Cell Therapy Will Transform the Future of Medicine

Bioprocess Economics, Tools, and Regulations Are Critical to Achieving Standard-of-Care Status

by S. Anne Montgomery with Phil Vanek

The third annual IBC Cell Therapy Bioprocessing conference was held in Bethesda, MD, on 21–22 October 2013. It brought pioneers in the development of cell-based therapies together with companies that have enabling technologies, such as bioreactors, cell culture media, and advanced monitoring software. After the conference, I discussed the highlights and key themes coming out of the event with Dr. Phil Vanek, general manager of cell bioprocessing at GE Healthcare Life Sciences in Westborough, MA. Also an instructor for advanced academic programs at Johns Hopkins University, Vanek was in business development, innovation, and cell therapy at Lonza for six years. Before that, he worked in marketing and business development positions with BD Biosciences, Invitrogen/Life Technologies, and Trevigen.

Montgomery: People are really starting to take notice of the cell therapy industry now. What is your assessment of the global impact that this wave of new therapies could have?

Vanek: Solving the technological challenges in cell therapy will facilitate affordable solutions that are well tolerated and more efficacious — and that potentially have a longer therapeutic effect — than treatments based solely on small and large molecules. What this means in practice is hard to predict fully, but we can say that for many patients for whom curative treatments are currently unavailable, the prognosis will be very different in the future.

Couple that with our growing understanding of the human genome, and as Dr. Robert Deans at Athersys Inc. said during this conference, “In the not-too-distant future, patients will have cells made to order, anticipating contingencies based on genetic disorders or stratification for treatment within indications.” The convergence of cell therapies and personalized medicine is clearly an inspiring prospect on the horizon.

Montgomery: Is 2014 the year when cell therapies finally become a truly viable industry sector?

Vanek: The pace of change and progress we’re seeing in the development of cell therapy applications is truly astounding. Some clinical outcomes we’ve seen in the past year or two are beyond even what we hoped for or expected. It is certainly true to say that we are now on the cusp of transforming the future of medicine, and that’s a very exciting place to be.

I wouldn’t go so far as to say that we’re through the woods yet, though. Clearly economic, technical, and regulatory challenges need to be overcome before successful adoption of cell therapies becomes widespread. A lot of discussion at this year’s conference was about fully describing those challenges and finding ways to address them.

Economics

Montgomery: If we examine the economics of the industry, where do you see problems at the moment?

Vanek: Let’s start with market predictions. Increasing therapeutic interest, manufacturing infrastructure demand, and clinical investments are driving market growth. According to a 2012 report from BCC Research, the major market segment for cell therapies is clinical application of these treatments to disease. BCC Research reported that the global market for stem cells was US$3.8 billion in 2011 and predicts that it could reach $6.6 billion in 2016, reflecting a five-year compound growth rate.
BIG PHARMA is willing to commit substantial resources to commercializing the right opportunities in cell therapy.

States at least, there exists a multiple-payer system that complicates things.

However, a number of things give us hope in this regard. For those therapies that are showing compelling clinical results in areas of unmet medical need — and we’ll come back to some examples — the cost/benefit assessment gets a major boost in favor of the therapy if you are talking about delivering a curative effect. Also, big pharma companies were much more in attendance at this year’s conference. Although they are waiting until therapies have sufficiently proven themselves in the clinic, once those milestones are reached, they are willing to commit their not insubstantial resources to commercialization of the right opportunities.

Finally, successful commercialized examples are already out there, with patients receiving treatments every day. The most established is, of course, blood stem cell transplant therapy. The milestone of a million transplants worldwide was reached in early 2013, and with the growing potential of using umbilical cord blood, that number will continue its upward trend. But we also had companies presenting at this conference that have reached the commercial stage. Organogenesis, for example, is treating many patients daily with a wound-healing product, as is Tigenix with its autologous chondrocyte therapy for injured knees.

Technologies

Montgomery: It’s interesting that you mention big pharma and the resources it could bring to bear. Do you see those companies’ involvement as a game-changer for commercialization of this field?

Vanek: Absolutely. The message coming from big pharma is that, although the challenges such as bringing down the cost of goods are by no means trivial, with time and resources they are solvable. Big pharma is willing to solve those problems if the clinical outcomes are compelling enough, particularly in areas of unmet medical need.

Alongside that, I want to highlight the commitment that the tools-and-technologies providers are making: GE and others are working closely with both academics and cell therapy companies to think ahead about how processes can be optimized at small scale to facilitate scaling up and scaling out. We’re also thinking about what larger-scale solutions will look like. As we know, two leading technologies will serve the cell therapy markets: large-population treatments from single cell lines (allogeneic therapies) and individual, custom treatments from a patient’s own cells (autologous therapies). The former is more about scaling up; the latter is about scaling out.

Montgomery: How do you plan ahead? What technical requirements must be met?

Vanek: Let’s look in more detail at an example. Autologous cellular immunotherapies have unique scalability requirements. A typical therapeutic dose could be around 1 × 10⁸ cells per kilogram (kg) of a patient’s weight, meaning 2 × 10⁹ cells would be required for a pediatric patient weighing 20 kg. The current commonly used cell growth vessel in clinical development is the T225 flask. With a 100-mL capacity, and based on achieving a density of 2 × 10⁶ cells/mL, you would need 10 flasks running in parallel to culture the required number of cells for that patient. For a 100-kg adult, the number would rise to 50 flasks.

So because of the autologous nature of immunotherapy, if we want to grow enough cells to treat larger numbers of patients, a similar number of growth vessels are required for each patient. Two difficulties need to be overcome here: One is a rationalization of the growth vessels allowing companies to work on a ratio of one vessel per patient to minimize labor costs. Then how can the burden on human operators be reduced so that it does not increase in line with the number of patients?
To address such questions, you need a system that allows robust and reliable expansion of ‘T’ cells. It needs to be able to culture T cells at high densities up to the required numbers in a functionally closed setting to minimize contamination risks and cell handling. Automating the system with multiple control and traceability features would then make it ideal for use in manufacturing for therapeutic purposes. It would reduce the need for human intervention and monitoring. In addition, understanding logistics, chain of custody, and process planning in a scale-out factory are all part of the recipe for cell bioprocessing success.

Montgomery: Where are we seeing the most exciting clinical results?

Vanek: I think many people are now familiar with the success that the University of Pennsylvania (UPenn) team has had, but it certainly warrants retelling. The first chimeric antigen receptor investigational therapy, or CART-19 as it is commonly known, is an autologous immunotherapy developed at UPenn to target and destroy cancer cells. To achieve that, T cells taken from a patient are sensitized to specific proteins found on his or her cancerous tumor. Once those cells have been manipulated, they are expanded to sufficient numbers for a therapeutic dose using the Xuri (WAVE) Bioreactor system before being reintroduced into the patient to seek out, bind to, and destroy cancer cells. A trial that included adults with advanced chronic lymphocytic leukemia (CLL) and children with acute lymphoblastic leukemia (ALL) showed some striking results, including continued remission of at least two patients after more than a year.

In August 2012, Novartis and UPenn entered into a multiyear collaboration and licensing agreement for CART-19. Knut Niss (senior technical project leader at Novartis) provided an interesting update at this year’s conference on how their alliance is progressing and described some of the logistical challenges they are facing. Sourcing raw materials is one example, both from a supply chain perspective and in regard to what documentation and auditing are needed, and what quality control (QC) testing of incoming raw materials must be performed. The scale of resources required ultimately depends on how large a lot size can be. Niss also highlighted that, as some experts have calculated, if one liter of serum is required per run on a typical cell therapy process, then current stocks and production rates of serum suitable for GMP manufacture may be sufficient only to support a single blockbuster cell therapy.

UPenn’s Bruce Levine also presented updated data along with plans for scale-out in development of a similar treatment for B-cell lymphoma. Plans are to broaden this immunotherapy to six indications in total, building capacity to treat about 5,000 patients per year using patient-specific therapies. The fact that some patients are seeing complete remission with CART-19 is incredibly exciting, but a lot of work needs to be done to understand why some patients responded and others didn’t. UPenn, however, has a deep understanding of the different parameters that may be affecting the success of these treatments. We hope that it will be just a matter of time and further trials before this particular element of the puzzle is solved.

Oversight

Montgomery: Where do we stand in terms of potential regulatory hurdles and challenges?

Vanek: The roundtable discussion at this conference emphasized the need for international standards. A first step most likely will be harmonization between the United States and Europe. Then, given that mainland Asia and Japan are developing their own guidelines and regulations right now, a second step will be toward global alignment.

A number of areas have been identified where discussion is still needed and agreement should be reached. These include developing and implementing universal bioprocessing current good manufacturing practice (CGMP) standards, developing approval steps for autologous stem cell treatments (which ensure that critical processing steps are well controlled), harmonizing and updating clinical document architecture (CDA) production documentation, and establishing cell-quality and cell-banking standards. That final element should guarantee product effectiveness and production quality to prevent contamination.

In addition, some at the conference raised the issue of raw materials and the supply chain in the context of regulations, with a push to develop global standards if possible. Resolving all these regulatory challenges will take coordinated efforts. Process developers will need to focus on tools for performing experimentation; adequate analytical techniques to predict performance upon scale-up and scale-out; and infrastructure to allow traceability and connections among patients, patient samples, and testing results.

To help address regulatory hurdles, GE is incorporating proven and regulatory-compliant software into our cell bioprocessing systems. Originally developed for large-scale chromatography, our Unicorn software can assist in quickly establishing appropriate process controls. The program is already 21 CFR part 11 compliant, which is necessary for use in a regulated environment.

Continued on page 33
THE NEAR FUTURE

Montgomery: Finally, what do you think is needed to keep the cell therapy field moving forward?

Vanek: I am very optimistic. The bioprocess industry can leverage engineering expertise and tools to solve technical challenges in process development and manufacturing facilities that will help accelerate the field of cell therapy. If we consider the manufacturing process for a cell-based therapy to sit at the interface of biology and engineering, then both disciplines must be seamlessly integrated to help move commercialization forward. Engineering a solution that provides consistent, high-quality cell therapies is possible with today’s new and improved instrumentation.

At GE, we are applying our core competencies in protein separation, biomanufacturing, cell biology, engineering, data management, and process development to innovate and provide integrated solutions throughout cell therapy workflows. Understanding how to make stem cells work and have the desired therapeutic effect is not the main difficulty anymore. Now the question is how to standardize and scale-up or -out these cell manufacturing processes.

In the next few years, remaining challenges probably will fall away as appropriate regulatory standards are formed and supply chain logistics are improved. As a result, the near future will provide more opportunities than ever before for life-saving cell therapies to enter mainstream medicine.

S. Anne Montgomery is cofounder and editor in chief of BioProcess International, 1574 Coburg Road #242, Eugene, OR 97401; 1-646-957-8877; amontgomery@bioprocessintl.com. Dr. Phil Vanek is general manager of cell bioprocessing at GE Healthcare Life Sciences, GE Healthcare, 14 Walkup Drive, Westborough, MA 01581; 1-508-616-3078; philip.vanek@ge.com.