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Combining engineering and medicine approaches to tackle tuberculosis (TB)

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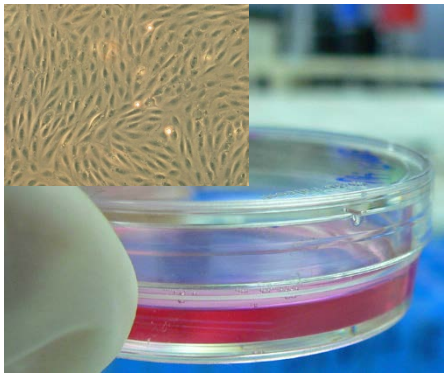
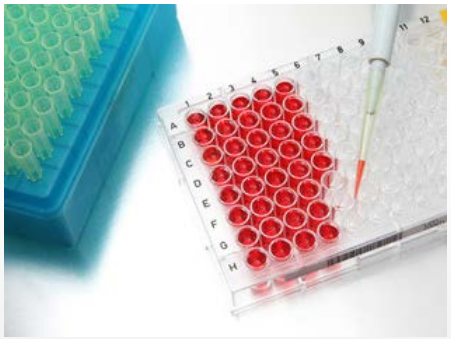
Outline

- Introduction – Challenges/Approaches
- Micro spherical 3-D models for cell culture, and regulation of response to tuberculosis (TB)
- Developing a microfluidic platform to model and detect physiological conditions
- Summary
- Acknowledgements

Challenges (in studying pharmacokinetics)



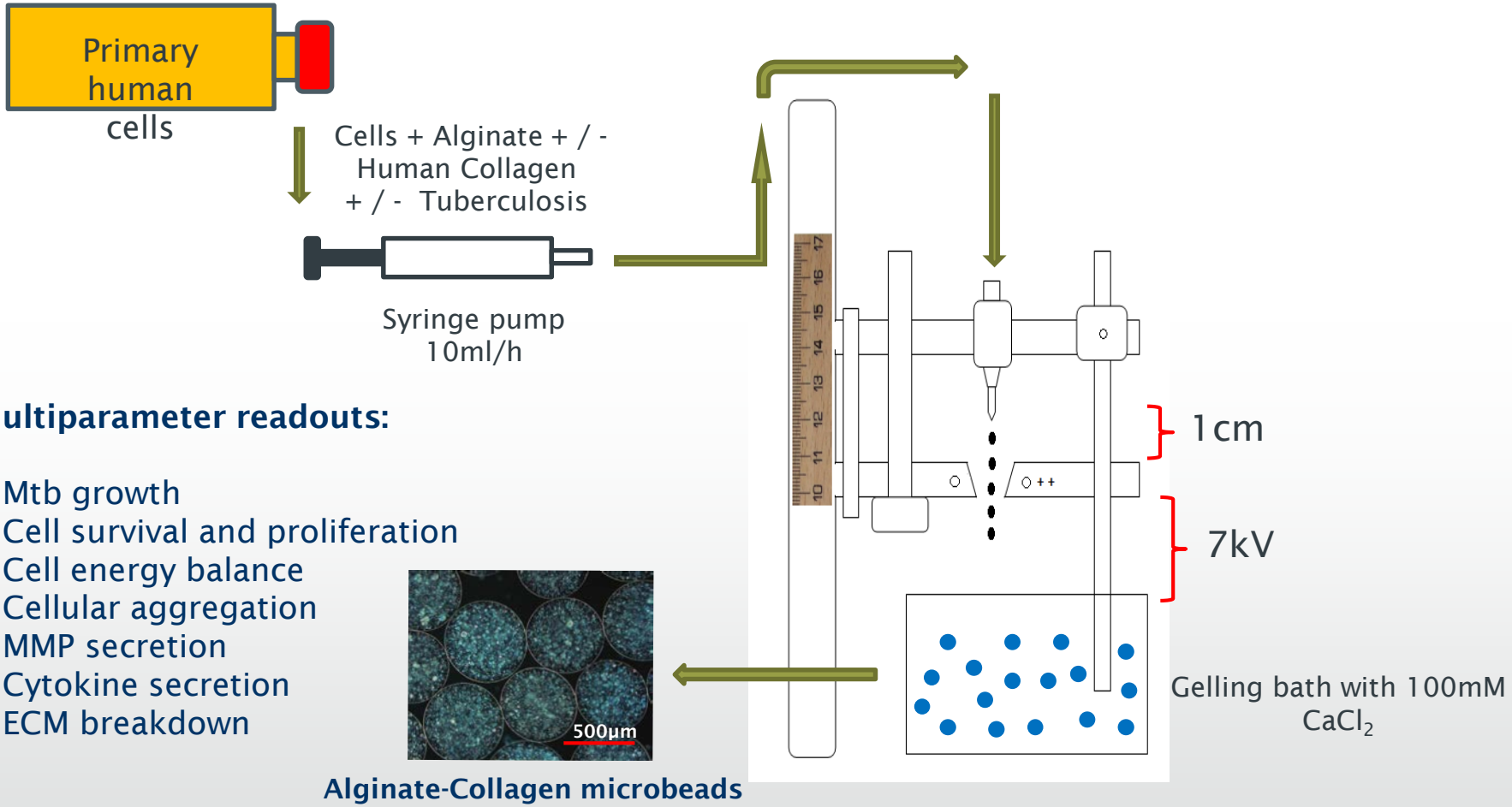
- Current **2-D** cell culture inaccurately reflects conditions in man
- Current drug testing protocols
  - **batch operation**
  - **static media**
  - **single concentration**



Our approaches

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

Generation of microspheres by electrospraying



Multiparameter readouts:

Mtb growth
Cell survival and proliferation
Cell energy balance
Cellular aggregation
MMP secretion
Cytokine secretion
ECM breakdown

Alginate-Collagen microbeads

Workman et al., *Adv Funct Mater*, 2014 24:2648 –2657

Microparticles formation by multiphase microfluidics

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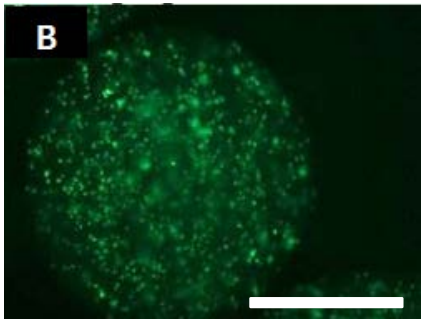
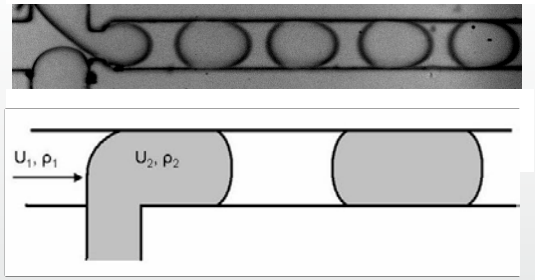
Microfluidic chips permit the formation of multiphase flows, that are flows constituted of two or more immiscible fluids, suggesting new routes to the production of microparticles.

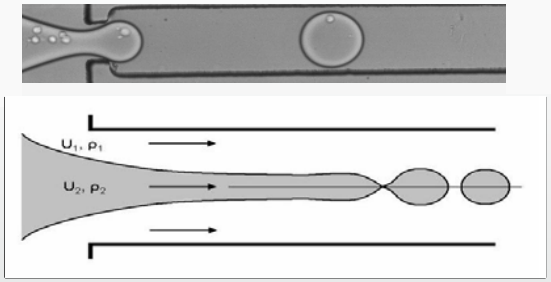


T-junction chips



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

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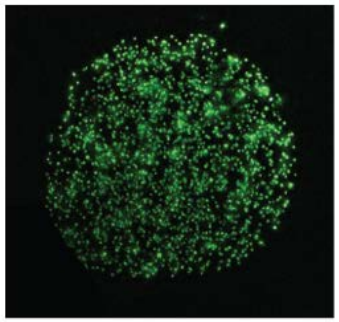
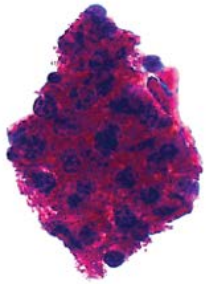
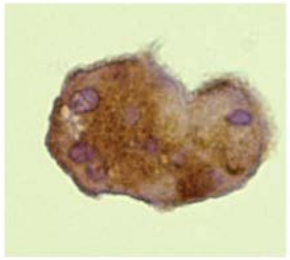


Cells in spheres

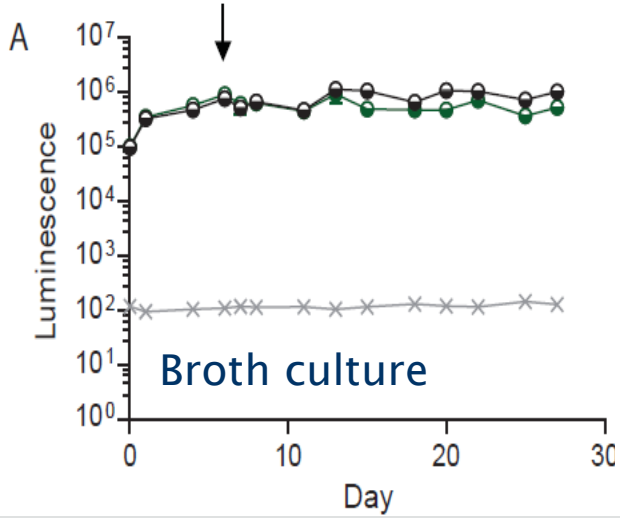


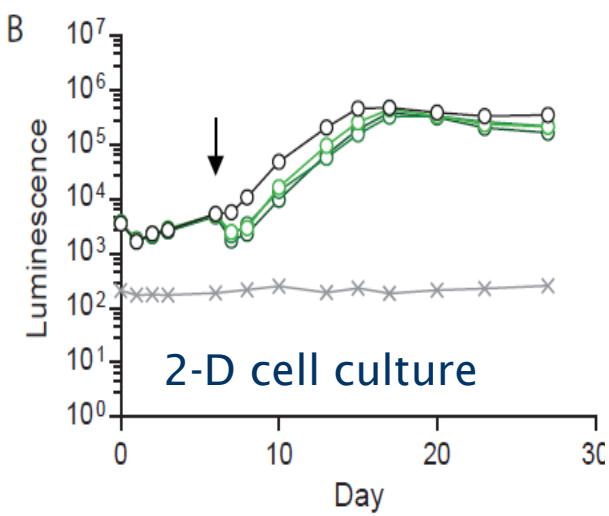
Granuloma formation

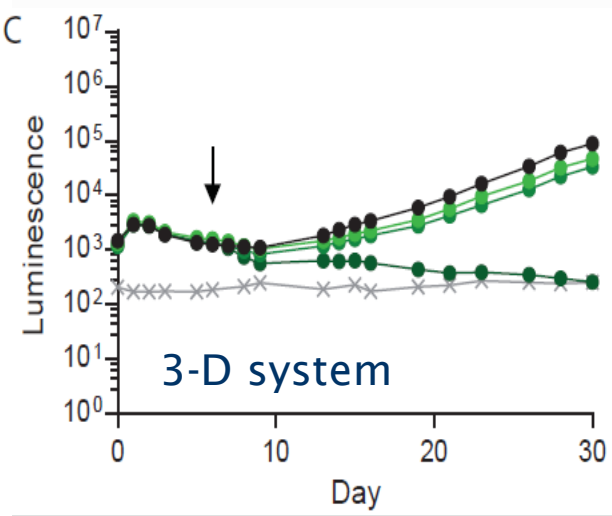


Multinucleate giant cell

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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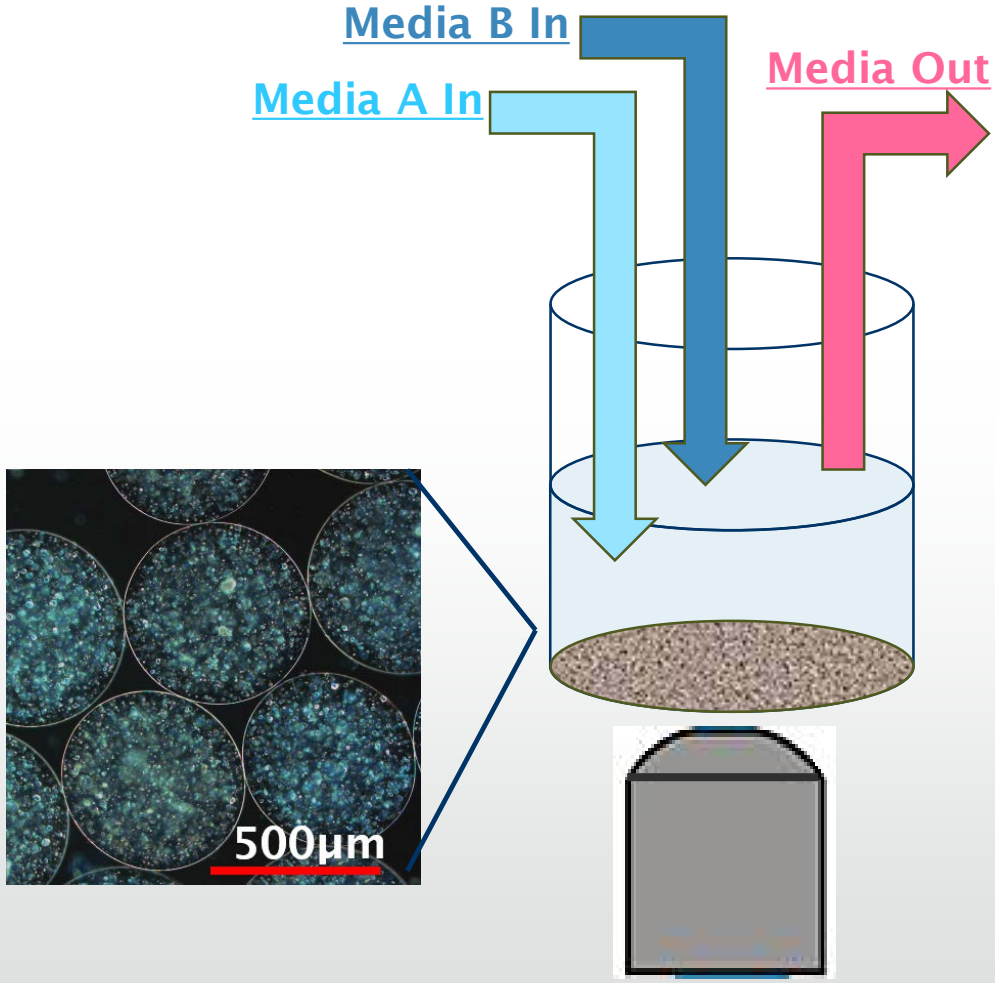
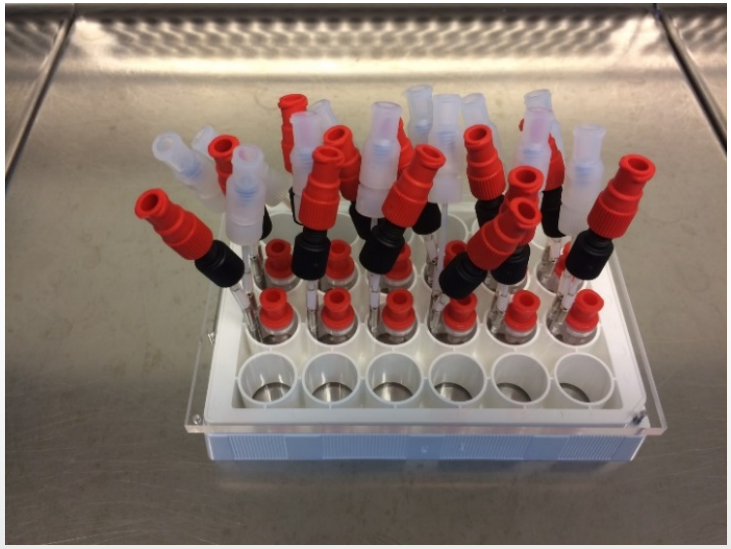
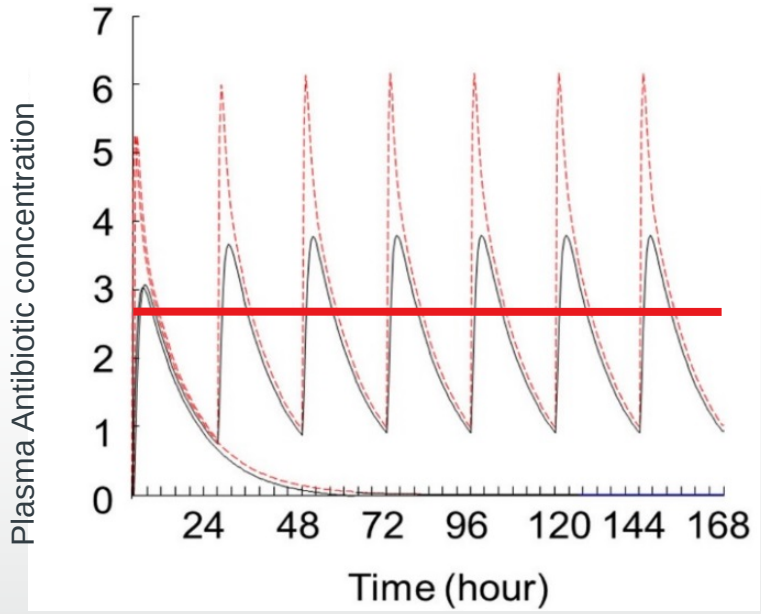


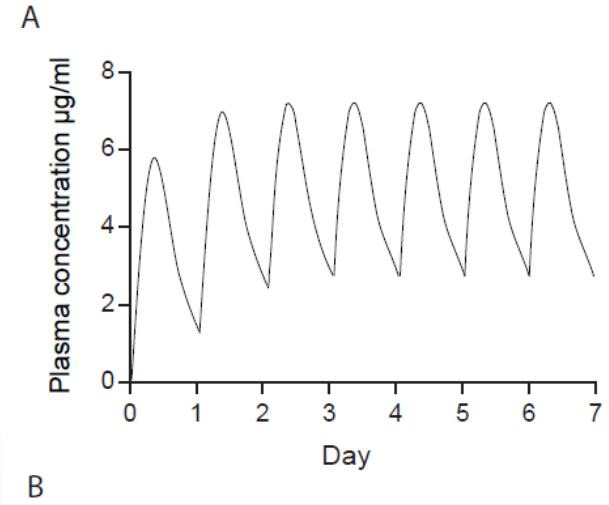
Microfluidic-based regulation of physiological conditions (1)

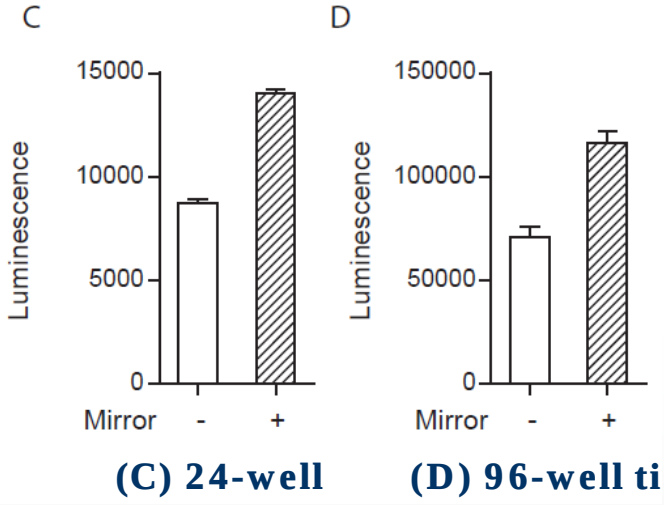




Bielecka et al., *mBio,* 2017, 8:e02073-16

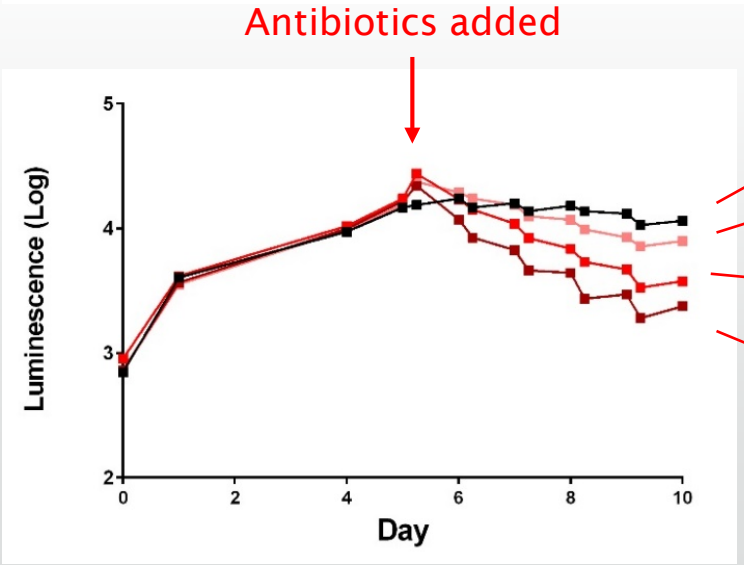
Microfluidic-based regulation of physiological conditions (2)





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

Luminescence from infected PBMCs in microspheres in a single well



No antibiotics

Low peak concentration

Standard peak concentration

High peak concentration

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

Developing a microfluidic platform to model & detect physiological conditions

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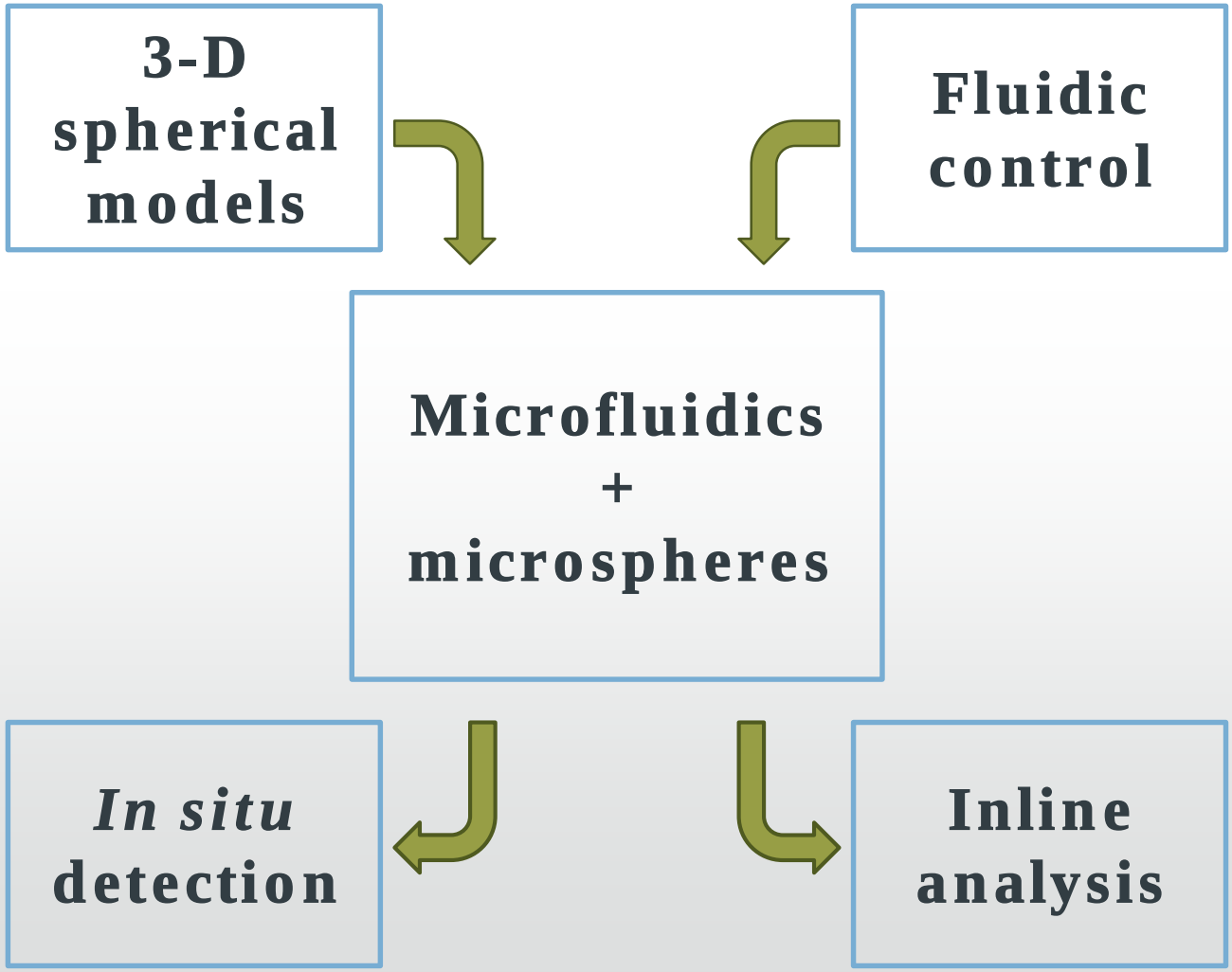

Summary

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- Microsphere-based 3-D extracellular matrix plays a previously unappreciated role in regulating the host pathogen interaction.
- Combining microfluidics and microsphere-based 3-D cell culture model can regulate and detect dynamic microenvironment surrounding cell culture microspheres with precise fluidic control.
- Ongoing work to integrate multi processes/units towards an effective platform/system for high throughput screening and kinetic modulation of pharmacokinetics by mimicking physiological conditions in patients.

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