Feature Article

Regenerative Medicine – Is It The Way Forward?

One phrase we have been hearing a lot about lately and undoubtedly will hear mentioned more often as the year unfolds is ‘regenerative medicine’.

According to the Medical Research Council, regenerative medicine is defined as:

“... an interdisciplinary approach that seeks to repair or replace damaged or diseased human cells or tissues to restore normal function, which holds the promise of revolutionising patient care in the 21st century.”

Sounds impressive; even to the layman. The MRC note that it may involve the transplantation of stem cells, progenitor cells or tissue, the stimulation of the body's own repair processes, the use of cells as delivery-vehicles for therapeutic agents such as genes, cytokines and small molecules or cell engineering and synthetic biology.

In the field of aesthetic medicine the quest for ‘make your own face-lifts’ and ‘take the fat from my bum to give me bigger boobs’ ideals have been around for many years but perhaps now is when these concepts are just beginning to become achievable as learning and development of techniques has moved on a pace.

The MRC summarises it nicely by stating; “all regenerative medicine strategies depend upon the harnessing, stimulation or guidance of endogenous developmental or repair processes”. Aesthetic medicine is looking to ‘harness’ valuable cells, be they platelets, fibroblasts or stem cell rich adipose cells, ‘guide’ them to the area needing treatment and hope that the ‘stimulation’ of new tissue such as collagen and elastin is achieved to ‘repair’ ageing or atrophic tissues without the need for synthetic substances or invasive tissue manipulation.

We are starting to achieve some of this via two forms of regenerative medicine, the autologous treatments, using a patient’s own cells harvested from themselves and cultivated or refined in some way, or by allogeneic means by using healthy, cultivated cells from a donor human source as seen with many growth factor treatments. In this article, I hope to look a little deeper into the growth of autologous and allogeneic applications now becoming more mainstream in aesthetic medicine.

Autologous Treatments

Platelet Rich Plasma (PRP) Therapy

Platelet Rich Plasma or PRP therapy has been around in the aesthetic marketplace for seven or eight years now, but momentum has increased for its widespread use in the last two. It has also been marketed (and trademarked in America) as the Vampire Facelift™ (this also uses hyaluronic acid as part of the ‘facelift’) and Dracula Therapy. Somewhat scary and sinister sounding names, but as the treatment involves the extraction of a small amount of the patient’s blood, to get at the platelet rich plasma which is the ‘liquid gold’, because of its yellow colouring, for reinjection into the skin, the term seems appropriate, even in the eyes of the general public and mainstream media, surprisingly!

The mechanism of action of the treatment is the release of cytokines and growth factors from the platelets once injected into the dermis as part of the wound healing process in the targeted area of introduction. The process is scientifically complex and is said to accelerate tissue regeneration by chemoattraction and deposition of extracellular matrix. The result of this tissue stimulation is the enhancement to the texture and tone of the skin.

Many different systems now exist to facilitate the process of extraction of the plasma from the red blood cells by the practitioner including brands such as MyCells, Regen, Selphyl and GLOPRP.

The general concept involves the use of a centrifuge to separate out the elements of the blood, done in the clinic environment whilst the patient is present for treatment. Differing brands of devices claim differing techniques to achieve this more reliably than their competitors, with a variety of equipment sizes and centrifuge parameters. Additional developments (both medical and cosmetic) have resulted in techniques such as the Platelet Rich Fibrin Matrix (PRFM) from Selphyl which is a substance created when the PRP is added to calcium chloride which turns the PRP into a gel like matrix, more commonly used in medical applications of PRP such as facilitating the closure of leg ulcers. The advantage in an aesthetic indication is said to be that the gel like substance means that the platelets will remain in the site of injection and get to work releasing growth factors in the desired location for treatment without the chance of migration.

PRP is being used for a variety of aesthetic indications, from facial cosmetic rejuvenation for lines and wrinkles in the crow's feet, nasolabials, marionette lines etc., to the rejuvenation of the backs of the hands and the décolletage. In fact anywhere that there is a crepey or slight wrinkling to the skin, including knees, elbows etc., PRP can be employed as it is of course derived entirely from the person who is in receipt of it.

The issue which can cause some problems with patients is the lack of immediate results, unlike with dermal fillers for example, they will need to wait several weeks to a couple of months for noticeable improvements to become apparent; hence, no doubt why the trademarked Vampire Facelift™ chooses to combine with HA to appease the consumer expectation.

Although the combination of PRP and HA also has advantages which are slightly less cynical. Dr. Daniel Sister enlightened us all at the BODY 2012 conference with his approach to non-surgical breast and décolletage rejuvenation where he uses hyaluronic acid placed just sub-dermally in the breast (not into the gland) and naps over it with PRP (or combines the two in the same syringe) for improvement to the cleavage area, correcting inverted nipples and breast asymmetry (natural or after breast reduction surgery).

Stem Cell Rich Fat Transfer

Fat transfer, fat grafting, fat transplantation or micro-lipoinjections are just some of the names used to describe the procedure of removing some adipose cells from a patient, refining them and then reintroducing them into a target area on the same patient to achieve a volume restoration. This is not a new concept; in fact it's been around a lot longer than you might think with the first published results for a procedure dating back to 1893 when a German doctor used fat from a patient's arm to correct a skin defect on their face.

According to the American Society of Aesthetic Plastic Surgeons (ASAPS), the percentage change in its own member statistics for 2011 versus 1997 for autologous fat transfer procedures is an increase of 82.6%, with even 2011 versus 2010 showing a 29.8% increase in the number of procedures performed. Similarly, the British Association of Aesthetic Plastic Surgeons (BAAPS) have reported in their 2012 members audit, an increase of 13% for fat transfer procedures compared to the previous year. It would seem that dermal fillers might perhaps need to start on the worry beads as more and more, plastic surgeons at least, are turning to fat transfer as the volumiser of choice.

What has changed and improved are the techniques for harvesting, processing and re-introducing the fat cells to achieve a better chance of survival of the adipose, post implantation, leading to increased long term viability and desired results for the intended procedure. This includes things like reductions in the speed of centrifuge used to separate the fat cells from the other liquids recovered during the liposuction harvesting, studies and research have shown that lower G-forces exerted during centrifuge processes reduce the likelihood of fat cell destruction.

The additional discovery which has augmented the usefulness and success of fat transfer procedures is the concept of using stem cell enriched adipose tissue for reinjection.

Often referred to as the 'building blocks of life' or 'mother cells'; stem cells have the ability to become any type of cell within the human body, from bones and skin to blood and muscles. By extracting adult stem cells along with the fat, and reintroducing them during transplantation, the theory is that the cells will become healthy new fat cells as well and augment both the results and their longevity.

One leading company involved in this marketplace and pioneering clinical trial work for reconstructive and cosmetic indications is Cytori. The company's Celution system was granted a European CE Marked in January 2006 for the 'extraction and concentration of stem and regenerative cells from adipose tissue for autologous re-implantation or reinfusion'. It is not yet available in the United States as FDA approval is pending.

The system enables the automated extraction, washing and concentration of a patient's own adult adipose-derived stem and regenerative cells or ADRCs. Having been introduced in European and Asia into the reconstructive surgical market a variety of physicians have undertaken trial work using ADRCs to enrich fat transplantations for a number of cosmetic applications including breast reconstruction and augmentation post-mastectomy, as well as for facial rejuvenation and buttock augmentation. Levels of patient satisfaction in the breast trials (known as RESTORE 1 and 2) were high at over 70% in both trials. The company also notes that the procedure can be used for other soft tissue defects such as those caused by disease and trauma, liposuction complications and congenital defects or asymmetries.

The company also produced the Puregraft™ system which allows the physician to wash and purify the fat in preparation for fat grafting in only 15 minutes. This received FDA clearance in January 2010 and European CE Mark approval in July 2010. The combined use of the two systems (Puregraft and Cellution) lowers the processing times and increases the volume of stem cell rich adipose for fat transfer treatment.

Studies are also being undertaken by the manufacturers of Selphyl to look at the combination of Platelet Rich Plasma treatment with autologous fat transfer to establish whether PRP will complement and improve on the results achievable with the fat transplant.

Autologous Fibroblast Injections

Hands up if you remember Isolagen®? Well it's still here, but wearing the emperor's new clothes!

Back in 2006, I covered the Rise and Fall of Isolagen (Autologous Cell Therapy) in a **feature article**. The concept behind the treatment was a good one, the company's rapid expansion following UK, European & Australian launches, combined with poor practitioner training and the marketing to the public and press was an exercise in what not to do, the company simply 'ran' with their product before the product could really 'walk'.

While all this was going on the company was running trials in an effort to gain American FDA approval for the process, which involved harvesting a skin sample from behind a patient's ear, cultivating the fibroblast cells over a period of weeks and shipping them back to the practitioner for reimplantation into the patient for facial skin rejuvenation and acne scare reduction.

Yet, the cost of this production process spiralled out of control and the company were forced to restructure and close many of the newly opened facilities including a complete pull-out from the UK. The American parent company later faced other financial difficulties and declared bankruptcy.

But like any good phoenix, it rose from the ashes of Isolagen at the end of 2009 and the company Fibrocell Science Inc. was born, along with a new name for the product, now known as azficel-T. This is now marketed in the USA as **Laviv™** following FDA approval for the treatment of moderate to severe naso-labial fold wrinkles in June 2011.

Hindsight is a wonderful thing and I'm sure that those behind Isolagen/Laviv have learnt the value of taking a product to market slowly. Only U.S. board certified dermatologists and plastic surgeons who have completed a Fribrocell approved training programme are permitted to use the product now, a stark contrast to the broad range of UK practitioners using it when the product was launched here as Isolagen.

As for the treatment itself, this was always in debate. As Isolagen there were those UK doctors who loved it and those who felt it showed no real rejuvenation results. Many argued that the time window for treatment was restrictive in terms of getting patients back in for treatment when the cells were 'ready' and others that so much of the success of the treatment relied upon pin point placement of the cells in the 'correct' place, which with a hefty price tag for the patient was too much of a gamble when the cells simply died and produces no results.

It seems that with Laviv, the situation is still a little uncertain; despite the FDA approval the regulator and Fibrocell point out that to date the efficacy of Laviv beyond six months has not been established, this puts it at a disadvantage when dermal filler longevity is increasing more and more. The recommended treatment is to inject the autologous cellular product at 0.1 millimetre per linear centimetre into the nasolabial fold during three treatment sessions spaced by 3 or 6 week intervals. A single vial of Laviv contains approximately 18 million fibroblasts. Those interested in it can read more in the package insert (PDF document) available from the **FDA website**.
The company is now in Phase II clinical trials to assess the potential of azficel-T for treating restrictive burn scars. It seems that there are no immediate plans however to return to market it across the pond.

Personalised Stem Cell Skincare

A U.S. company called **Personal Cell Sciences** launched a unique, autologous stem cell enriched skincare product line called U Autologous in the summer of 2012.

The product uses a small quantity (60cc) of adipose tissue (and the stem cells within) extracted by a plastic surgeon and shipped off to their laboratory. The stem cells (mesenchymal) are extracted from the fat, grown and some stored for future use and the rest cultivated to produce a blend of growth factors, cytokines and other proteins, which they call Autokine-CM™ and which are then the main ingredients in a daytime moisturiser, night time firming serum and eye cream set along with other ingredient including caffeine and green tea extract.

Consumers can expect to pay $3,000 for the 'set-up', to include the harvesting, storage, cultivation and creation of the first round of skincare products. After that it's $1,500 a month to receive new batches of the creams based upon the original set up and stored cells. Possibly the most expensive skincare range on the market currently!

The jury is still out in terms of efficacy and safety though as so far the only studies available are unpublished, company sponsored trials which are difficult to rely upon.

Allogeneic Treatments

Allogeneic Fibroblast Injections

VAVELTA®, produced by Intercytex was launched in 2008 as a skin repair and rejuvenation product, designed to restore and repair skin damaged by the ageing process or scarring.

The product, which also goes by the production name of ICX-RHY for medical applications, contains a suspension of 20 million human dermal fibroblasts per ml in cell storage medium contained in a sealed vial for injection into the skin. The fibroblasts used are allogeneic, that is, sourced from a human donor, in this case using neonatal cells.

Under current European Union regulation, the production is regulated under the European Human Tissue Directive on setting the standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, and as such, Intercytex is licensed by the UK Human Tissue Authority.

The company faced financial difficulties in 2009 but new investment a year later saw renewed activity and clinical trial work.

A Phase I trial, conducted in collaboration with Professor Nicholas Lowe at the Cranley Clinic, London, consisting of a placebo-controlled safety and tolerability study in ten healthy volunteers, has been completed. Each volunteer received a course of three injections given into the skin of the upper arm. VAVELTA was shown to be very well tolerated; no serious adverse events were reported and all adverse events were transient and resolved without treatment.

A Phase II dose-escalation trial of VAVELTA in nasolabial folds, also conducted at the Cranley Clinic, London has been completed. In this trial, six subjects received a low dose of VAVELTA and a second group of ten subjects was treated with a higher dose. All subjects have been being followed out to six months post-treatment. The average satisfaction scores for both groups, as assessed separately by both patients and the investigator on a scale of one to ten (ten being the highest), were 7.8 and 7.6 eight respectively. In addition, the investigator measured an improvement in wrinkle severity in 12 subjects (75%).

A second Phase II trial, for the use of VAVELTA in acne scarring, conducted by Dr David Eccleston at MediZen in Birmingham, has been completed. Subjects were followed out to six months post-treatment. The average satisfaction scores for the treatment, as assessed separately by both subjects and the investigator on a scale of one to ten, were 6.8 and 6.3 respectively.
No serious adverse events have been observed and the product has been well tolerated in both Phase II trials. To date, over 100 patients have been treated for a variety of skin damage including acne scarring and wrinkles.

However, when it was first developed in 2008 the MHRA agreed with Intercytex that it didn't require a marketing license. The regulatory situation in the rest of the EU member states concerning whether cell therapies were

Medicinal Products or not was not clear and in order to provide a coherent regulatory system throughout the whole EU the Advanced Therapy Medicinal Product (ATMP) legislation was developed. This classified VAVELTA as a "Tissue Engineered ATMP" as it was "administered to human beings with a view to regenerating, repairing or replacing a human tissue".

As a Tissue Engineered ATMP, it will require a full marketing license from the European Medicines Agency (EMA) from December 30th 2012. The company have noted that this will take time for them to obtain and will involve them carrying out a series of additional clinical trials and other studies. Until it is able to obtain a license, Intercytex will not be able to advertise, promote or market VAVELTA, but can continue to manufacture the product for its own clinical studies.

This is of course a set back, but having faced adversity before, we doubt this will halt progress and expect to see them commercialising the product again very soon.

Human Growth Factors in Topical Skincare Products

Growth factors in skincare have been one of the hottest trends to hit topical cosmeceuticals over the last decade.

Unlike growth factor released from a patient's own platelet cells, growth factors in topical products are extracted from laboratory cultured cells from donor human skin (e.g. cadavers or baby foreskins and placentas).

Growth factors are naturally occurring proteins which act as chemical messengers between cells, enabling them to turn on and off a variety of cellular activities. They can play a role in cell division, new cell growth and the production and distribution of collagen and elastin.

The term 'human growth factors' therefore covers a wide variety of different types or families of growth factor proteins, all with different jobs to do. Examples of human growth factors which are now being used in some cosmeceuticals include: transforming growth factor-beta (TGF-beta), which plays a role in tissue regeneration, fibroblast growth factor (FGF), involved in wound healing, keratinocyte growth factor (KGF) which stimulates the growth of cells in the surface layer of skin, and epidermal growth factor (EGF) which plays an important role in cell growth and proliferation.

Human growth factors applied topically have been used widely in the medical industry for treating wounds and have been shown to produce faster and more complete healing, and some research (mainly manufacturer backed) into the cosmetic use of human growth factors has shown that they can improve skin elasticity, uneven skin tone and thinning of the epidermis.

Skinmedica's TNS Recovery Complex®, a top five best selling cosmeceutical skincare brand in the USA for some time now, was one of the first to adopt the use of human growth factors and uses a patented ingredient called NouriCel® which is derived from bioengineered human skin, in this case an original donor baby foreskin.

This NouriCel® technology was originally developed by the manufacturers to treat burns and other wounds, before being developed for cosmetic skin rejuvenation. The composition of human growth factors used in the TNS Recovery Complex® includes TGF-Beta, KGF and vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), the latter of which stimulate new blood vessel formation.

As of last summer (2012), a new player emerged in the shape of ReGenica, manufactured by Histogen Inc. and marketed in the USA by Suneva Medical. **ReGenica** is a skincare system comprised of three products which have a Multipotent CCM Complex™, developed by the inventor of the key ingredient in SkinMedica's TNS, Dr. Gail K. Naughton. The company states that it is clinically proven to help reverse the signs of ageing and aid in scarless wound healing and they believe represents the next generation of growth factor skincare.

They note that their proprietary complex is created by growing fibroblasts, in a simulated embryonic environment, and then harvesting the naturally secreted proteins, growth factors and other synergistic bioproducts that are produced. ReGenica products contain a diverse mixture of active ingredients, including human growth factors such as Keratinocyte Growth Factor, soluble human ECM proteins such as collagen, and embryonic proteins which support the epidermal stem cells that renew skin throughout life.

In one study, ReGenica Day & Night Repair have been shown to reduce the appearance of fine lines and wrinkles, improve skin tone and generate smoother skin over a ten week period, and in two published studies, ReGenica Facial Rejuvenation Complex Post Procedure has been found to improve healing and more rapid re-epithelialization as early as three days post procedure.

Conclusion

So, should you all be throwing away your synthetic, cosmetic products and devices and getting set up to extract tissue and cells from your patients instead, so you can provide a complete DIY rejuvenation?

Well, the answer is clearly, not just yet. Techniques and technologies are improving and much research is ongoing (both in the medical arena as well as the cosmetic) to understand the exact mechanisms behind the application of regenerative medicine techniques to repair, replace, restore and regenerate human tissues and cells.

We're not there yet, so the combination of treatment options and products available to the aesthetic practitioner will be required for sometime to come to produce the natural and long lasting results demanded by the consumer of anti-ageing treatments.

However, there will be those who shun or fear the man-made options you have in your armament to date, so the attraction of regenerative medicine will grow as the science improves and the long term clinical data shows both safety and efficacy of some of these pioneering concepts.

A note of caution is always needed in any line of medicine, and just because these treatments revolve around using your own cells or other human cells to facilitate improvement, doesn't by default make them safe and nor should it make you complacent in their use.

A recent report in **Scientific America**, detailed the case of a woman who presented at the office of a cosmetic surgeon in California in 2009 complaining that she could not open her right eye without considerable pain and that every time she forced her eye open she heard a strange click, likened to a tiny castanet snapping shut. The surgeon, Allan Wu is said to have considered that the woman was making up stories but upon examination he could see that something was indeed wrong, he just wasn't quite sure what.

He operated on the woman's eye area which appeared swollen and with a drooping eyelid and removed small chunks of bone from her eyelid and the tissue surrounding her eye. The bone fragments were scratched but largely intact, so the tiny castanet was in fact bone on bone grinding sounds from the fragments as she opened and closed the eye.

A story to make you cringe indeed, but why had this happened? According to the report, three months prior the woman had received a 'face-lift' treatment using her own adult stem cells, harvested from abdominal liposuctioned fat. It is believed the doctor had extracted mesenchymal stem cells from the adipose tissue, which can turn into bone, cartilage or fat, amongst others. These cells were then reinjected into her face, particularly around the eye area.

It is thought this would not have been a problem as an individual treatment but the practitioner combined the stem cell application with calcium hydroxylapatite dermal filler, Radiesse™. This mineral encourages mesenchymal stem cells to turn into bone. The practitioner was apparently unaware of this and thus fragments of bone began to develop in the treated area, later to be removed by Dr. Wu.

We know that the human body, and the body of different patients can react in a variety of ways to the introduction of any foreign objects and substances, it is therefore always worth a practitioner bearing in mind the patient history when it comes to recent and even historical product applications and procedures in the same targeted treatment zone. The potential for undesirable reactions allied with the introduction of autologous and allogeneic therapies is something yet to be documented in the clinical literature, but no doubt more rare cases as highlighted above are as yet unknown.

Lorna Jackson
Lorna has been Editor of The Consulting Room™, the UK's largest aesthetic information website, for over nine years. She has become an industry commentator on a number of different areas related to the aesthetic industry, collating and evaluating statistics and writing feature articles, blogs, newsletters and reports for The Consulting Room™ and various consumer and trade publications, including *Aesthetic Medicine*, *Cosmetic News* and *Aesthetic Dentistry Today.*