Direct intralesional mTOR inhibition for targeted treatment of sporadic and syndromic venous and lymphatic malformations

- **Venous and lymphatic malformations** associated with pain, disfigurement, organ injury, hematologic derangements, venous thromboembolism, bleeding, infection, disability, death
- **No standard of care**; current options off-label, potentially lethal side-effects, prone to recurrence, costly
- Oral mTOR inhibition; needs frequent dosing, systemic exposure, side-effects, some efficacy
- **Working solution**: emulsion of a sterile, IV-compatible, mTOR pathway inhibitor for intra-operative direct intralesional delivery into venous and lymphatic malformations
- **In-human clinical data** with clinically and radiographically proven results; currently expanding clinical experience
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Venous and lymphatic malformations are morbid clinical entities

- Disease Outcome: Perpetual growth, pain, disfigurement, hematologic derangement, bleeding, infection, adjacent organ injury, venous thromboembolism, death
- Estimated US Population: 4 million
  - Likely underestimated due to decreased awareness
There is currently no disease modifying therapy

- Current therapies: surgery and/or embolization with off-label, toxic, and/or moderately potent agents
  - Cost to Treat per session: ~$25-50K (visits, imaging, surgery, embolic material)
  - Mean ~2 sessions per patient
- Unmet Need: Current treatments do not target the underlying etiologic mutated molecular pathway (mTOR) > recurrence, reintervention
mTOR pathway ubiquitously implicated in VM, LM pathogenesis

- Desired Biological Process: regression of vascular malformation via inhibition of the etiologic mutated pathway in affected endothelial cells

- Clinical Endpoint: Reduction in symptoms, size of lesion (detectable visually and/or radiographically [duplex ultrasound and MRI])

- Validity of Therapeutic Hypothesis:
  - Human: systemic oral sirolimus 82% partial or better regression
    - Daily dosing, frequent visits/blood draws, systemic exposure, side effects
• **Unmet Need:** Current approaches do not target the underlying etiologic mutated molecular pathway (mTOR) > recurrence, reintervention

• **Target:** intralesional mTOR inhibition (mTOR pathway is mutated in venous and lymphatic malformations)

• **Desired Biological Process:** regression of vascular malformation via inhibition of the etiologic mutated pathway in affected endothelial cells

• **Intervention:** direct stick embolization of venous/lymphatic malformation with the mTOR inhibitor temsirolimus

• **Clinical Endpoint:** Reduction in symptoms, size of lesion (detectable visually and/or radiographically [duplex ultrasound and MRI])
Current attempts being made at targeted therapy

- NCT04409145: First in Human Trial of Topical VT30 in Pts with cutaneous Venous/Lymphatic Malformations
  - VT30, a PIK3CA inhibitor, converted in skin to active form VT10
  - Limitations:
    - Cutaneous lesions only; limited generalizability
    - Non-target organ exposure
    - Daily BID dosing
    - Requires permeation through stratum corneum to achieve target engagement
Human clinical results via direct stick embolization, we deliver a pre-packaged, IV-compatible, drug solution to malformations

- Minimally invasive
- Avoids tissue toxicity of ethanol and detergents
- Targets the mutated molecular pathway directly
- Utilizes true and tried technique for intralesional drug delivery
- Maximizes culprit endothelial cell drug exposure
- Reduces systemic, non-target exposure
- Avoids repeat, daily dosing
- Reproducible
- On-going, in-human clinical experience
- Positive clinical AND radiographic follow-up up to 8-months
- Can be incorporated into a prepackaged formulation
  - Cost-reduction

MRI before and after embolization with temsirolimus shows lesion regression

Color-flow Doppler before and after embolization with temsirolimus shows flow cessation

Direct intralesional delivery of temsirolimus solution under ultrasound and fluoroscopic guidance
$150K to Optimize Formulation → ~12 months to pre-IND Meeting

- Validated Pathway
- Human clinical data on several patients
- IP for current formulations
- Clinical endpoints established

Blavatnik Support Deliverables Part 1:
- Formulation support ($150K)

12-15 months
Blavatnik Support Deliverables Part 2:
- Regulatory Support ($60K)
- Pre-IND Meeting ($60K)

15-18 months
File IND for Phase 2a

24-30 months
Analysis of clinical response

26 months
Interim indication of efficacy

✓ Commercial Interest:
  - Several confidential meetings with Pharma and biotechs
    - Preliminary human data is compelling.
    - Formalization of formulation and associated regulatory information to reduce investment risk

Partnering