

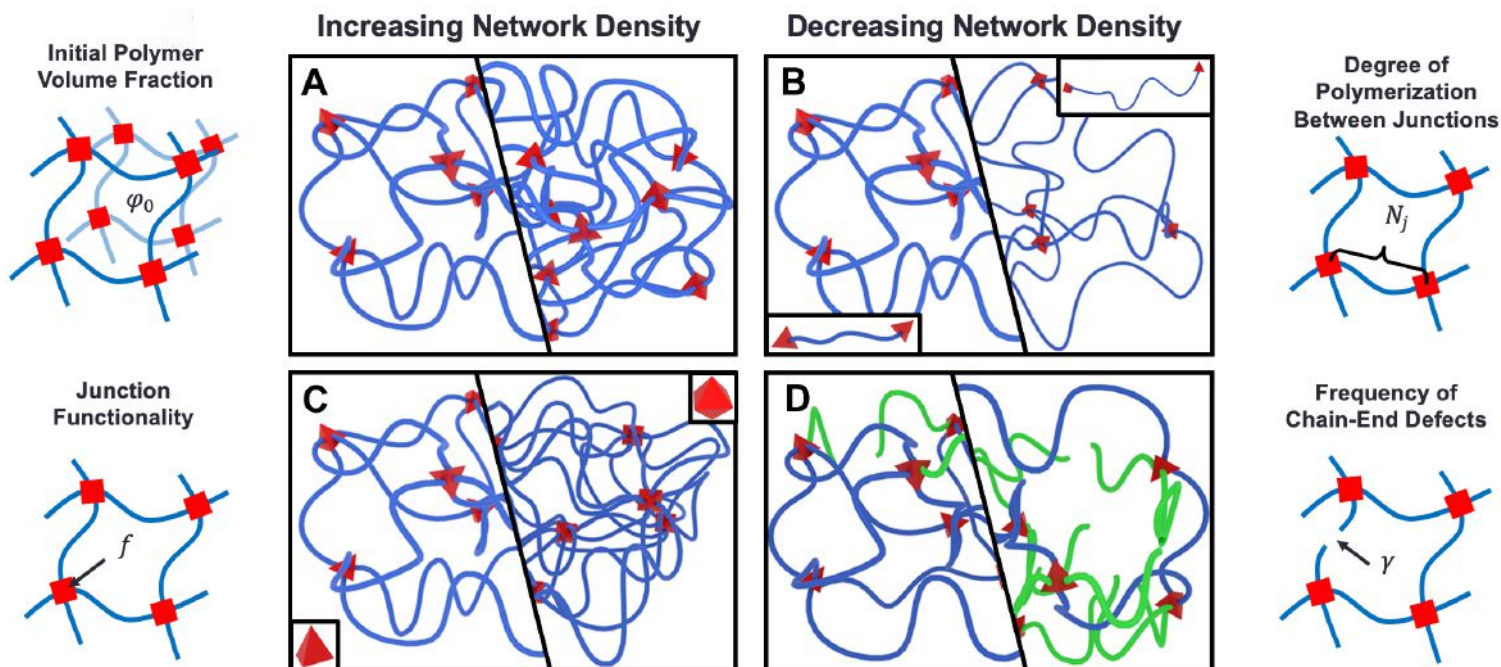
BIOMATERIALS FORUM

OFFICIAL NEWSLETTER OF THE SOCIETY FOR BIOMATERIALS



FOURTH QUARTER 2022 • VOLUME 44, ISSUE 4

Hydrogel Structural Parameters



ALSO INSIDE

FIFTY YEARS AGO BIOMEDICAL HYDROGELS WERE VERY UNUSUAL;
ALMOST USELESS MATERIALS

BIOMATERIALS FORUM!

The official news magazine of the **SOCIETY FOR BIOMATERIALS** • Volume 44, Issue 2

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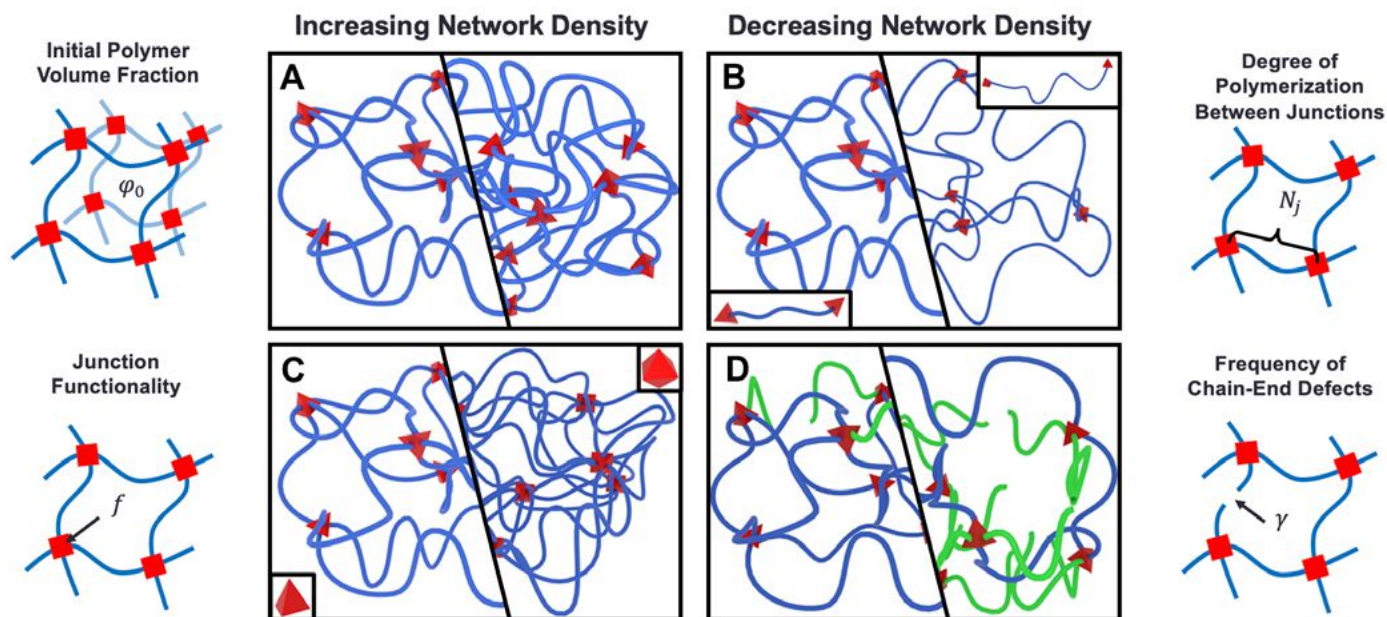
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Hydrogel Structural Parameters



ON THE COVER

Representation of the complex structure of hydrogels and networks. Four structural parameters control hydrogel (swollen polymer networks) density and can predict swelling, stiffness, and solute transport properties (Figure by Nathan Richbourg, UT Austin, PhD '2002 and Nicholas Peppas).

From the Editor

By Roger Narayan, *Biomaterials Forum Executive Editor*



I am glad to share this fourth quarter issue of *Biomaterials Forum*. This issue features a brief discussion of the emergence of hydrogels as an important class of biomaterials by Nicholas A. Peppas, ScD. The issue also includes a letter from Elizabeth Cosgriff-Hernandez regarding new initiatives to support trainees and industry members as well as an update on the upcoming 2023 Annual Meeting. Stephanie K. Seidlits, the Society's Member-at-Large, reviews recent achievements by Rena Bizios, Joachim Kohn, Cato T. Laurencin, Chad Mirkin and emerging leaders of our field. Gopinath Mani describes efforts to commercialize biomaterials research by BIOCORP, Novian Health, Hemosonics LLC, NanoVibronix Inc. and other companies. Carl Simon, our Government News Editor, considers the innovative use of a human-on-a-chip model in an investigational new drug (IND) application to the U.S. Food & Drug Administration, the implantation of 3D-printed tissue

containing living cells, which was developed by 3DBio Therapeutics, and the use of induced pluripotent stem cells (iPSCs) for patient treatment in the United States.

I am glad for the contributions from members, volunteer leadership, and staff to prepare this issue. I hope that this issue provides you and your team with timely information about our fellow members and recent advances in the field. Please do not hesitate to reach out to me at roger_narayan@ncsu.edu if you are interested in sharing an article for an upcoming issue of the *Forum*.

Yours truly,
Roger Narayan

CALL FOR COVER ART

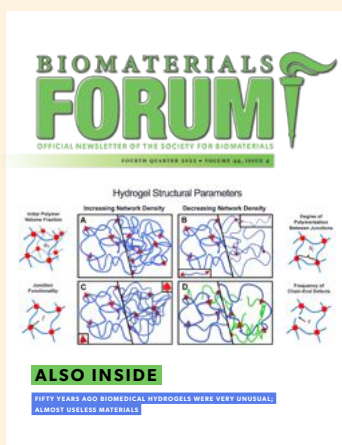
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From the President

By Elizabeth Cosgriff-Hernandez, SFB President



Dear friends and colleagues,

As 2022 comes to an end, I hope this message finds you well and you were able to celebrate the holiday season with family and friends.

This has been an exciting year for SFB as we continue to focus on building a stronger and more inclusive society. The Council met in November to continue our strategic planning to increase the value added for our members while maintaining fiscal responsibility for the long-term viability of our society. Please feel free to reach out if you have suggestions for activities or action for the Board and Council — we would love to hear from you!

We are excited for the upcoming Annual Meeting in beautiful San Diego on April 19-22, 2023 — “Riding the Translational Waves to the Future!” A big shout out to the Program Committee and all of our abstract reviewers for their hard work this fall. The conference will provide many opportunities for networking and community building for all members — make sure that you take full advantage of everything that SFB offers. In addition to outstanding scientific and technical sessions, professional development and networking opportunities are being developed to increase value to our members. We are especially targeting initiatives to increase the opportunities for our trainees and value to our industry members. Thanks to the sponsorship from the Royal Society for Chemistry, we will again be hosting the Three Minute Thesis and Postdoctoral Research Award competitions. We are also offering a brand new Industry Rising Star Award this year due to the generous sponsorship of Evonik. Be sure to submit your application when these competitions open! There are still a myriad of sponsorship opportunities that can be found on our meeting website. As part of our contract with the hotel, SFB conference attendees are responsible for covering a minimum number of nights, so please consider staying there so we avoid any financial penalties. You can keep up to date on meeting information, register and book your room at 2023.biomaterials.org

The Awards, Ceremonies, and Nominations Committee was hard at work this fall to select awardees and officer nominees. Be sure to vote for your new SFB officer positions this spring! Awards recognizing the exceptional scientific, professional and service contributions of our members at all professional stages, including the new Diversity Award, will be recognized at the Annual Meeting in San Diego. We continued to improve the transparency of the award and nomination process with descriptions of rubrics made available at biomaterials.org/awards.

SFB sponsored a Student Poster Contest + Rapid Fire symposium at the 2022 Materials Science & Technology Technical Meeting and Exhibition October 9-12 in Pittsburgh. I would like to congratulate this year’s student awardees: Sierra Kucko, Durva Naik, Emily Montgomery, Lan Nguyen. I would also like to extend special thanks to the volunteers on the SFB/MS&T Program Subcommittee: Roger Narayan (Chair), Guillermo Ameer, Danielle Benoit, Jeff Capadona, Thomas Dziubla, Jordon Gilmore, Bob Hastings, Jessica Amber Jennings, Lynne Jones, SuPing Lyu, Chris Siedlecki and Carl Simon. We plan to continue our partnership with MS&T next year and if you would like to be involved in organizing this joint symposium, please reach out to Dan Lemyre at dlemyre@biomaterials.org.

Finally, I wanted to again bring your attention to the Call for Symposium and Workshops for the 12th World Biomaterials Congress (WBC), which will be held in Daegu, South Korea, May 26-31, 2024. This is a great opportunity for SFB members to be involved in WBC programming. More information is available at wbc2024.com/

Thank you for your devotion and contributions to the Society For Biomaterials! I invite you all to continue your involvement with the society (including renewing your membership) to enhance the impact of our work improving healthcare through the use of biomaterials. Please share your ideas and suggestions with me directly at cosgriff.hernandez@utexas.edu.

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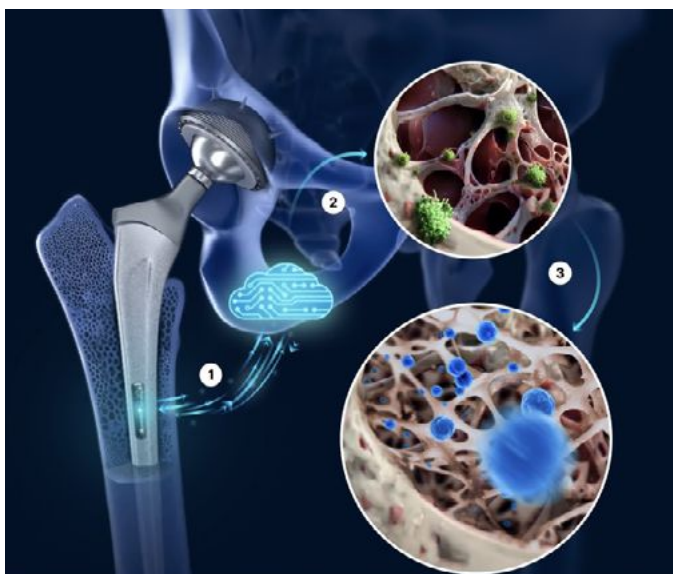
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Member News

By Stephanie K. Seidlits, PhD, Member-at-Large



Nurreddin Ashammakhi, Michigan State University, and team including first author **Mladen Veletić, Norwegian University of Science and Technology**, recently published a review article in *Chemical Reviews* discussing the future of sensor-integrating implants that can detect changes in their microenvironment. These implants will also be able to communicate data to enable remote management, and ultimately will be developed so they can be self-healing, self-correcting. The full article, titled "Implants with Sensing Capabilities," can be found [here](#).



Kaivalya Deo, Texas A&M University, a PhD candidate in the department of Biomedical Engineering, has received the 2022 Association of Former Students Distinguished Graduate Student Award for Excellence in Doctoral Research. Kaivalya is advised by Dr. Akhilesh

Gaharwar. His research focused on developing advanced bioinks for conceiving physiologically relevant 3D printed tissue models to evaluate therapeutic interventions.



Michael Gower, an Assistant Professor in Chemical Engineering at the **University of South Carolina**, was recently awarded an NSF CAREER grant to investigate macrophage-adipocyte interactions with biomaterials and advance treatment of obesity-related disease.

More details can be found [here](#).



Daniel Harrington, University of Texas Health Science Center at Houston and his team BIO have recently completed a scientific paper, accepted for publication in *Advanced Healthcare Materials*, demonstrating the co-culture of prostate cancer tumors with associated stroma and endothelium in 3D hyaluronic acid-based hydrogels, on MIMETAS' perfusable microfluidic OrganoPlate®. This work was funded by a NIH NCI SBIR contract to expand available platforms for studying health disparities in cancer, and leverages the rare bank of prostate cancer specimens from racially diverse individuals maintained at the MD Anderson Cancer Center. The manuscript offers a first glimpse at automated drug screening potential for a broader range of specimens in an advanced, biomimetic platform. The research was conducted in collaboration with both academic and industry partners at UTHealth Houston, Rice University, MD Anderson Cancer Center, and ESI BIO, MIMETAS US.

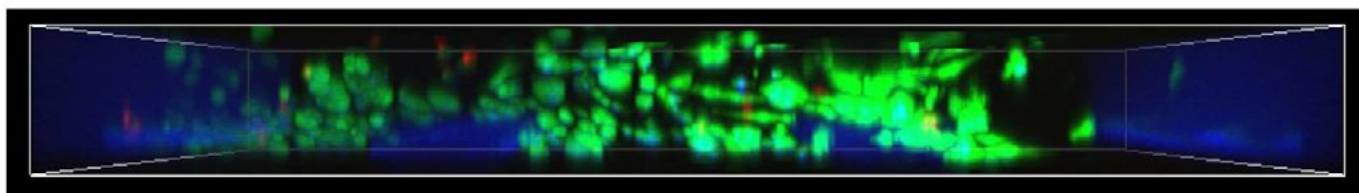
Cross-sectional reconstruction of cancer-stroma co-cultures on a perfusable microfluidic platform. Shown are human prostate cancer clusters in 3D hyaluronan-based hydrogel (left), bone marrow-derived stromal fibroblasts in peptide-customized hydrogel (center), and an adjacent open lane for continual media perfusion (right). Channel height is ~140 μm. Cells are stained with live/dead viability reagents, showing live cells in green, dying cells in red and nuclei in blue.

Mahdieh Heydarigoojani, University of Ottawa, is a PhD Candidate in Biomedical Engineering who recently gave a talk on her research at the Muskuloskeletal Symposium in Ottawa, CA.

Cancer Lane
(MDACC PCa-2b clusters)

Stromal Fibroblast Lane
(HS27a bone marrow cells)

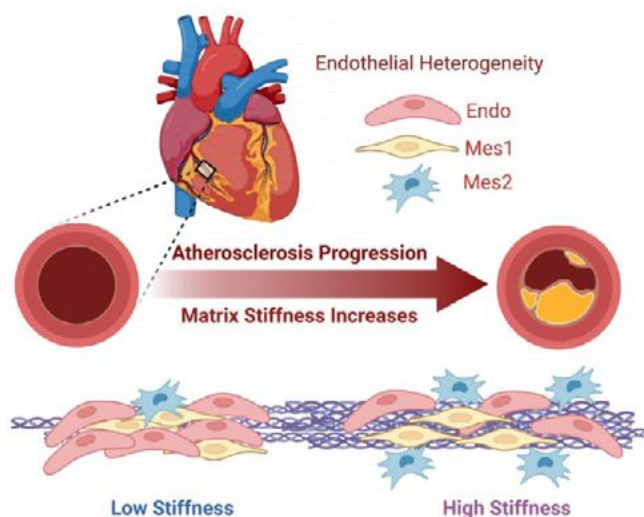
Media Perfusion
Lane



Member News (Continued)



Ngan F. Huang, an Associate Professor of Cardiothoracic Surgery at **Stanford University** led a study recently published in *Advanced Functional Materials*. Using single cell RNA Sequencing, the team showed the fundamental underpinnings by which substrate stiffness modulates endothelial-to-mesenchymal transition and the heterogeneity associated with the process.



Graphical abstract illustrates how the stiffness of the vascular environment modulates endothelial-to-mesenchymal transition in the setting of atherosclerosis



Christopher Jewell, the MPower Professor and Minta Martin Professor in the Fischell Department of Bioengineering at the **University of Maryland**, and his team recently published two new immune engineering papers on therapeutic vaccination, one in *Advanced Science* and one in *Nature Communication*. The first uses self-assembly of immune signals for combinatorial adjuvant design to create synergistic responses during cancer vaccination (J. M. Gammon, S. T. Carey, V. Saxena, H. B. Eppler, S. J. Tsai, C. Paluskiewicz, Y. Xiong, L. Li, L. H. Tostanoski, E. A. Gosselin, X. Zeng, J. S. Bromberg, and C. M. Jewell. Engineering the lymph node environment to promote durable antigen-specific tolerance in type 1 diabetes and allogeneic islet transplantation, *Nature Communications* 2022, in press). The latter reveals potent antigen specific tolerance with a single biomaterial depot treatment during type 1 diabetes and transplantation (M. L. Bookstaver*, Q. Zeng*, R. S. Oakes, S. M. Kapnick, V. Saxena, C. Edwards, N. Venkataraman, S. K. Black, X. Zeng, E. Froimchuk, T. Gebhardt, J. S. Bromberg, and C. M. Jewell. Self-assembly of immune signals to program innate immunity through rational adjuvant design, *Advanced Science* 2022, 2202393. doi: 10.1002/adv.202202393). These reports

contribute new insight to translation of safe and selective immunotherapies.



Astha Khanna, Graver Technologies, LLC, recently published a review article, in collaboration with Assoc. Prof. Ngan F. Huang at Stanford University, titled: "Engineering Spatiotemporal Control in Vascularized Tissues" in the journal *Bioengineering* (doi: 10.3390/bioengineering9100555). This publication highlights spatiotemporal engineering approaches to promote vascular networks in tissues and organs.



Joachim Kohn, President of the **International Union of Societies for Biomaterials Science and Engineering** and Distinguished Professor Emeritus at **Rutgers University**, was recognized by two prestigious international awards. First, in September 2022, he received the International Award from the European Society for Biomaterials for "having made major contributions to the field of biomaterials." Then, in November 2022, he received the Contribution Award of the Japanese Society for Biomaterials for "many years of work in the biomaterials field and his contributions to the global biomaterials community." Joachim Kohn has previously served on the Board of SfB and was the Treasurer when SfB hosted the World Biomaterials Congress in Hawaii in 2000.



Katharina Maisel, an Assistant Professor in the Fischell Department of Bioengineering at the **University of Maryland**, and her team recently published a research article titled "Multiple particle tracking (MPT) using PEGylated nanoparticles reveals heterogeneity within murine lymph nodes and between lymph nodes at different locations" with authors Ann Ramirez, Brooke Merwitz, Hannah Lee, Erik Vaughan, and Katharina Maisel in *Biomaterials Science*. In this work, Maisel and her team found that dense coatings with polyethylene allow nanoparticles to diffuse within the lymph node extracellular spaces, revealing pore sizes range from 500 nm – 1.5 μm , contrary to previous literature that predicted pores to be in the range of 10 – 20 μm . In addition, they found no significant difference in interstitial spacing between T and B cell zones, and a slight decrease in nanoparticle diffusion in interstitial tissue of mesentery lymph nodes compared to skin draining lymph nodes. This work shows that nanoparticles with the right surface chemistry can be used to characterize tissue interstitium, particularly immune tissues like the lymph nodes, which could shed new light on tissue biomechanical properties that are known to affect cell behavior.

Member News (Continued)



Amir Miri, Assistant Professor, and **Elvan Dogan**, PhD Student, in the Department of Biomedical Engineering at the **New Jersey Institute of Technology**, recently published a manuscript titled "A Novel Education Module to Teach 3D Printed Microfluidic Devices for Minority and College Students in Engineering."



Nashaita Patrawalla, a PhD candidate in the Department of Biomedical Engineering at **Florida Institute of Technology**, authored four recently published scientific manuscripts with the lab of **Vipul Kishore**: 1) Patrawalla, et al. "A Comparative Study of Bone Bioactivity and Osteogenic Potential of Different Bioceramics in Methacrylated Collagen Hydrogels", *J Biomed Mater Res A*, 2022, doi: 10.1002/jbm.a.37452. 2) Ali, et al. "Species-Based Differences in Mechanical Properties, Cytocompatibility, and Printability of Methacrylated Collagen Hydrogels", *Biomacromol*, 2022, doi: 10.1021/acs.biomac.2c00985. 3) Kajave, et al. "Design-Build-Validate Strategy to 3D Print Bioglass Gradients for Anterior Cruciate Ligament Enthesis Reconstruction" *Tissue Eng Part C Methods*, 2022, doi: 10.1089/ten.TEC.2022.0035. 4) Shokrollahi, et al. "Finite Element-Based Machine Learning Model for Predicting the Mechanical Properties of Composite Hydrogels" *Appl Sci*, 2022, doi: 10.3390/app122110835. In addition, Patrawalla has received several recent awards, including 1) First Place, ERAU Launch your Venture Business Contest 2022, 2) Outstanding Student of the Year 2022, Florida Tech, 3) First Place, BMES Medtronic Design Challenge, 4) Top 5 ranking in 2021 Impact Ventures Contest, 5) Residence Life at Florida Tech, 5 years of Service Award, and 6) Residence Life at Florida Tech, "Moving Mountains" Award for Succeeding While Overcoming Challenges.



Michael F. Wolf, **Medtronic**, was this year's recipient of the notable Excellence in Biomaterials Science Award given out by the Surfaces in Biomaterials Foundation (SiBF) at the 2022 BioInterface annual meeting. Mike joins a highly distinguished list of award recipients since SiBF started 31 years ago.



Silviya Zustiak, Associate Professor in the Department of Biomedical Engineering at **Saint Louis University**, and her team recently have three new scientific papers accepted and in press: 1) #M. Khachani, #S, Stealey, #E. Dharmesh, M. S. Kader, S. Buckner, P. Jelliss,

*S. P. Zustiak, "Silicate Clay-Hydrogel Nanoscale Composites for

Sustained Delivery of Small Molecules," *ACS Applied Nano Materials*, 2022, in press. 2) #A. Clancy, D. Chen, #J. Bruns, #J. Nadella, *A. Timperman, *S. P. Zustiak, "Hydrogel-based microfluidic device as a 3D in vitro drug screening platform", *Scientific Reports*, 2022, in press. 3) #J. Bruns, T. Egan, P. Mercier, *S. P. Zustiak, "Glioblastoma spheroid growth and chemotherapeutic responses in single and dual-stiffness hydrogels", *Acta Biomaterialia*, 2022, in press.



Chad Mirkin, **Northwestern University**, was awarded the 2022 John P. McGovern Science and Society Award by Sigma Xi, the Scientific Research Honor Society, honoring his "pioneering contributions to nanochemistry that have led to inventions that benefit society and monumental efforts in entrepreneurship, education, public understanding and national service/public policy."



Rena Bizios, **University of Texas at San Antonio**, was recently honored with two prestigious awards: 1) the 2022 William Procter Prize for Scientific Achievement from Sigma Xi, the Scientific Research Honor Society, "for being a true leader and visionary of modern materials, biomedical and chemical sciences, and engineering" and 2) the 2022 Margaret Hutchinson Rousseau Pioneer Award for Lifetime Achievement by a Woman Chemical Engineer, sponsored by AIChE (American Institute of Chemical Engineers) and Pfizer, was awarded to Dr. Bizios for "significant contributions to chemical engineering" and helping "women to have a greater impact on the profession."



Robert Langer, **Massachusetts Institute of Technology**, was awarded the 2022 Balzan Prize for Biomaterials for Nanomedicine and Tissue Engineering in honor of his "groundbreaking discoveries have paved the way for breakthroughs in the controlled release of macromolecules, with many medical applications."



Guillermo Ameer, **Northwestern University**, has been named a 2022 Honoree in the Academy of Distinguished Chemical Engineers at the University of Texas at Austin.

Member News (Continued)



Nicholas Peppas, University of Texas at Austin, was honored with the Biomaterials Global Impact Award for 2022, which was presented during the 32nd Annual Conference of the European Society of Biomaterials in Bordeaux, France. The award recognizes

established researchers in the field of biomaterials who have accomplished great achievement.



Subrata Saha, University of Washington, was awarded the 2022 Evan Ferguson Award for Service to the Society from Sigma Xi.



Cato T. Laurencin, University of Connecticut, was recently honored by AIChE (American Institute of Chemical Engineers) with the 2022 Founder's Award and by BMES (Biomedical Engineering Society) with the 2022 Robert A. Pritzker Distinguished Lecture

Award. Additionally, Prof. Laurencin recently gave the opening remarks at the inaugural U.S.-Africa Frontiers of Science, Engineering, and Medicine Symposium in Nairobi, Kenya.

**CALLING ALL
BOOKWORMS!**

If you'd like to contribute a review of your recent favorite read to the ***Biomaterials Forum***, send it for consideration to the Editor at ***Roger_narayan@ncsu.edu***. If it's approved, it will be published in a future Forum Book Review column!

Fifty Years Ago Biomedical Hydrogels Were Very Unusual; Almost Useless Materials

By Nicholas A. Peppas, ScD

When I open recent issues of journals such as *Science*, *Nature* or *PNAS*, when I read typical introductory remarks such as “these hydrogels are promising materials for biomedical or pharmaceutical applications” or when I check a journal issue and half of the publications are directly or indirectly related to hydrogels, I cannot but smile and think of earlier days in our field, days when hydrogels were rather unimportant, rarely mentioned polymeric materials. But how did macromolecular networks and hydrogels, an obscure class of polymeric materials, become a favorite subject of polymer physicists (often under the guise of “soft matter”) and a versatile family of biomaterials?

Hydrogels are of course three-dimensional, hydrophilic, polymeric networks able to imbibe small or large amounts of water or biological fluids. Early work on crosslinked polymers and networks appeared in the German literature in the early 1930s. Significant work on the behavior of “natural hydrocolloids” appeared in the late 1930s, but without structural insight. Such research was reported mostly on reaction kinetics and mechanical properties/behavior of the ensuing materials. It was in the early 1940s and specifically from 1944 to 1952 that a superb polymer chemist, Paul Flory (1910-85; Nobel Prize Chemistry, 1974) set the main framework of analysis of gels providing or developing along with collaborators the associated thermodynamic theories, statistical mechanics, first analysis of critical miscibility characteristics, etc. It was interesting that Flory developed his main theories while in two companies, Standard Oil of New Jersey and Goodyear with the latter portion of that period spent at Cornell University at the invitation of Peter Debye (1884-1966) who was chairing the chemistry department at Cornell at that time. Concurrently, there was pioneering work on networks and gels also in the Soviet Union (Valentin Kargin, 1907-69, Sergei Ushakov, 1893-1964, Victor Kabanov, 1934-2006, Nikolai Platé 1934-2007). Japanese scientists were also interesting in poly(vinyl alcohol) gels and fibers, starting with German educated Ichiro Sakurada (1904-86) who was the earliest scientist to study the swelling and dissolution of cellulose acetate in organic solvents in Leipzig in 1928, under the renowned colloid chemists Wolfgang Ostwald and Kurt Hess in Berlin-Dahlem (1928-1929). Sakurada was one of the scientists originally questioning the macromolecular ideas of Hermann Staudinger (1881-1965) but by 1932 he had become one of his supporters. He returned to Japan on the mid 1930s and promoted the important work on water swollen polymers, gels and fibers that was conducted in Kyoto.

Biomedical applications of these crosslinked structures came somewhat later through the great work of Czech scientists Otto Wichterle (1913-1998) and Drahoslav Lim (1925-2003) who were the first who identified important biomedical properties of crosslinked poly(2-hydroxyethyl methacrylates) (PHEMA) in their seminal 1960 *Nature* paper on “*Hydrophilic gels for biological use*” and, US Patent) and their 1961 US Patent on “Process for producing shaped articles from three-dimensional hydrophilic high polymers.” This pioneering biomedical work allowed scientists to initiate studies in other applications of PHEMA and related hydrogels in the medical field. But while translational research aspects of hydrogels in the biomedical field was already becoming strong and the results were promising with hydroxylated poly(meth(acrylates, poly(vinyl alcohol) and copolymers and poly(ethylene glycol) gels, fundamental research on the 3-D structure of some systems had remained at the level of the studies of the late 1940s.

THERE WAS ALSO A MAJOR PROBLEM WITH ACADEMIC RESEARCH ON HYDROGELS. THAT WAS INDEED THE SAGA OF GETTING FUNDED IN THE 1970S AND EARLY 1980S.

There was also a major problem with academic research on hydrogels. That was indeed the saga of getting funded in the 1970s and early 1980s. Polymer physicists were not yet interested in gels and the American Physical Society had no polymer network sessions in the 1970s. Fifty years ago my chemist and chemical engineering colleagues (ChEs) were ambivalent about the field. “Are you sure you are studying something important?” they were asking. In general, the subject was considered “too applied” and “not of significant intellectual interest” as a reviewer of NSF proposal had written to me in February 1978. And “JBMR? What kind of journals are you publishing in?” was a distinguished visitor to my University saying in October 1978. Surprisingly and pleasantly enough, Elsevier had a journal on “Polymer Gels and Networks.” But this journal lasted only five years (1993-1998).

Fifty Years Ago Biomedical Hydrogels Were Very Unusual; Almost Useless Materials (Continued)

However, the late 1960s and early 1970s became a fruitful period of cross-fertilization of hydrogel research and applications (translational research). For example, in 1972 MIT's Edward Merrill (1923-2020) who was a pioneer in biomaterials science had invited Paul Flory to MIT for a year of teaching and research (Figure 1). Flory obliged and brought with him a young Jim Mark (1937-2014). Eric Baer of Case Western was also invited along with Theodor Overbeek (1911-2007) from Utrecht; yes, this was Overbeek of the DLVO theory. So, the stage was set for a reexamination of the molecular and structural characteristics of hydrogels. Multifunctional crosslinked systems were studied. Non-Gaussian chain distributions gave new statistical mechanic models, etc. A few years later, in a trip to Nice France where he had his second home, Ed Merrill met Pierre-Gilles de Gennes (1932-2007, Nobel Prize Physics 1991). Some of these early summer discussions led to the significant and important analysis of network structure and gels based on scaling concepts.

Of course, hydrogels are three-dimensional, hydrophilic, polymeric networks able to imbibe large amounts of water or biological fluids. The networks are composed of homopolymers or copolymers and are insoluble due to the presence of chemical crosslinks (tie-points, junctions) or physical crosslinks such as entanglements or crystallites. The latter provide the network structure and physical integrity. These hydrogels exhibit thermodynamic compatibility with water which allows them to swell in aqueous media. Hydrogels could be neutral, anionic, cationic or amphiphilic based on the nature of the pendent groups and their ionization capabilities. According to their mechanical and structural characteristics, they can be classified as affine or phantom networks. Additionally, they can be homopolymer or copolymer networks based on the method of preparation. Finally, they can be classified based on the physical structure of the networks as amorphous, semicrystalline, hydrogen-bonded structures, supermolecular structures and



Figure 1. Drs Paul J Flory of Stanford and Edward W Merrill of MIT discuss a moisture-permeable polyurethane block copolymer containing hard and soft segments (May 1973) at the US Army Materials and Mechanics Research Center in Watertown, MA.

Fifty Years Ago Biomedical Hydrogels Were Very Unusual; Almost Useless Materials (Continued)

hydrocolloidal aggregates. An important observation was offered by Merrill and Edward Saltzman of Harvard in a seminal 1979 paper in the *ASAIO Journal* "Polyethylene oxide as a biomaterial." They proposed polyethylene oxide (PEO) as a highly biocompatible material and did significant studies to analyze its structure and blood response. Their ideas on PEO as a non-thrombogenic biomaterial led to an explosion in the use of PEG- and PEO- decorated biomedical systems.

The pH sensitive characteristics of these hydrogels are associated to their ability to ionize. Let us not forget that Aharon Katzir-Katchalsky (1914-1972) in a seminal 1949 paper on "*Rapid swelling and deswelling of reversible gels of polymeric acids by ionization*" in the journal *Experientia* defined and analyzed what has become 74 years later to be known as "intelligent hydrogels."

These early observations led to the realization that due to their chemical and structural tunability, hydrogels can be made to undergo volume transitions in response to a variety of environmental stimuli. Factors which can trigger a volume response in hydrogels are most commonly pH, ionic strength, temperature and the nature of the diluent. However, other response stimuli have been used to induce volume swelling responses in gels, including electric and magnetic fields, sound waves, analytes and biomarkers, ionizing radiation, pressure, and redox potential. In the last 25 years, we have seen also the design on novel hydrogels that can be responsive to one or more analytes, to a peptidic structure, a protein or an antibody. These are physiologically-responsive hydrogels that are based on judicious balance of non-equilibrium thermodynamics with the complex 3-D structure of the simple or complex networks. So, we can only imagine what the next 10-15 years of research, by a young generation of great, imaginative, diverse and science-converging scientists will bring up in the field of biomaterials based on hydrogels.

Two last personal comments. When I sat down to write, compile and edit the well known 3-volume treatise on "Hydrogels in

Medicine and Pharmacy" (CRC Press, 1986) I could not imagine that 37 years later the field of hydrogels would be so vibrant and so exciting for innovative research to solve major biomedical problems. The book provided, in a concise way, parameters that, although known before the mid 1980s, were reintroduced, measured and calculated by various techniques, parameters such as the average molecular weight between crosslinks or tie-points, and the related measure of distance between crosslinks, mesh size, ξ , the effective number of crosslinks, the junction functionality, etc.

The second comment is related to a biomedical and polymer scientist, who, because he wanted to help patients and had understood the importance of hydrogels in medical devices, coated surfaces and micro- and nanoparticulate systems, spent his life on the field, taught thousands and educated many. This is of course our former MIT colleague Edward Wilson Merrill (1923-2020) whose centennial we celebrate this year. So, in conclusion, it is interesting how converging ideas from various areas, statistical mechanics, thermodynamics, non-Gaussian structures, scaling concepts used in physics, molecular biology, biochemistry and hematology and pathophysiology have changed our field and have made hydrogels an important family of biomaterials.

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THESE EARLY OBSERVATIONS LED TO THE REALIZATION THAT DUE TO
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ENVIRONMENTAL STIMULI.

Industry News

By Gopinath Mani, Industry News Editor



BIOCORP, a company specialized in the design, development, and manufacturing of innovative medical devices, recently announced that they have received 510(k) clearance from the U.S. Food & Drug Administration (FDA) to market Mallya, its smart medical device that connects insulin pens.¹ The Mallya medical device is a smart sensor that is directly attached to insulin pen injectors, making them connected devices.¹ Mallya automatically collects and records key treatment information (selected insulin units, date, and time of injection) and transmits it to a dedicated digital application.¹ Mallya is capable of automatically connecting different types of insulin & GLP-1 drugs.¹ Mallya offers the possibility to connect to different types of injection pens and thus to follow a patient in a multitherapy notably with a use of basal and rapid insulin.¹ This smart sensor for insulin injection pens allows reliable monitoring of injected doses and thus offers better compliance in the treatment of patients with diabetes.¹

Novian Health has received Frost & Sullivan's 2022 European New Product Innovation Award in the breast tumor ablation industry for its [Novilase® Breast Therapy](#) system.² Novilase is a minimally invasive procedure that uses laser ablation to destroy tumors as an alternative to surgery.² Novilase is a thermal ablation device that uses laser heat to destroy tumor cells without lumpectomy surgery.² The intended use is for the focal destruction of malignant and benign tumors of the breast up to 20 mm; for general surgery procedures including incision, excision, and ablation of soft tissues; and coagulative necrosis and interstitial laser coagulation of soft tissues.² During a Novilase procedure, doctors insert a laser probe directly into the tumor using ultrasound guidance, similar to a breast biopsy.² The tumor is then heated by the laser and destroyed.² Intra-procedure confirmation of focal destruction is provided by a parallel temperature probe which records temperature at the periphery of the target ablation zone.²

HemoSonics, LLC, a medical device company delivering individualized diagnostic solutions for Patient Blood Management (PBM), recently announced that it has received 510(k) market clearance from the U.S. Food and Drug Administration (FDA) for the Quantra Hemostasis System with QStat Cartridge.³ The Quantra System leverages innovative SEER Sonorheometry, a proprietary medical-grade ultrasound technology, to measure the coagulation properties of a whole blood sample.³ The System enables clinicians to deliver patient-centered coagulation therapy that improves care and optimizes blood product usage.³ With its rapid results, ease of operation, and dials screen for straightforward interpretation, the Quantra System is the whole blood hemostasis testing system specifically cleared for use in point-of-care settings, such as operating rooms, emergency departments, and intensive care units.³

NanoVibronix, Inc., a medical device company utilizing the Company's proprietary and patented low intensity surface acoustic wave (SAW) technology, today announced U.S. Food and Drug Administration (FDA) 510(k) clearance of its PainShield® MD PLUS, its dual-actuator ultrasound pain therapy device.⁴ PainShield Plus, like the original PainShield, utilizes ultrasound therapy for the treatment of pain and various soft tissue injuries either directly over joints or orthopedic hardware and without the need for ultrasound gels.⁴ The device consists of a reusable driver unit and disposables, which includes a proprietary therapeutic transducer and cover adhesive to deliver a localized ultrasound effect to treat pain and induce soft tissue healing in a targeted area, while keeping the level of ultrasound energy at a safe and consistent level.⁴ Its range of applications includes acute and chronic pain resolution through its many mechanisms of action and can be used by patients at home, work or in a clinical setting and can be used even while the patient is sleeping.⁴ Patient benefits include ease of application and use, faster recovery time, high compliance, and increased safety and efficacy over existing devices that rely on higher-frequency ultrasound.⁴

CurvaFix, Inc., a developer of medical devices to repair fractures in curved bones, recently announced that it has received 510(k) clearance from the U.S. Food & Drug Administration (FDA) for its smaller-diameter CurvaFix® IM Implant indicated for fixation of fractures of the pelvis.⁵ The new 7.5 mm device is designed to simplify surgery and to provide strong, stable, curved fixation in smaller patients.⁵ Clinical case reports have indicated that the [CurvaFix IM Implant](#) achieves strong, stable fixation that follows and fills the natural curvature of each patient's anatomy, which may immediately reduce pain, allow for earlier mobility, and improve patient recovery.⁵ There are over 186,000 hospitalizations for pelvic fractures in the U.S. every year.⁵ Due to an aging population, the incidence is growing at 9% per year.⁵ Of the hospitalized, 108,000 are due to FFP injuries in geriatric patients, 80% of whom are female.⁵ The CurvaFix IM system simplifies pelvic fracture fixation surgery with a fast, easy, repeatable, minimally invasive procedure.⁵ The system has been shown to address many pelvic fracture fixation challenges, including dysmorphic sacra, curved superior rami, and to enable surgeons to address challenges of fragility fractures of the pelvis (FFP) in geriatric patients by providing strong fixation in weak bone with a minimally invasive procedure.⁵

Transit Scientific, a medical device company to treat calcified cardiovascular disease, dilate stenosed intimal hyperplasia, and access, cross and deliver to distal vessels, recently announced that the XO RX 2.2F and XO RX 3.8F Platform received FDA clearance to crack, break, and dilate stenoses in peripheral arteries and arteriovenous dialysis fistula associated lesions.⁶ XO RX and XO OTW (over-the-wire) exoskeleton devices include up to (22) rotating

Industry News (continued)

struts that slide onto a broad range of off-the-shelf angioplasty balloons.⁶ During balloon inflation, the struts rotate 90 degrees to crack, break, and dilate calcified stenotic atherosclerotic lesions, and intimal hyperplastic lesions, and can be used for vessel prep for other treatment options.⁶ The XO RX and XO OTW technology is designed to reduce shear and facilitate balloon rewrap by counter-rotating 90 degrees upon deflation.⁶ Clinicians can deliver fluids from the hub to the balloon before, during, or after inflation with XO OTW.⁶ The XO RX Percutaneous Transluminal Angioplasty System is intended to be used in conjunction with a PTA balloon to facilitate dilation and apposition of the scoring surface to the stenotic material in the iliac, femoral, ilio-femoral, popliteal, infra-popliteal, and renal arteries, and for treatment of obstructive lesions of native or synthetic arteriovenous dialysis fistulae.⁶ Not for use in the coronary or neuro-vasculature.⁶

Mesh Suture, Inc., recently announced that it has received 510(k) clearance from the [U.S. Food and Drug Administration \(FDA\)](#) for DURAMESH™ non-absorbable polypropylene mesh suture, a medical device for the surgical closure of soft tissues including muscles, fascia, tendons, and ligaments.⁷ DURAMESH™ aims to mitigate the intractable problem of surgical failure due to suture pull-through.⁷ The sharp leading edge of a conventional suture can slice through otherwise intact tissue, potentially leading to dehiscence, hernia formation, and poor tendon function.⁷ DURAMESH™'s novel architecture flattens at the suture-tissue interface to resist pull-through.⁷ DURAMESH™'s open-walled hollow design also allows tissue ingrowth for implant incorporation with no capsule formation.⁷

Advanced NanoTherapies, Inc., a medical device company recently announced that the U.S. Food and Drug Administration (FDA) has granted the company a Breakthrough Device designation for its SirPlux Duo Drug-Coated Balloon (DCB) for coronary artery disease in vessels less than 3.0 mm.⁸ Small vessel disease (SVD), defined as atherosclerosis within small (<3mm) coronary vessels, reaches roughly 1 in 3 of patients with symptomatic coronary artery disease (CAD), especially patients with chronic kidney disease (CKD), diabetes mellitus, and active smokers.⁸ The most powerful predictor of angiographic restenosis following treatment is the diameter of the vessel, with a 60% higher risk of restenosis for each decrease of 0.50 mm.⁸ The clinical profile of SVD patients translates into poor long-term outcomes, including a higher rate of target lesion failure when using drug-eluting stents (DES).⁸ DCBs are becoming an attractive therapeutic strategy for de novo lesions, with potential advantages of lower risk of acute thrombosis, favorable vascular remodeling, and shortened dual antiplatelet therapy.⁸ The SirPlux Duo DCB combines the synergistic power of Sirolimus and Paclitaxel to create a next-generation, front-line therapy engineered to provide stent-like patency and restenosis prevention while leaving no implant behind.⁸ SirPlux Duo DCB delivers low-dose, long-term release of both compounds to

inhibit cell growth, resulting in maximum potency exceeding any other DCB or drug-eluting stent.⁸ The Company's proprietary nanoparticle drug-encapsulation and delivery platform provides safe, reliable, and sustained bioavailability of the two synergistic drugs in tissue for long-term outcomes.⁸

Glaukos Corporation, an ophthalmic medical technology and pharmaceutical company focused on novel therapies for the treatment of glaucoma, corneal disorders and retinal diseases, recently announced that it has received 510(k) clearance from the [U.S. Food and Drug Administration \(FDA\)](#) for the *iStent infinite*® Trabecular Micro-Bypass System indicated for use in a standalone procedure to reduce elevated intraocular pressure (IOP) in patients with primary open-angle glaucoma uncontrolled by prior medical and surgical therapy.⁹ The *iStent infinite* includes three heparin-coated titanium stents preloaded into an auto-injection system that allows the surgeon to inject stents across a span of up to approximately six clock hours around Schlemm's canal, the eye's primary drainage channel.⁹ Once in place, the stents are designed to lower IOP by restoring the natural, physiological outflow of aqueous humor.⁹ The *iStent infinite* has a similar mechanism of action to the company's two-stent *iStent inject*® W Trabecular Micro-Bypass System, which is approved by the FDA for the reduction of IOP in adult mild-to-moderate primary open-angle glaucoma patients undergoing concomitant cataract surgery.⁹

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Government News

THREE FIRSTS FOR TISSUE ENGINEERING IN 2022

By Carl Simon, Government News Editor



FIRST FIRST: FIRST USE OF A HUMAN-ON-A-CHIP MODEL TO SUPPORT AN IND FILING

In a likely first, a human on a chip (Hoac) model has been used to provide “efficacy data included in an investigational new drug (IND) application” submitted to the FDA.^{1,3} The investigational drug is a monoclonal antibody (mAB) called TNT005 that is being tested for the treatment of multifactor motor neuropathy (MNN), which is a rare autoimmune neuropathy that causes muscle weakness, difficulty ambulating and impaired hand function. In MNN, patients produce autoantibodies in their serum that react to gangliosides (such as GM1) in peripheral nerves leading to activation of the classical complement pathway followed by peripheral nerve demyelination and loss of function. TNT005 inhibits C1s, a key protease of the classical complement pathway. The Hoac system was developed by Hesperos, Inc.² using co-culture of primary human Schwann cells and iPSC-derived (induced pluripotent stem cell) human motor neurons. The cells are cultured over a microelectrode array for measuring action potential frequency (APF) and conduction velocity (CV) (Figure 1).

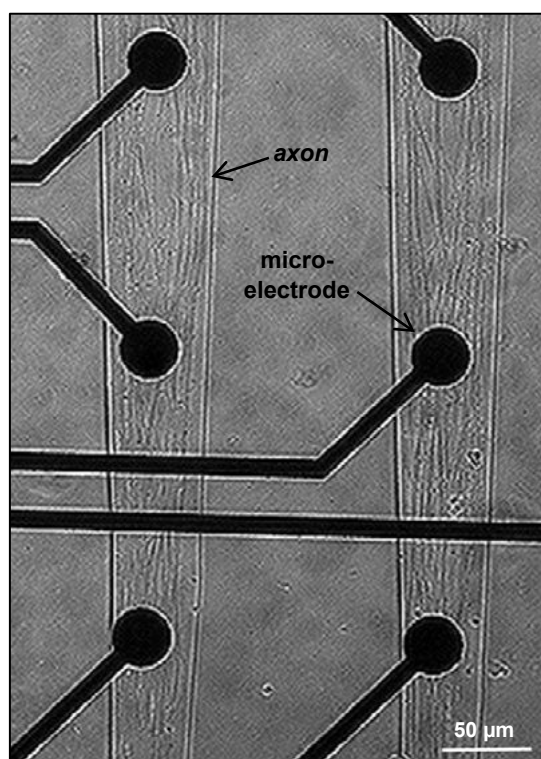


Figure 1. Human-on-a-chip model of autoimmune axon demyelination. Image shows human axons growing in PDMS (polydimethylsiloxane) tunnels over a microelectrode array that measures action potential. Scale bar is 0.05mm. Image is used under a Creative Commons License.¹

When HoacS were cultured with serum from MNN patients, a decrease in APF and CV was observed, which could be rescued by the addition of TNT005 but not by control mABs. [“The data shows the ability to take a molecule that has existing clinical safety data and use only a microphysiological model to repurpose the drug and provide efficacy evidence for a different indication without the need for preclinical animal experiments,”](#) commented [Michael Shuler, President and CEO of Hesperos.](#)²

SECOND FIRST: FIRST 3D-PRINTED TISSUE CONTAINING LIVE CELLS IMPLANTED IN PATIENT

The first 3D-printed tissue containing live cells has been implanted into a human.^{4,6} The implanted tissue was an ear that was used to treat a birth defect called microtia, a condition where the external part of the ear, called the auricle, is small and not properly formed.⁷ The 3D-printed auricle, a product named AuriNovo, was developed by 3DBio Therapeutics and is being tested in a single-arm Phase 1/2a clinical trial.⁸ Auricular cartilage cells were harvested from a biopsy of the patient’s ear and expanded in vitro using 3DBio’s proprietary cell expansion process. The expanded cells were incorporated into 3DBio’s collagen bioink and fabricated into the shape of an ear using a 3D printer (Figure 2). The 3D-printer was designed and built by 3DBio to meet key manufacturing requirements required by FDA, such as sterility. The precise shape of the patient’s other ear, which was properly formed, was imaged by a 3D scanner⁹ and used to create a matching design to replace the deformed ear. The trial is set to enroll 11 patients and preliminary efficacy will be assessed using the FACE-Q Questionnaire, which asks the patient how their ears look (shape and size), and how they look in photos, from the side and when they wear a hat. AuriNovo was granted an Orphan Drug and Rare Pediatric Disease Designation by FDA.

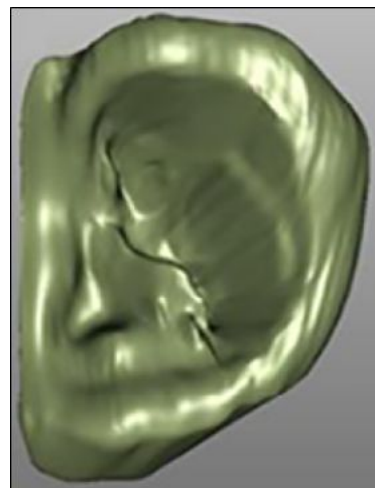


Figure 2. 3D scan of a patient’s ear that can be used as a design for 3D printing a tissue-engineered ear. Image is used under a Creative Commons License.⁹

Government News (continued)

THIRD FIRST: FIRST PATIENT TREATED WITH IPSCS IN THE U.S.

For the first time, a patient in the U.S. has been treated with induced pluripotent stem cells (iPSCs).¹⁰ In 2006, Shinya Yamanaka famously demonstrated that adult cells could be reprogrammed to be pluripotent using four factors, Myc, Oct3/4, Sox2 and Klf4, and he subsequently won the Nobel Prize in 2012 for this incredible discovery.^{11,12} The first patient treated with iPSCs was in Japan in 2014.¹³ She was treated for age-related macular degeneration (AMD) using a sheet of iPSC-derived retinal pigment epithelium (RPE) cells. The U.S. patient was also treated for AMD using a similar therapy developed by a team led by Kapil Bharti at the National Eye Institute at the National Institutes of Health. First, cells are isolated from the AMD patient and are reprogrammed during lab culture into iPSCs. The iPSCs are differentiated into RPE over several months using a panel of induction factors. Next, the RPE cells are seeded onto a degradable electrospun polymeric fiber-based scaffold that supports RPE maturation and gives the construct mechanical integrity so that it can be handled during surgery. A tiny, 2 mm by 4mm RPE-scaffold construct (Figure 3) is then implanted into the back of the patient's eye during surgery using a special surgical tool developed by the team. The RPE is a layer of cells that supports the photoreceptor cells in the retina. The photoreceptor cells absorb light to enable vision. In AMD, the RPE degrades, leading to the loss of photoreceptors and vision. The goal of the treatment is to replace the patient's degraded RPE with lab-grown RPE to rescue the photoreceptors and prevent vision loss. The U.S. patient was treated at Johns Hopkins University in a Phase 1/2a clinical trial.¹⁴

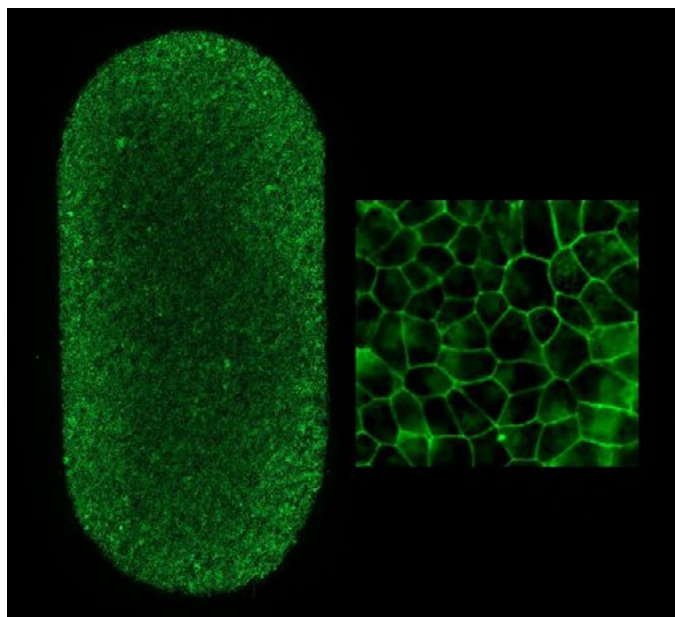


Figure 3. Left shows an image of a mm by 4 mm RPE patch that is used to treat patients for AMD. Cell borders are stained for green fluorescence. Right image is a higher magnification image showing the individual RPE cell borders. Right image is 0.18 mm across. Courtesy of Kapil Bharti, PhD, the National Eye Institute.

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