
http://s2.favim.com/orig/34/cute-dog-superman-Favim.com-272935.jpg

# D-Peptide Therapeutics: Empowering Nature's Fragile Warriors

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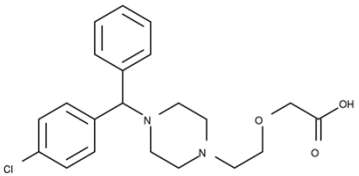
Disclosure
I have a stake in Navigen

# The Problem:
# Blocking Protein-Protein Interfaces

## Small Molecule Drugs

-cheap/easy to synthesize
-orally available




but…
-protein-protein interfaces are "undruggable"

## Biologics

-excel at disrupting protein-protein interfaces

but…
-expensive
-immunogenic
-bulky (slow/poor penetration)

## Peptides

-excel at disrupting protein-protein interfaces
-cheaper than Abs (synthetic)
-much smaller than Abs (more nimble)

but…
-short half-life due to proteolysis & filtration

## Our solution:

Mirror-image D-peptides

# ABC's of D-peptides

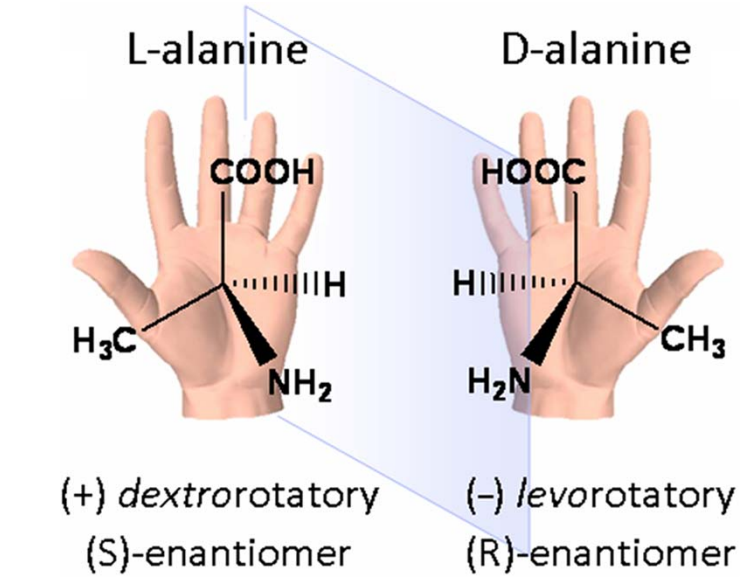
- D-amino acids are the mirror-images of natural L-amino acids

  -Not degraded by proteases

  -Enable less frequent/lower dosing

  -Reduced immunogenicity

- No examples in nature – so how do we design them?



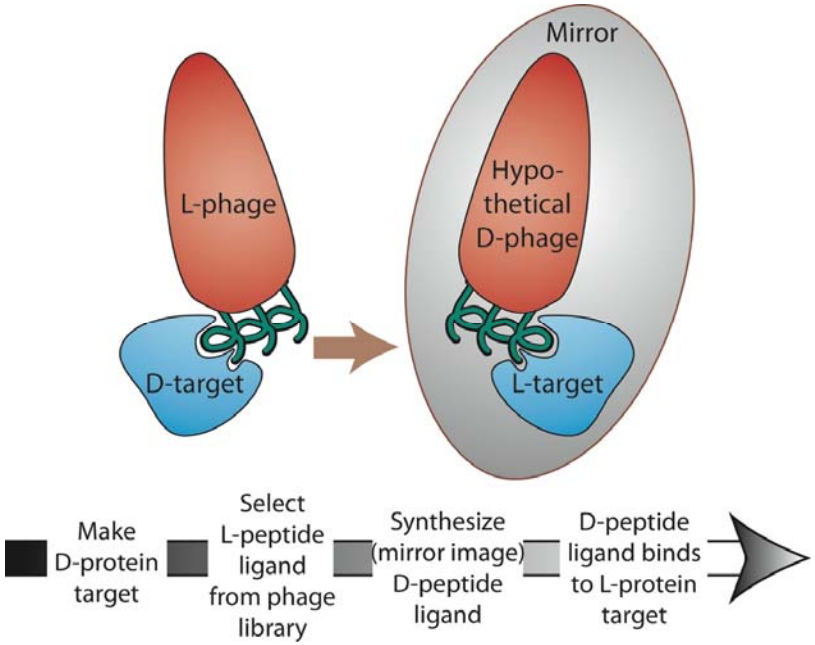

http://paleonerd.com.br/wp-content/uploads/2015/07/chirality-alanine.jpg

## Mirror-image phage display

-screens >$10^{10}$ peptide sequences

-requires chemical synthesis of D-protein target

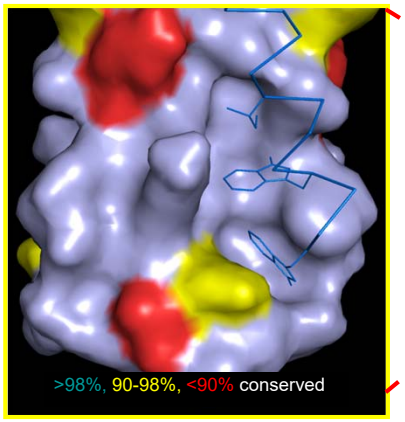
-hit optimization via structure-guided design & additional rounds of phage display

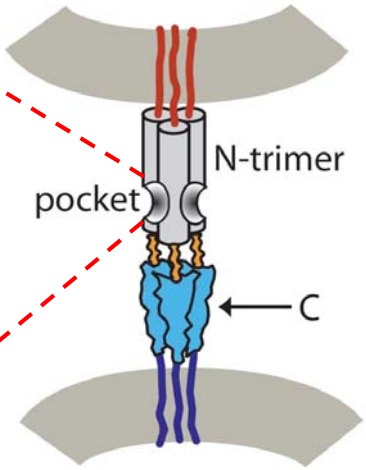


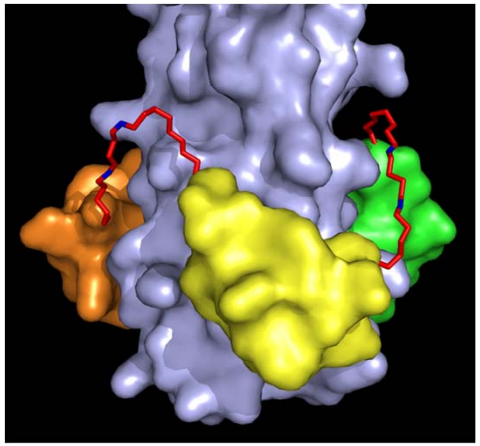

Schumacher et al. (1996) Science

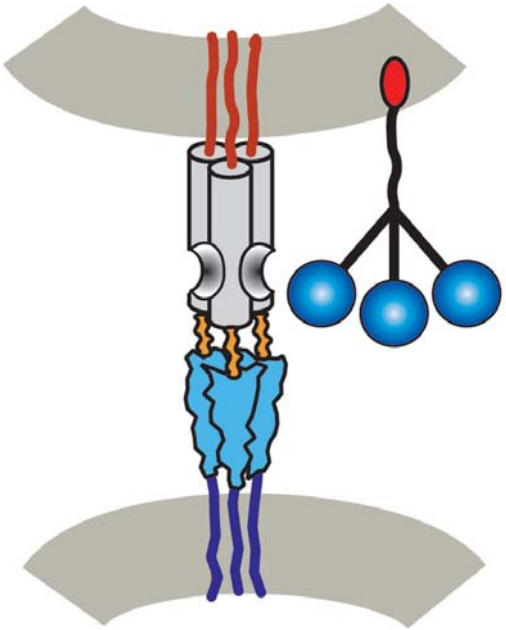
# From Idea to Lead: D-peptide HIV Entry Inhibitor

- The HIV “pocket” region is an ideal drug target
  - functionally essential and highly conserved
  - undruggable by traditional small molecule approaches
- PIE12 (Pocket-specific Inhibitor of Entry) is our optimized D-peptide
- PIE12-trimer has three D-peptides connected by a flexible PEG linker
- Potent inhibitor against all major HIV clades
- Conjugation to cholesterol further improves potency by >100-fold (low pM)





PIE12-trimer binding to three pockets

**Lead Inhibitor:**

cholesterol-conjugated PIE12-trimer (CPT31)

# How to advance a lead to a drug?

KAYAK BIOSCIENCES


http://activerain.com/image_store/uploads/agents/jeffrelc/files/iStock_000021267657Large.jpg

SBIR/STTR
SMALL BUSINESS INNOVATION RESEARCH
SMALL BUSINESS TECHNOLOGY TRANSFER

SBIR review: “The PI has limited experience in the development of a pharmaceutical drug”

SBIR resubmission review: “It also appears the team might be too highly qualified”

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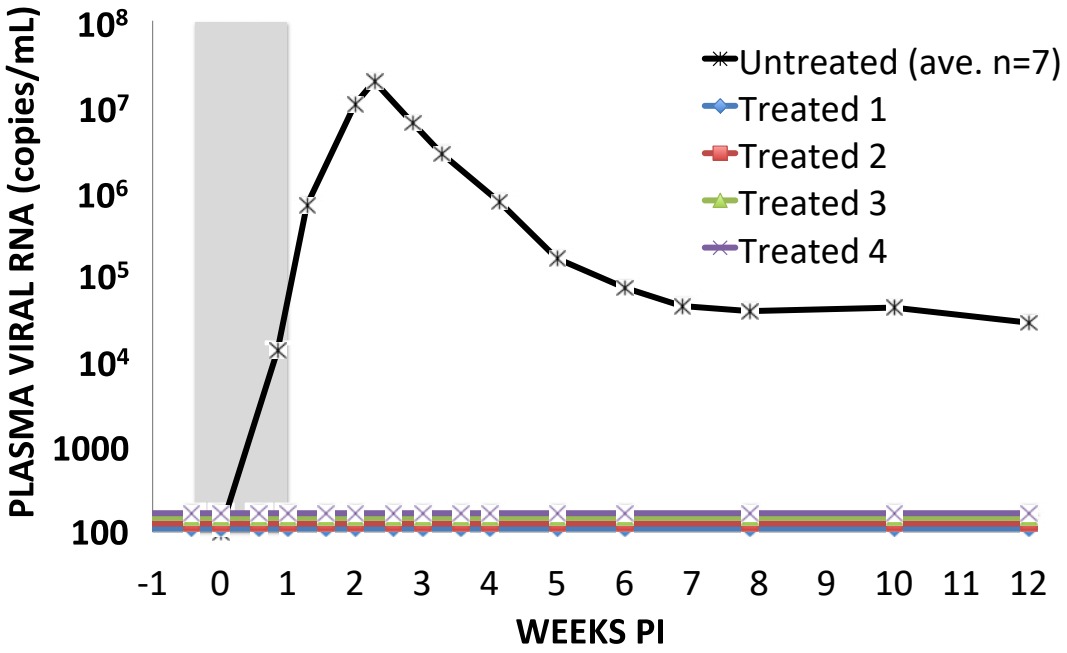
>$15M in NIH grants to date (mostly SBIR)

# In Vivo Efficacy: CPT31 Prevents Infection in NHPs

(with Yoshiaki Nishimura & Malcolm Martin, NIAID)

- 100% infection rate in 7 untreated controls
- No infection with 3 mg/kg/day dosing
- No infection with 0.5 mg/kg/day upon repeat challenge
- 1/4 animals protected with 0.125 mg/kg/day

## Four Animals Treated Showed No Viremia in Two Consecutive Prevention Studies




All values for treated animals are below the detection limit (100 copies/mL), curves staggered for clarity

# D-peptide Development
# Three Avenues

## PrEP

- Systemic agent for prevention of HIV
- Targeting monthly subcutaneous dosing

## Treatment

- Systemic agent for treatment of HIV
- Targeting monthly subcutaneous dosing
- Ideal for treating drug-resistant strains

## Microbicide

- Topical agent for the prevention of HIV
- Vaginal/rectal mucosa are hostile environment for traditional peptides
- Protective in human vaginal & rectal explants
- Ideal for formulation in monthly vaginal ring

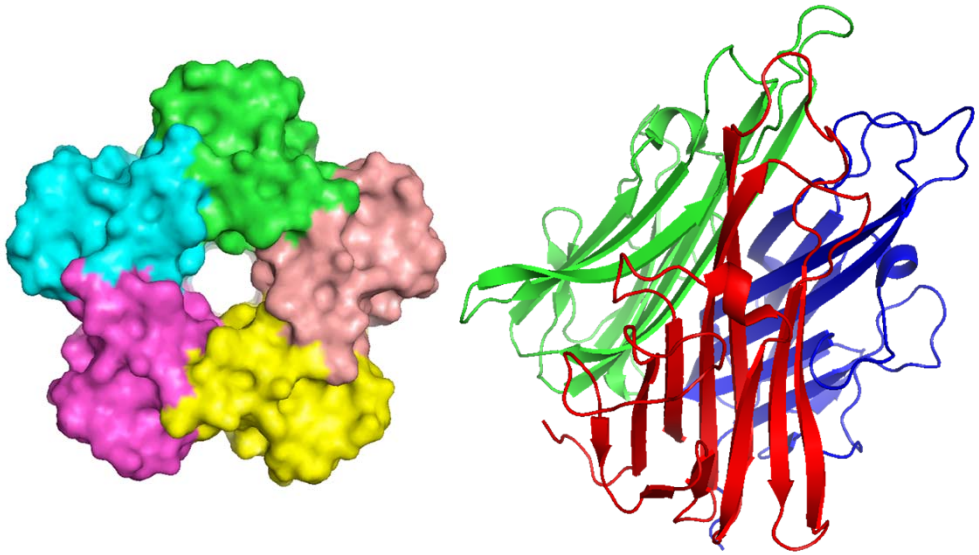
## Cost estimate

- Estimate ~500 mg/year for systemic uses ($50)
- Estimate ~50 mg/year for topical uses ($5)

# Future Directions

- Depot formulation
- Fundraising for phase I trial
- Application to other viruses (RSV/Ebola)
- Application to LARGER targets...

•"Gutsy" targets (oral-topical)
  -TNF-α (IBD)
  -Shiga toxins
•Ongoing development of chemical tools to address bottlenecks in D-protein synthesis




Helping Hand (solubilizing tool)

Aligator (automated ligator)

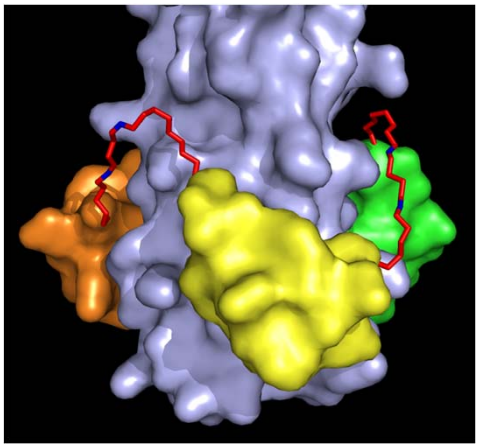
*D. coli*

http://www.adweek.com/digital/wave-goodbye-to-hamburger-helper-or-at-least-the-hamburger-part/

http://www.ren-ex.com/wp-content/uploads/2011/11/3931203_thumbnail.jpg

# Summary

- D-peptides are a potentially transformative new drug class
  - Excel at blocking protein-protein interactions
  - Insensitive to digestion, minimal immunogenicity
  - Greatly reduced dosing/cost, ideal for depot formulation
- We have developed an efficient D-peptide drug discovery plaform
  - Combining expertise in virology, protein design, peptide chemistry, and structural biology
  - Industrial partner experienced in drug development
  - Early-stage input from clinicians
- Our lead HIV D-peptide is effective in monkeys and poised for human trials
- Our ongoing peptide chemistry research is expanding D-peptide drug discovery to larger targets



Clinical Consultants

Adam Spivak (HIV)

Carrie Byington (RSV)

Daniel Leung (Shiga)

John Valentine (TNF)

# Enterprise Take-Home Messages

- Drug development requires professional help
  - No individual group has all of the required skills, experience, and resources (IP, $, FDA, pharma contacts)
  - Academic grants
    - ideal for target ID and drug discovery
    - suboptimal for subsequent drug development (high cost/low innovation)
  - Starting shell companies is not productive

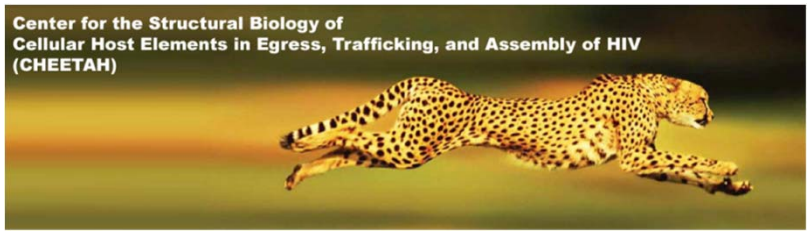
- SBIR/STTR grants are a vital (but underutilized) lifeline
  - Need affordable biomedical incubator space
  - Need experienced business partners

- Academic labs and startups have a symbiotic relationship
  - Excellent science benefits from the validation provided by translation
  - Startup companies need the ongoing engagement of inventors

# THE D TEAM


## Funding

AI76168 (R01), AI95172, AI102347, AI98197, AI120414 (SBIR), GM82545 (P50), DoD Discovery Award











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