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How artificial intelligence is enabling T cell receptor screening for cell therapy discovery

Exogene is using artificial intelligence to find rare, natural T cell receptors with a view to treating solid tumors and, ultimately, rejuvenating the immune system.

T cells use T cell receptors (TCRs) to identify and eliminate diseased cells. T cells equipped with cancer-targeting TCRs can detect and eliminate cancer cells, and TCR-based T cell therapies have the potential to eradicate otherwise untreatable solid tumors. Unfortunately, therapeutically relevant TCRs are rare and hard to find. Faced with a needle-in-a-haystack problem, Exogene has combined artificial intelligence (AI) with cutting-edge lab-based technologies to create a fast, scalable TCR screening platform to identify TCRs for cell therapy applications.

Artificially generating or engineering TCRs against disease-associated targets can introduce unwanted TCR cross-reactivity and cause toxic side effects, so to avoid this problem the field has shifted to identifying TCRs from natural human TCR repertoires. However, identifying natural TCRs against disease-associated targets is a huge challenge. For example, every human naturally produces billions of different TCRs, but less than one in 100,000 is specific for a cancer target. The scale of the problem means that comprehensive screening of natural TCR repertoires is impossible using current wet-lab technologies. So, although it is known that human blood may contain TCRs with the potential to help cure solid tumors, it is difficult to find such rare, target-specific TCRs.

Reliance on systems that fail to identify target-specific TCRs is holding back healthcare. For cancer, it is known that T cells genetically engineered to express cancer-specific TCRs can facilitate the eradication of solid tumors, but there isn't a good way of finding these rare TCRs. In the future, ready access to TCRs could support the development of completely novel cell therapies designed to eliminate senescent T cells, thereby rejuvenating the immune system and tackling a potential driver of cardiovascular disease and neurodegeneration (Fig. 1).

Harnessing AI to find T cell receptors

Exogene, a startup based in Oxford, UK, is developing an AI-based platform to identify target-specific TCRs and enable the development of TCR-based cell therapies. Exogene sequences millions of TCRs from patient and donor-derived T cells and uses its technology to comprehensively screen these natural TCR repertoires and identify rare, potent TCRs against targets of interest.

To identify TCRs, Exogene has developed AI that uses the protein sequences of millions of receptors and potential targets to predict interacting TCR–target pairs. The AI solves the scalability problem that is at the heart of 'why finding TCRs is hard' using current wet-lab technology.

"With AI, you can screen billions of TCRs in a matter of seconds. That means you have much higher chances of finding a potent cancer-targeting TCR because you cast a much wider net, and you can do it much faster and at a much lower cost than with any other platform," said Federico Paoletti, CEO and co-founder of Exogene.

Exogene's deployment of AI differentiates it from conventional TCR biotech companies, which mostly rely on wet-lab technologies that lack the speed and scalability of the computing-enabled approach. Other companies have also identified AI as the way to perform comprehensive, scalable screening of TCRs but they often lack Exogene's in-house, high-throughput data generation capabilities.

Using novel high-throughput display technologies coupled with deep sequencing, Exogene tests TCRs identified by its AI in the laboratory. Exogene can generate functional data for up to 100 million TCR-target pairs during each lab testing step. The display libraries are deep sequenced and the results are then fed back into the AI, creating a virtuous cycle that continually improves the output of the AI (Fig. 2). Laboratory testing also enables Exogene to determine which TCRs to advance for use in T cell therapies.

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"Our high-throughput data generation capabilities enable the continuous improvement of our AI-based TCR screening platform. This means we can generate massive training data sets in-house and we do not depend on limited external data sources to improve our AI platform," said Andrea Mambrini, CTO and co-founder of Exogene.

Exogene's combination of advanced AI and lab-based data-generation technologies sets it apart from both conventional, wet-lab-based TCR biotech companies and startups focused

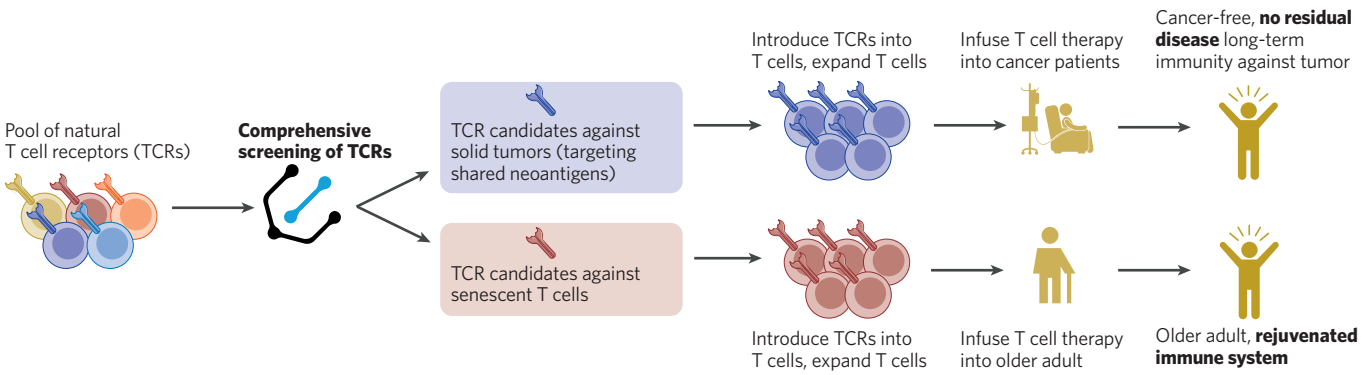

Fig. 1 | Screening natural T cell receptor repertoires. The screening enables the identification of T cell receptors to develop cell therapies targeting solid tumors (and in the future, targeting senescent T cells).

on AI. With a foot in each world, Exogene has the full suite of technologies needed to identify natural, target-specific TCRs.

Tackling solid tumors

Mutations in tumor cells cause them to express neoantigens on their surface. Evidence points to neoantigens as promising T cell targets to drive regression of cancer in patients receiving immuno-oncology therapies[1]. A subset of these neoantigens are derived from oncogenic driver mutations and are thought to be shared across patients and be present on most cancer cells in a specific patient, but not on any healthy cells. These are known as shared neoantigens.

Neoantigen-specific T cells are particularly rare, however. In one study, T cells specific for neoantigens represented as little as 0.002% of the peripheral T cell population[2], making it unfeasible to find these rare T cells using established wet-lab technologies and highlighting the need for more scalable AI approaches.

Exogene is using its AI platform to screen TCR repertoires from patients with solid tumors and identify rare, natural TCRs against shared neoantigens. As shared neoantigens are thought to be present on most cancer cells in a given patient, but not on healthy cells, TCR-based cell therapies targeting shared neoantigens have the potential to be both safe and highly effective.

Exogene's upcoming goals include the identification of initial TCR candidates for shared neoantigen programs. By comprehensively screening a pool of natural TCRs, Exogene will identify TCRs that target shared neoantigens expressed by solid tumors. It will then use these TCRs to develop its own pipeline of TCR-based cell therapies to cure patients who have advanced solid tumors presenting specific driver mutations.

"The field has found it very difficult to find natural, potent T cell receptors against shared neoantigens because they are very rare. Our AI unlocks the opportunity to find them by comprehensively screening natural TCR repertoires," said Paoletti. The rarity of neoantigen-specific T cells and their promising role in the treatment of some solid tumors makes them an ideal proving ground for Exogene's technology.

TCR-based therapies have attracted considerable dealmaking activity, despite the limitations of existing methods for identifying TCRs. GlaxoSmithKline and Roche have both entered into billion-dollar TCR deals in recent years, while Immunocore, the first company to receive approval from the US Food and Drug Administration (FDA) for a TCR therapy in January 2022, has gone public at a $1 billion valuation. Exogene potentially has a better way of finding receptors than the first generation of TCR biotechs.

Rejuvenating the immune system

Solid tumors are a major, near-term opportunity for TCR-based cell therapies, but an even bigger market awaits Exogene in the future. Exogene plans to validate its technology and establish its business in the solid-tumor space, and then use that position of strength as a launchpad to work on a completely novel therapeutic approach: TCR-based cell therapies to rejuvenate immune systems and prevent disease.

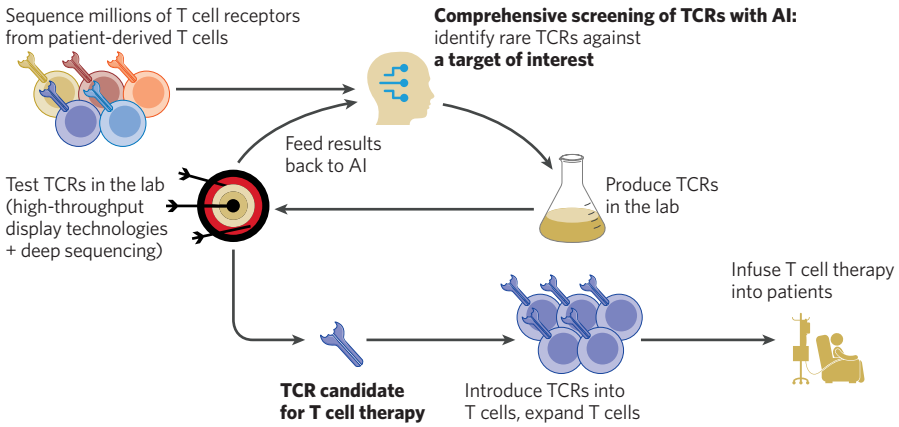

Fig. 2 | Exogene combines AI with cutting-edge wet-lab technologies to identify natural T cell receptors against targets of interest. TCR, T cell receptor.

The immune rejuvenation strategy is underpinned by evidence that senescent T cells accumulate as we age[3], weakening the immune system and raising the risk of developing cardiovascular disease, neurodegenerative disorders and other chronic conditions[4]. Although the evidence currently centres on mice data, researchers think senescent T cells may have a similar effect in humans. If that is true, therapies that eliminate senescent T cells could potentially prevent a wide range of major age-related diseases.

Immune rejuvenation is still a far more speculative concept compared to TCR-based cell therapies for solid tumors, but both fields pose a similar challenge to drug developers. In both cases, a key problem is finding rare, natural TCRs that can guide immune cells to eliminate diseased cells in a targeted, effective manner. Exogene is building its platform to solve that problem.

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The nascent nature of the immune rejuvenation field means Exogene has plenty of work to do before it can use its platform to find TCRs against senescent T cells. First, it needs to build an initial target library for senescent T cells because there is currently a shortage of characterized senescent T cell targets. Once Exogene has built its library, it will use its platform to match natural TCRs to these targets to support the development of immune rejuvenation therapies.

Exogene's immune rejuvenation work could position it to prevent many of the chronic diseases that are the biggest unmet medical needs faced by our ageing societies. By specifically targeting senescent T cells, a common root of several chronic diseases, Exogene could unlock a wide range of therapeutic opportunities and realize the full potential of its platform for finding TCRs.

"The aim would be to eliminate senescent T cells," Paoletti explained. "There's evidence showing that as you age, you accumulate these senescent T cells, and that potentially harms you and actually increases the chances of you developing chronic diseases. If this is true, we could develop TCR-based cell therapies to specifically eliminate these senescent T cells while leaving other immune cells untouched. The approach is of course still speculative, but it could potentially result in a major shift towards preventing age-related diseases."

Partnering with pharma and biotech

Exogene is looking to enter into partnerships to capitalize on its ability to rapidly identify TCRs. The business development strategy has two strands. First, Exogene wants to partner with pharma and biotech companies to help them discover TCRs from scratch for therapeutic applications they are pursuing. Second, Exogene is developing internal TCR T cell therapies that could be the focus of out-licensing deals.

Both types of deal present pharma and biotech companies with opportunities to gain access to the fruits of a platform that is positioned to realize the long-unfulfiled potential of TCR-based cell therapies. Exogene is addressing the scalability barrier to TCR screening by developing an AI capable of almost instantly screening billions of TCRs, and has set up wet-lab capabilities that will drive continual improvement of the system.

Equipped with this platform, Exogene is positioned to address major unmet medical needs through the use of TCR-based cell therapies, both through its internal programs and partnerships. Pharma and biotech companies that partner now will gain early access to AI-based technology that is poised to unlock the identification of natural, target-specific TCRs.

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2. Cohen, C. J. et al. *J. Clin. Invest.* **125**, 3981–3991 (2015).
3. Nikolich-Žugich, J. *J. Nat. Immunol.* **19**, 10–19 (2018).
4. Desdín-Micó, G. et al. *Science* **368**, 1371–1376 (2020).

CONTACT
Federico Paoletti, CEO & Co-founder
Exogene Ltd.
Oxford, United Kingdom
Email: f.paoletti@exogene.co.uk