EVINCE Biosciences

Reimagining Drug Discovery Through Artificial Intelligence

AVO – Next Generation Drug Discovery Platform

Simply stated, without a dramatic increase in R&D productivity, today's pharmaceutical industry cannot sustain sufficient innovation to replace the loss of revenue due to patent expirations for successful products (Nature Reviews, March 2010).

AVO (Autonomous Virtual Organism) employs **contemporary computational techniques and machine learning** to modernize drug discovery – it is extraordinarily powerful and disruptive. AVO's underpinnings come from structural biology and computational chemistry rather than systems biology.

The platform accurately predicts activity, toxicity and drug-like properties (ADME) **simultaneously**. This means millions of molecules can be screened against…

- The target of interest
- Counter-screens to determine selectivity
- ADME filters to identify "drug-like" leads

AVO applies **virtual medicinal chemistry** to optimize leads that result from an initial screen. New molecules are designed based on the drug-like leads and evaluated in AVO. AVO algorithms can predict which chemical changes provide an advantage and prioritize the molecules to be synthesized. A few rapid cycles of intensive **in silico compound optimization**, synthesis and testing replace the many cycles of synthesis and testing required by the traditional drug discovery processes. The AVO paradigm, therefore, requires far less time and money.

AVO has a dramatic economic impact on the drug discovery process. Reduction in cycle time and cost through discovery and lead optimization can lower the capitalized cost by 63%, based on Evince's analysis of a pharmaceutical productivity study published in Nature Reviews (March 2010). For a biotech company, lower cost enables prosecution of more molecules in parallel and higher probability of success. (Full analysis is available)

Partner Proof of Concept. AVO has worked with two partners and recently signed a third deal. With one partner, AVO analysis successfully identified 8 of the 10 most potent compounds from the partner's proprietary library. Further, AVO analysis suggested novel starting points that could be used in a possible back-up program.

In a second on-going collaboration, AVO was used to screen Evince's library of repurposing candidates against an undisclosed target. The prioritized molecules are in the process of being screened by our partner. If a molecule is found that reasonably affects the target, the partner can initiate Phase 2 studies with a compound that has a known safety profile.

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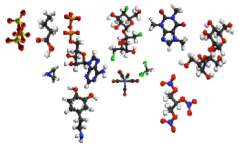
[1]ADMET = Absorption, Distribution, Metabolism, Excretion, Toxicity

The Approach…

Virtual biological simulations generate 25,000 descriptors to "fingerprint" molecules



Molecules are used for
1. Building a library
2. Training a target

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"Train" a target with known active and inactive molecules that have been fingerprinted 

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AVO uses **machine learning** to determine what makes molecules active and inactive.

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Screen a very large library of fingerprinted molecules against the target and ADMET[1] filters to find "drug-like" leads.

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Apply AVO medchem to optimize leads and find **preclinical candidates**

- AVO finds actives, not binders.
- AVO does not use target crystal structures

Partnering

Evince will engage in multiple types of partnerships, including (a) screening client targets and libraries, (b) collaborations, (c) repurposing projects, (d) co-discovery deals with shared risk, and (5) joint ventures. Projects may focus on a single target or a "franchise" such as cystic fibrosis or diabetes, as examples. Evince will also develop internal projects that will be partnered when animal proof of concept is generated.

Evince is interested in accessing novel biology. Application of AVO can add value quickly to projects through lead optimization.

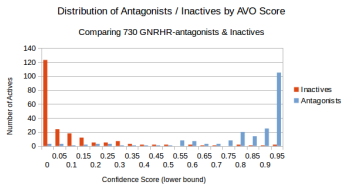
GnRH Example

The GnRH example demonstrates (1) training of the GnRH receptor, (2) screening approved drugs, (3) screening novel compounds, and (4) using ADMET filters to identify "drug-like" novel compounds. The **"repurposing screen"** tested 1293 FDA drugs. The **novel compound screen** tested over 750,000 compounds and resulted in 613 novel actives with an AVO score of 0.90 or higher. These 613 actives were "filtered" through two **ADMET screens** (human intestinal absorption and plasma protein binding) to narrow the focus to 62 actives. Additional ADMET filters can be applied as appropriate and desired. **Elagolix** was used as a reference molecule and received an AVO score of 0.989 (out of 1). This is expected for a molecule that has been optimized for activity against the GnRH receptor.

The human intestinal absorption filter used in the GnRH example is compelling because Caco-2 cells are normally used to predict human intestinal absorption, but this assay only reliably discriminates poorly permeable from highly permeable compounds. Evince has been able to "train" the human intestinal absorption prediction into AVO (the core technology) to **directly predict intestinal absorption in vivo** – this is a significant improvement on the Caco-2 test.

1 Train the GnRH Target

Train the GnRH receptor with a mix of known active and inactive compounds to enable AVO to recognize actives and inactives in compound libraries.



The histogram shows the accuracy of the training at a threshold of an IC50 <10nM. Known active compounds (blue) should be at an AVO score toward "1". Known inactives should be toward an AVO score of "0". Based on the training, compounds with an IC50 of 10 nM or better will be identified.

2 Screen Approved Drugs

Evince can screen approved drugs or compounds that have been "placed on the shelf" because of poor efficacy in clinical trails. In this repurposing screen, AVO evaluated 1293 FDA-approved drugs. The top five scores ranged from 0.9294 to 0.8517. Two of these drugs have literature links to beneficial activity in endometriosis and two have links to endometrial cancer.

Compound	AVO Score
EV000001	0.9294
EV000002	0.9201
EV000003	0.9138
EV000004	0.8630
EV000005	0.8517

Elagolix (Phase 3) received an AVO score of 0.989.

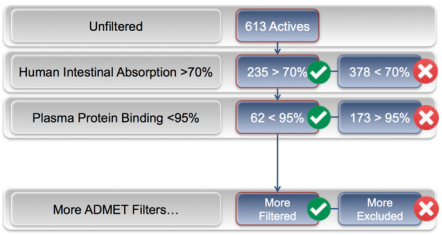
3 Screen Novel Compound Library

775,361 compounds were screened against GnRH by AVO, resulting in 613 compounds with an AVO score of 0.90 or better. Compounds with a higher AVO score have a higher probability of meeting the threshold IC50<10 nM.

These 613 compounds can be "filtered" through ADMET screens

4 ADMET Filters

Two ADMET filters were applied in AVO to the 613 novel compounds. This resulted in 62 compounds with the combination of (a) 0.90 or better AVO score for GnRH and (b) acceptable scores in the ADMET filters.



AVO enables selection of compounds that are active against a target and have drug-like characteristics.