Engine Biosciences
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Deciphering complex biology to discover next-generation therapeutics

Engine Biosciences has developed a multi-layered platform, NetMAPPR, which integrates machine learning and combinatorial CRISPR to decode biological networks, pinpoint crucial units, and design specific therapeutics.

Drug developers have long known that many diseases are the product of complex biology involving interactions between multiple genes and molecules. Yet that complexity has overwhelmed traditional drug discovery technologies, forcing researchers to take a simplified single-target, single-gene, single-molecule approach that only partly addresses the underlying causes of disease. Engine Biosciences seeks to shift that paradigm by applying machine learning and combinatorial CRISPR screens to the problem.

Led by the oncology field, biopharma is beginning to tap into the power of combination therapy and treatments that target two linked genes through a biomarker and a drug target. However, the complexity of human biology makes it difficult to systematically discover such therapies and treatments.

Humans have approximately 20,000 genes. Scientists can explore the therapeutic value of individual genes using existing tools such as genome-wide CRISPR screens, but the task becomes significantly more challenging when the search expands to cover combinations. A researcher searching for two genes involved in a disease would need to go through around 200 million unique pairs. Adding a third gene increases the number of possibilities to above 1 trillion.

Engine Biosciences has developed a platform, NetMAPPR, to make those numbers far more manageable (Fig. 1). Since starting out 3 years ago, the company has raised $17 million in venture funding and built a 30-person team across sites in San Francisco and Singapore, enabling its multi-pronged approach to deciphering complex biological networks and converting the resulting insights into validated R&D programs.

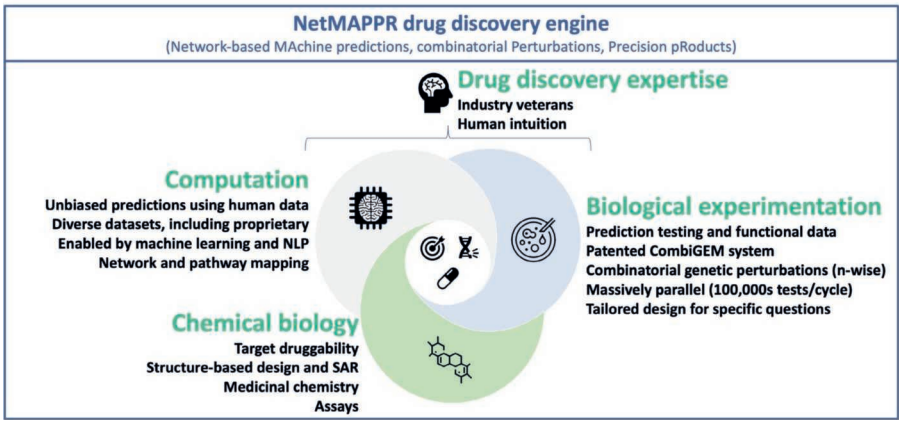

Fig. 1 | NetMAPPR drug discovery engine. The three-pronged platform analyzes complex biological networks to drive the development of next-generation therapeutics.

Analyzing gene networks at scale

The first layer of Engine Biosciences' platform is a suite of algorithms leveraging machine learning and natural language processing. By training the models to spot patterns using public and proprietary datasets, the company has gained the ability to make predictions about larger biological networks and identify potentially crucial gene combinations. The algorithms quickly identify thousands of gene combinations worth investigating.

To avoid a bottleneck between in silico identification and experimental validation, Engine Biosciences exclusively licensed patented technology from the Massachusetts Institute of Technology to run massively parallel experiments. Having industrialized the technology, Engine Biosciences can quickly and easily create custom n-wise combinatorial knockout CRISPR libraries that support time- and cost-efficient experiments that test the platform's predictions.

The third layer of the platform comes into play once Engine Biosciences has identified crucial biology that could form the basis of a drug discovery program. Engine Biosciences' team of drug discovery experts work to validate druggable targets and design small-molecule inhibitors against them. The team uses structure-based design and structure-activity relationships to accelerate progress.

Engine Biosciences has validated the effectiveness of its three-pronged platform through in vitro and in vivo testing of the most advanced programs to emerge from it. Those programs target oncological indications, which the company identified as an attractive proving ground for its approach.

Although chemotherapy remains widely used in cancer care, combinations and targeted approaches are starting to redefine the treatment of some tumors. Engine Biosciences' network biology approach is well suited to the identification of drug combinations and gene combinations that enable synthetic lethality, a process through which the simultaneous perturbation of multiple genes causes cell death.

Engine Biosciences has already demonstrated proof of principle with novel discoveries of a precision oncology program and a combination therapy. The precision oncology program targets a kinase in the presence of a separate loss-of-function mutation found in several solid tumors, including those originating in the liver, ovaries and gastrointestinal tract. The company has validated the pan-cancer efficacy of the inhibition across these three tumor types.

The combination therapy is supported by in vitro and in vivo data linking the simultaneous targeting of two genes underlying tumor growth to the synergistic killing of cancer cells. Engine Biosciences is working to optimize small-molecule leads, nominate candidates and start clinical testing of these two programs.

Partnering to realize potential

The two lead assets are trailed closely by earlier-stage programs, most of which are also in precision oncology, as well as efforts that target indications outside oncology. Engine Biosciences has shown the applicability of its platform to therapeutic areas such as neurodegeneration and dermatology, the latter through a collaboration with a major multinational healthcare company.

Engine Biosciences intends to leverage its unique platform, which feeds data from its combinatorial CRISPR screens back into its machine learning algorithms for continual improvement, to expand the scope of its efforts, but the potential of the approach is too broad for even such an ambitious biotech to realize on its own. As such, the company is open to partnering with companies with complementary capabilities to advance its earlier-stage programs and further explore the potential of its platform.

Through its internal and partnered programs, Engine Biosciences is well positioned to continue deciphering complex biological networks to inform the development of next-generation therapeutics that tackle major unmet medical needs.

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