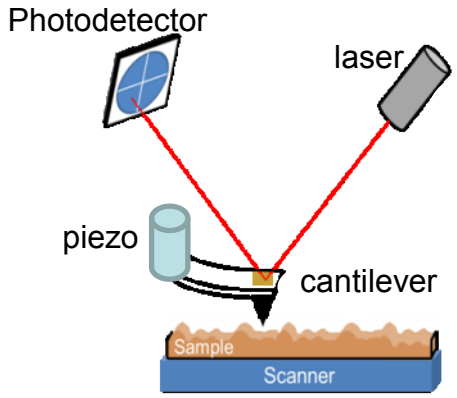
ATOMIC FORCE MICROSCOPY AND BIOMEDICAL APPLICATIONS

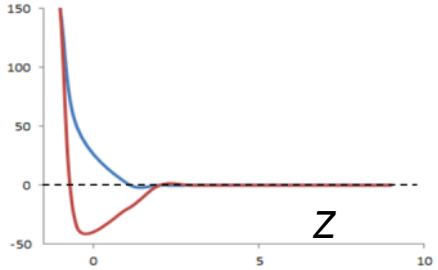
Nanoinstrumentation and Force Spectroscopy Section, Laboratory of Cellular Imaging and Macromolecular Biophysics
NIBIB/NIH

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)

$F(\delta)$



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:

Hertz model

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

Sneddon model

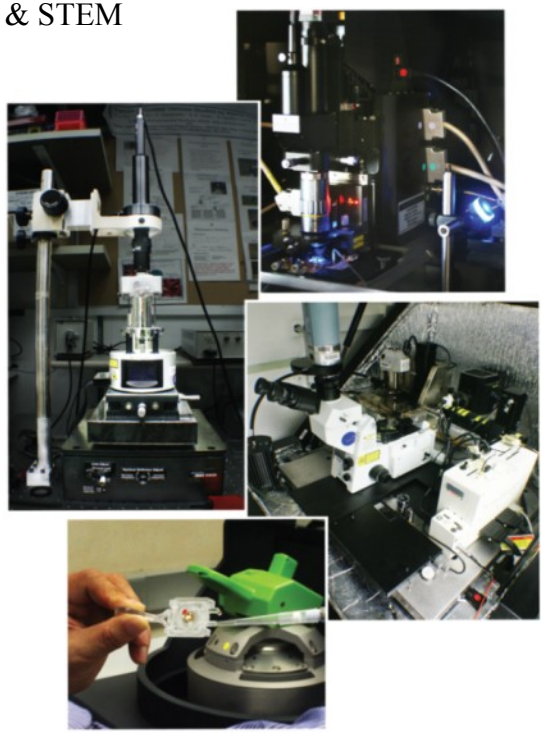
$$F = \frac{2}{\pi}\frac{E}{(1-\upsilon^2)}\tan(\alpha)\delta^2$$

Linear spring constant

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

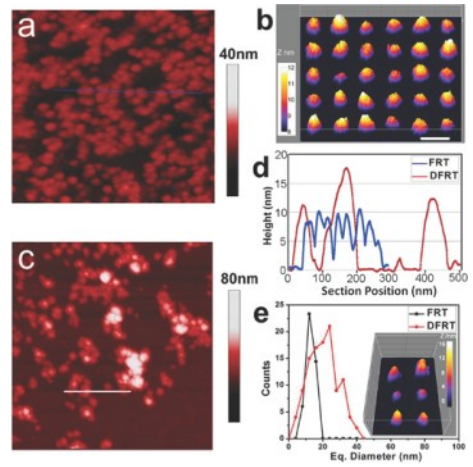
Improving Tools:

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



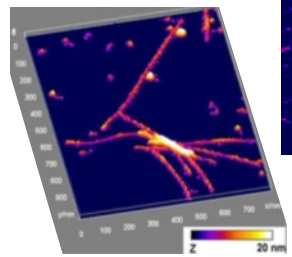
Examples of a large collection of BioAFM platforms at NIBIB/NIH

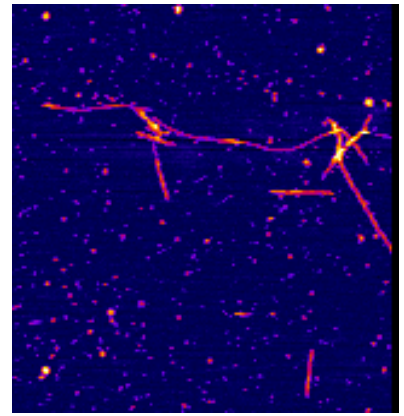
Biomedical Applications



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: $A\beta_{40}$ dynamical assembly (2019)





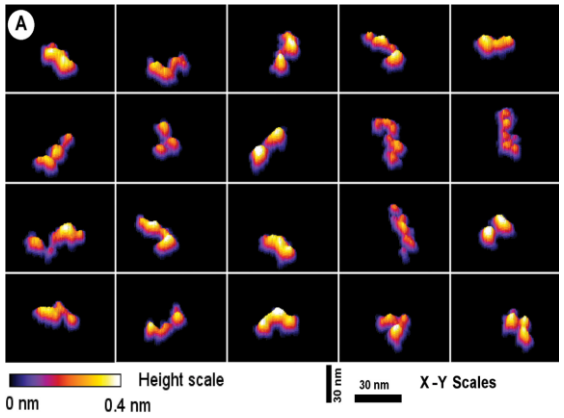
Movie
(9 minutes per frame)

Albert Jin, Ph.D (NFSS/LCIMB/NIBIB)

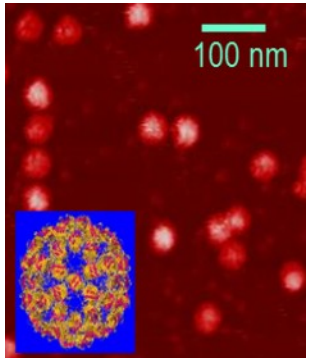
jina@mail.nih.gov

BIOMEDICAL ATOMIC FORCE MICROSCOPY (BioAFM)

Malaria Vaccine Development, Biopolymers, ECM, & Nanomedicine Characterizations



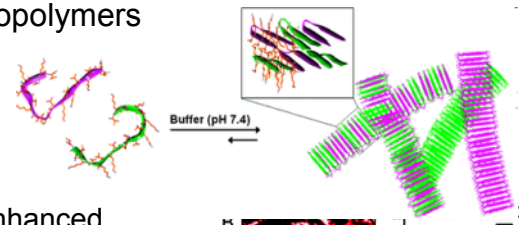
Structure of the **Plasmodium falciparum Circumsporozoite Protein**, a Leading Malaria Vaccine Candidate. Plassmeyer, ML., K. Reiter, RL Shimp, S Kotova, PD Smith, DE Hurt, B House, XY Zou, YL. Zhang, M Hickman, O Uchime, R Herrera, V Nguyen, J Glen, J Lebowitz, AJ Jin, LH Miller, NJ MacDonald, YM Wu,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



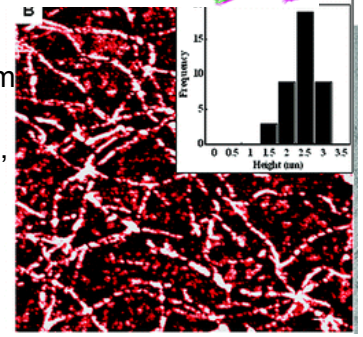
Many additional **malaria vaccine candidates** and **potential vaccine carriers** like Qβ virus-like-particles (PDB:1QBE, d ~ 25 nm)

- MSP3 Study: 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).
- MTRAP and PTRAMP Study: Uchime, O, R Herrera, K Reiter, S Kotova, J Shimp, RL, K Miura, D Jones, J Lebowitz, X Ambroggio, DE Hurt, AJ Jin, LH Miller, and DL Narum. Eukaryotic Cell 11:615-25 (2012).
- Native CSP study: R Herrera, C Anderson, K Kumar, A Molina-Cruz, V Nguyen, M Burkhardt, K Reiter, R Shimp, RF Howard, P Srinivasan, MJ Nold, D Ragheb, L Shi, M DeCotiis, J Aebig, L Lambert, KM Rausch, O Muratova, A Jin, SG Reed, P Sinnis, C Barillas-Mury, PE Duffy, NJ MacDonald, DL Narum. Infection & Immunity 83 (10), 3771-80 (2015)

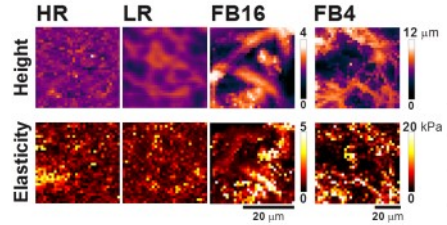
New Biopolymers



e.g. 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)



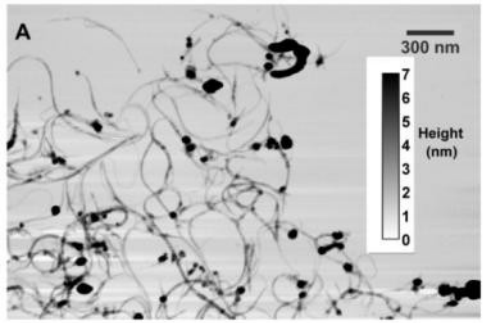
Mechanosensing & MechanoBiology:



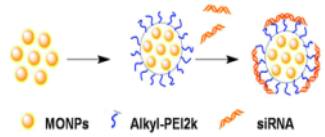
(1) Local 3D matrix microenvironment regulates cell migration through spatiotemporal dynamics of contractility-dependent adhesions. AD Doyle, N Carvajal, A Jin, K Matsumoto, KM Yamada. *Nature Commun*.6, 8720 (2015)

(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

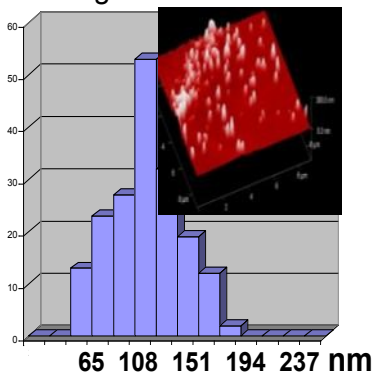
Many Developing Nano-theranostics, e.g.:



(1) Nuclear Mapping of Nanodrug Delivery Systems in Dynamic Cellular Environments. AA Bhirde, 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).



NP height



(2) Functional MnO nanoclusters for efficient siRNA delivery. R Xing, G Liu, Q Quan, A Bhirde, G Zhang, A Jin, LH Bryant, A Zhang, A. Liang, HS Eden, YL Hou, X Chen. *Chem. Commun*.47: 12152-4 (2011).

Latest Examples: (1) Zhu G., et al., *Nat Commun* 8:1482 (2017); 2) Zhu G., et al., *Nat Commun* 8:1954 (2017); (3) Yu, et al. *Nat Commun* 9 (1), 766 (2018)

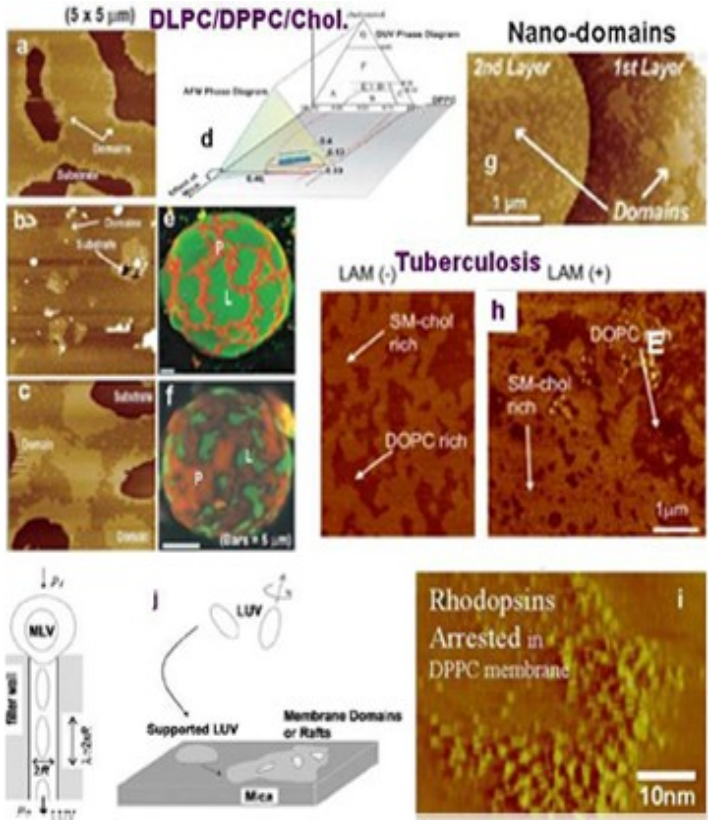
Albert Jin, Ph.D (NFSS/LCIMB/NIBIB)

jina@mail.nih.gov

BIOMEDICAL ATOMIC FORCE MICROSCOPY (BioAFM)

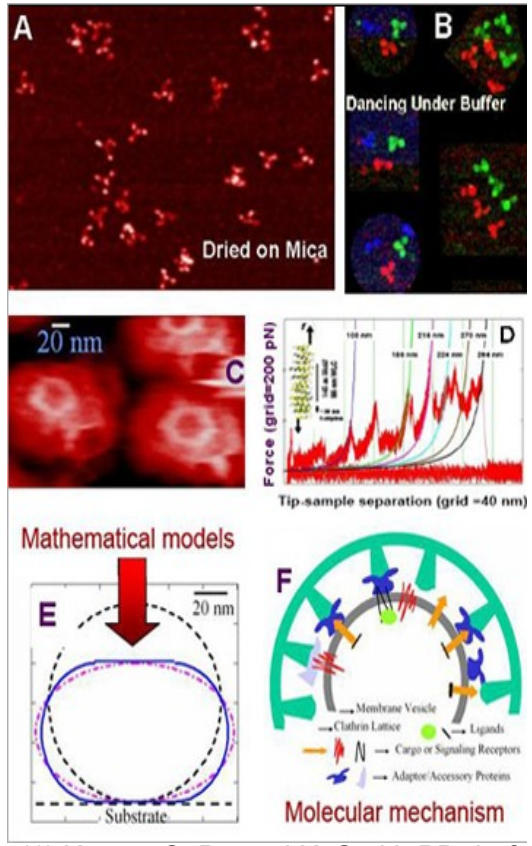
Biomembranes, Clathrin/CCV, Endocytosis/Exocytosis, Biophysics

Membrane "Rafts"

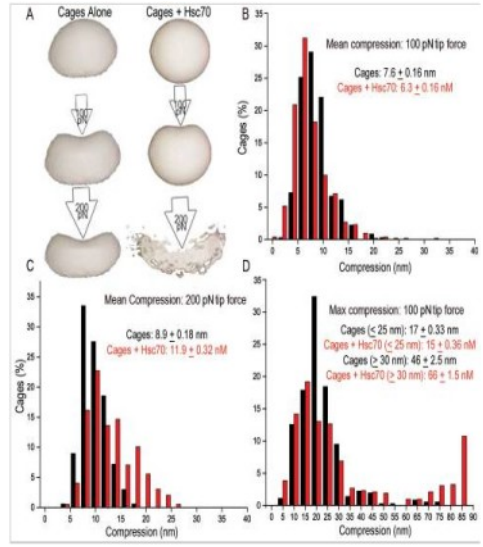


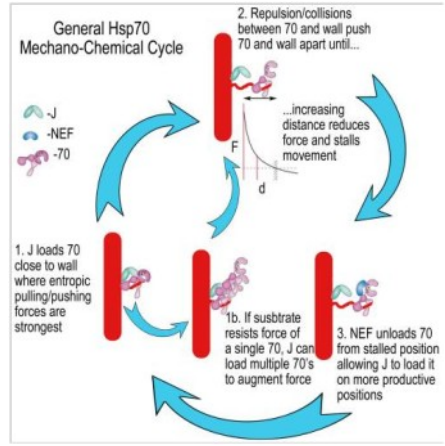
e.g. (1) Tokumasu F, Jin AJ, Feigenson GW and **Dvorak JA**. Biophys J, 84: 2609-2618 (2003). (2) D. Huster, AJ Jin, K Arnold, and K Gawrisch. Biophys. J. 73:855-64 (1997). (3) AJ Jin, M Edidin, R Nossal, NL Gershfeld. Biochem.38 (40), 13275-8 (1999).

Dancing Triskelia & Subcellular Trafficking



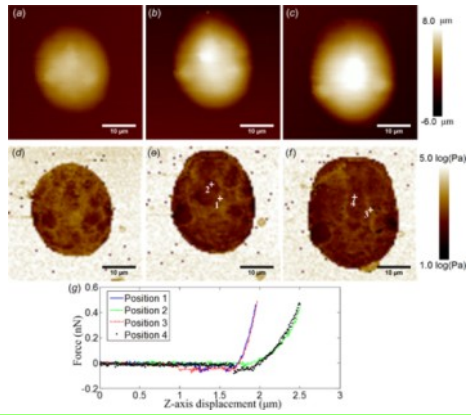
e.g. (1) Kotova S, Prasad K, Smith PD, Lafer EM, Nossal RJ, and Jin AJ. FEBS Lett 584: 44-8 (2010); (2) Measuring the elasticity of clathrin-coated vesicles via atomic force microscopy. AJ Jin, K Prasad, PD Smith, EM Lafer, R Nossal. Biophys. J. 90 (9), 3333-44 (2006)





Collision pressure model
for CCV uncoating,
entropic force, subcellular transport.

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



(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 (5), 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)

Albert Jin, Ph.D (NFSS/LCIMB/NIBIB)

jina@mail.nih.gov