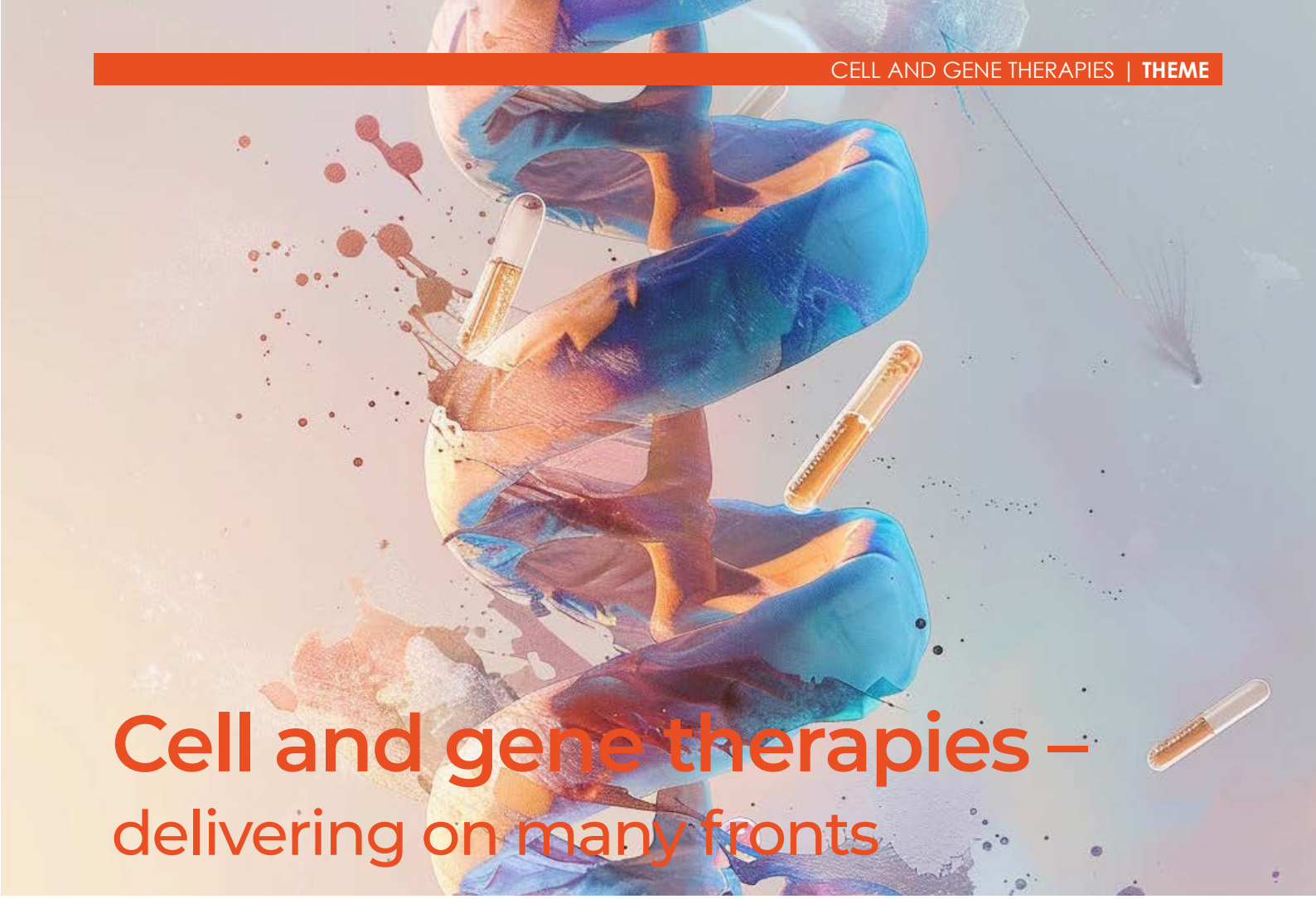

Cell and gene therapies – delivering on many fronts

There is a great deal of excitement in the fields of cell and gene therapy as the findings of painstaking research aimed at uncovering the cellular and molecular nature of human disease are now beginning to bear fruit. This is also true for the cutting-edge genetics research being done in South Africa, and could even lead to advanced therapies for certain cancers and HIV.

As a medical student, I recall being overwhelmed by the amount of information we were asked to internalise, even if only for long enough to get through the next exam. During my brief passage through clinical medicine, I was constantly in awe of the infinitely complex networks of cells, molecules and signalling pathways that were in operation to ensure the successful recovery of the patients under my care. Since then, during my time in biomedical research, I have been reminded daily of the miracle that is life, and the incredible beauty of seeing an organism that is structurally and functionally intact, given the number of things that could potentially go wrong. And I am not alone.

Driven by an insatiable curiosity to understand how things work and what happens when they do not, researchers in biomedicine have for many years been painstakingly identifying the cellular and molecular basis of disease, with the aim of one day being able to utilise this information to combat the very diseases they have been studying. These efforts are now bearing fruit.

Precision-targeting of diseases

Let us begin with the human genome, the blueprint that underlies structure and function in human and other organisms. Three billion base pairs of DNA (the proverbial As, Cs, Gs and Ts) are inherited from each of our parents. They contain 20,000 genes that code for those proteins that underpin biological structure and function. The remaining DNA (95% of the genome) contains regulatory and other sequences that ensure the co-ordinated integration of all of this information.

The change in a single base (nucleotide) in this ocean of information can cause aberrant structure and function, resulting in disease. One of the benefits of identifying the culprit with such exquisite precision is that it is now possible, through gene editing, to replace the offender with a nucleotide that is 'correct', resulting in a normalisation of structure and function. Alternatively, this technology can be used to re-awaken pathways that have become dormant as a consequence of normal development. CRISPR-Cas9, imported from the world of microbiology, is the tool that is used to effect

this change, and its use to treat human disease has progressed into clinical trials. One area of intense activity, highly relevant to the African continent, is blood disorders. These include sickle cell disease and thalassemia.

Cancer, and in particular haematological malignancies (blood cancers), are characterised by a notoriously poor survival rate, despite the use of powerful chemotherapeutic agents and radiotherapy. Following the identification of molecules that are expressed on the surface of the malignant cells and characterise these cancers, researchers have successfully developed therapies that are targeted at these molecules, and by combining these with the body's own immune functions, are able to specifically target and destroy the cancer cells. This has resulted in remarkable rates of cure, including complete remission with no detectable residual disease. The technical term is 'chimeric antigen receptor T-cells' (CAR T-cells). This approach has thus far worked well in blood cancers, but less well for solid tumours, although this is likely to change as the specific features of the latter are carefully laid bare for researchers to target.

Equally exciting is the application of these technologies outside the field of oncology, in particular in the area of autoimmune diseases such as systemic lupus erythematosus (lupus) and scleroderma. More recently, CAR T-cell technology has been applied successfully for the treatment of asthma. The possibilities are apparently endless; watch this space as we witness the very exciting evolution of modern medicine in real time!

South Africa joining the fight

From a South African perspective, application of these technologies for the treatment of disease is as relevant as it is elsewhere in the world, perhaps even more so given the high disease burden in our country. Equally important is the fact that in sub-Saharan Africa we harbour the greatest degree of genetic diversity on the planet, which means that genetic variants specific to our populations need to be catered for when designing advanced therapeutic technologies.

Why then has uptake been slow in our country? Some of the barriers include cost, lack of technical and human resources, and a grossly inadequate regulatory environment that is unable to accommodate the needs of this rapidly evolving technology.

With regard to cost, one needs to take a medium-to-long term view rather than focus on immediate expense. From a health economics perspective, by curing previously incurable diseases, and thereby reducing the high cost associated with their ongoing/lifelong management (and their impact on society), it is likely that the initial outlay will be less than the lifetime cost of managing these serious disorders. And of course there are the benefits to the patients, their families and society as a whole, which is why we undertook to work in this field in the first place.

In terms of our own work, the Institute for Cellular and Molecular Medicine (ICMM) at the University of Pretoria undertakes translational research aimed at addressing critical elements of the disease burden in South Africa. The ICMM promotes research that is multidisciplinary in nature, with strong links to national and international partners and collaborators. Specifically, we work in the fields of HIV (with an HIV 'cure' project underway), cancer (including CAR T-cells), a multi-faceted approach to broadening the donor base for transplantation, and the development of a 'universal donor cell', also for transplantation purposes. The ICMM is well positioned to make major contributions to the alleviation of the high disease burden in South Africa, and will also contribute to global efforts to reduce morbidity and mortality in previously incurable diseases, and the impact that they have on all facets of our lives.

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