e therapeutics

Computing the Future of Medicine

Is Drug Discovery a Data Science Problem?

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Forward looking statement

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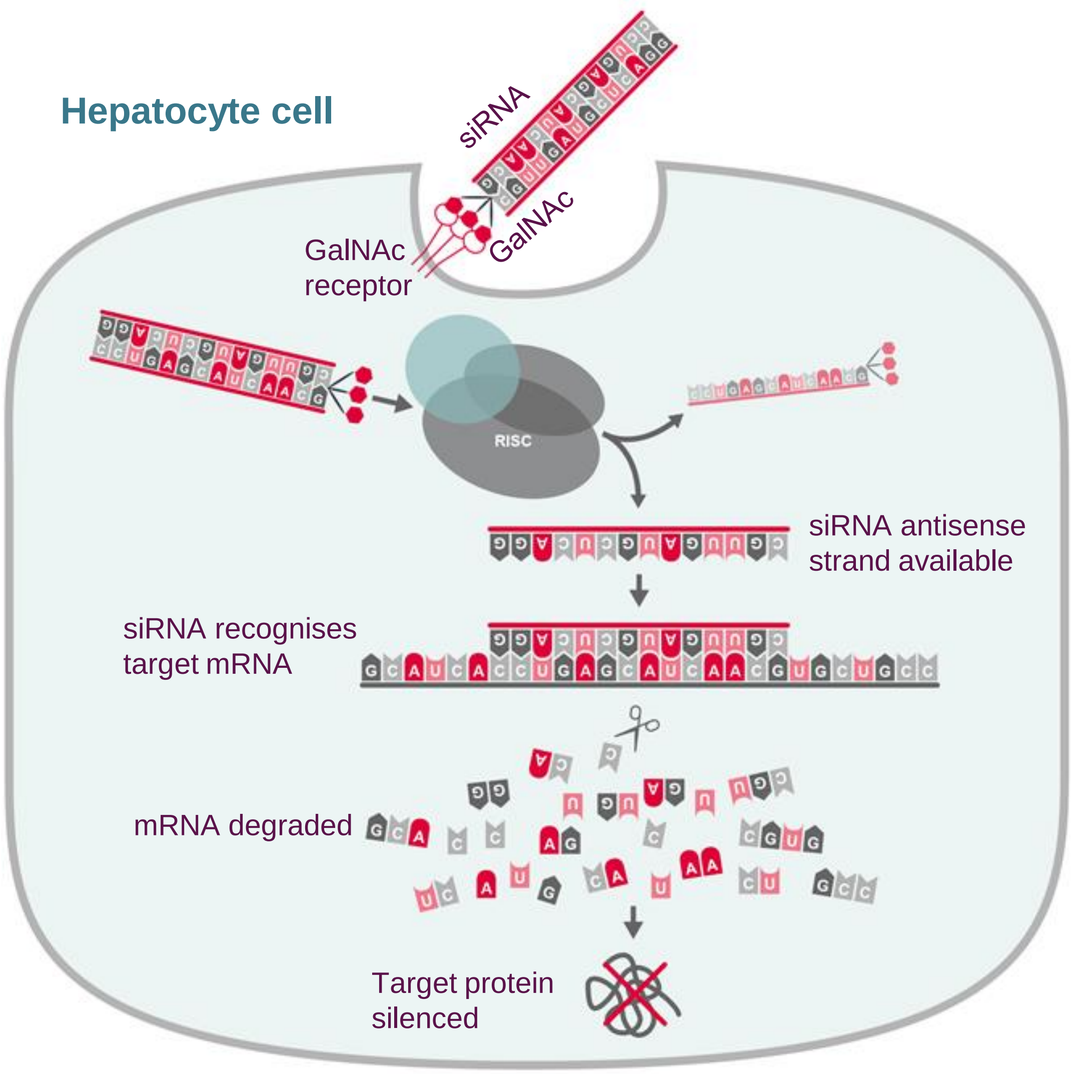
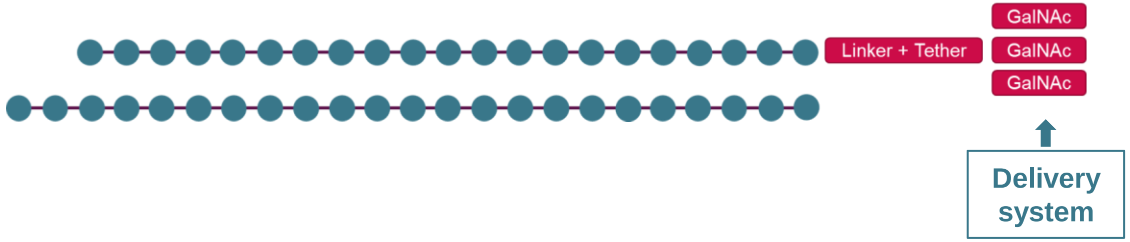
GalOmic – ETX RNA Drug Platform

ETX RNA Drug Platform: Information Molecules

RNA drugs are a form of computation





1. We know the DNA sequence of hepatocytes, and the corresponding **mRNA code** for all genes
2. Design complementary **'anti-code' siRNA sequences**, opposite to a region of the mRNA code
3. We **deliver** siRNAs to **hepatocytes** using **GalNAc** to trigger the natural intracellular interference process
4. The cell **silences the expression** of the target disease-associated gene (no protein made)

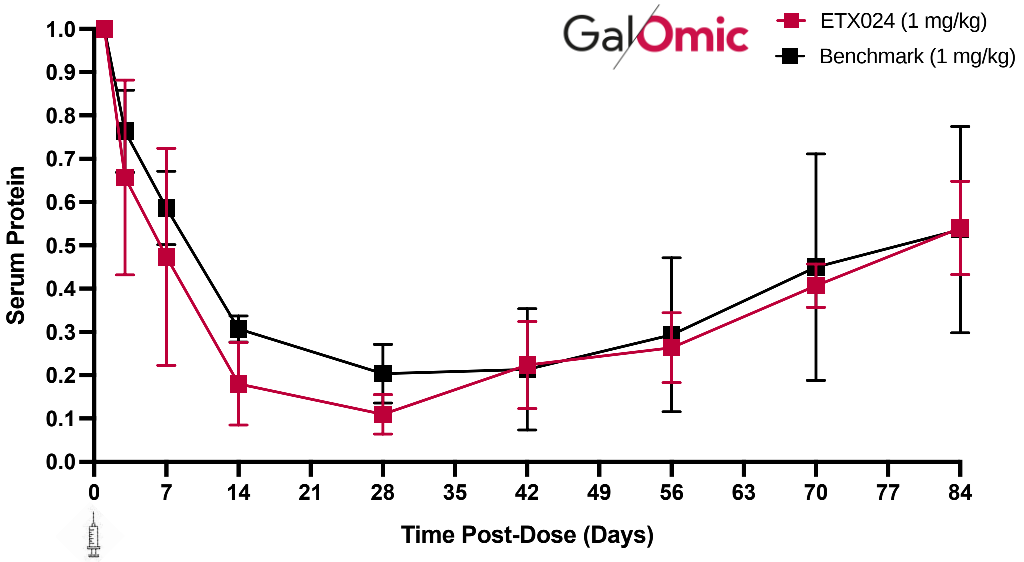
GalOmic: ETX RNAi Platform

Novel target prosecution at pace and with a patient-friendly profile

Management team has >10-year track record and scientific experience in RNAi therapeutics

- We can **inhibit any gene in hepatocytes**
- Commercial stage modality, with 5 approved drugs
- **Powerful, validated technology:** highly specific, well tolerated, long duration of action, subcutaneous administration
- Generated data demonstrating **at least equivalent performance** to market lead across multiple genes
- **17 patent applications filed** to protect novel GalOmic platform and target inventions

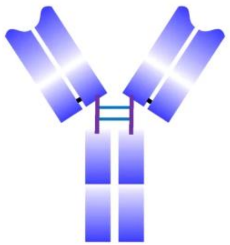
Typical performance profile of our RNA platform



We go from gene target selection to *in vivo* dose response experiments in 6 months, costing only ~£500,000

mAbs History as Precedent of new Therapeutic Modality

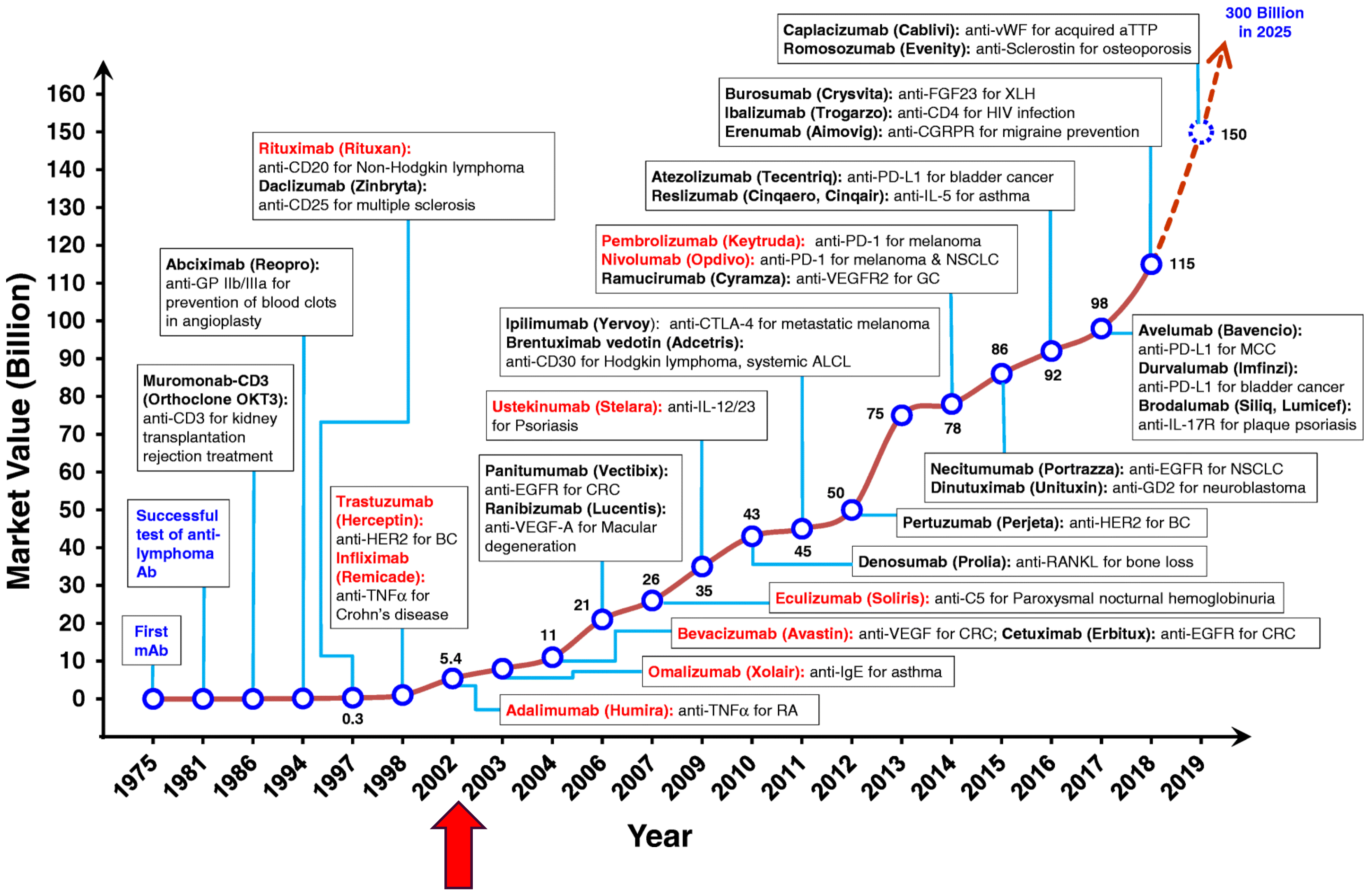
Monoclonal antibodies are now established as a drug class



100th mAb product approved by the FDA in May 2021

mAb market estimated to reach **$300B** in 2025

Limitations: extracellular targets only, duration of action



Development of therapeutic antibodies for the treatment of diseases. J Biomed Sci Jan 2020

HepNet: Our Computational Biology Platform

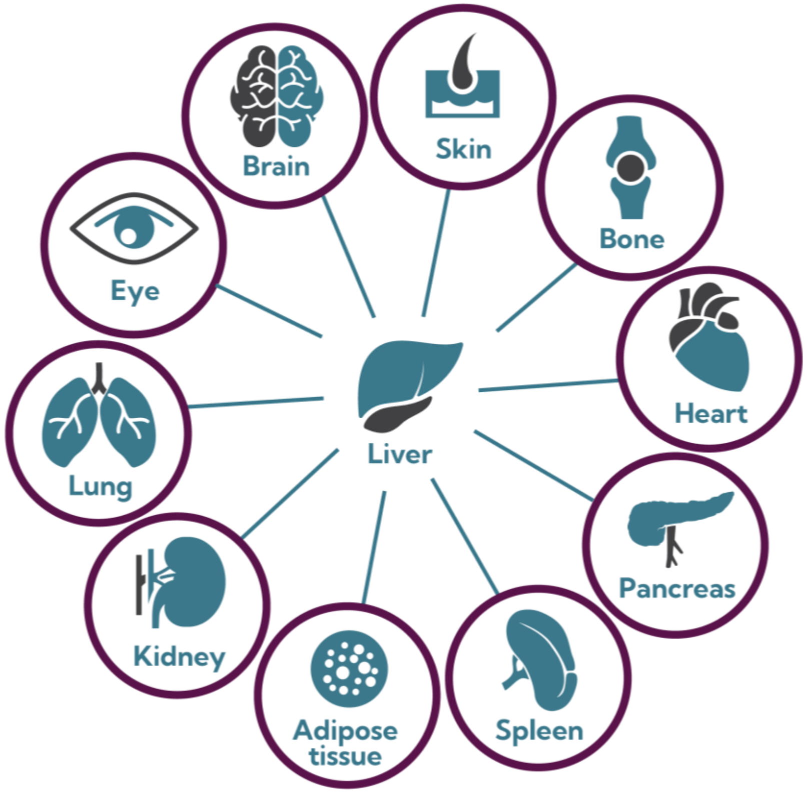
Which gene, in which disease?

Hepatocyte Biology – A Central Trafficking System

Hepatocyte associated disease areas

- Cardiovascular
- Metabolic
- Diabetes
- Haematology
- Obesity
- NASH
- Renal
- Rare
- Other

Hepatocytes have a high degree of influence over other cell types and tissues



ETX data and knowledge covers…

- **12,091** Expressed genes
- **1039** Secreted proteins
- **461** Proteins secreted to blood
- **700** Biological Processes

Please note numbers are derived from ETX proprietary curation and analysis of public 'omics data, proprietary data derived from NLP processing of literature and network-aware ML-driven analysis of curated pathway data

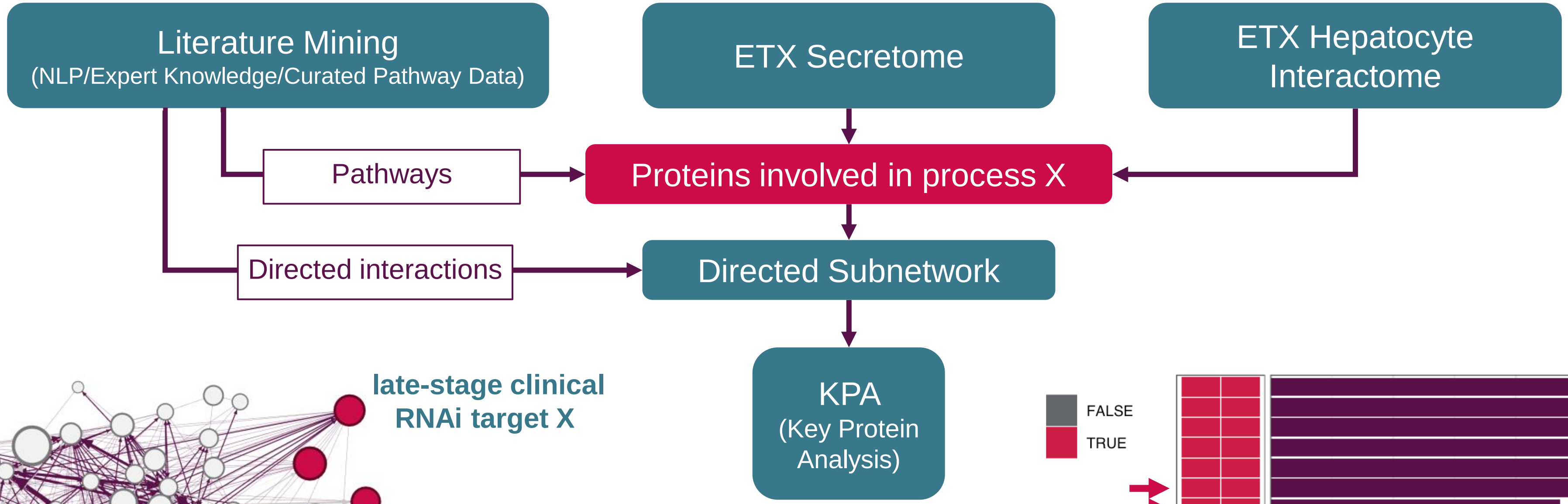
High Degree of Overlap in Competitive Landscape

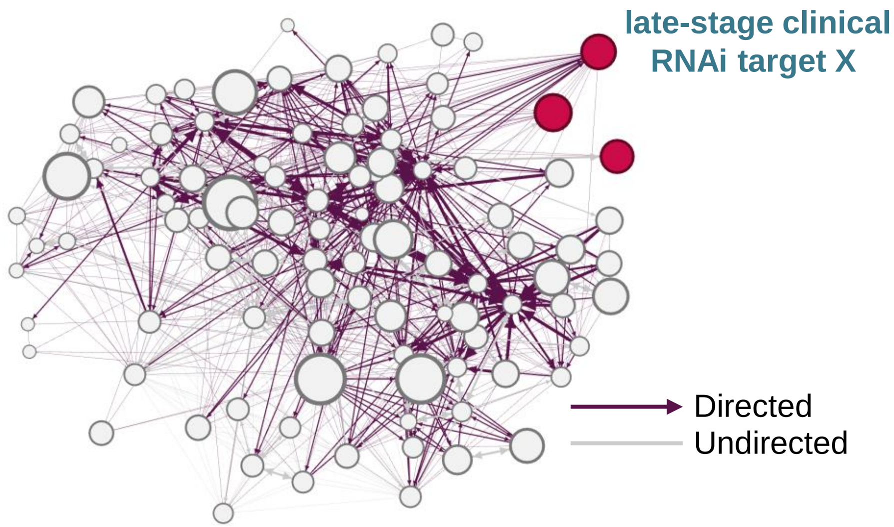
Multiple players are targeting obvious liver-expressed genes

Hepatocyte Genes	HBV	LP(a)	AAT	PCSK9	TTR	HSD	XDH	C3
Alnylam Pharmaceuticals	X		X	X	X	X	X	
arrowhead pharmaceuticals	X	X	X			X	X	X
Dicerna pharmaceuticals (acquired by Novo Nordisk for $3.3bn)	X	X	X					X
SILENCE THERAPEUTICS		X						X
IONIS*	X	X		X	X			

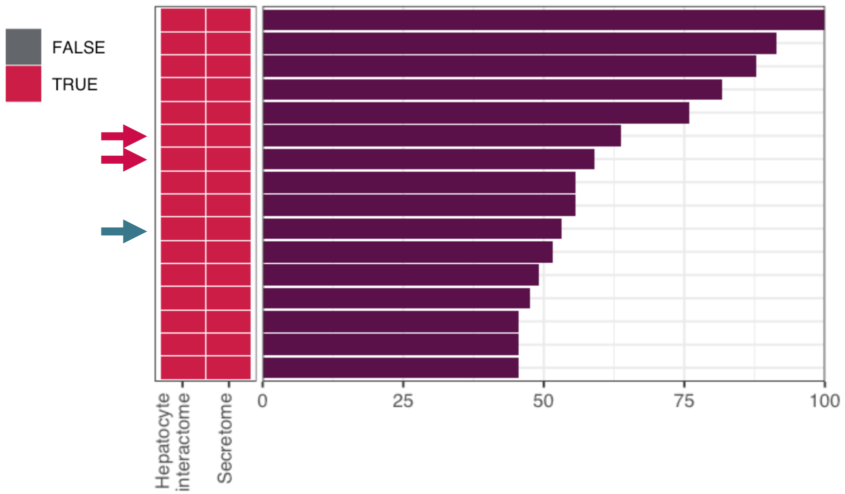
*antisense oligonucleotides

Modelling Biology In A Computer: Clotting Cascade





Directed biological process network model
Directed network containing 100 nodes constructed using ETX proprietary interactome which includes directed interactions from NLP and curated pathway data.



Target identification using KPA on the network model
Top ranked proteins using the KPA approach. Triage of the top decile led to the identification of two RNAi targets and selection for evaluation (magenta arrows)

HepNet: a Centralised ‘Google for Hepatocytes’

A discovery resource and engine for target ID, under a user-friendly GUI (in progress)

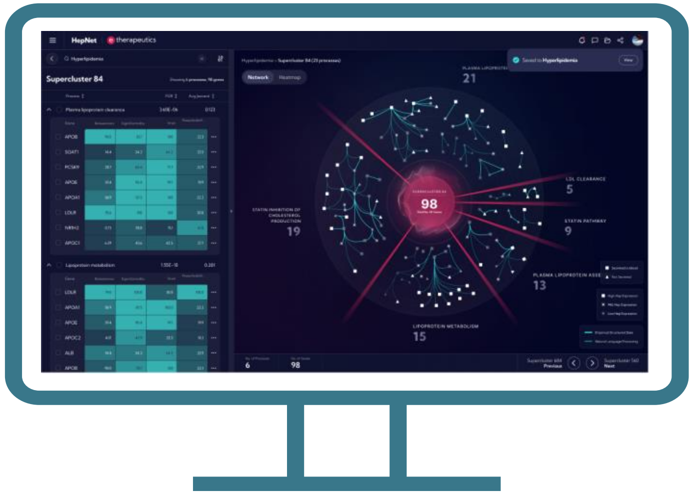
Unstructured Data

Papers, grants, proteins, ncRNAs, drugs, pathways, omics, GWAS, patents, clinical trials, animal models

Structured Data (Knowledge Graph)

Proprietary Network Analytics

HepNet GUI



- The most comprehensive hepatocyte knowledge resource
- Enhanced with AI, mined by AI
- ETX modelling and analysis functionality embedded

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Expert review and Competitive Intelligence

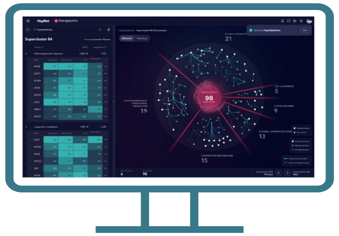
Outputs

- Novel gene targets
- Patents
- Biological insights
- Predictive siRNA drug design
- Automation

A Highly Differentiated Pipeline of RNAi Candidates

We are prosecuting several preclinical candidates drugging our novel targets

HepNet™



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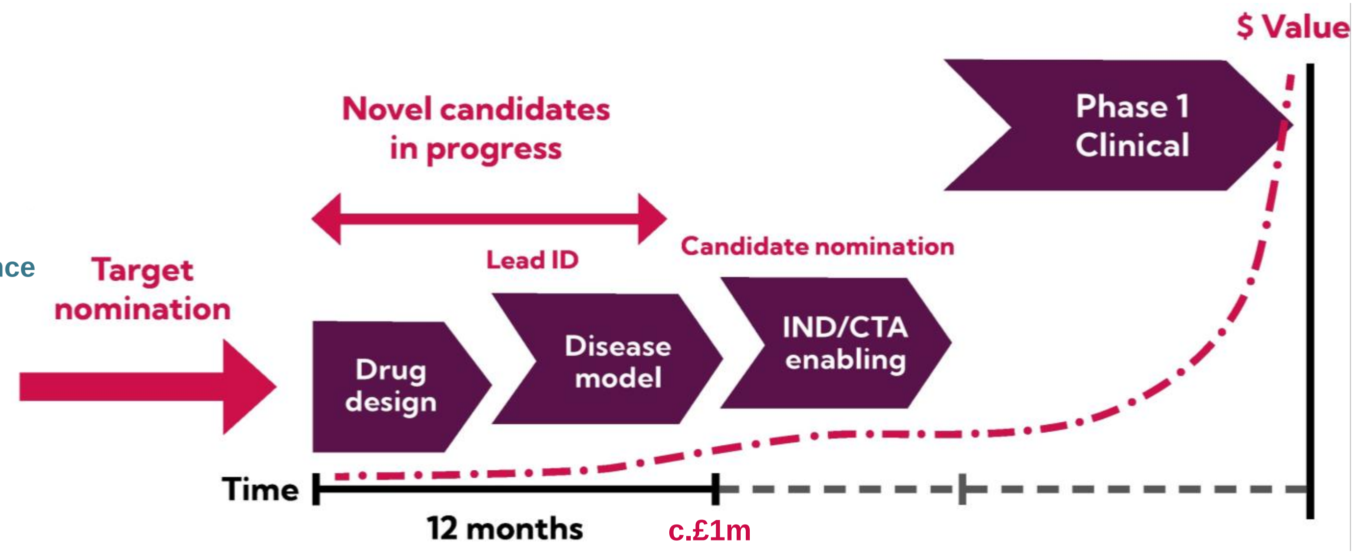
Expert review and Competitive Intelligence



In-house Pipeline generating PoC datasets:

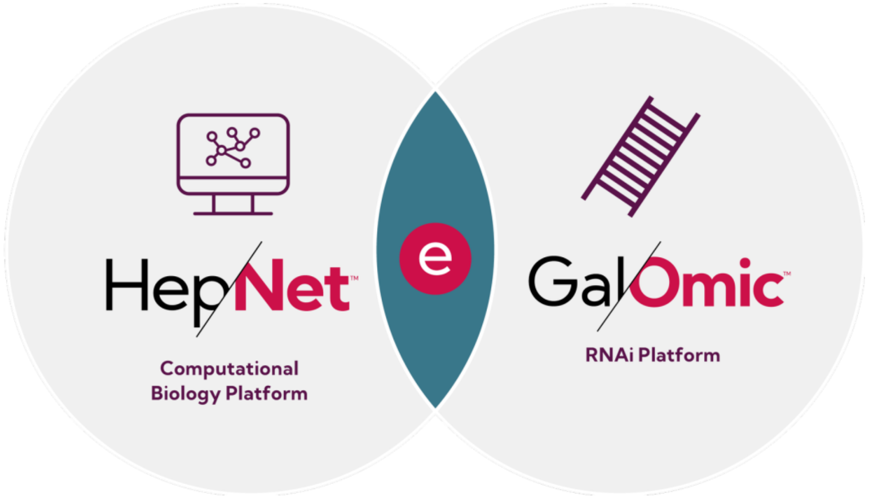
IP generation: 17 patents filed

6 Novel Targets

5 TA

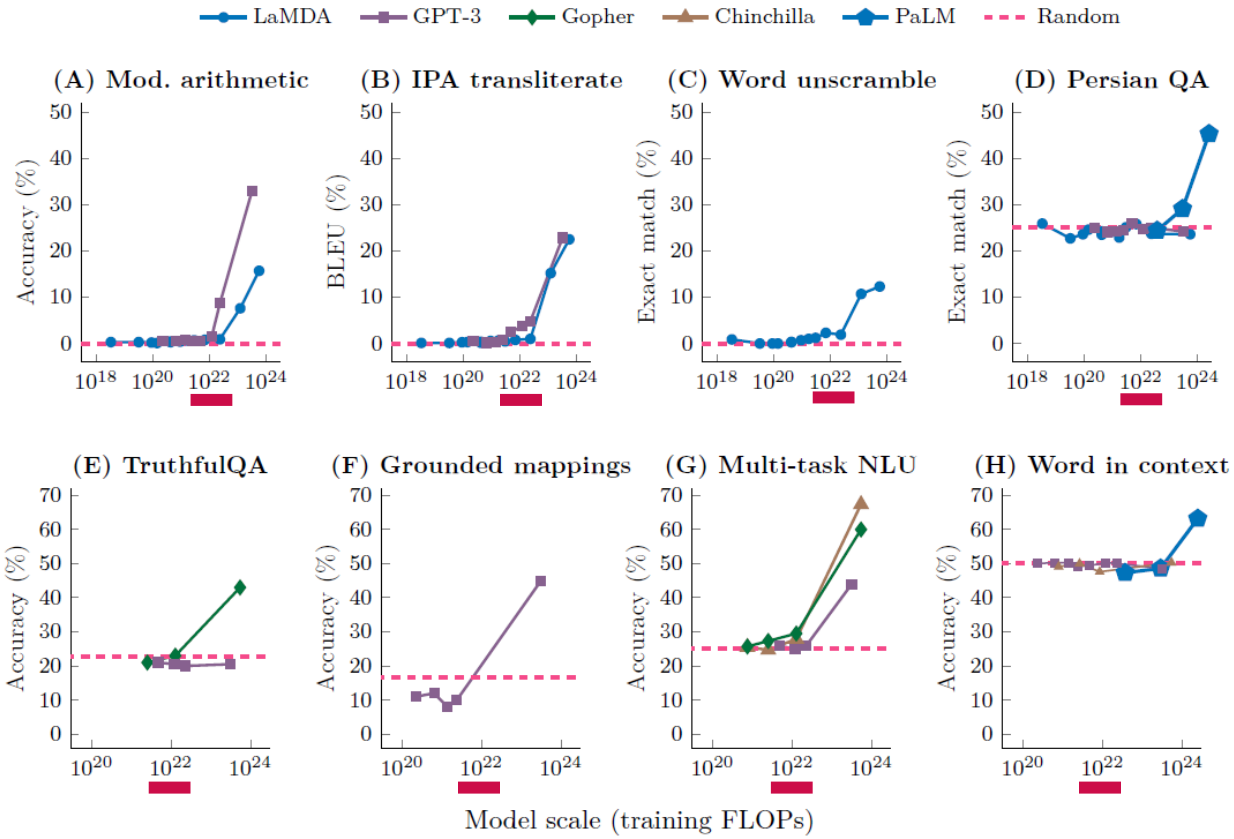
- Haematology
- Cardiovascular Disease
- NASH
- Others (undisclosed)

ETX Powered by Generative AI



How do Generative AI Models work?

In simple terms, they predict the next word…



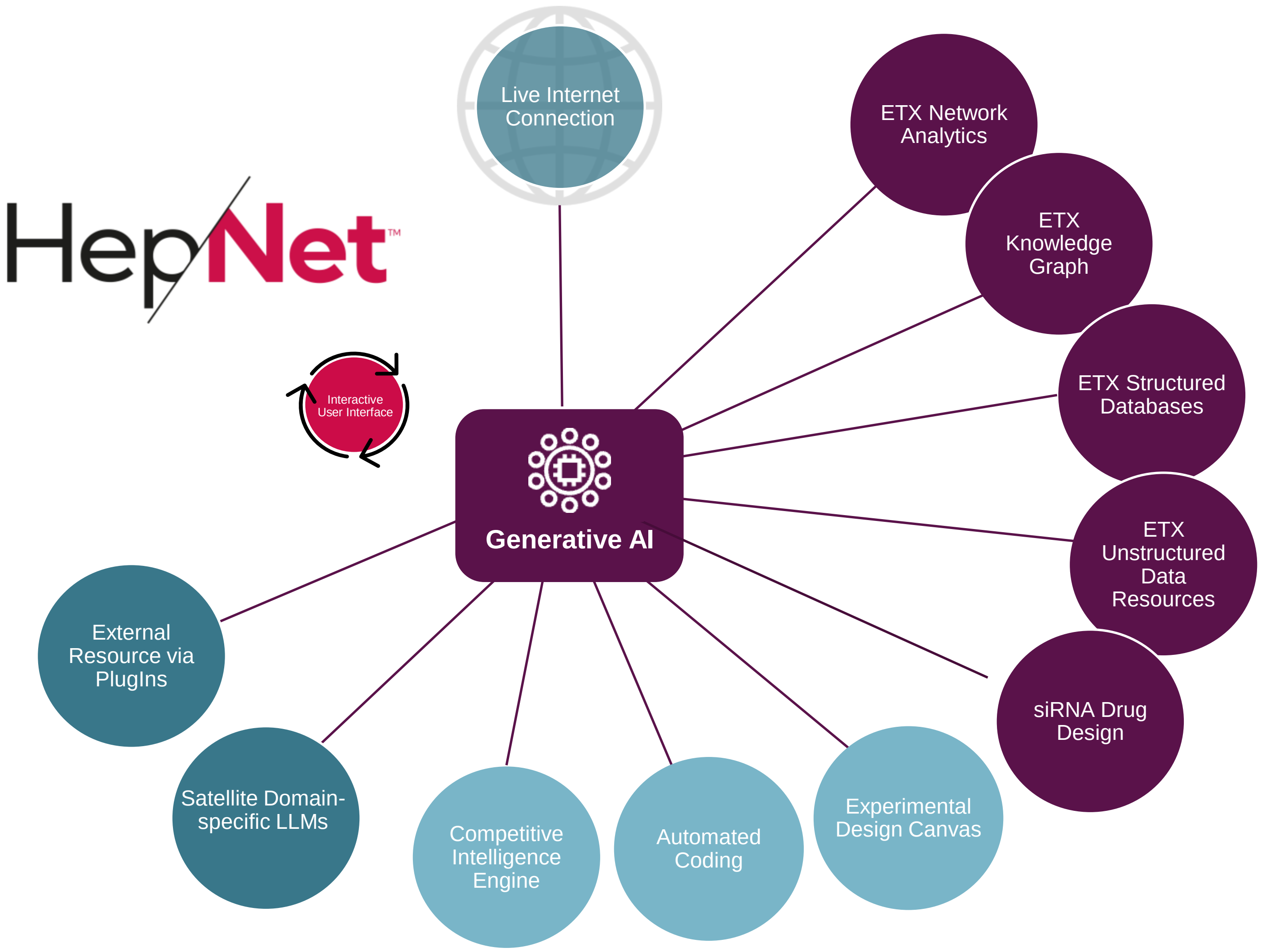
How do emergent properties arise?

"Emergent properties are a necessary result of the task of predicting the next word as in order to perform that prediction task more perfectly, a machine must derive an understanding of the reality described in the various materials used in training."

lya Sutskever, Chief Scientist at OpenAI

Integration of Generative AI

Further evolving HepNet with creation of ETX specialist agents



Adding AI Language Capability

Not a ChatBot

HepNet™ + Generative AI

ETX Specialist 'AI Agents'

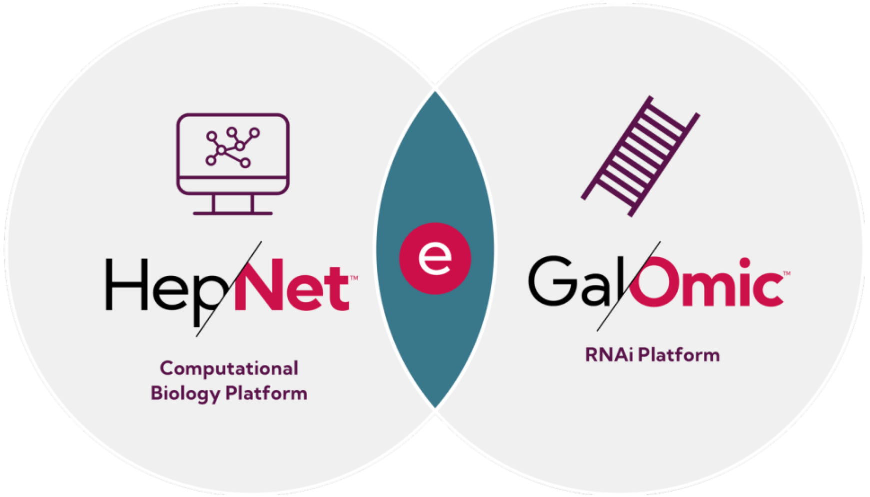
- Fine-tuned to our business, projects and processes
- Trained with hepatocyte-specific data
- Trained with siRNA sequences/constructs
- Trained on all relevant scientific papers

Impact of LLM addition Allows ETX AI Agents To:

"Understand"
"Reason"
"Infer"
Code/Self Code
Access the Internet

Computing the Future of Medicine™

ETX Powered by Generative AI – Use Cases



Use Case: HepNet Powered by Generative AI

An 'intelligent' System

HepNet™ *'Google' for Hepatocytes*

Inputs:

- Data
- Network analytics

Limitations:

- Search heavy
- Limited NLP

Expert review and Competitive Intelligence

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HepNet™ + Generative AI

Inputs:

- Any data
- Any format

Added Generative AI capability:

- Understanding
- Reasoning
- Inference
- Ability to invent
- Automation

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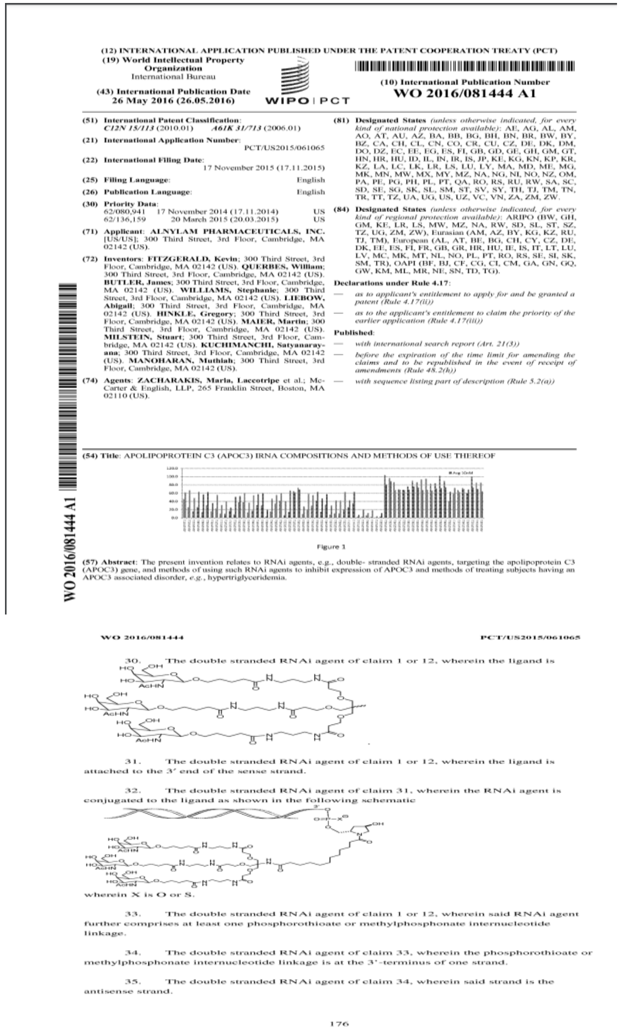
Expert review and Competitive Intelligence

Use Case: Unstructured Data Patent Mining

To extract, analyse and formulate a patent strategy that accounts for all 400,000 RNAi-related patents from 2001



	Old Approach	ETX AI Patent Agent
Extract and store all relevant patents	+++	✓
Summarise and categorise patents	+	✓
Extract all sequences, constructs and performance	++	✓
Cross-talk with HepNet	+	✓
Understand the syntax of patent documents	Manual	✓
Find gaps for FTO and new IP	Manual	✓
Find new learnings to infer new information	Manual	✓
Find patents in other drug modalities relevant to our targets	Manual	✓
Write new patent applications	Manual	✓

Use Case: Is There A Secret Language in Genetic Sequences?

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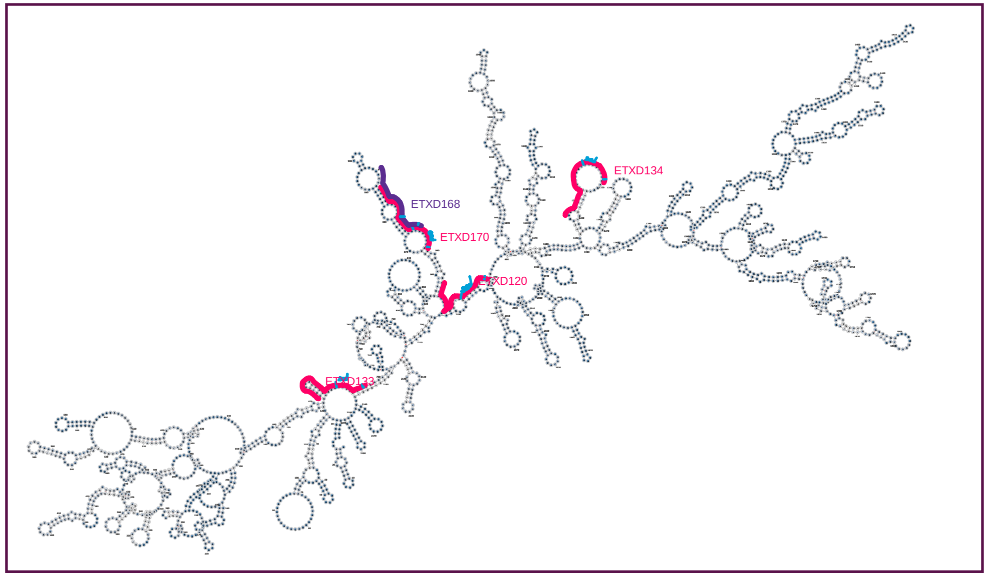
CCCCGCAGCGCCGGAGTCAAAGCCGGTTCCCGGCCCAGTCCCGTCCTGCAGCAGTCTGCCTCCTCTTTCAACATGACAGA
TGCCGCTGTGTCCTTCGCCAAGGACTTCCTGGCAGGTGGAGTGGCCGCAGCCATCTCCAAGACGGCGGTAGCGCCCATCG
AGCGGGTCAAGCTGCTGCTGCAGGTGCAGCATGCCAGCAAGCAGATCACTGCAGATAAGCAATACAAAGGCATTATAGAC
TGCGTGGTCCGTATTCCCAAGGAGCAGGGAGTTCTGTCCTTCTGGCGCGGTAACCTGGCCAATGTCATCAGATACTTCCC
CACCCAGGCTCTTAACTTCGCCTTCAAAGATAAATACAAGCAGATCTTCCTGGGTGGTGTGGACAAGAGAACCCAGTTTT
GGCTCTACTTTGCAGGGAATCTGGCATCGGGTGGTGCCGCAGGGGCCACATCCCTGTGTTTTGTGTACCCTCTTGATTTT
GCCCGTACCCGTCTAGCAGCTGATGTGGGTAAAGCTGGAGCTGAAAGGGAATTCCGAGGCCTCGGTGACTGCCTGGTTAA
GATCTACAAATCTGATGGGATTAAGGGCCTGTACCAAGGCTTTAACGTGTCTGTGCAGGGTATTATCATCTACCGAGCCG
CCTACTTCGGTATCTATGACACTGCAAAGGGAATGCTTCCGGATCCCAAGAACACTCACATCGTCATCAGCTGGATGATC
GCACAGACTGTCACTGCTGTTGCCGGGTTGACTTCCTATCCATTTGACACTGTTCGCCGCCGCATGATGATGCAGTCAGG
GCGCAAAGGAACTGACATCATGTACACAGGCACGCTTGACTGCTGGCGGAAGATTGCTCGTGATGAAGGAGGCAAAGCTT
TTTTCAAGGGTGCATGGTCCAATGTTCTCAGAGGCATGGGTGGTGCTTTTGTGCTTGTCTTGTATGATGAAATCAAGAAG
TACACATAAGTTATTTCCTAGGATTTTTCCCCCTGTGAACAGGCATGTTGTATTATATAACATATCTTGAGCATTCTTGA
CAGACTCCTGGCTGTCAGTTTCTCAGTGGCAACTATTTACTGGTTGAAAATGGGAAGCAATAATATTCATCTGACCAGTT
TTCTCTTAAAGCCATTTCCATGATGATGATGATGGGACTCAATTGTATTTTTTATTTCAGTCACTCCTGATAAATAACAA
ATTTGGAGAAATAAAAATATCTAAAATAAATTTTGTCTGCAGTATATTTTCATATAAAAATGCATATTTGAGTGCTACAT
TCGAATAAATACTACCTTTTTAGTGAA
```

Gene ‘string’



3D view of gene

Can we design & predict the activity of our drug computationally?

Use Case: ETX RNA AI Agent

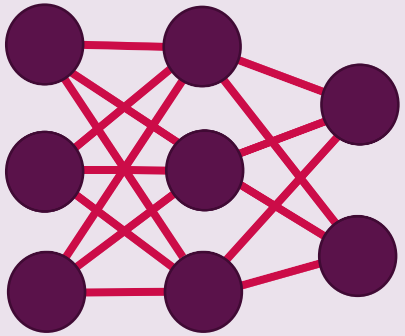
Is there a secret language in genetic sequences?

Aim: To treat mRNA sequences as a language and predict siRNA efficacy in downstream tasks

1 Pre-Training Model to understand mRNA structure

AGGCUAGUC<MASK>UCAG<MASK>UCCA

Input



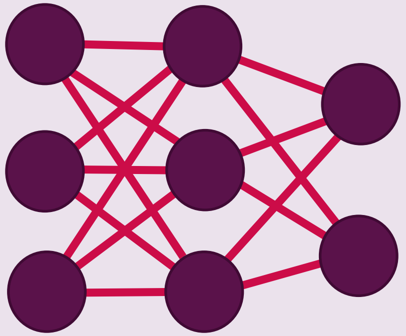
Output

AGGCUAGUCUUCAGCUCCA

2 Downstream task to make siRNA efficacy predictions using mRNA structure knowledge

mRNA: AGGCUAGUCUUCAGCUCCA
siRNA: UCCGAUCAGA

Input



Output

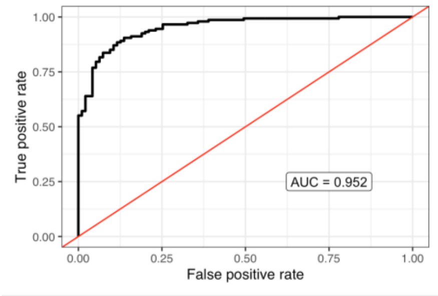
Efficacy: 0.75

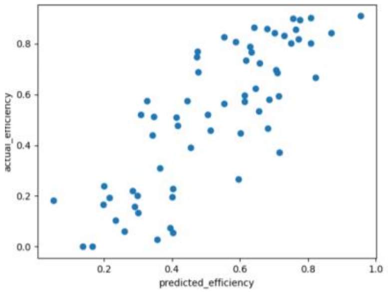
Fully Computational siRNA Drug Design

ETX siRNA designR

- Proprietary deep learning algorithm for predicting siRNA efficacy
- Ranks siRNAs to minimise, and potentially eliminate, *in vitro* screening
- Can currently accurately predict 6 of the top 10 siRNAs per gene (ranked by knockdown efficacy)
- Working on enhancing predictive performance using large language (transformer) models to represent information of RNA sequences

Validated using ETX designs





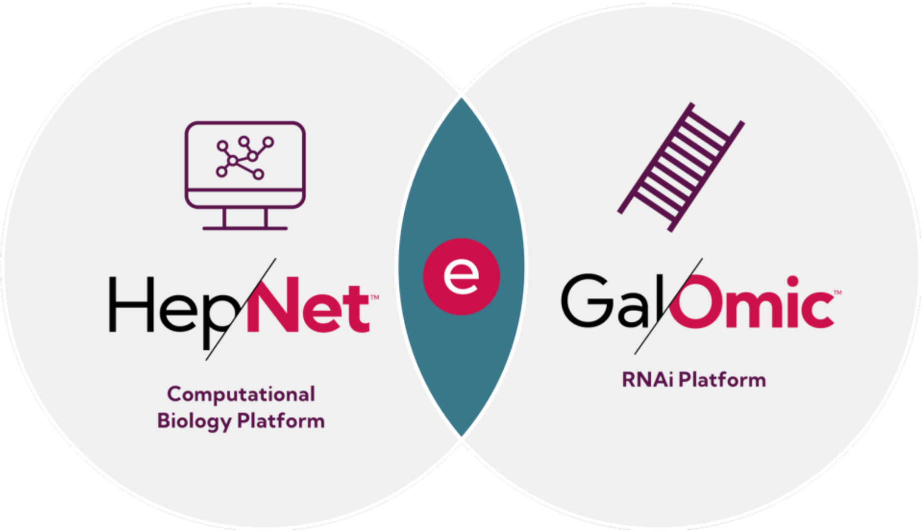
Classification Performance Metrics

Strong performance classifying siRNAs as active vs inactive (AUC : 0.952)

	Current Approach	ETX RNAi Agent
Number of siRNA screened	Up to 400	**<10**
Time to lead identification (potential clinical candidate)	6 months	**1 month**
Cost of screening	£500,000	**£50,000**

A Unique Generalisable Model for Drug Discovery

Significant reduction in wet lab work & even clinical trials



Computing the Future of Medicine™

Drug Discovery Is A Data Science Problem

- Unparalleled ability to **model complex human biology**
- Identification of **novel gene targets**
- **Rapid** design of safe and potent **RNAi medicines** that silence those genes
- **Accelerated** progress of in-house **pipeline** across multiple diseases

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