A Case Study of AI Applied to ALS Drug Discovery

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BenevolentAI

- 5-year, $200M investment into unique & proprietary Knowledge Graph built for the biomedical domain
- 200 life scientists, AI researchers, informaticians work side by side across 4 locations
  - 81% scientists
- Cross-functional squads organised for rapid experimentation, innovation and feedback loops
- Technology validated by scientific experimentation
The BenevolentAI Knowledge Graph

1 billion + relationships ingested, integrated and accessible through a domain and user-centric API layer.

Over a third of unique disease and target edges are algorithmically derived from unstructured data and proprietary.

Unstructured data
- 140mn documents
- 1bn relationship edges

Structured data
- 30mn structured relationships
- 3bn omics data points

Patient level data
- 400bn public/commercial data points
- 1mm partner/programmed data points
The BAI Platform - End to End Drug Discovery

**The Right Foundations**
- Benevolent Knowledge Graph including algorithmically derived new knowledge

**The Right Drug Target**
- Underlying mechanisms of disease for hypothesis generation and target identification

**The Right Drug**
- AI-augmented molecular design to design the most effective drug more efficiently

**The Right Patient**
- Patient stratification and homogeneous patient subgroups to design better clinical trials
ALS - *Target ID*
Amyotrophic Lateral Sclerosis (ALS)

- Cognitive impairment
- Behavioural impairment
- Dysphagia
- Dysarthria
- Respiratory insufficiency
- Muscle cramps
- Spasticity
- Muscle weakness
- Muscle atrophy

Median survival is ~3 years with no effective treatment.

Nat Rev Dis Primer 3, 17071 (2017)
Amyotrophic Lateral Sclerosis (ALS)

Non-cell autonomous

~35 Associated Genes

85% of patients do not have mutations in known gene
Direct conversion of patient fibroblasts demonstrates non-cell autonomous toxicity of astrocytes to motor neurons in familial and sporadic ALS. [PNAS 111, 829-832 (2014)]

Assay tackles the clinical heterogeneity up front.
Hypothesis Generation - First Iteration
Nilotinib Rescued Motor Neurons In Coculture
ABL Inhibition is not Sufficient for Robust Rescue
Nilotinib as a Tool Molecule

- ABL assays
  - $pIC_{50}$ (Biochem) = 8.0
  - $pIC_{50}$ (Cell) = 7.5

- Poor Properties
  - Highly Insoluble
  - Moderate Clearance
  - $cLogP$ = 6.4

- Nilotinib has some Safety Liabilities
  - HERG $pIC_{50}$ = 6 ($\&$ QT Prolongation in Clinic)

- Low brain exposure
  - $Br:Pl$ = 0.2
  - $Kpu$ = 0.03

ALS - Chemistry Optimisation
The Complex Process of Drug Design

- Safety
- Efficacy
- PK
- Developability
- Patentability

It is iterative, slow, and expensive:
- 3-4 years
- 100s molecules

Inside the Mind of a Medicinal Chemist

How to improve R&D productivity, the pharmaceutical industry's grand challenge: Art Rev Drug Disc 9

BenevolentAI Proprietary
The Complex Process of Drug Design
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The Complex Process of Drug Design

- Safety
- PK
- Efficacy
- Reliability
- Developability

BenevolentAI Proprietary
EvoChem - Chemist augmentation, not replacement

EvoChem no preconceptions and extrapolates from vast datasets vs Scientists plenty of preconceptions

- BUT... preconceptions and experience are 2 sides of the same coin. Some bias is good
- Both scientists and algorithms use related but distinct criteria to assess compounds

We combine the best of both

- All EvoChem structures can be augmented by chemists and rescoring with the MPO
- Scientist feedback is provided to EvoChem (vetted structures, project data)

The interplay between algorithms and scientists is key - the best results come from a hybrid approach
Drug Design - powerful products and methods

Scientists

Synthesis planner
Find the best way to make your molecule

Ligand based models
Predictive Modelling for Multiple Experimental Endpoints

Novelty models
Explore novel Markush space

Structural models
Augmenting ligand based models with AI based structural design

All products are used by both EvoChem and scientists to power drug design.
Predicting Activity

**pIC50: % predictions within 0.5 Log units (n = 24)**

- Human 1
- Human 2
- Human 3
- BA 2D
- BA 3D
- Random number (-1)

- **Train**
- **Test**

**Metrics:**
- R²: 0.99
- MAE: 0.00
- RMSE: 0.00
Chemistry Progress

- Lead Exploration: ~30 Compounds
- Scaffold Hopping: ~35 Compounds
- DFG-Loop Binders: ~15 Compounds

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Time to First Registration: 4 Months

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Lead Profiling

Nilotinib

**ABL (Biochemistry) pIC$_{50}$:** 8.0

Molecular Weight: 344
Ligand Efficiency: 0.42

**ABL Cell (BaF3) pIC$_{50}$:** 7.5

SITraN ALS Patient Coculture pEC$_{50}$: 7.0

**hERG pIC$_{50}$:** <5

Lots of related IP

BenevolentAI Proprietary

BEN-XX1

**ABL (Biochemistry) pIC$_{50}$:** 7.9

Molecular Weight: 530
Ligand Efficiency: 0.29

**ABL Cell (BaF3) pIC$_{50}$:** 7.1

SITraN ALS Patient Coculture pEC$_{50}$: 7.3

**hERG pIC$_{50}$:** 6

 Lots of related IP

Patent application prepared

BenevolentAI
ALS - Precision Medicine
Translational Medicine Strategy

Patient cohort

Multi-modal omics data

Longitudinal clinical observations

ML models applied to high-dimensional datasets

Disease trajectories

Latent variable models

Map latents to Patient stratification

Patient endotypes

Novel therapeutic targets

Clinical trial design
Summary and Next Steps
Summary and Conclusions

**THE RIGHT DRUG TARGET**
We have built workflows that traverse the Knowledge graph to find key biological nodes.

**THE RIGHT FOUNDATIONS**
We are learning what works, and what doesn't. Everything is validated in the lab.

**THE RIGHT DRUG**
We have built tools designed to make the most of scientists AND algorithms. We are using these to design better molecules faster, aiming for Lead to Candidate selection in <12 months.

**THE RIGHT PATIENT**
We hope to balance arms based on progression. The ultimate goal is identification of responder endotypes. Access to data is key.
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