NuvoBIO
Intellegent peptide design

DARWIN: An evolution-inspired algorithm for target-specific peptide inhibitor engineering

What is DARWIN?

DARWIN is a genetic algorithm that can evolve target-specific peptide binders using sequence information. **Darwin** can generate (1) binding/ therapeutic, (2) anti-viral/ microbial, and (3) target/delivery peptides.

Case Study 2: Can DARWIN converge on the peptide sequence of an FDA approved therapeutic peptide?

An experiment was designed to determine if **DARWIN** can independently reconverge on a peptide that contains significant homology to an FDA approved peptide. Nesiritide peptide was chosen for this study as a highly specific for Natriuretic Peptide Receptor (NPR) 1-3 with established clinical implications. **DARWIN** works by designing *de novo* binding peptides based on large datasets of protein interaction information and evolving these peptides *in silico* over multiple generations to obtain the fittest peptides that prioritize target selectivity.

- *Nesiritide is an FDA-approved peptide for the atrial NPR1-3 target (2001)*
- *Nesiritide is therapeutically used for the treatment for congestive heart failure*
- *Relatively long linear B-type natriuretic peptide; 32 amino acids*
- *Indicated for intravenous delivery; established 18-minute half-life*

Mechanism of Action

Nesiritide binds to the NPR guanylate cyclase receptor of vascular smooth muscle and endothelial cells, leading to increased intracellular concentrations of guanosine 3'5'-cyclic monophosphate (cGMP) and smooth muscle cell relaxation. Cyclic GMP serves as a second messenger to dilate veins and arteries. *Nesiritide* has been shown to relax isolated human arterial and venous tissue preparations that were precontracted with either endothelin-1 or the alpha-adrenergic agonist, phenylephrine. In human studies, *Nesiritide* produced dose-dependent reductions in pulmonary capillary wedge pressure (PCWP) and systemic arterial pressure in patients with heart failure. In animals, *Nesiritide* had no effects on cardiac contractility or on measures of cardiac electrophysiology such as atrial and ventricular effective refractory times or atrioventricular node conduction. Naturally occurring atrial natriuretic peptide (ANP), a related peptide, increases vascular permeability in animals and humans and may reduce intravascular volume. The effect of Nesiritide on vascular permeability has not been studied.

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NRRYPTTSKMVQRSGCFGRKMDRIGSLKGENM (Darwin peptide)
        |||| |||||||||||  |   |
------SPKMVQGSGCFGRKMDRISSSSGLGCKVLRRH (Nesiritide)
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DAWIN was able to design *de novo* peptides that specifically target NPR1 (target rank 1), NPR2 (target rank 2), and NPR3 (target rank 3). The peptide sequence of the top-ranked anti-NPR1 peptide is shown (above) along with sequence homology to Nesiritide. **DARWIN** successfully designed an *in silico* target-specific anti-peptide that converges on the Nesiritide sequence using independent training data. This data demonstrates the ability of **DARWIN** to identify key principles of highly-specific peptide interaction and then apply this information towards the convergence of new *de novo* peptide inhibitors for therapeutic development.

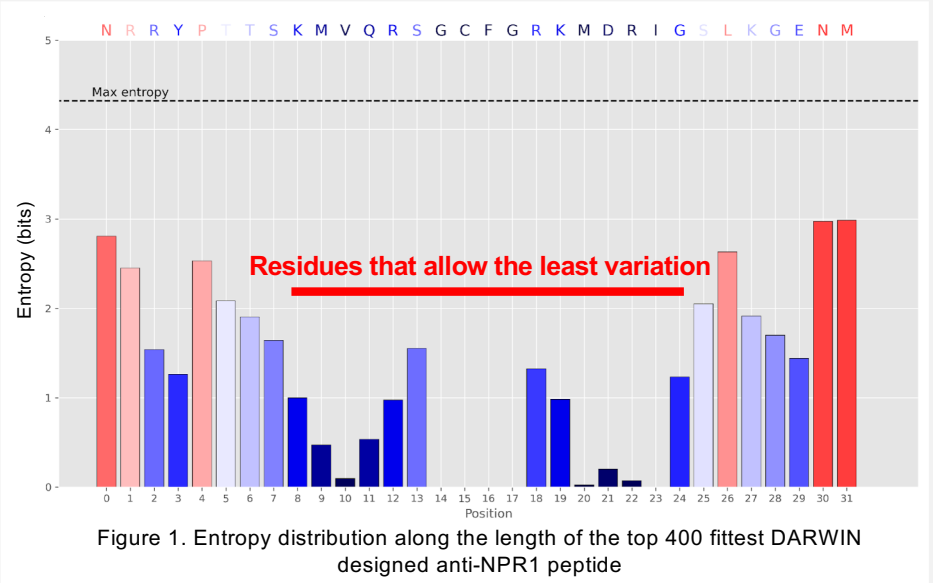

Figure 1. Entropy distribution along the length of the top 400 fittest DARWIN designed anti-NPR1 peptide

From it's top 400 fittest peptides, **DARWIN** converges on a specific region (i.e., residues with the least sequence variation) of anti-NPR1 peptides. Notably, this region shows the greatest homology to the *Nesiritide* peptide. These results demonstrate the capability of **DARWIN** to identify functional regions of peptide therapeutics for *de novo* design and focus peptide evolution on these regions of interaction over multiple generations.

For complete study information, please reference:

Charih *et al.* (2022) Assessing sequence-based protein-protein interaction predictors for use in therapeutic peptide engineering (2022). *Scientific Reports* 12(9610), 1-13.