Neoantigen-based cancer immunotherapy: One step closer to the promise of personalized medicine

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Executive Summary

The human immune system is the latest conscript in the war on cancer. One part of this immuno-oncology (IO) revolution has already proven its worth: checkpoint inhibitors that work by blocking the ability of the tumor to hide from the immune system. In some patients, results have been remarkable. For others, the response has been weaker, possibly hindered by a lack of cancer-specific "signposts" which mark the tumor for destruction.

Neoantigens—new proteins generated by dividing tumor cells—may be these better oncological signposts, unlocking the power of immune therapies in a larger number of patients, for longer periods of time. Well aware of this breathtaking potential, scientists, patient groups, and the industry charge ahead, driving a groundswell of emerging technologies that harness a neoantigen approach.

But the road ahead is beset with complex questions to answer before high science becomes clinical practice: What is the best neoantigen to use in a given patient? What are the best ways to present neoantigens and connect them to an immune system primed for a fight? How best to mix and match neoantigen strategies with other IO therapies? And, importantly, what is the path forward for companies developing neoantigen-based therapy to make a real impact for cancer patients?

Back Bay Life Science Advisors analyzed the companies making inroads here and looked at the most promising approaches, from those that rely most on the patient’s own body, to those that use bioengineering to produce entirely new cells in the lab, as well as some that lean on the power of machine learning to develop individualized treatments. We examined how emerging companies with novel approaches can make headway and engage innovators in IO to help their methodologies come to market and save lives.
Glossary

**Checkpoint Inhibitor** – Checkpoint proteins keep immune cells from attacking healthy cells. Tumor cells hide from attack using the immune checkpoint system. Examples of checkpoint proteins found on T cells or cancer cells include PD-1/PD-L1 and CTLA-4/B7-1/B7-2.

**T cell** – Any of several types of white blood cell. T cells are part of the immune system and develop from stem cells in the bone marrow. They help protect the body from infection and may help fight cancer. Also called T lymphocyte and thymocyte. A few types of T cells are of particular interest for immuno-oncology applications:

a. **CD4 (Helper) T cells** — A type of immune cell that stimulates killer T cells, macrophages, and B cells to make immune responses. A CD4-positive T lymphocyte is a type of white blood cell and a type of lymphocyte. Also called helper T cell.

b. **CD8 (Killer) T cells** — A type of immune cell that can kill certain cells, including foreign cells, cancer cells, and cells infected with a virus. Killer T cells can be separated from other blood cells, grown in the laboratory, and then given to a patient to kill cancer cells. Also called cytotoxic T cell and cytotoxic T lymphocyte.

**Antigen (often abbreviated Ag in the literature)** — Any substance that causes the body to mount an immune response against that substance. Antigens include toxins, chemicals, bacteria, viruses, or other substances that come from outside the body. Body tissues and cells, including cancer cells, also have antigens—in this case, proteins—on their cell surface that can cause an immune response. These antigens can also be used as markers in laboratory tests to identify those tissues or cells.

**Neoantigen** – Small protein fragments that arise as the result of the high number of mutations found in the DNA of tumor cells. Neoantigens are never found in normal tissue.

**Vaccine** – A substance or group of substances meant to cause the immune system to respond to a tumor or to microorganisms, such as bacteria or viruses. A vaccine can help the body recognize and destroy cancer cells or microorganisms.

**CAR-T (chimeric antigen receptor T cell)** – A type of treatment in which a patient's T cells are changed in the laboratory so they will attack cancer cells. T cells are taken from a patient's blood and a gene is introduced into the T cells.
This gene codes for a special receptor that binds to a protein on the patient’s cancer cells. This receptor is a natural T-cell receptor that has been spliced to a segment designed to bind to neoantigens; it is called a chimeric antigen receptor (CAR). Large numbers of the CAR-T cells are grown in the laboratory and given to the patient by infusion. CAR T-cell therapy has been successfully used against certain blood cancers and is being studied in the treatment of some types of tumors.

* https://www.curemelanoma.org/blog/article/neoantigens-what-are-they-and-why-do-they-have-researchers-excited

Unless noted all terms are from The National Cancer Institute (NCI) glossary
Checkpoints in Check

In 2014, the Wall Street Journal profiled a retired teacher named Thomas Telford who, in 2005, was diagnosed with Stage 4 melanoma with a prognosis of one year to live. Undaunted, Telford enrolled in a clinical trial to combat his cancer. Nine years after receiving an experimental cancer therapy called a checkpoint inhibitor (CPI), Telford had beaten the odds. The Journal noted that he had joined “... a growing group of super-survivors (who are) transforming the world of oncology. In both total numbers and duration of survival, they are charting new territory.”

The idea of manipulating a patient’s own immune system to fight cancer was considered novel—even implausible—only twenty years ago. Today, it has taken hold as a true paradigm shift in foundational science as scientists develop treatments that manipulate the patient’s immune system to ferret out and kill cancer but spare healthy tissue, and cancer immuno-oncology (IO) is an ever-larger part of the cancer marketplace. While the immune system was thought only to confront and destroy biological “invaders,” intriguing clinical clues, elegant basic science research, and a flurry of translational studies have finally led to acceptance that the immune system can recognize and eradicate growing tumors.

However, tumors employ a variety of insidious strategies to hide from, de-activate, and even usurp the immune system in their quest for unrestrained growth. As these pathways and mechanisms have been identified, a variety of immune-targeted cancer therapies have made their way into clinical studies. In this quest to use the immune system to keep cancer at bay, a key player has been the T cell: the drug that saved Thomas Telford was one of a class that releases some of the power of T cells, but there is a whole other range of T cell behaviors that researchers are using to fight cancer.

As the workhorses of the adaptive immune system, T-cells play a critical role in identifying and killing potentially threatening cells. T cell responses are stimulated by proteins on the surface of target cells—antigens—but one of the ways that the body keeps its T cells under control is through other cell-surface proteins called “checkpoints.” In healthy tissue, checkpoints restrain T-cell activity, preventing auto-immune reactions. One of the ways in which tumors pose as healthy tissue and “hide” from the immune system is by turning on these checkpoints and dialing down T-cell activity, turning deadly T cells passive. This latter discovery has resulted in a spate of checkpoint inhibitor therapies to release this “brake” on a patient’s T cells to kill cancer. As of this publication, there are five checkpoint inhibitors approved by the U.S. Food and Drug Administration (FDA) in 11 tumor types.

However, not everyone treated with CPIs becomes a super-survivor like Telford, and many eventually become resistant to CPI therapy. Even within tumor types where CPIs have shown remarkable effectiveness, such as melanoma, less than half of patients have what are referred to as “hot” tumors, those that respond most effectively to CPIs.
Some Make It Hot

Tumors are classified as "hot," "warm," or "cold" based on their responsiveness to CPIs. Scientists are now grappling with how to turn cold or even warm tumors into hot tumors. Unlocking this mystery could mean a dramatic increase in rates of patient survival. Within these classifications, there are intriguing differences that suggest other avenues for treatment.

One avenue may be found in the groundswell of new vaccines and cell therapies directed against neoantigens—new proteins generated as tumor cells divide and mutational programs carelessly make mistakes copying cell DNA. Because neoantigens are only expressed in tumors, they may be the ideal signposts needed by T cells to identify and spare healthy cells while targeting cancerous ones. Therefore, uncovering these signposts is critical to the next step. Neoantigen vaccines and cell therapies may be an answer.

Cancer vaccines are not new. But thus far, vaccines have only been developed against an array of antigens that also occur in healthy tissue, albeit at low concentrations. Therefore, even if a tumor has high amounts of antigen and the rest of the body low amounts, the body will not naturally produce T cells that recognize the antigen to spare healthy tissue—even low expressions of

![Figure 2: Neoantigens are only expressed in the tumor](image)

Because neoantigens are only expressed in tumors, they may be the ideal targets of new cancer vaccines and cell therapies.

- **TISSUE SPECIFIC ANTIGEN**
  - Tissue-specific antigens are specific to the tissue but upregulated in cancer cells, including MART-1, gp-100, TRP-1/gp75.

- **CANCER-TESTIS ANTIGEN**
  - Cancer-testis antigens are expressed mainly in tumors or testis but have low-level expression in normal tissues and include MAGE-A1 and NY-ESO-1 2017.

- **OVEREXPRESSED IN TUMOR**
  - Overexpressed tumor antigens are expressed in both tumor cells and healthy cells but have high expression in tumor cells.

- **NEOANTIGEN**
  - Neoantigens are new proteins created as the cancer cell goes haywire and mutation rates intensify.

- Expression of antigen in normal tissue
- Expression of antigen in the tumor
antigens would result in an auto-immune response. Neoantigens, on the other hand, are only formed when the tumor is developing and are restricted to those rogue cells.

Hot tumors have higher mutation rates than cold tumors and therefore may generate more neoantigens than cold tumors. Even some patients may be more prolific at producing neoantigens than others. As a result, even within the same tumor type, a patient's response to CPIs can be stratified based on differences in the mutation burden as well as how prevalent a neoantigen is within the tumor.

Figure 3:
Neoantigens may be the difference between ‘Hot’ and ‘Cold’ Tumors

Tumors with higher mutational loads have higher response rates to checkpoint inhibitors

SOURCE:
The Difficult Road to Neoantigen Therapies

To turn the neoantigen hypothesis into therapies, scientists are developing neoantigen vaccines that help activate tumor-killing T cells. And, thanks to advances in cellular and genetic engineering, they are also engineering T cells to recognize neoantigens. If these therapies work as predicted, they could increase the number of super-survivors and help them live even longer, especially when combined with CPIs.

Developing vaccines and cell therapies that kickstart the immune system is a tantalizing idea, but any new path in drug development is a tangle of turns to navigate. Translating promise into reality means that companies developing treatments must progress through three initial steps:

**Step 1:** Selection: Decide which neoantigens will be the most effective. Does this differ by patient and/or tumor?

**Step 2:** Priming: Once the neoantigen is identified, choose the ideal way of administering the vaccine to elicit a T-cell response

- Consider skipping the vaccine altogether and just engineer a novel neoantigen-recognizing T cell

**Step 3:** Therapeutic strategy: Map out how these neoantigen therapies could be combined with other IO drugs

A successful first step is critical because without targeting a neoantigen that cleanly discriminates between self and tumor, the T cells will not be able to recognize and eradicate the tumor and the promise will be lost. For many research groups, the process starts with sequencing the tumor tissue to determine whether there is a “public” neoantigen available. Public (also called “shared”) neoantigens are known neoantigens that repeatedly occur in many patients, often because they are the product of strong driver mutations responsible for the transformation from healthy to cancerous cell. For people with tumors bearing a specific public neoantigen, an off-the-shelf vaccine can be developed and administered to multiple patients.

For patients without a public neoantigen, a vaccine needs to be tailored to their tumor. Identifying the right “private” neoantigen is akin to finding a needle in a mutation haystack. The powerful mutation programs that are turned on as a cell becomes cancerous can generate thousands of mutations, many of which are random changes that are not conserved across patients, even those patients with the same tumor type. Further, even if we could identify all the mutations in tumor DNA by sequencing, mutations in the DNA don't always correlate to a neoantigen, much less to a neoantigen that activates T cells.

Thus, personalizing treatment for each patient's neoantigen repertoire is complex, costly, and potentially a shot in the dark. But with significant improvements in computational power and big data analytics, the daunting feat of identifying all the mutations and predicting actual neoantigens is being
tackled in silico; given the complexities of the problem, these techniques fall under the umbrella of Artificial Intelligence (AI).

While this approach is promising, according to Nature: International Journal of Science “… prediction algorithms return a vast number of candidates, of which only a tiny handful are ever found to trigger bona fide antitumor responses in patients”. Therefore, even if sophisticated machine learning methods are used to winnow down candidates, scientists must go back to wet lab experiments to validate that the potential neoantigen is active. Therefore even companies using state of the art computational methods must use biological assays to enrich for neoantigens and their cognate T cells so that only the candidates of interest are isolated in a test tube.
Primed for Expansion

Once a neoantigen is selected, the next decision is about priming, or how to use the neoantigen to activate the right T cell and nudge the body's immune system to generate an army of cancer specific T cells.

The first strategy, a vaccine approach, exposes a repertoire of T cells to a specific neoantigen to prime and expand the appropriate T cells—to quickly replicate them in sufficient quantity for an effective immune response. This is analogous to traditional infectious disease vaccines; by exposing the immune system to pathogen associated antigens in the form of attenuated/killed pathogens, we can stimulate production of T cells that respond to those antigens in live pathogens.

Figure 5:
Two main priming strategies

There are two ways to PRIME a T-cell

1. DEVELOP A VACCINE to boost neoantigen levels

2. ENGINEER OR SELECT T CELL to recognize neoantigen

Once the neoantigen is selected, the next decision involves priming, or how to use the neoantigen to activate and expand the right T cell to generate an army of cancer specific T cells. The first strategy, a vaccine approach, exposes a repertoire of T cells to a specific neoantigen to prime and expand the appropriate T cells.

As a second approach, and instead of using the neoantigen to stimulate a T-cell response, scientists can engineer or select T cells such that the main recognition domain, called the T-cell Receptor (TCR), is a good match to the neoantigen.
Instead of using an existing neoantigen to stimulate a response in existing T cells, the second strategy involves artificially engineering or selecting T cells whose main recognition domain, called the T-cell Receptor (TCR), recognizes the neoantigen.

Two Main Priming Strategies

With a vaccine strategy, direct vaccines can be generated in multiple ways:

1. Inject purified neoantigen into the patient, eliciting a T-cell response.
2. Inject a genetic template—RNA or DNA—to stimulate the body’s protein-making machinery into creating antigen itself, or in a similar in vivo antigen-production strategy, inject engineered bacterial cells to produce antigens.
3. Use a virus to infect cancer cells, lysing and spilling the neoantigens into the environment.

Figure 6: Multiple methods to develop vaccines
4. In the lab, generate antigen presenting cells (APCs) from a patient’s own blood and reinject it back into the patient, where the APCs will stimulate T-cell activity.  

Multiple Methods to Develop Vaccines

Given the complexity and uncertainty in developing a vaccine, some groups have simply begun with the end in mind and focused on creating significant quantities of high quality T cells that recognize tumor neoantigens and which can be infused into the patient. This approach has taken one of two forms:

Figure 7: Engineering T cells that Recognize Neoantigens

Expansion and Selection of Autologous Tumor-Specific T Cell

- Excise tumor
- Plate fragments
- Culture with T cell growth factors
- Select and expand tumor specific clones
- Assay for specific tumor recognition
- Reinfuse

Isolation and Engineering of Antigen-Specific T-Cell Receptors

- Isolation and Expansion of Tumor Antigen-Specific T-Cell Clone
- Isolation of TCR and creation of vector infect lymphocytes
- Assay for specific tumor recognition
- Infusion of clones into patient
- Inflection of cells with vector and expansion of TCR expressing clones
- Isolation of cancer patients’ lymphocytes
- Infusion of clones into patient

TYPES OF T-CELL-BASED PRIMING APPROACHES.

Left: T cells are isolated from a patient’s own tumor, expanded in the presence of tumor sample and T-cell growth factors, and re-infused into the patient.

Right: T-cells from a patient are assayed for activity against a public neoantigen. Reactive clones are selected, and the T cell receptor is sequenced and subsequently used to transduce lymphocytes from any patient sharing the public neoantigen, creating a transgenic T-cell product.
1) tumor-infiltrating lymphocytes (TIL) approach, and 2) an engineered T-cell receptor (TCR) approach.

In the former, clinicians simply let the patients’ own tumor instruct their immune system as to the best target to seek out and destroy. Initially developed at The National Cancer Institute (NCI), this approach involves harvesting TILs from the patient, and then reproducing them \textit{in vitro} in the presence of the patient’s own tumor tissue along with select T-cell growth factors. The T cells that emerge are the ones likely to recognize the patient’s specific tumor antigens. Specific clones of these cells are selected, grown to sufficient quantities and subsequently re-introduced into the patient.

The success of chimeric antigen receptor T cell (CAR-T) approaches in treating blood cancers has ignited an interest in tweaking a patient’s own T cells to “force” these cells to recognize a known tumor target. This engineered approach introduces a lab-created, high-affinity T-cell receptor into a patient’s own cells and then reintroduces the engineered cells back into the patient. To do so, researchers isolate samples from tumors, identify T cells that are highly reactive to the neoantigen of interest, and subsequently clone out the TCR sequence. This process has undergone proof-of-principle studies with antigens which are expressed in healthy tissue but over-expressed in cancers, but there is keen interest in applying this technology to public neoantigens of many different cancers, and perhaps one day, personalized neoantigens.\textsuperscript{12,13}

\textbf{Cancer Wars: A Neo Hope}

As described above, any neoantigen strategy confronts a sequence of challenges and choices that generate an almost infinite array of possibilities. A few groups have successfully navigated the options to demonstrate the concept in melanoma patients, whose hot tumors have many neoantigens due to high mutational load. Three recent high-profile studies in particular outline proof-of-concept for scaling up prediction-based technology to produce personalized vaccines.

- One study used predictive methods to develop peptide vaccines containing up to 20 private neoantigens. After patients received the vaccines, survival data showed four patients had no relapse after 25 months. Two patients relapsed but responded after they were treated with a CPI.\textsuperscript{14}

- Another study using a very similar sequence of steps delivered an RNA vaccine encoding up to ten personalized neoantigens and a potent immune stimulator. Nine of the thirteen patients remained relapse-free during follow-up (12-23 months) and all but two patients survived during the study time. Interestingly, one individual’s cancer progressed but the patient successfully mounted a complete response when given a CPI after vaccination.\textsuperscript{15}

- A study in melanoma taking the TIL-focused approach demonstrated \~20% complete tumor regression in heavily pretreated melanoma patients.\textsuperscript{16} Importantly, this and other TIL studies reveal many of the lymphocytes used as part of this process do indeed recognize neoantigens.\textsuperscript{17}
These results have led to initiation of around 70 new neoantigen trials since 2013. One-third of these have started in the first four months of 2018 alone. The neoantigen field is no different from other IO modalities where combinations are the order of the day: a third of neoantigen trials initiated this year are expected to test vaccines in combination with a CPI.

The Next Wave

Even as scientists explore which neoantigens and methods will work best in different patients, companies have already marked their territory as they develop science advances into medical treatments. Back Bay Life Science Advisors cataloged the activity of more than 30 companies who have laid claim to a neoantigen selection and/or priming method.

**LANDSCAPE OF NEOANTIGEN COMPANIES**

The current class of neoantigen hopefuls have products in various stages of development (view a comprehensive list of companies involved in neoantigen therapy development at bblsa.com). All are buoyed both by the promise of next-generation immunotherapy as well as the momentous potential impact of personalized neoantigen therapy.

Interest in this area has not escaped the public capital markets and venture capital—or big pharma. Of more than 30 companies identified by Back Bay, 11 have accessed public capital, and the remainder have stayed private. The latter group raised over $1.3 billion in venture money with the majority coming over eight financings within the last two years (exclusive of Moderna and their eye-popping $1.6 billion in VC cash).

**Financings of Neoantigen Companies**

One aspect of this market to note is that investors are keenly interested in RNA-based vaccines. From a priming perspective, the ability to engineer these treatments is provocative: RNA is easy to synthesize and can encode any neoantigen. In addition, it is immunogenic and can be delivered by injection directly near the tumor, where expression of mRNA will likely yield enough of the neoantigen to jumpstart local T cells, ideally without provoking a more system-wide effect. This hypothesis is why BioNTech, a German start-up company developing personalized immunotherapies, has garnered an enormous Series A round of funding. and a lucrative partnership with Genentech. BioNTech showed that it can predict neoepitopes and manufacture a personalized vaccine, Ivac Mutanome, that leads to a significant reduction
 Alongside these proprietary methods for predicting effective neoantigens, a good deal of their value may be generated by their RNA platform.

Other start-up companies are highlighting their unique approaches to neoantigen discovery. Faster computers and more economical sequencing methods mean that companies can now use big data and AI techniques to crack this problem. Two companies, Neon Therapeutics and Gritstone Oncology, both founded in 2015, are pursuing this path to discovery.

Neon Therapeutics has a strong roster of scientific founders, including Catherine Wu, whose work proved the potential of neoantigens in melanoma, and Jim Allison, a revolutionary in the IO field—famously referred to as “The Scientist Who Just Might Cure Cancer.”

Neoantigen Vaccines: Nucleotide/Protein Based
- e.g. bacterial vectors, oncolytic viruses, heat shock proteins

Neoantigen Vaccines: Other Vector Priming Technology
- e.g. T cells, DCs

Neoantigen-Specific Cell Therapy
- Undisclosed/TBD

Priming Approach
- Undisclosed/TBD

Sources: Back Bay analysis, company press releases and websites
personalized protein vaccine or, as appropriate, they can engineer T cells to recognize a neoantigen, skipping the vaccination step. Their proficiency in T-cell biology allows them to develop tools to monitor how well either approach is working as the patient is dosed. With almost $170 million in venture funding and partnerships with BMS and Merck, Neon is seeking to differentiate itself with its predictive methods (branded as Recon) as well as its dual vaccine and cell therapy neoantigen delivery strategies.

Figure 11:
Snapshot of BioNTech, an mRNA company

### Technology and Capabilities

BioNTech's mRNA technologies center around antigen-encoding mRNA and its overall goal is to develop an immunotherapy platform that utilizes tumor-specific information to develop personalized treatments for each patient, with 3 levels of personalization:

- **FixVAC**: vaccine approach that uses combinations of shared tumor-associated antigens across patient populations (currently being tested in melanoma)
- **RNA WAREHOUSE**: a personalized combination of antigens against shared tumor-associated antigens
- **IVAC MUTANOME**: NGS sequencing to completely tailor the antigen combination to the individual patient (currently tested in multiple tumors)
- **RiboMAB**: Platform announced in June 2017 focused on antibody production, announced with data showing BITE production in mouse tumor model

### Partnerships

**MAB DISCOVERY / SEPTEMBER 2017**

Extension of 2013 partnership, MAB will use its platform to discover monoclonal antibodies against BioNTech selected targets

**GENENTECH / SEPTEMBER 2016**

Collaboration combines Genentech's immunotherapy portfolio and research program with BioNTech's mRNA cancer vaccine platform, and personalized medicine expertise to develop individually tailored cancer immunotherapies against a range of cancers; ~$310M in upfront and milestone payments

**SANOFI / NOVEMBER 2015**

Sanofi will pay BioNTech for the rights to 5 discovery-stage immunotherapies, each relying on proprietary mRNA platform; ~$60M upfront and up to $1.5B in milestones

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<td>Fixed combo of shared antigens</td>
<td>Melanoma (2 studies), H&amp;N</td>
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<td>Personalized combo of shared antigens</td>
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<td>Individualized cancer vaccine</td>
<td>Melanoma, TNBC, multiple cancer indications</td>
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<td>Cell &amp; Gene (CAR-T)</td>
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<td>Protein therapeutics</td>
<td>Pancreatic cancer</td>
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<tr>
<td>Small molecules (TLR)</td>
<td>Solid tumors</td>
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Gritstone’s approach is based on work by Timothy Chan and Naiyer Rizvi, researchers who published early on the efficacy of IO in non-small cell lung cancer (NSCLC) linked to both mutational burden\(^7\) and the levels of a neoantigen among the tumor cell population.\(^{21}\)

Even with significant competition, investors have seen fit to fund Gritstone Oncology’s large Series B funding round to enable the company, which has no candidates in the clinic, to construct a ~45,000 square foot manufacturing facility for their eventual commercial product.

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**INCEPTION:** Cambridge, MA; founded 2015

**FOUNDERS:** Robert Schreiber, PhD, Ed Fritsch, PhD, Catherine Wu, MD, James Allison, PhD, Nir Hacohen, PhD, and Ton Schumacher, PhD

**BACKGROUND:** Leverages proprietary prediction and T-cell selection methods to build both Public and Private neoantigen therapies; marquee Cancer Immuno-Therapies (CIT) founders

**FUNDRAISING:** Private; Series A: $55M (2015); Series B: $106M (2018)

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**Technology and Capabilities**

Neon plans to use both Public (Neon Select) and Private (Neon One) neoantigens to make cancer vaccines as well as engineer T-cells. These two programs will be enabled by the following proprietary technology:

- **RECON:** Proprietary statistical methods that can predict specific neoantigen-binding peptides based on binding properties, validated by proprietary peptide data sets
- **PEPTIDE CHEMISTRY:** Uses specific peptide neoantigens for priming. Potentially offers superior manufacturing, lower costs, and reduced risks
- **NEO STIM:** Proprietary method for inducing neoantigen-specific T cells outside the body, allowing the company to engineer cell therapies that are targeted specifically to immune-stimulating neoantigens. This method also allows the company to build diagnostics that can monitor how products influence each patient’s immune system and how these immune changes affect tumors.

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**Partnerships**

**MERCK /// DECEMBER 2017**

Entered into an agreement with Merck to evaluate Neon’s NEO-PV-01 in combination with Keytruda (pembrolizumab)

**CRISPR THERAPEUTICS /// JULY 2017**

CRISPR and Neon are exploring the combination of each company’s proprietary technologies to develop novel T-cell therapies. This will likely be best applied to Neon’s engineered T-cell therapies.

**BRISTOL MEYERS SQUIBB /// DECEMBER 2015**

Entered into an agreement to combine NEO-PV-01, and Opdivo® (nivolumab), a PD-1 immune checkpoint inhibitor. In melanoma, NSCLC, and bladder cancer.

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**Internal Programs**

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**Figure 12:**

Snapshot of Neon Therapeutics, a neoantigen vaccine and cell therapy company
Because they are both well-funded neoantigen-directed companies relying on AI to develop therapies (i.e., Neon ~$160M and Gritstone ~$200M in the three years since inception), the two companies are often mentioned in the same breath, but it is too early to judge whether one will be more successful. AI utility is based on so many different components, including the real-world data on which its models are built. In the absence of clinical performance, it is hard to guess at who will ultimately succeed.

INCEPTION: Emeryville, CA; founded 2015

FOUNDERS: Andrew Allen, MD., PhD., Naiyer A. Rizvi, MD., Graham Lord, MD., PhD., Mark Cobbold, MD., PhD., Timothy A. Chan, MD., PhD., Jean-Charles Soria, MD., PhD.

BACKGROUND: Built on foundational work coming from the lab of Timothy Chan and Naiyer Rizvi, and predicated on specific ‘Deep Learning’ algorithms for neoantigen prediction


Technology and Capabilities

Gritstone is identifying neoantigens using “Deep learning” algorithms that are iteratively refined based on the analysis of DNA, RNA, and protein of hundreds of actual tumor samples.

Based on their ability to develop the “Deep learning” algorithm, Gritstone believes “[o]ur estimate, when we test ourselves on fresh data, is that we’re operating at something like ten-fold better than the public domain approach that many of our competitors are using.” Their approach relies on two fundamentals:

• NEOANTIGEN PREDICTION: “Deep learning” algorithm refined by analysis of tumor samples
• IMMUNOGENIC ANTIGEN DELIVERY: Uses viral vectors to package neoantigen vaccines and stimulate immune response. The company plans to be able to efficiently manufacture personalized vaccines in its newly built 43,000 square foot California manufacturing facility

Internal Programs

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<td>Neoantigen based vaccines</td>
<td>Preclinical (IND expected mid-2018)</td>
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Figure 13:
Snapshot of Gritstone, a neoantigen company
On the Horizon

It remains to be seen how neoantigen approaches within the clinic will succeed and how these vaccines will be used in combination with other IO therapies. Currently, the majority of neoantigens in play are predicted to activate a specific type of T cell called CD8. In the future, groups could develop neoantigens that interact with the CD4 class of helper T cells. Another direction could derive neoantigens from different genetic sources. While most approaches have looked at neoantigens encoded by the tumor cell’s main DNA cache, effective neoantigens could possibly also be developed from mitochondrial DNA.12

Beyond the vaccine target, the ability to mix and match vaccines with other IO modalities offers a variety of ways to impact tumors with poor to moderate responses to CPIs (e.g. ovarian, breast, head and neck, pancreatic). Neoantigen combinations could provide synergistic tumor killing but without some of the immune toxicity seen with other combination approaches. For example, some tumor tissues are notoriously inhospitable to T cells because of the variety of signaling molecules and cell types these tumors can enlist to dampen any T-cell response. Mixing vaccines with agents that reverse the pro-tumor advantage, such as indoleamine-2,3-dioxygenase (IDO), T-regulatory cells, and macrophages/myeloid-derived suppressor cells, is another future horizon.

Conclusion

Scientists, investors, and big pharma are channeling resources to pursue the development of neoantigen priming technologies and prediction techniques in the hope of building on the impressive advances in the IO. However, several big questions remain as to how this technology will impact patients.

For instance, some tumors are surrounded by a fibrotic coat, limiting the ability of T cells to enter the environment22—pancreatic cancer is one example of a fibrotic tumor. Whether a vaccine or T-cell infusion therapy can penetrate the fibrotic tumor environment will be critical in understanding whether these approaches can impact these deadly tumors.

Further, while bioinformatics is a growing area, the distinct approaches under development are little more than a “black box” to clinical experts who are unable to compare the relative merits of each approach. Even as companies develop their own methods, there must some way of comparing their ultimate utility.

Answering these core clinical questions is still a substantial hurdle to overcome, as access to patients for IO clinical studies is becoming of increasing concern to industry watchers.23

From an implementation perspective, practical questions remain, which may determine their clinical and commercial success or failure. First, how will the necessity of the bedside-to-bench-to-mainframe-to-bedside workflow impact
the rollout and utilization of personalized neoantigen vaccines? What will be the clinical and business impact of logistical considerations, such as the time lag between antigen identification and vaccination? What are the implications for cost of goods in scaling up a safe and quality product individualized for each patient? How will the hurdles that plague a first mover for any truly novel product be overcome? Furthermore, how neoantigen vaccines are combined with CPIs and/or other IO modalities, and how that may vary from tumor to tumor, remains to be seen.

Lastly, competitive pressures may not be ideally aligned with scientific discovery. As an increasing number of large consolidators make their bets on partnerships with proprietary predictive technologies and/or vaccine platforms, the freedom to take a broad view and experiment with various combinations of predictive and vaccination technologies may shrink, as discoveries become the exclusive domain of competitive organizations. Nevertheless, given the advent of “personalized” medicine heralded over the last 20 years, the neoantigen field has the chance to bring the promises of a truly bespoke cancer therapy to fruition, offering hope to patients and physicians who battle cancer every day.

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Bibliography


