Jellagen
MARINE BIOTECHNOLOGIES

COLLAGEN

IN THE LAB

WHY COLLAGEN IS THE BEST MATRIX TO GROW CELLS

FOREWORD

We are entering a new era of tissue engineering. An era of next-generation therapies for chronic disease, advances in regenerative medicine and new avenues for stem cell research. But to grow a garden, one needs soil, and to develop the biomaterials industry, one needs the right cell culture protein.

Culturing cells is no easy task. Every cell type has its own unique needs, and a protein surface matrix that can nicely nurture one cell may kill another. Thus, a scientist must think wisely before selecting their substrate.

Collagen is a very important extracellular matrix protein for biological structures. It can accurately mimic the *in vivo* micro-environment to develop high-quality cells for a wide variety of applications.

Stories of bovine-based cultures housing bovine spongiform encephalopathy (BSE), cancers and other autoimmune diseases have led many to question the future of animal-derived collagen. Coupled with a rising sense of sustainability, regulatory and religious concerns, the industry is wondering how the bright future of cell culture and regenerative medicine will be facilitated.

Jellyfish have been relatively unchanged genetically for over half a billion years and can be harvested sustainably. They have a high collagen content, with wide biocompatibility and zero risk of BSE and disease transfer. This enables them to offer the ultimate precursor collagen – a safe and highly adaptable material that can act as all its mammalian collagen descendants rolled into one.

The future of tissue engineering is bright. But to get there, the biomaterials industry must take the necessary steps. From its current state to its future rewards with expert opinion throughout, this report outlines the challenges faced in cell culture and tissue engineering and also demonstrates how jellyfish collagen can overcome them.

Professor Andrew Mearns Spragg
FOUNDER & CHIEF SCIENTIFIC OFFICER, JELLAGEN

What does the future have in store for the use of collagen in cell culture and tissue engineering? At Jellagen, we have the answer.

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WHAT A CELL NEEDS

Cells are the building blocks of life. Their ability to adapt and perform critical functions are the basis of every living being that has ever been. In research they have been a key part/factor of almost every medical advancement in the last century.

But cells did not evolve to live in a lab. Instead, human cells prefer the body's extracellular matrix, the three-dimensional network of collagen, enzymes, and glycoproteins that give cells their unique structural and biochemical support. When the preference of every cell type are taken into consideration, the challenge to nurture and grow each one successfully, seems impossible.

But to achieve medicine's next series of advancements, from oncology to spinal cord research, these challenges must be met.

This section outlines key criteria for effective cell culture and the difficulties each pose.

MORPHOLOGY

When studying the development of cells in culture, a simple but important question, arises: what do they look like? From their shape to their colouring, their formation to their size, examining a cell's morphology is the first and most essential aspect of successful culturing experiments. And as a safety measure, a quick visual inspection can often reveal signs of contamination far quicker than any technology.

Indeed, cells do not always respond well to their new accommodation. If contaminated by a toxin or unsuited to their medium, a cell can rapidly detach from its substrate, lose its nucleus granularity and stop its cytoplasmic vacuolation – all of which jeopardize an experiment.

WHAT THE EXPERT SAYS

"Hepatocytes tend to express levels of enzymes closer to those in vivo in a 3D matrix rather than in 2D. It is often more complicated to culture them in 3D: it becomes difficult to count them and to image them for instance."

Marion Paolini, PhD,
LEADING SCIENTIFIC US INSTITUTION

WHAT THE EXPERT SAYS

"Collagen is the most abundant protein within the human body; from skin up to brain, we have collagen everywhere, so we need it to mimic the in vivo situation."

Dr Mike Barbeck, BERLIN ANALYTIX

CELLULAR DIVERSITY

Fundamentally, a cell is adapted to perform a few specific functions. And when these functions can range from forming bone tissue to transferring electrical signals, cells must diversify to carry them out.

Even typical mammalian cell culture can be divided into three broad classes.

- Fibroblastic cells: elongated cells that grow best attached to substrates.
- Epithelial-like cells: regular-shaped cells that attach to substrates in discrete patches.
- Lymphoblast-like cells: spherical cells and usually grown in suspension without attachment.

These diverse cell types necessitate diverse substrates. Hepatocytes, for example, are liver cells that synthesize proteins, bile salts and phospholipids all while thriving in the toxin-rich liver system. To study these cells in culture requires replicating this unique environment.

ATTACHMENT

Animal cells typically grow only when attached to specially coated surfaces. This attachment allows cells to interact with each other and their environment as they would in the body's extracellular matrix. But facilitating these physical connections can become tricky without the right medium.

WHAT THE EXPERT SAYS

"At Swansea University, we study gynaecological cancers. The cells that we target in our research are anchorage dependent. They must be anchored to something in order to grow, to proliferate and to move. And in our *in vitro* studies, many cells don't like to anchor to plastic and they're very difficult to culture if they can't anchor."

Dr Lewis Francis, SWANSEA UNIVERSITY

In order to overcome this issue, cell cultures must contain an attachable collagen that mimics a cell's *in vivo* environment.

MIGRATION

Like attaching to a substrate, some cell types can only survive if they can migrate across a substrate. This phenomenon involves the coordinated action of cell movement in a four-step motion pattern: a cell will protrude from the leading edge of a cluster of cells, it will form new adhesions near the front, then contract and release the real adhesions, which creates mobility.

When grown on a gradient, migratory cells such as fibroblasts and smooth muscle cells often move from softer substrate regions to stiffer ones. Another challenging requirement of many cell types, researchers looking to culture migratory cells should anticipate motion and search for a traversable substrate.

WHAT THE EXPERT SAYS

"The culture method is extremely important because I need my hepatocytes to express specific enzymes involved in drug metabolism as they usually do *in vivo*. This expression is extremely sensitive to the mechanical properties of the culture matrix. If they don't 'believe' they're in a liver environment, they will stop expressing those proteins."

Marion Paolini, PhD,
LEADING SCIENTIFIC US INSTITUTION

GENETICS

Fundamentally, those studying cells are looking at which genes they express. But if a cell culture does not have the right collagen, its weak structure can destabilize the cells and inhibit gene expression.

EXPANSION

Cell growth benefits from the 3D spatial expansion capability that collagen gels and matrices can provide. This enables more natural and higher yield cell growth and development processes, as well as enabling technicians and analysts to better manage and understand the spatial orientation and structure of the cells at different stages.

WHAT A CELL NEEDS
THE KEY POINTS

☐ Culturing cells outside the body is no easy task - every cell type requires **its own bespoke conditions.**

☐ There are those that attach to substrates and those that float in solutions, **there are cells that migrate and those that stay still.**

☐ For successful cell culture it is vital to **know the cell's requirements and find** an accommodating, biocompatible substrate, such as collagen, that can cater for those needs.

ASK THE EXPERTS

WHAT ARE **THE CHALLENGES** OF CELL CULTURING?

"You know, not every collagen is the right collagen for every type of cell and vice versa. So, you have to optimize that process, you have to select the type of collagen that you want and then optimize the culture conditions by paying attention to cell doubling time, cell morphology or cell functional molecules. You need to know what your cell culture needs."

Dr Lewis Francis, SWANSEA UNIVERSITY.

"Although many collagen products are highly purified, they might still constitute a risk for cells that would undergo transplantation. Moreover, there needs to be a consideration of the immunogenicity of any matrix used when growing cells from one species on collagen from another species. In addition, one has to consider the potential impact of the purity of any product and what influence any contaminants will have the consistency of the desired results."

Dr Chris Adams, KEELE UNIVERSITY

"Hepatocytes [liver cells] are pretty difficult to culture. You always have to have sufficient collagen and coat the plates with it, so the hepatocytes feel like they're in a liver environment. And culturing in two dimensions is more difficult than in three dimensions. It's hard because collagen is pretty expensive, and also it's hard to have batch-to-batch consistency, especially in 3D."

Marion Paolini, PhD, LEADING SCIENTIFIC US INSTITUTION

THE IMPORTANCE OF COLLAGEN

Collagen is considered by many to be the hallmark protein of animals. It is the most abundant protein in all mammals, constitutes over 25% of the human body and quite literally holds entire species together.

It is this relevance to the human body and its incredible ability to reproduce its inner environments that helps make collagen the Gold Standard for cell culture substrates.

Unlike synthetic polymer-based scaffolds, collagen is biologically active and typically promotes strong cell adhesion and growth. And as a biodegradable structure, a collagen substrate allows host cells to replace it and produce their own extracellular matrix. Cells also interact with scaffolds via the ligands and pores on the material's surface. As a surface, collagen naturally possesses these ligands and contains pores wide enough for cell migration, but small enough to allow for attachment.

These characteristics make collagen an ideal substrate to help cells grow in culture. The *in vivo* environment can be very closely mimicked through the use of stable and homogeneous biocompatible collagen material.

"Porosity is of fundamental importance, so cells can survive,"
Marion Paolini,
PhD, LEADING SCIENTIFIC US INSTITUTION

But while a gold standard overall, not every collagen is suitable or even safe enough for in vivo applications such as medical devices, drug discovery and therapeutic applications. Indeed, collagen substrates have been associated with scandalous cases of infectious diseases, sustainability issues and rejection for religious and regulatory reasons.

This section outlines the limitations of each collagen source and the challenges this protein faces as a substrate for future research.

WHAT THE EXPERT SAYS

"In the research lab collagen is an excellent substrate on which to grow cells, particularly cells that are difficult to grow with other materials. It is a very versatile substance that can be cast in 3D shapes and cross-linked as needed. We often make 3D gels of collagen to create useful models of skin cells for non-clinical purposes."

Professor Sheila Macneil
PhD, UNIVERSITY OF SHEFFIELD

BATCH-TO-BATCH CONSISTENCY

Collagen is found throughout the body in all kinds of organs and tissues, making up around 75% of the dry weight of human skin for example, and this makes it the most important and versatile material for growing cells.

There are over 28 types of identified collagen, all of which have a characteristic triple helix consisting of three polypeptide chains, which differ in length and size depending on the type. The five most commonly used in cell culture are:

- Collagen Type I: The main component of organic bone
- Collagen Type II: The main constituent of cartilage
- Collagen Type III: Found in reticular fibres
- Collagen Type IV: Sourced from the basement membrane and the basal lamina
- Collagen Type V: The main protein of connective tissue and 90% of the collagen in the human body

The reliable and studied properties of these collagen types make them invaluable to researchers, who require substrates to be a constant variable over multiple experiments. A simple change in pH or ionic concentrations between collagen batches can nullify an entire research project. As complex organisms, cows, pigs and rats can vary in age, sex, size, levels of fitness for example, could all lead to batch-to-batch inconsistency in collagen products. Such batch-to-batch inconsistency is often due to poor production and storage, but even when these are tightly regulated, the source of the collagen itself can create inconsistency.

WHAT THE EXPERT SAYS

"I'm making a hydrogel that can be injected and deliver drugs over a long period of time. As this is something that has to be implanted into the human body, obviously I don't want to use mammalian collagen."

Marion Paolini, PhD,
LEADING SCIENTIFIC US INSTITUTION

BOVINE COLLAGEN

For decades, cows have been the prime industrial source of collagen. Plentiful, manageable and easy to breed, the animal's collagen products have transformed reconstructive surgery and, as a culturing bio-material, advanced global medical research. Collagen types I, II and IV can be sourced from the animal's Achilles tendon, nasal cartilage and placental villi, respectively.

But bovine collagen's successful status has not come without criticism. As a fellow mammal, cows can transfer multiple diseases to humans that non-mammalian sources cannot. And as outbreaks of transmissible spongiform encephalopathies (TSEs) and foot and mouth disease (FMD) continue to be reported in bovine collagen-producing countries. Consequently, many researchers are looking for safer alternatives.

WHAT THE EXPERT SAYS

"The potential risk of BSE associated with bovine collagen requires us to carry out additional testing for safety and compliance purposes. Jellyfish collagen could have potential in reducing this risk which will make our translational stage faster and easier."

Professor Chaozong Liu,
UNIVERSITY COLLEGE LONDON (UCL)

WHAT THE EXPERT SAYS

"One of the main reasons we don't use bovine collagen for clinical applications is a lack of confidence in the source. Unless it originates from herds that have only ever fed on grass there is always some risk of BSE being present - which is very hard to detect until it is too late."

Professor Sheila Macneil
UNIVERSITY OF SHEFFIELD

WHAT THE EXPERT SAYS

"I think as we progress developing new tissue engineering products, sustainability will become a big factor. And if we continue using bovine materials in medical devices, the risks in this industry will only get bigger and potentially worse."

Marion Paolini, PhD,
LEADING SCIENTIFIC US INSTITUTION

PORCINE COLLAGEN

Unlike bovine -sourced collagen, porcine proteins do not cause a significant allergic response in humans, perhaps owing to a closer homology to human collagen. Thus, the dermis and small intestinal mucosa of pigs have been widely used for biomaterial, tissue repair and cosmetic purposes.

But, just like bovine collagen, porcine sources also come with a risk of disease and contamination. As a mammalian relative, the bacterial and viral pathogens of pigs are often transferable to humans, as most infamously demonstrated during the Swine Flu pandemic of 2009-10. As a pig product, porcine collagen is a prohibited substance for the nearly two billion people who follow certain religious orthodoxies. And, just like bovine products, pig-derived collagen is sourced from a relatively complex organism that can have multiple variables and lead to the aforementioned batch-to-batch inconsistency.

WHAT THE EXPERT SAYS

"We're interested in transplanting cells into the nervous system to repair it after injury or disease. To do that, we've tried rat tail collagen, which is mammalian type I. It's easy to use, it's viscous, which is something we like in the nervous system, but we've also found that it's mechanically very weak in the end. Its stiffness is around 300 pascals, compared to brain and spinal cord which are around 10,000 pascals."

Dr Chris Adams, KEELE UNIVERSITY

Aside from the disease risk, it has been estimated that approximately 3% of the population experi-ence allergic reactions to bovine collagen. When the environmental sustainability of the meat industry is also taken into consideration, it is easy to understand why many scientists are turning their backs on bovine and porcine sources.

WHAT THE EXPERT SAYS

"I'm not the biggest fan of porcine or bovine collagen because there's no homogeneous quality of the collagen. That's my big problem, and that's why I'm working now with jellyfish collagen"

Dr Mike Barbeck,
BERLIN ANALYTIX

RAT TAIL COLLAGEN

While bovine and porcine collagen serve the larger biomaterials industry, on the smaller, laboratory scale, rat tails are the preferred source for type I collagen. Due to its high accessibility and homogeneity, the animal's protein is now the dominant source for laboratory slides, cover slips and gels.

But there is a good reason that rat tail collagen is not as popular with the larger industry: its low yield and poor immunogenic profile. With its commercial collagen content limited to just its tail, the animal can hardly match the yields of its mammalian contemporaries. And when its structural fragility is considered, it is no wonder that industry projects tend to avoid rat tail collagen completely.

PLANT-DERIVED COLLAGEN

As the dangers and limitations of animal-derived collagen become clearer, many alternative sources are rapidly gaining interest. And one such burgeoning source might be unexpected: plants. Collagen is, after all, only found naturally in animals, so any plant-derived collagen is the product of genetic engineering.

Now used for the treatment of various chronic and infectious diseases, plant collagen is quickly gaining a reputation for being economical, scalable, and safer than its bovine contemporaries. However, as an unnatural source, plant collagen has its limitations. Most plant scaffolds form weaker and smaller fibre diameters than bovine materials[1] and due to its farmed nature, production is at the mercy of environmental con-ditions such as droughts and blights. Thus, compared to animal-derived collagen, the market for plant-derived collagen is expected to increase at the slowest rate until 2025, growing to just $46.5 million com-pared with animal market's value of $480.5 million.

Tobacco leaves are also used as a source for the derivation of medical-grade human type 1 collagen. Tobacco-derived collagen is homogeneous and bioactive, it produces no immunogenic response and does not transmit diseases or pathogens. However, questions remain over production volumes and efficacy for demanding applications. Tobacco plant cultivation requires substantial use of land, fertiliser, and water while producing substantial toxicity to land and water ecosystems. Both land clearance for cultivation.

SYNTHETIC COLLAGEN AND ALTERNATIVE MATERIALS

For more limited applications collagen derived from synthetic peptides (short chain amino acids) is sometimes used. Synthetic collagen can be chemically synthesised in small chains relatively easily and may be purified to a highly homogeneous material.

Synthetic collagen doesn't contain pathogens or disease, nor does it typically produce an immune response in humans. It can also be used to develop biomaterials with specifically tuned attributes for different research and clinical needs. However, due to the complexity of synthesis only relatively short chain collagen molecules can be produced compared to natural samples, making them of limited use.

Finally, in some clinical research settings alternatives to collagen are used for cell culture and other biomedical processes. Polymers for example are often employed for applications that require mechanical strength and support. Polymers can be precisely controlled and have very high longevity in the body, along with no risk of disease.

However, they can cause local inflammation and swelling when deployed in clinical settings, so care must be taken to protect patients. Research is also underway to investigate modifying polypropylene meshes with collagen to see how well they can be tolerated by the body.

WHAT THE EXPERT SAYS

"Cells like to grow on collagen because it has been optimised by biology to provide the perfect conditions for their development. Synthetic biomaterials still have a long way to go to compete with nature. Collagen has tremendous potential in clinical applications if we can make it safe and usable."

Dr Vanessa Hearnden, UNIVERSITY OF SHEFFIELD

THE IMPORTANCE OF COLLAGEN

THE KEY POINTS

- ☐ There are **five common types of collagen** that can culture the majority of cells used in research.
- ☐ These five types are traditionally sourced from bovine and porcine sources, but due to concerns of batch-to-batch consistency and disease, there is now **a great investment in alternative sources.**
- ☐ One safer source, plant collagen, is gaining interest, but its market is not expected to increase at a great rate due to **poorer performance and production worries.**

JELLAGEN

THE FUTURE OF COLLAGEN IN CELL CULTURE AND REGENERATIVE MEDICINE

Major advances in disease therapies and regenerative medicine are on the horizon. But to reach them, researchers need a consistent, disease-free substrate that better mimics the *in vivo* environment and can stimulate growth in all cell types.

Considering the constraints of many collagens, to many this may seem unfeasible. But there is a solution. Marine animals have been found to be the safest and one of the most applicable sources for obtaining collagen there is. Due to their safety and high natural collagen levels, animals such as fish, starfish, sponges and squid have been welcomed as exciting new collagen candidates. But one marine animal has a collagen content potentially different to any other: Jellyfish.

Thanks to collagen contents exceeding 40% in certain species, evolutionary ancient lineage, no risk of BSE and a compatibility with every common collagen type, jellyfish-derived collagens are set to reshape the biomaterials industry.

By exploring these benefits and more, this section will demonstrate both jellyfish's viability as the future of substrate sources and Jellagen's ability to provide it.

WHAT THE EXPERT SAYS

"At the UCL IOMS at the Royal National Orthopaedic Hospital we regularly use collagen as a scaffold for cartilage, hard tissue and soft tissue repair and regeneration. Jellyfish collagen has shown similarities to type 1 and type 2 and this could be very useful for improving tissue regeneration in the future and opening up new opportunities."

Professor Chaozong Liu,
UNIVERSITY COLLEGE LONDON (UCL)

MATCHING MAMMALIAN CELL CULTURE

As this review has detailed, cells in culture need supportive, nurturing substrates to promote growth. But this structure must also suit a cell's unique morphology and requirements. Traditionally, these different needs were served by the common collagen types, I,II,III, & IV, sourced from mammals. Jellyfish collagen can now be defined as "collagen Type 0" due to its evolutionary ancient chemical lineage and homogeneity to the mammalian types I, II, III, V, and IX. It also has a a highly flexible surface, able to act like many of its mammalian collagen descendants rolled into one, without posing a disease risk – a highly flexible surface, able to act like all its mammalian collagen descendants rolled into one, without posing a disease risk.

- Collagen from *Rhizostoma pulmo* (Barrel Jellyfish) jellyfish shares sequence homology to vertebrate collagen type I[2]
- Protein sourced from *Stomolophus meleagris* species make a near perfect match for type II[3]
- The common edible jellyfish *Stomolophus nomurai* contains collagen similar to type IV and V[4]

This biocompatibility means human fibroblasts grown on jellyfish collagen can survive and proliferate just as they would on any mammalian collagen contemporary, but without any of the associated risks.

WHAT THE EXPERT SAYS

"Jellyfish have an evolutionary conserved structure to their collagen. This means they have functional peptides in their collagen protein sequence, which is common to many of the collagen types that we see in mammalian biology. So Jellagen provide jellyfish-derived collagen which is functional, inert, and doesn't create a cytotoxic effect that kills cells. It benefits us because we have an inert scaffold that we can then decorate with specific supplements like marks or motifs that our cells will interact with. So it's almost like a blank scaffold that you then add your biological variation to."

Dr Lewis Francis, SWANSEA UNIVERSITY

WHAT THE EXPERT SAYS

"Cell culture is a critical first step for us to establish the biocompatibility and cellular performance of a sample before moving on to the animal or human tissue model. We do most of the tissue culture analysis (on histology, immunoresponses etc.) manually, and reproducibility and efficiency can sometimes vary between researchers. The better the substrate we have available, the more we can speed up these processes."

Professor Chaozong Liu,
UNIVERSITY COLLEGE LONDON (UCL)

2. https://www.mdpi.com/1660-3397/9/6/967/htm
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IMPROVEMENTS ON MAMMALIAN CULTURING

Many studies[5] have shown that jellyfish collagen is able to replicate the cell adhesion, proliferation and migration that mammalian collagen is known for. But marine scaffolds do not just copy their mammalian counterparts. In many instances, they improve upon them. In one study[6], new jellyfish-based therapeutics showed improved cartilage differentiation and repair actions, a finding that could help advance the field of regenerative medicine. And in another[7], jellyfish collagen was found to preserve chondrogenic phenotypes better than mammalian type I collagen. More recently jellyfish collagen was found to be anti-inflammatory, produced a weaker immune response and also created vessel-rich connective tissue that is an optimal basis for (bone) tissue regeneration[8].

Current challenges with mammalian cell culture methods include the ability to maintain the primary function of patient derived cancer cell lines. On mammalian derived biomaterials, patient derived cancer cell lines lose their primary function and differentiate. By using Jellagen® 3D scaffolds, researchers have noticed that patient cell lines do not differentiate and therefore maintain their primary function. This holds great promise for the creation of better and more accurate disease models with better predictive outcomes in drug discovery.

WHAT THE EXPERT SAYS

"Jellyfish-derived collagen can be an easier matrix to use than mammalian collagen to culture hepatocytes. It may allow a better well-to-well consistency for 3D cultures, and with better cell viability, more pores and the nutrient circulation is better. Because collagen is necessary to culture hepatocytes, both in 3D or in 2D, jellyfish-derived collagen may be a better alternative to mammalian collagen."

Marion Paolini, PhD, LEADING SCIENTIFIC US INSTITUTION

WHAT THE EXPERT SAYS

"We have used Jellagen collagen in a number of studies. In all our tests from HEK cells to hepatocytes the Jellagen product performed as well as or exceeded the performance of standard rat tail collagen."

Dr Joe Mee, SCIENTIFIC AND BUSINESS MANAGER AT CENSO BIOTECHNOLOGIES.

WHAT THE EXPERT SAYS

"It was clear in these intense studies that not only was the Jellagen collagen functional in allowing ad-herence of these cells, but it performed the best in preventing their activation in culture when grown without stimulus of the cells. This was a very exciting result and related to some of the properties of the collagen being derived from the Jellyfish rather than mammals."

Dr Joe Mee, SCIENTIFIC AND BUSINESS MANAGER AT CENSO BIOTECHNOLOGIES.

5. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3131555/
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A DISEASE-FREE, SUSTAINABLE SOURCE

But while meeting and exceeding other collagens' properties is important to researchers, no factor is more salient than safety. When so much of the research that requires collagen is conducted on human tissue, with the aim of improving human health, there is no room for unsafe sources, such as those that harbour BSE or provoke an unwanted immune response in patients. Instead, the biomaterials industry must search for safe, disease-free sources that can give lab professionals the sanitary assurance they need.

Sources like jellyfish. As an ancient marine animal with few similarities to human immunobiology (low immunogenicity), jellyfish offer a safe, biocompatible collagen material, ideal for translational research thanks to a lower risk of immune reactions.

Coupled with its safety, jellyfish collagen's sustainability only furthers its value in the modern age of biomaterials. As the meat industry is considered one of the major contributors of CO_2 emissions, many researchers now long for a more responsible source. Again, jellyfish collagen can answer these calls for change.

Due to human marine activity, jellyfish blooms now blight coastal regions, causing dangerous problems for both marine life and shipping activity.

But from its Cardiff base, Jellagen's operations remove these growing pests and turn their abundant collagen into valuable, biocompatible cell culture products. These products can be used in innovative new approaches to tissue engineering, cell culture, medical devices, drug discovery and therapeutic applications.

WHAT THE EXPERT SAYS

"Jellyfish collagen will benefit my research by providing me with a very useful material for translating cells into the nervous system. Indeed, and since it's derived from a sustainable source, Jellyfish Collagen will cause less of an immune reaction, particularly when you compare it to bovine collagen - one that's badly affecting the planet."

Dr Chris Adams, KEELE UNIVERSITY

Collagen is also used in advanced therapies for bone repair. In cases where a defect, injury or tumour has left a hole or cavity in a bone, it is possible to surround the area with a titanium scaffold and seed it with collagen to enable the bone to regrow and repair. A disease-free and high quality collagen source is vital for this process.

JELLAGEN, THE FUTURE OF COLLAGEN IN CELL CULTURE AND REGENERATIVE MEDICINE

THE KEY POINTS

- ☐ Jellyfish collagen can now be defined as "collagen Type 0" due to its evolutionary ancient chemical lineage and homogeneity to the mammalian types I, II, III, V, and IX
- ☐ Due to its evolutionary conserved structure, collagen sourced from jellyfish can **replicate the major mammalian collagens** without the risk of disease or batch-to-batch inconsistency.
- ☐ In certain areas, jellyfish-derived collagen even improves on its mammalian contemporaries as it can **nurture enhanced cartilage differentiation and preserve chondrogenic phenotypes** better than mammalian type I collagen.
- ☐ These benefits are provided by Jellagen, a UK marine biotechnologies company that **sustainably sources its collagen from jellyfish blooms in the South Wales area.**

CONCLUSION

Culturing cells is hard work. To replicate a cell's unique environment requires a deep understanding of its needs and the right substrates to meet them. Can this collagen provide attachment? Can it allow for migration? Will it help the cells proliferate? These are just some of the questions one must ask before choosing a suitable biomaterial.

And in recent times, researchers have had to ask themselves some more troubling questions, too. Will this collagen provoke an unwanted immune response or cause inflammation? Do I fully trust the mammalian source of the collagen or could this bovine substrate transfer BSE? Are these materials ultimately safe for human use?

With the field of tissue engineering poised to revolutionize regenerative medicine and stem cell therapies, these are not the sort of questions the industry should be asking of itself.

Instead, a bolder question must be asked: what is the future of collagen? What collagen can resolve these serious source of issues and facilitate the industry's great ambitions to protect and improve humanity's health?

Paradoxically, the answer might just come from far in the past.

WHAT THE EXPERT SAYS

"Collagen is a great structural agent and a very good medium in which you could introduce cells for certain tissue engineering applications in the body, and it will be very interesting to see how these opportunities are addressed in the future."

Professor Christopher Chapple,
SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST