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nanoTECHNOLOGY news
from the University of Minnesota

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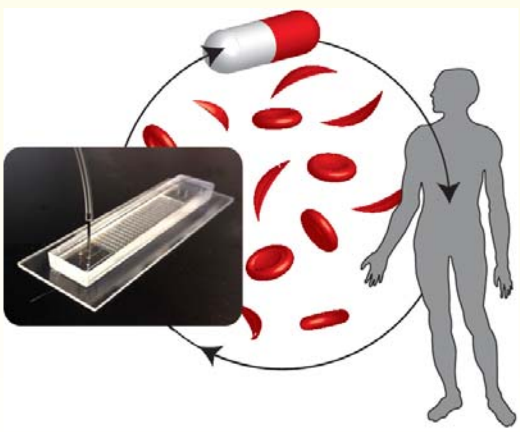
What's Blood Got to Do with It? A Role for Microtechnology in Treating Sickle Cell Anemia

Xinran Lu and David K. Wood
Department of Biomedical Engineering
University of Minnesota

In healthy individuals, red blood cells are sufficiently flexible to distort and reorganize so that blood flows smoothly through the vascular system. In some diseases, such as sickle cell anemia, red blood cells become rigid, and they can obstruct blood flow (vaso-occlusion), which deprives the surrounding tissue of oxygen and nutrients. For people with sickle cell anemia, the result is chronic anemia, episodes of intense pain, increased risk of stroke, frequent infections, and a significantly shortened lifespan. The Living Devices Lab, directed by Professor David Wood in the Department of Biomedical Engineering at the University of Minnesota is using microtechnology to combat sickle cell anemia. The group is developing new tools that allow them to study the changes in blood that occur during vaso-occlusions and to discover new methods for treatment.

A major obstacle in studying sickle cell anemia is the difficulty of imaging the deep tissue in humans where vaso-occlusions occur. To get around this problem, the Living Devices Lab has developed a microfluidic device that mimics the conditions inside the body under which vaso-occlusions naturally occur. At the heart of the devices, which are made in the Minnesota Nano Center, is a microfluidic channel about the size of a human capillary. The researchers perfuse the microchannel with whole blood from sickle cell patients and measure changes in flow that result from changes in blood oxygen concentration, which is the trigger for changes in red blood cell rigidity that lead to vaso-occlusion. In a clinical study published in the journal *Science Translational Medicine*, the group showed that measurements made in their microfluidic device could serve as a biomarker for disease severity. This means the devices could be used to monitor patients and predict when patients might need more intensive care. They also showed that the devices might be able to predict the efficacy of drugs. Together these findings suggest that the devices could be used to test new therapies before clinical trials and to monitor patients during clinical trials, thus significantly improving the pipeline to develop new treatments for sickle cell anemia.



Professor Wood's group is currently studying some of the basic mechanisms in vaso-occlusion with the hope of finding new targets for therapy and to predict the efficacy of potential new therapies. They are also working on a new generation of microfluidic devices that more fully mimic the structure of the vascular system in the body. This work is supported by funding from the College of Science and Engineering and a Scientist Development Grant from the American Heart Association.

REMINDER: If your work uses the Minnesota Nano Center (formerly NFC) please add the following in the acknowledgements section of any publication: "Parts of this work were carried out in the Minnesota Nano Center which receives partial support from NSF through the NNIN program."

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CHARFAC DIRECTOR'S MESSAGE

CharFac Director,
Greg Haugstad

As of June a new field-emission scanning electron microscope, the Hitachi SU8230, is being installed in the CharFac's Nils Hasselmo Hall site, replacing the 25-year old Hitachi S-900. The new instrument is the latest addition to our suite of cryo-active EMs (two SEMs, two TEMs) positioned in Hasselmo and Moos Tower. The complete cryo system ultimately will include new ancillaries, a Leica VCT-100 Cryo stage and sample shuttle and a Leica ACE600 cryo sample preparation and metal coating unit. Other ancillaries include a desktop UV cleaner for samples and a new-generation Thermo-Noran System 7 for energy dispersive spectroscopy (EDS, characteristic X-ray emission for elemental imaging). The complete ($1M) system was primarily funded through the NSF Major Research Instrumentation program. Proposal authors included lead PI Lorraine Francis of Chemical Engineering and Materials Sciences and co-PIs from several departments in the College of Science and Engineering, the Medical School and the College of Pharmacy, underscoring the trans-disciplinary need for next-generation systems.

The SU8230 delivers 1.1 nm resolution at 1.5 mm working distance at 1.0 kV landing voltage, and 0.8 nm at 4.0 mm working distance at 15 kV accelerating voltage. Beam landing energies range from 30 kV to 0.01 kV using beam deceleration with variable retarding bias. For electron detectors, the SU8230 utilizes (1) an in-column upper ExB detector with a lens-integrated control electrode to provide either pure secondary electron (SE) signal or variable percentages of SE and inelastically scattered backscattered electrons (BSE); (2) an in-column top detector which receives elastically scattered BSE for high-resolution atomic-number contrast at short working distances; (3) a chamber-mounted Everhart-Thornley detector; (4) a 4+1 segment retractable below-lens semiconductor type BSE detector. The SU8230's 8" sample chamber (with dedicated loading chamber) includes an integrated LN_2 cryo trap and a 5-axis motorized stage with an 11 cm x 11 cm range (X,Y).

As we enter the busy summer season – a time when many students launch into their research – it is worth restating that training is meant to enable heavy, ongoing usage spanning at least months if not years. Usage statistics confirm that as much as 40% of the time spent training users has been effectively wasted: either the trainee did not go on to use the instrument at all, or used so little that analytical services by the CharFac scientific staff would have been more appropriate (and likely would have generated better data). Moreover, one should seek neither training nor services for a technique that is inappropriate to the research questions or sample types. It is not uncommon to receive an email wherein a student simply states, "I need training" (on instrument X). But upon inquiry it becomes clear that the student knows essentially nothing about the analytical technique: the nature of the data acquired, the caveats in interpreting this data, restrictions on sample type/size, and more. If there is uncertainty on technique appropriateness, it is best to *send an email query to the relevant staff member with a detailed description of the research issues.* In the spirit of the University's push for "operational excellence", CharFac continually seeks to eliminate fruitless effort and enhance the quality of research performed.

CHARFAC AT THE UNIVERSITY OF MINNESOTA

12 Shepherd Labs
100 Union Street SE
Minneapolis, MN 55455

Website: www.charfac.umn.edu
Email: charfac@umn.edu
Telephone: 612-626-7594

Greg Haugstad, Director

MNC DIRECTOR'S MESSAGE

NFC Director, Steve Campbell

I wanted to update you on our progress in moving into the new Physics and Nano (PAN) Building. During the move-in process we encountered several delays. The code office mandated a change in how hazardous materials are stored. This required changing some ventilation systems. This work is done and as a result, a full certificate of occupancy will shortly be issued. The other major problem was that the contractor did not carry out the clean room certification as per specifications. Most of the certification problems have been resolved. The major remaining issue is the noise level in the lab, especially the south-most bays. We hope to resolve this over the summer.

The equipment move from Keller is just about complete. As to new equipment, we are planning to add another ALD tool as the existing system is heavily loaded. We also have submitted a proposal to the OVPR's infrastructure program to fund a refurbished contact aligner for PAN and to replace the very old PECVD system in Keller with a much more modern high density PECVD system. Thanks to our colleagues who helped me write this proposal. Other new capabilities can be found in the new bionano wet lab, and the new nanomaterials wet lab as described in the last newsletter.

Finally, let me bring you up to date on the National Nano Infrastructure Network (NNIN). Minnesota has participated in NNIN since 2004. NNIN income represents about 15% of our lab funding. We joined the Cornell/Stanford/MIT/Berkeley team for the competition for Next Generation (NG) NNIN. Although we had a very strong proposal NSF declined to make an award and instead decided to recompete NG-NNIN. So, we get to go through this again during the 2014-15 academic year. I have been asked by NSF to serve on the team to draw up the RFP. I will let you know how this goes.

MINNESOTA NANO CENTER AT THE UNIVERSITY OF MINNESOTA

140 Physics & Nanotechnology Bldg
115 Union Street SE
Minneapolis, MN 55455

Website: www.mnc.umn.edu
Email: mnc@umn.edu
Telephone: 612-624-8005

Steve Campbell, Director
Greg Cibuzar, Lab Manager

OPTICAL LITHOGRAPHY AND ALD

Our Canon i3-2500 i-line stepper is set up for 100mm wafers, and is capable of defining 400 nm lines and spaces with overlay accuracy of about 150 nm. Die sizes as large as 20 mm by 20 mm are possible. With our maskmaking system we can fabricate the reticles on site. This tool fills a gap in our lithography capabilities between contact lithography and electron beam lithography.

Atomic Layer Deposition (ALD) systems allow very well controlled growth of extremely thin films, even over highly nonplanar structures such as nanopores, nanowires, and nanoparticles. Typical films are metal oxides such as HfO_2 and Al_2O_3. The process involves the sequential exposure of the substrate to two gases. The gases are chosen such that at least one of them saturates the surface at one monolayer of coverage and the process conditions are such that neither gas, by itself, will decompose to form a solid. After exposure to the first gas, the system is flushed, but one monolayer of this gas remains on the substrate where it can react with the second gas to form a monolayer of the desired film. The process is repeated until the desired film is grown.

MNC currently has source materials for the deposition of HfO_2, Al_2O_3, SiO_2, TiO_2, and ZnO. We are currently in the process of adding ozone capability, which will improve the SiO2 process, as well as allow new processes. Please contact us if you have interest in this capability.

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115 Union Street SE
Minneapolis, MN 55455

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Minnesota Nano Center: www.mnc.umn.edu

The MNC is a state-of-the-art facility for interdisciplinary research in nanoscience and applied nanotechnology. The Center offers a comprehensive set of tools to help researchers develop new micro- and nanoscale devices, such as integrated circuits, advanced sensors, microelectromechanical systems (MEMS), and microfluidic systems. The MNC is also equipped to support nanotechnology research that spans many science and engineering fields, allowing advances in areas as diverse as cell biology, high performance materials, and biomedical device engineering.

The MNC is composed of two main facilities. Our current clean room and associated labs, formerly known as the Nanofabrication Center, are housed in Keller Hall. The Keller Lab has a 3000 square foot Class 100 clean room, and an additional 4000 square feet of labs and support areas.

In late 2013, the MNC will open a new research facility in the Physics and Nanotechnology (PN) building. The new PN Lab facility will offer a larger and more advanced clean room, with state-of-the-art tools for fabricating structures under 10 nanometers in size. The MNC will also offer two new specialized labs to support interdisciplinary research in bio-nanotechnology and nano-and micrometer-scale materials.

The National Nanotechnology Infrastructure Network: www.nnin.org

The National Nanotechnology Infrastructure Network (NNIN) is an integrated networked partnership of user facilities, supported by the National Science Foundation, serving the needs of nanoscale science, engineering and technology. The mission of the NNIN is to enable rapid advancements at the nano-scale by efficient access to nanotechnology infrastructure. The NNIN supports the Minnesota Nano Center at the University of Minnesota. As a node in NSF's National Nanotechnology Infrastructure Network (NNIN), the NFC provides access to advanced multi-user facilities to both industry and academic researchers, the latter at a subsidized rate.