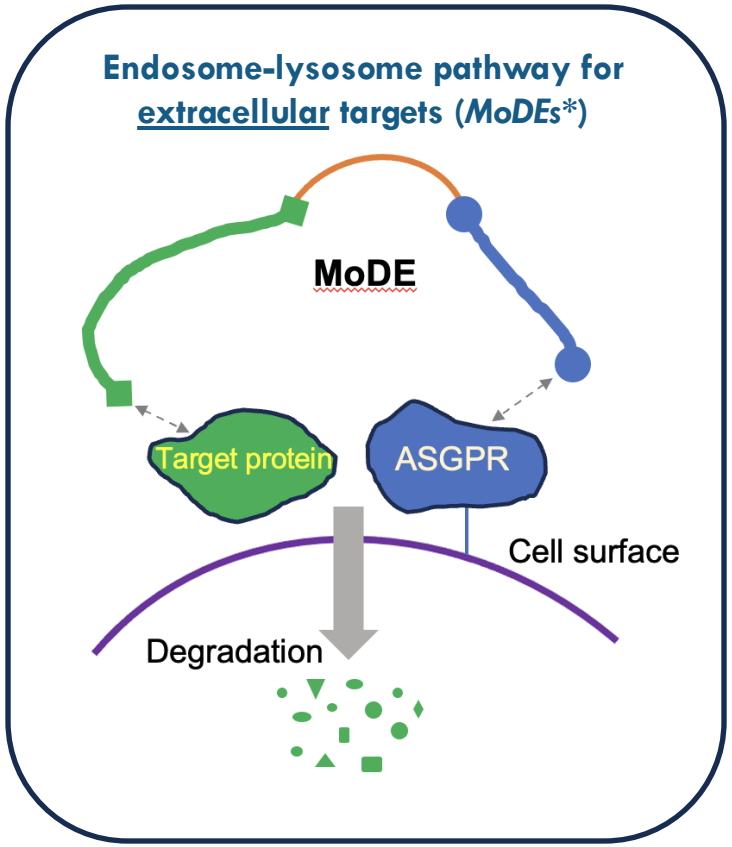
Universe of drug discovery with AI (by Microsoft Designer)

Yale Blavatnik Fund Semifinalist Pitch
December 5, 2024

How to destroy pathogenic proteins?

Targeted protein degradation (TPD) has emerged as a promising therapeutic approach by exploiting cellular degradation mechanisms and induced proximity.





EDDIT

*MoDEs = molecular degraders of extracellular proteins

TPD approaches have significant room for improvement

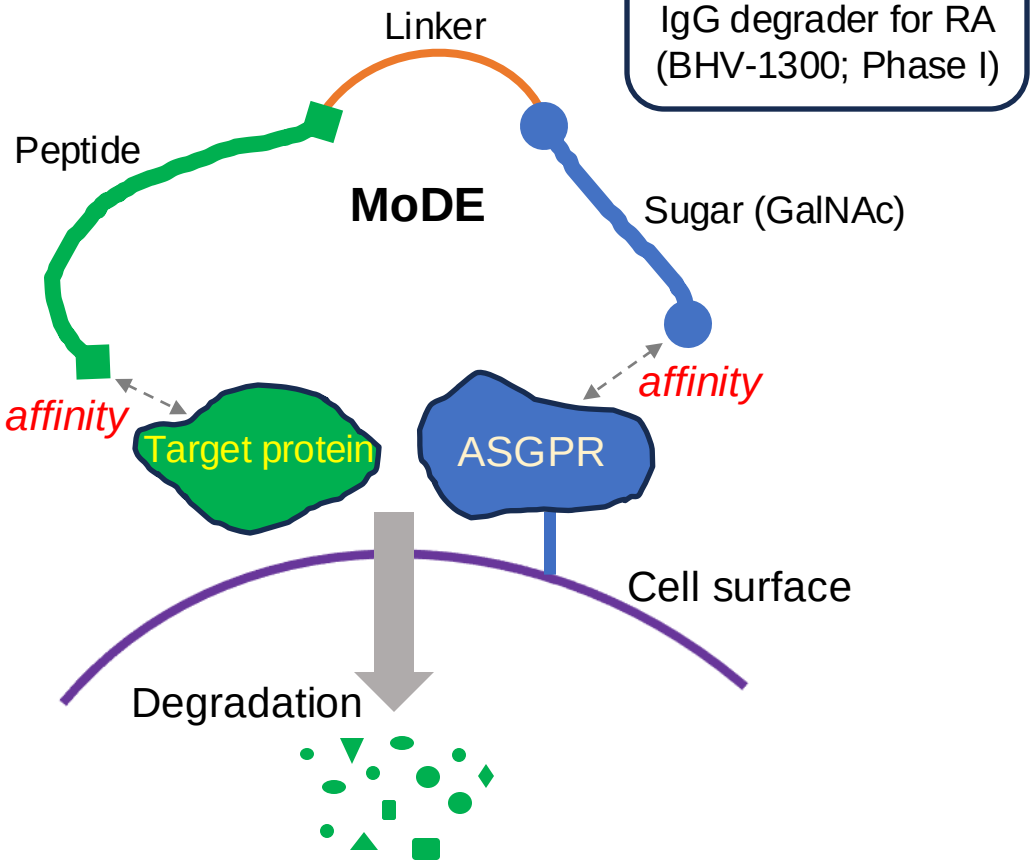
MoDEs were pioneered by the Spiegel lab at Yale and licensed to Biohaven (**1st gen MoDEs**)

Key limitations of 1st gen MoDEs

Composed of sugars and peptides: limited oral bioavailability and weak PK/PD profiles

***Goal*: Develop non-sugar small molecule-based MoDEs to improve degradation of extracellular targets using our AI-based platform technology, *EDDY*.**

biohaven®
IgG degrader for RA
(BHV-1300; Phase I)



- **Lee** and Emani. Provisional patent filing. May 30, 2023
- **Lee**, Emani, Gerstein. *EDDY: Scalable early drug discovery by computational meta-modeling.* Yale Innovation Summit. June 1, 2023

ASGPR = asialoglycoprotein receptor

Scientific Team

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Research Scientist in Genetics Systems Biology @ Harvard
Part III Math @ Cambridge
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Mihir Khambete, PhD

Postdoctoral Associate, Chemistry, Spiegel Lab
Visiting Faculty @ Institute of Chemical Technology, Mumbai

Advisors

David Spiegel, PhD
Professor of Chemistry,
Inventor of 1st gen MoDE technology licensed to Biohaven

Mark Gerstein, PhD
Albert L. Williams Professor of Biomedical Informatics and Data Science at Yale

David Stowe, MBA
Founding Partner at Adventus Consulting

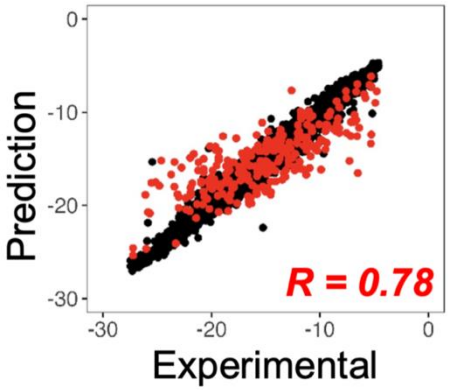
EDDY exhibits cutting-edge performance for small-molecule ligands

- Novel meta-modeling framework by taking advantage of diverse datasets and tools (*no need of structural data*)
- Validated against public experimental reference datasets of binding affinities between small molecules and proteins

Reference data performance ($-1 \leqslant R \leqslant 1$)

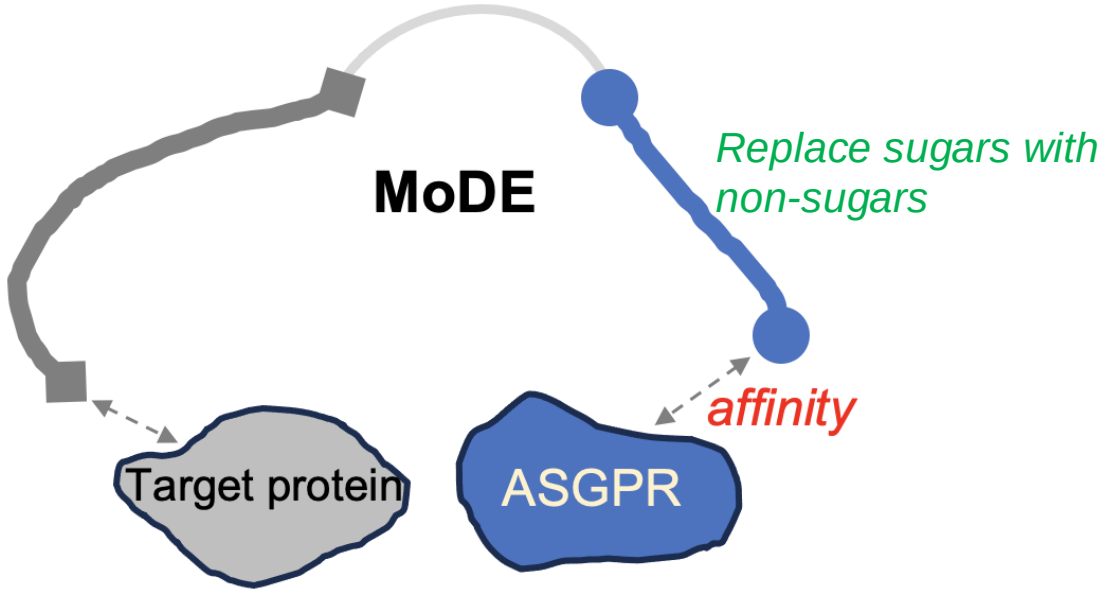
Existing base models (Structures or Sequences)	**EDDY DL models (*>1,000*) (Sequences)**	**EDDY Meta-models (*>200*) (Sequences + Structures + Molecular properties)**
0.47	**0.76**	**0.78**

Flexible & Competitive



- **Lee and Emani. Pending patent (PCT/US2024/031704)**
- **Lee, Emani, and Gerstein. 2024. *J. of Chem. Inf. Model.***

EDDIT: Replace old with new for 2nd gen MoDEs



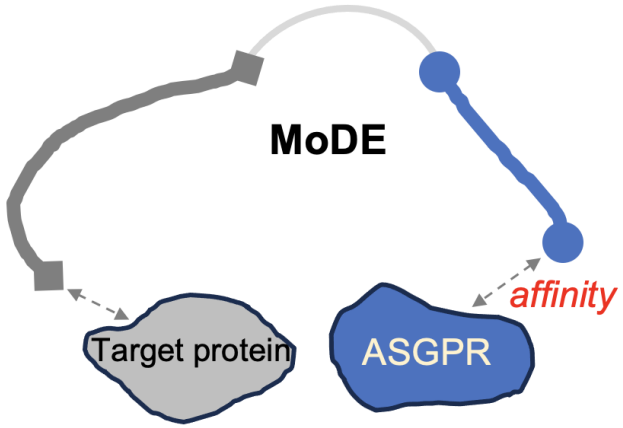
EDDY enables the discovery of non-sugar small-molecule ligands for both **ASGPR** and **targets of interest.**

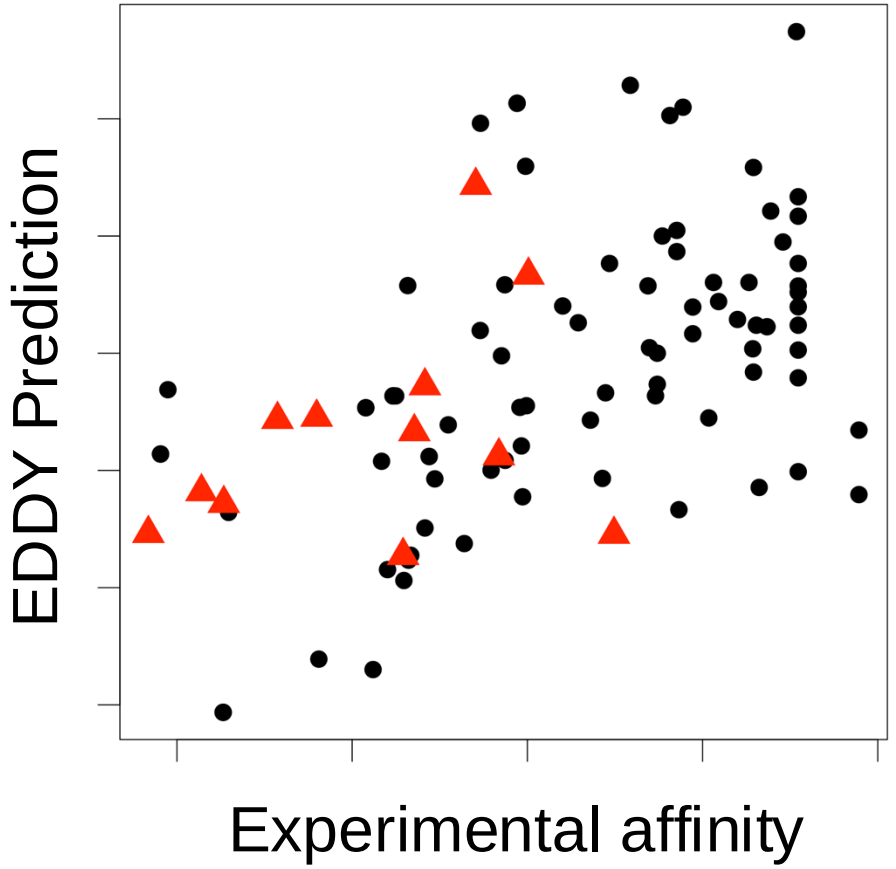
We will first address ASGPR, because its current sugar ligands make MoDEs ***sub-optimal.***

Predict ***high-affinity non-sugar ligands to replace sugar ligands for ASGPR***, expanding the potential of a new/general therapeutic modality

EDDY has been validated for known ASGPR ligands (*in silico* proof of concept)

Capable of identifying high-affinity small-molecule ligands for ASGPR (never seen before by EDDY).





R = 0.52

p < 5.2e-8

Private (Spiegel lab)

Public

Masked partial results (unpublished)

EDDIT has made further progress with federal AI funding and NSF I-Corps

1. National AI Research Resource (NAIRR) pilot grant (federal initiative)

(June 2024 – May 2025)

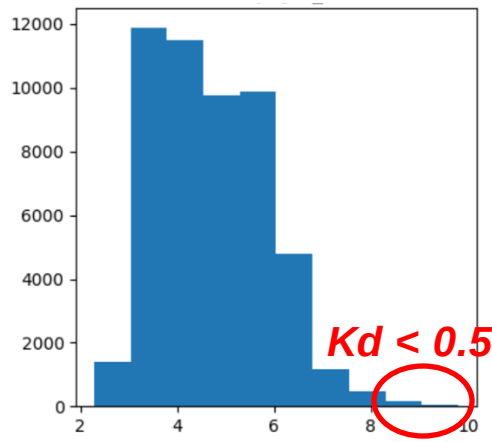
: Virtual screening of 51,000 small molecules (Maybridge library) for ASGPR (with David Spiegel)

2. NSF I-Corps National Program

(Feb – May 2025, pending)

- $50k for 100 customer interviews
- Completed the Northeast Regional program (Summer 2023)
- Plans for spinout and NIH SBIR (mid 2025)

Masked partial results (unpublished)



Best sugar ligand

- TriGalNAc, Kd < 15nM

Blavatnik $200K Ask

Milestone 1 ($100K): Platform optimization and asset identification

- Target-specific optimization of EDDY by fine-tuning
- Virtual screening of the YCMD collection of 300,000 synthetic small molecules
- In vitro validation of top-ranking ligands by SPR (YCMD)

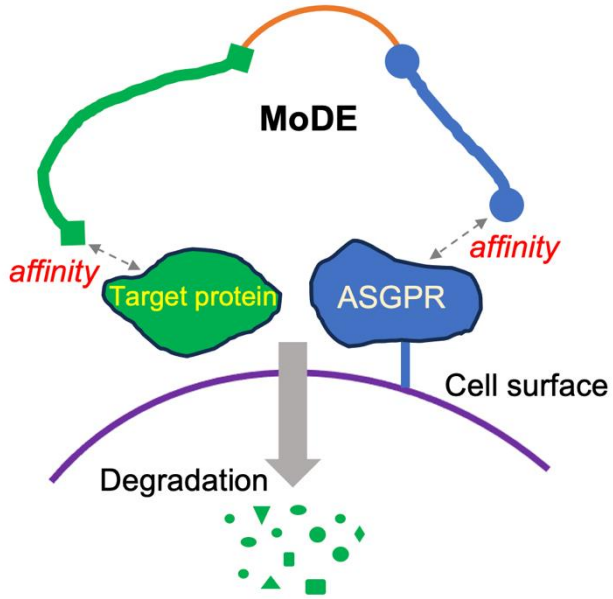
Milestone 2 ($100K): In vitro head-to-head comparisons with 1st gen MoDEs

- Anti-DNP model antibody
- Pan-IgG AAb (RA; BHV-1300)
- anti-b1AR AAb (HF; BHV-1600)

Milestone 3 ($$$): In vivo validation (YCC-PCM for preclinical evaluation)
Milestone 4: Partnership with Biohaven to share IP

*Development of other assets:

1. PROTACs with small-molecule ligands for 600 E3 ligases
2. Pan-cancer therapeutic targets (with the Gerstein lab)
3. Discovery of SRSF3 small-molecule inhibitors (with Dr. Christine Ko)
4. TFs, other endocytic receptors, undruggable dark proteome



- **Hits**
  : 100s of ASGPR ligands with sub-nM Kd
- **New IP**
  : IgG AAb, anti-b1AR AAb, others