Use newly discovered mechanism of intermediate filament assembly to develop topical vimentin assembly inhibitors that prevent and treat hypertrophic and keloidal scarring

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**Dermatologic & Aesthetic Need:**

An effective, targeted, and patient-friendly **topical** therapy for hypertrophic and keloid scars

- Common reason for dermatology visits, since hypertrophic or keloidal scarring develop in:
  - ~10% of all people
  - 5-15% of all wounds
  - 5-16% of all Blacks and Hispanics
  - ~38% of all burn patients

*Bolognia et al., *Dermatology*, 3rd Ed.*
Vimentin Intermediate Filaments Play a Central Role in Scarring

Vimentin regulates fibroblast proliferation, collagen production, and EMT-like differentiation

Vimentin expression correlates with keloid formation

The Problem

- There are no reliable, topical methods to prevent and/or treat hypertrophic and keloidal scarring.
- There are currently no intermediate-filament targeting drugs currently in medical practice.
We discovered a knob-pocket mechanism critical for intermediate filament assembly

**Key advance:** This knob-pocket interaction was previously unknown in its importance to intermediate filament assembly.

Develop **peptide therapeutics** that prevent and treat hypertrophic and keloidal scars by disrupting the vimentin cytoskeleton.

**The Product: Stapled Peptides**

**Advantages of Stapled Technology**
- Increased cell permeability
- Increased target affinity
- Decreased proteolysis
Market Opportunity for Topical Vimentin Assembly Inhibitors

The Market

- The global market for hypertrophic and keloid scar treatment was $4.8 billion in 2017 (Grand View Research)
- The global market for hypertrophic and keloid scar therapy is expected to reach $10.5 billion by 2026 (Acumen Research and Consulting)
- Topical vimentin assembly inhibitors could be expected to achieve ~$200-300 M USD per year based on this market analysis

<table>
<thead>
<tr>
<th>Competition</th>
<th>Topical Treatment</th>
<th>Specific Molecular Target?</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Corticosteroids</td>
<td>No</td>
<td>Risk of steroid atrophy; high cost of steroid-impregnated tapes; poor efficacy</td>
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<tr>
<td></td>
<td>Silicone</td>
<td>No</td>
<td>Poor efficacy</td>
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<tr>
<td></td>
<td>Retinoids</td>
<td>No</td>
<td>Poor efficacy</td>
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<tr>
<td></td>
<td>Imiquimod</td>
<td>No</td>
<td>Poor efficacy; risk of irritant contact dermatitis</td>
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<td></td>
<td><strong>Our Vimentin Knob-Pocket Inhibitor</strong></td>
<td><strong>YES</strong> – vimentin assembly</td>
<td></td>
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<tr>
<th>Non-topical Treatments</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Intralesional Corticosteroid</strong></td>
<td>No</td>
<td>Best efficacy to date, but requires repeated treatments, pain with injection, risk of steroid atrophy, risk of hyperglycemia in diabetics</td>
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<tr>
<td><strong>Intralesional 5-FU</strong></td>
<td>No</td>
<td>Not routinely used in dermatology clinic, pain with injection</td>
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<td><strong>Cryotherapy</strong></td>
<td>No</td>
<td>Painful, generates skin ulcerations, unrealistic for patients with numerous scars</td>
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<tr>
<td><strong>Radiation Therapy</strong></td>
<td>No</td>
<td>Not patient-friendly, risk of radiation-related adverse events, not practical if patient has numerous scars</td>
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<tr>
<td><strong>Laser Technologies</strong></td>
<td>No</td>
<td>Painful, expensive</td>
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Timeline, Milestones, and Budget

**Objective 1: $50,000**
- **Goal:** Evaluate effect of lead vimentin peptide inhibitor on fibroblast cell lines and compare to keratinocyte cell lines
- **What:** Characterize alterations in fibroblast and keratinocyte proliferation, apoptosis, and cell migration due to inhibition of vimentin cytoskeleton
- **How:** transient transfection technology; cell culture with inhibitor
- **Milestone:** Validate that inhibitor disrupts vimentin cytoskeleton and effectively reduces fibroblast proliferation and migration
- **Timeline:** Q3 2020

**Objective 2: $75,000**
- **Goal:** Lead optimization: Improve design of and synthesize stapled peptides for inhibiting vimentin cytoskeleton
- **What:** variety of “optimized” stapled peptides that are “knob” mimics and “pocket” mimics will be synthesized
- **How:** direct synthesis
- **Milestone:** Production of a set of optimized lead peptides for therapeutic screening
- **Timeline:** Q4 2020

**Objective 3: $75,000**
- **Goal:** Assess the effect of synthesized peptides on multiple fibroblast cell lines
- **What:** Identification of a specific, best lead therapeutic effective against fibroblast proliferation and migration
- **Desired endpoints:** reduced cell proliferation, enhanced apoptosis, and/or reduced cell migration
- **Milestone:** A specific ‘best’ lead peptide that reduces the viability of and cell migration potential of fibroblasts in scar tissue
- **Timeline:** Q1 2021

**Objective 4: $100,000**
- **Goal:** Evaluate ‘best’ peptide inhibitor of vimentin filament assembly in mouse model of keloidal scarring (NOG mice: Shang T et al. Int Wound 2018, 15(1)).
- **What:** Top performing peptide inhibitor(s) identified in Objective 3 will be tested for topical efficacy in mice with humanized keloids
- **Desired endpoints:** prevention of de novo scar formation and/or reduction in size and firmness of established keloids
- **Milestone:** Value Inflection point–targeted vimentin peptide therapy that topically treats scar formation
- **Timeline:** Q2 2021
Blavatnik Funding will enable the Bunick Laboratory to reach a Value Inflection Point with its technology. Specifically, first-in-class vimentin therapeutics will be positioned for Preclinical Investigation at the conclusion of this funding period.

Because the knob-pocket mechanism is utilized in multiple intermediate filament types (e.g. neurofilaments, keratins), Blavatnik Funding can position our technology for future use in other indications. The peptide technology may be leveraged into small-molecule discoveries for systemic use.