

Can Microbubbles Replace Magnetic Beads In Cell Therapy Manufacturing?

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Bracco's Thierry Bettinger explains how BubbleGen is simplifying cell isolation workflows while supporting the scalability demands of next generation cell and gene therapies.



Cell and gene therapy developers continue to face mounting pressure to improve manufacturing efficiency while maintaining product quality and scalability. Traditional magnetic bead based cell isolation methods, although widely adopted, often introduce additional processing steps, specialised equipment requirements, and operational complexities that can impact yield, cost, and manufacturing consistency. Bracco's BubbleGen platform is seeking to address these challenges through a novel microbubble based approach designed to simplify cell selection and activation workflows. **In this Q&A with BioSpectrum Asia, Thierry Bettinger, PhD, Director of Research and Development at Bracco,** shares insights into the technology's advantages, emerging applications, and its potential role in shaping the next generation of cell and gene therapy manufacturing.

What specific manufacturing or scalability limitations in magnetic bead-based workflows does BubbleGen aim to solve?

Magnetic bead isolation has become the default for cell therapy workflows, although their limitations are well known. Introducing them for isolation requires specialized equipment such as a magnetic bead column, and additional steps to remove the magnetic beads, adding significant time and cost to the manufacturing process. Certain cell types, like CD34+ stem cells, can get stuck in magnetic columns, leading to inconsistent recovery.

In addition, even though it's the current operational technology for cell selection, magnetic beads-based systems do not provide a perfectly efficient process, often meaning that some tradeoff is required between the risks related to residual magnetic material left behind after processing versus reductions of yield.

BubbleGen has been designed to address these limitations. Since no magnetic separation is required, no specialized equipment or dedicated bead removal steps are needed for cell isolation, enable more cost-effective, potentially less manual-intensive, and shorter workflows. The technology is platform agnostic, meaning no additional machinery is required and isolation can be simply integrated into automated workflows.

The new technology also expands workflow possibilities beyond today's limitations. Sequential separation to hone in more specifically on certain cell populations, for example, can only be performed in specific permutations with magnetic beads, as it is challenging to remove them between steps. By enabling a variety of combinations of positive and negative selection, BubbleGen can make various protocols more scalable. The applications could include improving purity of a CAR population through an additional enrichment step, as well as positive-positive selection for memory T cell phenotypes and Tregs, for example. Additionally, BubbleGen can enable separation and activation in a single step, avoiding the sequential processing requirements of bead-based approaches.

How does the BubbleGen platform impact cell viability, recovery rates, and downstream manufacturing consistency compared to conventional approaches?

Based on initial results, with BubbleGen, we expect that the gentler cell handling and compatibility with downstream genetic modification and expansion workflows will lead to more viable cells recovered. Unlike the vigorous requirements for removing magnetic beads, microbubbles can be removed by popping with gentle pressure or simply by waiting for natural deflation through gas exchanges, thanks to their lipid shell composition.

Additional published data is forthcoming, but data from an early experiment presented by an external academic partner showed BubbleGen-based workflows produced cells with functionality that matched magnetic beads following CD3 separation, suggesting the same or better quality can be achieved in less time and without additional specialized equipment.

Which cell therapy applications or modalities are currently seeing the strongest interest for this technology?

Since launching our early access program, we've seen broad interest from academics, biotechs, and device manufacturers.

In particular, we're hearing many requests to support workflows with CD34+ stem cells, the type used in approved gene/gene-edited therapies approved for sickle cell disease. CD34s(+) are relatively rare, representing about 1% of cells in a typical mobilized apheresis leukopak. They are also challenging to isolate with magnetic bead-based approaches, in part because a magnetic column is not gentle enough on fragile cells and can result in substantial loss. Also, initial data suggests that BubbleGen can be used to isolate CD34 cells in as much as half the time of a magnetic column, possibly more. So developers are very interested in alternative technologies.

Another common request is CD3+ depletion for immune cells. This can be used for removing T cells from the starting material, and there is a significant and growing interest in using it for selecting the rare NK cells. That's a primary reason why our first product, newly available through an early access program, is a CD3 isolation kit.

We're also hearing interest from developers of cutting-edge platforms, likely because new technology adoption in this space skews toward early-stage programs. In particular, developers of iPSC cell therapies are very interested. There is also an appeal for developers of T cell-based therapies, given the flexibility of the technology and the ability to combine selection and activation into a single step.

How important is accessibility to enabling technologies at the early development stage for emerging CGT developers?

One crucial lesson over the past decade of CGT development has been the importance of optimizing processes where possible during early-stage development. Regulators have continued to grant flexibility in CMC, so some processes can be finalized for late-stage trials. However, just because it can be done later doesn't mean it should be, given the expense, time, and complexity of making a change after Phase 1. Late changes require comparability studies and redoing the intensive characterization required to ensure cell therapy manufacturing quality.

We hear regularly from developers who are not yet even approaching clinical trials who want to know about BubbleGen – to understand our pathway to GMP, and how it compares to other products. Innovators in particular are eager to access enabling technology early, so they can make faster decisions and lock in processes as early in development as possible.

Looking ahead, do you see microbubble based activation and sorting becoming part of mainstream CGT manufacturing workflows?

Given the versatility of the BubbleGen platform, the internal and external data we've seen so far and the potential to reduce time and cost across workflows, we do expect microbubble-based technologies to enter broad usage. We recently made a major facility investment to support the manufacture of GMP-grade microbubbles to enable the next wave of CGT innovation.

Magnetic bead-based sorting was invented for research, and adds significant cost, time, and processing steps at a moment when cell therapy developers are struggling with commercial scalability. BubbleGen is platform-agnostic, ideal for automated technologies and workflows without the need to purchase additional equipment and reagents as is required to run a magnetic column.

As with many technologies, what is perhaps most exciting is the possibilities we haven't seen yet: because there are no magnetic residuals to complicate or interfere with downstream processes, BubbleGen can make possible the isolation of extremely rare cells for therapeutic development and further enrichment steps towards the end of the manufacturing process, when purity of the final product is a concern. We anticipate the platform will inspire new technologies and methodologies that had not been plausible until now.