panorama

Issue no 19 December 2005

Innovation with a mission

From ischemia to cerebral malaria

Inhaled carbon monoxide

The state of the art research

Latest findings

Distinguished speakers presented their latest research in gas medicine

One million dollars in research grants for nine researchers in GEMI Fund second round

The 2005 GEMI Fund Grantees. From left: Ana Pamplona Santos (for Maria M Mota), Portugal, Ajay Verma, Brian Zuckerbraun, Benjamin Williams, USA, Nick Plesnila, Germany, Martin Bienengraeber, USA, Michael Fries, Germany, Bastiaan Driehuys, USA and Gaio Paradossi, Italy.

At the second international scientific seminar and grant award ceremony of the GEMI Fund (Gas Enabled Medical Innovations), nine researchers shared a total of USD one million for research into gas enabled medical innovation.

The meeting was held in Stockholm on 15 September, 2005. It also provided the platform for the 2003 GEMI Fund grantees to present findings of the research they have been conducting over the past two years.

Attending were nearly 100 scientists, distinguished guests and grantees, and in his opening address Head of Linde Gas Therapeutics, Lars Källsäter noted with satisfaction the notable rise of interest in, and awareness of, the GEMI Fund among the scientific and medical community as well as the leading position Linde Gas Therapeutics has established in this field. The GEMI Fund was founded in 2003 by Linde Gas Therapeutics in co-operation with Harvard Medical International of Boston, USA and the Karolinska Institute of Stockholm, Sweden.

The role of Linde Gas Therapeutics as benefactor was highlighted by GEMI Fund Board member, Dr David Pinsky, MD, Professor of Cardiovascular Medicine at the University of Michigan. 'The GEMI Fund is unique in the world. Here we have industry demonstrating a genuine interest in science. I really feel the Fund's work is going to leverage further development in the field of gas enabled medical innovation.'

As well as presentations of the findings of the GEMI-funded research, attendees also heard from Professor Göran Hedenstierna, MD, (from Uppsala University Hospital, Sweden) how, with the support of Linde Gas Therapeutics in the form of gas and devices, he and his Chinese and Swedish team achieved positive outcomes with patients of the SARS epidemic in China.

THE GEMI FUND

Increased focus on clinical benefit

The Scientific Secretary of the GEMI Fund is Professor Jörg Weimann, MD, of the Charité Campus Benjamin Franklin, Berlin. He spoke highly of the range and quality of the applicants for the 2005 round of funding, but also of the Fund in general.

Application proposals are all reviewed by an independent panel and the grants are enough for a lab to work for two years.' He went on to praise the increased focus on clinical benefit.

'Projects this year seem more focused on clinical applications. This is needed in medicine - not just the bench work, but also the clinical practice.' He commented with interest also on the growing focus on carbon monoxide and its possible potential in therapeutic applications.

The seminar and award ceremony was held at the Opera Terrace in Stockholm, offering a magnificent view of the Swedish royal palace. Lively questioning followed each presentation and the lunch and refreshment breaks saw animated discussion and networking on a major scale. The session culminated in the presentation of the awards, which were handed out by Professor Warren Zapol, MD, Massachusetts General Hospital, Boston, MA and Chairman of the GEMI Fund Board together with Lars Källsäter.

Dr Warren Zapol, Anesthesist-in-Chief at Massachusetts General Hospital, Boston, MA and Chairman of the GEMI Fund Board, spoke enthusiastically of the role of the GEMI Fund. The international goodwill produced by the Fund is immense. Its 'no strings attached' support of gas related research is noticed widely by clinicians and scientists and it is noteworthy that nearly one hundred top-notch investigators made the effort to submit GEMI Fund applications.

EDITORIAL

The GEMI Fund seminars and grant award ceremony brings together researchers, representatives of the clinical and scientific community and the industry.

Clinical benefit: a shared goal

In some respects, the occasion of the second GEMI Fund Seminars and Grant Award Ceremony represents just the very tip of the iceberg. Yes, it brings together researchers, the Fund founders and representatives of the clinical and scientific community. But at the same time, working in the background is an extensive and highly committed network. This network is linked by the GEMI Fund and actively engaged in working towards bringing gas enabled medical innovation into the light of the mainstream and, one day, into the clinic. The GEMI Fund, and this event, gives this network a public face. That this round of Fund applications increased so notably in number, and that it encompassed quality products from across the whole globe, is further evidence that the hitherto rather neglected field of gas research is finally beginning to get the attention it deserves.

As a representative of Linde Gas Therapeutics, a 'gas' company, it is natural that I am biased in favour of research into the therapeutic effects of gas. But I feel fully justified in this; living organisms appear to make very specific use of gas molecules to which they have been exposed throughout the process of evolution and there are many very compelling arguments pointing to both diagnostic and curative properties of gases. To over-simplify, we could say that different diseases are associated with an under- or over-supply of a certain gas molecule. Research is needed to determine how these effects can be exploited for clinical benefit. We therefore fully support the work of the Fund in researching these properties, linking them clearly to clinical outcome and, ultimately, making them globally available to enhance patients' lives.

It is my sincere hope that the GEMI Fund continues to support this work and to foster the active networking among researchers in different parts of the world and among clinical practitioners. The results of the first round of GEMI funding, and the potential of the projects awarded in this 2005 round, point to research that will bear fruit in the clinic, both in the short and the long-term, and I am very proud to be a part of it.

Lars Källsäter,
Heaf of Linde Gas Therapeutics

Dr Ben Williams

Dr Brian Zuckerbraun

Dr Nick Plesnila

Innovation with a mission

At the heart of the GEMI Fund's raison d'être is innovation. All nine grantees' research projects revolve around exploration of perhaps unconventional uses of gas in a medical application.

Dr Maria M. Mota, PhD, (Instituto de Medicina Molecular, Universidade de Lisboa, Lisbon, Portugal) and her team are looking into how CO could be used to fight cerebral malaria. Dr Mota was represented at the ceremony by Ana Pamplona Santos, a post-doc at the laboratory. 'We are very glad to have more money to tackle this disease that attacks millions of people around the world. Cerebral malaria is the lethal form of malaria that kills 2 million children under five every year and I hope we can demonstrate that CO can be used as a therapeutic gas for the treatment of cerebral malaria. If we could reverse the spread of cerebral malaria it would be a great breakthrough.'
Ana Pamplona Santos also spoke enthusiastically of the GEMI Fund seminar and how it brought together exponents of different gases and applications.
Equally enthusiastic was Dr Ben Williams, PhD, of Dartmouth Medical School, Hanover, NH, USA. His research topic is electron paramagnetic resonance measurement of brain tissue pO2 and oxidative stress during hyperbaric oxygen therapy following stroke. 'The GEMI Fund has been really instrumental in supporting some of the research staff and the equipment we need. Specifically we will be measuring tissue oxygen concentration in a rat stroke model. It's a therapy that has been used before in a number of animal studies and it is shown to be effective. Adequate studies have not yet been done, however, to refine the technique with regard to dosage and timing.' Dr Williams confessed he was impatient to get back to the lab to continue doing the research. 'We've done a number of preliminary studies and have been making some of the measurements but now, with this funding, we can have the instrumentation and the equipment we need to carry out the research we've proposed. We can really dig in now.'

FORUM FOR COLLABORATION
Fellow grantee Dr Brian Zuckerbraun, MD, (Assistant Professor of Surgery at the University of Pittsburgh School of Medicine, Pittsburgh, PA, USA) is studying the use of carbon monoxide as a treatment for pulmonary arterial hypertension. In particular he praised the way the seminar brought together so many potential collaborators and other researchers with whom to exchange information, observations and contacts. 'It's been a fantastic day, with a great programme and plenty of stuff I knew nothing about before. I have made some very good contacts.' On the impact of the grant on his work he commented, 'I'm aiming high but I think it's a very worthwhile area. In two years I hope I can come back and report on the efficacy of carbon monoxide with pulmonary arterial hypertension in humans.'

Representing the Institute for Surgical Research, University of Munich, Munich, Germany, Dr Nick Plesnila, MD PhD, is looking at the inhalation of NO for the treatment of cerebral and cardiac ischemia.
'We are working primarily at stroke and traumatic brain injury models, and we're trying to find out what NO actually does in this context. We are investigating how NO goes from the lung to the brain and then what effect has there. We want to know exactly how NO is transported to the brain and then how we can use the cerebral effect of NO therapeutically.' On the day's presentations, Dr Plesnila noted that he had received some excellent input on xenon and CO that sounded really interesting.

New roles for gases

Ajay Verma, MD PhD, Associate Professor of Neurology at the Uniformed Services University of the Health Sciences, Bethesda, MD, USA is looking at the role of xenon therapy in the treatment of traumatic brain injury.

Dr Verma compares brain injury with dropping a rock in a pool, with a corresponding cascading ripple effect. 'One of the biggest things in the last ten years has been the understanding that the initial injury is not all. There is a large window of opportunity to come in and do something. We just haven't had anything good to come in with. Now we hope to show that xenon can act as one of those agents that will shut down the cascade of injury.'' For a long time we have been working on examining the role of gases as messengers, starting with carbon monoxide back in 1993 and over the last four years with oxygen and how it regulates brain metabolism and gene expression. What we are hoping to do is look at brain metabolism and how it can be regulated by general anesthesia. We're looking to slow down brain metabolism - right after an injury such as a stroke or brain injury. The plan is to start using general anesthetics as drugs.'

Dr Verma would like to see a time when general anesthetics could be used, for example, after a car accident or sports injury. 'It's so easy to administer gases and their action on the brain is so quick that they represent an ideal way to immediately shut down brain metabolism.' He will be experimenting with xenon by producing an injury in a rat brain, allow it to develop and then administering a brief period of general anesthesia to try and stop the injury cascading.'

Also examining xenon is fellow grantee Dr Martin Bienengraeber, PhD, Assistant Professor at the Department of Anesthesiology at the Medical College of Wisconsin, Milwaukee, WI, USA. His project is looking at the mechanisms of cardioprotection by xenon.
'We are aiming to protect the heart from ischemia by exposing it to xenon before, or immediately after, ischemic attack. We have demonstrated that there are several pathways involved when xenon is introduced in this way. My special interest is with the mitochondria and we will also be looking at how the mitochondria's 'energy factory' functions. This is a specific part of our proposal.' Dr Bienengraeber has a background in volatile anesthetics and he heard of similar mechanisms being observed with volatile anesthetics as with xenon leading to his decision to research what he describes as such a 'technical gas.'

Dr Martin Bienengraeber

> "We're looking to slow down brain metabolism - right after an injury such as a stroke or brain injury"
>
> **Dr Ajay Verma**

'This has been a great meeting and I've been really impressed by the quality of the presentations. I've got new ideas from nearly every talk. Very often meetings like this are too big and you don't really get the opportunity to exchange ideas.'


Dr Michael Fries


Dr Bastiaan Driehuys

THE RISE AND RISE OF XENON

Xenon certainly seemed to be very much the 'molecule of the moment' with no fewer than four grantees' projects involving the gas. Among these was Dr Michael Fries, MD, of the University Hospital of RWTH Aachen, Aachen, Germany. His project is to research the neuroprotective effects of xenon in a pig model of cardiac arrest. He lamented that though there were a number of neuroprotective agents that yielded good results in animal studies, this did not seem to be the case with clinical trials. There's still a pressing need to relieve the symptoms of people who are suffering brain injury or stroke or global ischemia. We're testing the hypothesis that xenon might act as a neuroprotective agent in a model of global ischemia and reperfusion in cardiac arrest. In two years my hope is to show a positive effect of xenon on pig brains that are globally ischemic.'

The final xenon project was that of Bastiaan Driehuys, PhD, Assistant Professor at the Centre for In Vivo Microscopy, Duke University Medical Center, Durham, NC, USA. The GEMI Fund awarded its grant for research into the hyperpolarized 129Xe imaging of lung function. This research involves imaging of hyperpolarized xenon gas, ordinary xenon gas that people can inhale but specially treated so that the signal on the magnetic imaging screen is enhanced by a factor of a million. 'Using this we can make images of gases with a very high resolution in diseases like asthma and emphysema. Xenon is extremely interesting - not only when we inhale it and it crosses into the blood stream and into the brain and beyond, but because it gives us different frequencies. Because of this we can tell what tissue the gas is dissolved in, opening up a completely different way of looking at images of blood flow and inhalation and so forth. Really, the sky's the limit.'

Multifunctional gas use

Dr Gaio Paradossi, Associate Professor of the Dipartimento di Scienze e Technologie Chimische at the University of Rome Tor Vergata in Italy will be using the GEMI Fund grant to explore the use of gas carrier microballoons with diagnostic and therapeutic features.


Dr Gaio Paradossi

'We are looking to fabricate microballoons containing therapeutic gases, such as NO, and to use them in a multi-functional way - both as an ultrasound contrast agents, and also as a mechanism for releasing gases close to the tissue. For this end we will try to use some sort of ultrasound procedure as a drug delivery system.' He describes the project as a 'frontier project' on the borders of physics, biology and chemistry, and cites the usefulness of the Fund in bringing together researchers from various disciplines.

Distinguished speakers present latest news about gas enabled medicine at Stockholm ceremony

From the opening address through to the day's culmination with the award ceremony, the seminar was filled with presentations from right across the spectrum of gas enabled medical innovation.

The latest in gas enabled medical innovation

2003 grantee Markus Rehm, MD, of Ludwig-Maximilian Universität in Munich presented the results of his work on NO and the endothelial glycocalyx. His research examined the inner layer of blood vessels and their role in maintaining vascular patency. Professor Rehm and his group demonstrated, for the first time, that this layer is protected by inhaled NO after an interruption in the blood flow.

From Ohio University, Athens, Ohio, USA, 2003 grantee Tadeusz Malinski, PhD, presented his work on wound healing with gases. Professor Malinski showed that several gases including NO and CO applied periodically to a wound area have a wound healing effect and can reduce the time to full recovery by around 40%.

GEMI FUND GRANTEES 2005

Martin Bienengraeber, PhD
Assistant Professor,
Department of Anesthesiology
Medical College of Wisconsin,
Milwaukee, WI, USA
Subject: Mechanisms of cardioprotection by xenon

Bastiaan Driehuys, PhD
Assistant Professor,
Department of Radiology Center for In Vivo Microscopy, Duke University Medical Center, Durham, NC, USA
Subject: Hyperpolarized 129Xe imaging of lung function

Michael Fries, MD
Department of Anesthesiology
University Hospital of RWTH Aachen,
Aachen, Germany
Subject: Neuroprotective effects of xenon in a pig model of cardiac arrest

Maria M Mota, PhD
Principal Investigator
Instituto de Medicina Molecular,
Universidade de Lisboa, Lisbon,
Portugal
Subject: The role of CO during the course of a malaria infection
Represented at the ceremony by Ana Pamplona Santos Instituto de Medicina Molecular, Universidade de Lisboa, Lisbon, Portugal

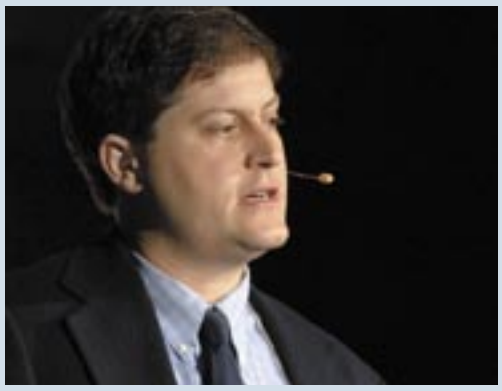
Dr Gaio Paradossi
Associate Professor,
Dipartimento di Scienze e Tecnologie Chimiche
Università di Roma "Tor Vergata",
Rome, Italy
Subject: Gas carrier microballoons with diagnostic and therapeutic features (NO)

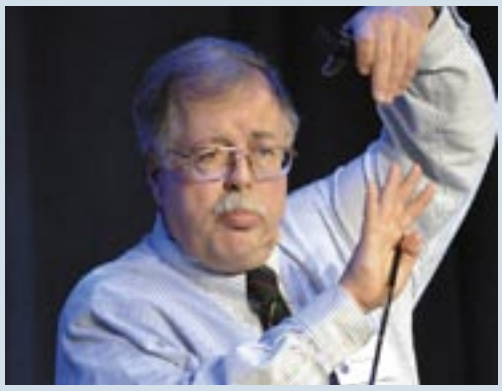
Nick Plesnila, MD PhD
Experimental Neurosurgery
Institute for Surgical Research,
University of Munich, Munich, Germany
Subject: Inhalation of NO for the treatment of cerebral and cardiac ischemia

Ajay Verma, MD PhD
Associate Professor of Neurology
Uniformed Services University of the Health Sciences, Bethesda, MD, USA
Subject: Xenon therapy in traumatic brain injury

Benjamin B. Williams, PhD
Research Associate, Department of Radiology Dartmouth Medical School,
EPR Center for the Study of Viable Systems, Hanover, NH, USA
Subject: Electron paramagnetic resonance measurements of brain tissue pO2 and oxidative stress during hyperbaric oxygen therapy following stroke

Brian Zuckerbraun, MD
Assistant Professor of Surgery,
University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
Subject: The use of carbon monoxide as a treatment for pulmonary arterial hypertension





Inhaled carbon monoxide State of the art research

From Harvard Medical School in Boston, USA, Professor Leo Otterbein, PhD reviewed the state of the art in inhaled CO research.

One of the world's leading researchers in this field, Professor Otterbein is behind most of the findings and innovation of the hemeoxygenase and carbon monoxide inhalation. He spoke eruditely on its possible role in the origin of life, its therapeutic effects as well as on its negative sides. 'It's been a long road getting people to think of CO as more than just a toxin. Now we want people to think think of it in another way as a substance with beneficial effects. It's been a long road, but we're getting there.'

The potential clinical benefits of CO therapy in treating the fatal and particularly burdensome disease, pulmonary fibrosis, formed the basis of Dr Danielle Morse's presentation. From the University of Pittsburgh School of Medicine, Professor Danielle Morse, MD, is a 2003 GEMI Fund Grantee. No effective therapy exists for pulmonary fibrosis and the mean survival time is just four years. Dr Morse and her team have confirmed that CO administered in low doses and for short periods can inhibit lung fibrosis. The mechanism appears to involve a decrease in matrix production by fibroblasts, the cell type responsible for scar formation.

Also from University of Pittsburgh School of Medicine, and also a 2003 grantee, Dr Atsunori Nakao's research focused on CO in organ transplantation. Doctor Nakao presented the results of his researching showing that inhaled low doses of CO after transplantation surgery exhibits anti-inflammatory effects. Various animal models were explored showing strong further potential.

FROM TRANSPLANT TO THERAPY

From the Instituto Gulbenkian de Ciencias, Oerias, Portugal and Harvard Medical School, Boston, Professor Miguel Soares has investigated multiple sclerosis in animal models. A 2003 grantee, he and his group demonstrated that the progression of MS in mice can be controlled by heme oxygenase-1 (HO-1), a gene that generates CO. There is also a suggestion that inhaled CO alone could have the same effect though it has to be shown that this also works in other species.

Professor Mark Conradi of Washington University, St. Louis, Missouri focused on diagnostic imaging of lungs with perfluorinated gases. 'The idea is to develop this into a superior technique for detecting emphysema, in identifying where it is in the lung - more than just diagnosing emphysema but locating it for surgeons performing lung reduction surgery.'

Above: **Dr Leo Otterbein, Dr Mark Conradi, Dr Miguel Soares**

Below: **Dr Danielle Morse**

The Gemi Fund Board

Professor Warren M. Zapol
Anesthesiology, Massachussetts General Hospital, Boston, USA

Professor Timothy W. Evans
Intensive Care Medicine, Royal Brompton Hospital, London, UK

Professor Dag Linnarsson
Physiology and Pharmacology, Karolinska Institute, Stockholm, Sweden

Professor David J. Pinsky
Internal Medicine, University of Michigan, USA

Professor Rolf Rossaint
Anesthesiology, University Hospital Aachen, Germany

Professor Ignacio Sanchez
School of Medicine, Pediatrics, Universidad Cátolica de Chile, Santiago, Chile

Professor Jörg Weimann
Anesthesiology and Intensive Care Medicine, Charité Campus Benjamin Franklin, Berlin, Germany

Rolf Petersen
Director, Product Search & Development, Linde Gas Therapeutics, Sweden

THE GEMI FUND

Practical results

The presentation by Professor Göran Hedenstierna, MD, of the Academic Hospital, Uppsala University in Sweden both moved and impressed the audience. Recounting a rescue trial in 2003 with SARS patients in Beijing, China, he detailed how four out of six patients treated with inhaled NO in combination with steroids were discharged to their homes after 28 days. Two remained in the Intensive Care Unit. Of those not treated with NO, two out of eight went home, two died and four remained in Intensive. The hypothesis was that iNO can enhance the efficacy of steroid treatment.

The GEMI Fund was founded in 2003 by Linde Gas Therapeutics in co-operation with Harvard Medical International, Boston, MA, USA and the Karolinska Institute, Stockholm, Sweden.

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Panorama is published by Linde Gas Therapeutics

Publisher Per Blom, MD PhD, Senior Vice President

Managing Editor Agneta Skröder

Editor Peter Whitby

Linde Gas Therapeutics
AGA AB
SE-181 81 Lidingö, Sweden
Tel +46 8 731 1000
Fax: +46 8 765 5287

Email: ask@linde-gas.com

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Jan Carlstedt-Duke, Dean of Research of the Karolinska Institute, Stockholm, Sweden

'Medical gas research is an area that has been well established at the Karolinska Institute for some time, and we have enjoyed a long-term relationship with Linde Gas Therapeutics, but I think the GEMI Fund has really opened up this field even more.' 'This Fund brings together scientists from different countries with different areas of research and they get exposed to a broader opportunity within their field - not just in the field of their own specific interests.'

Dr Walter Koppensteiner, Head of Institutional Business, Linde Gas Therapeutics, Munich

'This forum is the right platform to bring together people from the industry, regulatory bodies, inventors, research people and the day-to-day practitioners who work with patients every day. These researchers are pointing to new opportunities with gas, contributing to better health care.'

"This occasion, both the presentations and the awards, honours the work that we are all doing"

2005 Grantee Dr Michael Fries