In-house Mass Spectrometry Becomes Essential in Supporting Research and Process Development

The client: MacroGenics, Inc.

INTRODUCTION

MacroGenics, Inc., a clinical-stage biopharmaceutical company with facilities located in Rockville, MD and South San Francisco, CA, focuses on discovering and developing innovative monoclonal antibody-based therapeutics for the treatment of cancer, as well as autoimmune disorders and infectious diseases. To drive its aggressive and efficient clinical program with a reduced risk of downstream failure, MacroGenics constructed a rigorous product development model. To support that model, the company deployed the Waters Biopharmaceutical Platform Solution with UNIFI® to:

- Accelerate analytical turnaround times
  - top-down analysis from 1–3 weeks to 2–3 days
  - bottom-up peptide mapping studies from 3–6 weeks to about 1 week
- Eliminate high-cost outsourcing of mass spectrometry analyses
  - $400 per sample for outsourced top-down MS analysis
  - $3,000 per sample for outsourced LC-MS peptide mapping studies
- Confirm identity and quality attributes of biotherapeutic candidates
- Confirm expected drug products
- Speed results interpretation using in-house experts
- Support research and process development programs

THE CHALLENGE: CRO OUTSOURCING IS NOT SUSTAINABLE

MacroGenics has two Fc-optimized monoclonal antibodies (mAbs) in clinical trials as well as five Dual-Affinity Re-Targeting, or DART®, molecules that have entered clinical testing in the last two years. When these five programs were rapidly moving towards the clinic and major biopharmaceutical collaborators wanted to routinely review mass spectrometry data, MacroGenics determined that it needed in-house LC-MS capabilities for its analytical program. The company decided it could no longer rely on contract research organizations (CROs) for the identification of impurities and detailed characterization of its biologics.

“It was costing several thousand dollars and taking two to three months for a full MS analysis to be completed by the outside CRO,” said Eric Yearley, Ph.D., a research scientist in the Antibody Engineering and Analytical Departments at MacroGenics, who was responsible for evaluating MS platforms. “It was clear that these costs and timeframes were inadequate going forward.”

“Having a mass spec onsite was really critical to meet the demands of our collaborators.”

ERIC YEARLEY, Ph.D., Research Scientist at MacroGenics
In addition, outsourcing precluded MacroGenics from troubleshooting or modifying experiments; for example, if sample preparation based on past standard operating procedures stopped working with a new drug candidate. “With our own mass spec, I can immediately see the data coming off the instrument and say, ‘Okay, we need to do something else. We need to think about preparing the sample differently or optimizing the MS parameters,’ which would be very difficult with a CRO,” Yearley said.

Investing in a biopharmaceutical mass spec solution is critical, he said, because biologics must be analyzed for a multitude of different structural and quality questions that mass spectrometry analysis enables.

THE SOLUTION:
A DEDICATED BIOPHARMACEUTICAL SOLUTION

Yearley, who was hired by MacroGenics in large part to bring MS capabilities in-house for the confirmation and characterization of drug products, said he identified five goals for the program:

1. Reduce total cost per sample analysis
2. Reduce total cycle time
3. Improve timely results delivery
4. Improve quality of analytical results, meet higher standards
5. Enable experimental optimization

He then contacted a number of vendors with electrospray quadrupole time-of-flight (ESI Q-Tof) mass analyzers to set up real-time demonstrations.

“I employed actual data, collected on our biologics, to determine overall sensitivity and resolution of each instrument,” Yearley explained. “Then I ranked each vendor in terms of the LC and MS biopharma applications’ performance. Third, I rated the ease of use of the mass spec solution, based on my own demo experience. After conducting a number of demos with some of our Fc-optimized mAbs and DART® molecules, I concluded that the Waters Biopharmaceutical Platform Solution with UNIFI met or exceeded all of our current mass spec needs.”

Yearley said he did not consider purchasing individual components from multiple vendors “because of the inherent complexities... and their differing service contracts.” He also noted that single-vendor solutions were “much more cost effective.” In addition to meeting MacroGenics’ budget, the Waters UPLC®/QToF MS solution was selected for its high reliability, industry reputation, and Waters’ application expertise for building the biopharm solution, particularly with UNIFI Software.

The Waters Biopharmaceutical Platform Solution with UNIFI features the ACQUITY UPLC® H-Class System and Xevo® G2-S QTof Mass Spectrometer for robust characterization and the comprehensive UNIFI Scientific Information System. The associated Glycan Application Solution also integrates optimized released glycan analysis workflows, the Waters Glucose Unit (GU) Glycan Library, columns, and calibration and system check standards for released glycan analysis.

“It took several weeks to get fully installed, but once we got it all set up, there weren’t any problems,” Yearley said. “We were able to hit the ground running.”

Since its deployment, Waters has continued to support Yearley as his team optimizes their analytical methodology and takes on additional responsibilities. Once, Waters sent a service technician from outside the region for support when Yearley was up against a tight deadline. Another time, when he called for support, the Waters service technician shared a new, Waters-optimized method for the collection of top-down intact protein analysis, “which increased the overall response and resolution between our glycoform peaks of our glycosylated biologics,” Yearley said.

“I was somewhat concerned that once MacroGenics purchased the Waters solution I would be alone to face any problems encountered, but exactly the opposite was true. Whenever we needed assistance in terms of hardware, software, methods, or support, Waters was extremely quick to find a solution.”

ERIC YEARLEY, Ph.D.,
Research Scientist at MacroGenics
Before You Buy

Having been through a robust purchase decision-making process, Eric Yearley offers some recommendations for researchers who are considering investing in a biopharmaceutical mass spectrometry platform.

- **Invest as early as possible.**
  “It is a large initial expense, but in my opinion, the future benefits outweigh the upfront and future maintenance costs.”

- **Get references.**
  “Purchase a biopharma mass spec solution that has a history of results and success. You’ll learn about that through interacting with many of the mass spec scientists throughout the community, and based on your experience as well.”

- **Determine your needs.**
  “Sit down and construct a list of requirements and determine the type of instrument you’ll need to meet those requirements. For us, we chose the electrospray ionization and quadrupole TOF mass spec – which is ideal for a fast-growing, small to mid-size biopharmaceutical company.”

- **Demo with real samples.**
  “Determine if the mass spec results are accurate and reliable and then that the hardware/software solution is user friendly.”

THE RESULTS: INFORMING PROGRAM DIRECTION DECISIONS

By the numbers, it is easy to see the benefit MacroGenics has enjoyed by bringing its confirmation capabilities and characterization in-house. The company has significantly increased its turnaround times while lowering costs. Top-down intact protein mass analysis now takes 2–3 days, instead of one to three weeks at $400 per sample. Bottom-up peptide mapping now takes a week or less, compared to three to six weeks at $3,000 per sample analyzed. Yearley estimates a return on investment in the Waters Biopharmaceutical Platform Solution with UNIFI within three to five years.

“But that’s not taking into consideration, as programs advance and we get more analytical data, that we can quickly make very, very important decisions on the direction of a program,” he said. “It’s hard to calculate those savings, in terms of turning the direction of a program, but it’s quite significant. Based on my experience, the Waters Biopharma Solution is key to a lot of our early success in changing the direction of our programs.”

He noted that the Xevo G2-S QTof Mass Spectrometer detected a modification of a construct from a top-down experiment that resulted in a change of direction, and thus reduced the potential liability for lead molecules later in development. “It’s a lot more cost effective if you can solve these problems right away, at the very beginning of early discovery or the research stages of your pipeline.”

Yearley was also able to, within a week of first using the Waters Biopharmaceutical Platform Solution with UNIFI, generate results for one of its DART® molecules that had previously been run, unsatisfactorily, by a CRO. “They got the analysis done, but it wasn’t good quality, so management gave me a week and said, ‘Can you get better in terms of sequence coverage?’ Currently, I do all the analyses in terms of sequencing.”

In another example, with peptide mapping analysis, Yearley said he’s able to perform high confidence primary structural analysis in two to three days. “Not only do we match up the monoisotopic masses with the theoretical sequence, but we also use fragmentation data as well, because there is additional information on the sequence of amino acids. We can verify not only by the mass of the peptide, but also the specific order of individual amino acids. That is really key to meeting regulatory requirements for biotherapeutic characterization.
“If we had to send that to a CRO, most of the time we’d just get the identification of peptides based on monoisotopic mass,” he said. “And it’s two to three months for an analysis like this to be completed.”

With more than 100 DART® molecules, sample preparation and mass spec analyses “is a challenging endeavor,” Yearley said. “My group is constantly optimizing our mass spec procedures for each biologic that comes through our lab. With the Waters Biopharmaceutical Platform with UNIFI, our methods are uniquely tailored. Our lab has a really strong starting point to commence our optimization experiments so we don’t have to start from scratch each time, and we can easily save our revised analysis within UNIFI.”

The system has been easy to learn and use. Yearley trained an assistant on the system to both run samples and analyze results within a couple of months. The Biopharmaceutical Platform Solution with UNIFI is running all day and sometimes overnight and weekends. “What’s really nice is I have remote access, so I can check it any time, even using my smartphone,” said Yearley. “It’s highly stable and I trust that I can run it remotely.”

**NEXT STEPS**

The Waters Biopharmaceutical Platform Solution with UNIFI supports early-stage development as well as the GLP and GMP environment for later development stages. Yearley said, “It serves as a really important tool to develop and optimize the characterization assays that can be transferred to the right environment.”