Genocea Aims To Take The T-Cell Century By The Horns

Although cancer grabs the spotlight for harnessing the immune system against tumors, other therapeutic areas and modalities are being developed in the shadows. Genocea Biosciences thinks it has a surefire way to identify novel antigens for T-cell vaccines. It hopes to shake up large infectious disease markets, and more.

BY MICHAEL GOODMAN

The global vaccine market is on a tear, growing at an annual rate of 11.5%, far outstripping drugs and devices. Although 80% of the $30 billion market is held by Merck & Co. Inc., Sanofi, GlaxoSmithKline PLC and Pfizer Inc., a raft of biotechs are working on transformative technologies that could shake up established brands. Standing at the forefront of these upstarts is Genocea Biosciences Inc., one of a handful of clinical-stage companies, laboring in the shadow of immuno-oncology firms, which are harnessing T-cell immunity in vaccines for non-cancer therapeutic areas. It is starting with viral and bacterial infections, but has the technology and ambition to eventually expand into cancer and autoimmune disease.

The road won’t be easy. Genocea dodged a bullet on May 20 when it reported topline Phase II data for GEN-003, a therapeutic T-cell-directed vaccine against HSV-2 (genital herpes). Although the trial met its primary endpoint of reducing viral shedding – defined as when the active virus rises to the surface of the skin and becomes contagious at the site of infection – the interpretation of its secondary endpoint, the reduction of herpes lesions, was confounded by a similarly steep reduction seen in the placebo group.

Although a secondary endpoint, reduction of viral lesions is the kind of hard clinical outcome that FDA will require in GEN-003’s Phase III trial. Genocea’s stock flatlined for a couple of weeks as investors digested the data, then steadily rose to re-touch $16, its yearlong high.

GEN-003 is one of two lead programs at Genocea, and is furthest along, having notched proof-of-concept in a Phase I/II trial that read out in October 2014. The other program, GEN-004, is a universal, prophylactic T-cell vaccine against pneumococcal disease. “Universal” means that the vaccine aims to cover all 90+ serotypes of the disease compared with the handful covered by Pfizer’s market-leading pneumococcal vaccine Prevnar 13.

Genocea puts the HSV-2 market opportunity at $1 billion in the US. The pneumococcal vaccine is targeting Prevnar’s $6 billion market. Genocea is positioning itself to prosper in what, according to the
Tufts Center for the Study of Drug Development, will be a $40 billion global vaccine market by 2020.

But to achieve that goal Genocea is relying on a few bold assumptions: about the need for T-cell vaccines in markets currently served by the established vaccines that work through B-cell responses, about the centrality of viral shedding to HSV clinical symptoms and risk of transmission, about the extent to which pneumococcal serotype replacement is a growing factor in places where serotype-specific vaccines like Prevnar are available and about the ability of its ATLAS platform to identify antigen targets that drive protective T-cell responses.

So far, the biopharma has produced compelling data in rigorous trials for both leads. Clinical catalysts over the next year will determine whether investors stay on for the ride. Specifically, the catalysts will show whether 004 with its novel mechanism of action is a viable vaccine, and whether Genocea can demonstrate six-month durability in its 003 vaccine and that it has identified the right dose of antigen and adjuvant to take into Phase III.

TARGETS MATTER


Pre-IPO investors were betting on Genocea’s strategy to develop vaccines using a T-cell antigen discovery platform called ATLAS developed by scientific co-founder Darren Higgins, PhD, professor of microbiology and molecular genetics at Harvard Medical School.

Over the past 12 years, scientists have developed different methods to discover T-cell antigens; however, many require prohibitively expensive or complex, rate-limiting steps, or are not sufficiently high-throughput.

ATLAS enables the rapid, cost-effective, high-throughput discovery of protective T-cell antigens for human vaccines. Scientists can use primary T cells from the pathogen of interest as input, bypassing the need to purify recombinant proteins. Antigens can be identified in diverse human subjects; there is no need to generate cell lines or for deconvoluting pools of antigens, a laborious process for identifying which of numerous antigens are provoking a T-cell response.

“We take the T cells and antigen presenting cells from hundreds of people who have been exposed to either a pathogen or a disease,” says Genocea CEO Chip Clark. “We then identify the antigen target of people who have been making a protective T-cell response against a disease.”

In the case of the HSV-2 vaccine 003, Genocea scientists interrogated 150 subjects and found that 40 of them made protective T-cell responses against genital herpes. Comparing those 40 with subjects who were not making protective responses, scientists identified ICP4.2 (infected cell polyepitope 4) as a novel T-cell antigen. It is one of two used in 003, the other being gD2, a B-cell antigen.

ATLAS is fast, too. Genocea took four programs in three diseases from project initiation to animal proof-of-concept, and two vaccines into the clinic, all in seven years. This compares favorably against the traditional 10- to 12-year pace of discovery in the vaccine space.

Genocea’s mantra is “targets matter.” The company believes that the current approach to vaccine discovery is largely trial and error. Consequently, Clark maintains that competing T-cell vaccine companies focus their efforts on the adjuvant; Genocea is unique in focusing on the right antigen. ATLAS not only underwrites the company’s ability to create proprietary vaccines that elicit the right immune response, it also positions it to collaborate with any party and with any novel adjuvant or delivery system to create a successful vaccine.

Thus, in a 2009 deal with Isconova AB, a subsidiary of Maryland-based vaccine specialist Novavax Inc., Genocea licensed the saponin-derived Matrix-M adjuvant used in the 003 vaccine. Novavax gets modest clinical milestones and low single-digit royalties based on clinical success. More importantly, it gets to marry its novel adjuvant with a cutting-edge target of T-cell response, as it frequently reminds investors in its quarterly earnings calls.

SVP Research Jessica Flechtner, PhD, notes that some companies with antibody-targeted vaccines in development “haven’t been able to see if those antibodies also produce TH17 cells. It gives us comfort that we’re on the right track.” Genocea’s 004 vaccine contains three antigens: SP0148, SP1912 and SP2108. These antigens have been shown by ATLAS to be associated with protective TH17 T-cell responses against pneumococcus, and to be conserved across known pneumococcal serotypes.

The ATLAS platform is ideally suited to diseases whose proteome provides a large number of proteins that can be T-cell targets. With viruses like influenza or hepatitis, there are only a few well-known protein targets. But once you get into pneumococcus (2,200 antigens), malaria (5,000 antigens) or chlamydia (1,000 antigens), the complexity is such that a discovery engine like ATLAS is necessary. Even HSV-2 with only about 80 antigens required ATLAS to home in on the one that drove a protective T-cell response. Chip Clark says that there are several large proteome pathogens for which good solutions don’t yet exist. He numbers Staphylococcus aureus, pseudomonas, Epstein-Barr virus and cytomegalovirus among them.

PHASE II PLANS FOR THE TWO LEAD PROGRAMS

HSV-2, or genital herpes, affects approximately 400 million people worldwide. In the US, it affects one out of six people age 14 to
49, 80% of whom go undiagnosed because their symptoms are mild or mistaken for another skin condition. HSV-2 causes recurring, painful genital sores and concomitant psychological stress due to social stigma. It can increase the risk of HIV transmission two- or three-fold, and pose considerable risk to newborns if transmitted from the mother during birth. In rare cases, it can cause serious complications including blindness, encephalitis and aseptic meningitis.

Genocea showed a determination in the HSV-2 clinical plan to conduct a rigorous, multi-trial Phase II program primarily to optimize the dose, both antigen and adjuvant, and the frequency of administration for Phase III. The repeated trials also had the benefit of re-confirming, even bettering, previous clinical results, and of generating an ongoing stream of news.

Chip Clark credits the ATLAS platform, and its promise of generating "truly novel vaccines" with freeing the company from battles over minor points of differentiation or speed-to-market pressures. "Novelty gives us the luxury of being able to be thoughtful," he says. Chief Medical Officer Seth Hetherington, MD, a veteran of biotech, big pharma and academia, concurs: "If you are thoughtful up front, you’ll regain the time you’ve spent later on because you’ll have a more efficient Phase III program – you’ll have captured all the efficacy in your product, and you’ll know a lot about its safety."

The ’003 Phase II program includes four trials. (See Exhibit 1.)

The Phase II program confirmed the viral shedding and lesion reduction rates seen in the Phase I/IIa trial, even bettering them. Viral shedding was chosen as the primary endpoint, according to Hetherington, "because that is how we measure the total efficacy of the vaccine."

Importantly, it produced a more optimal antigen/adjuvant dose compared with the 30 µg/50 µg dose used in the earlier trial. In May 2015, Genocea announced that the 60 µg/75 µg dose used in the Phase II trial produced superior, dose-dependent viral shedding rate reduction of 55% (post dose 3) versus 52% in the earlier trial. The higher dose also produced superior genital lesion rate reduction, a secondary endpoint, of 60%-69% in the 60 µg per protein group versus 48% in the earlier trial. However, a 62% genital lesion rate reduction seen in the placebo group made it difficult to say that any treatment arm achieved significance.

Hetherington says the Phase II trial used a 6:1 (treatment:placebo) randomization design to test six different antigen/adjuvant dose combinations. He claims that this may have influenced how patients, who self-reported herpes eruptions during the trial, interpreted their lesions. "We believe that there was a true placebo effect driven by the extent to which patients anticipated the trial and the fact that they knew they had a 6 in 7 chance of getting active drug." Apparently, there is enough variability in herpes lesions – they can be fleeting, they can be atypical, they can resemble other symptoms, etc. – that patients can, as one of his investigators put it, "talk themselves out of it because they want so much for the vaccine to work."

Florian Schodel, MD, PhD, founder of vaccine consultancy Philimmune LLC and a former VP vaccines clinical research at Merck Research Labs, agrees. "If you go by anecdotal evidence, frequency of eruptions in herpes are often linked to other malaises – febrile diseases, mood alterations, etc. So it’s not impossible that an assumption that you are being effectively treated can have a positive effect on frequency of eruptions, maybe even on your immune system. There is also both a natural variability in the frequency of eruptions and often a decline over time without any treatment."

Hetherington maintains that the placebo issue can be remedied in Phase III by using a more balanced randomization, 1:1 or 1:2. Clark believes that Genocea’s investors understood the connection between “no viral shedding” and “no transmission, no lesions” and so shrugged off the placebo issue.

The next read-out in the Phase II program will be six-month data in the fourth quarter, followed by 12-month data in the first quarter of 2016. These read-outs will answer important questions about the durability of ’003, and whether or not a booster shot will be needed before the end of the year. It will also determine whether, with the new dosage, ’003 can improve on the already impressive six-month durability demonstrated in the earlier study.

Phase III for ’003 is slated to begin in the second half of 2017. FDA will require a clinical endpoint for the trial such as reduction of lesions or frequency of eruptions. Genocea intends to repeat the same rigorous Phase II program for ’004 and for its other pipeline assets. It will finalize its thinking around the Phase II program after having analyzed the data from ’004’s ongoing trial.

The pneumococcal vaccine ’004 is currently in a Phase Ila human challenge trial. The company says it will yield proof-of-

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### Exhibit 1

**Phase II Program For GEN-003 HSV-2 Vaccine**

<table>
<thead>
<tr>
<th>CLINICAL STAGE</th>
<th>PURPOSE OF TRIAL</th>
<th>READ-OUT (DATE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II</td>
<td>Dose optimization (determine optimum dose of antigen and Matrix-M adjuvant)</td>
<td>Post dose 3 (May 2015) 6 month (4Q15) 12 month (1Q16)</td>
</tr>
<tr>
<td>Phase IIB</td>
<td>Bridging study (compare profile of scaled-up product)</td>
<td>Post dose 3 (1Q16)</td>
</tr>
<tr>
<td>Phase IIB</td>
<td>Dose regimen (compare effect of number of doses)</td>
<td>6 month (1H17) 12 month (2H17)</td>
</tr>
<tr>
<td>Phase IIB</td>
<td>Antiviral combination</td>
<td>Post dose 3 (2H16) 6 month (1H17) 12 month (2H17)</td>
</tr>
<tr>
<td>Regulatory</td>
<td>Meet with regulatory bodies</td>
<td>EU national advice (1H16) FDA end of Phase II (2H16)</td>
</tr>
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**Source:** Genocea corporate presentation, August 2015
concept evidence of ’004’s ability to reduce the frequency, magnitude or duration of colonization of pneumococcus in the nasopharynx of healthy adults. The trial is expected to report out in fourth-quarter 2015.

After that, the vaccine will go into an extensive Phase II pediatric study that will start around mid-year 2016 and extend to the end of 2017. Genocea deliberately chose a well-established adjuvant, aluminum, for ’004, whose target population will be children. Using a novel adjuvant in a pediatric population – such as the AS04 adjuvants used by GSK in some of its vaccines – would arouse regulatory scrutiny.

The World Health Organization estimates that up to 1.6 million people, including 800,000 children, die each year from pneumococcal infection. Although commonly treated with antibiotics, antibiotic resistance is taking hold worldwide; up to 40% of infections are caused by pneumococcus resistant to at least one antibiotic.

’004’s mechanism of action whereby it generates a TH17 T-cell mediated response preventing pneumococcal colonization in the nasal passages is unprecedented in a pneumococcal vaccine. TH17 CD4+ T cells help to control colonization and immunity to pneumococcal infection. They recruit other immune cells to fight off pathogens at mucosal barriers such as the nose and throat before they can invade the body. Young children whose immune systems are still developing, and older people whose immune systems are waning, are more susceptible to sustained colonization and resulting pneumococcal disease.

Hetherington says that the idea of reducing colonization in the nose is embraced by many in the field. "Despite the fact that people knew it, there wasn't really a way to develop a vaccine that could work in the nose to drive TH17 responses against all pneumococcus serotypes." He adds that The PnumoCarr Consortium, a group of academicians who have devoted their careers to studying pneumococcus, is a strong proponent of the colonization theory. They've published their research, and spoken with regulatory bodies about it, proposing that impact on pneumococcus colonization can actually be a useful endpoint in the development of a product.

In the human challenge trial, Hetherington says healthy adults will be treated either with placebo or ’004. "Then they get challenged intra-nasally, and then over a period of two weeks they get cultured to see how many of them actually get colonized with pneumococcus. We expect the placebo group will have a colonization rate of about 50%. Our goal is to show that we can substantially reduce that."

Precisely how much pneumococcus has to be cleared to have a clinical effect on the disease is unknown; however, Hetherington said in Genoceca’s second-quarter earnings call that, based on the input of his scientific advisory board, "a 50% reduction in overall colonization would be a meaningful endpoint, because it would be a magnitude of reduction that, replicated over a series of years, would end up in reduction of total colonization – the real goal of a universal pneumococcal vaccine such as GEN-004." Current pneumococcal vaccines on the market do not impact total colonization.

Schodel agrees that if ’004 has an effect on nasal colonization, then it is very likely that it will have an effect on pneumococcal pathogens. "But you still have to show it. The difficulty will be in showing it clinically at a time when very effective pneumococcal vaccines are already broadly available."

COMPETITION AND UNMET NEED

Genocea competes on two planes. The main competitors in T-cell vaccines for infectious diseases are Genocea, Vical Inc., Novadigm Therapeutics Inc. and Agenus Inc. In June, Vical reported topline Phase I/II data for its therapeutic hSV-2 vaccine – it did not meet the primary endpoint of reduction of viral shedding. Clark explains, "We chose different T-cell antigens. Ours, ICP4.2, came from our platform. Theirs did not distinguish itself in our platform as being associated with distinctive T-cell responses."

Likewise, in June 2014, Agenus reported a modest reduction in the primary endpoint of hSV-2 viral shedding for its T-cell vaccine candidate in a Phase II trial: 15% post administration of the vaccine, and 14% post booster shot at six months.

Novadigm is still in a Phase Ib/la trial of its T-cell vaccine against candidiasis.

Agenus has decided not to advance its hSV candidate to Phase III. Vical will make a decision whether to continue based on 9 and 12 month follow-up data. Clark ascribes the weak clinical performance of their vaccines to an inferior antigen component. He says of their experience that it provides validation Genocea’s ATLAS platform.

As for potential product competition, Genocea sees significant unmet need in both its lead indications. The standard of care for hSV are the oral antivirals such as acyclovir, valacyclovir and famiclovir. Even with the availability of antivirals, the genital herpes epidemic has only worsened. The company estimates that of the approximate 7 million Americans treated by antivirals, about half of them are not adequately controlled. "That’s our initial population," says Clark. In many cases, patients don’t comply with a daily pill. In some cases, eruptions of genital lesions are not controlled.

Hetherington points out that antivirals have been tested at very high doses, but no matter how high the dose, "you can only get shedding down to a certain point. Antivirals can reduce transmission, but only by a little less than 50%. You can reduce the amount of recurrence, you can reduce symptoms, but it’s a bit tougher to reduce shedding."

Beyond that initial treated population who are uncontrolled on antivirals, there are pre-symptomatic patients who have no outbreaks and may not even know they’re infected. Even if they knew it, they probably wouldn’t be motivated to go to a physician twice a year for injections. For this population, Genocea’s pipeline lists an hSV-2 prophylactic vaccine in preclinical testing.

Also, the majority of patients who treat with antivirals do so episodically during visible outbreaks that may last a few days or a week or more. But when the lesions abate, they go off medication. Most transmission occurs when people have no symptoms but they are shedding. Antivirals have no effect on reducing hSV-2 asymptomatic shedding.

Many patients who are well controlled on antivirals are very concerned about spreading it to one of their sexual partners. Consequently, there will probably be a segment of the asymptomatic population who will be interested in receiving a vaccine to reduce their likelihood of transmission.

Management has said that efficacy against hSV-2 may translate into efficacy against hSV-1 (oral herpes). Although Genocea does not list an hSV-1 program on its website, Cowen & Co. in a recent research note suggested that
The pneumococcal vaccine ‘004 will compete primarily with Pfizer’s Prevnar 13, which is sold globally, and less so with GSK’s Synflorix (covers 10 serotypes), which is sold ex-US in the EU and 90 other countries, or with Merck’s Pneumovax (covers 23 serotypes), an older vaccine. Genocea believes that the commercial vulnerabilities of Prevnar involve manufacturing complexity and the concept of serotype shift.

When pneumococcus colonizes the nose and throat, it just sits there without causing symptoms. At some point, no one knows why, it becomes activated and starts invading some otherwise sterile site where it can cause upper airway infection such as sinusitis and ear infection. It can also cause pneumonia, and it can invade the bloodstream to cause sepsis associated with pneumonia and meningitis, so-called invasive pneumococcal diseases.

Pfizer’s Prevnar 7 contains seven serotypes, or strains, of pneumococcus. When the vaccine was introduced in 2000, it significantly reduced incidence of pneumococcal disease. Schodel says, “There was even a reduction of disease in the non-vaccinated population that came in contact with the vaccinated population – a herd effect, if you will.” However, within a few years, other serotypes not contained in Prevnar 7 became important, like serotype 19A. Schodel notes that the appearance of serotype 19A did not result in a net increase in the number of cases of pneumococcus disease. Rather, many of the cases that physicians saw were no longer the vaccine types; they were new types. (See sidebar, “Serotype Shift.”)

In 2010, Pfizer added six additional strains to Prevnar 7, one of which was serotype 19A, and called the improved vaccine Prevnar 13. Hetherington says that cases of serotype shift reported around the world argue for the introduction of a universal vaccine that doesn’t go after one serotype at a time.

Another opportunity for a universal, T-cell-directed pneumococcal vaccine has to do with the complexity of the manufacturing process for Prevnar 13. The vaccine comprises fragments of the polysaccharide shells from 13 different pneumococcal serotypes. These fragments must then be conjugated into a single product. Moreover, the introduction of multiple vaccines in a conjugated vaccine means that they are all vying for the immune system. Some are better at it than others. “You will lose the immunogenicity of some serotypes if you add more, so you won’t get as good an antibody response,” says Hetherington.

Even if Pfizer wanted to improve on Prevnar 13, there are limits to how many pneumococcal strains can be added. Affinivax Inc.’s MAPS technology, still in preclinical, claims to get around these limitations of conjugate vaccines.

**BUSINESS DEVELOPMENT FOLLOWS ON THE HEELS OF DATA**

Clark says that even a year ago “there was no real proof that our platform worked in the sense that there was clinical data to validate it.” Fast-forward to today: ‘003 has achieved and recently reconfirmed proof-of-concept in genital herpes; and ‘004 will shortly report PoC data from its human challenge trial in pneumococcal disease. The accumulating data enable business development.

Genocea thinks about retaining US rights for ‘003. OB-GYN physicians are significant prescribers of antivirals for genital herpes in the US, accounting for about 40% of the market. It’s a population that Clark feels the company can manage, certainly smaller than office-based primary care physicians. It would also be possible to establish agreements with the major distributors, and to put together a medical and policy organization that interacts with the Centers for Disease Control & Prevention’s Advisory Committee on Immunization Practices. Clark leans toward a co-promote for ‘003 in the US with a partner detailing PCPs. But he’d only consider a partner that would allow Genocea to develop the label or to reach more customers faster. And he’d look to enter into such a deal closer to approval or launch, the better to maximize its economics. Given the company’s ability to bring ‘003 forward on its own in the US, Clark says “we would look at those offers in a more jaundiced way than we would offer ourselves outside the US.”

Here Clark emphasizes that it’s not in Genocea’s sights at this time to be a global company. “We would certainly entertain partnership discussions with an ex-US partner provided they can give us the right kind of value, some combination of money and capabilities to allow us to develop ‘003 to maximize its potential.”

Validation of the ATLAS platform opens the possibility of licensing it in exclusive or non-exclusive target discovery collaborations. One area is infectious disease. “There are 20 or more infectious disease areas where it’s thought that T-cell-based protection can be helpful,” says Clark. “We’d love to see in the coming years if we can partner in diseases that we’re not currently working on.”

Genocea believes that ATLAS will have applications outside of infectious disease, in the cancer and autoimmune space. It recently entered into a collaboration with the Dana-Farber Cancer Institute to find targets of tumor response, focusing on patients who are responding or not responding to iplimumab. The idea is that ATLAS can help identify which T-cells are being unleashed by checkpoint inhibitors, and what those tumor-shrinking T cells were targeting. Unlike Agenus, which appears to be moving away from its vaccine heritage, striking recent immuno-oncology antibody development deals with Incyte Corp. and Merck, Genocea sees the immuno-oncology opportunity as complementary to its core business of proprietary T-cell vaccines for infectious diseases. (See “Incyte Will Tap Agenus Platform To Move Into Checkpoint Modulator Space”— “The Pink Sheet” DAILY, January 9, 2015.)

Looking ahead, Clark thinks that TCR therapeutics (T-cell receptor) may be a fertile area for alliances in that they target both intracellular and extracellular cancer proteins, which greatly increases the breadth of targets over technologies such as CAR-T.

One final frontier of growth for the company is expanding from established markets into pathogens that afflict emerging and developing markets. HSV-2 is thought to affect more than 400 million worldwide. Much of the prevalence is in places like Africa (31.5%). Companies like GSK and Sanofi, convinced of the possibility of capturing established and developing markets through tiered pricing, are close to launching vaccines for scourges like malaria and Dengue fever.

Genocea is aware of the opportunity and also the profound logistical challenges of commercializing vaccines in less-developed regions of the world. (See “Vaccine Funding And Access Key To Pharma Success In Developing World”— “The Pink Sheet,” November 11,
PNEUMOCOCCAL SEROTYPE SHIFT

There are currently 90+ serotypes of pneumococcus. Before any pneumococcal vaccine became available, there were roughly a dozen serotypes that caused about 70% to 80% of infections. As vaccines were introduced against these serotypes, other serotypes have taken their place. Many of the serotypes represented in Prevnar have disappeared; the serotypes that weren’t targeted are flourishing. Genocea Chief Medical Officer Seth Hetherington, MD, says, “If you go to Boston and swab the noses and throats of infants, you’ll find plenty of pneumococcus – serotypes 15, 35, 36 will be the predominant ones, and they’re not in Prevnar. You’ll find very few vaccine-type serotypes represented. Other serotypes have taken up residence in the upper airways of those infants in Boston, and their incidence is increasing. That’s serotype shift. If you look at all reported cases of pneumococcal disease in the US, maybe 40%, maybe less, is caused by vaccine serotypes.”

Philimmune’s Florian Schodel, MD, PhD, is not so sure. He acknowledges that when a serotype is prevalent that causes serious disease, and is not covered by a vaccine, it will not go away; effectively, it may increase a little bit under the circumstances of vaccination. Serotype shifts have also been observed in the absence of vaccination. “The question is, in the long run, if you have a vaccine that protects against 13 or more serotypes, will you see other types of pneumococcal serotypes? The answer, in all probability, is yes, but some of them are fairly rare. Will they take over and become as frequent as the other serotypes used to be? Unknown. If that were to happen it could be a very long process.”

Michael Thomas, senior managing director at Red Team Associates, and former head of GSK’s US vaccines business and Merck’s global vaccine business, thinks of serotype shift as a “theoretical concern.” He also notes that Prevnar 13 has only been on the market for a few years, and it’s only been available in higher income countries. “In order to see serotype shift, you have to see broader global use over time where the vaccine is effectively continuing to stamp out those 13 serotypes. Maybe I’ve missed it, but I haven’t seen it.” He adds that if Genocea can document that there is an emerging problem with serotype shift in the US or some other established market where Prevnar has been available, “that would give them a huge opportunity.”

Hetherington is confident. He points to articles on the CDC website and in the journals Clinical Infectious Diseases and Journal of Infection and Chemotherapy describing global cases of serotype shift in regions where Prevnar 13 is available giving rise to pneumococcal otitis media and pneumococcal meningitis in pediatric populations.

But Thomas thinks there’s a difference in appetite among the four. Pfizer, for instance, is interested in growing its business, most recently spending $130 million for GSK’s vaccines, $635 million for Baxter International Inc.’s vaccine business and an undisclosed amount for Redvax GMBH. “If they saw something they thought was a reasonable valuation, like Genocea, I think they’d go for it,” he says. Though Pfizer may not wish to jettison its Prevnar franchise, Thomas didn’t think it had anything early stage in either HSV or chlamydia.

Takeda Pharmaceutical Co. Ltd., too, has shown itself to be a serious and acquisitive player on the global vaccine stage, having acquired Ligocyte and Inviragen in 2012 and 2013.

Clark is lukewarm toward the idea of being bought. “Any such offer would have to be at a very significant level to be attractive.”

Genocea’s current market cap is about $360 million. Although it harnesses the power of T-cell immunity much like any immuno-oncology company, albeit with none of the safety concerns or variability in patient response, it lags far behind those companies in valuation. It’s possible its forays into cancer collaborations, like the one with Dana-Farber, could help investors appreciate the broad commercial potential of the ATLAS platform, and to see Genocea as a product company with a platform that positions it to play in infectious disease, cancer and autoimmune disease. If ’003, and especially ’004 go on to capture their market, it could even wake investors to the idea that ATLAS, with its ability to identify novel antigens for infectious disease vaccines, can be as commercially rewarding, or even more so, as immuno-oncology modalities.

At this point, Genocea still has much to prove – about the durability and dosing regimen of ’003 or about using T cells in the nasopharyngeal passages to eliminate total pneumococcal colonization. Clark thinks the company is on track and headed for great things. “If our technology is as promising as it appears to be, we’re in a position to pursue our own destiny.”

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