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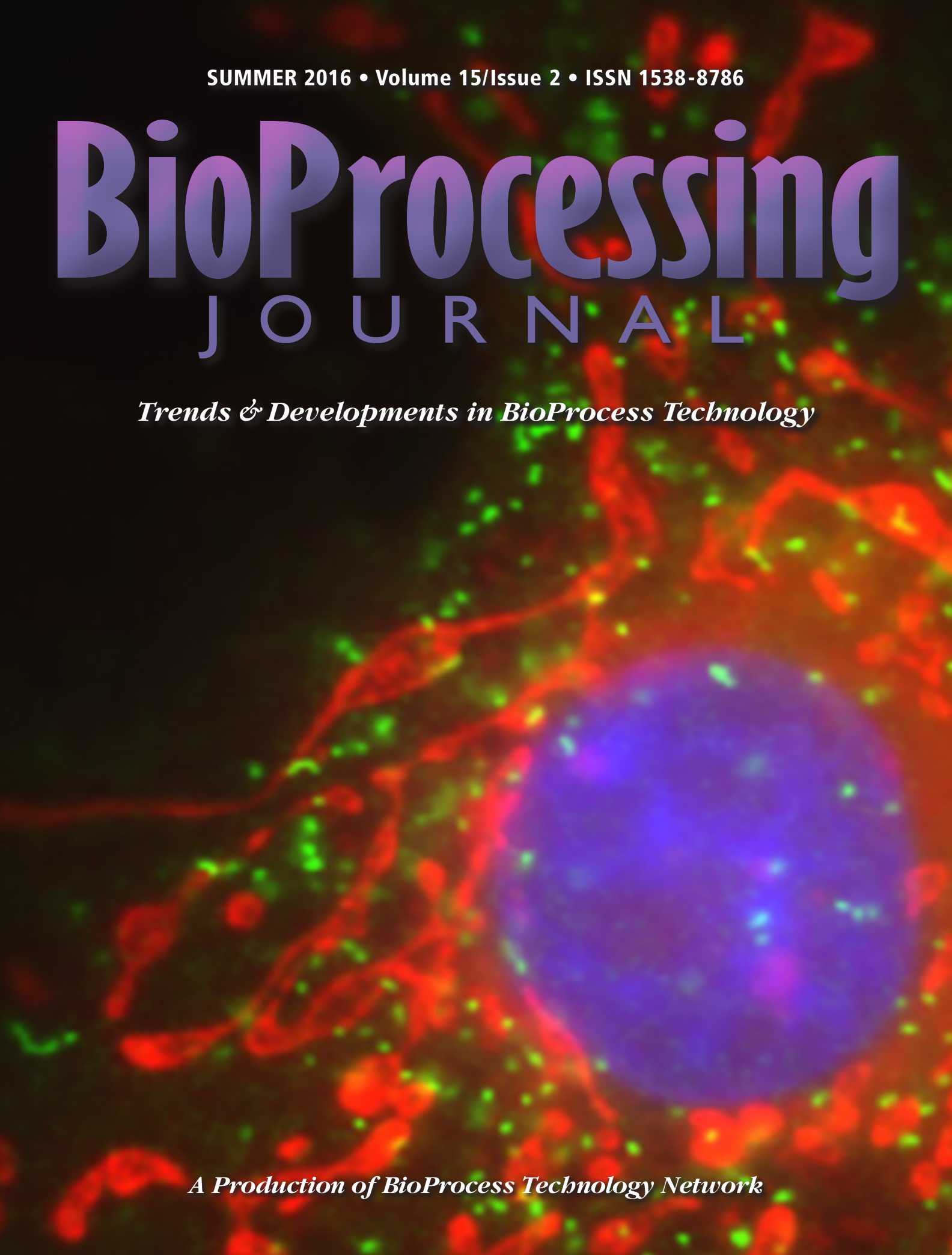
Trends & Developments in BioProcess Technology



A Production of BioProcess Technology Network

From The Editor-In-Chief:

As biologics continue to advance at a dizzying pace, I want to take this opportunity to outline what I see as the major successes, as well as the primary challenges facing the industry. First, the science of antibody production appears to be quite settled. The industry knows how to express antibodies at very high levels and then purify them with well-established techniques, which also provide satisfactory viral clearance. Then the characterization and comparability techniques have also been well-established. "Platform" techniques for upstream and downstream processing provide acceptable starting points for expression levels, purity, and product safety, while chemically defined media are readily utilized and result in much cleaner harvests. The chance of viral contamination from animal-derived components has been virtually eliminated.

The dominant challenges in antibody production remain their formulation, cell-based assays, drug linking, and delivery systems. Then significant value can be gained by finding ways to limit production batches to volumes that can be accommodated by single-use bioreactor systems. If a batch exceeds the volume of these systems, then fed-batch and perfusion techniques can be used. However, continuous clarification and purification techniques remain challenging, and it may make more sense to plan on sufficient "hold" steps during these unit operations.

Then the growth of applications for "personalized medicine" is resulting in smaller batch sizes which are perfect for single-use systems. But until these applications can be satisfied with allogeneic/donor cells, or can be used for broader patient populations, each treatment will be very expensive.

Then concerning development and production facilities, more applications can now be accommodated in modules that are rolled in and then plugged into air-handling systems and power. These modules can be set up to use shared, recirculating clean air systems, or can be operated off separate recirculating, or single-pass air systems. With these modules and the use of single-use process systems, a facility can be set up and qualified within a matter of weeks.

However, bigger challenges exist for other biologics such as viral gene vectors and cellular therapies. Here, and in the case of personalized medical applications, the small batches result in a challenge of "scale-out" — many parallel process systems — instead of "scale-up." With these batches, a production suite must be able to handle multiple "closed" systems, plus each suite must be turned around very quickly after each batch. Then there is the heightened concern of product cross-contamination unless single-pass air handling is used, or a recirculating air system can be validated to prevent such a contamination.

And for cellular therapies, understanding the product's mechanism of action and developing a suitable potency assay remain the biggest hurdles. In addition, their essential limitation to patient-specific, or autologous applications makes them very expensive. Otherwise, "closed" systems are readily available to take a patient's cells through selection, transfection, media / buffer exchange, and final dose filling. But then, cryopreservation remains a serious challenge, and many products are administered before proper sterility testing can be done. In addition, multiple doses are difficult to store, and each dose must start with new patient cells.

More recently, cell banking has become an area of increased interest as we've discovered that many cell lines have not been properly identified and cleared of adventitious agents. The cells used in thousands of research experiments and QC testing have been found to be contaminated with other cells, and in many cases, have been determined to be from a different species. Then more powerful tools such as massively parallel sequencing have identified viral contaminants that were previously undetected. And again, cryopreservation deficiencies have resulted in unacceptable process variability.

Finally, one of the biggest challenges moving forward is obtaining sufficient, real-time data so that a process can be automated and properly reproduced. Regulators want to see the industry show consistent product characteristics at numerous points throughout the process, and not simply from the final, pooled production lot. A number of new disposable sensors have become available, as well as analytical techniques that can be used in-line, or immediately off-line. These capabilities will be even more critical if more continuous processing is to be implemented.

It appears to me that we have made major advancements in the development and testing of biologics, and we appear to have a good idea of what our next steps should be.

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