from Tsukuba, Japan to the world

NIMS NOW International

National Institute for Materials Science

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Special Features

Introduction of 20 New Projects and Recent Achievements - Biomaterials Center -

Preface "Diverse Efforts in the Field of Biomaterials"

Tetsuya Tateishi
Director-General
Biomaterials Center

Three necessary and indispensable elements in tissue engineering are a cell source, a cell carrier (scaffold), and a cell stimulating factor (**Fig. 1**). However, cells, materials, and stimulating factors alone are not sufficient for regenerative medicine. Engineering design technology is also necessary in order to design a medical instrument, in other words, a cell device, which can be used to place the cells in the matrix, manufacture the cell device automatically and aseptically under an environment which maintains safety, and secure some means of transporting the device while maintaining its activity, and the support of cell engineering technology is required for mass production of cell devices. Control of the differentiation/migration and proliferation of cells until the desired tissue or organ is realized requires design/production of multi-functional high-order cell matrix materials utilizing bio-nanotechnology and bio-informatics for monitoring information on genes and proteins which exist between cell populations. More than anything else, to enable tissue which has been regenerated outside of the body to demonstrate the expected functions after transplantation into the body, a non-invasive assessment as to whether the regenerated tissue possesses adequate strength and mechanical properties and satisfactory biochemical properties must be performed in advance, and the requisite properties must be ensured. This is the field where science and engineering display their greatest strength. In other words, tissue engineering is only materialized through a fusion of science/technology and medicine. < Continued on p.2

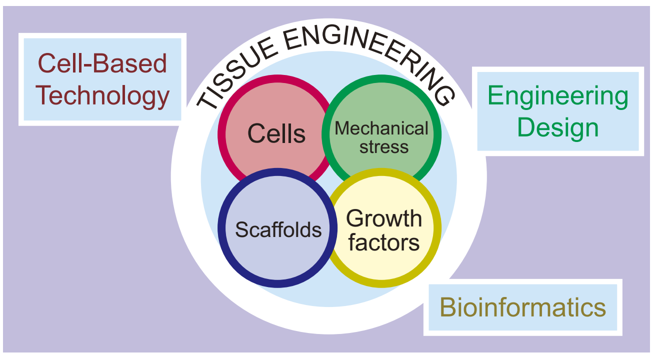


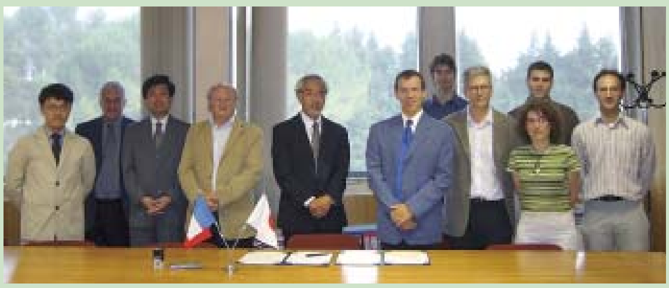
Fig. 1 Seven factors for tissue engineering.

in this issue

NIMS News

MOU with INSA Toulouse, France

(June 27, France) -- The NIMS Quantum Dot Research Center signed an MOU with the Laboratory for Nanophysics Magnetism and Optoelectronics (LNMO), INSA Toulouse (Institut National des Sciences Appliquees), France. LNMO is noted for outstanding research and development focusing on spintronics research applying optical techniques to semiconductor nanostructures. The Quantum Dot Research Center and LNMO plan exchanges of researchers and research information, joint research, and related activities in the field of semiconductor nanostructural materials, beginning with joint research on the creation and property evaluation of semiconductor nanostructures, represented by quantum dots.



From left, Dr. Kuroda, Nano Photonics Group of NIMS, Prof. Erschler, Director of Research, LNMO, Dr. Sakoda, Group Leader of the Nano Photonics Group of the Quantum Dot Research Center, Prof. Castex, Director of INSA Toulouse, Dr Koguchi, Managing Director of the Quantum Dot Research Center, Prof. Marie, LNMO, and the laboratory staff.

For more details: http://www.nims.go.jp/qdr/

Research on Nano-Structured Ceramic Biomaterials

Tetsuya Tateishi, Masanori Kikuchi,
Yasushi Suetsugu, Toshiyuki Ikoma
Nano-Structured Biomaterials Group
Biomaterials Center

Many of the cells in our bodies live surrounded by a "scaffold" composed of polysaccharide or protein. This scaffold is called an extracellular matrix (ECM). When cells construct tissues such as skin or blood vessels by differentiation and proliferation, it is thought that they recognize and are strongly influenced by the physiochemical properties of the ECM. For example, the ECM of bone is a nano-composite consisting of hydroxyapatite, which is a type of calcium phosphate, and the fibrous protein collagen. In addition to giving bone its hard, pliant mechanical properties and storing calcium and phosphorus, which are indispensable elements in the living body, this substance also provides an environment for the normal activity of bone cells.

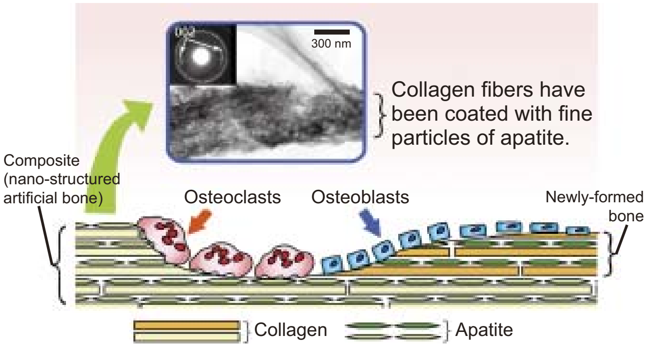


Fig. Biological reaction of apatite/collagen composite. Replacement with the patient's own bone is possible using osteoclasts which dissolve bone and osteoblasts which create bone. The figure at the top shows transmission electron microscope (TEM) and electron beam diffraction images of the composite.

We succeeded in reproducing in the test tube the conditions under which bone forms in the body and artificially synthesizing a nano-structured apatite/collagen composite which closely resembles the bone matrix (see **Fig.**). In this material, the apatite crystals and collagen fibers are arranged at the nano-level in the same way as bone. Investigation by the electron beam diffraction method revealed that the direction from the center of an arc which shows the 002 orientation of the apatite crystal coincides with the direction of the collagen fibers. When this composite is embedded in organic bone, the cells recognize it as bone, and it is gradually replaced by real bone by metabolism.

High expectations are placed on tissue engineering as a new treatment for restoring damaged tissue. For practical application of this technology, the development of scaffold materials which control cell proliferation, differentiation, and migration is indispensable. Focusing on nano-topologies which have been overlooked in past biomaterial development, the Nano-Structured Biomaterials Group plans to contribute to the development of new medical technologies such as tissue engineering by developing ceramic materials which can express cellular functions by controlling this nano-topology.

For more details: http://www.nims.go.jp/bmc/index_e.html

Special Features Introduction of 20 New Projects and Recent Achievements - Biomaterials Center -

< Continued from p.1

Preface "Diverse Efforts in the Field of Biomaterials"

While it is undoubtedly true that Japanese engineers have made extremely important contributions to research and development of medical technology in some areas, it would be exceedingly questionable to claim that they have played a leading role in promoting the medical industry. At present, Japan must still depend on imports from Europe and the United States for the larger part of artificial tissues and organs of types implanted in the deep interior of the human body. The root cause of this situation lies in the fact that medicine and engineering have each clung stubbornly to their own cultures, and methodologically and organizationally, a mutual fusion was impossible. Of course, there are also several other factors in this problem, such as Japan's lack of a diverse, flexible American-type system of corporate evolution, in which venture companies accept the high risk inherent in the R&D stage of new technologies, and the harmful effects of the government's vertically-compartmentalized administrative system and one-year budgeting system. Perhaps it can be said that we have not been making efforts to break down the intractable cultural barriers which have existed between governmental ministries and agencies, medicine and engineering, and industry and academia. A repetition of this kind of failure cannot be permitted in the fields of regenerative medicine and genetic therapy, which are likely to become the "star" medical industries of the 21st century (**Fig. 2**).

In the Biomaterial Center, our objectives are to contribute to the development of regenerative medicine, next-generation medical technologies such as nano drug delivery systems (nano-DDS), and safety evaluation technologies such as bioelectronics with the aim of realizing a society where the Japanese people can live safe, healthy, and comfortable lives. We are of course involved in medical/engineering collaboration and joint work with industry and academia, and we are devoting great effort to the construction of a medical/engineering collaborative network for an interdisciplinary integration of specialties on the national scale and to realizing the Medical Industry Highway concept for inter-industry/regional integration.

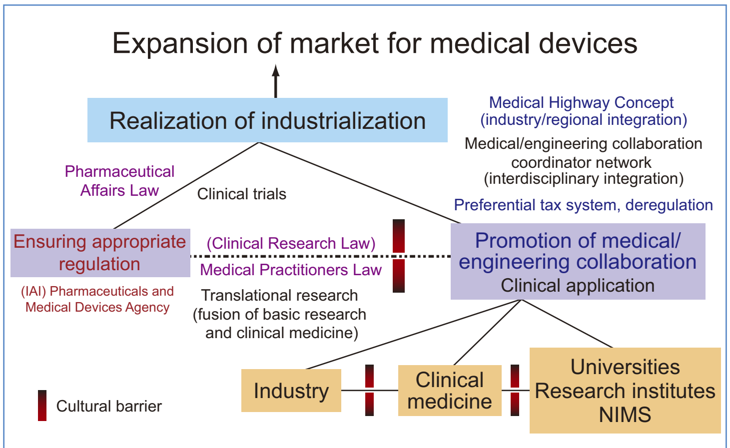


Fig. 2 Organization for promoting medical industry.

For more details: http://www.nims.go.jp/bmc/index_e.html

Research on Creation of Polymeric Biomaterials and High-Order Control of Expression of Functionality

Hisatoshi Kobayashi, Tetsushi Taguchi
Biofunctional Materials Group
Biomaterials Center

Nanostructured molecular assemblies which maintain homeostasis in the body exist in the area around cells. These are called the extracellular matrix (ECM). Except in the case of hard tissue such as bone, the ECM consists almost entirely of collagen and other macromolecules. Therefore, up to the present, living tissue which has become functionally imperfect has been reconstructed using a combination of cells and a material which mimics ECM. Some clinical application has already begun with comparatively simple tissues such as cartilage, bone, and skin. On the other hand, because organs such as the liver and pancreas consist of multiple cells and require blood vessels, research on the regeneration of organs of this type is still in its infancy. Regeneration of these complex organs requires biomacromolecular materials which are controlled from the nanostructure to the micro and macro structure. This report introduces (1) a nanofiber sheet for neovascularization and (2) an intercellular adhesive.

In order to achieve (1), we developed a nano co-fiber sheet (**Fig. 1a**) consisting of collagen, which has a cell adhesive property, and polyglycol acid (PGA), which maintains shape, using the electron spinning method aiming at early functioning of regenerated materials and achieving their long-term stability in the human body. In this method, a voltage is impressed on a macromolecular solution, and fibers are formed by ejecting a jet of the solution. An investigation of the neovascularization (angiogenetic) capacity of the prepared material confirmed adhesion of blood vessel endothelial cells in groups in which the angiogenetic factor (fibroblast growth factor (FGF)) was adsorbed on the nanofiber (**Fig. 1b**). An evaluation of genetic expression revealed that a high level of genes related to angiogenesis existed in the endothelial cells which were in contact with the nanofibers.

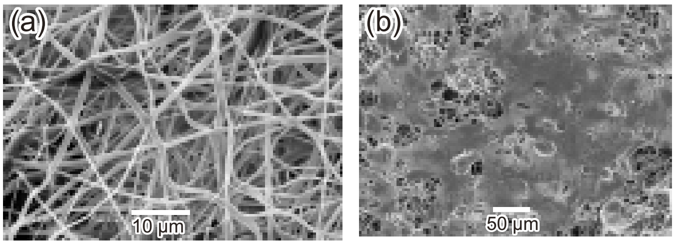


Fig. 1 (a) Prepared nanofiber sheet, (b) view of cell adhesion and penetration.

On the other hand, we are also engaged in research on adhesives for intercellular bonding. Spheroids, in which multiple cells form a pseudomass by intercellular interaction, are known to display enhanced cellular functionality in comparison with single cells. However, the existing spheroid forming method has various problems, for example, requiring special equipment and techniques. Therefore, we synthesized a polymeric cross-linking agent (adhesive) which enables quick, simple formation of spheroids. As shown in **Fig. 2a**, this adhesive has a hydrophobic group such as lipid molecules at both termini and has a structure which possesses biodegradability. When this adhesive was added to cells, spheroids were obtained, as shown in **Fig. 2b**. As the mechanism of spheroid formation, it is thought that the hydrophobic groups of the adhesive function as anchors in the lipid bilayer comprising the cell membrane, and thus physically cross-link pairs of cells (**Fig. 2c**). In spheroid formation using this adhesive, it was clear that the speed of spheroid formation and the size of the spheroids obtained varies depending on the adhesive/cell concentration, molecular weight, and presence or absence of serum, among other factors. We are currently conducting a biochemical evaluation of the spheroids formed by this process and collecting basic data for medical applications.

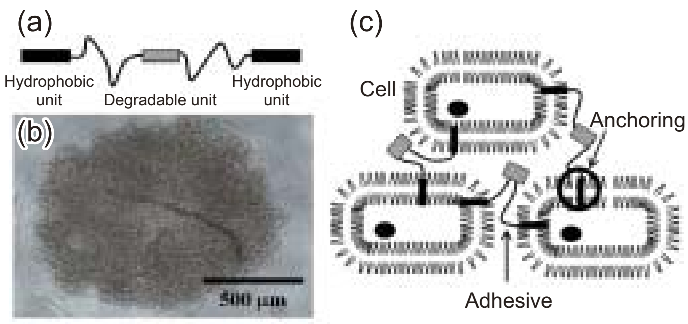


Fig. 2 (a) Structure of synthesized adhesive, (b) spheroid, (c) mechanism of psuedomass formation.

For more details: http://www.nims.go.jp/bmc/index_e.html

NIMS News

MOU with Engineering Research Institute, Gyeongsang National University, Korea

Prof. Dong-Woo Shin, Gyeongsang National University (left) and Dr. Hidehiko Tanaka, Leader of Non oxide ceramics group, Nano ceramics center, in front of ERI at Jinju, Korea.

(June 20, Tsukuba) -- The NIMS Nano Ceramics Center (NCC) signed an MOU with the Engineering Research Institute (ERI), Gyeongsang National University, South Korea on the "Theory and Practice on Structural Ceramics." Japan and Korea both have long histories of research on modern ceramics and have accumulated extensive technical knowledge. The two countries have also collaborated actively in research at the governmental and private-sector levels by exchanging scientists. Structural ceramics have recently found wide application in the precision machinery, semiconductor, and environmental materials industries. NCC and ERI intend to maintain mutual cooperation and will work intensively in research in the above-mentioned field in order to develop advanced technologies for creating special fine ceramics for these applications.

Research on Interaction of Cells and Materials for Regenerative Medicine

Akiyoshi Taniguchi,
Junko Okuda
Cell Engineering Technology Group
Biomaterials Center

Research on regenerative medicine is a comprehensive research field encompassing both biomaterials and stem cell research. As a scaffold for cells, biomaterials occupy an important place in regenerative medicinal technology. With progress in research in recent years, it is increasingly possible to induce differentiation in the cells which comprise the object tissue or organ from undifferentiated cells (for example, ES cells and bone marrow stem cells). However, if these cells are transplanted individually into the human body, the cells will not survive, and efficient regeneration of the tissue or organ will be impossible. This means that it is necessary to develop tissue from cells in advance so that the cells can be transplanted in a form which approximates the organ. From this viewpoint, interaction with cells is important in biomaterials for regenerative medicine. Construction of organs model is undoubtedly an important technique for optimizing the interaction between cells and biomaterials. Therefore, it is thought that an investigation of the kinds of interactions which take place between the cell groups of tissues/organs and other cell groups will provide crucial knowledge for designing the surface of biocompatible materials. In other words, it is important to reproduce the interaction between these cell groups on the surface of the biomaterial. If it is possible to clarify the key factors in intercellular interaction and reproduce these molecules on the surface of biomaterials using nanotechnology, it is also expected to be possible to design materials which maintain cellular functions and have high biocompatibility.

To investigate these issues, we constructed a system for analyzing genes which display changes in expression due to interaction between cells using a bi-layered co-culture method involving different types of cells. The hepatic lobule, which is the smallest unit of the liver, is composed mainly of endothelial cells and hepatocytes. This suggests that interaction between the endothelial cells and hepatocytes is important in the function of the liver. We therefore measured liver cell-specific gene expression in a bi-layered co-culture system using endothelial cells and hepatocytes, as shown in **Fig. a**. The results revealed that expression of the albumin gene in a bi-layered co-culture system of endothelial cells and hepatocytes increases in comparison with a monolayer culture (**Fig. b**). An increase in albumin gene expression indicates an increase in liver function. This result demonstrates the importance of the extracellular matrix and proliferation factor produced by the endothelial cells, cytokines (proteins produced by cells which induce proliferation and differentiation in itself and foreign cells), and other factors for the expression of liver function.

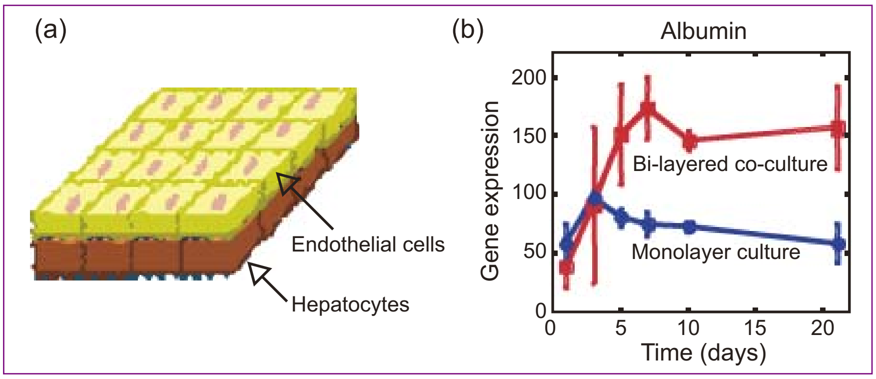


Fig. (a) Hepatocyte/endothelial cell bi-layered culture, (b) change in gene expression.

For more details: http://www.nims.go.jp/bmc/index_e.html

Research for Clinical Application of Biomaterials

Yoshiyuki Uchida, Norio Maruyama, Guoping Chen
Akiko Yamamoto, Sachiko Hiromoto, Yoko Shirai
Clinical Technology Group
Biomaterials Center

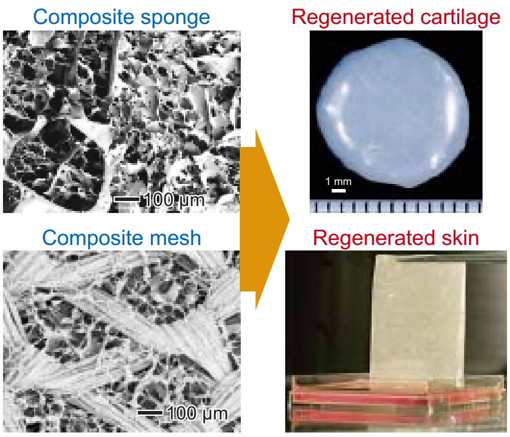


Fig. 1 Tissue regeneration using porous substrate materials.

The Clinical Technology Group consists of researchers who specialize in scaffold materials for tissue engineering, implant metals, and drug delivery systems. Based on exchanges of information which go beyond the frameworks of these individual specialties, the Group develops medical materials from the viewpoint of medical researchers who are actually involved in clinical situations.

For example, we developed a bioabsorbable polymer with a precisely controlled porous structure. This material is being used as a porous scaffold in cultivation of somatic cells and stem cells and in the regeneration of living tissues such cartilage and bone, skin, ligaments, and the pancreas (**Fig. 1**).

Because metallic materials have excellent strength, toughness, rigidity, electrical conductivity, and other properties, they are used in artificial joints, bone fixation devices, and similar applications. Recent years have also seen a rapid increase in the use of stents (metallic mesh tubes) which expand constrictions that have formed in blood vessels, the esophagus, and other body parts. Among the conditions which can be predicted in stents for use in blood vessels, corrosion and fatigue of the metallic material are accelerated by the blood flow, and the shear forces applied to the cells of the blood vessel walls and the blood

Research and Development of Biochips Based on Nano-Biotechnology

Yuji Miyahara,
Nobutaka Hanagata,
Toshiya Sakata
Biosensing Group
Biomaterials Center

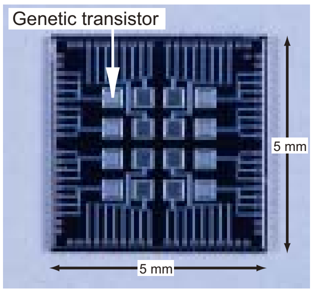


Fig. 1 Genetic transistor.

Decoding of the entire base sequence of the human genome was completed in April 2003, and active research (polymorphism analysis) is now underway worldwide with the aim of clarifying how differences (polymorphism) in certain parts of the base sequence are linked to individual differences (for example, susceptibility to disease).

As part of these efforts, we are engaged in research and development of biochips which enable simpler, more accurate, and quicker analyses of individual polymorphism, in other words, DNA chips. At present, a variety of techniques and principles are used in DNA chips, and in our group, we are attempting the world's first introduction of semiconductor nanotechnology using the field effect transistor (FET), as illustrated in **Fig. 1**.

As a distinctive feature of this genetic transistor, because the chip is effective in detecting molecules such as DNA which have electrical charges, direct monitoring of changes in these charges as electrical signals is possible. As a second advantage, chips which are compact and have integrated functions, and which also have a high degree of simplicity, can be produced easily using conventional semiconductor processing technology.

With the genetic transistor which is object of research and development in our group, it is possible to detect various DNA molecule recognition reactions. Recently, it has also become possible to detect individual base sequences of DNA. Thus, high expectations are placed on this device as a tool for polymorphism analysis. **Figure 2** shows the results of DNA sequence analysis using the genetic transistor. When the substrates (C, A, G, T) which form the individual base pairs (bp) of DNA are introduced in order together with the enzyme polymerase, the electrical signal changes corresponding to the sequence undergoing the extension reaction. In the DNA sequence in the upper part of **Fig. 2**, a double chain structure has formed between 9 bp of the probe DNA and 17 bp of the target DNA which have a complementary sequence to the probe DNA. If an extension reaction is caused in the direction of the arrow in the sequence TGCACGGG (shown in blue), which corresponds to the remaining 8 bp, the sequence can be identified from the changes in the electrical signals, as shown in the graph.

We are also engaged in work in bioinformatics in order to evaluate the effects of biomaterials on cells by a comprehensive analysis of gene expression using an integrated DNA chip in which virtually all human, mouse, and other genes are mounted on the slide glass. This technique makes it possible to predict the effects when materials are transplanted into a living body without performing animal experiments. Because the integrated DNA chip can easily discover gene groups which display changes in expression due to differences in the surface structure or chemical properties of biomaterials, it is possible to predict molecular level phenomena at the interface between cells and biomaterials. By constructing an integrated database for genetic expression and material properties embodying a fusion of nanotechnology, biotechnology, and IT technology, our aim is to break free of the conventional paradigm of "phenomenological/empirical biomaterial development" and establish a "theoretical system and technology for a new biomaterial development process understood from the viewpoint of biological reactions."

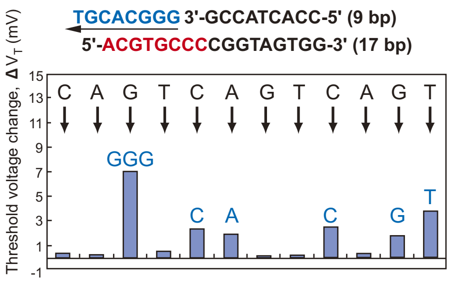


Fig. 2 Result of DNA sequence analysis using the genetic transistor.

For more details: http://www.nims.go.jp/bmc/index_e.html

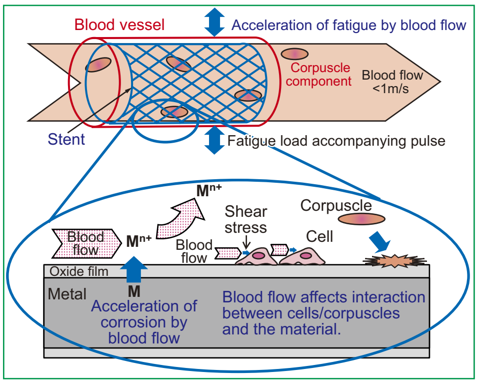


Fig. 2 Blood flow causes the increase in mass diffusion, accelerating corrosion, and as a result, fatigue of a metal by pulsating loads is accelerated. The shear forces caused by the blood flow also influence the interaction between cells and the material.

corpuscles affect the interaction between the cells and the material (**Fig. 2**). However, there is still no technique for evaluating the effects of these conditions under a blood flow. Therefore, we are developing techniques for evaluating the corrosion behavior, fatigue property, and biocompatibility of materials under a flow environment. The establishment of these evaluation techniques is expected to reduce the need for animal experiments and accelerate the development of new materials.

Various defense systems exist in the living body, and the effects of these systems cannot be avoided when drugs are administered. Nano-inhalers are extremely effective in comparison with oral administration of drugs, and development as an alternative to invasive drug injections is progressing. When inhaled, nano-sized drug particles are delivered to the alveoli in the lungs with high efficiency, and are then transported from inside the capillaries distributed in the alveoli to organs throughout the body. We established a technology which keeps nanoparticles in their original dispersed condition on nanofibers, and thereby succeeded in developing the world's first nanoparticle inhaler. Because the adhering nanoparticles are separated by the velocity of the patient's respiration, we are currently studying application to mask-type inhalers (**Fig. 3**).

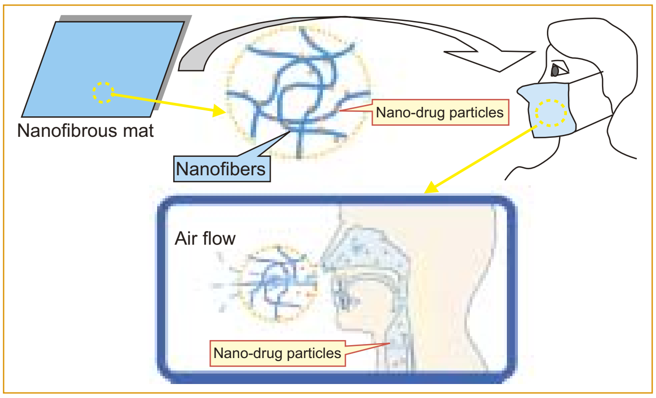


Fig. 3 Mask-type inhaler.

For more details: http://www.nims.go.jp/bmc/index_e.html

Hello from NIMS

A Balanced Research Career and Family Life

Hello, I am Manisha Kundu. I am from Pune City in India, where I completed my Ph.D. in Physics in 1995. I came to Japan in 1997. After working in various institutes/university in Tsukuba and Tokyo, I joined NIMS as a Post-Doctoral Research Fellow in Dr. Tsuyoshi Hasegawa's Group in April 2004. My present research focuses on the growth and development of high-quality solid electrolyte materials such as Ag_2S and Cu_2S under ultra-high vacuum conditions. These materials have potential applications as nanoscale switches in present-day electronic devices. I am interested in understanding the film properties of such materials. NIMS is undoubtedly one of the best institutes in the world to carry out research activities.

I have been in Japan for nine years and definitely enjoy living in Tsukuba. Come spring and it is a unique experience to walk down the pedestrian road surrounded by blooming cherry blossoms. The kindness and warmth of Japanese people is heartwarming. I love Japanese food, and "gyu-don" (beef over rice in a bowl) is one of my favorites.

Finally, my husband Kazuo Nagata (who is Japanese) makes my life much easier and comfortable by helping me understand various customs and traditions of Japan.

Manisha Kundu (India)
Research Fellow (April 2004 - March 2007)
Atomic Electronics Group, Nano System Functionality Center

[Enjoying a pleasant time with all my colleagues at a party arranged by my supervisor, Dr. Hasegawa (front row, first from right) on the occasion of my marriage. Me and my husband: front row, second and third from right.]

A Rewarding 4 Month Stay

Peter Mayr (Graz University of Technology, Austria)
Visiting Researcher (May 2006 - August 2006)
Physical Metallurgy Group, Structural Metals Center

[With NIMS Metal Masters team members. (Dr. Muneki: front row, center left, author: front row, center right)]

Hello from the Heat Resistant Design Group at NIMS. Although I will most likely be back in Austria when you read these lines, I would still like to share some of my impressions of NIMS and Japan with you. My name is Peter Mayr and I am a Ph.D. student at the Institute for Materials Science, Welding and Forming at Graz University of Technology in Austria. My research work deals with the development of new steels and improvement of existing steels for high temperature applications in thermal power plants. I came to Tsukuba for a 4 month visit to obtain some final results for my thesis and have interesting discussions with my new colleagues. Having access to the most advanced equipment under the guidance of experts in my research field produced many valuable results for my work.

Beside research work, I started to play baseball with the NIMS Metal Masters Team. My trainer, Dr. Muneki, had a really hard job teaching a person from a skiing and soccer playing nation how to play baseball. In any case, for me this was a great experience and I had lots of fun with my Japanese colleagues.

I also really enjoyed staying in what is - for a European - still a mysterious country like Japan. I used every weekend to travel together with my friends from Ninomiya House (foreign researcher's residence) to different places all over Japan in order to get to know the Japanese culture and people better. Besides Mt. Tsukuba, I visited Tokyo, Kamakura, Hiroshima, Kyoto, Nikko, and many more interesting and impressive sites. After almost four months, I can say that this stay here at NIMS was very successful and improved my research work, but also opened my eyes to a different culture.

NIMS
National Institute for Materials Science

PUBLISHER
Dr. Hisao Kanda

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