



Drug

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Tomorrow's cures today: navigating drug discovery

Revolutionising osteoarthritis treatment

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Angry@Arthritis

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Tomorrow's cures today: navigating drug discovery

In the ever-evolving landscape of drug discovery, the latest issue of *Drug Target Review*. This issue signifies a substantial journey, during which esteemed experts and industry professionals explore future developments in the field. Within these pages, we feature articles on topics including artificial intelligence (AI), regenerative medicine and neuroscience.

We begin on page 6 where we explore brain cell interactions, guided by the expertise of Dr Olga Chechneva from Shriners Children's Northern California. We also discover on page 8 how neurons stimulate the brain's microglia, uncovering the mysteries of neurological function.

Next on page 12, Randolph Kerschbaumer, representing the OncoOne Foundation for the National Institutes of Health, reveals insights into the next wave of undruggable cancer targets.

Dr Jason Park, CEO of Empress Therapeutics, takes us on a journey to decode genetic programmes powered by AI. We also explore models for success in improving drug metabolism prediction, presented by Dr Peter Hunt of Optibrium.

On page 22, we examine the challenges and advancements in COVID-19 vaccine development with Alexandre Le Vert of Osivax. Further on page 24, we discuss why innovation is the key to unlocking a universal pneumococcal vaccine, as shared by Dr Marie O'Brien from ReNewVax. Dr Cristina Ureche from Hannover Medical School (MHH) walks us through the aseptic process of viral vector-based vaccines on page 26 and Dr Mark J Newman of GeoVax, Inc. illustrates the foundation for next-generation vaccines.

Turning our attention to page 32, Dr Emily Richardson from CN Bio takes organoids to the next level. On page 36, we uncover the pioneering advancements in muscle repair for various disorders, courtesy of Frank Gleeson from Satellos Therapeutics. Additionally, Steve O'Keefe of Angry@Arthritis and Dr Ivan Martin of the University of Basel lead the charge in revolutionising osteoarthritis treatment through innovative regenerative approaches. Following on page 42, Dr Brian Kaspar of Insmad Incorporated takes us on a journey from bench to bedside, addressing some of gene therapy's most pressing challenges. We also dive into promising preclinical data for drug-resistant epilepsy with Dr Cory Nicholas from Neurona Therapeutics.

Last but not least, hear the results of our brand new Drug Discovery Article Competition in association with ELRIG, celebrating excellence in the industry. The winning article is featured in the following pages and will be showcased at ELRIG 2023 next month..

Throughout this issue, you will find a tapestry of insights, discoveries and innovations that collectively pave the way for tomorrow's drug discovery. We invite you to explore, engage, and be inspired by the journey ahead.



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Regenerative Medicine

This In-depth Focus explores developments in the field of regenerative medicine and innovative therapies. Dr Cory Nicholas, Founder and CEO of Neurona Therapeutics, shares compelling insights into their promising preclinical data concerning NRTX-1001, a regenerative neural cell therapy designed to combat drug-resistant focal epilepsy, derived from human pluripotent stem cells. Steve O’Keeffe, the visionary behind Angry@Arthritis, and Dr Ivan Martin from the University of Basel engage in a conversation about the transformative potential of regenerative approaches in revolutionising the treatment of osteoarthritis, offering hope to those affected. Dr Brian Kaspar, Chief Scientific Officer at Insmmed Incorporated, discusses the challenges faced in the development of gene therapies today, shedding light on the evolving landscape of healthcare research and development, and how we can push the boundaries to address these challenges. Lastly, Frank Gleeson, Cofounder, CEO and Board Member of Satellos Therapeutics, dives deeper into the world of muscle repair, exploring advancements and possibilities in regenerative medicine.

Q&A

Revolutionising osteoarthritis treatment: hope and innovative regenerative approaches

Osteoarthritis (OA) afflicts hundreds of millions worldwide – but today, there is no disease modifying treatment, other than flawed joint replacements. In May of this year, the U.S. federal government launched Novel Innovations for Tissue Regeneration in Osteoarthritis (NITRO) – a moonshot to cure OA with regenerative solutions in five years.

THIS ARTICLE focuses on the latest in Osteoarthritis treatment with Dr Ivan Martin University of Basel innovative Nasal chondrocyte Tissue Engineered Cartilage (N-TEC) programme, the most promising disease modifying regenerative treatment for osteoarthritis that is in clinical trials in multiple joints in the body. The University of Basel harvests nasal cartilage and cultivates it to create autologous cartilage implants that are surgically transplanted to restore joints compromised by OA. Dr Ivan Martin, OA cure innovator and Chair of the Department of Biomedicine at the University of Basel in Switzerland and Steve O’Keeffe, founder of Angry@Arthritis, an OA patient advocate nonprofit, chime in on the promise of new regenerative treatments to cure OA.

How does regenerative medicine offer a promising solution for the millions of people worldwide suffering from osteoarthritis? What makes it stand out among other treatment approaches?

IVAN: Current treatment approaches for osteoarthritis are not good enough. They are either palliative, to temporarily reduce pain and improve mobility; or,

at the end stage of the disease, joint replacement with a prosthetic implant. Regenerative medicine targets a disease modification strategy, namely the possibility to restore the structure and function of the native cartilage, rather than replacing it with synthetic materials.

What role does regenerative medicine play in the process of cartilage regeneration? Can you explain the potential benefits of using regenerative techniques compared to traditional treatment methods?

IVAN: Regenerating cartilage offers greater joint function, durability, and quality of life for the patient. A considerable percentage of patients who undergo knee replacements are not fully satisfied with the outcomes. For all patients, knee replacements limit function – high-impact activities such as running and jumping are discouraged. Further, prosthetic joints need to be replaced in 10 to 25 years. This makes joint replacements a poor fit for all patients, especially for younger, active individuals, with a long expected lifetime. Regenerative procedures for osteoarthritic cartilage could be a game changer in this landscape, in order either to avoid a

prosthetic device all together or at least to delay joint replacements.

As of the present time, how advanced is the science of regenerative medicine for osteoarthritis treatment? Are there any notable breakthroughs or successful pre-clinical studies?

IVAN: Currently, there is no approved regenerative treatment for osteoarthritis – all proposed procedures are in pre-clinical or clinical trials. That said, the Nasal Chondrocyte-based Tissue Engineered Cartilage or N-TEC procedure that we have developed at the University of Basel offers an innovative and highly promising new approach to treat OA in multiple joints in the body. N-TEC harvests cartilage from the nose and grows out new cartilage patches to repair damage in the joints. N-TEC takes regenerative medicine in cartilage repair from lab concept to real clinical success in humans. Leading an international clinical trial with five centers in Europe, our team at Basel has successfully treated more than 100 patients for focal lesions – 2 to 8 cm² – in the knee since 2012, and those patients have already returned to robust sporting activities. We expanded those trials

beyond focal lesions five years ago and have treated two patients with advanced knee OA. Moving beyond those trials, we are now conducting clinical trials focused on patella-femoral OA in the knee, as well as OA in the ankle and shoulder – and we plan to launch a trial for elbow OA next year.

In what ways is regenerative medicine contributing to a better understanding of the mechanisms behind cartilage regeneration? How does this understanding translate into improved therapies?

IVAN: Researchers in our field have experimented a lot with stem cell injections as well as other injections of cartilage growth factors as well as agents to reduce inflammation – and even early work on senolytic treatments to remove aging cells from the joint. Regrettably, none of these approaches has proven successful in producing repeatable positive results required to get official approvals as a disease modifying OA treatment. We have also learned that OA is not simply about cartilage loss, it can be a disease of the whole joint. N-TEC is different, in that it replaces the cartilage and at the same time, the attributes of the nasal-derived cartilage patches possess anti-inflammatory characteristics that enhance their ability to persist and thrive in the joint.

OA is not one disease – it manifests variously in different patient populations, or phenotypes. We will need multiple OA treatments to address different patient populations – and we will likely need to take a combinant approach to care for some patients, bringing together multiple therapies (cartilage replacement, inflammation suppression, etc.) to deliver results for all patients.

Some therapies claim to be regenerative but have not yet demonstrated consistent success in restoring hyaline cartilage. What specific research efforts are underway to enhance the efficacy of regenerative treatments for osteoarthritis?

IVAN: There are many different OA regenerative approaches currently in clinical trials – and patients can see

them as well as sign up to participate in clinical trials via the new Angry@Arthritis OA Fix – <https://www.angryarthritis.org/oa-fix-trials-in-the-mix/>. We are very excited about the progress we are making with N-TEC. Considering the path forward, two thoughts. First, we need to recognise that OA is not a single disease – and that it is manifest in different patient populations in different ways. As such, we need better definition of the subcategories or phenotypes of patients and identification of associated biomarkers. Ultimately, we will look to take a precision medicine approach, prescribing multiple forms of treatment to specific patient populations based on their biomarkers. Second, as we move out on this biomarker-driven approach, we need to twin regenerative therapies with treatments to address mechanical factors (eg, leg axis correction, joint instability, obesity), inflammation (eg, with additional drugs) and/or enabling post-treatment restoration of proper mechanical loading of the joint (eg, through personalised rehabilitation and physiotherapy).

Apart from cartilage repair, how else can regenerative medicine contribute to osteoarthritis management and prevention? Are there any potential long-term implications for patients and the healthcare system?

IVAN: As we look at regenerative interventions to restore joint function and replace expensive, flawed, and short-term joint replacements, we also need to take a proactive approach to stop joint degeneration before it even develops into OA. The cost burden of joint replacements on our collective quality of life as well as our economies is enormous. We need to fund innovative new OA treatment options, explore the science behind the disease, and deliver better, more durable joint therapy solutions. It's time to break the failing status quo in OA. Through these investments, we will deliver not just better treatment options, but also less expensive and less invasive procedures. We have a lot of promising science that has already crossed from the lab into the clinic. I applaud the researchers and clinicians making a difference on the frontier of the war on OA. I also applaud patient groups like Angry@Arthritis who are engaging with the healthcare system

and government leaders to push for new, improved therapies for the world's OA problem. It's time to fund new innovative OA cures.

Steve, as someone who personally experiences arthritis, how do you view the potential of regenerative medicine in providing solutions for millions of people worldwide with osteoarthritis? What excites you the most about regenerative therapies?

STEVE: Every OA sufferer is cheering for new regenerative therapies – specifically, ones that work. There are many pirate doctors selling stem cell “magic cures” in the Cayman Islands – better for doctors' incomes than patient outcomes.

Treatments like N-TEC fill OA patients with hope – we're thrilled to see these new, next-generation therapies that offer light for the millions of us trapped in the dismal OA dungeon. I can't talk about what excites me most, without name dropping the US government Novel Innovations for Tissue Regeneration in Osteoarthritis (NITRO) OA cure moonshot programme – patients need to pay attention and support this critical OA regenerative initiative. NITRO calls for three regenerative cures for OA – injections to regrow bone, injections to regrow cartilage (in one and multiple joints), and new, organic, bioresorbable joint replacements (that will mark the end of today's flawed synthetic joint replacements).

Could you share your thoughts on how regenerative medicine might be a game-changer in the treatment of osteoarthritis compared to conventional approaches? What benefits do you believe it can offer to patients?

STEVE: The opioid crisis is fuelled by chronic pain and OA is a significant factor in propelling that pain. Regrettably, the healthcare industry's attitude to OA is benign neglect.

The only “treatments” today for OA are NSAIDs for pain, physical therapy and weight loss – and then joint replacements when OA becomes advanced. Weight loss is not a solution for people that are not overweight. It is not a solution for OA in non-weight-bearing joints – hands, shoulders, elbows, etc. »

We need new innovative pain management and joint regeneration treatments to break the physical and mental OA downward spiral that's damaging the lives of hundreds of millions of people around the globe and wreaking havoc on our economies. While OA is not lethal, it makes people sedentary and that fuels heart disease, diabetes and other lethal comorbidities. In short, new regenerative OA treatments promise to give patients their lives back and unlock massive dividends in global productivity while slashing the world's healthcare bills.

Through your organisation, Angry@Arthritis, you advocate for advancements in arthritis research and treatments. How do you see regenerative medicine fitting into your vision for improving the lives of those affected by arthritis?

STEVE: In short, regenerative approaches are clearly the answer to liberating people from the OA dungeon. Pain management is a must. We also need to regenerate these joints so that people can go back to an active, healthy lifestyle.

I will point out the early successes at the University of Basel. Also, to the US government NITRO programme – which is focusing on three regenerative approaches to cure OA in five years. Hundreds of millions around the world cannot wait to see the innovative new therapies you deliver.

The launch of the first-ever clinical trial locator, the OA Fix, is a significant development. How do you think this tool can help individuals with arthritis explore regenerative medicine options and access potential clinical trials?

STEVE: Thank you. Yes, the OA Fix empowers patients with the first visibility into emerging innovative OA regenerative treatments. Plus, the ability to sign up for clinical trials. For folks in the OA dungeon, regular healthcare gives you palliative options – and you are left alone with google desperately searching for options and trying to make sense of academic papers. That's just not good enough – you can feel like your life is over.

Angry@Arthritis wants to give patients a ray of hope and to help guide the

OA developer investment community to recognise the promising treatments that need funding to advance the state of the cure. What treatments are in the pipeline for approval? What joints do they address? What kind of procedure – injection or surgery? We want to make it simple for normal people to navigate the current state of the science – we developed the OA Fix as a lifebelt for folks shipwrecked in the OA sea.

This is a very exciting time considering the breakthroughs at the University of Basel and the US federal government's launch of the NITRO OA cure moonshot. You will see that the University of Basel N-TEC is the OA Fix innovation and clinical leader.

As both a patient and an advocate, what role do you think patient involvement and feedback play in the development and adoption of regenerative medicine therapies for osteoarthritis?

STEVE: We patients are the most powerful force in the battle to cure OA. We need to empower patients with information on new promising regenerative treatments so that they realise that a cure is not impossible. We also need to get smarter about questionable promises and dodgy treatments – we're vulnerable and we need better protection.

We patients need to get familiar with the NITRO programme – and we need to talk with politicians about helping fund cures for this terrible disease that afflicts hundreds of millions worldwide. And, yes, patients that have the means can also get involved directly in cure hunting by helping to fund promising new OA research and clinical trials.

With regenerative medicine being a relatively new field, how do you plan to support and promote its research and implementation through Angry@Arthritis? Are there any specific initiatives or collaborations in the regenerative medicine space that you are excited about?

STEVE: Yes, we're excited about all of them. We would point specifically to the work at the University of Basel N-TEC and at Cytex Ortho – <https://cytexortho.com/>.

Today, these seem to be the most promising. The OA Fix provides the first easy-to-navigate chart that shows patients what innovative, new treatments are out there and how to sign up for those clinical trials.

Angry@Arthritis hosts a podcast that allows regular patients to hear directly from the leading research and clinical experts on emerging OA treatments. We're also working actively with the NITRO programme, with the US Department of Defense, and policy leaders in the US Government to advocate for increased funding for OA research – and transparency into the outcomes of that research.

Last, but certainly not least, Angry@Arthritis provides a vehicle for people to get into the fight on OA – you can donate to directly fund new OA research and clinical trials. www.angryarthritis.org.



Steve O'Keeffe

A focused osteoarthritis cure hunter, Steve O'Keeffe founded Angry@Arthritis to provide a patient's guide to OA, offering consumer's direct access to the leading science and treatments focused on curing OA.

Angry@Arthritis hosts a podcast with leading research and clinical OA experts and publishes the OA Fix the first map of promising OA treatments and clinical trial locator – <https://www.angryarthritis.org/oa-fix-trials-in-the-mix/>



Professor Ivan Martin, PhD

Dr Ivan Martin studied Biomedical Engineering at the University of Basel where he obtained his PhD in 1996. Between 1996 and 1999, he was a postdoctoral associate at Harvard/MIT. He joined

the Department of Biomedicine (DBM) at the University Hospital of Basel in 1999 as leader of the Tissue Engineering Research Group, in close coordination with the surgical units. In 2007, he was appointed Professor for Tissue Engineering at the University of Basel and from 2021 he is Director of the DBM. From 2004 to 2009, he was the first president of the European section of the Tissue Engineering Regenerative Medicine International Society (TERMIS), and later Chair of the TERMIS Strategic Alliance Committee. In 2018, he was elected as member of the Swiss Academy of Medical Sciences. He is currently Chair of the 'Mesenchymal Stromal Cell Committee' and member of the 'Orthopaedics and Musculoskeletal Committee' of the International Society for Cellular and Gene Therapy (ISCT). He is part of the editorial boards of six international journals.