ISA Pharmaceuticals
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Designing next-generation immunotherapeutics

With two established technologies, SLPs and AMPLIVANT, ISA Pharmaceuticals is developing fully synthetic immunotherapeutic vaccines to target cancer and persistent viral infections.

Netherlands-based ISA Pharmaceuticals is a science-driven immunotherapeutics company with a difference. "Decisions are based on a clinically validated and well-understood mechanism of action of our immunotherapeutics," said CEO Ronald Loggers. "This unique approach leads to a growing portfolio of T cell–activating immunotherapeutics, proven to be safe and easy to combine with standard of care."

ISA's approach is based on the pioneering work of Leiden University Medical Center immunohematologist Cornelis Melief, who became the company's CSO in 2008. With the medical center as its primary research partner, ISA is the first company to decipher the immunopharmacology of its compounds, designed via its two proprietary drug development platforms: synthetic long peptides (SLPs) and a Toll-like receptor adjuvant (AMPLIVANT).

SLP immunotherapeutics typically contain between 5 and 15 different, carefully selected SLPs. Each peptide is between 20 and 35 amino acids in length, which is longer than an immunogenic epitope itself. "The length of the peptides is crucial for how they are processed and presented to the immune system," said Melief. When administered, the SLPs are directly taken up and processed by antigen-presenting cells, which in turn educate and direct a strong systemic immune response against the diseased cells. The SLPs contain epitopes designed to elicit both $CD4^+$ helper and $CD8^+$ killer T cell responses, independent of a patient's human leukocyte antigen profile. They are applicable to a variety of targets expressed by diseased cells and recognized as foreign to the human body.

SLPs are designed to harbor multiple T cell epitope sequences of a given target. Once taken up by dendritic cells, they are processed into the smaller peptides that are loaded onto either MHC class I (the epitope recognized by a $CD8^+$ T cell receptor) or MHC class II (the epitope recognized by a $CD4^+$ T cell receptor) molecules (**Fig. 1**). Antigens presented on the cell surface of dendritic cells activate naive $CD4^+$ and $CD8^+$ T cells. A $CD4^+$ helper T cell response is key to the maturation of dendritic cells and the subsequent strength of the $CD8^+$ killer T cell response. Costimulatory components such as Montanide and AMPLIVANT substantially contribute to the induction and magnitude of responses. As a result, SLP-based therapy elicits strong and lasting immunity capable of killing the diseased cells expressing the pathogenic antigens without affecting healthy tissues.

Targeting HPV16

ISA's lead product, ISA101, is closing the gap between preventive cancer vaccines and standard cancer treatments. It treats human papilloma virus 16 (HPV16)-induced diseases, which occur when the cancer-associated virus becomes integrated into cell DNA and activates processes that can lead to cancer.

Specifically, ISA101 targets cells expressing HPV16 proteins—the strain responsible for over 50% of human cervical cancers and more than 85% of HPV-positive head and neck cancers. ISA101 is derived from two HPV16 oncogenic proteins. Clinical trials have shown proof of concept in patients with vulvar intraepithelial neoplasia and proof of principle in cervical cancer[1,2]. "We are the first and only ones to show a direct correlation between vaccine-induced immune responses and clinical responses," said Melief. "We deciphered optimal timing for T cell activation in concert with standard-of-care chemotherapy regimen, resulting in unprecedented immune responses."

ISA Pharmaceuticals is also developing a complementary AMPLIVANT adjuvant technology to enhance the activity of its SLP immunotherapeutics by 100- to 1,000-fold. It is based on a lipo-peptide that targets Toll-like receptors expressed by dendritic cells. SLP-AMPLIVANT conjugates lead to longer-term, more effective antigen presentation and T cell response, thereby allowing for lower dosing at higher efficacy. AMPLIVANT can substantially enhance any type of targeted immunotherapy. SLP-AMPLIVANT conjugates are currently in clinical trials for patients with HPV16-positive head and neck cancer.

ISA has several other programs in development, including ISA203, an SLP therapeutic derived from the human antigen PRAME (preferentially expressed antigen in melanoma), which is mis-expressed by many tumors, including lung, breast, kidney, brain and skin cancers, and ISA204, an SLP composite of hepatitis B antigens and ISA's AMPLIVANT technology for treatment of chronic hepatitis B infection.

Recent results published in high-impact journals show that SLP therapeutics offer synergistic benefits when combined with standard chemotherapy and immunomodulatory compounds. Currently ISA101 plus chemotherapy is being assessed in the CervISA study[3] in advanced cervical cancer, and ISA101 plus checkpoint inhibitor nivolumab is being explored in a phase 2 study by the MD Anderson Cancer Center.

Personalized approach

ISA is also developing personalized SLP immunotherapies to tackle cancers with a high mutational load and resistance to standard treatments (e.g., lung cancer and melanoma). "The best results can only be achieved by choosing antigens that are unique to the cancer, thereby avoiding central immunological tolerance," said Melief. "While off-the-shelf immunotherapeutics work well in virus-induced cancers, addressing nonviral cancers needs antigens specific to the tumor. Therefore, we are focusing on patient-specific neoantigens, originating from mutations in the cancer cells."

These treatments require an individual set of SLPs designed from patient tumor samples. Such on-demand, personalized treatments would provide a highly specific and sustained immune response. The approach could signal a paradigm shift in both treating cancer and developing therapies, and ISA is well placed to take on this challenge. "As a true pioneer in the cancer immunotherapy field, we are dedicated to exploring it to provide therapeutics for previously untreatable cancers at affordable costs," said Loggers.

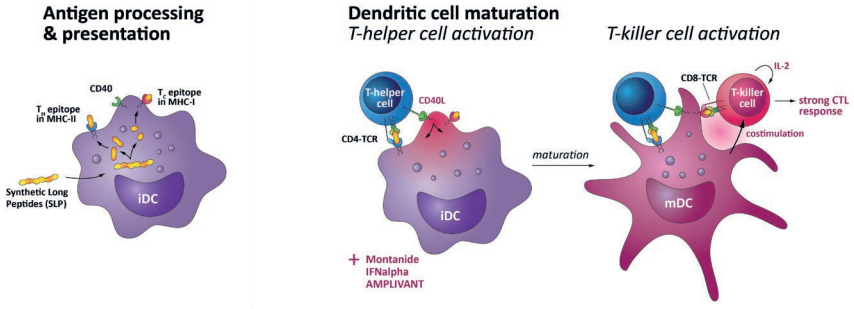

Figure 1: The synthetic long peptide (SLP) concept and costimulation induce strong T cell–mediated immunity and memory. Image designed by Scicomvisuals.

1. Kenter, G.G. *et al. N. Engl. J. Med.* **361**, 1838–1847 (2009).
2. van Poelgeest, M. *et al. Clin. Cancer Res.* doi:10.1158/1078-0432.CCR-15-2594 (2016).
3. ISA Pharmaceuticals. Study of therapeutic vaccine (ISA101) to treat advanced or recurrent cervical cancer (CervISA). *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02128126 (2016).

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