#### **Benevolent**<sup>Al</sup>

# Language models for target prioritisation

Genome-wide | Multimodal | Explainable

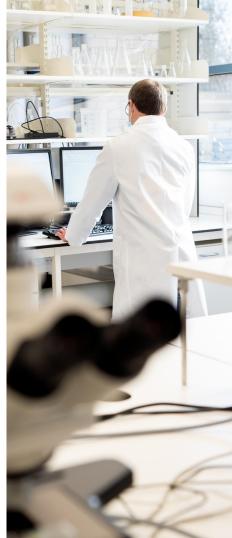
Ravi Patel | July 16, 2023

BenevolentAI | ravi.patel@benevolent.ai

Oxford Machine Learning Summer School







# **Contents**

- Drug discovery and BenevolentAl
- Drug discovery biologist's approach
- Masked-language modelling approach

Evidence synthesis with attribution approach

Large-language models: What role do they have?

# Drug discovery & BenevolentAl

## Huge burden on society demands a new approach

failure rate in clinical development

in average R&D and to market cost per drug

to market

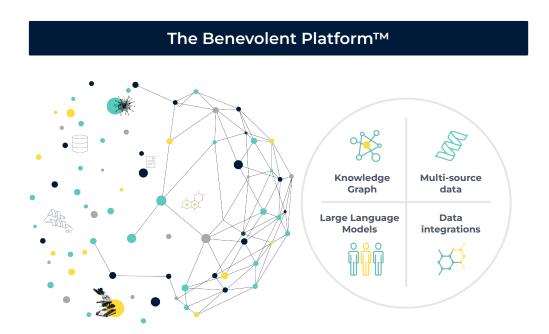
10 years 30-50%

of patients respond poorly to leading drugs

Gaining a clear understanding of the underlying molecular mechanisms of disease based on the totality of available biomedical data is a vital step in the development of successful and efficacious treatments

## BenevolentAl develops technology in the service of science

BenevolentAl applies deep expertise in developing **biology-specific Al models**, including sophisticated and **comprehensive data foundations** and **NLP**, to enable novel biomedical discoveries.



#### **COMMERCIAL VALIDATION**

**5 novel targets** selected for **AstraZeneca's** portfolio

#### **REGULATORY VALIDATION**

**FDA approval** of **COVID-19 treatment** identified by BenevolentAl

#### **SCIENTIFIC VALIDATION**

Robust wholly owned drug pipeline

### Data modalities

#### Patient-level data

Omics, genetics, clinical data etc.



#### **Unstructured Literature**

Millions of ingested full-text biomedical publications.

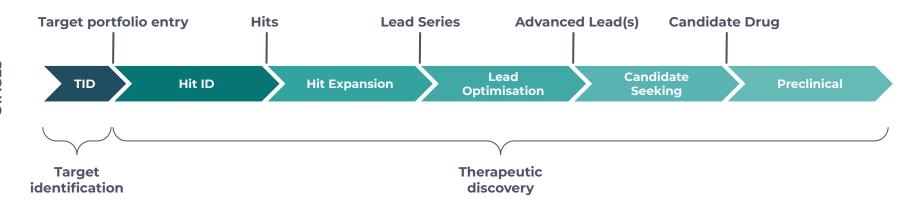


#### **Knowledge Graph**

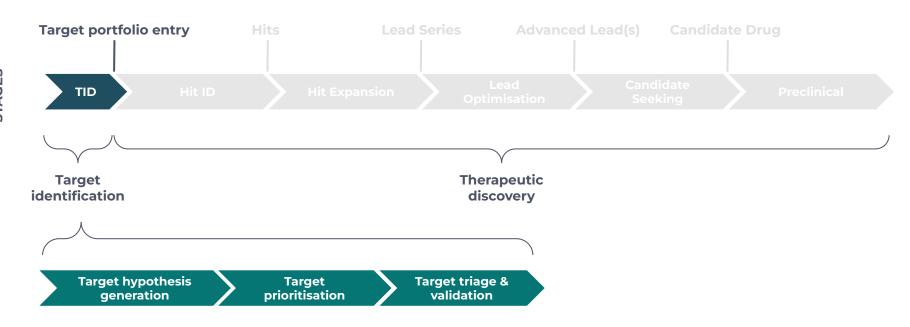
A large-scale biomedical knowledge graph combining patient-level data, literature and structured sources.



# Early stages of drug discovery

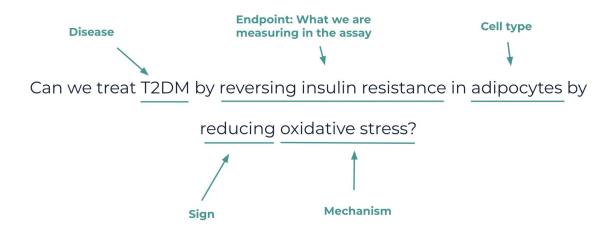


# Early stages of drug discovery



# Target hypothesis generation

Drug discovery biologists explore our data and **define strategic hypotheses** aligned with assay strategies to use as inputs into our Al models and custom data queries







Target Prioritisation



Target triage and Validation

# Target hypothesis generation



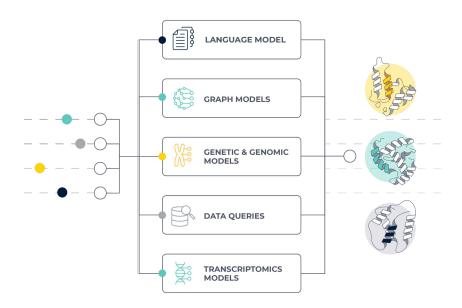
Target
Prioritisation



Target triage and Validation

# Target prioritisation

Our **models** combine our large literature corpus, knowledge graph and patient data to predict which targets are the most **efficacious** and **progressible** for the user's biological context



# Target hypothesis generation



Target Prioritisation



Target triage and Validation

## Target triage & validation

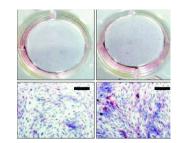
Biology and chemistry expert **triage of targets** for biological relevance and suitability for portfolio entry

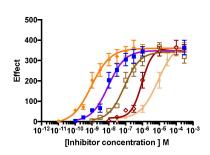
Shortlisted targets are validated in **assays** 



Triage

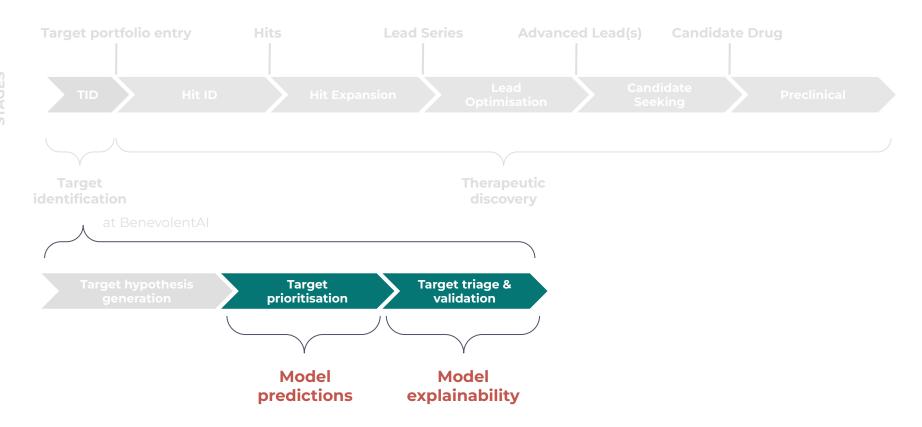






**Validation** 

## Our focus today: Target prioritisation and validation



# Drug discovery biologist's approach

Drug discovery scientists:

 Can integrate multiple tradeoffs and evidence from different data modalities, but can only consider a limited number of targets



Drug discovery scientists:



Can integrate multiple tradeoffs and evidence from different data modalities, but can only consider a limited number of targets

	<b>Tradeoffs</b> Disease relevance	Data modalities	
		Literature	
	Mechanism relevance	Patient-level data	
	Novelty	•	Genetics Expression
	Expression	•	Differential
	Assayability		•••
	•••	Knowledge graph	
		•••	

expression

Drug discovery scientists:

- Can integrate multiple tradeoffs and evidence from different data modalities, but can only consider a limited number of targets
- Gain deep insight from papers and datasets, but can only look at a limited number



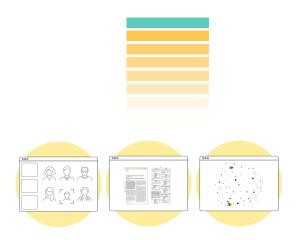
#### Drug discovery scientists:

- Can integrate multiple tradeoffs and evidence from different data modalities, but can only consider a limited number of targets
- Gain deep insight from papers and datasets, but can only look at a limited number



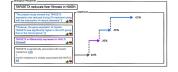
 Could be complemented by model-based prioritisation, but have a strong requirement for explainability

## Target prioritisation model wishlist



Genome-wide predictions (relevant and novel)

Reason from multiple data modalities



Explainable predictions

# Masked-language modelling approach

- Direct and indirect evidence
- User workflow
- Model setup: Training, inference, post-processing
- Explainability

# Direct and indirect evidence

# Levels of insight from the literature

Simple Pattern Matching

Semantic Awareness



# Levels of insight from the literature

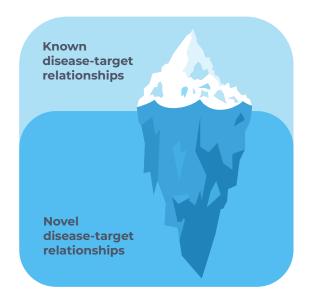
# Simple Pattern Matching

Identify direct relationships between target and disease

E.g. **NTRK1** and **atopic dermatitis** co-occur in many papers

→ Can find **known** (published) relationships

Semantic Awareness



## Levels of insight from the literature

#### Simple Pattern Matching

#### Identify direct relationships between target and disease

E.g. NTRK1 and atopic dermatitis co-occur in many papers

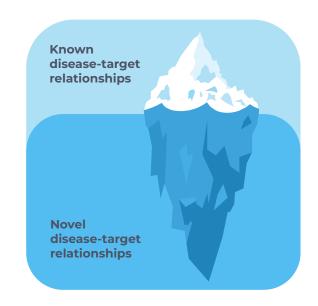
Can find **known** (published) relationships

#### Semantic **Awareness**

#### Identify indirect relationships between target and disease

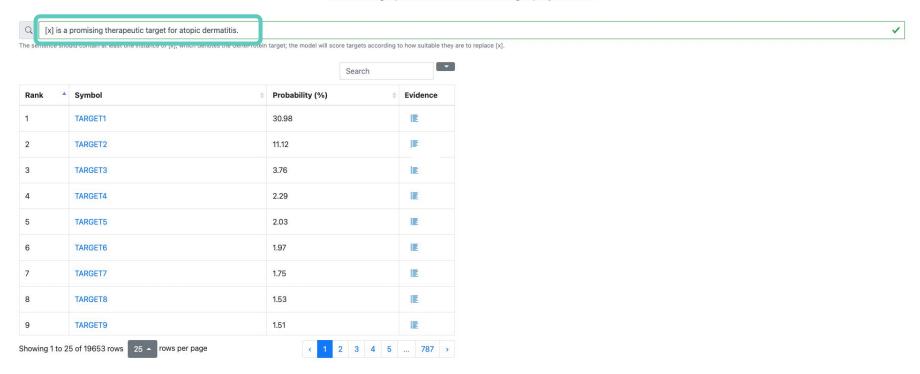
E.g. NTRK1 found to be involved in other similar diseases of allergic inflammation or mechanisms related to atopic dermatitis

Can uncover **novel** relationships.

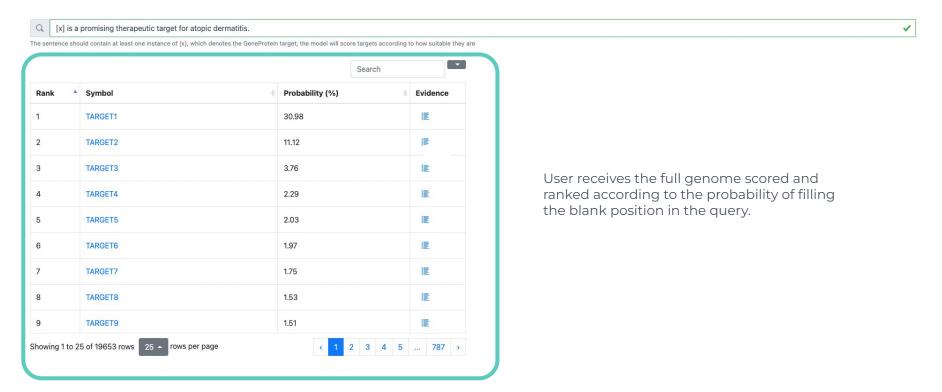


User enters a query sentence containing a blank. This can be a **completely novel sentence** that hasn't appeared in any publication.

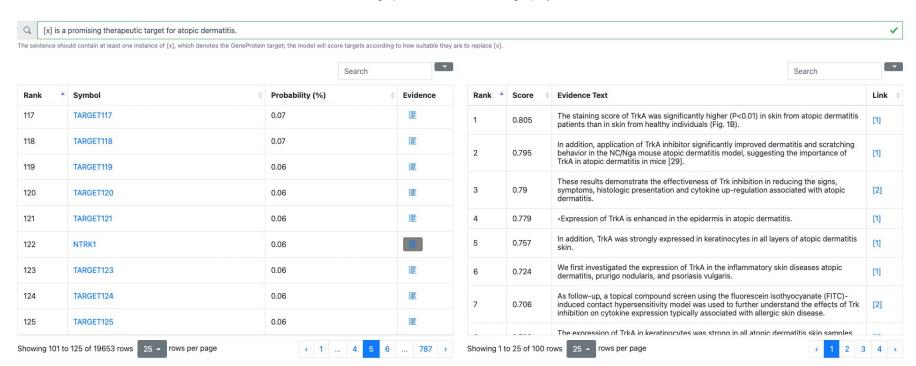
Generate target predictions and evidence using a query sentence.



Generate target predictions and evidence using a query sentence.



Generate target predictions and evidence using a query sentence.



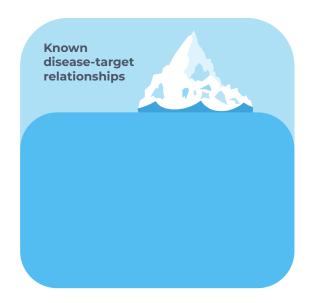
Generate target predictions and evidence using a query sentence.

Q

[x] is a promising therapeutic target for atopic dermatitis.

~

The sentence should contain at least one instance of [x], which denotes the GeneProtein target; the model will score targets according to how suitable they are to replace [x].



**Rank 1:** The staining score of [NTRK1] was significantly higher (P<0.01) in skin from **atopic dermatitis** patients than in skin from healthy individuals (Fig. 1B).

**Rank 2:** In addition, application of [NTRK1] inhibitor significantly improved dermatitis and scratching behavior in the NC/Nga mouse **atopic dermatitis** model, suggesting the importance of [NTRK1] in **atopic dermatitis** in mice [29].

**Rank 3:** These results demonstrate the effectiveness of [NTRK1] inhibition in reducing the signs, symptoms, histologic presentation and cytokine up-regulation associated with **atopic dermatitis**.

**Rank 4:** Expression of [NTRK1] is enhanced in the epidermis in **atopic dermatitis**.

Generate target predictions and evidence using a query sentence.

[x] is a promising therapeutic target for atopic dermatitis.





Rank 12: Translational studies showed elevated expression of [NTRK1] in allergic tissue from patients with EoE.

#### relevant pathology

Rank 15: Our results demonstrate that inhibition of [NTRK1] decreases IL-4-induced proliferation of keratinocytes and that [NTRK1] overexpression in keratinocytes enhances cell proliferation.

#### relevant symptomatic mechanisms

Rank 17: [NTRK1] is also involved in NGF-related allergic reaction

#### relevant pathology

Rank 21: In summary, we conclude that significant enhancement of [NTRK1] expression by Th2 cytokines regulates proliferation and differentiation of keratinocytes as well as allergic inflammation.

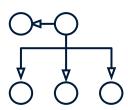
relevant symptomatic and causative mechanisms

Generate target predictions and evidence using a query sentence.

[x] is a promising therapeutic target for atopic dermatitis.

The sentence should contain at least one instance of [x], which denotes the GeneProtein target; the model will score targets according to how suitable they are to





The masked language model enables fast full-genome ranking for a textual target discovery hypothesis, accounting for both direct and indirect evidence

Rank 12: Translational studies showed elevated expression of [NTRK1] in allergic tissue from patients with EoE.

#### relevant pathology

Rank 15: Our results demonstrate that inhibition of [NTRK1] decreases IL-4-induced proliferation of keratinocytes and that [NTRK1] overexpression in keratinocytes enhances cell proliferation.

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relevant symptomatic and causative mechanisms

# **Model setup**

## **Model setup:** Overview

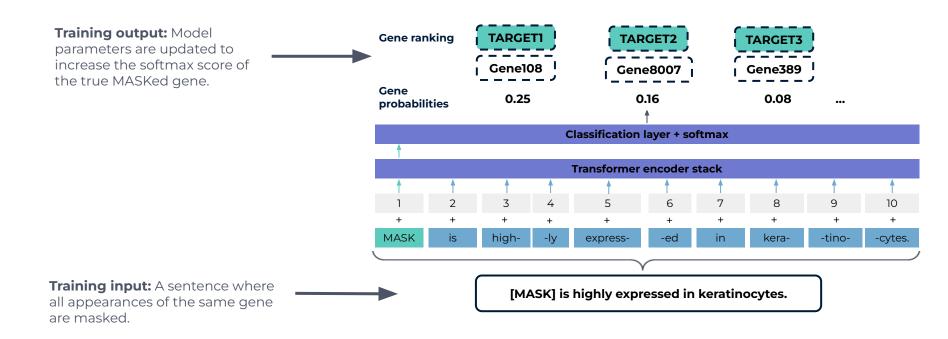
#### Transformer-based masked language model

150million+ entity-linked real-world scientific literature sentences

Trained to predict **genes** from a **text-based query** 

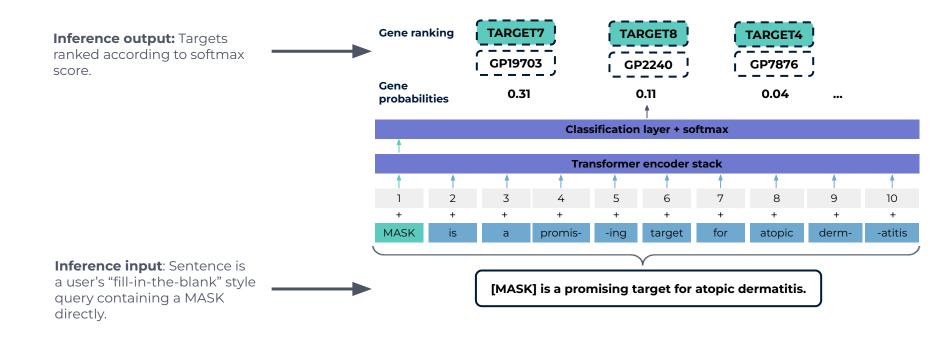
- → Semantic representation of biology
  - → Predict novel targets

## **Model setup:** Training



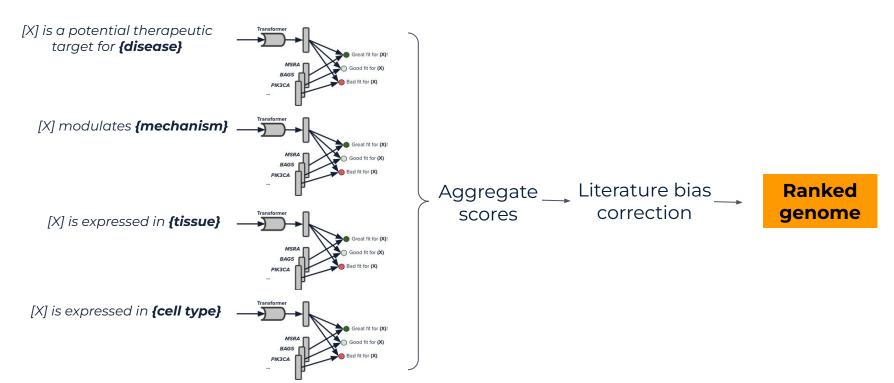
BERT: Pre-training of Deep Bidirectional Transformers for Language Understanding. Devlin et al., 2018.

# Model setup: Inference



BERT: Pre-training of Deep Bidirectional Transformers for Language Understanding. Devlin et al., 2018.

# **Model setup:** Post-processing



# **Model setup:** Post-processing

#### **Correcting for literature bias**

```
score(target|query) = log(p(target|query)) - c*log(p(target))
```

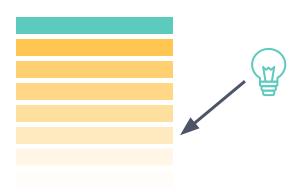
```
Where 0 \le c \le 1
```

and **p(target)** = (nb of sentences with target) / (nb of sentences)

#### **Model setup:** Evaluation

Tens of thousands of in-house target annotations from drug discovery scientists

- Wide range of diseases
- Biological rationale and novelty annotations
- Highly relevant targets near the top of the list (e.g. Ranks 1-10)
- Continues to find **promising, novel targets** further down in the list (e.g. Ranks 100-200)

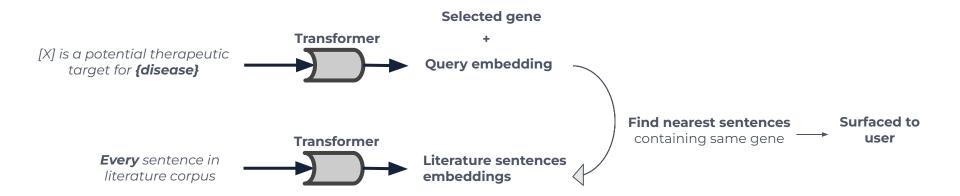


# **Explainability**

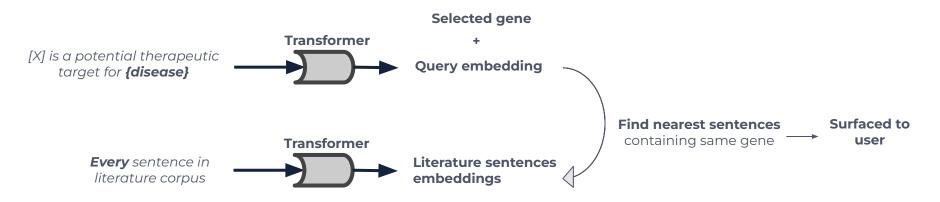
### Indirect explainability via retrieval



### Indirect explainability via retrieval



#### Indirect explainability via retrieval



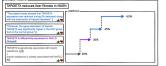
Literature sentence embeddings stored in **per-gene FAISS\* indices** - for efficient vector similarity search

\*Johnson, J et al. (2019). Billion-scale similarity search with GPUs. IEEE Transactions on Big Data, 7(3), 535–547.

## Target prioritisation wish list

#### Target prioritisation model wishlist





Explainable predictions



## A moment to breathe and ask questions

Before breath: 😴

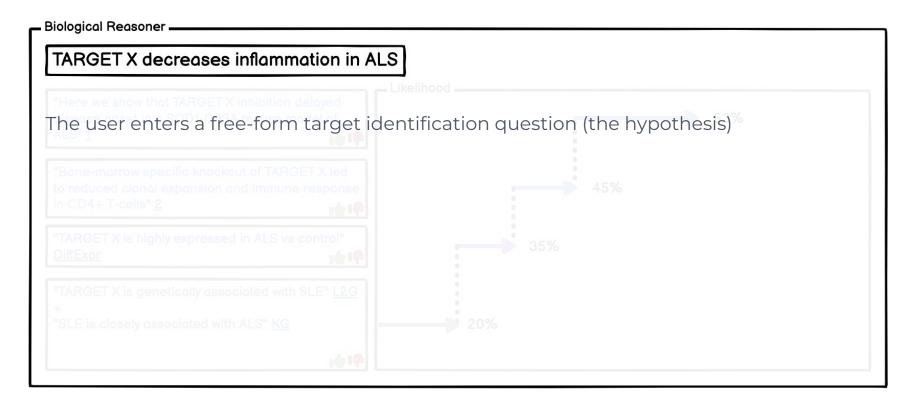
After breath: 👶

## Evidence synthesis with attribution

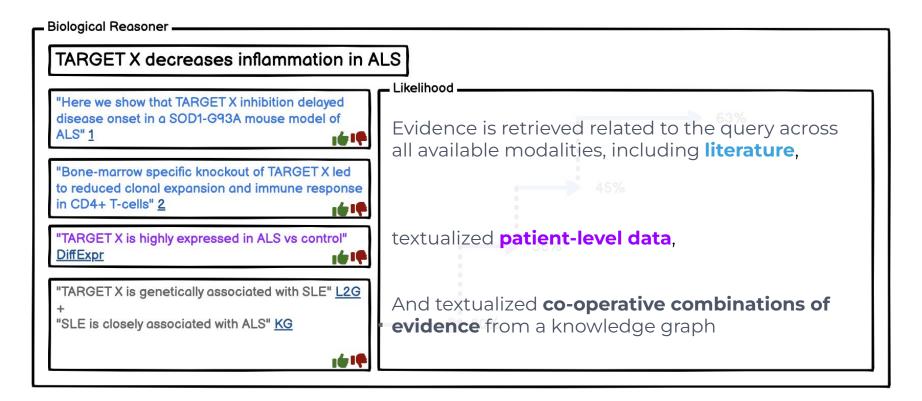
- User workflow
- Model setup: Training, finetuning, inference
- Explainability and multimodality

## **User workflow**

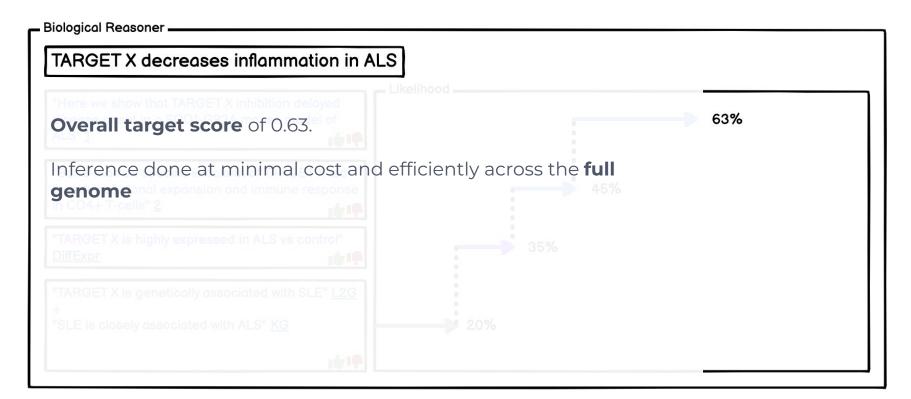
#### **User workflow:** User query



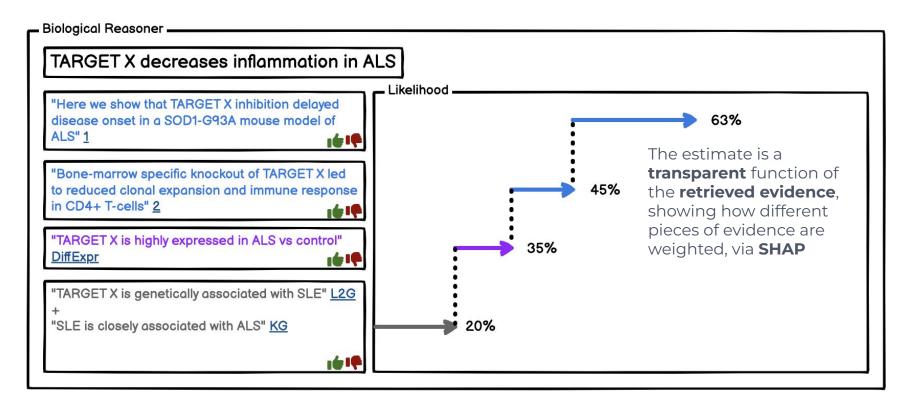
#### User workflow: Multimodal evidence



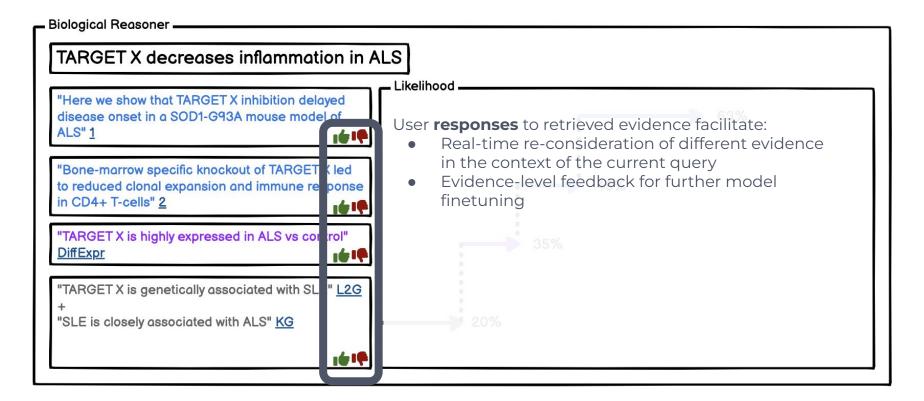
### User workflow: Overall prediction, full-genome



#### **User workflow:** Explanation via SHAP



#### User workflow: User feedback



#### User workflow: Example

Query:

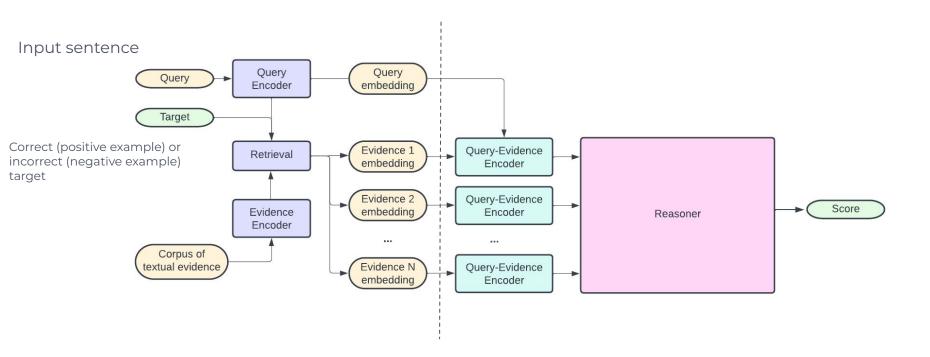
[x] is a novel promising therapeutic target for atopic dermatitis.

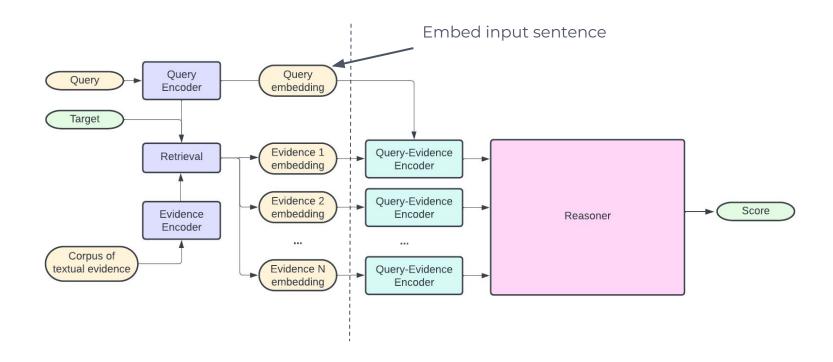
**Evidence Sources** 

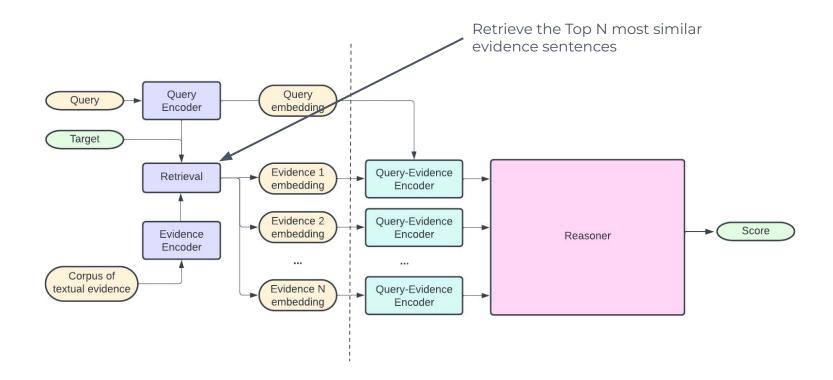
O Literature & Differential Expression

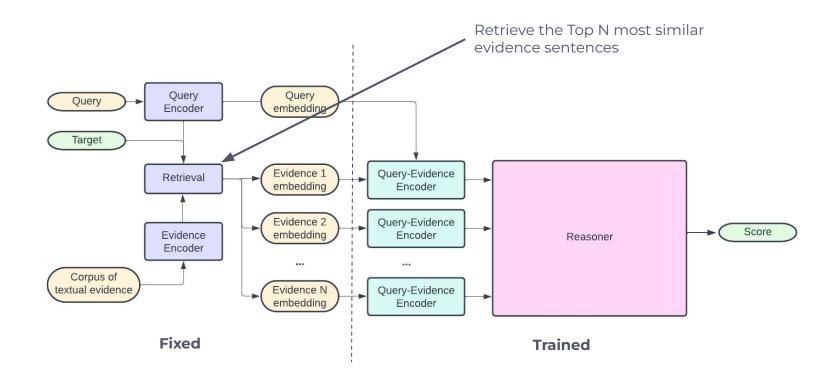
**Target:** NTRK1

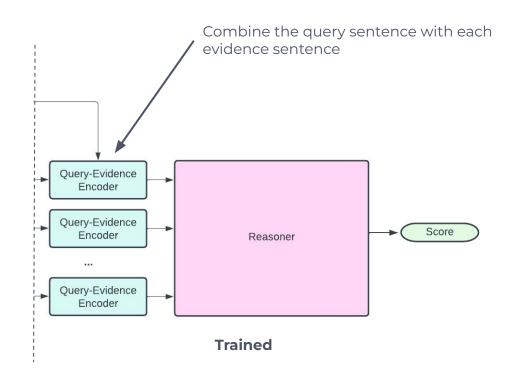


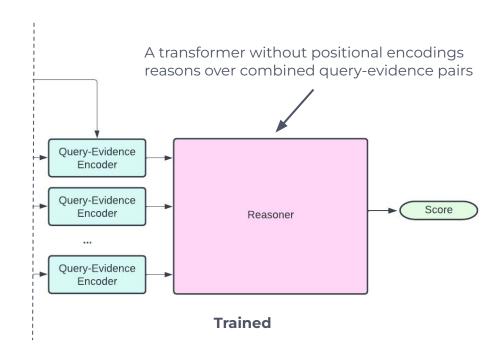






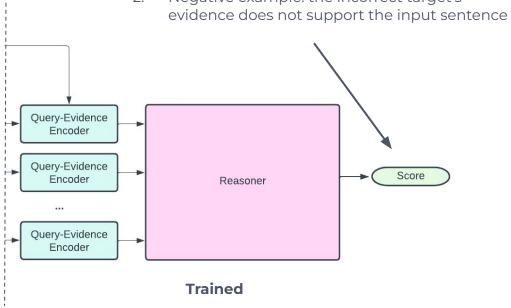




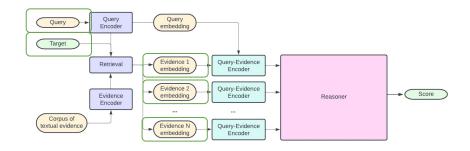


#### Objective is to predict that:

- Positive example: the correct target's evidence supports the input sentence
- Negative example: the incorrect target's



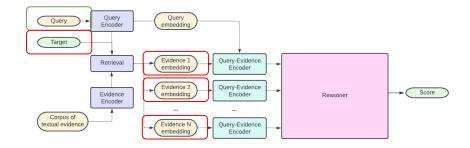
#### Positive example



Retrieved evidence corresponds to correct target for the input sentence.

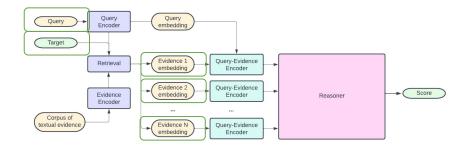
During training the query is a sentence with a known target, such as an entity-linked sentence from the literature.

#### Negative example



Retrieved evidence corresponds to an incorrect target for the input sentence.

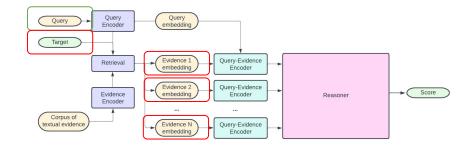
#### Positive example



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During training the query is a sentence with a known target, such as an entity-linked sentence from the literature.

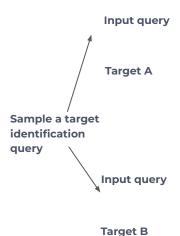
#### Negative example



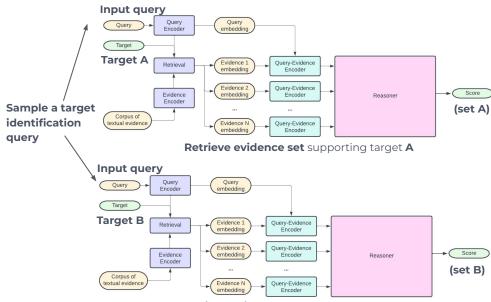
Retrieved evidence corresponds to an incorrect target for the input sentence.

To **limit literature bias**, the negative evidence **target** is randomly sampled according its frequency of mention in the literature, so that so well-studied targets come up equally often in negative and positive examples.

Constitutional evidence set finetuning with an LLM



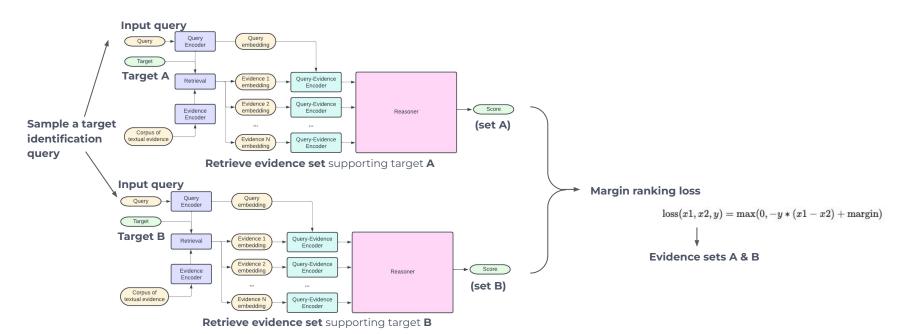
Constitutional evidence set finetuning with an LLM



Retrieve evidence set supporting target B

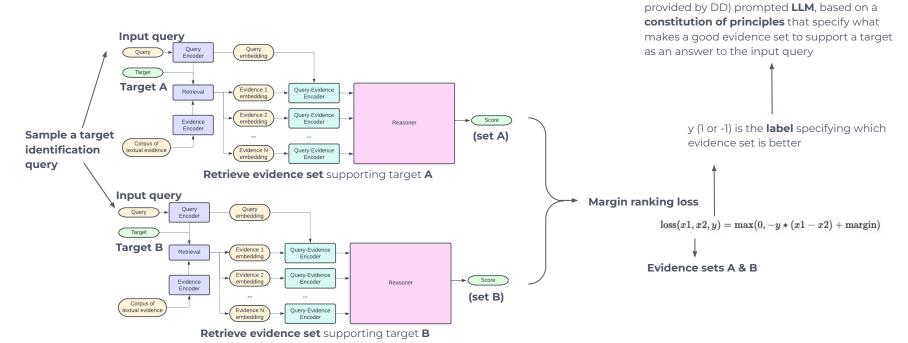
Yuntao Bai,et al. (2022). Constitutional Al: Harmlessness from Al Feedback.

Constitutional evidence set finetuning with an LLM



Yuntao Bai,et al. (2022). Constitutional Al: Harmlessness from Al Feedback.

Constitutional evidence set finetuning with an LLM



Yuntao Bai,et al. (2022). Constitutional AI: Harmlessness from AI Feedback.

label is determined by few-shot (examples

#### A constitution of principles for few-shot LLM ranking of two sets of evidence

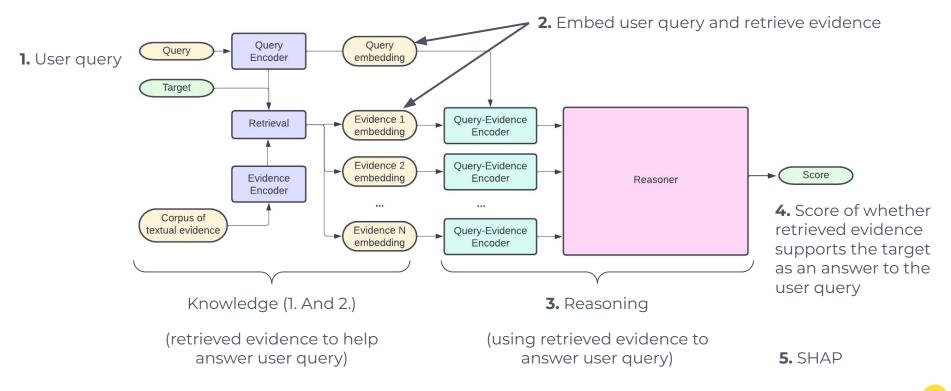
The better evidence set is the one which offers most support to set of principles

Principles in the constitution relate to:

- Disease relevance
- Mechanism relevance
- Tissue and cell type expression

## Model setup: Inference

#### Model setup: Inference



# **Explainability & Multimodality**

## **Direct explainability with SHAP**

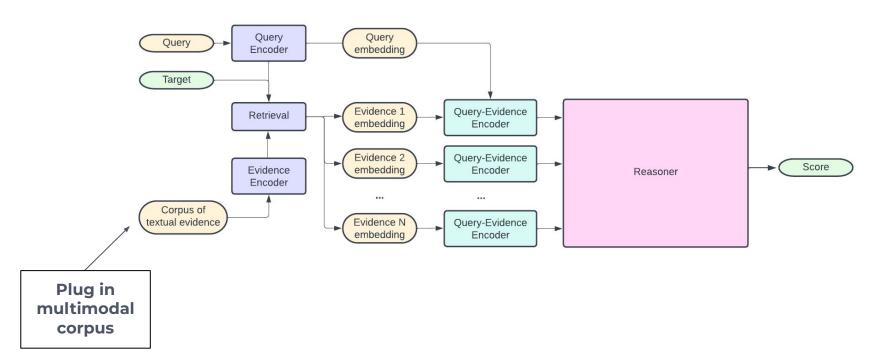
#### **SHapley Additive exPlanations (SHAP)**

- Approximate output of a model as a linear combination of binary input features
- The model output is an additive sum of Shapley values ( $\varphi$ ) attributed to the input features, plus a bias ( $\varphi$ 0):

$$g(z') = \phi_0 + \sum_{i=1}^{M} \phi_i z_i',$$

- o (z') is binary, the feature is present [1], or absent [0].
- φi is the average difference between the score with and without feature i, considering all combinations of other features
- g(\*) is the output

# Multimodality



**Example modality:** Differential expression

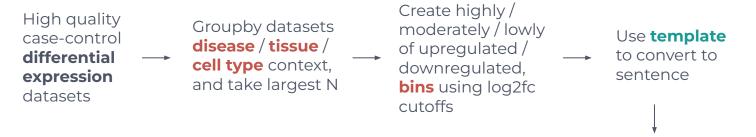
High quality case-control differential expression datasets

Groupby datasets

disease / tissue / cell type context, and take largest N

Create highly / moderately / lowly of upregulated / downregulated, bins using log2fc cutoffs

**Example modality:** Differential expression



Target X was {bin} in {cell type}s within the {tissue} in {disease}.

Target X was highly upregulated in keratinocytes within the skin in atopic dermatitis.

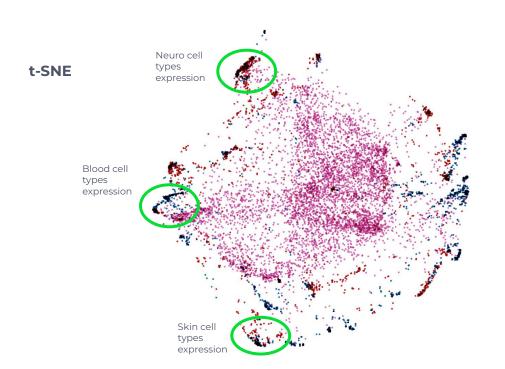
**Example modality:** Differential expression



Target X was {bin} in {cell type}s within the {tissue} in {disease}.

Target X was highly upregulated in keratinocytes within the skin in atopic dermatitis.

Embed sentence with literature-trained encoder and add to vector search index

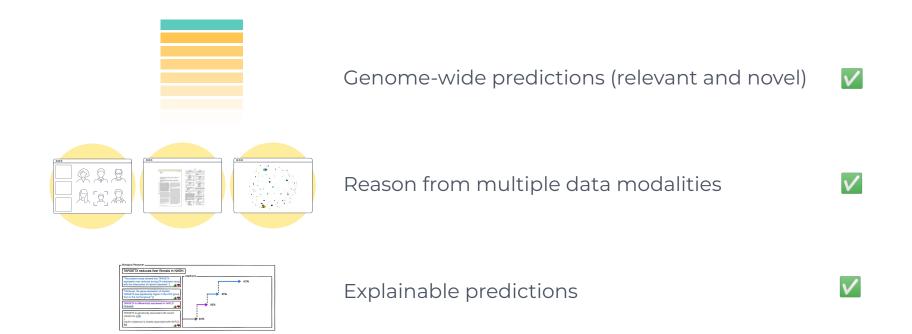


**Literature trained encoder** → overlap of literature and textualised (omics) sentences covering similar aspects of biology

Literature
Differential expression
Expression

# Target prioritisation wish list

## Target prioritisation model wishlist



# Large language models:

What role do they have?

## Target prioritisation model wishlist: LLMs

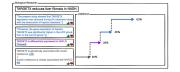


Genome-wide predictions (relevant and novel)



Reason from multiple data modalities





Explainable predictions



# The flexibility / performance tradeoff



Teach users how to use a model or data source optimally.

Develop guardrails around a limited number of use cases to ensure ease and high performance.

# The flexibility / performance tradeoff

Large language models can help to mitigate this tradeoff as both

a translator and orchestrator at a source optimally.



Easy to use, high-performance

Develop guardrails around a limited number of use cases to ensure ease and high performance.

# The flexibility / performance tradeoff

Large language models can help to mitigate this tradeoff as both

a translator and orchestratorata source optimally.



Adapt user needs into the right language for underlying models and databases.

Easy to use, high-performance



Navigating complex workflows involving a series of complex analysis steps leveraging a large range of tools and data sources

Develop guardrails around a limited number of use cases to ensure ease and high performance

Can you find me novel targets to modulate neuroinflammation in ALS?

An LLM is initialized with a set of instructions about how to format queries to an underlying specialist model or data source.

It knows the relevant best practices and can flexibly apply them.

Can you find me novel targets to modulate neuroinflammation in ALS?

#### Requirement (in LLM context):

Phrase the query in the form of a statement, using an "[x]" to denote the desired target.

Can you find me novel targets to modulate neuroinflammation in ALS?

Example Best Practice (in LLM context): When considering novelty, use two separate queries for novelty and biological function, aggregating results post-hoc.

Can you find me novel targets to modulate neuroinflammation in ALS?

Example Best Practice (in LLM context): When considering novelty, use the phrase "well-known" and invert the score.

Can you find me novel targets to modulate neuroinflammation in ALS?

#### Query:

"[x] modulates neuroinflammation in ALS" AND NOT "[x] is well-known in ALS".

Can you find me novel targets to modulate neuroinflammation in ALS?

Details about best practices can be **abstracted away** for non-technical users (but available for experts to tweak).

#### Query:

"[x] modulates neuroinflammation in ALS" AND NOT "[x] is well-known in ALS".

Certainly. My top choice is TARGETX. It has been linked to neuroinflammation by ...

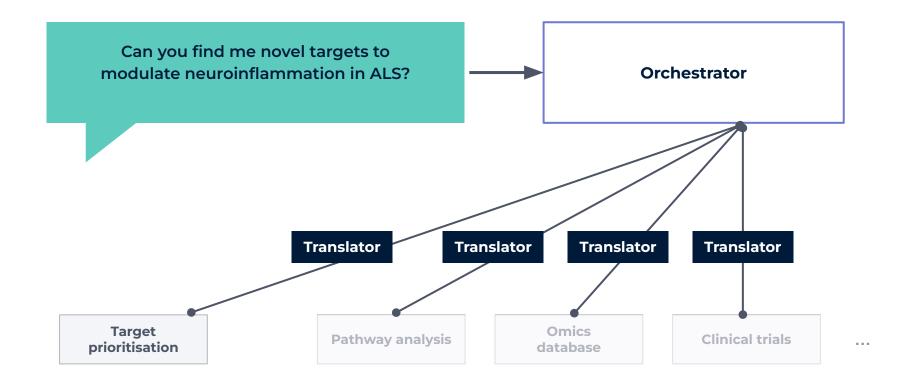
Can you find me novel targets to modulate neuroinflammation in ALS?

Users can **flexibly** interact with the underlying model, while applying best practices for **high performance**.

#### Query:

"[x] modulates neuroinflammation in ALS" AND NOT "[x] is well-known in ALS".

Certainly. My top choice is TARGETX. It has been linked to neuroinflammation by ...



Can you find me novel targets to modulate neuroinflammation in ALS?

Certainly. My top choice is TARGETX. It has been linked to neuroinflammation by ...

Can you find me novel targets to modulate neuroinflammation in ALS?

Is there anything interesting upstream of TARGETX?

Certainly. My top choice is TARGETX. It has been linked to neuroinflammation by ...

TARGETY upregulates TARGETX. TARGETY ranked 834th overall; there doesn't appear to be any strong evidence linking it to neuroinflammation...

Can you find me novel targets to modulate neuroinflammation in ALS?

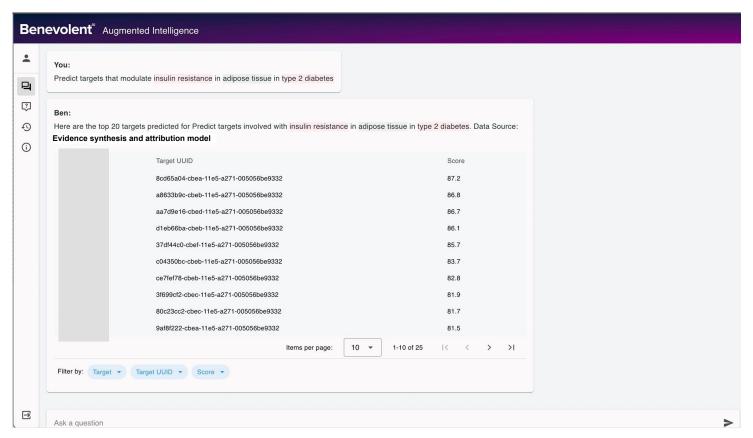
Is there anything interesting upstream of TARGETX?

Can you filter the Top 200 results to those without any clinical results at or beyond Phase II?

Certainly. My top choice is TARGETX. It has been linked to neuroinflammation by ...

TARGETY upregulates TARGETX. TARGETY ranked 834th overall; there doesn't appear to be any strong evidence linking it to neuroinflammation...

Yes. There are 128 targets remaining. The top remaining target is...



# Summary

# Summary: Language models for target prioritisation

Genome-wide

Multimodal

**Explainable** 

Drug discovery and BenevolentAl

**Drug discovery biologists:** In depth, multimodal reasoning

Masked-language models: Genome-wide, literature-based target prioritisation

**Evidence synthesis with attribution:** Explainable, genome-wide, multimodal target prioritisation

**Large-language models:** What role do they have?

#### Thanks to the team

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Many others

Any questions?

Email: ravi.patel@benevolent.ai







