DR DAVID SASSOON, PROFESSOR JÖNS HILBORN, AND **DR JONATHAN DANDO** INDICATE WHAT NEEDS TO BE DONE IN THE FIELD OF REGENERATIVE MEDICINE AND HOW THESE GOALS CAN BE ACHIEVED

2090…or 2020?

The doctor holds the vial up to the window and lightly shakes it by the lid. A fine cloud of desiccated dust fills the chamber; perfect. She has selected this vial as the material inside, based on a PEG-hyaluronic conjugate, provides a better environment for the tissue to be repaired. Other materials exist in her cabinet: fibrins in various formulations, silica, carbon nanoparticles, calcium and zinc based materials, all specifically designed for different tissues and effects and all very affordable (at only €5). The treatment in her hand is the most expensive.

After an injection of 1ml of saline containing epigenetic modifiers, myostatin inhibitors and antifibrotics into the vial to dissolve the material and a quick spin in the centrifuge, it is ready.

The 77-year-old patient outside – a builder with at least 15 years of working life left – had come in two weeks ago with mild chest pain, and immediate imaging at the clinical centre had revealed early onset acquired genetic cardiac muscle disease; detailed analysis indicated that it would be better to be safe than sorry and a combination approach would be more effective. The doctor could have opted for just the materials and factors, but the patient needed to have total functionality restored within 48 hours due to professional requirements.

This is why she submitted an online request to the patient's hospital that same day for them to pull his iPS (induced stem) cells, created 78 years earlier, out of the freezer, expand them and send them across for today's treatment.

Combining the liquid with the cells, the doctor walks into the next room, where one of her colleagues has prepped the patient with a local anesthetic ready for the key-hole application; the imaging agent used two weeks previously is still in the patient and functional, and is used by the doctor to guide the cell-material-factor combination direct to the location of damage. A little pressure on the plunger and the mix is delivered directly to the area to be repaired; pulling out the macroscopic device, the imaging agent is changing colour on the screen, indicating that the combination therapy is already starting its action. Two hours later, and following another check on the scan, she lets the patient know he has the all clear; he can go home.

The damaged tissue is repaired, and while it will take another day to be fully functional, she can see that the resident cells have been recruited into the material and are correctly integrating and aligning with the injected cells in the damaged space. There has been limited fibrotic infiltrate, clear blood vessel growth and innervation, while the inflammatory cells are busy cross-talking with the stem cells to figure out what is best to repair the tissue and restore function.

- **Total cost of treatment (labour, infrastructure, goods): €200;**
- **Days of work lost due to illness: 1.5 days;**
- **Duration of therapy effect: life span of patient.**

The doctor's day is full, in addition to the 77-year-old man who had iPS developed from his placenta at birth in 2013. Using similar approaches but with different combinations, she has an 85-year-old road cleaner whose diabetes has flared up again, a five-year-old infant who fell off their bike and whose Achilles tendon has torn completely through, and a 30-year-old postman who has the early onset of Parkinson's disease; she can successfully treat and send home all of these patients today.

In the department next door, her prescription nurse is spending the day eradicating cancer from his patients using the inter-body equivalent of a calamine lotion; he is basically providing anti-cancer patches, which contain targeted delivery vehicles which pass through the skin, scour the body and destroy all relevant cancer cells within three hours before passing out through the urine.

A snapshot of future medicine

The 'snapshot' indicated above is achievable but has to be placed in the context of the real world, in that all patient-focused therapies must be:

- **Cost-effective** (resolve direct and indirect costs);
- **Reimbursable** (it is affordable for customers; governments and HMOs);
- **Reproducible** (so it is worth reimbursing);
- **Broadly applicable** (a platform to be tailored and expanded);
- **Exportable** (it works for everyone, everywhere);
- **Generating a return on investment greater than 3%** (so it is worth it).

This 'must have' list to some extent represents the Holy Grail of all medical development, with the exception that this particular grail can be achieved. To be clear: what is being referred to above is an apothecary which contains, on one side, materials, in the middle, factors or drugs, and, on the other side, the patients' cells. They are clinically-approved products in their own right, but, more importantly, they have been approved to be used in any number of combinations based on the patients' need as determined and tailored by the doctor following diagnosis.

Projects such as Endostem and Biodesign are well on the way to developing the three major components that will permit this. Through collaborative funding, alignment of strategies, portfolio project management and integration of quality infrastructures, a foundation has been laid and a structure created. This structure permits innovative, insightful and quality academic and industrial research teams to work within a series of small collaborative projects which focus on project-specific and long-term strategic objectives. This is permissible in spite of the large geographic distance between the different teams involved.

As knowledge and advances within these collaborative structures is shared between the partners, the outcome is that the significant prior public investment in the laboratories and personnel is leveraged to reduce financial burden, enhanced by the cash injections which focus the translational development, the blueprint for the apothecary is established.

Global issue; globalised solutions

The increase in the ageing population globally is known, as are the burdens. Treating ageing *per se* isn't going to change anything; the focus has to be on keeping people functional; they must feel empowered and strengthened and the sensation of age related fragility replaced by a sense of well being linked to a motivation to continue actively contributing to the socio economy.

However, some things could be changed to accelerate the speed at which the goals are reached in order to maximise their impacts. Fundamentally, the healthcare need and market must be perceived as global, predisposing better support for mechanisms that permit the partnering of teams from across the globe to work together addressing the import and export of knowledge, innovation and development.

For global application, the outcomes of these developments, the therapies themselves, need to be supported by a global framework of Mutual Recognition Agreements (MRA) on the production of medical products. This would mean that products made in any country, if produced to the correct standard, can be applied and sold in any other country that has signed the MRA. At present, however, there are not many MRAs in place that deal with global markets, but having more would pave the way for better cost-effective exploitation of developed innovations. The right balance has to be struck between developing cost-effective therapeutics and maintaining a margin above the cost of capital so that it makes sense for all stakeholders.

Critically, this ties in with the necessity for an easier clinical translation process. While internal projects within Endostem and Biodesign attempt to increasingly address the quality of the decision making at earlier stages, so that those concepts which clearly will not be applicable are removed as early as possible to enable an enhanced focus on those that will, there also needs to be a re-evaluation of the trial process itself, specifically with regard to publicly developed therapeutics.

Streamlining and cost reduction at these later stages of development, matched with social innovation and the integration of all of society in understanding their own health management, will bring forward Regenerative Medicine 2090 by 70 years.

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