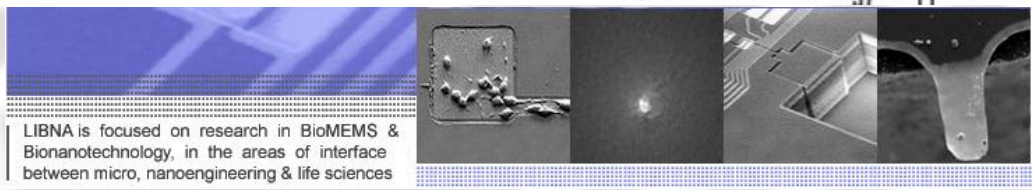
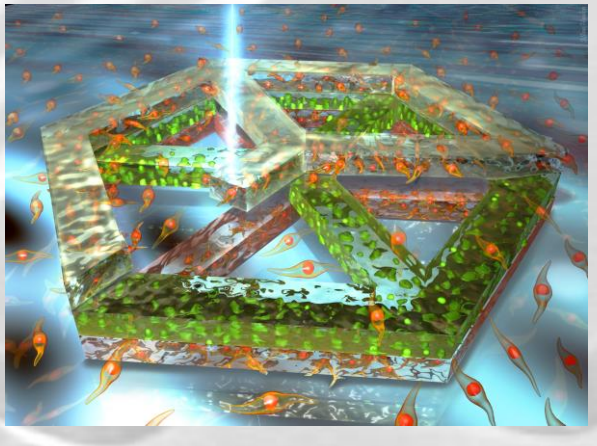
LIBNA

Laboratory of Integrated Bio Medical Micro/Nanotechnology & Applications



BIOMEMS AND BIOMEDICAL NANOTECHNOLOGY: FROM LAB ON CHIP TO PRINTING CELLULAR MACHINES



Rashid Bashir
Department of Bioengineering
Micro and Nanotechnology Laboratory
Carle Illinois College of Medicine
University of Illinois, Urbana-Champaign
http://libna.micro.uiuc.edu/

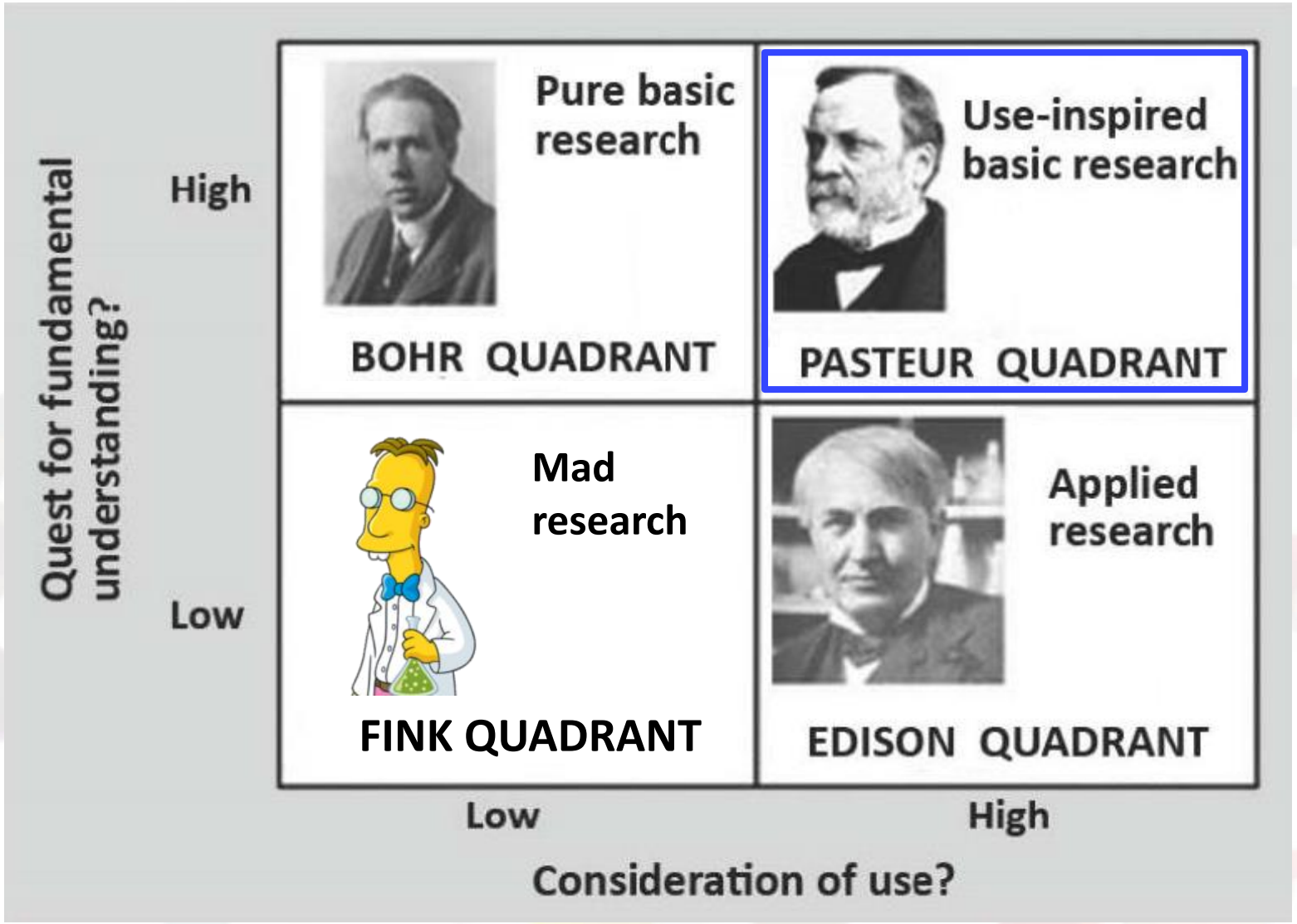
March 5 - 6, 2018

Integrated Cellular Systems

NSF

XI Annual Conference of Spanish Technological Platforms in Biomedical Research, Barcelona, Spain

What Drives Our Research ?



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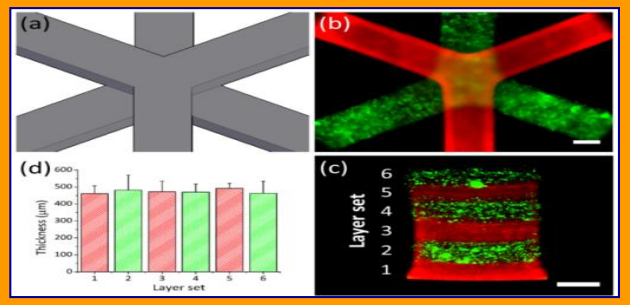
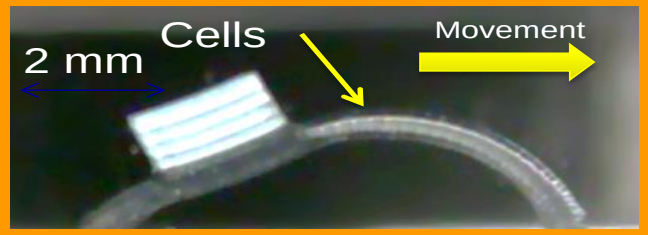
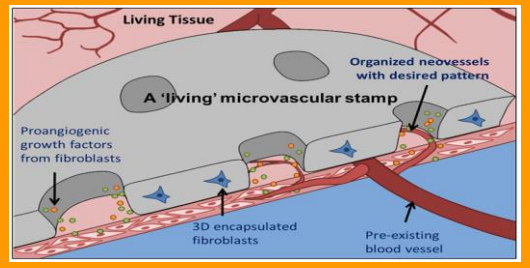
libna.mntl.illinois.edu



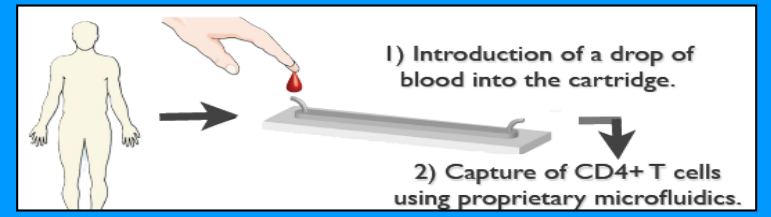
Emergent Behavior of Cell Systems



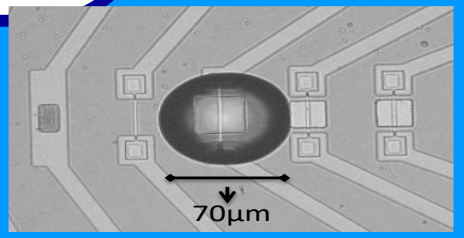
Biological Soft Robots



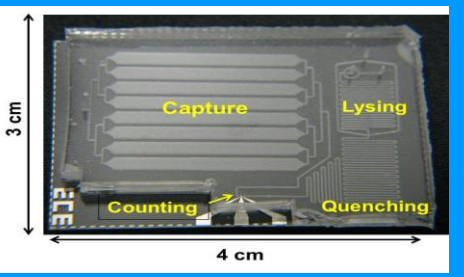
Vascular Patch for Angiogenesis

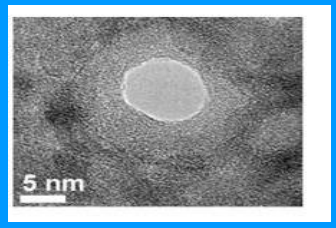


POC Sensors and Systems



Point of Care PCR – Droplet Heating





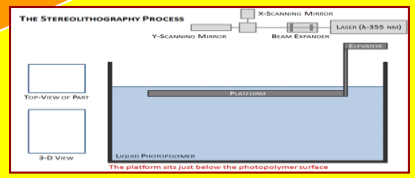
Nanopores for DNA Methylation and Sequencing

Drug Screening, Bio-Robotics, Hyper-organs

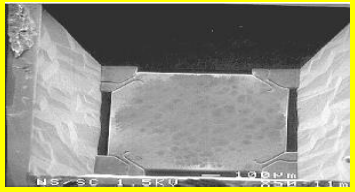
Cancer, Global Health, Sepsis

3-D Bio-fabrication and Cellular Systems

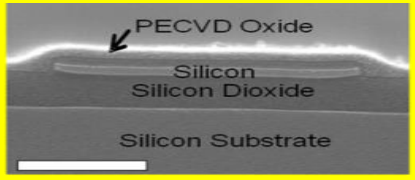
Tools for Precision and Personalized Medicine



PDMS and 3-D Bio- Stereo-lithography



Silicon MEMS Fabrication

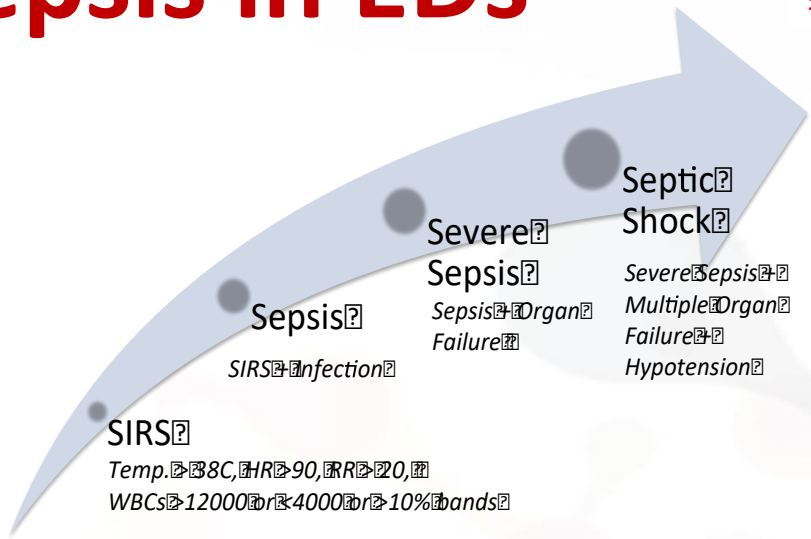


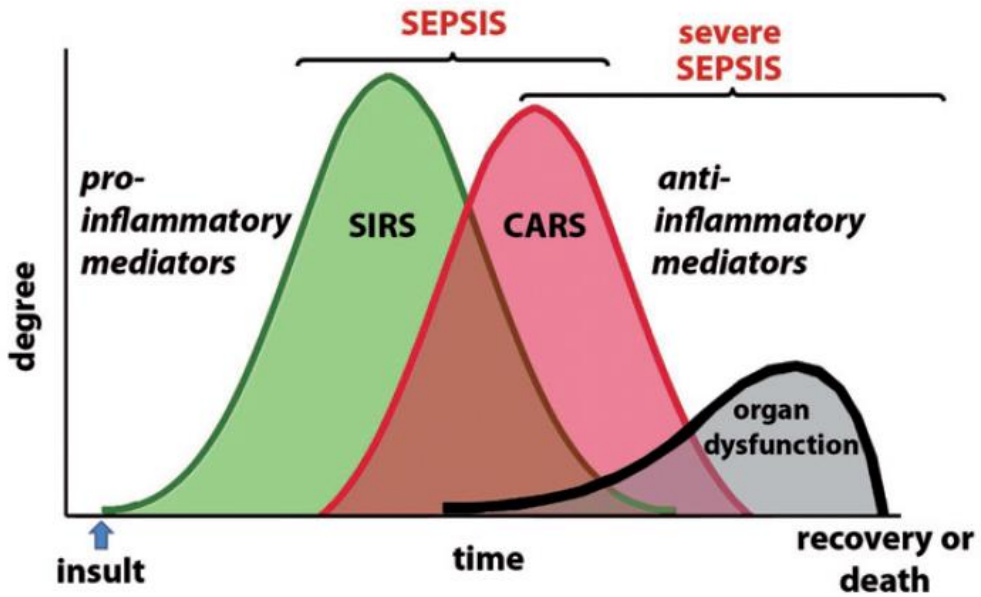
Silicon Nanofabrication

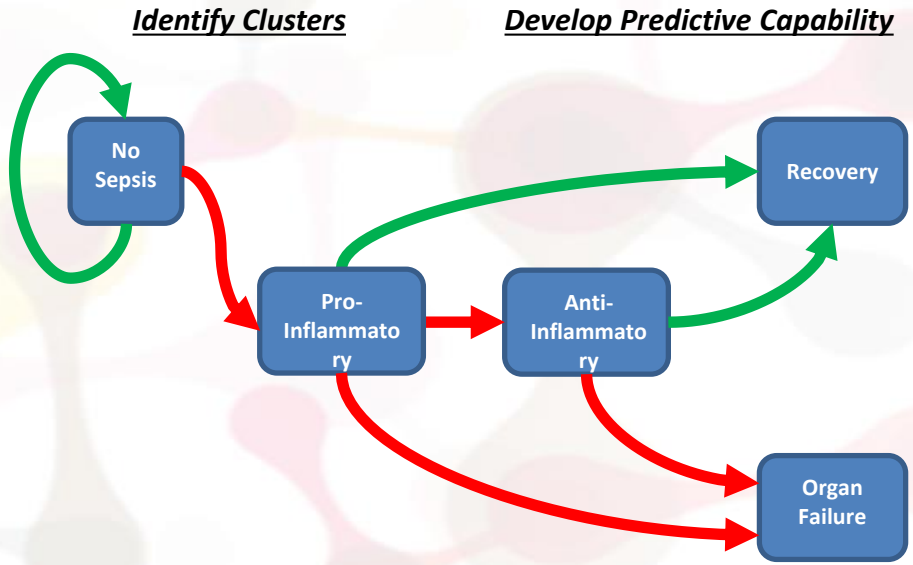
Macro, Micro, Nano - Fabrication

Stratification of Sepsis in EDs

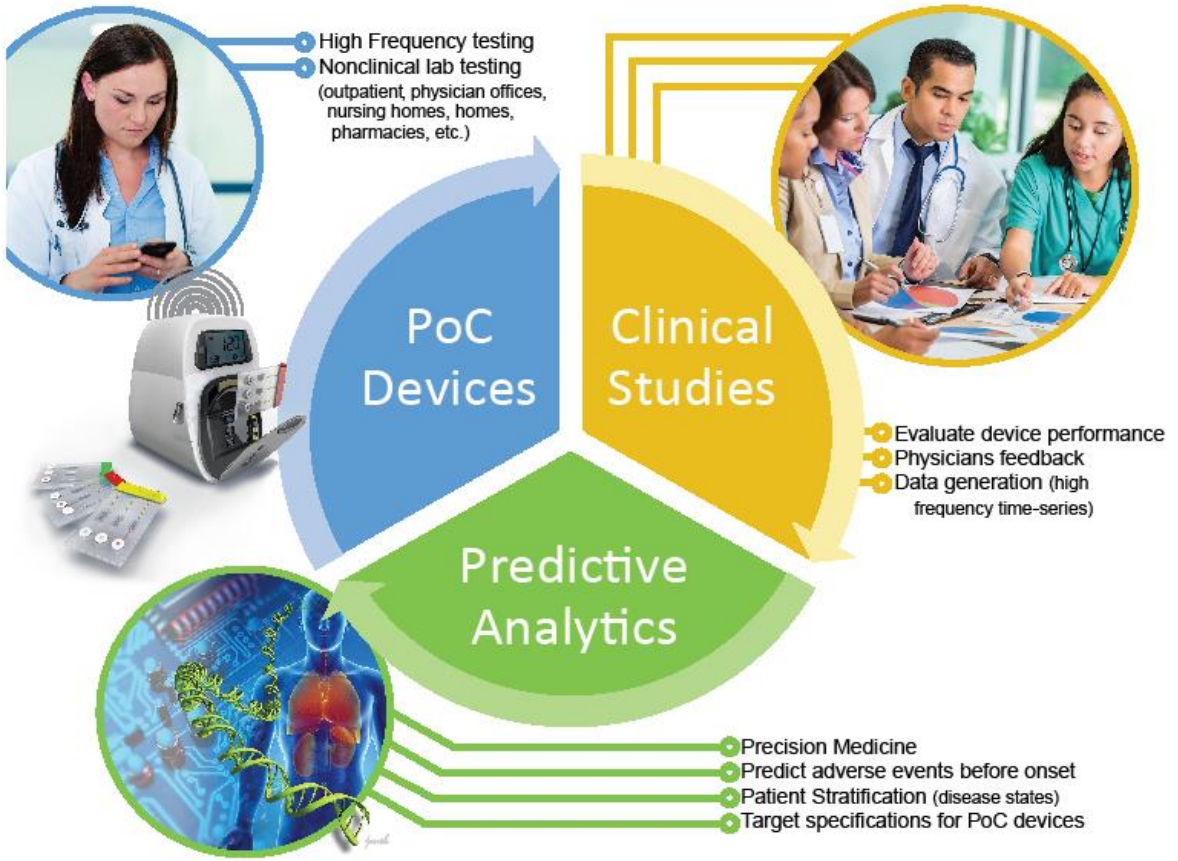
- Leading cause of death in critical care
- 1,150,000 cases in the US per year
- 20-50% die! 215,000 deaths per year
- Estimated $26 billion annual cost to the U.S. healthcare system







A Team Approach



Rashid Bashir

Novel Devices

Bobby Reddy

Translation

Enrique Valera

Umer Hassan

Karen White

Director of ICU

Benjamin Davis

Director of ED

Jennifer Eardley

Carle Research

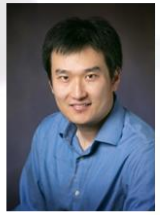
James Kumar

Internal Medicine

Dave Zhao

Biostatistics

Ruoqing Zhu



Biostatistics for Machine Learning

Ali Dunnett

Director of Clinical Lab

Jamie Holley

Quality Services

Brad Weir

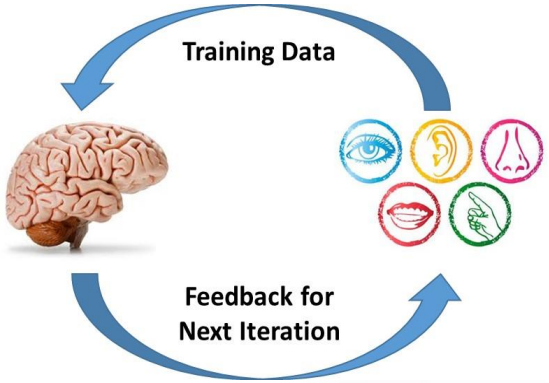
Sepsis Champion

Ongoing Sepsis Biomarker Study (900 samples and counting)

SAMPLES TAKEN FROM PATIENTS FOR WHICH A BLOOD CULTURE HAS BEEN ORDERED

Precision Medicine + Critical Care

Predictive Analytics Algorithm
The Brain
- **Learn:** Add to database using training data
- **Predict:** Refine the model
- **Validate:** Test the model
- **Instruct:** Request more relevant training data for next iteration



Point of Care Device
The Senses
- **Diagnose:** Collect information of critical value
- **Observe:** Collect information of unknown but promising value
- **Adjust:** Focus on different information and adjust frequency of information as per feedback

Pro-Inflammatory
- **Neutrophil CD64**
- **IL-6**
- **TNF-α**
- **IL-1β**
- **sTREM-1**
- **MMP-3**
- **C5a**

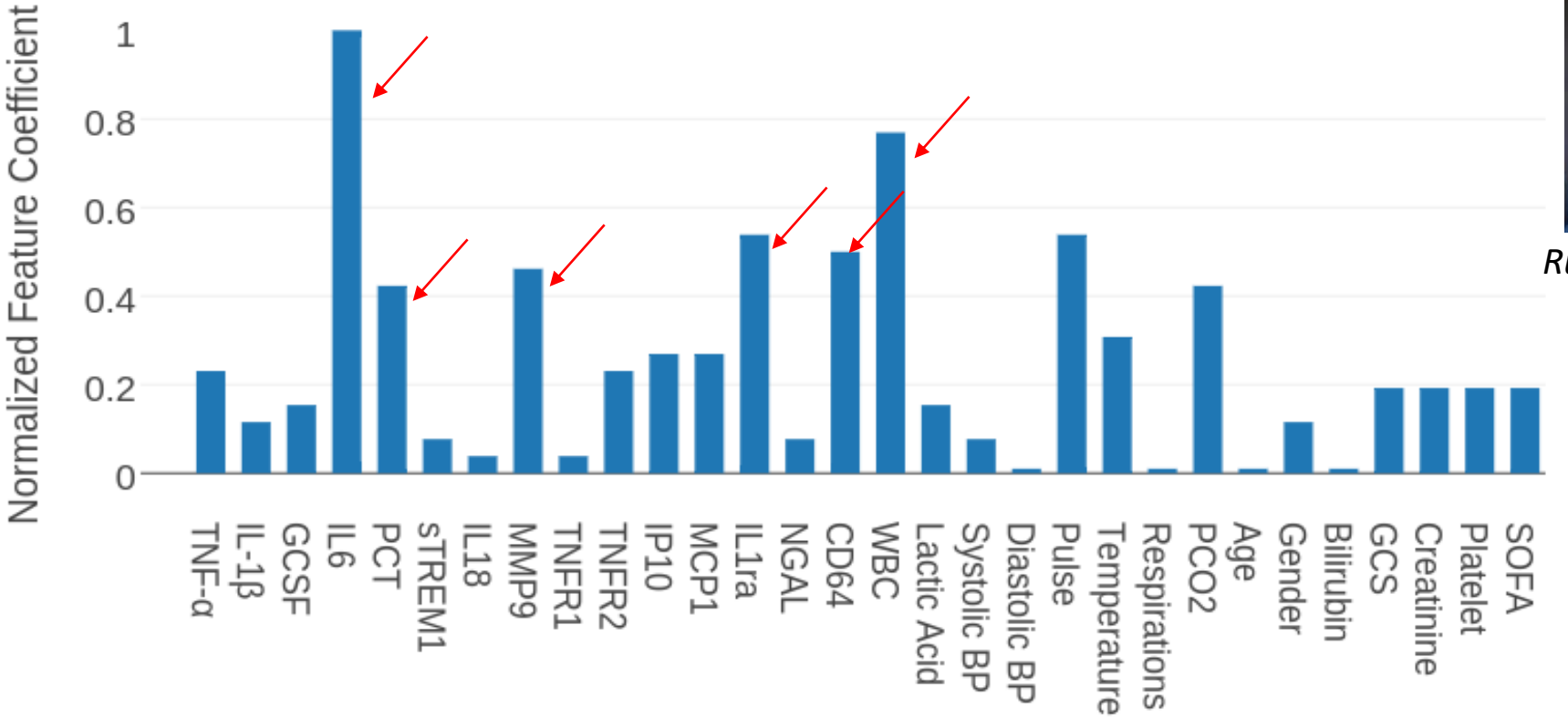
Others
- **PCT**
- **NGAL**

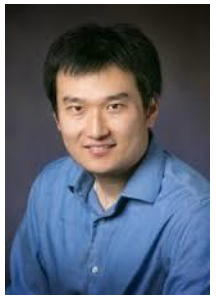
Anti-Inflammatory
- **Monocyte HLA-DR**
- **IL-10**
- **IL-1α**
- **IP-10**
- **sTNF-R2**
- **MCP-1**

Clinical Information

- Every single vital measurement **throughout entire hospital stay**
- All clinical diagnoses including time of diagnosis
- All CBC results, BMP results, PCT, CRP, blood culture, lactic acids **throughout entire hospital stay**
- All medications and time administered

Machine Learning Models Indicate which Biomarkers are Important ?





Ruoqing Zhu *David Zhao*

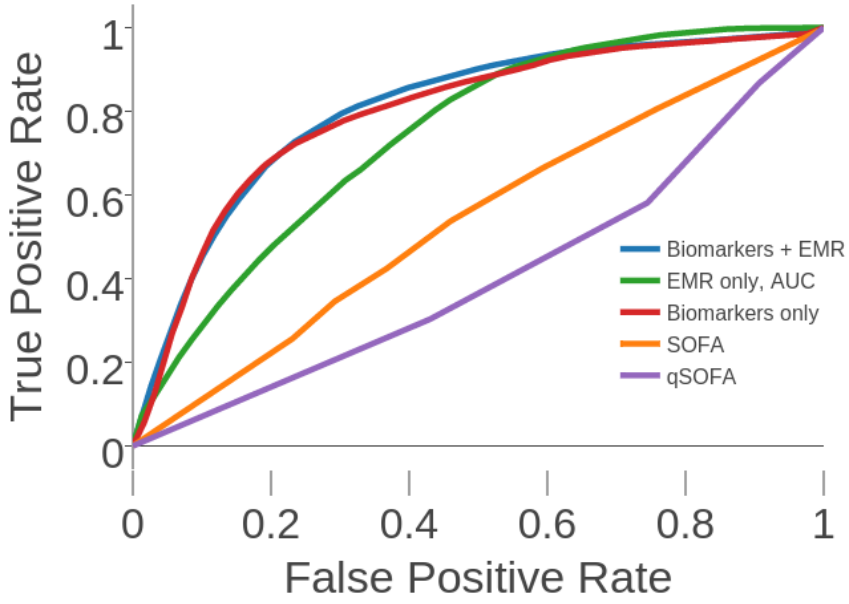
Normalized feature coefficients outputted by SVM for clinical adjudication label set. The absolute value of each feature coefficient in SVM corresponds to its relative importance.

Taneja, et al. *Scientific Reports*, 2017

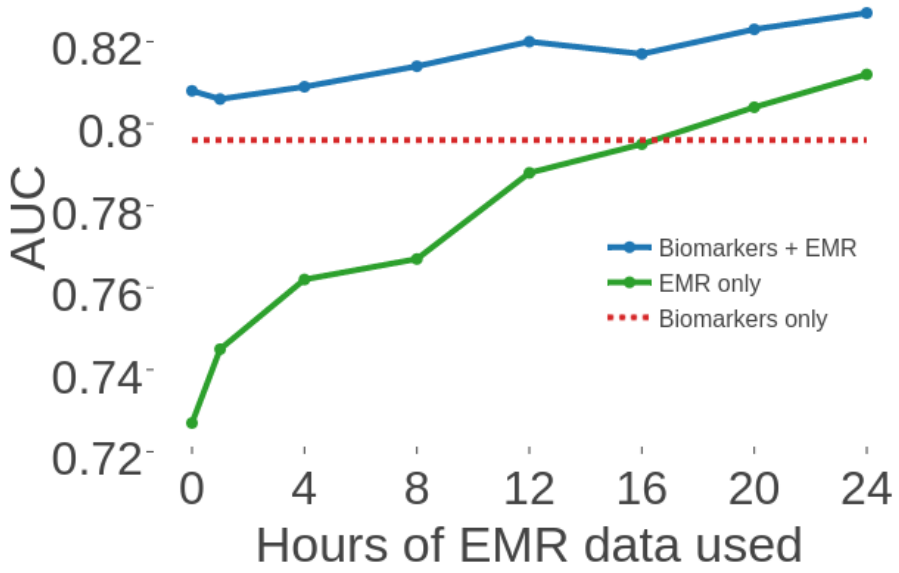
Prenosis

Carle

Power of Biomarkers



	Features Decreasing in Importance	AUC
—	IL-6, nCD64, pulse, WBC, MMP9, IL-1ra, PCT	.81
—	WBC, pulse, temperature, lactic acid, SOFA	.75
—	IL-6, nCD64, PCT, IL-1ra, MMP9, TNFR2	.80
—	SOFA score	.54
—	qSOFA score	.40



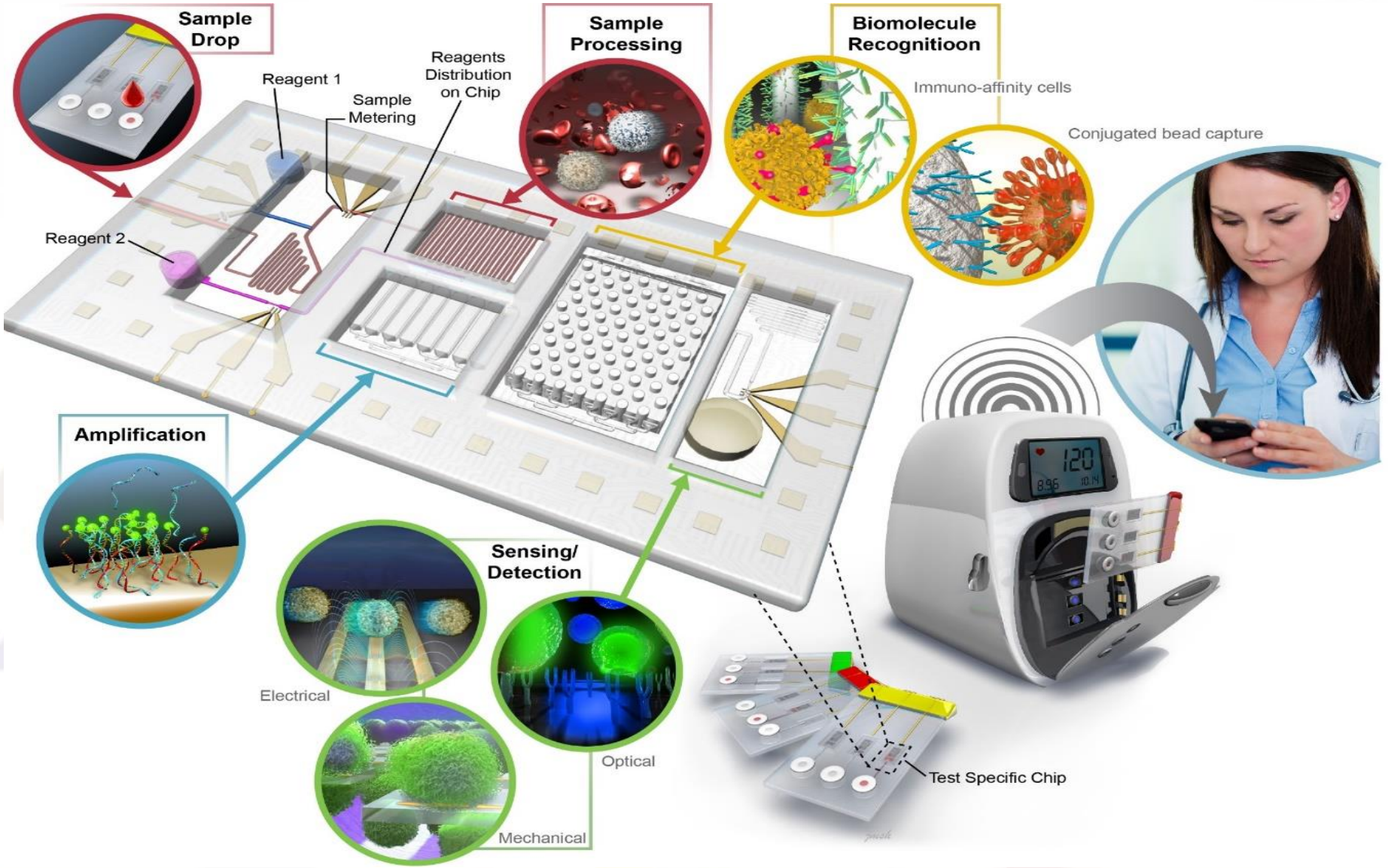
1 drop of blood at T=0 is same as 16 hrs of EMR data !!

Taneja, et al. *Scientific Reports*, 2017

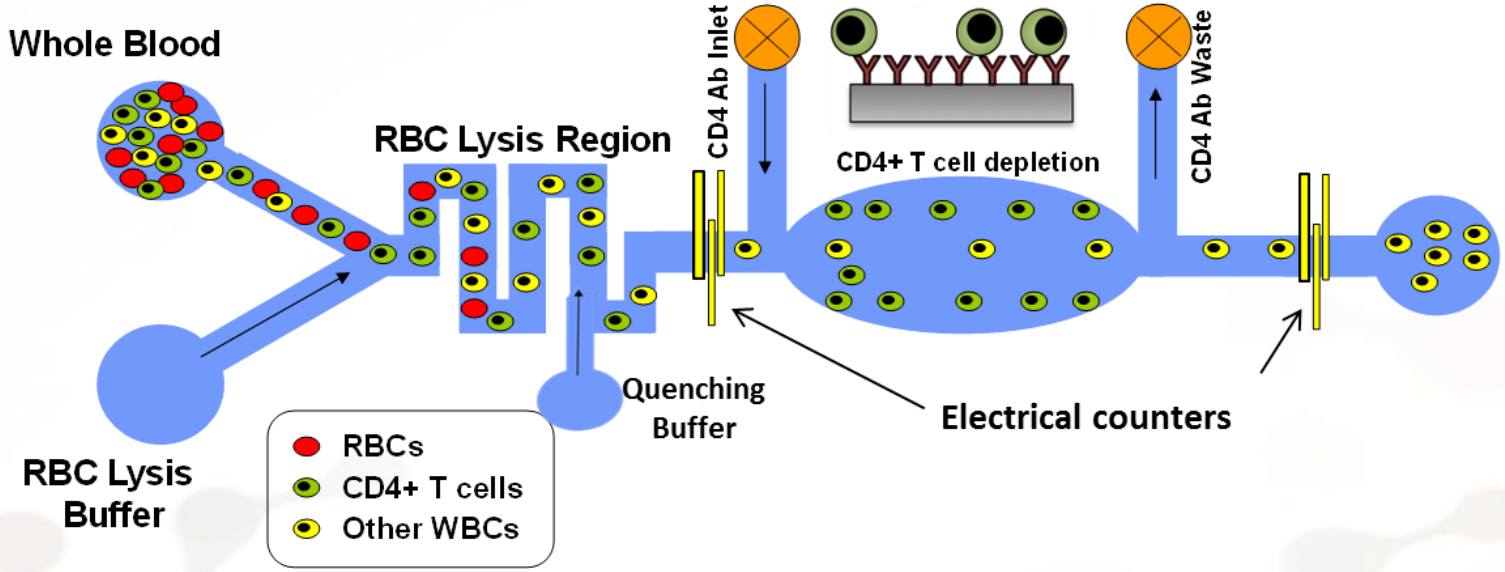
Prenosis

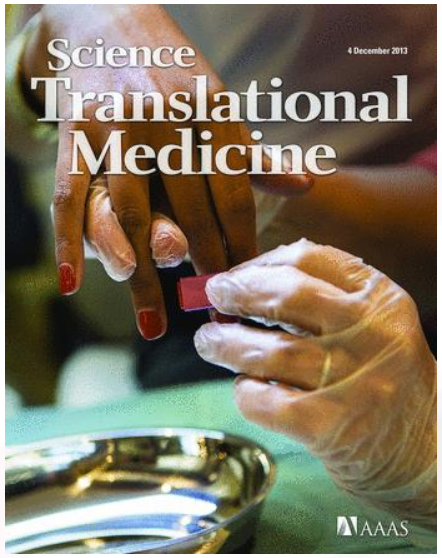
Carle

From Sample to Results

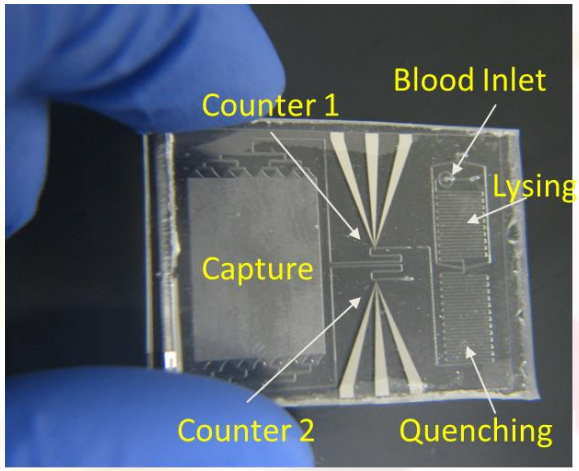


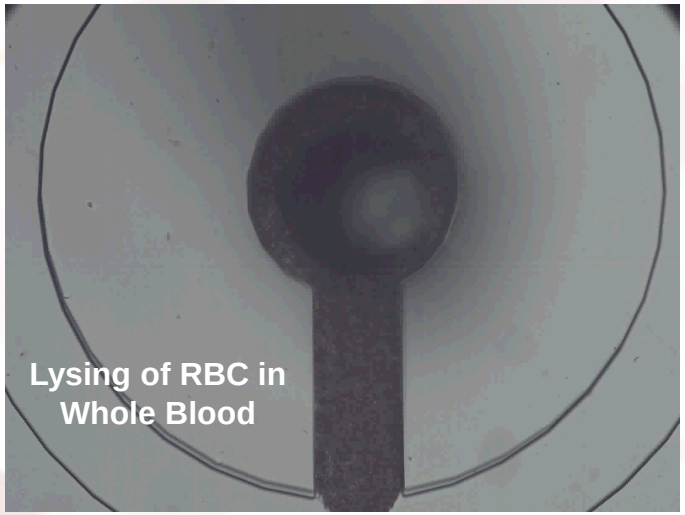
Can We Measure WBC and Subtypes from a Drop of Blood?





- **A point of care CBC from a drop of blood**
  - **WBC, Neutrophils, Monocytes**
  - **CD4+, CD8+, CD64+ other sub types**
  - **Protein biomarkers**

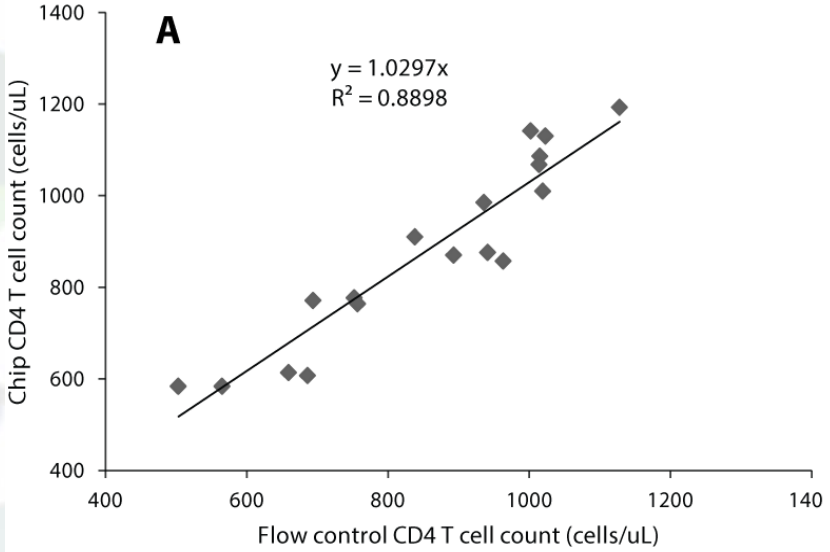


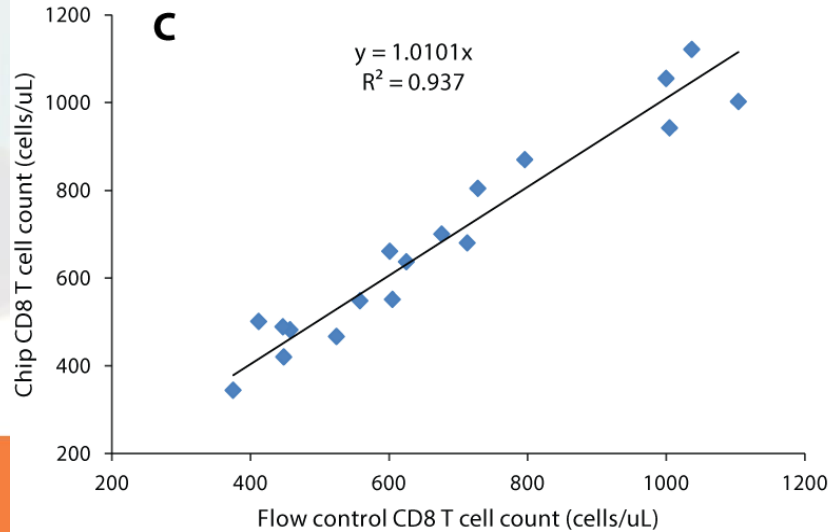


Watkins, et al. *Sci. Trans. Med*. 2014
Hassan, et al. *Nature Protocols*, 2016
Hassan, et al. *Nature Comm*., 2017

T Cell from Healthy Donors

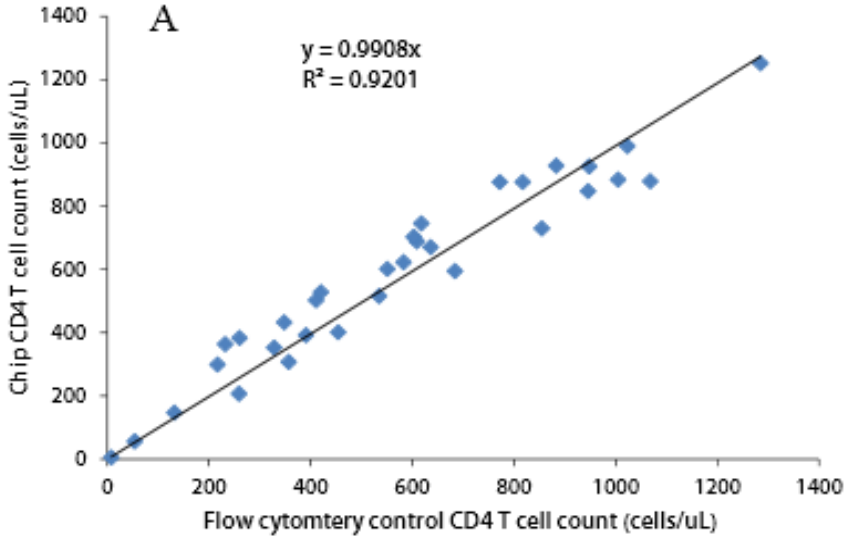
- IRB approved
- De-identified samples
- Healthy Subjects from UIUC

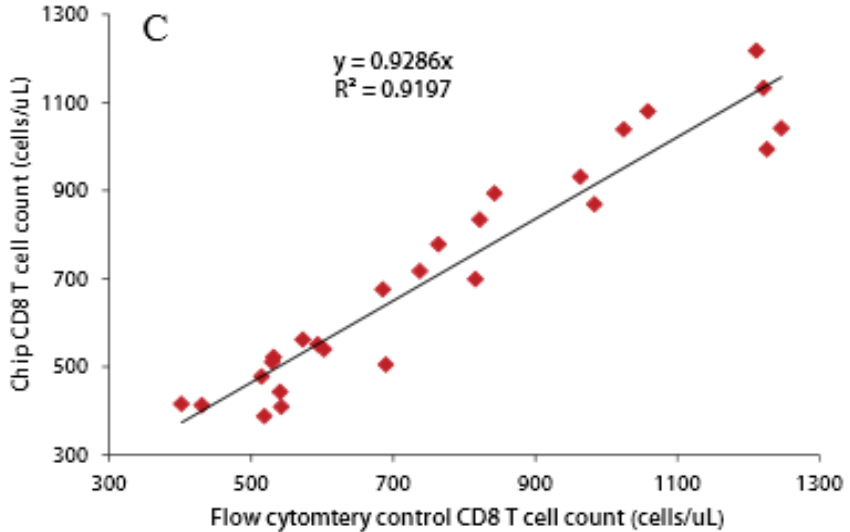


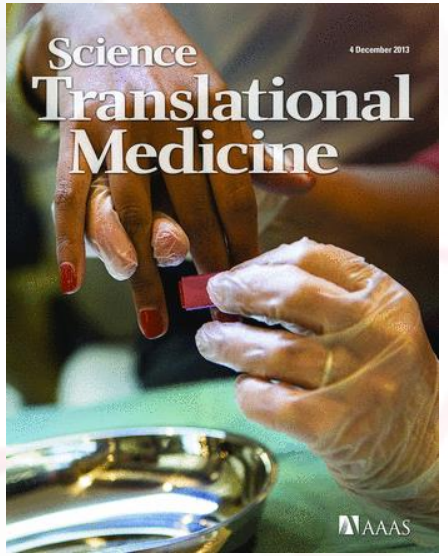


T Cell from HIV Infected Patients

- IRB approved
- De-identified samples
- Infected Subjects from CUPHD

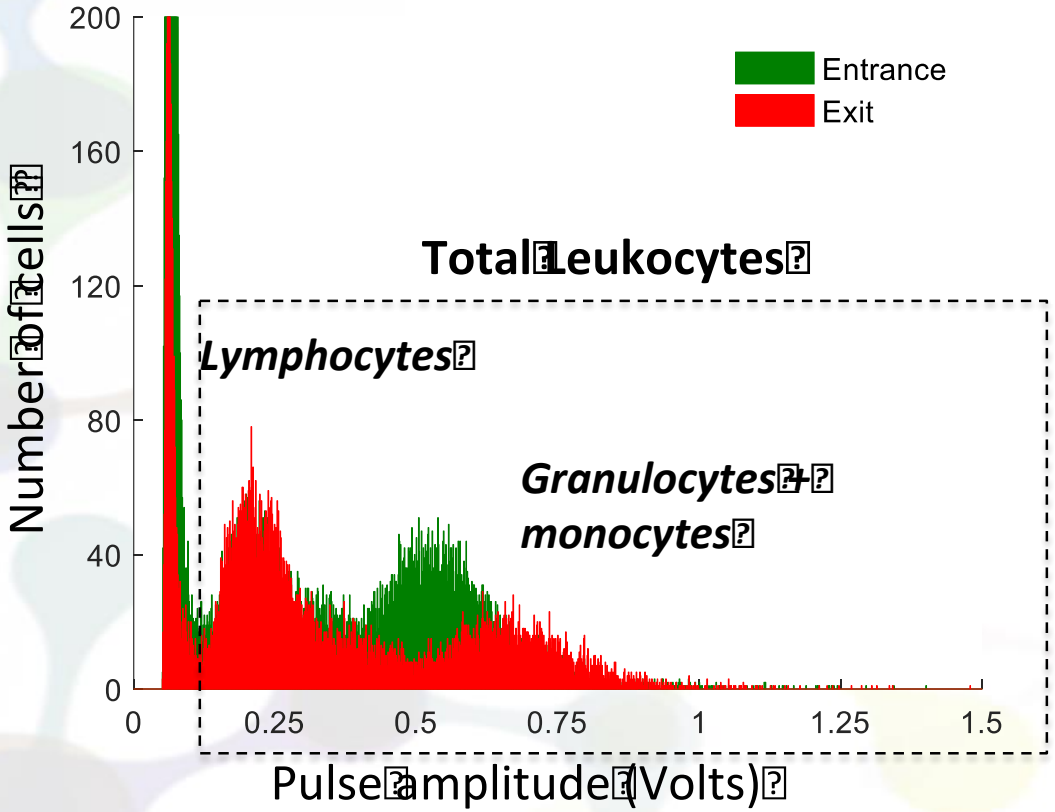


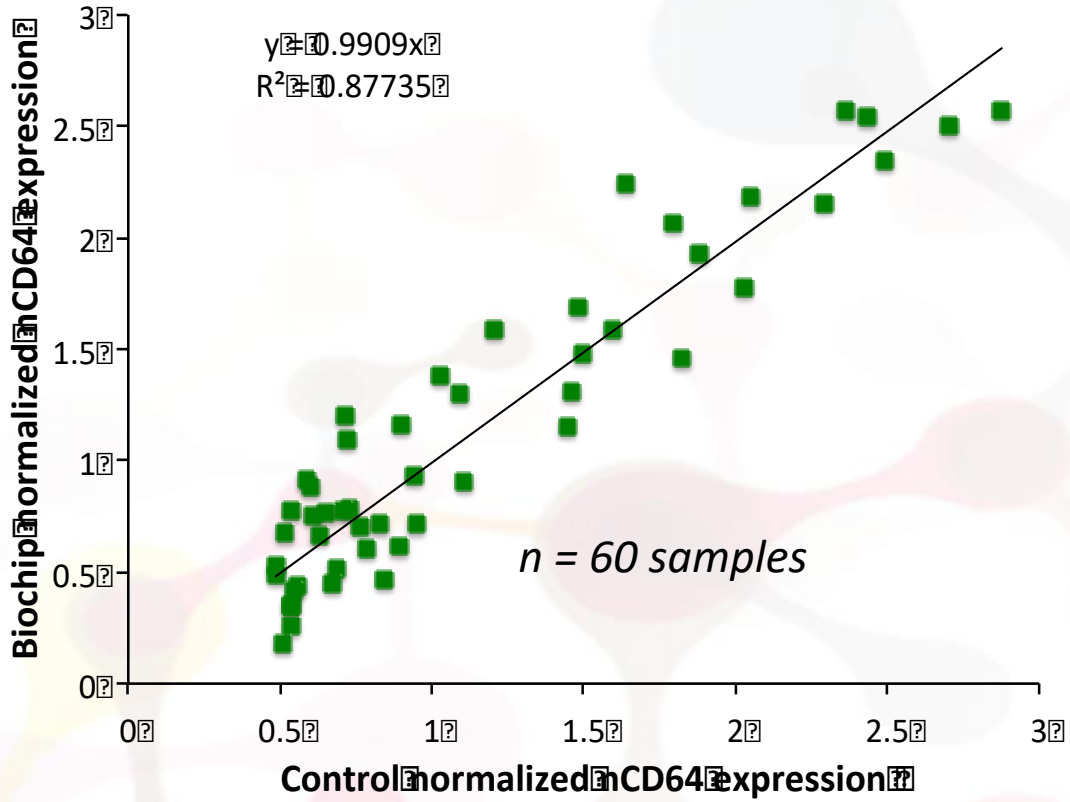




Watkins, et al. *Sci. Trans. Med*. 2014

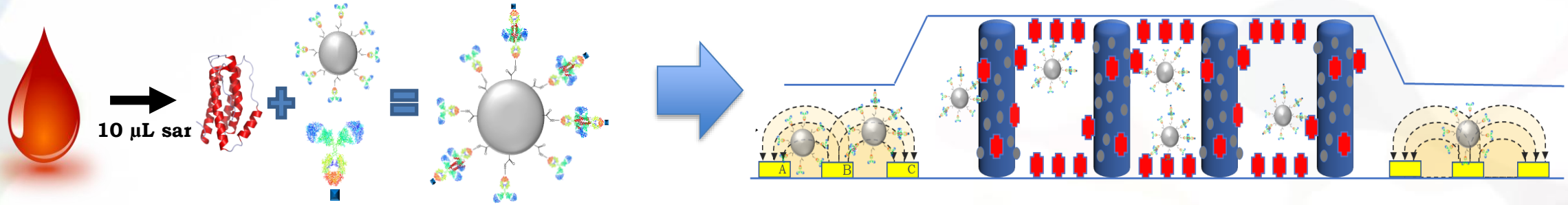
CD 64 expression based capture as marker for sepsis





U. Hassan, et al. *Nature Comm. 2017*

Protein Capture on Chip



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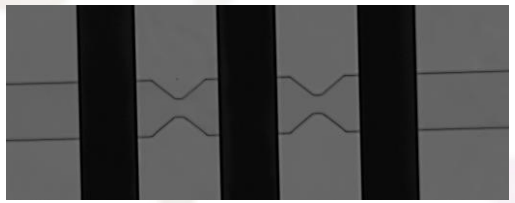

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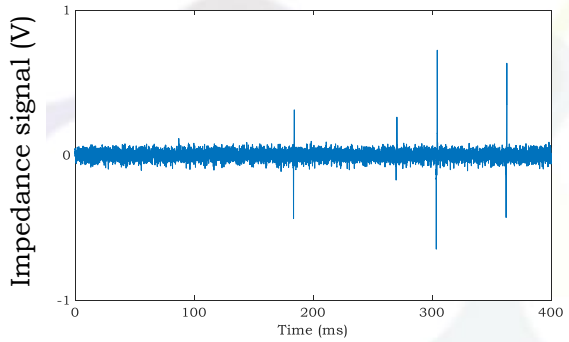

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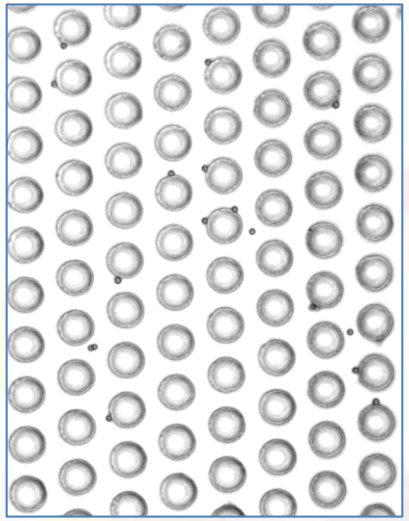
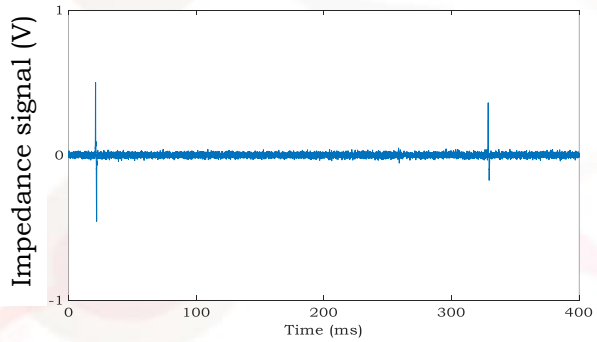


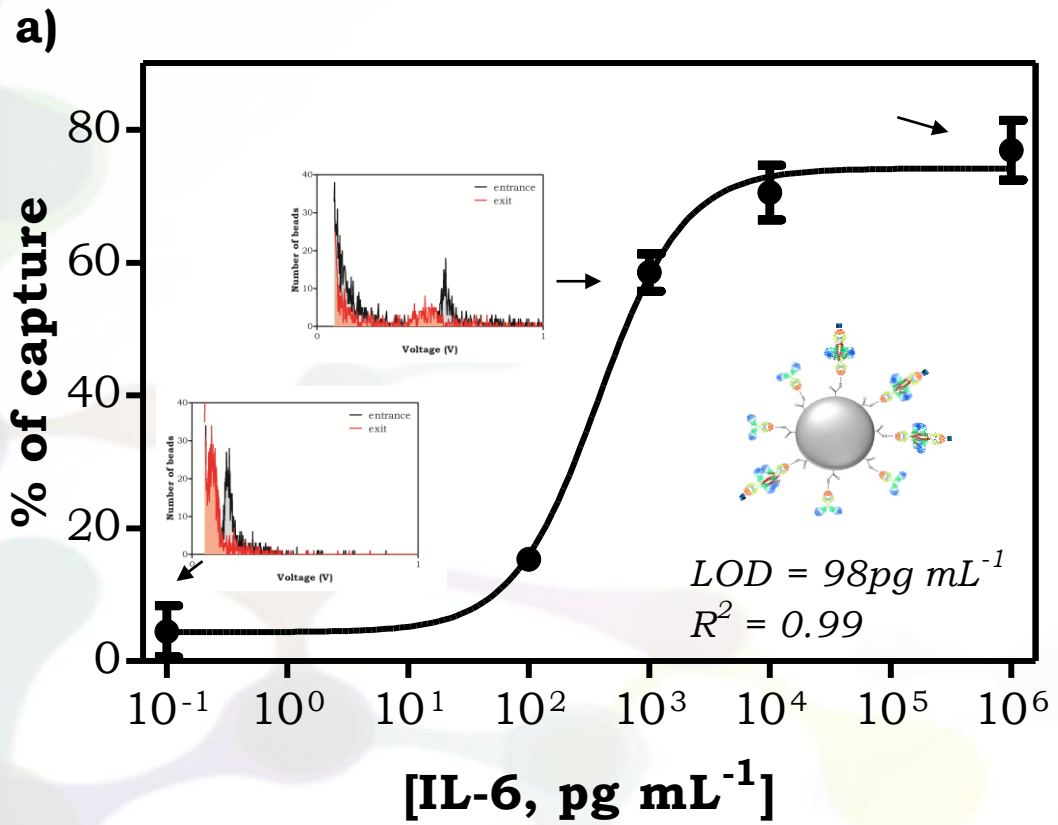
4. **Figure of merit: % of capture**

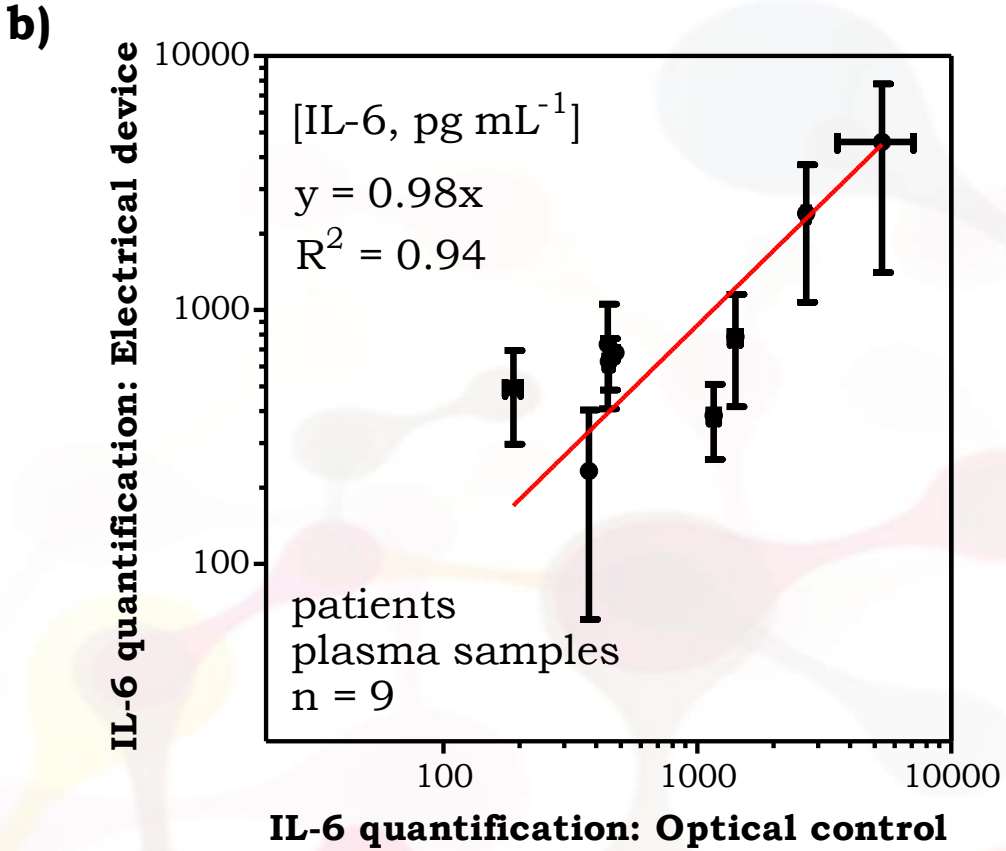
$$\frac{Entrance\ Count - Exit\ Count}{Entrance\ Count} * 100 = Percent\ Capture$$



Valera et al. Unpublished, 2017

Protein Capture on Chip





Valera et al. *Unpublished*, 2017

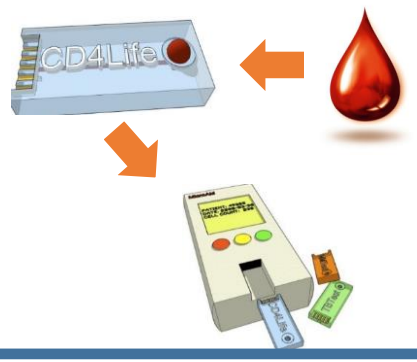
bobby.reddy.jr@prenosis.com
rashid.bashir@prenosis.com
angela.mcfarland@prenosis.com

Creating products to help hospitals understand and track sepsis.

http://www.prenosis.com/

Point of Care Device

Cell + Protein Measurements

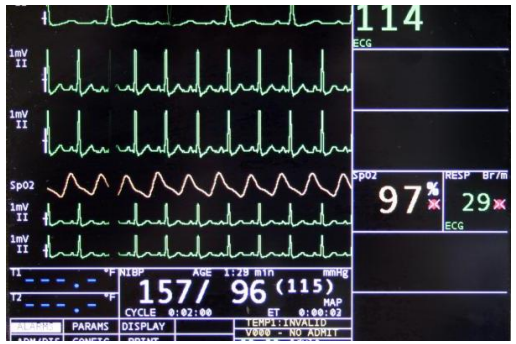


Central Platform

Algorithm for Predicting Sepsis

Relevant Patient Data

Vitals, Labs, Medications
Medical history, Co-morbidities



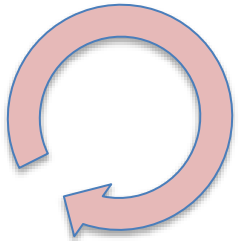
Sepsis Diagnosis & Stratification

Discovery and Reverse Engineering

Developmental Biology

Reverse Engineering and bio-mimicking - Regenerative Medicine

Tissue Engineering



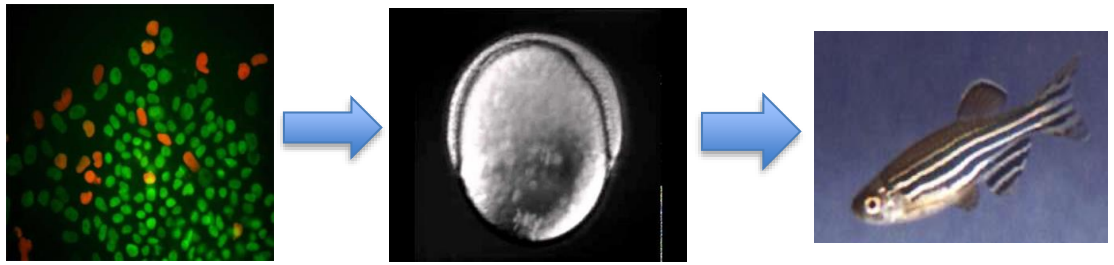
"Progenerative" Medicine

Engineered Living Systems

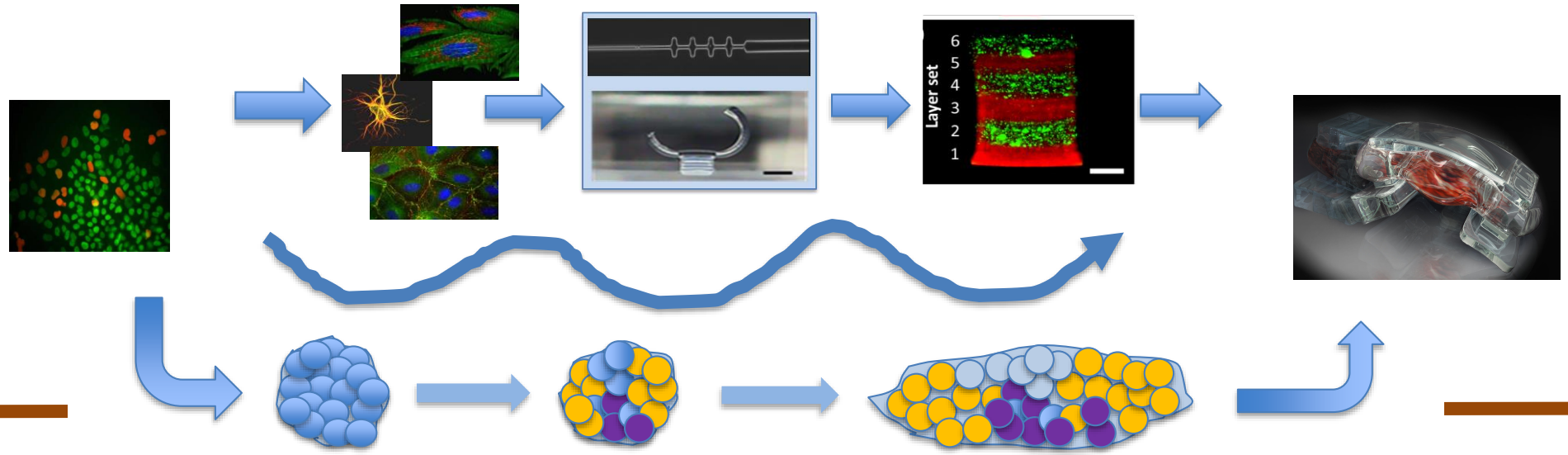
Forward Engineering and use of Emergence for 'Non-natural functions'

Engineered Living Systems

Developmental Biology



Engineering & Emergence

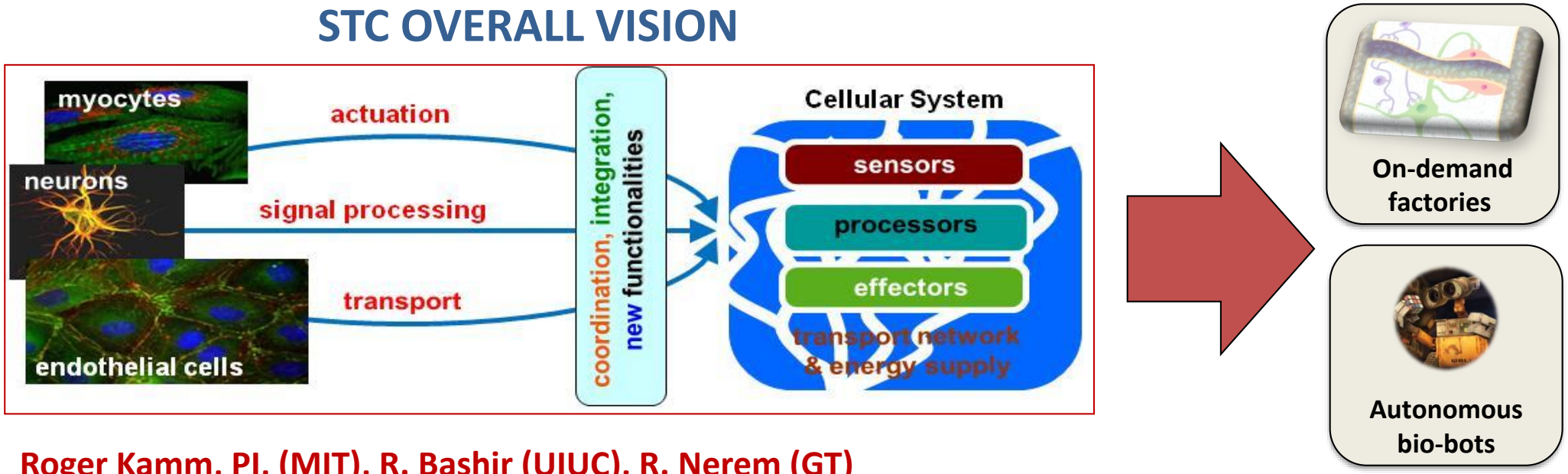


NSF STC: EBICS

Emergent Behavior of Integrated Cellular Systems

www.ebics.net

STC OVERALL VISION



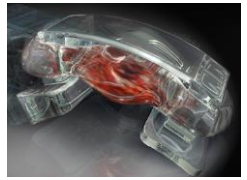
Roger Kamm, PI, (MIT), R. Bashir (UIUC), R. Nerem (GT)

30 faculty from MIT, GT, UIUC, CCNY, UC Merced, Morehouse College

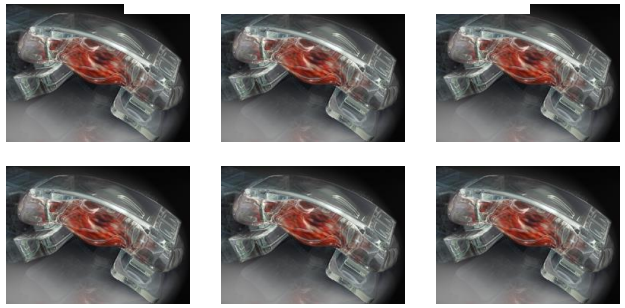
- **Basic Science**: To gain a deeper understanding of how cooperative cell behavior leads to the formation of large organized cellular structures.
- **Applications**: To create biological "machines" in which multiple cell types coordinate to perform a specified function.

Many Possibilities Ahead

Single Devices



Swarms of Devices



in-vivo

- Hyper-organs and enhanced function
- Augmented physiology
- Continuous bio-sensing and therapeutics

- Drug Screening
- Tissue on Chip
- Robotics and Automation
- Sensing and Monitoring

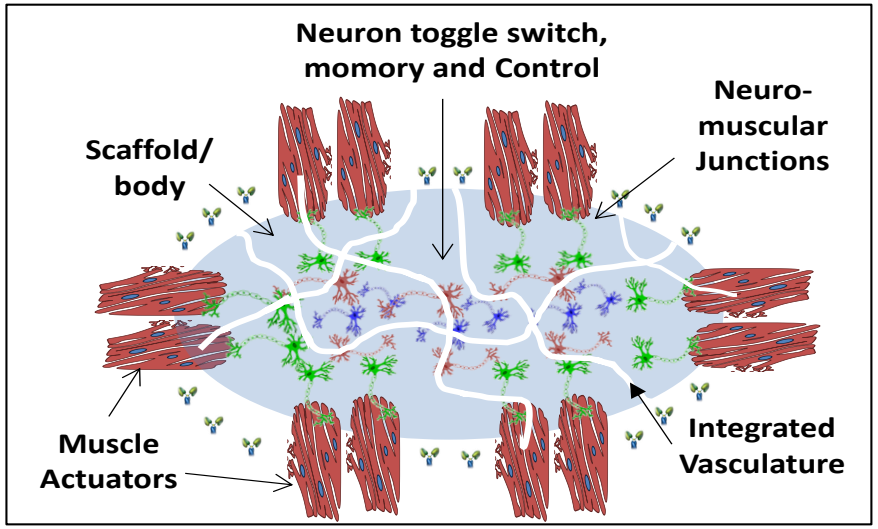
in-vitro

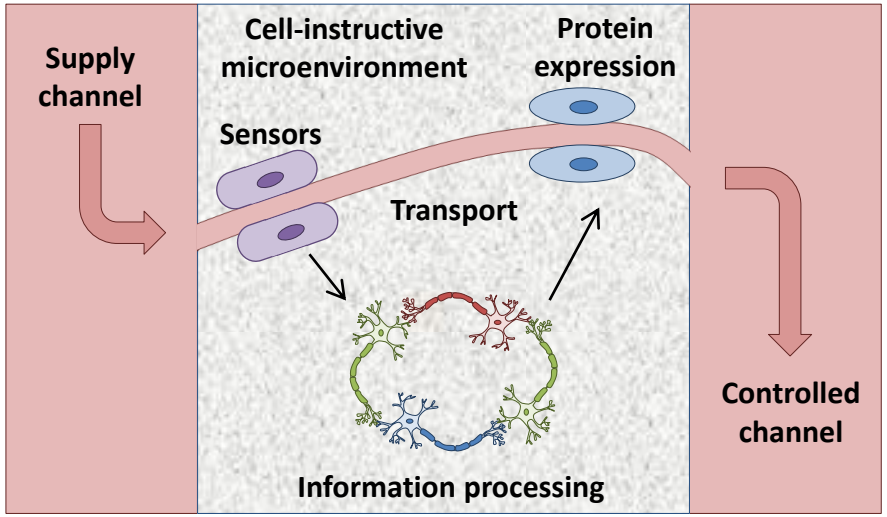
- Emergent Manufacturing
- Water purification
- Higher order functions
- Self healing bio-matter (structures, building, furniture)

Health & Medicine, Energy, Environment, Agriculture

Biological Machines – 'BioBots'

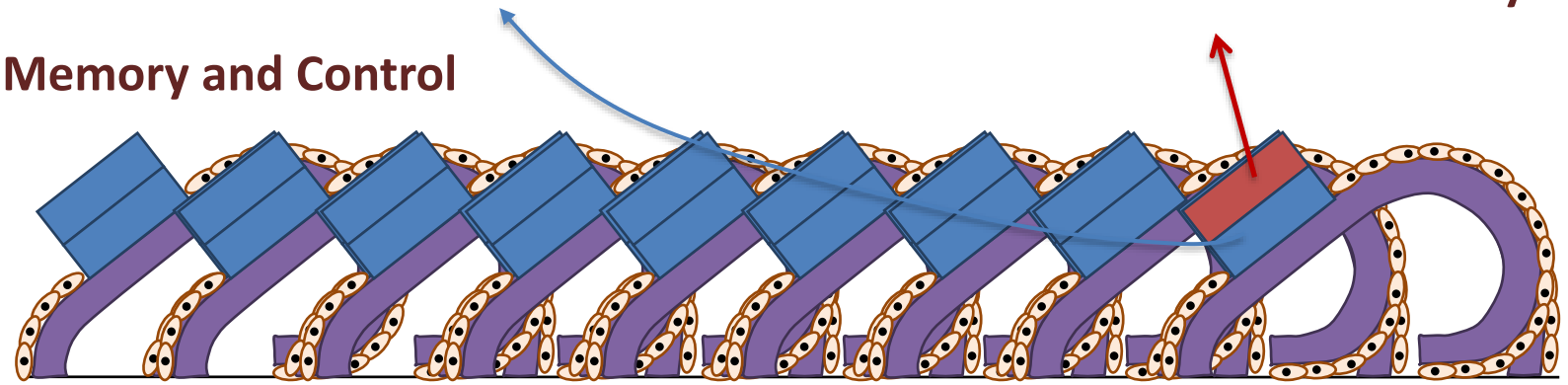
Prescribed tasks include sensing, information processing, transport, protein expression, and movement.





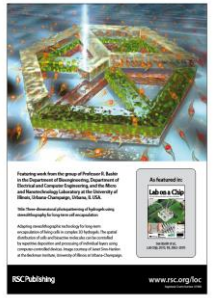
Vasculature & Cell-Based Factory

Memory and Control



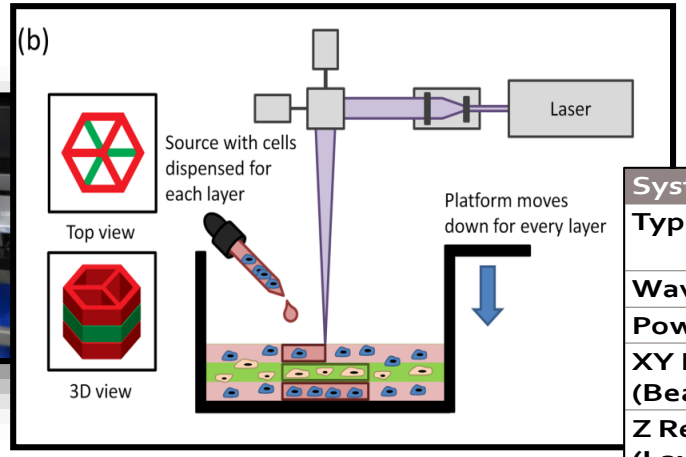
Bio-Bot

3D Bio-Printing and Bio-fabrication

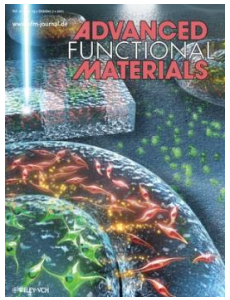


Chan, et al. 2010

Macro-SLA

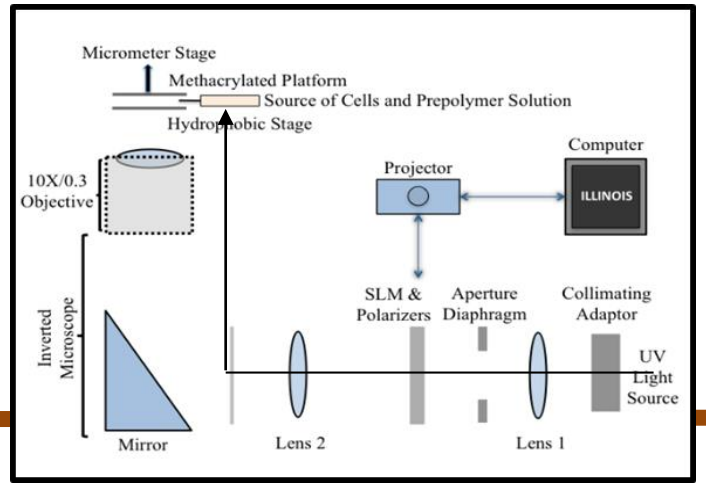


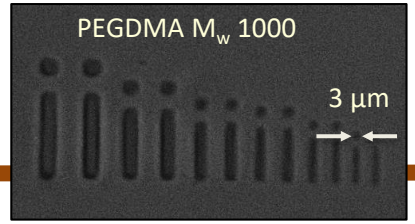
System	SLA 250/50
Type	HeCd (Gas)
Wavelength	325 nm
Power	40 mW
XY Resolution (Beam ϕ)	250 µm
Z Resolution (Layer)	0.1 mm

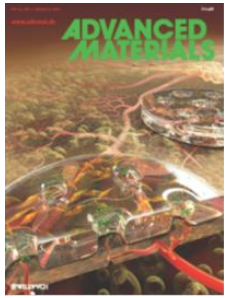


Zorlutuna,, et al. Adv. Func. Mat., 2011

Micro-SLA



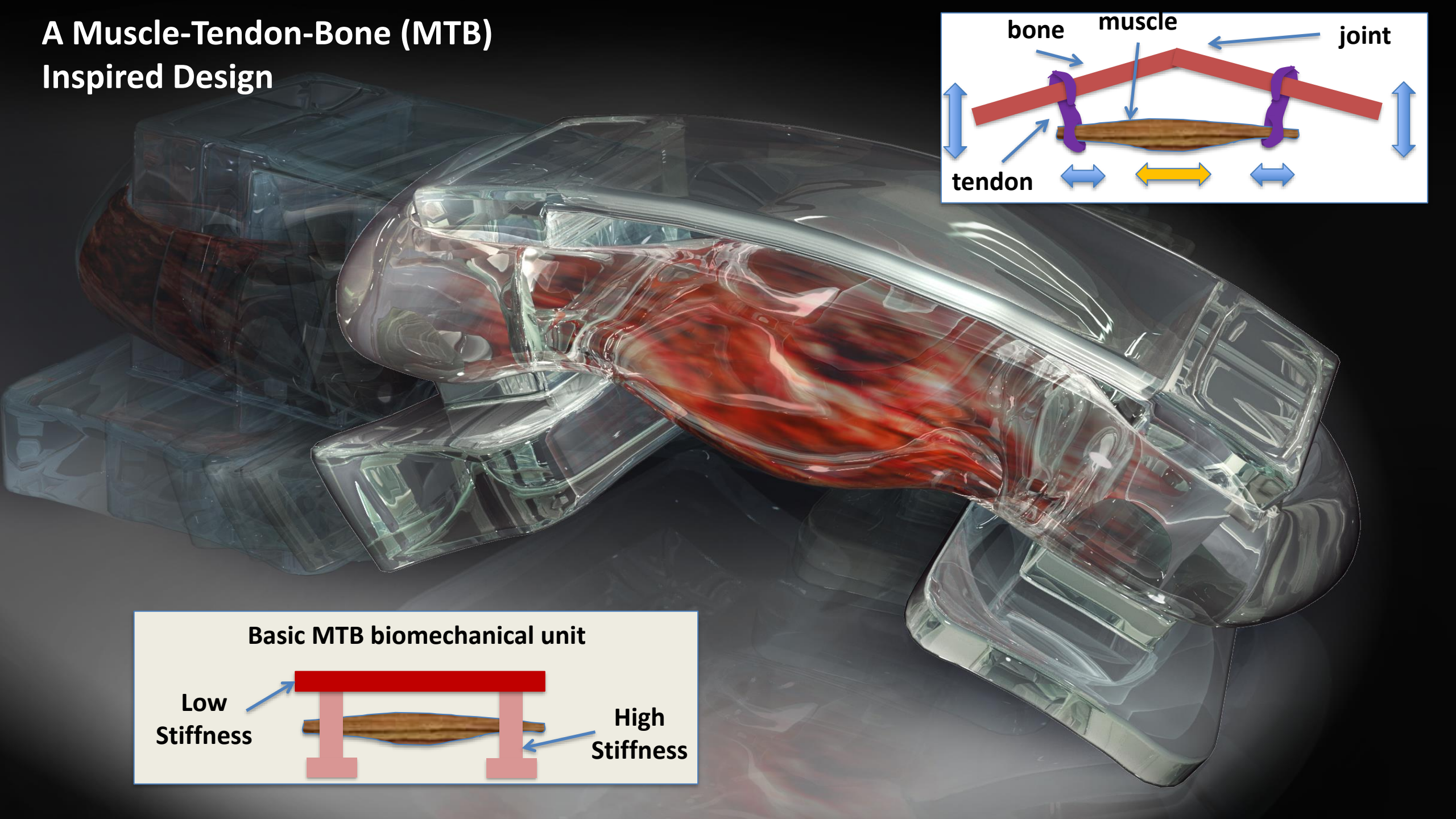




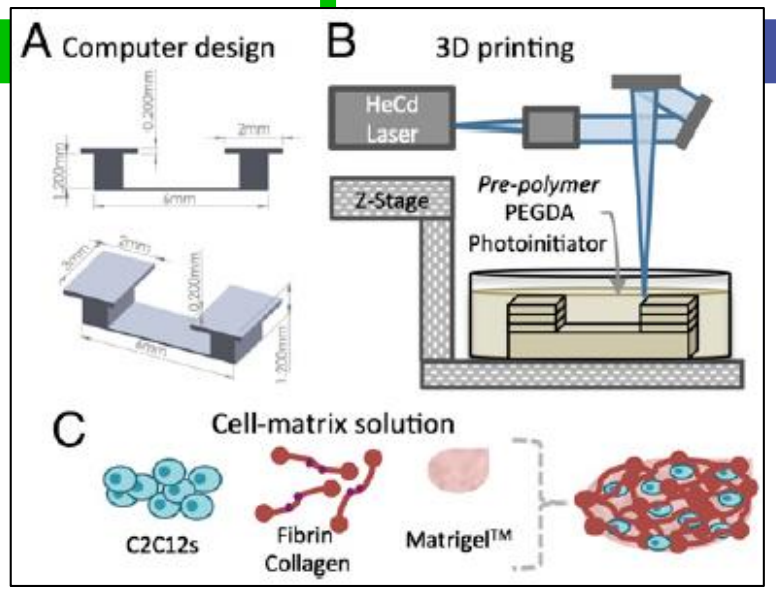
Jeong et al, Adv. Mater. 2012

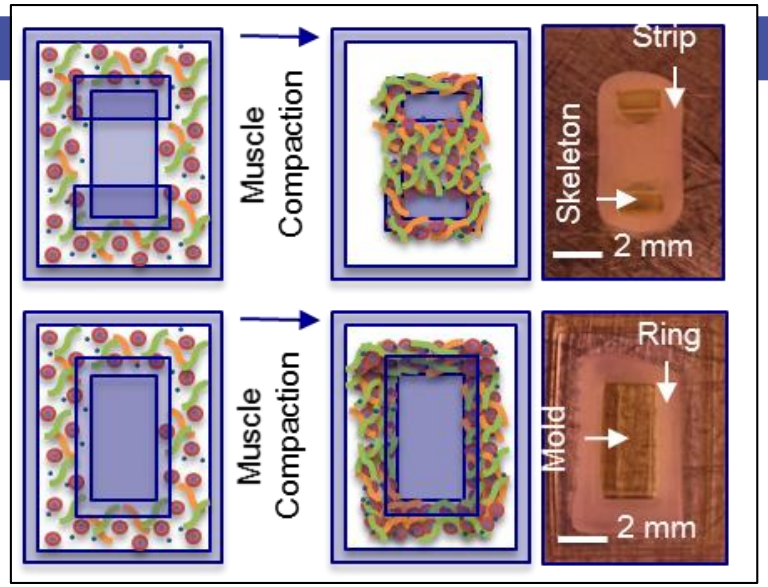
Raman, et al. 2016

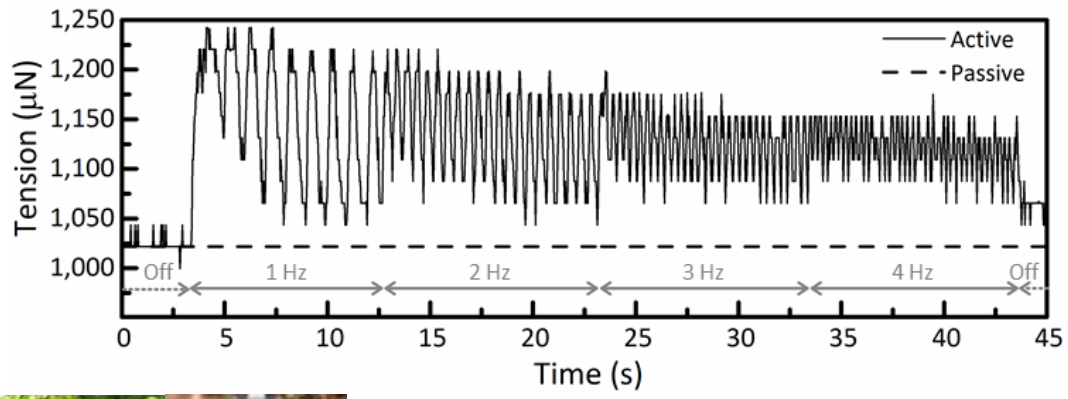
A Muscle-Tendon-Bone (MTB) Inspired Design

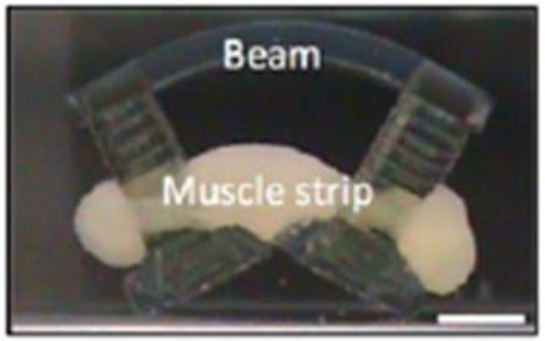


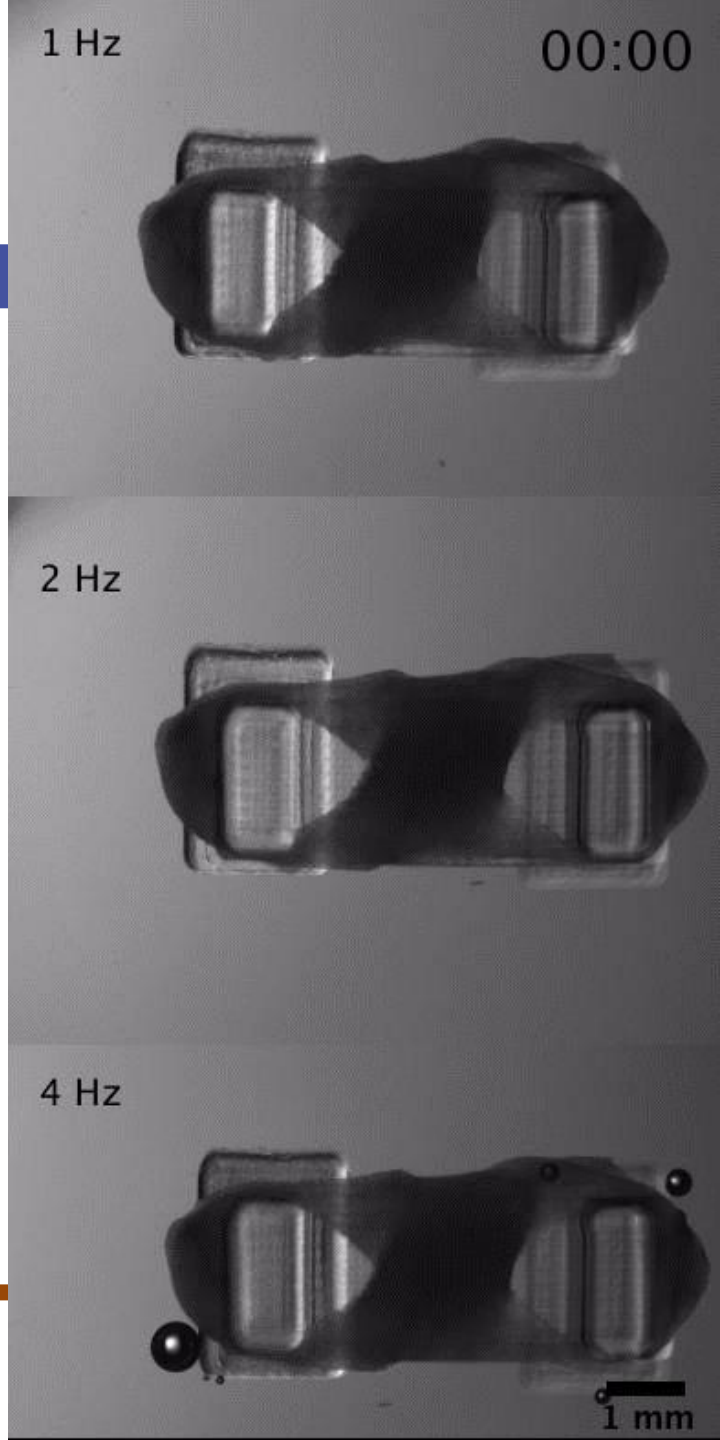
Skeletal Muscle Cell Driven Biobots - Gen 2





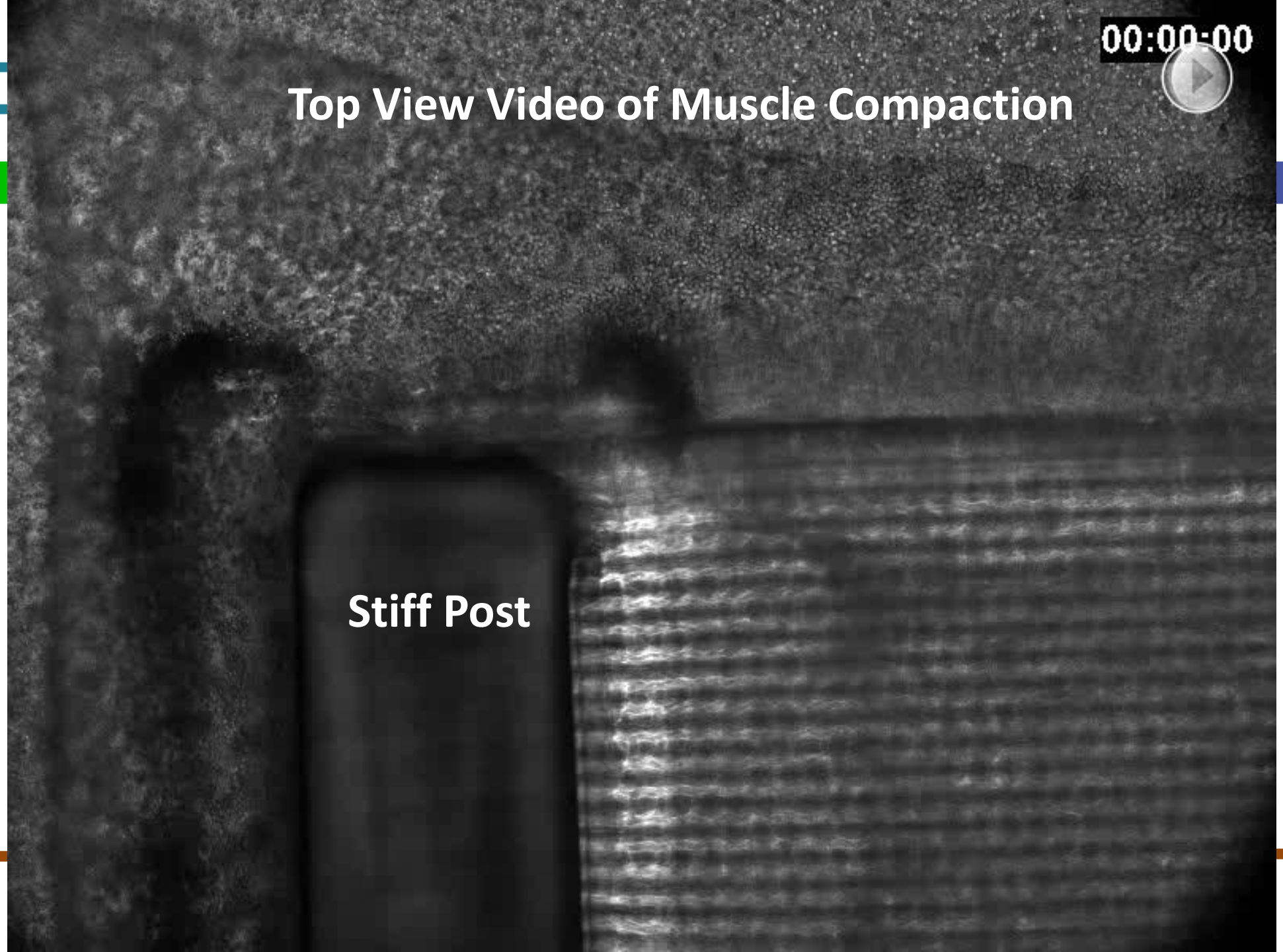




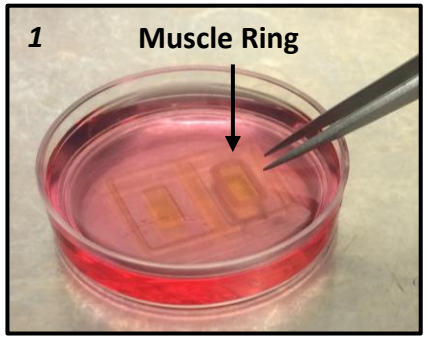


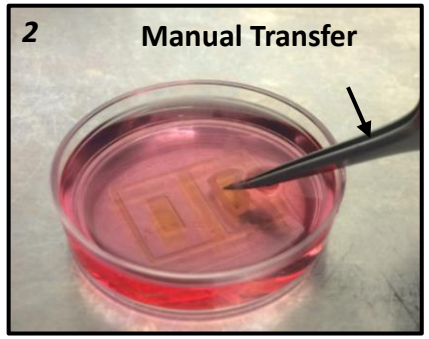
Cvetkovic, Raman, et al. PNAS, 2014

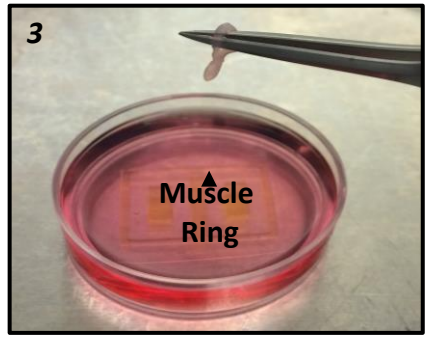
Top View Video of Muscle Compaction

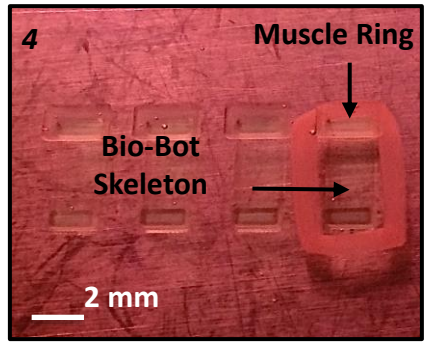


3D Printed Optogenetic Skeletal Ring Muscle Powered BioBots

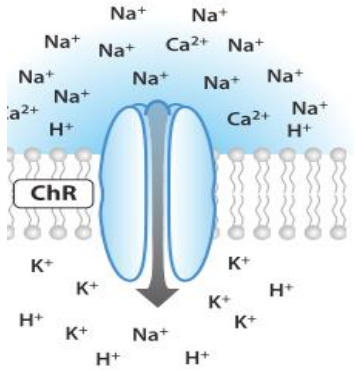


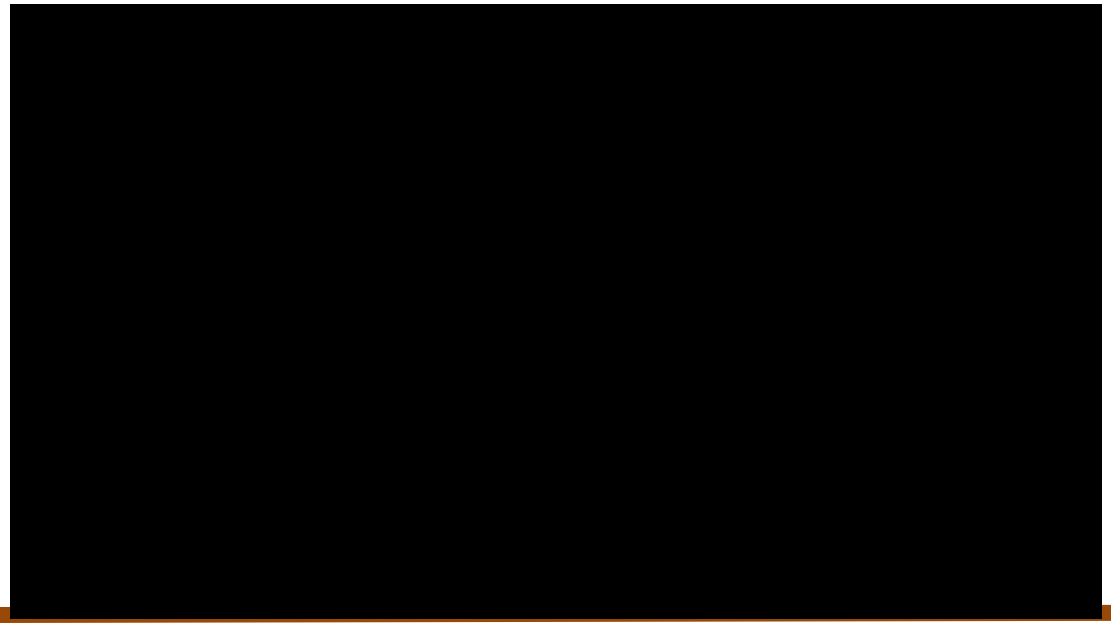






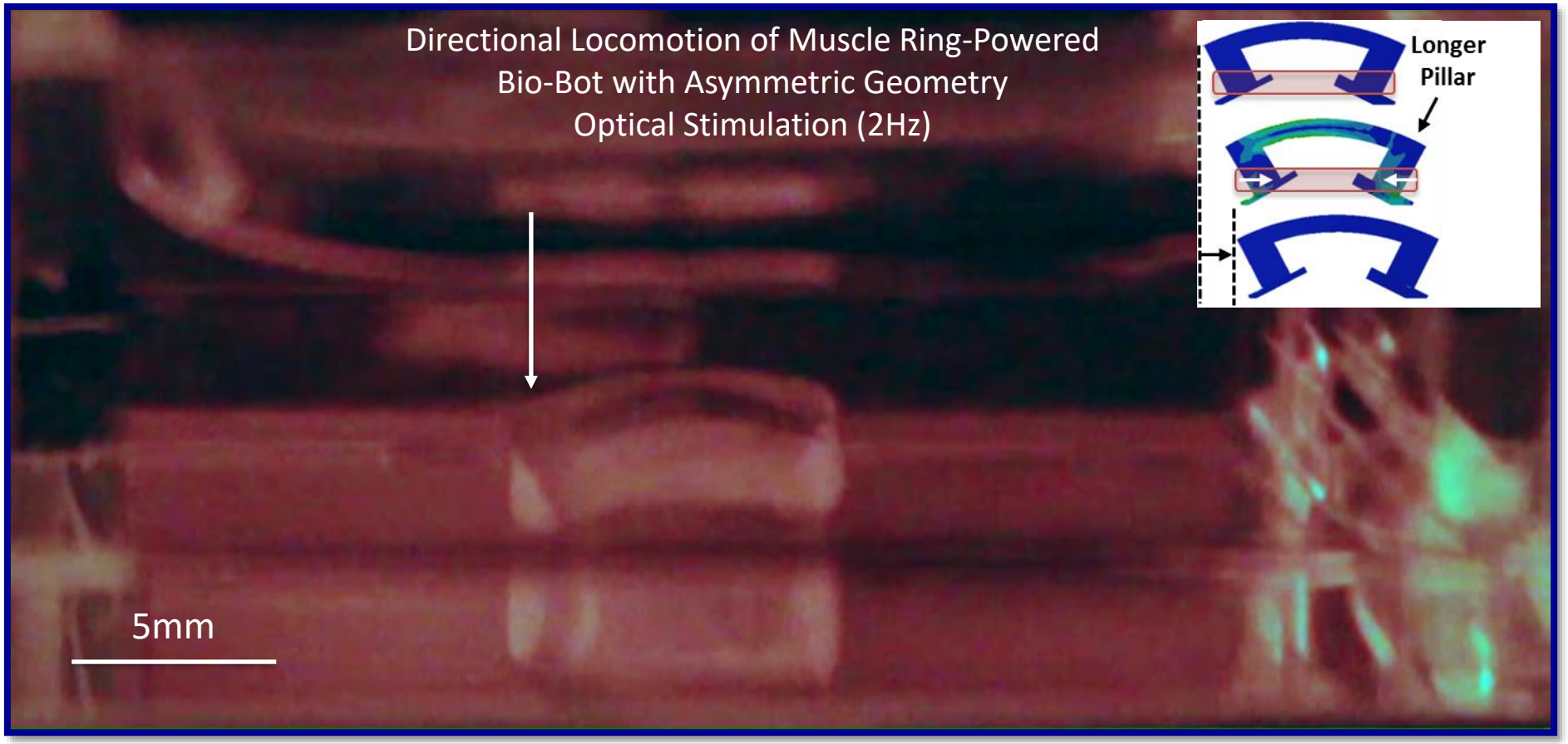
ChR2
Cation channel
Depolarizing
Blue light, Excitatory

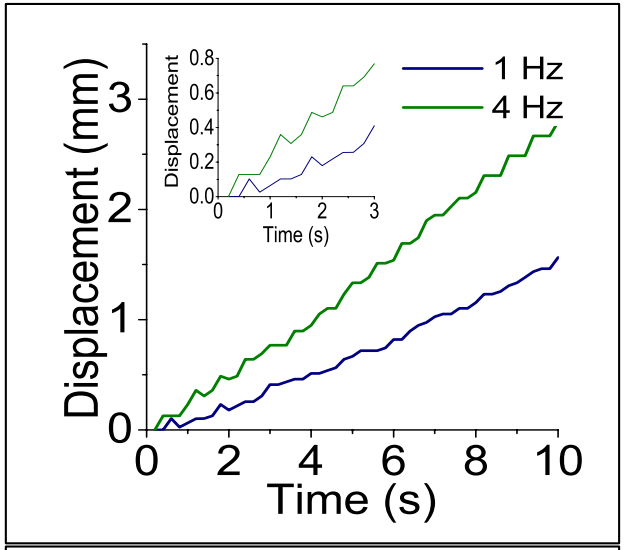


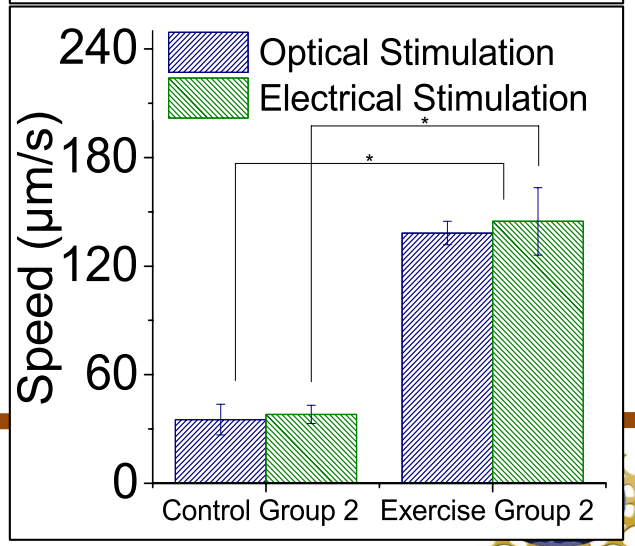


Raman et al, PNAS, 2016

Biobot Control with Light – Gen 3



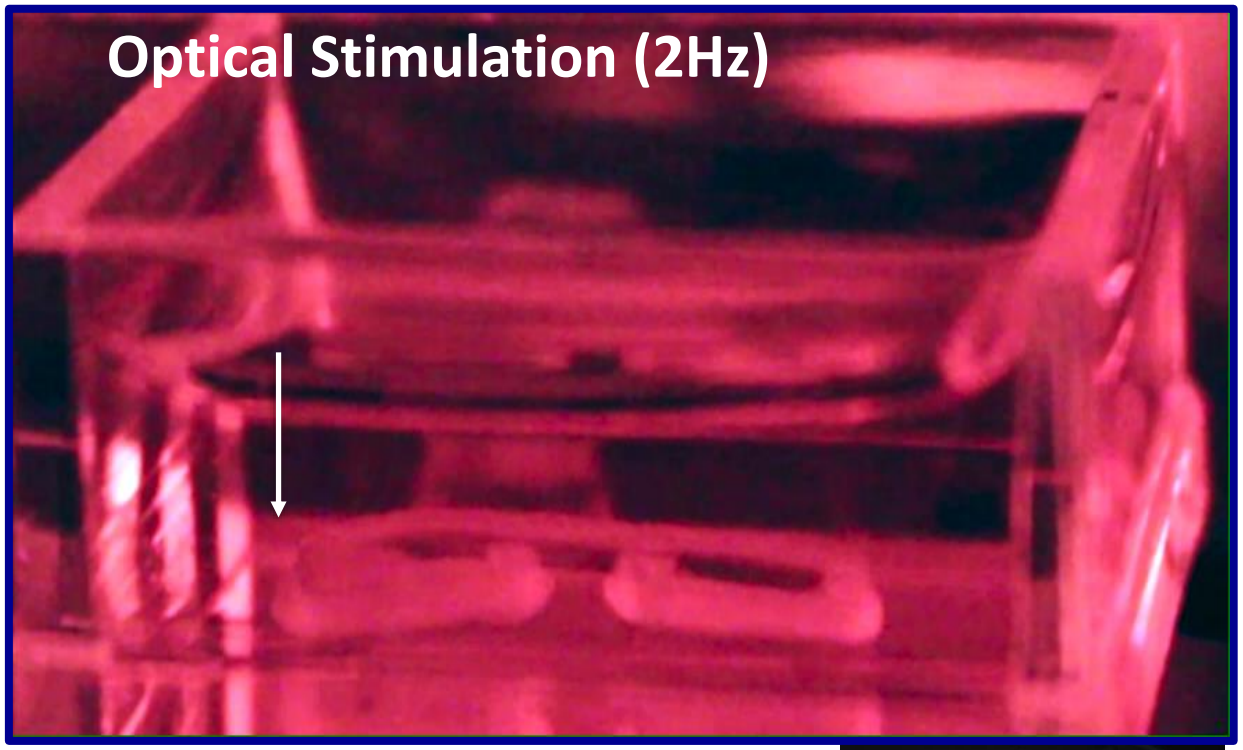


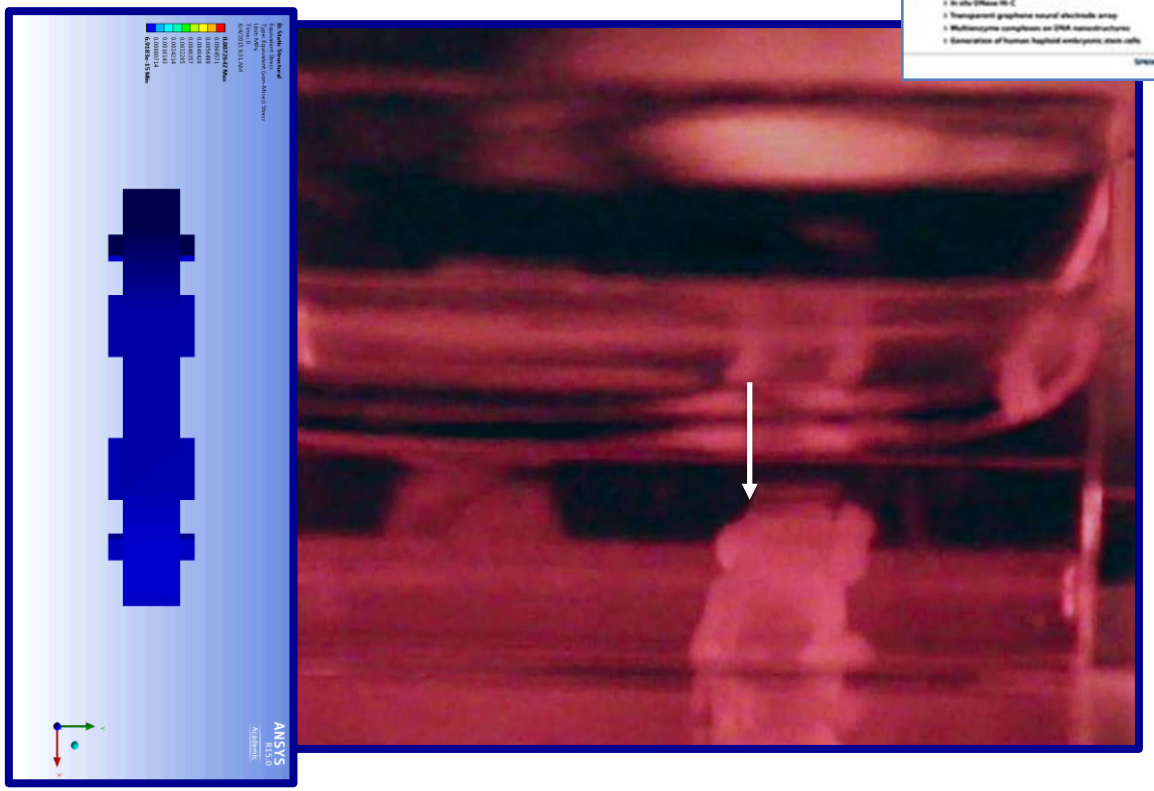


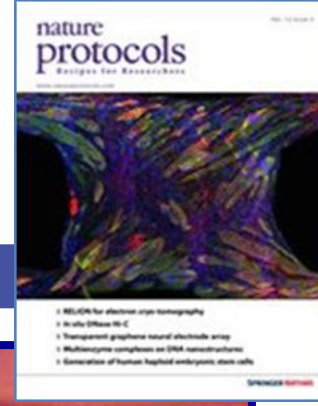
Raman et al, PNAS, 2016

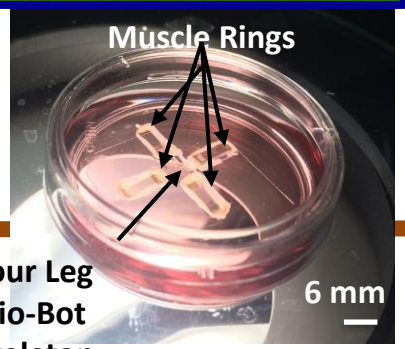
Raman, et al. Nature Protocols, 2017

Directional Locomotion of Muscle Ring-Powered Bio-Bot





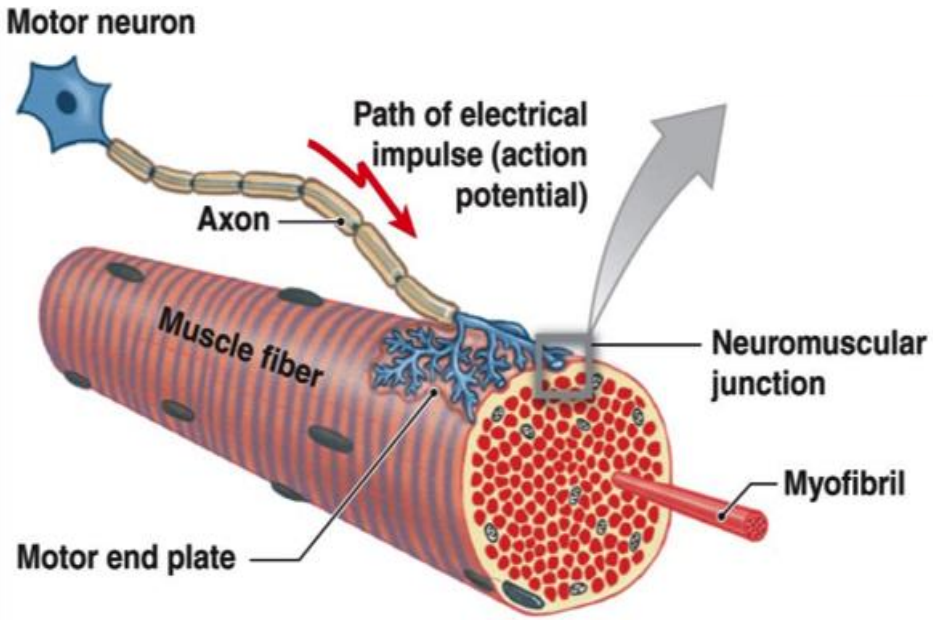




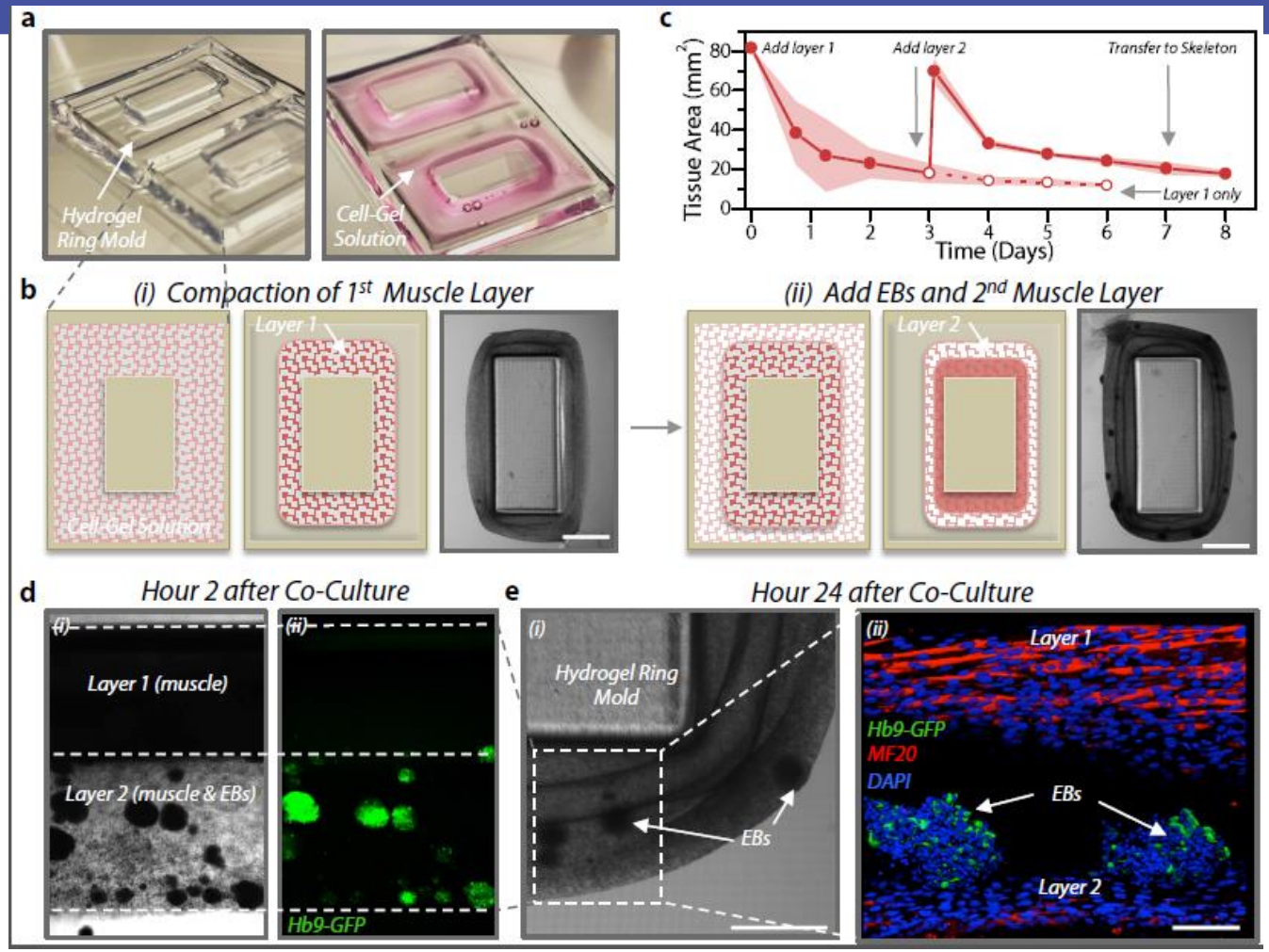
Four Leg Bio-Bot Skeleton

Cvetkovic, et al. PNAS, 2014
Raman, et al. PNAS 2016
Raman, et al. Nature Protocols, 2017

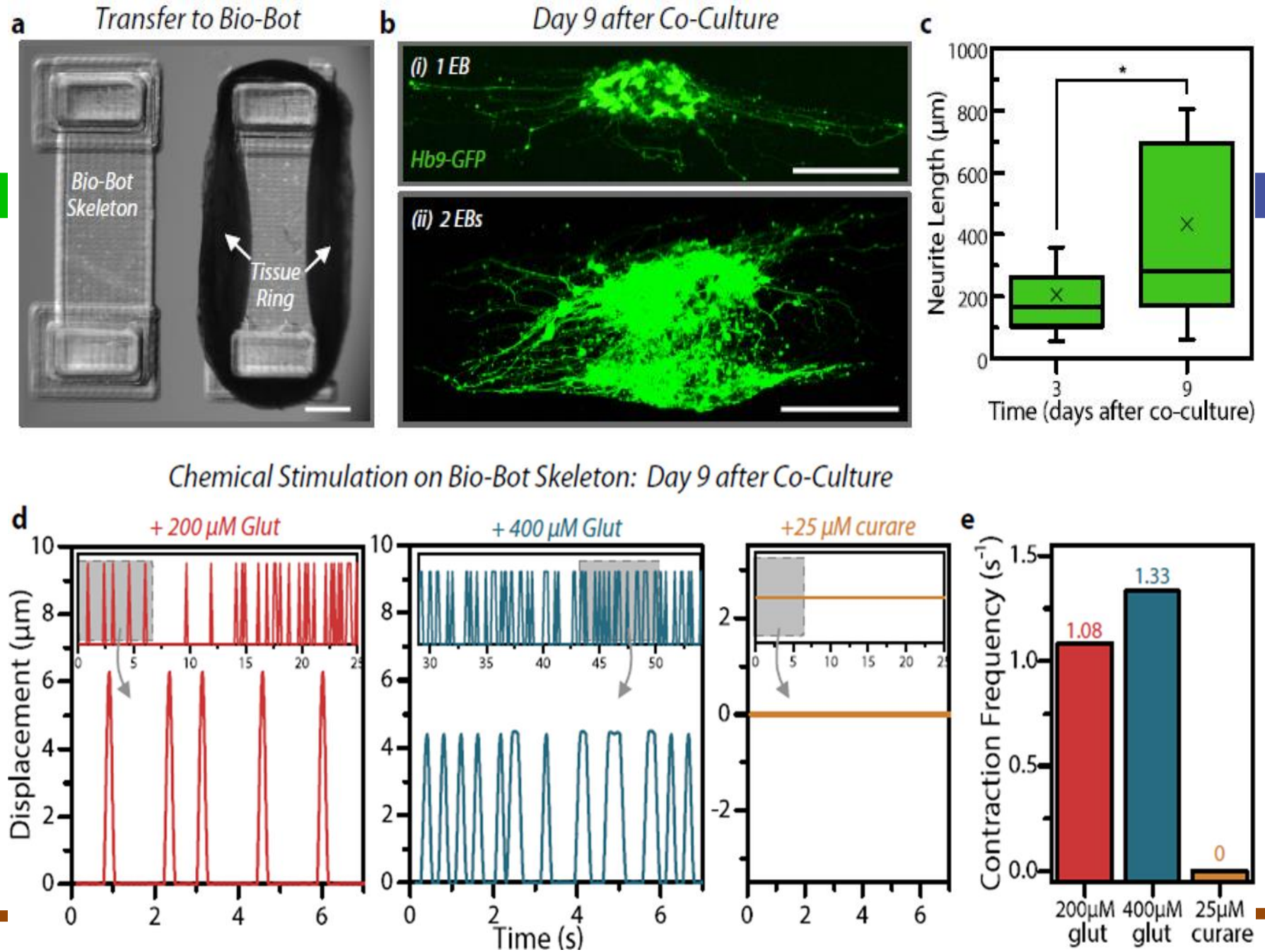
Neuromuscular Junction Integration in 3D



Pearson Education, 2011



Cvetkovic, et al, *Microsystems and Nanoengineering, 2017*



Cvetkovic, et al, *Microsystems and Nanoengineering*, 2017

Important Ethical Considerations

- At what level of complexity does a biological machine ‘become’ a living organism?
- What features distinguish one from the other?
- What if the biological machines can self-repair, learn, adapt?
- 5 Ethics modules on the EBICS website

Where We Are, and Possibilities Ahead

- 3 generations of locomotive machines demonstrated
- Control with electric fields and light
- Complex 3D geometries
- Neuro-muscular junction and control
- Vasculature
- Self repair and self healing
- Self Replication !! neuronal oscillator and toggle switch - Learning and memory –
- Adding skin and exoskeleton (function in dry ambient)
- Adding pump and gas exchange system

1st International 'Engineering Living Systems' Workshop

Chicago, IL. August 3-4, 2016

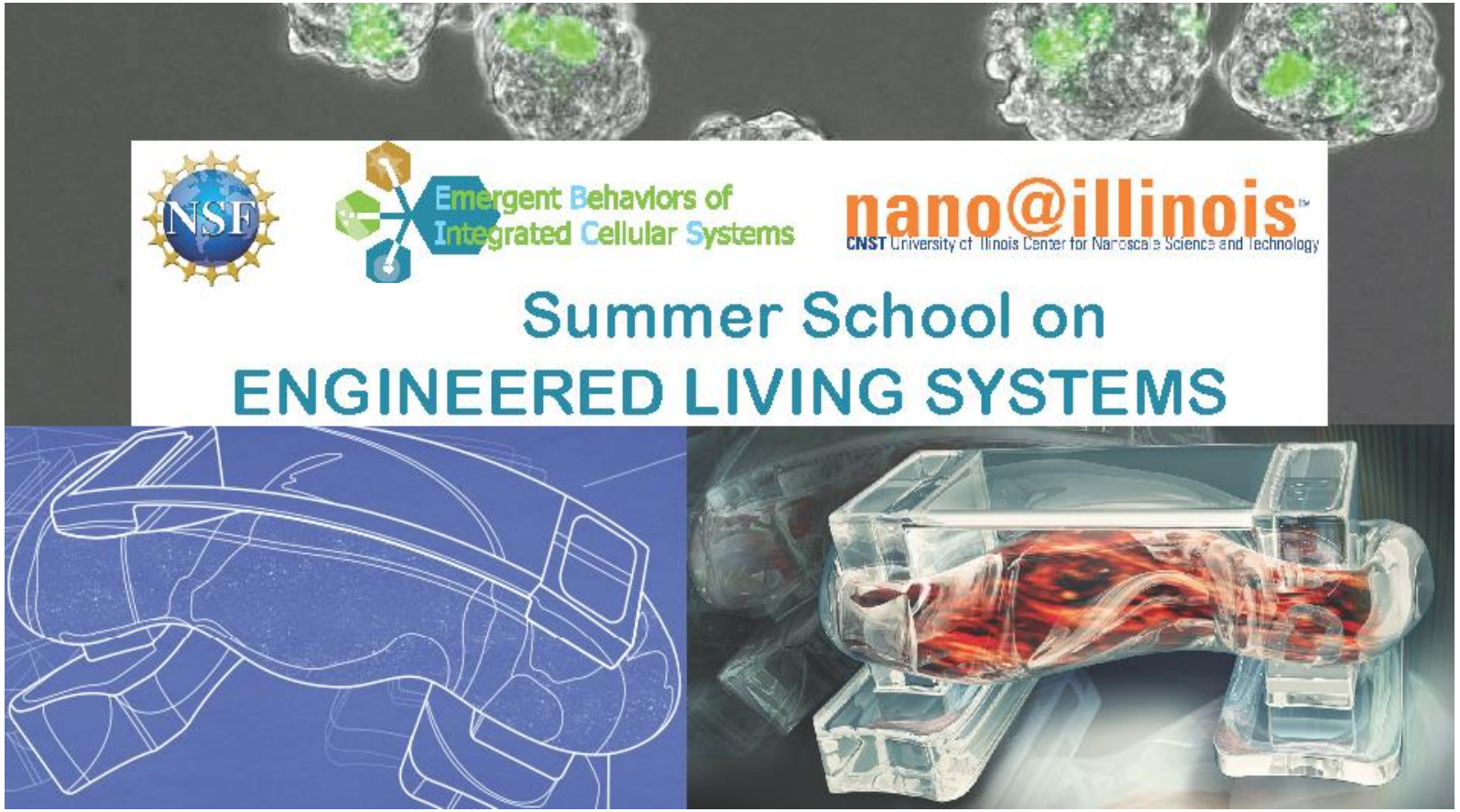
Engineering Cellular Systems Summer School

August 6, 2018 – August 10, 2018

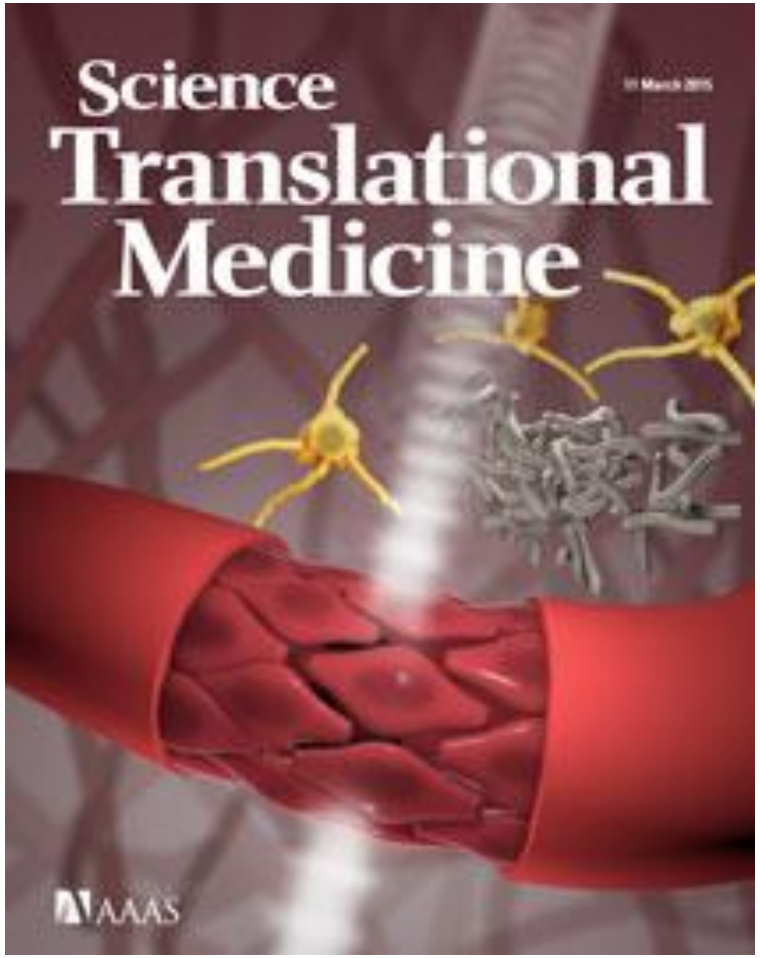
An exciting new summer opportunity – EBICS Engineering Cellular Systems Summer School is being offered in 2018 on the University of Illinois at Urbana-Champaign campus.

LEARN ABOUT ENGINEERED LIVING SYSTEMS THROUGH HANDS-ON LABORATORY MODULES and LECTURES ON:

Cell Culture/Transfection/Patterning + Matrix/Biomaterials + Advanced Imaging + Fabrication/3D Printing + Microfluidic device fabrication + Computational Modeling+Biobots+Organ on a Chip + Organoids



http://ebics.engr.illinois.edu/ebics-engineering-living-systems-workshop/

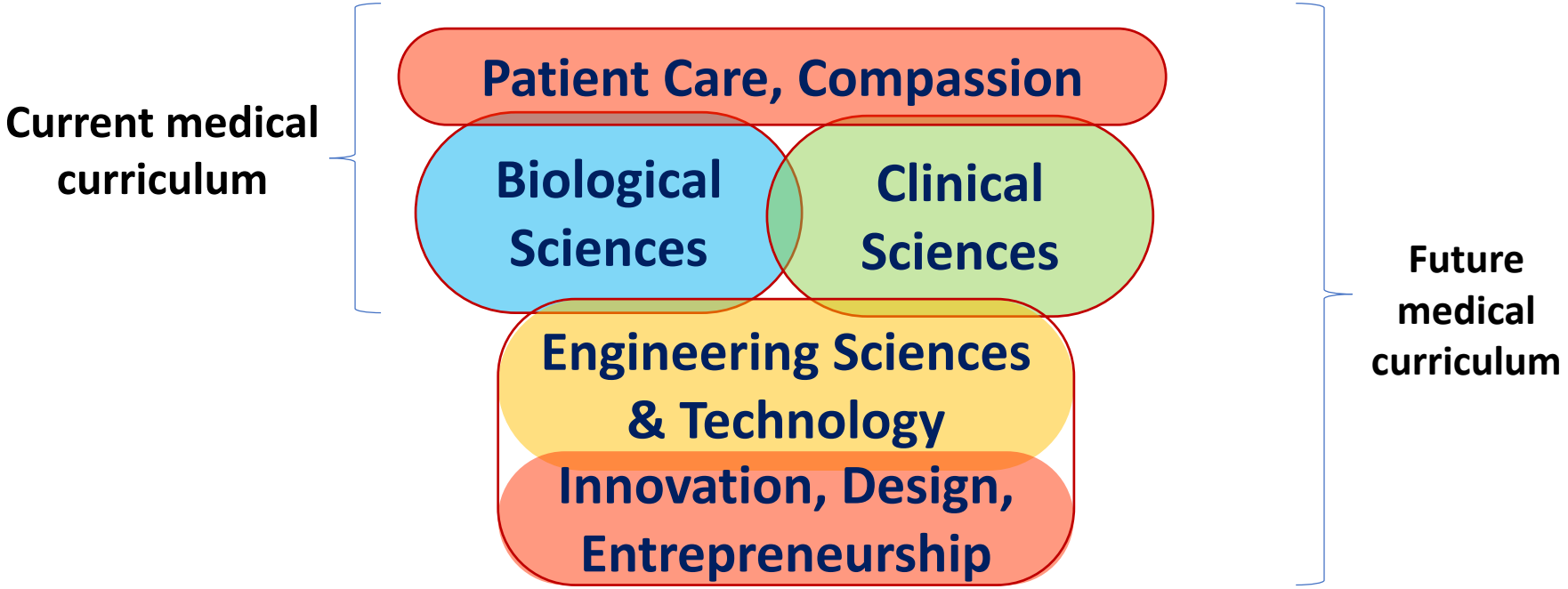


S Chien, R Bashir, RM Nerem, R Pettigrew, ***Engineering as a new frontier for translational medicine***. Sci. Transl. Med, April 1 2015

The inclusion of engineering ideas and approaches makes medicine a quantitative discipline that facilitates precision diagnostics and therapeutics improving healthcare delivery for all……Achieving this vision of higher-quality healthcare globally while containing or reducing its rising costs presents conflicting demands and is a challenge for engineering and medicine ….. We posit that the integration of engineering into medicine, and medicine into engineering—until boundaries vanish—will play a critical role in achieving these broad and specific goals

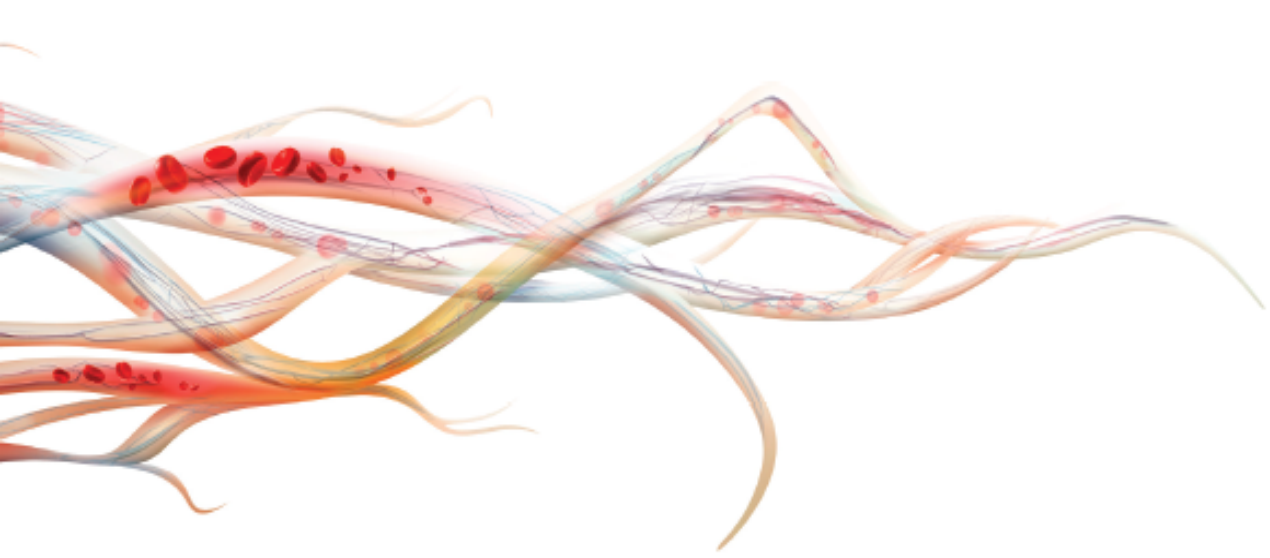
Medical Education Must Change

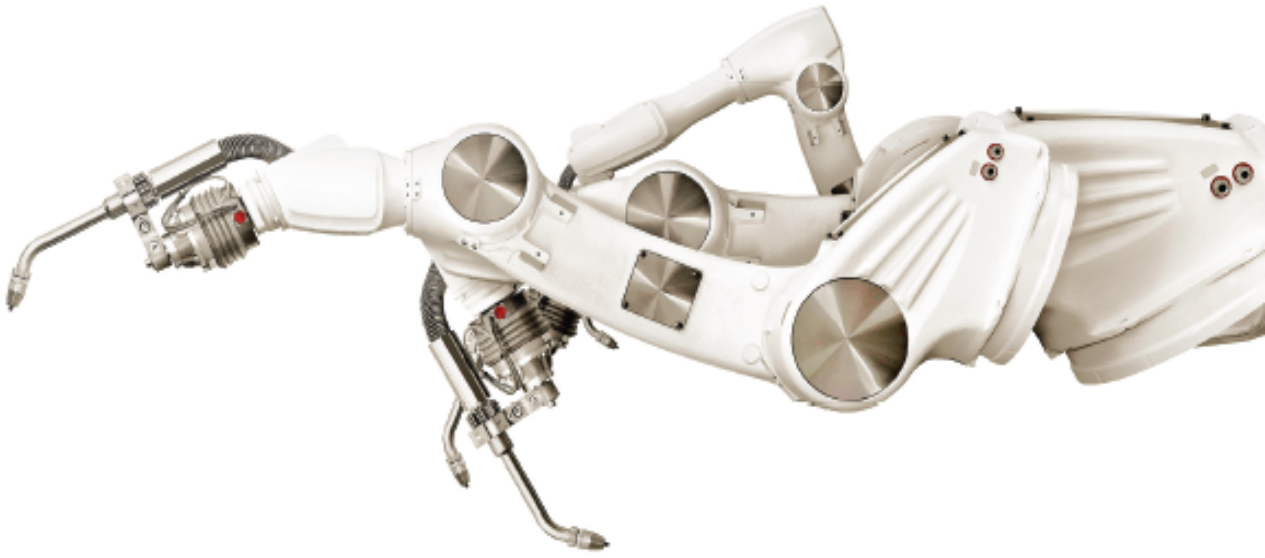
Quantitative Biology → Quantitative and Precision Medicine



New College. New Medicine.

The first College of Medicine specifically designed
at the intersection of engineering and medicine.

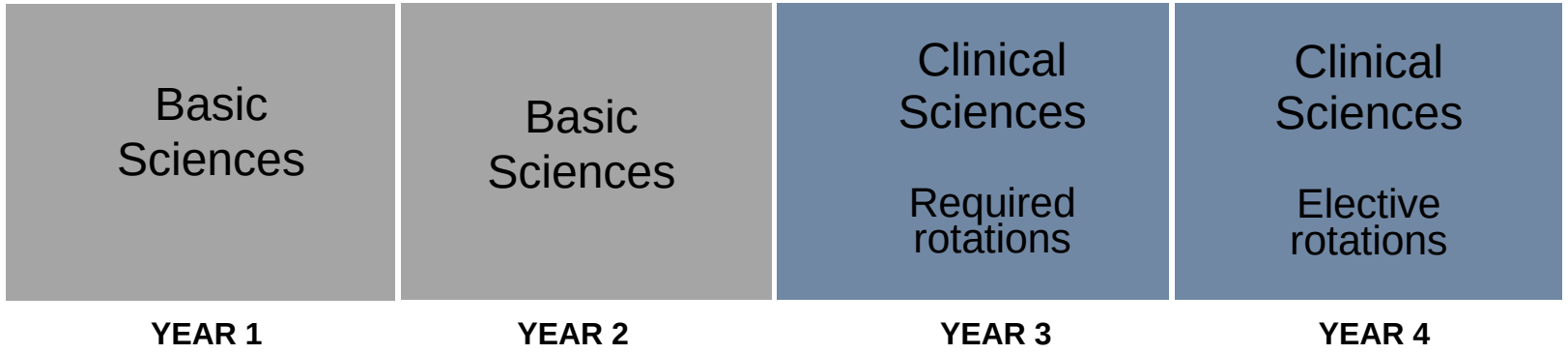




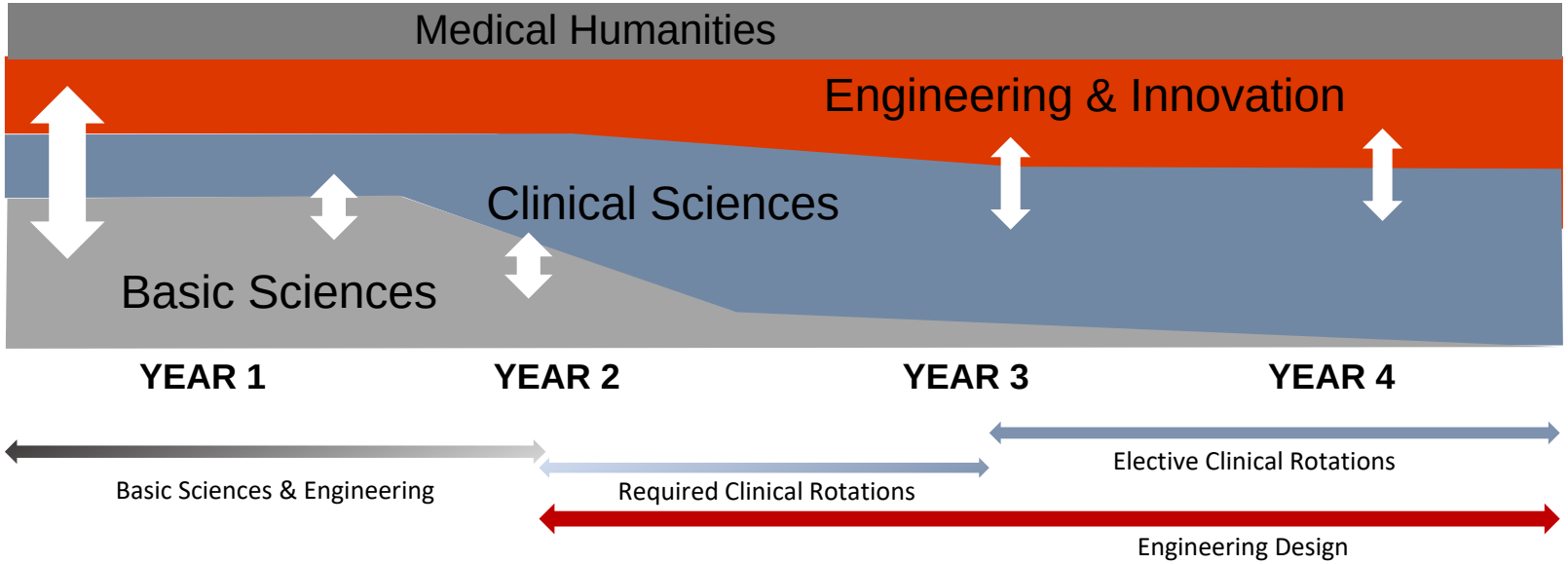
Starting Summer 2018

Curriculum Framework

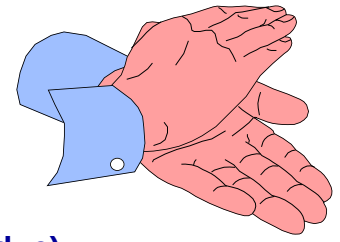
Flexner Report, 1910



Illinois Model, 2016



Acknowledgements



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- Dr. Umer Hassan
- Dr. Enrique Valera
- Dr. Michael Hwang
- Olaoluwa Adeniba
- Jacob Berger
- Sihan Chen
- Gelson Josue Pagan Diaz
- Anurup Ganguli
- Tanmay Ghonge
- Lauren Grant
- Aaron Jackelow
- Yongdoek Kim
- Akid Ornob

Funding Agencies (2014)

- Abbott
- NSF IGERT CMMB
- NSF STC EBICS
- NIH NCI M-CNTC
- NSF IUCRC CABPN
- TSMC
- NIH NCI
- National Science Foundation
- USDA ARS, Center for Food Safety Engineering at Purdue

Faculty Collaborators

- Prof. A. Alam (ECE, Purdue)
- Prof. A. Bhunia (Food Science, Purdue)
- Prof. B. Cunningham, (UIUC)
- Prof. R. Kamm (MIT)
- Prof. H. J. Kong (CheBE, UIUC)
- Prof. Gabi Popescu
- Prof. W. Rodriguez (Daktari)
- Prof. John Rogers (UIUC)
- Prof. T. Saif (MechSE, UIUC)
- Prof. M. Toner (Harvard Med School)
- Dr. G. Vasmatzis (Mayo Clinic)

Abbott
A Promise for Life

Integrated Cellular Systems

NSF

tsmc

USDA

Daktari Diagnostics

Prenosis

National Institutes of Health


Thank You.