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New biospleen blood cleansing excites experts

Molecular diagnostics for infectious diseases takes a forward leap

A new extracorporeal nanotech device addresses the root cause of sepsis by removing pathogens and endotoxins simultaneously from blood even before their identification – this genetically engineered mannose-binding lectin protein can also latch on to the Ebola virus...

Report: Cynthia E Keen

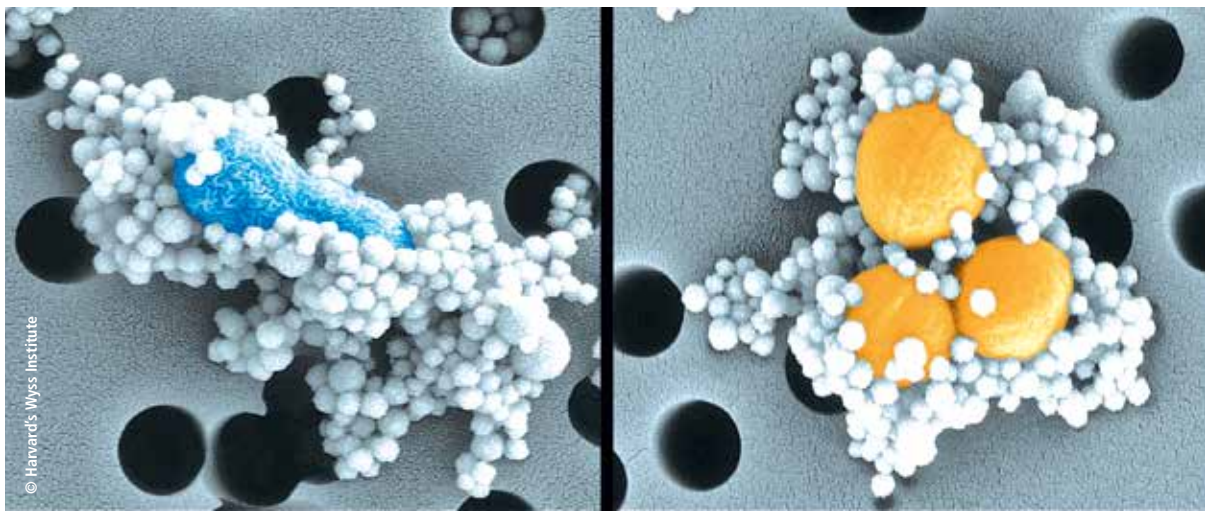

Image demonstrates the effectiveness of the genetically engineered protein-coated magnetic beads binding to pathogens. Here, the magnetic beads (128 nm) are bound to two pathogens (*E. coli* on the left and *S. aureus* on the right)

Sepsis is on the rise worldwide, in all likelihood exceeding the 2003-2013 estimates of 18 million cases. 30-50% of patients die, whether treated in a high-tech intensive care unit (ICU) or a resource-constrained hospital ward. In developing countries, sepsis causes 60-80% of all deaths (source: Global Sepsis Alliance). It also kills around six million infants and young children and 100,000 new mothers annually.

No specific anti-sepsis drugs are commercially available. Thus the presentation from Harvard University's Wyss Institute for Biologically Inspired Engineering in Boston of a dialysis-like blood cleansing biospleen device that can filter live and dead pathogens from human blood, generated tremendous excitement at the 6th Annual Molecular Diagnostics for Infectious Disease conference held in Washington, D.C. in late August*.

Inspired by the spleen, the extracorporeal blood-cleansing device is revolutionary in its ability to continuously remove pathogens and toxins from blood without first identifying the infectious agent. Time is vital – sepsis mortality rates increase as much as 9% for every hour before a correct antibiotic therapy is administered – the device offers the potential to rapidly treat systemic blood infections and prevent sepsis progression.

'The biospleen device addresses the root cause of sepsis by removing pathogens and endotoxins simultaneously,' principal investigator Michael Super PhD, Senior Staff Scientist, told *European Hospital*. 'Blood pathogen load is known to be a major contributor to both disease severity and mortality in patients with sepsis. Many patients respond to appropriately targeted antibiotic therapies that work exclusively by lowering the number of live pathogens, but antibiotic therapy does not treat endotoxins in a patient's blood. Therefore, we set out to develop an extracorporeal blood-cleansing therapy, similar to dialysis, that can rapidly remove microorganisms and endotoxins from the blood without the need to first identify the source of the infection and without altering blood contents – and it has exceeded our expectations, by being able to filter these out in a matter of hours.'

Magnetic micro-bead magic

The biospleen unit uses magnetic nanobeads coated with a genetically engineered human opsonin – mannose-binding lectin (MBL) that binds to a wide variety of pathogens. In its innate state, MBL has a branch-like 'head' and a stick-like 'tail'. In the body, the head binds to specific sugars on the surfaces of all types of bacteria, fungi, viruses, protozoa and toxins. The tail cues the immune system to destroy them. 'The protein is part of the innate immune system that has been binding sugars for 500 million years. It's a very robust pathogen capture mechanism,' he explained.

Because other immune system proteins can bind to the MBL tail and activate clotting and organ damage, Dr Super used genetic engineering tools to remove the tail and graft on a similar one from an antibody protein that does not cause these problems. This genetically engineered 'secret sauce' protein binds the pattern of sugar on the surface of the pathogens – more than 100 different species, but does not bind to mammalian host cells.

Dr Super described how the engineered MBL 'secret sauce' protein is attached to magnetic beads 128 nanometers in diameter. The beads are added to blood removed from the patient and bind to the pathogen. Magnets in the biospleen device pull the now pathogen-coated magnetic beads through the channels to cleanse the blood, which is then returned to the patient.

Dr Super and his colleagues tested the device on anaesthetised laboratory rats infected with bloodstream infections that human sepsis patients experience. Approximately 90% of live *S.aureus* and *E. coli pathogens* were removed within 60 minutes. Rats were challenged with lethal doses of endotoxin and 90% of the biospleen-treated rats survived, while only 14% of the control rats survived.

Tests of human blood *in vitro* removed more than ninety percent of key sepsis pathogens when the blood flowed through a single device at a rate of half to one litre per hour.

Dr Super advised that many devices could be linked together to obtain levels required for human

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The potential of cardiovascular magnetic resonance imaging

Cardiomyopathy – the chameleon disease

MRI benefits and potential should be communicated better and to a wider clinical audience to be used more frequently

Cardiomyopathy is a disease with many faces, a 'chameleon', according to Professor Jeanette Schulz-Menger. As Head of the working group Cardiac MRI at Charité, Campus Buch and head of Non-invasive Cardiac Imaging at Helios-Klinikum Buch, Berlin, she uses cardiac MRI to understand the disease better. 'Cardiac MRI plays different roles in the diagnosis of the different forms of cardiomyopathy,' the professor explained during our EH interview.

The 'crucial feature' of this imaging modality is its ability 'to differentiate possible myocardial damages' in all forms of this cardiac disease, she pointed out, even when the pump function of the heart is intact. Even if echocardiography, for example, recorded normal cardiac performance in a patient, cardiac MRI can detect scar tissues and inflammations.

Cardiac MRI is the modality of choice to record right ventricular pump function, because echocardiography cannot handle the complex anatomy of the right heart. 'The right ventricle is shaped like a backpack –it simply does not fit in any geometrical assumption,' Prof. Schulz-Menger explained. While echocardiography tries to cut the right ventricle into many sections to be able to calculate pump function, she added, 'MRI can generate a 3-D image of the heart, which allows us to evaluate the actual pumping performance.'

In dilated cardiomyopathy – the pathological enlargement of the heart muscle – MRI is used to identify the cause of the condition, such as perfusion problems, inflammations or scar tissue. 'Scar tissue is easily visualised with contrast-enhanced techniques,' she said. This is of utmost importance because patients with scar tissue on the myocardium are at a higher risk of sudden cardiac death or on-going weakening of the heart muscle.

Moreover, cardiac MRI is increasingly used to examine the hearts of professional athletes, although this particular area has not yet been acknowledged in the relevant guidelines. Here, the task of cardiac MRI is to show whether a heart is enlarged due to intensive activity or due to a hypertrophic cardiomyopathy.

While echocardiography can visualise a thickened heart muscle, unlike MRI it cannot unambiguously identify cardiomyopathy. Furthermore MRI can identify heart muscle inflammation. Athletes who suffer this condition, and continue training, might experience life-threatening arrhythmias, which may lead to sudden cardiac death.

Professor Schulz-Menger is particularly pleased that other disciplines have begun to recognise the value of this: 'Cardiac MRI is used for risk stratification purposes in non-cardiac diseases.' In certain lung diseases such as sarcoidosis MRI can contribute to a more complete picture of the patient status. 'Many young sarcoidosis patients die of sudden cardiac death due to conduction disorders,' she explained. Conventional diagnostic methods, however, detect only eight percent of cardiac involvement, while pathological studies have shown cardiac involvement in 40 percent of patients. Cardiac MRI could identify these patients – 'and,' Professor Schulz-Menger said, 'that's great'.

She would like to see MRI used more frequently and in a more targeted fashion, but that would need its benefits and the potential to be communicated better to a wider clinical audience. Close relatives of patients with hypertrophic cardiomyopathy also need to undergo an MRI scan because there could be a familial predisposition for the disease. 'If I am serious about diagnostics, each relative has to have a cardiac MRI,' the professor pointed out, particularly since echocardiography is known for its poor detection of early signs of a hypertrophic cardiomyopathy. Additionally, a cardiac MRI scan is indicated when contradicting findings are reported, for example when an ECG yields different data than the echocardiography.


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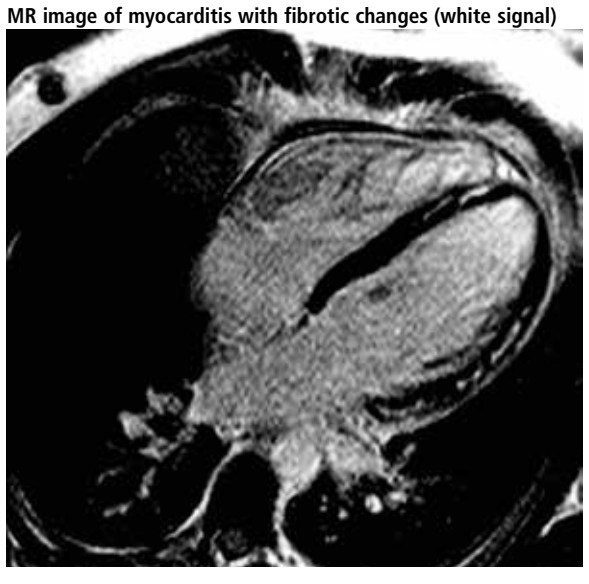
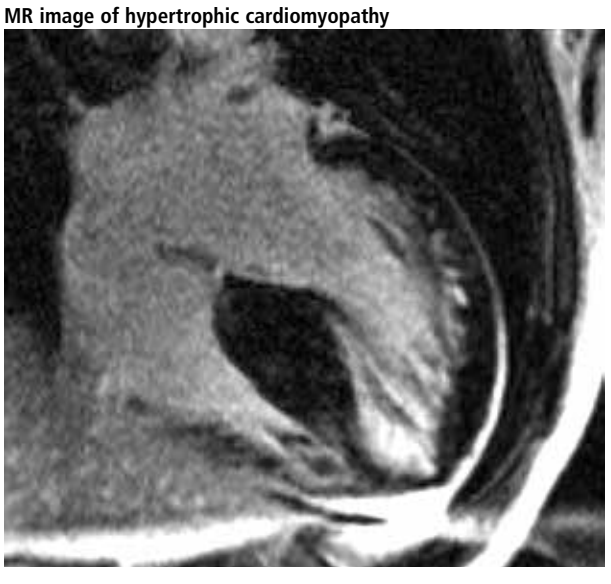
Jeanette Esther Schulz-Menger has chaired cardiovascular magnetic resonance imaging at the Experimental and Clinical Research Centre (ECRC) in Berlin since 2008. The Max Delbrück Centre (MDC) and Charité jointly operate the centre. The professor's research focus is on the evaluation of myocardial damage with cardiac MRI. A driving force behind the implementation of a 7T MRI scanner at MDC, she also sets great store by translating MRI research results into clinical practice.

MR image of myocarditis with fibrotic changes (white signal)



MR image of hypertrophic cardiomyopathy



Spain's Institute for Cardiovascular Research

Stepping towards CD disease prevention

Report: Dr Eduardo de la Sota

Cardiovascular disease develops in a slow and subclinical manner over decades, only to manifest suddenly and unexpectedly. Prevention is crucial, both before and after clinical appearance, and evidence is ample of the effectiveness of early detection of at-risk individuals and lifestyle modifications or pharmacological approaches.

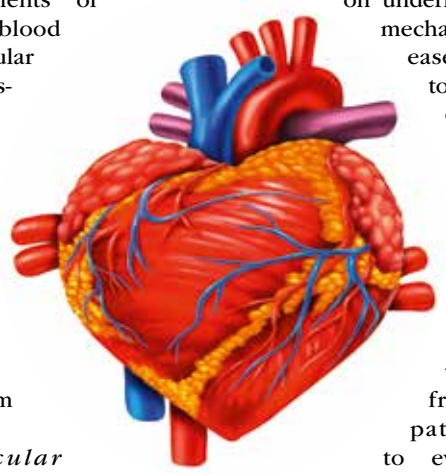
However, those approaches require time, perseverance, and continuous development. Special focus must be made in e.g. diet, weight control (obesity is a disease) and physical activity, among others.

Led by Dr Valentín Fuster, The Spanish Institute for Cardiovascular Research (CNIC) was founded because – despite enormous advances in diagnosis and treatment over the last 20 years – cardiovascular diseases remain the major cause of death in the developed world. The costs generated in economic, social and human terms are also immense.

In response, the Spanish Government, through the Carlos III Institute of Health, created the CNIC to amalgamate the best Spanish cardiovascular research and provide a modern infrastructure and ample funding for biomedical research.

CNIC research is grouped into three departments:

- *Vascular biology and inflammation* (VBI). Here the complex interactions between the components of circulating blood and the vascular wall are investigated, with emphasis on vessel wall remodelling, inflammation and cell-cell biology and signalling in metabolism and disease.
- *Cardiovascular development and repair* (CDR). Researchers are investigating cell-cell interactions and signalling pathways operating during heart morphogenesis and vascular development, the origin and maintenance of the pluripotent state, and the metabolic regulation and repair of the adult cardiovascular system.
- *Atherothrombosis, imaging and epidemiology.* This department develops non-invasive technologies for molecular-resolution imaging that can identify and characterise vulnerable plaques. Combined with epidemiologic analyses, this approach provides invaluable information on underlying molecular mechanisms of disease, leading to tools for accurate diagnosis and targeted drug delivery.



At the 19th World Congress on Heart Disease in Boston, MA, topics ranged from clinical pathophysiology to evaluation and stratification techniques and molecular and cellular biology, including neurohumoral, immunological and genetic studies. The most relevant studies presented approached cardiovascular disease prevention and prognostic algorithms. These included two interesting Spanish studies.

In the first, according to Dr R C Hermida from the University of Vigo, sleep blood pressure (SBP) is an independent predictor of cardiovascular events. That study involved 11,255 subjects, 6,028 men/5,227 women. Dr Hermida concludes that mean SBP, but not daytime clinically measured BP, is a significant and independent prognostic marker of cardiovascular disease morbidity and mortality. These findings indicate ABPM (Asleep Blood Pressure Measurement) is a clinical necessity to accurately detect abnormal sleep-time BP and assess cardiovascular disease risk.

In the second study, Dr M J Sanz from the University of Valencia), presented a study to address effective strategies to treat and prevent atherosclerosis, using combined concentrations of Rosuvastatin (Rosu) and bexarotene (Bex) on angiotensin II (Ang-II)-induced arterial mononuclear cell (MC) recruitment. Research data suggest that combined administration of Rosu+Bex at suboptimal doses may constitute an alternative therapy to control vascular inflammation, minimising the appearance of drug-associated adverse effects.

Thus, CD prevention is advancing slowly, but showing clear evidence that physical and mental hygiene, medical controls, education and healthcare information will minimise mortality and morbidity of cardiovascular diseases, which cause much suffering, mortality and healthcare expenditure.

2nd artificial heart implanted in France

Firm imposes press embargo over new transplants

Another patient in the final stages of heart failure has received an artificial heart at Nantes University Hospital Centre, according to Carmat, the manufacturer of the device. John Brosky reports

Carmat announced, in a press release, its active recruitment of two more patients to complete its first-in-human clinical trial of the artificial heart against a primary endpoint of 30-day survival with secondary criteria for assessing the impact of the reinvigorated blood supply from the mechanical heart on internal organs. 'We warmly thank, particularly today, the experienced team at CHU-Nantes,' stated Carmat CEO Marcello Conviti. 'Passing this step was made possible thanks to their confidence as well as that of our participants, partners and investors.'

The company was forced to issue the press release after the newspaper Liberation reported a second implantation.

Although the news leak was reported by all French media, none could report any further detail about the patient's condition. The company imposed a news blackout regarding implantations after the media circus that followed the news of the first implantation and the subsequent death of the patient 74 days later. The company's stock price jumped on the first news and then fell dramatically with the death of the patient and statements by the inventor of the mechanical heart, renowned cardiac surgeon Alain Carpentier MD, that the device had stopped abruptly.

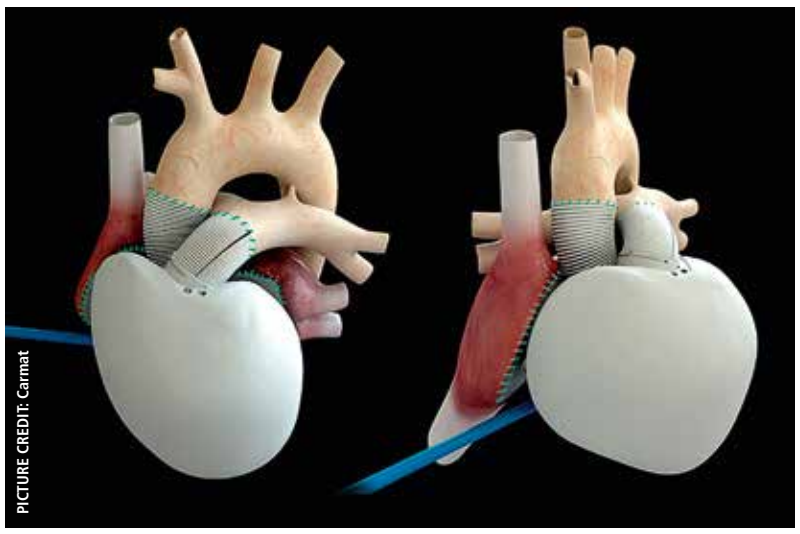
One of the surgeons who participated in the implantation procedure, Daniel Duveau MD, said that the heart did not stop brutally. 'During two hours, each time the device stopped, the system did everything it could to restart the pump. Despite a possible dysfunction, the system intelligently demonstrated its capabilities,' he said, comparing the action to that of a doctor performing a cardiac massage.

Dr Duveau was the lead surgeon for the implantation procedure at CHU-Nantes.

The first patient, Claude Dany, 76, lived 74 days, which, noted lead surgeon Christian Latremouille MD, from the Hôpital Georges-Pompidou in Paris, widely exceeded the end point for the safety study.

After a four-month review of the device and the causes of death of the first patient, French authorities approved the continuation of the clinical trial for safety and feasibility. In its press release, Carmat reported that two independent control committees monitoring the trial had met on 4 September 2014 and issued a report approving a continuation of the trial for the final two patients.

The Carmat artificial heart is the first device to completely replace a human heart and is fully contained within the thorax requiring no external pumps. Only two wires exit the body at the abdomen, one to supply power and the second to monitor device performance.


PICTURE CREDIT: Carmat

Carmat's artificial heart

It is also the first artificial heart capable of adapting the blood supply according to a patient's activity, varying from three to nine litres per minute, rather than having a constant blood supply.

Carmat repeated in its press release that, in conformance with good clinical practices, there would be no reporting of results of any of the implantations until the end of this safety and feasibility trial, unless required by 'particular circumstances'.

Low energy, cold light, long life

A surgical led lamp illuminates countless conditions

The Starled3 NX suits many applications in the operating theatre and diagnoses in, for example, gynaecology, dermatology and general medicine.

'The lamp grants a homogeneous and shadow-less light thanks to its special LED optics created by ACEM Medical Company, which directs light beams at best according to the needs,' the Italian manufacturer reports. 'The visual area is perfectly illuminated assuring both excellent visual comfort and working conditions. Its next generation LEDs produce an unparalleled quality of light with a colour temperature (CCT) of 4.500 °K and a colour rendering index (CRI) of 95.'

Light intensity is 130.000 lux with low energy consumption of 69W, and the life cycle of their LEDs is around an impressive 50,000 hours.

The model has three reflectors producing a blended and intense cone of light, focused through automatic adjustment of the light spot diameter, the firm points out. 'The slim, practical, compact design makes it perfect for several uses. The lamp is ergonomic, easy to move and to position and suitable for the laminar flows of the operating theatre.'

The Endo function (light for endoscopy) also enables the lamp's valuable use during Minimally invasive surgery. Other functions include touch-screen adjusted via the I-Sense control panel – covering light intensity, DoF (depth of field), Size (light spot diameter adjustment), Sync (optional - to synchronise controls of the Acem Medical Company's combined lamps when also used for exams or proceduresC).

Details: www.acem.it