

# Preventing thrombosis and infection with nitric oxide releasing polymers

Every day, thousands of patients receive medical device implants and while these implants can be life-savers they have inherent risks, such as thrombosis, infection and, in the worst cases, death. **Dr Hitesh Handa** at the University of Georgia who has been awarded grants from NIH, CDC, and VA and his team are developing novel NO releasing materials to find innovative solutions to decrease morbidity, mortality and costs associated with hospital stays.

the haemodialysis patient's blood takes outside of the body) has shown tremendous potential in preventing the thrombosis and infections these medical devices cause. His novel polymeric coatings not only provide superior adherence to the medical device but protect it from and/or eliminate corrosion, adhesion and fouling. Most important is their potential to save lives.

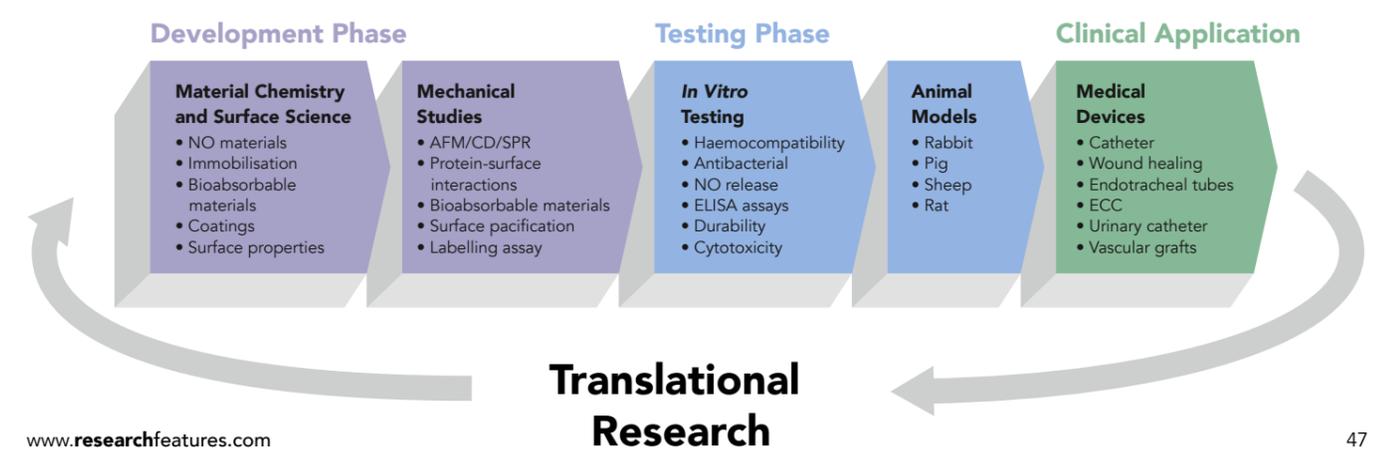
**M**edical devices are at risk from infection and thrombus formation. Blood flows through our arteries and veins without clotting. That is, unless, you put a medical device, even one as simple as a catheter, in contact with it. Within seconds, the blood clots (thrombosis) which causes fouling (proteins and bacteria attach to medical device) infections and sometimes, death. The CDC estimates that 1.7 million hospital-associated infections cause up to 99,000 deaths each year.

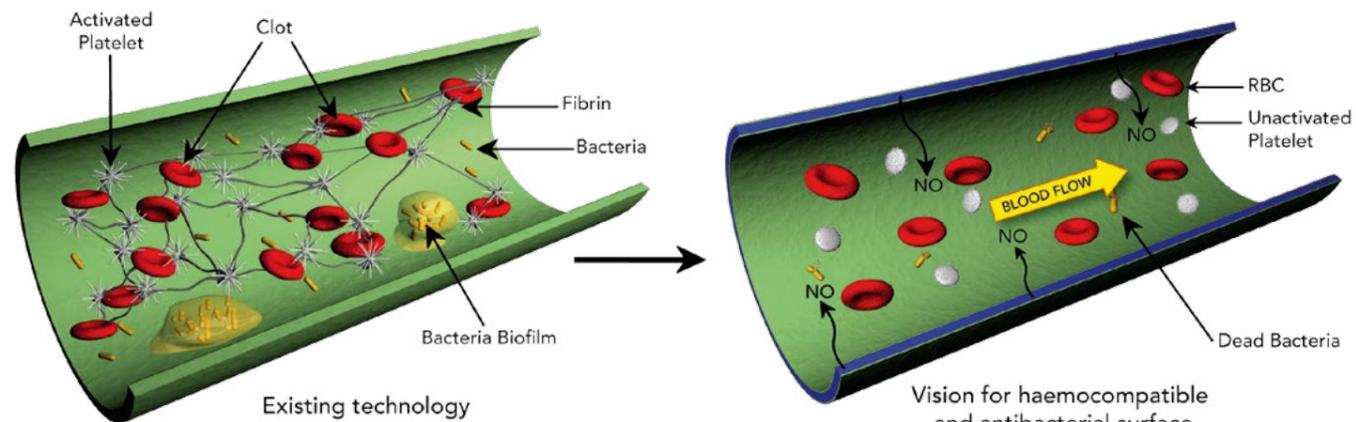
**BIOCOMPATIBLE MEDICAL DEVICE COATINGS**  
Dr Handa's research focuses on designing novel materials or coatings that make medical devices biocompatible with the endothelium. Using his extensive translational research experience, he puts materials/surface science, polymeric coatings, blood-surface interactions and animal models into medical practice for meaningful health outcomes. The result? The development of biocompatible medical device coatings.

**WHAT MAKES DR HANDA'S COATINGS SPECIAL?**  
In these novel polymeric coatings, Dr Handa's special ingredient is NO (nitric oxide). Nitric oxide is a free radical, water-soluble, ubiquitous gas with a very short half-life. In mammals, including humans, NO is an important cellular signalling molecule involved in many physiological and pathological processes. It is important for cognitive function, sleep, even gastric motility. Dr Handa's interest also lies in NO's antimicrobial (bacteria-killing) properties, its vasodilation effects (widening of blood vessels, which decreases blood pressure) and its ability to naturally inhibit the clotting

For over a hundred years, researchers have focused on improving this blood-material interaction, but now improving interactions between medical devices and blood by mimicking the endothelium (lining of the interior surface of lymphatic and blood vessels) have taken centre stage.

**This research has forged the way for a new generation of biocompatible medical devices**





process by blocking platelet adhesion and activation. More specifically, he is interested in the effect of NO when released in a controlled way from the polymeric coatings of implanted medical devices, from simple catheters to implantable vascular grafts and stents to complex artificial organs.

It's an extremely fine balancing act. Dr Handa's team explores ways to release the right amount of NO in a reproducible way for prolonged periods without compromising the device's mechanical properties, stability or shelf life. All while attaining the highest biocompatibility.

In their 2016 study, the team tested the physical properties and biocompatibility of SNAP (an NO donor molecule called S-nitroso-N-acetylpenicillamine) when incorporated into Elast-eon E2As polymer. Elast-eon E2As is a copolymer of mixed soft segments of polydimethylsiloxane and poly(hexamethylene oxide). This combination passed rigorous tests with flying colours, including tensile strength, surface chemistry, surface roughness, storage and sterilisation analysis. In addition, excellent haemocompatibility and cytotoxicity results give SNAP-E2As polymers outstanding translational potential, making this material excellent for biomedical device and implant applications, vital for commercial and clinical success.

## Dr Handa's research has made significant progress towards decreasing the risks associated with medical implant use

### FINE-TUNING NO RELEASE

Since the physical effects of NO release are dose dependent, Handa and team have explored fine-tuning NO release. Take Cu-SNAP (Copper- S-nitroso-N-acetylpenicillamine) for example: by varying its copper concentration, the team discovered that the amount of NO released can be fine-tuned. From there he expanded the use of his Cu-SNAP combination for numerous biomedical applications, showing that these composites show exceptional promise for fabricating a whole new generation of life-saving medical devices that have the ability to not only control NO release and reduce platelet adhesion but have a superior degree of microbial inhibition for outstanding biocompatibility.

Handa's team show that NO release can be effectively controlled and fine-tuned using a dual-layered surface containing the NO releasing hydrophobic polymer linked to a hydrophilic polymer topcoat. It proved two important points: this combination reduces bacterial adhesion compared to hydrophobic polymer topcoats alone, and that incorporating SNAP into the hydrophobic layer significantly reduces bacterial growth (*S. aureus*). Hydrophilic polymers are therefore perfectly suited as NO and other biocide releasing materials, that reduce microbial adhesions and control the release of antibacterial agents.

Animal studies show the exciting potential of Dr Handa's polymers. NO release was shown to be controlled over nine days in a central venous catheter implanted into the veins of a rabbit. The Elast-eon E2As polymer used showed significant inherent haemocompatibility properties (platelet preservation and limited clot formation). Previous experiments using common polymers such as PVC, exhibited an initial NO burst on day one, hence limiting NO release to an unacceptable period of less than one week. Using two PLGA additives with ester end groups as their proton donor source for the DBHD/NONO (a diazeniumdiolate NO donor molecule)-based catheters caused NO release to last for two weeks. A significant *in vivo* result!

### FURTHER IMPACT OF DR HANDA'S PIONEERING RESEARCH

Dr Handa's research has made significant progress towards decreasing the risks associated with medical implant use, and equally significant is their bacteria-fighting abilities that help them avoid the drug resistance and toxicity to cells seen with current antimicrobial agents. This is an exciting step forward in helping reduce our dependency on antibiotics at a time when we're losing ground against 'super bugs'. In addition, his work to promote angiogenesis (formation of new blood vessels) and prevent platelet activation show great promise for solutions in coronary artery disease.

Not only that, Dr Handa's knowledge, expertise and future research could bring basic engineering and biological science to the benefit of patients in every field of medicine. Perhaps in many applications outside medicine not yet even considered.

## Q&A

### What was your most significant discovery or breakthrough which led your research to where it is today?

When I started working on this technology nine years ago the biggest challenge was that release rates of NO from the NO donors were extremely low and short lived. I believe developing new materials that are more stable, sterilisable and can release NO for months (unpublished work) is the breakthrough that can take this technology to the next level.

### How far away are we from seeing your ground-breaking technology put into practical use to save lives?

We are working with medical device companies to conduct large animal studies and clinical trials. I hope in the near future we can have NO-releasing catheters in the market. I hope this technology can help reduce morbidity and mortality in our hospitals.

### You have tackled wound healing, endotracheal tubes, ECC and catheters, what's next?

Basically wherever there is a risk of infection and/or clotting, these coatings can be applied. Examples include stents, bone implants and urinary catheters.

I hope this technology can help reduce morbidity and mortality in our hospitals

You mentioned the need for a more elaborate study comparing the overall healing process of these new NO releasing polymers to appropriate controls, including silver-based materials. How is this significant? Is it currently under investigation?

Silver and heparin coated materials are currently used clinically, so the next step is to compare our materials with the existing technology.

### In what surprising new applications, unrelated to medicine, would NO releasing technology be compatible?

Food packaging! We have already published in the area and have a patent pending. More preliminary tests are being conducted in my lab.



Handa Biomaterials Research Group at the University of Georgia. The lab is committed to developing biocompatible coatings for medical devices through highly translational and interdisciplinary research. Find out more at [handalab.uga.edu](http://handalab.uga.edu)

## Detail

### RESEARCH OBJECTIVES

Dr Handa's translational research explores the use of novel materials that can prevent thrombosis and infection for potential medical device applications. His achievements in designing innovative nitric oxide (NO) release formulations have been tested in animal models and have led to multiple funded proposals, publications, and patent applications. Using his experience in biomolecular interactions, materials/surface science, polymeric coatings, blood-surface interactions and animal models, Dr Handa's goal is to bridge the gap between the engineers and clinical researchers in the field of biocompatible materials.

### FUNDING

National Heart, Lung and Blood Institute (NHLBI), National Institute for Health (NIH), Centers for Disease Control and Prevention (CDC), Department of Veteran Affairs, Industrial funding.

### BIO

Dr Hitesh Handa received his PhD in Material Science and Engineering from Wayne State University, where he developed biomimetic surfaces for biosensor application for the US Department of Defense. Dr Handa then worked as a Development Engineer in a Biomedical Device company. In 2010, he joined the Department of Surgery, University of Michigan as a Research Investigator where he published more than ten peer-reviewed articles and received an NIH Career Development Award. Dr Handa is currently Assistant Professor at the College of Engineering, University of Georgia.

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