CELL & GENE THERAPY RAW MATERIALS:
GETTING IT RIGHT FROM THE START

SPOTLIGHT

INNOVATOR INSIGHT

Strategic & practical considerations in raw material selection & sourcing for cell therapies

Dr David Wellis is a cell biologist with over 25 years experience in the life science industry and currently serves as the CEO of the San Diego Blood Bank (SDBB), which is a member of Blood Centers of America (BCA). David serves as Chair of the Cellular Therapies Leadership Committee within BCA. David joined SDBB following his tenure at a variety of companies that developed tools for biomedical research, diagnostic and applied markets, including Illumina, GenVault and Axon Instruments. David received his B.S. from UC Irvine, an M.S. and Ph.D. from Emory University, postdoctoral training at Tufts University and UC Berkeley, and business training at Leavey Business School of Santa Clara University and Haas Business School at UC Berkeley.

Dr Robert Tressler is Vice President of Laboratories for the San Diego Blood Bank where he oversees the Public Cord Blood Bank and Cell Therapy research program. Previously he held leadership roles in Biotechnology companies, serving as head of Preclinical Oncology Research at Geron, Inc., overseeing their oncology and anti-aging research programs. He also was VP of Research and Development at Cellerant Therapeutics, heading up research and development efforts for stem cell and oncology programs.

Q What are some of the factors that can impact the quality of this type of starting material?

RT: One of the key cell therapy manufacturing challenges is the inherent variability of the product. Right now there isn't a strong consensus across the research, translational and manufacturing communities about the best way

to develop the product, the optimal method to isolate the starting material, or even the ideal attributes of the starting material itself. Understanding that inherent variability is crucial, for example, if I take CD34 stem cells from a 20-year-old and compare them with the same cells from a 60-year-old, the 'quality' of those cells may be different in terms of clonogenicity, proliferative capacity and development of specific lineages, and these factors could impact the therapies developed from these cells.

In addition to the age of the donor, other factors to consider when sourcing your starting material are genetic diversity, health status and gender. If you are developing a cell therapeutic, we know that the potency of your final product can be affected by the age and health status of the donor.

It's essential to understand what factors can impact your starting material and that's something we have a great deal of experience with. All of the participating centers within the Blood Centers of America's (BCA's) network have strong expertise in the area of raw material collection. This sits at the core of our business and therefore we have developed and follow standardized and compliant methods of collecting material from donors. In addition to the standard venous collection you would expect a blood center to carry out, we also have expertise in cord blood collection and apheresis technology.

Q Cell selection is a critical step in ensuring your starting material meets the requirements of your end product – what techniques do you typically employ and what determines this decision?

RT: We carry out routine apheresis and whole blood collections, from which we generate mononuclear cell fractions, red blood cell enriched fractions, platelet fractions and serum and plasma fractions for different needs throughout the medical community. Apheresis protocols are highly standardized and consistent from patient to patient, which again ensures consistency of your product.

However, say for example a company requires high cell yield because they're carrying out large manufacturing campaigns and need substantial amounts of starting material for expansion and potential refinement of their product, there may be additional steps required such as standard Ficoll-Paque isolation or bead separation technologies. Within the community we have specific centers that routinely use these techniques of cell selection and have developed standardized protocols that help achieve not only high yield but also a high-purity, well-characterized product. This enables optimal collection, enrichment and purification in a cost-effective manner.

DW: I think a key challenge with yield arises when you try to isolate a specific cell type out of a crude mixture. Mesenchymal stem cells (MSCs) are a great example – when we refer to this cell type we're actually talking about a broad continuum of cell types. So there's a big opportunity and need to better define and therefore isolate specific cell types.

RT: On that note, a variety of automated systems are now available. These include STEMCELL Robosep platform as well as a variety of

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systems offered by Miltenyi and Terumo, some of which are cleared by the FDA for clinical use. The standard ficoll isolation system is also a viable option, but requires the appropriate lab environment and equipment if one is carrying out a cGMP cell processing procedure. Yield, purity and viability requirements need to be determined here to select the optimal method, and this must be coupled with a robust system to characterize the end product, which can include multiparametric FACs analyses of surface markers as well as potency assays.

Q Working with a variety of different stakeholders, from biopharma, cell therapy companies, diagnostic companies and hospitals, do you find the cell material requirements differ significantly?

DW: Absolutely. One of the benefits of working with such a variety of stakeholders from industry, academia and hospitals, is that we learn a great deal about their processes and what the cell starting material will undergo as part of their research or manufacturing process. This helps you guide and advise the client on the optimal starting material for their needs.

RT: One needs to understand that while an autologous product may be easier to bring into the clinic due to lower 'safety and identity' hurdles, you are 'locked in' as far as the donor source material and have more limitations in terms of collection of optimal starting material because of this. With allogeneic products one has a higher hurdle to clear in terms of safety and identity, such as the need for HLA typing or assessing other potential incompatibilities, but has greater latitude to identify optimal donor populations to assure higher yields and potentially a more effective starting cell population for the desired indication.

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RT: The first step in understanding the type of materials the company requires is to identify the intended use – whether it's for research, translational research, or Current Good Manufacturing Practice (cGMP) product development and manufacture. If the client requests research-grade material, but the intent is to take that product to the clinic then it's sometimes prudent to do everything under full or near-full cGMP upfront so as to enable an easy transition from research to clinical application.

Next it's essential to understand what's your active pharmaceutical ingredient (API) in the end product? Currently, when you treat a patient with a cell therapy, often the API in that population of cells isn't all of the cells. We're fairly certain that for CD34 cells there's a significant bystander effect from cells we are injecting that don't really have a therapeutic impact but that we're considering part of the actual product. For example, a

significant fraction of the injected cells could be CD34 positive, but are not carrying out the desired pharmacological effect.

If you think back to the early bone marrow transplants where the cells were obtained from a donor, crudely enriched and injected into the recipient – some patients responded well whilst others less so. We now suspect that the reason some of these worked so well was that the purification methods were likely inconsistent at that time and some bone marrow transplants might also have contained MSCs mixed in with the CD34 cells. Whilst these MSCs don't make hematopoietic stem cells, we now know they play a role in facilitating the engraftment of the CD34 cells in the marrow.

Therefore, the sector needs to better define cell identity, potency and purity, so that the API becomes the majority of the fraction injected. The tools and technology already exist, we just need to develop more thoughtful and standardized characterization assays to ensure a potent product. That's one of the concerns we have right now, and one of the things everyone is working on to address.

Q From these interactions with biotech and cell therapy companies, do you feel there's a strong understanding of the impact starting material selection can have on the path to commercialization of their product?

DW: We see a fair degree of variability between the different sized companies and institutions. Some of the larger pharmaceutical companies we work with have an established R&D focus on specific indications and are therefore very knowledgeable, but even there we find they need some assistance in terms of understanding consent protocols and regulatory aspects of donor collection, which are areas we have strong expertise in.

I think most organizations understand the impact of the quality of the starting material. One of the first pharmaceutical companies that approached the San Diego Blood Bank when I arrived was an organization working on developing platelets from cord blood stem cells. They came to us having previously worked with another organization in obtaining their starting material as they were having issues in their R&D and the quality of their output. Upon working closely with them and understanding their desired output and processes, we were able to provide them with a starting material of much higher quality and that resolved the R&D issues they were experiencing.

RT: Some of these issues included setting overly stringent criteria in the proposed certificate of analysis, unrealistic yield expectations for the targeted purity, unnecessary processing steps that incurred increased COGs, and lack of a systematic approach to optimization of the manufacturing process to assure a consistent, cost-effective high-quality cGMP compliant product.

When working with earlier-stage companies, even those that might be pre-translational but where the intent is to go into the clinic, we can play a key role in guidance in terms of starting material collection. Not only the type of material, but how to go about collecting it, in terms of homogeneity or methodology, whether it be apheresis, Ficoll or bead separation technologies.

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When a company says they want cGMP MSCs, stem cells or another cell type, one of the first things we ask is: Do you have the desired quality and functional attributes (CofA or specifications) already mapped out, or criteria you can share with us? In some cases with younger companies we've been given criteria that are not biologically possible to meet. That's where our experience will help them identify what is required and what's achievable.

Then you have other companies that have perfectly acceptable criteria but the variability they build into their CofA and specifications in terms of the dynamic range of the starting material product may be too broad or narrow, and we can help guide them on that. Our experience is that you don't need a 99% viable population starting material plus or minus 1%. You can adequately achieve your *ex vivo* expansions and differentiation studies with a 90% viable product.

Not only are these factors important when defining your starting material requirements, but they can have a major impact your timeline for manufacture and ultimately cost of goods (CoGs). We look at the CoGs upfront, otherwise you may develop cell processing and manufacturing protocols that may not be viable, because of excessive cost.

Q What are the key regulatory considerations that biotech and cell therapy companies need to be aware of in terms of their raw material selection?

RT: One of the key considerations regarding your starting material is your consent protocol – consent to collect, and the appropriateness of use beyond core use, i.e., blood transfusion or bone marrow transplant, for research use or clinical development. You have to make sure your consenting process, policies and regulatory oversight is well executed so that the various regulatory authorities (FDA, EU) will not have issues. For example, our supplying CD34 cells from cord blood to a Big Pharma company for use in the development of their CAR-T cell therapy would require that we have a robust and compliant informed consent in place to allow such activities.

Because of the nature of our business, we have all of our consenting protocols defined and in place within the facilities that participate in these aspects of cell therapy. This can be a critical factor for a client when they are perhaps considering working with a Contract Manufacturing Organisation (CMO) who then has to develop an institutional review board (IRB) protocol, an informed consent protocol and go through the required training and documentation steps before they can even touch the material. By already having this infrastructure in place at BCA facilities, this accelerates the ability of a company to develop a product, versus spending weeks or months, which can be of substantial cost in terms of time and dollars, just to put in place their ability to obtain starting material.

DW: I've been at the San Diego Blood Bank for 3 and a half years and blood banking is the most highly regulated industry I'm aware of. On the blood side of the business we are, of course, regulated by the US FDA and by the American Association of Blood Banks. Because we also ship plasma to Europe we are regulated by the European Medicine's Agency (EMA). At

San Diego Blood Bank, we are also regulated by the state of California. For BCA members such as the San Diego Blood Bank, who have cord blood banks as well, there are different regulations and standard operating procedures that apply to this side of the business and these more closely resemble those applied to cell therapeutics.

Because we are so tightly regulated this puts us in a great position to be able to share our knowledge with our clients in pharma and biotech and help guide them where required.

Q Where do opportunities lie across the CGT supply chain to expedite clinical translational and commercialization?

RT: From the perspective of raw and starting materials, there's a real opportunity to help address one of the biggest challenges of manufacturing within the sector: CoGs. We see this in particular with autologous products such as CAR-T cells where the CoGs are quite high. This is because it's a one-person-one patient system and therefore every CAR-T treatment requires a full cGMP manufacturing campaign. The ideal, therefore, might be to move towards a pooled allogeneic approach for CAR-T cells and other cell types such as MSCs whereby we can use pooled product from multiple donors as an acceptable starting material because HLA compatibility will not be an issue, or can be engineered out of the allogeneic product. This could have a huge impact on the cost of manufacturing and also the added benefit of dampening out variability of one manufacturing lot to another.

As we have millions of donors within the BCA network for whole blood, and tens of thousands of donors for cord blood, we are ideally placed to support the development of pooled allogeneic products.

DW: But more than this, from a manufacturing streamlining standpoint we can work with a company to stress test their manufacturing protocols and help define their infrastructure, personnel and equipment supply needs. Working that closely with a client really enables us to provide suggestions around how to better contain their costs and that's something we're actively doing now with a particular company who are in clinical trials.

We see this as a critical part in the early assessment of scale-up feasibility. Before I came to the blood bank I ran an antibody therapeutic company. One of the big challenges is when you develop an antibody for small cell lung cancer, for example, you engineer antibodies and produce them at small scale before moving into clinical trials. What typically happens in the industry is that what's developed on the research side is tossed over a wall for clinical trial scale up, which ends up being a very expensive step. So why not focus on what's critical for scale-up during the earlier development of your product? Maybe it's a bit more expensive during the development process, but because you've considered what's necessary to scale-up at a much earlier stage, you are more likely to get your drug to market more quickly, which is a big financial win.

If you're sitting on a billion dollar drug but it takes you an extra year to scale it up, you've lost a billion dollars in that delay. Whereas you could

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spend tens of thousands of dollars earlier on the development side to get that right from the get go. I think the same thing will apply in the cell therapy space: we need to pay attention to scale-up and -out as early as is feasible in development, just so those therapeutics get to the market and have the biggest financial impact on the companies.

RT: There are also opportunities downstream where we feel our expertise can be applied to support commercialization. For cord blood banking we carry out a lot of cryopreservation, all of which is performed under controlled, validated cGMP, FDA-compliant conditions so we can take that material and ship it for transplant into extremely ill patients. We developed a courier and transportation system that is fully validated and has legal chain of custody for shipping a cord blood unit from our facility to a transplant center, whether in the USA or Europe.

It sounds conceptually easy to do, but it involves a great deal of work to establish and validate your protocols, equipment and logistical coordination of that exercise. Having that tried and trusted network in place enables us to help companies with this critical but often overlooked biologistics issue.

Q How do you anticipate the field evolving over the next 5 years as more products enter the clinic?

RT: I think in the future, regenerative medicine and cell-based therapeutics are potentially going to exceed CAR-T cells as a therapeutic opportunity, because they'll treat a broader range of diseases and you can use pooled allogeneic products. Therefore, sourcing, characterizing and establishing MSC banks, for example, that can supply that as an off-the-shelf source material for development by companies is not that farfetched. It's actually one of the strategic priorities for BCA.

A key part of any type of cell therapy sourcing is maintaining a robust donor and recruitment base. We have established a societal relationship with our communities, so we can access in a timely fashion source material from donors that's appropriately consented and can then be transferred to biopharma for drug development.

I think one of the things we want to do, and need to do, as a community to serve biopharma and R&D efforts is to tailor the portfolio of products we can offer. Not just blood, white cells or cord blood, but characterized, high-quality subfractions, such as MSCs, that are essential materials for a number of these cell therapy products. We have already invested in the infrastructure at BCA to add these capabilities to our offering and are ideally placed to offer that service to clients.

> When thinking about innovation it's not just around characterizing cells and isolating cells, it's also about being innovative in partnering across different centers to offer a full and diverse set of products and services to this growing market.

DW: I think the industry is still new and growing. We mentioned the continuum of MSCs, which I think highlights a great opportunity for innovation in trying to better molecularly characterize cell types. We are used to characterizing cell types in the blood business with HLA typing and cross-matching being done as standard. I think the real opportunities lie in applying these skills and conceptual knowledge to impact and develop standards within the cell therapy market.

Being part of such an extensive network of blood centers also creates a very unique opportunity for us to collaborate and combine the complementary, synergistic capabilities between centers to better serve the cell therapy market.

So in thinking of innovation it's not just around characterizing cells and isolating cells, it's also about being innovative in partnering across different centers to offer a full and diverse set of products and services to this growing market.

For BCA there's a number of opportunities for diversification with both strategic imperatives and also with a broader desire to impact our communities' health. Blood banking itself is a low-margin business; therefore, to grow and sustain ourselves we need to look at related businesses we can be involved in which is why the cell therapy market looks interesting to us.

But even more importantly, I think BCA's blood center network can have even greater impact in our communities' health by extending into these cell therapy spaces. We save tens of thousands of lives a day with blood used for transfusion, for patients that need red blood cells or platelets. But I think we can have even greater impact on a potentially larger scale by engaging in research and clinical trials and translational science to cure disease.

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The Natural Resource for Cell and Gene Therapy Material

Blood Centers of America is a national network with more than 600 collection and testing sites that provide human blood products, cells and tissues to the therapeutic, diagnostic and cell therapy industries.

We work with doctors, researchers and scientists to provide specific, clinical grade bio-materials to a wide variety of incubator organizations, clinical testing facilities and biotech manufacturing customers including:

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- **Hospitals and Clinical Labs**
- **Pharmaceutical Companies**
- **Device Companies**
- **BioTech Companies**
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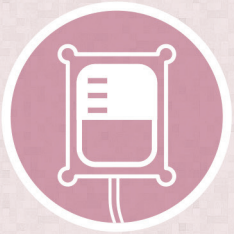

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