CELL THERAPIES

Argos Aims To Automate Cell-Based Cancer Therapy

Eventually, someone is going to have clinical and commercial success with a personalized cancer therapy. Learning from the mistakes of Dendreon and others, Argos expects to be first. Automation is its key.

BY DEBORAH ERICKSON

- Argos Therapeutics has developed a cell-based therapy to help the body's own immune system fight cancer already present, on a tumor-specific and patient-specific basis.
- The Arcelis platform technology can, in theory, boost immune response to many kinds of solid tumors. Argos aims to prove its worth, first as an add-on to standard-of-care treatment for advanced kidney cancer.
- Final Phase III clinical data should come in mid-2016. Preparing to launch product as soon as regulators say OK, Argos began automating its manufacturing process a decade ago.
- Intent on commercial as well as clinical success, Argos has applied lessons learned by others including the ill-fated cell-therapy pioneer Dendreon. Everyone in the field must confront similar challenges.

"There is a fine line between tenacity and insanity," says Jeff Abbey, president and CEO of Durham, NC-based **Argos Therapeutics Inc.** since February 2010. He has held several roles at the firm including VP of business development and chief business officer. Abbey claims to have attained some intimate understanding of the abyss in the course of his tenure, and no wonder. Argos is intent on creating the first cell-based, personalized cancer therapy to qualify as both a clinical and commercial success. The company has been working toward this goal since 1997, and is at last nearing the finish line.

Argos' *Arcelis* technology platform has evolved along with understanding that dendritic cells are the "teaching" cells of the immune system. Dendritic cells scavenge diseased cells and foreign invaders that they recognize via specific proteins or antigens. The dendritic cells then use these identifiers to educate other immune cells to attack the bad actors. Argos believes it has developed a means of stimulating this natural immune process in a directed way. The Arcelis approach relies on gathering RNA and white blood cells from a patient, then processing both in a way meant to create dendritic cells better educated to fight the disease already present in the body.

The company is now more than half-way through enrolling 450 patients for a Phase III clinical trial of AGS-003, its personalized dendritic cell therapy against metastatic renal cell carcinoma (mRCC), the most common form of kidney cancer. The experimental treatment is being given in addition to the current standard-of-care, which entails surgery and **Pfizer Inc.**'s oral targeted therapy *Sutent* (sunitinib). Abbey says the final Phase III results should arrive mid-2016, from over 130 clinical sites.

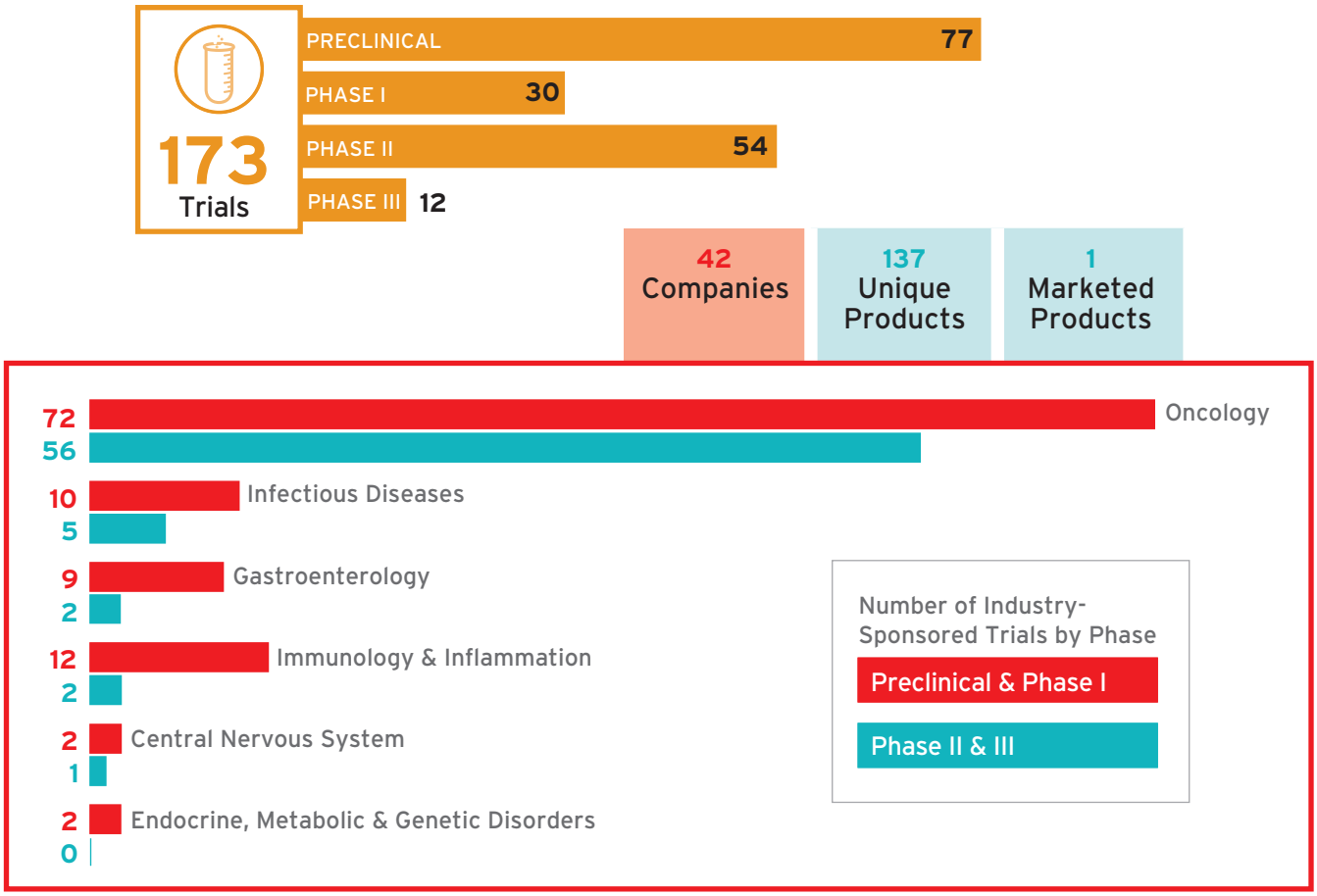
Argos is betting that adding its cell therapy to standard treatment will significantly extend the lives of advanced kidney cancer patients, with no additional toxicity. The goal is to show 38% improvement, which equates to about six months more life than the control arm. If the data bear out, the company hopes to get FDA's approval to sell the therapy for that purpose, as well as to test it in earlier-stage kidney cancer, again with standard-of-care treatment. Abbey says Argos believes that AGS-003 may be able to improve outcomes for cancer patients receiving standard treatment for many kinds of solid tumors. The cell-based therapy may also help patients with chronic infectious diseases such as HIV, where it has reached Phase IIb testing, he says.

Given the long, disappointing history of cell-based therapies, these are big "ifs." Argos knows it has little choice but to endure its doubters. Until Phase III results are in, the company's most advanced data on AGS-003 come from a Phase II trial in just 21 people. In that trial, median overall survival for the 21 intermediate and poor-risk patients was just over 30 months, versus expected survival of 15 months. In the intermediate risk patients only, median overall survival was about 60 months, compared to an expected 20.

Many, many companies have tried and failed to commercialize immunotherapies for cancer over the past 30-odd years. Enthusiasm for cell-based approaches in particular has waxed, waned, and at times been almost fully eclipsed by Phase III failures. (*See Exhibit 1 for a look at the current landscape.*) To date, the Food and Drug Administration has only ever deemed one cell-based cancer therapy sufficient. **Dendreon Corp.**'s "therapeutic vaccine" *Provenge* (sipuleucel-T), won approval in April 2010 as a treatment

Exhibit 1

Cell-Based Immunotherapy Companies



SOURCE: Alliance for Regenerative Medicine

for asymptomatic metastatic prostate cancer. But the pioneering product has not been successful in the marketplace. Dendreon filed for bankruptcy on November 11, 2014.

Argos insists that it will succeed where others have failed at commercializing a cell-based, personalized cancer therapy, largely by applying lessons learned the hard way by Dendreon and others, and also itself in earlier years.

FIGHTING CANCER'S CORRUPTION

"So many companies developing cell-based cancer immunotherapies did not take into account that patients' immune systems are corrupted by cancer," Abbey declares. But that was then and this is now. Increasingly, this awareness is becoming a guiding principle for drug developers such as those who created the new checkpoint inhibitors. (*See "Cancer Immunotherapy Reaches A Tipping Point"* — START-UP, *October 2014.*) The knowledge also informed Argos' development of its Arcelis technology platform, Abbey says: by growing and educating dendritic cells outside the patient's body, "we are not relying on a damaged immune system to function normally."

Abbey believes AGS-003 has the potential to help patients by converting CD8+ cells into CD28+ "memory" T cells capable of providing a sustained immune response against antigens they have learned to recognize. "They work in healthy people, but not in cancer patients," he says. This rationale appeals to immunologist and venture capitalist Brian Underdown, MD, whose Toronto-based firm Lumira Capital first invested in Argos in 1999. "Long before there was genomic proof, it was clear to me that everyone's tumors would be different," he declares. So to him dendritic cells that by nature respond to all sorts of aberrance seemed a better bet than single-antigen and peptide-based cancer immunotherapies. Argos maintains that inserting RNA from a patient's tumor into dendritic cells can, potentially, allow the cells to respond to multiple mutations specific to each individual patient, rather than just one antigen that might or might not be relevant in any individual.

AVOIDING OTHERS' MISTAKES

All the while Argos was working to resolve technical challenges of its particular approach to cell-based cancer treatment, the company was simultaneously concentrating on avoiding commercial problems that Abbey perceived at Dendreon. As far back as 2001, Abbey says, "We knew Dendreon was making mistakes." Knowing

that Dendreon would need to build three manufacturing facilities in the US, Argos determined that its own production process must work with just one facility in North America, to limit capital investment, costs and logistical challenges. Argos also decided at the outset that its manufacturing process should yield a final product that could be injected intradermally, rather than administered through an intravenous drip like Provenge. Injections would be simpler for both clinicians and patients, and less costly. Argos also decided it would formulate a product that could withstand being frozen because, Abbey observes, "Provenge needs to be administered within 18 hours after completion of manufacturing, and begins losing potency as soon as it leaves their facility."

Argos was not the only one to see Dendreon's manual production process as a real hindrance to commercialization. Financial analysts and journalists following Dendreon certainly expressed their concerns about it. Abbey says Dendreon's big Japanese development partner **Kirin Brewery Co. Ltd.** found the matter serious enough that it approached Ralph N. Steinman, MD, the Nobel prize-winner who discovered dendritic cells, in late 2001, asking whether he believed Argos' production process could be automated. After five years in partnership with Dendreon, Kirin terminated that contract in 2004 and signed a new one with Argos. Kirin agreed to share 50% of core costs in exchange for 50% of profits, but only if Argos could prove it had a scalable manufacturing process before even beginning clinical trials. Argos spent 4.5 years figuring out its manufacturing process, Abbey says, noting, "it was an ongoing struggle to bring our investors along with us. Venture capitalists don't like building the foundation first."

"Having Kirin with me when we went to the board to present plans was critical," Abbey recalls. Together, the partners convinced Argos' directors that it was worth developing a new and improved process for inducing dendritic cells; worth figuring out *before* gathering clinical data whether this Arcelis manufacturing process could be automated; worth re-running the same study it had run with an earlier candidate with AGS-003.

"The investors let us do all of this, including spending money on automation, when we didn't even have Phase II data yet," Abbey declares. It was a leap of faith that would have been unimaginable had Kirin not been paying 50% of the costs, he acknowledges. Argos also raised additional non-dilutive financing by licensing some of its technology. **Geron Corp.** paid $35 million, seeking to rev up its own experimental therapy based on the cancer antigen telomerase.

Argos began testing AGS-003, the first immunotherapy made with its Arcelis process, against mRCC in 2006. By 2008, the therapy was mid-way through Phase II testing, when suddenly Kirin announced a merger with Kyowa Hakko. The merged company, **Kyowa Hakko Kirin Co. Ltd.**, decided to pull the plug on the program, Abbey recounts, even though Kirin had invested some $50 million by that point, and gathering complete Phase II data would cost it only a few million more. Faced with handling 100% of the costs going forward, Argos had to make some quick adjustments. The company decided to wrap up the Phase II trial with 21 patients, instead of the 40 originally planned. Argos also told **Invetech**, the Australian design and engineering firm automating its manufacturing process, to halt work. Argos would manually prepare therapies for the Phase III trials, and later, when it could, show comparability between cells produced that way and by machine.

Argos' board of directors decided that the failure of other companies' cell-based therapies stemmed from problems that Argos had avoided, or could avoid. The potential of the Arcelis platform to raise antibodies to multiple antigens was just a start.

The hardship Argos experienced with the loss of its partner Kirin has turned out to be a blessing in disguise, Abbey suggests. Had Argos finished gathering data on 40 patients, with the same results seen in the 21, he figures the data would have been good enough to prompt some kind of staged acquisition of Argos, with the partner paying for Phase III trials and then a pre-negotiated buyout. But the sudden stop meant Argos did not have enough data to attract a Big Pharma partner, nor any more typical US venture investors. Especially not in light of what other, more advanced companies in the field were experiencing. **CancerVax Corp.**'s *Canvaxin* had failed its Phase III trial for melanoma in April, 2005. In 2007, the FDA told Dendreon its Phase III trial did not sufficiently show efficacy of Provenge, and it would need more data. In 2009, **Cell Genesys Inc.**'s *GVAX* failed its Phase III trial. Those were dark times for personalized immunotherapies.

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Dendreon had to employ and train thousands of people, many of them PhD-level workers, to carry out its manual manufacturing process. To house them, it built three facilities across the US, each bigger than 100,000 square feet. By contrast, Argos figured it could supply AGS-003 to qualifying kidney cancer patients in North America using a few hundred employees in one automated, centralized facility. Where Dendreon's process called for patients to have blood cells harvested via leukapheresis three times, for only three doses of therapy over six weeks, Argos could with one tumor sample and one leukapheresis collect enough material to prepare three to five years' worth of its immunotherapy per patient.

Where Dendreon's immunotherapy to treat asymptomatic prostate cancer faced tough competition soon after its launch from two new oral drugs approved for the same indication, AGS-003 is being tested in a cancer where the standard drug's high toxicity often forces patients off therapy. Patients will continue receiving AGS-003 even if they switch to other targeted therapies.

Argos' VP of medical and clinical affairs, Doug Plessinger, says the company took one lesson of Dendreon particularly seriously. He points

out that, "Dendreon took Provenge from Phase II through Phase III trials without identifying a biomarker that could help clinicians decide which asymptomatic prostate cancer patients should receive it." The lack was especially glaring, given the price tag of $93,000.

Argos managed to leverage studies done by leading kidney cancer experts, identifying some clinical factors of risk, so that it could more accurately stratify patients based on their prognosis. The company wanted, at minimum, to test its therapy in patients likely to live long enough to receive a full course of its treatment. In the Phase III trial of AGS-003, Argos is taking a minimum of 70% of patients with intermediate risk, while limiting poor-risk patients to no more than 30% of participants.

Plessinger acknowledges that Argos has not yet validated "a biomarker to serve as an indicator of how our cell-based therapy was designed to work, and whether or not it is working." But it's trying. Plessinger says Argos expects to gain better understanding of the correlation between memory T-cell response and survival after the Phase III trial. It may then offer the concept as "a blueprint for oncologists and urologists."

Like other advocates of immunotherapies, Plessinger argues that it is not necessary to completely eradicate cancer in order for patients to regain a normal quality of life. Argos originally tried to show complete remission with an earlier candidate, before realizing that even Sutent cannot make that claim. "We set the bar way too high [in that earlier trial]," and did not meet the clinical endpoint, he says. Since then, Plessinger explains that Argos has seen some of its long-term stable patients enjoying "pretty deep partial remissions. They may still have a small tumor burden, some stubborn nubbin of a lesion that refuses to go away, but they feel fine," he says.

Argos has gained some strategic advantages by luck. FedEx Express courier service now reliably delivers packages all over the world. Happily, someone also invented special shipping tubes containing liquid nitrogen that can keep contents frozen for two weeks. Both the packaging and the delivery options are key to Argos' strategy, observes Argos' chief operating officer Frederick Miesowicz, PhD.

TIME TO GET CREATIVE

After reviewing all these commercial factors, Argos' board agreed in 2011 that the company should commence a pivotal Phase III trial of AGS-003, knowing it would still have to raise a lot of money from no one knew where. Argos tried to go public in 2011, hoping to raise $60 million, but withdrew the offering. Jeff Abbey reminded himself that necessity is the mother of invention: "It was time to get creative." He began traveling to China, Hong Kong, Singapore, Korea, and Russia in search of fresh financing.

In Moscow in the summer of 2013, Abbey signed a licensing agreement with "a great new partner with deep pockets and a passion for commercial biotechnology." **Pharmstandard OJSC**, Russia's largest pharmaceutical manufacturer, had decided just a few years

earlier that it wanted to start making advanced biologics such as monoclonal antibodies, and established a $200 million venture investment fund to support the effort. The fund, Pharmstandard International Inc., was incorporated in Luxembourg and started operations in December 2012. It is being managed for the drugmaker by Inbio Ventures, a private independent Russian company charged with finding licensing opportunities and partners.

Andrei Petrov, PhD, Inbio's CEO, says that Argos' willingness to license product rights, and share manufacturing know-how, fit right in with Pharmstandard's vision for future growth. Petrov recommended that Pharmstandard be the company to exercise license to Argos' technology in Russia, and also that it take an equity stake in the US biotech company. That is just what happened. Pharmstandard led Argos' final venture financing, a Series E round of $42.5 million in August 2013, and six months later participated in Argos' IPO, investing over $40 million total and winding up with about 30% ownership of the company.

Pharmstandard recently finished the construction phase for a pilot manufacturing plant that will utilize Argos' Arcelis technology, Petrov notes. He says, "Pharmstandard's people will soon visit Argos, perhaps as soon as December, to spend some weeks and effect the technology transfer." The large Russian drug company may also sub-license some rights to strategic partners in Russia, Petrov suggests. One likely candidate is the **International Biotechnology Center Generium**. Founded less than a decade ago, the IBCG already manufactures and markets some "biosimilar" drugs in Russia and the Commonwealth Independent States. It also has some versions of monoclonal antibodies like *Rituxan* (rituximab) (Rituxan) and *Herceptin* (trastuzumab) in advanced clinical development. It even has some products in registration in Latin America and Asia. But the factor most likely to get IBCG involved in some way with the Arcelis platform, Petrov points out, is that it has its own R&D capacity.

Thanks to the new infusion of funds from its Russian partner and the US public stock offering, and certainly the past contributions of Kirin, Argos now has the increasingly rare opportunity to become a vertically integrated biopharmaceutical company. Frederick Miesowicz believes Argos must take that leap: "To truly show the world the value of what we have, we have to take this all the way to commercialization and show we can make money." He asserts, "The investor and biopharma worlds are all playing wait-and-see with us. Until we prove we can build a business on this technology, we remain under the shadow of Dendreon." Miesowicz says Argos plans to hold on to all product rights in North America and possibly also the EU, and "go it alone." In other territories, licensing partners like Pharmstandard in Russia may use Argos' methods. And **Green Cross Corp.**, which also participated in the Series E round, concurrently received rights to sell Argos' AGS-003 in South Korea.

Argos has come a mighty long way since it was a fresh spin-out from **Duke University** in the late 1990s. Back then, under a different name, Merix Bioscience Inc., it received a $10,000 loan from the North Carolina Biotechnology Center. Bill Bullock, now VP of bioscience industrial development there, knew the company then and now. At the start of October 2014, Argos broke ground in Durham on a new biomanufacturing facility it expects will employ hundreds of people. In appreciation, the state is giving Argos a $9.5 million grant that will begin paying out as the jobs do.

The company needed to commit to the manufacturing facility while its Phase III clinical trial was just getting started, Abbey says: it needs to be ready to quickly commercialize its cell-based cancer therapy, if and when regulators approve it. The Keith Corp. is building the facility to GMP specification, and is the one actually paying for the structure Argos will lease. So the developer is sharing risk with Argos to some degree, but Bullock points out "there is a very limited number of those kinds of facilities anywhere in the world. No one wishes failure upon Argos, but if it does turn out to be a bad-case scenario, the developer will fill that building."

As ever, Jeff Abbey continues going where he needs to go, to get what Argos needs. In early November 2014, he announced that Invetech, the Australian design and engineering firm that worked a decade ago on automating the company's Arcelis technology, is now a strategic partner. Invetech will "develop and supply manufacturing systems to support production needs for fully personalized immunotherapies," first for the Durham facility and potentially for other sites as needed (such as Russia and Korea). Richard Grant, now Invetech's director of cell therapy, was Argos' initial project manager.

Argos' original manufacturing process effectively took six people working for three weeks in two different clean rooms to create one person's therapy, Grant recalls: "That was never going to be commercializable." Invetech was able to translate typical operator workflows, and control temperature, pressure, and flow rates, to create an entirely sterile manufacturing process that involves proprietary disposable components. Argos can now process multiple patient samples in one room with one operator, while keeping an automated batch record. The possibility of human error is gone, and costs are dramatically lower, not only for sample processing but for the facility overall.

Abbey understands that many industry observers remain skeptical of Argos' chances, given the history of personalized cell-based cancer therapies. But he chooses to focus on the many things that have been done right by Argos, and are going well for it now. The company has put tremendous effort into managing clinical and commercial issues that have scuttled many another noble effort. Management has made some clever decisions and strong moves, and consequently, Argos is attracting allies around the world. The company's boldest action to date was, arguably, the decision to begin automating its manufacturing process before the Phase II clinical data were even in.

Every would-be developer of every fascinating theoretical approach to cancer immunotherapy must ultimately prove the method's worth through clinical trials. That challenge still lies ahead of **Novartis AG** in its alliance with the **University of Pennsylvania**, and Seattle's exceedingly well-funded start-up **Juno Therapeutics Inc.**, affiliated with both the **Memorial Sloan Kettering Research Center** and the **Fred Hutchison Cancer Center**. Eventually, if the data are good, every organization that envisions providing a cell-based cancer therapy to patients will have to process those cells. However the cells are collected or cultured, however they are manipulated, they will have to be formulated into a reliable product or process. Clinical and regulatory hurdles are unavoidable. So too, are the sorts of practical commercial challenges that Argos began working through in detail over a decade ago. **SU**

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COMMENTS?
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