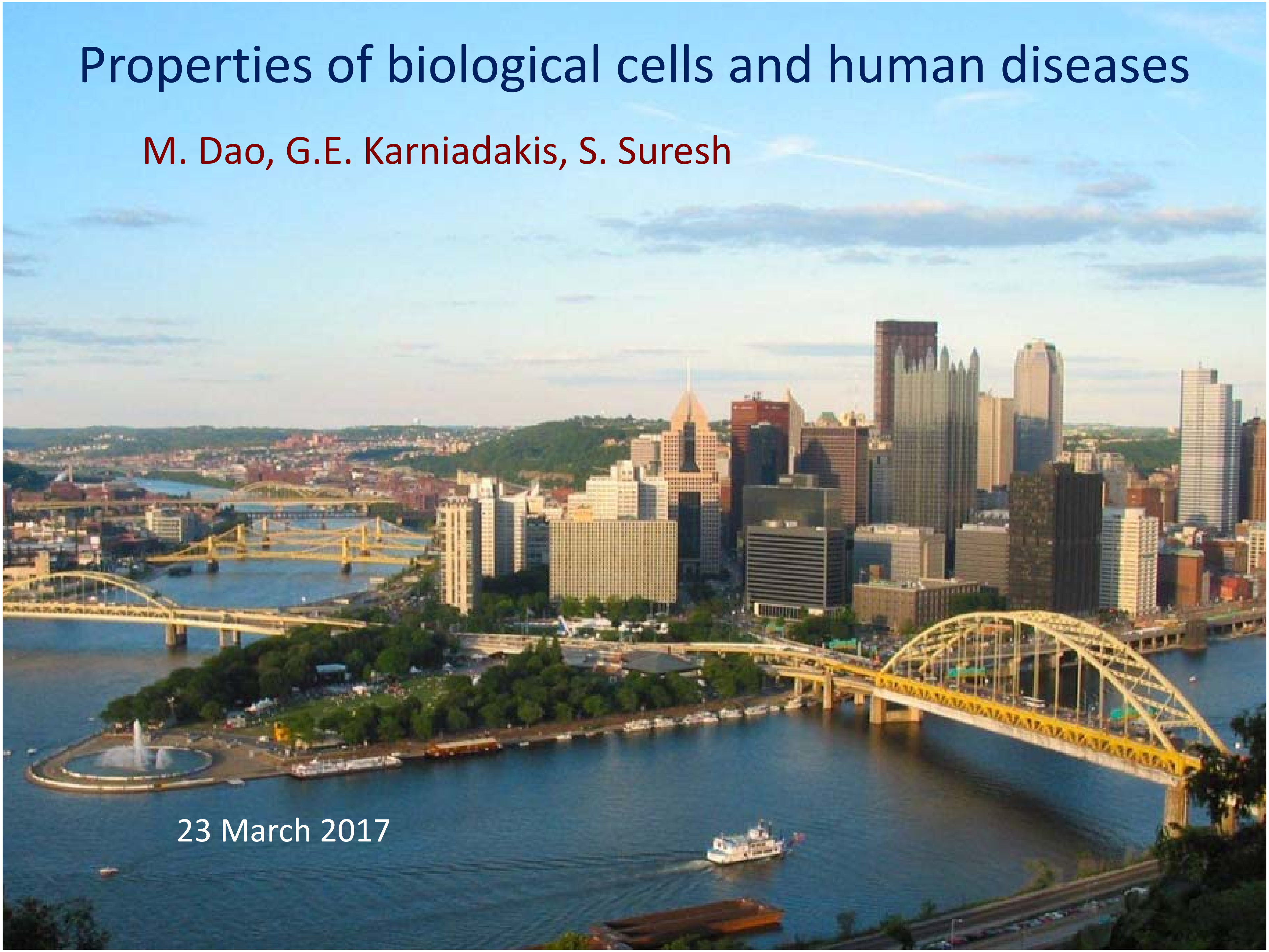
Properties of biological cells and human diseases

M. Dao, G.E. Karniadakis, S. Suresh



23 March 2017

Motivation

The role of "cell properties" in influencing diseases

The role of diseases in influencing cell properties

Multi-scale computational simulations, guided and validated by experiments, and *vice versa*

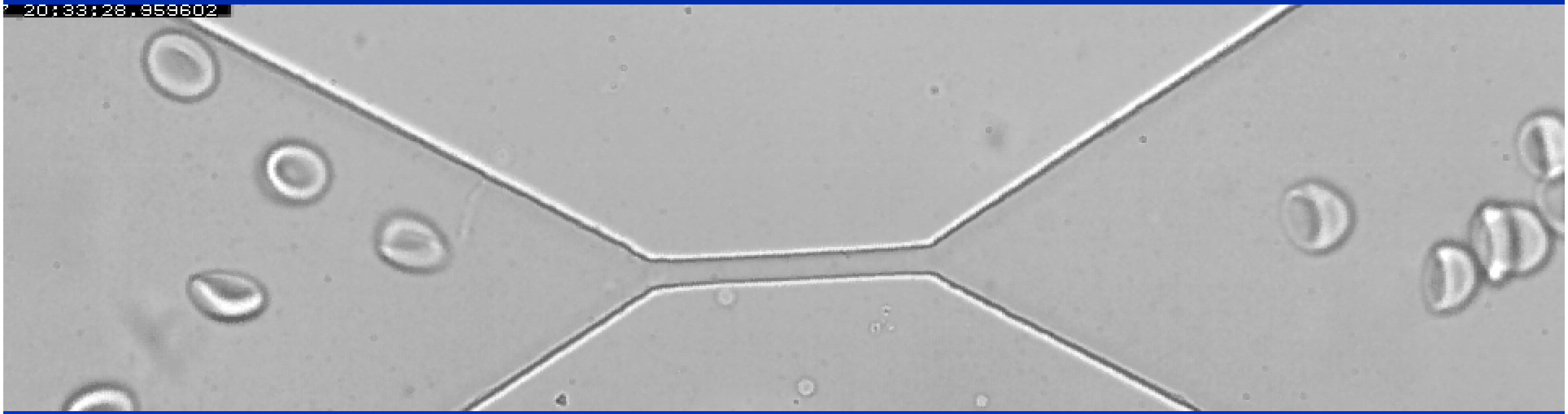
hereditary blood disorders – sickle cell disease

Plasmodium falciparum malaria

different types of human cancer

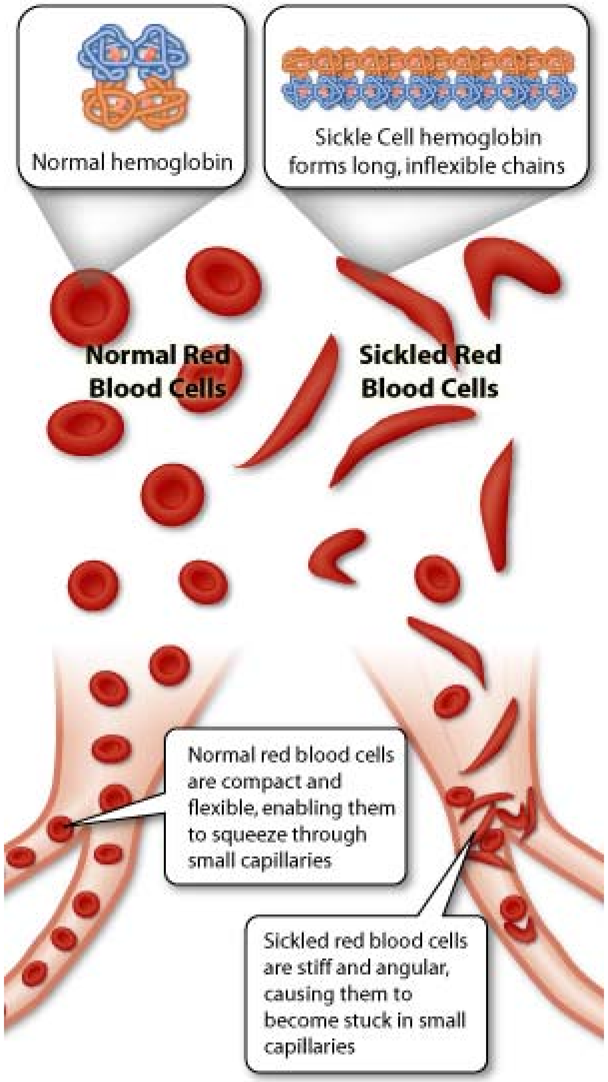
Microfluidics and cell pathology

Visualization of RBC flow *in vitro*



D.J. Quinn et al. (2010)

Sickle Cell Painful Vaso-Occlusive Crisis



http://learn.genetics.utah.edu/content/disorders/whataregd/sicklecell/

SCD may lead to acute and chronic complications

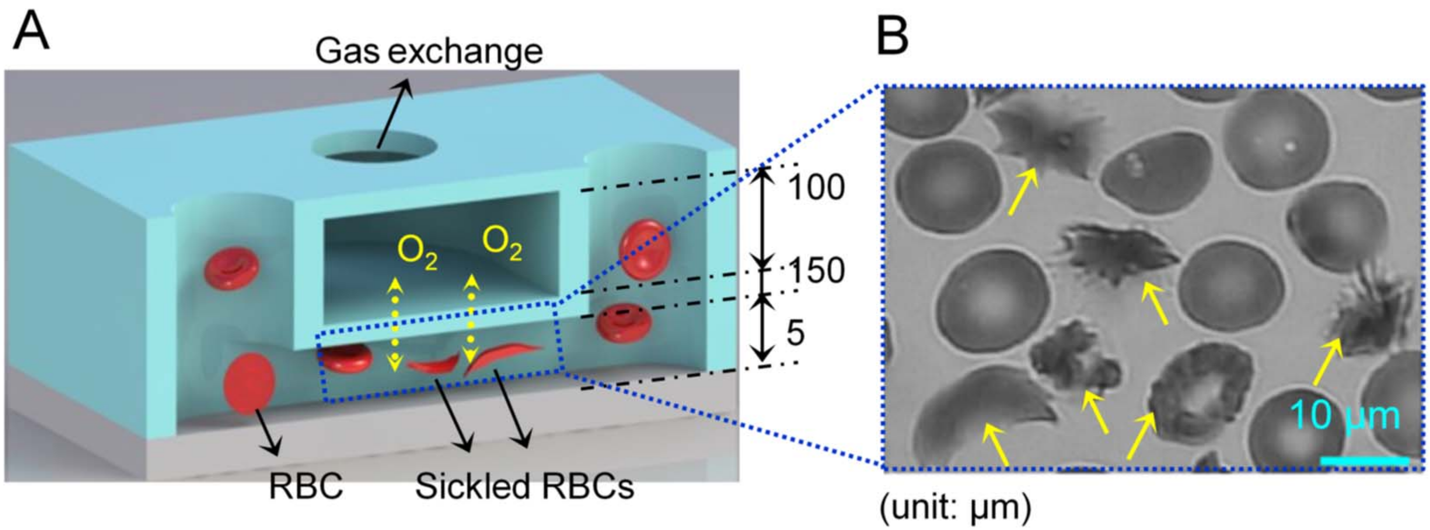
Anemia – the most common symptom

- o Complications from vaso-occlusion
  - Recurrent, painful episodes
  - Stroke
  - Organ damage
  - Swelling in hands/feet

http://www.childrenshospital.org/

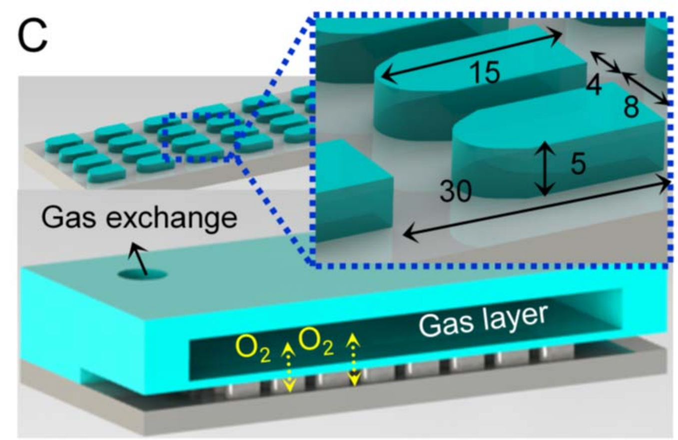
Microfluidic devices with controlled transient DeOxy states

Kinetics of cell sickling



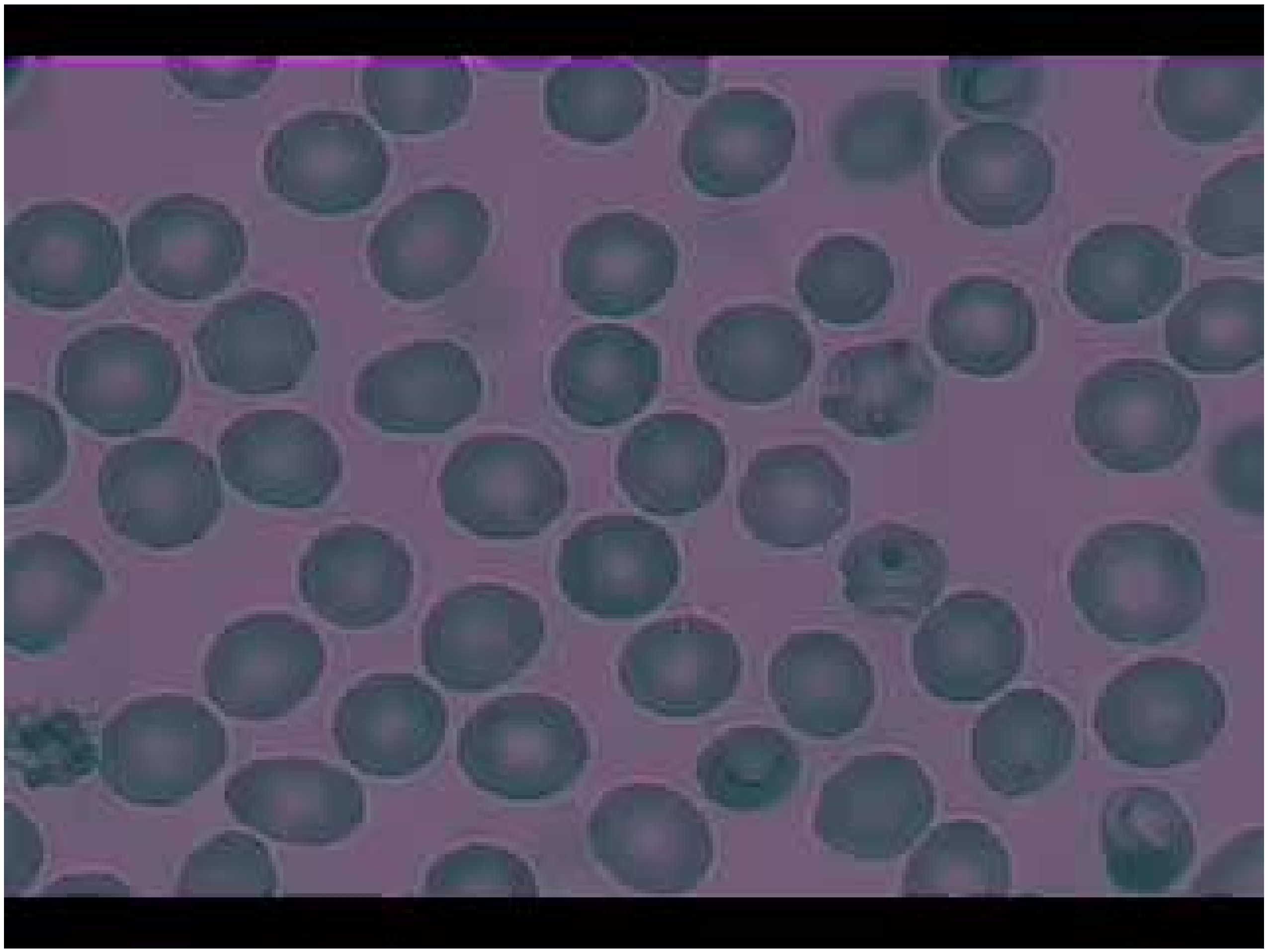
- **SCD patient samples tested**

  off-HU and on-HU



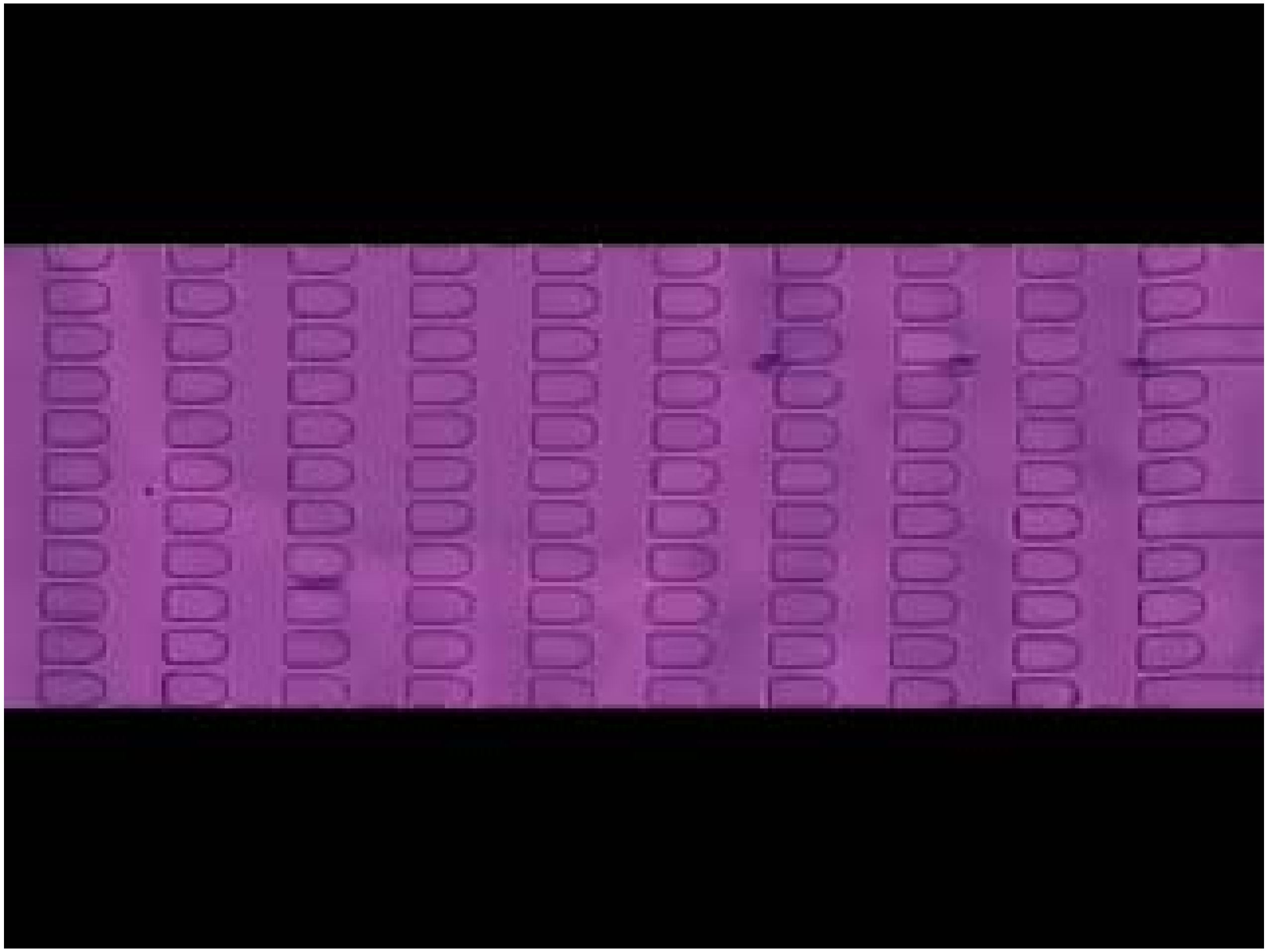
E. Du, M. Diez-Silva, G.J. Kato, M. Dao, S. Suresh, *PNAS* 2015

Sickle Cell Disease: in vitro sickling and unsickling



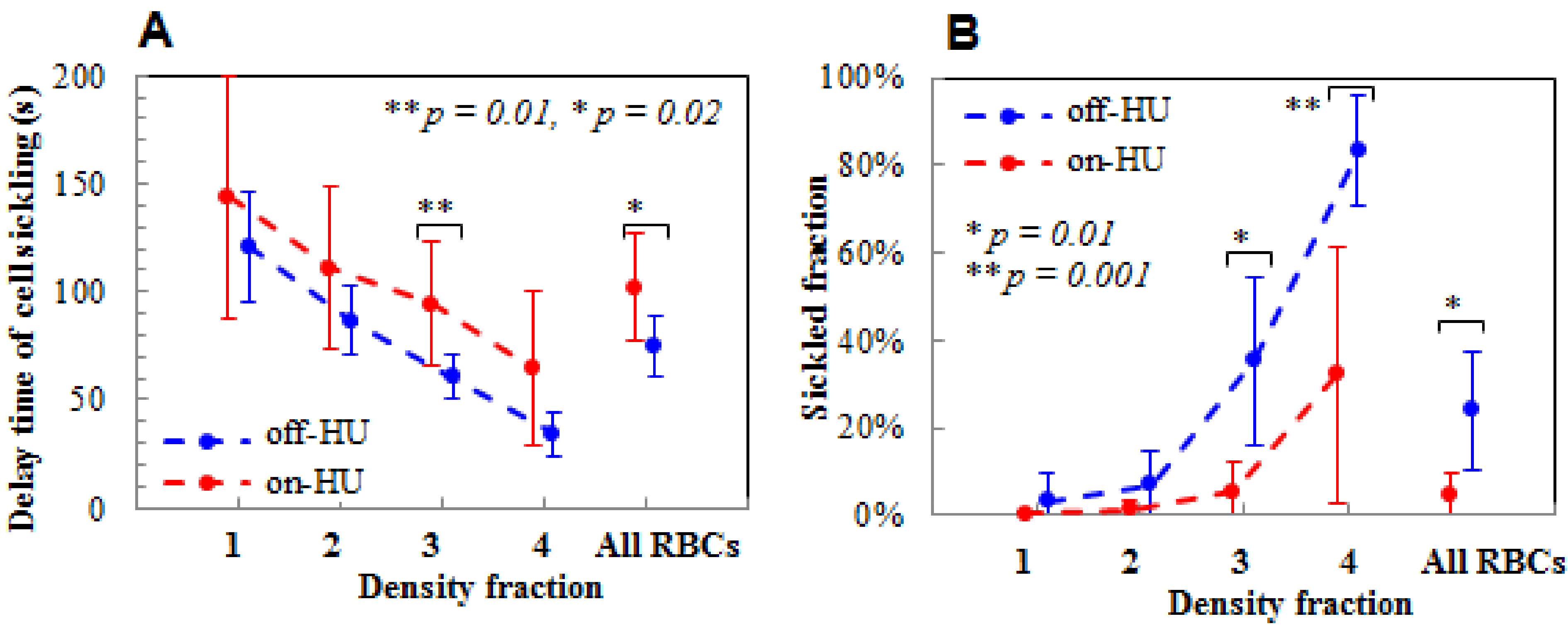
E. Du, M. Diez Silva, G. Kato, M. Dao & S. Suresh, *PNAS*, 2015

Sickle Cell Disease: Demonstration of vascular obstruction *in situ*



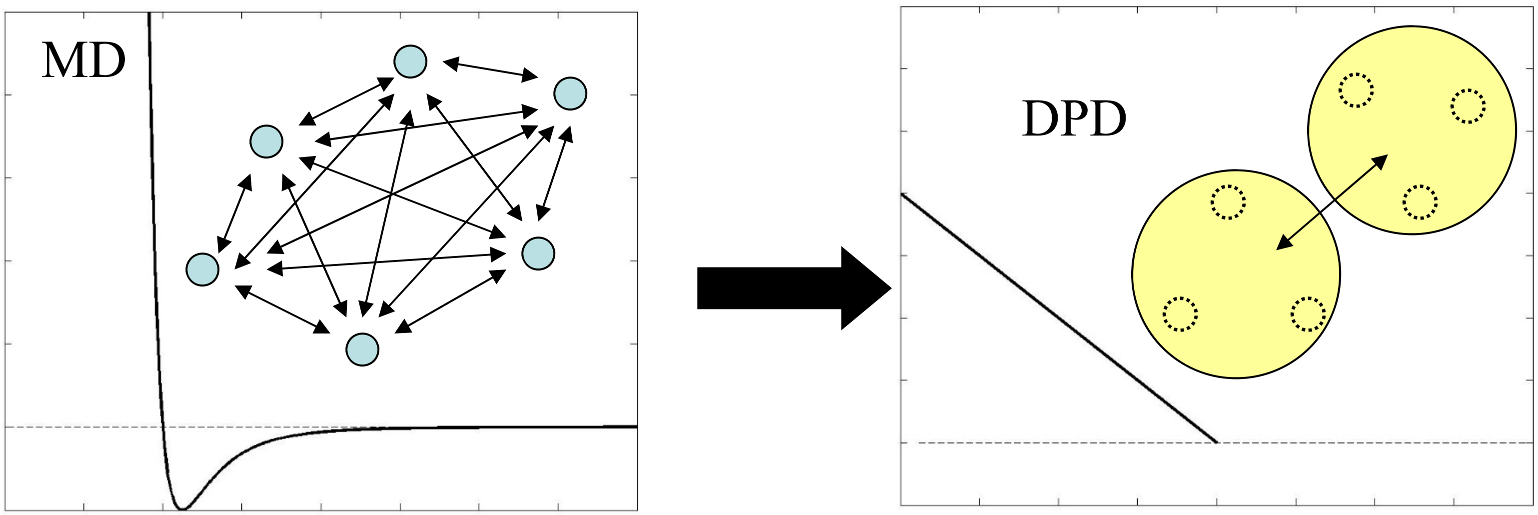
E. Du, M. Diez Silva, G. Kato, M. Dao & S. Suresh, *PNAS,* 2015

In vitro assays for risk assessment in SCD



E. Du, M. Diez Silva, G. Kato, M. Dao & S. Suresh, *PNAS*, 2015

Dissipative Particle Dynamics (DPD)

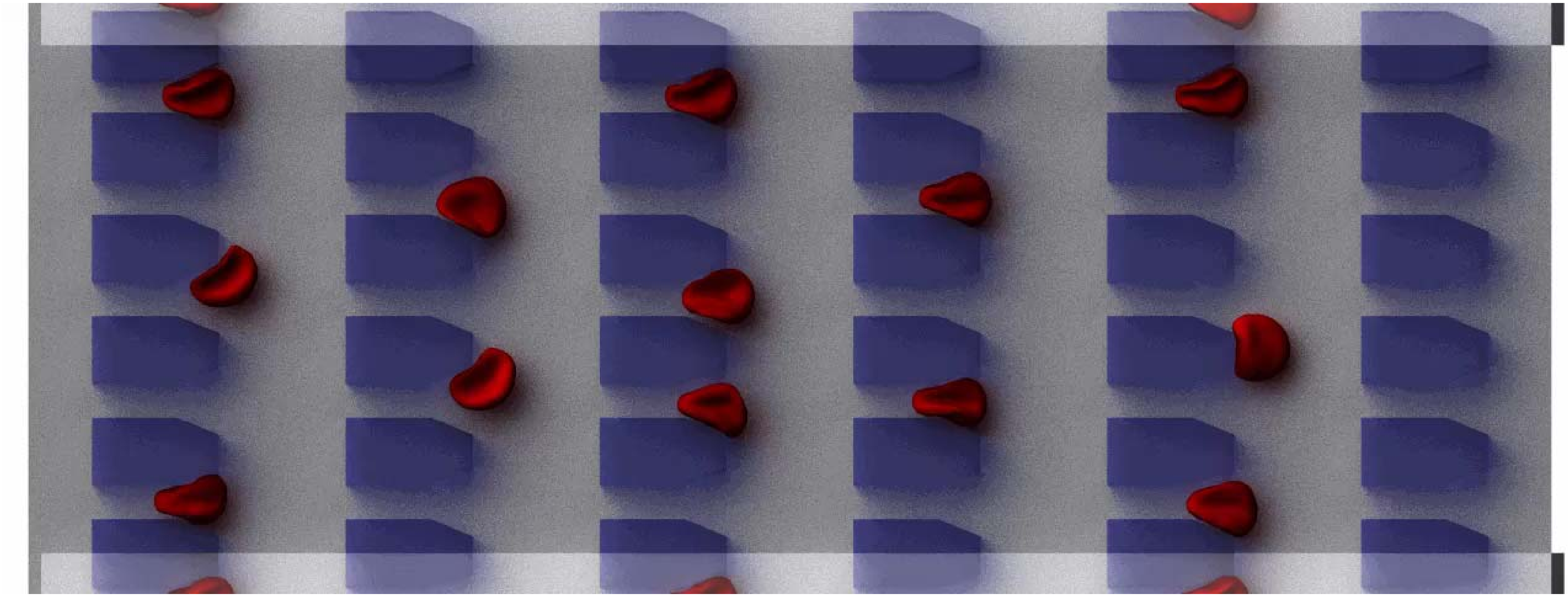


- DPD particles represent clusters of atoms or molecules
- Particles interact through a simple pair-wise potential
- Calculation of positions and velocities of interacting particles over time.
- Account for interactions through conservative, random and dissipative forces of fluids + dissipative membrane forces

P.J. Hoogerbrugge and J.M.V.A. Koelman, Europhys.Lett.,19:155-160, 1992

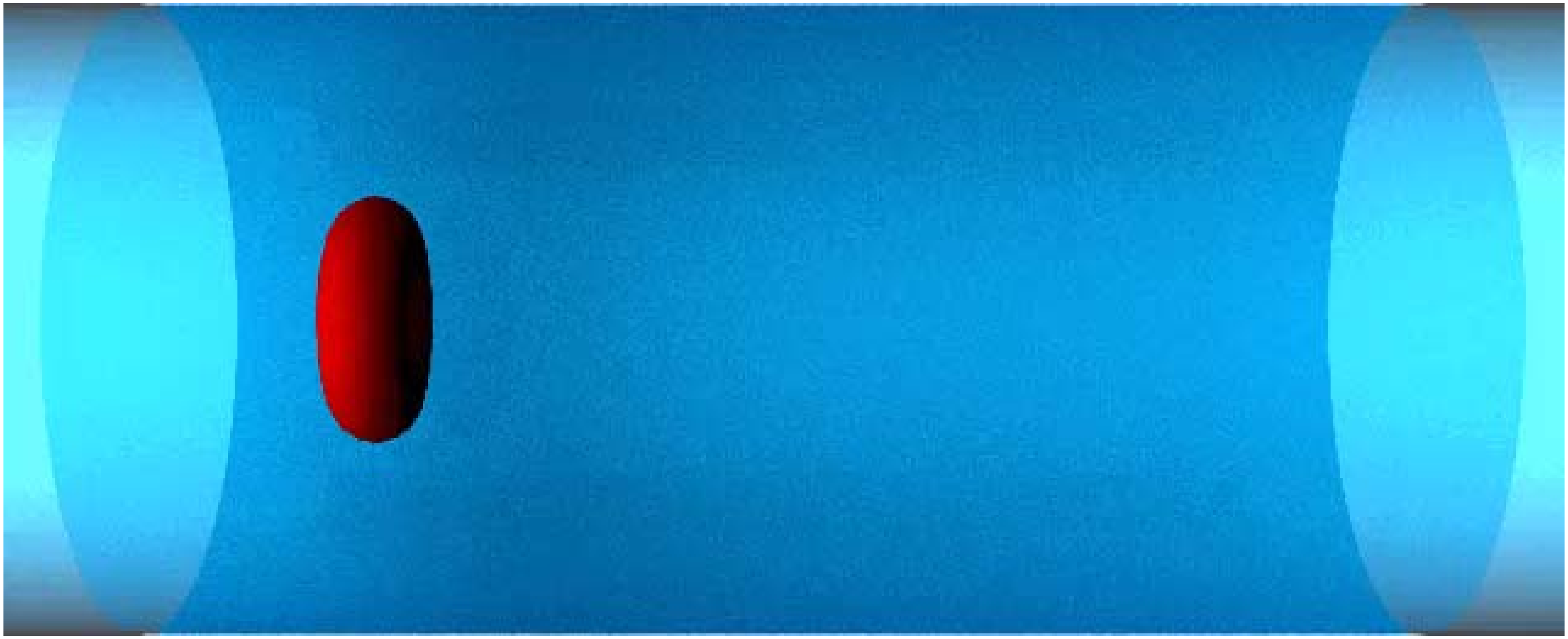
Dissipative particle dynamics simulations:

capillary-obstruction simulations



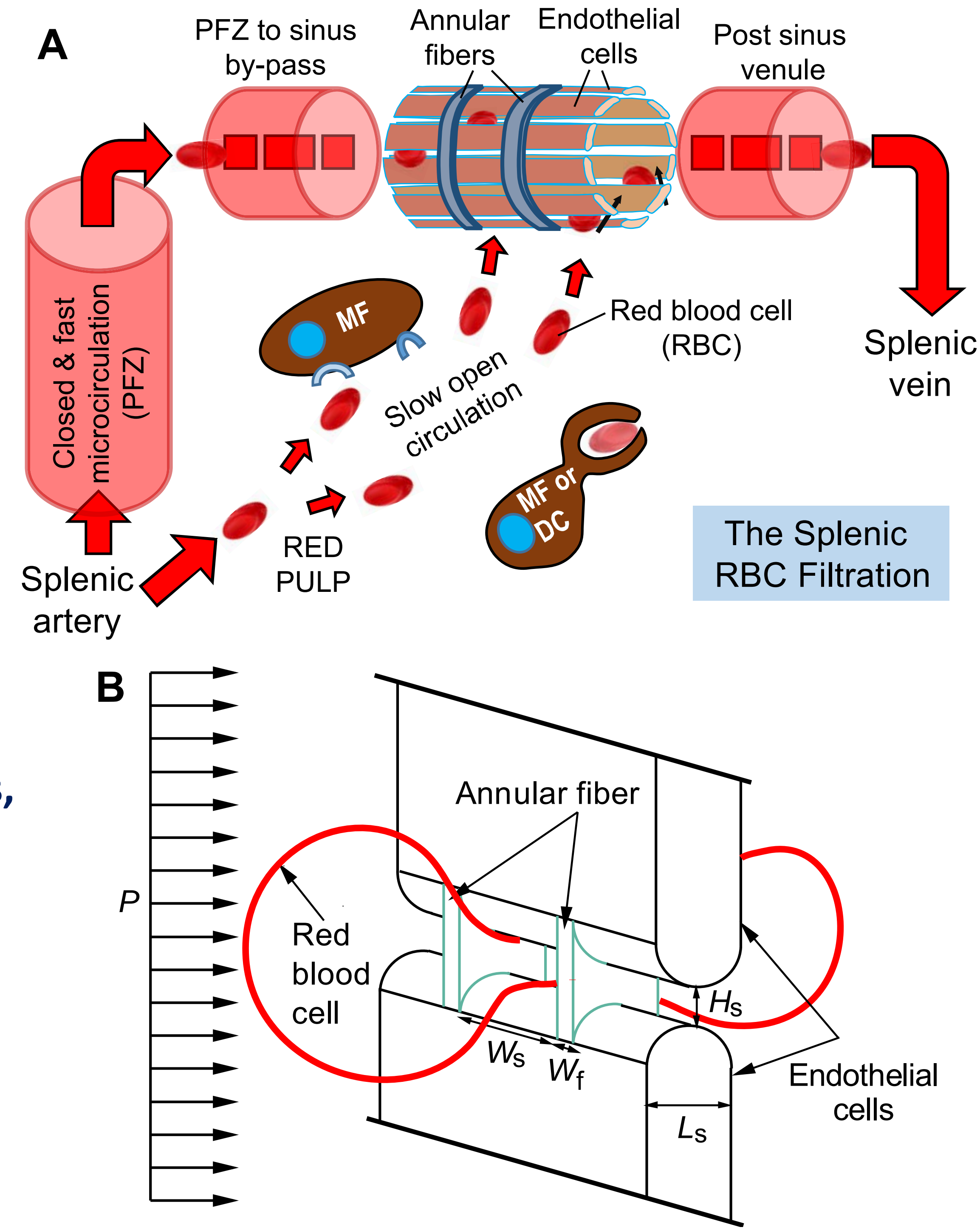
X. Li et al., *PLOS Computational Biology* (2017)

Dissipative particle dynamics simulations:
single cell transient sickling behavior



X. Li et al., *PLOS Computational Biology* (2017)

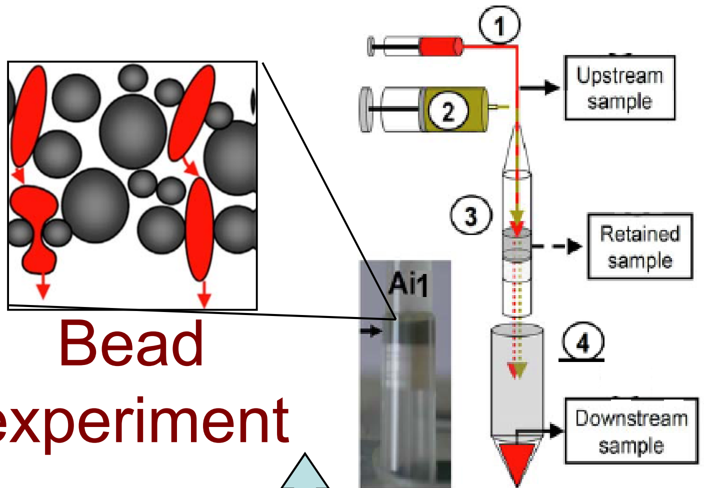
Biomechanics of human spleen



I.V. Pivkin, Z. Peng, G. Karniadakis, P.A. Buffet, M. Dao, S. Suresh

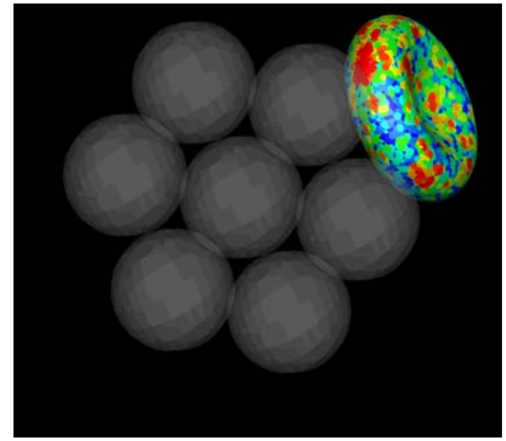
PNAS, June 2016

Cell mechanics to spleen mechanics



Bead experiment

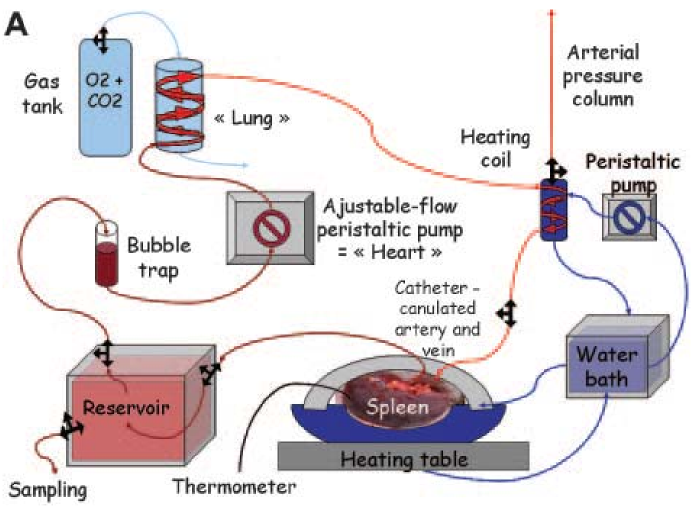
Microbeads to simulations



Bead simulations

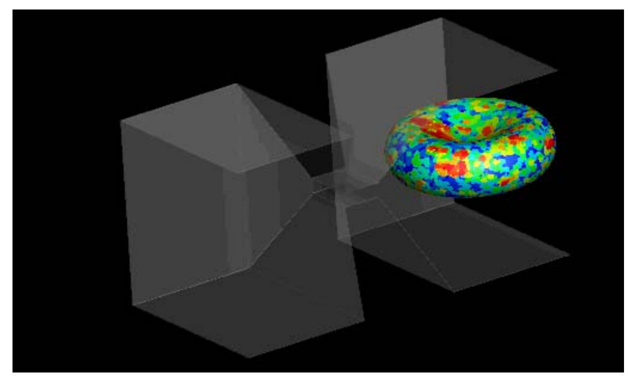
P. Buffet et al., 2012

The isolated perfused human spleen system



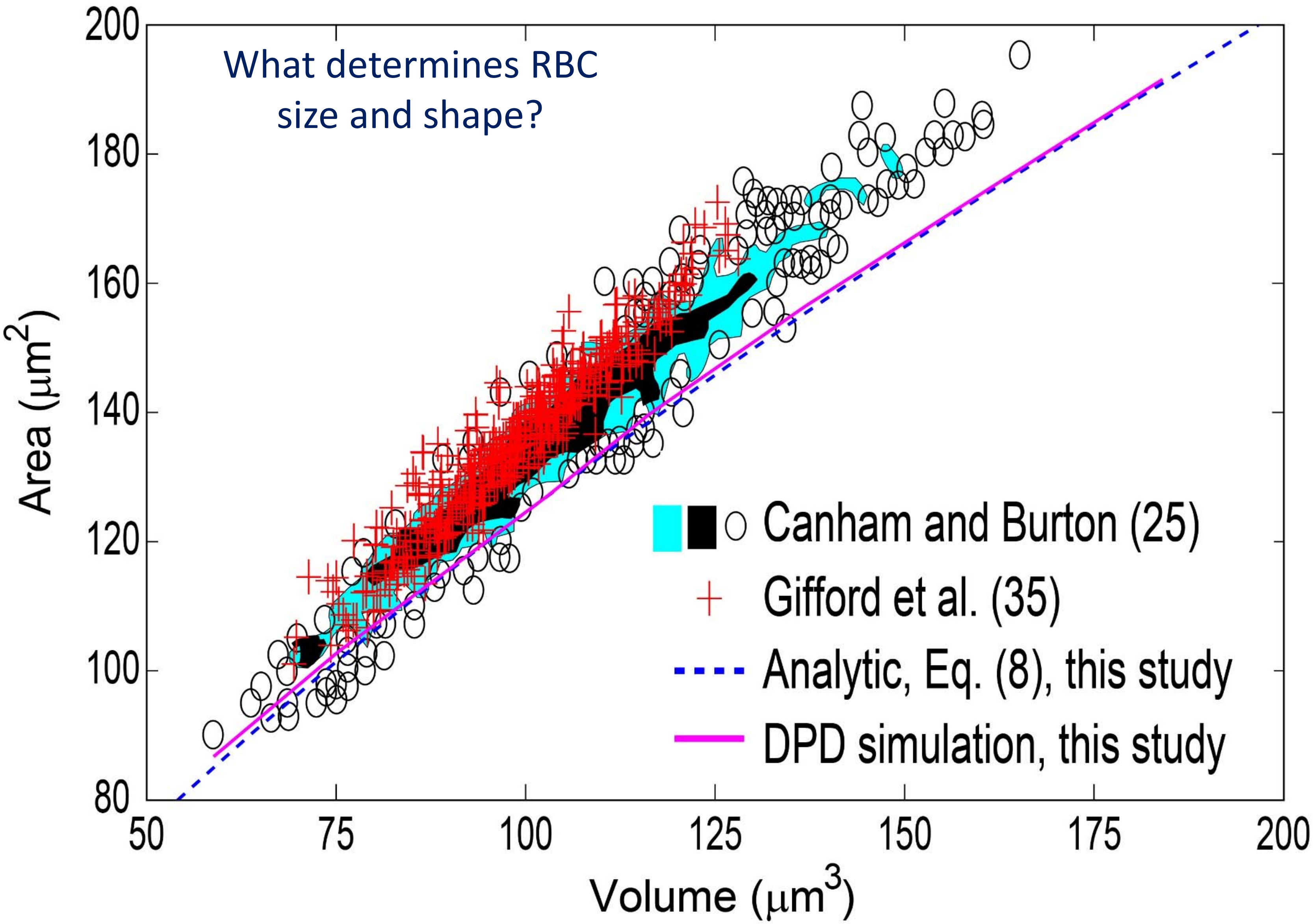
Simulations to real human spleen experiments

Human spleen simulations



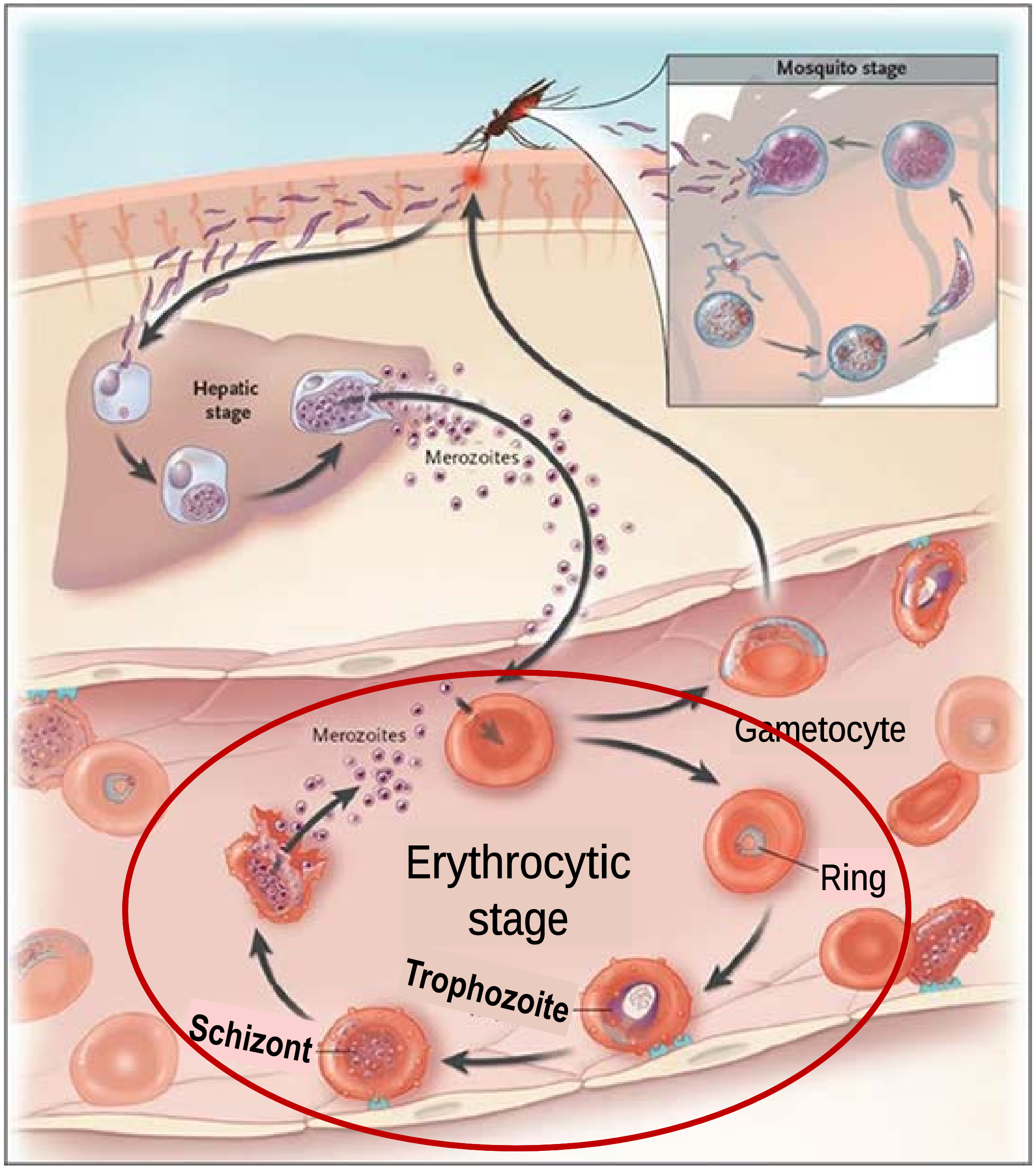
I.V. Pivkin, Z. Peng, G. Karniadakis,P. Buffet, M. Dao & S. Suresh, *PNAS* (2016)

Cell mechanics to organ mechanics – Role of MSM



I. Pivkin, Z. Peng, G. Karniadakis, P. Buffet, M. Dao, S. Suresh, *PNAS*, 2016

Malaria Biomechanics



http://www.mcwhealthcare.com/malaria_drugs_medicines/malaria.htm

Anti-malarial

Plasmodium infection of a RBC

Invasion

Host cell modification

RBC rigidity (shape)

asexual ↗

sexual ↗ ↘

Infected RBC sequestration

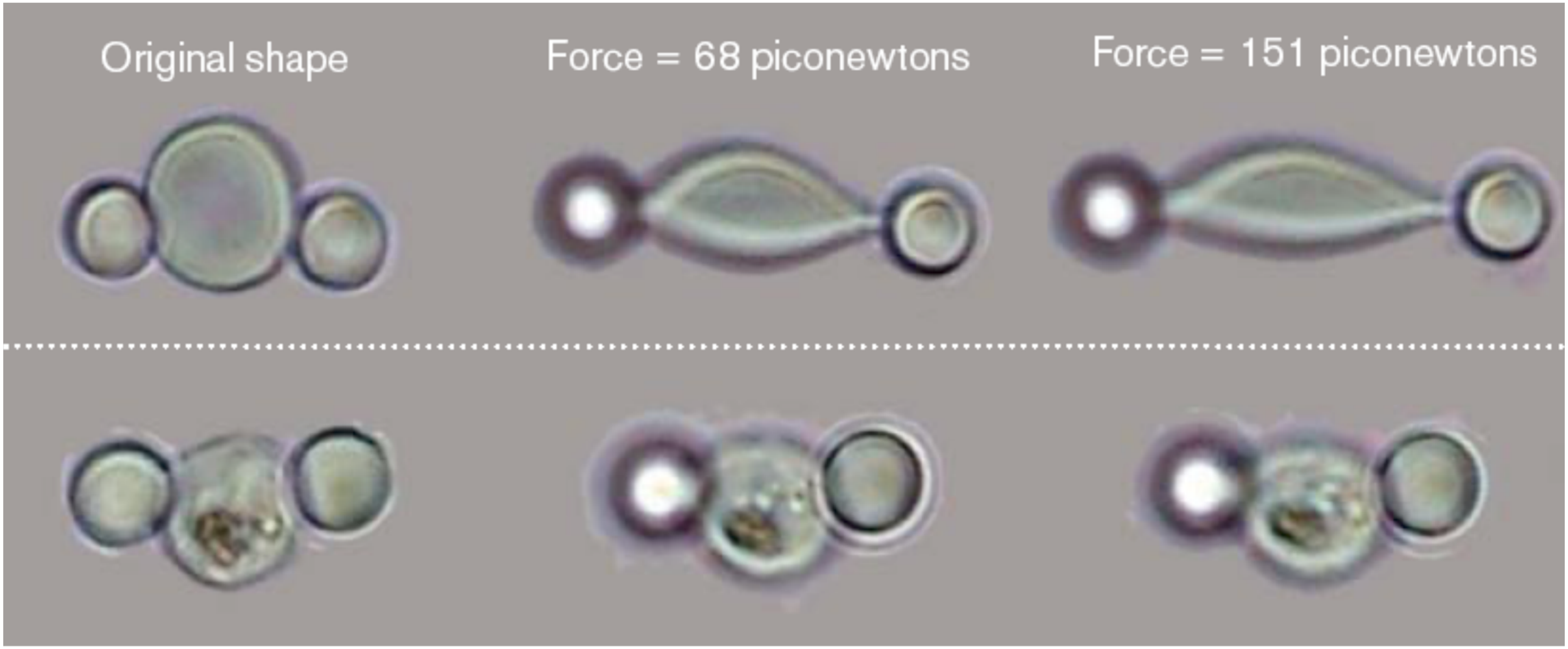
&

Spleen clearance

Mechanical vs Immunological

Pathology & Novel Drug Target

Laser optics, cell mechanics and diseases



More than an order of magnitude reduction in deformability

Suresh et al., *Acta* Biomaterialia 2005

J.P. Mills et al., *PNAS* 2007

C.T. Lim, S. Suresh et al. (2010)

In vitro Demonstration of RBC flow obstruction in microvasculature

Using sound waves to detect rare cancer cells

Collaborators:

Tony Jun Huang, *et al.*
Ming Dao

Proc. National Academy of Sciences (2014, 2015, 2016)

Circulating Tumor Cells (CTCs)

Current clinical applications

- Evaluation of tumor prognosis
- Therapy feedback

Potential applications

- Early cancer diagnosis
- Real-time disease progression monitoring
- Tumor staging criteria
- Personalized drug susceptibility test
- Treatment target

Currently 305 clinical trials in the US

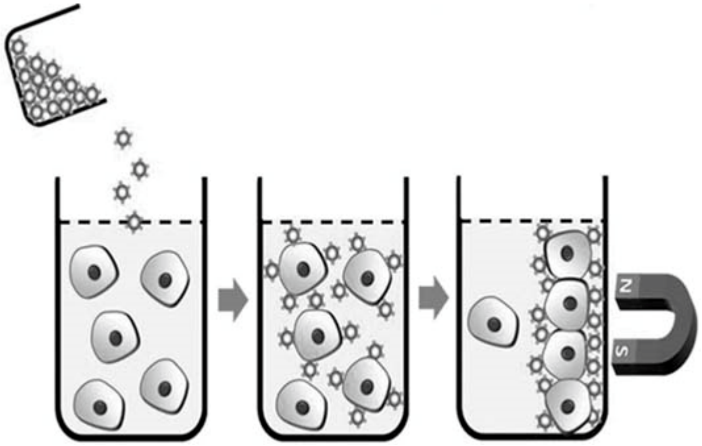
Source: BCC Research; clinicaltrials.gov

Existing Cell-Separation Technologies

Centrifugation

Fluorescence-Activated Cell Sorting

Magnetic beads



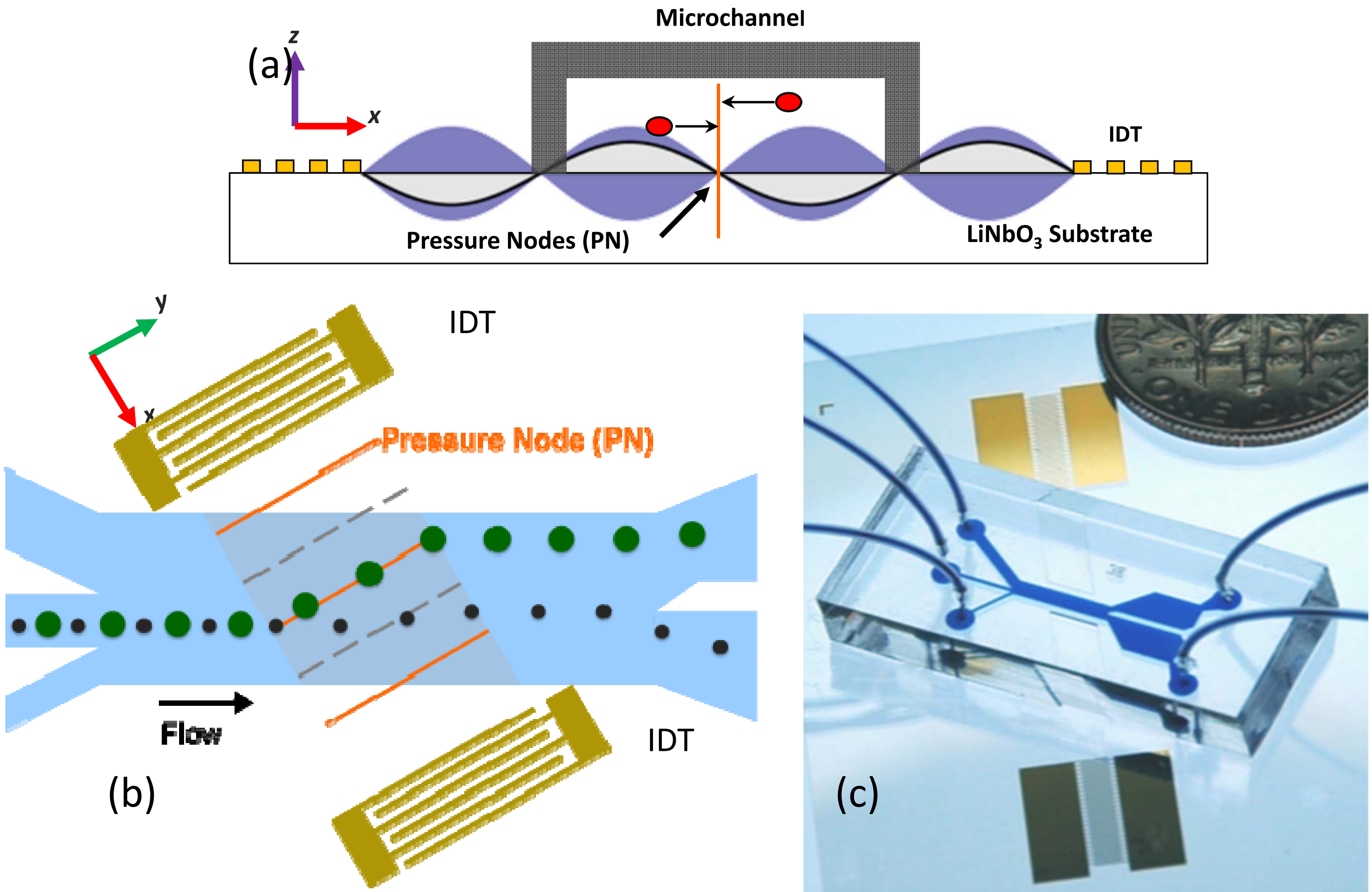
Affinity labeling

Filtration

Dielectrophoresis

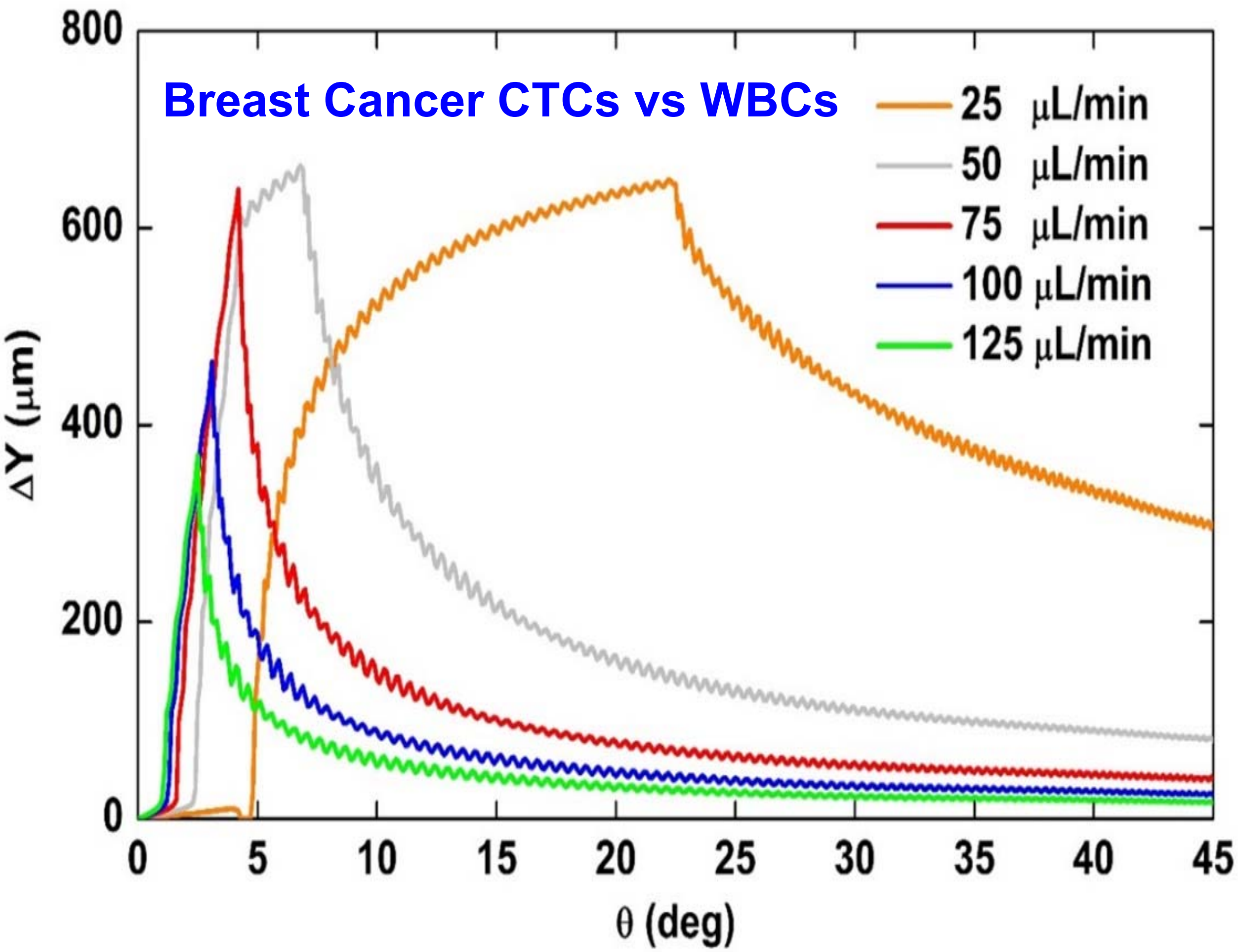
Tilted-angle standing surface acoustic wave (taSSAW)

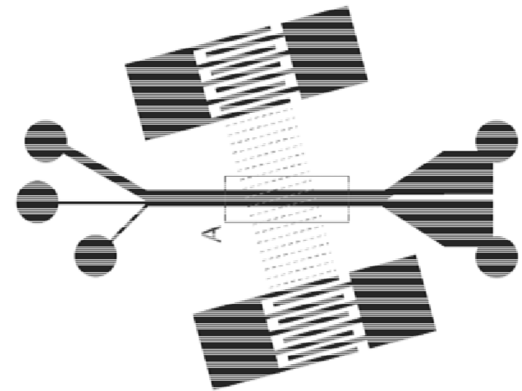
Microfluidics design through MSM



X. Ding, et al., *PNAS,* 2014.

Tilted-angle standing surface acoustic wave (taSSAW) Optimization for better separation & throughput



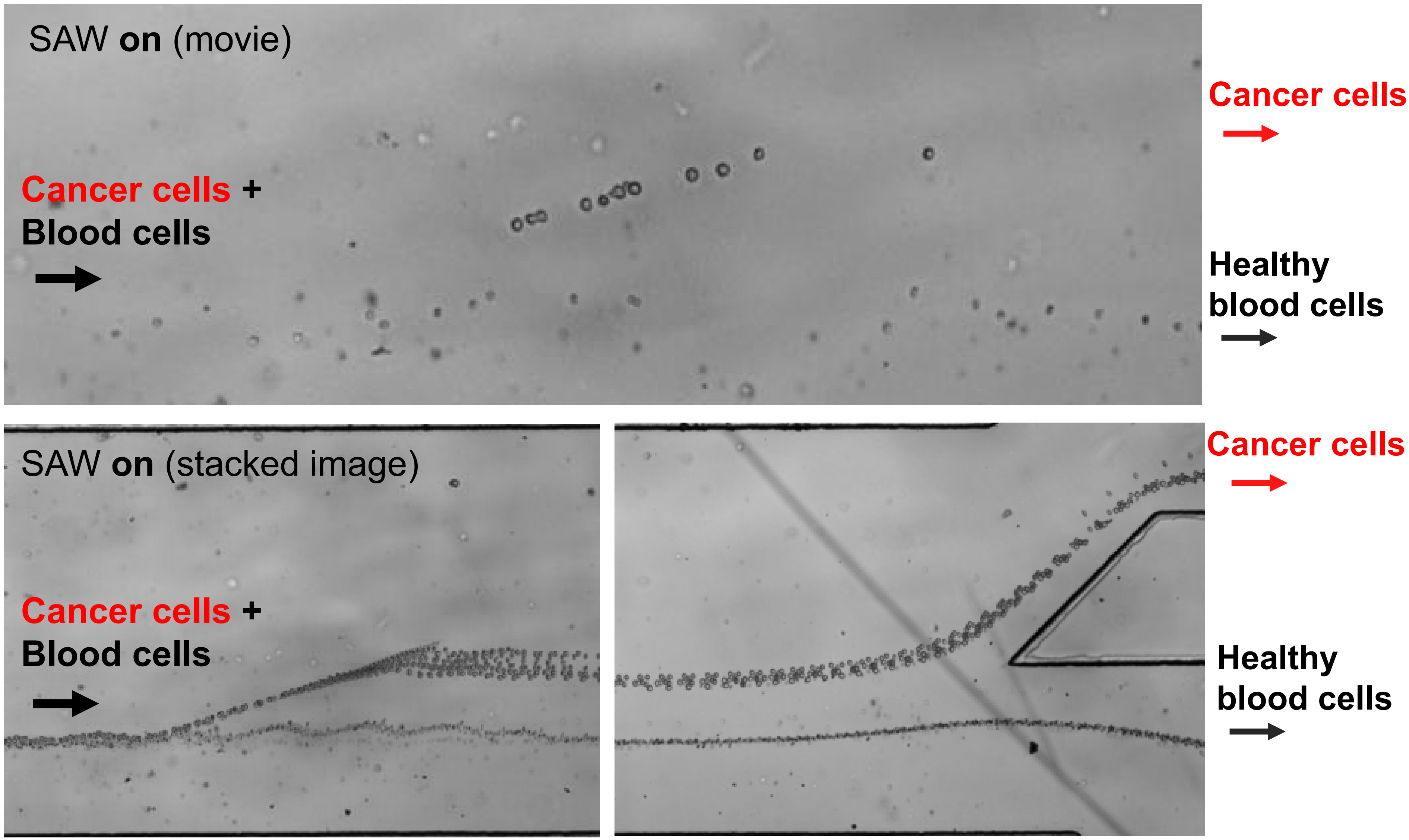


Optimized parameters

- IDT tilt angle
- IDT working length
- Sample flow velocity

P. Li et al., *PNAS,* 2015

Acoustic Separation of Cancer Cells from Blood



X. Ding, Z. Peng, S. Lin, M.Geri, S. Li, P. Li, Y. Chen, M. Dao, S. Suresh, T. Huang, *PNAS*, 2014

Tilted-angle standing surface acoustic waves

Cell line	Cells ratio (Cancer cells / WBCs)	No. of cancer cells (collection outlet)	No. of cancer cells (waste outlet)	Recovery rate
MCF-7	1:40000	121	20	86%
MCF-7	1:40000	90	11	89%
MCF-7	1:40000	52	2	96%
HeLa	1:6000	907	165	85%
HeLa	1:100000	49	10	83%
HeLa	1:40000	131	7	95%
UACC903M-GFP	1:100000	64	12	84%
UACC903M-GFP	1:100000	36	7	84%
UACC903M-GFP	1:100000	28	5	85%
LnCAP	1:20000	111	12	90%

P. Li, et al., *PNAS*, 2015

Concluding Remarks

Understanding human diseases at the intersections of different disciplines through

quantitative experiments, computational simulations, and connections to clinical relevance

Benefits:

fundamental mechanistic understanding,

diagnostic capabilities, novel therapeutics,

drug efficacy assays

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