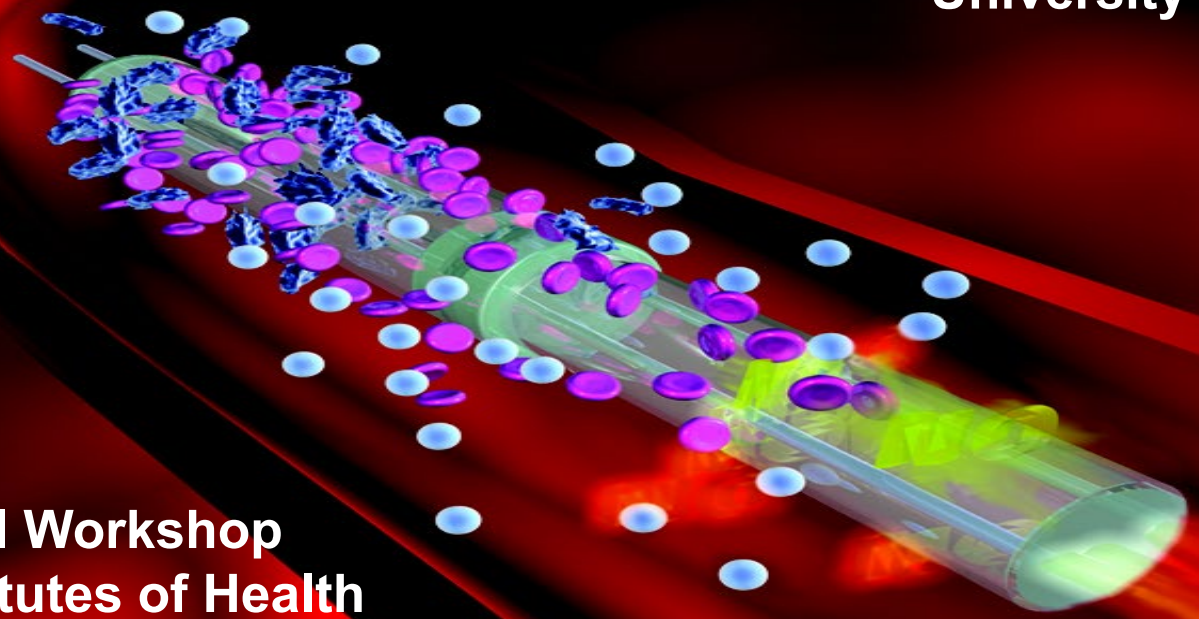
Nitric Oxide (NO) Releasing Urinary Catheters to Reduce the Risk of CAUTIs

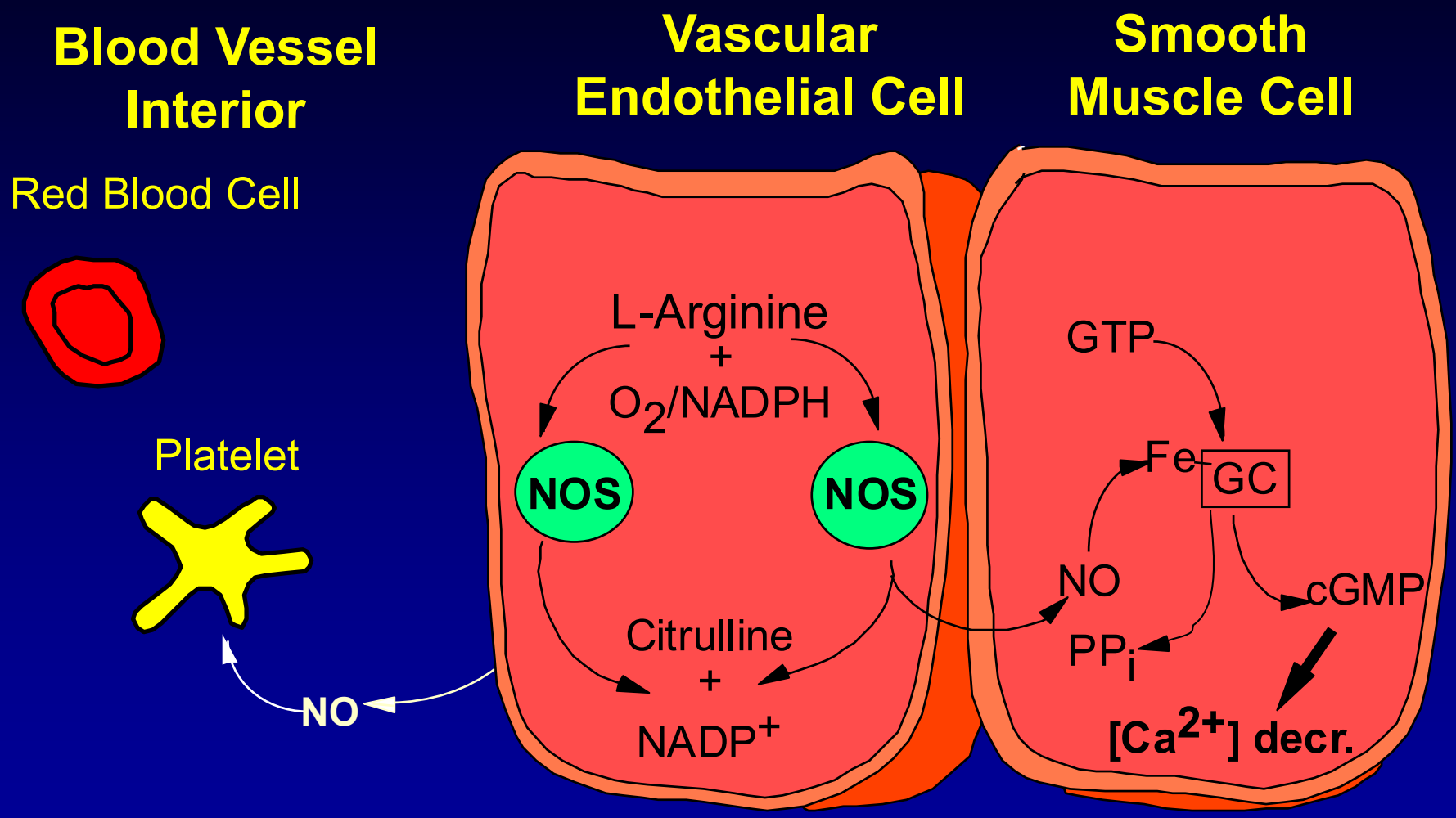


M. E. Meyerhoff
Department of Chemistry
University of Michigan

NIDDK CAUTI Workshop
National Institutes of Health
March 12, 2019

Current Research that May Lead to New Antimicrobial/Antibiofilm Catheters to Prevent Catheter Associated Infections

NO Production: Endothelial Cells (EDRF)



surface flux:

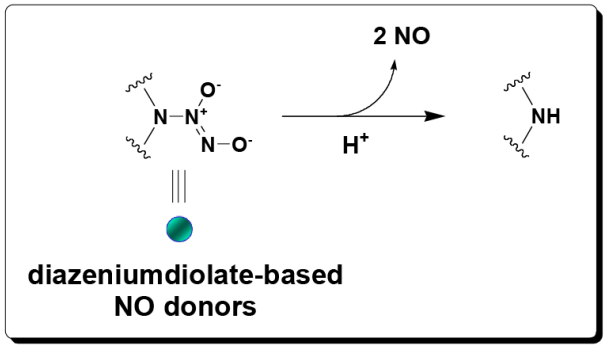
1×10^{-10} mol/cm^{2}min

NOS : Nitric Oxide Synthase

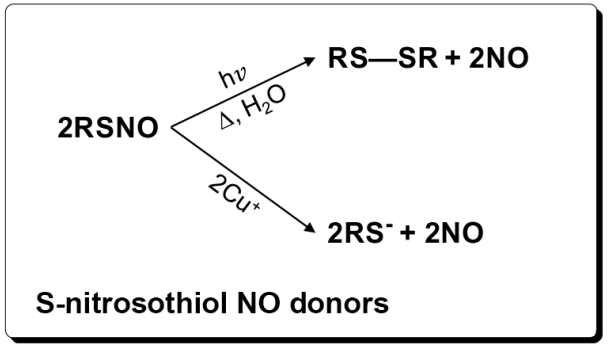
Nitric Oxide Release Chemistries Examined

Chemistry

I. Proton-mediated NO release

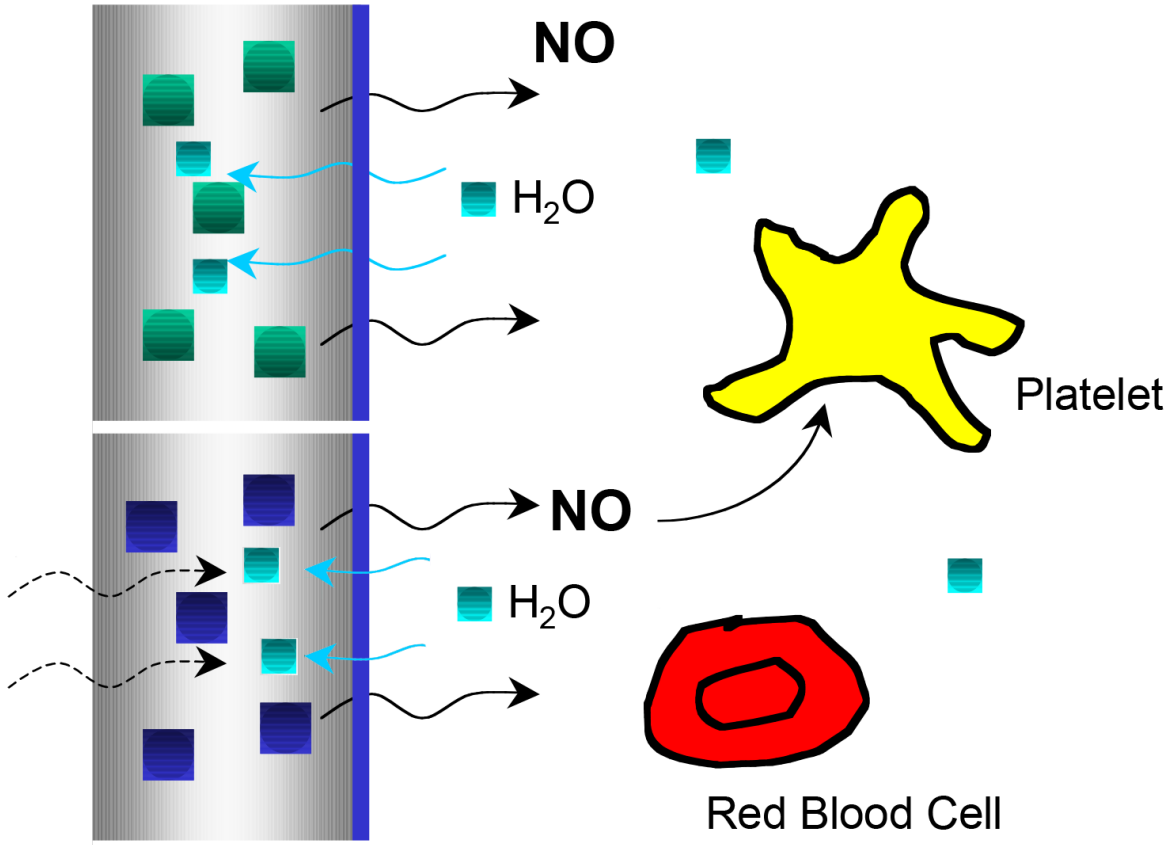


II. Thermal/Light/Water NO release

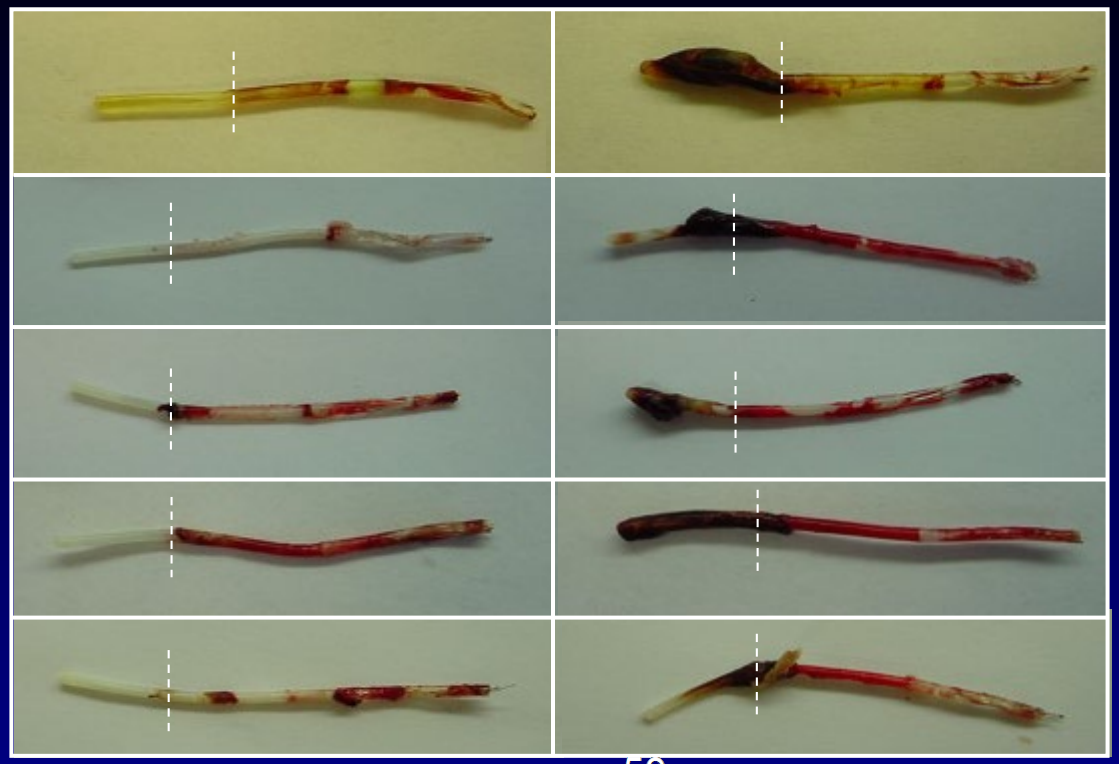


Polymer phase

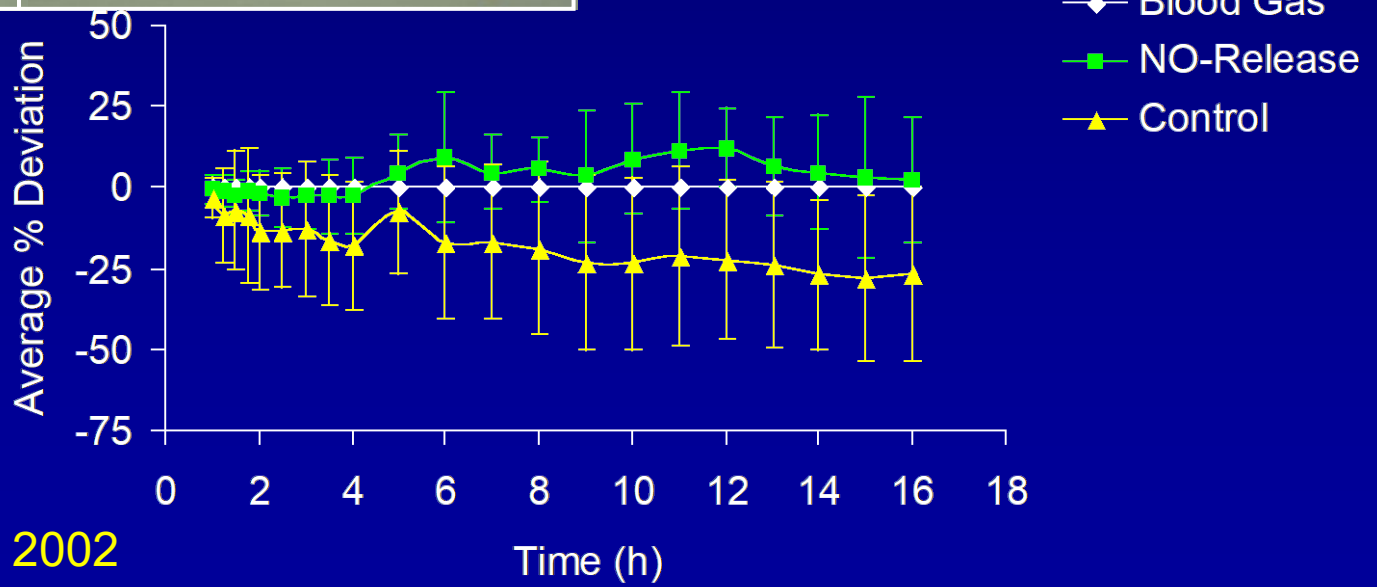
Blood phase



a) With NO-Release b) Without NO-Release

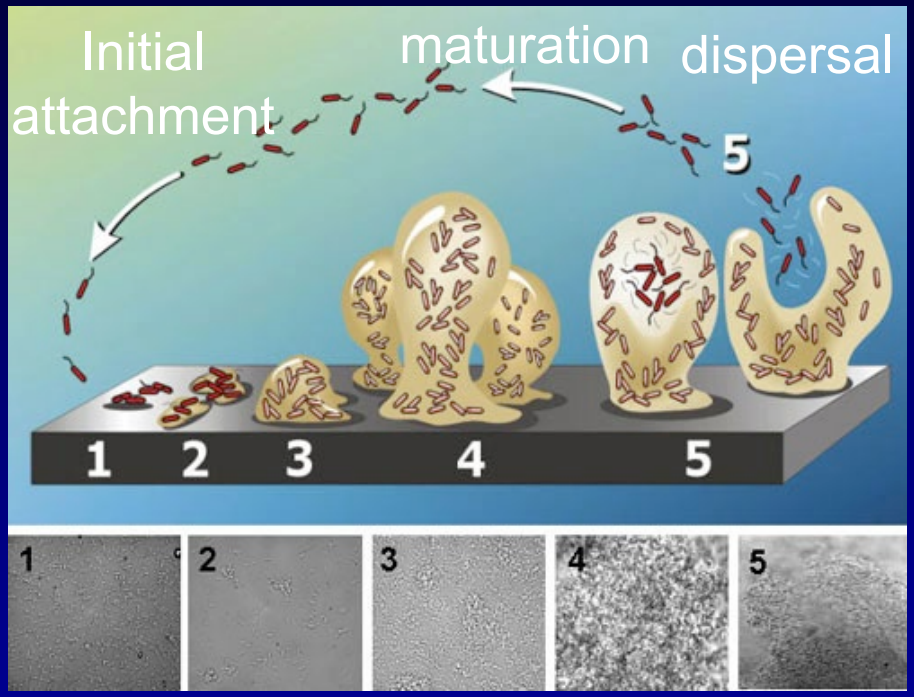


Oxygen Sensors After Removal From Porcine Arteries (16-18 h)



Frost et al., Anal. Chem. 2002

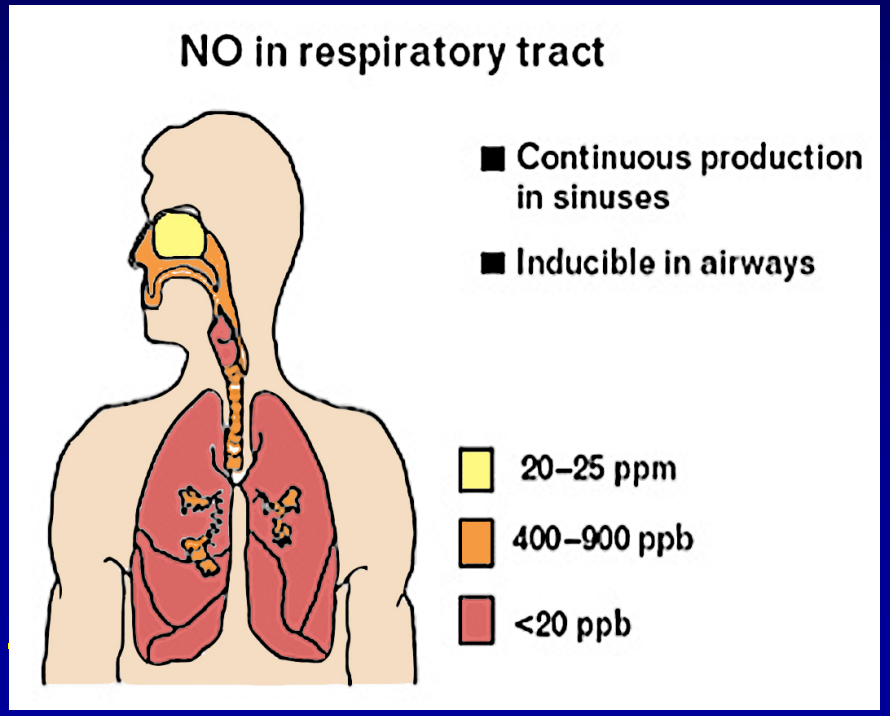
Bacterial Biofilms on Medical Devices: Can't be Treated Effectively with Antibiotics



Biofilm Development Stages

Nitric Oxide

Natural and potent antimicrobial and biofilm dispersal agent

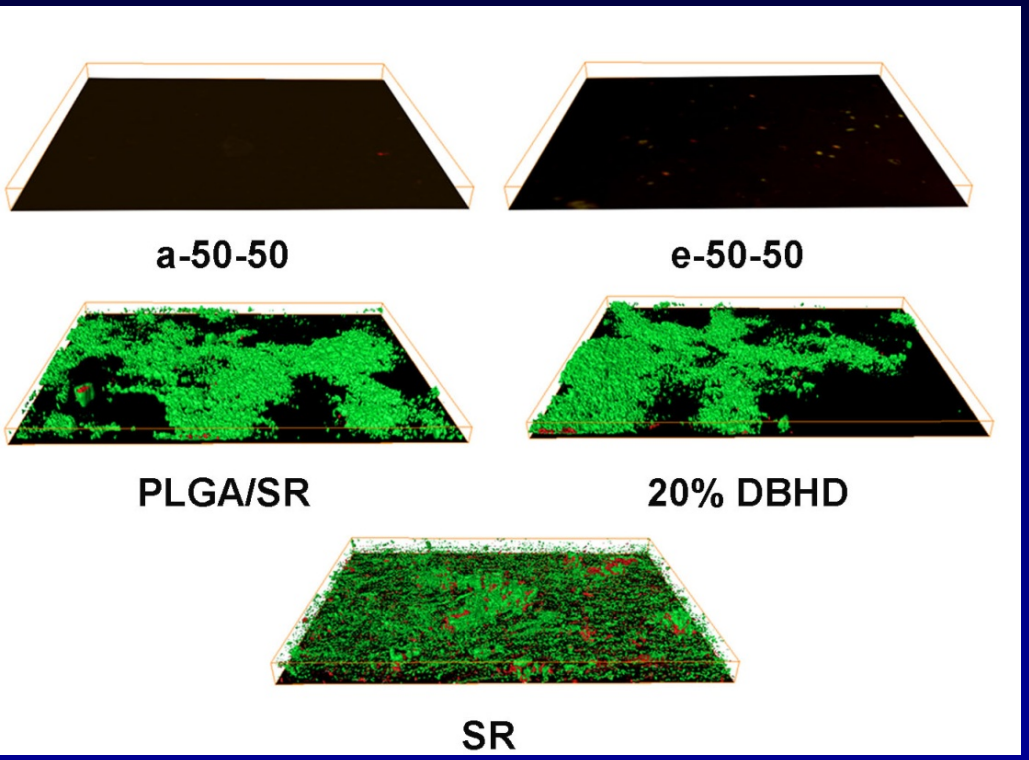


Macrophages produce high NO levels: This is how we fight infection!!

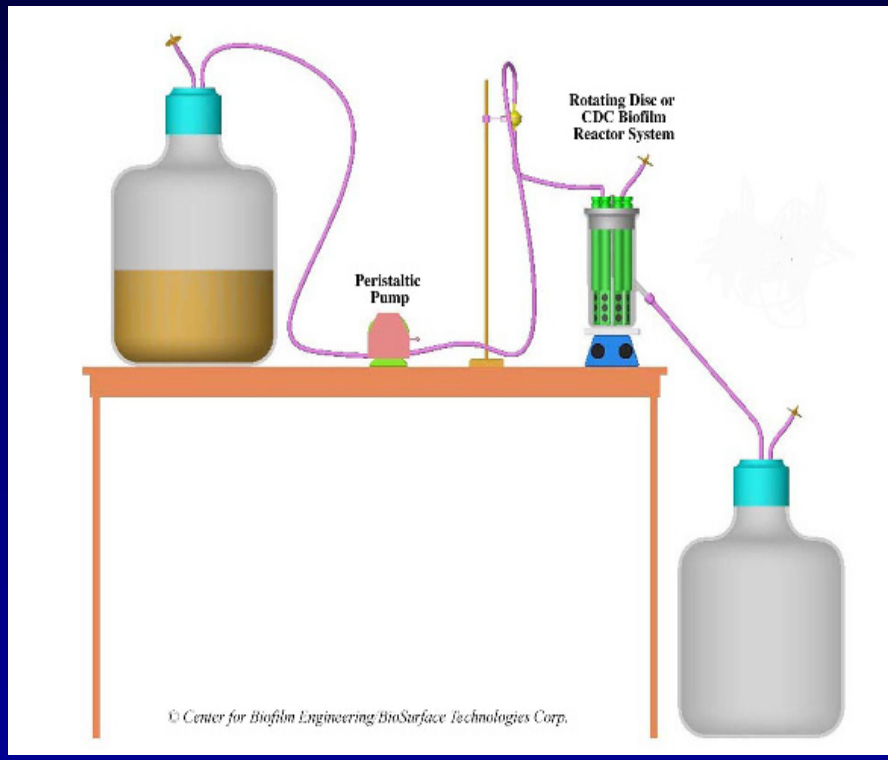
"Looking for Chinks in the Armor of Bacterial Biofilms" PLoS Biol, Vol 5, issue 11.

Chemical Release of NO Significantly Reduces Microbial Biofilm (*S. aureus*) Formation over 7 d

(DBHD/NONO in SR Films-w/PLGA Additive)

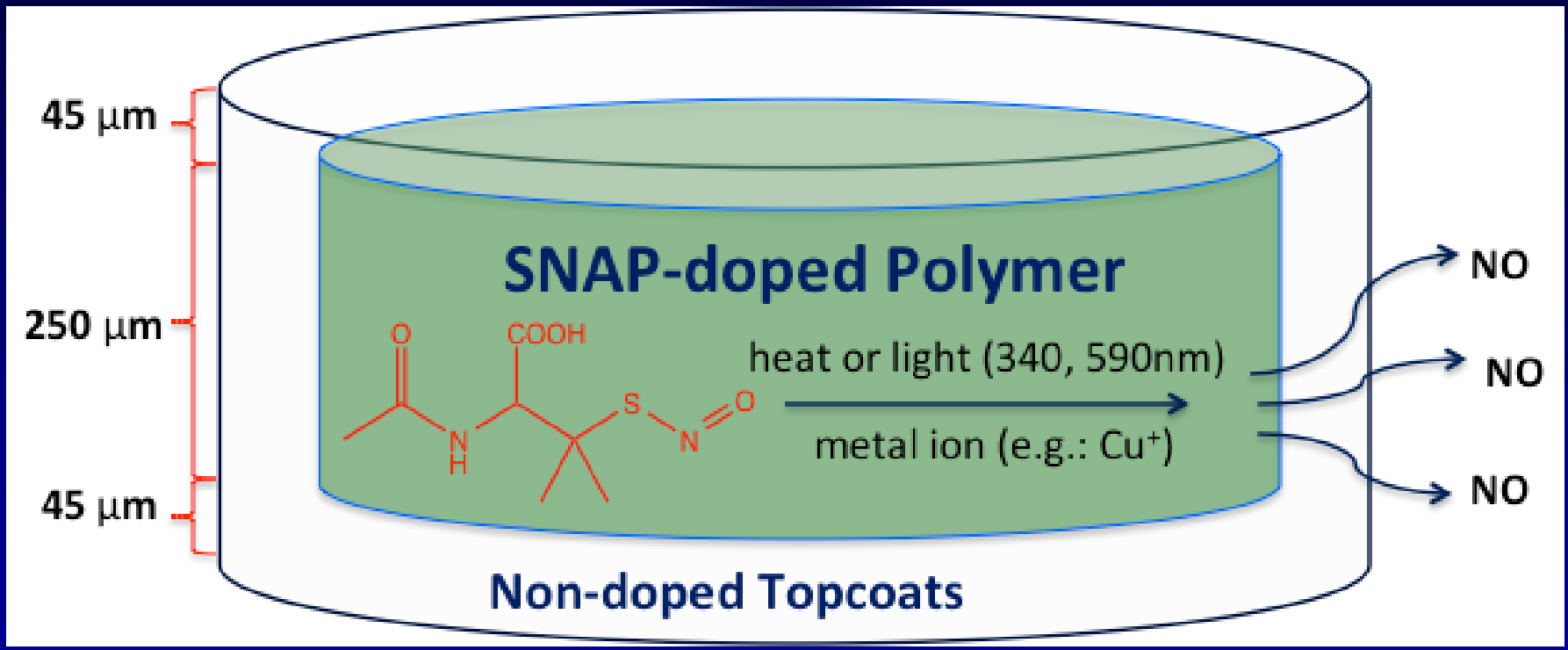


S. aureus biofilm formation on surfaces of NO releasing (top) and control silicone rubber films (lower three films are controls)



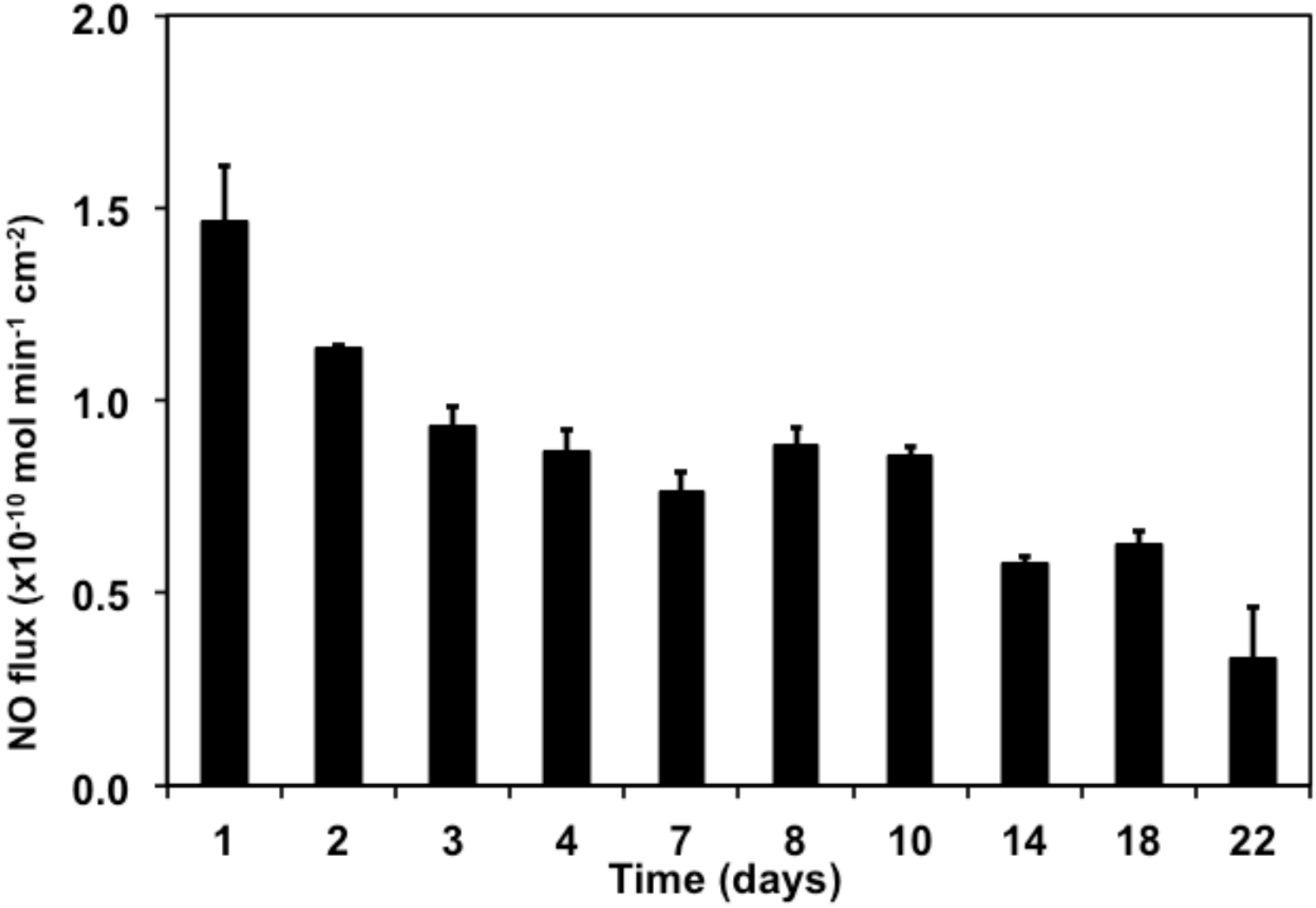
CDC Biofilm Reactor

S-Nitroso-*N*-Acetylpenicillamine (SNAP) Doped Polymers



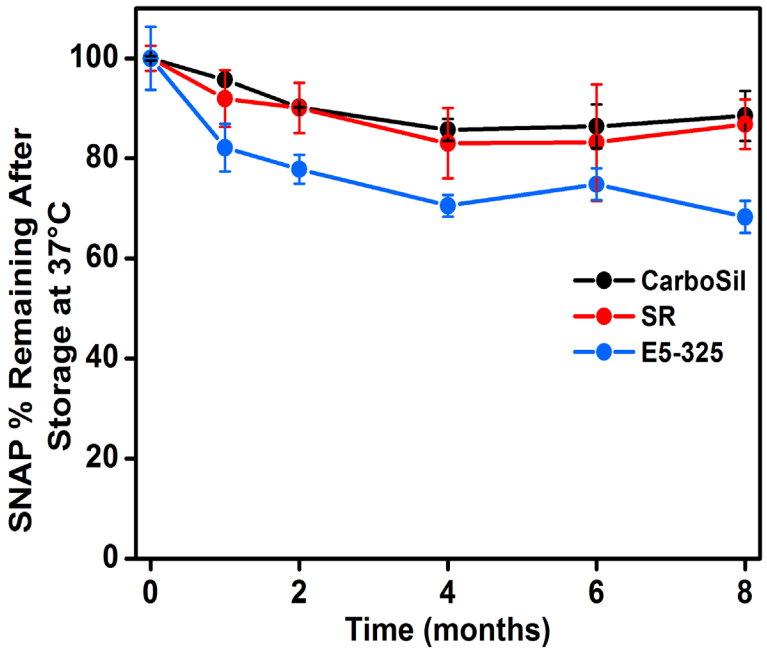
$$2RSNO \xrightarrow{\text{heat, light, metal ions}} RSSR + 2NO$$

10 wt% SNAP-Doped CarboSil Film NO Release at 37 °C (kept in PBS buffer)



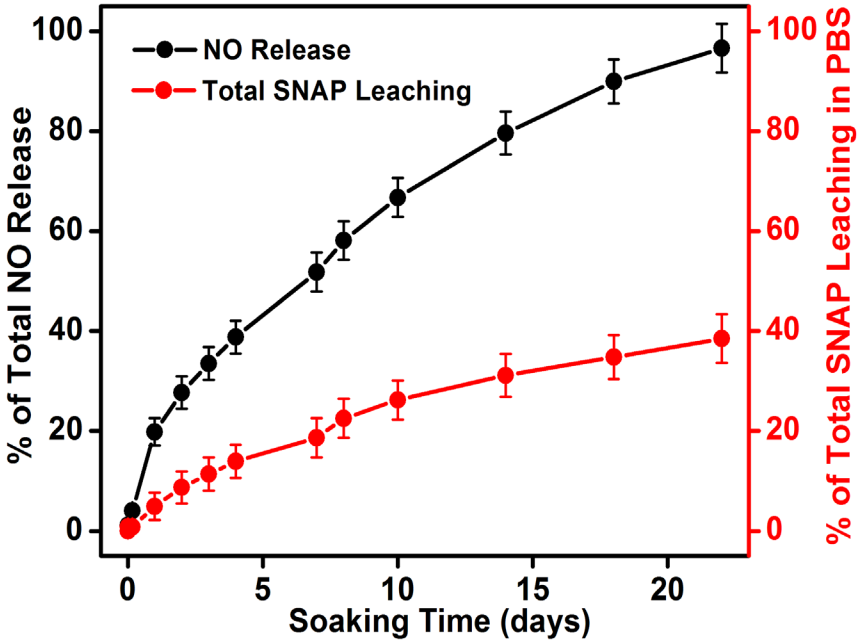
SNAP-Doped CarboSil Composite Material (Long-Term Behavior)

Shelf-Life Stability



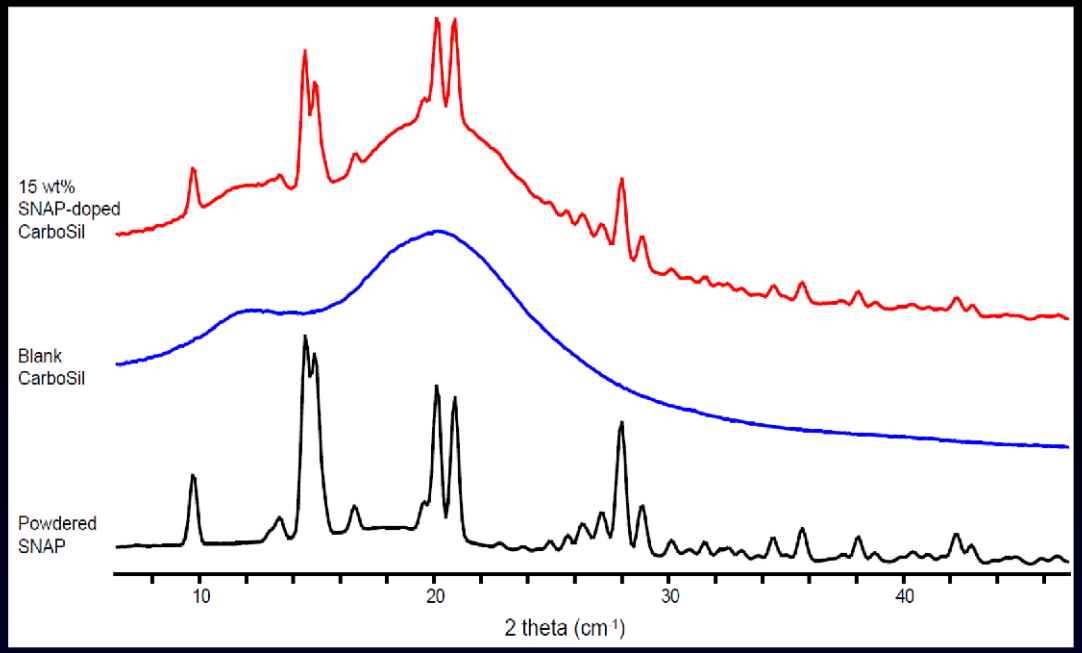
stored dry in dark at 37 °C

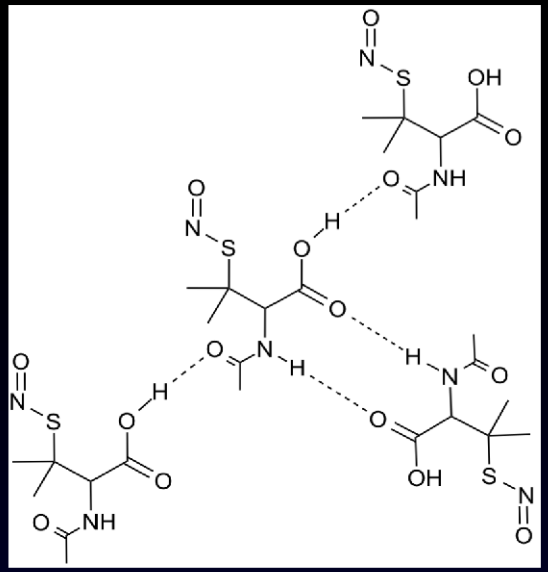
SNAP/NAP/$(NAP)_2$ Leaching



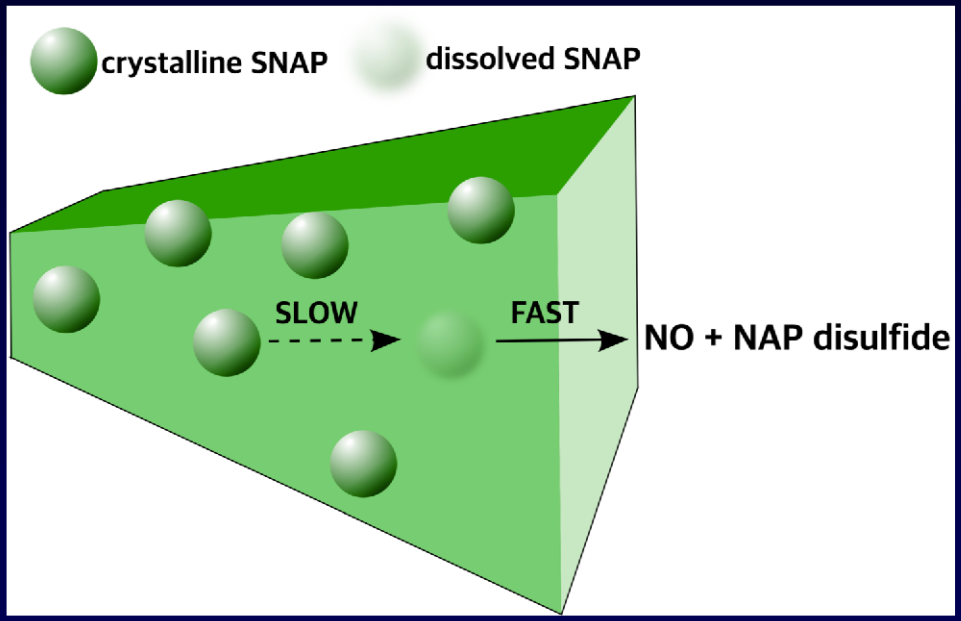
-stored in PBS (pH 7.4) at 37 °C
-soaking solutions changed daily
-SNAP/NAP/$(NAP)_2$ determined by LCMS

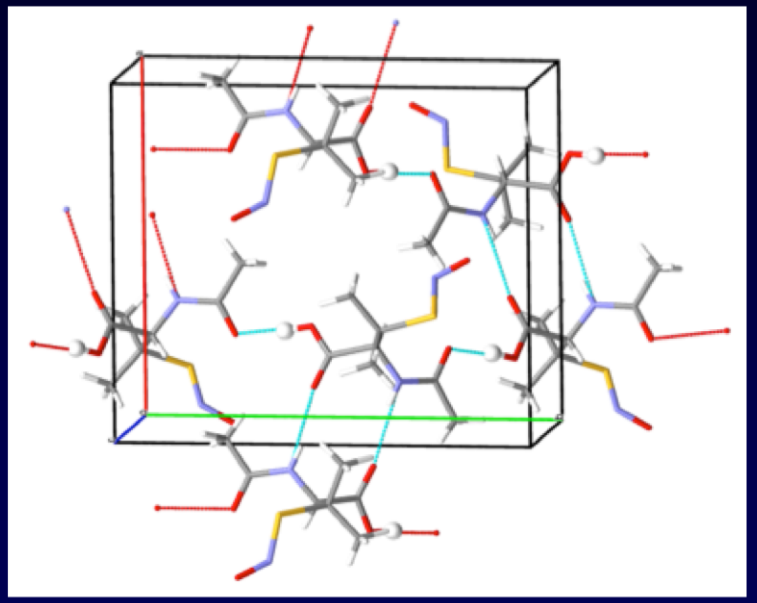
ACS Biomaterials Sci. & Eng., 2017

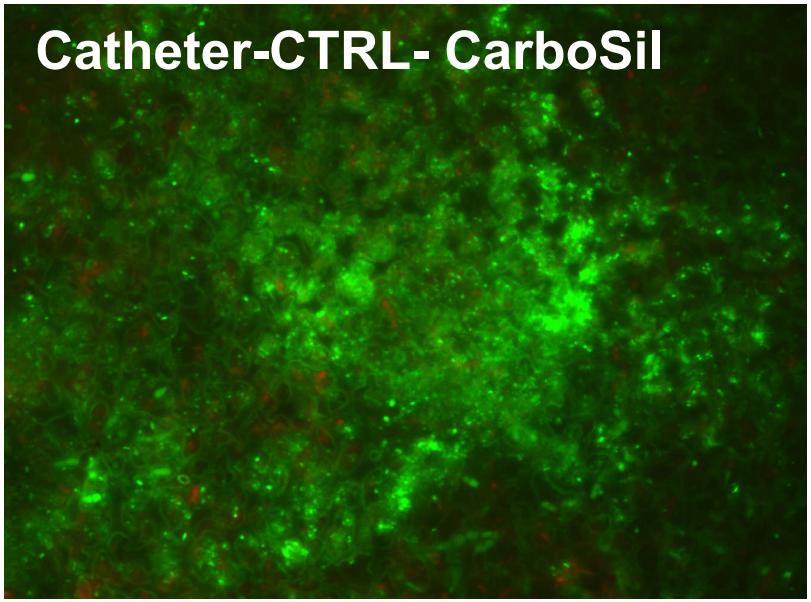


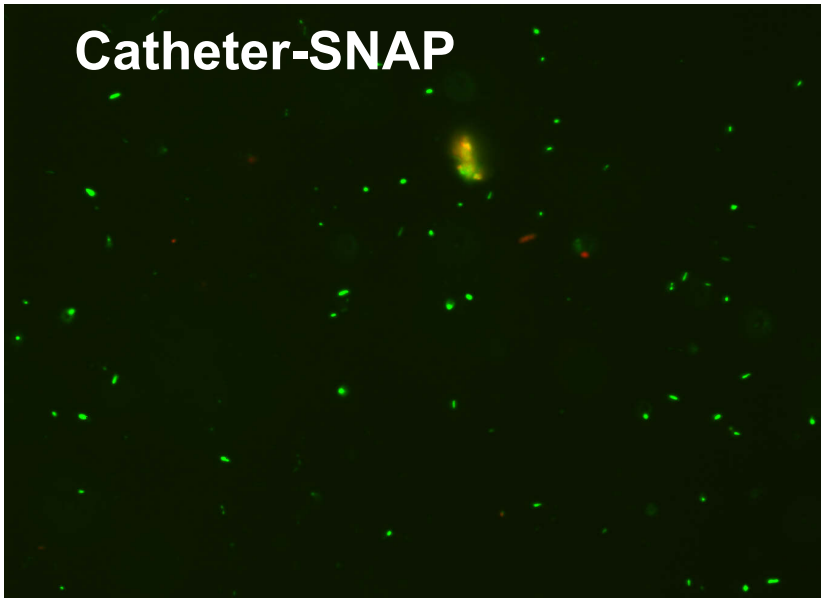


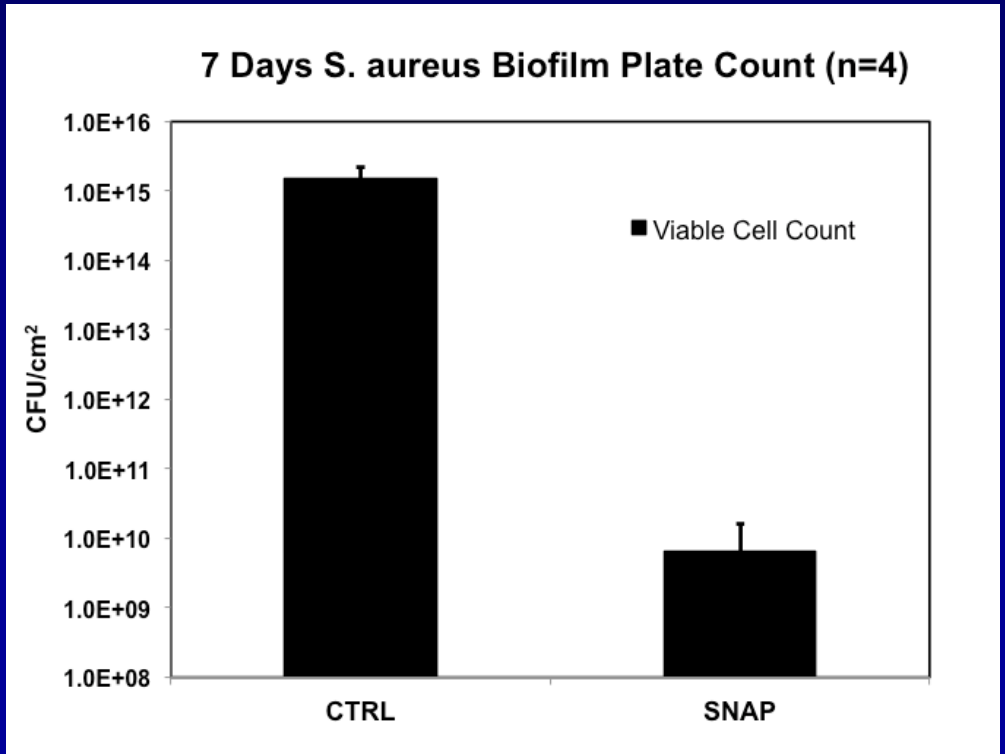
PXRD patterns of SNAP powder, blank CarboSil and 15 wt% SNAP-doped CarboSil film samples.



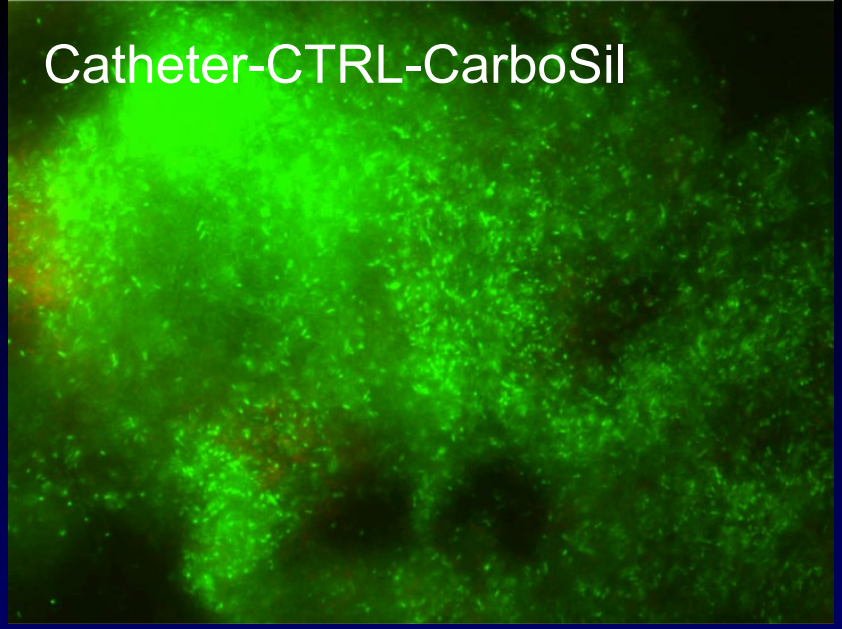


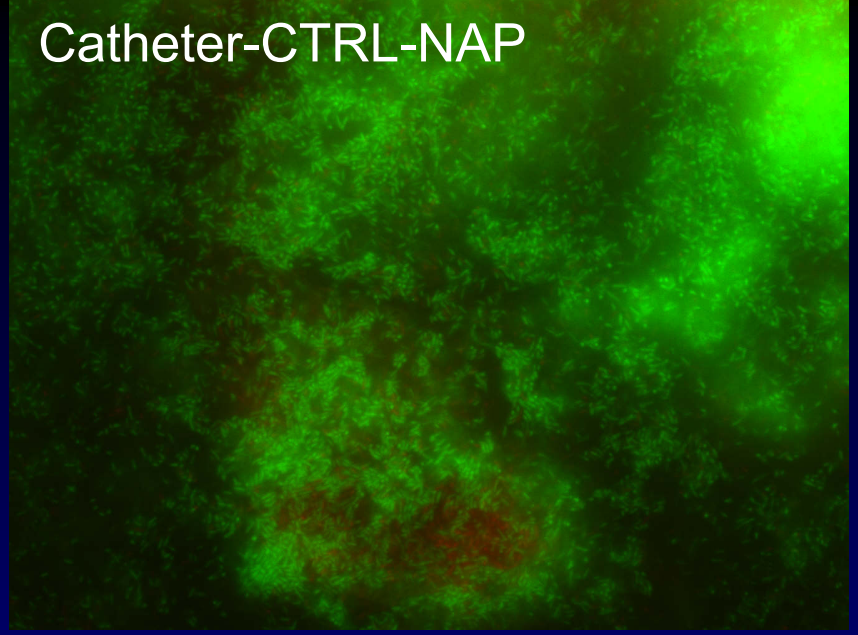




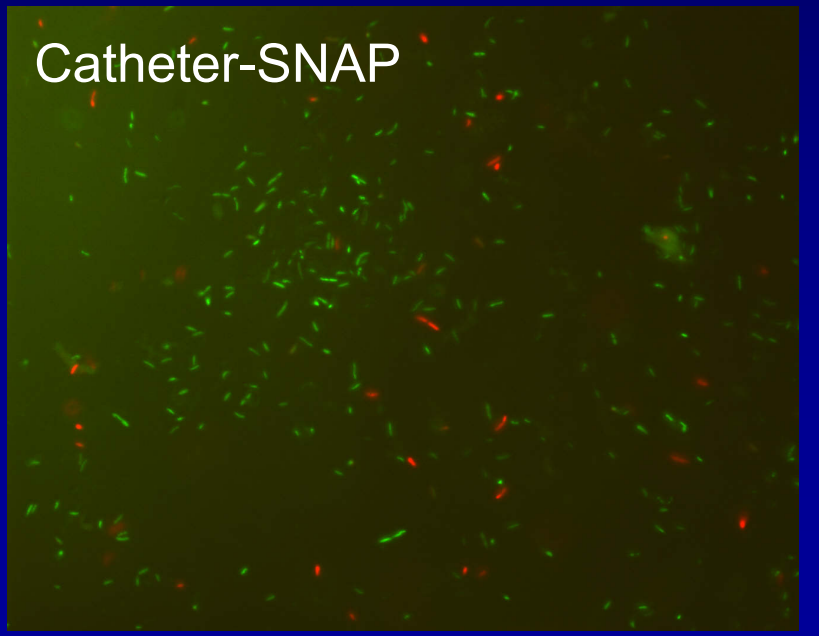


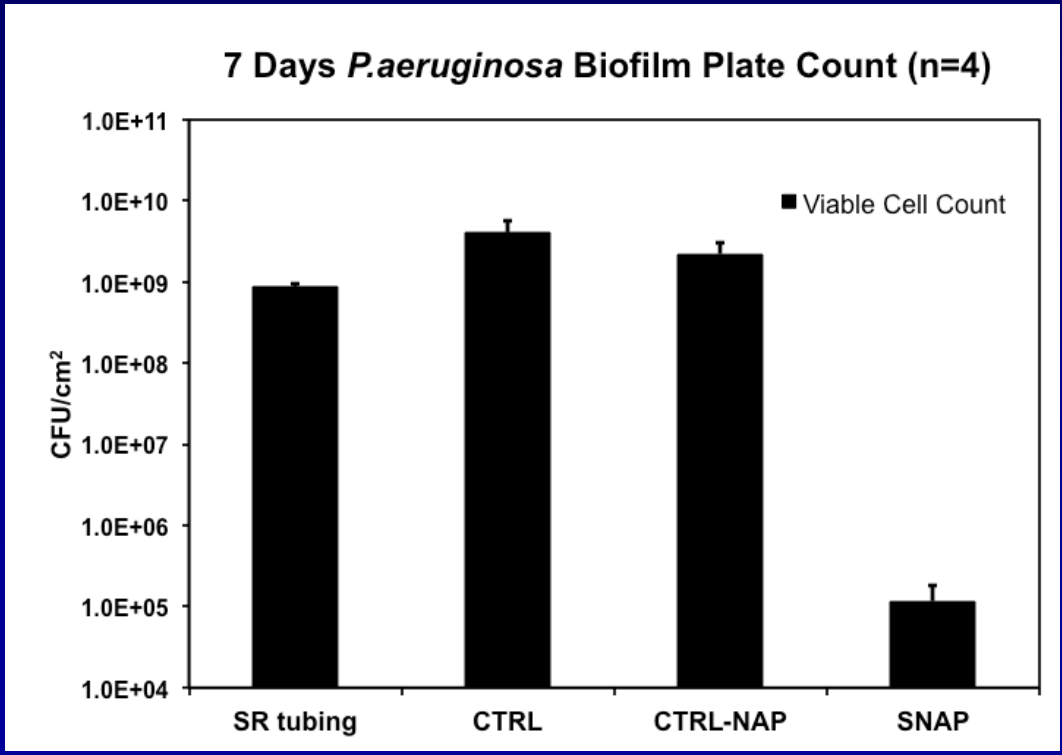
drip-flow bioreactor





CDC Bioreactor





ACS Biomaterials SCIENCE & ENGINEERING

Article

pubs.acs.org/journal/abseba

S-Nitroso-N-acetylpenicillamine (SNAP) Impregnated Silicone Foley Catheters: A Potential Biomaterial/Device To Prevent Catheter-Associated Urinary Tract Infections

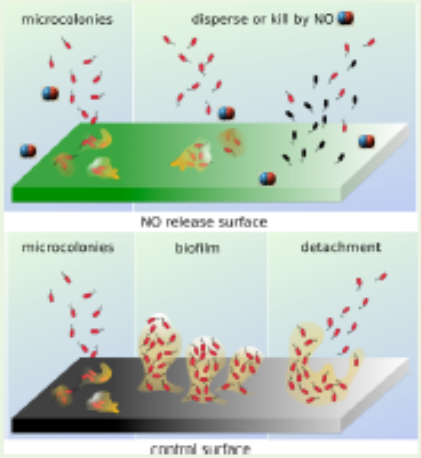
Alessandro Colletta,[†] Jianfeng Wu,[‡] Yaqi Wo,[†] Michael Kappler,[§] Hao Chen,[§] Chuanwu Xi,*[,‡] and Mark E. Meyerhoff*[,†]

[†]Department of Chemistry and [‡]Department of Environmental Health Sciences, University of Michigan, Ann Arbor, Michigan 48109, United States

[§]Biocrede Inc., Plymouth, Michigan 48170, United States

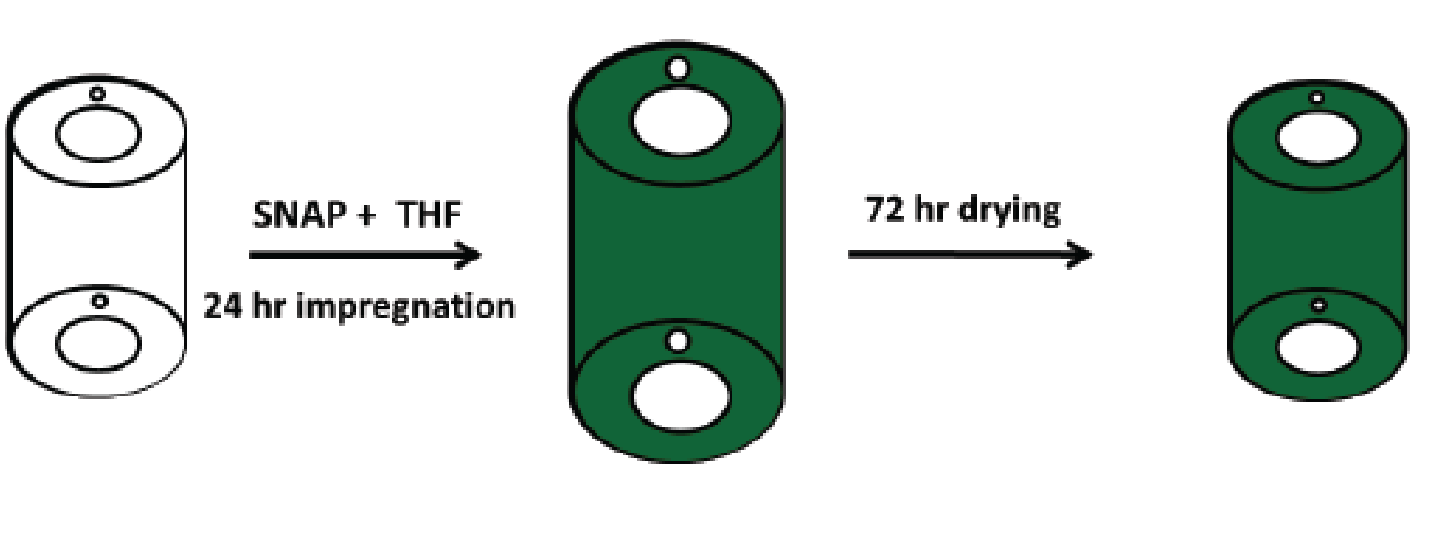
Supporting Information

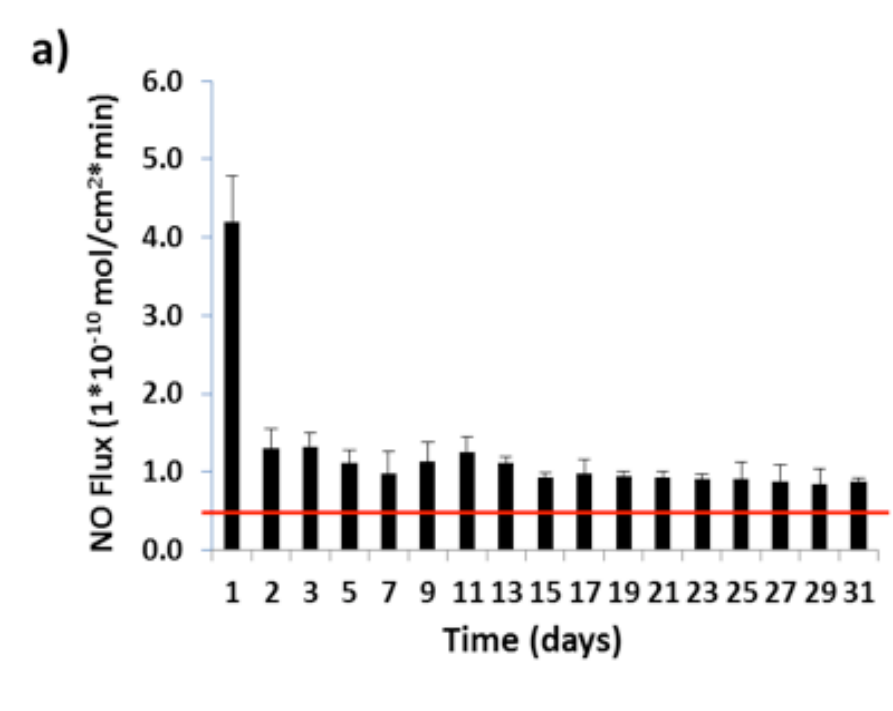
ABSTRACT: Urinary Foley catheters are utilized for management of hospitalized patients and are associated with high rates of urinary tract infections (UTIs). Nitric oxide (NO) potently inhibits microbial biofilm formation, which is the primary cause of catheter associated UTIs (CAUTIs). Herein, commercial silicone Foley catheters are impregnated via a solvent swelling method with *S*-nitroso-*N*-acetylpenicillamine (SNAP), a synthetic NO donor that exhibits long-term NO release and stability when incorporated into low water-uptake polymers. The proposed catheters generate NO surface-fluxes >0.7×10^{-10} mol min^{-1} cm^{-2} for over one month under physiological conditions, with minimal SNAP leaching. These biomedical devices are demonstrated to significantly decrease formation of biofilm on the surface of the catheter tubings over 3, 7, and 14 day periods by microbial species (*Staphylococcus epidermidis* and *Proteus mirabilis*) commonly causing CAUTIs. Toxicity assessment demonstrates that the SNAP-impregnated catheters are fully biocompatible, as extracts of the catheter tubings score 0 on a 3-point grading scale using an accepted mouse fibroblast cell-line toxicity model.



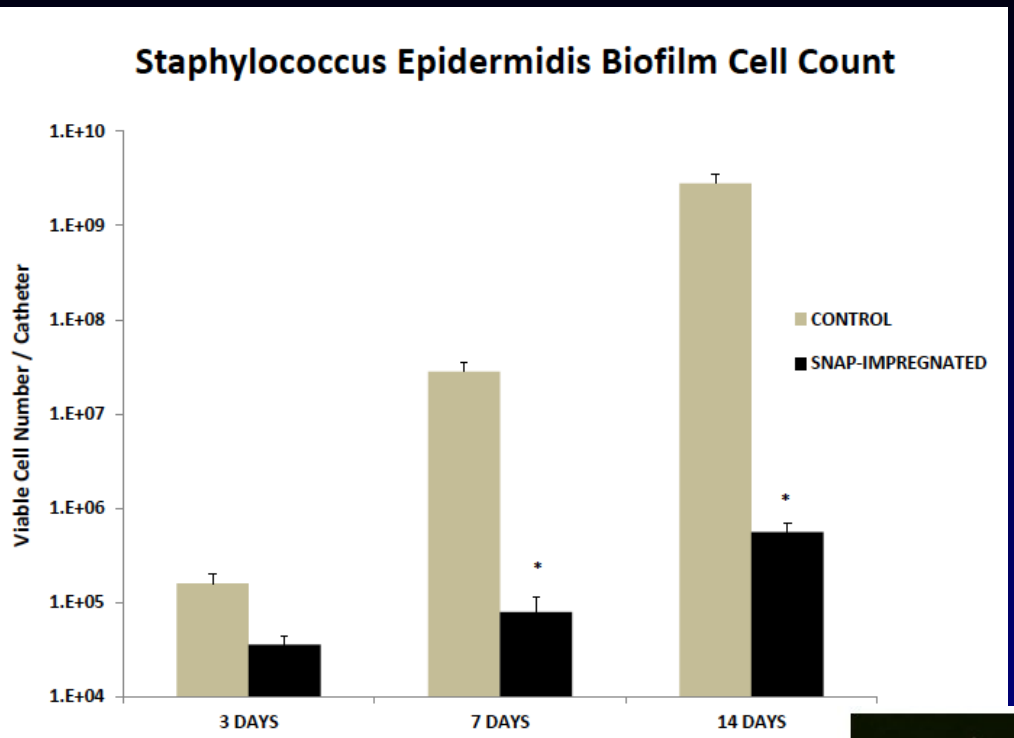
2015

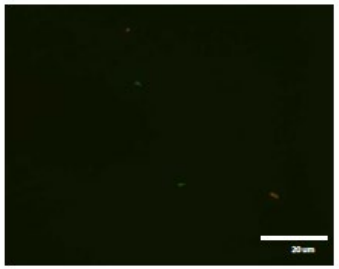
SNAP Impregnation into Catheter Tubing (e.g. Foley Catheters)

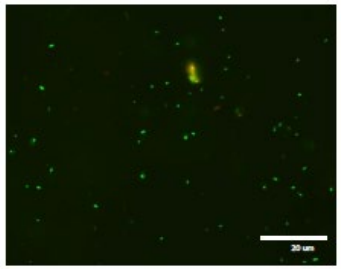


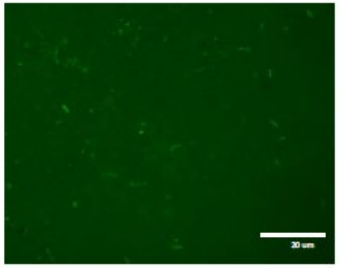


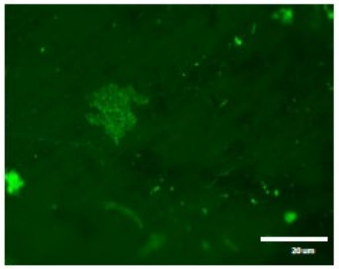
Antimicrobial Activity of SNAP Impregnated Foley Catheters Toward *Staph. epidermis* in CDC Bioreactor for 3, 7, and 14 d

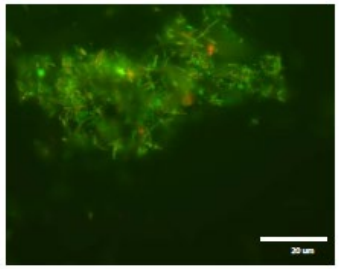


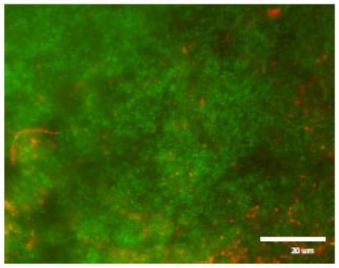

3 Days Biofilm – SNAP Catheter


7 Days Biofilm – SNAP Catheter


14 Days Biofilm – SNAP Catheter

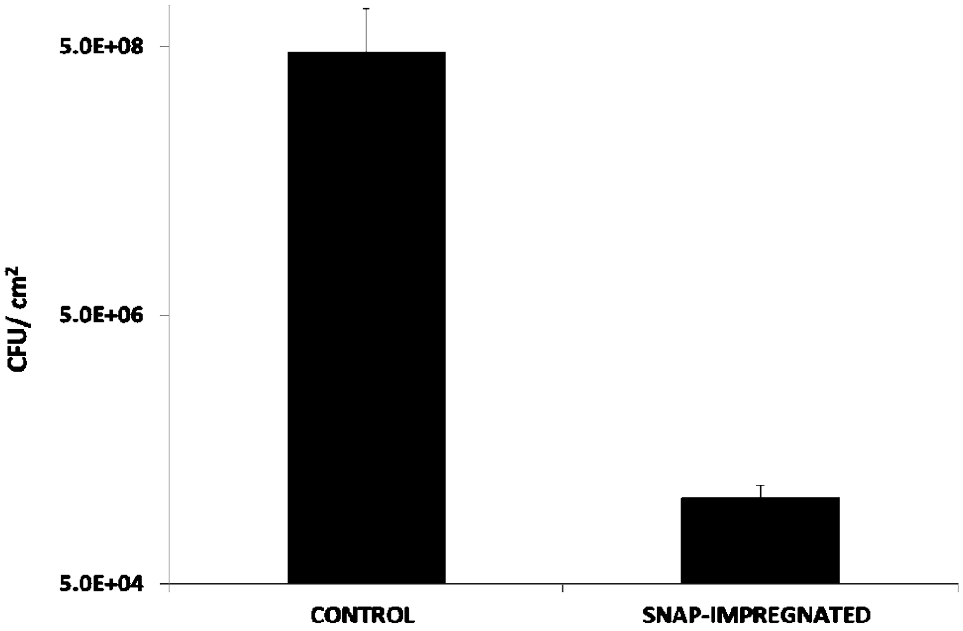

3 Days Biofilm – Control Catheter


7 Days Biofilm – Control Catheter

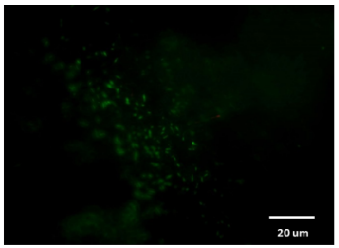

14 Days Biofilm – Control Catheter

Antimicrobial Activity of SNAP Impregnated Commercial Silicone Rubber Foley Catheters Toward *P. mirabilis* in CDC Bioreactor for 3 d

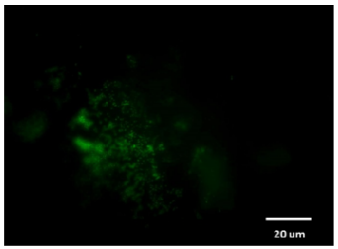
a)



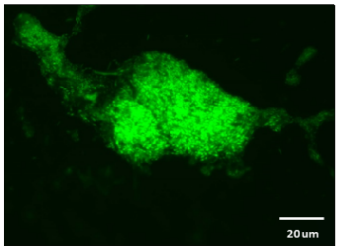
b)



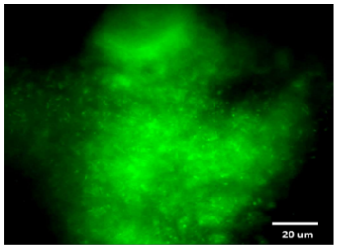
3 Days Biofilm – 24 Hr pre-soaked SNAP Catheter



3 Days Biofilm – 24 Hr pre-soaked SNAP Catheter

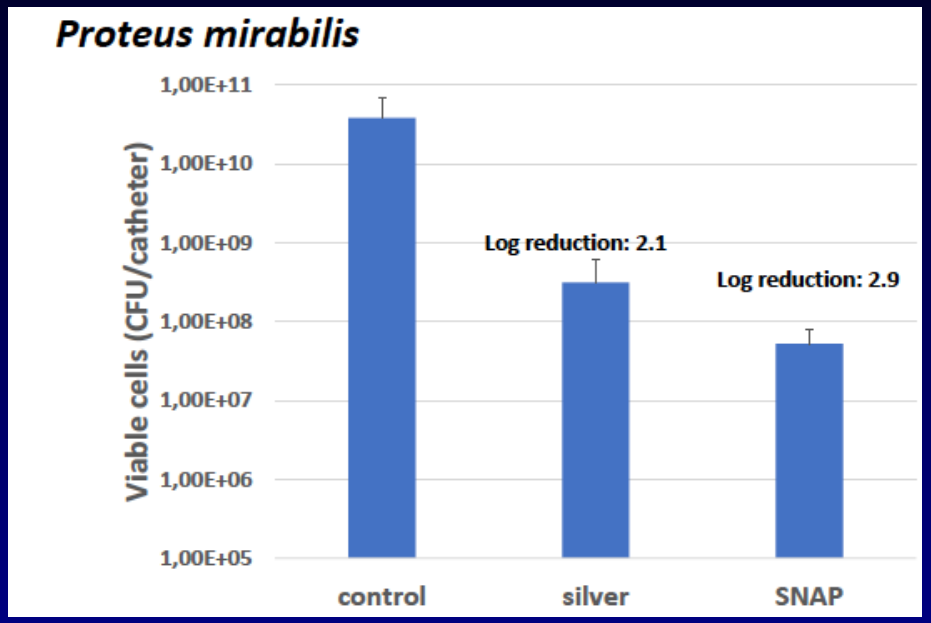


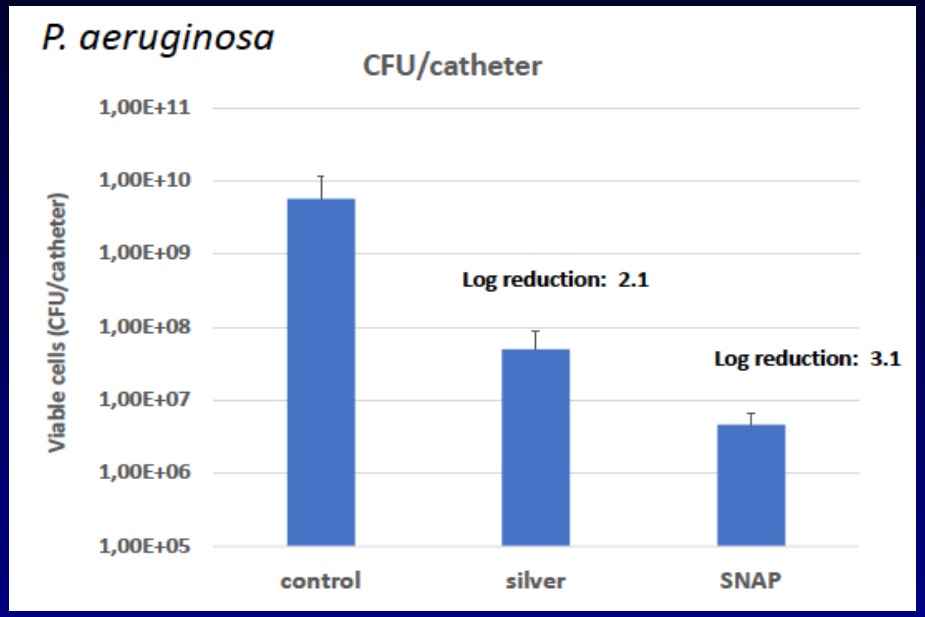
3 Days Biofilm – Control Catheter

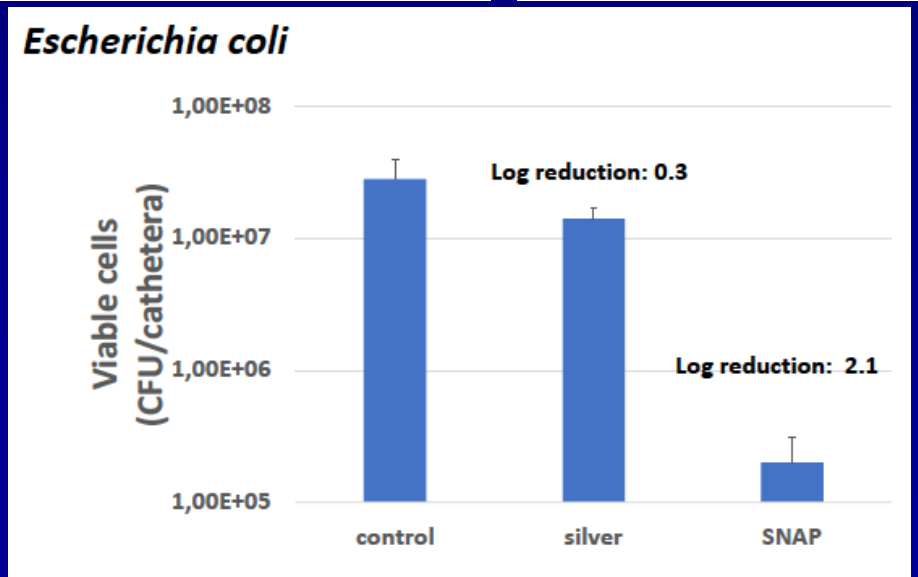


3 Days Biofilm – Control Catheter

Comparison of Commercial Ag^{o} Particle Impregnated Urinary Catheters vs. New SNAP-Doped Catheters



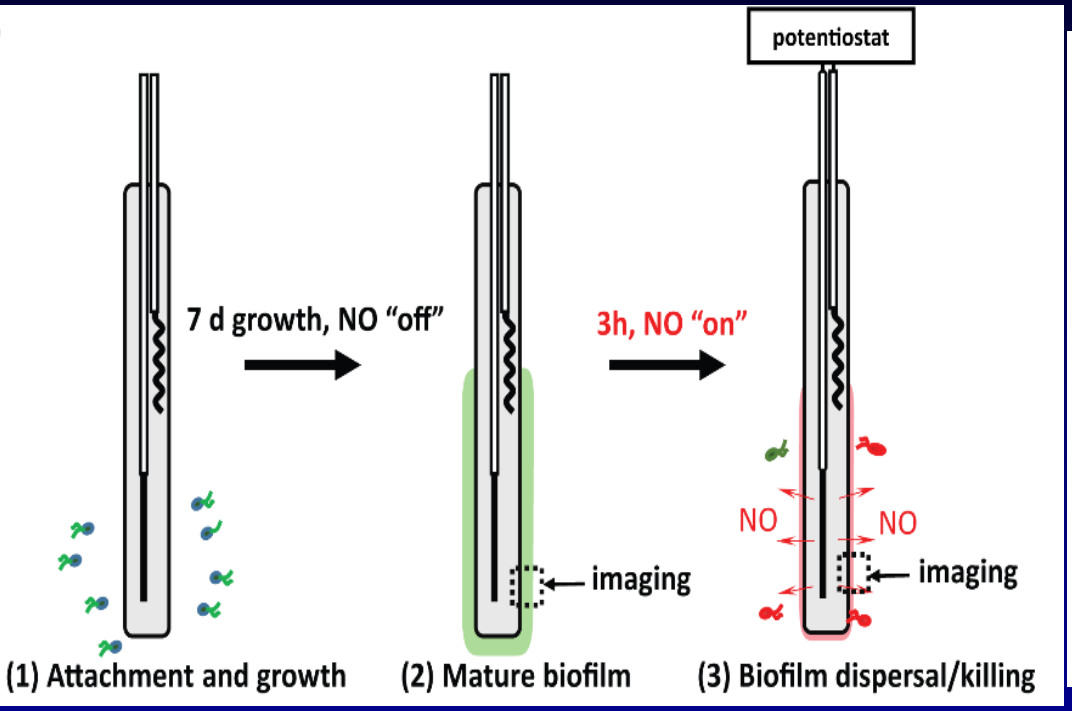


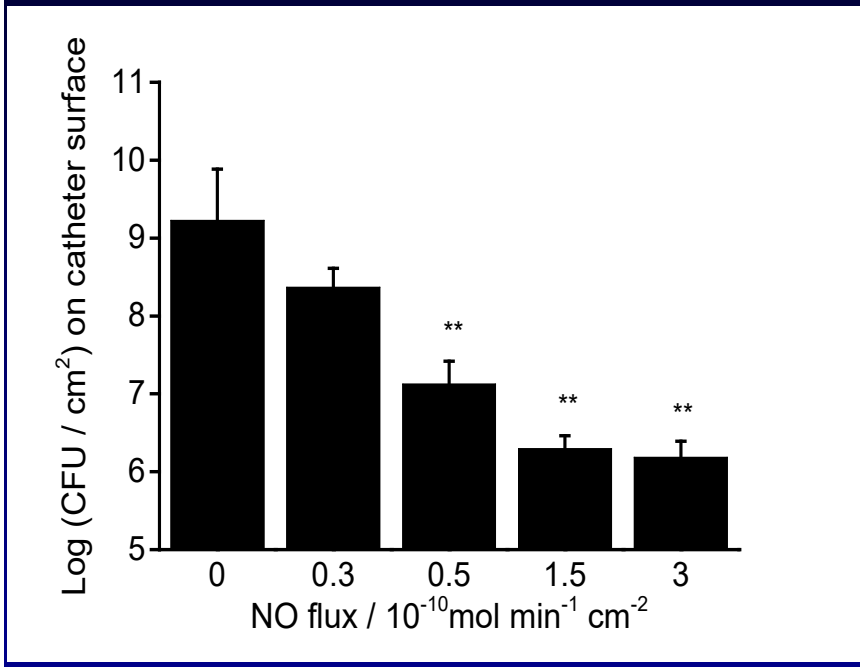


7-day experiments within CDC bioreactor

Note:
NO reléase
Catheter only had 4 wt% SNAP

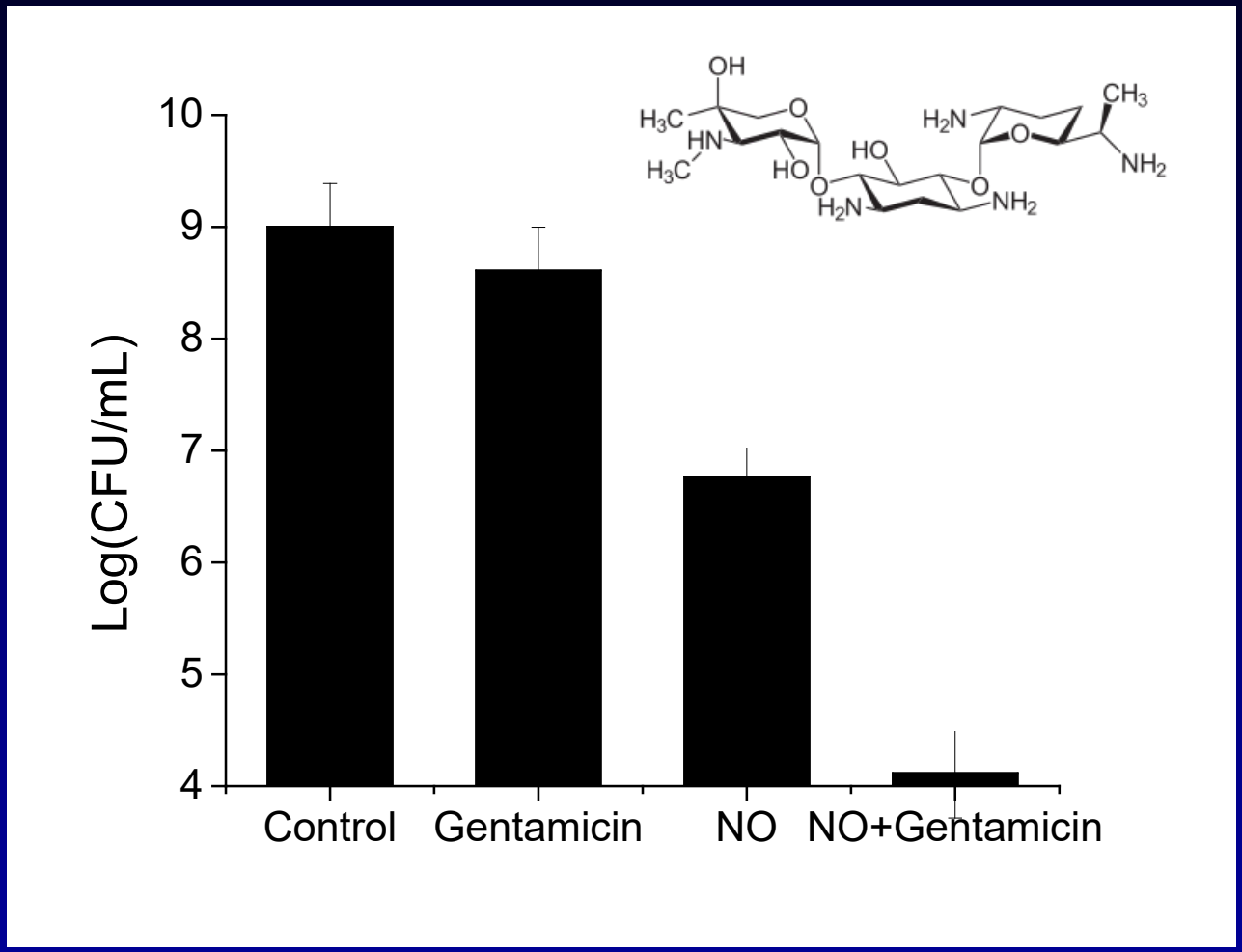
Removal of Mature Biofilms





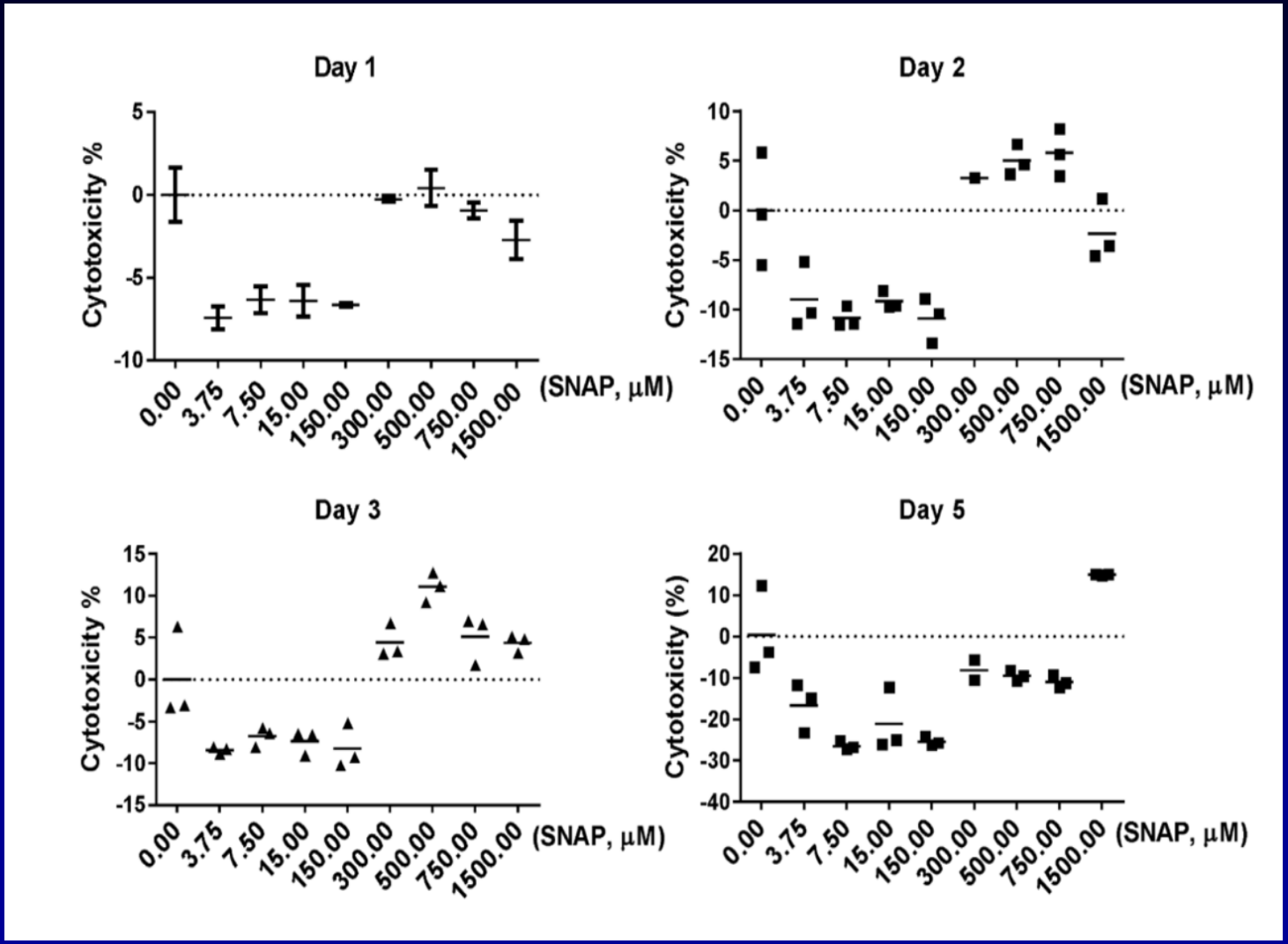
P. aeruginosa biofilm grown for 7 d before any treatment

Synergy of NO with Antibiotic Treatment



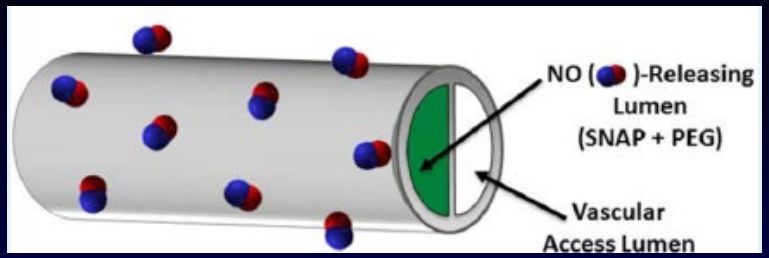
NO release + antibiotic (100 μg/mL) treatment for 3 h on 7 d *P. aeruginosa* biofilms

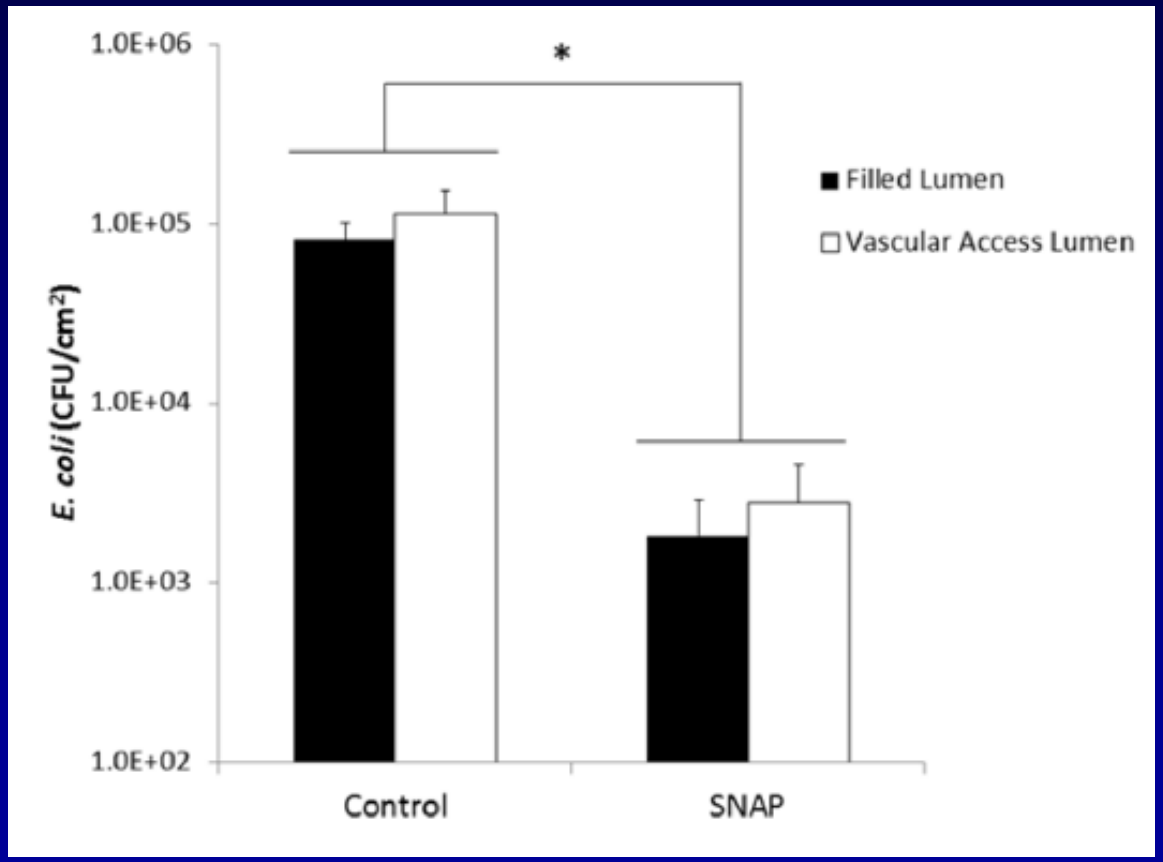
Cytotoxicity Study of SNAP on Human Cells (AD-293 cells—Embryonic Kidney Cell line)



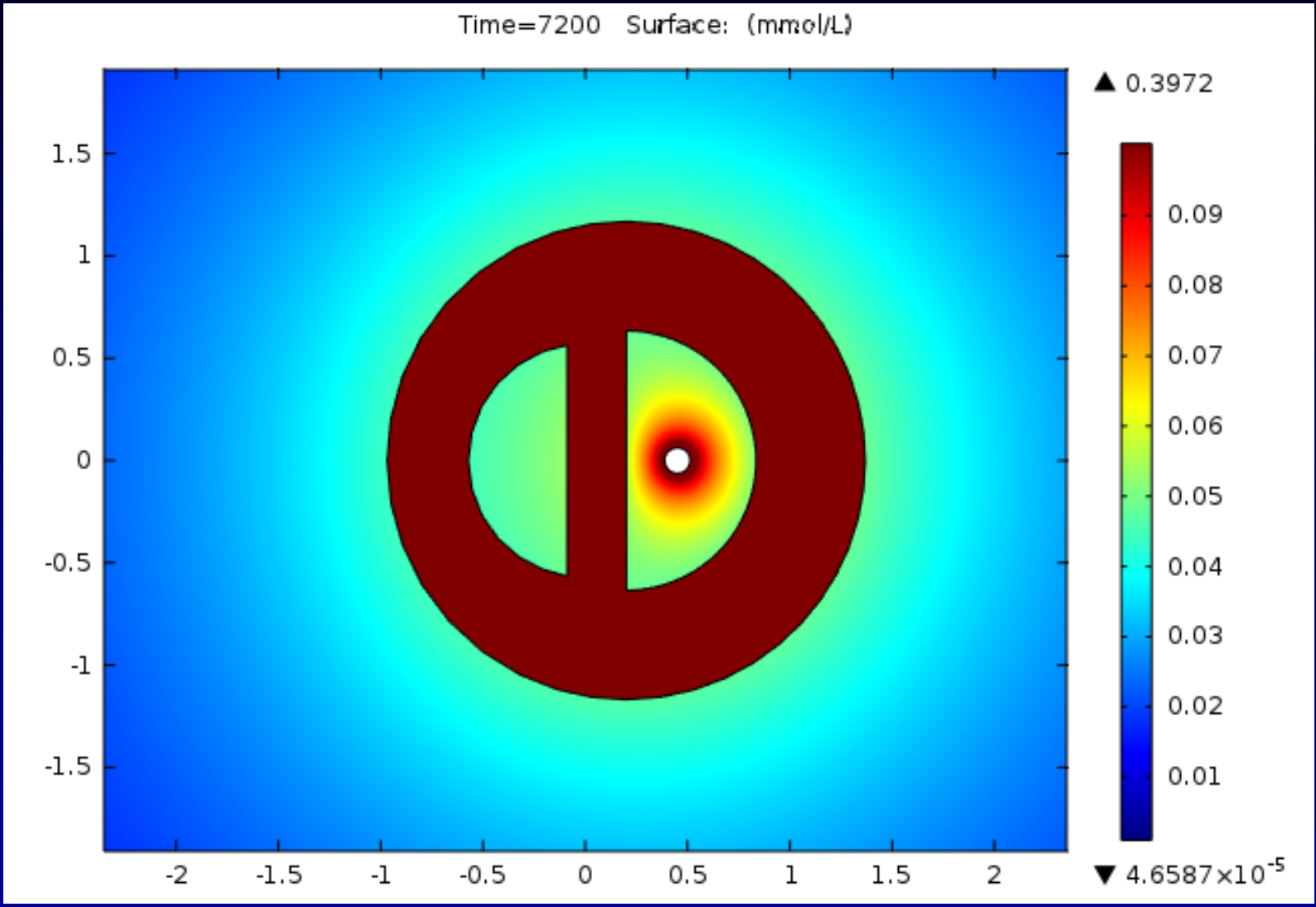
Toxicity assay based on LDH activity measurements

Alternate Configuration: Filling and Sealing One Lumen of Dual Lumen Catheters – Nothing Comes Out Except NO





Finite Element Simulations of NO Concentration Profile in Dual Lumen Catheter Configuration (Comsol Software)



Partition coefficient $K = S_{silicone} / S_{water} = 7$

D_{NO} (polymer) = D_{NO} (water)

NO-Release Collaborators/Support

Current/Recent Graduate Students/Undergraduates/Post-Docs

Alex Wolf
Hang Ren
Zheng Zheng
Gergely Lautner
Alessandro Colletta
Andrew Hunt
Bo Peng
Kamila Konopinska
Yu Qin
Dipankar Koley
Elizabeth Brisbois
Hitesh Handa
Xuewei Wang
Woonghee Lee
Jianfeng Wu
Melissa Reynolds
Qi Zhang
Orsi Lautner
Wenyi Cai
Yaqi Wo
Wen Wen
Kyoung-Ha Cha
Alex Ketchum
Joanna Zajda
Josh Doverspike

Faculty/Other

Nicolai Lehnert (U of M)
Prabir Roy-Chaudhury (U of Cinc.))
Robert Bartlett (UM-Surgery)
Chuanwu Xi (UM-SPH)
Yu Qin (U of M)

Current Financial Support

- NIH: HL-128337
- NIH: HL-132037
- NIH: EB-023294
- NIH: HD-087071
- NIH: EB-024038
- JDRF / NIH: EB-019566
- MC3 Inc./ NOTA Labs
- BICI/ Beijing-Epione
- Instrumentation Laboratory