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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ISSVA

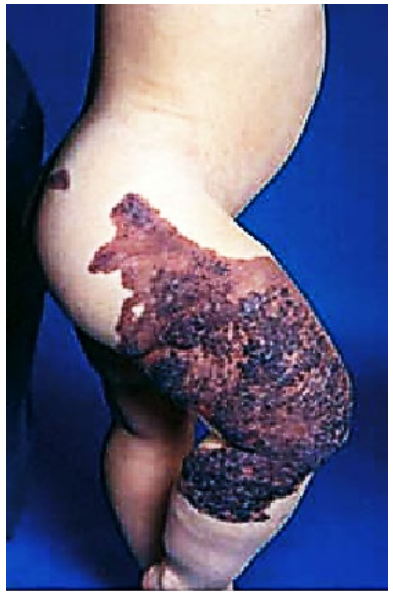
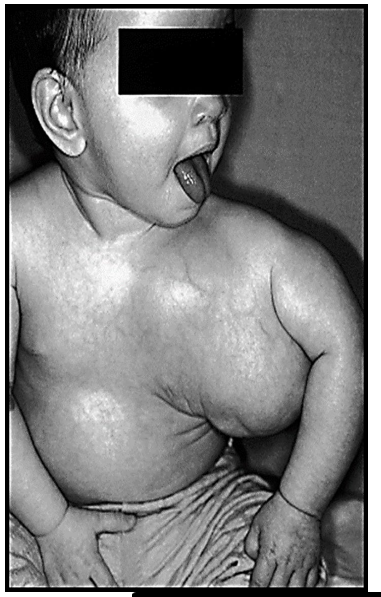
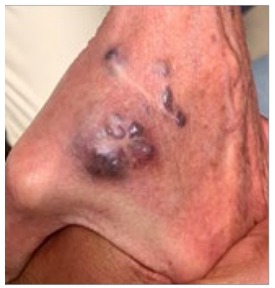
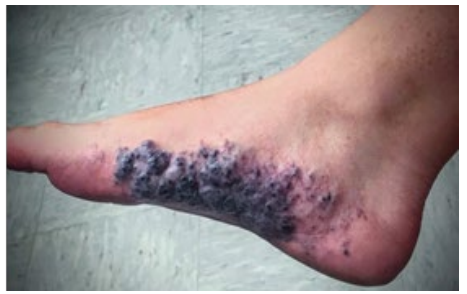
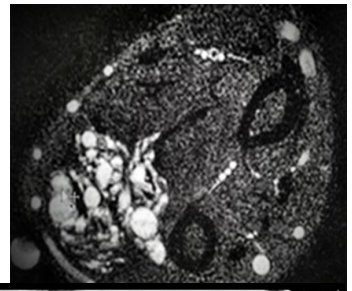
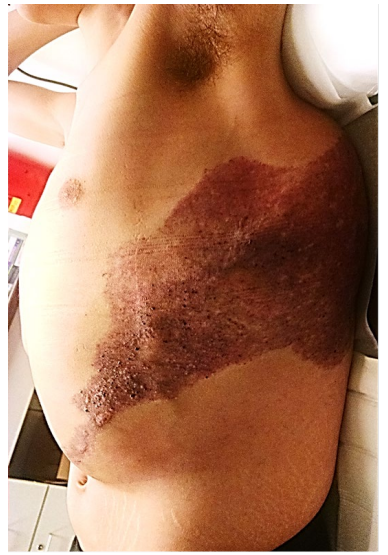
CLOVES SYNDROME COMMUNITY

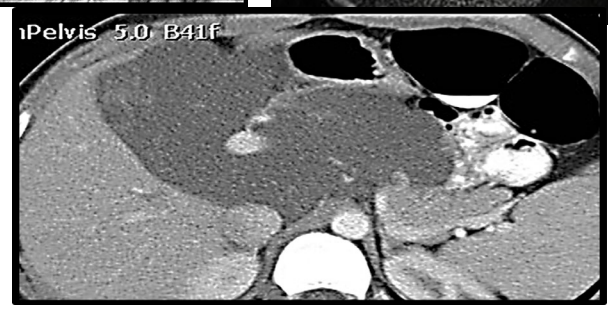
NORD® National Organization for Rare Disorders

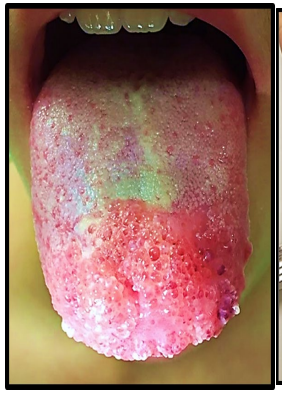
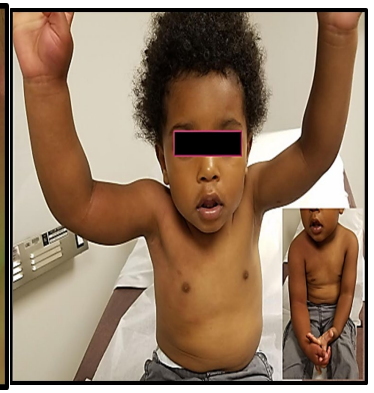
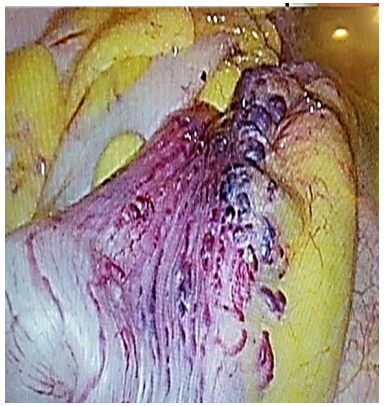
INTERNATIONAL SOCIETY FOR THE STUDY OF VASCULAR ANOMALIES

Venous and lymphatic malformations are morbid clinical entities

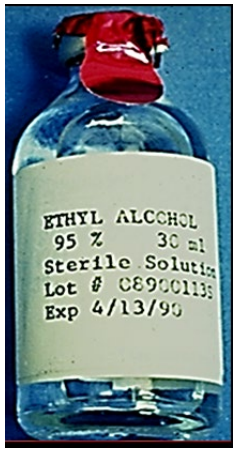
- Disease Outcome: Perpetual growth, pain, disfigurement, hematologic derangement, bleeding, infection, adjacent organ injury, venous thromboembolism, death
- Estimated US Population: 4 million
  - Likely underestimated due to decreased awareness

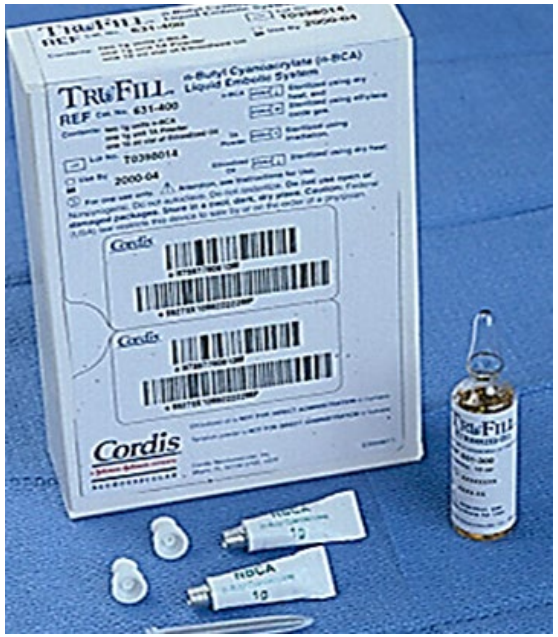







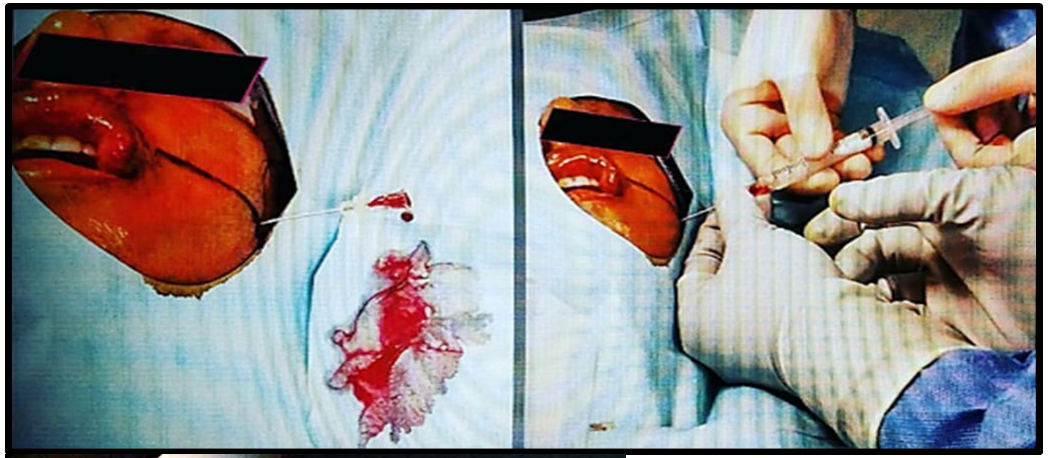



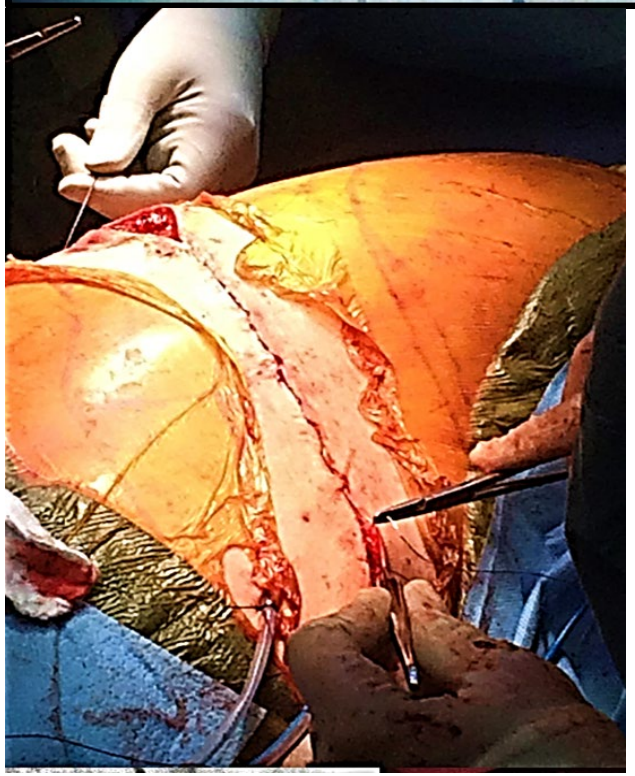




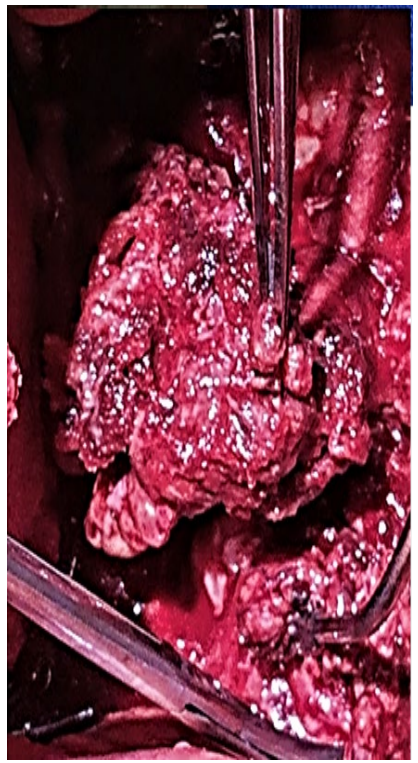
There is currently no disease modifying therapy





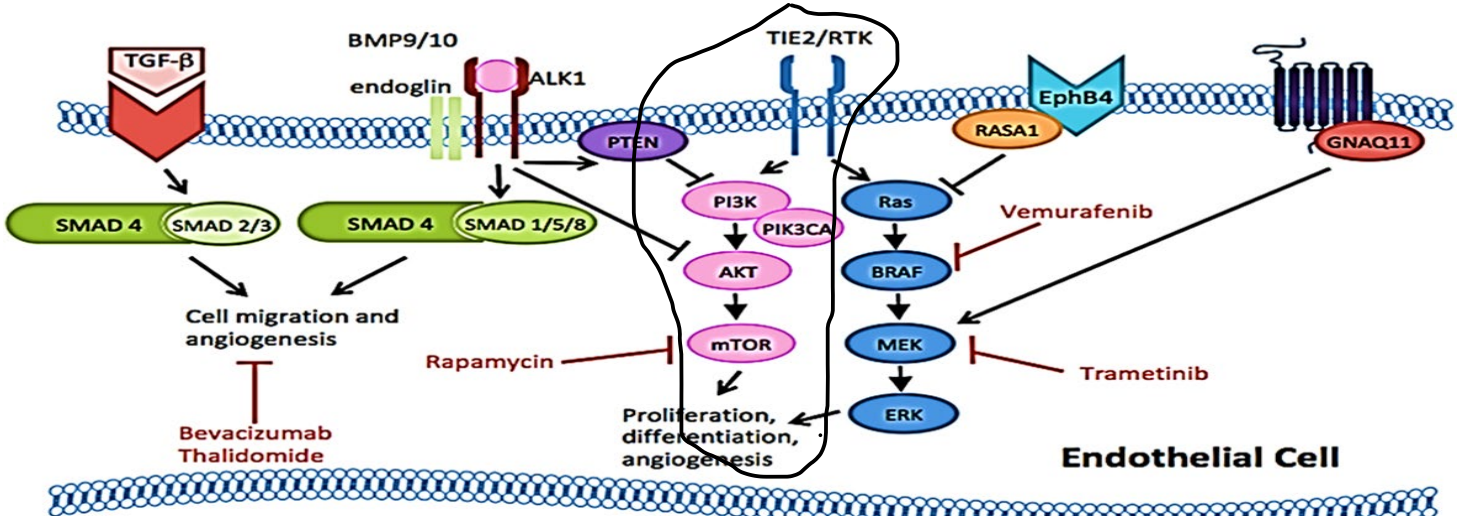






- Current therapies: surgery and/or embolization with off-label, toxic, and/or moderately potent agents
  - Cost to Treat per session: ~$25-50K (visits, imaging, surgery, embolic material
  - Mean ~2 sessions per patient
- Unmet Need: Current treatments do not target the underlying etiologic mutated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

mTOR pathway ubiquitously implicated in VM, LM pathogenesis



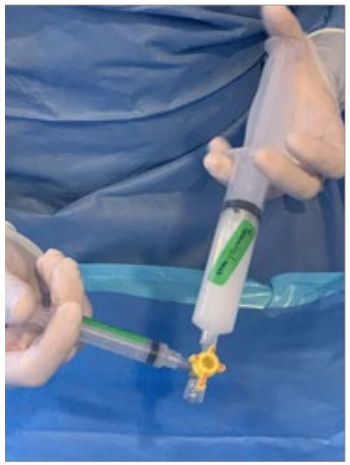
- Desired Biological Process: regression of vascular malformation via inhibition of the etiologic mutated pathway in affected endothelial cells
- Clinical Endpoint: Reduction in symptoms, size of lesion (detectable visually and/or radiographically [duplex ultrasound and MRI])
- Validity of Therapeutic Hypothesis:
  - Human: systemic oral sirolimus 82% partial or better regression
    - Daily dosing, frequent visits/blood draws, systemic exposure, side effects

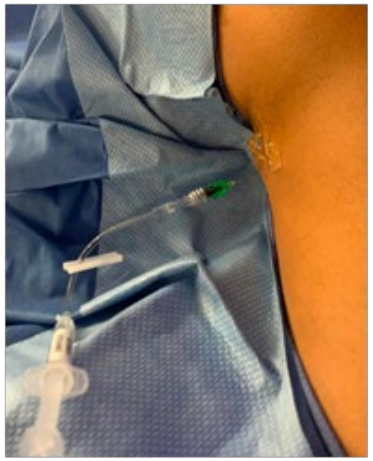
- Unmet Need: Current approaches do not target the underlying etiologic mutated molecular pathway (mTOR) > recurrence, reintervention
- Target: intralesional mTOR inhibition (mTOR pathway is mutated in venous and lymphatic malformations)
- Desired Biological Process: regression of vascular malformation 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])

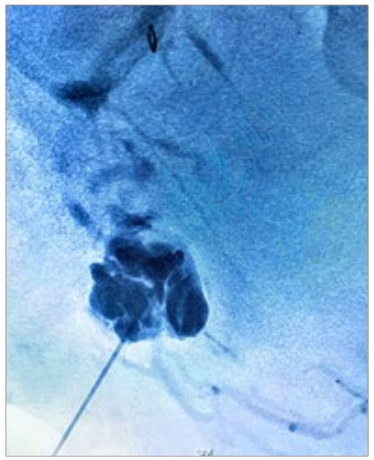
Current attempts being made at targeted therapy

- 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

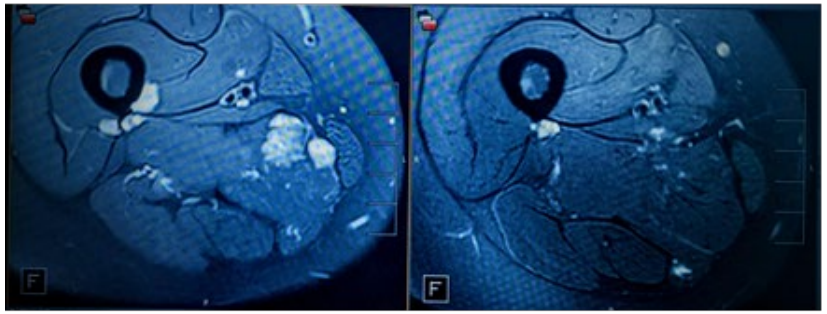
Human clinical results via direct stick embolization, we deliver a pre-packaged, IV-compatible, drug solution to malformations



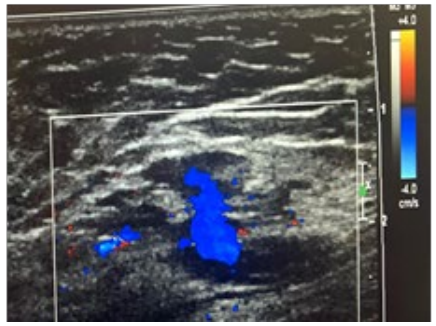


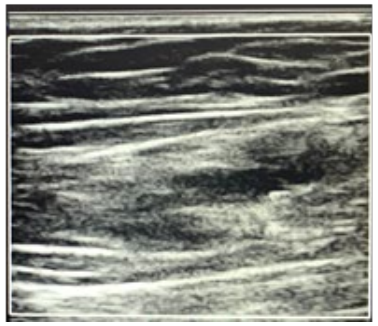


Direct intralesional delivery of temsirolimus solution under ultrasound and fluoroscopic guidance



MRI before and after embolization with temsirolimus shows lesion regression





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

- 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

$150K to Optimize Formulation → ~12 months to pre-IND Meeting

Now

- ✓ 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

26 months

Interim indication of efficacy

24-30 months

Analysis of clinical response

✓ **<u>Commercial Interest</u>**:

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

Partnering