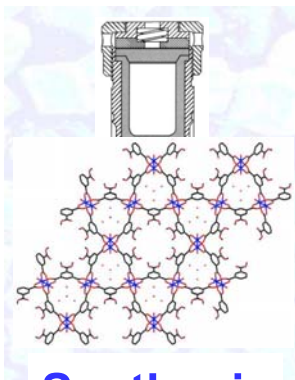




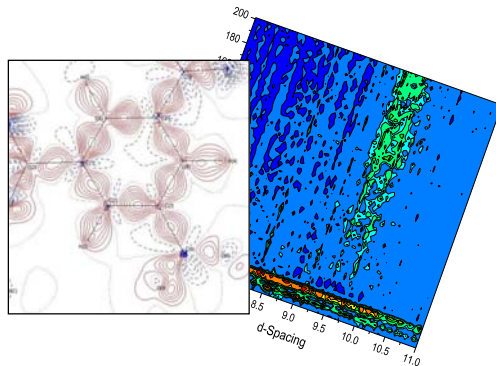
Storing and delivering gases using zeolites and MOFs



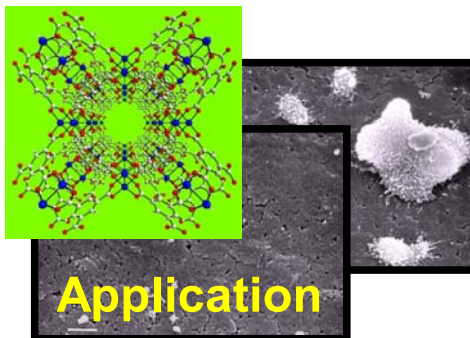
Russell Morris
University of St Andrews



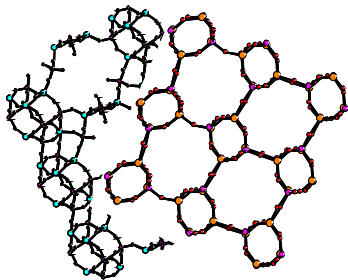
Synthesis



Characterisation



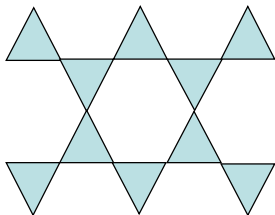
Application



Ionothermal Synthesis

Nature (2004)

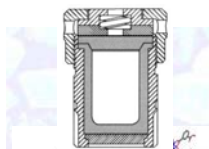
J. Am. Chem. Soc. (2006)



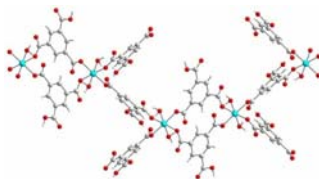
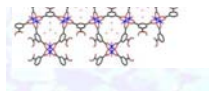
New Quantum Spin Liquids

Nature Chemistry (2011)

Angew. Chemie (2015)



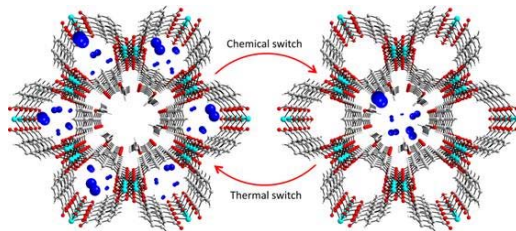
Synthesis



Chiral Induction

J. Am. Chem. Soc. (2007)

Nature Chemistry (2010)

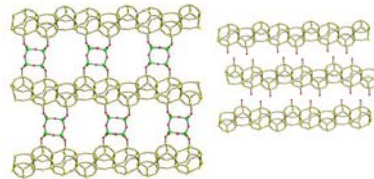


New MOFs with new properties

Nature Chemistry, (2009)

J. Am. Chem. Soc. (2010)

Nature Chemistry, (2011)



ADOR Chemistry

Nature Chemistry (2013)

Nature Chemistry (2015)

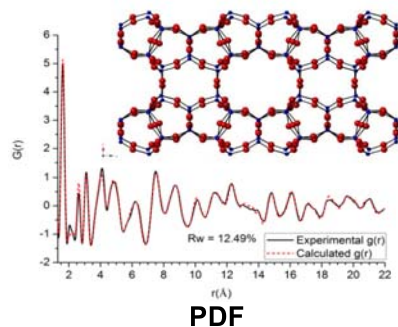
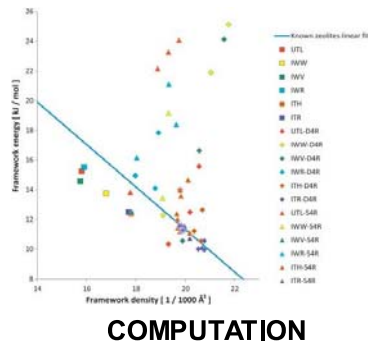
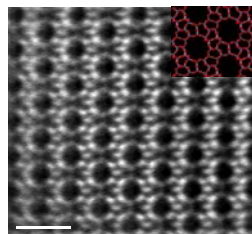
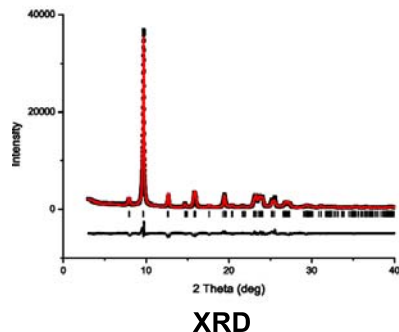
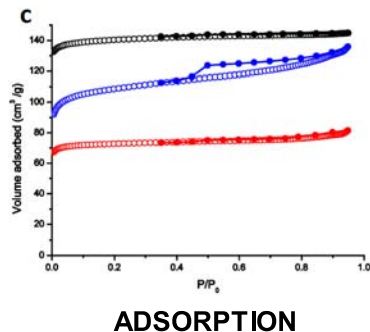
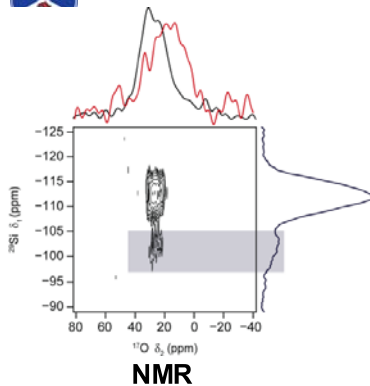
Nature Chemistry (2016)

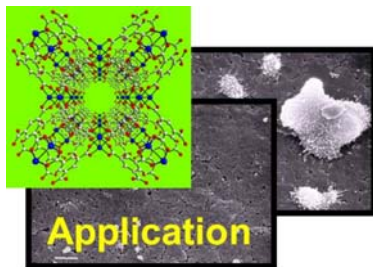
Nature Chemistry (2017)

J. Am. Chem. Soc. (2017)



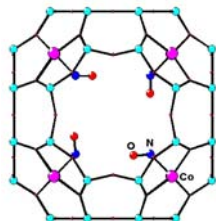
Characterisation





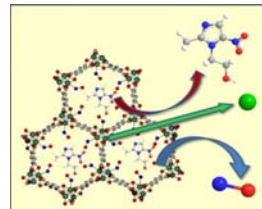
Zeomedix

Zeolites for medical applications



SASOL

Energy and Chemicals



MOFgen

MOF
Development
Spin Out
Company



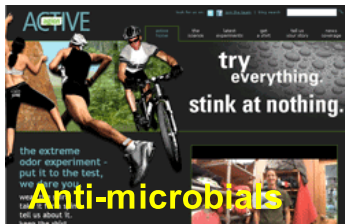
Pigments



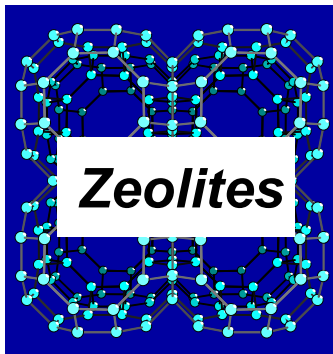
Ion exchange



Oil refining



Anti-microbials



Zeolites



Adsorption



Automotive Catalysis



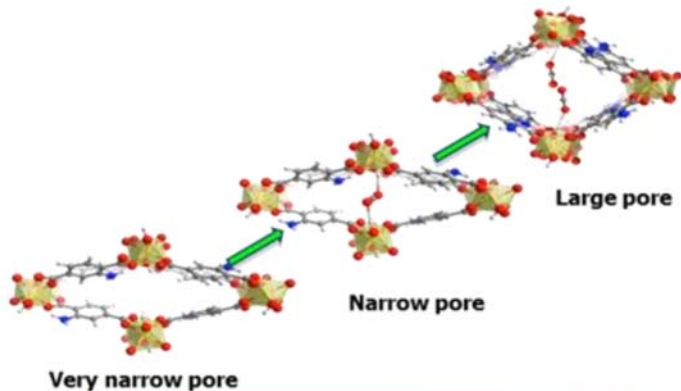
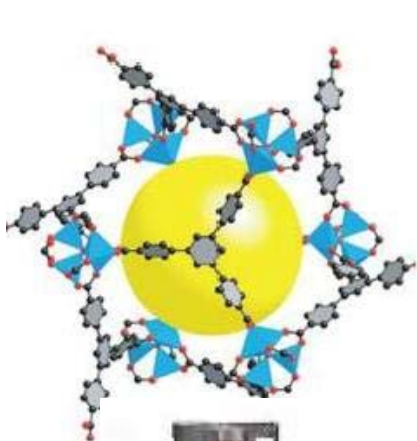
Medical Devices



Space exploration



MOFs - Gas tanks and wine racks



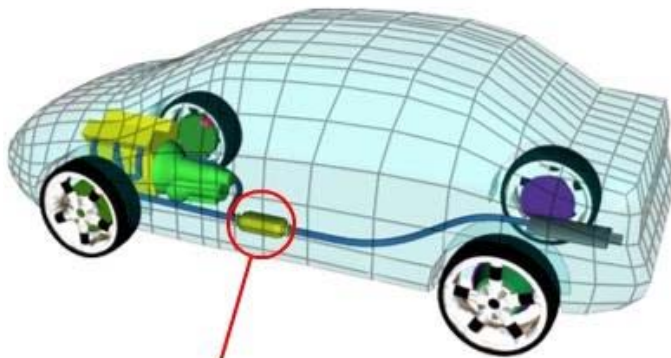


Which gases should we store (and why)?

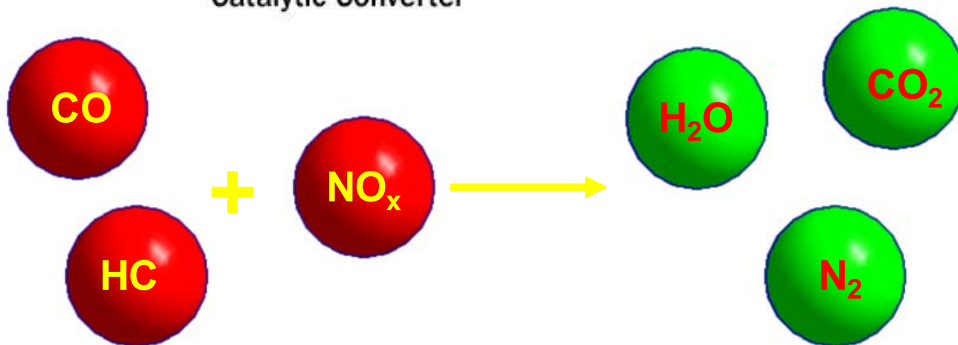
- Hydrogen *Energy*
- Methane *Energy*
- Other hydrocarbons *Energy*
- SO₂
Environmental
- CO₂
Environmental
- Ethylene *Agriculture/Food*
- Nitric Oxide *Biology/medicine*
- Hydrogen Sulfide *Biology/medicine*
- Carbon Monoxide *Biology/medicine*



Cleaner Cars and Greener Gases

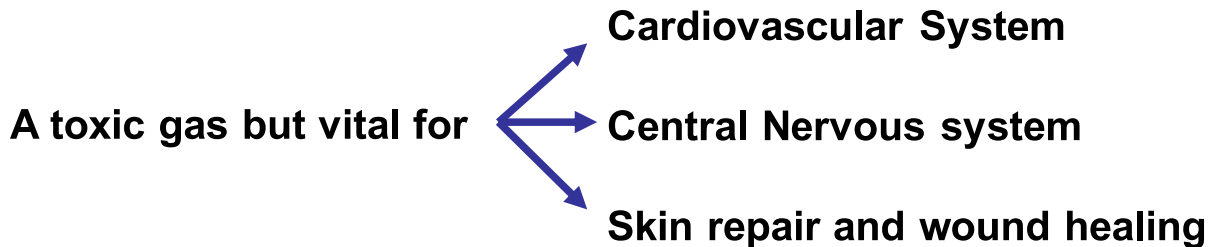


Catalytic Converter

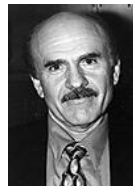




Nitric oxide – Friend or Foe?



The 1998 Nobel Prize for medicine awarded to Furchgott, Ignarro and Murad for discovery of NO as a signalling molecule in the cardiovascular system

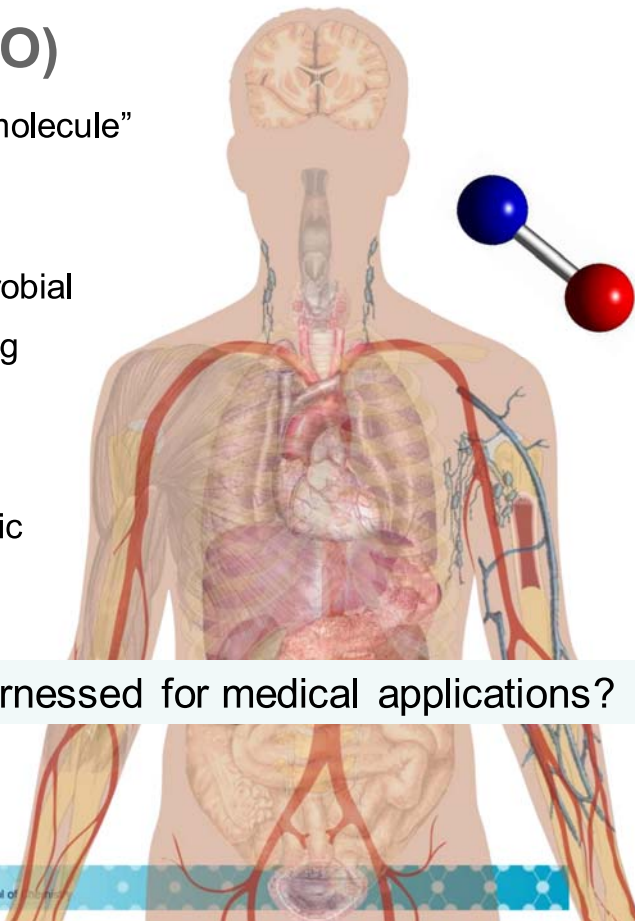
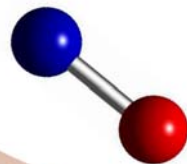




Nitric Oxide (NO)

“gaseous biological signalling molecule”

antimicrobial
wound healing
anti-thrombotic
vasodilatory
angiogenetic



Can its properties be harnessed for medical applications?

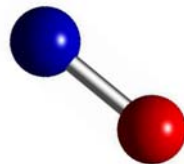


Nitric Oxide

difficult to administer

concentration dependent

toxic in high concentration



Requirement to deliver controlled dosage for specific durations

Market seeks a SAFE and effective delivery method



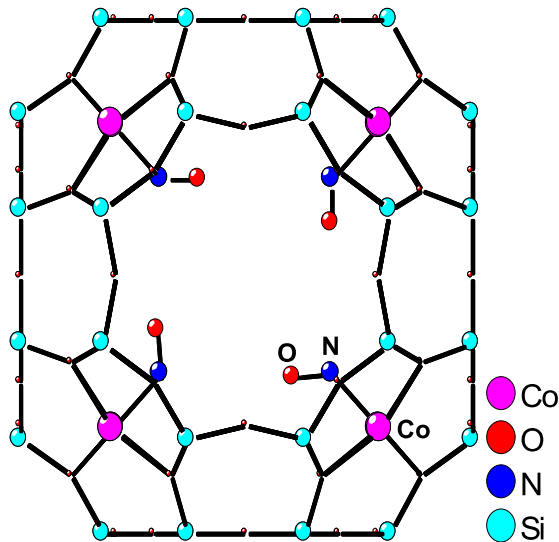
Zeolites and MOFs

- Can we use Zeolites or MOFs to store and deliver NO?
 - Issues
 - Toxicology
 - Chemical stability (particularly in contact with physiological solutions)
 - Opportunities
 - High gas storage capacities
 - Tailorable structures with unusual properties
 - Biocompatibility?
 - Which structures
 - Zeolites with high numbers of extraframework cations
 - MOFs with accessible metal sites



Crystal Structure of Co-LTA NO complex

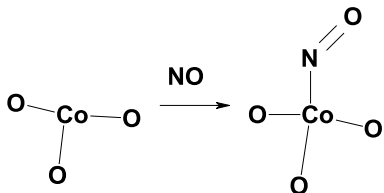
- XRD
 - K. Seff, Inorg Chem 1979
- Infra Red
 - Lunsford, Inorg Chem, 1978
- Theoretical
 - Henao, J. Mol. Cat. A, 2004



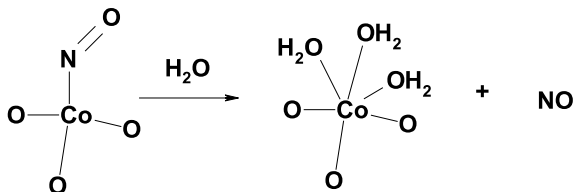


Can we use zeolites to deliver NO?

- From catalytic studies we know that NO makes a complex with the metal ions

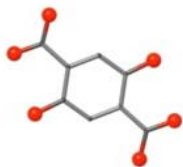


- Need a simple way of releasing NO from the complex?





MOFs – “Crystalline Sponges”

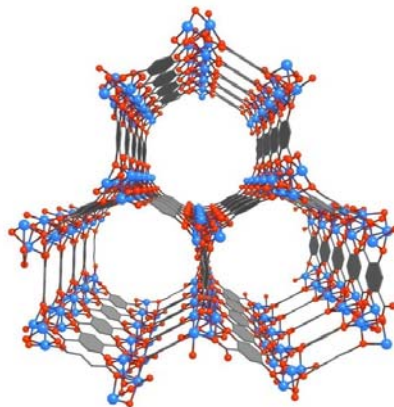


organic linker

+



metal ion or
cluster

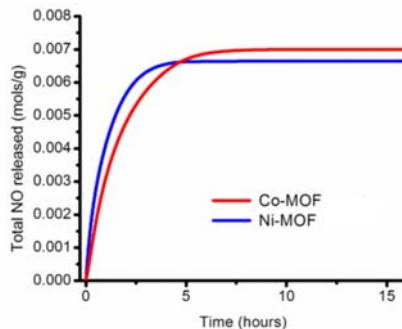
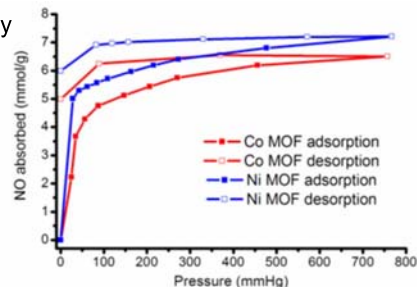
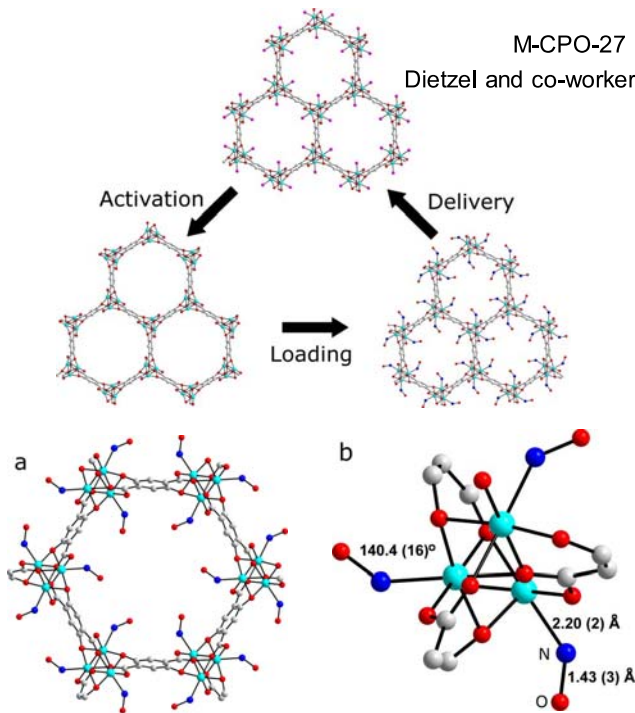


extended framework structures

- **flexible chemical composition**
- **many possible structures**
- **very high porosity**



M-CPO-27: Exceptional performance over the whole adsorption-storage-release cycle

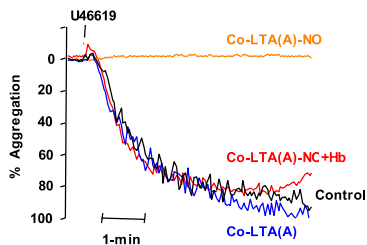
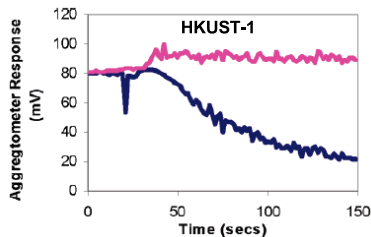


McKinlay et al, *J. Am. Chem. Soc.* 2008



Biology: Anti-thrombosis Materials

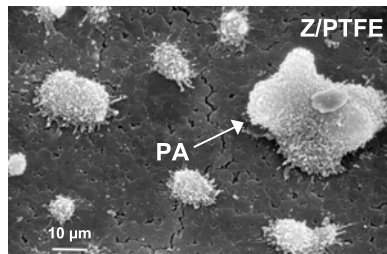
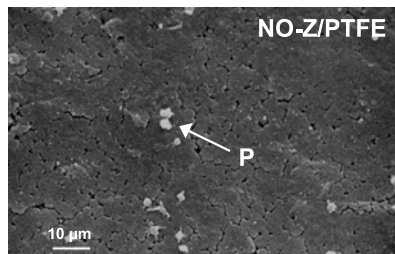
- Platelet aggregation
 - Both zeolites and MOFs inhibit platelet aggregation



Paul Wheatley

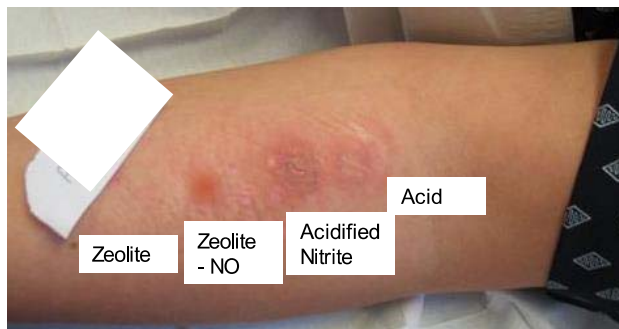
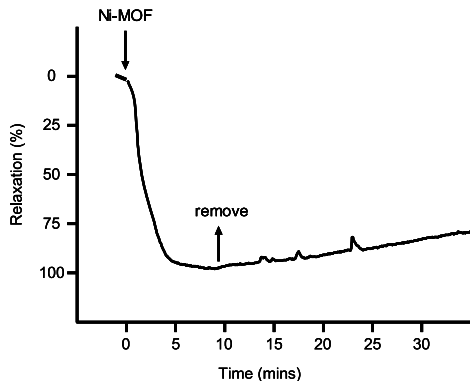
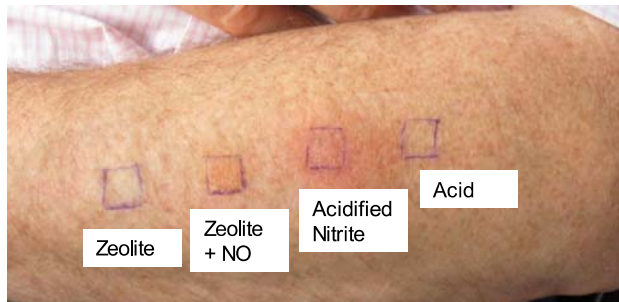
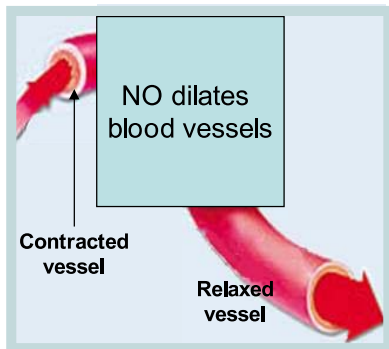


- Platelet Adhesion





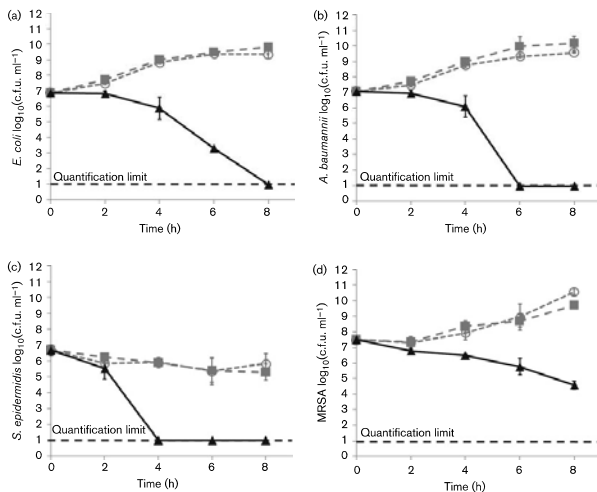
Dermatology Studies



No inflammation! Unlike competitor acidified nitrite



Anti-Bacterial NO zeolites



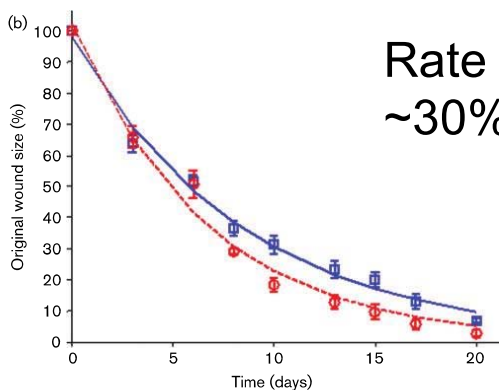
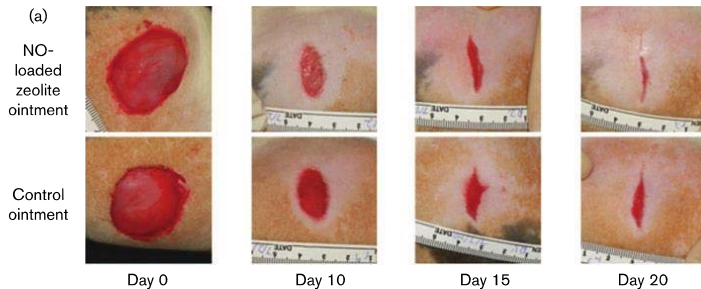
(a) *E. coli*, (b) *A. baumannii*, (c) *S. epidermidis*, (d) MRSA

Neidrauer et al Journal of Medical Microbiology (2014), 63, 203–209

Organism	Log reduction (NO–zeolite versus initial)	Log reduction (NO–zeolite versus untreated)
<i>E. coli</i>	5.9	8.4
<i>A. baumannii</i>	6.1	8.6
<i>S. epidermidis</i>	5.7	5.1
MRSA	2.9	6.0
<i>C. albicans</i>	3.0	3.1



Wound Healing study

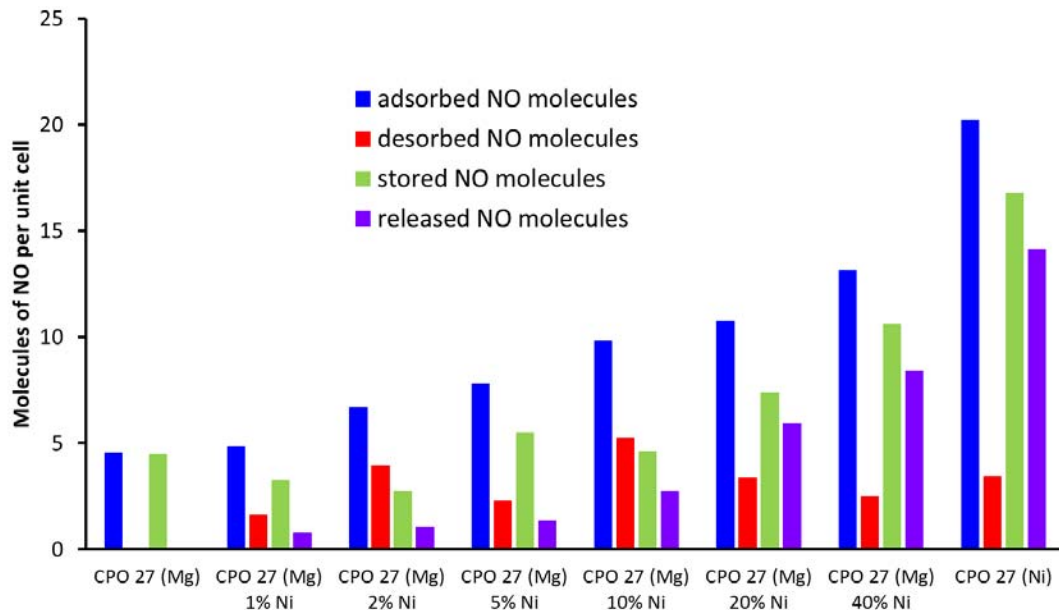


Rate of wound closure
~30% faster

Neidrauer et al Journal of Medical
Microbiology (2014), 63, 203–209
Zeomedix



Tuning NO Delivery from CPO-27



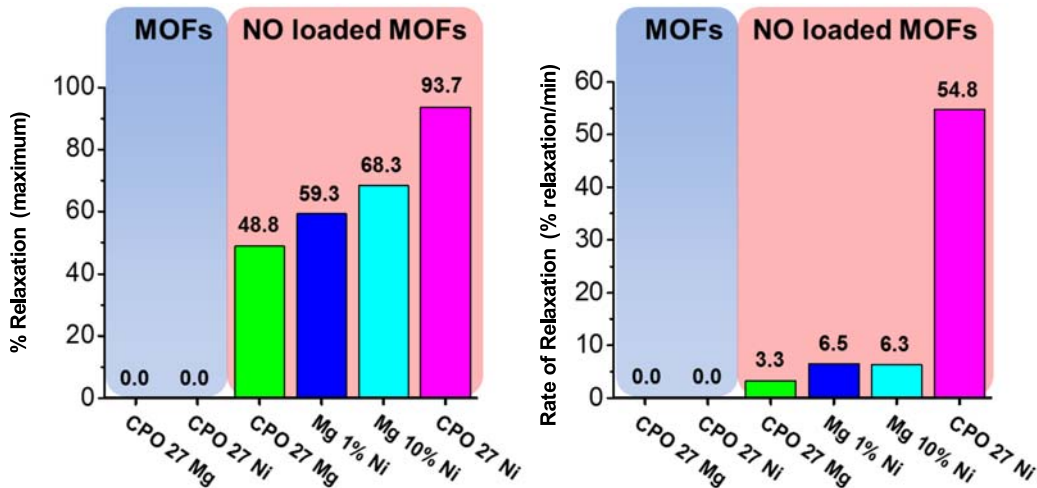
D. Cattaneo *et al*, *RSC Adv.*, 2016, 6, 14059



Tuning Biological Response

Porcine Coronary Artery Relaxation

measure the tension of artery at fixed length in the presence of NO loaded MOFs



% and rate of relaxation increase with NO dose, controlled by MOF Mg/Ni ratio



Multifunctional antibacterial properties

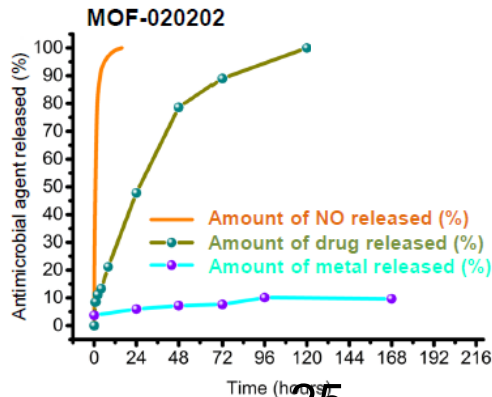
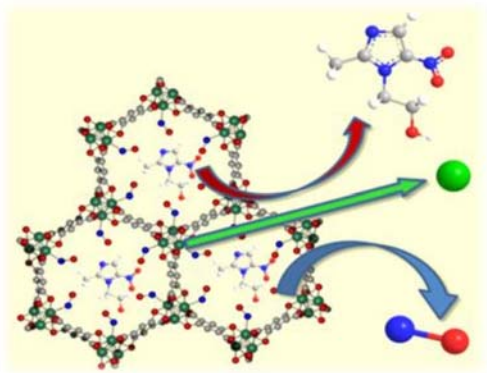
- The anti-bacterial nature of MOFs comes from 3 different areas.
- Bacteriostatic or bactericidal metal ions
- Anti bacterial gases (e.g. NO)
- Anti Bacterial organic molecules (e.g. antibiotics)
- A combination of all three can be used from the same MOF!



Multifunctionality of Antimicrobial MOFs

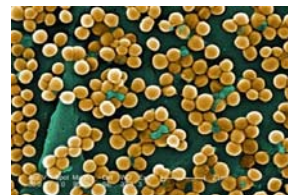
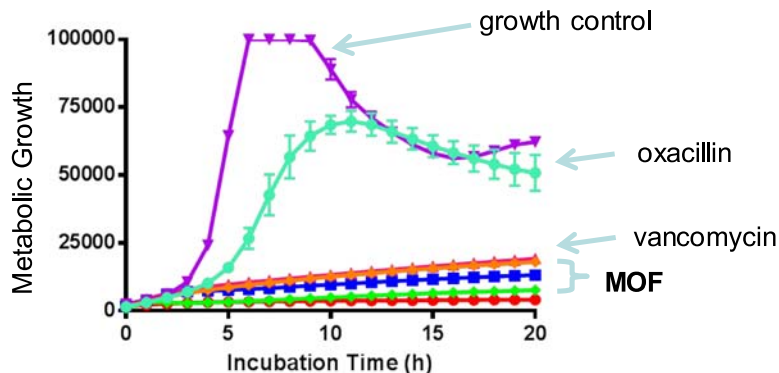
Store / Release

- antimicrobial metals from framework
- antibacterial gases (e.g. nitric oxide) from pores
- antimicrobial molecules from pores or framework (e.g. antibiotics, biocides, therapeutics)

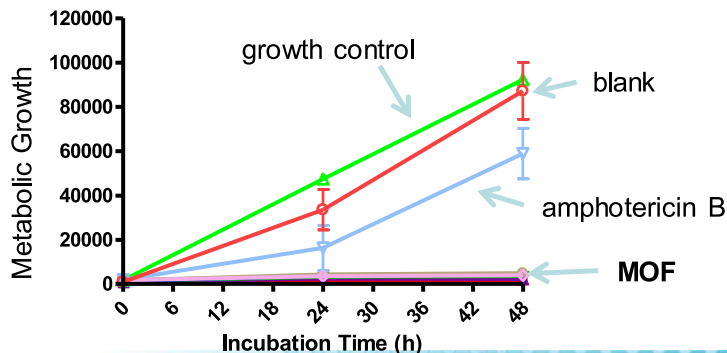




Proven Antimicrobial Efficacy



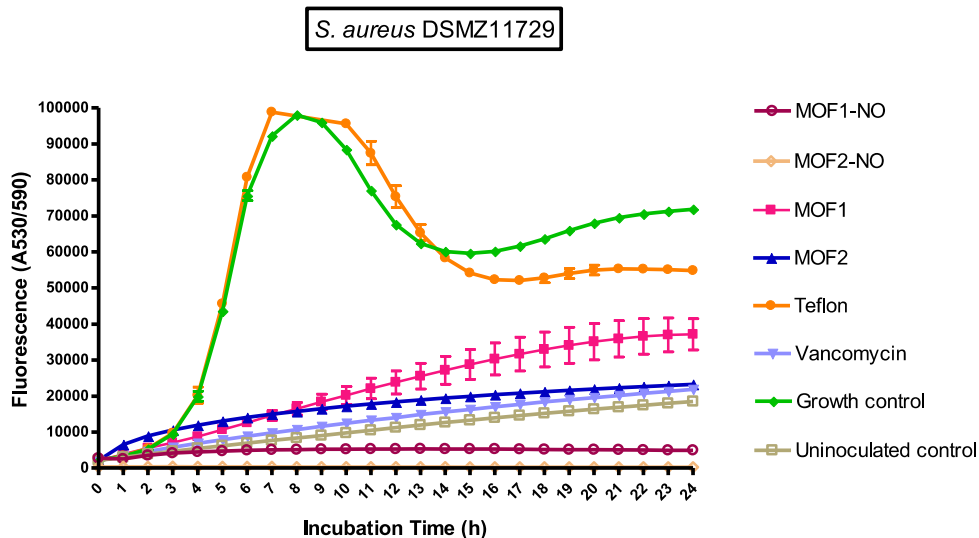
MRSA (Gram +ve)
top 5 of HAls
skin infection pneumonia,
sepsis



A. niger
black mould
contaminant of food



Multifunctional antibacterial Activity

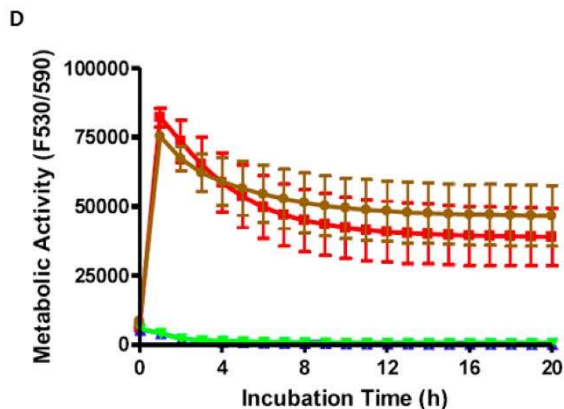
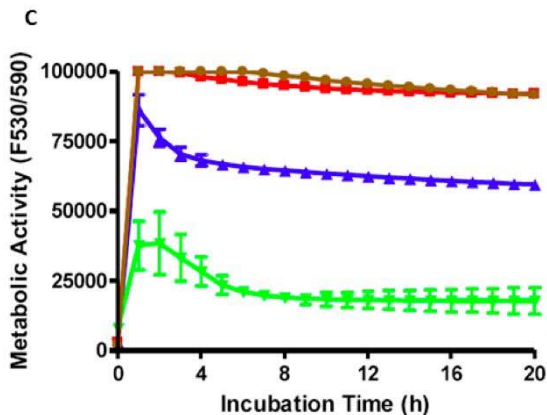


MOFs are antibacterial. MOF + NO shows outstanding antibacterial activity



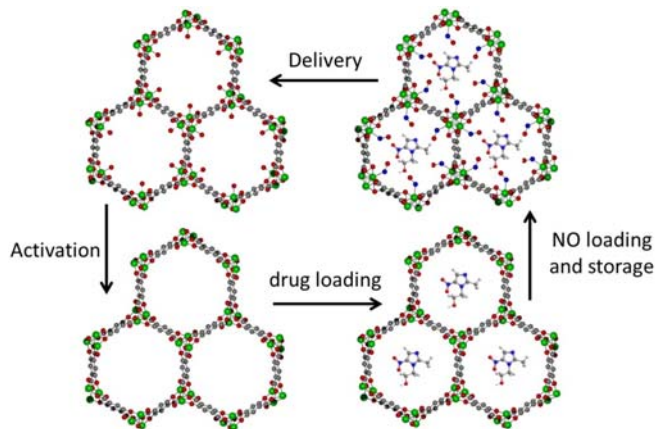
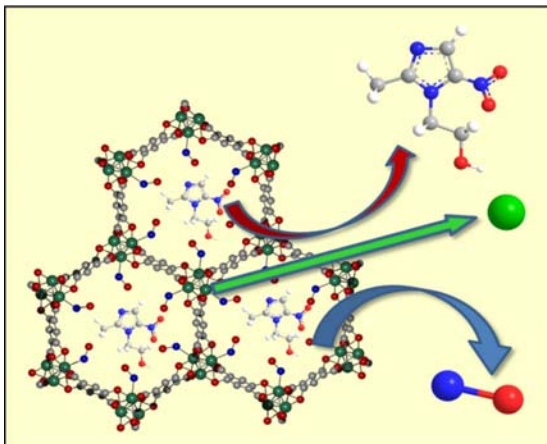
Anti-biofilm studies using MOFs

- *Pseudomonas Aeruginosa* and *Staphylococcus aureus*
- MOFs (blue), NO-loaded MOFs (green) compared with 100 x dose of preferred antibiotic (ciprofloxacin and vancomycin, brown)
- Red line is the biofilm control.





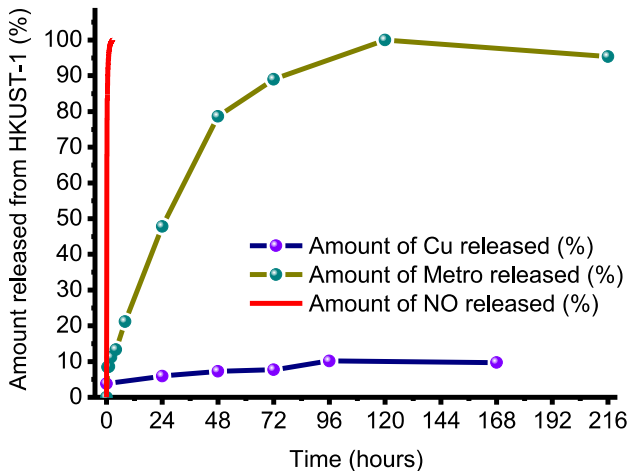
Multirate delivery of multiple therapeutic agents



Why is the rate of delivery important?



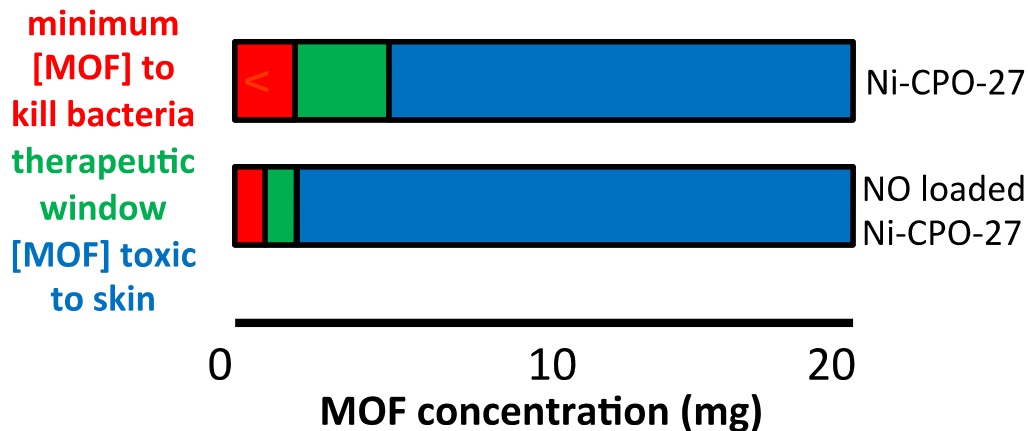
Multirate delivery of therapeutic agents



- Fast delivery of NO leads to 'sterilisation' of media
- Slow delivery of other agents (e.g. metals) prevents recolonisation over much longer timescale
- Relies on fundamental instability of the MOF



Toxicity



- Cytotoxicity against dermal fibroblasts and red blood cells.



Manufacturing at Large Scale



30ml



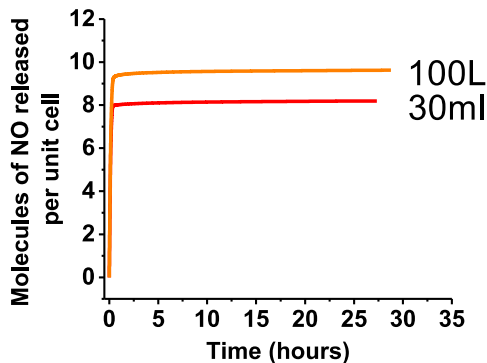
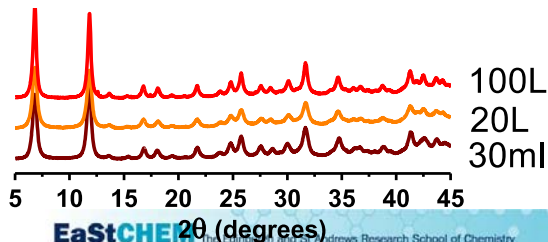
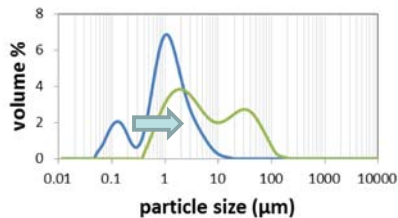
1L



20L



100L





Formulating products

- demonstrated compatibility with wide range of polymers using various techniques



solvent cast
polyurethane film



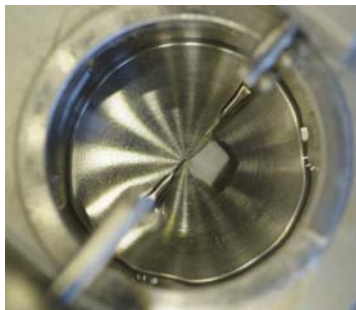
silicone
extruded
tubing



coated non woven
polyester



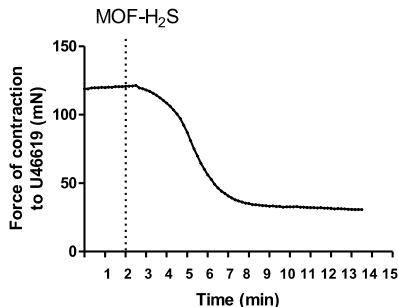
Myography : Relaxation to H₂S-loaded MOFs or NaHS



Porcine coronary arteries \pm EC:

1) Incubated for 30 min with or without channel inhibitors

2) H₂S-loaded MOF introduced for 30 min, or cumulative $\frac{1}{2}$ log concentrations of NaHS for 2 min per concentration, or time required to reach plateau

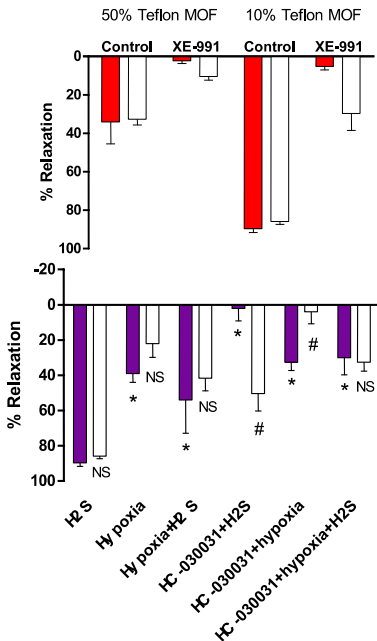


Relaxation response of PCA to an H₂S-loaded MOF of Mg(dhtp) 10% Teflon

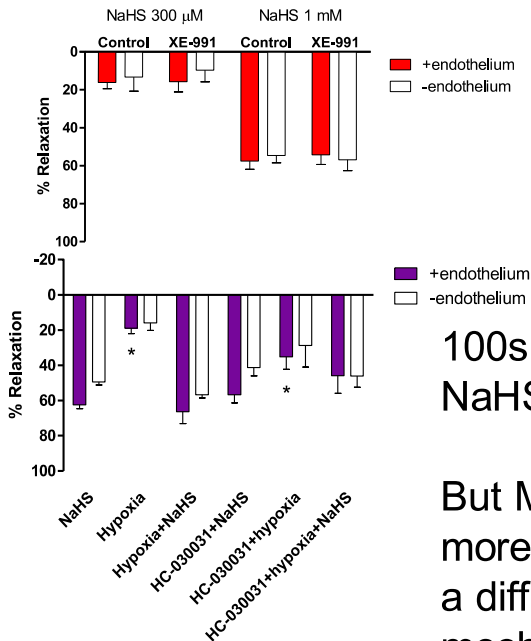


Comparison of relaxation responses to NaHS and H₂S gas

H₂S MOF



'NaHS'



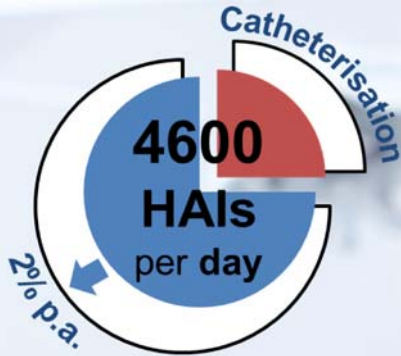
100s of papers using NaHS to deliver H₂S

But MOF-H₂S is more potent and has a different mechanism



- Biological applications of MOFs
 - Some instability (wrt MOFs) is actually an advantage
 - Functionality
 - Biodegradability
 - Controlling the rate of degrading is key
- Hemilabile MOFs
 - Engineering weakness into a MOF can lead to unusual properties that can be exploited
 - e.g. Ultrasensitive NO adsorption

Markets Seeking Solutions



Silver and chlorhexidine coatings

unsatisfactory
performance vs cost

do not treat root cause of
thrombosis

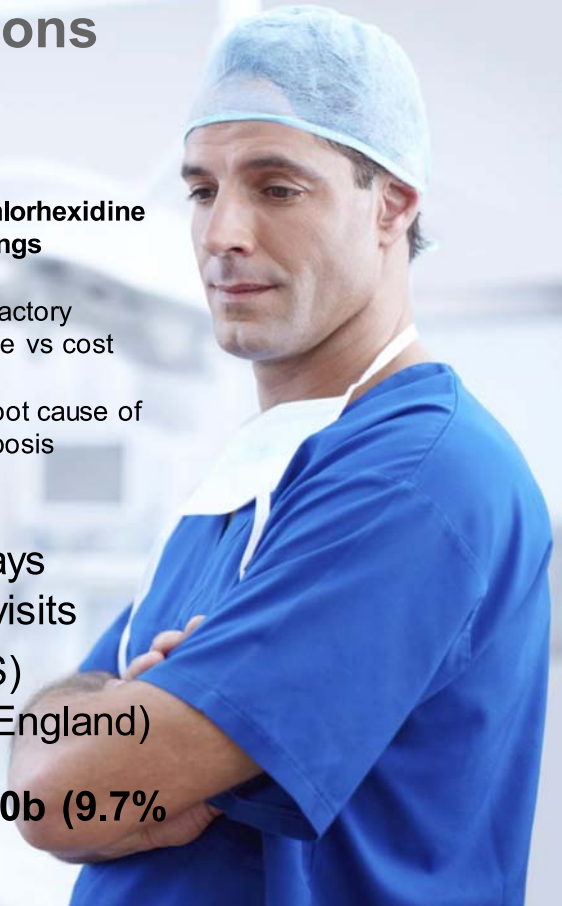
Increase hospital stay by 5-6days

Increased GP, nurse, hospital visits

CRBSI \$46k per infection (US)

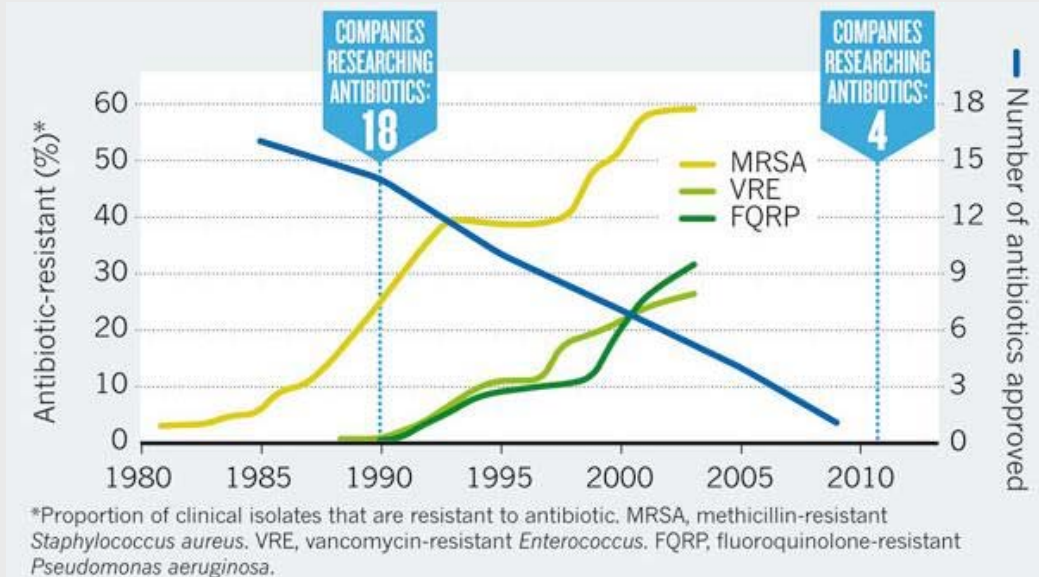
CAUTI £99 million p.a. NHS (England)

Catheters – Global Market \$30b (9.7% CAGR)



Increasing resistance

decreasing drug development



Markets Seeking Solutions

Chronic Wounds – global market \$5b

Annual incidence **600,000** (UK)
→ 6000 amputations p.a. (England)

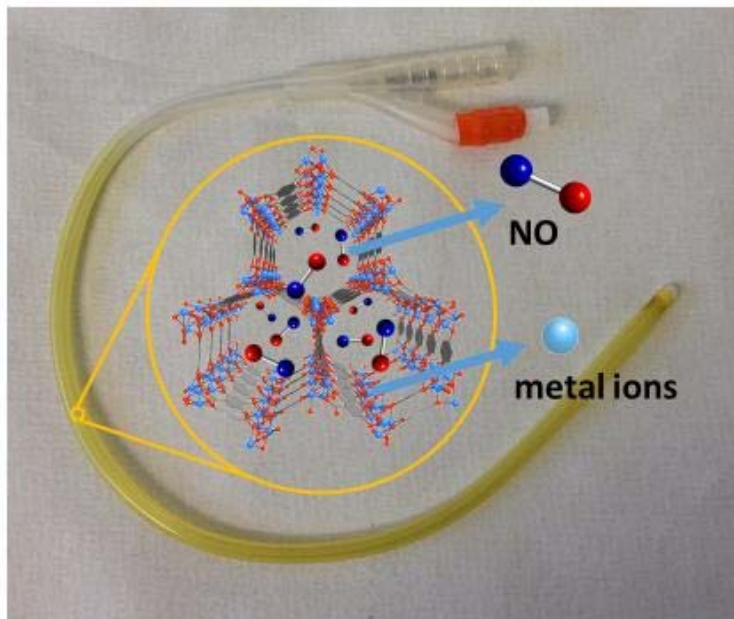
25-40% of beds
are occupied by wound care patients

Cost to NHS £2-3 billion p.a. (UK)





Commercial products in trials





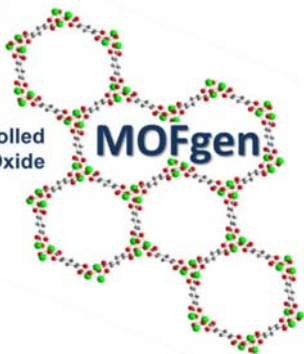
Emerging Technologies Competition 2016

First Prize - Health and Wellbeing Category



Delivery System for Controlled
Release of Nitric Oxide

MOFgen



funding



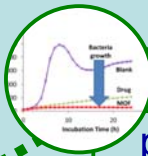
partnering



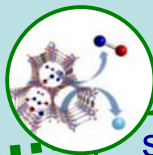
scale up



formulation



performance



solution



unmet need



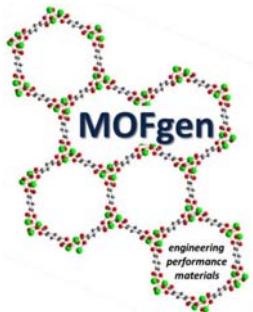
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Thanks



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