A physicist remembers 30 years after the "Woodstock of Physics"

By **Tim Palucka**

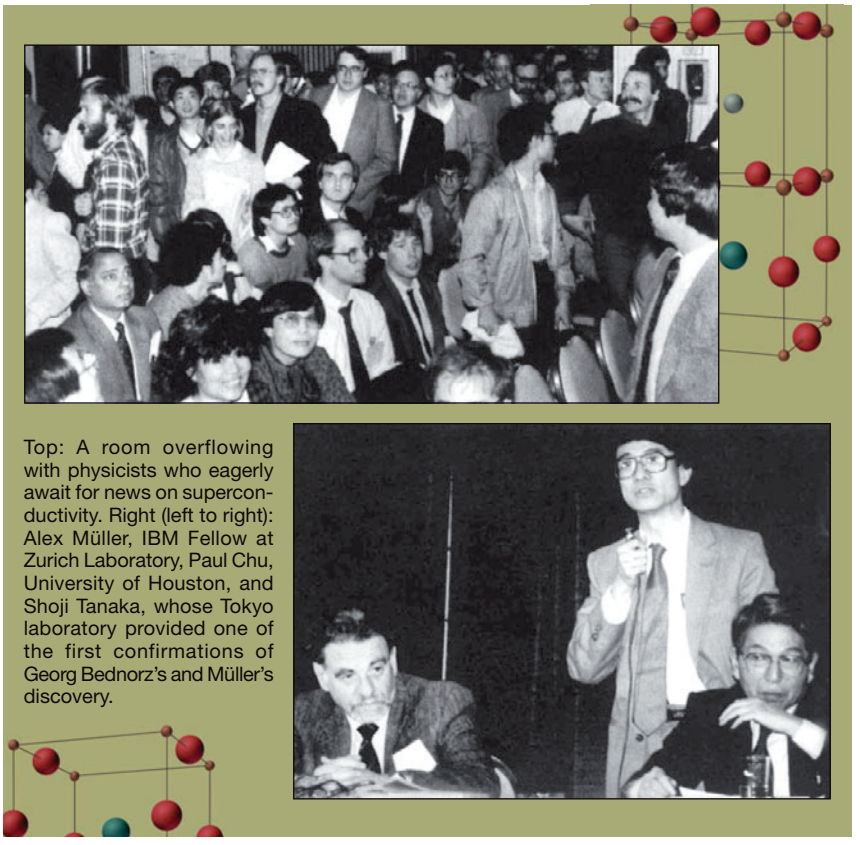
March 1987 was a heady time to be a physicist. At the annual meeting of the American Physical Society (APS), held that year at the Hilton Hotel in New York City, reporters followed physicists around town, trying to get interviews about the new high-temperature superconductors that were supposed to make electricity super-efficient. An APS meeting badge was sufficient to get you to the front of the line in at least one trendy New York night club, *and* free admission. Paul Michael Grant, then a physicist at the IBM Almaden Research Center in California (later with the Electric Power Research Institute and now the founder and principal of W2AGZ Technologies), was surprised to see a photograph of himself, blown up two stories tall on the side of the downtown Sony office building, performing a "dipper-stick" measurement of the transport properties in a liquid helium dewar of a sample of YBCO-123($YBa_2Cu_3O_{7-y}$), whose single-phase structure Grant and his group had identified only two weeks before the APS meeting, exhibiting a critical temperature (T_c) of 93 K. "Seeing that photo displayed in mid-Manhattan knocked my socks off," said Grant.

The highlight of the March meeting week was a special session of five-minute talks on the copper oxide perovskite high-temperature (high-T_c) superconductors. Starting at 7:30 Wednesday night, March 18, and continuing into Thursday morning, the session, dubbed the "Woodstock of Physics," due to its New York city location about 70 miles south of 1969's Woodstock rock music festival, drew 51 speakers and thousands of eager listeners who overflowed the meeting hall.

The path to this level of physics popularity in the United States was an unlikely one: High-T_c superconductivity (T_c > 20 K) seemed to be a research dead end only a few years earlier. In 1984, Grant had reviewed his team's work on organic superconductors that delivered a maximum T_c of only about 10 K and then shut the program down. Other researchers who had been trying to develop room-temperature superconductors had also stopped their efforts.

But K. Alex Müller, one of the early IBM Fellows, located in the company's Zurich lab, decided to leave his management position and return to the lab, and used his USD$50K discretionary funding which was available to all IBM Fellows at the time to explore their "wild notions." Müller had long harbored an idea that materials exhibiting the Jahn–Teller effect—a strong distortion of the lattice periodicity in metals arising from highly degenerate bonding states—might prove promising candidates for high-T_c superconductors. He persuaded J. Georg Bednorz, one of his former postdocs at ETH Zürich, later hired by IBM to work on semiconductor laser structures, to work after hours to investigate doped transition-metal nickel oxide materials that had demonstrated Jahn–Teller properties.

After a number of months of unsuccessfully exploring nickel oxides, Bednorz came across a paper published in 1984 by the French researchers Michel and Raveau titled, "Oxygen intercalation in mixed valence copper oxides related to the perovskites." Immediately, Bednorz



Top: A room overflowing with physicists who eagerly await for news on superconductivity. Right (left to right): Alex Müller, IBM Fellow at Zurich Laboratory, Paul Chu, University of Houston, and Shoji Tanaka, whose Tokyo laboratory provided one of the first confirmations of Georg Bednorz's and Müller's discovery.

and Müller began investigating the French team's La-Ba-Cu-O system, and Grant heard that they had found trace evidence of superconductivity between 20 and 30 K. After keeping the discovery quiet for a while, Müller sought out Alex Buchel, the editor of *Zeitschrift für Physik*, who was an expert in the field of superconductivity, and asked him to personally review the paper and publish it without further refereeing. After all this secrecy, their announcement of 30 K superconductivity finally appeared in late summer 1986 under the title "Possible high-T_c superconductivity in the Ba-La-Cu-O system."

Shoji Tanaka's group at The University of Tokyo in Japan noticed the paper and quickly reproduced the results, and then the word began spreading. Because LaBaCuO powder was easy to make, others around the world soon jumped into the field. Paul Chu's group at the University of Houston and Maw-Kuen Wu's team at The University of Alabama in Huntsville subsequently separately reported the discovery of 90 K superconductivity in a very mixed phase of the lanthanide cuprates.

The YBCO superconductor was the focus of the Woodstock of Physics session. Müller, Chu, Tanaka, and other luminaries spoke for 15 minutes, while the remaining speakers were limited to five minutes. Grant spoke about the unit-cell structure for the 123 phase of YBCO. As he recalls, no major discoveries were announced that night, but the excitement ran high as speakers confirmed reproduction of results and incremental advances.

Sadly, the excitement would not last long. All the hype in the press about how superconductivity would soon ease humanity's energy burden proved quite premature. In the April 1988 issue of *MIT Technology Review*, authors Simon Foner and Terry P. Orlando wrote, "High temperature superconductors are a scientific breakthrough, but technical and *economic* obstacles to useful applications remain." So "stay tuned."

Even today, the mechanism of high-temperature superconductors is not well understood, and the economics regarding its application remains an issue. Grant is now advocating the dual transport of chemical and electrical energy—natural gas and superconducting cables in the same right of way. Still, despite the disappointment of as-yet unfulfilled expectations, he fondly remembers the days 30 years ago when physicists were treated like rock stars, if only briefly. He also regrets that some scientists fed the media frenzy that led to an unrealistic promise of its impact on the energy enterprise. Nonetheless, the discovery of high-temperature superconductivity remains one of the great science stories of the latter half of the 20th century, and the struggle, competition, and secrecy surrounding the participants at our "Woodstock" recall the period around the formulation of the structure of DNA … the "double helix" story all over again.

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SPECIAL ISSUE PROSPECTIVE ARTICLES: BIOMATERIALS FOR 3D CELL BIOLOGY

Next Generation Tissue Engineering of Orthopedic Soft Tissue-to-Bone Interfaces

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Soft tissue-to-bone interfaces are complex structures that consist of gradients of extracellular matrix materials, cell phenotypes, and biochemical signals. These interfaces, called entheses for ligaments, tendons, and the meniscus, are crucial to joint function, transferring mechanical loads and stabilizing orthopedic joints. When injuries occur to connected soft tissue, the enthesis must be re-established to restore function, but due to structural complexity, repair has proven challenging. Tissue engineering offers a promising solution for regenerating these tissues. This prospective review discusses methodologies for tissue engineering the enthesis, outlined in three key design inputs: materials processing methods, cellular contributions, and biochemical factors. DOI:10.1557/mrc.2017.91

The need for advanced three-dimensional neural models and developing enabling technologies

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Neurological and psychiatric disorders account for an increasing proportion of the global disease burden. Correspondingly the neuropharmaceutical industry has experienced a significant contraction in recent years resulting in a poor variety of therapies available to treat an expanding range of conditions. Perhaps the greatest contributor to this failure in drug-discovery is the lack of understanding of the underlying biology of the nervous system and how molecular scale events translate into macroscale pathologies. Due to the unique nature of the human nervous system commonly used model organisms are often poorly representative of human pathologies resulting in a need for the development of advanced *in vitro* models that are capable of faithfully modeling complex structures within the brain. In this prospective, strategies for the generation of neuronal circuits and cultivation of complex three-dimensional (3D) cultures are explored. Frequently these constructs provide valuable insights into systems and processes that are difficult to explore *in vivo* due to the isolated and delicate nature of neuronal tissues. New developments are required to assess the physiological functions of 3D tissues *in vitro*. DOI:10.1557/mrc.2017.50

Three-dimensional neuronal cell culture: in pursuit of novel treatments for neurodegenerative disease

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To gain a better understanding of the underlying mechanisms of neurological disease, relevant tissue models are imperative. Over the years, this realization has fuelled the development of novel tools and platforms, which aim at capturing *in vivo* complexity. One example is the field of biofabrication, which focuses on fabrication of three-dimensional (3D) biologically functional products in a controlled and automated manner. Herein, we provide a general overview of classical 3D cell culture platforms, particularly in the context of neurodegenerative disease. Subsequently, the focus is put on bioprinting-based biofabrication; its potential to advance 3D neuronal cell culture and, to conclude, the relevant translational bottlenecks, which will need to be considered as the field evolves. DOI: 10.1557/mrc.2016.96

Tissue engineering towards organ-specific regeneration and disease modeling

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Tissue engineering has been recognized as a translational approach to replace damaged tissue or whole organs. Engineering tissue, however, faces an outstanding knowledge gap in the challenge to fully recapitulate complex organ-specific features. Major components, such as cells, matrix, and architecture, must each be carefully controlled to engineer tissue-specific structure and function that mimics what is found *in vivo*. Here we review different methods to engineer tissue, and discuss critical challenges in recapitulating the unique features and functional units in four major organs—the kidney, liver, heart, and lung, which are also the top four candidates for organ transplantation in the USA. We highlight advances in tissue

engineering approaches to enable the regeneration of complex tissue and organ substitutes, and provide tissue-specific models for drug testing and disease modeling. We discuss the current challenges and future perspectives toward engineering human tissue models. DOI:10.1557/mrc.2017.58

Modulated nitric oxide delivery in 3D biomaterials for vascular functionality

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Nitric oxide (NO) acts a pivotal role in regulating various physiological processes of vasodilation, platelet aggregation, and vascular smooth muscle cell mitogenesis and proliferation. This makes NO a promising candidate for the treatment of cardiovascular problems like hypertension and vascular stenosis. However, the high reactivity of NO poses an issue for effective NO delivery. To overcome this limitation, recent developments on three-dimensional (3D) materials have been explored with either physical or chemical incorporation of NO releasing donors, to provide spatiotemporal control over NO-signaling pathways in blood vessels. Here, we offer an overview on the current efforts, and propose future perspectives for precise regulation on NO delivery in advanced 3D materials toward proper vascular functionality. DOI:10.1557/mrc.2017.40

Dynamic bioengineered hydrogels as scaffolds for advanced stem cell and organoid culture

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Bioengineered hydrogels enable systematic variation of mechanical and biochemical properties, resulting in the identification of optimal *in vitro* three-dimensional culture conditions for individual cell types. As the scientific community attempts to mimic and study more complex biologic processes, hydrogel design has become multi-faceted. To mimic organ and tissue heterogeneity in terms of spatial arrangement and temporal changes, hydrogels with spatiotemporal control over mechanical and biochemical properties are needed. In this prospective article, we present studies that focus on the development of hydrogels with dynamic mechanical and biochemical properties, highlighting the discoveries made using these scaffolds. DOI:10.1557/mrc.2017.72

Take a deep breath and digest the material: organoids and biomaterials of the respiratory and digestive systems

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Human organoid models recapitulate many aspects of the complex composition and function of native organs. One of the main challenges in developing these models is the growth and maintenance of three-dimensional tissue structures and proper cellular organization that enable function. Biomaterials play an important role by providing a defined and tunable three-dimensional environment that is required for complex cellular organization and organoid growth *in vitro* or *in vivo*. This review summarizes organoids of the respiratory and digestive system, and the use of biomaterials to improve upon these model systems. DOI:10.1557/mrc.2017.61

The control of stem cell morphology and differentiation using three-dimensional printed scaffold architecture

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In this work, we investigated the interactions of human mesenchymal stem cells (hMSCs) with 3D printed scaffolds displaying different scaffold architectures. Pressure assisted microsyringe (PAM) system was used to fabricate scaffolds with square (SQR), hexagonal (HEX), and octagonal (OCT) architectures defined by various degrees of curvatures. OCT represents the highest degree of curvature followed by HEX, and SQR is composed of linear struts without curvature. Scaffolds were fabricated from poly(L-lactic acid) (PLLA) and poly(tyrosol carbonate) (PTyC). We found that hMSCs attached and spread by taking the shape of the individual struts, exhibiting high aspect ratios and mean cell area when cultured on OCT scaffolds as compared to those cultured on HEX and SQR scaffolds. In contrast, cells appeared bulkier with low aspect ratio on SQR scaffolds. These significant changes in cell morphology directly correlate with the stem cell lineage commitment, such that 80±1% of the hMSCs grown on OCT scaffolds differentiated into osteogenic lineage, compared to 70±4% and 62±2% of those grown on HEX and SQR scaffolds, respectively. Cells on OCT scaffolds also showed 2.5 times more alkaline phosphatase activity compared to cells on SQR scaffolds. This study demonstrates the importance of scaffold design to direct stem cell differentiation, and aids in the development of novel 3D scaffolds for bone regeneration. DOI:10.1557/mrc.2017.73

Polymeric scaffolds for 3D culture of nerve cells: a model of peripheral nerve regeneration

Radamés Ayala-Caminero, **Luis Pinzón-Herrera**, **Carol A. Rivera Martinez**, and **Jorge Almodovar**, University of Puerto Rico Mayaguez, Puerto Rico

Understanding peripheral nerve repair requires the evaluation of 3D structures that serve as platforms for 3D cell culture. Multiple platforms for 3D cell culture have been developed, mimicking peripheral nerve growth and function, in order to study tissue repair or diseases. To recreate an appropriate 3D environment for peripheral nerve cells, key factors are to be considered including: selection of cells, polymeric biomaterials to be used, and fabrication techniques to shape and form the 3D scaffolds for cellular culture. This review focuses on polymeric 3D platforms used for the development of 3D peripheral nerve cell cultures. DOI:10.1557/mrc.2017.90

Gelatin-based hydrogels for biomedical applications

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Gelatin-based hydrogels derived from hydrolysis of collagen have beenextensively used in pharmaceutical and medical applications because of their biocompatibility and biodegradability. For example, gelatin-based hydrogels are finding use in drug delivery and tissue engineering because they are able to promote cell adhesion and proliferation. In addition, these hydrogels can be used as wound dressings due to their attractive fluid absorbance properties. Manufacturing technologies such as UV stereolithography and two-photon polymerization (2PP) can be used to prepare structures containing photosensitive gelatin-based hydrogels. This review describes the preparation of gelatin-based hydrogels and use of these materials for biomedical applications. DOI:10.1557/mrc.2017.92

Shooting for the moon: using tissue-mimetic hydrogels to gain new insight on cancer biology and screen therapeutics

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Tissue engineering holds great promise for advancing cancer research and achieving the goals of the Cancer Moonshot by providing better models for basic research and testing novel therapeutics. This paper focuses on the use of hydrogel biomaterials due to their unique ability to entrap cells in three-dimensional (3D) matrix that mimics tissues and can be programmed with physical and chemical cues to recreate key aspects of tumor microenvironments. The chemistry of some commonly used hydrogel platforms is discussed, and important examples of their use in tissue engineering 3D cancer models are highlighted. Challenges and opportunities for future research are also discussed. DOI:10.1557/mrc.2017.86

SPECIAL ISSUE RESEARCH LETTERS: BIOMATERIALS FOR 3D CELL BIOLOGY

Three-dimensional nanofiber scaffolds with arrayed holes for engineering skin tissue constructs

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Three-dimensional (3D) scaffolds composed of poly(ε-caprolactone) and gelatin nanofibers were fabricated by a combination of electrospinning and modified gas-foaming. Arrayed holes throughout the scaffold were created using a punch under cryo conditions. The crosslinking with glutaraldehyde vapor improved the water stability of the scaffolds. Cell spheroids of green fluorescent protein-labeled human dermal fibroblasts were prepared and seeded into the holes. It was found that the fibroblasts adhered well on the surface of nanofibers and migrated into the scaffolds due to the porous structures. The 3D nanofiber scaffolds may hold great potential for engineering tissue constructs for various applications. DOI:10.1557/mrc.2017.49

Development of magnetically active scaffolds as intrinsically-deformable bioreactors

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Mesenchymal stem cell behavior can be regulated through mechanical signaling, either by dynamic loading or through biomaterial properties. We developed intrinsically responsive tissue engineering scaffolds that can dynamically load cells. Porous collagen- and alginate-based scaffolds were functionalized with iron oxide to produce magnetically active scaffolds. Reversible deformations in response to magnetic stimulation of up to 50% were recorded by tuning the material properties. Cells could attach to these scaffolds and magnetically induced compressive deformation did not adversely affect viability or cause cell release. This platform should have broad application in the mechanical stimulation of cells for tissue engineering applications. DOI:10.1557/mrc.2017.41

Electrospun aniline-tetramer-co-polycaprolactone fibers for conductive, biodegradable scaffolds

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Conjugated polymers have been proposed as promising materials for scaffolds in tissue engineering applications. However, the restricted processability and biodegradability of conjugated polymers limit their use for biomedical applications. Here we synthesized a block-co-polymer of aniline tetramer and PCL (AT–PCL), and processed it into fibrous non-woven scaffolds by electrospinning. We showed that fibronectin (Fn) adhesion was dependent on the AT–PCL oxidative state, with a reduced Fn unfolding length on doped membranes. Furthermore, we demonstrated the cytocompatibility and potential of these membranes to support the growth and osteogenic differentiation of MC3T3-E1 cells over 21 days. DOI:10.1557/mrc.2017.45

Spatially-graded hydrogels for preclinical testing of glioblastoma anticancer therapeutics

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While preclinical models such as orthotopic tumors generated in mice from patient-derived specimens are widely used to predict sensitivity or therapeutic interventions for cancer, such xenografts can be slow, require extensive infrastructure, and can make *in situ* assessment difficult. Such concerns are heightened in highly aggressive cancers such as glioblastoma that display genetic diversity and short mean survival. Biomimetic biomaterial technologies offer an approach to create ex vivo models that reflect biophysical features of the tumor microenvironment. We describe a microfluidic templating

approach to generate spatially-graded hydrogels containing patient-derived glioblastoma cells to explore drug efficacy and resistance mechanisms. DOI:10.1557/mrc.2017.85

Hydrogel-based microchannels to measure confinement- and stiffness-sensitive YAP activity in epithelial clusters

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Nuclear translocation of Yes-associated-protein (YAP) in single cells serves as a key sensor of matrix stiffness. On 2D polyacrylamide (PA) hydrogels, we found that nuclear YAP localization in epithelial clusters increases with gel stiffness and reduces with cell density. To measure YAP activity in 3D-like confinement of tunable stiffness, we fabricated PA-based microchannels. Here, narrower channels enhanced nuclear YAP localization even in softer ECM and denser epithelial clusters, both of which reduced YAP activation in 2D. Thus, the presented hydrogel microchannels-based platform may reveal new mechanosensitive cellular signatures in 3D-like settings, which cannot be captured on standard 2D hydrogels. DOI:10.1557/mrc.2017.87

Three-dimensional cell culture of human mesenchymal stem cells in nanofibrillar cellulose hydrogels

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Human mesenchymal stem cells (MSCs) are the most intensely studied and clinically used adult stem cell type. Conventional long-term cultivation of MSCs as a monolayer is known to result in a reduction of their functionality and viability. In addition, large volumes of cell culture medium are required to obtain cell quantities needed for their clinical use. In this proof of concept study, we cultivated human MSCs within a three-dimensional nanofibrillar cellulose (NFC) hydrogel. We show that NFC is biocompatible with human MSCs, and represents a feasible approach to upscaling of their culture. DOI:10.1557/mrc.2017.59

A living electrode construct for incorporation of cells into bionic devices

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A living electrode construct that enables integration of cells within bionic devices has been developed. The layered construct uses a combination of non-degradable conductive hydrogel and degradable biosynthetic hydrogel to support cell encapsulation at device surfaces. In this study, the material system is designed and analyzed to understand the impact of the cell carrying component on electrode characteristics. The cell carrying layer is shown to provide a soft interface that supports extracellular matrix development within the electrode while not significantly reducing the charge transfer characteristics. The living layer was shown to degrade over 21 days with minimal swelling upon implantation. DOI:10.1557/mrc.2017.44

Spheroid 3D culture enhances Notch signaling in cardiac progenitor cells

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Cardiac progenitor cells (CPCs) are a promising candidate for cardiac regeneration, and the interaction between CPCs and their microenvironment can influence their regenerative response. Notch signaling plays a key role in cell fate decisions in the developing and adult heart. Here, we investigated the effect of 3D spheroid culture, as a model of the 3D microenvironment, on Notch in fetal and adult human CPCs, under room air (20%) and physiological (5%) oxygen tension. Notch signaling is enhanced in 3D spheroids; spheroid culture under 5% O_2 further increases Notch signaling enhancement, and might ultimately improve the regenerative potential of CPCs. DOI:10.1557/mrc.2017.82

Decorin-containing collagen hydrogels as dimensionally stable scaffolds to study the effects of compressive mechanical loading on angiogenesis

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Angiogenesis is a critical component during wound healing, and the process is sensitive to mechanical stimuli. Current *in vitro* culture environments used to investigate three-dimensional microvascular growth often lack dimensional stability and the ability to withstand compression. We investigated the ability of decorin (DCN), a proteoglycan known to modulate collagen fibrillogenesis, incorporated into a collagen hydrogel to increase construct dimensional stability while maintaining vascular growth. DCN did not affect microvascular growth parameters, while increasing the compressive modulus of collagen gels and significantly reducing the contraction of 3% collagen gels after 16 days in culture. DOI:10.1557/mrc.2017.54

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