



Large-Scale GMP Manufacturing with Customized Bioreactor for Photoautotrophic Organisms

Promising pilot-scale project with the world's first 500L single-use bioreactor that can be adapted for any manufacturing process requiring light as an energy source.



Success Story

Sartorius fitted the BIOSTAT® STR 500 single-use bioreactor with more than 5000 LEDs for Greenovation's commercial moss production facility in Germany

BryoTechnology, a biopharmaceutical manufacturing technology based on moss-plants, is one of the next generation manufacturing technologies for biopharmaceuticals¹. The process developed by Greenovation (Heilbronn, Germany), uses the genetically modified moss *Physcomitrella patens* to produce complex human enzymes to treat rare diseases (orphan drugs)². Moss-aGal, a glycosylated α -galactosidase, is developed as Enzyme Replacement Therapy (ERT) for patients with Fabry disease in order to correct their enzyme deficiency. It is the first drug candidate world-wide produced in moss. Positive clinical Phase I data have been reported back in December 2017^{3,4}

For moss cultivation, Greenovation has been working with 200L wave-bag bioreactors equipped with LEDs to provide the light energy required for biomass production by the photoautotrophic organism. To progress to clinical phase II and III studies, the company now needs to expand its production and to scale-up its process. Their current wave-bag bioreactors are not suitable for scale-up, though. This is where Sartorius came into play. As a world renowned supplier to the biopharmaceutical industry Sartorius is well known for its capabilities to address specialized solutions. The Integrated Solutions Team in Guxhagen, Germany, worked closely with Greenovation's specialists to develop a customized BIOSTAT STR® 500 for commercial production of photoautotrophic organisms.

» The system is patent pending and can potentially be adapted to any manufacturing process requiring light energy.

Hannes Schmid,
Sartorius Stedim Systems

This stirred-tank bioreactor, which contains a single-use Flexsafe® STR bag, has been fitted with more than 5000 LEDs on the inside of the vessel to provide the essential light energy required for moss growth. The system is patent pending and can potentially be adapted to any manufacturing process requiring light energy.

In this unique pilot project the customized BIOSTAT STR® will now go into production at Greenovation's facility and will be integrated in the moss-aGal production process.

In an exclusive interview⁵, Greenovation's Chief Scientific Mr. Schaaf talked about the pilot project with the Sartorius Integrated Solutions Team and his plans for the future:

Sartorius: Mr. Schaaf, what do you see as the major advantages of the moss *Physcomitrella patens*, which you are currently using for the production of your products?

Mr. Schaaf: The advantages are a combination of issues... Since moss is a higher plant, the expression machinery is similar to that of CHO cells. Plants are photoautotrophic and use light energy and CO₂ as carbon source to create biomass. So we are able to use chemically defined media, which does not contain any organic compounds, and we are not using any animal derived components. Working with only water and inorganic salts helps create a risk-free system, which is biologically safe with no risk from viruses or pathogens.

The genetics of moss is also important. Moss is haploid meaning that there is only one copy of the genome, which is always dominant. Homologous recombination is a DNA repair mechanism, which every higher organism has, but moss does this at a very high rate, which is advantageous. We use this fact to target gene sequences very efficiently to modify the organism. In this way, we can e.g. eliminate proteases that are harmful during



The customized bioreactor for Photoautotrophic Organisms is equipped with 5000 LEDs on the inside of the vessel to provide the essential light energy required for moss growth.

protein production processes. Due to this fact, moss is very valuable for biopharmaceutical production.

Also, it's important to mention that in contrast to mammalian cell cultures, moss strains are regenerated complete plants, which are genetically very stable. This is important for long production processes, since there is no genetic drift as is sometimes observed in mammalian cultures. In the process we are only using antibiotics in the very beginning during strain development, but not later during production, which is another important advantage of producing drugs in moss.

Sartorius: We are very excited to work with you on this new pilot project with the customized BIOSTAT STR® 500 bioreactor for photoautotrophic organisms. May we ask why you have decided to run the project with our team?

Mr. Schaaf: In fact, this is not our first project with Sartorius. We have already had very good experience in a former project, so we are convinced that Sartorius is the right partner for a special engineering solution like this. We are very excited that Sartorius is open to trying new ways with us and that they are willing to enter into a new novel pilot project.

The advantage of working with Sartorius is that based on their current product portfolio, they are able to adapt these products according to the customer's bespoke needs and are addressing an individual engineering project.

We are very happy with the support, speed and management of this project by Sartorius.

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Andreas Schaaf,
Greenovation

Sartorius: Where do you see the biggest challenges of our common project?

Mr. Schaaf: Well, I do not have any doubts that Sartorius can manage this project, but the heat generated inside the fermenter, caused by the large amount of light given-off by the LEDs, will definitely be a challenge that the engineers will need to focus on.

Sartorius: How will you test the performance on site?

Mr. Schaaf: We will run moss cultures and aGal production processes and compare them to our established processes. The question will be whether we will obtain sufficient material for market supply and sufficient material with similar quality for market supply. But as the project looks now, I do not have any doubts on the success.

Sartorius: Which are your future plans for the development of your production pipeline?



Mr. Schaaf: We are thinking about Phase II and III as well as commercial production for aGal. Also, we have three more products in the pipeline with very good results in the pre-clinical evaluation. So we would like to expand our production for those molecules to GMP production.

Depending on the outcome of our current pilot project involving the customized BIOSTAT STR® 500, we are interested in scaling-up our production process further. Initially we will require 1000 – 2000L, but in a few years we will require ~8000 – 10000L production volume.

Sartorius: How do you value the Sartorius "Integrated Solutions" approach including upstream and downstream processes for this critical development phase of your production?

Mr. Schaaf: Currently we have not implemented downstream processes in this project, but we are in discussion with the Sartorius Integrated Solutions Team regarding the potential design of a new moss facility – taking advantage of the Sartorius expertise in executing special engineering solutions.

Sartorius would like to thank Mr. Schaaf for this exciting interview. Considering that BryoTechnology may be an important technology for biomanufacturing in the near future, the development of large-scale bioreactors for commercial production of photoautotrophic organisms is an important step on the way to drugs produced in plants without the risk of infection from viruses and pathogens. Combining such customized bioreactor solutions with the Sartorius approach of intensified bioprocesses could make biomanufacturing a little greener.

References

- ¹ <https://www.greenovation.com/technology.html> (as of June 9, 2018)
- ² <https://rarediseases.info.nih.gov/diseases/fda-orphan-drugs/F> (as of June 23, 2018)
- ³ <https://www.greenovation.com/press-releases-details/fabry-enzyme-replacement-therapy-ert-based-on-mannose-mediated-cellular-uptake-shows-encouraging-preclinical-results-that-allow-.html> (as of June 23, 2018)
- ⁴ <https://www.greenovation.com/press-releases-details/greenovation-bio-tech-gmbh-reports-positive-clinical-data-from-the-phase-1-safety-study-for-moss-agal.html> (as of June 9, 2018)
- ⁵ Interview by Bettina Renker, Sartorius Stedim Biotech, and Hannes Schmid, Sartorius Stedim System, with Andreas Schaaf, Greenovation on April 11, 2018; text has been shortened by the editor.

Sartorius Stedim Biotech GmbH
August-Spindler-Strasse 11
37079 Goettingen, Germany
Phone +49.551.308.0
www.sartorius-stedim.com