Biomaterials: Challenges, Characteristics, and Considerations

Dr Jeff Daelman, Business Development Manager, Innovations, at Rousselot Biomedical spoke to *EBR* about the role of biomaterials within the biopharmaceutical space, as well as the challenges and developmental considerations of biomaterials, and recent progress made in the field

***EBR:* What is the role of biomaterials in biopharmaceutical and biomedical applications?**

Dr Jeff Daelman: Biomaterials restore function and facilitate healing after injury or disease, and are used in applications including medical implants, tissue regeneration, molecular probes, wound dressings, and biosensors. They provide a physical structure that can be used as a drug delivery system for active pharmaceutical ingredients or other ingredients, or as a scaffold to which cells can attach. However, with such a diverse range of uses, the specific role of biomaterials is application-dependent.

Biomaterials can be natural or synthetic. For cellular applications, such as tissue engineering, we need to consider that the majority of the cells in our body are attached or anchored to an extracellular matrix (ECM). So, ECM-derived biomaterials – such as collagen and its denatured counterpart (gelatin) – can enhance the attachment and migration of cells promoting tissue repair. For that reason, collagen and other natural biomaterials are an ideal starting material thanks to the fact that they are well tolerated, promoting cellular adhesion and subsequent tissue formation to facilitate body integration, while their biodegradability allows for tissue remodelling.

What are the key challenges that come with developing biomaterials for sustainable and successful tissue engineering?

I think the answer to this question is threefold. Firstly, when it comes to tissue engineering, there is no such thing as one size fits all; all organs, tissues, and cells have their own specific properties. The challenge is to create a basic biological, functional construct that cells recognise, and then tune the mechanical properties to match the tissue properties and cell requirements. This means that we, as biomaterials experts, need to communicate effectively with our tissue engineering clients to help them select the best biomaterial for their application, whether that is an existing biomaterial or a new material we customise for a specific purpose.

Secondly, we need to provide biological benefits while maintaining consistency. Our clients are trying to replicate an immensely complex system with hundreds of components, including some with unclear roles. By using a natural biomaterial, such as gelatin derived from collagen (the body's biomaterial) we can better mimic the natural cellular environment. However, natural biomaterials are notoriously difficult to define and obtain consistently. By 'define', I mean listing the individual ingredients instead of something general like 'bone extract'. Poorly defined ingredients can lead to increased variability, and we know that clients buy and store whole batches of cell culture media, just to be sure they can minimise variability over time. Our challenge, as a biomaterial supplier of a natural product, is developing natural biomaterials that can provide all the biological benefits, while maintaining batch-to-batch consistency.

Thirdly, it is important to ensure purity. Endotoxins like lipopolysaccharides (LPS) can influence cell differentiation, potentially yielding unexpected or irreproducible results. For example, we investigated the effect of LPS contamination in several methacrylated gelatins (GelMAs) on the chondrogenic differentiation of equine mesenchymal stromal cells. At day 28 of differentiation, both glycosaminoglycan and collagen II production were inversely correlated to the LPS levels in the gelatin, and there was a clear trend towards improved chondrogenic differentiation in low-endotoxin gelatins.

What are some of the essential characteristics of biomaterials required to mimic the cell microenvironment?

Recapitulating the cell microenvironment enhances cell survival, adhesion, and functional performance. The most essential characteristic for this is biocompatibility. In addition, biomaterials ideally contain cell recognition motifs that bind to cell surface receptors (e.g., integrin). This interaction allows cells to physically adhere to the material, and provides cells with a signal that facilitates survival and growth – characteristics that are important for growing cells both in 2D and 3D.

The natural environment of a cell is 3D, so it is no surprise that many cell types perform better in 3D culture. Therefore, biomaterials that allow 3D culture (e.g., hydrogels) are often preferred. Besides containing cell recognition motifs, these materials need to provide sufficient mechanical stability at physiological temperatures and allow diffusion of oxygen and nutrients. The physicochemical properties of the biomaterial should be tunable because the preferences of cells vary significantly depending on the tissue of origin (e.g., liver cells will prefer a softer environment than bone cells). For most applications, the biomaterial should be biodegradable, ideally at a predictable rate, and should allow cells to interact and reorganise themselves into a living structure. Purity is equally important, as endotoxins like LPS cannot be removed by sterilisation alone.

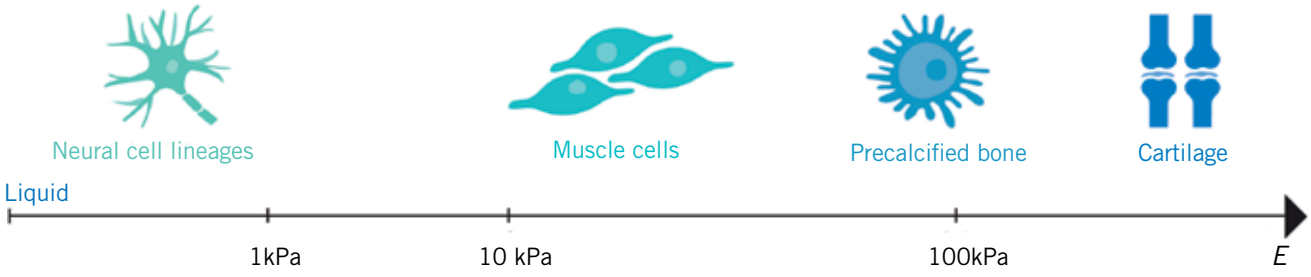
When we investigated the effect of different gelatin coatings on the proliferation capacity of adipose-derived mesenchymal stem cells, we found a higher proliferation capacity with highly purified, ultra-low endotoxin gelatins with a low molecular weight (like our 10 HGP X-Pure® gelatin). The results confirmed that the right gelatin can optimise expansion and maintenance.

What are some of the early considerations when developing biomaterials for optimal progression to the clinic?

The most critical consideration is whether the biomaterial is safe to use in the human body. There are many biomaterials with incredible functionalities that are restricted to R&D because they are not suitable for use in the human body. If the goal is progression to the clinic, then selecting a biomaterial that is biocompatible, biodegradable, and purified, is vital.

As a rule, biomaterials must serve their function in the body without affecting other bodily organs. A biomaterial that contains too many impurities can cause immune reactions affecting the entire body, resulting in rejection of the implanted tissue. Selecting low endotoxin gelatin is an important step to ensure compliance with regulations and to guarantee a smooth and successful translation from bench to bedside. We should consider the system as a whole; by trying to fix a problem in one location, we must not cause a problem in another.

Once you have a biomaterial that meets all the regulatory requirements to proceed to clinical trials, one very important question remains: can the production process be scaled to the quantities that are needed at a clinical stage? For biomaterials, the production process has a large impact on the final product. Sometimes this impact is measurable or quantifiable, sometimes it is not so obvious. If you don't consider upscaling, you might end up with a



E = Elasticity of microenvironment

Different cell types require different environments

product that is perfectly suited for the application you are developing, but cannot be sourced in sufficient quantities.

We have experienced the importance of early consideration of scaling up first-hand; a customer asked if we could provide a modified gelatin using a synthesis process often used in the literature (EDC-NHS). We discovered that this process was not suitable for controlled and consistent production at scale, so we found an alternative synthesis route that gave a similar biomaterial. This early evaluation of scalability meant no time was lost later on in the development or manufacturing process.

How can biomaterials help reduce clinical translation time?

For use in a clinical setting, biomaterials need to have an acceptable purity level, follow regulatory guidelines, be consistently produced, and be scalable. Selecting the appropriate biomaterial at the start of research can save time and money in the long run. Research involving a biomaterial unsuitable for clinical trials will require a revalidation of said data using a clinically suitable biomaterial before you can proceed to patient trials. This is the case even when clinical translation is not the goal, as cell growth and differentiation can be strongly influenced by the presence of contaminants like endotoxins, and cell performance can vary significantly depending on endotoxin levels. The use of contaminated biomaterial for research purposes can lead to data variability and misinterpretation, so using the right biomaterial from the start will help to reduce the risks and delays associated with changing biomaterial midway through development.

How have biomaterials developed over recent years to help better meet the needs of the biopharmaceutical and biomedical industries?

For tissue engineering, the goal is to have a natural, well characterised and basic functional matrix as a starting material to which we can add other specific cellular components that mimic our bodies' ECM, where cells can thrive. Such biomaterials are well tolerated, promoting cellular adhesion and subsequent tissue formation to facilitate body integration. Their biodegradability also allows for tissue remodelling.

There are very exciting possibilities in combining several biomaterials and production techniques to achieve the optimal environment, both in terms of structure and functionality. For example, the use of calcium phosphate ceramics and synthetic polymers in combination with gelatin can improve mechanical properties. Likewise, combining polyaniline and carbon-based nano substrates with gelatin-based systems can create the conductive properties needed for cardiac and nerve tissue engineering.

There is no limit to the possibilities of biomaterials, but their development should begin with the end application and scale-up potential in mind.

Dr Jeff Daelman has a bioengineering background and holds a PhD in Applied Biological Sciences. He spent several years working on parenteral process validation at Pfizer, before joining **Rousselot**. Jeff was instrumental in the commercial success of Rousselot's ultra-low endotoxin X-Pure® range of biomedical gelatins and he is responsible for the business development of a range of modified gelatins (GelMA and others) with customisable physical and chemical properties for use in a range of applications.