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Microfluidics as an Emerging Platform for Tackling AMR

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Global-NAMRIP network conference, Uganda

Monday 4th – Thursday 7th March 2019

Outline

- Introduction - Microfluidics
- Challenges in tackling AMR
- Our approaches
- Application examples
- Summary
- Acknowledgements

Lab-on-a-Chip & Microfluidics

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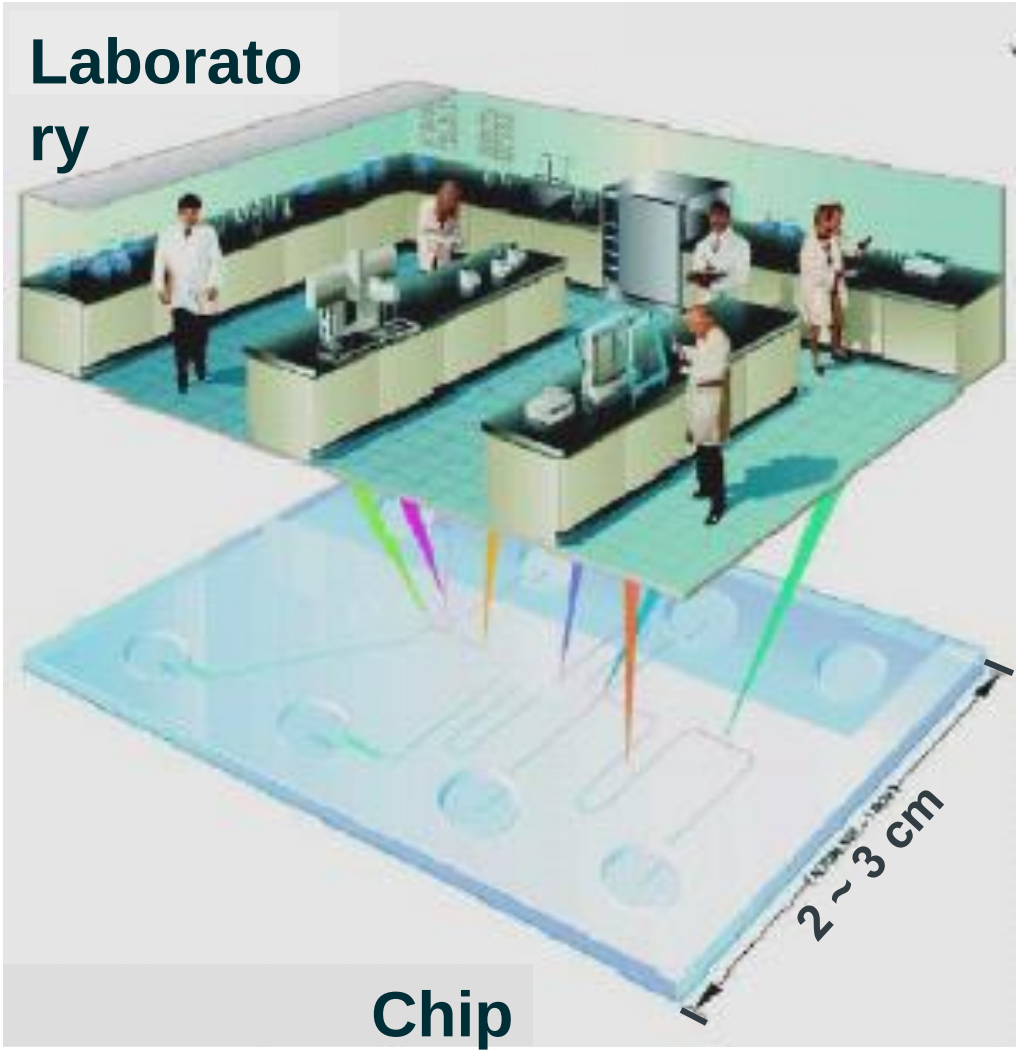

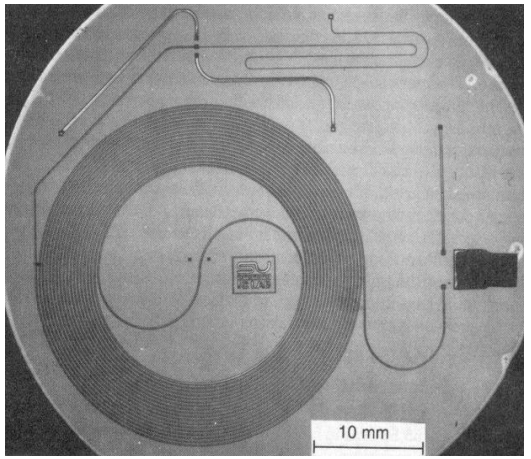

Stanford Chip

Capillary:

1.5m, 200 × 30 μm

Stationary phase:

OV-101

Detector:

Thermal conductivity

Terry, *et al*, *IEEE Trans. Electron. Devices*, ED-26: 1880, 1979

Laminar Flow within Microfluidic Channels

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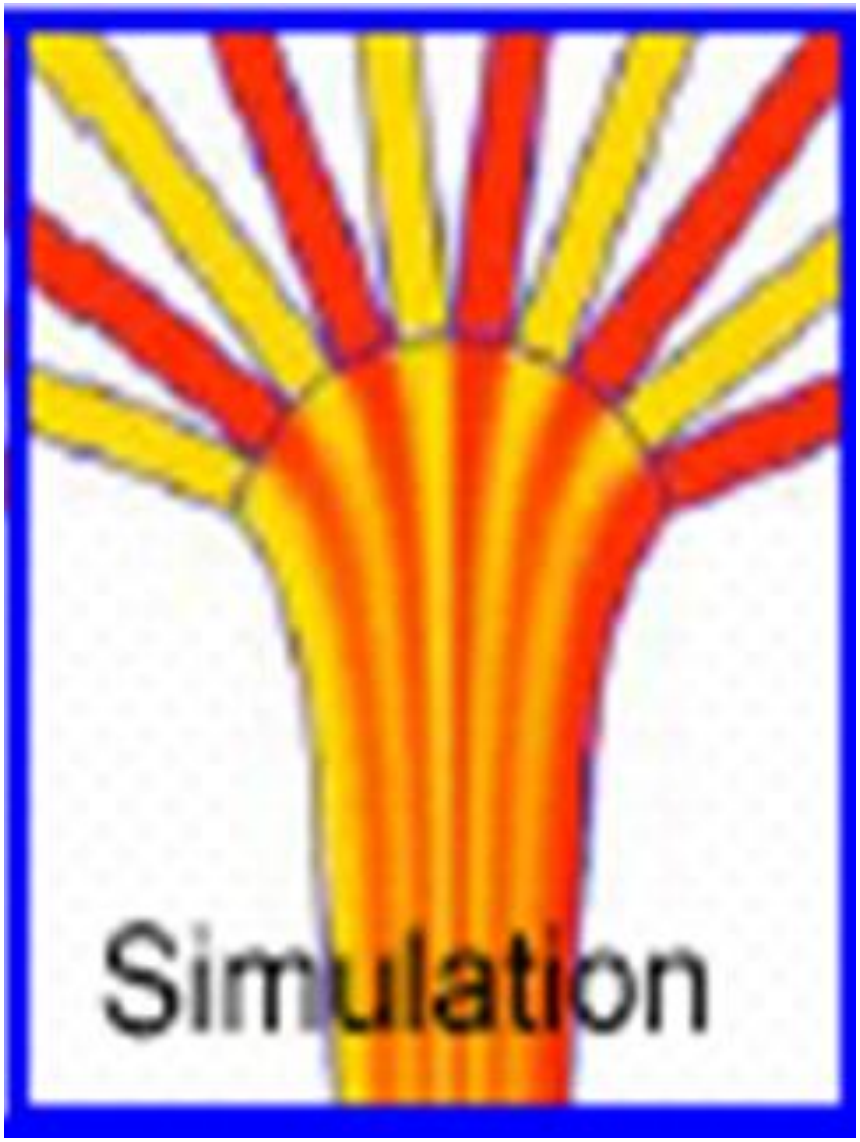
Whitesides, et al, *Science* (1999)

On the cover: Seven aqueous streams, each colored with a different dye, converge in a microchannel and proceed in parallel laminar flow, without turbulent mixing. Using laminar flows of reagents is the basis of a technique for fabricating microstructures inside capillaries. The stream presentation was designed with the help of F. Frankel, who also photographed the sample. [© Felice Frankel]



Laminar Flow and Diffusive Mixing

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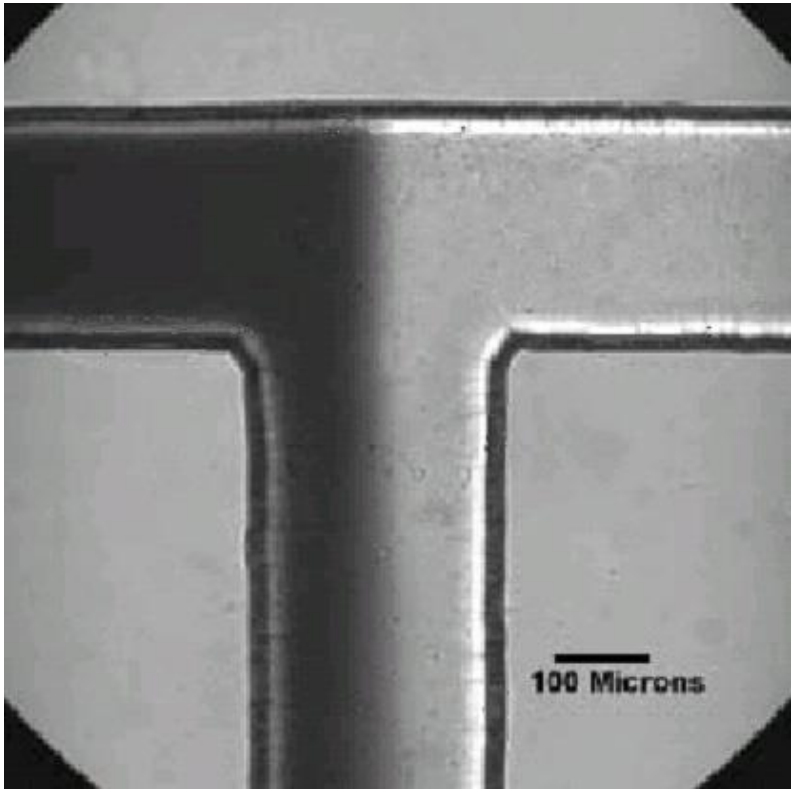
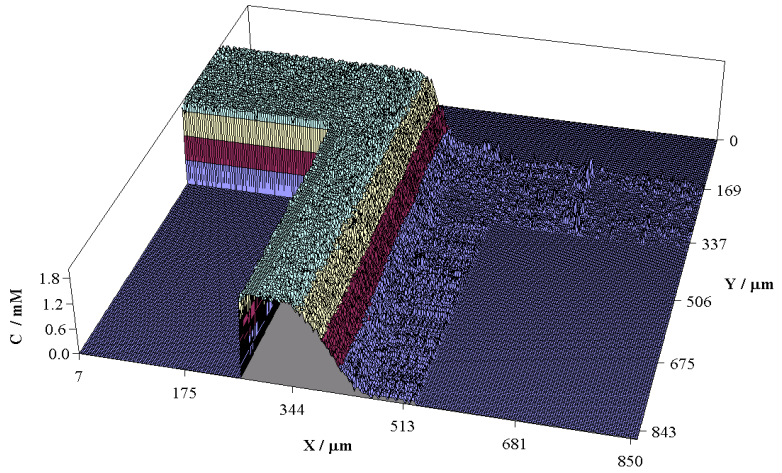
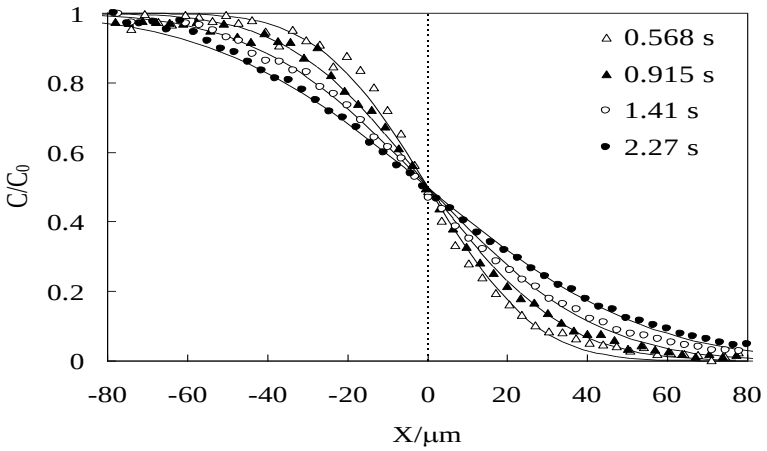
- Unique characteristics of microfluidics







$$Abs = \varepsilon d C$$

$$Abs = \log (I_0/I_1)$$

Tetrahedron, **58**, (24), 4735-4757 (2002)

Applications

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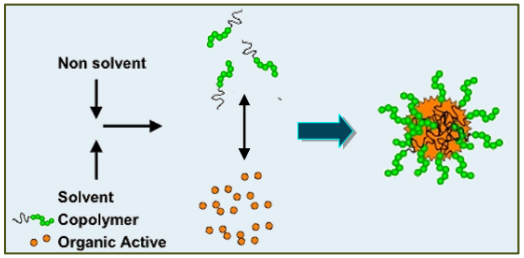
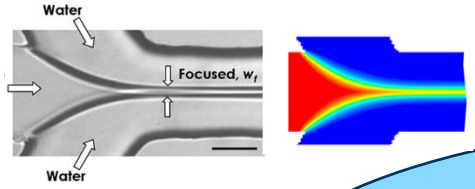
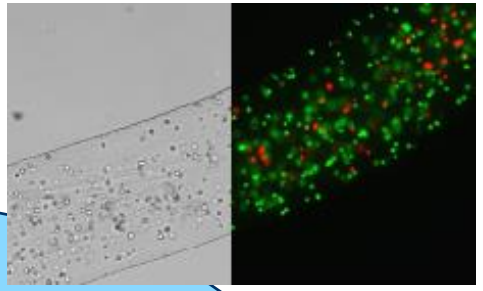
Drug Delivery



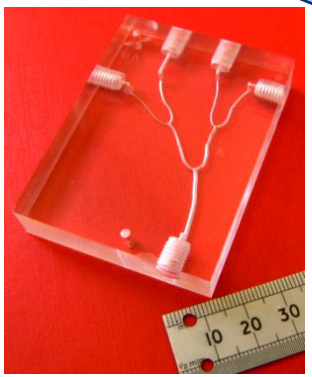
Microreactors



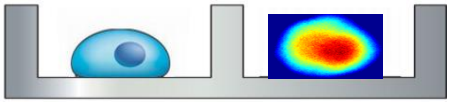
Biomaterials



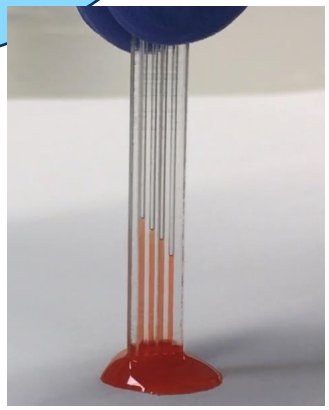
Microfluidics and Lab-on-a-Chip



Biomicrofluidics

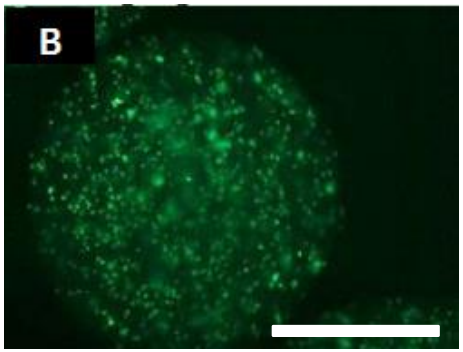


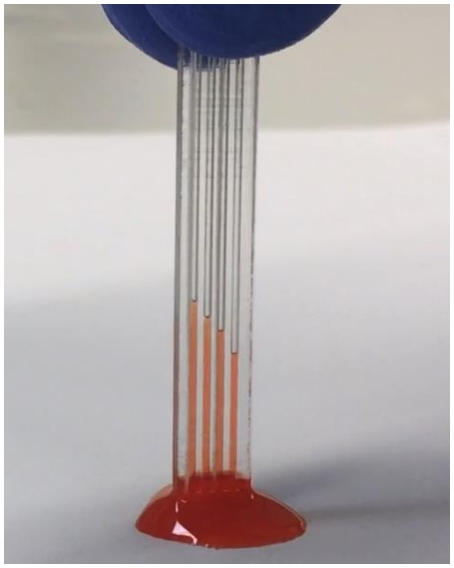
Cell Bioanalysis



Tackling AMR

Applications

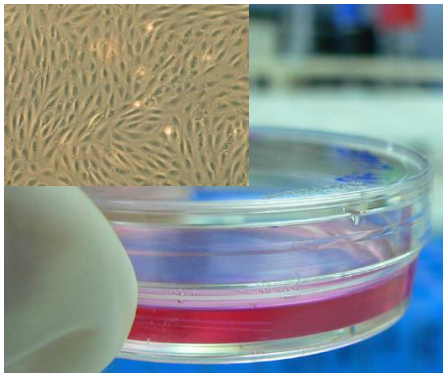




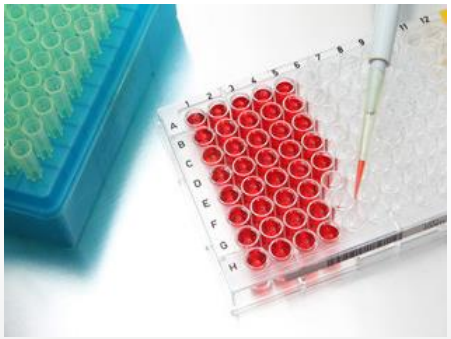
Tackling AMR

Challenges (1)

- in studying pharmacokinetics/AMR



- Current **2-D** cell culture inaccurately reflects conditions in man
- Current drug testing protocols
  - **batch operation**
  - **static media**
  - **single concentration**



Our approaches

- Using a microsphere-based **3-D cell culture model**
- Developing a **microfluidic-based platform** with precise fluidic control

Microparticles formation by multiphase microfluidics

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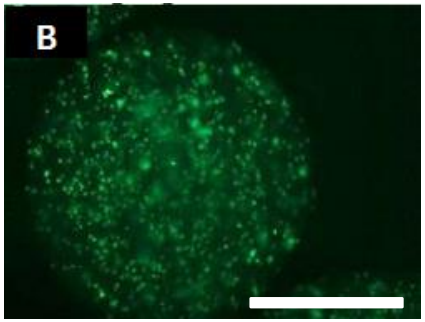
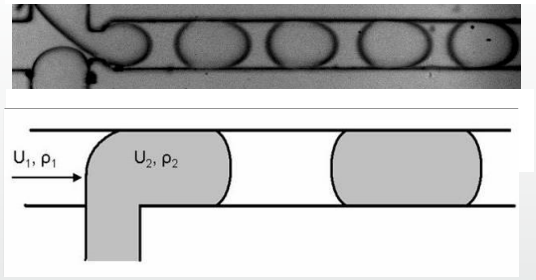
Microfluidic chips permit the formation of multiphase flows, that are flows constituted of two or more immiscible fluids, suggesting new routes to the production of microparticles.

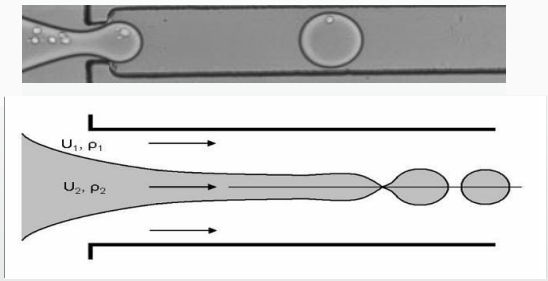


T-junction chips



The breakup process is driven by the build-up of pressure upstream of an emerging droplet

X-junction chips



The formation of droplets is due to the interplay between viscous forces and interfacial forces

The extracellular matrix regulates the host-pathogen interaction - Testing Tuberculosis (TB) drug resistance

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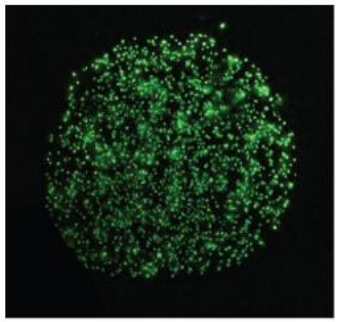
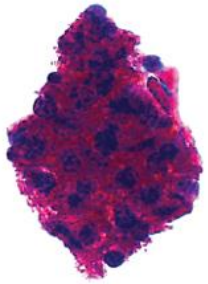
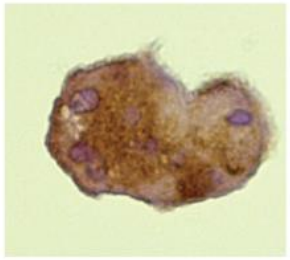


Cells in spheres

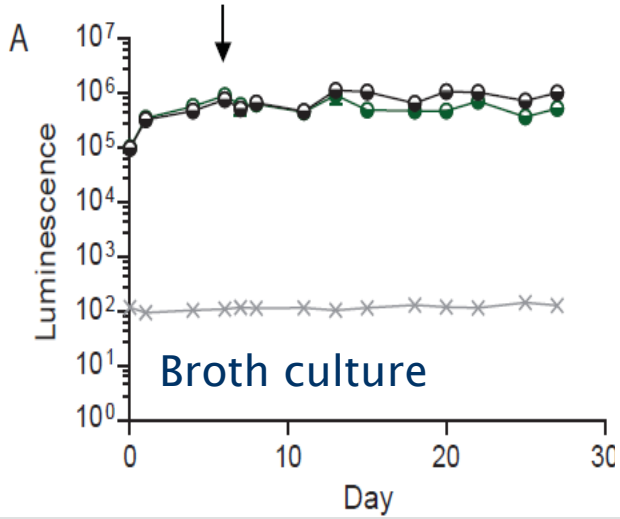


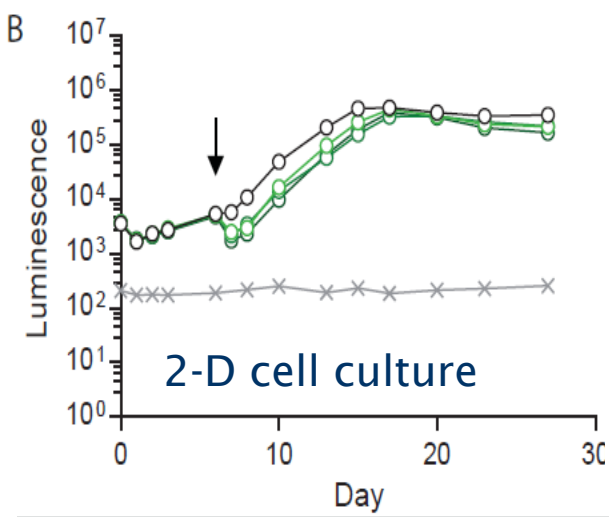
Granuloma formation

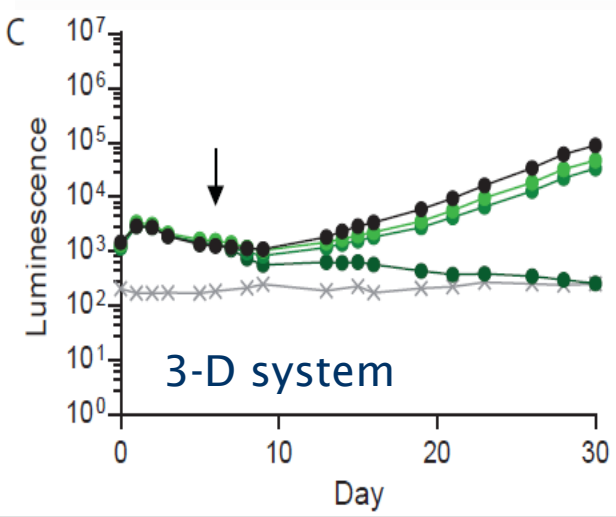


Multinucleate giant cell

Pyrazinamide kills Mtb in the 3-D model, but not in 7H9 broth or 2-D culture.







Al-Shammari et al., *J Inf Dis,* 2015, 212:463-473 Bielecka et al., *mBio,* 2017, 8:e02073-16

Microfluidics to model physiological conditions

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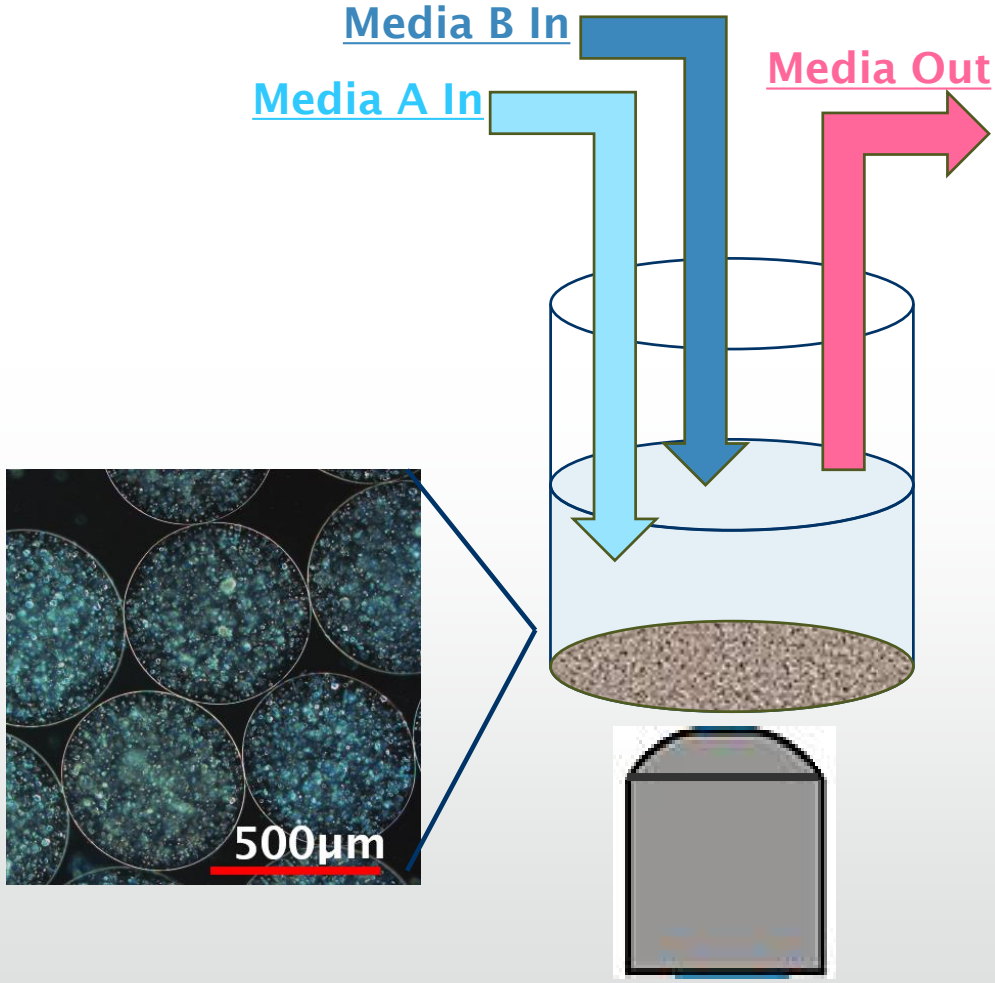
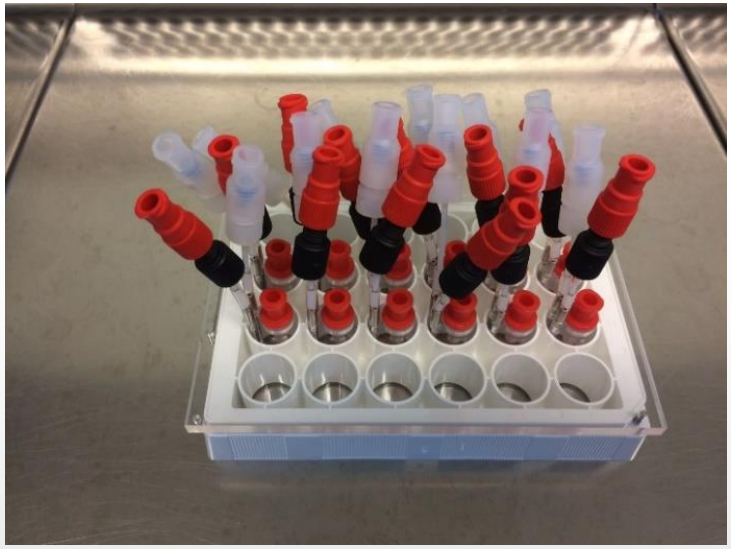
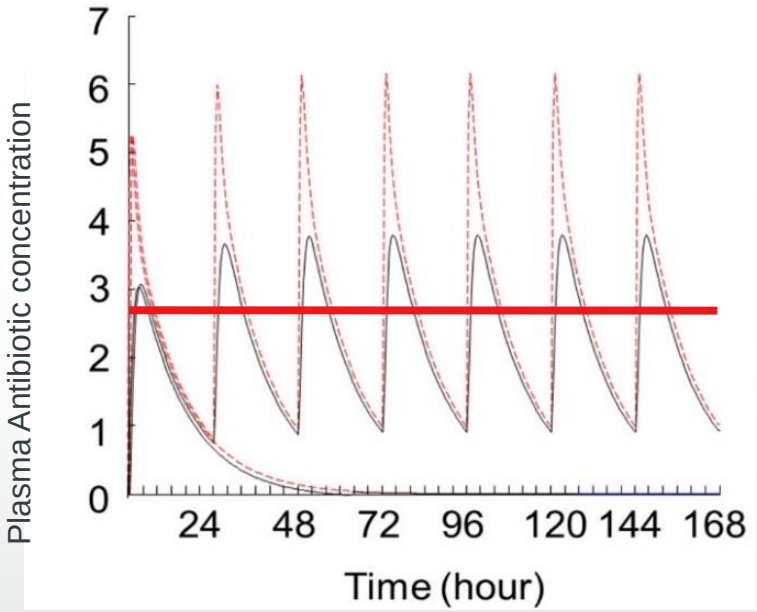


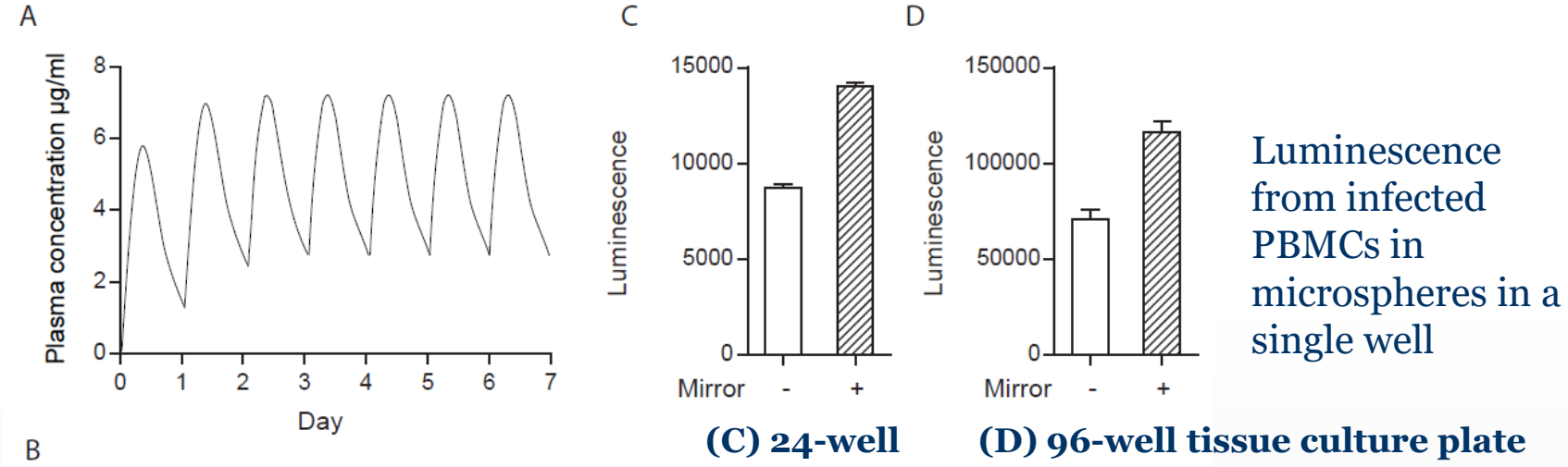
Microfluidic-based regulation of physiological conditions (1)





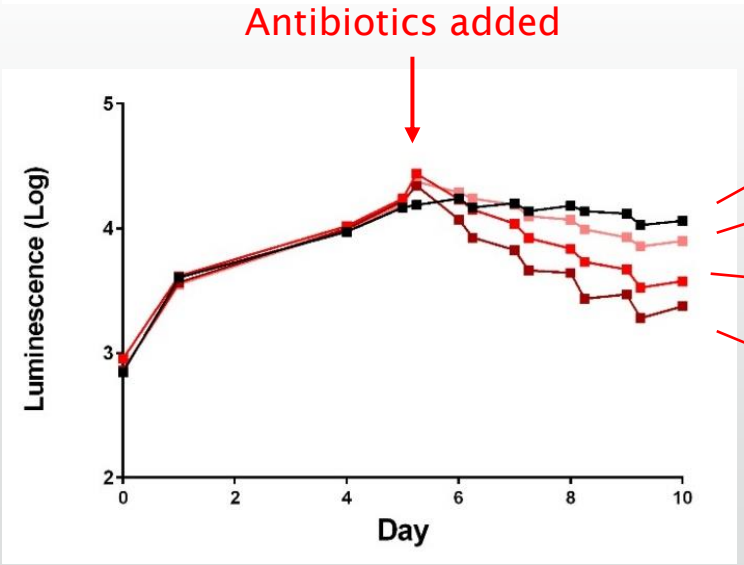
Bielecka et al., *mBio,* 2017, 8:e02073-16

Microfluidic-based regulation of physiological conditions (2)



Luminescence from infected PBMCs in microspheres in a single well

(C) 24-well **(D) 96-well tissue culture plate**



No antibiotics

Low peak concentration

Standard peak concentration

High peak concentration

Bielecka et al., *mBio,* 2017, 8:e02073-16

Challenges (2)

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- in rapid detection/diagnosis of AMR

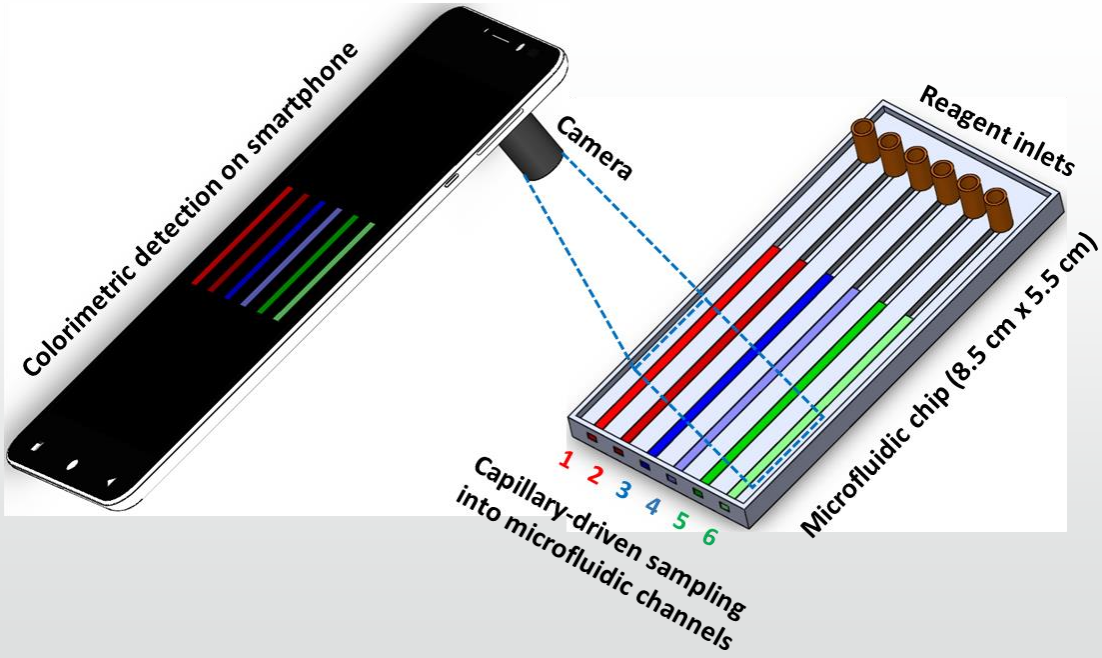
- Rapid and easy to use
- Low cost
- High sensitivity
- High specificity
- Portable
- Accurate
- Multiplex

Our approaches

- To miniaturise AMR assays into microfluidics devices and provide portable handheld systems for rapid and high throughput AMR testing.

Microfluidic-based AMR testing

- Antimicrobial susceptibility testing (AST)
- Minimum inhibitory concentration (MIC) determination



Microfluidic chips

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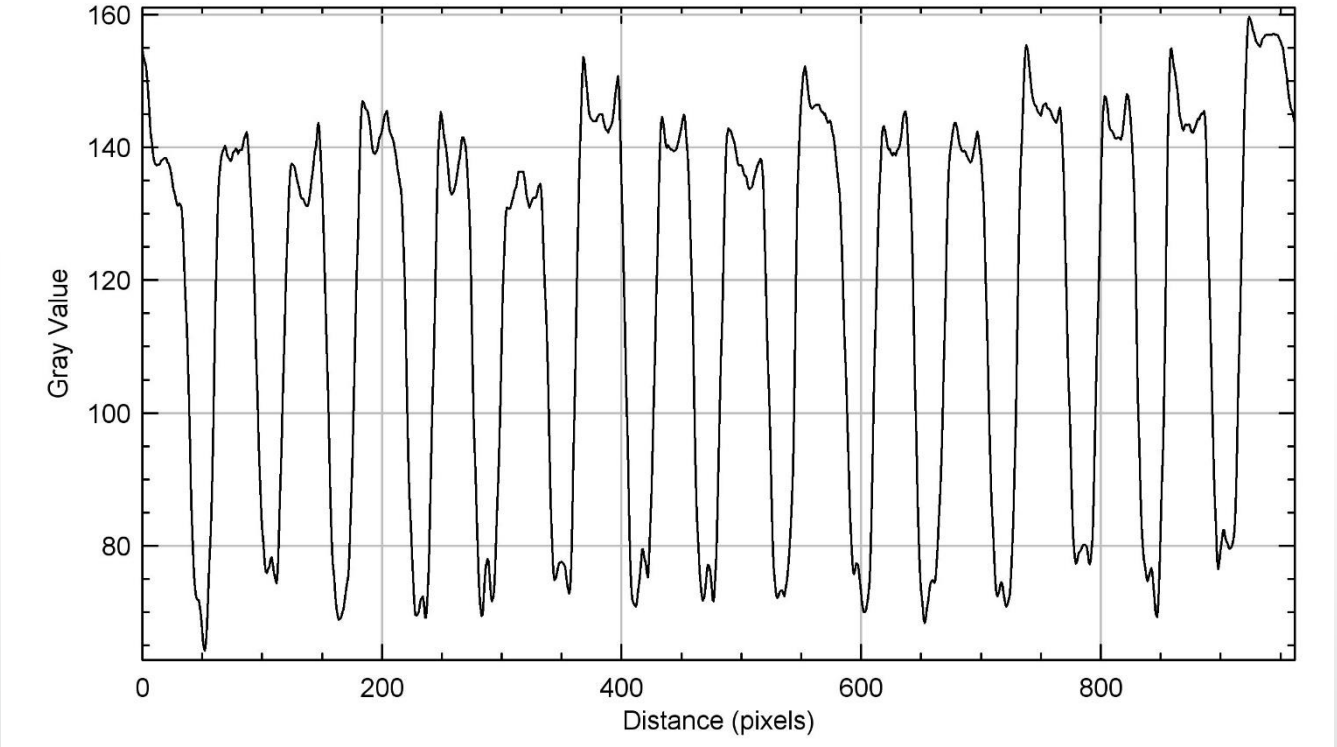
Microfluidic sampling / quantification



Smart phone based quantification

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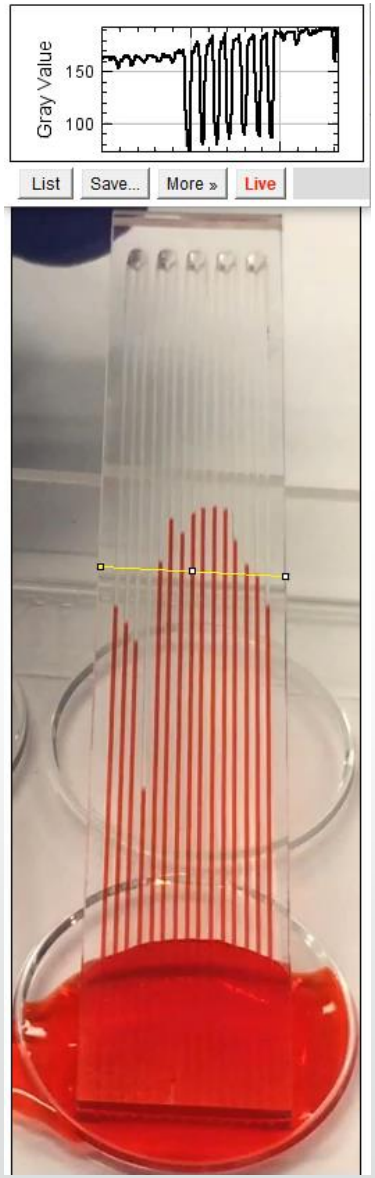

Summary

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- Microfluidics as powerful tools for tackling AMR.
- Combining microfluidics and microsphere-based 3-D cell culture model can regulate and detect dynamic microenvironment surrounding cell culture microspheres with precise fluidic control.
- Pump-free microfluidic chips provide essay-to-use and cost-effective approaches for rapid and high throughput AMR testing.

Acknowledgements

- Prof Paul Elkington (Medicine)
- Dr Magda Bielecka (Medicine)
- Dr Liku Tezera (Medicine)
- Dr Robert Zmijan (Engineering)
- Dr Sammer-ul Hassan (Engineering)
- Prof Suwan Jayasinghe (Biomaterials, UCL)
- Network on Antimicrobial Resistance and Infection Prevention (NAMRIP)

University of Southampton

EPSRC Engineering and Physical Sciences Research Council

MRC Medical Research Council

E·S·R·C Economic & Social Research Council

Department of BioTechnology, Government of India

सत्यमेव जयते

GCRF Global Challenges Research Fund