



15 years of *Regenerative Medicine*



In focus: 15 years of *Regenerative Medicine*, the field & the journal

The last 15 years have seen dramatic developments in the field of regenerative medicine, as it has grown from its infancy to an established field poised to become the next pillar in a modern healthcare system. This period has also seen the journal *Regenerative Medicine* grow from its launch to become one of the leading journals serving the field. In this special feature, RegMedNet and *Regenerative Medicine* reflect on 15 years in the journal and the field, with expert interviews, a special edition of the Industry Update and more.

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Ask the experts: 15 years of Regenerative Medicine, the journal and the field

In this feature, we've asked three experts from different areas of regenerative medicine (and members of the Regenerative Medicine editorial board) to discuss the last 15 years of the field and share their predictions for the next 15. Read an excerpt from the feature below or [read the full article on RegMedNet](#)>>

How has the field of regenerative medicine evolved over the last 15 years?

Paul Knoepfler (University of California, Davis)

Focusing first on the positive, I see the field as far more mature now. By that, I mean that we have a much better understanding of not only stem cell biology, but also the challenges faced in getting safe and effective cellular medicine products through the approval process and to patients. We also have far more trials ongoing including some that look very promising.

15 years ago, there may have only been one or two unproven stem cell clinics in the US, but now there are likely around one thousand. This explosion of clinics has harmed the health of scores of patients and muddied the waters. As to the former, there are now concrete data on patients being hurt including via vision loss, infection from contaminated products (at least a dozen patients became septic in just one incident), and other ways. In

addition, I see vast economic harm to vulnerable patients and their families. In terms of the muddied waters, it is now much more difficult for patients to be confident in what is a traditional clinical trial versus a strictly for-profit venture by a clinic firm. Sadly, a few universities are also routinely marketing unproven regenerative products.

Bernard Siegel (Regenerative Medicine Foundation)

In 2005, policy and advocacy issues were largely focused on funding and support for embryonic stem cell research. There were societal issues – ethics questions and religious mores to be considered. Somatic cell nuclear transfer (aka nuclear transfer, aka therapeutic cloning) was a red-hot topic and socially conservative lawmakers around were stamp laws criminalizing ethical scientific research. These issues have receded somewhat, as the field has evolved. We now have induced pluripotent stem cell (iPSCs) to deliver pluripotent cells.

Glyn Stacey (International Stem Cell Banking Initiative)

Clearly, the discovery of iPSC reprogramming technology by Professor Yamanaka at Kyoto University (Japan) led a revolution in various aspects of research. Many thousands of labs around the world suddenly found themselves in a position to carry out reprogramming and generate stable pluripotent stem cell lines. This drove a rapid development in research experience and technology development in this area, which was significantly accelerated by experience in working with human embryonic stem cells, but would not have been so readily achievable with the then relatively limited access to human embryonic stem cell lines.

Large collections of these iPSC lines are now available through centralized stem cell banks. Quality-controlled stocks of large numbers of cell lines will do much to enhance the reproducibility in pluripotent stem cell-based research. International coordination on hPSCs has also been marked since the mid-2000s with now well-established activities, such as the European Commission-funded hPSCreg hPSC database and the International Stem Cell Initiative, which has published numerous key papers on well-standardized research to enable better understanding of hPSCs.

The International Stem Cell Banking Initiative, started in 2007, has also brought many of the world's expert hPSC resource centers together to draw consensus on a wide range of banking issues for these challenging cell types. These early initiatives have also supported other international networking activities, such as GAIT. Further significant

developments have also emerged such as the NIST genome editing consortium, the Standards Co-ordinating Body and significantly increased interest in standardization within regenerative medicine supported by both established organizations and newer actors.

In more recent years molecular approaches such as combined antibody receptor (CAR) expression on immune cells have emerged and gene editing has diversified and rapidly progressed to the early stages of clinical application. As witnessed with iPSC technology, the broad accessibility to a new and exciting technology, in this case CRISPR/Cas9, has led to a fantastically dynamic science and technology environment in the last 5-10 years. Finally, gene therapy, a technology which emerged in the 1990s, is now beginning to deliver an ever-growing portfolio of medicinal products.

What has been the biggest surprise in the field?

Paul Knoepfler (University of California, Davis)

I think iPSC technology took the field by surprise and shook up our assumptions of cell biology and differentiation in a positive way. iPSCs are an exciting technology for many reasons but I also see them as a force to make people think more creatively.

Bernard Siegel (Regenerative Medicine Foundation)

BS: Coming into the field as a lawyer, not a scientist or clinician, I was hoping, and wistfully believed, that stem cells would be in

wide use in 15 years. Of course, underestimation of the scientific, regulatory and funding challenges was widespread. My thinking is far more realistic and has evolved way beyond championing a single type of cell or technology. We now have a GIANT convergence of technologies in our discovery toolbox – CRISPR, advances in microscopy, nanotechnology, bioprinting and AI – all in the age of the Internet and instant global communication!

Glyn Stacey (International Stem Cell Banking Initiative)

The early and dramatic potential benefits realized from CAR-T immunotherapy has led to very rapid and significant investment in this area which has stimulated interest in new versions of CAR-based treatments, as well as an even broader range of unrelated cell-based therapies. This stimulus has thrown the spotlight on the potential of advanced cell therapies which could drive new discoveries and elevation of roadblocks in the delivery of regenerative medicine.

What are your hopes for the next 15 years in the field?

Paul Knoepfler (University of California, Davis)

I hope that we'll see 5-10 approved regenerative products that truly help patients in some revolutionary ways. We've come a long way and the scope of trials out there is impressive. Even if most don't work out, I think there are going to be some game changers that do.

Bernard Siegel (Regenerative Medicine Foundation)

That the use of cells for effective treatments and cures will be in the doctors' black bags as tools to alleviate human suffering for everyday and chronic medical conditions, cheap and available for all populations.

Glyn Stacey (International Stem Cell Banking Initiative)

I hope that the progress to licensed medicinal products seen for gene therapies will be consolidated for a broader range of applications and that a complementary portfolio of successful targets for long-term effective CAR-T cell therapy, including solid tumors, can be established. The huge challenges of delivering safe and effective regenerative medicines will hopefully be eased by the development of greater reproducibility and consistency supported by enhanced bioanalytics and automation in regenerative medicine manufacturing.

[Read the full article on RegMedNet>>](#)

Industry updates with Dusko Ilic: 2005–2020

Since 2006, Dusko Ilic has discussed the latest developments and news in regenerative medicine and stem cell research in Regenerative Medicine, and since 2019 has summarized his key takeaways each month exclusively for RegMedNet. In this special edition of his industry updates to celebrate 15 years of Regenerative Medicine, Dusko shares his standout moments and surprises from the last 15 years in the field, and looks into his crystal ball about what the next 15 may hold.

What happened in the industry that you were expecting?

The rise of mesenchymal stromal/stem cells (MSCs) and a growing list of their nearly magical properties took me by surprise. I believe in science and I always wanted to see hard proof supporting the claims. For years, there was rarely any; it was inevitable that the MSC hype would end and people would have to embrace the reality of what these cells can or cannot do. However, papers deciphering MSC mechanism of action started coming out. Understanding of how to control their immunomodulatory potential has established MSCs as an efficient therapy for acute inflammatory diseases, such as graft-versus-host-disease.

What happened that surprised you?

The arrival of chimeric antigen receptor (CAR)-T and NK cell-based therapies was something that I did not see coming. It could

be just ignorance, because I am not an immunologist and did not follow the field closely. However, even more surprising was how quickly big pharma has jumped on the bandwagon and taken over the field. With large injections of capital, in a few years the field has blossomed.

What have been your standout moments from the last 15 years?

For me, some standout moments in the last 15 years of cellular therapy are: the fall of Geron Corporation (CA, USA), the rise of human embryonic stem cell (hESC)-based therapy for macular degeneration of the retina and the first clinical trials with induced pluripotent stem cell (iPSC)-derived cells in Japan.

Geron Corporation, a Silicon Valley company, was a pioneer in development of hESC-based therapies. Geron filed a 21,000-page Investigational New Drug (IND) application with the FDA and, after a long struggle, finally got a green light to start the trial in spinal cord

injury. The first patient was treated at the Shepherd Center in Atlanta (USA) in October 2010. With all the hype, positive and negative, about the use of hESCs in regenerative medicine, the results of the trial were highly anticipated.

Even though the trial was about the safety, not efficiency, the public and investors expected that the treated patients would walk shortly after the treatment. Of course, this did not happen and Geron's stock dropped nearly 60% in nine months. In spite of the safety results fulfilling all expectations, they had to give up on their stem cell program. That was a shock for all of us working with hESCs and we became seriously worried that the field may not recover for many years.

Robert Lanza and Irina Klimanskaya changed that in the summer of 2011. Their hESC-derived retinal pigment epithelial (RPE) cells become the first hESC-based therapy that successfully demonstrated clinical benefits in clinical trials. Macular degeneration of the retina was a much better choice for pioneering a new treatment than spinal cord injury. Other companies followed and today, ten years on, we have more than 20 hESC-based clinical trials worldwide in diseases of the eye and adnexa.

Masayo Takahashi from the Riken Centre for Developmental Biology (Kobe, Japan) seized the opportunity and initiated the first-in-man study with iPSC-derived RPE cells. The indication was the same – macular degeneration of the retina. Today, there are about 20 ongoing iPSC-based clinical trials worldwide for more than 10 indications.

Looking into your regenerative medicine crystal ball, what does the next 15 years hold?

Predictions of future development are, in general, unrewarding. I would still dare to make one, which is relatively safe. Lack of ethical controversy has made iPSCs more appealing than hESCs for drug discovery and toxicology-related studies. In years to come, I believe iPSCs will also take over from hESCs in clinical applications. The results of current hESC-based clinical trials are setting a gold standard for future iPSC-based cellular therapy.

[Read the full article and find more editions of Dusko's Industry Updates on RegMedNet>>](#)

A brief history of Regenerative Medicine: top 10 articles from 15 years of the journal

Since the birth of Regenerative Medicine in 2005, the field has moved forward in leaps and bounds. From the use of mesenchymal stem cells for the treatment of neurodegenerative disease, to a unified theory of aging, we look back at some of the most popular content from the last 15 years, in no particular order, and look forward to what the future has in store for our much-loved journal and the field as a whole. Read an excerpt from the feature below or [read the full article on RegMedNet](#)>>

2007: A brief definition of regenerative medicine

As the field of regenerative medicine continues to develop and stretch into the domain of government and public opinion, its defining terms become broader and more lengthy. In efforts to provide clarity on the subject, the authors of this article address the matter and the origins and relationships that help to define the field.

[Read the article](#)>>

2009: Stem cell paracrine actions and tissue regeneration

Another noughties vintage, this review paper describes the potential beneficial effects of stem cells in light of their transient paracrine actions, with subsequent research directions including efforts to elucidate, augment and harness stem cell paracrine mechanisms for tissue regeneration. The authors conclude that learning to modulate and harness the paracrine actions of stem cell populations provides researchers with a myriad of

treatment options for traumatic injury and diseases limited by cell sourcing issues. It's certainly exciting to see how the field has advanced since.

[Read the article](#)>>

2015: The translation of cell-based therapies: clinical landscape and manufacturing challenges

The ever-increasing number of cell-based therapies in the development pipeline means this industry has the potential to provide significant health and wealth benefits throughout the world. With this increase in regenerative medicine innovation comes a need for a better definition of the manufacturing requirements for cell-based products. This study, published in 2015, assesses a total of 1342 cell-based clinical trials to provide an overview of the then state of cell therapy clinical development and identify gaps in their manufacturing requirements.

[Read the article](#)>>

[Read the full article on RegMedNet](#)>>

Meet the experts



Paul Knoepfler

Paul Knoepfler is a Professor at UC Davis School of Medicine (CA, USA) in Cell Biology and Human Anatomy. He's a stem cell and cancer researcher, but also conducts research and writes about ethics and policy issues. He has run The Niche blog for more than 10 years now and have also written three books.



Glyn Stacey

Glyn Stacey is Director for the International Stem Cell Banking Initiative based in the UK and, together with the ISCBI Board and Steering Group, organizes regular international meetings. Glyn also holds a position as a President's International Fellowship Investigator with the Institute of Zoology at the Chinese Academy of Sciences (IOZ-CAS; Beijing, China). Glyn is also the CEO of the biosciences consultancy SSCBio Ltd (UK), which provides advice and support internationally to a broad range of government institutes and private not-for-profit organizations.



Bernard Siegel

Bernard Siegel is executive director of the nonprofit Regenerative Medicine Foundation (FL, USA) and founder and chair of the World Stem Cell Summit global meeting. He serves on numerous boards and committees in our field. Presently and of most topical interest, he co-chairs the advisory board of the Alliance for Cell Therapy NOW (DC, USA), serve on the governing board of Californians for Stem Cell Research, Treatments and Cures (Prop 14) and several National Science Foundation (VA, USA)-related organizations.



Dusko Ilic

Dusko Ilic is a Senior Lecturer in stem cell science, coordinator of the cross-divisional postgraduate program in stem cells and regenerative medicine, and Head of the Induced Pluripotent Stem Cell Core Facility at King's College London (London, UK). He is also Head of the Assisted Conception Unit's Human Embryonic Laboratories at Guy's Hospital (London, UK).