BIRC Biomaterials Innovation Research Center

TISSUE ENGINEERING
BIOMATERIALS
BWH
MICROFLUIDICS
BIOMEMS
ORGAN ON-A-CHIP

BIRC-*update*

NOVEMBER 2015 | VOLUME 1 | ISSUE 3

## IN THIS ISSUE



## AGENDA

Lab safety test 12-04
*65 Landsdowne street*

Tissue engineering meeting
*every Thursday 10AM-11AM*

Biomaterials meeting
*every Friday 2pm-3pm*

Organ-on-a-chip meeting
*every Monday 11:15AM-12:15AM*

Innovation subgroup meeting
*t.b.a.: contact Katelyn Bringer*

# Ali Khademhosseini wins *Kavli Early Career Award in Nanoscience*

The Kavli Early Career Award in Nanoscience: This honor recognizes significant novel contributions to materials science by a young researcher in early stages of his/her career. We would like to congratulate Prof. Ali Khademhosseini on receiving this award at the 2015 Materials Research Society Fall Meeting & Exhibit.

Prof. Khademhosseini has been on the forefront in the field of nano- and microscale tissue engineering. He has utilized the advances in nanotechnology and nanoengineering and created cutting edge solutions in the field of regenerative medicine and tissue engineering

## NEW: Regenerative Engineering and Translational Medicine

Springer has launched Regenerative Engineering and Translational Medicine in partnership with the newly formed Regenerative Engineering Society. The new international journal will cover the convergence of multiple fields, including tissue generation, advanced materials science, stem cell research, the physical sciences and developmental biology, and is actively seeking submissions.

The journal will offer exciting opportunities to translate work done in a laboratory – so-called "bench-top" research – into bedside methods. This approach allows for the possibility of moving beyond simply maintaining or repairing tissues, into ways of actually generating them. Dr. Laurencin is joined on the editorial board by Managing Editor Lakshmi S. Nair, M.Phil, Ph.D., also from the University of Connecticut, and News and Views Editor, **Ali Khademhosseini, Ph.D., of Harvard University.**

The journal is actively seeking submissions, and encourages both top-down engineering approaches and bottom-up strategies integrating materials science with stem cell research and developmental biology. Papers covering instructive biomaterials, stimuli-responsive biomaterials, micro- and nano-patterning for regenerative engineering, elastomeric biomaterials, hydrogels for tissue engineering, and rapid prototyping and bioprinting approaches are particularly welcome.

*[news source: http://www.springer.com]*

**Mini-review series** *By Hae Lin Jang, Katelyn Brinegar & Ali Khademhosseini*

## In vivo cellular reprogramming by nanoneedles

Lead: Nanoneedles can access in vivo intracellular targets to deliver biomolecules with an efficiency greater than 90%, inducing sustained neovascularization and an increase in blood perfusion in muscle tissue for regenerative engineering.

Regenerative engineering is a convergence of tissue engineering with advanced material science, stem cell science, and developmental biology, which aims to repair complex tissues[1]. In this regard, regenerative engineering can enhance complicated tissue healing by inducing vascularization, which can be done by reprogramming of cells through minimally invasive gene delivery system. Here, we introduce an innovative approach of nanoneedle material to demonstrate one example of regenerative engineering. The recent development in high-aspect ratio nanoneedle structures has enabled single cells to be monitored and small biomolecules to be directly delivered into the targeted area of intracellular space[2-4]. During penetration of cellular membrane with nanoneedles, cells can function normally as minimal intrusion occurs. Now, writing in Nature Materials, Ennio Tasciotti, Molly Stevens and colleagues from Imperial College London and Houston Methodist Research Institute in the USA reported an innovative approach of applying nanoneedles in vivo to directly reprogram cells to induce tissue regeneration (**Figure 1)[**5,6].

The team showed that biodegradable silicon nanoneedles can co-deliver DNA and siRNA into the cytosol of cells with an efficiency greater than 90%. As a result, neovascularization and blood perfusion were significantly enhanced in the selected tissue area. In addition, even with this early prototype, nanoinjection did not show any inflammation in muscle or skin and required only very small incision level (< 1~2 cm).

From hypodermic injection to nanoneedle injection, scale of the injection has been reduced to minimize tissue damage and enhance accuracy of targeting. Since the first patch was approved by the US FDA

in 1979, transdermal delivery has been dramatically expanded to overcome biological barriers for the effective drug delivery[7,8]. Starting from the first generation of basic patches, the second and third generation transdermal delivery systems increased skin permeability and provided driving force for drug transport into the skin by chemical enhancers and physical stimulation, respectively. Microneedles belong to the third generation delivery system and have been successfully created painless microscale pathway to deliver drugs through skin. As the scale of needles decreased into nanoscale, nanoneedles have enabled the efficient delivery of small hydrophilic biomolecules directly into the intracellular target by penetrating the cellular membrane.

To create silicon nanoneedles, Tasciotti and co-workers prepared patterned silicon nitride masking layer on top of the silicon wafers using photolithography. By metal assisted chemical etching, silicon pillars were formed underneath the silicon nitride pattern and then redesigned into conical needle shape by reactive ion etching. The prototype nanoneedles had 5 µm length, 50 nm apical width, and 600 nm base diameter with densities of approximately 25 million needles/cm2 on 8 x 8 mm2 chip, providing an over 300-fold increase in surface area compare to the cylindrical nanowire structures[9]. The diameter of the nanoneedles was controlled by changing the duration of the plasma etching. To load nucleic acids on nanoneedles, the surface of the chips were silanized to become positively charged and attract negatively charged nucleic acids.

Nanoneedles had sufficient mechanical strength (~260 nN) for in vitro and in vivo applications, as the force experienced during penetration of a cell is known as 2 nN. On the other hand, silicon nanoneedles were biodegradable in physiological condition that their shape ultimately dissolved within 72 hours. Therefore, silicon nanoneedles had unique characteristic of being both robust enough to penetrate the cellular membrane while, at the same time, biodegradable to completely dissolve over time. When cells were penetrated by nanoneedles, they maintained physiologic metabolic activity and normal proliferation level. There was no leakage of intracellular material. In addition, the team evaluated the efficiency of nanoinjection of VEGF165 plasmid DNA, which is a master angiogenic gene, in the in vivo mouse model. Small incision was made in the mouse model and VEGF-loaded nanoneedles were implanted in the muscle and compared with the group of direct injection of VEGF. Notably, only nanoinjected muscle exhibited much higher neovascularization with 6-fold increase in blood perfusion and the number of nodes in the vasculature, while the direct injection of VEGF group did not show significant enhancement in neovascularization.

The major innovation of Tasciotti and co-workers achieved is that they have made a nanoneedle platform with high transfection efficacy of loading and releasing nucleic acids directly inside cells in dynamic in vivo conditions which actually induced effective neovascularization. This approach extended previous single cell level of nanoneedle application into simultaneous reprogramming of cells in complex tissue level as a regenerative engineering. Also, nanoneedles showed high potential as a non-immunogenic delivery platform for small biomolecules to other tissues as well. Conceivably, nanoneedles can be used with other delivery systems to enhance accuracy of targeting and become multi-functional systems for sensing, stimulating and monitoring of cells in vivo, to facilitate development of regenerative engineering approaches.

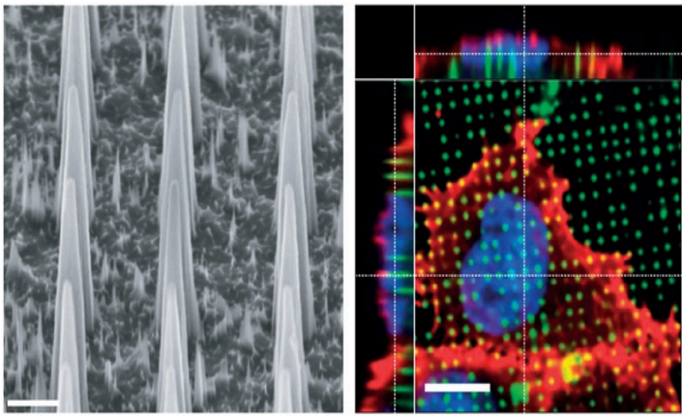

**Figure 1**: *Biodegradable silicon nanoneedles (left, scale bar: 2 µm) and cells interfacing nanoneedles (right, scale bar: 10 µm). Adapted with the permission of Macmillan Publishers Ltd. (Nature Materials)[5], copyright 2015*

## Active tumor targeting by homing lymphocytes

Lead: In vivo homing of autologous lymphocytes can deliver anticancer drugs to poorly accessible tumor-bearing lymph nodes with high efficiency to result in tumor reduction and tissue regeneration.

Development in active cell mediated delivery, which has grown in concurrence with tissue engineering, material science, stem cell science and biological pathway analysis, has led to repair complex tissues, as a facet of regenerative engineering[1]. Here, we introduce a novel cancer chemotherapy treatment that effectively targets disseminated tumors by using tissue-homing lymphocytes as a living drug delivery agent.

Lymphoma is a cancer developed in lymphatic system, which can lead to metastasis in multiple organs as it is derived from the lymphatic cells that circulate along the lymphoid organs. Once the lymphoma enters into the lymph nodes, it becomes difficult to treat with general cancer chemotherapy. The permeation of the drug throughout the blood vessels and tumor is often hindered by rapid metabolism, excretion, and biological barriers and thus inevitably requires excess dosage to induce the proper level of an anticancer therapeutic effect[10,11]. Even with the support of current advanced drug delivery systems using nanoparticles, issues such as low efficiency of targeting tumor cells in lymph nodes arose, as nanoparticles were often trapped outside the tumor while their delivery pathways were mostly limited to the presence of the leaking vasculature. To augment the therapeutic efficacy of drug delivery while reducing toxic side-effects of the drugs, writing in Science Translational Medicine, Darrell J. Irvine and colleagues from Massachusetts Institute of Technology designed and developed active targeting chemotherapy on cancer cell by using nanoparticle-carrying T cells with engineered homing receptors to access into tumor-bearing lymph sites [12]. The team expanded autologous polyclonal T cells ex vivo, functionalized their surface to carry drug-loaded nanocapsules, and transferred carrier T cells in a murine model of disseminated lymphoma. This "Trojan horses" strategy of nanoparticle-decorated T cells to actively target hidden tumor cells has increased potency of the drug more than 40-fold greater than dosing free drug, enhancing overall tumor recovery in vivo.

Since cancer has been one of the most critical causes of human death, many treatments have been investigated, including surgical intervention, radiation, and chemotherapeutic drugs[13]. To minimize toxic adverse effects of anticancer drugs by enhancing the efficiency of tumor targeting, drug delivery has been rapidly developed by the integration of nanotechnology and advanced organic/inorganic materials. Current chemotherapeutics target tumor cells either passively by extravasation of nanocarriers through the leaky vasculature based on enhanced permeability and retention (EPR) effect or actively by conjugating nanocarriers with molecules that can bind to target tumor cell[14]. To increase circulating time in blood and to enhance targeting efficiency, cell-mediated drug delivery system using circulating cells, such as red blood cells, white blood cells, and stem cells, have recently gained increasing attention due to their disease tracking capacities and homing properties[15]. Among circulating cells, T lymphocytes have generated promising results as carriers to deliver chemotherapy agents to treat hematologic malignancies[16,17].

In the recent literature, Darrell J. Irvine and colleagues used polyclonal T cells which can be obtained with large numbers (~250 to 500 million) from a single leukapheresis and quickly expanded (~5000-fold), whereas tumor-specific T cells can be only isolated from patients.
Nanocapsules were synthesized by divalent cation-mediated fusion of anti-cancer drug SN-38 loaded anionic bilayers and subsequent stabilization by the formation of covalent crosslinks between these liposome walls to build multilamellar lipid capsules. After crosslinking, remaining maleimide groups on the surface of nanocapsules were conjugated with thiols of T cells and the residual malemide groups were quenched by polyethylene glycol-thiol. Without malemide groups, nanocapsules

*Continued on next page*

and T cells had minimal nonspecific interactions. The direct conjugation of SN-38 loaded nanocapsules on the cellular membrane did not cause toxicity or alter the functions of carrier cells. After the injection of nanocapsule-loaded T cells (NC-T cells) into the tumor-bearing mice model, NC-T cells were dispersed throughout the tumor-bearing lymphoid organs. Concentration of SN-38 accumulation in tumor-bearing lymph nodes delivered by NC-T cells was 63-fold greater than free nanocapsules. As a result, animals treated with SN-38 NC-T cells exhibited 60-fold reduction of tumor burden. In addition, based on the result that one-fourth dose of NC-T cells showed a similar level of tumor burden with ten times more concentrated free SN-38 dose, NC-T cell mediated delivery had increased the potency of SN-38 by 40-fold while it simultaneously lowered off-target toxicity.

The active targeting strategy developed by Darrell J. Irvine and colleagues, using tissue-homing of autologous lymphocytes as chaperones for drug delivery, achieved a high efficacy of drug delivery to poorly accessible tumor sites. The efficiency of a drug-loaded cellular platform has a high potential to continuously increase by converging the ongoing progress of nanotechnology into carrier design. In addition, autologous T cells can be easily obtained from the blood and expand into mass quantity. As T cells are involved in the cell-mediated immunity of most tissues, tissue-homing of lymphocytes carriers can be applied into other organs as well by modifying homing ligands related to targeting of T cells. It is conceivable that these actively targeting pharmacytes will be applied to clinical trials to cure diseases and to regenerate tissues.

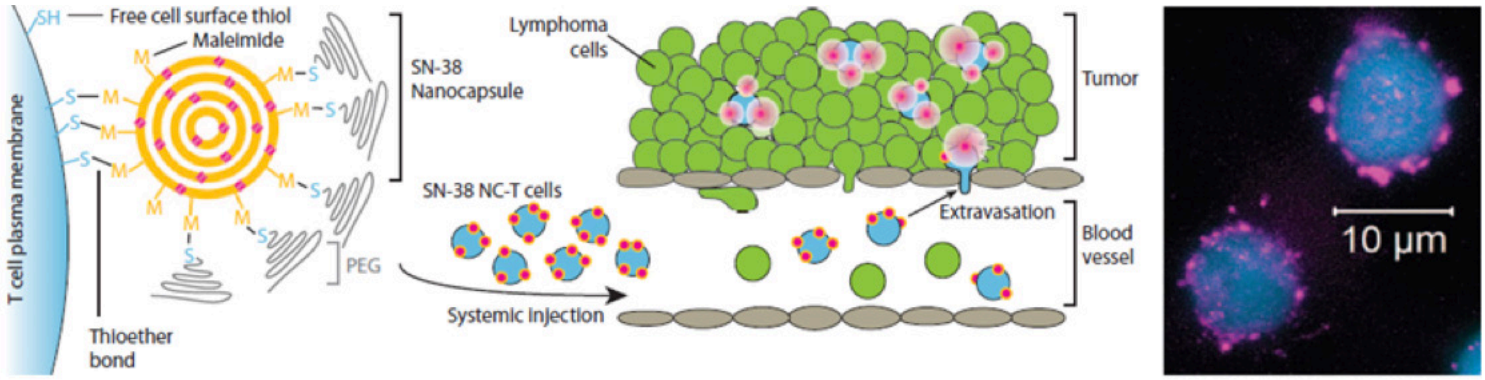


**Figure 2**: *Schematic of cell mediated delivery of drug loaded nanoparticles into poorly accessible tumors (left) and confocal microscopy image of T cells conjugated to nanocapsules. (From Huang et al. 2015. Science Translational Medicine, 7:291ra94. Reprinted with permission from AAAS.).*

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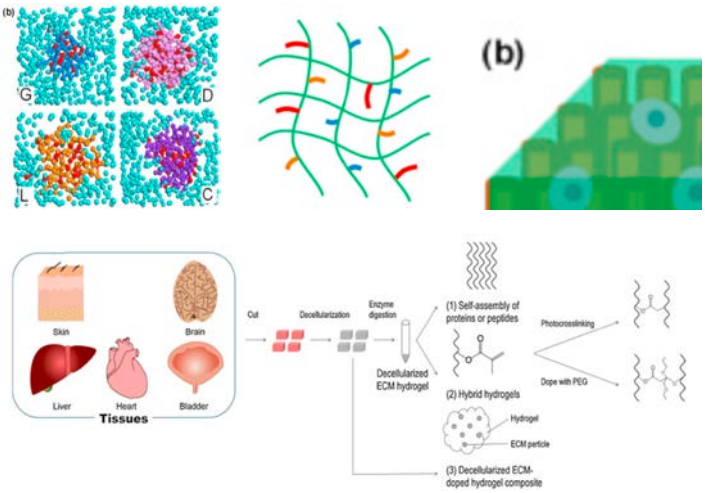
## Recent BIRC Publications

### The matrix reloaded: the evolution of regenerative hydrogels

*Esmaeil Jabbari, Jeroen Leijten, Qiaobing XU, Ali Khademhosseini.*
*published in: materials tody, november 2015*

**A/** Cell-laden hydrogels can regenerate lost, damaged or malfunctioning tissues. Clinical success of such hydrogels is strongly dependent on the ability to tune their chemical, physico-mechanical, and biological properties to a specific application. In particular, mimicking the intricate arrangement of cell-interactive ligands of natural tissues is crucial to proper tissue function. Natural extracellular matrix elements represent a unique source for generating such interactions. A plethora of extracellular matrix-based approaches have been explored to augment the regenerative potential of hydrogels. These efforts include the development of matrix-like hydrogels, hydrogels containing matrix-like molecules, hydrogels containing decellularized matrix, hydrogels derived from decellularized matrix, and decellularized tissues as reimplantable matrix hydrogels. Here we review the evolution, strengths and weaknesses of these developments from the perspective of creating tissue regenerating hydrogels.




## Highly Elastic and Conductive Human-Based Protein Hybrid Hydrogels

*Annabi N, Shin SR, Tamayol A, Miscuglio M, Bakhooshli MA, Assmann A et. al. Advanced materials 2015.*

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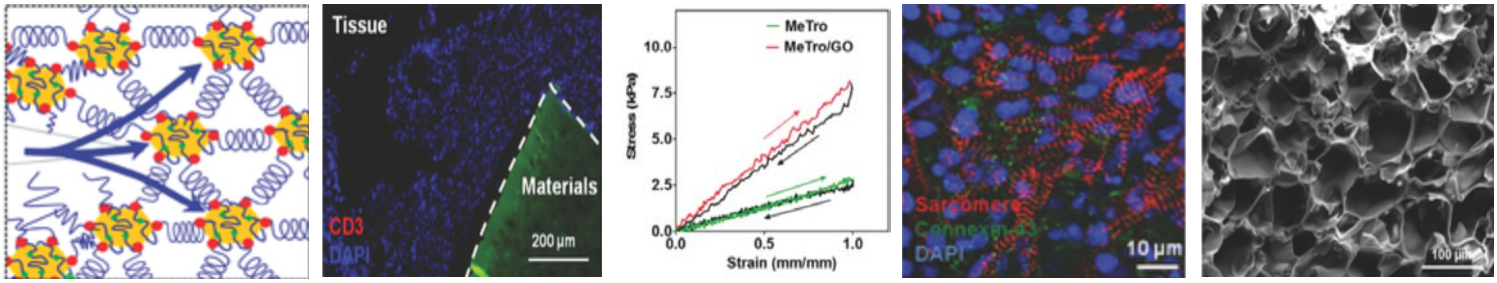
**A/** A highly elastic hybrid hydrogel of methacryloyl-substituted recombinant human tropoelastin (MeTro) and graphene oxide (GO) nanoparticles are developed. The synergistic effect of these two materials significantly enhances both ultimate strain (250%), reversible rotation (9700°), and the fracture energy (38.8 ± 0.8 J m−2) in the hybrid network. Furthermore, improved electrical signal propagation and subsequent contraction of the muscles connected by hybrid hydrogels are observed in ex vivo tests.




### *Bioprinting the Heart: Applications in Tissue Fabrication and Organs-on-a-chip*

*Y Zhang, A Arneri, V Dell'Erba, S Shin, J Aleman, F Busignani, S Bersini, et. al. Tissue engineering part A: 2015.*

### *Dermal Patch with Integrated Flexible Heater for on Demand Drug Delivery*

*Sara Bagherifard, Ali Tamayol, Pooria Mostafalu, Mohsen Akbari, Mattia Comotto. et al. Advanced Healthcare materials 2015.*

### *Evaluation of Lung Sealants as Suture Replacements in an Ex Vivo Pig Model*

*Sebastian Ochoa, Bijan Dehghani, George Cheng, Jennifer Wilson, Adnan Majid, Nasim Annabi, Ali Khademhosseini, Sidhu Ganghadaran. CHEST journal 2015*



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## BIRC News

# Joao Ribas wins prize at Athenahealth Hackathon!

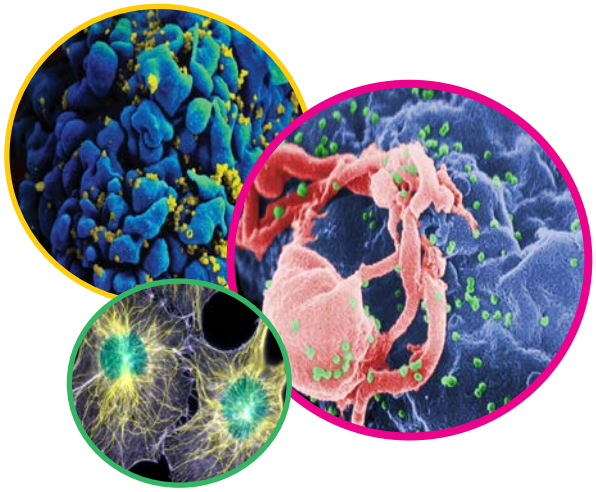

We are happy and proud to announce that Joao Ribas has received a $500 prize at the Athenahealth More Disruption Please Hackathon! His PhD reserach spans from organs-on-chip mechano-transduction to biomedical tools. We congratulate him on receiving the prize in recognition of his entrepreneurial skills.

## The Art of Science Award

# Show your artistic research skills by joining BIRC's the 'Art of Science' contest

To showcase the artistic side of our center's researchers, BIRC members may compete for the art of science award 2015!
A panel of judges will select 3 image as finalists for the yearly Art of Science Award. Judging of the images will be based on scientific value, originality and artistic/visual impact.

The winner's images will be framed and an example will be given to all finalists. In addition, the best image will receive an extra Prize. Winners will be announced in the next BIRC-update of December 2015. Please send you images (SEM/TEM/AFM/Fluorescecne/....) with a short description to **sadeghi@mit.edu** before December 20th. (one for each per person).



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