Buying into personalized cancer vaccines

Cancer vaccines based on tumor-specific neoantigens are becoming the next big immunotherapy partnering opportunity.

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First-generation cancer vaccines have disappointed drug developers, investors and clinicians, largely because so far they have targeted bits of protein that the immune system does not deem a threat. Such vaccines direct the immune system to target proteins overexpressed on cancer cells—so-called tumor-associated antigens—that it would otherwise recognize as normal (or 'self') because they are also expressed on healthy cells. But new efforts to identify key mutations that give rise to antigens that are unique to an individual's cancer are reigniting interest in the field.

By harnessing rapid and cost-effective genomic sequencing and bioinformatics tools, scientists are able to sleuth these tumor-specific neoantigens (also called neoepitopes) out of patient biopsies, load them into vaccine vectors with increasingly efficient manufacturing techniques, and administer them to patients, sometimes alongside drugs such as immune-checkpoint inhibitors that take the brakes off tumor-fighting T cells. Within each step of this process lie competing ideas, theories and technologies. Key questions facing the field include how to pick the right combinations of neoantigens, which vector can most effectively deliver those neoantigens, and what the right therapeutic combinations and clinical settings in which to test the vaccines are.

Over the past 18 months, biopharmaceutical partners have begun to support the strategies they believe are most likely to bear fruit. The opportunity has also been warmly embraced by venture capitalists, who have funneled hundreds of millions of dollars into the space in this period. That total doesn't include forays into the area by well-heeled biotechs such as the messenger RNA (mRNA) drug developer Moderna Therapeutics, which announced its Caperna personalized cancer vaccines unit in late 2015.

Identifying neoantigens

Interest in neoantigen cancer vaccine platforms is "extremely high" among pharma companies, said Andrew Allen, CEO of Gritstone Oncology, which raised $102 million in series A funding from Versant Ventures, the Column Group, Clarus Ventures and others in October 2015. In January 2016, Gritstone licensed neoantigen technology developed in part by its scientific founders from the Memorial Sloan Kettering Cancer Center. Commercial oncology players must make a raft of strategic decisions about whether they want to pursue personalized therapies or wait for tumor-specific antigen therapies that comprise antigens shared across patients with common mutations, he said. They're also exploring which therapeutic modalities they will invest in to achieve their personalized therapy objectives, said Allen, because vaccines, chimeric-antigen-receptor T cells, and T cell receptors offer different opportunities for pharma companies.

Much of the vaccine companies' potential competitive advantages come from how and why they choose specific neoantigens for their personalized vaccines. "If you think about it like a recipe from a cookbook, you can make a vaccine no problem, but if you don't know which parts of the recipe and what amounts, you will construct a vaccine that frankly won't do anything," said Neon Therapeutics CEO Hugh O'Dowd. "You need to be able to quickly and clearly identify the right epitopes" by using a powerful predictive algorithm such as Neon's, he said. In late 2015, Neon entered a partnership with Bristol-Myers Squibb (BMS) to test its neoantigen vaccine NEO-PV-01 in a phase 1 combination study with BMS's PD1 checkpoint inhibitor Opdivo (nivolumab). Investors have poured cash into the biotech. In January 2017, Neon said it had raised $70 million in a series B round led by Partner Fund Management. New investors included a handful of so-called crossover investors that fund private and publicly traded companies, and which tend to invest in companies during the lead-up to their initial public offerings. The financing was Neon's second haul in only 15 months: the company debuted in October 2015 with $55 million from investors—including founders Third Rock Ventures—to commercialize neoantigen biology from the Broad Institute at the Massachusetts Institute of Technology and the Dana-Farber Cancer Institute.

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Other companies have begun to eschew antigen prediction altogether, if including all the identifiable neoantigens is possible. Though several companies in the space argue that the use of proprietary algorithms to select the right neoantigens remains an essential step, "even to this day we're not very good at it as a field," said Advaxis EVP and CSO Robert Petit. Petit argued that more often than not, current algorithms fail to select the neoantigens that would effectively direct the immune system against tumor cells. "Do we want to use some predictive algorithm that is only going to give us the right epitopes probably less frequently than a flip of a coin?" By including all possible neoantigens in a vaccine, he said, as the Advaxis platform aims to do, "we don't have to run the risk of eliminating a useful epitope based on a predictive algorithm that hasn't been validated."

Early momentum

Advaxis teamed up with Amgen to develop its neoantigen vaccine ADXS-NEO, in August 2016, in a deal for $65 million up front ($40 million cash plus a $25 million equity investment). Amgen gets worldwide rights to ADXS-NEO and will fund all clinical and commercial activities. Advaxis, which will continue to lead the development of the program through clinical proof of concept and is responsible for manufacturing the vaccine, could receive development, regulatory and sales milestone payments of up to $475 million, plus royalties.

"For the players that are big and serious about immuno-oncology, there's enough promise there that they're very interested, but some are waiting to see if it's really going to be practical," said Petit. This is a typical response to any new technology, but "hats off to Amgen, because I think they have a clear understanding of the potential," he said. He also pointed to Amgen's appreciation for Advaxis' live-attenuated Listeria monocytogenes (Lm) vaccine delivery vector, gained in part because Amgen itself pioneered the approval of a live-attenuated anticancer agent, the genetically modified virus Imlygic (talimogene laherparepvec), which was approved by the US Food and Drug Administration in 2015 for treatment of a subset of melanoma patients.

Advaxis' various immunotherapies—in addition to ADXS-NEO, the company has multiple therapeutic programs directed against cancers associated with human papilloma virus—are all delivered using the Lm vector. One of the vector's features, said Petit, is its large capacity for the delivery of many neoantigens at once within DNA plasmid constructs. It's not alone: the biotech Immune Design Corp. and Gritstone partnered in May 2016 in part to leverage Gritstone's algorithm in vaccines delivered with Immune Design's proprietary viral vector ZVex, but the collaboration was short-lived. The biotechs said only that it was terminated after about six months, by mutual agreement. Immune Design now believes that ZVex has the potential to deliver enough neoantigens to render predictive tools unnecessary.

Several other biotechs say that algorithms able to predict the best neoantigens are necessary, and are getting better as more data are gathered. "One of our competitive advantages is that we're out in front, and we're out in front by a very long way," said Sean Marett, COO of the German biotech BioNTech, whose mRNA-based personalized cancer vaccine is in two phase 1 studies (in patients with melanoma and with triple-negative breast cancer). That speed advantage means BioNTech has more experience, and more data, with which to hone its predictive algorithm, he said. "The quality of the algorithm will determine the efficacy of the product, because you pick the best mutated epitopes to stimulate immune response," said Marett. The company has a strong competitive advantage because the data they put into the algorithm improve its predictive ability, he said, noting that BioNTech's program began in 2009. "The more patients you treat, the better it becomes, and so first to market automatically has a competitive advantage. That's where Genentech comes in for us."

This Genentech deal, which BioNTech signed with the Roche subsidiary in September 2016, is one of the field's largest to date, worth $310 million in up-front payments and near-term milestones that could speed the development of the biotech's therapies in combination with Genentech's products. Genentech and BioNTech will develop, manufacture and commercialize personalized cancer vaccines based on BioNTech's mRNA platform and in combination with Genentech's immunotherapy portfolio. The deal—structured as a cost- and profit-sharing arrangement—gives BioNTech the right to co-promote products in the United States and certain European markets (and to opt to take forward on its own products Genentech declines to advance). The companies will split manufacturing duties, with BioNTech manufacturing clinical supply and both companies manufacturing commercial supply.

Maturing field

Signaling that the field is both expanding and maturing, in December 2016 the newly hatched Parker Institute for Cancer Immunotherapy teamed with the nonprofit Cancer Research Institute to help further the study of neoantigens. The collaboration—known as the Tumor Neoantigen Selection Alliance, or TESLA—includes 30 neoantigen research groups within industry and academia, and aims to improve the identification and prioritization of neoantigens in cancers including melanoma, colorectal cancer and non-small-cell lung cancer. "Tesla allows us to understand best practices as a field for everything involved from the best methods for sequencing, best reagents to use, best processes for selection, and what people can share about algorithms," said Advaxis' Petit. Advaxis and Amgen are both members of the alliance, as are BioNTech, the Dutch biotech ISA Pharmaceuticals, Genentech, Neon, BMS, and a handful of other large and small biotechs.

Efforts like TESLA should help companies accelerate their technological development, say executives involved. Neoantigen vaccines are also helping to advance aspects of personalized medicine that may have an impact across multiple modalities. "Every manufacturing campaign we run here is for a single patient, which requires a completely new rewiring of how we think about manufacturing and really forces you to be truly patient-focused," said Neon's O'Dowd. "This is one of the key advantages of being more advanced in our development program," said Neon CBO Robert Ang. "We're learning a great deal about important nuances, whether it's in bioinformatics, or in practical elements such as the quality of these biopsies that you simply can't learn through computational models."

Improved and cheaper sequencing and bioinformatics technologies are luring others to the field. Diversified, clinical-stage immuno-oncology companies such as ISA Pharmaceuticals and Agenus have neoantigen vaccine programs nearing the clinic. In October 2016, the Wellcome Trust investment arm Syncona teamed up with Cancer Research Technology to form Achilles Therapeutics, staking the biotech with £13.2 million ($17.5 million) series A financing. Achilles aims to commercialize neoantigen-based immunotherapy technology from University College London and the Francis Crick Institute.

Partner interest

Neon remains among the field's best-capitalized biotechs. "We've certainly had our fair share of partner interest as well," said Ang. He pointed to Neon's recent crossover round as a means of relieving any dealmaking pressure on the company. "What's important to us is building the value of Neon as a lasting entity," he said, and although other neoantigen companies were able to ink deals with "great economics," those companies "really gave up a lot of product rights." Neon, he said, is exploring deal structures that will enable them to build their own oncology franchises. In the short term, access to a "broad catalog" of immunomodulators like the PD1 or PDL1 checkpoint inhibitors is the best reason to partner up with a pharmaceutical company, said Gritstone's Allen, who noted that the company could "source capital" in other ways. Moderna's Caperna signed a deal with Merck & Co. in June 2016 that ostensibly ticks both boxes. The biotech received $200 million up front, and the companies will explore combinations of Caperna's neoantigen vaccine platform with Merck's PD1 inhibitor Keytruda (pembrolizumab).

As a demonstration of the field's heightened interest, the lucrative neoantigen deals up until this point have all been struck "in the absence of convincing clinical data that this approach works," said Allen. He sees two critical technological dimensions that could lift the market for neoantigen vaccine deals even further: clinical evidence of the accuracy of a platform's neoantigen prediction and of the immunogenicity of its selected vector. "Specifically, can the vector generate high-potency, high-function $CD8^+$ T cells, which is what we think we need to kill the tumor cells," he said.

"Four years ago, if you talked to traditional pharma companies, neoantigen vaccines didn't fit with their models at all," said BioNTech's Marett. "But now, a good number of them are really engaged in this area." In fact, during the process that culminated in BioNTech's deal with Genentech, the two other companies with which BioNTech seriously negotiated were traditional pharma companies, he said. "There's a new willingness to move into personalized medicine because everyone is now realizing this is the way medicine is going." As the costs of sequencing continue to fall, it will continue to enable personalized approaches to the treatment of cancer and other diseases, he predicts.

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