CASE STUDY

Mustang Bio CAR-T Development Program Utilizes HemaCare Leukapheresis Products for Process Development Studies

Interview with
Dr. Knut Niss, Chief Technology Officer

Cell and Gene Therapy has now been proven in the clinic to treat or cure serious diseases for which there has previously been no effective treatment. Perhaps the most striking achievement in this new field of medicine is the introduction of a number of different CAR-T based drugs. CAR T-cell therapies triggered a well-deserved stir when the first treatment was approved by the FDA in 2017 following a series of highly successful clinical trials. Today, the number of cell and gene-based therapies entering clinical trial is growing exponentially, and consequently, there is an emergent need to prepare the industry for commercialization of these "living drugs".

Dr. Knut Niss, Mustang Bio's Chief Technology Officer, has an impressive background in cell and gene therapy. Prior to his current role, he directed the transfer of Novartis' first-in-class FDA-approved CAR T-cell drug, known then as CTL019, from its academic beginnings at the University of Pennsylvania over to pharmaceutical giant Novartis. Novartis is one of HemaCare's foremost clients,[1] and this is where Dr. Niss first became familiar with using HemaCare's products and services for cell therapy process development. Now that he is part of Mustang, Dr. Niss continues to be at the forefront of CAR T-cell and gene therapy. He recently took the time to discuss his research and his experience with HemaCare products.

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Mustang Bio is a Massachusetts-based clinical stage biopharmaceutical company focused on developing novel cancer immunotherapy products and other gene therapy treatments. Many of the therapies they are developing are based on CAR T-cell technology, where a patient's own immune system T cells are modified to fight cancer cells more effectively.

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Preserving Product Potency

One of the key concerns for any scientist working with cell-based products is that of maintaining the optimal function of the therapeutic cells. From his company's location in Massachusetts, Dr. Niss has been able to obtain HemaCare leukapheresis products from anywhere within the U.S. within 24 hours of collection. Freshly isolated leukapheresis products are fairly stable for up to 48 hours, so he knows that the cells are arriving well within acceptable time constraints.

Mustang Bio expects to grow as a company, however, and Dr. Niss wonders what will happen when they start shipping internationally. The company will need to work out a reliable method of manufacturing cell therapies in the U.S., then ship to Europe within 2 days, in order to maintain the therapeutic potency of their product. Current shipping practices for cell therapy starting materials provide a valuable lesson on that front. The company is well aware that there have been incidents where customs offices have mistakenly held cell therapy starting material products too long, resulting in a loss of viability and therapeutic function that renders them useless for the intended purpose.

> *"In Europe, regulations prohibit monetary compensation for donor material, so it's often shipped from the United States. When it comes to access to cell therapy starting materials, European research companies are being left behind, when in reality it may take only a few modifications of the international shipping process to serve that population as well."*
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> *- Dr. Knut Niss, CTO, Mustang Bio*

Even within the U.S., logistics often dictate that cell therapy starting material must be cryopreserved prior to processing to accommodate physician and patient schedules, as well as for shipping from the collection center to the processing lab. Dr. Niss has found great success working with cryopreserved leukopaks that he receives from HemaCare. He asserts that the leukopaks have reliable T cell quality and quantity, often more, in fact, than is strictly necessary for process development.

Cryopreservation, if it's done in a way that preserves optimal function, has proven to be a good answer to the issue of preserving product potency.[2] Another answer may be to tighten government shipping regulations on handling "living" medical products. Until that type of regulation is put in place, however, Dr. Niss suggests that fine-tuning apheresis collection and optimizing cryopreservation protocols and process development can significantly help protect product quality.

> *"One thing we struggle with, in all of the process development work, is that much of it must be done using healthy donor material. However, the profile of cell types in material collected from patients is very different from that of healthy donors. Access to material from patient populations is therefore very valuable."*
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> *- Dr. Knut Niss, CTO, Mustang Bio*

Product Availability is Critical to Commercialization

Reliable access to a sufficient quantity of cell therapy starting material is also a key concern for commercialization. Companies need to be sure that the supplier has access to a large, diverse donor network, so they can reliably source what they need, particularly if the product is difficult to obtain or has a short shelf

life. An experienced supplier will overestimate client needs from the start to account for losses during shipping and handling, or to the need for screening and quality control assays.

> *"We work with HemaCare because there are really not that many other apheresis providers who demonstrate the same level of both quality and responsiveness; when we have a specific request, they are able to procure the apheresis material we need. In the past, we have reached out to other apheresis providers, but we chose HemaCare because they devote a higher level of attention to our projects."*
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> *- Dr. Knut Niss, CTO, Mustang Bio*

Dr. Niss' work at Mustang Bio is focused on finding effective treatments for acute myeloid leukemia (AML), an aggressive cancer characterized by the rapid growth of abnormal cells in the bone marrow and blood. In order to carry out this research, Dr. Niss emphasizes the importance of product availability; in this case, having access to AML material, which he obtains from HemaCare.

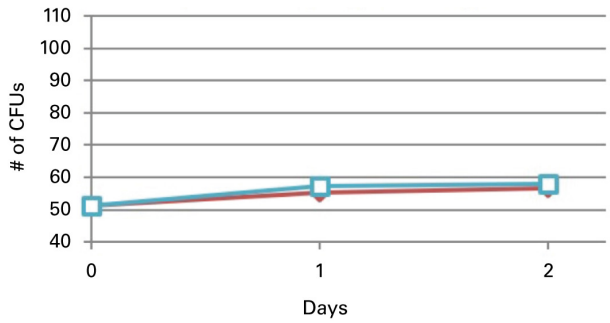
Dr. Niss explains that HemaCare's capacity to provide blood samples from AML patients has been invaluable to his preclinical research. HemaCare fosters close relationships with collaborators in order to boost clinical access. This allows the company to facilitate the procurement of disease-state materials by its clients. The availability of patient material helps clients to predict clinical outcomes, since such materials more accurately reflect patient responses.

Access to specific disease-state biological material is just one of the challenges pharmaceutical companies face when sourcing cell therapy starting material. [3] But it isn't all about accessing an expansive range of products. Dr. Niss explains that since his group is focused on optimizing conditions for several different drug candidates, being able to customize their starting material requests gives them a valuable advantage. Depending on their project, researchers may also need to customize cell separation techniques or cell handling and storage methods to identify the best production process.

Bringing Quality to the Clinic

At present, Mustang Bio has five cell-based drug candidates being tested in phase 1 and phase 2 clinical trials, and more in pre-clinical development. Four of these clinical candidates are autologous CAR T-cell treatments, including MB-102, a potential treatment for a rare blood cancer which just received Orphan Drug Designation from the FDA. Autologous CAR-T treatments use blood drawn from the patient as starting material for the therapy. Each of these CAR T-cell candidates are modified to recognize different surface proteins that are widely expressed on cancer cells, but not healthy immune cells. Due to the fact that these treatments are experimental, a patient being considered for clinical trial will already have failed to respond to more traditional treatments like chemotherapy, or have relapsed after initially responding. That means that the CAR-T treatment they receive may represent the patient's last hope of recovery. The starting material for these therapies has got to be of the absolute highest achievable quality.

Achieving that quality requires more than any one key factor; it requires a unified process that incorporates attention to detail. Dr. Niss feels that Mustang's proprietary CAR-T methodology is best-in-class, but



Leukapheresis-derived cells are functionally stable and retain their ability to form colonies for at least 48 hours. Storage temperature doesn't appear to have a meaningful impact in amount of CFUs quantified within this time period. (blue line = 4° C) (red line = 21° C)

he also recognizes that bringing their best product to the clinic involves more than the product itself. Researchers at cell therapy companies need access to high-quality starting material because that material will have a huge impact on the quality of the final product; this includes access to patient-donor starting material, which will allow better prediction of patient responses in the clinic. Methodology and quality management safeguards that protect the integrity of the product need to be in place from start to finish. This means working with the best materials and working out the best biopreservation techniques and shipping systems for a given therapeutic as early in the process as possible.

Looking Forward

The arrival of an entirely new form of medicine on the healthcare scene is driving researchers and physicians alike to rethink drug development and delivery strategies. When your product is a living cell, quality control and scale up become a much more complicated process. Cells are uniquely responsive and vulnerable to their surrounding environment. Their viability and functional capacity can be influenced by a variety of factors, such as culture media, temperature, age, biopreservation conditions, and so forth. Consistently delivering the optimum therapeutic potential of a cellular therapy entails careful starting material sourcing and meticulous quality control until the therapeutic can be administered to the patient. In the final analysis, CAR T-cell quality can make a life or death difference to a patient, and protecting therapeutic efficacy is the best way to ensure that these life-giving products fulfill their potential.

References

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