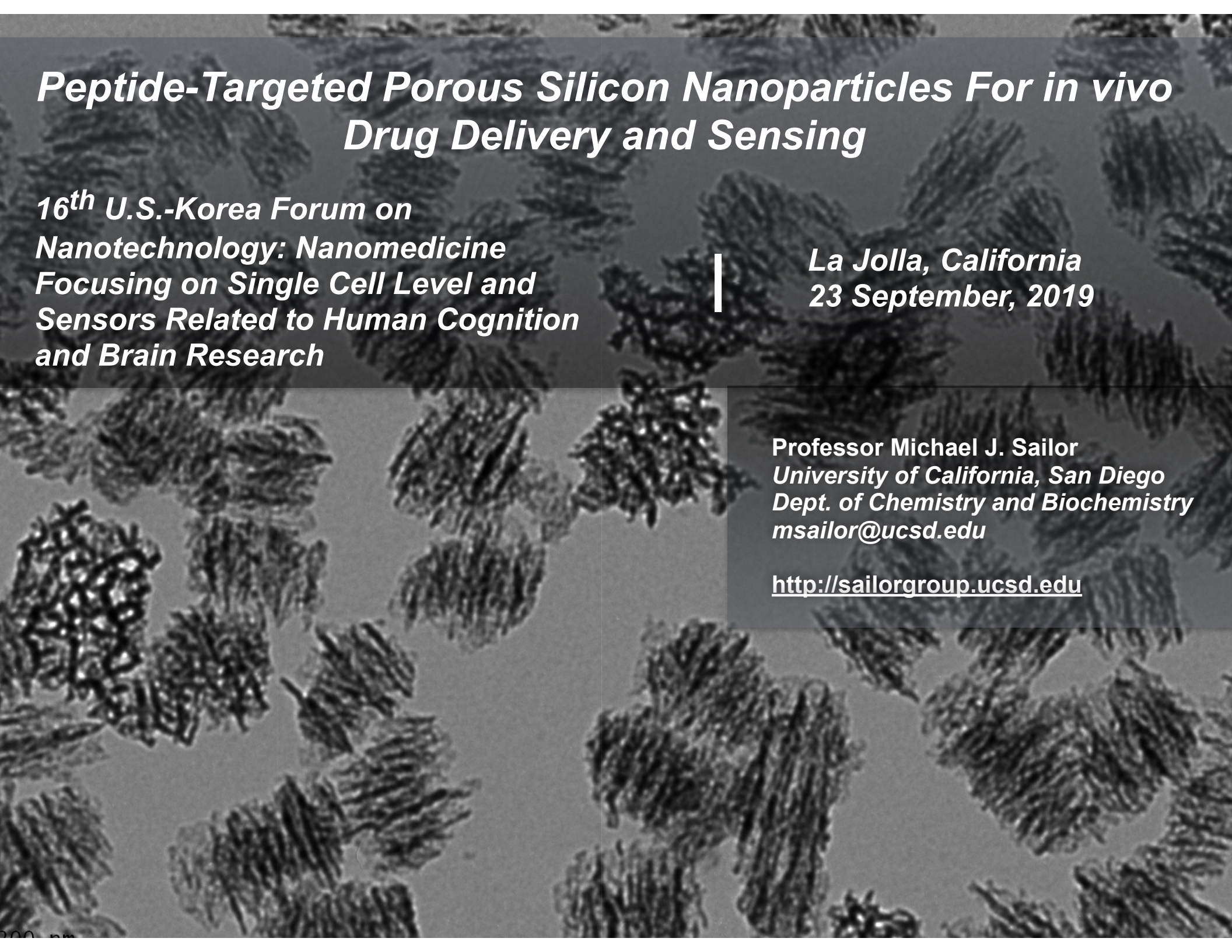
Peptide-Targeted Porous Silicon Nanoparticles For in vivo Drug Delivery and Sensing

16th U.S.-Korea Forum on Nanotechnology: Nanomedicine Focusing on Single Cell Level and Sensors Related to Human Cognition and Brain Research

La Jolla, California
23 September, 2019



Professor Michael J. Sailor
University of California, San Diego
Dept. of Chemistry and Biochemistry
msailor@ucsd.edu

http://sailorgroup.ucsd.edu

Conflict disclosure

MJS is a consultant, and/or scientific founder, and/or is a member of the board of directors, and/or has an equity interest in the following companies. The research findings included in this presentation may not necessarily relate to their interests. The terms of these arrangements have been reviewed and approved by the University of California, San Diego in accordance with its conflict of interest policies.

Prof Sailor is a compensated “High-Level Talent” at the Key Laboratory of Organosilicon Chemistry and Material Technology, Hangzhou Normal University and a Guest Professor at Zhejiang University.

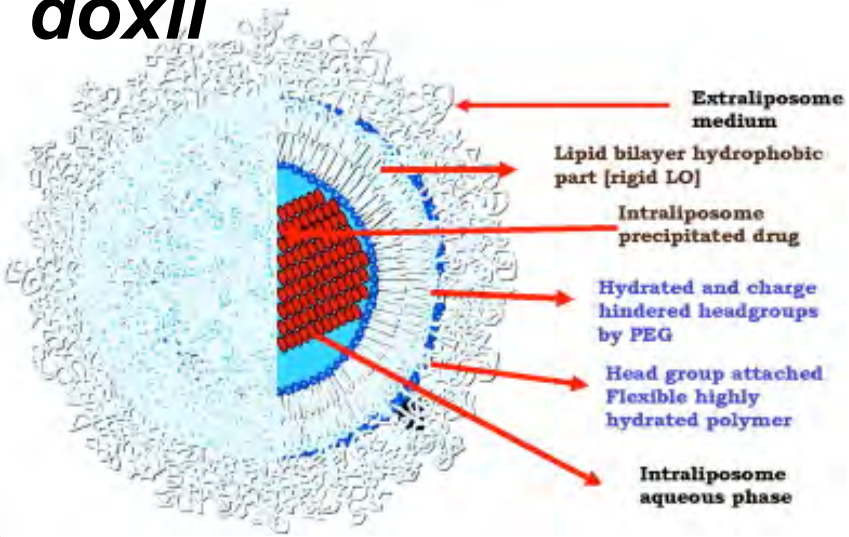
US-Korea Collaborations

Prof. Kyo Han Ahn (Chemistry, POSTECH)
Prof. Byoung-Yong Chang (Chemistry, Pukyong National University)
Prof. Wonyoul Choi (Metal and Materials Engineering, Kangnung-Wonju National University)
Prof Jinmyoung Joo (Biomedical Engineering, Ulsan Institute of Science and Technology)
Prof. Dokyoung Kim (Anatomy and Neurobiology, Medicine, Kyung Hee University)
Prof. Ki Hean Kim (Mechanical Engineering, Biosciences and Biotechnology, POSTECH)
Dr. Young Sub Kwon (Clinical Assistant Professor, Neurosurgery, Ilsan Hospital)
Prof. Sanghwa Lee (Chemistry, Gachon University)
Prof. Yoonkey Nam (Neural Engineering Lab, Dept of Bio and Brain Engineering, KAIST)
Prof Ji-Ho Park (Bio and Brain Engineering, KAIST)
Prof. Honglae Sohn (Chemistry, Chosun University, Korea)

*__Active collaboration__ (published in last 3 years)
**Past collaboration

Nanoparticles in medicine

doxil

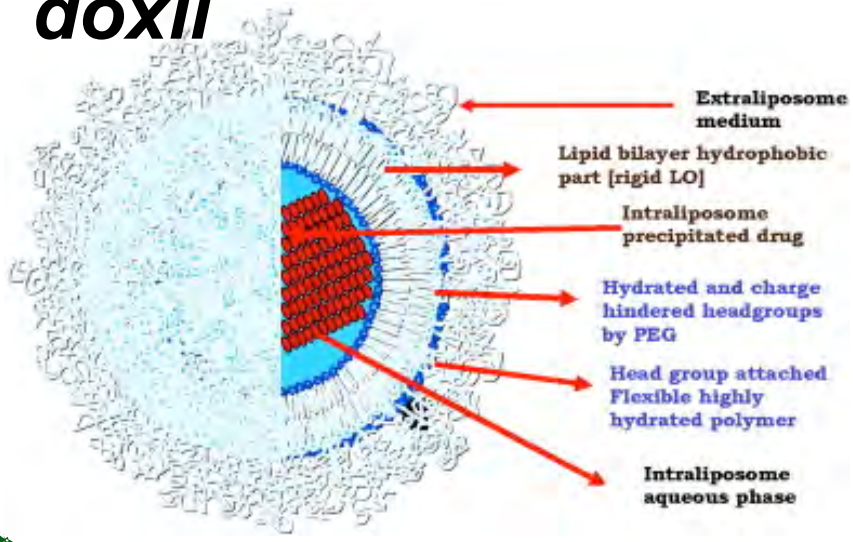


- **Improve efficacy of existing drugs**
- **Rescue "failed" drugs**
- **Enable emerging gene therapies (siRNA, mRNA, CRISPRa/i)**
- **Provide imaging modalities**

Barenholz, Y., Doxil (R) - The first FDA-approved nano-drug: Lessons learned. *J. Control Release* **2012,** *160*, 117.

Nanoparticles in medicine

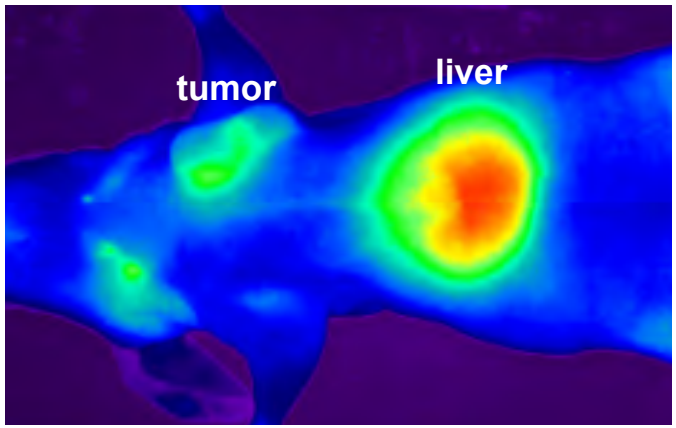
doxil



- **Improve efficacy of existing drugs**
- **Rescue "failed" drugs**
- **Enable emerging gene therapies (siRNA, mRNA, CRISPRa/i)**
- **Provide imaging modalities**

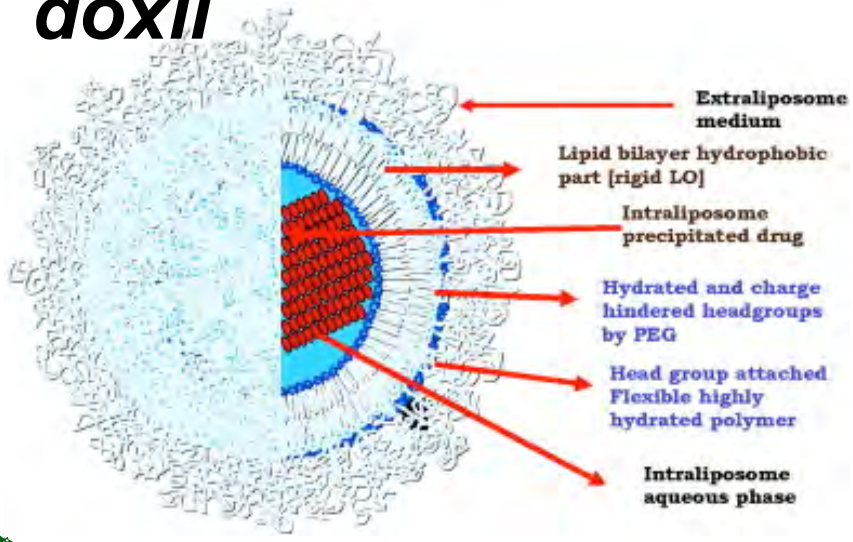
Barenholz, Y., Doxil (R) - The first FDA-approved nano-drug: Lessons learned. *J. Control Release* **2012,** *160*, 117.

- ***Nanoparticles can selectively target diseased tissues***



Nanoparticles in medicine

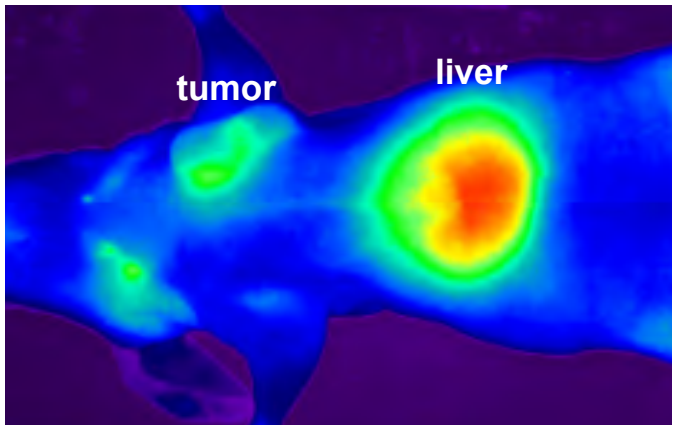
doxil



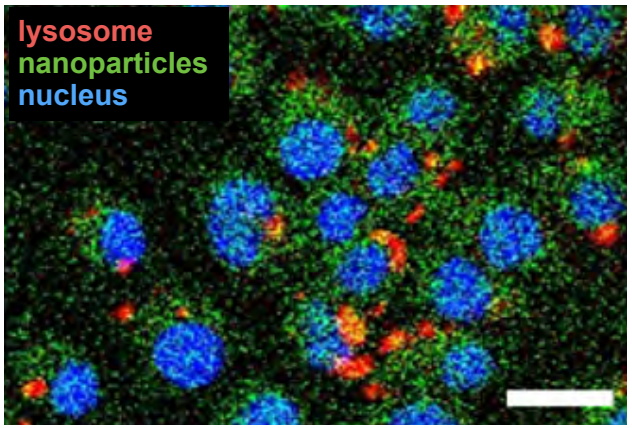
- **Improve efficacy of existing drugs**
- **Rescue "failed" drugs**
- **Enable emerging gene therapies (siRNA, mRNA, CRISPRa/i)**
- **Provide imaging modalities**

Barenholz, Y., Doxil (R) - The first FDA-approved nano-drug: Lessons learned. *J. Control Release* **2012,** *160*, 117.

- ***Nanoparticles can selectively target diseased tissues***

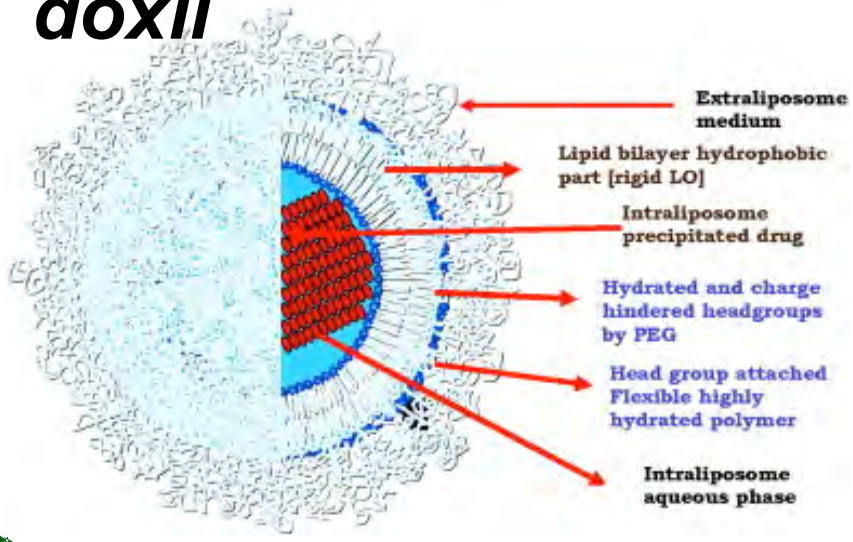


- ***Nanoparticles can reach privileged cellular compartments***



Nanoparticles in medicine

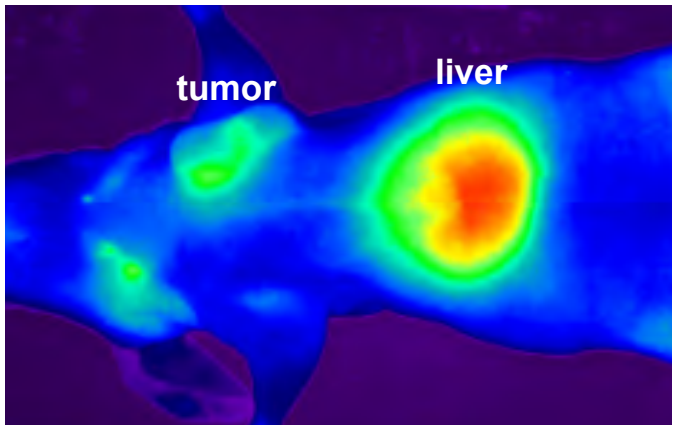
doxil



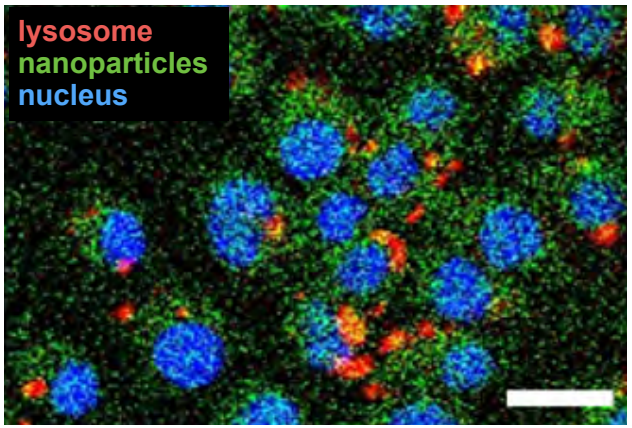
- **Improve efficacy of existing drugs**
- **Rescue "failed" drugs**
- **Enable emerging gene therapies (siRNA, mRNA, CRISPRa/i)**
- **Provide imaging modalities**

Barenholz, Y., Doxil (R) - The first FDA-approved nano-drug: Lessons learned. *J. Control Release* **2012,** *160*, 117.

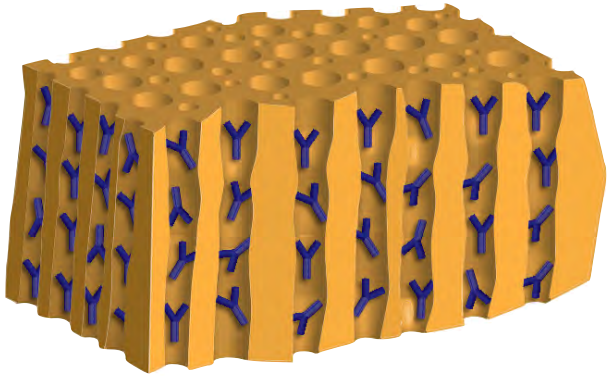
- ***Nanoparticles can selectively target diseased tissues***



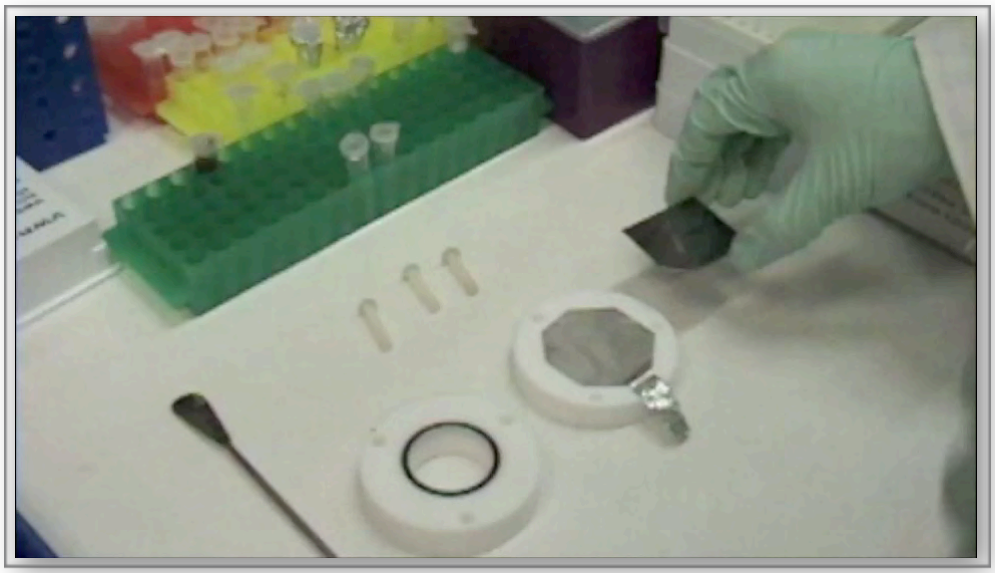
- ***Nanoparticles can reach privileged cellular compartments***



- ***Nanoparticles can Improve in vivo stability of a drug or imaging agent***

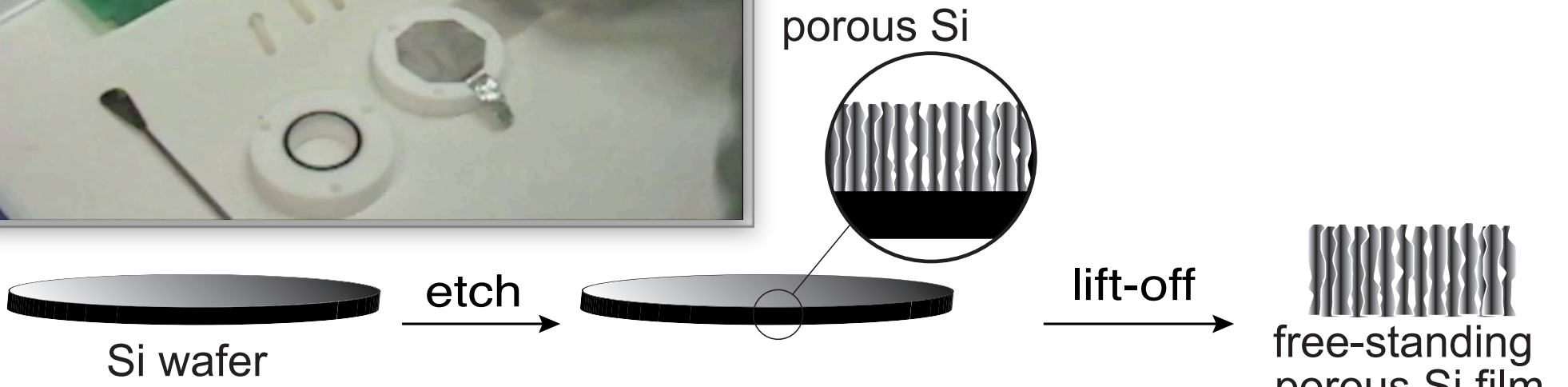


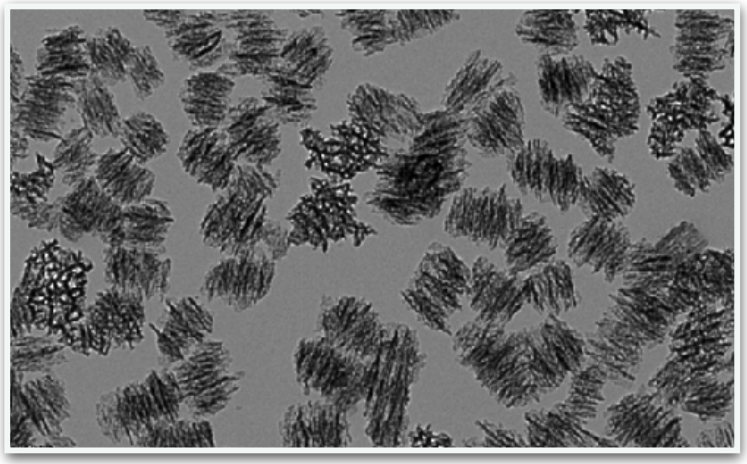
Synthesis of porous Si particles



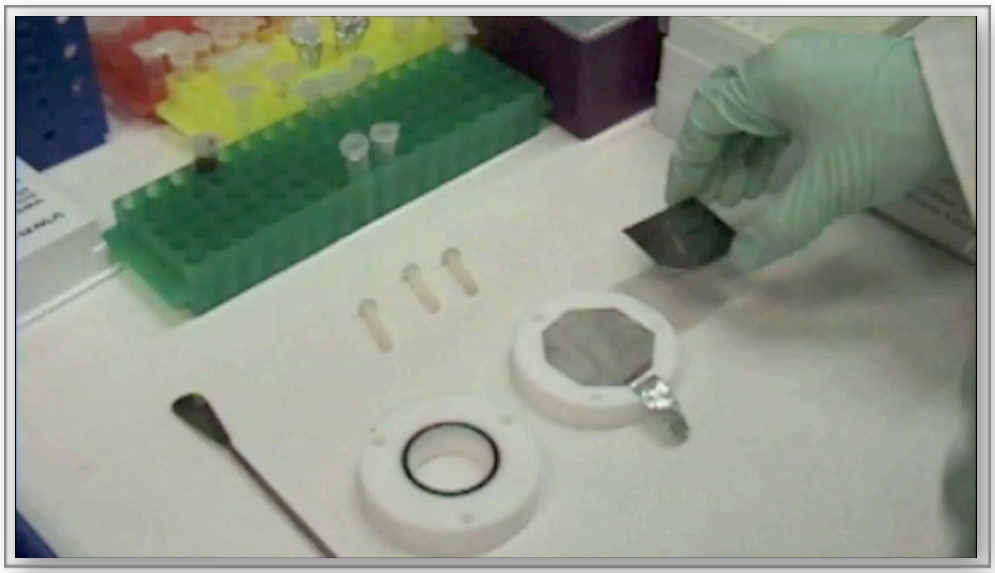
REVIEW: Sailor, M. J.; Wu, E. C., *Adv. Funct. Mater.* **2009**, *19*, 3195–3208.

$$Si + 2h^+ + 6HF \rightarrow SiF_6^{2-} + H_2 + 4H^+$$



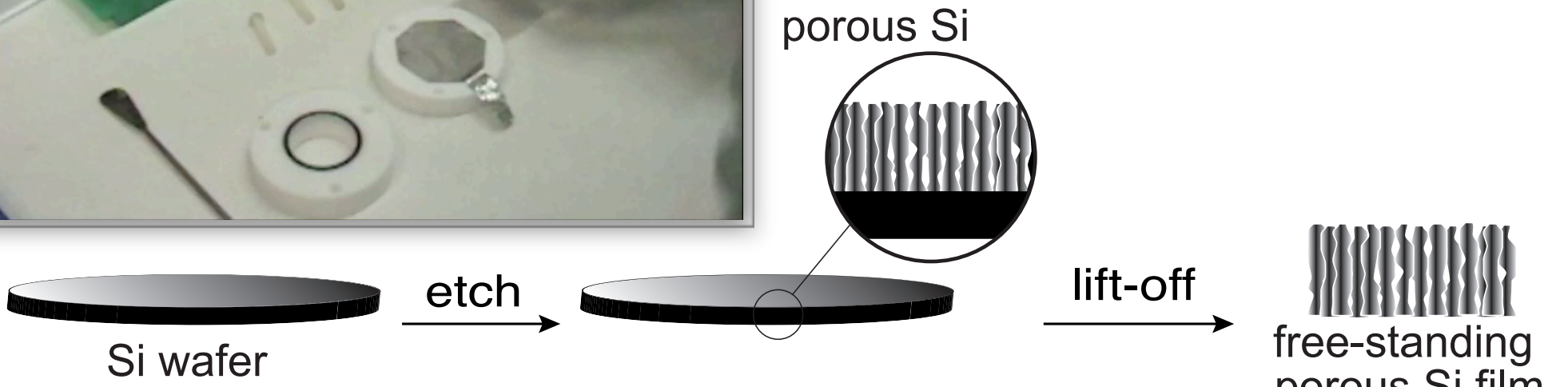


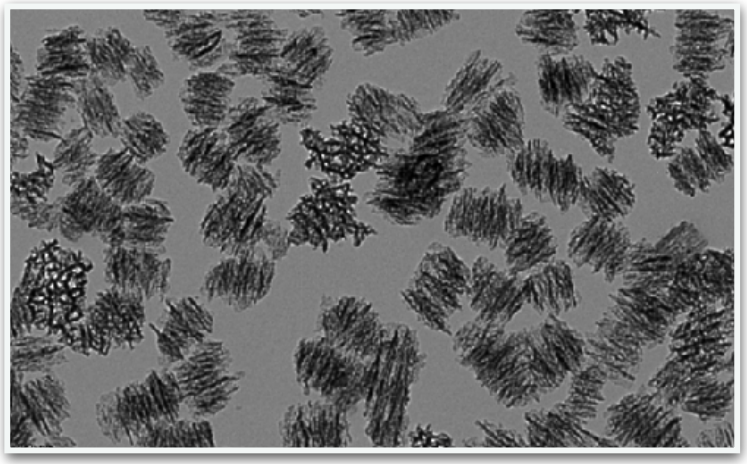
Synthesis of porous Si particles



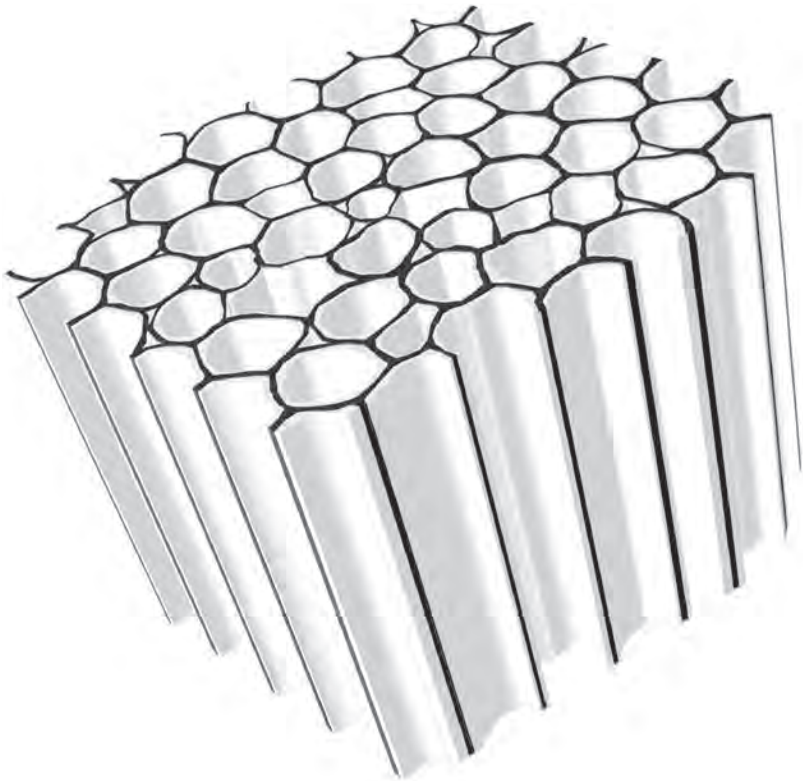
REVIEW: Sailor, M. J.; Wu, E. C., *Adv. Funct. Mater.* **2009**, *19*, 3195–3208.

$$Si + 2h^+ + 6HF \rightarrow SiF_6^{2-} + H_2 + 4H^+$$

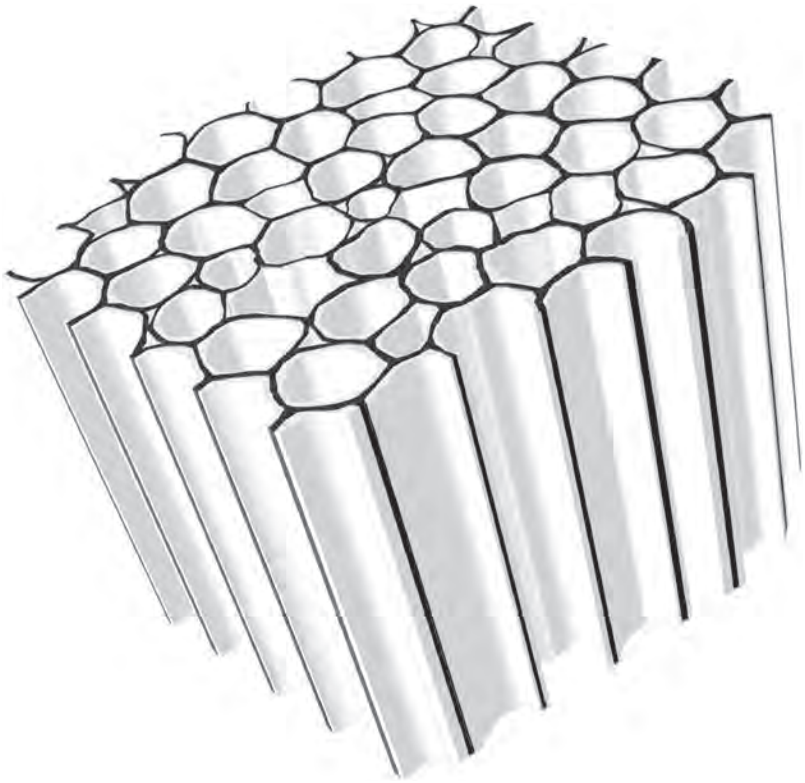


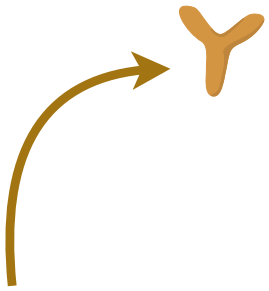


Preparation of silicon nanoparticles



Preparation of silicon nanoparticles

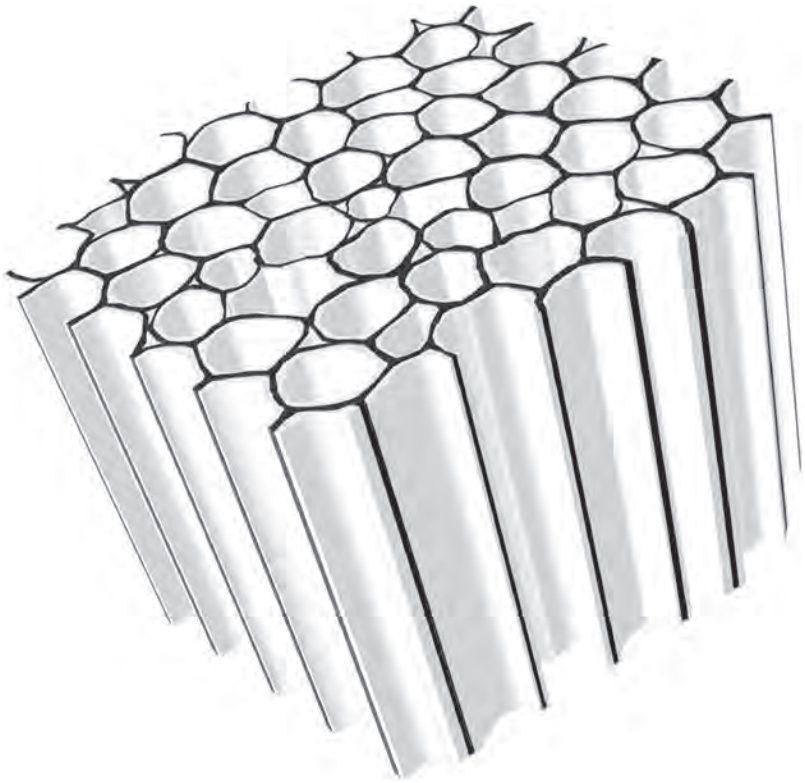




accommodate drug

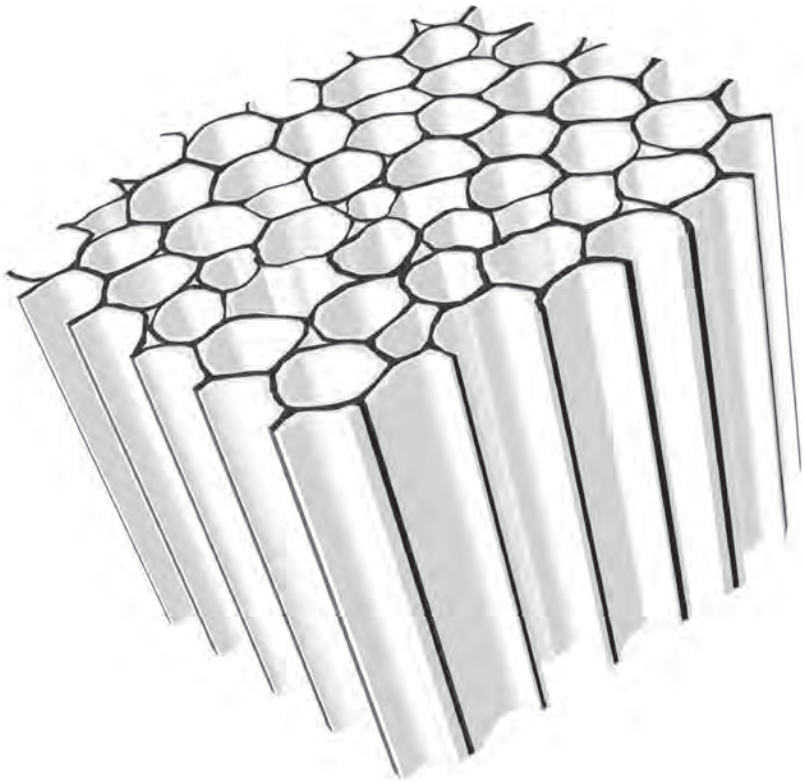
Preparation of silicon nanoparticles

accommodate drug



Preparation of silicon nanoparticles

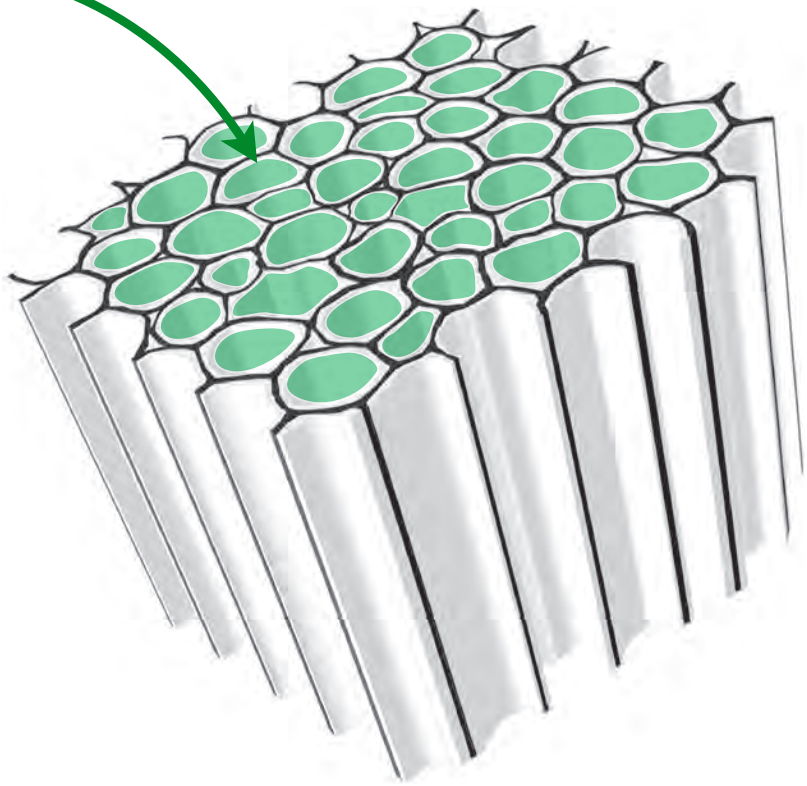
accommodate drug



Preparation of silicon nanoparticles

accommodate drug

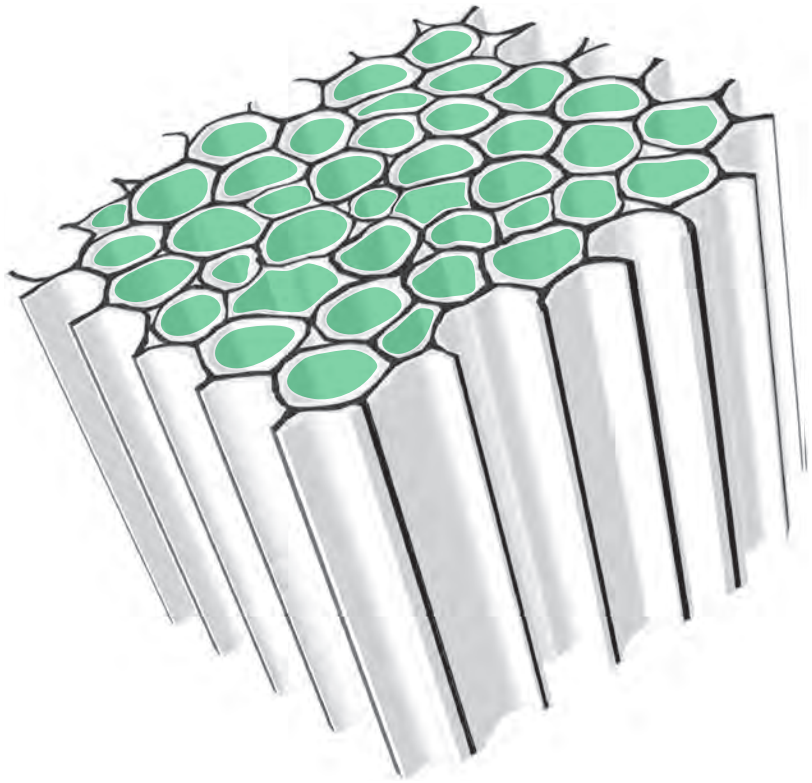
seal pores



Preparation of silicon nanoparticles

accommodate drug

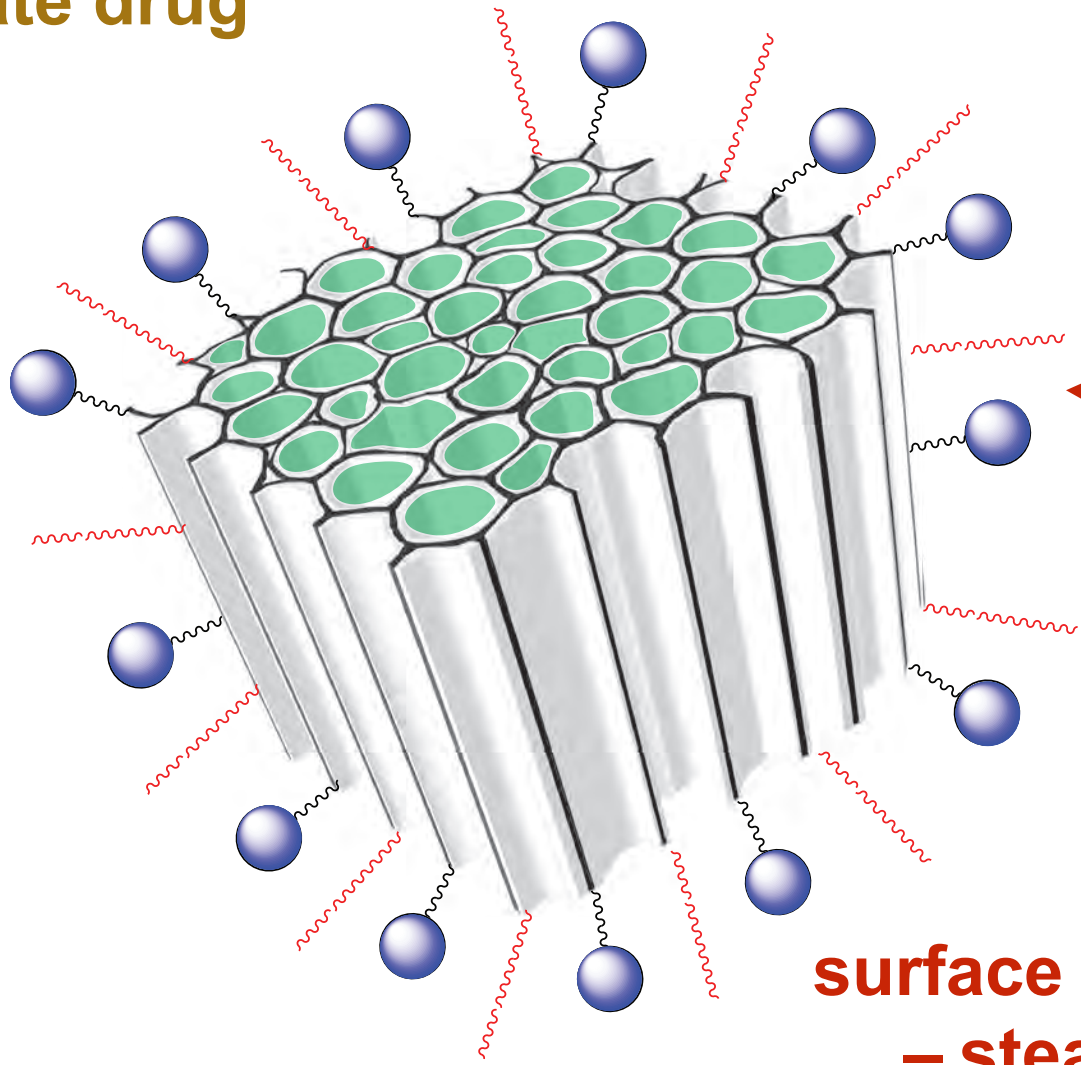
seal pores



Preparation of silicon nanoparticles

accommodate drug

seal pores



surface chemistry

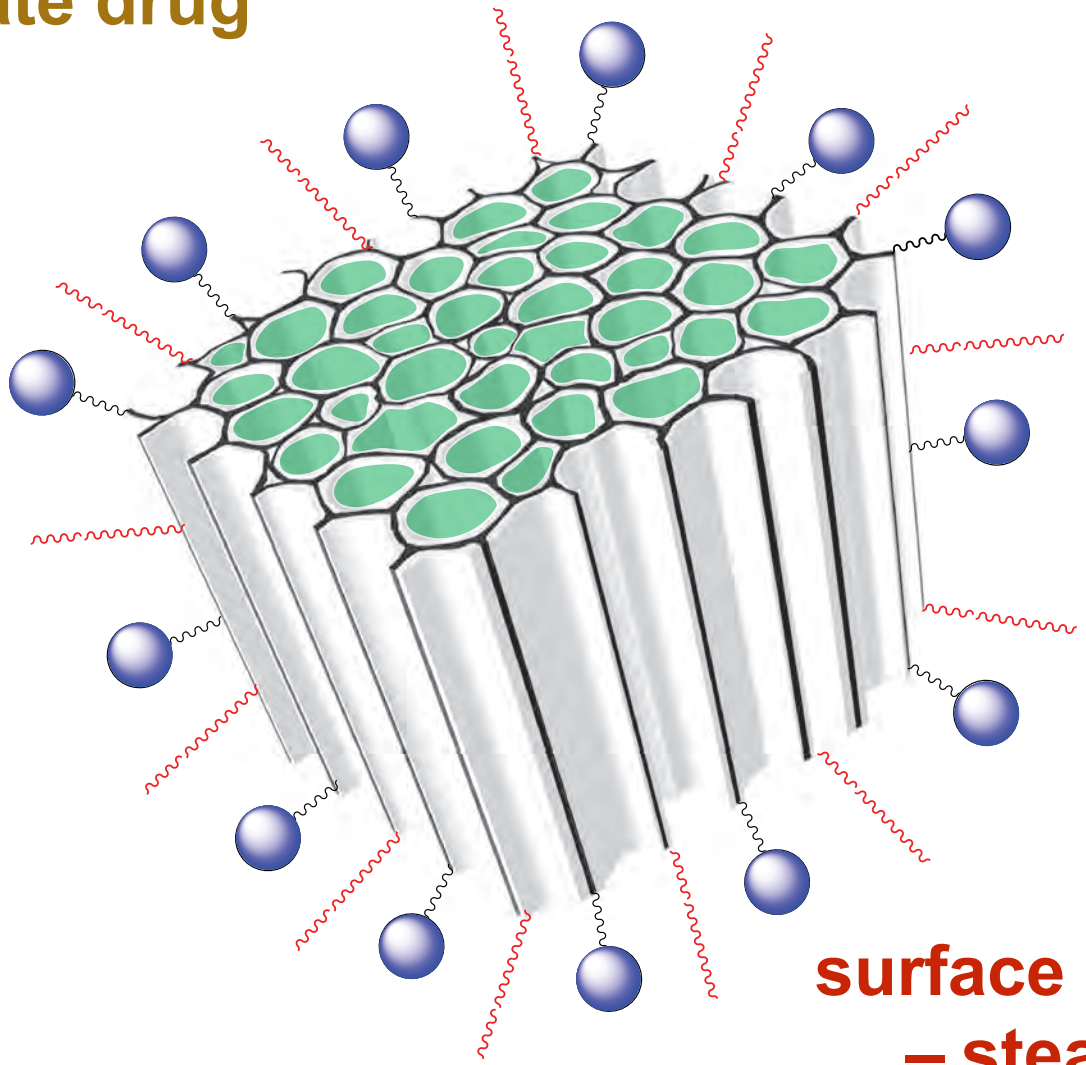
– stealth coatings

– targeting groups

Preparation of silicon nanoparticles

accommodate drug

seal pores



surface chemistry

– stealth coatings

– targeting groups

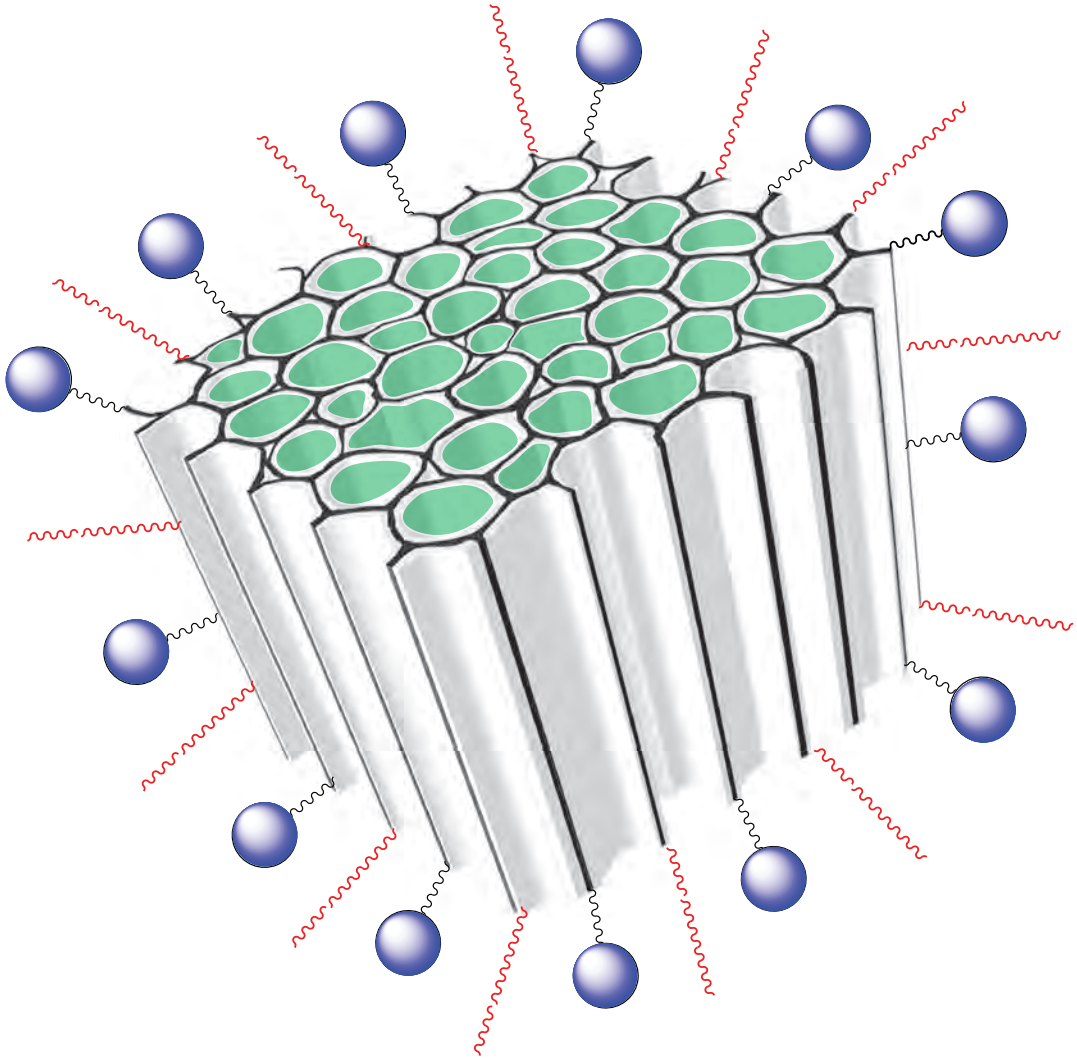
Preparation of silicon nanoparticles

accommodate drug

seal pores

surface chemistry

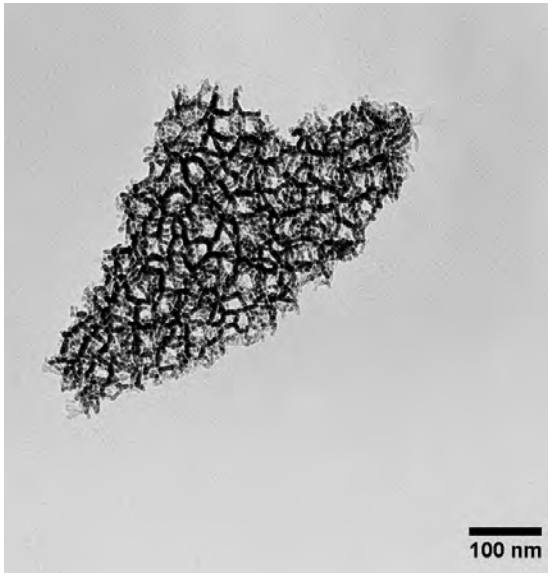
- stealth coatings
- targeting groups

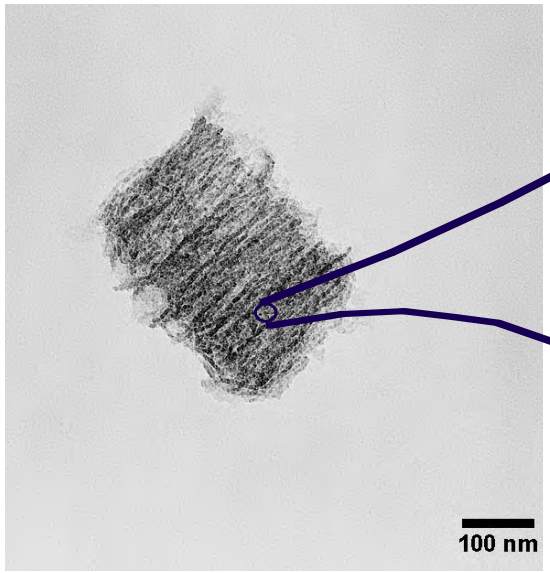


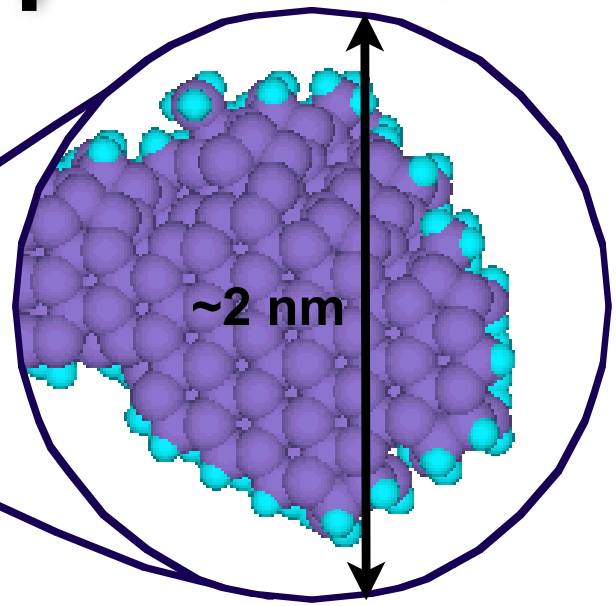
Quantum confinement in porous Si

Canham, L. T., *Appl. Phys. Lett.* **1990**, 57, 1046.
Nash, K. J.; Calcott, P. D. J.; Canham, L. T.; Kane, M. J. *J. Luminesc.* **1994**, 60-61, 297.
Canham, L. T. *Phys. Stat. Sol. (B)* **1995**, 190, 9.
Fauchet, P. M. *J. Lumin.* **1996**, 70, 294-309.
Collins, R. T.; Fauchet, P. M.; Tischler, M. A. *Phys. Today* **1997**, 50, 24-31.

Quantum confinement in porous Si







Nanoscale features in porous Si emit light

Quantum Confinement:

$$E^* \approx E_g + \frac{h^2}{8R^2}\left[\frac{1}{m_e} + \frac{1}{m_h}\right] - \frac{1.8e^2}{\varepsilon R}$$

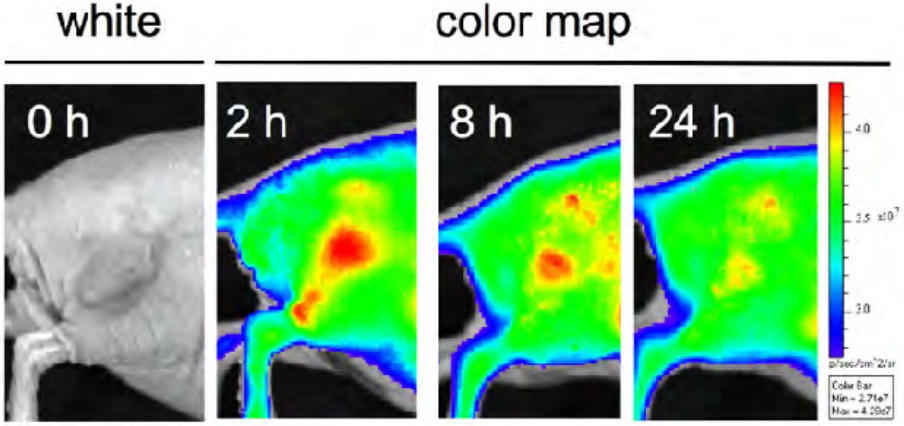
Canham, L. T., *Appl. Phys. Lett.* **1990**, 57, 1046.
Nash, K. J.; Calcott, P. D. J.; Canham, L. T.; Kane, M. J. *J. Luminesc.* **1994**, 60-61, 297.
Canham, L. T. *Phys. Stat. Sol. (B)* **1995**, 190, 9.
Fauchet, P. M. *J. Lumin.* **1996**, 70, 294-309.
Collins, R. T.; Fauchet, P. M.; Tischler, M. A. *Phys. Today* **1997**, 50, 24-31.

University of California San Diego

In vivo imaging with silicon nanoparticles

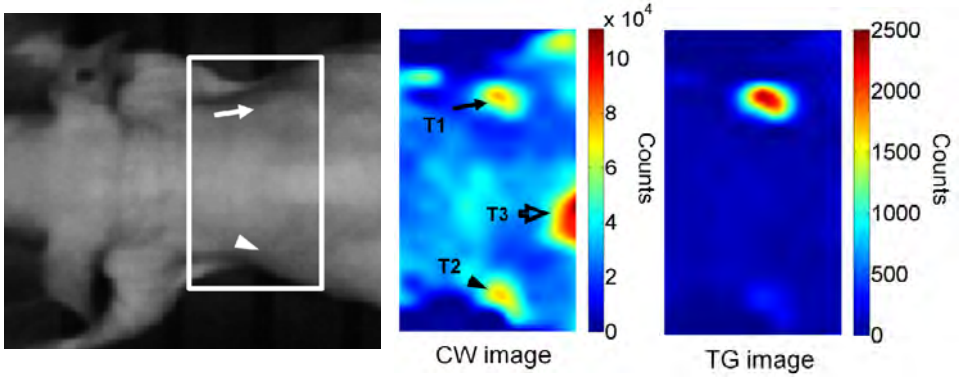
Photoluminescent imaging

Park, J.-H. et al., *Nature Mater.* **2009**, *8*, 331-336.



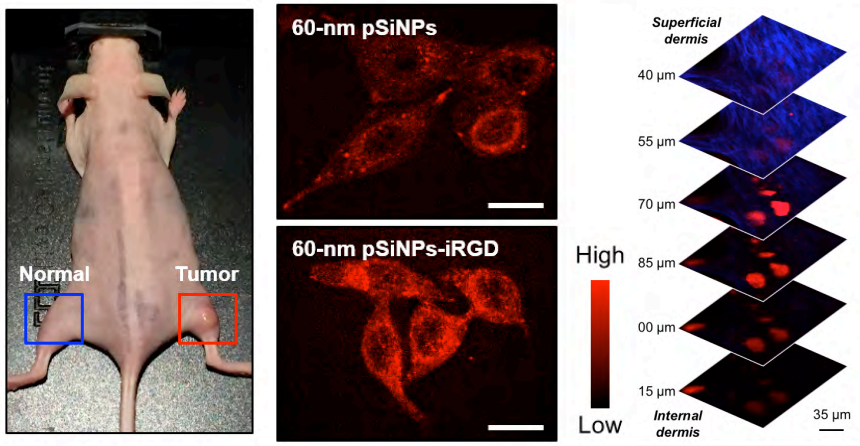
Time-gated photoluminescence imaging

Gu, L., et al. *Nat. Commun.* **2013**, *4*, 2326.



Two-photon imaging

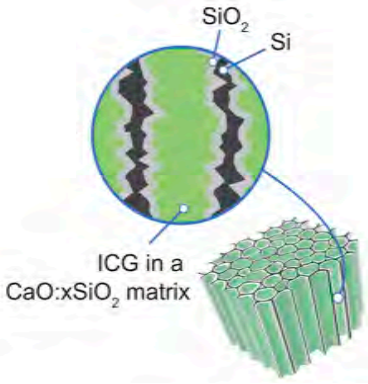
Kim, D. et al., *Adv. Mater.* **2017**, *29*, 1703309.



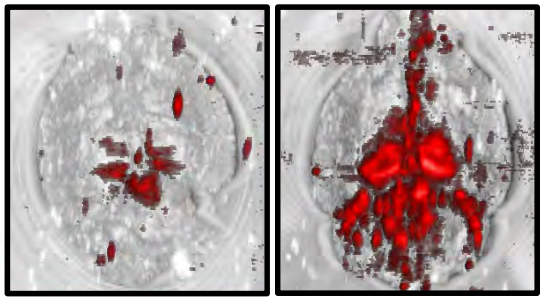
Photoacoustic imaging

Kang, J., et al., *Adv. Mater.* **2018**, 1800512.

Porous Silicon Nanoparticle

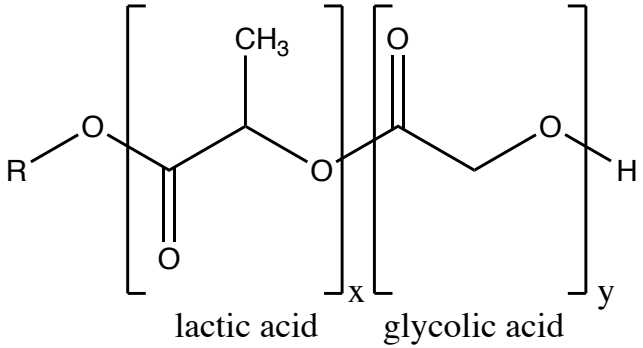


Photoacoustic Brain Images



Free ICG *ICG in nanoparticle*

Protein therapeutics are generally not compatible with “biocompatible” polymers



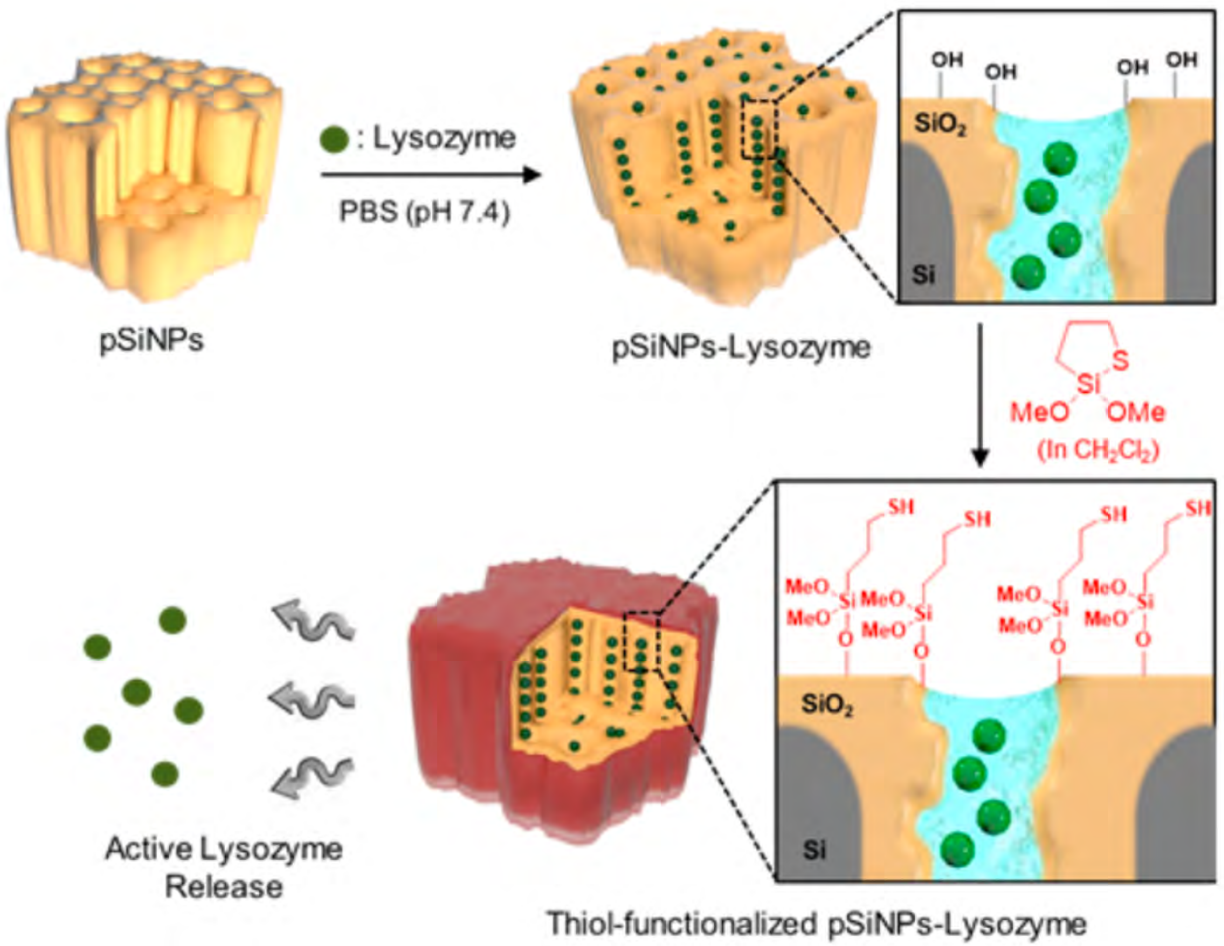
Structure of poly lactic-co -glycolic acid (x is the number of lactic acid units and y is number of glycolic acid units).

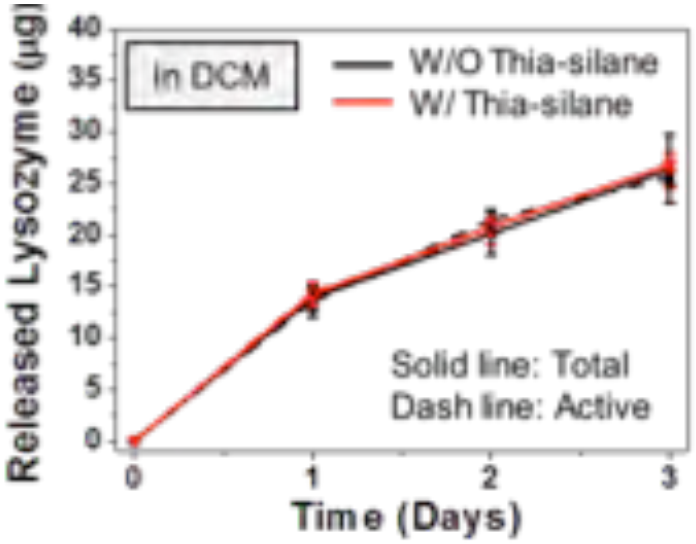
In past two decades poly lactic-*co*-glycolic acid (PLGA) has been among the most attractive polymeric candidates used to fabricate devices for drug delivery and tissue engineering applications. PLGA is biocompatible and biodegradable, exhibits a wide range of erosion times, has tunable mechanical properties and most importantly, is a FDA approved polymer. In particular, PLGA has been extensively studied for the development of devices for controlled delivery of small molecule drugs, proteins and other macromolecules in commercial use and in research…

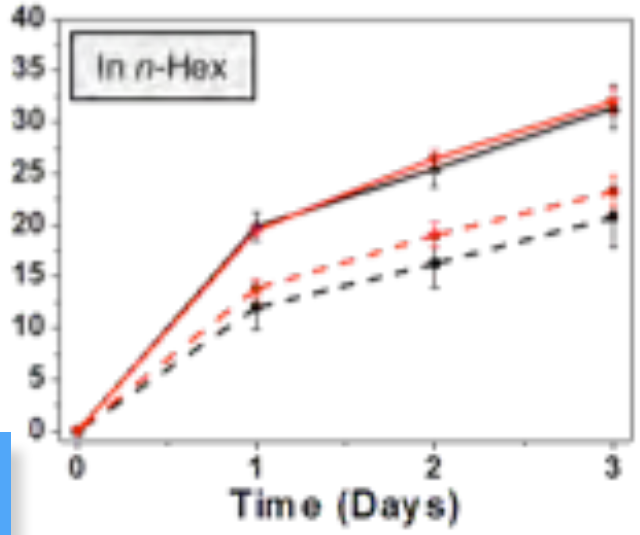
…Solvent-casting methods are not ideal for industrial scale-up for many reasons…such systems are also open to the risk of **denaturation of drugs and/or proteins during encapsulation because of the use of organic solvents**. Denatured species are therapeutically inactive and can cause unpredictable side effects, such as immunogenicity or other toxicity.

Makadia H. K., Siegel S. J. Poly Lactic-*co*-Glycolic Acid (PLGA) as Biodegradable Controlled Drug Delivery Carrier. *Polymers* **2011**, *3*, 1377-1397. doi:10.3390/polym3031377.

Heterocyclic silane allows encapsulation of sensitive biologics







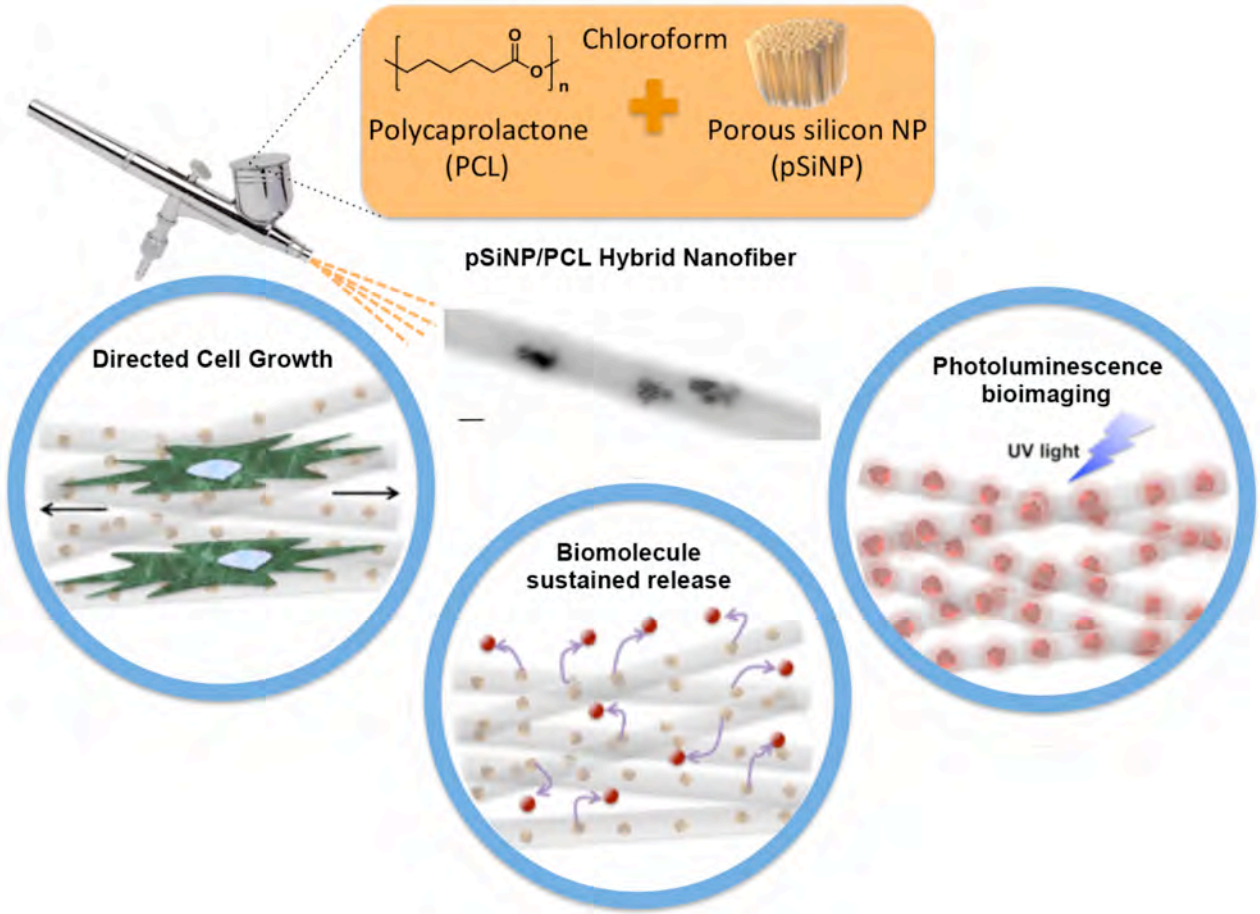
- **Water is retained in nanostructure**
- **Preserves activity of lysozyme**
- **Slow release with no burst**

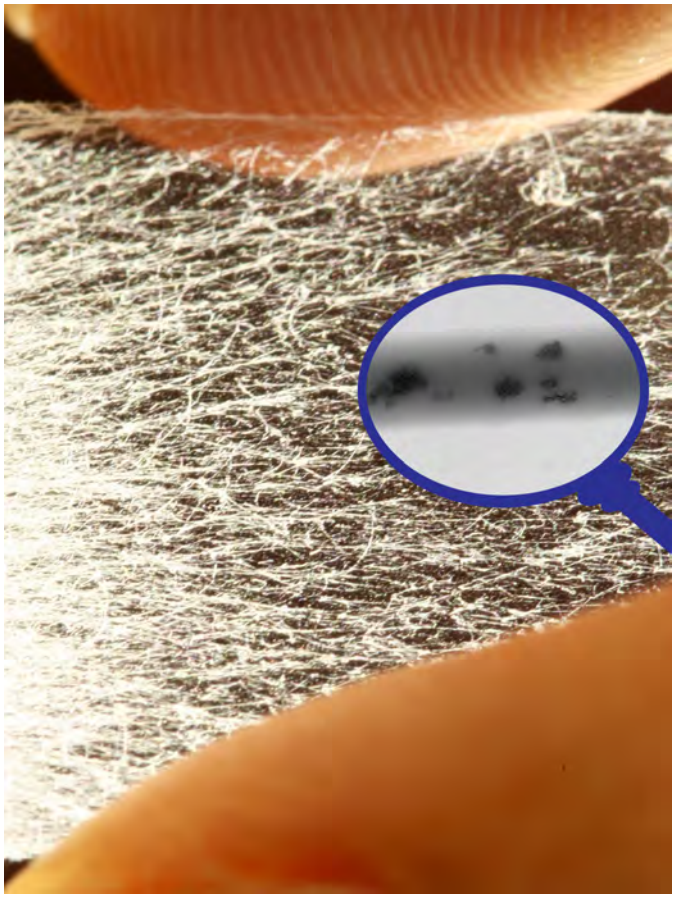
Total protein loaded: 76 µg
Release into PBS @ 37°C

Kim, D.; Zuidema, J. M.; Kang, J.; Pan, Y.; Wu, L.; Warther, D.; Arkles, B.; Sailor, M. J., *J. Am. Chem. Soc.* **2016**, *138*, 15106.

Loading and release of enzymatic payload

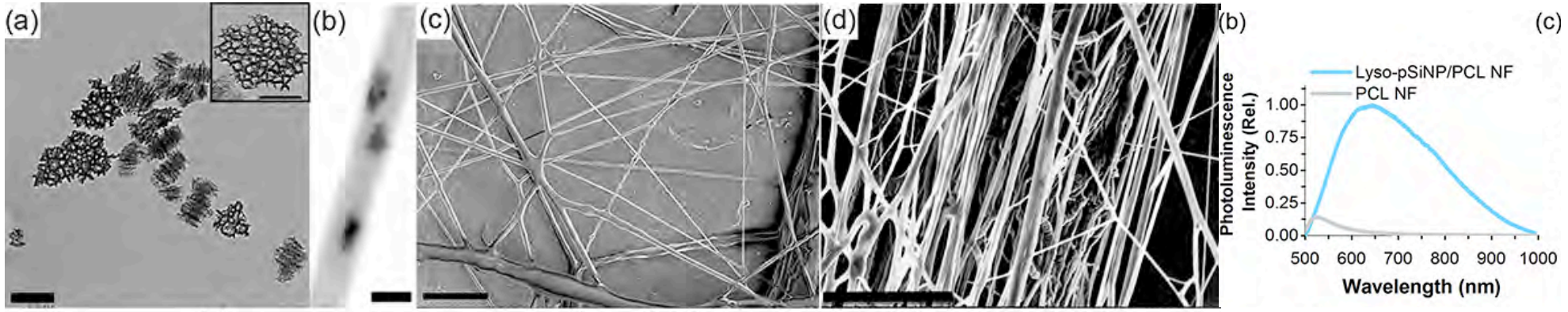
Zuidema, J. M., et al., *Adv. Mater.* **2018,** 10.1002/adma.201706785

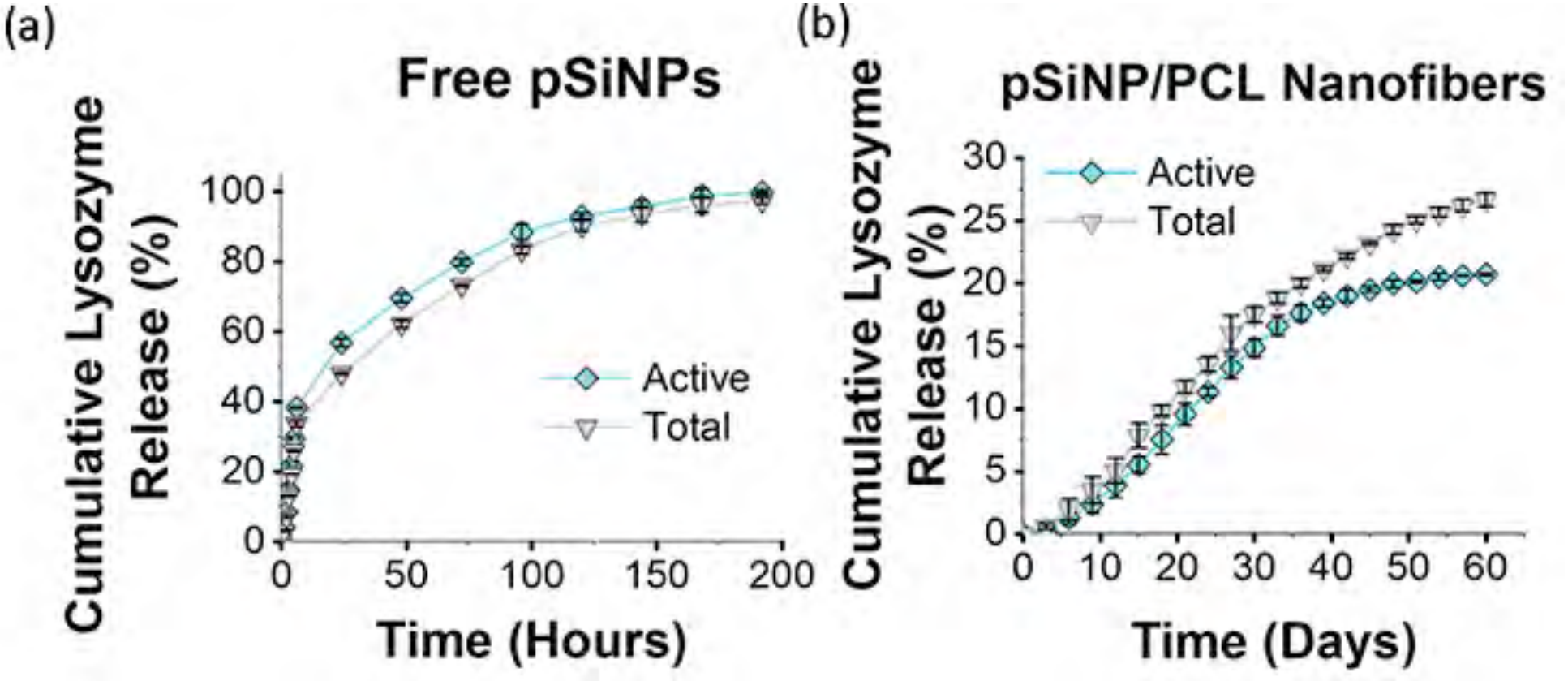




Loading and release of an enzymatic payload

Zuidema, J. M., et al., *Adv. Mater.* **2018,** 10.1002/adma.201706785





Targeted RNA delivery to macrophages

Harness the host's immune system to mitigate bacterial infection.

siRNA payload: silence *Irf5* gene

Silencing the Irf5 gene in M1 macrophages:
–suppresses inflammatory immune response
–activates phagocytic response against bacteria

Targeting peptide: CRV

Targets macrophages *in vivo*

tail vein injection

Coating: fusogenic liposomes

Fuses with cell membrane *in vivo*
delivers nanoparticle directly into the cytosol
avoids endocytotic uptake

Targeted RNA delivery to macrophages

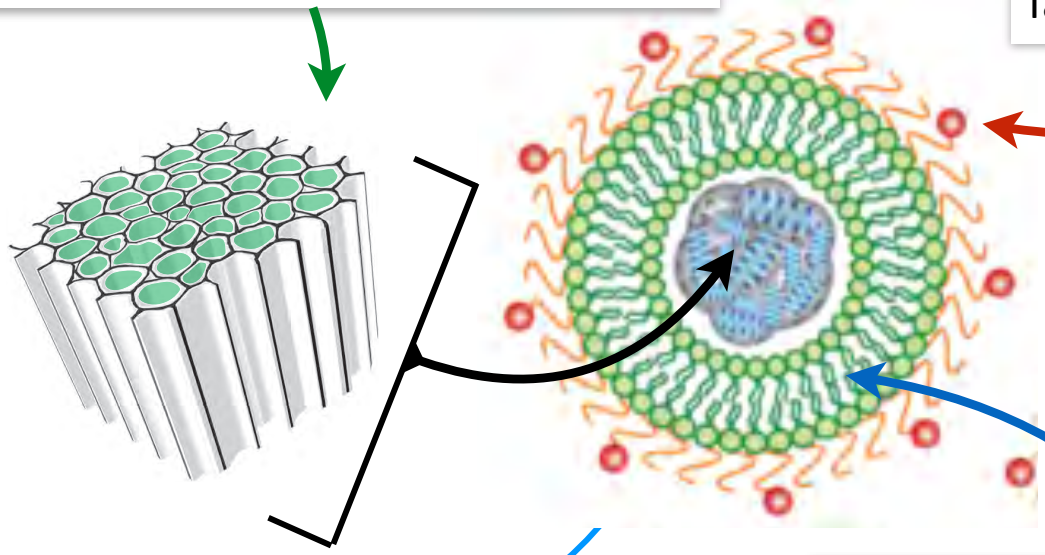
Harness the host's immune system to mitigate bacterial infection.

siRNA payload: silence *Irf5* gene

Silencing the Irf5 gene in M1 macrophages:
–suppresses inflammatory immune response
–activates phagocytic response against bacteria

Targeting peptide: CRV

Targets macrophages *in vivo*

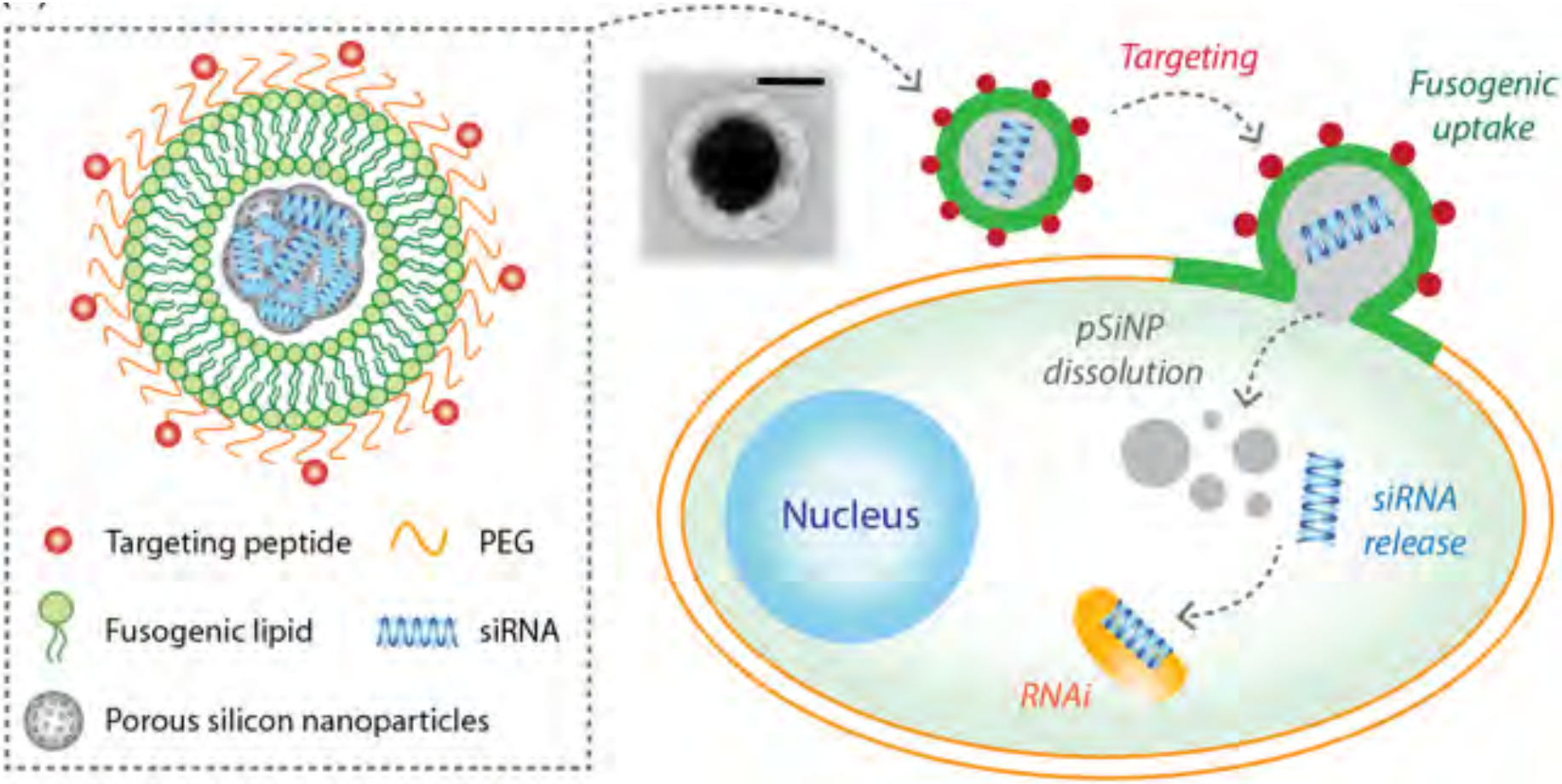


tail vein injection

Coating: fusogenic liposomes

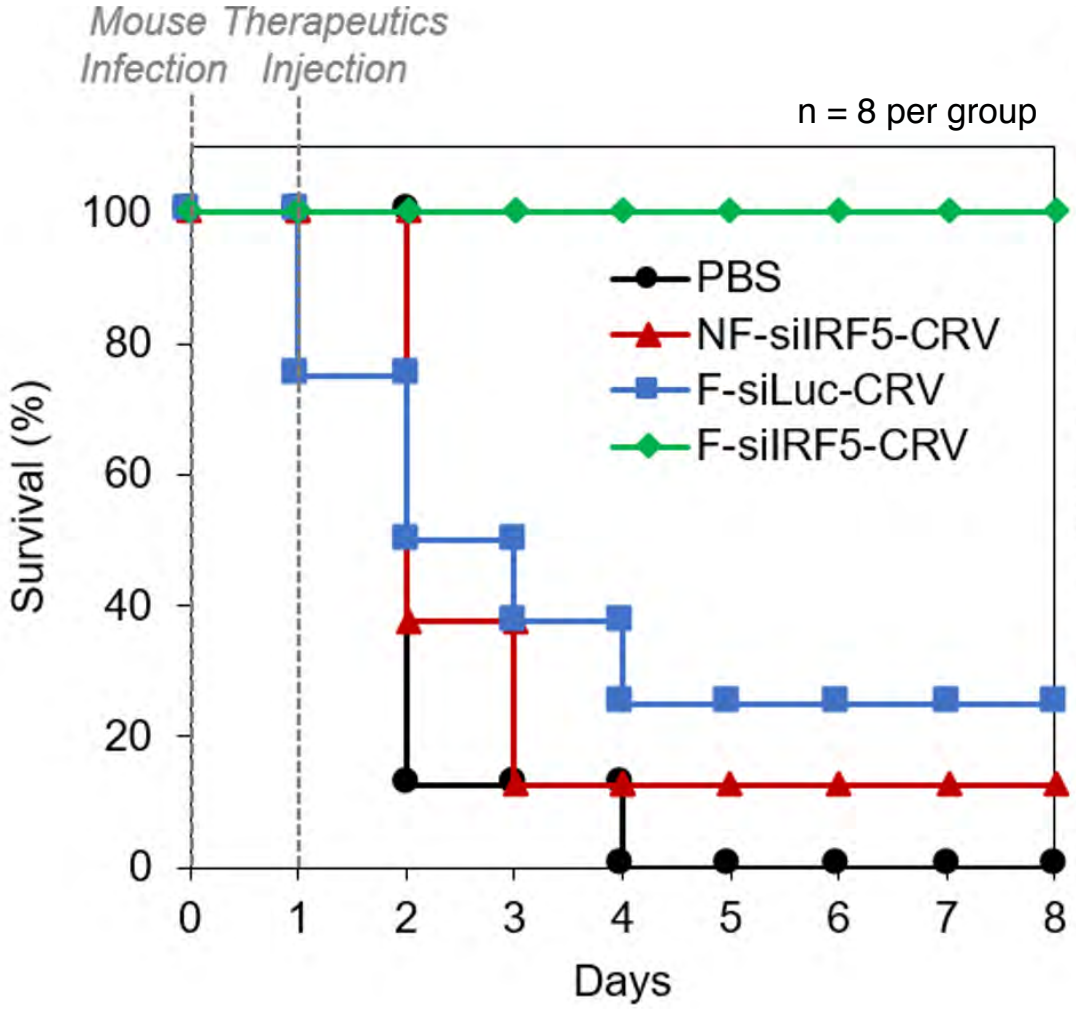
Fuses with cell membrane *in vivo*
delivers nanoparticle directly into the cytosol
avoids endocytotic uptake

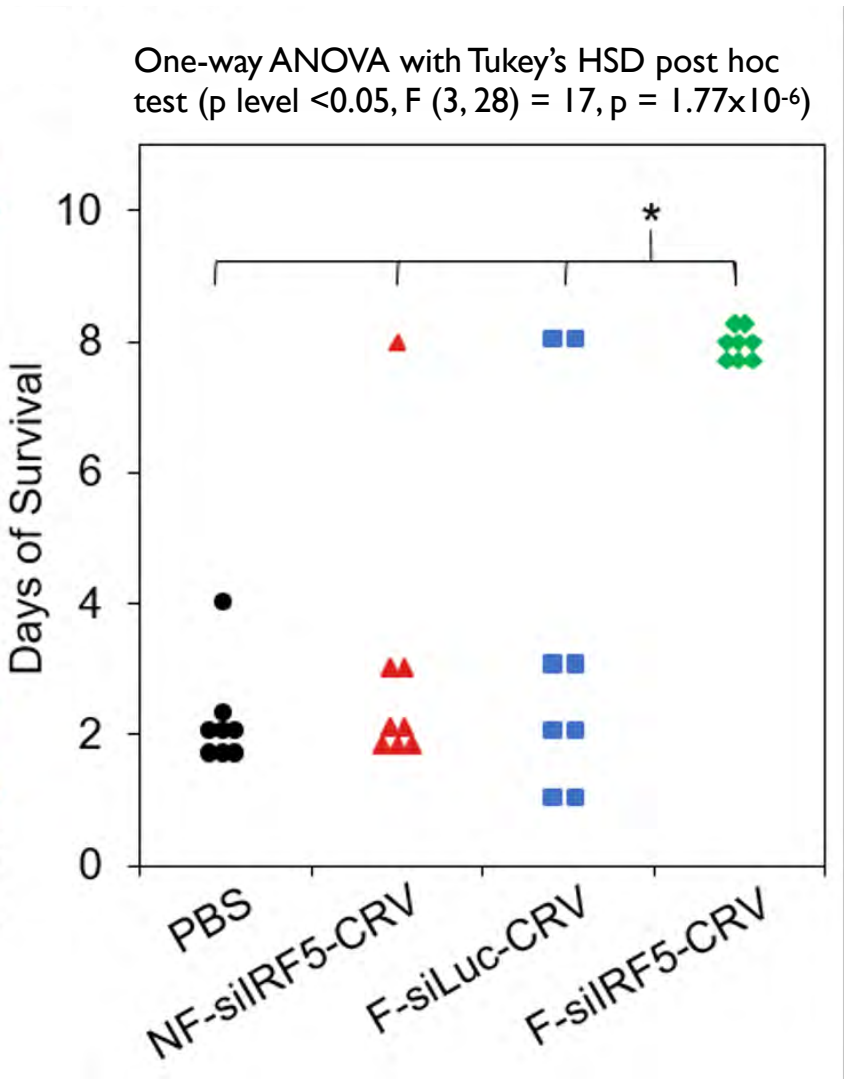
Fusogenic liposome-coated porous Si nanoparticles bypass endocytosis



Adv. Mater. **2019**, 1902952

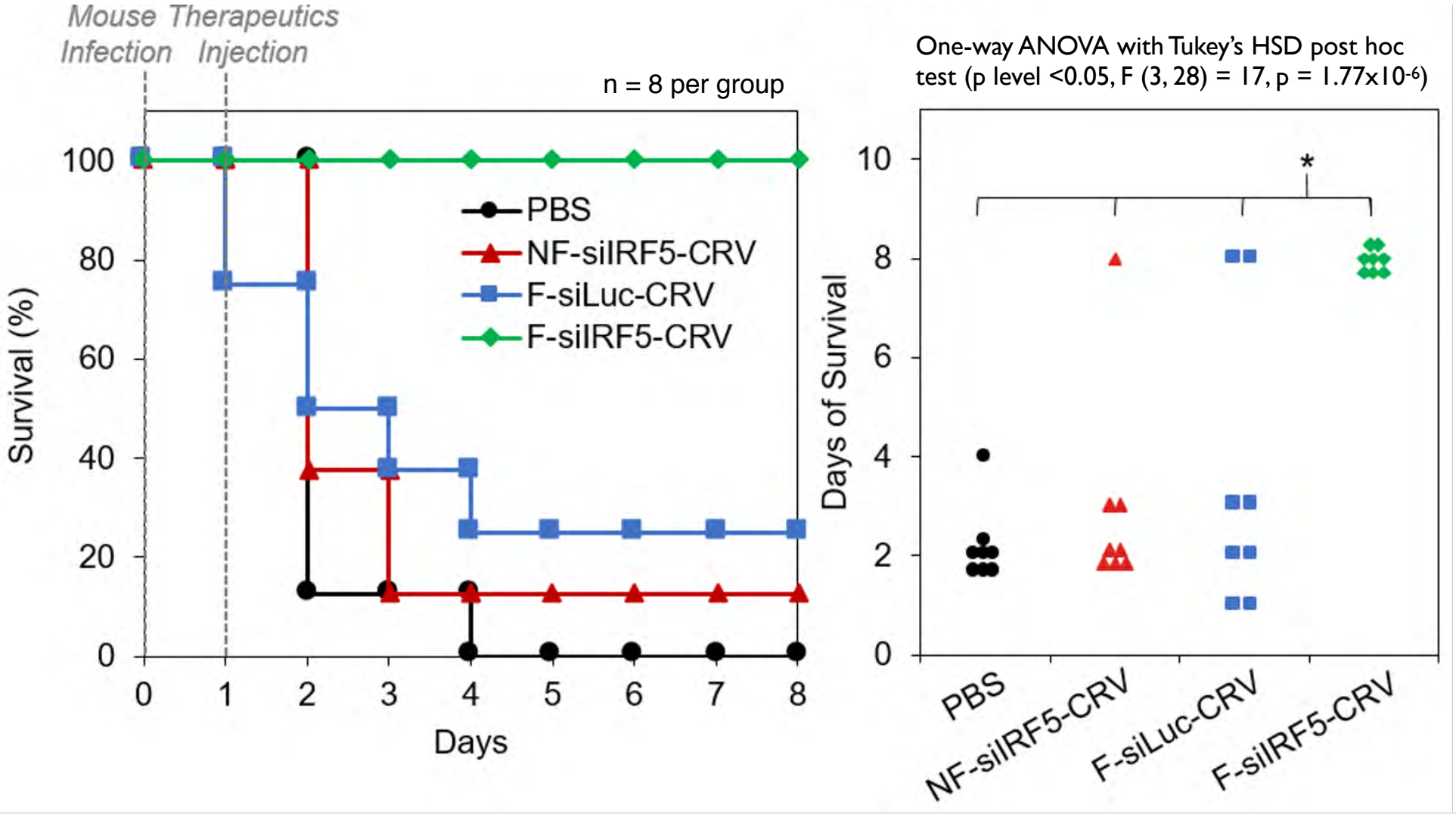
Macrophage-activating siIRF5 in CRV-targeted fusogenic particles show 100% survival rate





Kim, Byungji, et al., *Nature Commun.* **2018,** *9*, 1969.

Macrophage-activating siIRF5 in CRV-targeted fusogenic particles show 100% survival rate



- **Survival significantly higher than non-fusogenic formulations in S. aureus mouse lung infection model**

Kim, Byungji, et al., *Nature Commun.* **2018,** *9*, 1969.

Conclusions

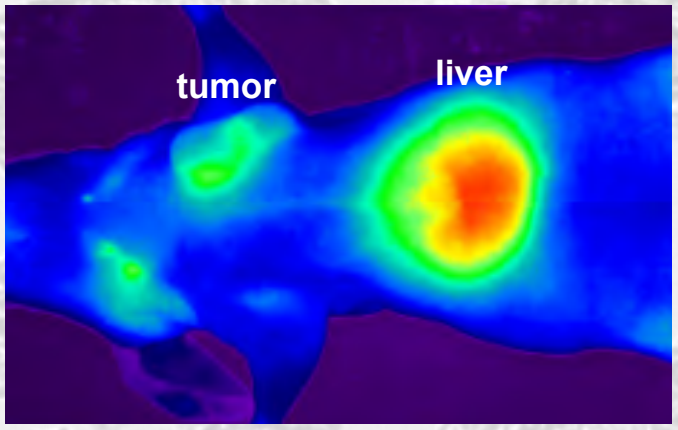
1. Porous nano-hosts allow loading and protection of protein, nucleic acid therapeutic agents

2. Targeting of the nanoparticles via peptides allows direct access to specific cells

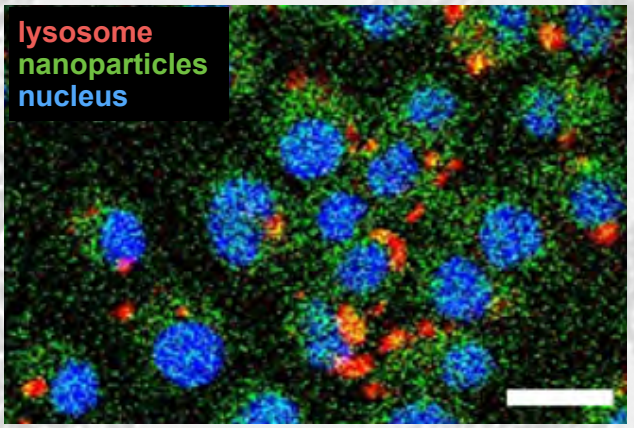
3. Fusogenic coatings allow access to the cellular interior, bypassing endocytosis

4. Delivered siRNA can shut down inflammatory macrophages in a lung infection

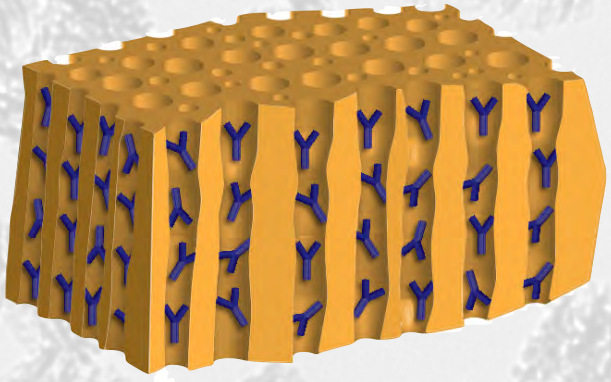
- *Nanoparticles can selectively target diseased tissues*



- *Nanoparticles can reach privileged cellular compartments*



- *Nanoparticles can Improve in vivo stability of a drug or imaging agent*



Acknowledgements

Coworkers:

Jinyoung Kang, Byungji Kim, Dokyoung Kim, Luo Gu, Jinmyoung Joo, Hongbo Pang, Gha Young Lee, Elizabeth Wu, Emily Anglin, Michelle Chen, Sanahan Vijayakumar, Zhengtao Qin

Collaborators:

Prof. Kyo Han Ahn (POSTECH)
Dr. Barry Arkles (Gelest)
Prof. Giuseppe Barillaro, Michela Sainato (University of Pisa, IT)
Dr. Ronald E. Betts, Emily Anglin (Spinnaker Biosciences)
Prof. Sangeeta N. Bhatia, Geoffrey von Maltzahn (MIT Bioengineering)
Dr. Frederique Cunin, Prof. Jean-Marie Devoisselle (CNRS Montpellier, FR)
Dr. William Freeman, Dr. Lingyun Cheng (UCSD Jacobs Retina Center)
Dr. David Hall (UCSD Moores Cancer Center)
Prof. Stephen Hedrick (UCSD Biology)
Dr. Stephen B. Howell (UCSD Moores Cancer Center)
Prof. Jesse Jokerst (UCSD Nanoengineering)
Prof. Sanghwa Lee (Gachon University)
Prof. David J. Mooney (Harvard)
Prof. Yoonkey Nam (KAIST)
Prof Ji-Ho Park (KAIST)
Prof. Erkki Ruoslahti (Sanford-Burnham-Prebys Medical Discovery Institute)
Prof. Honglae Sohn (Chosun University, Korea)
Prof. Lianbin Wu (Hangzhou Normal University)
Prof. Jianmin Wu (Zhejiang University)

Funding thanks: NIH, NSF, DARPA

Summer School for Silicon Nanotechnology

http://sailorgroup.ucsd.edu/courses/SummerSchool/

The Summer School for Silicon Nanotechnology is an intensive, 6-week hands-on workshop involving UCSD undergraduates, high school students, graduate students, post-docs, and international scholars.

Summer School for Silicon Nanotechnology

http://sailorgroup.ucsd.edu/courses/SummerSchool/

The Summer School for Silicon Nanotechnology is an intensive, 6-week hands-on workshop involving UCSD undergraduates, high school students, graduate students, post-docs, and international scholars.

Program Dates: July 6 - Aug 21, 2020

Web: http://sailorgroup.ucsd.edu/courses/SummerSchool/