BioProcess International eBooks

SENSORS

PROCESS ANALYTICS FOR MODERN BIOPHARMACEUTICAL WORKFLOWS

Brian Gazaille, with Mason A. Chilmonczyk and Andrei G. Fedorov



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Sensors

Process Analytics for Modern Biopharmaceutical Workflows

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Process analytical technologies (PATs) have improved significantly since establishment of the quality by design (QbD) paradigm. Thus, in-line sensors, at-line spectrometric instruments, and other such tools are bringing biomanufacturers closer than ever before to adaptive control of antibody production. That said, developers of next-generation therapies are finding that new in-line technologies are needed to enable identification and subsequent monitoring of critical process parameters and quality attributes. In this eBook, BPI's associate editor speaks with the founders of a new PAT developer about the biopharmaceutical industry's needs for process analytics and control.

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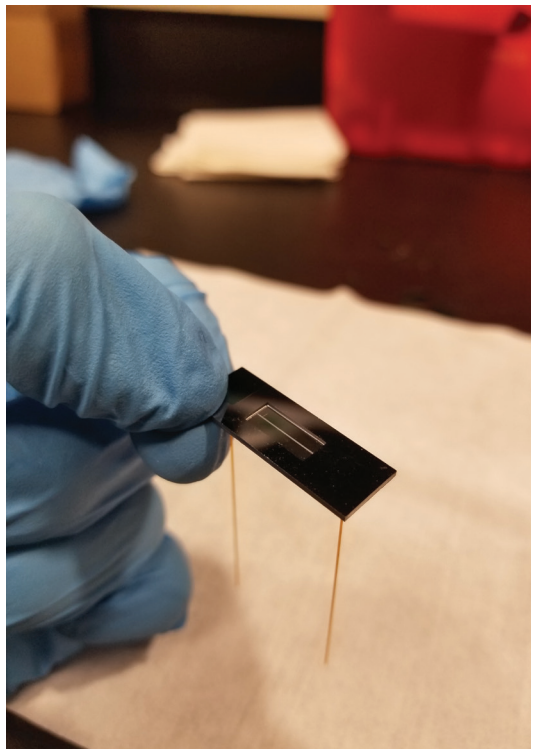
To achieve quality by design (QbD) in biopharmaceutical production, manufacturers need tools that can ensure the stability of critical process parameters (CPPs) and other performance indicators related to product critical quality attributes (CQAs). Over the past couple decades, sophisticated process analytical technologies (PATs) have emerged to meet such needs. Offerings are now abounding for single-purpose sensors that measure temperature, pressure, pH, glucose, protein concentration, or dissolved oxygen (DO). New in-line formats are enabling such instruments to provide data in real time, bringing manufacturers of monoclonal antibodies (MAbs) and other protein products closer than ever before to the goal of adaptive process control. Even spectroscopic methods that traditionally have been too difficult to perform in or at line are becoming commercially available.

However, much work remains to be done for monitoring cell therapy production processes. In February 2022, I spoke with Mason A. Chilmonczyk and Andrei G. Fedorov, past BPI authors and cofounders of the recently launched PAT developer Andson Biotech. Chilmonczyk noted that presenters at the 2022 Phacilitate Advanced Therapies Week in Miami, FL, highlighted urgent needs for process analytics "but weren't asking about methods that can measure what matters. They're still measuring pH, glucose, and DO" rather than indicators that could provide meaningful information about process and product quality — and such data would have significant value considering the inherent complexity of advanced-therapy discovery, process development, and commercial manufacturing.

During our discussion, Chilmonczyk and Fedorov mapped out their sense of the current PAT landscape, highlighting ways in which sensors and other technologies suffice for conventional biologics workflows but fail to meet the myriad needs of advanced therapy developers. They also described how real-time mass spectrometry (MS) of biomolecules could address such needs.

In addition to being chief executive officer of Andson Biotech, Chilmonczyk has worked as a postdoctoral researcher at the Georgia Institute of Technology (Georgia Tech, Atlanta, GA), from which he earned master and doctoral degrees in mechanical engineering. Fedorov has established and since advised several companies, including Andson Biotech, OpenCell Technologies, and Invisicool. He is Rae S. and Frank H. Neely professor and associate chair of graduate studies at Georgia Tech. He holds bachelor and master degrees in mechanical engineering from Bauman Moscow State Technical University (Moscow, Russia), bachelor and master degrees in applied mathematics from Lomonosov Moscow State University (Moscow, Russia), and a doctorate in mechanical engineering from Purdue University (West Lafayette, Indiana).



Andson Biotech's SecrAS (secretome analysis system) mass-exchanger technology

Current Requirements and Limitations

How do you think PAT needs have evolved over the course of the biopharmaceutical industry, and how would you characterize the current PAT landscape?

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Chilmonczyk: I would say that PATs have matured enough to meet the basic needs of current workflows for biologics manufacturing.

If you think back to the early 2000s, you'll recall a slew of articles — including a particularly famous paper in *Nature* (**1**) — talking about whether biologics would "boom or bust." Back then, writers weren't sure whether biologics manufacturing was ever going to work. They noted a lack of manufacturing capabilities and said that PATs were insufficient. Hindsight being 20/20, we know now that detractors couldn't have been more wrong. Scientists focused on the problems that needed to be solved, creating new methods for characterizing their processes, all the way from laboratory runs to commercial manufacturing.

Unfortunately, advances in PATs are lagging a bit behind innovations in medicine. Maybe measuring temperature, pH, glucose, and dissolved oxygen (DO) is enough for some processes. Maybe you need to do real-time measurement of such parameters. Those kinds of PATs suffice for some drugs. But as drugs become larger and more complex, especially when they are based on living cells, PAT needs increase. I think that we will soon find widespread application of advanced PATs in biologics workflows, such as adoption of real-time Raman spectroscopy and in-line technologies. At Andson, Andrei and I are working on real-time mass-spectrometric analysis of biomolecules.

That is a grand challenge. About five years ago, our technology was a solution in search of a problem, as some people would say. Such PATs could be important for many biopharmaceuticals, but especially for advanced cell and gene therapies. Analytical needs and complexities continue to grow every year for advanced therapies, but the PATs that are used for those processes are the same ones that were innovated maybe 20 years ago.

I believe that the development of new medicines underscores the need to develop new PATs, and the feedback loop between those advances has been too long. Andrei and I are designing solutions from the ground up to fit the needs — all the way from lab to market — of modern biopharmaceutical workflows, for which the difficulties are sometimes totally different than from those of first-generation biologics.

Fedorov: Historically, the PAT field (both in academia and in industry) has been a "sandbox" for scientists, not engineers. Traditionally, the field was composed of analytical chemists. That probably happened because biopharmaceutical companies have tended to hire biochemists and analytical chemists. I don't mean to take any accomplishments away from chemists. They are quite knowledgeable about different sensing modalities. But they are not engineers, who bring different expertise to the table.

The PAT field is still dominated by a semiempirical or maybe pragmatic approach to process analytics, following in the pathways made by the field's founders and making adaptations to existing systems — for instance, by simply making a sensor smaller.

The field is still dominated by a **SEMIEMPIRICAL** or maybe **PRAGMATIC** approach to process analytics, following in the pathways made by the field's founders and simply making adaptations to existing systems.

— A. G. Fedorov

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Engineers do not design systems in that way. If we were to build new airplanes in that way, I don't think they would ever leave the ground.

Sensing needs have become more complex than they were 20 years ago. Now sample volumes need to be very small. Your sensors need to work quickly. They must be disposable because you don't want to contaminate your cell culture media. All of a sudden, the biopharmaceutical industry has found that it can no longer approach PATs thinking, "We have been using this instrument in the lab this way. Let's just try to make it smaller and push it in, and it'll work."

Development of advanced PATs requires an engineering approach to synthesis of design, by which you identify user requirements, step back, and then consider how to design a system to address those specifications. You need to consider multiple perspectives: not only how to measure specific things, but also how to manufacture a system that can be assembled, incorporated, and integrated in the best way possible. Such an approach is based on first-principle understanding, not ad hoc design based on tales from our predecessors. And complicated advanced therapy workflows demand something more than adaptation of technologies that we already know.

What sensing needs arise with cell therapy workflows, and how do those compare with requirements for antibody production processes?

Chilmonczyk: Compared with antibody processes, cell therapy production requires greater capabilities for rapid characterization and real-time decision-making. A monoclonal antibody (MAb) product comes from a single clone that is cultured to produce identical cells that express a specified protein. Everything about those cells should be predictable; the proteins that they express should be predictable. That is not to say that challenges don't exist, and biomanufacturers still need to perform deep characterization to confirm expected quality attributes. But assuming that you develop your cell line appropriately, then expand and characterize it, you should have enough cells to make your protein product. You measure the protein levels in the cell's secretome and find what you need to do to optimize upstream production.

But with autologous cell therapies, the patients who contribute the starting material are experiencing different levels of illness and have diverse medical histories. Such patients contribute highly variable starting material — on top of cells' being as different as humans are. But the idea is to isolate (potentially unhealthy) patient cells, genetically engineer them, expand them into a bioreactor, and then manufacture them into a drug product — all in two to four weeks.

Developers of advanced therapies still are trying to understand why some of the cells they isolate from patients don't work. Why won't they proliferate? Why aren't they differentiating as expected?

Compared with antibody processes, cell therapy production requires greater capabilities for **RAPID** characterization and **REAL-TIME** decision-making.

— M. A. Chilmonczyk

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Why is metabolism different across these cells? In addition to such complications, developers must address other variable inputs — for instance, quality variations in cell culture media. Developers are finding that a lot of current production processes rely on animal-derived products and other raw materials that are not as well controlled as they need to be for advanced therapy workflows to succeed. The cell and gene therapy space also needs better ways than are currently available to measure parameters indicating how a product works. Developers want to gain a fundamental understanding of how their products behave in a process, and today they don't have many means for achieving that.

Our fundamental hypothesis at Andson is that the best quality indicators for cell therapies are biomolecules inside, on the surface, and outside of therapeutic cells. During a production process, your starting materials and their resulting biomolecules all change dynamically. The biopharmaceutical industry famously says that "the product is the process," but right now, cell therapy developers don't have the ability to characterize process parameters that matter.

Perhaps the largest difference between MAb and cell therapy production is that the latter uses extremely dynamic inputs, which in turn complicate workflows. And your output is not just a single protein anymore; it is hundreds of thousands of biomolecules that work in unison to deliver a therapeutic outcome. The process for making autologous cell therapies just demands new ways to measure many important factors.

The best analogy I've encountered is that biologics are like cars, whereas advanced therapies are like aircraft carriers. If you compare the requisite parts between those machines, you find that the scale is about right; and if you are thinking in terms of molecules, a cell therapy is that much more complex than a conventional biologic.

Fedorov: I want to emphasize, as Mason said, that a cell therapy product depends on what occurs inside, on, and outside of a therapeutic cell. Essentially, we have a machine, and the only way to make that machine work well is to have clarity about what happens inside and immediately outside it. No other modality requires monitoring and characterization of so many quality attributes. That brings a new level of manufacturing difficulty, which is why process analytics must be developed using a fundamentally different approach.

Perhaps the largest difference between monoclonal antibody and cell therapy production is that the latter uses extremely **DYNAMIC** inputs, which in turn complicate workflows.

— M. A. Chilmonczyk

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A Solution for Real-Time Mass Spectrometric Analysis

In March 2021, you wrote for BPI about your work with designing a next-generation in-line PAT (2). How might that technology address the sensing needs that you described?

Chilmonczyk: Our goal is to develop the technology into what we call the Triple-Shot Analysis System (TriAS) platform. It will be able to characterize biomolecules inside, on the surface, and outside of target cells, enabling biomarker analysis when and where it is important (Figures 1 and 2).

We are collaborating with the National Science Foundation Engineering Research Center for Cell Manufacturing Technologies (CMaT) at Georgia Tech, which is working on the same questions that we are trying to address: How do we ensure that biotherapeutics are safe, what can we measure to make such determinations, and how can we do that in ways that enable feedback control?

We believe that we can help to advance manufacturing — especially for cell therapies, but also for conventional biologics — in three key stages: drug discovery, development, and production. In terms of the discovery phase, we are working with academic clinicians who are developing therapies for conditions such as host-versus-graft disease (HGD). Sometimes researchers and even regulatory agencies are uncertain about how to ensure that a candidate therapy is safe and efficacious. Chimeric antigen receptor (CAR) T-cell therapies usually have clear targets, so researchers can say, "I am looking for this antibody." But some nascent therapies such as those based on mesenchymal stromal cells (MSCs) don't have such obvious targets or clinically relevant biomarkers.

Figure 1: Workflow for Andson Biotech's SecrAS, IntrAS, and TriAS systems for real-time mass-spectrometric analysis of biomolecules (IMAGE CREATED USING BIORENDER.COM)

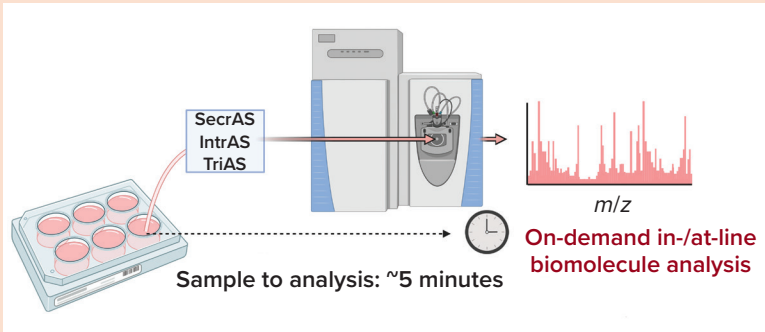
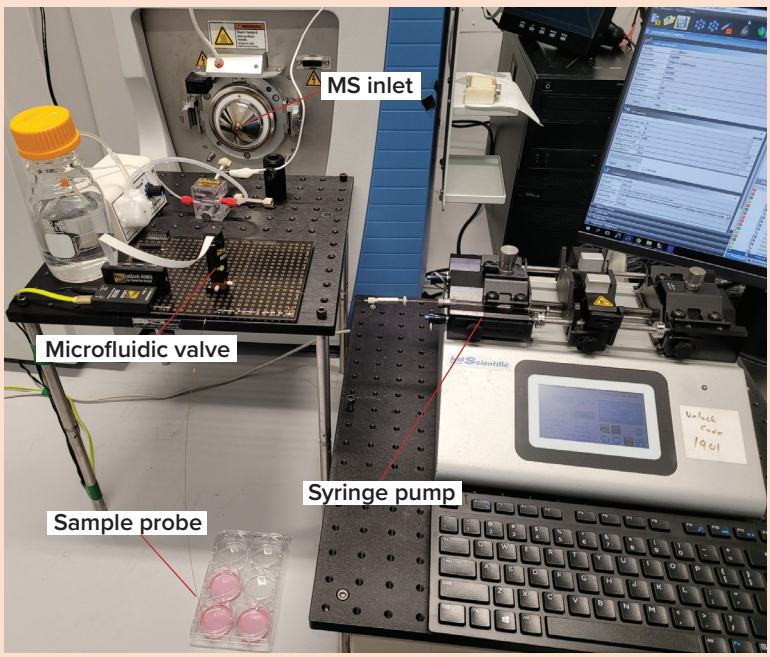


Figure 2: Sample flow system for Andson Biotech's SecrAS technology



The state of PAT is such that researchers culture their cells for three or four days, then do an endpoint assay and try to determine what happened to their cells in between. The TriAS technology is designed to monitor processes continuously to gather dynamic information about what is happening to cells as they are turned into therapies. Such work can help researchers to identify quality-indicating biomolecules and signatures that are associated with therapeutic potential — and developers and regulatory agencies alike are pleading for ways to identify better indicators of drug safety, efficacy, and potency.

A second use case occurs during drug development. After helping a developer to identify quality indicators and their correlation with a presumed mechanism of action (MoA), TriAS technology can be applied to optimize process parameters such as feed rate, cell seeding density, and media exchange rates.

Again, developers currently lack strong methods for verifying how process inputs influence the outputs. TriAS technology is designed to measure biomolecules that are, for instance, added, produced, and downregulated so that researchers can gain real-time insight into the dynamic activities of different process components. Eventually, you will have collected enough data to predict and control process outcomes.

We are actively working with developers of conventional biologics and advanced therapies regarding cell-surface analysis.

How might TriAS technology facilitate biomarker detection?

Chilmonczyk: What gives our systems an advantage over other mass spectrometry (MS) platforms — and over other PATs in general — is a microfabricated workflow that produces a platform system capable of interfacing with a bioreactor. To date, such interfaces haven't been realized because coupling those instruments has required an extremely complicated workflow. During my doctoral work, I essentially developed a rapid, robust, and repeatable method for cleaning up samples for MS analysis (**3–4**). That method enables us to perform repeatable mass spectrometric analysis in a scalable format.

The platform comprises three technologies to monitor the three cell-state aspects that we described. Those technologies have reached different levels of development. The most advanced part is the SecrAS secretome analysis system, which stemmed from my doctoral work at Georgia Tech (see opening image). The second most advanced aspect is the IntrAS intracellular analysis system, which isolates biomolecules in a completely different way than the secretome analysis system does (Figure 3) (**5**). I began that development work as a postdoctoral researcher, and Andrei is carrying it out with Austin Culberson, a senior doctoral student in his lab. Cell-surface profiling will complete the "triple shot."

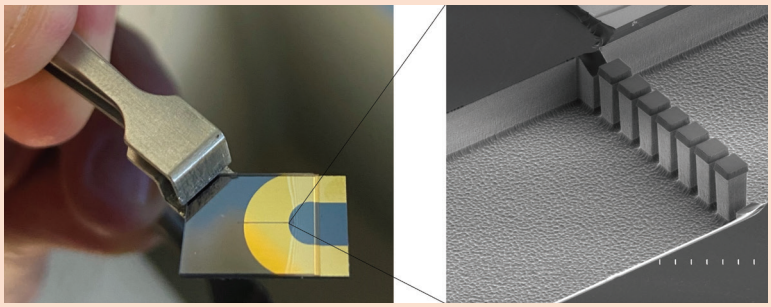
Fundamentally, the SecrAS system is what I would call a tangential-flow mass exchanger that we have miniaturized and tweaked. During my doctoral research, Andrei and I discovered that this unique approach to sample clean-up not only removed molecules that we didn't want to find, but also allowed us to add special molecules that we hadn't expected to benefit the MS in the ways they did, but that greatly expanded the utility of MS for cell therapies. The method could enable multicomponent detection and improve limit of detection (LoD), both of which are important for cell and gene therapies because biomolecules requiring detection often manifest in low concentrations. Our SecrAS technology basically samples from a cell's secretome (which bears all kinds of molecules produced by, consumed by, and added to the culture media), gently brings the captured biomolecules into a microchannel, and therein cleans up the sample in about one second such that we can obtain a meaningful result from a MS instrument. The process from sample to analysis takes about a minute, including the time needed to transport the sample from a reactor to the SecrAS technology.

To date, such interfaces [between mass spectrometers and bioreactors] haven't been realized because coupling those instruments has required an extremely **COMPLICATED** workflow.

— M. A. Chilmonczyk

One aspect of the SecrAS system that is particularly useful for drug-discovery applications is that it can probe cellular microenvironments. Consider solid tumors. They are among the hardest forms of cancer to treat because tumor microenvironments prevent bodies from figuring out that they are there. The microenvironment is where cells "talk" to one another. For engineers, it's the "boundary layer." Our technology can capture biomolecules when and where they are produced in a microenvironment. That could provide unprecedented, on-demand insights into cell states.

Figure 3: Andson Biotech's IntrAS intracellular analysis system (LEFT) takes up a small number of cells from a bioreactor or aliquot, then gently brings them into a restriction lined with microfluidic pillars (RIGHT).



The IntrAS technology works a little differently. We take up a small number of cells directly from a bioreactor or from an aliquot and bring them into a restriction. (Note that a *small number* means a few hundred or a thousand, whereas other MS techniques can require hundreds of thousands of cells to get any useful data.) The cells stop on those pillars, and the rest of the culture media flows past them (Figure 3). So we get rid of all the gunk that was outside the cells. Then the system gently lyses the cells and analyzes their contents for biomolecules of interest.

That lysis happens when we want it to, which is important because when to do so is not a trivial question. You need to figure out the isotonic points of different solutions, so that you don't cause osmotic lysing. That aspect of the IntrAS technology has been a major contribution of Culberson and of the whole Fedorov laboratory.

The final piece of the TriAS development process will be to generate cell-surface profiles. Large pharmaceutical companies have told us that they want to perform this type of testing. They also want to do such testing both in- or off-line. We definitely have the technical prowess to accommodate those needs, and we're excited to talk more about those considerations in the future.

Technical Considerations

Why is sample preparation critical to your systems and to MS methods more generally?

Fedorov: There is an interesting interplay here: The power of MS is exactly what makes it difficult to use for in- or on-line analytics. The method has extreme sensitivity, so it often is used as an "untargeted tool" that, by acquiring spectra and analyzing collections of peaks of mass to charge (m/z) ratios, gives analysts an idea of what is in a sample without their needing any knowledge about it. But extreme capability also presents challenges because the instrument can detect any type of molecule that is not your target molecule. Even "contaminants" such as cell-culture nutrients can produce noise that you cannot discriminate against.

There is an interesting interplay here: The **POWER** of mass spectrometry is exactly what makes it **DIFFICULT** to use for in- or on-line analytics.

— A. G. Fedorov

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Sample preparation enables you to sort out signals of relevance from such noise and to reduce the impacts on spectral behavior that are caused by molecules that simply cannot be removed.

My impression is that the SecrAS technology uses nanoelectrospray ionization (nESI)-MS. What advantages come with that ionization technique?

Fedorov: The method enables "soft" ionization of biomolecules. In essence, the electrospray phenomena can place a charge onto biomolecules without breaking them into unpredictable pieces.

A second factor is that cells, proteins, and peptides live in liquid environments. ESI is an effective way to take ions from a liquid environment and convert them into "dry ions" that can go into the vacuum of a mass spectrometer. That feature gives nESI-MS an appropriate, almost intrinsic reason for being a feature of the TriAS technology.

The method also tends not to be limited by molecular weight. ESI can place many charges on a given molecule. Mass spectrometers measure *m*/*z* ratios; the smaller the ratio is, the more capable a mass spectrometer will be in detecting a biomolecule. If you can place a lot of charge onto a large biomolecule, the ratio becomes smaller, making it easier to detect.

On the Horizon

What steps are next for Andson and the TriAS platform?

Chilmonczyk: We have big goals for the next couple of years. We recently received backing from Y Combinator, an accelerator company. Now that Andson is formed, our goal is to continue signing up companies for pilot programs. We will continue doing demonstrative work at the Georgia Tech Marcus Center for Therapeutic Cell Characterization and Manufacturing (MC3M), which provided the good manufacturing practice (GMP)-like, high-end mass spectrometer that we used for the studies mentioned in our previous article for BPI.

So our goal is to work alongside leaders in the field of advanced therapies to help them solve major problems. We are finding strong partners that are bullish about the TriAS approach and willing to partner with us to solve particular problems or develop new processes. We plan to have marketable products early in 2023, if only for the SecrAS and IntrAS technologies.

Fedorov: Experience shows that this kind of venture is possible only when you can create a diverse group of stakeholders that can bridge all of the business and technical divides that we've discussed today. That is difficult to do, but it will be a critical ingredient to our success.

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References

1 Thiel KA. Biomanufacturing, from Bust to Boom . . . to Bubble? *Nature Biotechnol.* 22, 2004: 1365–1372; https://doi.org/10.1038/nbt1104-1365.

2 Chilmonczyk MA, Fedorov AG. Improving Cell Manufacturing Outcomes Using In-Line Biomarker Monitoring. *BioProcess Int.* 19(3) 2021: 32–36; https://

bioprocessintl.com/analytical/pat/improving-cell-manufacturing-outcomes-using-in-line-biomarker-monitoring.

3 Chilmonczyk MA, et al. Localized Sampling Enables Monitoring of Cell State via Inline Electrospray Ionization Mass Spectrometry. *Biotechnol J.* 24 September 2020; https://doi.org/10.1002/biot.202000277.

4 Chilmonczyk MA, et al. Dynamic Mass Spectrometry Probe for Electrospray Ionization Mass Spectrometry Monitoring of Bioreactors for Therapeutic Cell Manufacturing. *Biotechnol. Bioeng.* 116(1) 2019: 121–131; http://doi.org/10.1002/bit.26832.

5 Culberson AL, et al. Sample-to-Analysis Platform for Rapid Intracellular Mass Spectrometry from Small Numbers of Cells. *Lab on a Chip* 21, 2021: 4696–4706; https://pubs.rsc.org/en/content/articlelanding/2021/LC/D1LC00884F.

Further Reading

Snapkov I, et al. Progress and Challenges in Mass Spectrometry–Based Analysis of Antibody Repertoires (in press). *Trends Biotechnol.* 14 September 2021; https://doi.org/10.1016/j.tibtech.2021.08.006.

Kling J. Bioreactor Sensors: Inside the Dynamics of Cell Culture. *BioProcess Int.* eBook 19(4) 2021; https://bioprocessintl.com/analytical/pat/ebook-bioreactor-sensors-inside-the-dynamics-of-cell-culture.

Chauhan VM. Fluorescent Nanosensors: Real-Time Biochemical Measurement for Cell and Gene Therapies. *BioProcess Int.* 18(5i) 2020: 4–8; https://bioprocessintl.com/analytical/pat/fluorescent-nanosensors-real-time-biochemical-measurement-for-cell-and-gene-therapies.

Rios M, Roesch M. Smart Sensors and Data Management Solutions for Modern Facilities. *BioProcess Int.* 17(10i) 2019: 8–11; https://bioprocessintl.com/analytical/pat/smart-sensors-and-data-management-solutions-for-modern-facilities.

Guerra A, von Stosch M, Glassey J. Toward Biotherapeutic Product Real-Time Quality Monitoring. *Crit. Rev. Biotechnol.* 39(3) 2019: 289–305; https://doi.org/10.1080/07388551.2018.1524362.

Patel BA, et al. Multi-Angle Light Scattering As a Process Analytical Technology Measuring Real-Time Molecular Weight for Downstream Process Control. *mAbs* 10(7) 2018: 945–950; https://doi.org/10.1080/19420862.2018.1505178.

Jiang M, et al. Opportunities and Challenges of Real-Time Release Testing in Biopharmaceutical Manufacturing. *Bioeng. Biotechnol.* 114(11) 2017: 2445–2456; https://doi.org/10.1002/bit.26383.

Kottke PA, et al. DRILL: An Electrospray Ionization-Mass Spectrometry Interface for Improved Sensitivity Via Inertial Droplet Sorting and Electrohydrodynamic Focusing in a Swirling Flow. *Anal. Chem.* 89(17) 217: 8981–8987; https://dx.doi.org/10.1021%2Facs.analchem.7b01555.

Matsuda F. Technical Challenges in Mass Spectrometry–Based Metabolomics. *Mass Spectrom.* (Tokyo) 5(2) 2016: S0052; https://doi.org/10.5702/massspectrometry.s0052.

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