3rd NOVEL FLUIDIC TECHNOLOGIES WORKSHOP WITH AN EMPHASIS ON TISSUE ENGINEERING

WORKSHOP

21-22 June 2018

IZMIR/TURKEY

3rd Novel Fluidic Technologies Workshop with an Emphasis on Tissue Engineering Workshop Abstract Book

ISBN: 978-605-65463-2-7

Dear Colleagues,

"3rd Novel Fluidic Technologies" workshop which is held on 21 - 22 June 2018 at Bioengineering Department, Ege University Izmir/TURKEY within the framework of our on-going (**117M843**) bilateral project titled as "**Synthesis of a novel stiff hydrogel for cartilage tissue engineering functionalized with nanoparticles fabricated by using a microfluidic platform along with *in vivo* studies**" supported by NRF Korea and TUBITAK.

Within the past two decades, microfluidic technology has evolved from a highly advanced tool for engineers to a versatile field at the interface of physics, engineering, medicine, chemistry and biology. Over the past years, microfluidic approaches have been used in biotechnology, pharmaceuticals, life sciences, defense and public health for a variety of applications, including point-of-care diagnostics, lab-on-a-chip, organ-on-a-chip platforms specifically focusing on detection of viral and bacterial infections, cell capturing, DNA microarrays, high throughput screening and toxicity of drug molecules and disease modelling. Likewise, the trends in supercritical fluids have been extended to major life science applications such as encapsulation of drug molecules, enzymatic treatments and drying of scaffolds.

The scope of the workshop is to bring together scientists and young researchers to discuss breakthrough research in the field of fluidic technologies, specifically microfluidics and supercritical fluids focusing on life science applications and to enhance skills of young researchers through knowledge exchange. Poster presentations by young researchers are carried out in a competitive environment and the selected best three poster presentations are rewarded by "Young Researcher Excelling in Novel Fluidics" award.

We look forward to the scientific exchange and the profile you bring to this meeting.

On behalf of the Organizing Committee,

Assoc. Prof. Dr. Ozlem YESIL-CELIKTAS
Workshop chair,
Ege University
Department of Bioengineering

3rd NOVEL FLUIDIC TECHNOLOGIES WORKSHOP WITH AN EMPHASIS ON TISSUE ENGINEERING

(21-22 June 2018)

	21.06.2018 (THURSDAY)
9.00-9.30	Registration
9.30-10.00	Opening session
10.00-11.00	Stretchable ionics – A promising candidate for oncoming wearable devices (Ass. Prof. Dr. Jeong-Yun SUN)
11.00-11.30	Organ-on-chip platforms for disease modelling (Assoc. Prof. Dr. Ozlem YESIL CELIKTAS)
11.30-12.00	Rapid prototyping and microfabrication of microdroplet generator for cell encapsulation (Assoc. Prof. Dr. Ahu ARSLAN YILDIZ)
12.00-13.30	Lunch
13.30-14.00	Microfluidic synthesis of precision microparticles for clinical applications (Dr. Wim van HOEVE)
14.00-14.30	Genetic applications of lab-on-a-chip (Assoc. Prof. Dr. Ayca AYKUT)
14.30-15.00	Development and application of an electrochemical biosensor system (Ass. Prof. Dr. Yalin KILIC)
15.00-15.30	Coffee break
15.30-16.00	Microfluidic applications in cancer research (Dr. Gizem CALIBASI KOCAL)
16.00-16.30	Hyaluronic acid nanocomposite hydrogels via precipitation process for biomedical applications (Dr. Seol-Ha JEONG)
16.30-17.00	Weightlessness and bone tissue (Assoc. Prof. Dr. Engin OZCIVICI)

3rd NOVEL FLUIDIC TECHNOLOGIES WORKSHOP WITH AN EMPHASIS ON TISSUE ENGINEERING

(21-22 June 2018)

	22.06.2018 (FRIDAY)
10.00-11.00	Engineering musculoskeletal organ by advanced biomaterials and microfluidic bioprinting technologies (Dr. Hae Lin JANG)
11.00-11.30	Microfluidic systems for bio-particle manipulation (Assoc. Prof. Dr. Barbaros CETIN)
11.30-12.00	Biosensors in health care: state-of-the-art developments and future perspectives (Assoc. Prof. Dr. Seda Nur TOPKAYA)
12.00-13.30	Lunch
13.30-14.00	Injectable shear thinning hydrogels for bone tissue engineering (Ass. Prof. Dr. Emine ALARCIN)
14.00-14.30	Cancer-on-a-chip (Assoc. Prof. Dr. Devrim PESEN OKVUR)
14.30-15.00	Biofunctionalization of electrospun nanofibers and their applications (Assoc. Prof. Dr. Dilek ODACI DEMIRKOL)
15.00-15.30	Coffee break
15.30-16.00	Microfluidics gene delivery platforms to study in vitro efficacy of DNA vaccination and gene therapy for cancer immunotherapy (Ass. Prof. Dr. Sultan GULCE IZ)
16.00-16.30	Clinical needs for novel techologies in lung research area (Assoc. Prof. Dr. Ozlem GOKSEL)
16.30-17.00	Poster presentations
17.00-17.15	Award ceremony and closing remarks

Invited Speakers

Stretchable ionics – A promising candidate for oncoming wearable devices

Jeong-Yun Sun

Department of Materials Science and Engineering, Seoul National University, Seoul 08826, Republic of Korea

e-mail (jysun@snu.ac.kr)

ABSTRACT

As many devices for human utility target fast and convenient communications with users, superb electronic devices have been demonstrated as hardware for Human-Machine Interface (HMI) in wearable forms. Wearable devices for daily health-cares and self-diagnosis desire more human-like properties unconstrained to deformation. In this sense, stretchable ionics based on flexible and stretchable hydrogels is on the rise as another field to develop wearable devices for bio-applications due to two major reasons; i) ionic currents, choosing the same signal carriers with biological areas, and ii) the adoption of hydrogel ionic conductors which are intrinsically stretchable materials with bio-compatibility. Here, forte and current status of stretchable ionics as well as future applications whose positive effects can be magnified by stretchable ionics are going to be introduced.

Keywords: flexible, stretchable, wearable devices

Organ-on-chip platforms for disease modelling

Ozlem Yesil-Celiktas

Department of Bioengineering, Faculty of Engineering, Ege University, 35100 Bornova, Izmir, Turkey

e-mail (ozlem.yesil.celiktas@ege.edu.tr)

ABSTRACT

Innovative technologies converged with more in-depth understanding of human physiology has opened new horizons for biologically inspired devices that mimic human tissue and organ functions. Microfabrication of such devices are based on microfluidic chips, which feature perfused chambers loaded with structured cells. These so-called organ-on-chip platforms recapitulate the multicellular architectures, cell-cell interactions, extracellular matrix and vascular perfusion of various organs such as gut, liver, kidney, lung, heart and brain. These platforms also allow high-resolution, real-time imaging and non-invasive analysis of biochemical, genetic and metabolic activities of living cells in a functional tissue and organ context. All these aspects make them perfect alternatives to animal models, where more than 30% of medications have failed in human clinical trials as proved to be toxic despite promising pre-clinical results. Developing platforms that model pathologies can yield information regarding the cause and progression of abnormal conditions as well as the structural and functional changes resulting from various diseases. Although animal models are often utilized to address this challenge, mimicry of human responses and interpretation of the results fail in many pathologies such as in murine models falling short in recapitulating human pathology. Therefore, more sophisticated models are required to mimic the pathology in human tissues and organs. So far, various disease models have been reported in the fields of neurodegenerative [1], cardiovascular [2], respiratory [3], liver disorders [4] and gastrointestinal diseases [5], as well as in cancer. In our group, we are currently developing a lung cancer-on-a-chip to study the effects of some potential drug molecules and have also investigated the effect of an anticancer compound on estrogen dependent and independent breast cancer cells in a butterfly shaped microfluidic chip allowing the cultivation of both cancerous and healthy mammary cells. Additionally, we have been involved in design and fabrication of a liver cancer-on-a-chip to mimic liver cancer metastasis to bone. Although the field is still in its infancy, we anticipate an exponential growth in the coming decade, particularly with models for chronic and more complex diseases.

Keywords: disease etiology, microfabricated devices, organ-on-a-chip, pre-clinical studies

References

[1] J. Park, S. Kim, S. I. Park, Y. Choe, J. Li, A. Han, Journal of neuroscience methods 2014, 221, 166.
[2] M. L. McCain, S. P. Sheehy, A. Grosberg, J. A. Goss, K. K. Parker, Proceedings of the National Academy of Sciences 2013, 110, 9770.
[3] K. H. Benam, R. Novak, J. Nawroth, M. Hirano-Kobayashi, T. C. Ferrante, Y. Choe, R. Prantil-Baun, J. C. Weaver, A. Bahinski, K. K. Parker, D. E. Ingber, Cell Systems 2016, 3, 456.
[4] L. A. Vernetti, N. Senutovitch, R. Boltz, R. DeBiasio, T. Ying Shun, A. Gough, D. L. Taylor, Experimental biology and medicine 2016, 241, 101.
[5] R. Villenave, S. Q. Wales, T. Hamkins-Indik, E. Papafragkou, J. C. Weaver, T. C. Ferrante, A. Bahinski, C. A. Elkins, M. Kulka, D. E. Ingber, PloS one 2017, 12, e0169412.

Rapid prototyping and microfabrication of microdroplet generator for cell encapsulation

Ahu Arslan-Yildiz

Izmir Institute of Technology (IZTECH), Izmir, Turkey

e-mail (ahuarslan@iyte.edu.tr)

ABSTRACT

Microfluidics offer promising experimental platforms for varied chemical and biological lab-on-a-chip applications, therefore microfluidics attracted significant attention over the past decade [1]. The conventional microfabrication techniques for microfluidic chip production requires cleanroom facilities and processes which are highly expensive and time consuming. To overcome this limitation, we have demonstrated a rapid, low-cost and time efficient methodology that enables the prototyping and microfabrication of microfluidic chips less than 1 hour including the design step. The method consists of three fabrication steps; (i)microfabrication via laser ablation, (ii)channel protection and (iii)polymer-based bonding. A commercial CO2 laser is used for laser ablation of polymethylmethacrylate (PMMA) substrates for rapid prototyping of microfluidic chips. The microdroplet generator is created by using a commercially available software and converted into designed microfluidic chips by direct-writing ablation technique. Later channels were protected using phase change material (PCM) followed by polymer-based bonding of PMMA layers. Surface quality and the aspect ratio of microfabricated channels were characterized by surface sensitive techniques. To demonstrate the feasibility of developed technique, microfluidic chip was utilized as microdroplet generator for cell encapsulation. Results confirmed that proposed microfabrication technique propose a rapid and cost-effective prototyping option compared to current alternatives [2-3].

Keywords: microfluidics, microdroplet generator, PMMA, rapid prototyping, bonding

References

[1] Mark, D., Haeberle, S., Roth, G., Stetten, F., Zengerle, R. Chemical Society Reviews, 39, 1153-1182 (2010).
[2] O'Neill, P.F., Azouz, A.B., Vazquez, M., Liu, J., Marczak, S., Slouka, Z., Chang, H.C., Diamond, D., Barabazon, D. Biomicrofluidics, 8, 052112 (2014).
[3] Duffy, D.C., McDonald, J.C., Schueller, O.J.A., Whitesides, G.M. Analytical Chemistry, 70, 4974-4984 (1998).

Microfluidic synthesis of precision microparticles for clinical applications

Wim van Hoeve

Tide Microfluidics, Capitool 41, 7521 PL, Enschede, The Netherlands

e-mail (w.vanhoeve@tidemicrofluidics.com)

ABSTRACT

The creation of controlled drug delivery systems, that enable personalised medicines and direct targeting of diseases is a major challenge in ensuring a reduction in healthcare cost while maintianing quality of care for patients [1,2]. Using ultrasound contrast agents (UCA) as drug carriers is an innovative solution to this challenge, whereby ultrasound imaging allows real-time monitoring of the affected area and confirmation of the drug delivery to the target site. Ultrasound contrast agents comprise of millions of microbubbles, smaller than a red blood cell in size, that oscillate in the ultrasound field increasing the image contrast to enable better visualisation of the patients affected organs. In order to optimise the the effectiveness of the UCA image enhancement and to control drug doses accurately the use of monodisperse UCAs is key.

To create uniformly sized UCAs Tide Microfluidics has developed a proprietary microfluidic technology for the production of microbubbles [3]. This technology is currently available as a research system, the MicroSphere Creator, that allows table top development of drug loaded monodisperse UCAs, enabling researchers to develop their own unique formulation for a specific disease. Current research has led to a variety of uniform microbubbles with various shell components such as targeting biomarkers and nanoparticle coatings being created with this technology. In addition to the MicroSphere Creator, product development is underway at Tide Microfluidics to create a table top production device to allow clinically validated production of personalised medicines at the bedside of the patient.

Keywords: microbubbles, microfluidics, monodisperse, targeted drug delivery, ultrasound contrast agent

References

[1] S. Hernot and A. L. Klibanov. Advanced drug delivery reviews. 10, 1153-1166 (2008).
[2] K. Ferrara, R. Pollard and M. Borden. Annual Review of Biomedical Engineering. 9, 415-447 (2007).
[3] E. Castro-Hernández, W. Van Hoeve, D. Lohse and J. M. Gordillo. Lab on a Chip. 11, 2023-2029 (2011).

Genetic applications of lab-on-a-chip

Ayca Aykut

Ege University Faculty of Medicine Department of Medical Genetics

e-mail (aycaaykut@gmail.com)

ABSTRACT

Precision medicine (PM) is a medical model that proposes the customization of healthcare, with medical decisions, treatments, practices, or products being tailored to the individual patient. In this model, diagnostic testing is often employed for selecting appropriate and optimal therapies based on the context of a patient's genetic content or other molecular or cellular analysis. Recent improvements in genomics and connected to the improvement of micro and nano-technologies open very interesting perspectives in the field of presicion medicine. Therefore, the development of highly integrated devices such as Lab-on-Chip (LoC) which is capable of scaling the single or multiple laboratory functions down to chip-format, able to rapidly and automatically perform various analyses such as, analitic chemistry, molecular biology, and genetics. LOCs are being applied in lots of molecular diagnostic steps: DNA extraction and purification, PCR, qPCR, molecular detection, electrophoresis. Due to the miniaturization of these applications, better diagnostic speed, cost efficiency, ergonomy, sensitivity can be achieved. This makes LOC applications suitable for clinical diagnostics and 'near-patient' or 'point-of-care' (POC) testing. Point-of-care diagnostic devices founded in microfluidic technologies will lead the change to presicion medicine, thereby, having a great effect in the diagnosis and treatment of diseases for future healthcare..

Keywords: genomics, lab-on-chip, point-of-care

Development and application of an electrochemical biosensor system

Yalin Kilic[1,2*], Ozlem Kilic[1] and Alper Demirhan[1]

[1]*Solar Biyoteknoloji İlaç Kimya ve Gıda San. Tic. Ltd. (SolarBiotec), Turkey*
[2]*Dokuz Eylül Üniversitesi, Adli Tıp Anabilim Dalı, Turkey*

e-mail (*yk@solarbiotec.com)

ABSTRACT

We have optimized and automatized the manufacturing of gold thin film electrodes on disposable sensor chips to reduce interlot variations and developed a synchronous multi-channel potentiostat system for electrochemical analysis on sensors with more than one working electrode. Automation of the manufacturing of the chips decreased their rejection rate to 15%, which was previously about 40% by manual processing. Changing the surface preparation method improved the response consistency to reach a variation of less than 2% in peak character. Also, synchronous measurement capability of the developed potentiostat device provides us to compansate variations, digitally.

All but dicing and optical evauation steps of the microelectrode manufacturing were automatized and various single, as well as multi electrode sensor designs were implemented. GalvanoPlot™, a USB powered, self contained, multi-potentiostat interface capable of scanning the ±2.0 V x 363 µA with a resolution of 736 µV and sensitivity of 390 pA, which is world's smallest in its class is designed and manufactured. On the other hand, twin working electrode chips recruiting common counter and reference electrodes were functionalized with unlabelled and labelled aptamers for cortisol and cocaine and tested as a whole.

The potentiostat design takes advantage of the low cost Texas Instrument LMP91000 analog front end to decrease end user costs and improved the performance results of a previous study [1]. We have also showed the performance of a previously described cortisol aptamer [2] on thin film gold electrode sensors, for the first time. To improve the repeatability and simplify the application, same sensor electrodes are functionalized to act as "signal-on". Methylene blue labelled cocaine aptamer that are shown to be successful in a previous study [3] is selected for further testing and is still being studied.

Keywords: aptasensors, biosensors, bipotentiostat, electrochemical, thin film electrodes

Acknowledgements

This project was partly supported by EU-FP7 Era-net European Framework Collaboration Grant Manu-net II Programme under the name "ManuMEMS" and in partnership with MicruX Technologies of Asturias, Spain.

References

[1] AF. Cruz, NR. Norena, A. Kaushik and S. Bhansali. Biosens Bioelectron 62:249-54 (2014).
[2] AS. Zainol Abidin, RA. Rahim, et al. Sensors (Basel). 17(5): 1180 (2017).
[3] JS. Swensen, Y. Xiao, et al. J Am Chem Soc. 131(12): 4262–4266 (2009).

Microfluidic applications for cancer research

Gizem Calibasi-Kocal[1,2]

[1]*Dokuz Eylul University, Institute of Oncology, Department of Basic Oncology, Izmir*
[2]*Dokuz Eylul University, Personalized Medicine and Pharmacogenomics/Genomics Research Center-BIFAGEM; Izmir, Turkey).*

e-mail (gizem.calibasi@deu.edu.tr)

ABSTRACT

Cancer is a leading and continuously increasing global health problem, hence cancer studies have significant impact on the future of scientific progress. However the heterogeneity and complication of cancer have hosted challenges to researchers in the field. Microfluidic technologies have been increasingly improved toward applications for medical problems. Among the increasing number of cancer related studies, these systems have emerged as promising platforms to elucidate cancer cell function. Especially they are well suited to cancer related applications for screening, diagnosis and treatment in terms of both routine or research based procedures [1, 2]. Microfluidics offer advantages on cancer investigation due to its high sensitivity, high throughput, micro-scale material-consumption, cost-effectiveness, controllability at cellular level and real-time monitoring. In recent years, the microfluidic applications have branched in several exciting directions to address longstanding challenges in cancer diagnosis and management, such as detection/isolation of circulating tumor cells from blood, molecular diagnostics, cell culture applications to study cellular characteristics of cancer cell and high-throughput screening for therapeutics [3, 4]. Here, these critical areas in cancer research and some of our lab's current research will be presented in the corresponding sections.

Keywords: cancer cell culture, circulating tumor cells, high-throughput screening, microfluidics, molecular diagnosis, tumor biology

References:

[1] Z. Zhang and S. Nagrath. Microfluidics and cancer: are we there yet? Biomed Microdevices 15(4), 595-609 (2013).
[2] D. Pappas. Microfluidics and cancer analysis: cell separation, cell/tissue culture, cell mechanics, and integrated analysis systems. Analyst 141(2), 525-35 (2016).
[3] W. Qian, Y. Zhang and W. Chen. Capturing Cancer: Emerging Microfluidic Technologies for the Capture and Characterization of Circulating Tumor Cells. Small 11(32), 3850-72 (2015).
[4] H.F. Tsai, A. Trubelja, A.Q. Shen and G. Bao. Tumour-on-a-chip: microfluidic models of tumour morphology, growth and microenvironment. J R Soc Interface 14(131), pii: 20170137 (2017).

Hyaluronic acid nanocomposite hydrogels via precipitation process for biomedical applications

Seol-Ha Jeong, Hyoun-Ee Kim*, Jeong-Yun Sun*

Department of Materials Science & Engineering, Seoul National University, Seoul, South Korea

e-mail (*kimhe@snu.ac.kr, *jysun@snu.ac.kr)

ABSTRACT

A general and simple approach to prepare nanocomposite hydrogels is to create a nanoparticle suspension in a hydrogel-forming solution before gelation, which is called "simple mixing" [1]. However, this approach has several drawbacks such as the low level of interaction between the polymer chains and nanoparticles [2] and aggregation of nanoparticles within the hydrogel networks [3].

Herein, we introduce an advanced procedure, called an "*in situ* precipitation process," that produces uniform nanocomposite hydrogels with a high level of integration between the precipitated particles and hydrogel networks. This precipitation process results in nanocomposite hydrogel systems with greatly improved mechanical properties and even enhanced biocompatibility. We present this approach for the precipitation of bioceramic nanoparticles within hyaluronic acid (HAc) hydrogels, which are representative hydrophilic polymers with high water uptake capability. HAc–calcium phosphate (CaP) nanocomposite hydrogel systems are introduced, and the enhancements of their mechanical properties and biocompatibility compared with those of nanocomposites fabricated using conventional methods are systematically evaluated. In addition, The applications of this system to injectable dermal fillers and hydrogel wound dressings are introduced, and the HAc–nanoHAp filler shows great potential as a soft tissue augmentation product by improving the biophysical and biological performance of skin tissue. The CaF_2 nanocomposite hydrogel, which is fabricated via *in situ* precipitation using $CaCl_2$ and NH_4F, shows great potential for application as an advanced hydrogel wound dressing with both antibacterial and accelerated wound healing effects.

Keywords: nanocomposite hydrogel, hyaluronic acid, injectable dermal filler, *in situ* precipitation, wound dressing

Acknowledgements

This research was supported by the R&D Program (S2174750) funded by the Small and Medium Business Administration (SMBA, Korea).

References

[1] Thoniyot, P., et al., *Nanoparticle-Hydrogel Composites: Concept, Design, and Applications of ThesPromising, Multi-Functional Materials.* Adv Sci (Weinh), 2015. **2**(1-2): p. 1400010.
[2] Richtering, W. and B.R. Saunders, *Gel architectures and their complexity.* Soft Matter, 2014. **10**(21): p. 3695-3702.
[3] Berts, I., et al., *Structure of polymer and particle aggregates in hydrogel composites.* Journal of Polymer Science Part B: Polymer Physics, 2013. **51**(6): p. 421-429.

Weightlessness and bone tissue

Engin Ozcivici

Department of Bioengineering, Izmir Institute of Technology, Urla, Izmir

e-mail (enginozcivici@iyte.edu.tr)

ABSTRACT

Mechanical loads are known to be important determinants of skeletal health [1-2]. Their omnipresence in skeletal tissue regulate bone mass and morphology continuously. Lack of mechanical forces such as bedrest, stroke and sedentary lifestyle induce deterioration in bone structure causing socio-economic costs. Similarly, cessation of mechanical loads caused by body mass during space missions is a major limiting factor for space exploration of humankind. During the event, I will be discussing the molecular and cellular basis of bone loss during weightlessness and extent of bone recovery during reambulation [3-5]. I will also discuss utilization of extrinsic high-frequency mechanical vibrations to interfere weightlessness induced deterioration [6-7]. Finally, I will briefly discuss cell-based microfluidic models in simulating microgravity [8].

Keywords: bone recovery, cell-based microfluidic models

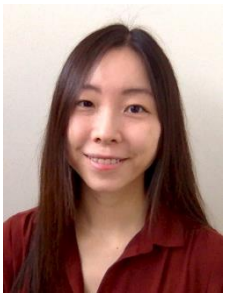
Acknowledgements

I would like to acknowledge institutional support from The Scientific and Technological Research Council of Turkey (Grants: 111T577 and 215S862), Turkish Academy of Sciences and Izmir Institute of Technology.

References

[1] E Ozcivici, YK Luu, B Adler, YX Qin, J Rubin, S Judex, CT Rubin. Nature Reviews Rheumatology 6 (1), 50 (2010).
[2] E Ozcivici. Turkish Journal of Hematology 30 (1), 1 (2013).
[3] S Judex, W Zhang, LR Donahue, E Ozcivici. Journal of Bone and Mineral Research 28 (7), 1537-1549 (2013).
[4] E Ozcivici, W Zhang, LR Donahue, S Judex. Bone 64, 25-32 (2014).
[5] E Ozcivici, S Judex. Bone 67, 122-129 (2014).
[6] E Ozcivici, YK Luu, CT Rubin, S Judex. Plos One 5 (6), e11178 (2010).
[7] L Demiray, E Ozcivici. Turkish Journal of Biology 39 (1), 88-97 (2015).
[8] M Anil-Inevi, S Yaman, AA Yildiz, G Mese, O Yalcin-Ozuysal, HC Tekin, E Ozcivici. Scientific Reports 8 (1), 7239 (2018).

Engineering musculoskeletal organ by advanced biomaterials and microfluidic bioprinting technologies



Hae Lin Jang[1,2]

[1] *Division of Engineering in Medicine, Department of Medicine, Harvard Medical School, Brigham & Women's Hospital, Cambridge, MA 02139, USA*
[2] *Harvard-Massachusetts Institute of Technology, Division of Health Sciences & Technology, Massachusetts Institute of Technology, Cambridge, MA 02139, USA*

e-mail (hjang@bwh.harvard.edu)

ABSTRACT

One in two people live with musculoskeletal diseases, which include nonunion, limb traumas, burns, arthritis, osteoporosis, and spinal cord injury. Unfortunately, the incidence rate of these musculoskeletal diseases is increasing due to the aging population, causing severe pain and economic burden to patients. However, there is no effective treatment in the clinic to rapidly restore the function of these musculoskeletal impairments, as it is difficult to heal large damage throughout multiple tissues, including bone, muscle, tendon, cartilage, blood vessels, and nerves. Most current implant materials are limited to function at a single tissue level, and thus require extensive recovery time, largely due to the lack of interactions with other surrounding tissues. Therefore, there is a significant need for the development of advanced biomaterials that can function instantly after implantation, by harmonizing with the patient's body. To address this need, we have developed advanced biomaterials and biotechnologies to treat currently incurable musculoskeletal diseases/injuries. Since each tissue dynamically communicates with other neighboring tissues, we have been using a holistic and interdisciplinary approach to design and engineer complex organs. At the same time, we used various types of biomaterials for supporting cellular growth and activities as cells of each tissue type seeks their microenvironment with distinct physicochemical properties. In this speech, we will introduce how to control the composition and structure of bone materials at the nanometer scale. We will also discuss various state-of-the-art bioengineering technologies including multi-channel microfluidic bioprinting for developing functional organs by understanding complex interactions among bone minerals, cell/proteins, and other neighboring tissues, including nerves, blood vessels, and muscles.

Keywords: multimaterial bioprinting, musculoskeletal organ implant

Acknowledgements

The authors would like to thank National Institutes of Health (Grant no: AR073135) for providing financial support to this project.

Microfluidic systems for bio-particle manipulation

Barbaros Cetin

Mechanical Engineering Department, Bilkent University, 06800 Bilkent, Ankara

e-mail (barbaroscetin@gmail.com)

ABSTRACT

One of the important challenges is the rapid development of biochips, miniaturized analysis systems or lab-on-a-chip (LOC) devices which are microfluidic platforms on which one can handle chemical and biological analyses, point-of-care testing, clinical and forensic analysis, molecular diagnostics and medical diagnostics for biological, biomedical and chemical applications. LOC devices can perform the same specialized functions as their room-sized counterparts. For chemical, biological and biomedical analysis in microfluidic systems, there are some fundamental operations such as separation, focusing, filtering, concentration, trapping, sorting, detection, counting, washing, lysis of bio-particles, and PCR-like reactions. Manipulation of the bio-particles is the key ingredient for the many aforementioned processes. Therefore, microfluidic bio-particle manipulation has attracted a significant attention from the academic community. Considering the size of the bio-particles and the throughput of the practical applications, manipulation of the bio-particles is a challenging problem. Many research groups and scientists have proposed utilizing different techniques to manipulate bio-particles such as hydrodynamic-based, electrokinetic-based, acoustic-based, magnetic-based, optical-based etc. In this talk, different microfluidic particle manipulation techniques and their assessment will be discussed. The recent numerical and experimental findings of the Bilkent University Microfluidics and Lab-on-a-chip Research Group will be presented.

Keywords: biochips, lab-on-a-chip, microfluidic particle manipulation

Biosensors in health care: State of the art developments and future perspectives

Seda Nur Topkaya

Department of Analytical Chemistry, Faculty of Pharmacy, İzmir Katip Celebi University, Izmir, Turkey

e-mail (sedanur6@gmail.com, sedanur.topkaya@ikc.edu.tr)

ABSTRACT

Pioneered by the first biosensor invention by Clark and Lyons in the 1960s, biosensors have gained tremendous attention in health-care. In addition to medical diagnostics, various market, e.g., pharmacy, food, environmental and agricultural industries demand biosensing technologies. Biosensors are self-contained analytical devices, that employ receptors to react with targeted analytes, where this reaction is converted to a meaningful signal by transducers [1]. Between different biosensing technologies, i.e., optical, electrical or mechanical; electrochemical biosensors have received significant attention as they are low-cost, easy-to-use and can enable the miniaturization of sensing platform for diagnosis applications. Their basic operation principle is based on a working electrode and reference electrode, which are separated by an electrolyte, which is very sensitive potential, current or impedance variations. Electrochemical biosensors are very good candidates for affordable sensing thanks to their simplicity arising from the use of inexpensive and miniaturized electrodes integrated to simple electronics. The continuous interaction between electrodes and electrolyte also enables a real-time detection of analytes, which could be very critical for understanding fundamental biomolecular phenomena. In this presentation, a summary of these electrochemical techniques and their use in health-care and future perspectives for medical diagnostic devices employing electrochemical biosensors will be given. Different electrochemical biosensor designs, i.e., material selection for electrodes and electrolytes and their manufacturing, which is very important for having a comprehensive guideline to achieve an ideal biosensor will be reviewed. We will briefly explain the related theory and practical examples related to these basics. Current electrochemical sensor designs and the trends in developing new generation electrochemical biosensors that enable detection in resource-poor settings will be summarized [2-4]. In addition, we will talk about hand-held electrochemical biosensors, paper-based cheap detection mechanisms, as well as wearable and real-time electrochemical technologies. We will also show commercial hand-held electrochemical devices to show the current status of this technology in improving public health and point-of-care diagnostics.

Keywords: biosensors, electrochemical sensors, point-of-care diagnostics

References

[1] R.K. Darsanaki, A. Azizzadeh, M. Nourbakhsh, G. Raeisi and M. A. Aliabadi. Journal of Biology and Today's World, 2, 53–61 (2013).
[2] D. Zhang, Y. Lu, Q. Zhang, L. Liu, S. Li, Y. Yao, J. Jiang, G.L. Liu, Q. Liu. Sensors and Actuators, 222, 994–1002 (2016).
[3] J. Gao, L. Jeffries, K.E. Mach, D.W. Craft, N.J. Thomas, V.Gau, J.C. Liao, P.M. Wong. SLAS Technology, 22, 466–474 (2017).
[4] C. Zhao, M.M. Thuo, X. Liu, Science and Technology of Advanced Materials. 16, 049501 (2015).

Injectable shear thinning hydrogels for bone tissue engineering

Emine Alarçin[1,2,3*], Tae Yong Lee[2,3,4], Sobha Karuthedom[2,3], Marzieh Mohammadi[2,3], Meadhbh A. Brennan[2,3], Dong Hoon Lee[2,3], Alessandra Marrella[2,3], Jin Zhang[2,3], Denata Syla[2,3], Yu Shrike Zhang[2,3,5], Ali Khademhosseini[2,3,5] and Hae Lin Jang[2,3,5]

[1]*Department of Pharmaceutical Technology, Faculty of Pharmacy, Marmara University, Istanbul 34668, Turkey.*
[2]*Division of Engineering in Medicine, Department of Medicine, Harvard Medical School, Brigham & Women's Hospital, Cambridge, MA 02139, USA.*
[3]*Division of Health Sciences & Technology, Harvard-Massachusetts Institute of Technology, Massachusetts Institute of Technology, Cambridge, MA 02139, USA*
[4]*Department of Chemical and Biomolecular Engineering, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 34141, South Korea*
[5]*Wyss Institute for Biologically Inspired Engineering, Harvard University, Boston, MA 02115, USA*

e-mail (*emine.alarcin@marmara.edu.tr)

ABSTRACT

Despite remarkable regenerative capacity of bone and advances in the treatment of fractures, complications related to impaired fracture healing associated with long bone defects represents a tremendous challenge. The impaired fractures result in nonunion which can occur in any bone due to unstable fracture, or insufficient blood supply, and leads to prolonged pain, disability and economic burden [1, 2]. The current treatment options are autografts, allografts and xenografts, but they have some drawbacks including donor site morbidity, disease transmission and the risk of immune response [3]. Currently, by the virtue of recent achievements in tissue engineering, a number of artificial bone implants were developed, but they haven't been sufficiently used in clinic yet due to ignoring vascularization. Furthermore, they cannot have the ability of filling the irregularly shaped bone defects. To address these limitations, here, we designed a novel injectable silicate-based shear thinning hydrogel to deliver cells and growth factors in a double layer structure. We controlled the solid composition of hydrogel to determine optimal conditions that enable extrusion of hydrogel while delivering both osteogenic and endothelial cells and further growth factors. Hydrogels were able to be simultaneously extruded into 3D constructs through the printhead composed of multiple channels. Extruded hydrogels were further able to fill any irregularly shaped defects in bone with its patterned structure in a continuous manner. Our injectable hydrogels with vasculogenic pattern could be applied for treating bone defects by providing a new platform of shape tunable material with a continuous vascular pattern.

Keywords: bone nonunion, injectable hydrogel, silicate nanoparticles, vasculogenesis

Acknowledgements

Emine Alarçin was supported by The Scientific and Technological Research Council of Turkey (TUBITAK) through a post-doctoral research grant 1059B191500017. The authors would like to thank National Institute of Health (EB021857, AR066193, AR057837, CA214411, HL137193, EB024403, EB023052, EB022403, AR070647), and Air Force Office of Sponsored Research under award #FA9550-15-1-0273 for providing financial support to this project.

References

[1] S. Olson and D. Hahn. Injury 37, 681-690 (2006).
[2] P.V. Giannoudis, T.A. Einhorn and D.Marsh. Injury 38, S3-S6 (2007).
[3] R.R. Rao and J.P. Stegemann. Cytotherapy 15, 1309-1322 (2013).

Cancer-on-a-chip

Devrim Pesen Okvur

Molecular Biology and Genetics, Izmir Institute of Technology

e-mail (dpesenokvur@gmail.com)

ABSTRACT

Cancer cell biology is complex in both space and time. Microfluidics based lab-on-a-chip (LOC) devices provide control at the nano/micrometer and seconds scales. We designed, fabricated and used LOC devices to investigate cell adhesion, invasion and migration, which are the cellular phenomena that are uncontrolled in cancer metastasis. With respect to cell adhesion, using basic LOC devices and complex nanopatterned surfaces, we showed that breast cancer cells better adapted to polarization inducing conditions such as interstitial flow and nano-patterned gradient surfaces, demonstrating their plasticity in comparison to normal mammary epithelial cells. In regard to invasion, it was not known whether the cellular distribution invadopodia, which are proteolytic structures formed by cancer cells, can be regulated by the organization of the extracellular matrix. Using nanometer scale surface protein patterns, our results showed that distribution of invadopodia were polarized towards non-adhesive areas. Furthermore, we investigated interactions of breast cancer cells with macrophages, a prominent duet of the tumor microenvironment. Our results showed that the EGF (epidermal growth factor) – CSF-1 (colony stimulating factor 1) loop is a paracrine – juxtacrine loop contrary to the generally accepted double paracrine loop. Finally, we are developing a new LOC based method for early detection of cancer metastasis. Here, we focus on the extravasation stage of the process, which we mimic in a LOC device.

Keywords: cancer, epidermal growth factor, lab-on-a-chip

Bio-functionalization of electrospun nanofibers and their applications

Dilek Odaci Demirkol

Ege University Faculty of Science Biochemistry Department Bornova-Izmir/Turkey

e-mail (dilek.odaci.demirkol@ege.edu.tr)

ABSTRACT

Diagnostic techniques based on biomolecules have huge a potential to be applied in the application in various areas such as food/beverage industries, diseases diagnostics, monitoring of bio-processes and environmental pollutants. Immobilization of biomolecules on a transducer is the key parameter to being able to prepare a highly stable diagnostic tests. Electrospun nanofibers are a good alternative to immobilize biomolecules [1]. Immobilization matrices provide a connection between the biomaterial and transducer. Additionally, they assist reproducible and repeatable biosensor design with higher stabilization. Biomaterials can be immobilized on to the transducer surface via physical adsorption, covalent binding, cross linking and entrapment techniques. The potential of the nanofibers is promising for human health, for example, tissue/organ regeneration, a vector to transport drugs and other therapeutics, biocompatible and biodegradable medical implants, medical diagnostics, fabrics against infection agents in hospitals, and even cosmetics and dental applications. The uses of these matrices in biomedical applications has a great advantage because of mechanical strength and ease of modification of nanofibers in, for instance, surface morphology and fiber orientation. Recently, nanofibers have been a novel tool for forming biopolymer sheets for tissue engineering. Electrospinning is an ancient and interesting technique and it is a widely-used fabrication technique for producing nanofibers. A variety of materials such as natural and synthetic polymer, polymer alloys, ceramics, composites, chromophores, as well as active metallic agents can be used to prepare nanofibers [2].

Here, optimization of electrospun nanofiber preparation conditions and their applications for the development of bio-functional surfaces were discussed.

Keywords: bio-functionalization, biosensors, electrospun nanofibers

Acknowledgements

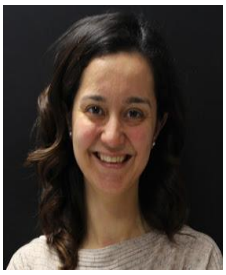
"The authors would like to thank The Turkish Academy of Sciences-Outstanding Young Scientists Award Program-2015 (TUBA-GEBIP), scientific research projects (Tubitak 215Z194 and Ege University Research Funds: 15-FEN-057 and 17-FEN-011) for providing financial support to this project".

References

[1] F. Ozturk Kirbay, E. E. Yalcinkaya, G. Atik, G. Evren, B. Unal, D. Odaci Demirkol, S. Timur. Biosensors and Bioelectronics 109, 286-294 (2018)

[2] O. Coauthor and A. Coauthor. Another Journal 324, 461-512 (2014). B. Unal, E. E. Yalcinkaya, D. Odaci Demirkol, S. Timur. Applied Surface Science 444, 542-551 (2018).

Microfluidics gene delivery platforms to study *in vitro* efficacy of DNA vaccination and gene therapy for cancer immunotherapy



Sultan Gulce-Iz

Ege University, Faculty of Engineering, Department of Bioengineering

e-mail (sultangulce@gmail.com)

ABSTRACT

DNA vaccination is a promising off the shelf candidate for cancer immunotherapy due to its several advantages such as easy to manufacture and cost-effective features. However, the immune response elicited after DNA vaccination is not at the desired level to translate preclinical studies into clinics. The most important step in DNA vaccination is the cellular delivery and uptake of plasmid DNA in which biomaterials are playing potent roles as delivery vehicles and adjuvants to increase the efficacy. In addition to DNA vaccination purposes, gene delivery is also used as gene therapy applications in which DNA, mRNA, miRNA, and RNAi molecules, such as siRNA or small hairpin RNAs (shRNA), and antisense oligonucleotides (AONs) are expected to be delivered as exogenous genetic materials. To study the efficacy of gene delivery *in vitro* has some shortcomings in two dimensional settings (2D). Thus, three dimensional (3D) settings recapitulating *in vivo* physiological conditions are needed where microfluidics platforms take place as promising solutions. *In vitro* gene delivery studies are done using adherent cells that caused undesirable nucleic acid aggregation and transfects cells which is not possible *in vivo*. In addition, *in vitro* experiments are done with very high concentrations of DNA at several hour-long transfections setting in a static closed cell culture flask contrary to circulatory flow *in vivo* settings. Thus, to study the transfection efficiencies 3D microfluidics systems with a continuous flow that mimics circulation is a promising alternative that represents the kinetics and transport conditions relevant for physiological gene delivery to assess mass transport challenges, physical forces, and cell microenvironment interactions [1]. In cancer immunotherapy using nucleic acid delivery both for DNA vaccination and gene therapy purposes are active therapeutic approaches. Targeting the tumor mass and the tumor microenvironment for nucleic acid delivery is a challenging task due to the transportation limitations. Therefore, the selective targeting of the desired tumor cells by using tumor specific monoclonal antibodies and the nucleic acid delivery method to enable transfection before clearance of nucleic acid cargo are becoming important. As well as selecting the nucleic acid delivery method, using specific cell types culturing them as 3D tumor spheroids to mimic tumor microenvironment and enable to express tumor specific antigens that are often down regulated in 2D cultured systems [2]. The state of the art in 3D microfluidics gene delivery platforms and the future expectations to build in vitro test systems to determine the DNA Vaccination and Gene Therapy efficacy for Cancer Immunotherapy will be discussed.

Keywords: DNA vaccination, gene delivery microfluidics, gene therapy, tumor microenvironment

References

[1] Hill AB, Chen M, Chen CK, Pfeifer BA, Jones CH, Overcoming Gene-Delivery Hurdles: Physiological Considerations for Nonviral Vectors, Trends in Biotechnology, Vol. 34, No. 2 http://dx.doi.org/10.1016/j.tibtech.2015.11.004 (2016)

[2] Boussommier-Calleja A, Li R, Chen MB, Wong SC, Kamm RD, Microfluidics: A new tool for modeling cancer-immune interactions, Trends Cancer, 2(1): 6–19. doi:10.1016/j.trecan.2015.12.003 (2016)

Clinical needs for novel technologies in lung research area

Ozlem Goksel

Ege University, Faculty of Medicine. Department of Pulmonary Medicine Division of Allergic Diseases and Asthma. Occupational Airway Diseases Laboratory.

e-mail (goksel.ozlem@gmail.com, ozlem.goksel@ege.edu.tr)

ABSTRACT

There is urgent need to use advanced technologies (e.g. microfluidics, biochips and sensor technologies) to develop novel point-of-care, personalized medicine tools and implement existing technologies in clinical settings with a goal to guide diagnostic and therapeutic efforts for the highly morbid and mortal lung diseases. Researchers from Ege University, Izmir have encouraged to form a multidisciplinary, translational team from laboratory/technical to clinical expertise to develop novel devices that will significantly empower patients, physicians, and clinical researchers to better manage or treat mainly chronic lung diseases including Lung Cancer, Asthma, COPD, Allergy and numerous others. With this speech it will be discussed the clinical needs for novel technologies in Lung Research area with current attempts of the EgeTPAG members.

Keywords: biochips, biosensors, lung diseases, microfluidics, personalized medicine, translational medicine

Poster Presentations for "Young Researchers Excelling in Novel Fluidics" Award

No	Presenting Author	Poster Name
P.1	Ali Kemal Bas	Generation of functional 3D lacrimal gland in microfluidics
P.2	Arzu Yildirim	Applications of microfluidics technology to enhance microalgae platform
P.3	Aslihan Kazan	Synthesis of thymoquinone loaded nanoparticles in a microfluidic system and its regenerative effect on a model organism
P.4	Begum Gokce	Lab-on-a-chip devices for drug screening
P.5	Beste Elveren	Microfluidic green synthesis of gold nanoparticles
P.6	Busra Yildiz	Fine-tuning hydrogel properties as porous tissue engineering scaffold
P.7	Ebru Gursoy	Development of nanobiosensor for dopamine detection
P.8	Ecem Saygili	Developing a micro paper-based analytical device for diagnostic purposes
P.9	Esra Ilhan Ayisigi	The comparison of β,β-dimethylacryl alkannin loaded Silica-PAMAM dendrimer hybrid nanoparticles obtained by a traditional batch production and microfluidic platform
P.10	Esra Turker	Scaffold-free three-dimensional cell culturing using magnetic levitation
P.11	Gizem Bati Ayaz	Optimization of a lab-on-a-chip device and method for quantification of extravasation
P.12	Gizem Evren	Effect of hydrophilic structures on the poly (ε-caprolactone) electrospun nanofiber morphology
P.13	Gozde Atik	Electrospinning clay-decorated hydrophobic-hydrophilic polymer blends to immobilize biological macromolecules
P.14	Gunes Kibar	Microfluidic based micro-particle synthesis
P.15	Hamdullah Yanik	Generation of bone-cartilage interface in microfluidic system
P.16	Irem Yezer	Toxic response of zinc oxide nanoparticles with different dimension on epidermal keratinocyte HaCaT cells
P.17	Olcay Burcin Akbulud	Neurodegenerative disease modeling in 3D microfluidic system
P.18	Ozan Yesiltepe	Testing of quantum dot bioconjugates toxicity on keratinocytes via digital holography
P.19	Pelin Saglam Metiner	3D lung spheroid cultures in microfluidic lung-on-a-chip system mimicking lung cancer disease
P.20	Rabia Onbas	Development of internal gelation based hybrid alginate-silica hydrogel for biocatalytic conversion in microfluidic platform
P.21	Sungsoo Lim	Hydrophilic treated silk fiber reinforced hydrogel with non-invasive, high modulus and toughness
P.22	Yong-Woo Kim	Highly stiff and tough pHEMA-alginate hydrogels

Generation of functional 3D lacrimal gland in microfluidics

Ali Kemal Bas, Olcay Burcin Akbulud, Hamdullah Yanik, Sinan Guven*

Dokuz Eylul University, Izmir Biomedicine and Genome Insitute, Turkey

e-mail (*sinan.guven@deu.edu.tr)

ABSTRACT

Dry eye syndrome (DES) is caused by a chronic lack of sufficient lubrication and moisture on the surface of the eye becuase of various reasons. Approximately 25% of patients referred to general ophthalmology clinics report DES indications[1]. Current methods for treatment of DES are not efficient enough to overcome disease completely. Especially inflammatory cases of this disease lack a proper treatment method. In this project, we aim to develop an artificial functional lacrimal gland from lacrimal gland cells in the precisely controlled microfludic system environment. The artificial lacrimal gland can be a potential treatment for dry eye syndrome especially in inflammatory cases. Tissue engineering is the use of a combination of cells, engineering and materials methods, and suitable biochemical and physicochemical factors to improve or replace biological tissues. The aim of tissue engineering is designing controlled artificial organ or tissue models to help medical treatment tools[2]. Microfluidic systems are interdisciplinary field which that are based on the control of very low volumes of fluids and have many applications in the fields of basic sciences (such as physics, chemistry and biology) as well as in engineering[3]. The objective of the project is to generate an artifical functional lacrimal gland inside of a 3D microfludic system with lacrimal gland cells. To do so, a microfludic system suitable for lacrimal gland generation will be designed. Inside this microfludic system different compartments of lacrimal gland will be cultured within the 3D hydrogel. So far, we achived to design and manufacture the microfludic system and run the flow tests. So far, we succesfully sysnthesized gelatin based photocrosslinkable hydrogel for 3D cell culture system. Design and manufacture of microfludic system is completed and tested. Epithelial and mesenchymal cells were isolated from mice. These cells were cultured.

Keywords: 3D Culture, dry eye syndrome (DES), lacrimal gland, microfludics, tissue engineering

Acknowledgements

This thesis is supported by TUBITAK 1001 - Scientific and Technological Research Projects Funding Program.

References

[1] The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf, 2007. 5(2): p. 75-92.
[2] Guven, S., A. Mehrkens, F. Saxer, D.J. Schaefer, et al., Engineering of large osteogenic grafts with rapid engraftment capacity using mesenchymal and endothelial progenitors from human adipose tissue. Biomaterials, 2011. 32(25): p. 5801-9.
[3] Tseng, P., A. Kunze, H. Kittur, and D. Di Carlo, Research highlights: Microtechnologies for engineering the cellular environment. Lab Chip, 2014. 14(7): p. 1226-9.

Applications of microfluidics technology to enhance microalgae platform

Arzu Yildirim

Ege University, Faculty of Engineering, Department of Bioengineering, Izmir-Turkey

e-mail (arzuyildirim78@gmail.com)

ABSTRACT

Microalgae are photosynthetic, single celled organisms, used in different areas of biotechnology such as food and feed industries, the production of biofuels and biochemicals [1]. They also have been used as a platform for recombinant dna technologies for over twenty years [2]. Their small size differing from 1 μm to over 2 mm, make them suitable as a material for the applications of microfliuidics technology. Like every system, microalgal platform has its own superiorities and drawbacks compared to other systems. Some of the problems faced in microalgal production systems such as cell culturing, cell screening, selection or even transformation have been addressed by microfluidics approach, and gave unique solutions for the advancement of the system [3,4,5]. Its economically convenient, robust, fast and sensitive features makes microfluidics a promising technology for the future studies of microlagae platform.

Keywords: microalgae, microfluidics, lab-on-a-chip

References

[1] R. Raj, S. Hemaiswarya, N. Ashok Kuma, S. Sridhar, R. Rengasamy. Critical Reviews in Microbiology, 34, 77–88 (2008)
[2] R.L. Banares, D.G. Ballester, A. Galvan and E. Fernandez. Trends in Biotechnology 22(1), 45-52 (2004)
[3] B. Qu, Y.J. Eu, W.J. Jeong and D.P. Kim. Lab on a Chip 12, 4483–4488 (2012)
[4] Y.J. Juang and J.S. Chang. Biotechnology Journal 11, 327–335 (2016)
[5] C.S. Luke, J. Selimkhanov, L. Baumgart, S.E. Cohen, S.S. Golden, N.A. Cookson and J. Hasty. ACS Synthetic Biology 5(1), 8–14 (2016)

Synthesis of thymoquinone loaded nanoparticles in a microfluidic system and its regenerative effect on a model organism

Aslihan Kazan[1]*, Kutay Deniz Atabay[2], Ozlem Yesil-Celiktas[1,3]

[1]*Department of Bioengineering, Faculty of Engineering, Ege University, 35100, Bornova, Izmir, Turkey*
[2]*Department of Brain and Cognitive Sciences, Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology, Cambridge, MA, USA*
[3]*Division of Engineering in Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Cambridge, MA 02139, USA*

e-mail (*aslihankazan@yahoo.com)

ABSTRACT

Thymoquinone is an attractive molecule with several therapeutic effects such as anti-inflammatory, analgesic, anti-diabetic, antihistaminic and anticancer. However its clinical applications are limited due to its hydrophobic nature [1,2]. To overcome this limitation, various nanoformulations were developed for encapsulation such as polymeric micelles, chitosan nanocapsules, silica nanoparticles, solid lipid nanoparticles and other lipid based delivery systems. For the success of these drug delivery systems, synthesis of monodisperse nanoparticles is highly important.

In this study, thymoquinone was applied to planarians in free and encapsulated forms to determine its effect on the planarian regeneration. Planarians are free-living nonparasitic invertebrates and are better known for their extraordinary regenerative capacity. They can detect the environmental stimuli efficiently and have bilateral symmetry, encephalization and ability to regenerate complete individuals from small body fragments [3,4]. Due to these properties, planarians were used as model organisms to determine the effect of thymoquinone on the neural regeneration.

A microfluidic device was used to prepare thymoquinone loaded albumin nanoparticles. The characterization tests of the prepared nanoparticles such as particle size distribution, *in vitro* release studies, SEM, FT-IR, and DSC analyses were carried out. Free and encapsulated thymoquinone were added to growth media of planarians. Then planarians were amputated and the fragments were observed in terms of head and tail regeneration, swimming pattern and behavior.

The results showed that microfluidic approach was more advantageous than the traditional nanoparticle preparation methods in terms of particle monodispersity since the obtained nanoparticles had narrower particle size distribution compared to the previous studies. Thymoquinone was applied to planarians at different concentrations and non-toxic dose was determined. At this non-toxic dose, effects of free and encapsulated thymoquinone on planarian regeneration were investigated. The results indicated that thymoquinone affected the behavior and regeneration capacity of planarians. In addition, it was shown that application of thymoquinone in free or encapsulated forms had a significant effect on planarians.

Keywords: microfluidics, nanoparticles, planarians, regeneration, thymoquinone

References

[1] J.M.M. Salmani, S. Asghar, H. Lv and J. Zhou. Molecules 19, 5925-5939 (2014).
[2] Y.S. Ong, L. Saiful Yazan, W.K. Ng, M.M. Noordin, S. Sapuan, J.B. Foo and Y.S. Tor. International Journal of Nanomedicine 11, 5905-5915 (2016).
[3] Alvarado, A.S. Cell 124(2), 241-245 (2006).
[4] J. Pellettieri, P. Fitzgerald, S. Watanabe, J. Mancuso, D.R. Green and A.S. Alvarado. Developmental Biology 338(1), 76-85 (2010).

Lab-on-a-chip devices for drug screening

Begum Gokce[1], Devrim Pesen Okvur[2]

[1]*Izmir Institute of Technology, Department of Biotechnology, Izmir, Turkey*
[2]*Izmir Institute of Technology, Department of Molecular Biology and Genetic, Izmir, Turkey*

e-mail (begumgokce35@gmail.com)

ABSTRACT

Breast cancer is one of the cancers with the highest incidence and mortality rates in women in Turkey and in the world. Research has shown that cell shape, adhesion, migration, response to growth factors and drugs are different in 2D and 3D culture. Today, only 8 out of 100 anti-cancer clinical trials give effective results. 3D cell culture systems have been shown to be a necessary step between *in vitro*, *in vivo* and clinical studies [1,2]. The most apparent disadvantage of widely used 3D cell culture setups is the lack of stromal cells [3]. The systems to be developed should provide both a 3D environment and comprise of multiple cell types. Here, we develop a 3D tri-culture platform for drug screening using a lab-on-a-chip (LOC) device,

SU-8 molds were prepared by UV lithography for LOC production. These molds were used for the fabrication of PDMS structures. By bonding PDMS structures with glass surfaces, LOC fabrication was completed. The LOC device has three parallel channels. Cells were loaded with matrigel in the middle channel to create a 3D microenvironment. Side channels were used for loading culture medium. MDA-MB-231 cancer cells, MCF-10A normal mammary epithelial cells and macrophages were used for tri-culture. As a control MDA-MB-231 cells were used as mono-culture. Our hypothesis is that drugs are less effective in tri-culture. Cells were labeled with fluorescent trackers and cell density was optimized to be at least 6 million cells/ml. Then cells were treated with doxorubicin and viability was determined after 48 hours. Following confirmation of preliminary results with doxorubucin, we will use this 3D tri-culture platform to screen novel compunds.

Keywords: breast cancer, drug screen, doxorubicin, lab-on-a-chip

Acknowledgements

Devrim Pesen Okvur is supported by TÜBA GEBİP 2016 and BAGEP 2016.

References

[1] Edmondson, R., Broglie, J.J., Adcock, A.F. ve Yang, L. "Three-dimensional cell culture systems and their applications in drug discovery and cell-based biosensors", Assay Drug Dev Technol, 12, 207-18 (2014).
[2] Kim, J.B., Stein, R. ve O'Hare, M.J. "Three-dimensional in vitro tissue culture models of breast cancer-- a review", Breast Cancer Res Treat, 85, 281-91 (2004).
[3] Ivers, L.P., Cummings, B., Owolabi, F., Welzel, K., Klinger, R., Saitoh, S., O'Connor, D., Fujita, Y., Scholz, D. ve Itasaki, N."Dynamic and influential interaction of cancer cells with normal epithelial cells in 3D culture", Cancer Cell Int, 14, 108 (2014).

Microfluidic green synthesis of gold nanoparticles

Beste Elveren[1], Umit Hakan Yildiz[2], Ahu Arslan Yildiz[1*],

[1]*Department of Bioengineering, Izmir Institute of Technology, İzmir, Turkey*
[2]*Department of Chemistry, Izmir Institute of Technology, İzmir, Turkey*

e-mail ([*]ahuarslan@iyte.edu.tr)

ABSTRACT

Microfluidic synthesis of metal nanoparticles enables controlling the amount of metal precursors and reducing agents, which affects the size, shape and other properties of nanoparticles. It is possible to control the dispersion of particles by changing channel design, size and fluid flow rate [1]. On the other hand, nanoparticles has huge potential in diagnosis, sensing and tissue engineering areas [2]. Different sorts of metal nanoparticle synthesis methods have been developed over the last decades. Most of the synthesis methods use harsh chemicals for the reduction of metals. The side-products of these chemicals are toxic to both environment and human health [3]. Green synthesis is a new methodology developed to reduce the toxicity of harmful chemicals and solvents. Most of the applications of nanoparticles are in the areas where there is a relationship between these particles and a biological systems [4] therefore an environmentally friendly synthesis approach is required. Green synthesis has been applied to various metals and metal-oxides using different parts of plants like; root, stem, fruit, leaf, seed, callus and/or flowers [5]. In this work microfluidic green synthesis was performed using both Melissa officinalis and Punica granatum extracts. Microfluidic chips were prepared via laser ablation technique that is easy to use and rapid for microfabrication of Poly-methyl methacrylate (PMMA) based microfluidic chips. To characterize the green synthesized gold nanoparticles (GNPs), absorbance, size, zeta potential measurements, SEM and EDX analyses were performed.

Keywords: gold nanoparticles (GNPs), green synthesis of GNPs, microfluidics

Acknowledgements

The authors would like to thank to Izmir Institute of Technology, Centre for Materials Research (MAM) and Biotechnology and Bioengineering Applications and Research Centre (BİYOMER) for their contribution. Scientific Research Project 2016IYTE70 by İzmir Institute of Technology.

References

[1] S.C.G. Kiruba Daniel, L.A.N. Julius, S.S. Gorthi, Microfluidics based Handheld Nanoparticle Synthesizer, Journal of Cluster Science 28(3) (2016) 1201-1213.
[2] G.L. Hornyak, Moore, J. J., Tibbals, H. F., Dutta, J., Fundamentals of Nanotechnology, (2008).
[3] L. Zou, W. Qi, R. Huang, R. Su, M. Wang, Z. He, Green Synthesis of a Gold Nanoparticle–Nanocluster Composite Nanostructures Using Trypsin as Linking and Reducing Agents, ACS Sustainable Chemistry & Engineering 1(11) (2013) 1398-1404.
[4] Y.-W. Lin, Y.-C. Chen, C.-W. Wang, W.-T. Chen, C.-M. Liu, C.-Y. Chen, H.-T. Chang, Gold Nanosponges: Green Synthesis, Characterization, and Cytotoxicity, Journal of Nanoscience and Nanotechnology 13(10) (2013) 6566-6574.
[5] K. Vijayaraghavan, T. Ashokkumar, Plant-mediated biosynthesis of metallic nanoparticles: A review of literature, factors affecting synthesis, characterization techniques and applications, Journal of Environmental Chemical Engineering 5(5) (2017) 4866-4883.

Fine-tuning hydrogel properties as porous tissue engineering scaffold

Busra Yildiz[1], Ahu Arslan Yildiz[2], Umit Hakan Yildiz[1*]

[1]*Izmir Institute of Technology, Department of Chemistry, Turkey*
[2]*Izmir Institute of Technology, Department of Bioengineering, Turkey*

e-mail (*hakanyildiz@iyte.edu.tr)

ABSTRACT

Hydrogels are polymeric networks able to absorb excess amount of water that exhibit high elasticity and mechanical strength similar to the extracellular matrix [1]. Thanks to their excellent biocompatibility in addition to porous morphology, swelling and responsive behaviors hydrogels are attracted high interests in the fields of biotechnology and biomedicine [2-5]. We here describe a modified methodology to synthesize GelMA hydrogels with photopolymerization reaction. The obtained hydrogels are highly porous with varying pore size between 10-95 μm and have high capacity of swelling at least % 336 depending on the modification degree of gelatin and concentration of pre-polymer solution. The further characterizations on structure, morphology and properties of the hydrogels were revealed that, swelling and water absorbance can be fine-tuned by crosslinking density. We currently focuse on the cell culture experiments to utilize synthetic tissues with high toughness.

Keywords: biomaterials, cell culture, gelatin, GelMA hydrogel, tissue engineering

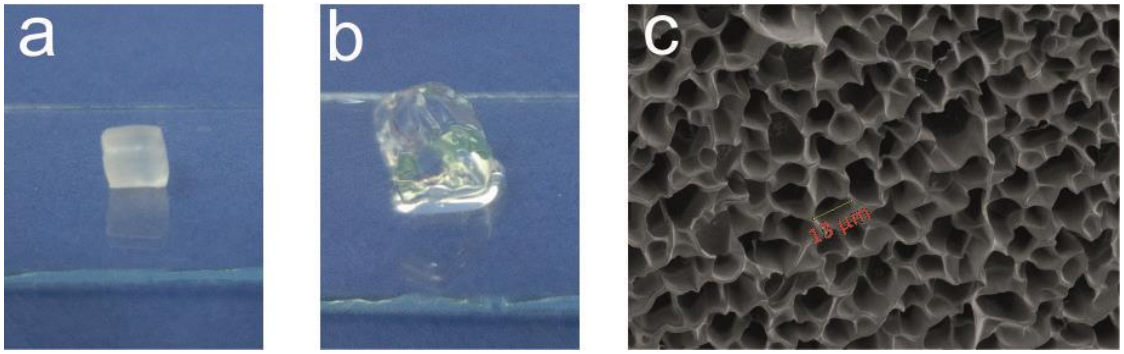


Fig.1 Image of the hydrogel; **a)** after synthesis; **b)** after swelling in water; and **c)** SEM image of freeze-dried hydrogel

Acknowledgements

We would like to thank TÜBİTAK 116Z547 for providing partial financial support to this project.

References

[1] D.A. Gyles, L.D. Castro, J.O.C. Silva, R.M. Ribeiro-Costa. European Polymer Journal 88, 373-392 (2017).
[2] Z. Cong, Y. Shi, Y. Wang, J. Niu, N. Chen, H. Xue. Int J Biol Macromol 107, 855-864 (2018).
[3] C.R. Weinstein-Oppenheimer, D.I. Brown, Rn Coloma, P. Morales, M. Reyna-Jeldes, M.J. Diaz, E.Sanchez, C.A. Acevedo. Mater Sci Eng C Mater Biol Appl 79, 821-830 (2017).
[4] M.C. Koetting, J.T. Peters, S.D. Steichen, N.A. Peppas. Mater Sci Eng R Rep 93, 1-49 (2015).
[5] M.Sepantafar, R. Maheronnaghsh, H. Mohammadi, F. Radmanesh, M.M. Hasani-Sadrabadi, M. Ebrahimi, H. Baharvand. Trends Biotecnol 35, 1074-1087 (2017).

Development of nanobiosensor for dopamine detection

Ebru Gursoy[1], Fulden Ulucan[2], Cansu Ilke Kuru[1], Raziye Hilal Senay[1], Sinan Akgol[3*]

[1]*Ege University, Graduate School of Natural and Applied Science, Department of Biotechnology, İzmir, Turkey*

[2]*Ege University, Graduate School of Natural and Applied Science, Department of Biomedical Technologies, İzmir, Turkey*

[3]*Ege University, Faculty of Science, Department of Biochemistry, İzmir, Turkey*

e-mail (*sinanakgol@gmail.com)

ABSTRACT

Dopamine is mainly produced in the nervous system and adrenal medullary and because of this reason it plays a role in brain functions such as behaviours and understanding. The hypothalamic-secreted dopamine interferes with the blood and acts as a neurohormone[1,2]. The alteration in the level of dopamine in the human body leads to many discomforts such as schizophrenia, involuntary tics, addiction, excessive joy, tension, hyperactivity, tension and carelessness due to acceleration in metabolism[3]. Detection of dopamine level is important to diagnose dopamine related disease. Dopamine measurement can be done by collecting 24 hour urine samples in hospitals. Many of the techniques developed for sensitive and selective monitoring of the level of dopamine require expensive, laborious, time consuming, complex steps and procedures. In recent years, biosensor applications have been found for the detection of neurotransmitters[4]. In this project, it was aimed to produce a nanomaterial which have ability recognize dopamine. For this purpose, p(HEMA) nanopolymer was synthesized with non-surfactant emulsion polymerization method and functionalized by APTES and PBA binding. The nanopolymeric material was optimized in terms of pH, time and concentration parameters and then used as a recognition layer on the surface of the gold electrode. Biosensor application was made to measure electrochemical changes on the surface by cyclic voltammetry and differential pulse voltammetry. Results showed that binding of dopamine to recognition layer cause the decrease on current. This drveloped system have potential to be used as a point of care diagnostic kit.

Keywords: dopamine, HEMA, nanopolymer, nanobiosensor

References

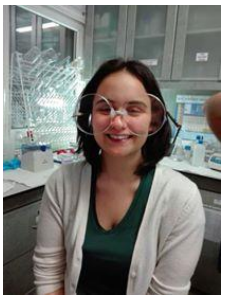
[1] Cooper, J., R., F., E., Bloom, Roth, R., H., Roth, R., H.,The Biochemical Basis of Neuropharmacology, UniversityPress, Oxford, UK, pp. 61–76, 1982

[2] Holloway, R., G., Biglan, K., M.,A review of pramipexole and its clinical utility in Parkinson's disease, Expert Opin. Pharmacother. 3, 197–210, 2002

[3] Li, D.,Sham, P., C., Owen, M., J., He, L., Meta analysis Shows Significant Association between Dopamine System Genes and Attention Deficit Hyperactivity Disorder (ADHD). Hum. Mol. Genet., 15, 2276–2284, 2006

[4]Florescu, M., David, M., Tyrosinase-Based Biosensors for Selective Dopamine Detection, Sensors, 17, 1314, 2017

Developing a micro paper-based analytical device for diagnostic purposes



Ecem Saygili*, Ozlem Yesil-Celiktas

Department of Bioengineering, Faculty of Engineering, Ege University, 35100, Bornova-Izmir, Turkey

e-mail (*ecem.sygl@gmail.com)

ABSTRACT

Enzymes are mainly globular proteins, having significant roles in the biological systems of all living organisms. The high concentration or absence of proteins in blood can further be used in diagnosis of a particular pathology at an early stage [1]. Current studies are intensely based on the analysis of interaction and detection of proteins, moreover, incorporation of multiple enzymes on a microfluidic platform instead of a single enzyme is getting more important for diagnosis of a diseases [2-3]. Microfluidic technology has high potential for developing different applications in medical diagnostics and therapeutic devices as well as in chemical and biological analyses. Micro paper-based analytical devices (μPADs) with high sensitivity and limited reagent consumption allow miniaturized and parallelized reactions simultaneously [4]. By taking into consideration of the current application of the μPADs, scope of this study was developing and enhancing more practical and affordable μPADs for the liver enzymes as they are the most commonly used enzymes in the clinical researches. Therefore, paper based microplatforms were designed, developed, and used to detect enzyme levels in body fluid samples. Electrical measurement and qualitative colour analysis were used as detection methods. The most significant results were obtained through the qualitative colour detection and it was observed that with the descending concentration of enzyme, the colour shade was changing as well. In regards to the electrical sensing model, it is concluded that the designed electrode system which requires more complex structure and optimization parameters, was not applicable for this study.

Keywords: electrical sensing, enzyme, micro paper-based analytical devices

Acknowledgements

Grant 16MUH109 provided by the Research Fund of Ege University is highly appreciated.

References

[1] Kiechle, F . L., Main, R. I. “Blood Glucose: Measurement in the Point-of-Care Setting”, *Laboratory Medicine*, 31, 5 (2000)

[2] La Cour,J. B, Generellia, S., Barbea, L., Guenatb, O. T, “Low-cost disposable ALT electrochemical microsensors for in-vitro hepatotoxic assessment”, *Sensors and Actuators B* 228, 360–365 (2016)

[3] Mark, D., Haeberle, S., Roth, G., Von Stetten, F., Zengerle, R., “Microfluidic lab- on-a-chip platforms: requirements, characteristics and applications” *Chem. Soc. Rev*. 39, 1153–1182 (2010)

[4] Pollock, N. R., Rolland, J. P., Kumar, S., Beattie, P. D., Jain, S., Noubary, F., Wong, V. L., Pohlmann R. A., Ryan, U. S., Whitesides, G. M, “A paper-based multiplexed transaminase test for low-cost, point-of-care liver function testing, *Sci Transl Med*, 19; 4(152): 152ra129 (2012)

The comparison of β,β-dimethylacryl alkannin loaded Silica-PAMAM dendrimer hybrid nanoparticles obtained by a traditional batch production and microfluidic platform

Esra Ilhan Ayisigi[1,2]*, Ecem Saygili[1], Ozlem Yesil-Celiktas[1]

[1]*Department of Bioengineering, Faculty of Engineering, Ege University, 35100, Bornova, Izmir, Turkey*

[2]*Genetic and Bioengineering Department, Faculty of Engineering and Architecture, Ahi Evran University, Kirsehir, Turkey*

e-mail (*esrailhan01@gmail.com)

ABSTRACT

Compared to conventional batch synthesis, microfluidic systems allow a precise control of the nanoparticle synthesis conditions, so the controlled synthesis of nanoparticles by rapid mixing in microfluidic platforms has been shown to improve their homogeneity and physicochemical properties (Ortiz de Solorzano et al, 2016). In this study, previously isolated and purified β,β-dimethylacryl alkannin which exhibits anticancer activity through their naphthazarin scaffold was encapsulated in silica-PAMAM dendrimer through a sol-gel technique using both a traditional batch production where magnetic stirrer is needed for 60 minutes, and continuous mode of microfluidic platform where mixing is in T-junction microchannel continuously. The objective of this study was to develop a continuous and less time-consuming silica-PAMAM dendrimer synthesis process with sol-gel technique based on our existing batch synthesis protocol (Yesil-Celiktas et al, 2017). The suitable concentrations of compounds were determined as 0.25 M TEOS and 0.0572 mM PAMAM in PBS (pH 7.4) through preliminary experiments and effects of different mixing protocols were investigated in terms of particle size distribution which was determined using dynamic light scattering by Malvern Zetasizer Nano-ZS (Malvern Inst. Ltd., UK).

The results show that using T-junction micromixer, the mean size of nanoparticles can be decreased to 161.05±1.45 (SEM) nm in sooner period than batch synthesis reaction. Microfluidic systems are a powerful tool to carry out nanoparticle synthesis reactions with high reproducibility, controllability and suitable for large-scale production of drug-loaded nanoparticles.

Keywords: β,β-dimethylacryl alkannin, microfluidics, nanoparticles, PAMAM dendrimer

Acknowledgements

This project is supported by the Research Fund of Ege University (16MUH052).

References

[1] Ortiz de Solorzano, I., Uson, L., Larrea, A., Miana, M., Sebastian, V., Arruebo, M. "Continuous synthesis of drug-loaded nanoparticles using microchannel emulsification and numerical modeling: effect of passive mixing", *Int J Nanomedicine* 11, 3397–3416 (2016).

[2] Yesil-Celiktas, O., Pala, C., Cetin-Uyanikgil, E. O. and Sevimli-Gur C., "Synthesis of silica-PAMAM dendrimer nanoparticles as promising carriers in Neuro blastoma cells" *Anal. Biochem* 519, 1–7 (2017).

Scaffold-free three-dimensional cell culturing using magnetic levitation

Esra Turker, Ahu Arslan Yildiz*

Department of Bioengineering, Izmir Institute of Technology (IZTECH), 35430 Izmir, Turkey

e-mail (*ahuarslan@iyte.edu.tr)

ABSTRACT

Cells and tissues are surrounded by extracellular matrix (ECM) that provides physical support and biochemical cues about the function. These properties of the natural ECM can be artificially simulated by fabricating three-dimensional (3D) scaffold that will provide temporary microenvironment for cells. A variety of cell culture methodologies [1, 2] and biomaterials [3, 4] provide 3D structure and microenvironment to overcome the limitations of traditional two-dimensional (2D) cell culture. Recently, new straightforward methodology for scaffold-free 3D cell culture via magnetic levitation has been developed in the presence of paramagnetic agents [5, 6]. The system is composed of mirrors, capillary tube and Neodmium (NdFeB) magnets. Magnets settled over capillary tubes in same poles and placed into a mirror system to reflect the light though capillary tube where 3D cell formation takes place, so the cellular behaviors can be easily examined. To magnetize the environment Gadobutrol (Gadovist, Bayer), Gadodiamide (Omniscan, GE) and Gadoteric Acid (Dotarem, Guerbet) were used as Gadolinium (III) chelates where cells levitated and assembled at a certain height. Balancing the magnetic and gravitational forces induce cell-cell interactions and provide 3D cellular formation without scaffold. NIH3T3 mouse fibroblast and HCC827 non-small-cell lung cancer cells were used for 3D cell culture, and their cellular behavior and viability were examined under these conditions. Thanks to the newly developed system, it provides a contactless manipulation of cells that can be used in many research areas such as drug screening, tissue engineering and regenerative medicine.

Keyword: 3D cell culture, contactless manipulation, Gadolinium (III) chelates, magnetic levitation, paramagnetic contrast agents

References

[1]G. R. Souza, J. R. Molina, R. M. Raphael, M. G. Ozawa, D. J. Stark, C. S. Levin, L. F. Bronk, J. S. Ananta, J. Mandelin, M. M. Georgescu, J. A. Bankson, J. G. Gelovani, T. C. Killian, W. Arap, R. Pasqualini, Nat Nanotechnol 2010, 5, 291.
[2]A. Arslan-Yildiz, R. El Assal, P. Chen, S. Guven, F. Inci, U. Demirci, Biofabrication 2016, 8, 014103.
[3]V. M. Merkle, P. L. Tran, M. Hutchinson, K. R. Ammann, K. DeCook, X. Wu, M. J. Slepian, Acta Biomater 2015, 27, 77.
[4]J. W. Nichol, S. T. Koshy, H. Bae, C. M. Hwang, S. Yamanlar, A. Khademhosseini, Biomaterials 2010, 31, 5536.
[5]E. Turker, A. Arslan-Yildiz, ACS Biomaterials Science & Engineering 2018, 4, 787.
[6]E. Türker, N. Demirçak, A. Arslan-Yildiz, Biomaterials Science 2018.

Optimization of a lab-on-a-chip device and method for quantification of extravasation

Gizem Bati Ayaz[1], Ismail Tahmaz[1], Muge Bilgen[1], Devrim Pesen Okvur[2*]

[1] *Izmir Institute of Technology, Biotechnology and Bioengineering, Izmir, Turkey*
[2] *Izmir Institute of Technology, Molecular Biology and Genetics, Izmir, Turkey*

e-mail (*devrimpesen@iyte.edu.tr)

ABSTRACT

Cancer is a worldwide disease, 90% deaths of which are due to metastasis. Metastasis comprises of intravasation, extravasation and new tumor formation at a secondary site in the body. Understanding the mechanism of metastasis and developing new platforms to study metastasis play a critical role in both the diagnosis and the treatment of cancer. Microfluidic technology provides the ability to mimic the *in vivo* microenvironment spatially and temporally. Lab-on-a-chip (LOC) devices produced with this technology can be used in metastasis studies.

Soft lithography was used for the fabrication of LOC devices. The design consists of a blood vessel channel, extracellular matrix/target tissue matrix channel and a medium reservoir. LOC devices were coated with APTES (3-aminopropyltriethoxysylan) followed by fibronectin, collagen or laminin to enhance adherence of endothelial cells for the construction of the endothelial barrier. Hydrogel mixture comprising of collagen:matrigel:target tissue cells (9:10:1) was loaded into the matrix channel. After the polymerization step, fluorescently labeled endothelial cells suspended in medium with or without 8% of 450-600 kDa dextran were introduced into the blood vessel channel. Media was added into the medium reservoir. 70 kDa fluorescent dextran was introduced into the blood vessel channel in static and flow conditions to determine the integrity of the endothelial barrier. Fluorescently labeled breast cancer cells were then introduced into the blood vessel channel. 3D images were acquired with a confocal microscope and analysis was performed using Fiji.

Laminin was better at promoting endothelial monolayer formation compared to fibronectin and collagen. Number of endothelial cells to be seeded was optimized to be 19736 cells / height of the blood vessel channel (μm) to form a continuous monolayer. Presence of dextran in the endothelial cell suspension prevented formation of cluster. Real time imaging and analysis showed that 70 kDa flourescent dextran did not diffuse from the flow channel into the matrix channel in static and flow conditions. Interactions of fluorescently labeled breast cancer cells with the endothelial monolayer and their extravasation into the matrix channel was quantitatively determined.

We have optimized surface coating, cell density and medium composition for successful mimicking of a blood vessel in a LOC device. The optimized method was used to quantitatively determine extravasation of cancer cells.

Keywords: metastasis, e**xtravasation, lab-on-a-chip, microfluidic**

Acknowledgements

The authors would like to thank TUBITAK (Grant no: 115E057 and 115Z428) for providing financial support to this project.

References

[1] Myers, D.R., Sakurai, Y., Tran, R., Ahn, B., Hardy, E.T., Mannino, R., Kita, A., Tsai, M., Lam, W.A. J. Vis. Exp. (64), e3958, DOI : 10.3791/3958 (2012).
[2] Siddique A, Meckel T, Stark RW, Narayan S. Colloids Surf B Biointerfaces 1;150:456-464 (2016).

Effect of hydrophilic structures on the poly (ε-caprolactone) electrospun nanofiber morphology

Gizem Evren*, Dilek Odaci Demirkol

Ege University, Faculty of Science, Biochemistry Department, 35040 Bornova, İzmir, Turkey

e-mail (*gizemmevrennn@gmail.com)

ABSTRACT

Nanofibers is a definition used for fibers of 100 nanometers or smaller. Nanofibers are suitable for new technologies that require very small environments because the existing high surface area can cause special characteristics [1]. Electrospinning is one of the production techniques of nanofibers. Electrospinning is an electrostatic method that uses electric forces to produce polymer fibers from 2 nm to several micrometer diameter using polymer solutions of both natural and synthetic polymers. This method is the easiest method to apply fort he production of nanofibers [2]. PCL [poly (Ɛcaprolactone)] is one of the polymers used in this method and it is hydrophobic, semi-crystalline polymer. PCL has a low melting temperature and is well soluble. For these reasons the biomedical field has led to extensive research into the potential application [3]. In this study, the effect of Chitosan and Polyamidoamine (PAMAM) dendrimer on PCL nanoparticles was investigated. Dendrimers; high branched structures, and polymerisation grades are macromolecule classes defined by the gaps in which functional groups can be placed. PAMAM dendrimers; an ethylenediamine core, a repetitive branching amidoamine internal structure, and a primary amino terminal surface [4]. Chitosan (CHIT) is a linear polysaccharide composed of glucosamine and N-acetylglucosamine units linked to β (1-4) glycosidic bonds and resulting from deacetylation of chitin (Martino and Risbud, 2005). It is also biodegradable, non-toxic and hydrophilic, has a significant affinity for proteins, and exhibits antibacterial, hemostatic, fungistatic, antitumoral and anticholesteric properties [5]. CHIT can be chemically modified easily. It is soluble in weak acids (pH 6.3) and can easily be made into film and porous scaffold [6]. In this work, PCL/PAMAM G5 nanofibers using PCL and PAMAM G5 solutions and PCL/CHIT nanofibers using PCL and CHIT solutions were obtained by electrospinnig. The prepared biofunctional surfaces can be used as an immobilization material for biological materials.

Keywords: chitosan; dendrimer; electrospun nanofibers; functional surface; PCL

Acknowledgements

This work was supported by the Scientific and Technological Research Council of Turkey (TUBITAK; grant number 215Z194). Dr. D.O. Demirkol thanks to The Turkish Academy of Sciences-Outstanding Young Scientists Award Program (TUBA-GEBIP 2015).

References:

[1]Homayoni, H., Ravandi, S.A.H. and Valizadeh, M., Carbohyd. Polym, 77, 656-661 (2009).
[2]Bhardwaj, N. and Kundu, S.C., Electrospinning: A fascinating fiber fabrication technique, Biotechnology Advances, 28, 325–347 (2010).
[3]Chandra, R. and Rustgi, R., Biodegradable polymers, ProgrPolymSci, 23, 1273–1335 (1998).
[4]Cloninger, M.J., " Biological applications of dendrimers ", Current Opinion in Chemical Biology, 6, 742–748 (2002).
[5] Martino, A.S.M. and Risbud M., Chitosan: a versatile biopolymer for orthopaedic tissue-engineering, Biomaterials, 26, 5983 (2005).
[6] Madihally, S. and Matthew, H., Porous chitosan scaffolds for tissue engineering, Biomaterials, 20, 1133–42 (1999).

Electrospinning clay-decorated hydrophobic-hydrophilic polymer blends to immobilize biological macromolecules

Gozde Atik[1*], Hamdiye Atilgan[1], Betul Unal[1], Esra Evrim Yalcinkaya[2], Fatma Ozturk Kirbay[1], Gizem Evren[1], Dilek Odaci Demirkol[1], Suna Timur[1]

[1]*Ege University, Faculty of Science, Biochemistry Department,35100 Bornova, Izmir, Turkey*
[2]*Ege University, Faculty of Science, Chemistry Department,35100 Bornova, Izmir, Turkey*

e-mail (*atikgozde9@gmail.com)

ABSTRACT

The use of nanomaterials as potential supports for enzyme immobilization has grown in popularity in recent years. Electrospun nanofibers show a high degree of porosity, large surface area to volume ratio, flexibility in surface functionalities, and interconnection properties, thus greatly preserving the enzyme immobilization efficiency and catalytic activity [1]. Poly (Ɛ-caprolactone) (PCL) is a hydrophobic, biocompatible, synthetic polymer with properties such as high tensile strength, low melting point and neutral charge [2]. PCL is one of the most studied polymers and recent studies show that it is mostly blended with alginate [3], polyethylene glycol (PEG) [4] and other polymers. To increase the selectivity and hydrophilicity of this synthetic polymer, chitosan was added as another polymer in the structure and Poly (Ɛ-caprolactone)-chitosan (PCL-CHIT) nanofibers were arranged using electrospinning technique. Addition of clay on the nanofiber structure changed some speficifications. Here, PCL-CHIT/clay structures were formed by electrospinning technique. Enzyme immobilization was carried out on the obtained structure and was used as an electrochemical biosensors.

Keywords: biosensors, chitosan, electrospun nanofibers, enzyme immobilization, poly (Ɛ-caprolactone)

Acknowledgements

This work was supported by the Scientific and Technological Research Council of Turkey (TUBITAK; grant number 215Z194). Dr. D.O. Demirkol thanks to The Turkish Academy of Sciences-Outstanding Young Scientists Award Program (TUBA-GEBIP 2015).

References

[1] Z.-G. Wang, L.-S. Wan, Z.-M. Liu, X.-J. Huang and Z.-K. Xu. Journal of Molecular Catalysis B: Enzymatic 56, 189-195 (2009).
[2] T. Prasad, E.A. Shabeena, D. Vinod, T.V. Kumary and P.R. Anil Kumar. J Mater Sci: Mater Med, 26:28 (2015).
[3] W.-W. Hu, Y.-C. Wu and Z.-C. Hu. Carbohydrate Polymers 183, 29-36 (2018).
[4] R. Rramaswamy, G. Mani, S. Venkatachalam, R.Y. Venkata, J.S. Lavanya and E.Y. Choi. Journal of Drug Delivery Science and Technology 44, 342-348 (2018).

Microfluidic based micro-particle synthesis

Umutcan Caliskan[1], Barbaros Cetin[1], Gunes Kibar[2*]

[1]*Bilkent University Mechanical Engineering, Ankara Turkey*
[2]*Adana Science and Technology University, Materials Engineerin, Adana Turkey*

e-mail (*gkibar@adanabtu.edu.tr)

ABSTRACT

In the past few years, microfluidic systems have given new horizons to science communities and become a new particle synthesizing system by providing to work in differential volume [1]. Comparing with conventional techniques microfluidic systems have many advantages while proceeding experiments such as providing more controlled synthesizing medium, less material consumption and time consuming [2]. The aim of this study is synthesizing particles having different properties by using micro/nano particles. Microfluidic systems were specifically designed for synthesizing particles and produced by use of proper materials for different synthesis procedure. In microfluidic system, the temperature, flow and other parameters were modelled and analyzed by computer aid designed program "*COMSOL* Multiphysics®" [3]. Within the scope of this project, the applicability of model which designed by computer aid program were tested by producing the successful designed models and using for experimental trials of appropriated synthesis procedure. Obtained products in micro-fluidic system were characterized by morphological (SEM) and surface structural analysis (EDAX). As a result, in the scope of the project, particles, which have not been synthesized in the literature, were obtained with different properties in polydisperse and monodisperse form in size range between 10μm to 5μm.

Keywords: composites, COMSOL modelling, microparticles, micro-reactor, polymerization

Acknowledgements

This study: Adana Science and Technology University-Scientific Research Project 17103007 (Budget: 10000TL Coordinator: Dr.Güneş KİBAR, Researcher: Assoc. Dr.Barbaros ÇETİN)

References

[1] Marre, S. and K.F. Jensen, Synthesis of micro and nanostructures in microfluidic systems. Chemical Society Reviews, 39(3): p. 1183-1202,2010.
[2] Faustini, M., et al., Microfluidic approach toward continuous and ultrafast synthesis of metal–organic framework crystals and hetero structures in confined microdroplets. Journal of the American Chemical Society, 135(39): p. 14619-14626,2013.
[3] Cetin, B., M.D. Asik, and S. Taze, Design and fabrication of a microfluidic device for synthesis of chitosan nanoparticles. Journal of Nanotechnology in Engineering and Medicine, 4(3): p. 031004,2013.

Generation of bone-cartilage interface in microfluidic system

Hamdullah Yanik, Olcay Burcin Akbulud, Ali Kemal Bas, Sinan Guven*

Dokuz Eylul University, Izmir International Biomedicine and Genome Institute

e-mail (*sinan.guven@deu.edu.tr)

ABSTRACT

Bone-cartilage interface is one of the most important area that is affected in bone and cartilage disorders. Tissue engineering approaches have been extensively utilized to regenerate the damaged skeletal tissues. Despite the significant progress in clinics there is still unmet need *for in vitro* osteogenic models to study the mechanisms of diseases. In their native environments cells are spatially organized within complex structures known as the extracellular matrix. Current *in vitro* 2D culture platforms have limited capacity to recapitulate the physiological clues. Bioengineered systems with 3D cell culture potential provide new venues for generating *in vitro* disease models. Microfluidic systems enable to mimic native habitat of cells and tissues in microscales [1]. Such systems are perfect platforms to examine the natural responses of the tissues like their native microenvironments. Some of advantages using tissue and organ models as, i) minimizing the number of animals used in research, ii) identification novel therapeutics, iii) defining the drug administration techniques [2].

In this study, we aim to generate a novel *in vitro* disease model for bone-cartilage defects by combining 3D cell culture systems with stem cell technologies. Here we design a microchip that allows the direct differentiation of adipose derived stem cells (ADSC) in 3D hydrogel based culture environment. The capacity of this unique microfluidic system provides simultaneous formation of osteogenic and chondrogenic tissues in the same channel.

We show the administration of two differentiation media in a single channel for osteogenic and chondrogenic differentiation of stem cells. Such bioengineered platform can be used to mimic the bone-cartilage interface and potentially utilized in pre-clinical tests of therapeutics. Additional work will be required to establish if this positive outcome could be due to the very early generation of human blood vessels in the constructs documented in this study.

Keywords: b**one-cartilage interface, GelMa, microfluidics, tissue engineering**

Acknowledgements

This research is supported by TUBITAK 115C125 and TUBA-GEBIP funds.

References

[1] Loessner, D., F. P. W. Melchels, A. Khademhosseini et al. Nat. Protocols 11(4): 727-746 (2016).
[2] Namkoong, B., S. Güven, S. Ramesan et all. Acta Biomaterialia 31: 301-311 (2016).

Toxic response of zinc oxide nanoparticles with different dimension on epidermal keratinocyte HaCaT cells

Irem Yezer[1]*, Astrid Pflieger[2], Dilek O. Demirkol[1], K.-H. Feller[2], Suna Timur[1]

[1]Ege University, Faculty of Science, Department of Biochemistry, Izmir, Turkey
[2]Department of Medical Engineering and Biotechnology, Ernst-Abbe-University of Applied Sciences Jena, Jena, Germany

e-mail (*iremyezer@gmail.com)

ABSTRACT

The rapid development of nanotechnology has resulted in an increasing number of nanomaterial-based consumer products and industries [1]. Because of their unique physical properties, nanomaterials have dramatically transformed the function and application of commercial products, including wound dressings, cosmetics, detergents, food packaging, drug delivery, biosensors, and antimicrobial coatings. Recently, zinc oxide (ZnO) and titanium dioxide (TiO2) nanoparticles (NPs) have gained popularity as inorganic physical sunscreens because they can reflect and scatter UVA and UVB radiations while preventing skin irritation and disruption of the endocrine system typically induced by chemical UV filters [2]. In addition, they contribute to wound healing and also have remarkable antimicrobial activity. Therefore, taking into consideration that they are special candidate for cosmetic products. However, safety concerns regarding their utilization in consumer products have recently emerged [3]. Reports have suggested that sunscreen NPs induce cyto- and genotoxicity through oxidative stress. In this study, cytotoxicity of commercial ZnO NPs with different dimension was tested by MTT (3-(4, 5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide) cell viability assay on HaCaT cell line. According to results, cytotoxic effect of three different dimension of ZnO NPs was evaluated. After cytotoxicity assay, oxidative stress assay (CellROX Oxidative Stress Assay) was carried out to determine the stress level of HaCaT cell line after it was exposured with NPs.

Keywords: cytotoxicity, HaCaT, oxidative stress, zinc oxide nanoparticles

References

[1] R. P. Chandra, Y. Hongtao and F. P. Peter, J Environ Sci Health C Environ Carcinog Ecotoxicol Rev. January 27(1), 1–35 (2009).
[2] S. Threes G and P. Stanislav, Nanotechnol Sci Appl. 13;4, 95-112 (2011).
[3] L. Pei-Jia , H. Shou-Chieh , C. Yu-Pen , C. Lih-Ching , S. Daniel Yang-Chih , Journal of Food and Drug Analysis 23, 587-594 (2015).

Neurodegenerative disease modeling in 3D microfluidic system

Olcay Burcin Akbulud, Ali Kemal Bas, Hamdullah Yanik, Sinan Guven*

Dokuz Eylul University, Izmir Biomedicine and Genome Institute, Turkey

e-mail (*sinan.guven@deu.edu.tr)

ABSTRACT

The necessity for novel *in vitro* and *in vivo* disease models to study neurodegenerative diseases is increasing every day. Novel approaches to utilizing bioengineering principles have high potency to provide *in vitro* culture settings that are capable to provide 3D neural tissues to study neurological disorders.

Microfluidic systems can provide venues to observe the effect of external stimuli of a biological system (e.g., pH, temperature, signaling factors, and interstitial flow) on *in vitro* bioengineered platforms under well-controlled miniaturized volumes and microenvironments. These systems can be utilized to investigate the biological processes such as cell-cell and cell-material interaction, chemotherapeutic drug administration, single cell analysis, tumor metastasis. Microfluidic systems can also be incorporated with 3D hydrogels and tissue engineering approaches, so that mimicking the *in vivo* conditions can be achieved better than 2D cell culture systems while using a very low amount of fluids. [1, 2]

Glioblastoma multiforme (GBM) is the most common malignant cancer in adults, which causes severe damage to brain. In this study we use U87, U138 and U251 glioblastoma cell line and evaluate the effect of microfluidic interstitial fluid flow in 3D culture on a bioengineered microfluidic chip. Gelatin based natural biopolymer is synthesized and validated for cell encapsulation application. Microfluidic chips were designed and fabricated to be single channel or multiple inlet and outlets. The clinical potency of the bioengineered platform was assessed with therapeutic drugs. Using such platform, we aim to design a novel *in vitro* disease model for neurodegenerative diseases by combining a microfluidic system with bioengineered 3D neural tissue. Using such platform, we aim to examine the behavior of the cells under various shear stress conditions, and test drugs with several chip designs.

Keywords: GelMA, glioblastoma, microfluidic, microglia, tissue engineering

Acknowledgements

This study is supported by DEÜ-BAPKB.SAG.029, TÜBİTAK 115C125 and TÜBA-GEBİP funds.

References

[1] G. Calibasi Kocal, S. Güven, SciRep.Dec2; 6:38221 (2016).
[2] C. Bouyer, P. Chen, S. Güven et al., Adv Mater.28, 161-167, doi:10.1002/adma.201503916 (2016).

Testing of quantum dot bioconjugates toxicity on keratinocytes via digital holography

Ozan Yesiltepe[1*], Guliz Bozokalfa[2], Dilek Odaci Demirkol[2], Suna Timur[2,3]

[1]Ege University, Graduated School of Naturel and Applied Sciences, Biotechnology Department,35100 Bornova, Izmir, Turkey
[2]Ege University, Faculty of Science, Biochemistry Department,35100 Bornova, Izmir, Turkey
[3]Central Research Testing and Analysis Laboratory Research and Application Center, Ege University, 35100 Bornova, Izmir, Turkey

e-mail (*ozanyesiltepe@gmail.com)

ABSTRACT

There is a raised concern about potential toxic effects of nanoparticles (NPs) on environment, ecosystem and human health. In case of quantum dots, their usage is limited on living cells and animals because of toxic metals in their composition and physicochemical properties such as size, capping materials, color, surface chemistry, and coating bioactivity [1]. Especially, cell culture studies are one of the most commonly used nanotoxicity approach, based on direct and indirect measurements of cell viability or on biophysical assessment of changes in cell population and morphology [2]. Digital holographic microscopy (DHM) is a technique which uses a laser or coherent light sources for recording 3D data of an object. In this technique, laser or other light source allows wave interference [3]. Practically, DHM was recently applied to live cell imaging [4], cell death studies [5-8], monitoring cell cycle [5,9], and toxicity analyses [7].

In this study, the effects of QDs and QD/FA on cell viability were assessed using human keratinocyte cell line (HaCaT) as a model. In order to determine if DHM method can be used to evaluate cell viability as efficient as MTT, we compared results obtained from both viability assessment methods. Results of MTT cell viability studies, half-maximal inhibitory concentration (IC50) of QD and QD-FA were respectively found 94.65 µg/mL and 38.47 µg/mL. For DHM studies, IC50 of QD and QD-FA were found 126.4 µg/mL and 36.03 µg/mL, respectively. According to the result's, IC50 values of QD and QD-FA fairly close. Previous studies show that there was a good correlation for cell viability identification between DHM and fluorescence based methods [7]. There is a favorable correlation between cytotoxicity dose response curves and calculated IC50 values

Keywords : DHM, MTT, QD, nanotoxicity

Acknowledgements

This work was supported by the Scientific and Technological Research Council of Turkey (TUBITAK-COST; grant number 114Z058). (COST TD 1204: Modelling Nanomaterial Toxicity (MODENA)).

References

[1] T. Jamieson, R. Bakhshi, and D. Petrova, et. al., *Biomaterials*, 28, 4717–4732 (2007).
[2] W. S. Cho, R. Duffn, and C. A. Poland, et. al., *Environ. Health Perspect.*, 118, 1699–1706 (2010).
[3] A. Mölder, M. Sebesta, and M. Gustafsson, et. al., *J. Microsc.*, 232, 240–247 (2008).
[4] H. Persson, C. Købler, and K. Mølhave, et. al., *Small*, 9, 4006–4016 (2013).
[5] A. Khmaladze, R. L. Matz, and T. Epstein, et. al., *J. Struct. Biol.*, 178, 270–278 (2012).
[6] N. Pavillon, J. Kühn, and C. Moratal, et. al., *PLoS One*, 7, 1–9 (2012).
[7] J. Kühn, E. Shaffer, and J. Mena, et. al., *Assay Drug Dev. Technol.*, 11, 101–7 (2013).
[8] M. Kemmler, M. Fratz, and D. Giel, et. al., *J. Biomed. Opt.*, 12, 064002 (2007).
[9] B. Rappaz, E. Cano, and T. Colomb, et. al., *J. Biomed. Opt.*, 14, 034049 (2014).

3D lung spheroid cultures in microfluidic lung-on-a-chip system mimicking lung cancer disease

Ece Yildiz-Ozturk, Pelin Saglam-Metiner, Sultan Gulce-Iz, Ozlem Yesil-Celiktas*

Department of Bioengineering, Faculty of Engineering, Ege University, Turkey

e-mail (*ozlem.yesil.celiktas@ege.edu.tr)

ABSTRACT

Lung is one of the most challenging organ system to study *in vivo* due to its mechanically dynamic nature and presence of a variety of physical forces.[1] Microfluidic cell culture platforms enable the creation of cellular environments that mimic a number of important in vivo attributes, including cell–cell interactions, oxygen and nutrient delivery, metabolite removal, and shear stress.[2] Microfluidic lung-on-a-chip platform is especially suited for the *in vitro* simulation of physiological environments involving flow and shear stress.[3] Flow-derived mechanical stimulation controls fundamental biological processes such as cell differentiation, proliferation, migration and adhesion. Cultivation of adherent cells under perfusion reflects their physiologic environment more closely than traditional static conditions.[4] 3D cell culture models are bridge the gap between cell culture and living tissue. Many cells are often typified by organized and aggregated structure *in vivo* that develop physiologic cell–cell contacts. Cellular spheroids share similar characteristics with in vivo tumors, which makes them excellent models used for cancer biology research.[5] This study aims to develop a novel, *in vivo*-mimicking, spheroid based 3D lung on-a-chip platform with perfusion function and investigate the effect of a potential drug molecule on lung carcinoma cell lines formed into spheroids. In this study, the cytotoxic activity and IC_{50} values of panaxatriol were determined on A549 (human lung carcinoma cell lines) and MRC-5 (human normal lung fibroblast cell lines) cells by MTT assay. Peristaltic pump was used in order to generate microfluidic dynamic systems. For these, two Ibidi µ–Slide I Luer microchip were fed with drug-free medium (for control) and drug medium continuously. Spheroids were generated on MicroTissues® 3D Petri Dish® micro-mold in 10 days. After harvesting from the mold, they had embedded into 3D matrigel matrix before they were seeded into the channel of microchip. After the matrigel was completely frozen, the flow was applied at 2 µl / min for 48h. Morphologies of tissue spheroids were observed by light microscopy at 0, 24 and 48th hours and spheroid size and counts were analyzed by ImageJ analysis. Cell viability on the spheroids of the groups was also compared with the live&dead flourescent dying test at the end of the study period. The size of the spheroid structures embedded in the matrigel matrix within the microchip was found to increase gradually in the static and dynamic microfluidic control groups, while gradually decreasing and becoming more fragmented in the drug groups. The potential drug is more effective on single cells around the spheroid structure, but less in the 3D-spheroid tissues with a more firm texture.

Application of such mimetic dynamic systems will contribute to advancing basic research and increasing the predictive accuracy of potential drug molecules which may accelerate the translation of novel therapeutics to the clinic, possibly decreasing the use of animal models.

Keywords: cytotoxicity, dynamic system, lung-on-a-chip, panaxatriol, spheroid culture

Acknowledgements

The authors would like to thank to TUBITAK (113M050) for providing financial support to this project.

References

[1] F. Zheng, F. Fu, Y. Cheng, C. Wang, Y. Zhao, and Z. Gu. Small 12(17): 2253–2282 (2016).

[2] S.A. Lee, D.Y. No, E. Kang, J.Ju, D.S. Kim, and S.H. Lee. Lab on a chip 13: 3529-3537 (2013).

[3] D. Huh, B.D. Matthews, A. Mammoto, M. Montoya-Zavala, H.Y. Hsin, D.E. Ingber. Science 328: 1662-1668 (2010).

[4] A.O. Stucki, J.D. Stucki, S.R.R. Hall, M. Felder,Y. Mermoud, R.A. Schmid, T.Geiser, and O.T. Guenat. Lab Chip 15: 1302-1310 (2015).

[5] D. Konar, M. Devarasetty, D.V. Yildiz, A. Atala, and S.V. Murphy. Biomedical Engineering Computational Biology 7(S1): 17–27 (2016).

Development of internal gelation based hybrid alginate-silica hydrogel for biocatalytic conversion in microfluidic platform

Rabia Onbas[1], Ozlem Yesil-Celiktas[1,2]

[1]*Biomedical Technologies Graduate Programme, Graduate School of Natural and Applied Sciences, Ege University, 35100 Bornova, Izmir, Turkey*
[2]*Department of Bioengineering, Faculty of Engineering, Ege University,35100 Bornova, Izmir, Turkey*

e-mail (rabiaonbas@gmail.com)

ABSTRACT

Alginate is one of the most attractive materials for the encapsulation of biomolecules due to the ability of forming gels by ionic cross-linking with calcium cation. However, environmental changes such as buffer condition, temperature or pH can easily effect calcium alginate gel and induces degradation leading to loss of encapsulated biomolecules [1]. These problems can be overcome by using organic-inorganic hybrid materials that combine the advantages of silica with organic materials and it provide suitable diffusion properties which help to retain biological activities of immobilized enzymes [2]. For that reason, sodium silicate was used as the silica precursor because during the sol-gel reaction there is no release of cytotoxic by-products which can cause a negative effect on enzyme activation [3]. Micro-channel reaction systems provide large surface area and interface areas which are beneficial for many chemical processes such as extraction and catalytic reactions [4]. In this study, ionic crosslink based internal gelation method was applied to prepare the hybrid alginate-silica hydrogel for the application of biocatalytic conversions in microfluidic systems. This method allows controlled gelation rate ensuring proper injection to the microfluidic system. Characterization of hydrogel was carried out by SEM, EDS/mapping, BET, BJH, FTIR analyses and the shrinkage of monoliths was evaluated. Subsequent to optimizing the enzyme concentration (40 µg), hydrolytic conversion of pNPG was performed to understand the behavior of the bioconversion in the microfluidic system. The yield was 94 % which reached the equilibrium at 24 h indicating that the alginate-silica gel derived microsystem overcome some drawbacks of monolithic systems. This study will contribute to the design of new catalytic systems, particularly for microfluidic systems. Furthermore, alginate-silica hybrid hydrogels will have diverse applications in life sciences due to their high surface areas, injectable and homogenous natures.

Keywords: alginate-silica hybrid hydrogel; enzymatic hydrolysis; internal gelation; microfluidics; microreactor

Acknowledgements: The authors would like to thank the Scientific and Technological Research Council of Turkey, TUBITAK (113M050) and Ege University Research Fund (15-FBE-012) for providing financial support to this project. Also, the grant from TUBITAK 2210-C National Graduate Scholarship Program is highly appreciated. Additionally, we thank Dr. Ozgur Tag for his support in HPLC analysis.

References

[1] S.Y. Lim, K.O. Kim, D.M. Kim, C.B. Park, J Biotechnol, 143, 183-189(2009).
[2] T. Coradin, N. Nassif, and J. Livage, Appl Microbiol Biotechnol, 61, 429-434 (2003).
[3] V.G. Gavalas, S.A. Law, J. Christopher Ball, R. Andrews, L.G. Bachas, Anal Biochem, 329, 247-252 (2004).
[4] M. Miyazaki and H. Maeda, Trends Biotechnol, 24, 463-470 (2006).

Hydrophilic treated silk fiber reinforced hydrogel with non-invasive, high modulus and toughness

Sungsoo Lim[1], Jinwoo MA[1], Ramesh Subbiah[2], Kwideok Park[2*], Jeong-Yun Sun[1*]

[1]Department of Materials Science and Engineering, Seoul National University Seoul, Republic of Korea
[2]Center for Biomaterials, Biomedical Research Institute, Korea Institute of Science Technology Seoul, Republic of Korea

e-mail (*kpark@kist.re.kr, *jysun@snu.ac.kr)

ABSTRACT

The degeneration of intervertebral disc(IVD), which is composed of elastic annulus and soft absorbable Nucleus pulposus, is one of the major health issue. Current treatments attempt to reduce the pain by administering medicine and intervention therapy and surgical treatment. Many biomaterials for repairing of IVD have not been conservative with removing annulus fibrosus. So we targeted to replace only nucleus pulposus maintaining annulus, which compensates high durability, biocompatibility, stiff ness and toughness for IVD treatment[1].

Here, we fabricated biocompatible non-invasive, fiber reinforced hydrogel, Using surface treated silk fiber for enhancing hydrophilicity as the reinforcement and poly(vinyl alcohol)(PVA) as the matrix via physical crosslinking. The mechanical properties of composites increased on PVA concentration dependent manner and by addition of the fraction of silk fiber. As a result, The fiber reinforced hydrogel shows high elastic moduli(~13MPa) and high fracture toughness(~5,300 J/m^2). *In vitro* cell viability test shows over 90% of cell alive.

Keywords: fiber-reinforced, high toughness, hydrogel, hydrophilic surface treatment, non-invasive

Acknowledgements

This work was supported by funds from a National Research Foundation of Korea (NRF). J.-Y.S. and S.S.L. acknowledge support from a National Research Foundation of Korea (NRF) Grant funded by the Korean Government (MSIP) (No.10052783).

References

[1] Long RG, Torre OM, Hom WW, Assael DJ, Iatridis JC. Design Requirements for Annulus Fibrosus Repair: Review of Forces, Displacements, and Material Properties of the Intervertebral Disk and a Summary of Candidate Hydrogels for Repair. *J Biomech Eng.* **2016**, *138*, 1.

Highly stiff and tough pHEMA-alginate hydrogels

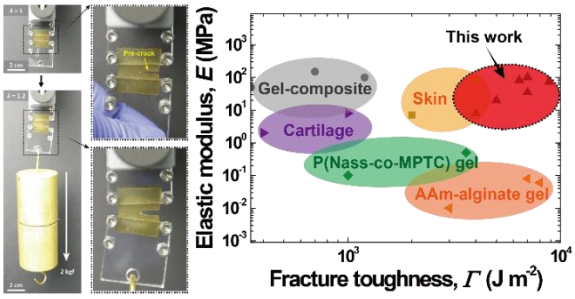
Yong-Woo Kim[1], Ji Eun Kim[2], Youngmee Jung[2*], Jeong-Yun Sun[1*]

[1]*Department of Materials Science and Engineering, Seoul National University Seoul, Republic of Korea*
[2]*Center for Biomaterials, Biomedical Research Institute, Korea Institute of Science Technology Seoul, Republic of Korea*

e-mail (*winnie97@kist.re.kr, *jysun@snu.ac.kr)

ABSTRACT

Human skin exhibits high stiffness (up to 100 MPa)[1] and toughness (up to 3,600 J m^{-2})[2] despite its high water content (40~70 wt%)[3]. Engineering hydrogels have rarely possessed both high stiffness and toughness, because compliant hydrogels usually become brittle when excess crosslinker is added to make the gel stiff. Furthermore, conventional hydrogels usually swell under physiological conditions, weakening their mechanical properties. Here, we designed a non-swellable hydrogel with high stiffness and toughness by interpenetrating covalently and ionically crosslinked networks. The stiffness is enhanced by utilizing ionic crosslinking sites fully, and the toughness is enhanced by adopting synergistic effects between energy-dissipation by ionic networks and crack-bridging by covalent networks. Non-swelling behaviors of the gel are achieved by densifying covalent and ionic crosslinks. The hybrid gel shows high elastic moduli of up to 108 MPa and high fracture energies of up to 8,850 J m^{-2}. *In vitro* and *in vivo* swelling tests prove non-swelling behaviors of the gel. Live/dead assays show 99% cell viability over a period of 60 days.



Keywords: cytocompatible hydrogels, non-swellable hydrogels, pHEMA-alginate hydrogels, stiff hydrogels, tough hydrogels

Acknowledgements

This work was supported by funds from the ILJIN GROUP. J.-Y.S. and Y.-W.K. acknowledge support from a National Research Foundation of Korea (NRF) Grant funded by the Korean Government (MSIP) (No.2016R1C1B2007569). J.-Y.S. acknowledges support from the Creative-Pioneering Researchers Program through Seoul National University (SNU).

References

[1] A.N. Annaidh, K. Bruyere, M. Destrade, M.D. Gilchrist, M. Ottenio, J Mech Behav Biomed Mater 5(1), 139-148 (2012).
[2] K.S. Koutroupi, J.C. Barbenel, J Biomech 23(3), 281-7 (1990).
[3] H. Arimoto, M. Egawa, Skin Res Technol 21(1), 94-100 (2015).

www.patenteffect.com

MICROFLUIDICS AND SUPERCRITICAL FLUIDS FOR LIFE SCIENCE APPLICATIONS.

TECHNOLOGY INSIGHT REPORT BASED ON PATENT DATA

JUNE 10, 2018

POWERED BY: patent effect

patent data-driven innovation insights

www.patenteffect.com

THE MAGIC OF PATENT INFORMATION

Your guide to develop strategic business intelligence coupled with emerging technology trends in your industry. We help you to discover your key partners/competitors and technology flows that will effect your business.

WHAT'S IN THIS INSIGHT REPORT

- Key Players
- Key Universities
- Countries of Technology Developers
- Top Technology sub-groups
- Top Inventors
- Top Cited Applicants
- Foothprints of Competitors
- Technology Flow
- Bonus

KEY FINDINGS

Microfluidics and Supercritical Fluids for Life Science Applications

This field has a total of **58.824** patent applications (17.155 of them are granted) distributed into **17.465 patent families**. According to the priority countries of patent applications, **the key markets of this field are USA, S. Korea and Germany.** The top companies in this industry are **SAMSUNG ELECTRONICS, CALIPER and AGILENT**. The top universities in this field are **UNIVERSITY OF CALIFORNIA, HARVARD COLLEGE and CALTECH.**

The critical technology sub-groups are '**Supercritical solvents used for life science purposes, integrated microfluidic structures (lab on a chip) and rectangular shaped lab. apparatus.**'

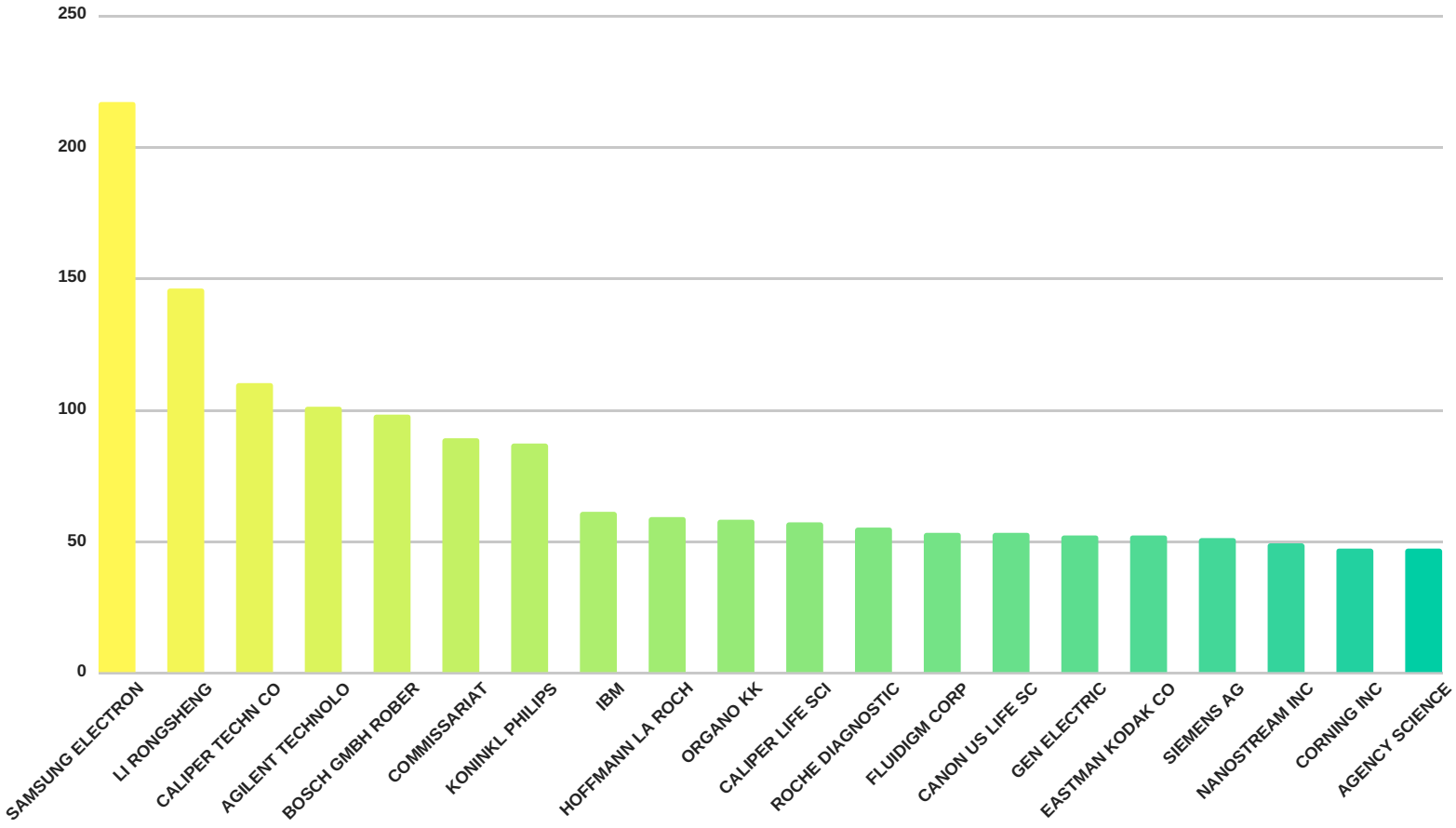
01
KEY
PLAYERS

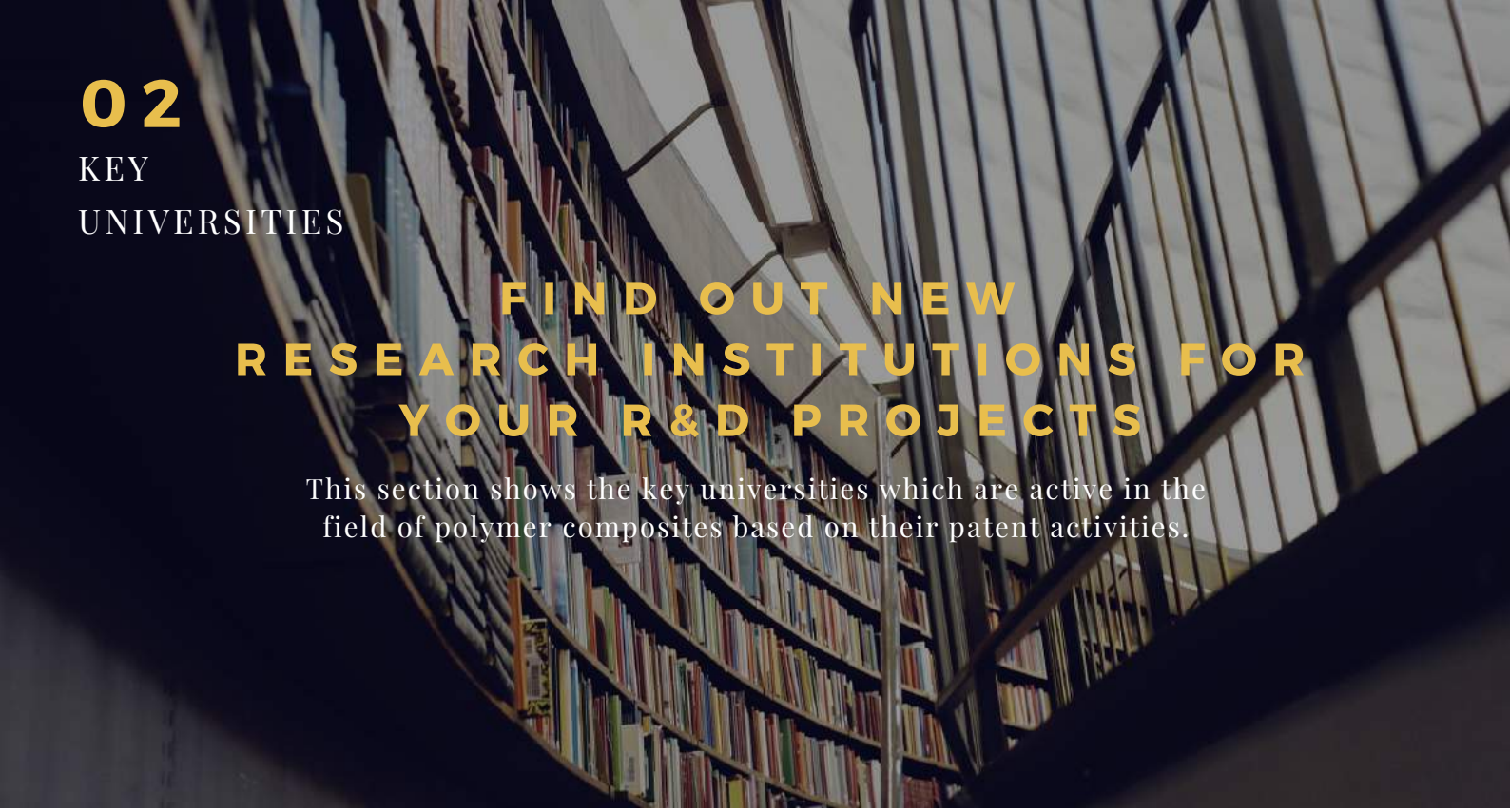
PARTNER OR COMPETITOR?

This section shows the key companies in the industry of polymer composites based on their patent activities.

TOP 20 KEY PLAYERS

These companies (+1 individual innovator) are focusing on microfluidics and supercritical fluids for life science applications.





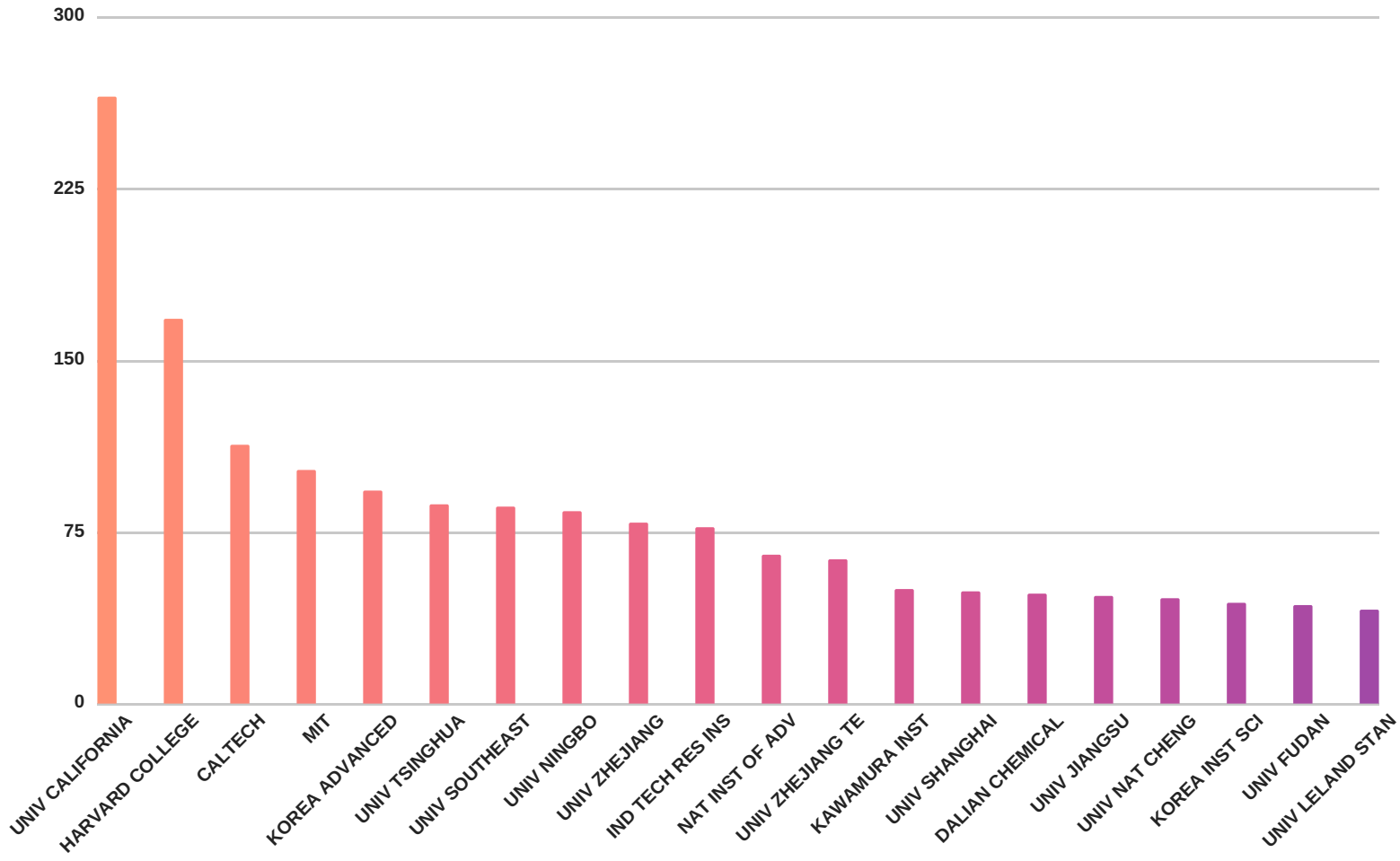
02
KEY
UNIVERSITIES

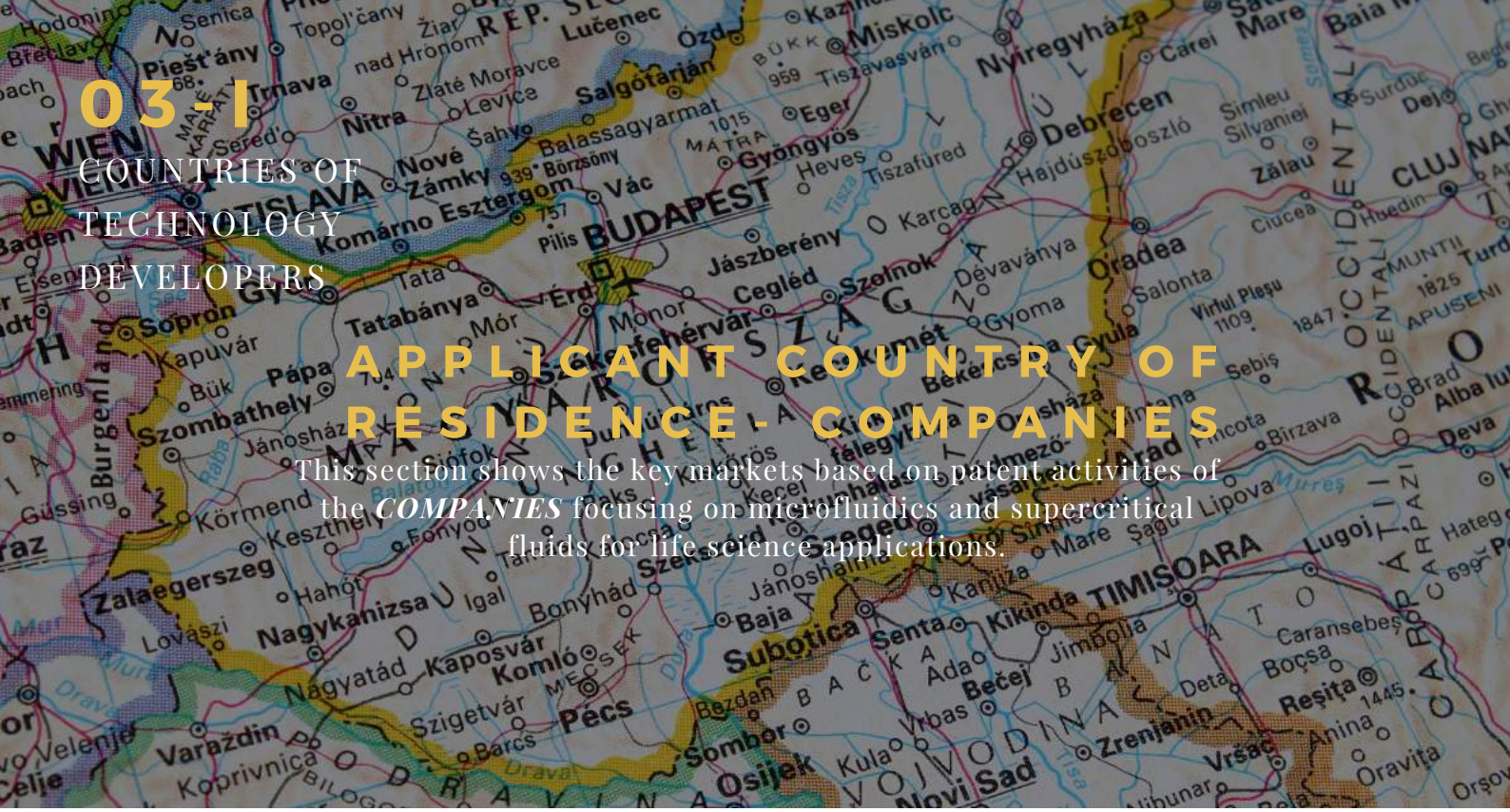
FIND OUT NEW RESEARCH INSTITUTIONS FOR YOUR R&D PROJECTS

This section shows the key universities which are active in the field of polymer composites based on their patent activities.

TOP 20 KEY UNIVERSITIES

These universities are focusing on microfluidics and supercritical fluids for life science applications. Contact with us to discover related patents of these universities.





03 - I

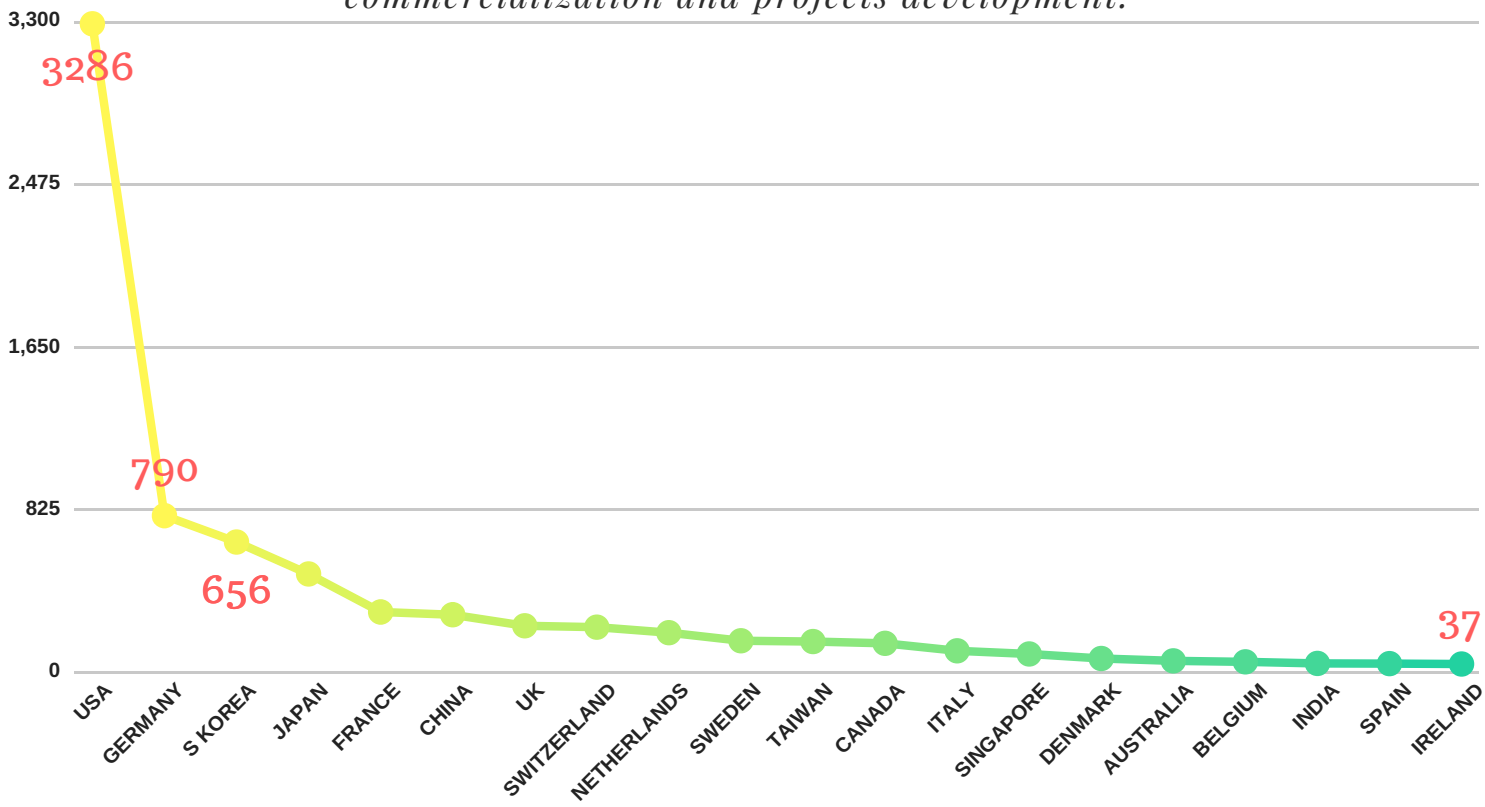
COUNTRIES OF TECHNOLOGY DEVELOPERS

APPLICANT COUNTRY OF RESIDENCE - COMPANIES

This section shows the key markets based on patent activities of the ***COMPANIES*** focusing on microfluidics and supercritical fluids for life science applications.

TOP 20 KEY MARKETS

You can find out the territorial markets in which the technology field is prominent or which markets have opportunities for commercialization and projects development.



USA, GERMANY AND S. KOREA

ARE THE TOP 3 PIONEER COUNTRIES

03-11

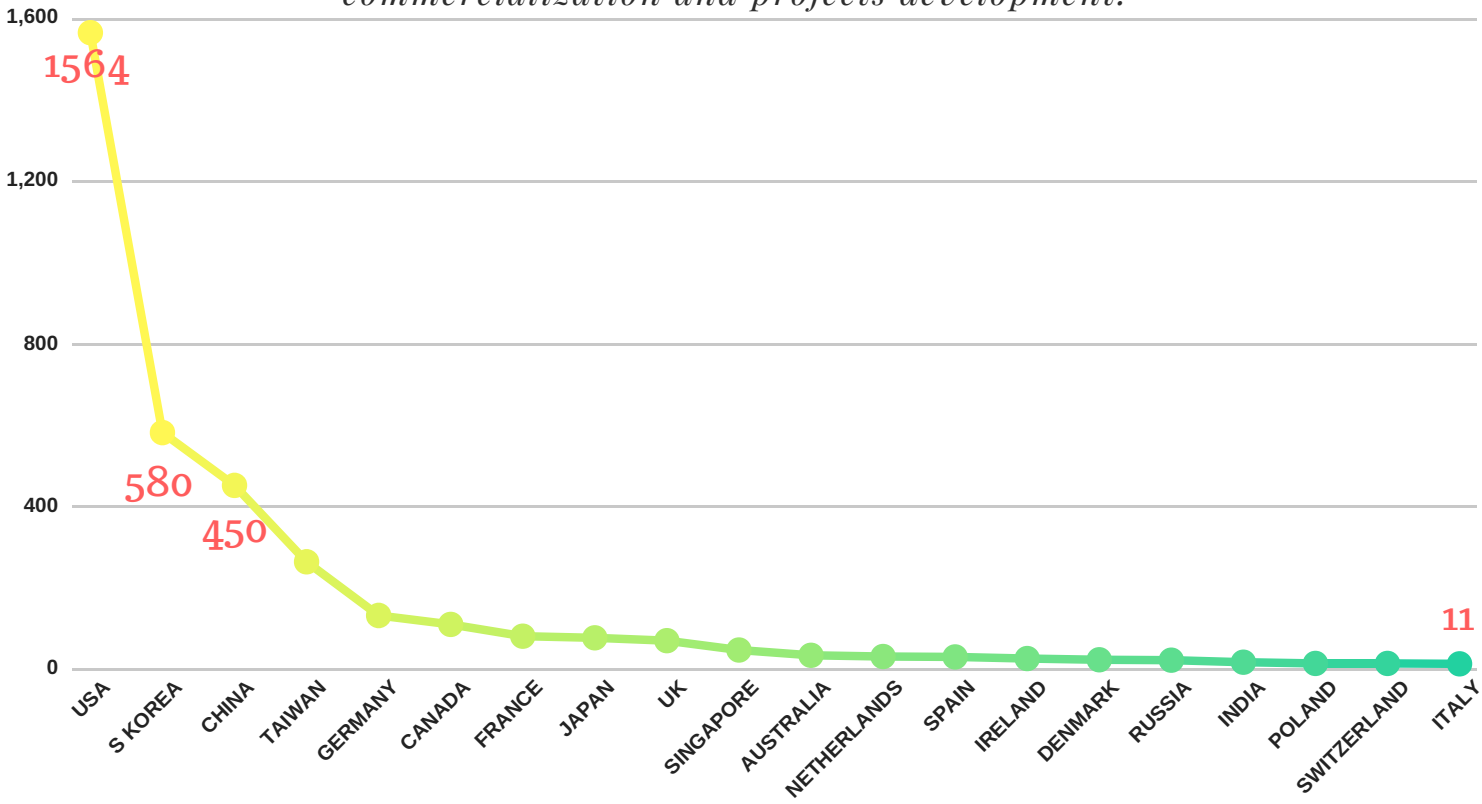
COUNTRIES OF TECHNOLOGY DEVELOPERS

APPLICANT COUNTRY OF RESIDENCE- UNIVERSITIES

This section shows the key markets based on patent activities of the **UNİVERSITIES** focusing on microfluidics and supercritical fluids for life science applications.

TOP 20 KEY MARKETS

You can find out the territorial markets in which the technology field is prominent or which markets have opportunities for commercialization and projects development.



USA, S. KOREA AND CHINA
ARE THE TOP 3 PIONEER COUNTRIES

04

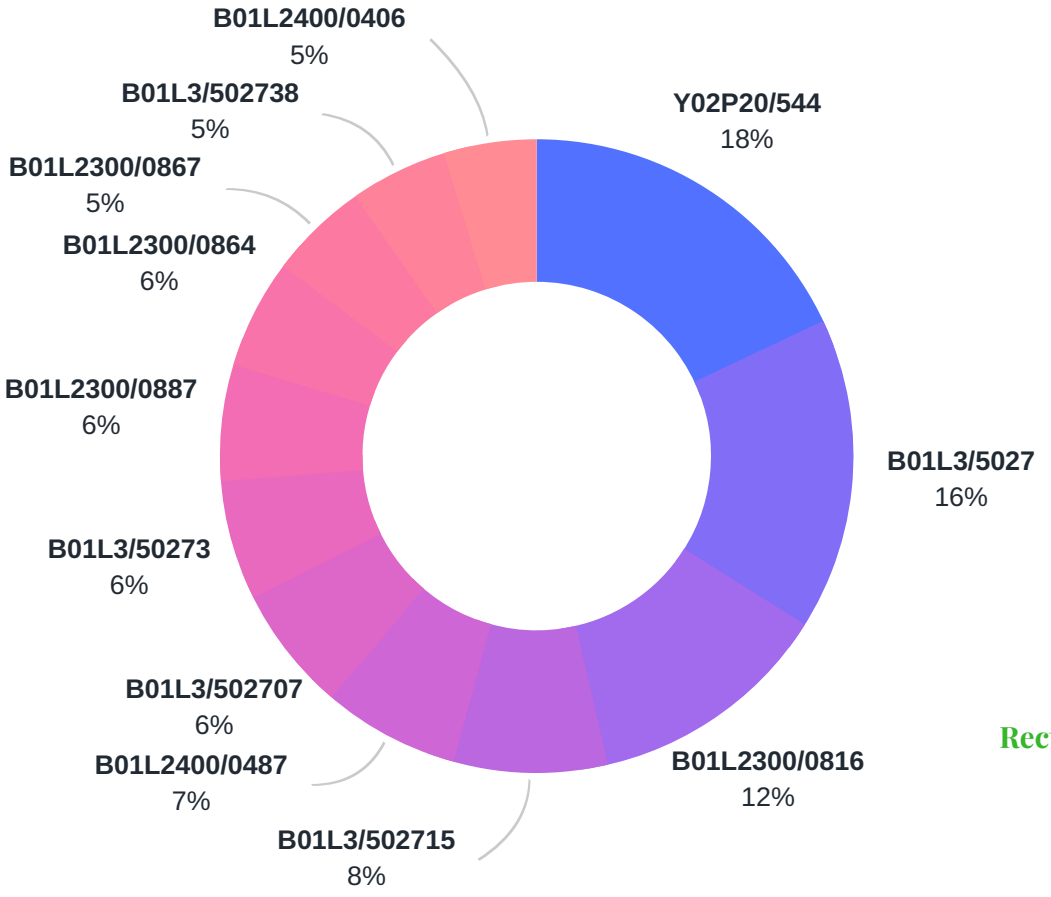
TOP
TECHNOLOGY
SUB-GROUPS

TRENDS OF TECHNOLOGIES

This section shows the key technology sub-groups based on patent activities of the **applicants** focusing on microfluidics and supercritical fluids for life science applications. These sub-groups can be used as an indicator of technology trend in that field.

TOP TRENDS FOR MICROFLUIDICS

You can discover the core technology areas of this field to be used for the opportunities of new project developments.



Y02P20/544
Supercritical solvents

B01L3/5027
Lab on a chip

B01L2300/0816
Rectangular shaped lab. apparatus

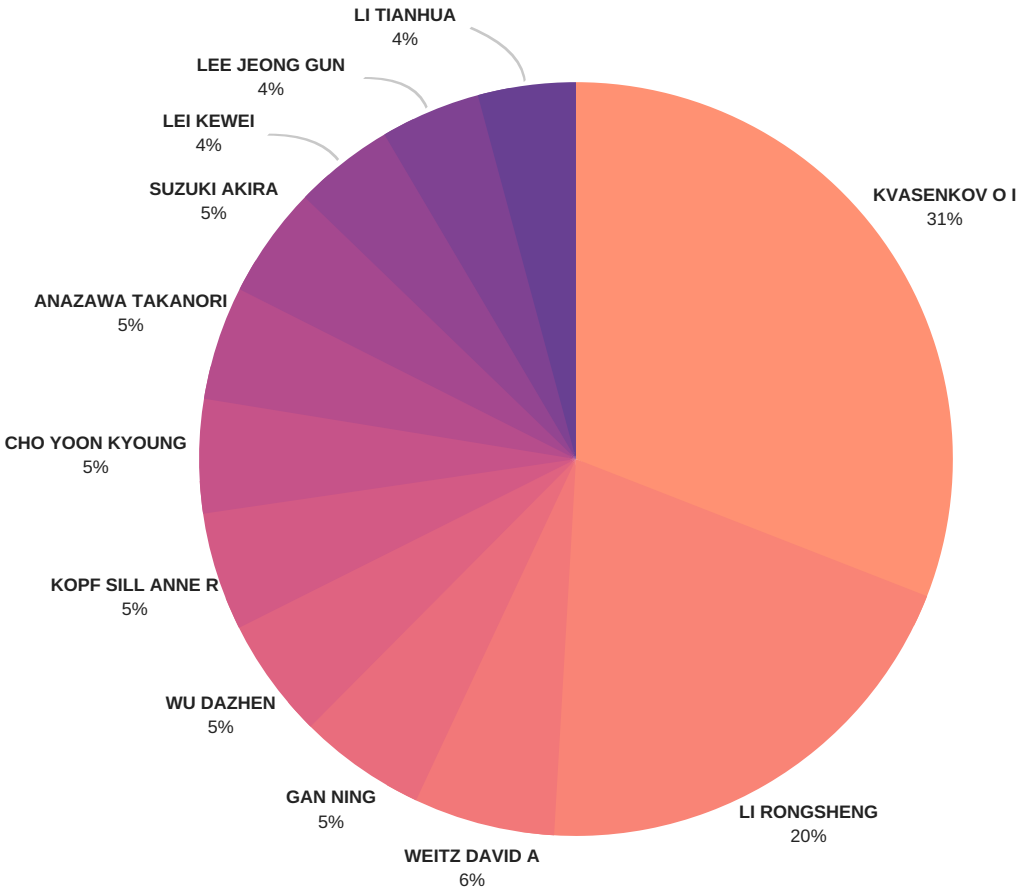
05
TOP
INVENTORS

DISCOVER NEW EDISONS

This section shows the key inventors who play an active role in the field of microfluidics and supercritical fluids for life science applications.

TOP INVENTORS FOCUSING ON MICROFLUIDICS AND SUPERCRITICAL FLUIDS FOR LIFE SCIENCE APPLICATIONS

You can identify the genius engineers for the opportunities of new collaboration projects.



06

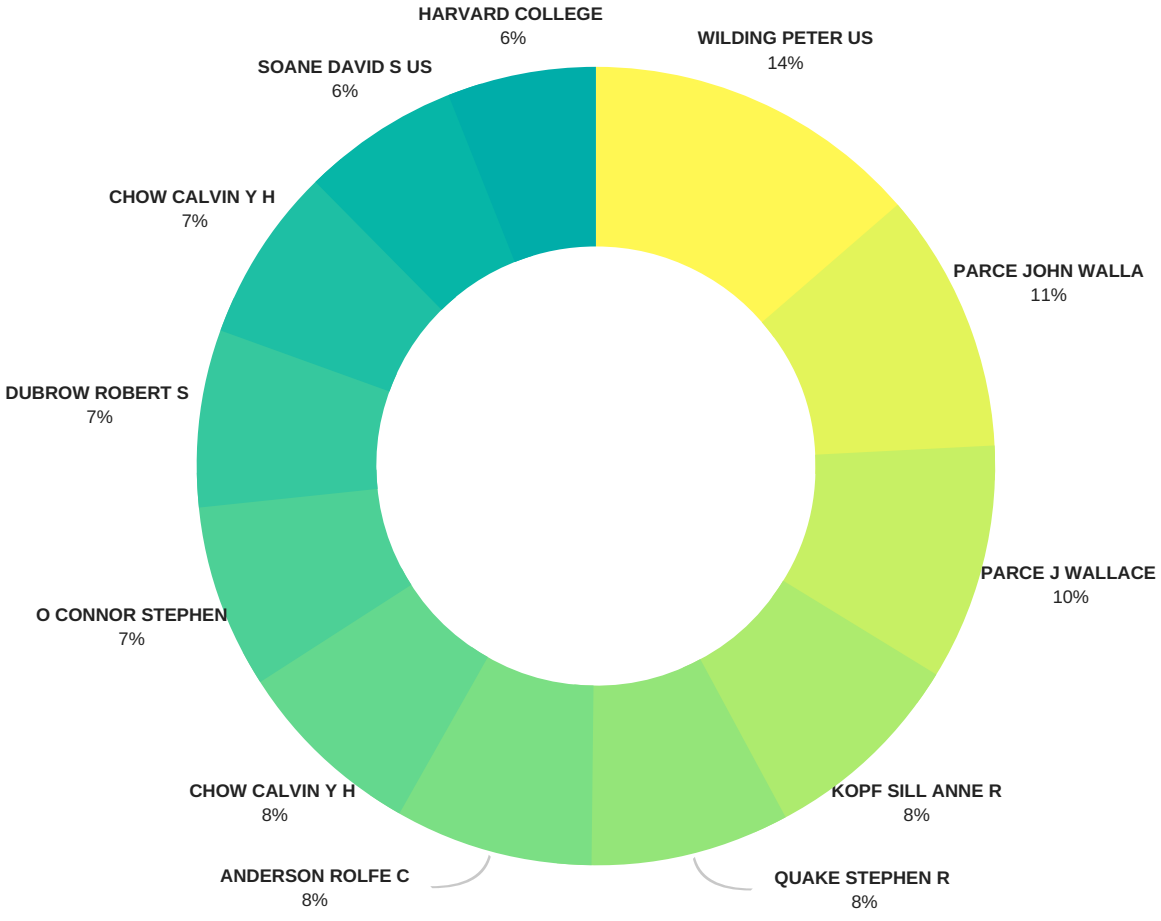
TOP CITED APPLICANTS

VALUABLE PARTNERS

This section shows the most cited applicants who play very critical role in the field of microfluidics and supercritical fluids for life science applications.

TOP CITED APPLICANTS

You can discover more valuable partners according to their most cited patents. They can be your competitor as well.



07-I

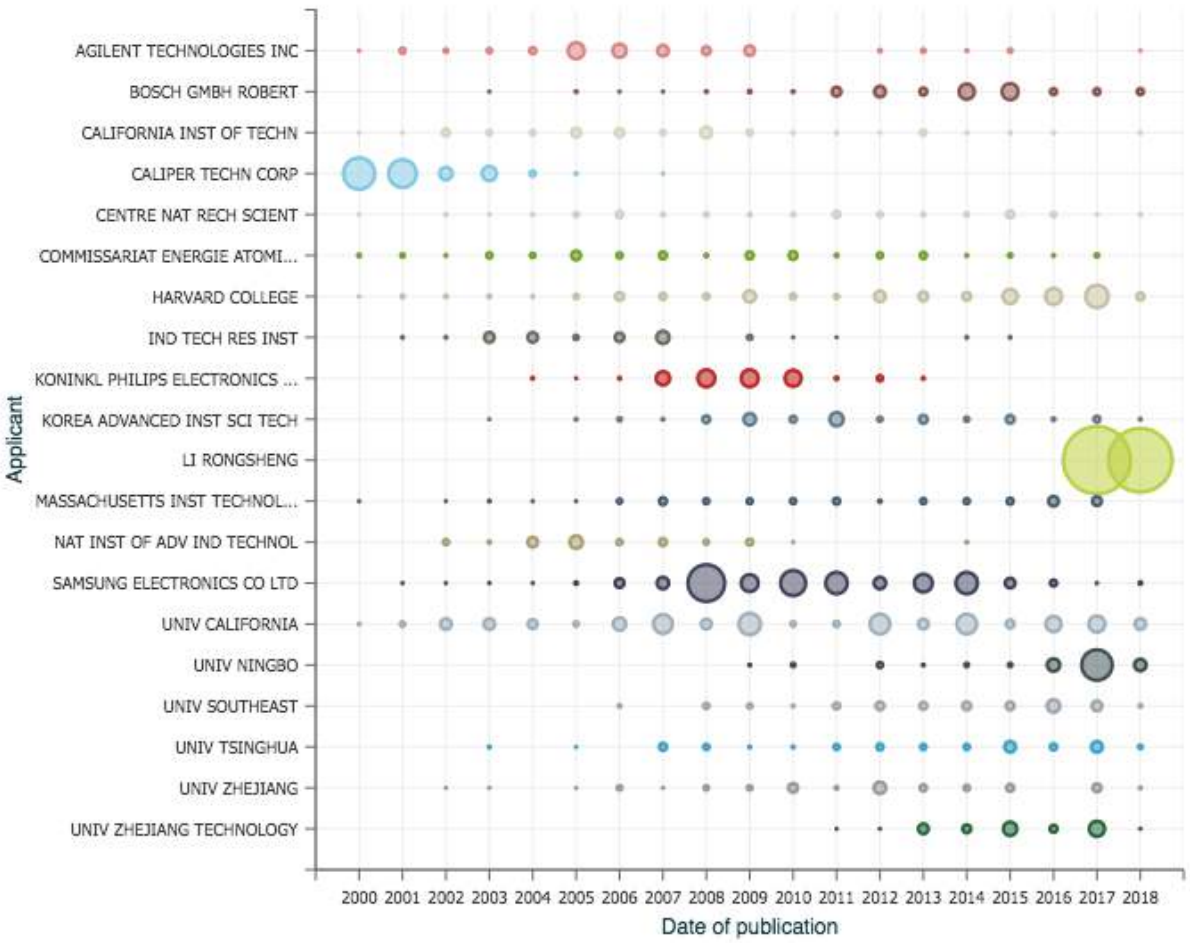
FOOTPRINTS OF COMPETITORS

PATENT PUBLICATION TRENDS 2000-2018

This section shows the trends of patent publications filed by the key players who are active in the field of microfluidics and supercritical fluids for life science applications.

PATENT PUBLICATION NUMBERS OF THE KEY PLAYERS BETWEEN 2000-2018

You can follow the filing trends of your competitors or you can identify newly active players in this field



07-II

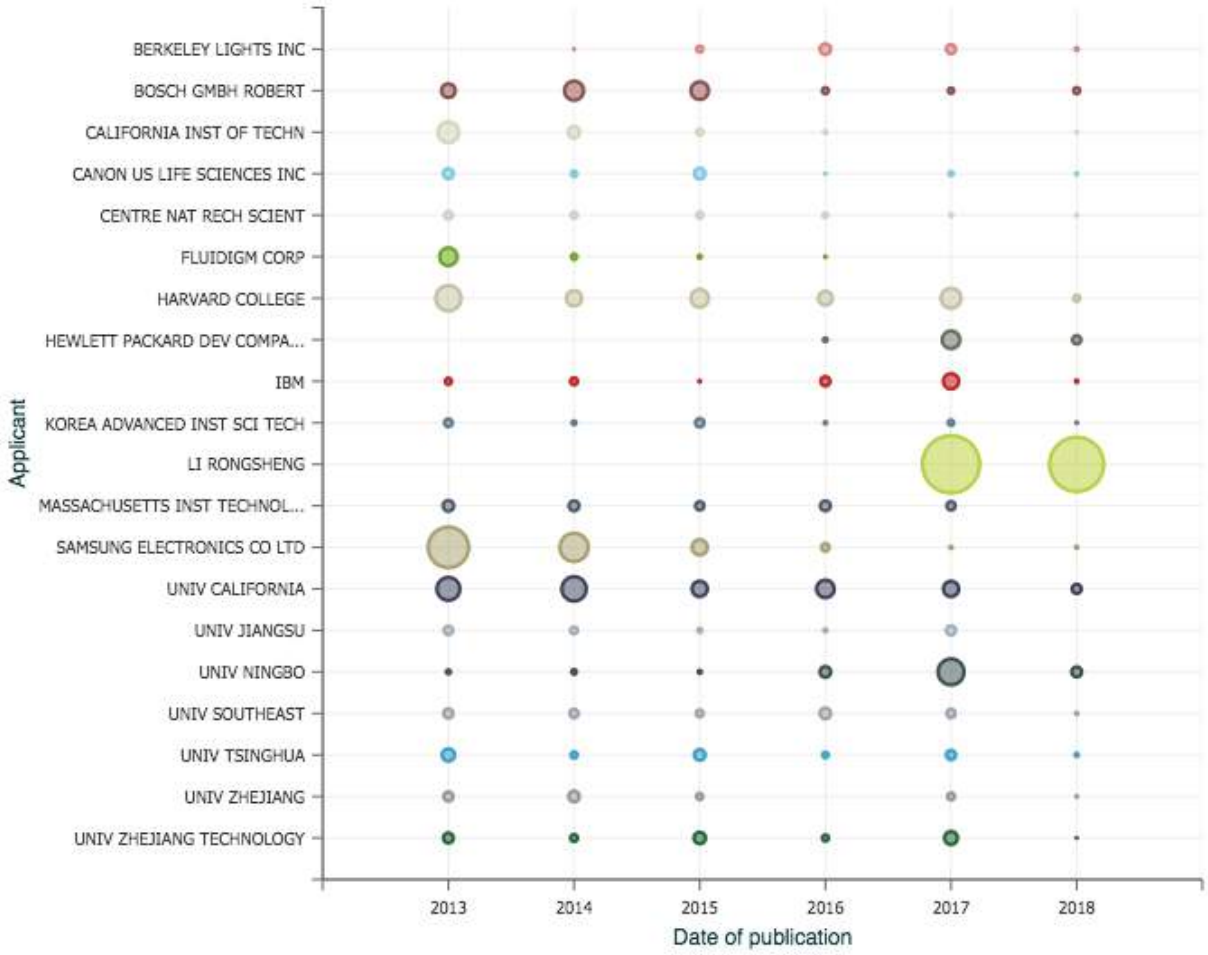
FOOTPRINTS OF COMPETITORS

PATENT PUBLICATION TRENDS 2013-2018

This section shows the trends of patent publications filed by the key players who are active in the field of microfluidics and supercritical fluids for life science applications.

PATENT PUBLICATION NUMBERS OF THE KEY PLAYERS BETWEEN 2013-2018

You can follow the filing trends of your competitors or you can identify newly active players in this field



08

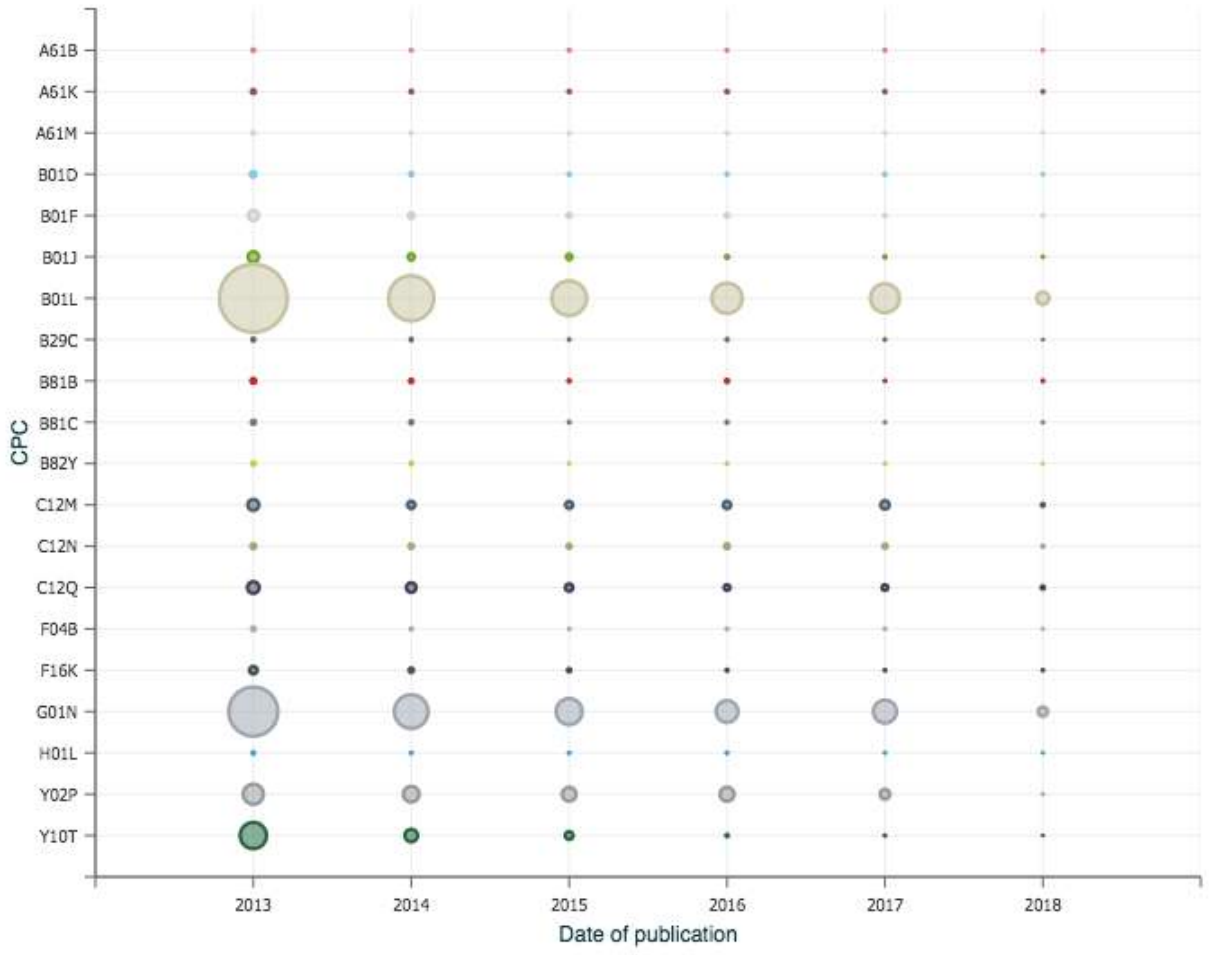
TECHNOLOGY
FLOW

TRENDS OF EMERGING TECHNOLOGY AREAS

This section shows the trends of emerging technology areas covered by the key players who have the most patent applications in the field of microfluidics and supercritical fluids for life science applications.

PATENT TRENDS OF THE KEY PLAYERS BETWEEN 2013-2018

You can follow the filing trends of your competitors or you can identify new technology areas in this field



09

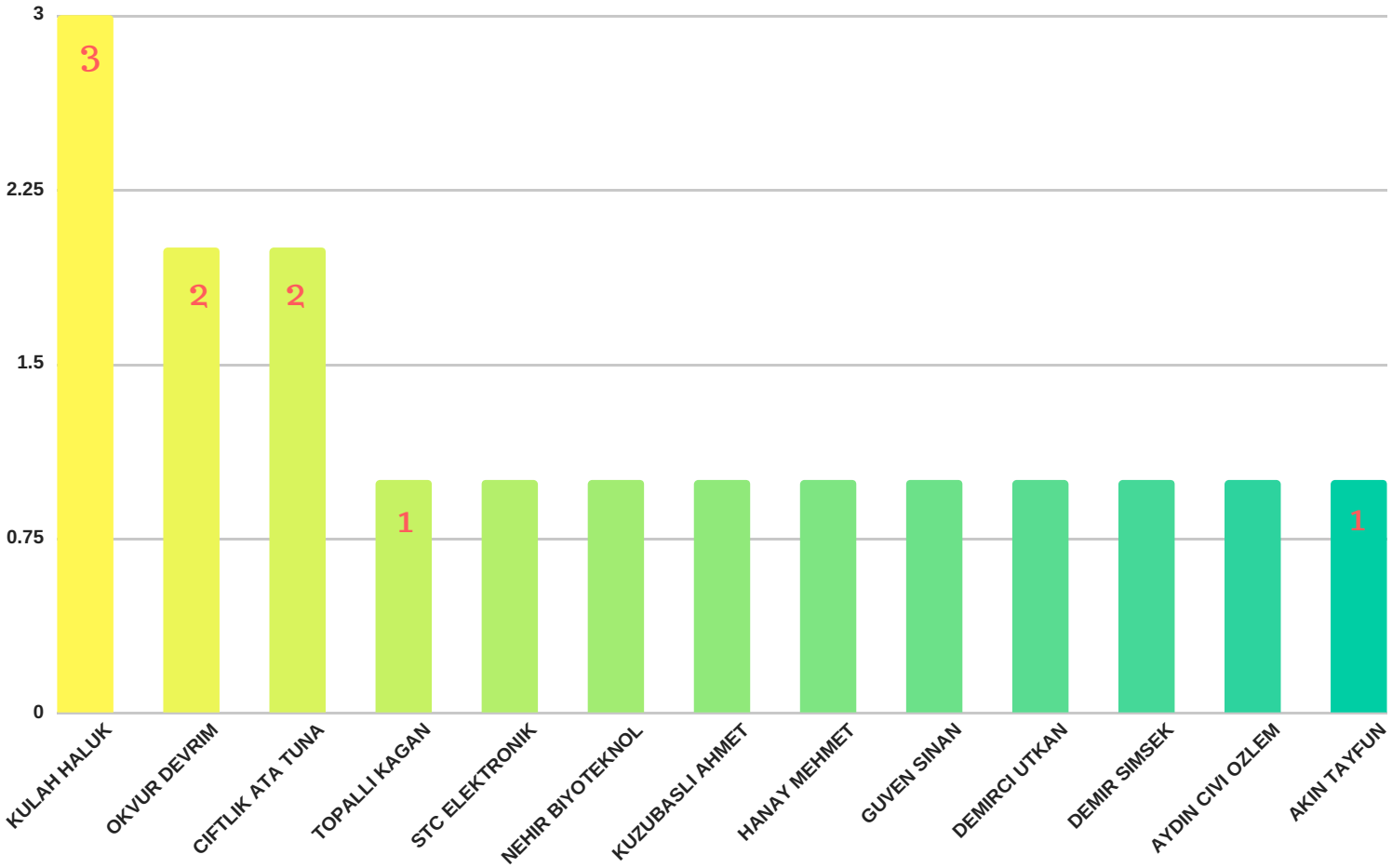
BONUS

TOP TURKISH APPLICANTS

This section shows the top Turkish applicants which have the most patent applications in the field of microfluidics and supercritical fluids for life science applications.

PATENT NUMBERS OF THE TOP TURKISH APPLICANTS

You can follow the most active Turkish companies and researchers in this field.



FOLLOW US

Please let us know your comments and suggestions.

info@patenteffect.com

DISCLAIMER

This document is provided for information purposes only and the contents hereof are subject to change without notice. This document should not be considered as a business advice and the insights written in this report are not to be used as the basis for investment or business decisions of any kind without your own research and information validation. Patent Effect disclaims all warranties whether express, implied or statutory, of reliability, accuracy or completeness of results, with regards to the information contained in this report.

Data Sources: Espacenet, WIPO Patentscope, USPTO

patent effect

patent data-driven innovation insights

BLOG **blog.patenteffect.com**

@patenteffect