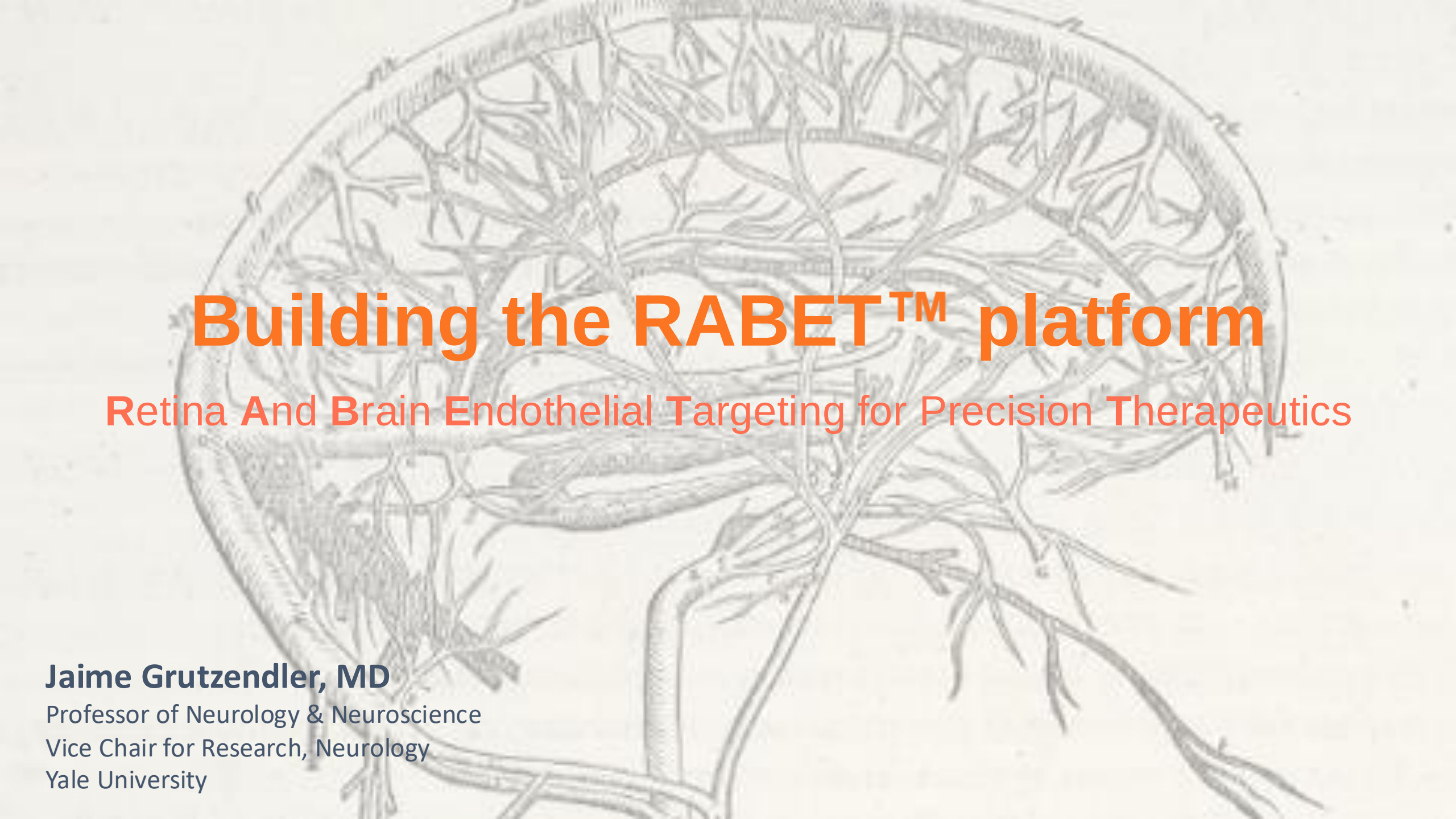

Building the RABET™ platform

Retina And Brain Endothelial Targeting for Precision Therapeutics

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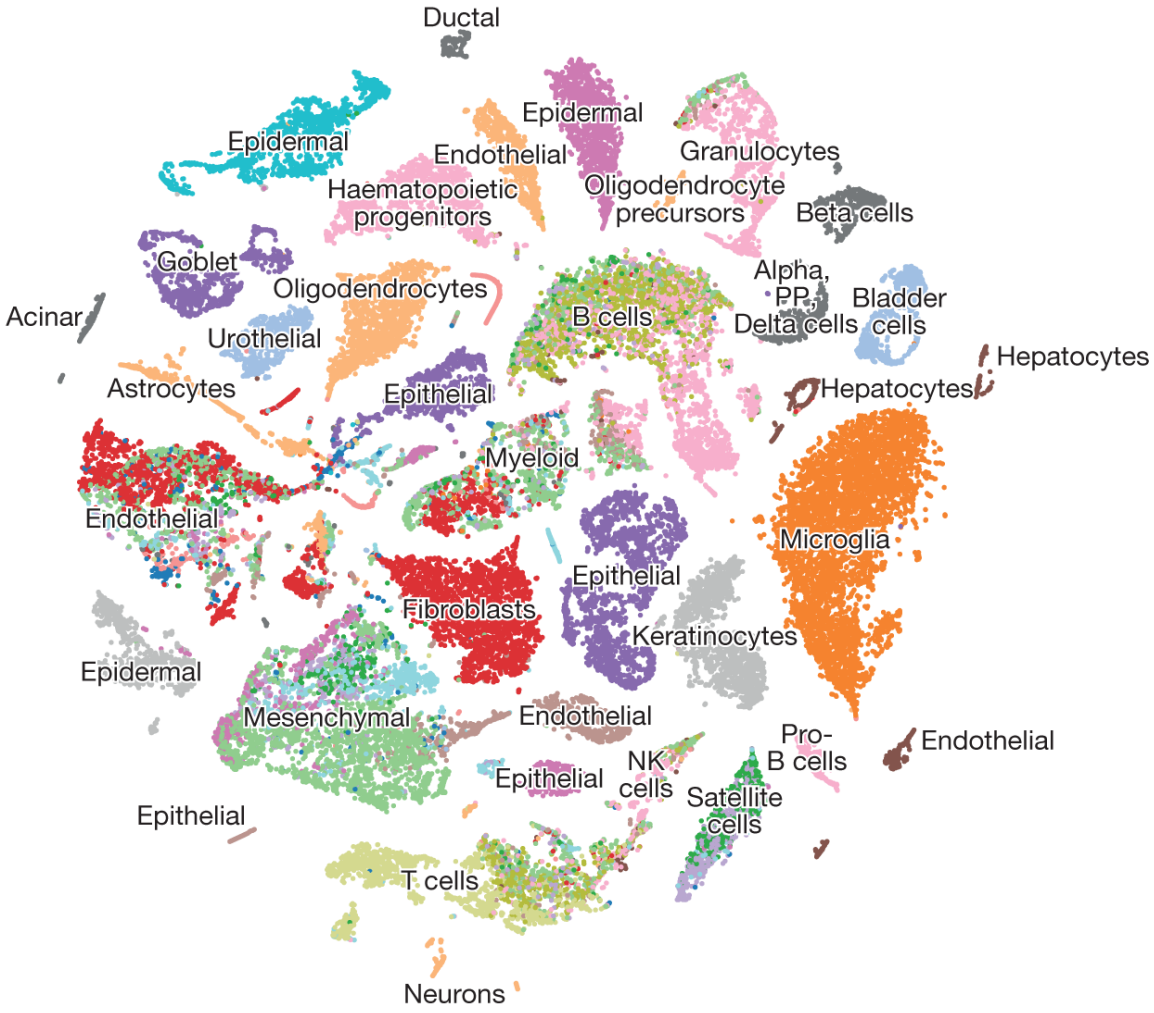
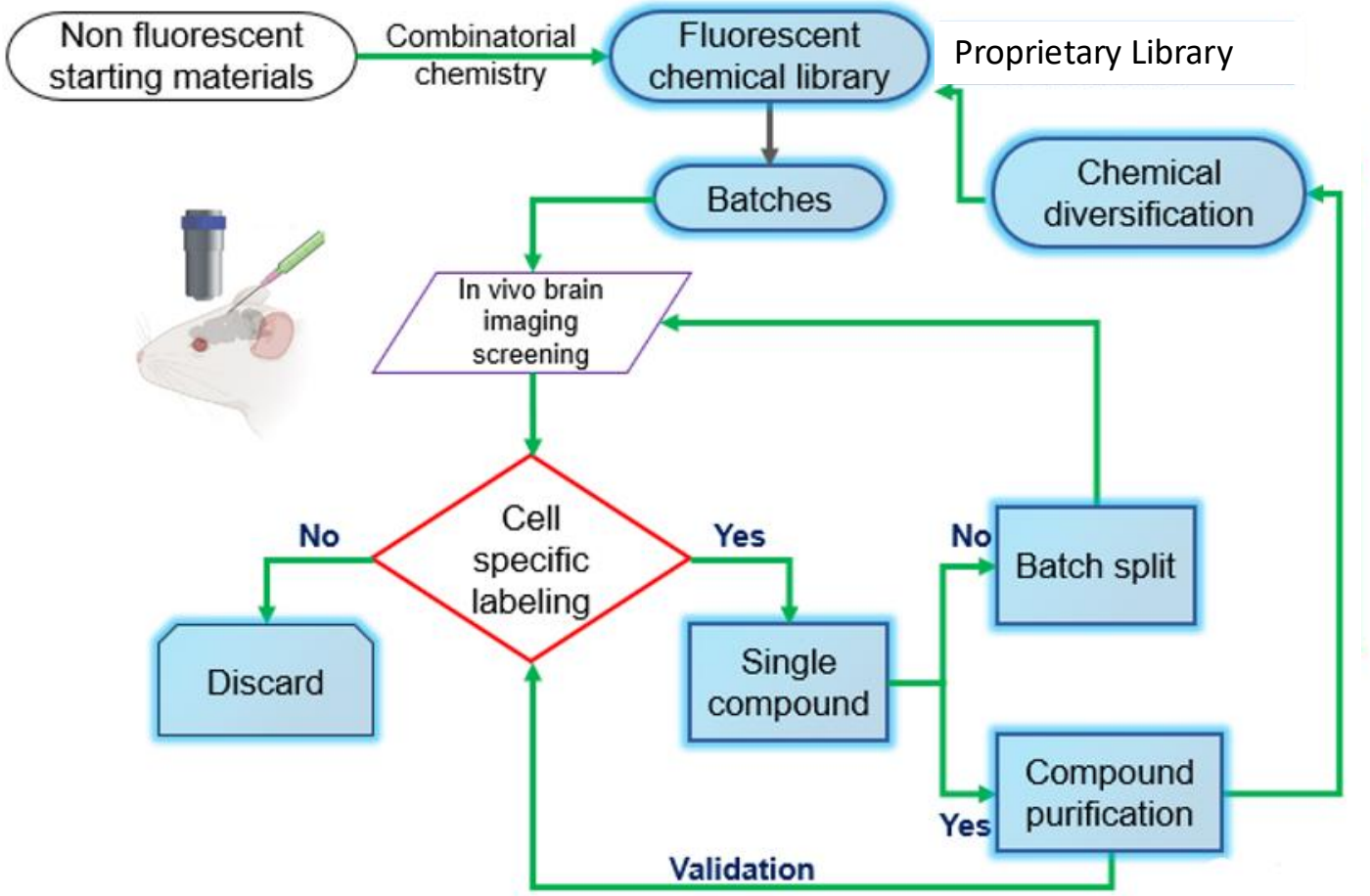
Platform to deliver diverse payloads to retina and brain

- Pharmacotherapies are rarely cell-type selective
- Achieving therapeutic intracellular drug levels in affected cells without impacting non-affected cells or organs is challenging.
- No systematic method exists for developing molecules that target intracellular pathways in a cell-type-specific manner.
- Platform will allow cell-type specific targeting of payloads to brain (mRNA, ASOs, Peptides and Small molecules).



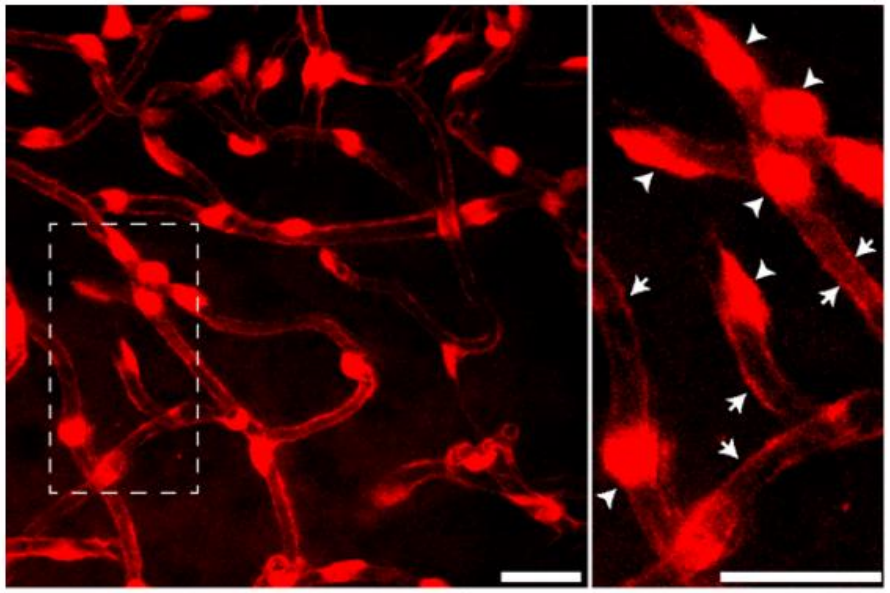
Combinatorial library screening in the live mouse brain allowed discovery of small molecules with cell type selective uptake



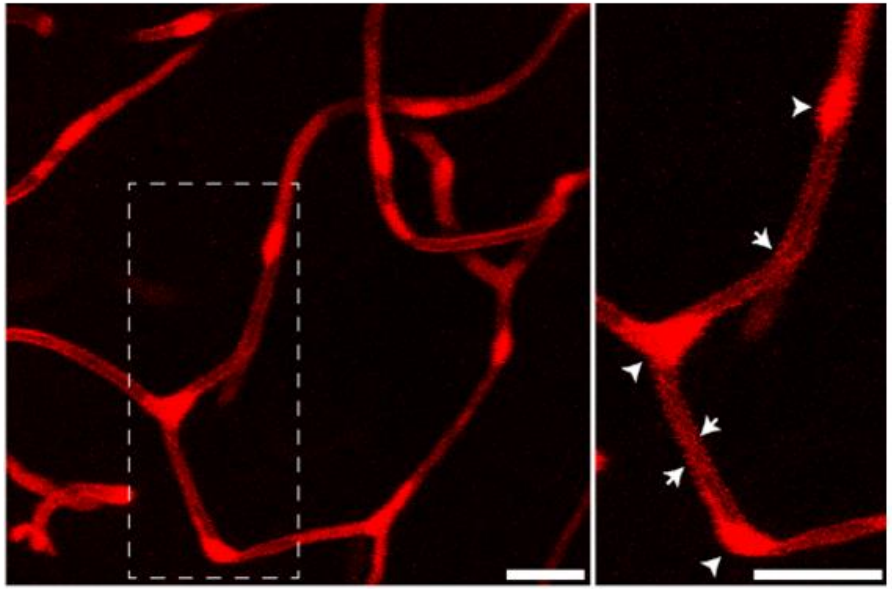
- Combinatorial chemistry fluorescent library enables *in vivo* screen.
- Identified molecules showing selective intracellular uptake in specific cell types (endothelial cells, neurons, astrocytes, pericytes)
- Molecules may act as "Trojan horses" for targeted pharmacological delivery in vivo.

Discovery of orally bioavailable molecules that target brain and retina endothelium

RABET



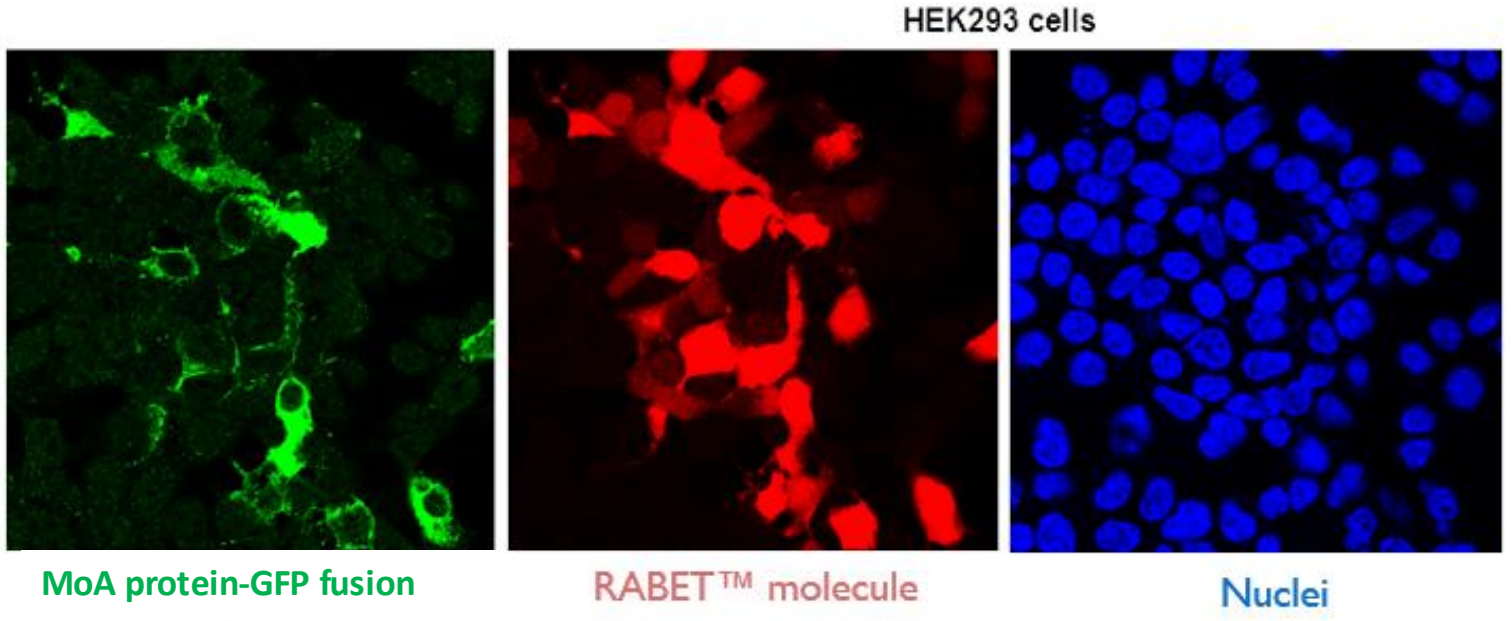
Brain



Retina

Patents pending

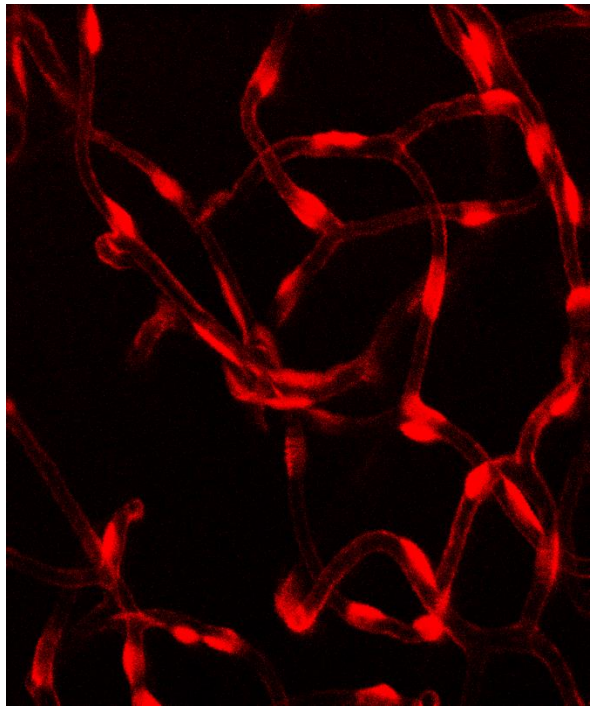
The RABET mechanism of action (MoA) is understood and conserved in humans



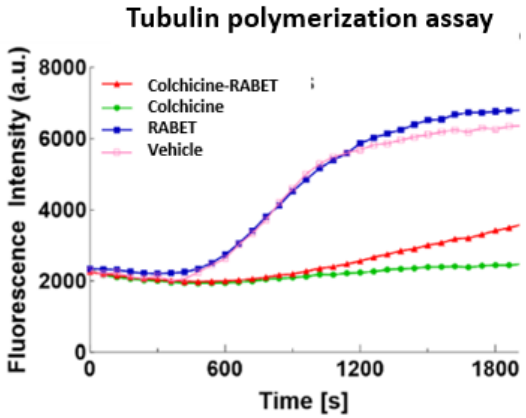
- Mouse overexpression and knockout experiments confirm MoA specificity
- Transfection of human protein orthologue leads to robust RABET™ uptake in vitro and in vivo
- The RABET™ molecule has affinity for mouse and human cellular entry MoA

Proof of Concept: Colchicine-RABET Conjugate Retains Cell Specificity Pharmacological Potency and Eliminates Systemic Side Effects

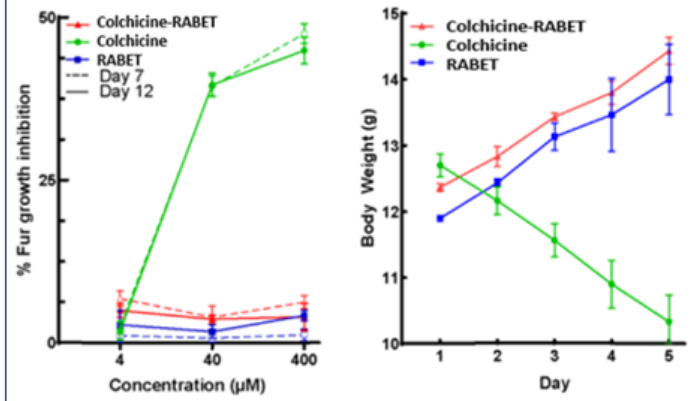
RABET-Colchicine preserves selective endothelial uptake *in vivo*



RABET-Colchicine retains pharmacological properties



Markedly reduced local and systemic toxicity at high dose RABET-Colchicine



Fur re-growth assay after local injection

Weight loss after systemic injection

- **Biodistribution:** minimal RABET uptake in non-target organs and cells, sparing immune cells (blood, spleen), heart, and skeletal muscle.
- **Clearance:** Kidney and Liver
- **Platform Pay Loads tested-** up to 20 Kd in Size (PEGylated compounds and GAPmer ASOs)

Common conditions that could benefit from RABET conjugates

- Vascular dementia
- Vascular malformations
- Diabetic retinopathy
- Age-dependent macular degeneration
- Multiple sclerosis
- Diseases with BBB disruption
- Neurodegeneration/Neuropsychiatric

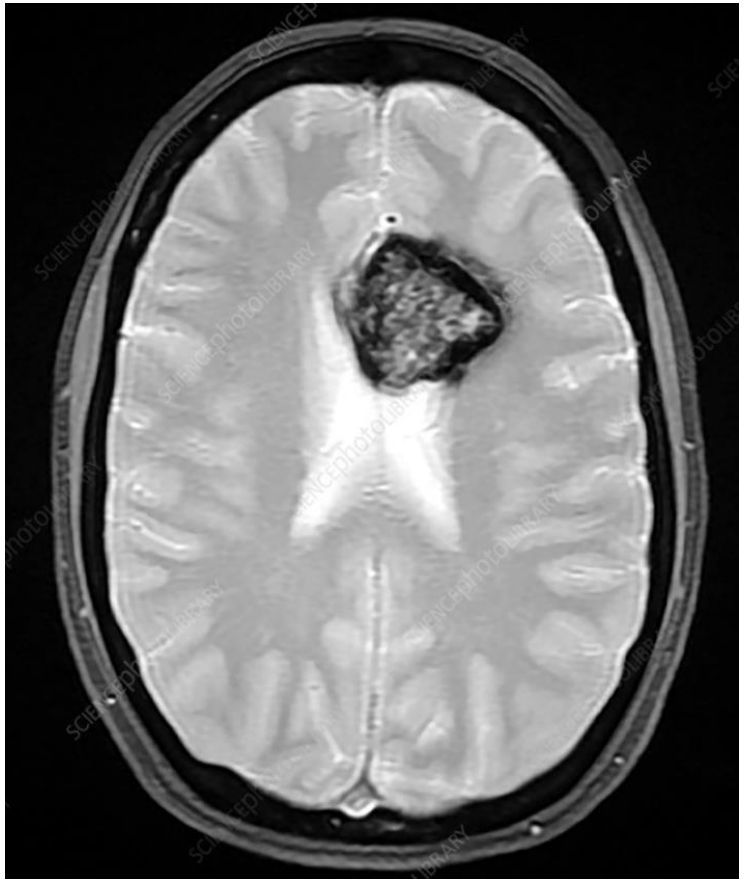
- Advanced conversations (NDA) with a large pharmaceutical company interested in platform
- Trojan horse across BBB and targeting brain cells with large payloads (siRNA and Peptides)

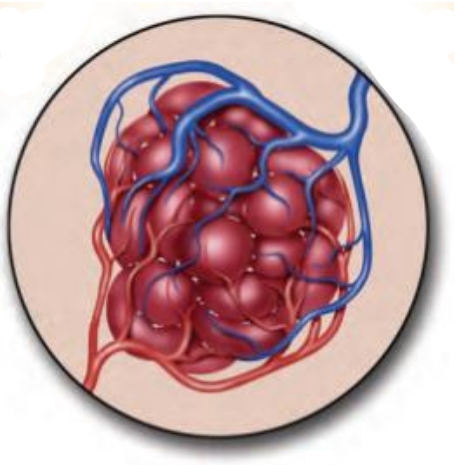
GOALS:

- Investigate a single endothelial-targeted indication with a clear path to commercialization
- Will also serve as POC of the overall platform

POC of RABET Platform
Cerebral Cavernous Malformations (CCM)

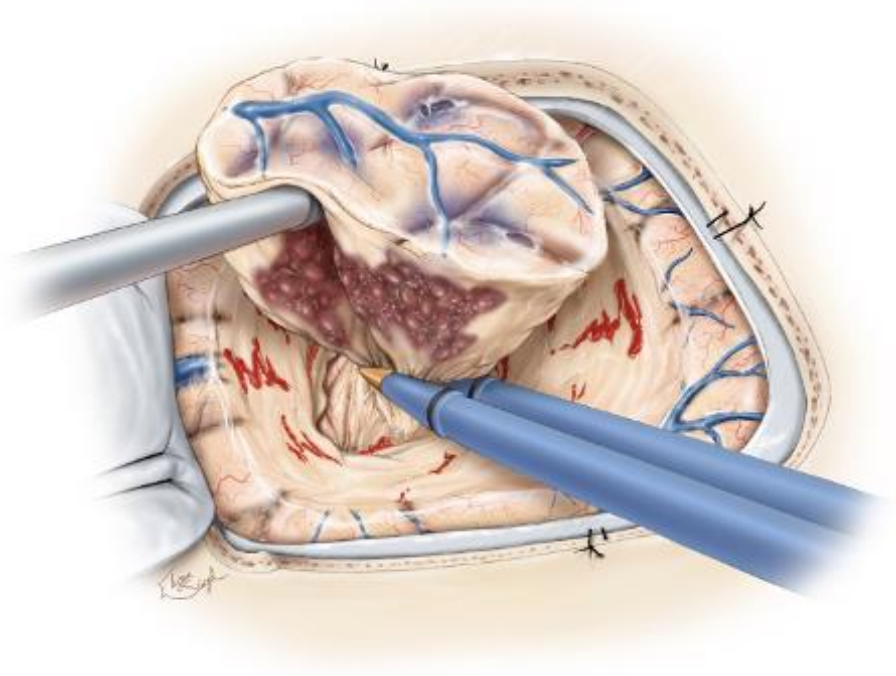
- CCM has a clear path to commercialization
- A brain endothelial-predominant pathology
- Clusters of enlarged tightly packed capillaries in brain, brainstem and spinal cord.
- Thin walls prone to leakage, rupture, and hemorrhage.
- Symptoms (repeated bleeding, compression)
  - Seizures.
  - Brain Hemorrhage
  - Headaches.
  - Weakness in the arms or legs.
  - Memory and attention deficits.
- Prevalence ~1 in 200 individuals





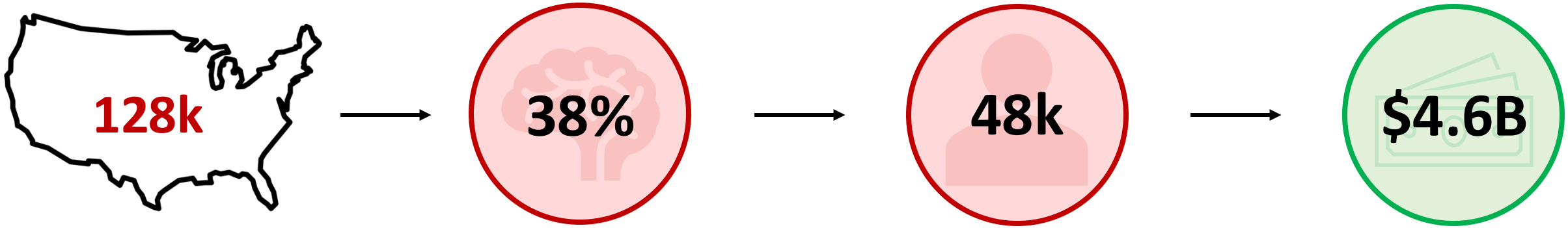
Management and Prognosis

- Medical Management
  - Analgesics for headaches
  - Antiepileptics for seizure control
  - Regular MRI monitoring
  - Avoiding trauma, anticoagulants
- Surgical Resection (For symptomatic CCM)
  - Lesions causing symptomatic hemorrhage
  - Risk of recurrent bleed 4-6%/year
  - Patients with medically refractory epilepsy
  - Surgery is limited to lesions in non-essential brain regions
- Prognosis
  - Seizures likely require lifelong medical treatments
  - Surgery can reduce rebleeds but carries significant risk



From https://www.aaroncohen-gadol.com/

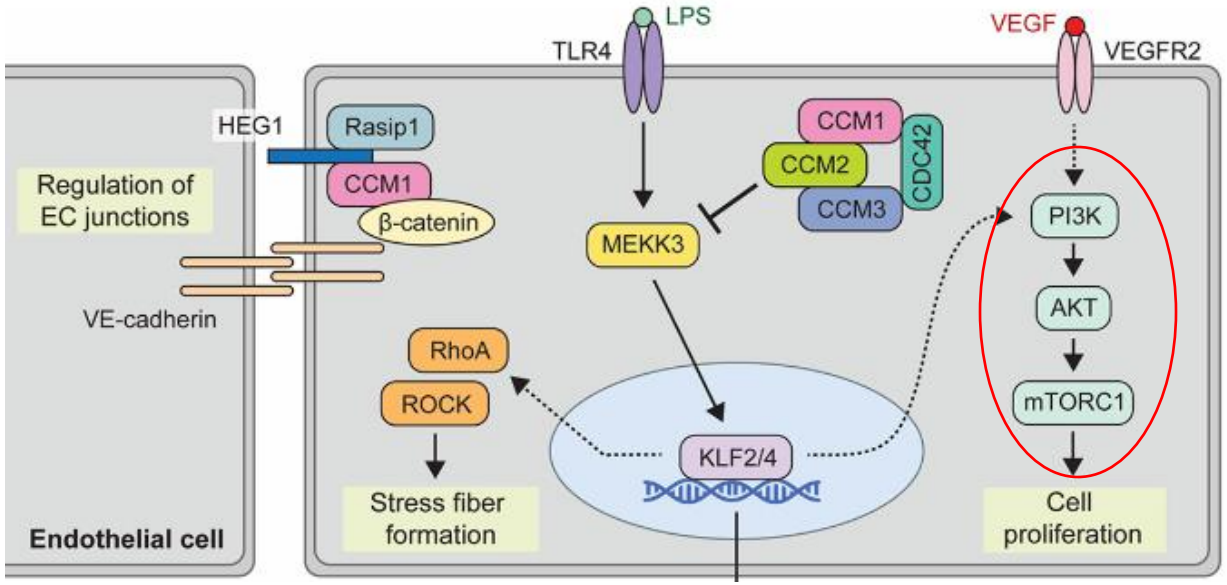
Targeted pharmacological therapeutics are an attractive alternative to surgery



- Large portion of CCM patients require surgical intervention
- Surgery is invasive, risky and expensive $$
- Addressable market based on an inflation-adjusted cost of surgery of $95,070 per patient

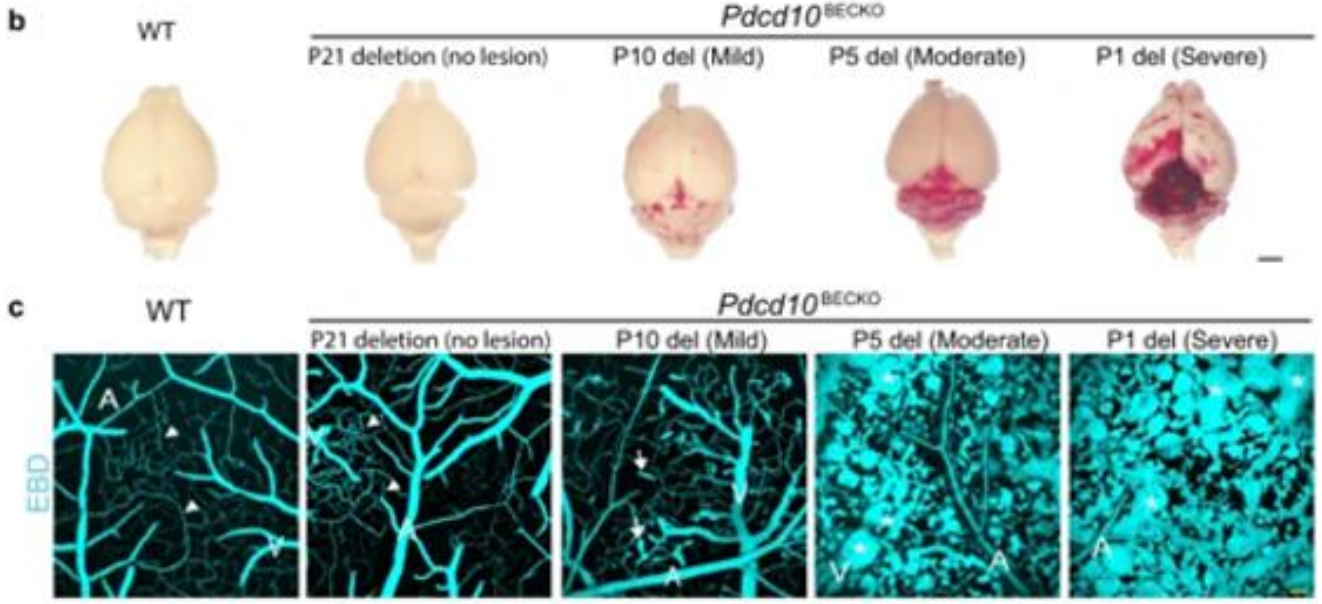
Disease Mechanisms- mTOR pathway hyperactivity

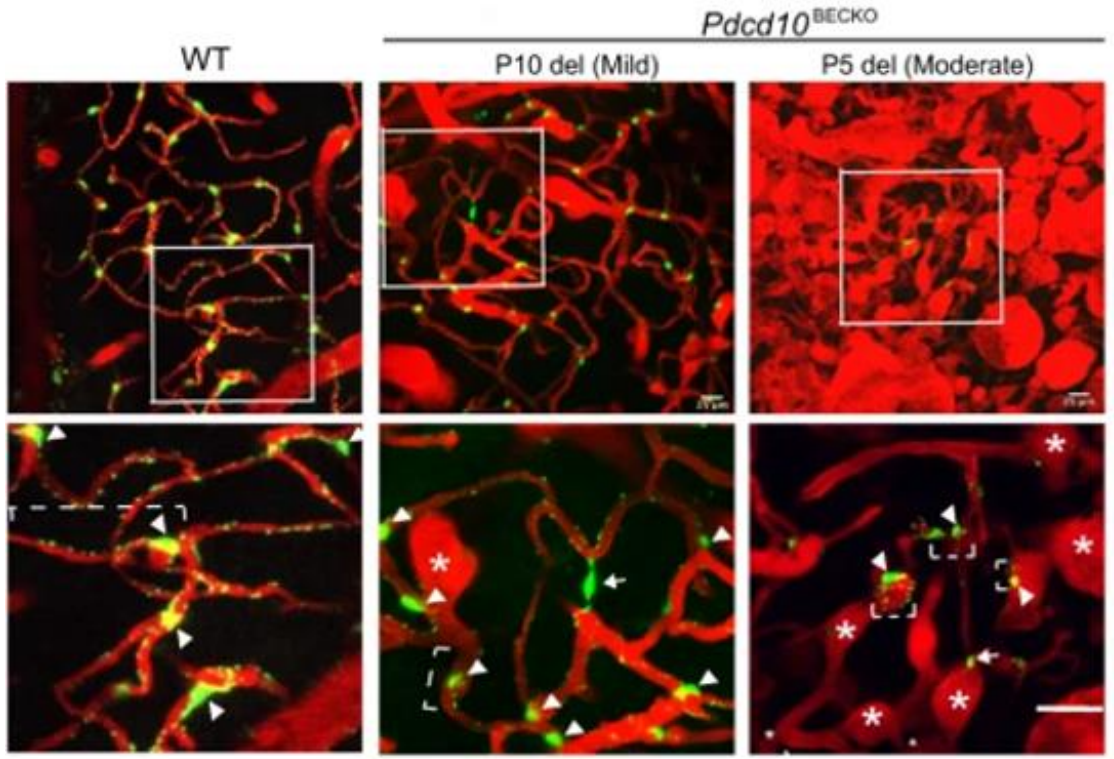
- *Familial (20%)* mutations in CCM1 (KRIT1), CCM2 (MGC4607), and CCM3 (PDCD10)
- *Sporadic (80%)* somatic mutations in related pathways PI3KCA/mTOR
- Mechanism related to aberrant endothelial proliferation (angiogenesis)



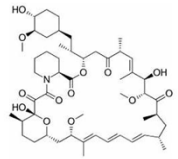
Modified from Snellings et al Circ Res, 2021

Endothelial CCM3 *deletion in mice* recapitulates pathology and hemorraghe



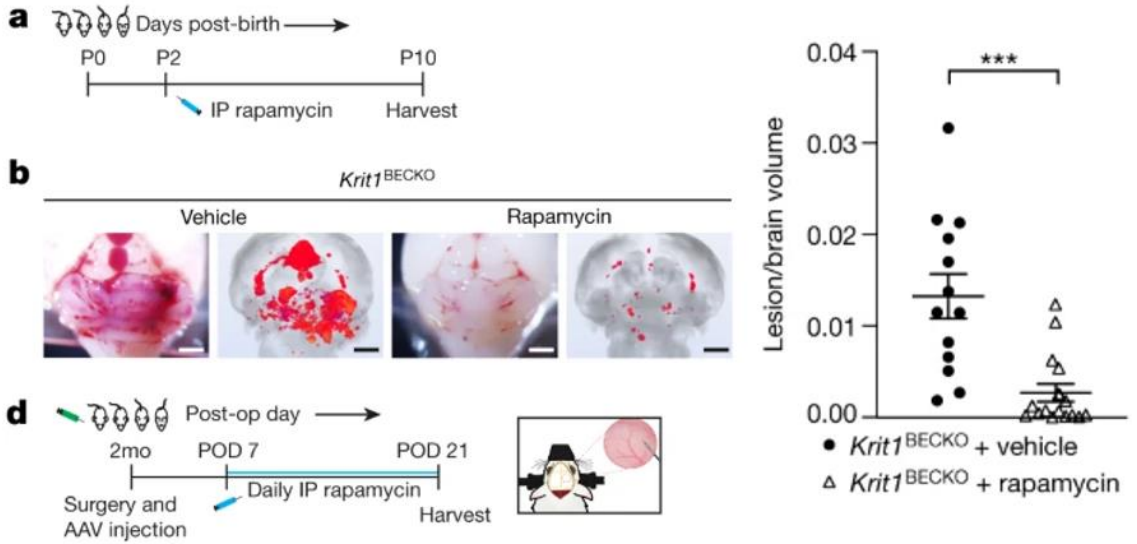


Zhou et. al. *Nature Comms*, 2021
(Jenny Huanjiao Zhou lab in collaboration with Grutzendler lab)
)



Rapamycin reduces CCMs in several mouse models

- *mTOR hyperactivity* involved in familial and sporadic cerebral cavernous malformations (CCM)
- Rapamycin (mTOR inhibitor) prevents formation of CCMs in mice.
- Antiproliferative, anti-inflammatory and autophagy-modulating properties

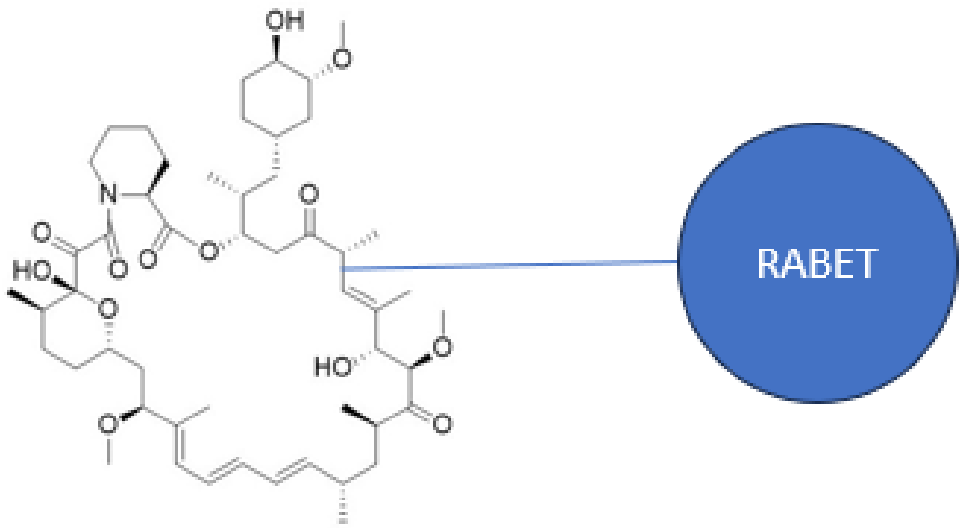


!! Chronic Rapamycin has major side effects !!

- Immunosuppression
- Diabetes and dislipidemia
- Stomatitis and mucositis
- Impaired wound healing
- Interstitial pneumonitis
- Nephrotoxicity

Modified from Ren, et.al. *Nature* 2021

Rapamycin-conjugates as POC for RABET platform



RAPAlog

Conjugation chemistry is well understood with known sites that preserve pharmacological potency

GOAL: RAPAlog-RABET conjugates to eliminate immune and metabolic side effects

Have already designed Rapalogs with and without cleavable linkers

Ongoing CCM trials demonstrate commercial interest and feasibility

Recursion Phase II CCM Trial (NCT05085561)	
Primary Endpoint	Secondary Endpoints
Safety/Tolerability	• CCM Health Index **(patient reported)** • Modified Rankin Scale **(patient reported)** • SymptoMScreen Score **(patient reported)** • Lesion size/number **(MRI)** • Number of cerebral hemorrhagic events **(MRI)** • Incidence of clinically significant changes **(physical examination)**

- Recursion is evaluating a small-molecule superoxide scavenger in **Phase II** clinical trials
- Key takeaways:
  - Industry interest and POC in treating CCM
  - Feasibility of patient recruitment and trial design
  - Clinically relevant endpoints to assess therapeutic efficacy.

https://www.alliancetocure.org/

Blavatnik funds for POC and lead optimization *in vitro* and *in vivo* CCM mouse model

$100K (0-4 months)- SYNTHESIS

- Synthesis of ~ 10 RABET-Rapalog conjugates. (CRO)

$80K (5-9 months)- IN VITRO CELL TYPE SPECIFICITY AND EFFICACY

- PK and Cell type specificity profiling of conjugates
- *In vitro* testing of pharmacological effect on mTOR pathway. (Grutzendler lab + CRO)

$120K (10-18 months) - IN VIVO EFFICACY

- Mutant mouse model of CCM to determine prevention and reversibility of CCMs and sparing of immune side effects *in vivo*. (Grutzendler lab)

Team with complementary skills to launch the RABET™ platform

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Composition of matter and utility patents pending