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## **Orchestrating the immune system** for precision immunity

Elicio's lymph node-targeting Amphiphile technology delivers potent T cell activation and boosts the effects of engineered cell therapies.

Immune cells are naturally gifted in recognizing antigens and fighting off infection and disease. But, just like talented people, they need nurturing and the right training to fulfil their true potential. For immune cells this means a spell in lymph nodes the training camps of the immune system—where they receive specialized instruction in the art of immune surveillance and attack.

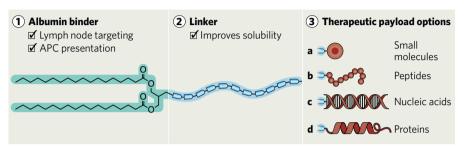
Today's immunotherapies do not make use of this powerful immunological form of education. The promise and effectiveness of immunotherapies are widely recognized: chimeric antigen receptor T (CAR-T) cell therapies directed against the CD19 tumor antigen have been particularly effective against hematological malignancies, and checkpoint inhibitors (CPIs) have emerged as a major focus for treating solid tumors.

Yet the full potential of these therapeutic approaches has not yet been unleashed. CAR-T cell therapies can struggle to achieve clinically beneficial T cell expansion and persistence, often lack the ability to effectively infiltrate the tumor microenvironment and over time lose their tumor-killing functions. At the same time, CPI therapies have demonstrated the ability of the immune response to kill solid tumors, but their efficacy has been limited because in these therapies few spontaneously arising T cells infiltrate tumors that have a low rate of neoantigen mutation. The key to overcoming these limitations, Elicio Therapeutics believes, is to make use of the specialized immunological training environment of the lymph nodes, to prime T cells to become more effective at their job.

## Transporting immunomodulatory payloads

Elicio is tackling this challenge with next-generation immunotherapies based on its proprietary Amphiphile (AMP) technology, which can effectively ferry immunomodulatory payloads—from small molecules and peptides to DNA and proteins—to the lymph nodes, where immune cells learn how to recognize these immunomodulators and react appropriately to them. Elicio is applying the AMP platform to developing new cancer vaccines, creating more potent responses from CAR-T cells and delivering cytokines, immunomodulators and adjuvants to lymph nodes. The unique, broadly applicable lymph node-targeting AMP technology has the potential to address many unmet medical needs and bring enormous benefits to patients.

The AMP technology grew out of the multi-disciplinary lab of Darrell Irvine, a biological engineer at the Koch Institute for Integrative Cancer Research



**Fig. 1 | A modular conjugation approach for delivery of immune therapeutics to the lymph node.** The technology enables a lipophilic tail to bind to a linker domain, which is then able to attach to various types of immunomodulatory payload molecules.

at the Massachusetts Institute of Technology. Irvine brought together materials scientists, immunologists and oncologists to work at the interface of materials science and immunology in an effort to solve the problem of how to target payloads to the lymph nodes.

Lymph nodes are one of the key secondary lymphoid tissues where immune cells congregate and where adaptive immune responses are initiated. It is here that the complex cellular interactions required for an effective immune response are finely orchestrated, and is why the lymphatic system is said to be the brain or command centre of the immune system. The learning environment of the lymph node endows immune cells with skills that are harder to learn elsewhere, such as how to achieve T cell expansion and persistence; how to effectively hone in on and penetrate solid tumors; and how to promote immune memory and antigen spreading.

Getting molecules of interest into lymph nodes, and making sure they stay there long enough to do useful work, faces some key hurdles. One of the most fundamental is that the smaller the molecule, the less likely it is to accumulate in the lymph nodes—an issue that affects small molecules, peptides, proteins and other biopolymers. The AMP strategy is to piggyback on a very large molecule, one that naturally accumulates in lymph nodes: albumin.

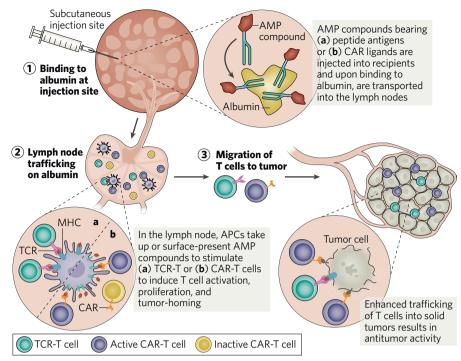
The core of the AMP technology is a lipophilic tail that mimics fatty acids that albumin naturally binds to, connected to a linker domain to which various types of immunomodulatory payload molecules can be attached (Fig. 1). When injected into tissue, cargo-loaded AMPs bind to locally present albumin, are transported through the lymphatic vessels and finally accumulate in lymph nodes. Here, the immunomodulatory payload ferried to the lymph nodes is taken up by antigen-presenting cells (APCs), which then interact with effector immune cells as part of their training to become potent antigen-targeting cells (Fig. 2).

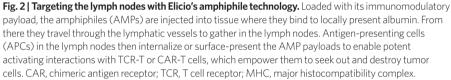
## **Portfolio of candidates**

Elicio has a range of candidates based on AMP technology in its proprietary pipeline: cancer vaccines that combine antigenic peptides and adjuvant with an AMP molecule; AMP-linked activators of CAR-T cells for hematological and solid tumors; AMP cytokines; and AMP adjuvants.

Elicio's most advanced cancer vaccine program is focused on patients with tumors carrying mutations in KRAS, which make up roughly 25% of all human solid tumors and are even more prevalent in specific cancers-up to 90% of pancreatic cancers, 50% of colorectal cancers and 30% of nonsmall-cell lung cancers. KRAS is widely recognized as promising in immunotherapy, and has been singled out by the National Cancer Institute as one of the only true public neoantigens, meaning that it is not only highly prevalent and clinically relevant, but also a target that the immune system is especially well suited to recognizing as a tumordifferentiating marker. And the biology of KRAS is compelling as mutations in this gene need to be maintained in all the tumor cells in most of the tumor types in which it is implicated. So if all tumor cells carrying KRAS mutations can be eradicated in a tumor, there is potential for a long, durable response.

Elicio's ELI-002 comprises AMPs carrying common KRAS-mutated peptides, along with a powerful immune-activating adjuvant, to elicit an immune response that engages both innate immunity (dendritic cells) and adaptive immunity (T cells) to increase tumor targeting. ELI-002 targets the seven position 12 and 13 KRAS mutations that are seen in more than 99% of KRAS-driven cancers,





and contains seven AMP peptides containing these mutations plus an AMP carrying a CpG Toll-like receptor 9 agonist.

Preclinical in vivo models have demonstrated that ELI-002 is precisely targeted to lymph nodes, where it creates a powerful T cell response that is more than 100 times greater than that achieved with conventional therapies. These lymph nodeprimed T cells, which become prolific producers of cytokines that are important for an effective antitumor response, are highly effective killers of KRAS-specific targets, and are able to specifically recognize all seven mutational variants of KRAS. Similar AMP vaccine approaches developed by Elicio and tested in other models have produced complete cures and resistance to otherwise lethal doses of tumor re-challenge.

In colorectal cancer care, patients with KRAS mutations are excluded from treatment with monoclonal antibodies against epidermal growth factor receptor, so that a therapeutic candidate for this subgroup holds potential to address a large group currently in need of an effective therapy.

Elicio is poised to begin a prospective, multicenter phase 1/2 clinical trial of ELI-002 in patients with locally advanced pancreatic ductal adenocarcinoma, colorectal cancer and other tumors after standard therapy. In the clinical trial of ELI-002, patients will be screened to identify those with tumors containing KRAS mutation and with minimal residual disease assessed by the presence of circulating tumor DNA-a group of patients that almost universally relapse. The trial is designed to allow crossover of patients assigned to the control arm to ELI-002 at the time of relapse, so that RECIST radiographic data on metastatic disease can be assessed. The trial is planned to begin in 2020.

Elicio has recently begun a collaboration with James Yang's laboratory at the National Cancer Institute, which has pioneered T cell therapies for solid tumors, to characterize T cell responses to ELI-002 in mice genetically engineered to carry human leukocyte antigen (HLA) genes important for the immune response. This study will not only inform how patient responses are monitored in the clinical study of ELI-002, but will also help use trial data to identify novel T cell receptors for future T cell therapies.

Elicio's other major application of AMPs is to unleash the full potential of CAR-T cell therapies. CAR-T cell therapies have demonstrated remarkable therapeutic results and have been shown to completely eliminate tumors in some forms of cancer, especially hematological malignancies, in some patients. Yet they have failed to show similar benefits in most other cancer settings, with solid tumors posing a particular challenge—largely due to the fact that current CAR-T cells lack the ability to properly expand their numbers, to efficiently infiltrate solid tumors and to effectively kill cancer cells. A major reason for these limitations is that CAR-T cells, as currently used, do not engage the lymph nodes at all. As a result, they are not activated at these key immune-orchestrating sites, and miss out on the education and training that lymph nodes provide to ensure that T cells become the best cancer-destroying cells they can be and remain functional and expanded over time.

Elicio is using its AMP technology platform to bring out the best in CAR-T cell therapies. The approach is to attach CAR-T activators to AMPs. which, once carried to lymph nodes by albumin, insert themselves into the surface of APCs through their fatty acid tails. These APCs then present the activator molecules to CAR-T cells in the lymph nodes, priming them to mount a potent response to tumor cells carrying the antigen they have been engineered to recognize (Fig. 2).

Elicio's proof-of-concept studies have shown how effective AMP CAR-T activators are. In a standard CAR-T cell approach, at best 20% of a patient's T cells are converted to recognize the tumor antigen that the CAR-T cells have been engineered to detect. When combined with AMP CAR-T activators, however, this jumps to as much as 70% or more in animal models. In addition, a number of current CAR-T therapies that have shown potent anticancer activity have been hampered in practice by toxicity caused by the high doses required for systemic delivery. The AMP technology can rescue these CAR-T therapies by targeting lower doses to the lymph nodes so they become highly effective tumor-destroying cells, while limiting exposure to other sites in the body.

Compared with CAR-T cell therapy alone, Elicio's AMP-CAR-T combination leads to a tenfold increase in the infiltration of solid tumors, a tenfold greater cytokine response, enhanced cytolytic function and the induction of 'antigen spreading', in which the native immune response is triggered to recognize tumor-specific antigens other than the one targeted by the CAR-T cell. In models in which CAR-T cell therapy by itself provides no detectable therapeutic effect, the AMP-CAR-T combination leads to durable cure in a large proportion of animals

Beyond developing AMP cancer vaccines and CAR-T cell activator, Elicio is developing ELI-004, an AMP-adjuvant with applications in a variety of indications and therapies, including as the adjuvant component of ELI-002. Finally, Elicio has earlier-stage programs using AMP technology to deliver cytokines, immunomodulators and other adjuvants to the lymph nodes for stimulating a potent immune response.

Immunotherapies have proved their worth, but for many specific therapies their full effectiveness has remained untapped, or they have been beset by problems linked to toxicity. AMP technology addresses both issues. Elicio's strategy is to continue developing AMP applications to expand the range of diseases to which it can be applied, and to focus on building a proprietary pipeline around this core platform. At the same time, Elicio is keen to partner with companies developing complementary technology, specifically in the cell therapy space, to usher in a new era of immunotherapies.

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