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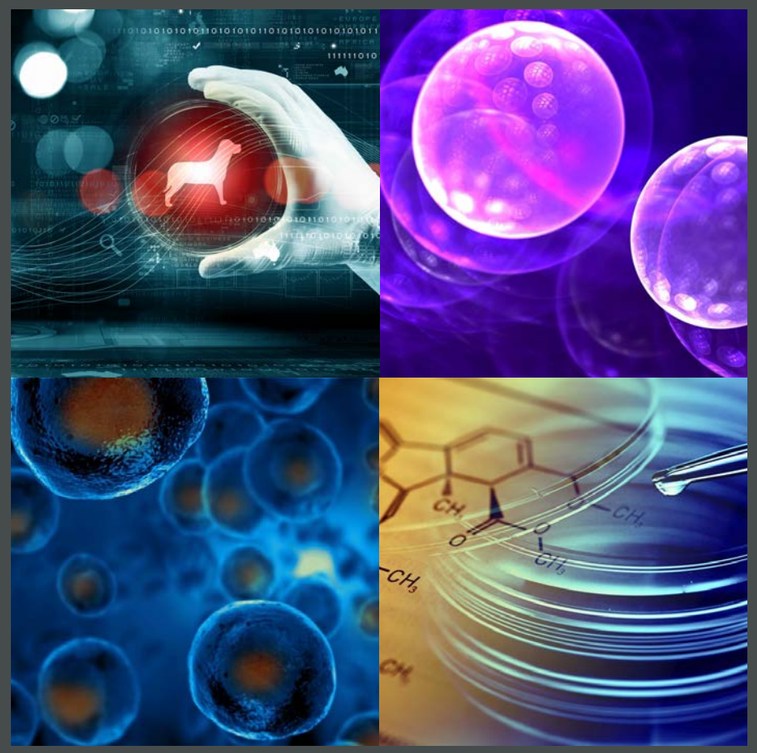

Veterinary Regenerative Medicine: Vision for the 2020s

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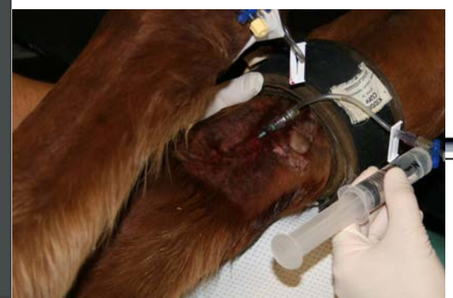

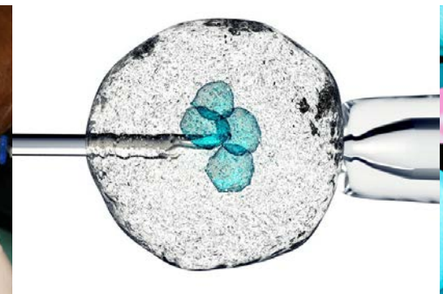

Veterinary Regenerative Medicine research overview

Veterinary Regenerative Medicine is a multidisciplinary field aiming to restore and/or regenerate damaged tissues and organs in veterinary patients. The plasticity and differentiation ability of stem cells, combined with the support of scaffolds mimicking biological structures and growth factors and cytokines providing guiding cues for the regeneration processes, represent the basic pillars of the field.

The first application in veterinary medicine involved the use of stem cells to treat tendon lesions in equines. The initial development of the field was focused in musculo-skeletal diseases, especially for treatment of tendon, ligament and joint injuries in sport animals. Since then the field has advanced in applying cell-based therapies in horses, companion animals and wildlife species for multiple chronic and degenerative diseases currently treated only with symptomatic therapies.

Mesenchymal stem/stromal cells (MSCs) and point of care blood-derived products such as platelet rich plasma (PRP) and autologous conditioned serum, are the main biologic therapeutics used in veterinary regenerative medicine. The positive preliminary data from animal models and veterinary patients are promising, however there are still many challenges on both pre-clinical and clinical levels that need to be addressed to achieve implementation in routine clinical practice. Starting from adequate cell manufacturing according good manufacturing practice (GMP), identifying the optimal tissue source and cell product, up to defining clinical therapeutic protocols and standardised outcome measures, there are still critical parameters to be defined. The lack of species-specific reagents and defined protocols for culture of animal-derived cells represents a big limitation for the development of the field, compared to human cell manufacturing. Currently within the EU there is no central legislation defining the use of cell-based therapies in veterinary medicine. Each member country regulates the field independently, contributing to a variability in cell manufacturing and clinical application.

Why is Veterinary Regenerative Medicine important?

Veterinary medicine has always had an important role in the translational process between basic sciences and human medical applications. Similarly, the innovation and development of regenerative medicine as an extremely dynamic and multidisciplinary field is based on collaborative efforts between cell scientists, human and veterinary doctors. A wide array of diseases affecting the human population spontaneously occurs in veterinary species such as equines and companion animals. They are known to be critical translational models of human disease due to similarities in anatomy, physiology and biochemical processes. Compared to laboratory animals, veterinary patients are exposed to similar environmental and external risk factors associated with conditions such as diabetes, osteoarthritis, cancer and traumatic injuries.

Results from pre-clinical and clinical veterinary studies in dogs and horses have provided valuable insight on the biology, immunomodulation and biodistribution of cell-based therapeutics for orthopaedic conditions. Animal models with defined and controlled genetic background are a critical step in the validation of in vitro findings. However, induced diseases and conditions rarely reflect spontaneous pathological process. Veterinary clinical trials represent an important intermediate tool for the assessment of safety and efficacy of novel cell therapeutics. Clinical studies involving animal patients are characterised by a similar variability in disease background, mirroring the conditions occurring in human clinical trials. The translational value of Veterinary Regenerative Medicine is well-defined in the so-called “One Health Initiative” concept developed by WHO, OIE and FAO which states that the global health is strongly defined by human, animal and environmental health.

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Application of Veterinary Regenerative Medicine in the current climate

The increased interest in using cell therapies in animals is driven by multiple factors. Innovation in veterinary medicine and better focus on animal health and welfare have increased the longevity of animals. This led to increased prevalence of chronic diseases for which there are no cures available yet, and cell therapies can potentially offer a disease-modifying treatment. The initial focus was on musculoskeletal disorders, however the field is expanding as cardiac, renal, orodental, hepatic, respiratory, dermal, reproductive and digestive system disorders have been treated with cell therapies.

Adipose tissue is the main source of MSCs due to ease of isolation and high proliferation rate. Fetal adnexa including amniotic membrane, placenta and umbilical cord are currently being explored, because of their lower immunogenicity and isolation from young and healthy donors allowing an establishment of cell banks. Autologous and allogeneic cell products are actively studied and present on the market. The advantage of autologous products is the absence of immune reactions as cells from the same animal are used for treatment, but extensive in vitro expansion is needed to obtain a high number of cells for clinical use. However, allogeneic “off-the shelf” products, from selected donors and subject to a set of quality control assays prior use. The current focus on academic and industrial level is on development of allogeneic products that can be readily available for use in veterinary clinics for treatment of mainly horses and dogs.

Currently there are no animal cell-based therapies approved by the U.S Food and Drug Administration. In the EU, the product Arti-Cell Forte composed of chondrogenic induced equine allogeneic peripheral blood-derived MSC, for lameness treatment is the only cell-based product that has received a marketing authorisation from the European Medicine Agency (EMA) in March 2019.

Potential impacts of Veterinary Regenerative Medicine in both academia and industry moving forward?

The potential of cell-based therapies in veterinary medicine is going the stimulate the field progression in the upcoming years as research interests and market demands are increasing. The current lack of precise guidelines to date is due to the limited amount of scientific knowledge we have on cell-based products for animals. In their absence, companies and laboratories worldwide are offering products without any substantial scientific background, quality control data, therapeutic protocols and indications.

However, it is important that new guidelines are developed by a team of experts from different backgrounds such as cell biology, cell manufacturing, human and veterinary doctors, and regulatory professionals, in order to meet all needs.

Potentially a disease-oriented approach might be considered, where cells with certain immunomodulatory, secretory or genetic profile from verified donors would be used to generate cell banks for the treatment of a precise condition. In order to obtain an unlimited number of cells, the field could increase the research and use of induced pluripotent stem cells (iPSCs) to generate MSCs for clinical use. Another approach that will grow in the next years are the ‘’cell-free” or ‘’cell-inspired” therapies, based on extracellular vesicles produced by the cells, containing a set of bioactive molecules involved in the intercellular communication. This process can be potentially easier to control and manufacture, eliminating a set of variables and challenges in cell manufacturing. As of now, minimally manipulated autologous point-of-care products are mainly used in veterinary clinics and will continue to be the first choice, due to the lack of evidence-based medicine for more complex therapies. On the clinical side, there is the need of properly designed gold standard clinical trials that will be placebo-controlled, double-blinded, randomised and multicentric, which are fundamental to obtain evidence-based data on what is the real efficacy and safety of cell-based products.

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Summary of thoughts and how is your institution working towards utilising this to drive innovation:

The exciting and dynamic field of veterinary regenerative medicine has a great potential in offering novel therapies for conditions which up to date are treated with conventional medical or surgical treatments which do not offer disease treatment, but merely a symptomatic relief approach. Veterinary Regenerative Medicine has a critical translational role in connecting basic sciences and human medicine and investing in its advancement has a two-fold value: development of novel therapeutics for animals and providing valuable data for the advancement of human medicine.

The research in animal stem cell biology and its clinical applications is ongoing with many questions that still need to be answered. The future evolution of the field is closely related to collaborations and exchange of ideas between cell biologists, veterinary scientists and surgeons, in order to develop a therapy that one day would be part of a therapeutic protocol.

Within CALIN, we are collaborating with specialised veterinary orthopaedic surgeons from Ireland and Wales on creating a Veterinary Regenerative Network, with the main aim to develop science-driven stromal cell therapies for companion animals. The experience, expertise and facilities of REMEDI have provided significant advancements in the area of cell therapies for osteoarthritis and advanced cell manufacturing. We are aiming to translate our knowledge and develop competitive products for the animal stem cell market that will be covered by scientific evidence. The collaboration with enthusiastic veterinary surgeons will allow us to offer cell therapeutics with application guidelines, that can be readily used in the veterinary clinical practice based on the evidence-based medicine approach. To maximise our output, we are working on delivering workshops and webinars that will offer the latest scientific and clinical developments to veterinary surgeons and scientists worldwide, a fundamental first step towards the correct use of the advanced therapeutics in veterinary regenerative medicine.

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