



National Institute of
Biomedical Imaging
and Bioengineering

ATOMIC FORCE MICROSCOPY AND BIOMEDICAL APPLICATIONS

Albert J. Jin (jina@mail.nih.gov)

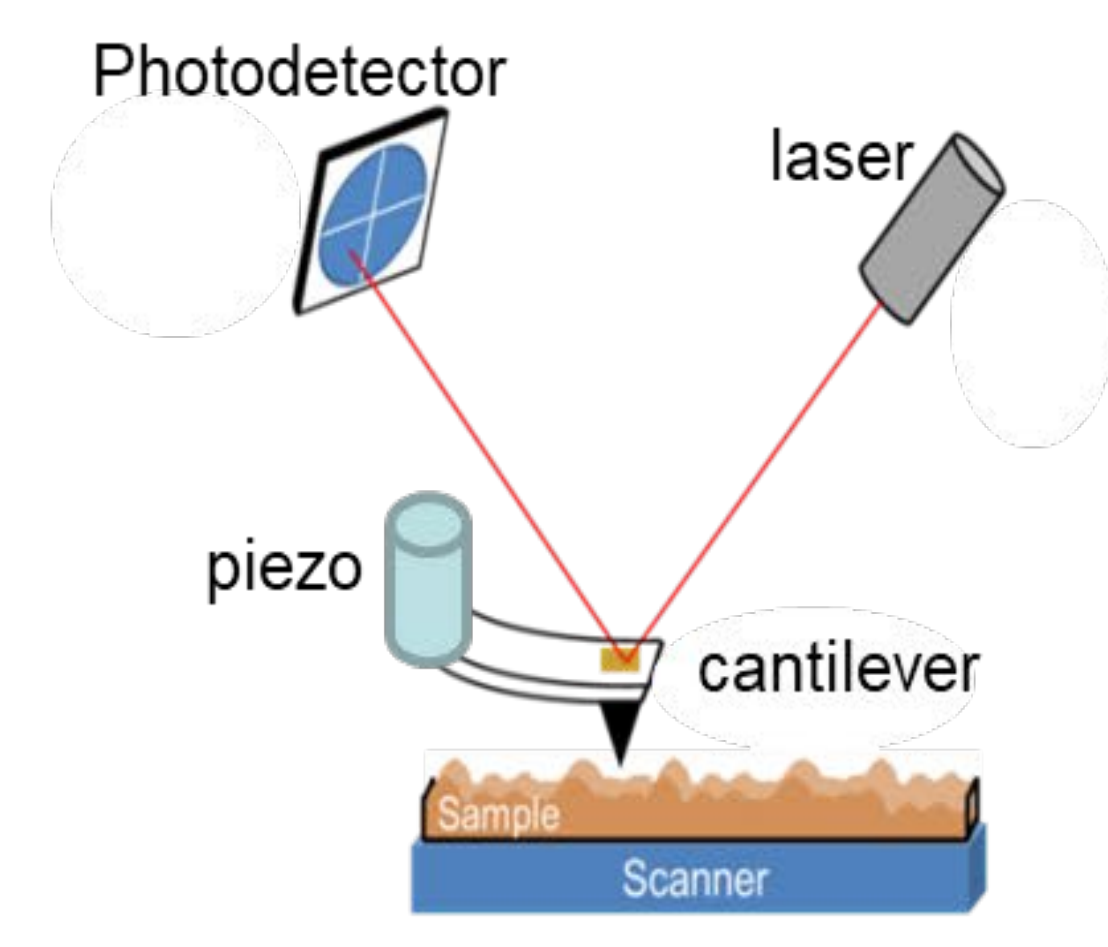
Nanoinstrumentation and Force Spectroscopy Section

Laboratory of Cellular Imaging and Macromolecular Biophysics, National Institute of Biomedical Imaging and Bioengineering, NIH, Bethesda, MD

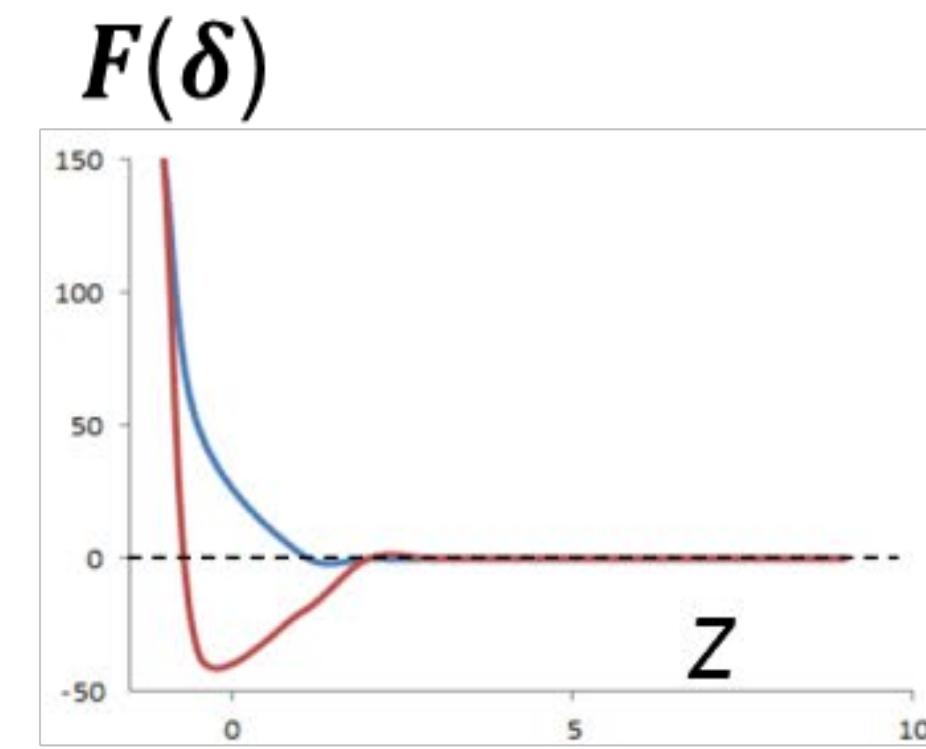


Biomedical Atomic Force Microscopy (BioAFM)

Principle of AFM:



- Binnig, G.; Quate, C. F.; Gerber, C. (1986). *PRL* **56** (9): 930–933
- Control force (pN) in Z (nm)
- Raster X-Y (nm)



Many operational modes

Contact, Tapping, Non-contact,
MAC Mode, QNM, FV, FM, EFM,
Multi-modal combinations

Single Molecule Force
Spectroscopy (SMFS),
unfolding/unraveling, molecular
recognition

Nanomechanics:

$$\text{Hertz model}$$

$$F = \frac{4}{3} \frac{E}{(1-\nu^2)} \sqrt{R\delta^3}$$

$$\text{Sneddon model}$$

$$F = \frac{2}{\pi} \frac{E}{(1-\nu^2)} \tan(\alpha)\delta^2$$

$$\text{Linear spring constant}$$

$$k_s = (1/k_{hs} - 1/k_{cl})^{-1}$$

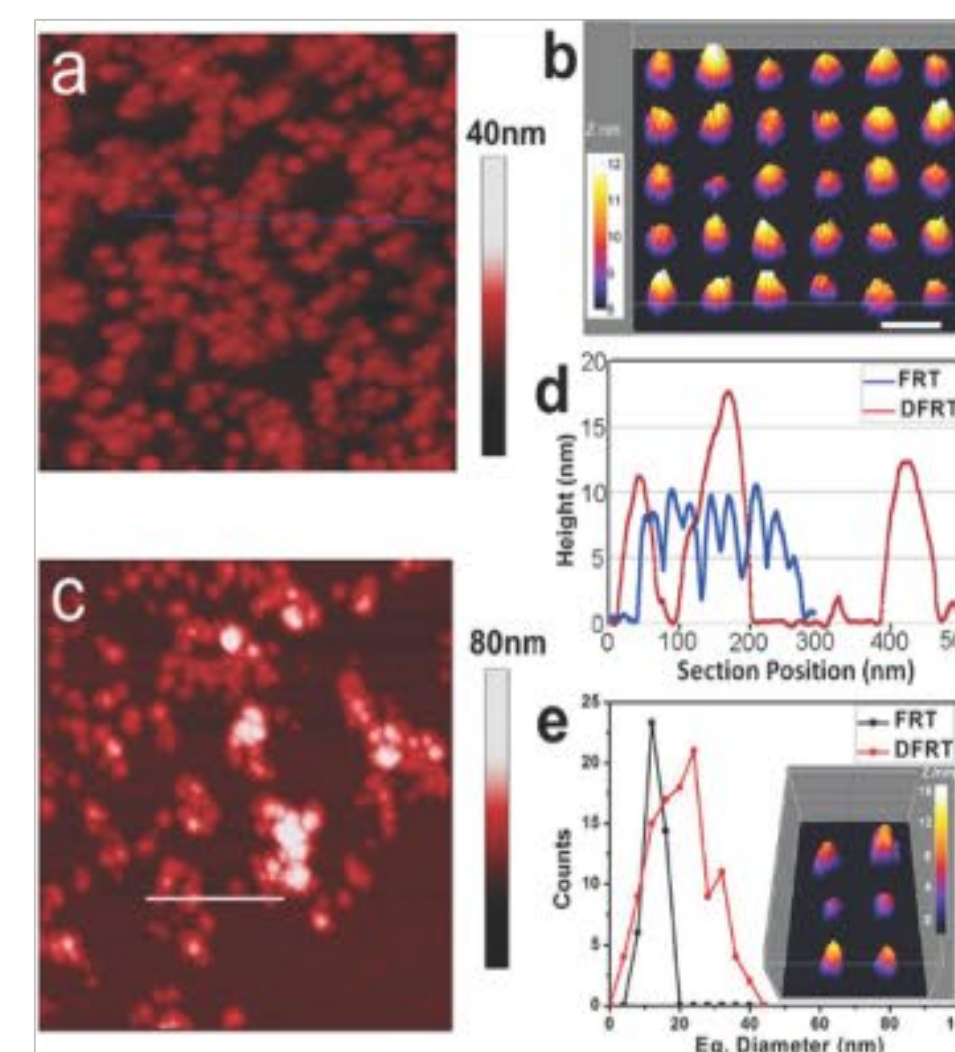
Improving Tools:

Multi-modal Bio-AFM (Raman-TIRF-SMFS-cellular- macromolecular-biomaterials) & complementary technologies (EM- super-resolution optics) & STEM

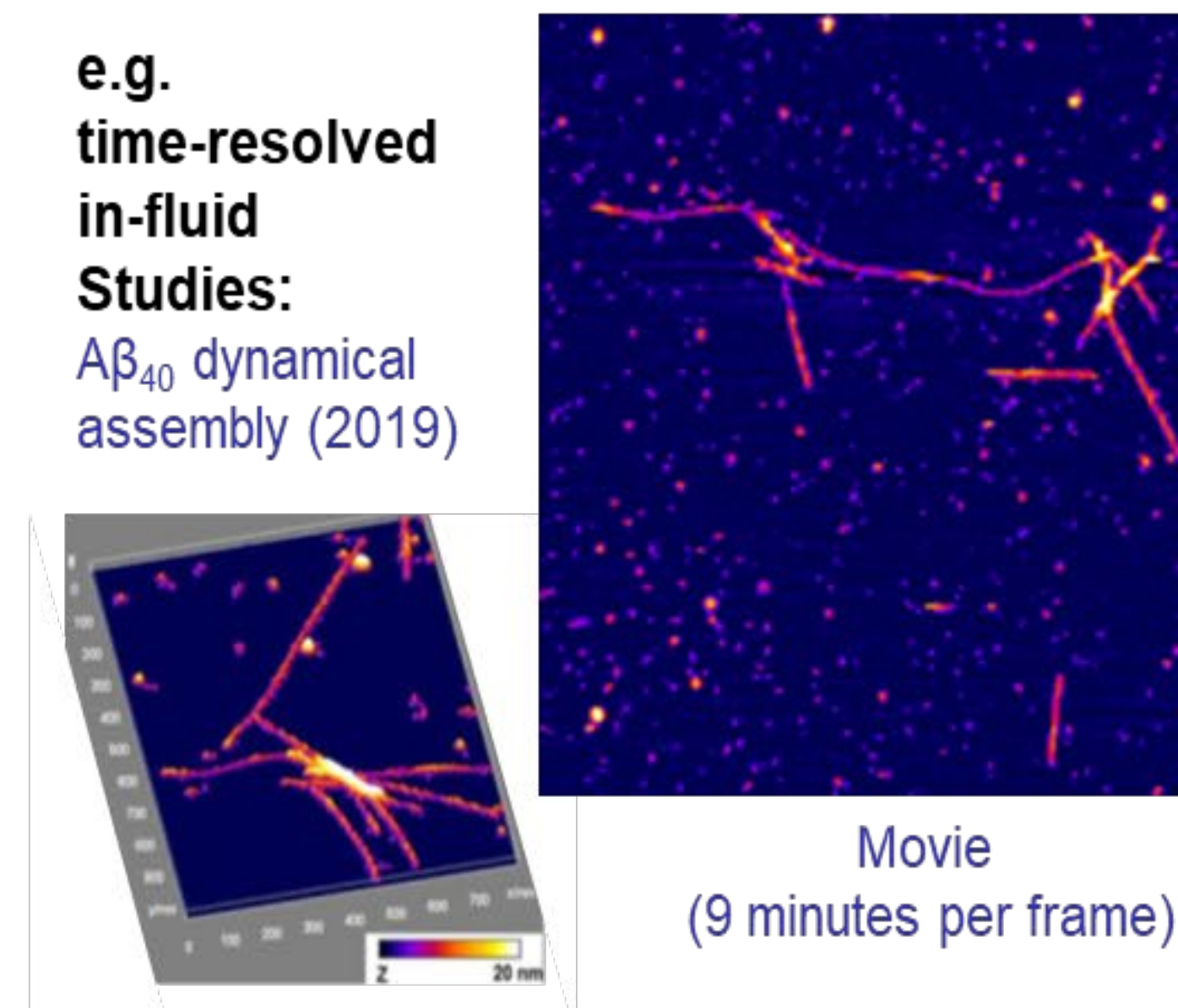


Examples
of a large collection
of BioAFM platforms at NIBIB/NIH

Biomedical Applications

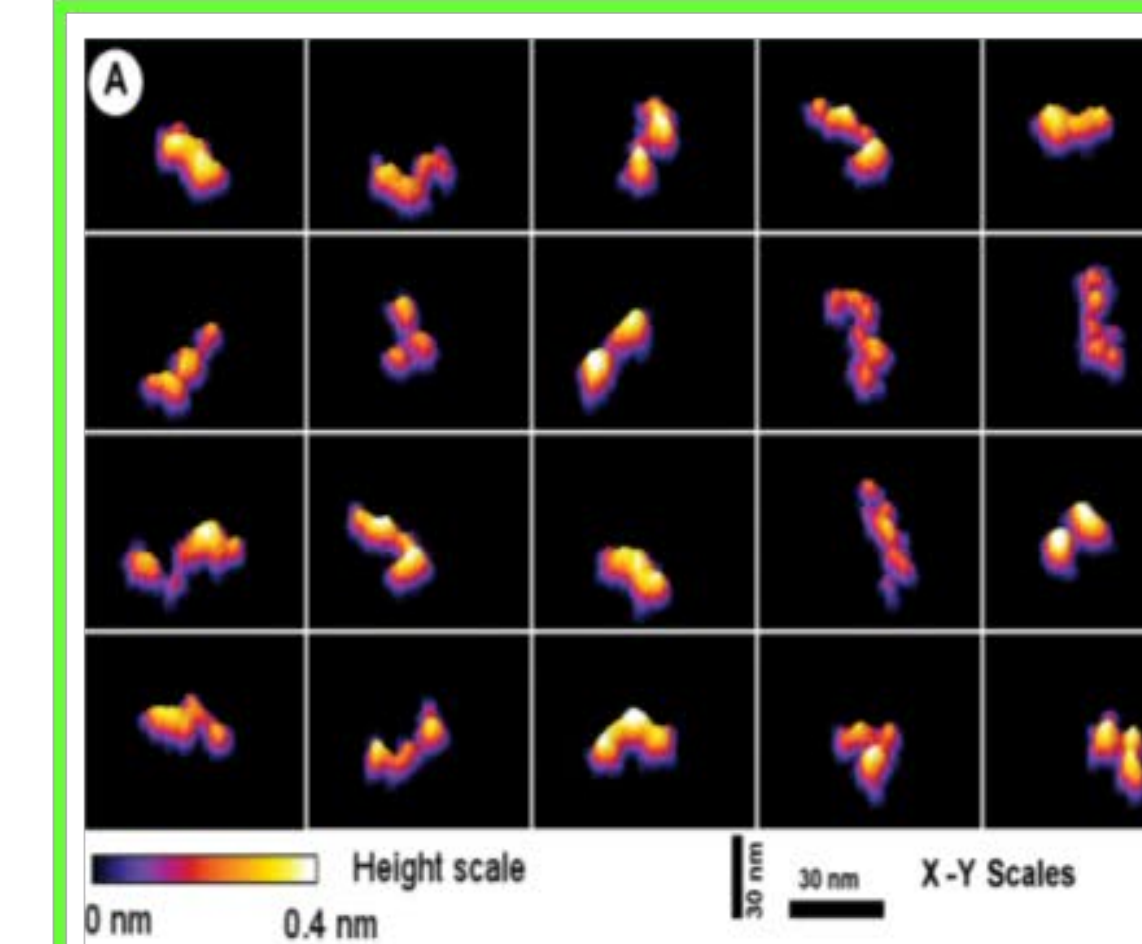


e.g. many
novel
Theranostics
like:
Dye-Loaded
Ferritin
Nanocages for
Multimodal
Imaging and
Photothermal
Therap. *Advanced
Materials*, 26 (37):
6401-8 (2014)

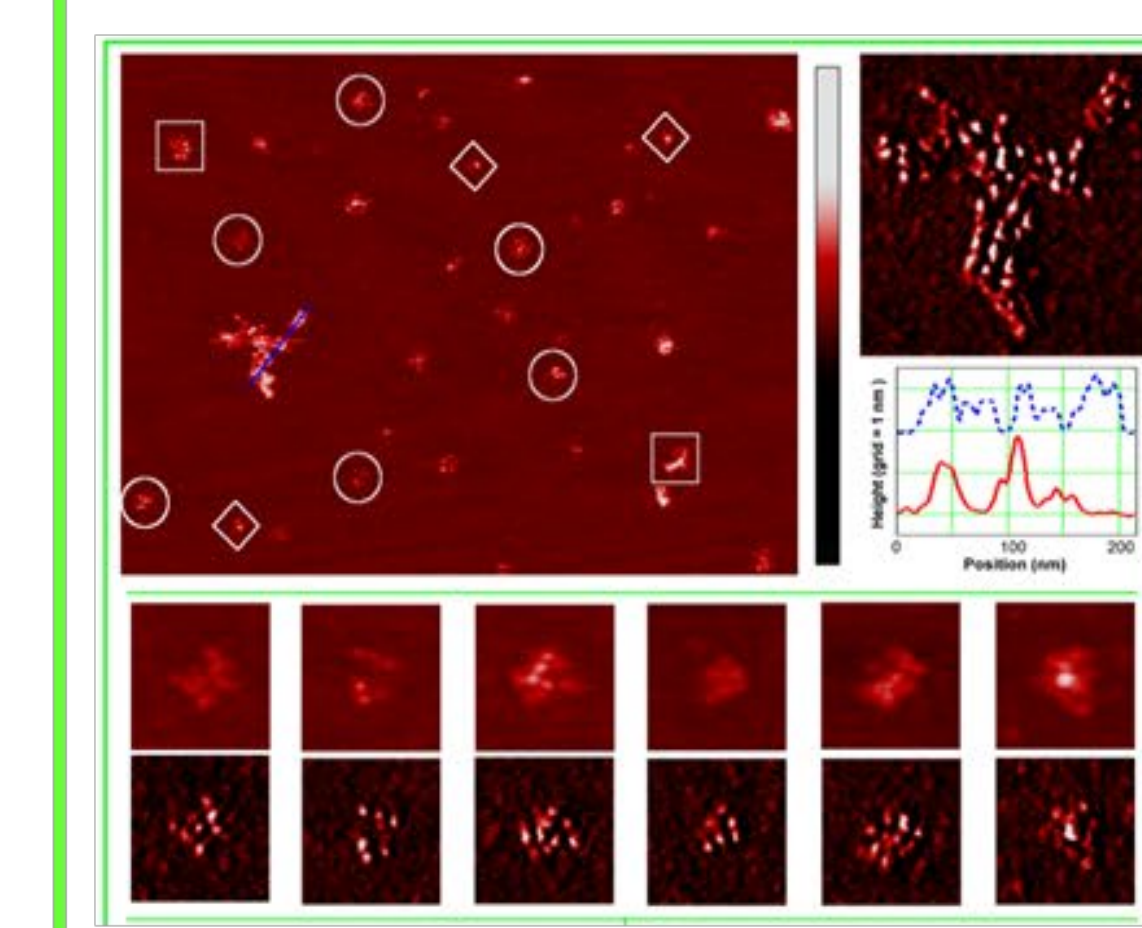


e.g.
time-resolved
in-fluid
Studies:
 $\text{A}\beta_{40}$ dynamical
assembly (2019)

Malaria Vaccine Development & Parasitology



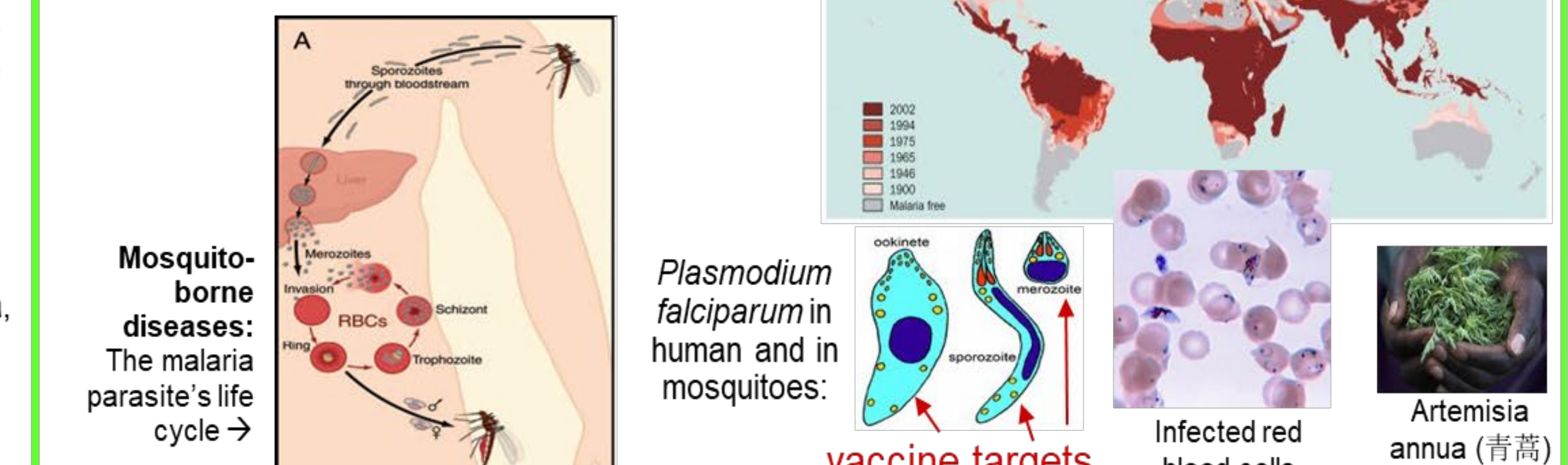
MSP3 Vaccine candidate:
Tsai, CW, PF Duggan, AJ
Jin, NJ MacDonald, S
Kotova, J Lebowitz, DE
Hurt, RL Shimp, L Lambert,
LH Miller, CA Long, A Saul,
DL Narum. *Mol. Biochem.
Parasitol.* 164:45-56 (2009).



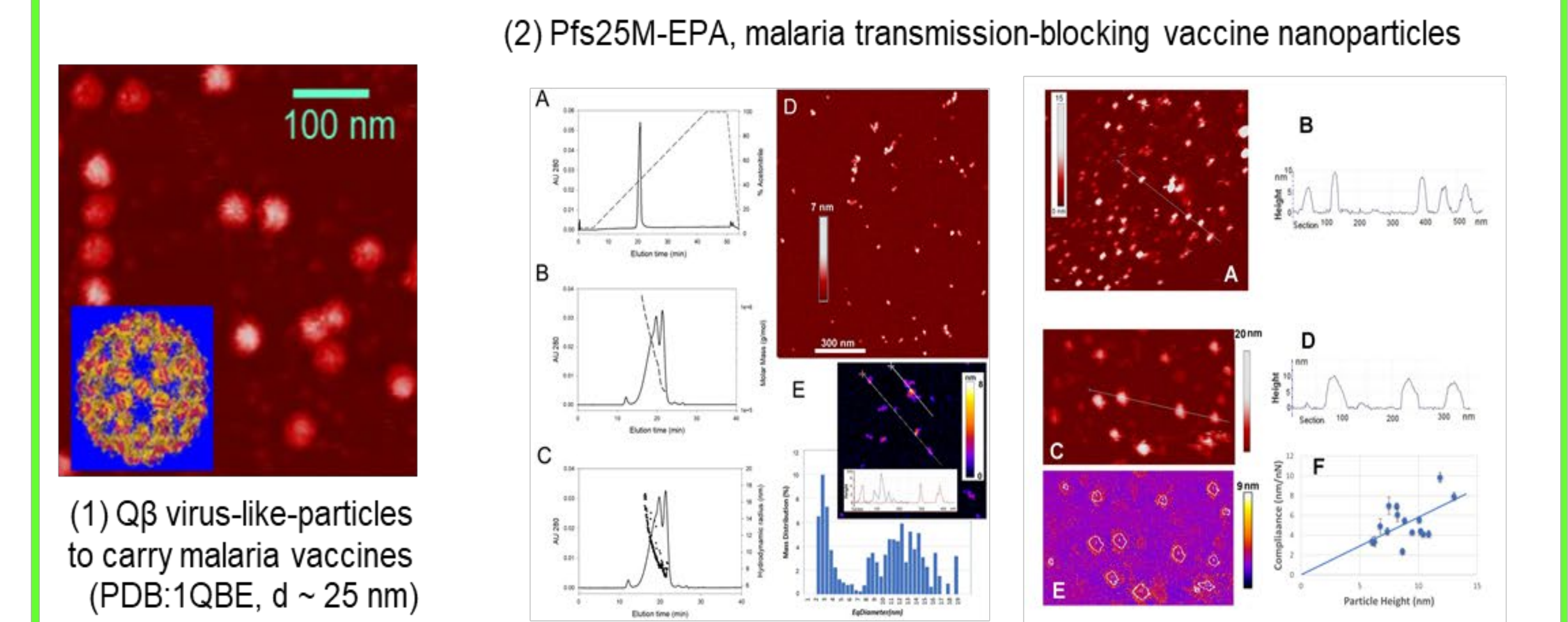
Structure of the *Plasmodium falciparum* Circumsporozoite Protein, a Leading Malaria Vaccine Candidate. Plassmeyer, ML., K. Reiter, RL Shimp, S Kotova, PD Smith, DE Hurt, B House, XY Zou, YL Zhang, M Hickman, O Uchime, R Herrera, V Nguyen, J Glen, J Lebowitz, AJ Jin, LH Miller, NJ MacDonald, YM Wu, DL Narum. *J. Biol. Chem.* 284:26951-63 (2009)

The fight against malaria

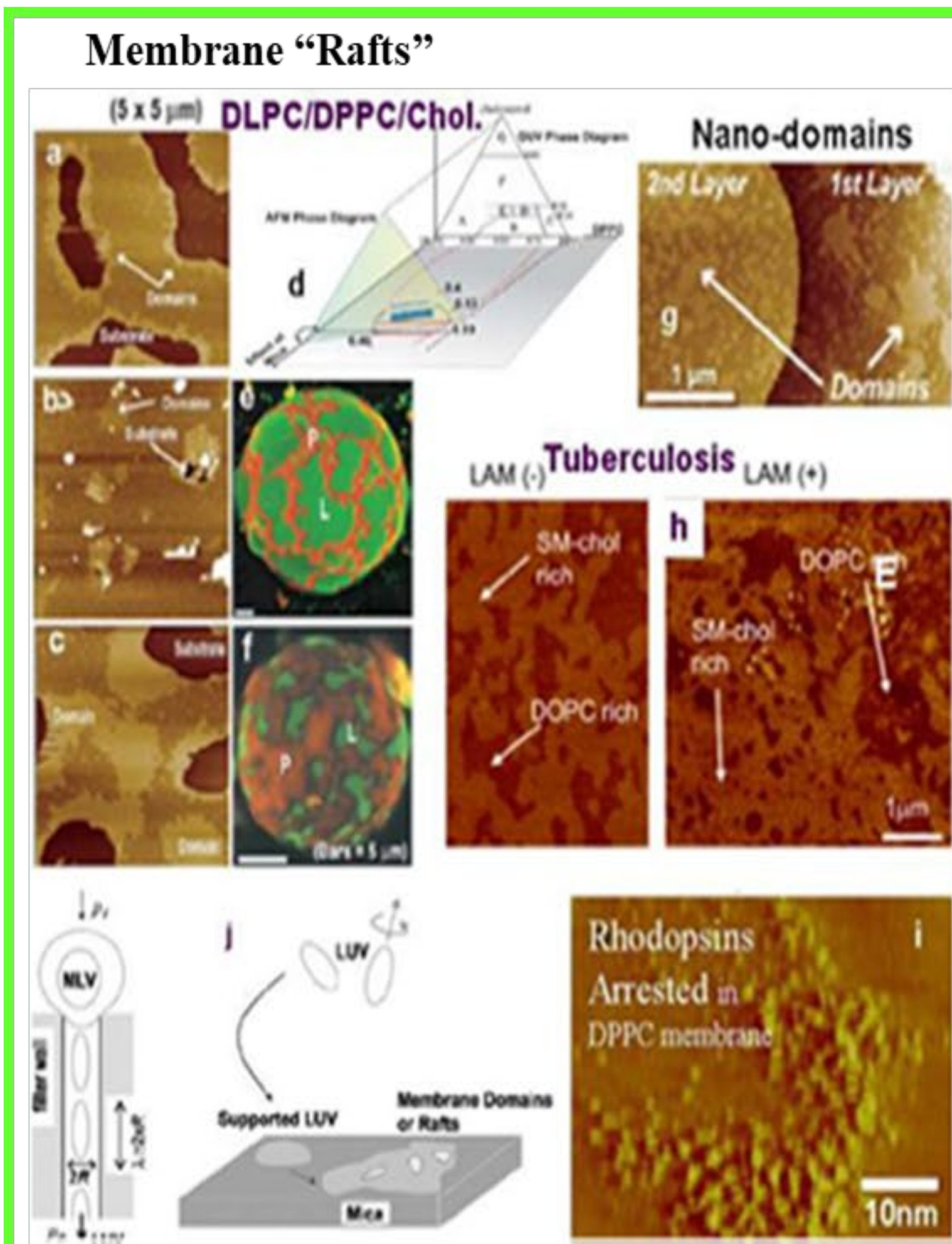
- Kills about half million people (mostly babes) each year
- Collaboration with Dr. David Narum (NIAID) & large team



Many additional malaria vaccine candidates and potential vaccine carriers (ongoing)

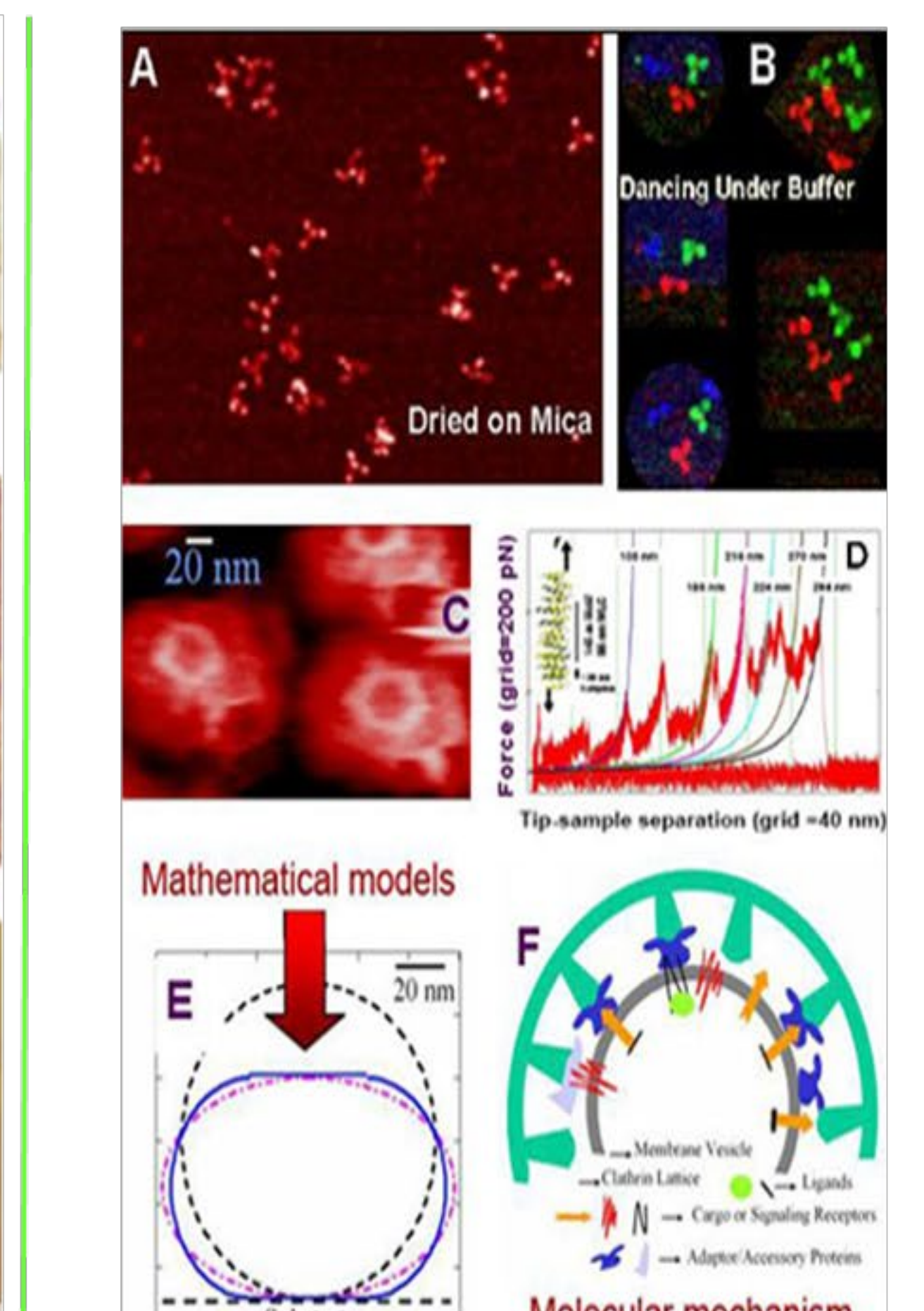


Biomembranes, Endocytosis/Exocytosis, Clathrin/CCV, Biophysics

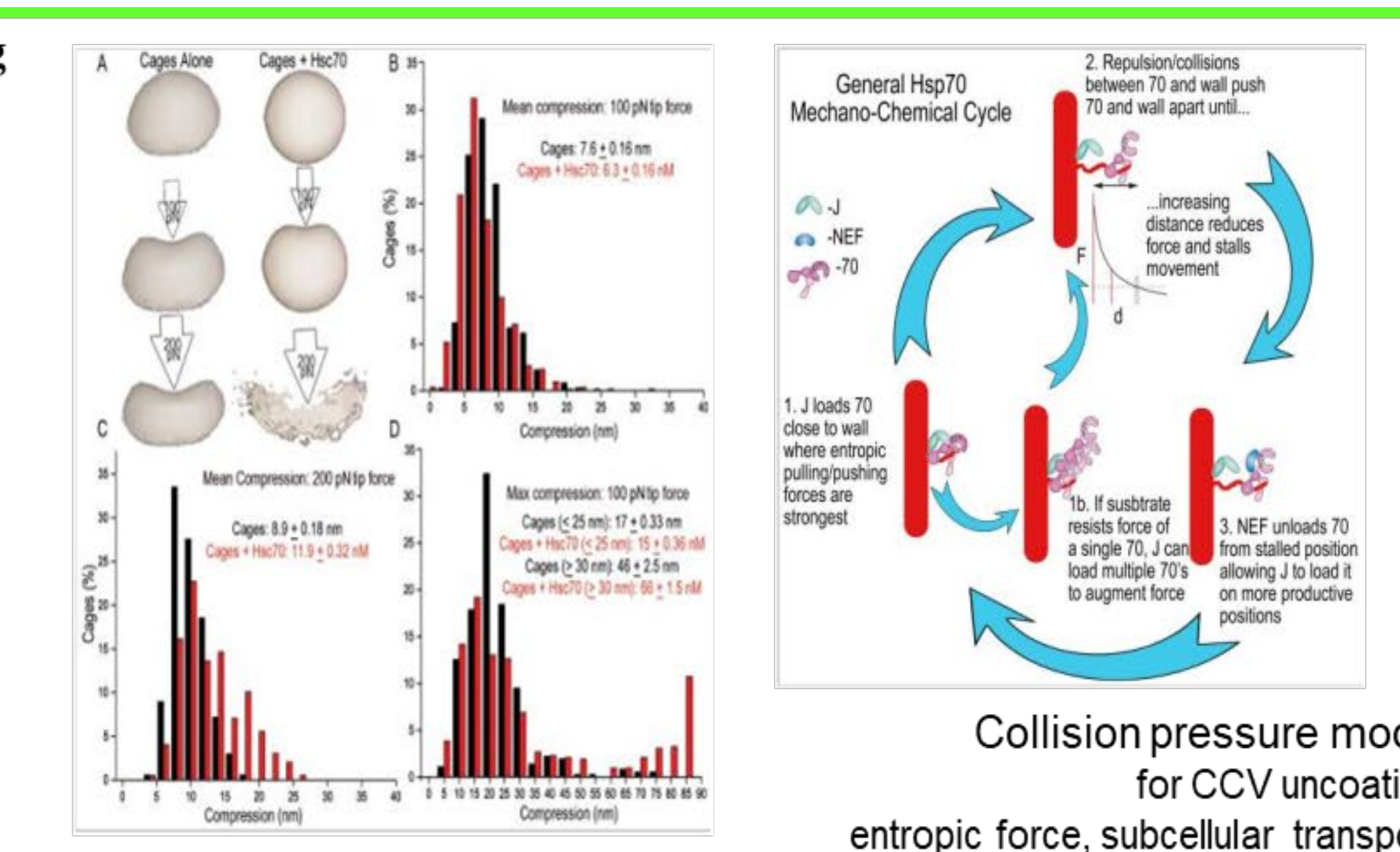


e.g. (1) Tokumasu F, Jin AJ, Feigenson GW and Dvorak JA. *Biophys J*, 84: 2609-2618 (2003). (2) D. Huster, AJ Jin, K Arnold, and K Gawrisch. *Biophys. J.* 73:855-64 (1997). (3) AJ Jin, M Edidin, R Nossal, NL Gershfeld. *Biochem.* 38 (40), 13275-8 (1999).

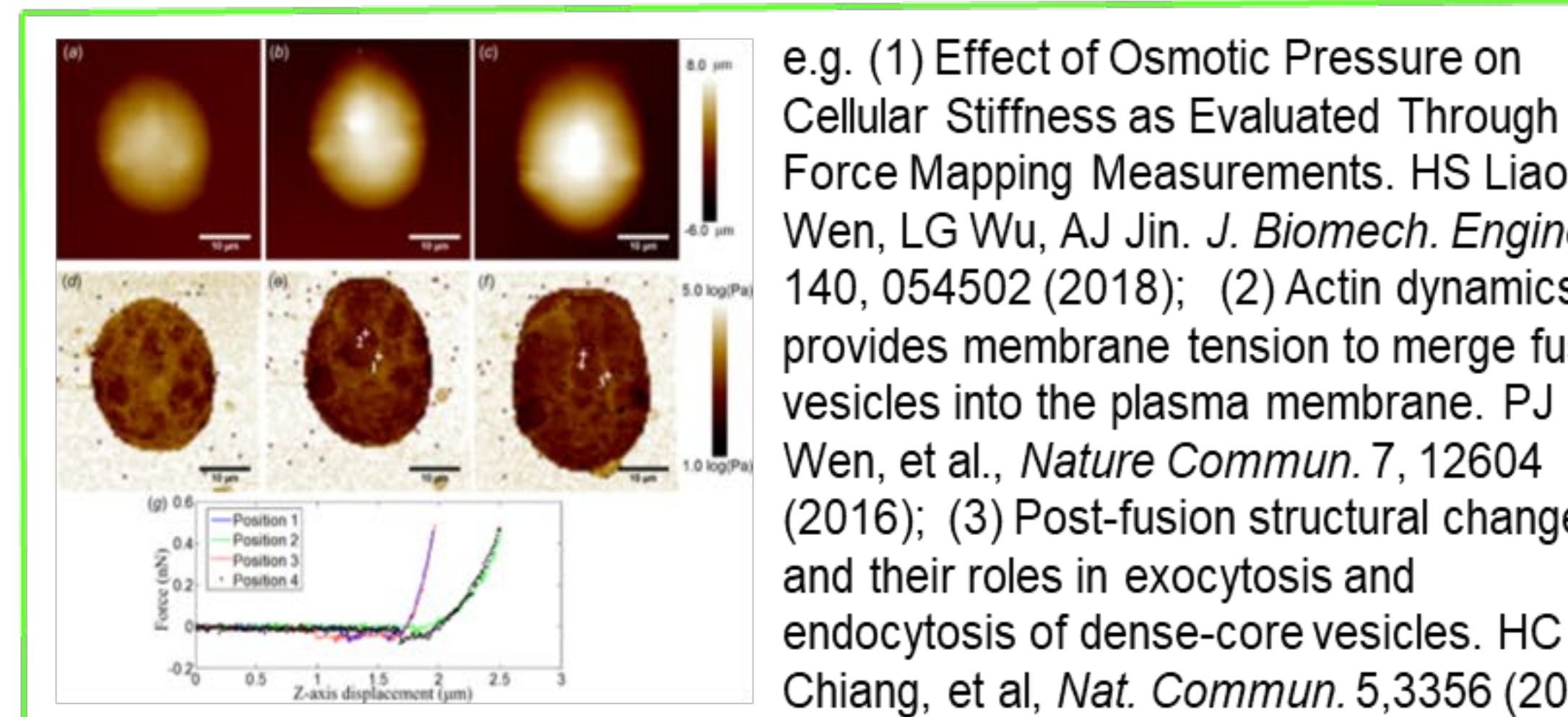
Dancing Triskelia & Subcellular Trafficking



e.g. (1) Kotova S, Prasad K, Smith PD, Lafer EM, Nossal RJ, and Jin AJ. *FEBS Lett* 584: 44-8 (2010); (2) Measuring the elasticity of clathrin-coated vesicles via atomic force microscopy. AJ Jin, K Prasad, PD Smith, EM Lafer, R Nossal. *Biophys. J.* 90 (9), 3333-44 (2006)



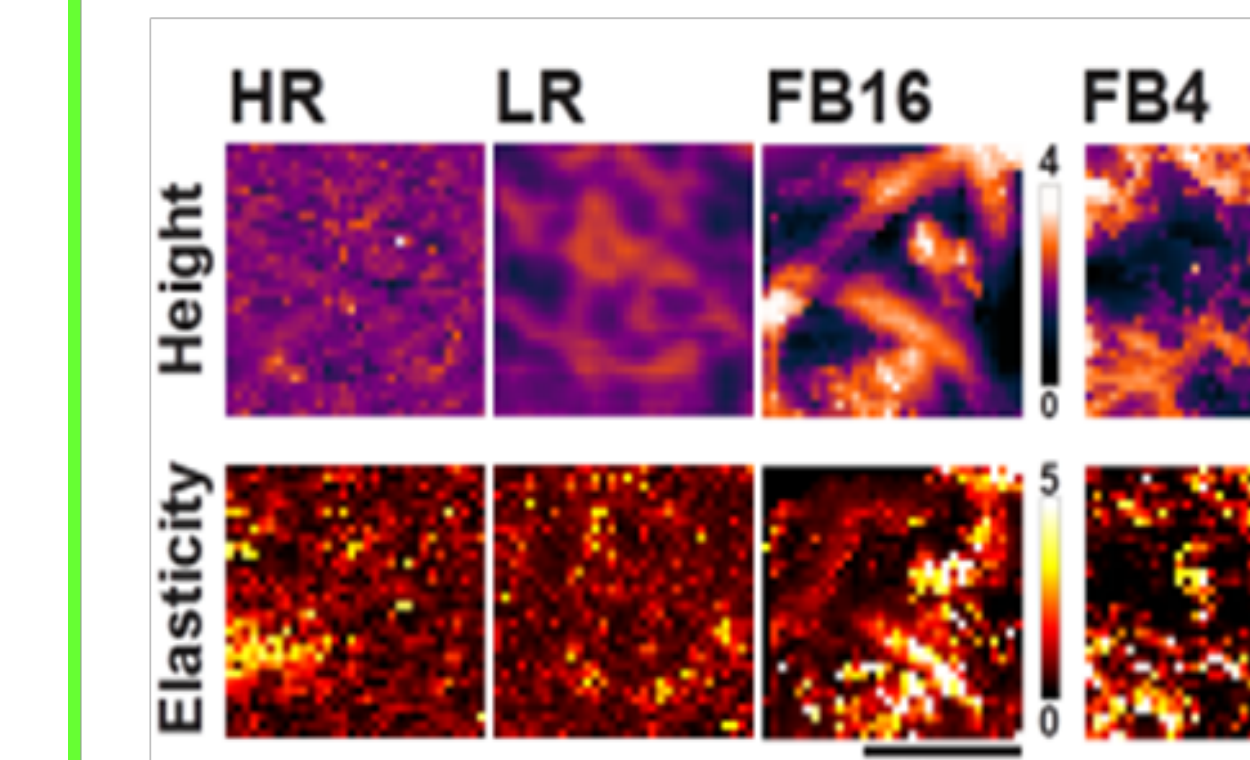
From "Clathrin-coat disassembly illuminates the mechanisms of Hsp70 force generation." Sousa R, Liao HS, Cuéllar J, Jin S, Valpuesta JM, Jin AJ, Lafer EM. *Nat. Struct. Mol. Biol.*, 2016 Sep 23(9):821-9



e.g. (1) Effect of Osmotic Pressure on Cellular Stiffness as Evaluated Through Force Mapping Measurements. HS Liao, PJ Wen, LG Wu, AJ Jin. *J. Biomech. Engineer.* 140, 054502 (2018); (2) Actin dynamics provides membrane tension to merge fusing vesicles into the plasma membrane. PJ Wen, et al., *Nature Commun.* 7, 12604 (2016); (3) Post-fusion structural changes and their roles in exocytosis and endocytosis of dense-core vesicles. HC Chiang, et al., *Nat. Commun.* 5, 3356 (2014)

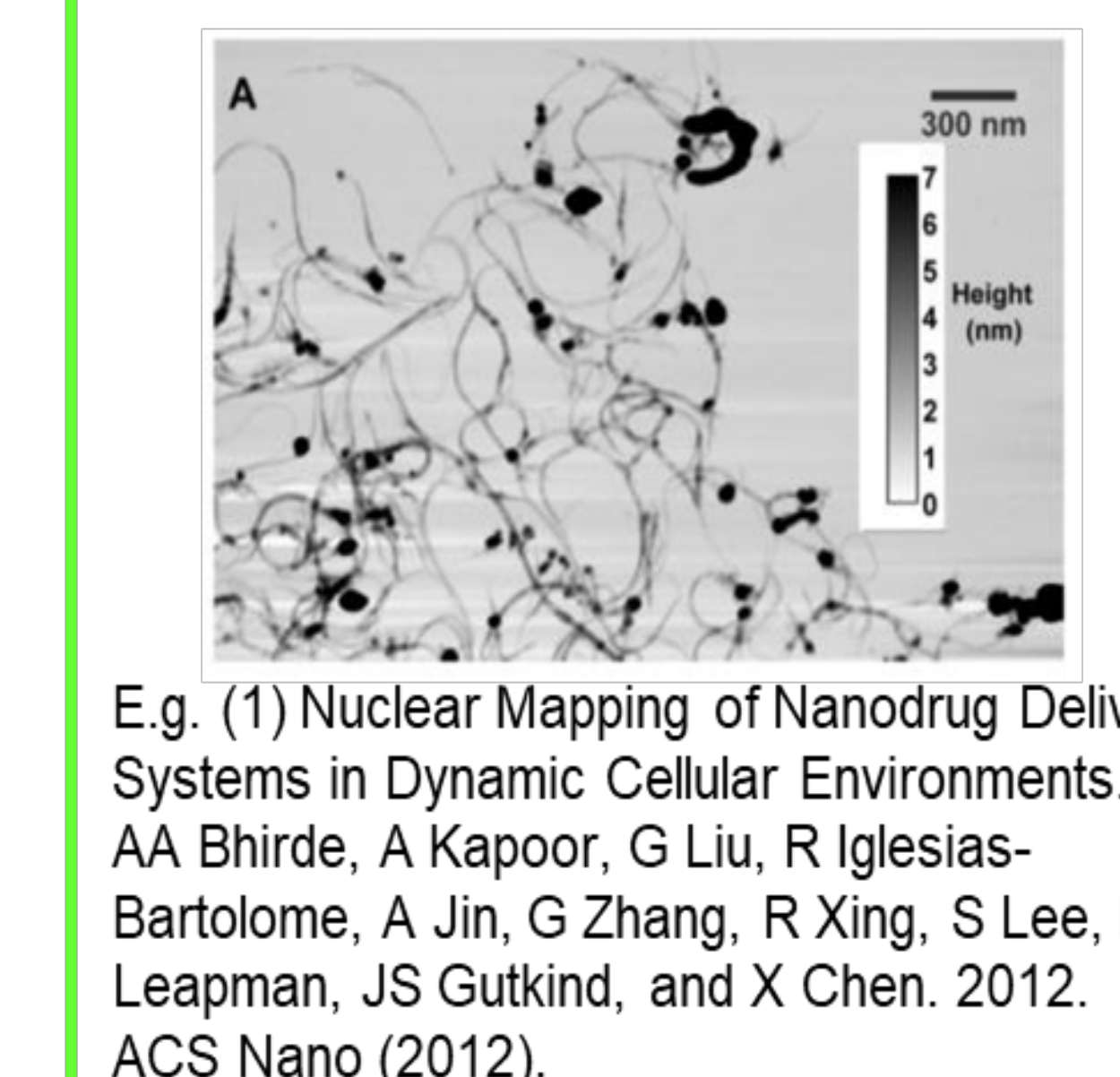
Nanomedicine Development, Biopolymers/ECM, Cellular Studies

Mechanosensing & MechanoBiology:

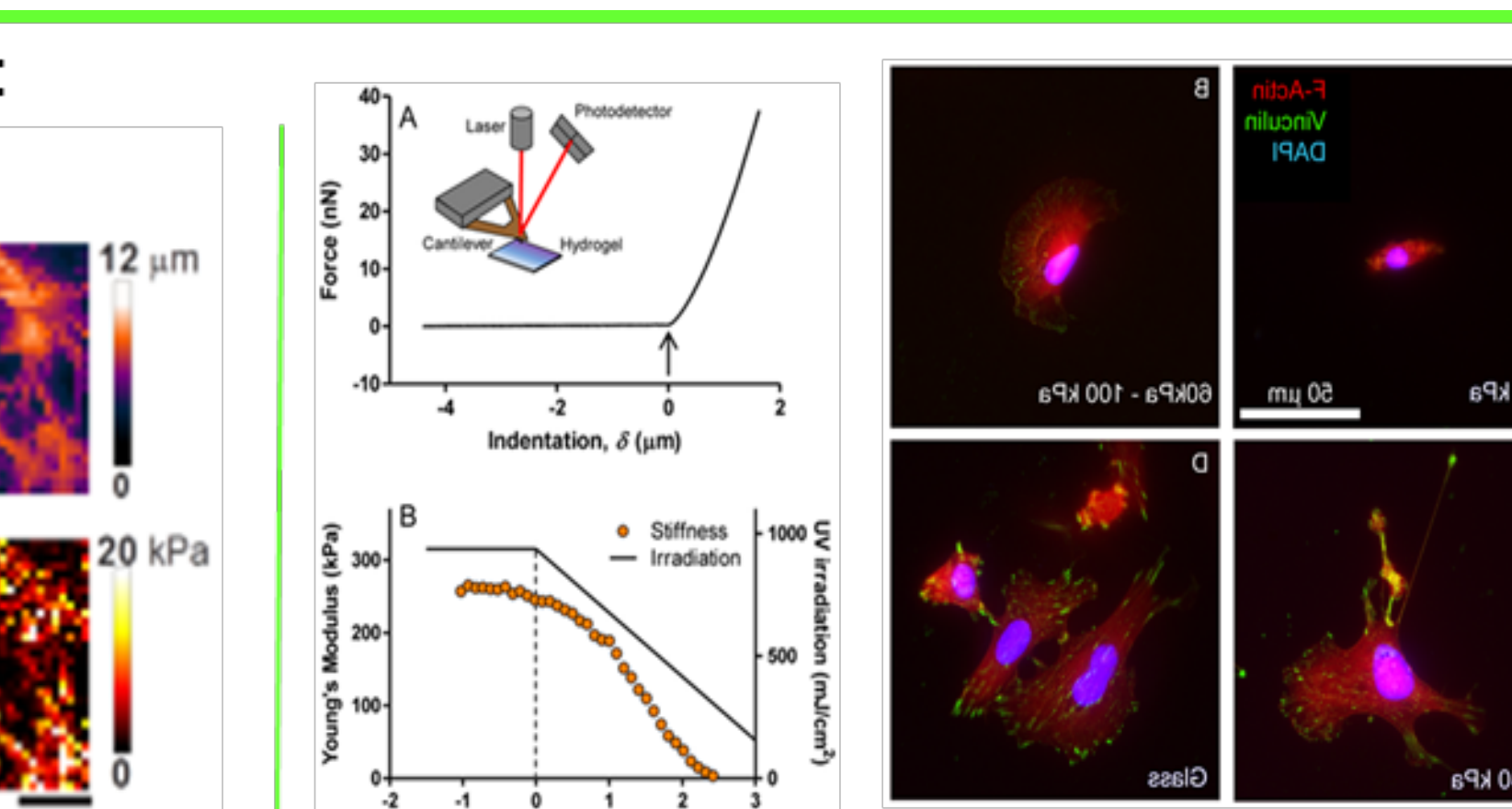


(1) Local 3D matrix microenvironment regulates cell migration through spatiotemporal dynamics of contractility-dependent adhesions. AD Doyle, N Carvajal, A Jin, K Matsumoto, KM Yamada. *Nature Commun.* 6, 8720 (2015)

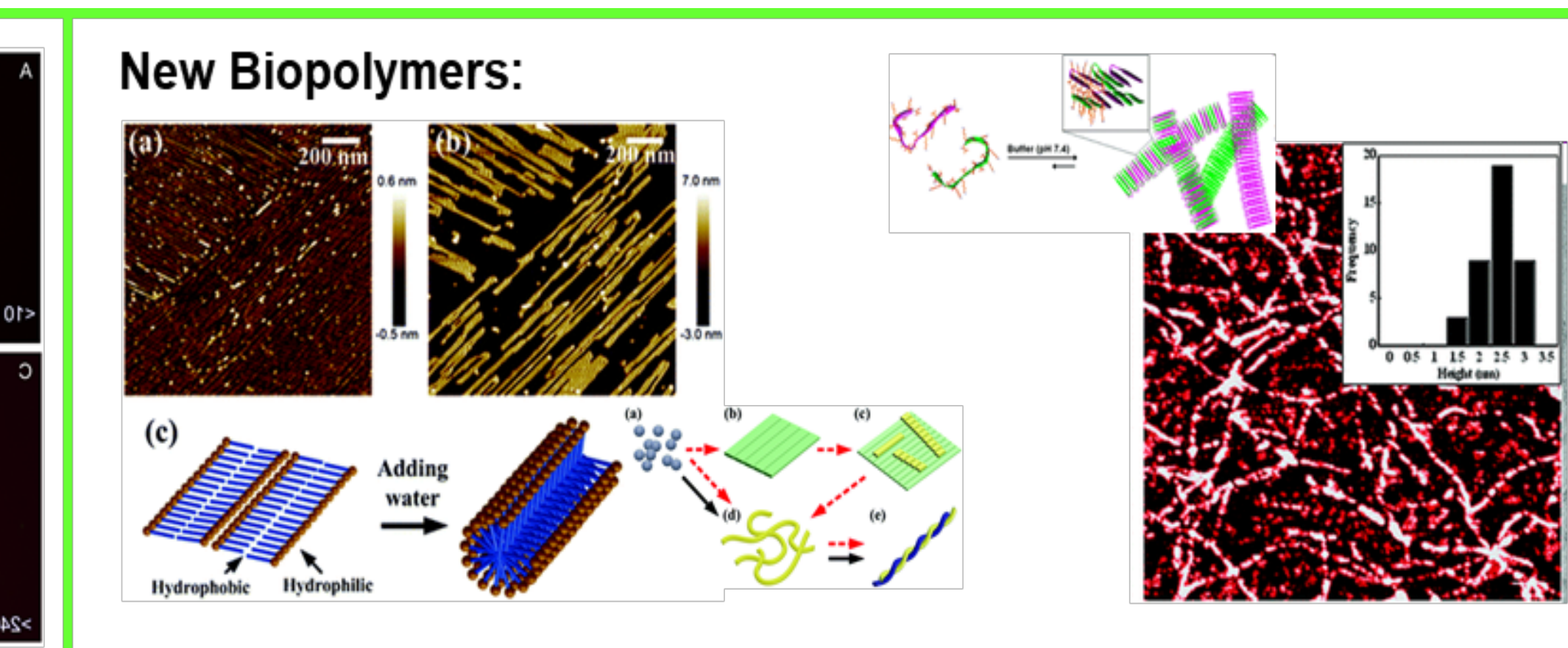
Developing Nanomedicine/theranostics:



E.g. (1) Nuclear Mapping of Nanodrug Delivery Systems in Dynamic Cellular Environments. AA Bhird, A Kapoor, G Liu, R Iglesias-Bartolome, A Jin, G Zhang, R Xing, S Lee, RD Leapman, JS Gutkind, and X Chen. 2012. *ACS Nano* (2012).

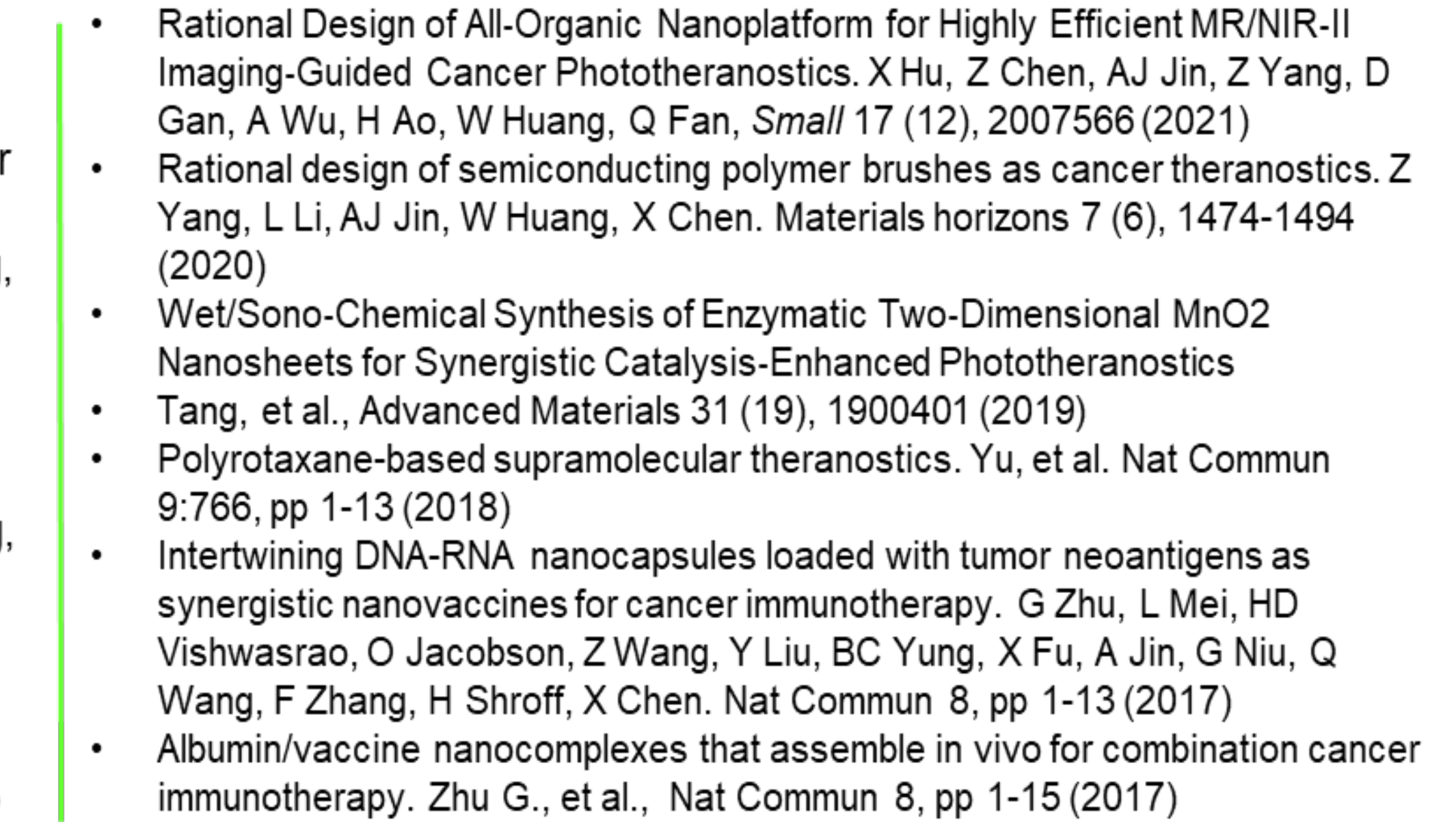


(2) Cell migration in 2D: Fabrication of hydrogels with steep stiffness gradients for studying cell mechanical response. Sunyer R, Jin AJ, Nossal R, Sackett DL, PLoS One. 2012



e.g. (left) Self-assembly mechanisms of nanofibers from peptide amphiphiles in solution and on substrate surfaces. HS Liao, J Lin, Y Liu, P Huang, A Jin, X Chen *Nanoscale* 8 (31), 14814-14820 (2016); (right) Enhanced Mechanical Rigidity of Hydrogels Formed from Enantiomeric Peptide Assemblies. Nagy, KJ, MC Giano, A Jin, DJ Pochan, and JP Schneider. *J. Am. Chem. Soc.* 133: 14975-77 (2011)

New Biopolymers:



(3) More Examples

- Rational Design of All-Organic Nanopatform for Highly Efficient MR/NIR-II Imaging-Guided Cancer Phototheranostics. X Hu, Z Chen, AJ Jin, Z Yang, D Gan, A Wu, H Ao, W Huang, Q Fan, *Small* 17 (12), 2007566 (2021)
- Rational design of semiconducting polymer brushes as cancer theranostics. Z Yang, L Li, AJ Jin, W Huang, X Chen. *Materials horizons* 7 (6), 1474-1494 (2020)
- Wet/Sono-Chemical Synthesis of Enzymatic Two-Dimensional MnO2 Nanosheets for Synergistic Catalysis-Enhanced Phototheranostics
- Tang, et al., *Advanced Materials* 31 (19), 1900401 (2019)
- Polyrotaxane-based supramolecular theranostics. Yu, et al. *Nat Commun* 9:766, pp 1-13 (2018)
- Intertwining DNA-RNA nanocapsules loaded with tumor neoantigens as synergistic nanovaccines for cancer immunotherapy. G Zhu, L Mei, HD Vishwasrao, O Jacobson, Z Wang, Y Liu, BC Yung, X Fu, A Jin, G Niu, Q Wang, F Zhang, H Shroff, X Chen. *Nat Commun* 8, pp 1-13 (2017)
- Albumin/vaccine nanocomplexes that assemble in vivo for combination cancer immunotherapy. Zhu G., et al., *Nat Commun* 8, pp 1-15 (2017)