

Stem Cells

Embryonic stem cell potential

Biological implants

Research retrospective

Overcoming infertility

Neurogenesis in the brain

Ethical issues with human-animal hybrids

Blood stem cell transplantations

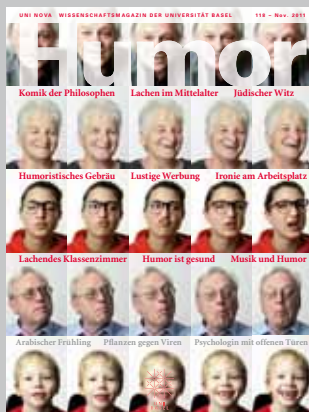
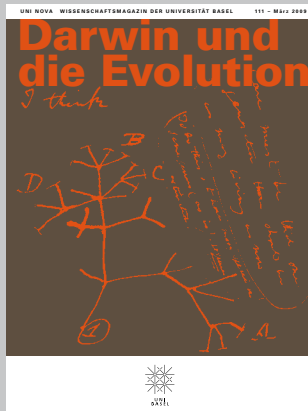
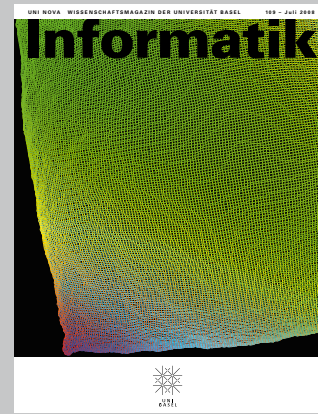
“Foreign” bodies

Bone marrow secrets

On depression in old age • Researching text, space and place • Web 2.0 and the Humanities



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The potential of stem cells

A few weeks ago, the world's one-millionth blood stem cell transplantation took place. Successful treatments of this type are literally life saving today for vast numbers of people suffering from leukemia or other severe blood disorders. Since the tissue characteristics of donors and patients must match exactly, suitable donors are often hard to find. Specialized stem cells from various tissues, for example from the bone marrow or skin, are referred to as somatic (or adult). Throughout an entire lifespan they constantly regenerate new cells, such as indeed blood or skin cells. Embryonic stem cells are considered to have much higher potency: Since they develop as part of the normal growth of embryos, they have the potential to differentiate later into any type of cell in the body. A relatively new discovery is the ability to "reprogram" tissue cells taken from adults back to an earlier embryonic state, which means that cells and even entire organs might be cultivated. In short: Stem cells bear the possibility to treat and heal a range of diseases. And yet, our knowledge of how exactly the various types of stem cells function, how they expand, how they are regulated and influenced by their environment is still limited, even today, but grows continuously. Researchers across the globe are working on finding new ways to use the supposed "totipotent" and "pluripotent" cells in clinical applications. The accompanying ethical issues – such as extracting stem cells from "supernumerary" embryos following in vitro fertilization – must be addressed. As always, the hopes must be weighed against the risks. Our current issue focuses on stem cell research and portrays the work of researchers belonging to the Basel Stem Cell Network (BSCN). This Competence Center at the University of Basel unites experts from the fields of biology, medicine and tissue engineering, but also from ethical and legal fields who, together with partners from industry, are seeking answers to the pressing questions in stem cell research. Treatment based on stem cells – "regenerative medicine" – is often described as the future of therapeutic applications. I hope you find this issue interesting and insightful!

Christoph Dieffenbacher, Editor UNI NOVA

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Cover page and photography sequence

Section through bone marrow cells showing mature and immature red blood cells (pink and pink spotted) and white blood cells (blue and grey). Bone marrow is the site of new blood cell production (Image: Keystone/SPL/Dr Gopal Murti). The images in the focus section come mainly from electron microscopes and have been colored retrospectively.



Newt detection with DNA

Animals leave genetic traces in the natural environment, and these traces are called environmental DNA. New technologies have been recently developed allowing us to track down rare species that are difficult to detect by conventional methods. Using molecular genetic analysis, researchers from the University of Basel have successfully detected DNA from the Great crested newt in water samples from ponds in the Basel area. Dr Sylvain Ursenbacher and his colleagues from the Conservation Biology section of the Department of Environmental Sciences adapted the technology to the genetic material of the Great crested newt, a highly endangered species in Switzerland. They took water samples from 30 ponds in which Great crested newts had already been spotted and then compared the molecular genetic methodology with the traditional approach, which consists of counting individuals in the ponds. The probability of detecting the species with environmental DNA techniques from water samples is 60%, whereas the traditional visual method was slightly better (about 70%). No method is 100% reliable in detecting the Great crested newt; consequently the two techniques are complementary and, when used simultaneously, can yield better detection probability.



Register of charitable foundations

Switzerland is home to more than 12,700 charitable foundations, a comparatively high figure by international standards. Despite the sector's growing social and economic importance, monitoring its activities remains as difficult as ever, and the lack of transparency and accessibility of foundations and private nonprofit organizations (NPOs) has come to be seen as increasingly problematic. The call for better data to be made available has now been endorsed by an international comparative study by the University of Basel's Centre for Philanthropy Studies, which has examined registers of foundations in seven European countries and proposed recommendations for the establishment of a national register for Switzerland. The study sets out a data quality framework and funding principles and presents three different models, which vary in terms of organizations to be included, target group and structure. These models are: a) a register of foundations, as a legal entity, including all charitable foundations; b) a register of funding bodies, including all private funding organizations and public funding agencies; and c) a register of all NPOs with charitable status.



Cannabis and psychosis

The association between cannabis consumption and the development of schizophrenic psychoses is a topic of much discussion. One possible mechanism behind this is that cannabis might enforce a reduction in brain volume in the early stages of psychoses. This assumption was analyzed by the psychologists Charlotte Rapp and Hilal Bugra together with Professor Anita Riecher-Rössler and Professor Stefan Borgwardt of the University Psychiatric Clinics (UPK) Basel. They summarized all studies examining the effect of cannabis use on the brain of people with beginning and chronic psychoses using magnetic resonance imaging (MRI) or so-called "post-mortem" methods. The review revealed an association between the use of cannabis and a volume reduction in various regions of the brain in patients with psychosis – for example, in the cingulum, the prefrontal cortex and the cerebellum – which was not clearly evidenced in healthy subjects. This may indicate that the brain of psychosis patients is particularly sensitive to reductions in brain volume caused by cannabis. This effect became apparent in very early stages of the illness, and even before the onset of the psychosis itself.

“Age-related depression is curable”



Depression, the most common mental illness during old age, is generally diagnosed too late or not at all – yet it affects every second person in our old age and nursing homes. Interview: Christoph Dieffenbacher

When we talk about age-related psychiatric conditions, we often focus on Alzheimer's and Parkinson's disease, even though depression is far more common. Why is that?

Depression affects people of all ages, whereas dementia is linked to old age. It is true that depression tends to be ignored because of the emphasis on dementia in public debate. That is a mistake, as much more could be done to help older people suffering from depression. It is often said that old people are entitled to feel withdrawn, tired and sad, but we know for a fact that this isn't normal. Generally depression is treated too late, and this is especially true in old age. Yet the disease is very treatable – there is nothing inevitable about it.

What factors put people at risk of becoming depressed in old age?

Predisposition is an important risk factor. You are more likely to be at risk if you suffered from depression earlier in life and if you have or had a relative with the disease. Women are affected more frequently than men. The link between depression and physical illnesses is also more pronounced than for any other psychiatric condition.

What sort of illnesses are we talking about?

Pain and sleep disorders, primarily, as well as physical disabilities that impede social interaction, such as difficulty walking, and visual or hearing impairment. Poverty in old age and experiences of bereavement also play a role; if they are unexpected, the danger is particularly acute. Suicide is common among older people in these circumstances, although again the extent of the problem is underestimated. It is also something of a taboo subject.

Professor Gabriela Stoppe (b. 1958) was appointed Associate Professor of Psychiatry and Psychotherapy at the University of Basel in 2003. Until 2012, she was Medical Director of General Psychiatry at the University Psychiatric Clinics (UPK Basel). After studying medicine in Giessen and obtaining her doctorate in Marburg, she worked at the neurological and psychiatric clinics in Bern, Hanover and Göttingen. She is the author of several textbooks on mental illness in old age and serves on a number of committees dealing with the issue, both in Switzerland and abroad, as an expert adviser and member (<http://www.gabriela-stoppe.com>).

How is age-related depression linked to dementia?

In principle they are different illnesses, but the symptoms often overlap. If someone has a manic depressive condition, this still remains even if they develop senile dementia. During the initial phase of dementia, around 30 to 40 percent of sufferers display symptoms of depression, such as withdrawal, loss of interest and listlessness. In some cases, depression is associated with cognitive impairments, and these then have to be differentiated from dementia.

Are there preventive measures that could be taken?

We should intervene much earlier to identify and prevent depression. If we did that, we could avoid a lot of unhappiness. There is also a need for increased suicide prevention measures. We could, for example, increase older people's resilience by offering them courses on problem solving or advice on dealing with day-to-day life. Many older people today want to help themselves and to take charge of their own health. We should take advantage of that.

How can age-related depression be treated?

The main form of treatment provided is with psychoactive drugs, but in old age it can be risky to use them in combination with other medication. At present there is an urgent need to increase the availability of psychotherapy for older people, as this is in very short supply. And yet we know that the brain can undergo dynamic changes – even in old age. It is always very gratifying for me to see how older people react when they hear that their condition can still be treated effectively, and how happy this makes them.



Bone marrow in cancellous (spongy) bone tissue. Cancellous bone is characterized by a honeycomb arrangement, comprising a network of fibrous tissue. The spaces between the fibrous tissue are filled with bone marrow (purple), which produces blood cells. White blood cells (dark orange) are also seen here (Image: Keystone/SPL/Steve Gschmeissner).

Stem cell research – a historical perspective

The history of the transplantation of hematopoietic – or blood-forming – stem cells illustrates all possibilities and limitations of modern medical stem cell research. Expectations, fears of misuse, disappointments and successes have alternated over a long period of time under changing external influences. Today, as a result of intensive international collaborative research hematopoietic stem cell transplantation has become reality and a success. It serves as fundamental proof that missing or failed organ function can be restored by healthy stem cells. Alois Gratwohl

Our basic understanding of stem cells stretches far back. In the 17th and 18th centuries, scientists determined that the different organs in the human body develop from the three germ layers, the endoderm, ectoderm and mesoderm, through a process of cell division and differentiation during prenatal development. However, they were still unaware of the mechanisms behind this process. This period also saw the first scientific attempts at “replacement treatment”. At the beginning of the 20th century, Alexander Maksimov posited that all blood cells come from the same original cell, and called it the “stem cell”. Yet, the scientific principles regarding stem cell fate remained fragmented, and there was no significant clinical application.

The radiation syndrome

With Hiroshima and Nagasaki came a turning point. Thousands of people were dying of hemorrhages and infections one or two weeks after they had been exposed to radiation. They appeared to have a lack of bone marrow function, which is responsible for new blood formation. A hitherto unknown disease with potentially huge effects demanded attention: In the words of Heraclitus, it was “war as father of all” that opened the door to stem cell research. Large sums of money were invested in finding medicines and methods for treating this radiation syndrome. Soon after the end of the war, animal testing helped scientists to determine that the failure of blood formation in the bone marrow (aplasia) following exposure to radiation could be prevented by shielding the spleen, or through the transplantation of bone marrow cells. Healthy stem cells clearly had the ability to renew the bone marrow that had been damaged by the radiation, and blood began to form again. This strategy was quickly adopted: In 1958, workers in a nuclear reactor accident in Vinča (former Yugoslavia) were taken to Paris and given what was then considered to be a successful bone marrow transplant using bone marrow from voluntary donors.

The next logical step was to use full body radiation in order to eradicate bone marrow that had been damaged from leukemia. Transplantation offered a way of replacing the diseased bone marrow with healthy bone marrow, and so the first wave of bone marrow transplants began. For patients suffering from leukemia, the method succeeded in curing their untreatable disease. However, disillusionment quickly set in following this initial phase of excitement: Though the transplants were successful, every one of the patients died, either from a relapse of the disease or from a new, unknown illness – the “secondary disease”.

Years of intensive basic research and experimentation with animals followed this initial phase and deepened scientists’ understanding of stem cell development. In the next breakthrough, the cause of the secondary disease was determined. During the transplantation, the donor’s bone marrow as well as his or her immune system is transferred to the patient. Therefore, a patient may reject the transplanted bone marrow cells after organ transplantation. However, in addition, successful engraftment of bone marrow cells may result in the graft rejecting the patient as well, the so-called graft-versus-host reaction. The challenge was then to overcome both of these hurdles.

The experiments resulted in the discovery of human leukocyte antigens (HLAs): These structures are present on all tissue cells and can cause the rejection of an organ as well as graft-versus-host disease. In transplants between monozygotic (single-egg) twins, neither a rejection nor a graft-versus-host reaction occurs. HLAs are part of the so-called histocompatibility complex, a genetic structure that dates back in evolution to the tunicates (marine filter feeders), and which allows individuals to differentiate between “self” and “other”. The HLAs reside on chromosome 6 in humans and are usually passed down as a unit. The probability that siblings have identical HLA molecules is around 25%.

Enthusiasm and disillusionment

Based on this knowledge, clinicians began to perform bone marrow transplants again in 1968, this time on children with a severe congenital immunodeficiency and where the bone marrow donor was a sibling with an identical HLA match. Again, expectations were high. Patients with aplastic anemia and leukemia were also treated and new transplant centers were opened. In 1973, Professor Bruno Speck arrived at the hospital in Basel from Leiden (Netherlands) and brought with him his expertise and experience, laying the foundations for today's Stem Cell Center of Competence, the Basel Stem Cell Network (BSCN) at the University. Once again there followed a period of disillusionment, as the procedure did not live up to expectations. Only a few patients survived in the long term, while many continued to suffer from rejections, graft-versus-host disease, infections and hemorrhages. Even when the treatment was successful, a relapse occurred all too often. In 1975, the renowned National Institute of Health in the USA decided to discontinue its bone marrow transplant program, as other treatment types seemed more promising. Only a few centers were convinced of the potential of the treatment; they continued to invest in research and share experiences and expertise.

The next breakthrough came in the mid-1980s as a result of several factors. For a long time, transplantation was considered the "method of last resort" when all other conventional treatments had failed. Doctors began to perform the treatment at an early stage of the disease. This was now possible for a number of reasons: Cyclosporine, a highly effective immunosuppressant drug produced by the former Sandoz AG became available; the transfusion of specific blood products (erythrocytes, thrombocytes or granulocytes) replaced the over simplistic use of "fresh blood" donation; and more effective and targeted medicines were being continually improved allowing doctors to treat the frequent infections caused by bacteria, viruses or fungi. The spectrum of indications grew quickly, and the transplantation of hematopoietic stem cells won recognition.

Nowadays, stem cell treatment is an established form of therapy. More than 60,000 stem cell transplantations are performed every year around the world; the one-millionth stem cell transplantation was carried out at the end of December 2012. For a bone marrow transplant, stem cells can be extracted from bone marrow; for peripheral blood stem cell transplantation, they are extracted from the peripheral blood stream; and for umbilical cord blood transplantation, they are extracted from cord blood. These transplantations all fall under the umbrella term "hematopoietic stem cell transplantation". The donor may either be the patient themselves in the case of an autologous transplantation; a single-egg twin for a syngenic transplantation; or a sibling with an identical HLA match, another family member or a matched, voluntary non-related donor for an allogeneic transplantation. Each of

these methods has its respective advantages and disadvantages; the choice depends on the illness, the health of the patient and the availability of the donor. Indications include severe congenital and acquired illnesses of the hematopoietic system as well as aggressive tumors that respond well to high-dosage chemotherapy, radiotherapy or immunotherapy. The awarding of the Nobel Prize for Medicine to Professor E. Donnall Thomas in 1990, a pioneer in the field of stem cell transplantation, illustrates the scientific recognition of this kind of treatment by the scientific community as a whole.

Hopes for many disease treatments

Almost overnight, the birth of Dolly the cloned sheep in 1996 raised hopes that a number of severe diseases in individual organs could be treated using stem cell transplantation. Stem cell research became a beacon of hope for many people suffering from all kinds of different illnesses, for patients with diabetes, Parkinson's disease or with dementia, for people with spinal paralysis, osteoarthritis, multiple sclerosis, and for people with heart, liver or kidney failure. It seemed that organ transplants would soon no longer be necessary. In 2004, the Swiss voted "yes" to a law on stem cell research in 2004 with an overwhelming majority. Companies were founded in anticipation of potential profit, studies were commissioned, and numerous promising cases were presented.

The results today, almost a decade on, appear sobering. As yet, there is no one certain indication for a transplantation of non-hematopoietic stem cells, or for a transplantation of hematopoietic stem cells for non-hematopoietic indications. The hope of a cure remains distant. Seemingly untouched, however, is the so-called "patient tourism" to questionable institutions promising cures at a high price.

It is interesting to consider these developments from a different perspective and to question why the application of stem cell therapies remains so limited. The transplantation of hematopoietic stem cells has evolved in several stages, with successes and setbacks, and some wrong turns along the way. It has evolved in large part without commercial support or claims for patents. The European Patent Office rejected an application for the use of cryopreserved (frozen in liquid nitrogen) umbilical cord blood cells. Yet stem cell research has always managed to find the right window of opportunity for its pursuits. During the Cold War, a large amount of funding and logistical support was provided for researching radiobiology. It is no coincidence that the leading clinical institutions such as Leiden and Paris in Europe, or Cooperstown in the USA worked closely with the nearby institutes for radiobiology. This ensured that pure research and clinical application remained closely linked.

Twenty million donors worldwide

The conviction that the objective of stem cell research is fundamentally sound has been unwavering. Difficulties at the

start forced clinical researchers to seek international cooperation at a very early stage, since no individual person or team could gain enough experience on their own. The key data for every single transplantation was recorded centrally by international associations – initially by the International Blood and Marrow Transplant Registry IBMTR (now CIBMTR) together with the European Group for Blood and Marrow Transplantation (EBMT), now the Worldwide Network for Blood and Marrow Transplantation (WBMT), which allowed researchers to determine the criteria for a successful transplantation one step at a time, to recognize mistakes and to improve the techniques. Data recording and standardized data analysis at regular intervals by national and international institutions, as part of a quality management system, are now considered integral and indispensable elements of the treatment process.

Stem cell research has always been supported and promoted by patients as well as donors. They were – and often still are – uncertain of the outcome of the treatment. They support the research by allowing their data to be used for scientific evaluation, and they encourage others to register as donors. It is quite unique in the field of medicine that in 2013, over 20 million people worldwide are willing to donate stem cells. This network stretches across the world and ensures that, regardless of gender, background, occupation, nationality and religion, those in need can receive help from donors with matched HLAs.

Science and society

From the perspective of hematopoietic stem cell transplantation, the development of stem cell research and its clinical application is right on track. True, the simple idea of “turning blood into brain and brain into blood” was wishful thinking. It is not surprising that this initial research on the plasticity of cells coincided with the end of the Cold War. Once the wall came down, changes that were previously unimaginable suddenly seemed possible. Science was influenced by the optimism of social politics; changing the lives of cells also seemed possible and data was interpreted differently than it would be today. And yet Dolly is no longer just a one-off coincidence: The reprogramming of adult cells is a reality, and it has become reproducible and repeatable using different methods. Creating cells is not a one-way street; it is carried out according to transparent laws and is influenced by internal and external regulatory systems. Generally, these ensure that the procedure can be controlled. The significance of this research was officially acknowledged in 2012, when pioneers in the field of reprogramming stem cells were awarded the Nobel Prize for Medicine.

It is therefore merely a question of time before stem cells find their clinical application in other fields, too. This does not mean a quest for eternal youth: The objective is still to replace or to restore missing or damaged organ functions. We

can predict that the same problems will occur as with the transplantation of hematopoietic stem cells: rejection, graft-versus-host disease and a return of the original disease. The same principles that applied to the transplantation of hematopoietic stem cells will also help scientists to attain the goal more quickly: intensive, networked basic research, international cooperation, and standardized data collection and analysis in the framework of a quality management system. Reform is needed at every level: Institutions must adjust the framework conditions, researchers will have to sacrifice their individual approaches for the sake of standardization, and the public will need to show more patience. A look back in 50 years' time is bound to be interesting.

Professor Alois Gratwohl is Professor Emeritus for Hematology and Stem Cell Transplantation at the University of Basel.

Basel Stem Cell Network

Stem cell research has a long tradition at the University and the University Hospital of Basel. The Department of Hematology was one of the first institutions worldwide to develop and implement clinical stem cell transplantations. Now there are around 40 research groups in various institutions working on issues related to stem cells. Aleksandra Wodnar-Filipowicz, Antoine Peters

The last decade witnessed groundbreaking scientific and technological developments in stem cell research. The importance of these developments was recently acknowledged by the awarding of the 2012 Nobel Prize for Medicine to Sir John Gurdon and Shinya Yamanaka, two pioneers in stem cell research. The major progress in this research field has also raised high expectations in modern society, that novel therapies for regenerative medicine will soon be developed.

The Basel Stem Cell Network (BSCN) was formed in 2007 as a bottom-up initiative led by Professor Alois Gratwohl from the University Hospital of Basel and Professor Yves-Alain Barde from the *Biozentrum* at the University of Basel. Scientists and physicians from the local basic research and medical communities took part in the network. In appreciation of this initiative and of the importance of studies on stem cell biology and stem cell based therapies, the BSCN was officially recognized as the Stem Cell Center of Competence at the University of Basel in 2008.

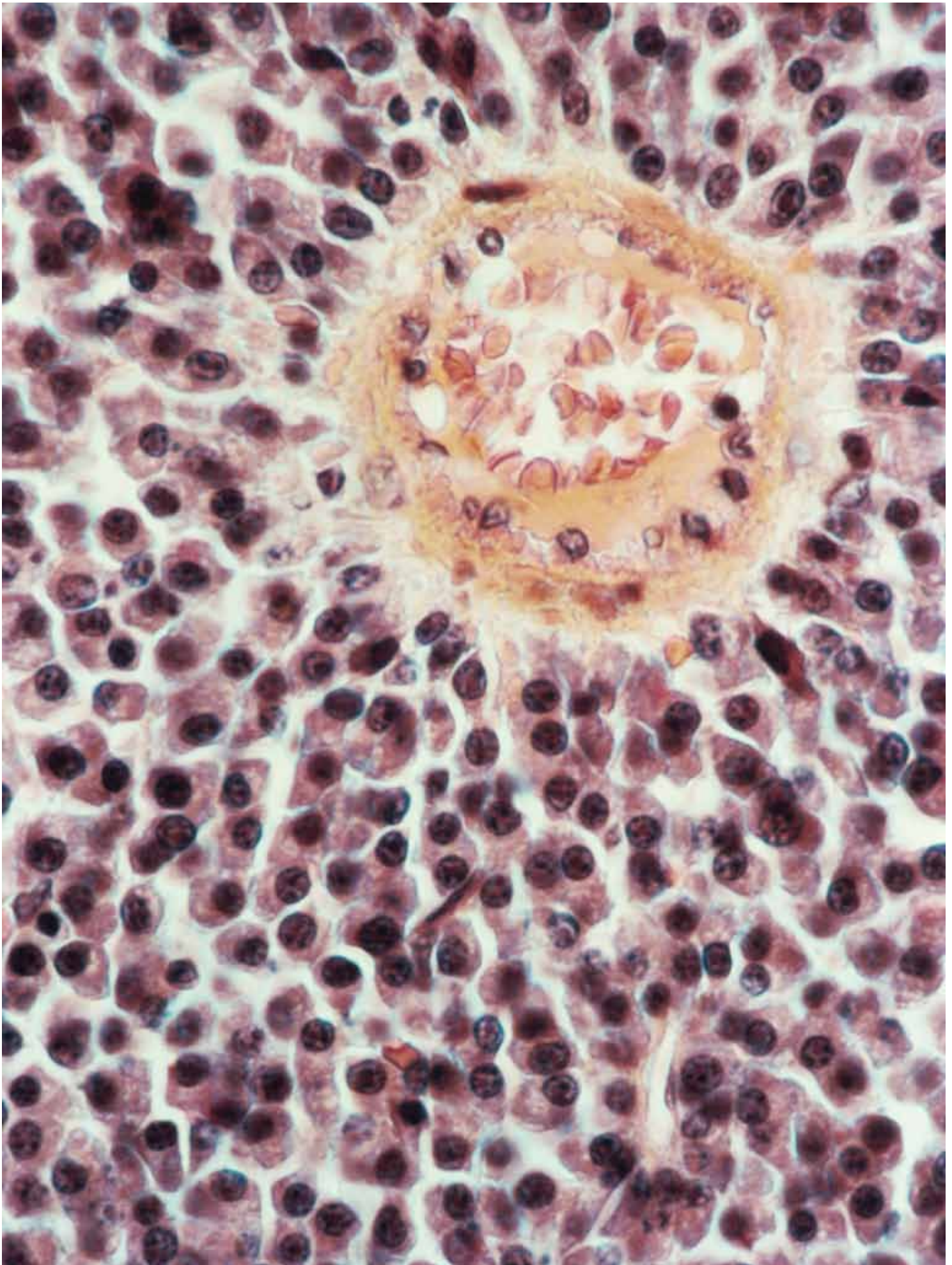
The BSCN is an assembly of scientists from research institutions at the University of Basel's faculties of science and medicine together with the Friedrich Miescher Institute for Biomedical Research (FMI), the Department of Biosystems Science and Engineering of the ETH Zurich in Basel (D-BSSE) and the pharmaceutical industry at Novartis and Roche. Within the BSCN there is internationally recognized expertise in research on germ-line and embryonic stem cells, the hematopoietic system, neuronal stem cells, and tissue engineering with artificial matrices. Research in these areas is supported by extensive knowledge about cell growth and differentiation, organ development, epigenetics, and cutting-edge molecular technologies.

The network maintains strong links with the local pharmaceutical industry, which is developing an increasing interest for regenerative medicine and the use of stem cells in drug screening. Groups addressing ethical, legal and regulatory issues related to stem cell studies complement

the interdisciplinary character of research within the network. Activities at the BSCN are primarily channeled towards exchange of information and knowledge through series of lectures and meetings which involve experts available in Basel and internationally. The network aims at exploiting the unique opportunities resulting from the close proximity of clinicians and basic researchers working in Basel in addressing a wide range of important questions related to stem cells. A further goal of the network is to educate and train young scientists at doctoral and postdoctoral levels.

Details of the organization, scientific expertise, and educational activities of the BSCN can be found at <http://www.baselstemcells.ch>.

Professor Aleksandra Wodnar-Filipowicz is the coordinator and Antoine Peters is the chairman of the Steering Committee of the BSCN.



Myeloma, a bone marrow cancer: Cancerous cells (purple) have replaced most of the healthy tissue leaving a patch of dying normal cells (pink) needed for immune response and blood clotting (Image: Keystone/SPL/CNRI).

Blood stem cell transplantation

Blood stem cell transplants have been used for decades to treat diseases of the blood and the immune system such as lymphoma and leukemia. What are the types of transplants, where do stem cells come from, who is eligible to receive or donate stem cells, and what are potential complications? Jakob R. Passweg

Stem cells were used to replace a patient's hematopoietic – or blood-forming – system as early as 45 years ago, when a patient suffering from a congenital immune deficiency received bone marrow from a matched sibling as a substitute for his own. Two different types of stem cell transplant are used: The patient's own stem cells are used for what are known as autologous transplants, whereas allogeneic transplants involve the use of another person's stem cells. Autologous and allogeneic stem cell transplantation are considered under the same heading because they share the same technologies for processing and administering blood stem cells.

Autologous vs. allogeneic

Autologous stem cell transplants are used to provide high-dose chemotherapy for lymphoma and leukemia in patients in whom the disease is sensitive to this treatment. The background is that such intensive treatment suppresses bone marrow function for a considerable period, and blood stem cells can help bridge the time until bone marrow function is restored. Autologous stem cell transplants are performed mainly to treat tumors of the lymphatic system, lymphoma, multiple myeloma and, less frequently, leukemia. An autologous stem cell transplant is not a transplant in the strict sense of the word in that no tissue is transferred from one person to another.

By contrast, allogeneic stem cell transplantation uses stem cells provided by another person, who is required to have the same tissue type as the patient. This procedure is used to treat a wide variety of acquired or congenital diseases. For instance, it helps treat leukemia by making it possible to harness the anti-leukemic activity of the donor's immune system; in the case of congenital failure of the bone marrow or immune system, it provides a functional substitute.

Blood stem cell transplants are a common procedure: More than 33,000 blood stem cell transplants were carried out in Europe in 2010, 13,000 of which allogeneic and 20,000

autologous. The principal risks associated with autologous stem cell transplantation are the toxicity of high-dose chemotherapy and infectious complications during the period of bone marrow aplasia, i.e. before the transplanted cells have started working. The main risks of allogeneic stem cell transplantation also include graft-versus-host disease, an inflammatory reaction caused by the donor's immune cells.

Stem cell sources

Originally, blood stem cells were harvested directly from bone marrow, extracted from the pelvic bone through a needle. It was later discovered that growth factors can stimulate stem cells to leave their niche in the bone marrow and circulate in the bloodstream. Once they are in the bloodstream, they can be harvested through an extracorporeal circulation using a procedure called apheresis. Another source of stem cells is cord blood: Blood which remains in the umbilical cord and placenta after the cord has been cut is rich in blood stem cells. This resource has been made available for use in allogeneic stem cell transplantation through the establishment of banks storing cord stem cells. In Europe, around 900 allogeneic stem cell transplants every year use stem cells from this source.

Allogeneic stem cell transplantation depends on a good tissue match between donor and recipient. The reason for this is the risk of rejection, which can occur in either direction, i.e. either as a reaction to the donor tissue by the recipient or – since allogeneic stem cell transplantation involves the transfer of an immunocompetent organ – as a reaction of donor tissue against the recipient. A matched donor can be found within the family: Siblings have a 25% chance of having the same tissue type. Alternatively, there are large registries of more than 20 million tissue-typed donors worldwide who are available to donate stem cells. Anybody under the age of 55 can become a stem cell donor. Donors can decide whether they want to donate bone marrow stem cells or mobilized

blood stem cells and are carefully informed about the procedure. Since the stem cell pool replenishes itself, the donor will not be left with an insufficient amount of stem cells.

Weighing the benefits

In deciding whether or not to carry out a stem cell transplant, a multiplicity of factors need to be taken into account: Is the disease in question known to be responsive to allogeneic or autologous stem cell transplantation? Is the disease so dangerous as to justify the risks associated with a stem cell transplant? Is it too advanced for a positive outcome to be likely? Is the patient too old or too ill to cope with the procedure?

Anybody up to the age of about 70 can receive a stem cell transplant, with the patient's general state of health and comorbidity often more important than their chronological age. Before a stem cell transplant can take place, it is necessary to carefully weigh its potential benefits against the risks, and a decision is made jointly with the patient after a detailed discussion of treatment options.

Both autologous and allogeneic stem cell transplants are preceded by a careful assessment of the patient and by chemotherapy. Under certain circumstances, chemotherapy is combined with total body irradiation in order to destroy malignant cells and – in the case of an allogeneic stem cell transplant – to weaken the immune system and so allow the transplanted cells to engraft. With allogeneic stem cell transplants, this preparative regimen can be relatively mild, depending on the age of the patient. The stem cells are administered via an intravenous infusion and find their own way to their niche in the bone marrow, where they then begin to multiply. After 14 to 18 days, the new cells produced can be measured in the blood. Depending on the chosen level of treatment intensity, the patient will need to remain in the hospital for a few weeks or longer.

Risks and complications

Intensive chemotherapy carries the dangers of toxicity and of infections occurring before the transferred cells engraft; these risks are similar for allogeneic and autologous stem cell transplantation. If the transplant involves another person's stem cells, there is a risk both of the recipient rejecting the graft (which is rare) and of the opposite problem, i.e. an immune response of the graft to its recipient. Graft-versus-host disease is an inflammatory reaction that can affect any part of the body, but occurs most frequently in the skin, intestine and liver. It can be mild or severe, can progress from an acute to a chronic stage and may be fatal.

Graft-versus-host disease is by far the most serious complication associated with allogeneic stem cell transplants. It does not occur with autologous transplants, as the recipient is also the donor. However, apart from the obvious negative impact, this immune response also has beneficial effects

in that the "rejection" of leukemia cells creates a powerful graft-versus-leukemia effect, which is often more effective than chemotherapy. In many cases, this anti-leukemic effect justifies the risks of the treatment.

Following an allogeneic stem cell transplant, patients with acute leukemia have a 20 to 65 percent chance of long-term leukemia-free survival. Success depends on whether the transplant is performed at an early stage of the disease, on whether there was a fully matched donor available and also on the patient's general state of health. Roughly half of the cases of treatment failure are due to complications and to leukemia recurring despite the allogeneic stem cell transplant. The success rate is higher if the disease being treated is not malignant: The long-term survival rate of patients with bone marrow failure is 80%, and as high as 90% in children and adolescents.

In the future, improved methods for manipulating the immune system will make blood stem cell transplants safer; particularly promising are current attempts to genetically modify immune cells to specifically target leukemia cells.

For information on how to become a stem cell donor visit: www.sbsc.ch/de and www.blutspende-basel.ch/stammzellspende.html

Professor Jakob R. Passweg holds the Chair of Hematology at the University of Basel and is Chief of Hematology at the University Hospital of Basel.



Blood cell production in bone marrow: White blood cells, part of the body's immune system (orange), and red blood cells, which carry oxygen around the body (red). Reticular fibers (brown) make up the connective tissue framework of the bone marrow (Image: Keystone/SPL/Steve Gschmeissner).

Adult stem cells to fight autoimmune diseases

In autoimmune diseases, the immune system mistakenly turns against its own host: The immune system considers the body's own tissue as "foreign" and fights against it. This can lead to serious inflammation and organ damage. Currently, there is intensive investigation into the use of adult stem cells for the treatment of serious, life-threatening autoimmune diseases. Alan Tyndall, Thomas Daikeler

The key characteristic of autoimmune diseases is that the immune system fights against its own structure instead of against foreign invaders. The only effective method of controlling this is to suppress the entire overactive immune system in general using particular drugs – however, these drugs also affect the normal desired immune responses. While in most cases a balance between the necessary immunosuppression and the maintenance of essential immune system function can be achieved, so far it has not been possible to suppress specific auto-aggressive immune reactions completely and without serious side effects. In other words: We can control autoimmune diseases but not cure them.

Treatment using the body's own blood stem cells

Sixteen years ago, a concept was developed in Basel, based on experience from hematocology. Since then techniques used in leukemia treatment have made it possible to block the immune system and, at the same time, the hematopoietic (i.e. blood-forming) system of patients suffering from life-threatening autoimmune diseases. During this process, blood stem cells are first taken from the patient; these stem cells will later be able to restore the entire blood-forming system. In a subsequent step, all "good" and "bad" immune cells are completely eliminated via strong chemotherapy and antibody treatment. The patient then receives his own stem cells back, which find their way into the bone marrow and there they begin to form new immune and blood cells. The new immune system that develops over the following weeks will now, hopefully, be "tolerant" and no longer auto aggressive.

The first patient with an autoimmune disease was successfully treated using this method in Basel in 1995. Since then there have been around 2,000 such autologous stem cell transplantations worldwide. Considering all indications, a third of the patients had excellent long-term results with this treatment, another third suffered a relapse, and the final third did not respond at all. These initial, encouraging

results have led to an international cooperation followed by several prospective randomized clinical trials.

The first of these, the Autologous Stem cell Transplantation International Scleroderma (ASTIS) trial was recently completed and showed a highly significant increase in the survival rate of scleroderma patients who had undergone such transplantations, but the treatment also led to a significant mortality of 10%. Scleroderma – a hardening of the skin's connective tissue as well as parts of the inner organs – is a serious and rare autoimmune disease for which no other treatment is available at the moment. Up to half of those patients who are severely affected die after five years. At present, refinements of the procedure are underway to optimize the treatment for scleroderma patients. Results of scleroderma trials in the US (SCOT trial) and in Europe for Crohn's disease (ASTIC trial) are expected soon. There are already positive results from non-randomized studies of patients with systemic lupus erythematosus (SLE) – another autoimmune disease, Crohn's disease and multiple sclerosis.

Hopes for mesenchymal stem cells

During the past five years, other adult stem cells – the mesenchymal stem cells – have increasingly attracted the attention of researchers due to their effect on the immune system. These cells can be obtained from several sources, such as bone marrow, fat tissue, placenta or umbilical cord, and then be expanded manifold in the laboratory. They are delivered either locally into diseased tissue or intravenously, where they find their way to damaged or inflamed tissue and exert some healing effects. This has been demonstrated in vitro as well as in animal models. There are probably several mechanisms involved, such as the release of anti-inflammatory messengers and the suppression of cell activation by direct cell-to-cell contact.

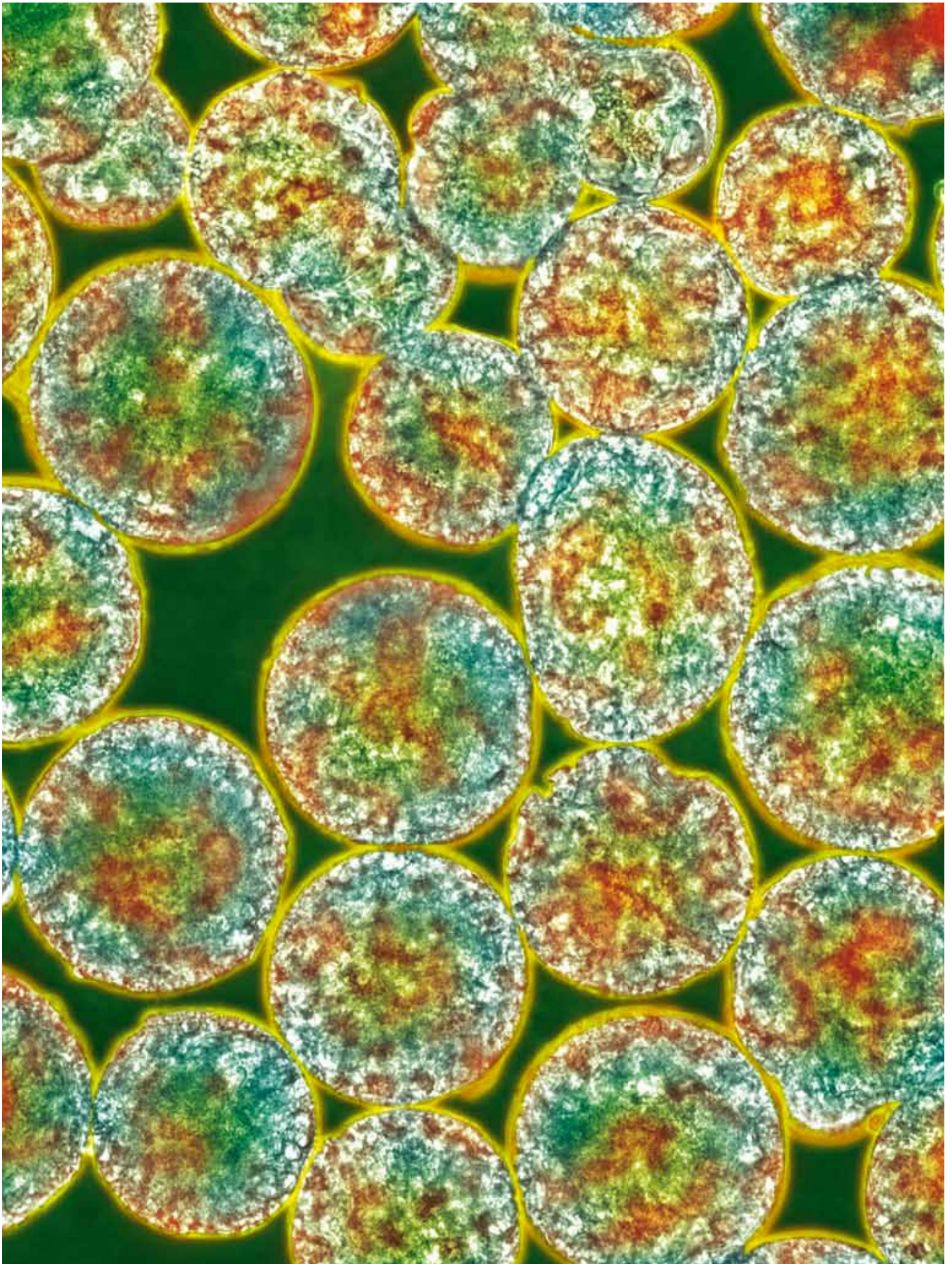
Research from Basel shows that mesenchymal stem cells obtained from patients with autoimmune diseases are equal-

ly effective in suppressing unwanted cell proliferation in the laboratory as those obtained from healthy donors. This opens up the possibility of using the patient's own mesenchymal stem cells from bone marrow or fat tissue in treatment. However, clinical application has not fulfilled the promise of the pre-clinical trials. Although in some trials a few patients with autoimmune diseases have been treated successfully with mesenchymal stem cells without significant side effects, two large trials applying these stem cells in Crohn's disease and acute graft-versus-host disease – an immunologic reaction – failed to reach their primary end points. It is uncertain whether this may have been due to trial design.

Further research necessary

Certainly, further studies are required to define the role of mesenchymal stem cells in the treatment of autoimmune diseases including SLE, scleroderma, Crohn's disease, multiple sclerosis, rheumatoid arthritis and type 1 diabetes. The application of these stem cells is also being investigated for the treatment of other diseases such as critical ischemia and fibrosis or for organ transplants. Definitive results can only be gained, however, from sufficiently large, prospective and randomized trials. One such trial has recently started for patients with systemic sclerosis and several others are running for patients with arthritis and Crohn's disease.

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Stem cells are precursor cells that can differentiate spontaneously or in a directed fashion to form specialized cell types. Appropriate therapies could potentially be used to treat various diseases and conditions (Image: Keystone/SPL/NIBSC).

The secrets of bone marrow

Bone marrow houses a tiny but mighty population of hematopoietic stem cells and produces billions of blood cells in the human body every day. Aleksandra Wodnar-Filipowicz

Bone marrow is found – well-protected – in hollow areas within our bones. This bone-shielded environment houses blood cells at all stages of development embedded in a framework of connective tissue supplied with blood vessels. These particular structures provide an ideal habitat for hematopoietic (blood-forming) stem cells – HSCs – and therefore also for lifelong production of all types of blood cells. Bone marrow is one of the most active organs in the body: The minute population of HSCs generates several billion mature blood cells daily to be deployed to peripheral tissues where they exercise their functions. The remarkable regenerative potential of human HSCs is exploited clinically: Bone marrow transplantations are a perfect example of the success of cellular therapies.

HSCs are among the longest studied stem cells, and the blood-forming system serves as a paradigm for understanding the function and clinical utility of somatic tissue stem cells. However, many questions as to stem cell biology, regulation and therapeutic potential remain unanswered. After decades of dedicated experimental and clinical research, the bone marrow still protects many of its secrets.

How hematopoietic stem cells work ...

The exact number of HSCs in the human bone marrow remains unknown. The most primitive human HSCs cannot be identified according to their morphology, and also their phenotypic characteristics based on the cell surface expression of specific antigens – so-called Cluster of Differentiation (CD) molecules – remains poorly defined. Studies in mice are much more precise in this respect; with the use of specific antibodies against several well-defined CD molecules a minute population of HSCs can be isolated and studied. These murine HSCs are precisely defined and represent less than 0.01% of all bone marrow cells. Transplantation of even a single purified mouse HSC is capable of reconstituting the entire blood system, which may have been destroyed, for example,

by irradiation. Under physiological conditions hematopoiesis has its origin in not just one HSC, but is rather oligoclonal, that is maintained by the offspring of several HSCs – both in mice and in humans.

How hematopoietic stem cells function ...

Stem cells are defined as undifferentiated cells capable of self-renewal and of generation of functional progeny of highly specialized cells. HSCs are multipotential, since they generate several lineages including red blood cells, platelets, and cells of the immune system. Under normal conditions, most HSCs are quiescent, and only some of them enter the cell cycle and progress towards the hematopoietic differentiation cascade.

Quiescence is important, since it prevents stem cell exhaustion and also protects them from acquiring mutations leading to malignant transformation. The quiescent cells form a dormant reservoir of cells that can be efficiently activated to self-renew and, subsequently, accelerate blood cell production in response to stress conditions, such as blood loss, infection or bone marrow injury by, for example, chemotherapy. Upon re-establishment of homeostasis – a steady state – activated HSCs return to quiescence. Understanding the mechanisms that allow the most primitive HSC to self-renew and to reversibly switch from dormancy to active state is one of the most exciting questions addressed by research in this area.

... and where they hide

The bone marrow provides a framework of microenvironmental domains – called niches – that support the function of HSCs and their descendants. Methodological progress in immunohistochemical analyses and recent introduction of in vivo imaging with confocal microscopy have enabled insights into the bone marrow tissue in situ and provided a functional definition of the niche. HSCs are found in differ-

ent areas of the bone marrow space. The inner bone-lining connective tissue (endosteum) harbors quiescent HSCs. Osteoblastic cells, which are responsible for bone formation and which line the inner surface of the bone, are critical components of the endosteal niches. HSCs have also been found in association with the endothelium of small blood vessels known as sinusoids. Vascular niches for HSCs are formed by a complex system of sinusoid capillaries branching throughout the bone marrow cavity. The vascular niche is thought to be the site where actively dividing HSCs and their progeny are located, and where trafficking into and out of the bone marrow occurs. Most likely, the endosteal niches help to sustain the quiescence or self-renewal of HSCs during steady-state hematopoiesis, whereas the vascular niches play a dominant role in stress response.

Complex regulatory pathways

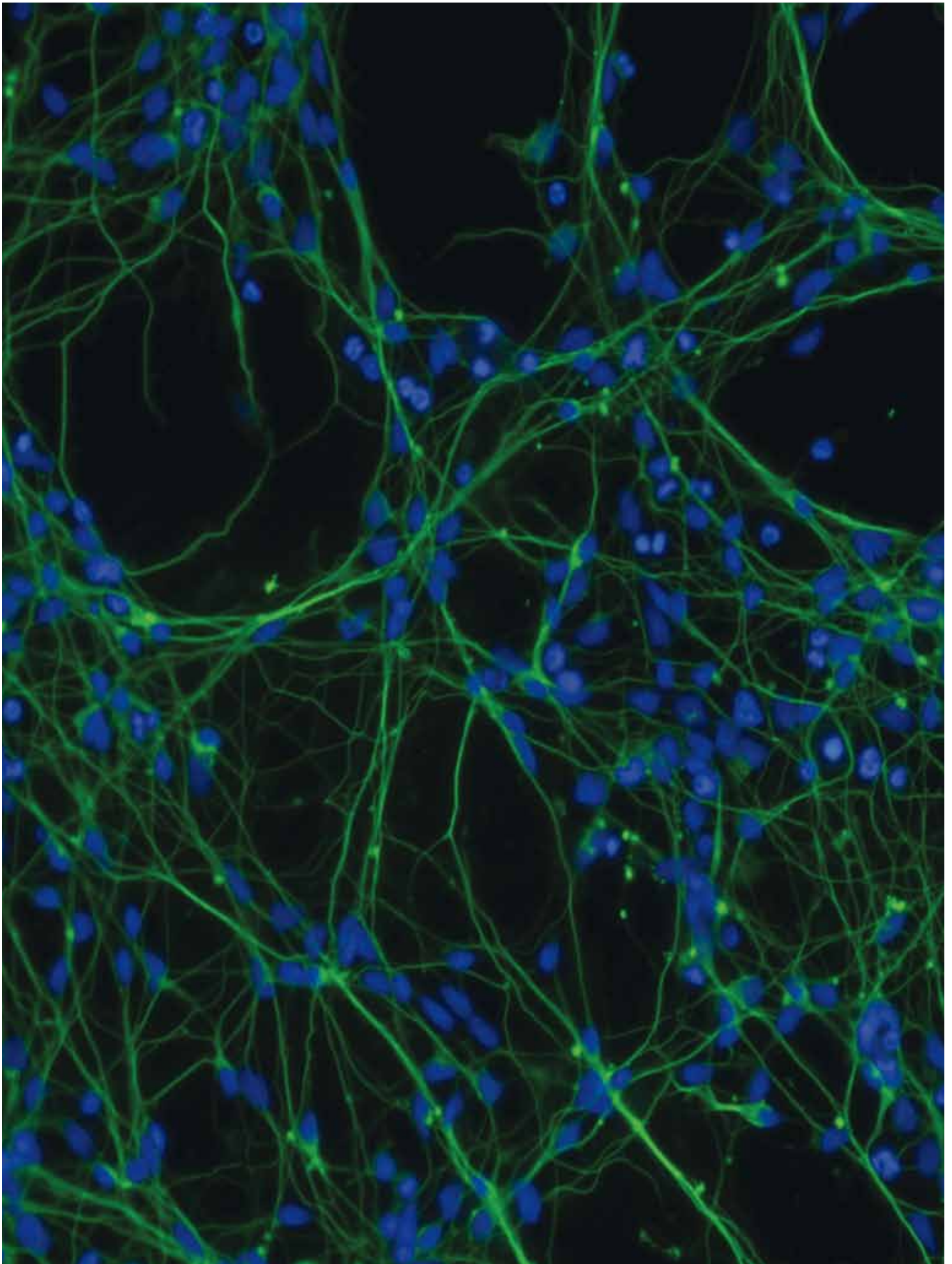
A complex interplay of cell-extrinsic cues and cell-intrinsic regulatory pathways regulate the fate of HSCs, defining the homeostatic balance between the quiescence or cycling and differentiation. The extrinsic mechanisms are dictated by the environment of surrounding supporting (stromal) and bone-forming (osteoblastic) cells. The intrinsic mechanisms involve downstream signaling molecules, including the transcription factors and epigenetic regulators acting through remodeling of the chromatin.

Small signal proteins, known as chemokines, are responsible for HSC migration into the niche. The chemotaxis is of particular importance for efficient “homing” of HSCs following their intravenous transplantation. Direct physical interactions between HSCs and niche cells are mediated by adhesion molecules. Various growth factors, produced locally in the bone marrow niches, act synergistically as positive regulators of stem and progenitor cells. HSC quiescence is also dependent on negative regulators, which can slow down the activity of HSCs. Recent research findings show that even hormones and the sympathetic nerve system can influence HSCs through the regulation of niche components. The oxidative conditions in the niche are another important regulator of HSCs. Since the endosteal niches are close to the bone and far from the capillaries, they are low in oxygen and therefore favor a slow metabolism. This is the hallmark of quiescent HSCs with their profound long-term repopulating potential.

Understanding of the cellular components and molecular mechanisms that regulate HSC-niche interactions has dramatically increased in the past few years. However, despite intensive efforts, it is still not yet possible to expand HSC numbers *ex vivo*, under laboratory conditions. This supports arguments for the complexity of humoral and cellular components that regulate hematopoiesis *in vivo*. Unraveling a dialogue between HSCs and their niches will provide an insight into the physiology of HSCs, and just as importantly, the

pathophysiology of diseases originating from HSC abnormalities. This information will guide future developments towards therapeutic possibilities based on this tiny and yet powerful population of stem cells.

Professor Aleksandra Wodnar-Filipowicz is the coordinator of the Stem Cell Center of Competence at the University of Basel.



Neurons created from human stem cells: Neural projections (axons and dendrites) are shown in green, while the nucleus is blue (Image: Valérie Crotet, Barde laboratory).

On pluripotent stem cells

Embryonic stem cells are pluripotent, which means that they can generate any cell type found in the adult organism. They have revolutionized biomedical research. In the years to come, induced pluripotent stem cells may have an even greater impact. Yves-Alain Barde

A stem cell has the unique property of self-renewal: Upon cell division, it can make an identical copy of itself and divide for an unlimited period of time. A pluripotent stem cell also has extraordinary developmental potential: It can generate all cell types found in the adult organism, including germ cells, i.e. oocytes and spermatozooids. These two properties combined, self-renewal and pluripotency, characterize embryonic stem (ES) cells.

These cells should not be confused with the fertilized egg. While the latter is totipotent, it needs a few rounds of cell division and serious re-programming to unfold its full differentiation potential. Indeed, the fertilized egg starts off as a highly specialized cell, and following cell division and de-differentiation it eventually gives rise not only to all cell types found in the adult organism, just like ES cells, but also to extra-embryonic tissue including the trophoblast (placenta in mammals). By contrast, ES cells cannot generate cells of the trophoblast unless manipulated, for example made tetraploid. This is why they are qualified as “pluripotent” and not “totipotent” – the distinctive characteristic of the fertilized egg.

Not all stem cells are pluripotent

When a stem cell divides symmetrically, both daughters are identical and remain stem cells, a property that applies to ES cells as well as to adult (or tissue) stem cells. Adult stem cells also have an unlimited self-renewal capacity like ES cells, though their differentiation potential is more limited. These properties allow adult stem cells to ensure a continuous supply of specific sub-sets of differentiated cells needed by the organism for its entire life. Most tissues are made of cells that only have a limited lifespan and that need to be continuously replaced. In the case of the hematopoietic (blood-forming) system, for example, literally billions of cells are replaced every day in humans. The progeny of hematopoietic stem cells is remarkably diverse and includes red blood cells

(erythrocytes) as well as B-lymphocytes and other terminally differentiated cell types.

The fact that tissue stem cells have a restricted differentiation potential – they are qualified as “multipotent” – should not be taken to imply that their properties are less spectacular than those of ES cells. On the contrary, this restricted potential is critical to ensure that the organism is supplied with a meaningful, organ-specific progeny, a key condition of a lifelong state of equilibrium, also known as homeostasis.

The symmetric cell division of stem cells is an elaborate and well-controlled process that can proceed for very long period of times, even beyond the normal lifetime as revealed by transplantation of hematopoietic stem cells. These stem cells must then benefit from special surveillance and maintenance mechanisms ensuring cell division without mistakes and preservation of genome integrity. Also, special features must be at work to prevent what is typically seen with “ordinary” dividing cells, namely the shortening of the chromosomes.

While a variety of cell types can divide, cells typically age upon cell division. This includes chromosome shortening and limits the number of cell division to about 15 rounds or 40–50 for cultured mouse and human cells respectively. This process is often referred to as “senescence” and is efficiently prevented in stem cells by various mechanisms, one of them consisting of a high telomerase activity. This enzyme prevents chromosome shortening upon cell division, a process that typically accompanies the cell division. High telomerase activity not only characterizes stem cells, but also cancer cells, which is an additional reason why the study of the biochemistry and cell biology of stem cells is a highly relevant area of current research in biomedicine.

Why are ES cells so useful?

Pluripotency and unlimited self-renewal capacity are such an extraordinary set of properties that one wonders why such

Are ES cells more than a very useful tissue culture artefact?

Mouse ES cells are typically cultured in the presence of a specific growth factor designated leukemia inhibitory factor (LIF). It is needed to maintain cultured ES cells pluripotent. This oddly named protein turned out to be the key ingredient secreted by the “feeder cells” used to isolate ES cells. For a long time, the relevance of LIF to normal mouse development was left unclear as embryos develop without any problems in the absence of LIF.

However, rodents are hitherto the only reliable animal source of true ES cells and this may be related to a special adaptive feature called diapause. This refers to a state of developmental arrest of the blastocyst, the tissue of origin of ES cells. In rodents, eggs can be fertilized while the mother is still lactating, but development is arrested at the blastocyst stage. It will only resume after weaning and these arrested blastocysts need a functional LIF signaling system to be maintained. When key elements of the pathway are eliminated, the inner cell mass of blastocysts arrested at diapause is not viable. It appears then that ES cells represent the culture equivalent of the inner cell mass of arrested blastocysts. These experiments, as with several key others related to the biology of ES cells and mentioned in the text, were performed in the laboratory of Austin Smith, Cambridge (UK). He was awarded the Louis Jeantet Prize in 2010.

a cell should exist and where it may come from (see box on the left). This field has a long history that started with tumorigenic properties of germ cells of certain mouse strains, a curiosity-driven research effort that culminated in a major milestone with the isolation and culture of ES cells in 1981 by the laboratories of Martin Evans in Cambridge, UK, and Gail Martin in San Francisco, USA. The potential of these cells was quickly realized and soon exploited to specifically manipulate the mouse genome with the generation of specific mutants.

This achievement revolutionized biomedical research and was recognized by the Nobel Prize Committee with the award for physiology or medicine given to Mario Capecchi, Martin Evans and Oliver Smithies in 2007. As with viruses or bacteria, the isolation of cells carrying specific mutations involves the selection of mutant cells, typically using resistance to an antibiotic. This implies that the cells can self-renew while remaining pluripotent. Indeed, to be really useful, a mutation introduced into the genome of ES cells needs to be transferred to the progeny, i.e. the mutated ES cell must be able to colonize the germ line so that the mutation can be transmitted to the next generation.

Mouse ES cells are easy to grow under well-defined, reproducible conditions and, as a result, their pattern of gene expression has been analyzed in considerable detail. Key transcription factors have been identified and the LIF pathway dissected and thoroughly analyzed. This body of work culminated with the notion put forward by the Smith lab that pluripotency corresponds to a “ground state”, i.e. it is the actual default state of an ES cell in the absence of extracellular signals. This system appears to be built in such a way that it is unstable, ensuring that no cells with the characteristics of ES cells are left behind during development.

As mentioned, ES cells have molecular characteristics close to those of cancer cells, including unlimited cell division potential and high telomerase activity. As it turned out, two of the transcription factors that characterize pluripotency, Oct4 and Sox2, directly activate the expression of the growth factor known as fibroblast growth factor 4 (FGF4). This mechanism ensures then that the pluripotent state is unstable by design and destined to rapidly disintegrate during normal development. Remarkably, blocking the FGF pathway is sufficient to maintain ES cells pluripotent, a landmark discovery that also allowed the isolation of ES cells from a variety of mouse genetic background and of rat ES cells. This latter goal had been intensely pursued ever since mouse ES cells were isolated but remained unsuccessful, presumably because rat ES cells are less responsive to LIF addition compared with mouse cells.

Do human pluripotent cells exist?

Given the pluripotent character of mouse ES cells and their ability to differentiate into various cell types under well-defined culture conditions, the question of whether or not human

ES cells exist is of considerable importance. Cells resembling mouse ES cells were isolated from human blastocysts in 1998 by Jamie Thomson in Madison (Wisconsin, USA), but whether or not these cells are truly pluripotent is still unclear. The final proof of pluripotency is ultimately the demonstration of germ line transmission, a test that is not an option with humans. In this regard, work with primates represents a useful alternative that is actively pursued in several laboratories.

Thomson's success, however, indicates that human cells with interesting properties and very significant differentiation potential can be isolated and even maintained in culture and used *in vitro* to generate elaborate structures. For example, as with mouse ES cells, the laboratory of Yoshiki Sasai in Kobe (Japan) succeeded in generating *in vitro* earlier this year an organ as complex as the eye. In the context of organ replacement based on cultured stem cells, this is a very significant and encouraging result.

Still, the conditions needed to maintain and expand human ES cells undifferentiated are still poorly understood. These cells do not seem to be LIF-responsive unless selected, an approach actively followed in our laboratory at the University of Basel's Biozentrum. Most groups use fibroblast growth factor instead to propagate human cells, although it is unclear whether this allows the propagation of truly pluripotent stem cells. It seems instead that human cells grown resemble "primed" mouse ES cells, i.e. cells that are no longer truly pluripotent but committed instead towards certain differentiation lineage. Much more work is needed in this area, if only to establish a reliable standard to be used in comparison with reprogrammed human cells or induced pluripotent stem (iPS) cells.

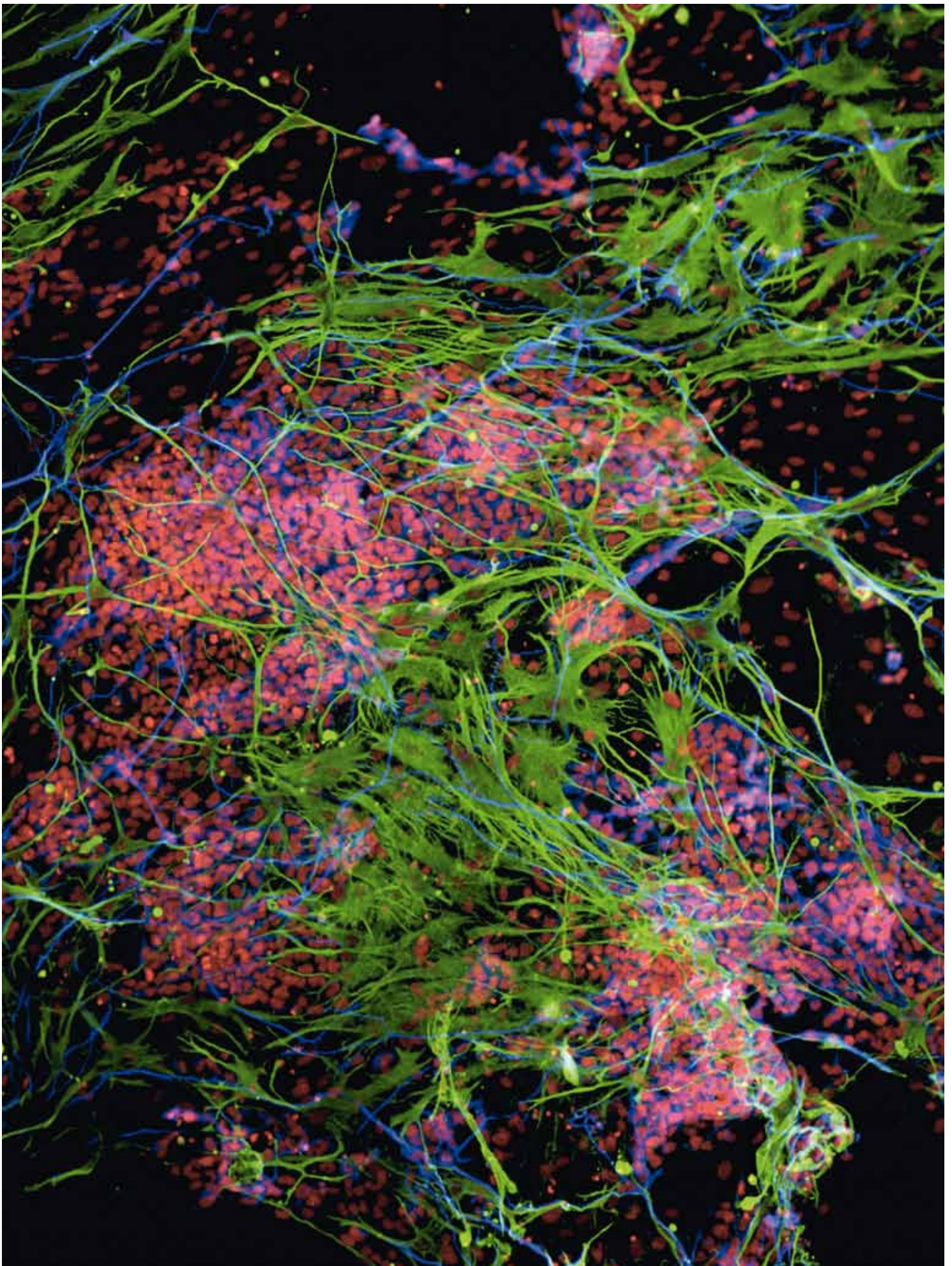
Reprogramming stem cells

Progress made in exploring the nature of pluripotency as well as the spectacular demonstration that differentiated mammalian cells can be completely reprogrammed by activated oocytes (the so-called Dolly experiment by Ian Wilmut and his colleagues) led to the field-transforming experiment by Shinya Yamanaka from Japan, which won him the 2012 Nobel Prize for Medicine. He succeeded in reprogramming cells *in vitro*, under well-defined, reproducible conditions. Briefly, the addition of four key nuclear factors to differentiated somatic cells, coupled with an efficient selection system allows reprogramming, i.e. de-differentiation of cells already committed to specific lineages. With the mouse, it has been possible to demonstrate that such iPS cells are reprogrammed to such an extent that they can even contribute to the germ line.

The generation of iPS cells is of critical importance as it allows human cells to be grown in unlimited numbers and differentiated into specific cell types, opening the path to studies of the impact of mutations of interest in a relevant

cellular context. This also makes it possible to develop and test new drugs targeting human molecules with a degree of relevance that was impossible to achieve in the past. By contrast, the use of iPS cells as a reasonably safe substitute for organ transplantation still has a long way to go, not least because studies related to the genome stability of human iPS cells are still in their infancy. Meanwhile, work with mouse iPS cells indicates that such studies are much needed.

Professor Yves-Alain Barde is Professor of Neurobiology at the University of Basel's Biozentrum.



Neural (nerve) stem cells that have been derived from human embryonic stem cells: Two specific proteins are shown (blue and green) as well as the cell nuclei (red). Embryonic stem cells can differentiate into any of the 200 cell types in the human body (Image: Keystone/SPL/Silvia Riccardi).

Stem cells in human brains?

Scientists have long debated whether the human brain also contains stem cells. Today, it is certain that new neurons are formed in specific regions of the brain throughout life, sometimes in response to certain stimuli. Neural stem cells that generate these neurons also play a part in some brain tumors. Verdon Taylor

Our brain is not only the most complex organ in our body, its elaborate connections and remarkable plasticity enable us to dominate and control our environment. Remarkably, the billions of neurons in the human brain are organized and connected in defined patterns to ensure functionality. Most neurons in the brain must last a lifetime as they are generated before or shortly after birth. Unlike the cells of some tissues, neurons are not replaced with age. Therefore, in contrast to its immense plasticity, the brain has a poor capacity to regenerate after disease or traumatic injury.

The inability of the mammalian brain to replace lost neurons was long thought to be due to a lack of stem cells that retain the potential to divide and generate new neurons upon demand. This is different in the skin, intestine and blood, where cells are continually replaced and the tissue repaired by populations of stem cells. However, even in the 1960s, scientists hypothesized that new neurons might be generated in the brains of adult mammals, implying the presence of undifferentiated progenitor cells. Subsequently, the first compelling evidence for stem cells in the brains of adult vertebrates came from the finding that male songbirds regenerate neurons of the vocal region in a seasonal cycle. These stem cells are activated by hormones at the onset of the breeding season to replace neurons necessary for the males to sing. These neurons die off after the breeding season.

New neurons on demand

In rodents, stem cell populations have been studied extensively in various regions of the brain. The largest neural stem cell population generates neurons of the olfactory bulb, replacing cells that are continually lost and thereby maintaining the sense of smell. It has been estimated that an adult rodent can generate 80,000 new neurons per day and these newly generated neurons are important to maintain the animal's sense of olfaction. By contrast, the same neural stem cells in humans stop generating new neurons during infancy.

Although humans have a relatively poor sense of smell compared to most other mammals, it is not known whether these neural stem cells are lost or simply become dormant.

Even in older people, neural stem cell-like cells can be isolated from the brain, cultivated and expanded in vitro seemingly indefinitely. This is potentially promising for therapy, as these human neural stem cells can generate not only neurons of the olfactory system, but also other new neurons, for example those that migrate to the neocortex, a region of the brain affected by degenerative diseases. The hope therefore remains that, once we understand the mechanisms that control their activation and differentiation, these cells could be induced to generate neurons later in life.

Memory and disease

The other region of major neuron production in the adult brain, including in humans, is the hippocampus. This region of the cerebrum is responsible for the formation and retrieval of specific forms of memory, during which new neurons are generated and integrated into an established neuronal circuitry. Studies with rodents have shown that these new neurons are used for memory formation. In addition, physiological stimuli can induce activation of hippocampal neural stem cells and the generation of neurons. For example, physical exercise increases the production of neurons and an enriched environment, combined with cognitive stimulation, increases the integration of these new neurons into the hippocampal circuitry. Although it has not been shown equivocally that these new neurons are required for memory formation in humans, experimental findings imply that moderate physical exercise and intellectual stimuli may help to stave off some aspects of brain aging and cognitive decline.

The stem cells in the human hippocampus are also implicated in disease. In rodent models of temporal lobe epilepsy, hippocampal stem cells rapidly activated and proliferated, generating many new neurons. These neurons disperse into

the hippocampus to form potentially diffuse and sometimes aberrant connections in the brain. Similarly, in humans, temporal lobe epilepsy is associated with increased proliferation and dispersion of neurons in the hippocampus. It remains to be clarified whether the activation of stem cells and the likely associated generation of new neurons is a response to the disease or even a contributing factor in epilepsy.

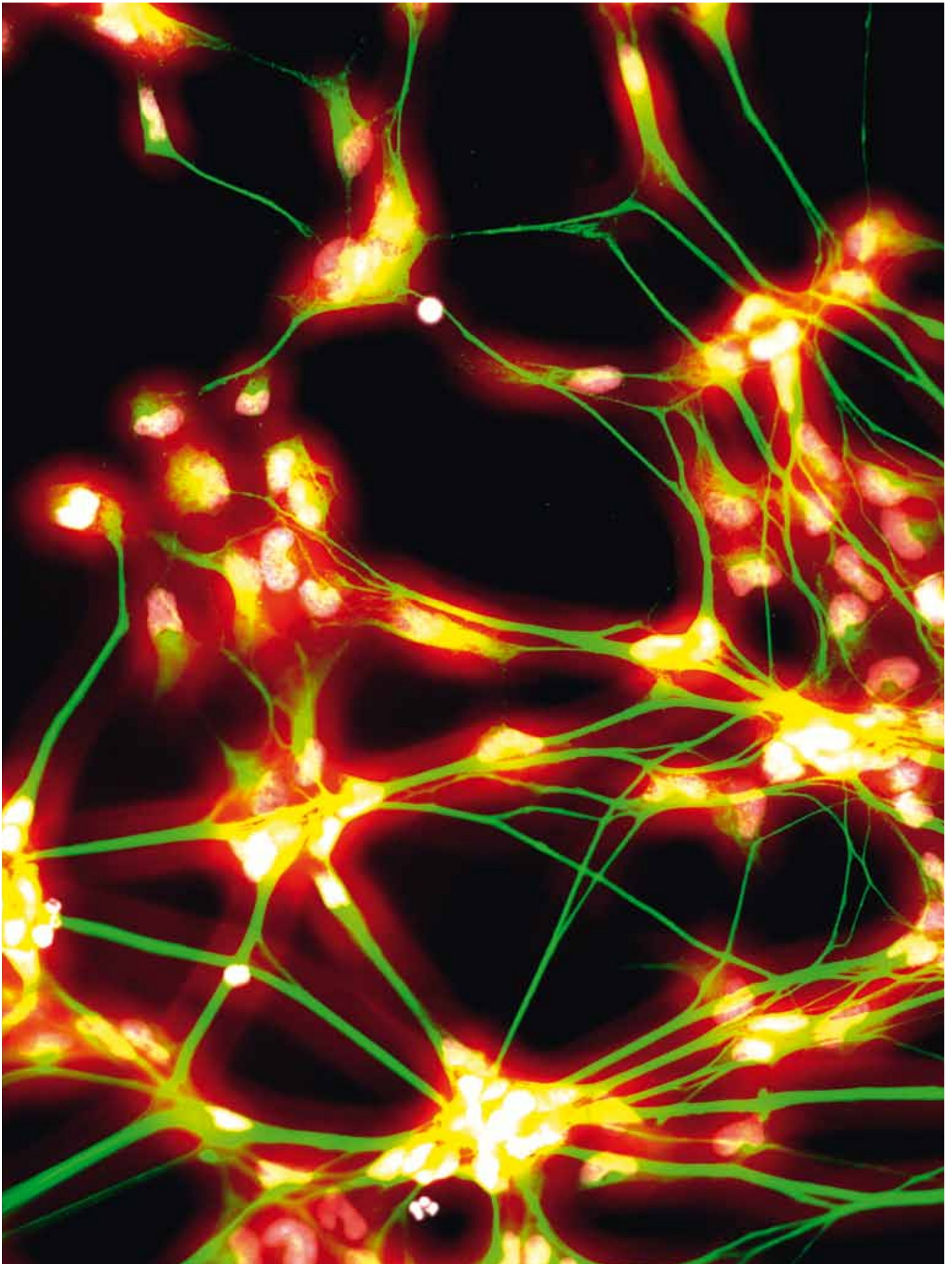
Recently, scientists concluded that a link exists between the actions of some anti-depressant drugs and the regulation of neurogenesis, suggesting that neural stem cells may be involved in depressive and bipolar disorders. While the precise mechanisms of action of anti-depressants on neurogenesis remain unclear, it is now evident that neural stem cells and their progenitor cells respond to neurotransmitters released by neurons and therefore may monitor neuronal signaling and respond to changes in brain activity.

Neural stem cells in brain tumors

In some tissues, cancers are formed by stem cells and progenitors that have acquired mutations and lost control of their proliferation and differentiation programs. Evidence is accumulating that some brain tumors are caused by aberrant stem cells. Glioblastomas and high-grade gliomas are aggressive cancers with poor prognosis and potential for treatment. Glioblastomas contain cells with stem cell characteristics, and together with experimental evidence it has been proposed that stem or progenitor cells in the adult human brain may contribute to or even cause these tumors. Here, the tumor-initiating cells would hijack the mechanisms that normally maintain neuron producing stem cells in the adult brain. Furthermore, it is assumed that glioma cells occupy and transform local niche environments, leading to the uncontrolled expansion of these tumorigenic cells. Consequently, understanding the mechanisms that control neural stem cell maintenance and differentiation could be critically important to understand brain tumor formation in humans and to develop novel therapies.

The presence of stem cells in the human brain has long been the subject of intensive discussion. However, it is now broadly accepted that new neurons are generated in some regions of the brain throughout life and in response to certain stimuli. The task still facing scientists is to investigate further the mechanism and local signals that regulate neural stem cell maintenance and differentiation and, not least, to understand the contribution of these stem cells to brain homeostasis and disease.

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Neural stem cell culture: Neural stem cells are able to differentiate into nerve cells or support cells (glial cells). They are a potential source of cells to replace damaged or lost brain cells (Image: Keystone/SPL/Riccardo Cassiani-Ingoni).

Stem cell use in reproductive medicine

Reproductive medicine deals with the diagnosis and treatment of infertile couples. Many of the causes of infertility can be treated with assisted reproductive medicine. In addition, assisted reproductive medicine enables stem cell research to gain new insights and develop alternative methods, for example modeling diseases in the laboratory. The interaction between assisted reproduction and stem cell research is strictly regulated by law. Christian De Geyter, Oliver Sterthaus, Anne-Catherine Feutz, Maria De Geyter

Many pregnancies can result naturally after a short period of time with targeted treatments. Some of the reasons for long-term infertility, however, can no longer be reversed medically, or there may be insufficient time left due to the advanced reproductive biological age of the affected person to wait for a spontaneous pregnancy.

Assisted reproductive medicine

In these cases, assisted reproductive medicine may offer help: This technology offers the opportunity to induce a pregnancy without eliminating the actual cause of infertility. The term assisted reproductive medicine today essentially refers to two forms of treatment: In vitro fertilization (IVF) and Intracytoplasmic Sperm Injection (ICSI), which differ in the method of fertilization. In IVF, eggs and spermatozoa are simply put together in the laboratory. In IVF the physiological location of fertilization, for example the Fallopian tube, is bypassed; and IVF is therefore predominantly applied to cases with dysfunctional or absent tubes. In ICSI on the other hand, a single vital spermatozoon is injected directly into the egg using a micropipette, so that successful fertilization is possible despite a distinct reduction in male fertility.

As a result of the limited efficiency of assisted reproductive medicine with individual eggs that have matured naturally, this procedure is mostly carried out within the framework of a hormonal stimulation of the menstrual cycle, so that several eggs can be used simultaneously. In this way, several embryos may be created, which can be transferred in one single treatment cycle. Since assisted reproductive medicine enables access to embryos, there is also huge potential for abuse requiring the establishment of a legal framework for its application. This was achieved in January 2001 with the enactment of the Law on Reproductive Medicine (FMedG), which stipulates that no more than three embryos can be created in the course of each individual treatment cycle. Furthermore,

it prohibits the conservation of embryos by freezing. Instead, eggs in the pronucleate stage (before final fusion of the genetic material of both parents) may be cryoconserved.

Supernumerary embryos resulting from assisted reproduction as vehicles for stem cell research

Before the law came into effect, i.e. prior to 2001, more than 200 excess embryos, which were no longer required by the infertile couples for a variety of reasons, had already been cryoconserved in 25 Swiss centers involved in medically assisted reproduction. This triggered the passing of a Stem Cell Research Law in 2004, which regulates the use of such excess embryos for the derivation and characterization of new embryonic stem cell lines (hESC) in Switzerland. In a close cooperation between several research groups at the universities of Geneva and Basel and a group of ethicists and lawyers, a working group was established to develop the concepts and methods for the derivation of new hESC lines on the basis of this legislation. The result was the Joint Embryonic Stem Cell Project (JESP). The Geneva Group was the first to produce and characterize a new hESC line in Switzerland out of 203 excess and anonymized embryos donated for research: CHES1. Although this line has all of the characteristics of a human embryonic stem cell line, its chromosome complement is significantly damaged, so that it can scarcely be used as a standard line.

Building on the experiences of the Geneva Group, we decided to develop a different approach at our own treatment centre in Basel. Since the circumstances of assisted reproduction are decisive for the production of new hESC lines, the procedures for assisted reproductive medicine at the University Hospital of Basel were adapted. If an excess embryo arises and may be donated for stem cell derivation, all of the criteria for “good manufacturing practice” must be met. Without these criteria, none of the newly developing lines may ever be used.

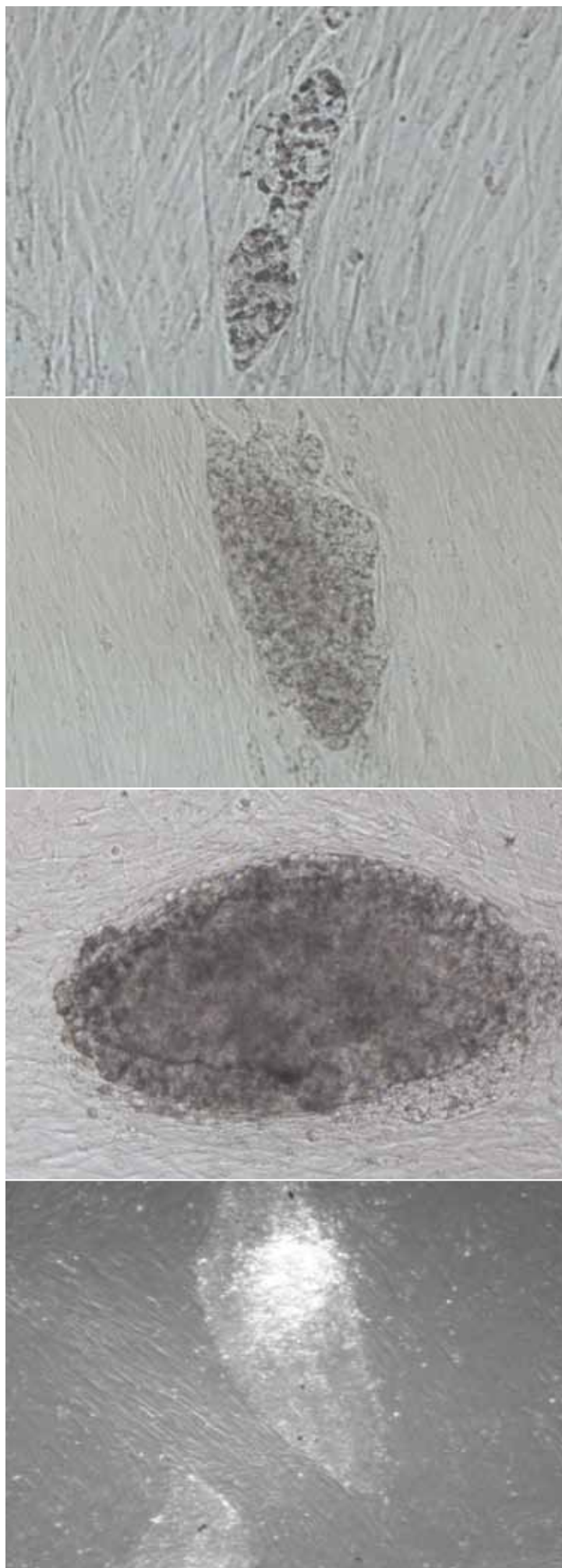
Consequently, all of the procedures involved in assisted reproductive medicine were critically reviewed and modified. Moreover, the infrastructure has been adapted to include a new particle-free laboratory (Grade A) and to enable long-term culture of embryos up to the blastocyst stage. These measures have had an extremely positive impact on the outcomes of assisted reproductive medicine, as well. It was possible therefore not only to increase significantly the probability of a transferred embryo implanting, but also to reduce the number of multiple pregnancies.

Dealing with excess embryos

With the support of legal experts and as part of the JESP project, a protocol was developed in which couples who undertake treatment with assisted reproductive medicine are given several options for dealing with their fertilized eggs and embryos. All couples are given the option as to whether the embryo transfer is carried out at an early embryonic stage (on the second or third day after fertilization) or at the blastocyst stage (five days after fertilization). Couples can also decide whether just one, two or three eggs at the pronucleate stage may be kept in the culture and later transferred as an embryo. Any remaining eggs will be cryoconserved at the pronucleate stage. The decision by both partners must be recorded in writing at the latest immediately before extraction of the eggs. This flexibility allows for individualized treatment, something that is greatly appreciated by many couples. Furthermore, in this way a maximum degree of transparency can be guaranteed in the decision making.

The couple's decision is usually influenced, on the one hand, by the desire for a pregnancy and by the fear of a multiple birth on the other. It can therefore occasionally happen that a couple decides to leave three pronucleate eggs in the culture, since on average only 50 to 60 percent of cultivated embryos develop into blastocysts. In the exceptional case that all three develop to blastocysts and are transferred at this stage, there is a higher risk of a multiple pregnancy, including a triplet pregnancy. Such pregnancies involve both for mother and child significant risks of morbidity and, indeed, mortality. Consequently, a couple in this situation can opt for the transfer of just two embryos. The couple may discuss with an external medical team the options for dealing with excess embryos; in this way an independent decision can be made. The details of this discussion and the decision about the destruction or donation to stem cell research are recorded in writing. Permission for the creation of new hESC lines is reapplied for each year to the Swiss Federal Office of Public Health. Equally, the maximum number of embryos

Induced pluripotent stem cells (iPS) on "feeders" after introduction of foreign DNA with the help of lentiviruses (from above): cell colonies after ten days; after 15 days; after 20 days; and after 25 days. The first three pictures are 200-fold, the fourth is enlarged 50-fold (Images: Basel University Hospital, Women's Hospital).



donated for stem cell research is set; until now it has been a maximum of 25 embryos per year. The procedures are monitored annually by a team of experts from the public health office: The data – including the number of embryos donated for stem cell research – is sent to the Swiss Federal Statistical Office. Furthermore, the procedures in the biological reproductive laboratory and in the stem cell laboratory have been ISO-certified and ISO-accredited by external experts.

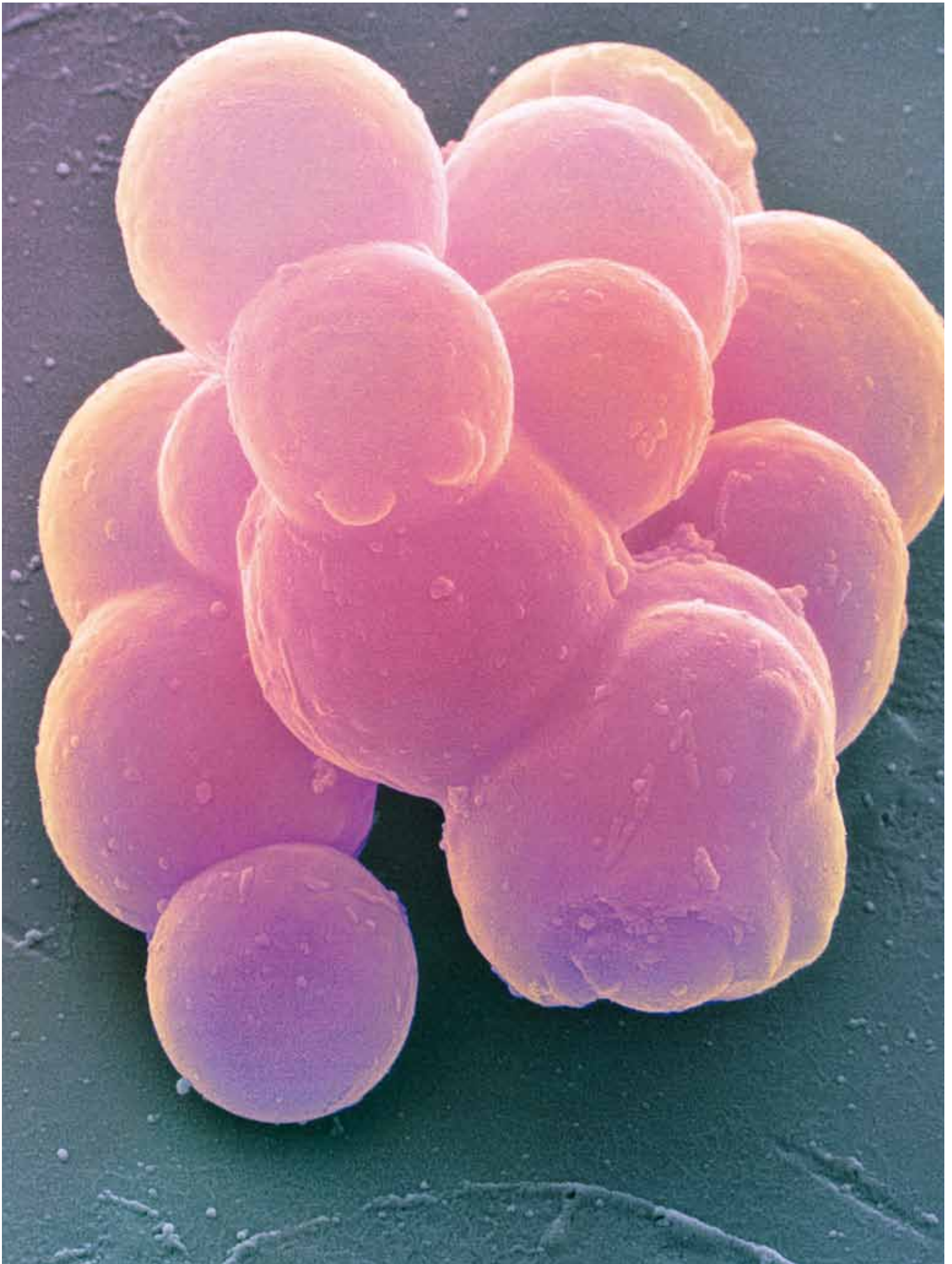
Investigating the modeling of disease in the laboratory

In the time between August 2008 and December 2012, a total of 59 embryos were donated to stem cell research, far fewer than the maximum of 25 per year that the federal public health office has authorized until now. In our research laboratory in Basel five new hESC lines in total have been derived and characterized (CHES₂, CHES₃, CHES₅, CHES₆ and CHES₇). They are registered with the authorities. These new lines have since been used in other institutions in Switzerland for research work.

In the research laboratory in Basel, the donated embryos are used to develop newer, more efficient derivation methods for hESC. Our next goal is to derive new hESC lines in the absence of feeder cells. In addition, our expertise in deriving and culturing hESC lines has made it possible to establish alternative methods in stem cell research. We have therefore succeeded in creating so-called induced pluripotent stem cells (iPS) from somatic cells. Even though iPS cells may not be identical to hESC lines, they represent an important instrument in researching the inheritability of certain characteristics that can cause diseases.

At the Swiss Centre for Applied Human Toxicology (SCAHT), the available lines are being used for the in-vitro modeling of disease. We have succeeded in proving that chemical substances which cause neural tube malformations in the early embryo, also induce these defects during the neuronal differentiation of our stem cell lines. Other substances that do not have these effects on the early embryo do not cause these changes to the stem cells either. It has now also become possible to differentiate embryonic cells to teratoma in a bioreactor, in which these are continually provided with nutrients and oxygen in a circulating medium. This culture system should enable us to test the effects of sexual steroids on the development of insulin resistance during embryonic and fetal development, which are probably also responsible for development of polycystic ovary syndrome as the female fetus grows in the womb. Progress in stem cell technology benefits not only infertile couples, but also researchers who can work with the hESC lines newly created in Switzerland.

Professor Christian De Geyter is Professor of Gynecology and Obstetrics; Dr Oliver Sterthaus works at the division of gynecological endocrinology and reproductive medicine at the *Frauenspital* (University Women's Hospital of Basel), Dr Anne-Catherine Feutz is a research associate with the research group on Gynecological Endocrinology in the Department of Biomedicine, and Dr Maria De Geyter is head of the Gynecological Endocrinology and Reproductive Medicine laboratory at the *Frauenspital*. These are all part of the University of Basel and the University Hospital of Basel (UHBS). Christian De Geyter and Dr Anne-Catherine Feutz are also employed at the Swiss Centre for Applied Human Toxicology (SCAHT).



Stem cells taken from umbilical cord blood: These cells are known as multipotent because, as a type of precursor, they can produce all the body's specialized blood cells, for example red or white blood cells (Image: Keystone/SPL/Jürgen Berger).

Biological implants for cartilage and bone repair

Current implant substitutes to replace damaged or lost tissue, typically based on metal or plastic materials, suffer from several limitations often leading to limited functionality and durability. Now recent advances in materials science and cell biology have opened up ways to induce tissue and organ regeneration. The goal of tissue engineering is to generate implantable biological tissues based on the association of cells with scaffolding materials, which then serve as a template for long-standing tissue regeneration. Ivan Martin, Anke Wixmerten, Marcel Jakob, Dirk Schaefer

In the past 13 years, the Tissue Engineering group at the University Hospital of Basel (UHBS) has been actively engaged in the development as well as pre-clinical and clinical application of advanced biological substitutes for cartilage and bone repair. Research activities initially addressed ways to control growth and differentiation programs for human cartilage cells and mesenchymal stromal/stem cells, based on the presentation of biochemical, physical or material-based cues. In order to translate the developed protocols to a clinical setting, the group then established a comprehensive quality management system (QMS) addressing the requirements of GMP (good manufacturing practice) and GCP (good clinical practice) guidelines. In 2010, Swissmedic approved the use of a small GMP facility at the UHBS for the “generation of transplant products for clinical trials”. The following describes two ongoing clinical programs using autologous cell-based implants to address critical patient needs in skeletal tissue regeneration.

Nasal cells for cartilage repair

First program: The treatment of articular cartilage injuries using autologous cells was first proposed about 20 years ago. Cartilage cells (chondrocytes) are harvested from a small biopsy of an articular (joint) surface, expanded in vitro and the cartilage cell suspension is then injected. However, the clinical outcome is still a subject of controversy. As opposed to “cellular therapy” – which relies on the injection of a cartilage cell (chondrocyte) suspension – the implantation of a mechanically functional graft – known as “tissue therapy” – could offer several biological and surgical advantages. In both cases, the unpredictable variability in the regenerative capacity of autologous articular chondrocytes presents a challenge for the reliable engineering of cartilage grafts.

Recently, it was discovered that human nasal cartilage-derived cells, which can be harvested under minimally invasive conditions, have a higher reproducibility in their tissue

regenerative capacity compared with articular chondrocytes, allowing engineering of cartilage tissues with superior structural and functional properties. Thanks to the active commitment of scientists and surgeons from the Plastic and Reconstructive Clinic at the UHBS, an initial clinical study (“nose to nose”) has been carried out to reconstruct the alar side of the nose following a deep tumor excision, using engineered autologous nasal cartilage. For all five patients treated so far, it was possible to demonstrate the stability and functionality of the regenerated tissue.

Can the same engineered nasal cartilage be used to heal cartilage defects in the knee? The Tissue Engineering group discovered that nasal chondrocytes respond similarly to mechanical loading as articular ones and can adapt their “molecular memory” program (defined by the Hox code) on implantation in a new joint environment. In a goat model, nasal chondrocytes were seen to participate in the repair of experimental articular cartilage defects. Building on this research, a second clinical study (“nose to knee”) is currently in progress. Here, engineered nasal cartilage tissue is used with the aim of regenerating large traumatic articular cartilage defects for which no satisfactory treatment is available. The study, bringing the Traumatology, Plastic and Reconstructive, as well as the Orthopaedic Clinics at the UHBS together with the Orthopaedic Units at the Bruderholzspital and the CrossKlinik, will test the safety and feasibility of the strategy in ten patients, of which two have been already treated with satisfactory outcomes and promising clinical results. This treatment could later be extended to degenerative pathologies (e.g., early osteoarthritis) – most likely in combination with surgical and/or pharmacological protocols that address the etiology of the disease.

Adipose tissue progenitor cells for bone repair

Second program: Despite a generally efficient bone regenerative capacity, several bone injuries fail to heal properly due

to the critical size, the compromised environment, or patient characteristics. The use of autologous mesenchymal stromal/stem cells (MSC) isolated and expanded from bone marrow to enhance fracture repair has been available for some time, but with no convincing benefits for the few patients treated so far. Beyond the controversial issue of the heterogeneous and not properly defined nature of MSC – which cannot be formally described as “stem cells” – one of the challenges in this field is how to achieve a fast and efficient graft vascularization, which is critical for bone formation.

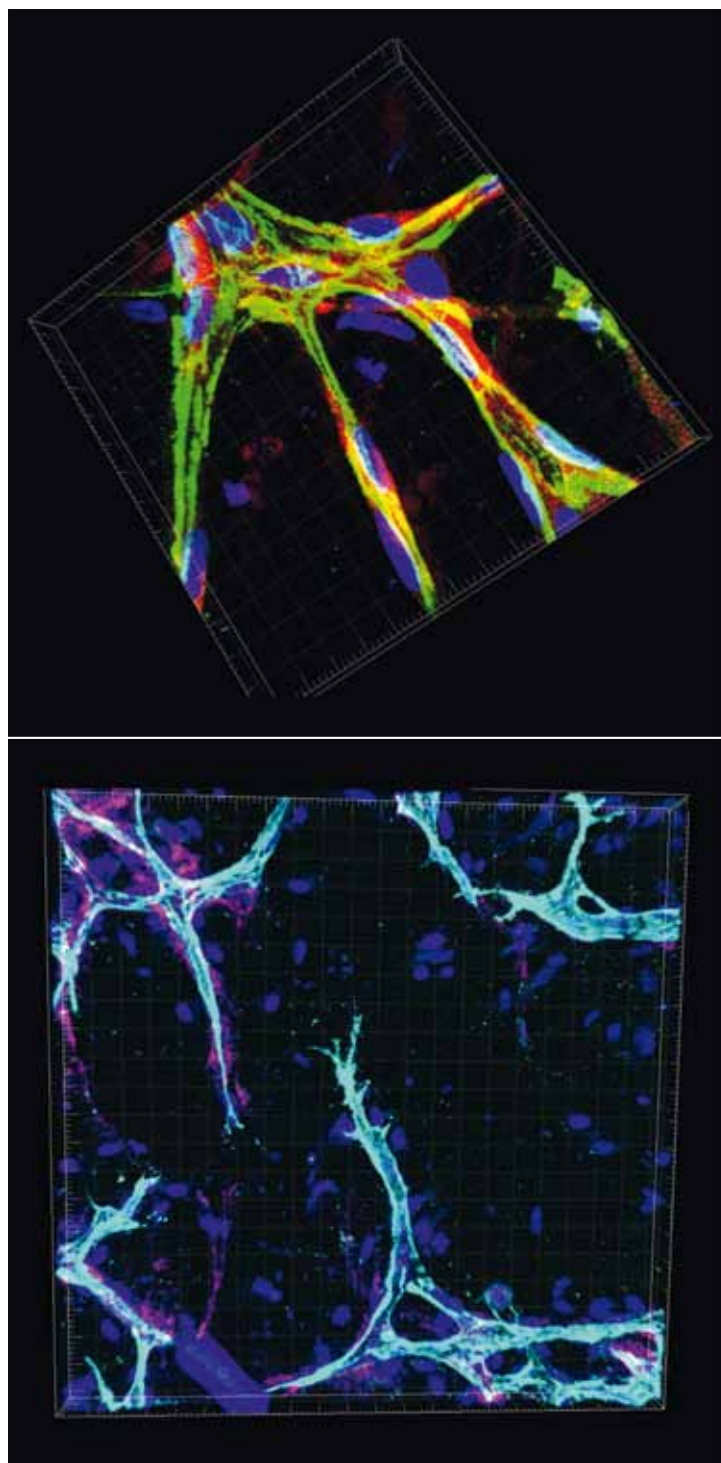
Levels of MSC along with endothelial lineage cells – which are responsible for the formation of blood vessels – are about 100 times higher in adipose tissue cells than in bone marrow. These adipose tissue cells are easily available through lipoaspirates. The Tissue Engineering group was able to demonstrate that human adipose tissue derived cells, directly implanted in animal models of bone formation, not only form bone tissue without being expanded – thanks to the high number available initially – but also promote accelerated graft vascularization, thanks to the presence of the endothelial cell population.

Based on these findings, we have started a clinical study to test the effect of autologous, intraoperatively harvested adipose tissue-derived cells in the healing of upper arm fractures in older, typically osteoporotic individuals. The goal is to reduce the rate of complications and re-operation, which is generally high due to the fragility of the native bone. The first patient in a series of 20 planned recently participated in a pilot study to test the safety and feasibility of the procedure. A larger patient cohort will later be necessary to assess efficacy compared with a control procedure without cells, as well as to identify possible correlations between the phenotype of implanted cells and clinical outcomes.

The longer term perspective of the program is to generate larger grafts (a few cubic centimeters in size) and pre-vascularize them prior to implantation for repair of critically sized defects, which currently represent a considerable clinical challenge for traumatology and for plastic and reconstructive surgeons.

Modern tissue engineering

From a biological standpoint, successful implementation of tissue engineering strategies in routine clinical practice requires a better understanding of the mechanism of action and the fate of the implanted cells, as well as the definition of cellular markers to predict regenerative potency in individual patients. From an engineering point of view, the field would greatly benefit from the introduction of more robust, standardized and automated manufacturing processes. By analogy with other biotechnology products (e.g., antibodies, vaccines and recombinant proteins), this could be achieved with “bioreactors”, i.e. closed systems for controlled production. With this ambitious goal in sight, the Tissue Engineer-



Tridimensional reconstructions of engineered vascular structures generated from human adipose-derived progenitor cells (above) and of angiogenic sprouting by engineered vascular structures (below) [Images: PD Dr A. Scherberich].

ring group in Basel has founded a start-up company (www.cellecbiotech.com) and is coordinating an EU-funded project (www.biocomet.eu) that is expected to lead to a unique clinical study for the implantation of engineered cartilage manufactured in an automated bioreactor system.

In a longer term perspective, the field of tissue engineering should progressively evolve towards more modern concepts of “regenerative medicine”, whereby the implant would not need to have the required characteristics of the target tissue, but would contain only sufficient signals necessary to activate resident stem/progenitor cells towards regeneration programs. The identification of such signals could be inspired by the recapitulation of developmental processes in the embryo and delivered by “smart materials”, according to spatially and temporally defined patterns. Future research will bring together expertise in developmental biology, material science as well as computational modeling.

Although as yet on a small scale, the set-up in Basel is unique in fostering close, efficient collaboration between different research and clinical disciplines on the development of biological implants for tissue repair. The structural framework is also being shaped by the Stem Cell Center of Competence at the University of Basel and the Center for Regenerative Surgery at the University Hospital of Basel’s Department of Surgery. These concerted efforts are also expected to lead to the infrastructure (e.g., GMP facilities) required to boost international competitiveness in a field that has the potential to link scientific discovery to patient satisfaction and economic benefits.

Professor Ivan Martin is Professor of Tissue Engineering, Anke Wixmerten is a research associate with the Tissue Engineering group, Professor Marcel Jakob is Professor of Traumatology, and Professor Dirk Schaefer is Professor of Plastic, Reconstructive and Aesthetic Surgery, and hand surgery at the University of Basel.



Section through a chondrocyte cell with typical large nucleus (pink): Cartilage is a type of connective tissue formed of cells embedded in a matrix (green) of collagen fibers and proteoglycans in a space called a lacuna (Image: Keystone/SPL/Steve Gschmeissner).

Germ cells: Origin of life

What gives embryonic cells the potential to develop into many different types of cells? DNA modifications and certain proteins contribute to the specification of cell types. New procedures enable cells to be reprogrammed as well. Antoine Peters

In mammals, life starts at fertilization with the fusion of two highly specialized cells, the sperm and the egg, to form a single-cell embryo, called the zygote. This zygote has the potential to form all cell types in the developing embryo and adult individual. In addition, cells derived from the zygote, together with cells of maternal origin, form the placenta that nurtures the embryo during its growth and development in the womb of the mother. Given this “all-inclusive” potential, the zygote and cells of early pre-implantation embryos, called blastomeres, are totipotent. During embryogenesis, however, cells differentiate and become progressively restricted toward specific cell fates, being able to only develop into certain cell types and organs.

Cell identity and developmental potential

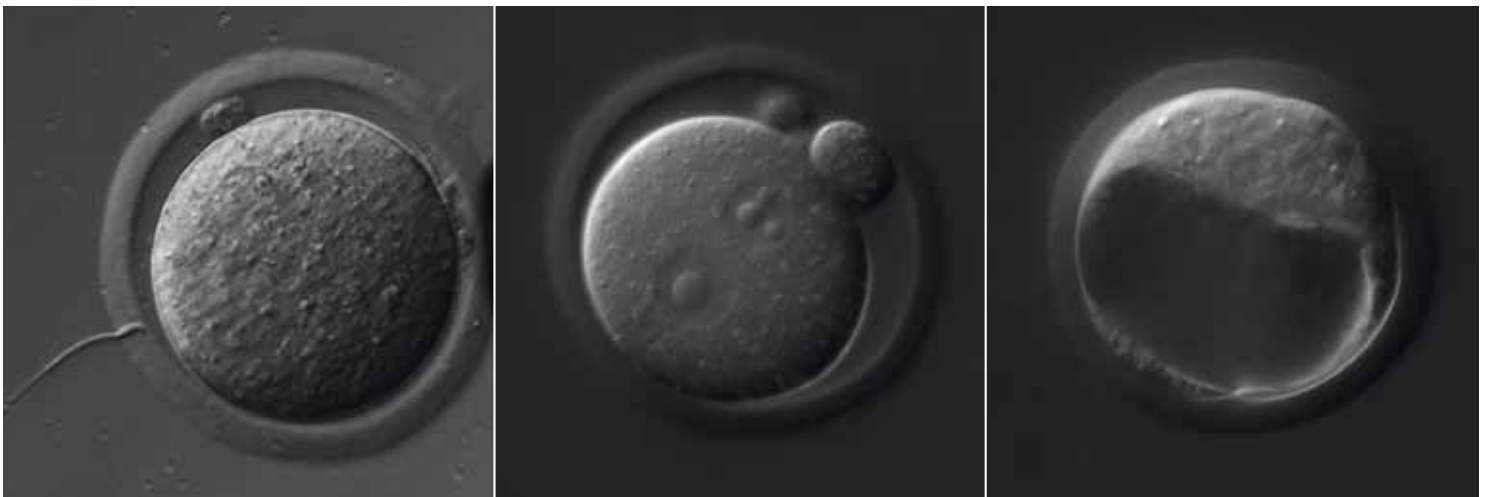
What is the mechanism that specifies cell identity and developmental potential? All cells harbor DNA molecules that contain genes, which encode proteins that serve structural and regulatory functions in an organism. Though hundreds of different somatic cell types exist in a human body, they almost all contain identical DNA molecules with the same set of genes, forming together the genome. Cell identity and the loss of developmental potency during embryonic growth are therefore not due to irreversible changes of the DNA.

Instead, it is determined by regulatory DNA sequences present in the genome that define the level of activity of genes in a given cell type. These regulatory sequences are interpreted by special “reader” molecules such as transcription factors and RNA molecules driving cell type-specific gene expression.

Furthermore, like humans wearing different clothes depending on the season and their personal identity and activity, DNA is not naked within a cell, but is nicely dressed by histone proteins and DNA-binding proteins. This complex of DNA and proteins, chromatin, forms an open or closed configuration within the nuclei of cells. The kind of chromatin packaging of genes and their neighboring sequences influences the level of expression of individual genes.

At the time of implantation of the blastocyst embryo into the uterus, a specific group of cells has developed inside the embryo known as the inner cell mass (ICM). These cells express a set of specific transcription factors and contain many chromatin regulatory proteins that are important for gene expression during this stage and regulate the degree of DNA packaging. Their chromatin states are relatively open and flexible. Together, these chromatin characteristics and transcription factors enable ICM cells to differentiate into all different cell types of the embryo (but not the placenta), a property defining ICM cells as pluripotent.

Stages of development: sperm and egg (left), zygote (middle) and blastocyst (right) of the mouse (Images: Antoine Peters, FMI).



During subsequent differentiation, key genes that orchestrate embryonic gene expression become packaged into repressive chromatin configurations, which are subsequently inherited by progeny cells. In addition, cells within distinct developmental paths adopt various specific chromatin states that are also maintained during further development. Such a mode of inheritance of gene expression acting beyond the direct genetic code is called epigenetic memory. It is widely thought that epigenetic memory mechanisms contribute to the hierarchy of cellular differentiation by controlling the progressive limitation of differentiation potential during development, as well as by disabling the possibility of de-differentiation.

Reprogramming mature cells

Seminal studies by Sir John Gurdon, one of the 2012 Nobel laureates for Medicine, have, however, shown that the chromatin landscape in a differentiated cell, the epigenome, can be reprogrammed to an embryonic-like state that is able to support development and generation of viable offspring. This procedure entails the transfer of the nucleus of a fully developed somatic cell into the cytoplasm of an enucleated mature egg and is called nuclear transfer or reproductive cloning. Gurdon made his discovery using cells and eggs from frogs. Later work has shown that eggs and blastomeres of early embryos of a variety of species, including mouse and cow, can reprogram mature nuclei. Mechanistically, it is thought that large numbers of chromatin regulatory factors in the egg remove repressive chromatin states in differentiated nuclei in such a manner that important pluripotency genes required for embryogenesis can become expressed and then instruct embryonic development.

Recently, Shinya Yamanaka, the second recipient of the 2012 Nobel Prize for Medicine, demonstrated that the presence alone of certain transcription factors can directly reprogram mature cells to pluripotency, thereby forming induced pluripotent stem (iPS) cells that resemble pluripotent embryonic stem (ES) cells derived from the ICM of pre-implantation embryos. When placed back into a pre-implantation embryo, ES and iPS cells have the potential to differentiate into all embryonic cell types and generate living offspring. Moreover, they are able to generate various mature cells under different in vitro growth conditions and are thus ideally suited for disease modeling and drug testing. Knowledge obtained from such basic research studies may contribute to the development of novel and safe applications in personalized regenerative medicine.

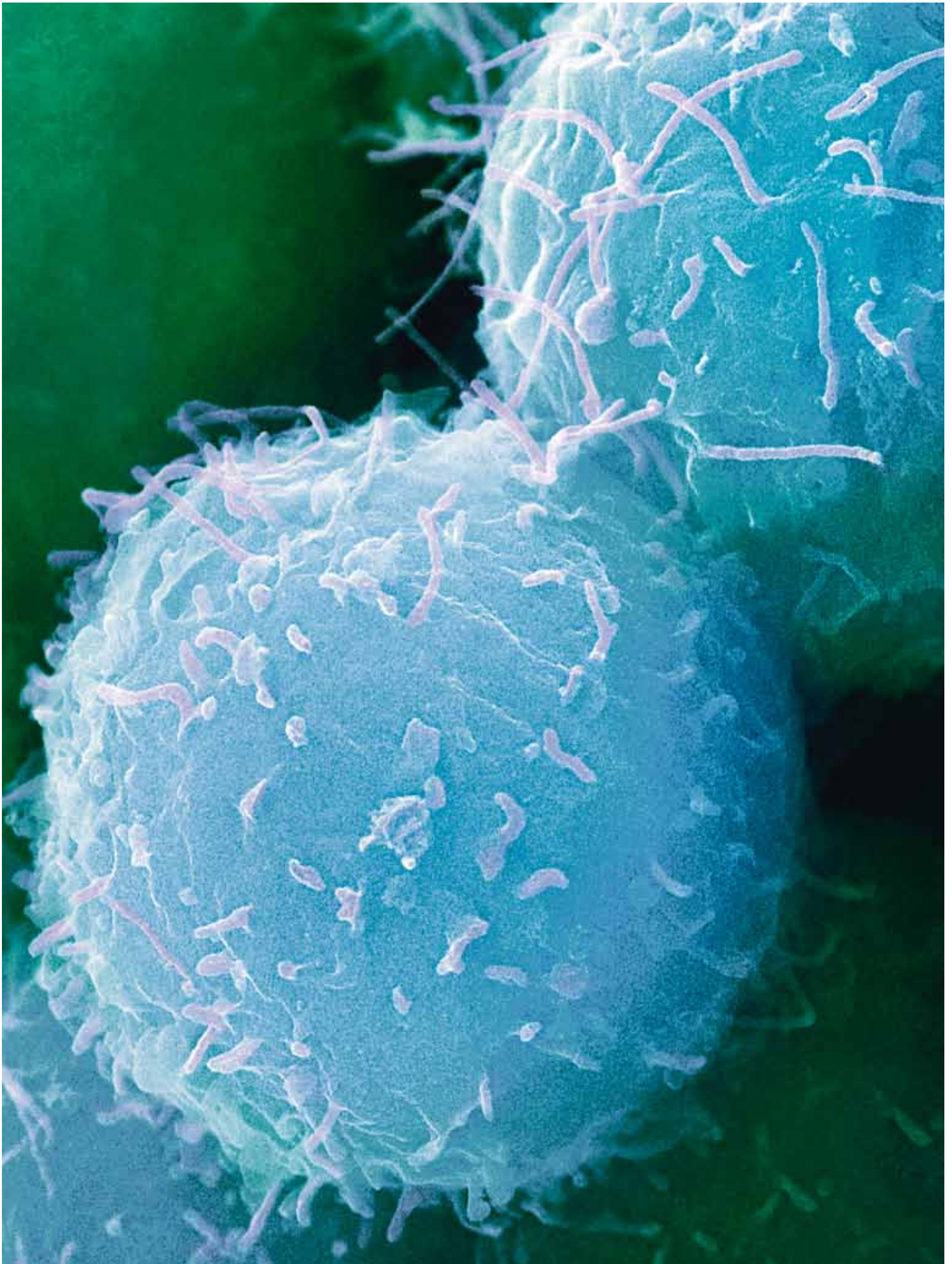
Epigenetic inheritance

From the experiments described, it becomes clear that the efficiency of transcription factor-induced reprogramming is low, illustrating the robustness of epigenetic memory and the complexity of gene expression mechanisms. Interestingly,

the success rate of reproductive cloning is also very low compared to that of natural reproduction. These latter observations suggest that, compared with those of normal somatic cells, the epigenome of mature eggs and sperms is prepared to effectively support the acquisition of totipotency after fertilization. Possibly, there are certain chromatin states transmitted from the egg and sperm to the embryo that do not become reprogrammed in early embryos. How would such germ line chromatin states be formed? Germ cells in mammals arise early during gestation from a group of cells differentiating towards a somatic fate. Newly specified germ cells then undergo extensive epigenetic reprogramming during their long path of development, providing opportunities for preparing their epigenomes for successful embryogenesis. An increasing number of studies in rodents and humans show that parents' nutrition, smoking habits and exposure to pesticides can cause physiological changes in offspring.

In many laboratories worldwide, research is focused on identifying the mechanisms of epigenetic reprogramming in developing germ cells and in early embryos, and of epigenetic inheritance between generations. The insights obtained will, for example, help to identify mechanisms underlying human infertility in the future. Furthermore, pure research on reprogramming somatic cells will stimulate the development of new forms of treatment in regenerative medicine. Finally, these studies will one day reveal the secrets of the germ line in reestablishing totipotency as the basis for new life, thereby preserving immortality of the species.

Professor Antoine Peters is Senior Group Leader at the Friedrich Miescher Institute for Biomedical Research in Basel and Professor of Epigenetics at the University of Basel.



Mouse embryonic stem cells: Stem cells of this type are able to differentiate into any of the cell types in the animal's body. The type of cell they mature into depends upon the biochemical signals received by the immature cells (Image: Keystone/SPL).

Ethical issues with human-animal hybrids

Embryonic stem cell research offers the hope of tailored treatments for severe diseases such as Alzheimer's and Parkinson's disease. At the same time, it raises a range of ethical issues. In an attempt to defuse the controversy, researchers in the UK employed a novel technology that does not require the use of human embryos. Instead, they inserted nuclei of human cells into animal eggs. However, this merely prompted a new ethical debate. Sabrina Engel

The acceptability of research using embryonic stem cells has long been a subject of debate among researchers, politicians, church leaders, patient organizations and other groups. The issue took on a new dimension in the UK in 2008, when British researchers experimented with a novel strategy for producing tailored stem cells without recourse to human embryos. They introduced nuclei of human cells into animal eggs that had their nuclei removed. In genetic terms, the cell thus created is 99.9% human and 0.1% animal. After these experiments became public, the UK Parliament voted on a proposal to ban any future research of this nature. The proposal was defeated, and the research was allowed to continue, at least in the United Kingdom. In Switzerland, by contrast, it is illegal to combine human and non-human reproductive and genetic material, and all over Europe the controversy continues over whether it is permissible to mix human and animal material in this way.

Violation of human dignity?

Opponents of the new technology appeal to arguments similar to those voiced in connection with embryonic stem cells. They criticize the experiment as unnatural and accuse the researchers involved of playing God and of violating human dignity. In addition, the experiment is seen as unacceptably blurring the distinction between man and animal. Moreover, it is argued that the experiments create a slippery slope towards fully developed hybrid creatures with an undefined status.

On the opposing side, however, advocates of this type of research make the point that it could yield huge benefits for the treatment of severe diseases. Above all, they argue that the technology would make it possible to continue stem cell research without destroying human embryos or using human gametes. Furthermore, they point out that any hybrid embryo created would on no account be allowed to grow for more than two weeks, so that a fully developed hybrid creature could never come into being.

No new concerns

In response to the ongoing debate about such hybrids, ethics committees established in several European countries (including the United Kingdom, Switzerland and Germany) published separate reports in 2011. None of them fundamentally questions the acceptability of animal experimentation or of mixing human and non-human cellular and genetic material, provided that steps are taken to protect animal welfare and provided that the experiments are aimed at developing new therapeutic approaches. Moreover, none of the committees found any ethical concerns that had not been raised in the context of previous debates over biomedical research. However, the German and Swiss reports, in particular, emphasized that the more human material is transferred, the more serious the associated ethical concerns will be.

The transfer of individual genes or a limited amount of tissue from humans to animals raises relatively few concerns. By contrast, considerable ethical concerns exist about transferring human cells to an animal during development to create entire human-like organs or other human structures. In particular, the reports warrant caution regarding the transfer of human neural stem cells to animals. This might lead to animals acquiring human characteristics such as human-like consciousness. The reports concur that the boundary between man and animal could theoretically become blurred in that case, also stating that the use of primates for such experiments in particular could lead to the existence of hybrid creatures with no defined moral status.

In its report "Animals containing human material", the UK's Academy of Medical Sciences suggests the use of three categories to define experiments. Experiments in the first category pose no concerns beyond animal ethics issues, which are sufficiently regulated by animal welfare legislation; experiments of this type would not need to be individually assessed. Category two comprises experiments that give rise to further ethical concerns, e.g., experiments involving non-

human primates. The report proposes a special committee to scrutinize experiments in this category in advance. Category three experiments raise strong ethical concerns and therefore should not be conducted. This includes implantation of hybrid embryos in an animal or human uterus. Experiments of this type are illegal in Switzerland.

Stem cells in animal brains

The recommendation in the UK and German reports that the transfer of neural stem cells to animal brains, in particular brains of non-human primates, be placed under special scrutiny, and possibly monitored by a special committee, has raised concern in the scientific community. Researchers are worried about additional hurdles that may impede the translation of novel therapeutic approaches into practice, for example treatments targeting Alzheimer's and Parkinson's disease. These treatments would need to be tested on animals, ideally primates, before clinical trials could be initiated. However, the ethics committees' recommendations are not binding for the respective national legislators. It remains to be seen what conclusions will be drawn from the reports and whether research will be hindered as a result.

Dr Sabrina Engel is a postdoctoral researcher at the University of Basel's Institute for Biomedical Ethics.

Educational Ideal – (Media) Competencies



Even the classic intelligence quotient, the IQ, is no longer what it used to be. For some time now, experts have even considered it to be misleading. Intelligence, according to recent studies in Canada, is not a single unitary talent, but is instead made up of three independent factors: short-term memory, logical thinking and verbal abilities. A strong correlation between these factors is said to indicate true intelligence. The same is true for our understanding of mass media (newspapers, television) and individual media (PC, Internet). Media education used to take a single and straightforward do-it-yourself approach: By making their own radios at school, it was hoped that children would come to understand the way the media system worked inside out. However, the shiny new media world of Facebook, Google, YouTube & co. has made things more complicated. A more differentiated set of skills is now required. Following the Bologna Declaration on higher education in Europe, the European Qualifications Framework (EQF) was introduced specifying exactly what students need to do to acquire the competencies of each corresponding qualification level. In this context, the general model used by language schools provides direction. Students learn – just like an automatic processing system – how to transform a calculated input to fit a pre-defined goal: the competency. Organizational sociologist Stefan Kühl calls this the “automatic transmission” of the Bologna Process.

But how does Geist – the “human mind” – even fit into this concept of machine technology? Life teaches us that ed-

ucation does not work this way: Some of us learn systematically, some of us learn “bit by bit”, some of us learn alone, and others need guided instruction in a classroom, or discussions with peers over a coffee, beer or glass of wine. Even a resurgence in the idea of sending professors into classes and seminars to act as digital media experts to enlighten the students (just as Theodor W. Adorno did in his time, traveling from the cities to rural areas to campaign for convertees) cannot make up for the shortcomings of this kind of educational approach. And how could it? The Internet has created an unprecedented culture of participation in which young people (so-called “digital natives”) learn media competencies themselves, alone as well as through a network of friends and like-minded young people all over the world. However, when navigating this networked and daily life that has become so extraordinarily complex, a commentary by more-knowledgeable peers is often helpful and sometimes necessary. Decision architects are what we need.

In the field of political governance, economist Richard H. Thaler and lawyer Cass R. Sunstein introduced the term “nudge” into debates. Libertarian paternalism suggests that the mature citizen should be given a nudge in the right direction when it comes to making political decisions. Top-down dictating is about as outdated as technocratic or ideological superiority. Instead, we need to “nudge” in a way that suits the person, question or situation, to initiate the process, and to provide flexible “framing” – this also applies to the appropriate teaching of media competencies.

Professor Klaus Neumann-Braun (b. 1952) is Professor of Media Studies at the University of Basel. He studied sociology, social pedagogy, psychology, education and ethnology in Tübingen and Freiburg im Breisgau, where he gained his doctorate in 1982. He completed a post-doctoral “Habilitation” at the University of Oldenburg in 1993, where he worked in the field of media studies. Since then, he has held positions at a variety of universities in German-speaking countries.

Researching space and place in literature

Ina Habermann has been Professor of English Literature for five years now. She is currently interested in the interplay between texts and cultural spaces. The Centre of Competence Cultural Topographies, which she founded three years ago and where she is director, is the outcome of her distinctive cultural studies approach. Anna Wegelin

Literary scholar Ina Habermann is quietly industrious, and she also has a good instinct for topics of popular interest. This is how she came to study discourses of Europe in Britain and “Englishness”, that is, particular conceptions of national identity. She focuses on two different eras and genres: early modern drama in the Shakespearean period, and popular prose literature from the first half of the twentieth century, including such bestselling novels as Daphne du Maurier’s “Rebecca” from 1938, with a focus on mythmaking and national identity.

For the love of literature

Ina Habermann’s first job after leaving school was as a bilingual secretary. “Because of my family situation, it seemed a good idea at the time to do a job that I could make a living from,” she explains, now sitting in her corner office located in a listed building in Basel’s old town. Finally, she chose to study simply for the love of literature and embarked on an academic career: “I soon realized that this was my world.” She majored in English with German and Sociology at the University of Frankfurt between 1989 and 1995, and worked at the University’s Renaissance Institute. She wrote her Master’s thesis on cross-dressing and gender identity in Renaissance drama of the Elizabethan and Jacobean periods. On completion of her Master’s, she won a three-year scholarship to study with the Research Training Group on Gender Difference and Literature at the University of Munich. Her university career – which she

describes as a troika of “research, research-based teaching, and administration” – began in 1998 at the University of Erlangen, where she worked for nine years as an assistant. In her dissertation, for which she was awarded the highest possible grade by the University of Frankfurt in 2000, she researched discourses of slander in English Renaissance drama and legal texts from the period around 1600.

“Middlebrow” and common sense

She successfully completed her postdoctoral “Habilitation” at the University of Erlangen shortly before coming to Basel. In this research project, Habermann turned her focus to “Englishness” (as a symbolic form) in literature and films that were considered “quality” entertainment between the interwar period and the 1940s. Such works are often condescendingly called “middlebrow”, in contrast to “highbrow”; both of these terms stem from phrenology, the practice of determining intelligence from the height of a person’s forehead. In a book published in 2010, Ina Habermann suggests that

“mediocre” literary and filmic output deserves more scholarly attention since it can offer representative insights into social identity formation.

“I take a cultural studies approach to English,” explains Ina Habermann. As well as the artistic merit of a literary work, “I am interested in the relationship – and the distinction – between literature and real life.” Her years spent studying in Frankfurt, home to the Frankfurt School of critical thought, together with the

Ina Habermann was appointed Professor of English Literature since the Renaissance at the University of Basel in 2007. Born in 1965, she studied English, German and Sociology in her home city of Frankfurt am Main and in Exeter, UK. She spent the years between 1995 and 1998 researching gender relations and literature at the University of Munich and in London. She completed her doctorate in 2000 in Frankfurt, and her postdoctoral “Habilitation” in 2007 at the University of Erlangen, where she worked at the Institute for English and American Studies from 1998 to 2007. She has been director of the Centre of Competence Cultural Topographies at the University of Basel since 2009.



Exploring space: Ina Habermann in the studio theater in the cellar of the English Department (Image: Andreas Zimmermann).

countless books that she devoured as a young girl, are two significant factors that have influenced her approach of reading every text in its context. “I always wanted to understand the role of literature in society,” she explains. She finds “middlebrow” literature particularly insightful, since it often explores women’s activities and stories: for example, the 1946 novel “The Pavilion of Women” by Pearl S. Buck, which has remained a favorite, as well as popular English literature classics by the Brontë sisters and Jane Austen.

The “middle style” is “highly typical of the British intellectual landscape,” says the English professor. It stands for an anti-intellectual, generally intelligible culture of common sense: from empiricism and pragmatism in British cultural history, to the supreme writing form, the essay, “an accessible form for anyone who wants to deal with complicated content.” These practices are all based on a “long democratic tradition where the voices of a wide range of people were heard more clearly than in other countries.”

Love, death, and the nuclear family

“Middlebrow” literature and “Englishness” constitute one of three main topics of Habermann’s research to date. However, she is planning to broaden her focus historically to include the reception of Vergil’s “Georgica” didactic poems in England. She also keeps returning to Shakespeare, her second main research focus. In his tragedies especially, explains Habermann, he takes the “highly adaptable, archaic themes of love, death, and the problems of the nuclear family,” and packages these into multifaceted, complex stories that always allow us to discover something new. According to Habermann, the Elizabethan-Jacobean drama was the main creative form around 1600: “The theatre was the place where important social conflicts were acted out, and where burning issues were addressed.”

Her third research area, which is linked to her activities at the Centre of Competence Cultural Topographies, addresses British literary and cultural discourses on Europe. Habermann calls this the “cultural-political element” of her work. She claims that while Great Britain is a “very hesitant member of the European Union,” it continues to play a particular role in Europe. The cultural topography of Basel and Switzerland favors this approach: Switzerland also plays a marginal role in Europe, despite its geographical position at its center.

Bodies connected in space

Ina Habermann personally took the initiative in founding the Centre of Competence Cultural Topographies, where she is currently the director. The Centre was established by the University of Basel in 2009, and was originally conceived as a mid-term project. Habermann explains that she has always been fascinated by interdisciplinarity and so, when she found out that a number of colleagues at the University were

working on space and cultural topographies, she wanted “to join forces” and tackle the research questions together. The Centre of Competence currently has two primary strands of research: Firstly, the “borders of Europe”, with a focus on Eastern Europe; Habermann’s research on British Europe discourses is also part of this strand. The second research strand is centered on Basel city and regional development from human-geographical and historical perspectives.

Researching cultural topographies – defined as “geographical, imagined, described and invented spaces” – is more than just a useful approach, according to the literature scholar. Space represents a “paradigm of today’s world” and a move beyond the “body” and gender debates of the 1990s. “Bodies are located in space,” says Ina Habermann, situated within landscapes and living in interpersonal “topographical” relationships: “Spatial studies highlight the connection between discourse and the material world.” In the context of “Englishness”, one question might be: “How does national identity correspond to the geography and topography of the insular state?” William Wordsworth offers a tentative answer in his literary evocation of the Lake District, the epitome of the English countryside. “Research-based teaching generally takes some time to develop,” admits Ina Habermann, “yet the Centre of Competence is becoming more and more productive.”

Raison d’être as a professor

Habermann loves her work, although she also has a life outside university that she shares with her partner and child. Many of her hobbies, including acting and music, are momentarily on the back burner. She explains that the University is distinctive in the way that teaching and research are interwoven: “There is a need to produce excellent research, while at the same time ensuring a broad scope of activity.” Her *raison d’être* as a professor is to impart her knowledge and experience to students, and to continue to develop alongside them, she explains. “The students should leave university equipped with knowledge and intellectual tools and full of enthusiasm for the subject.” For students, Ina Habermann is something of a role model – living proof that a woman can have a successful university career. For the love of it.

Anna Wegelin is a freelance journalist based in Basel.

Interdisciplinary research on wetlands

When pile dwellings were first discovered in Switzerland more than 150 years ago, they became a sensation all over Europe. Since then, archaeology has developed into an interdisciplinary field of study. Combining methods from both the natural sciences and the humanities, the University of Basel's Centre for Integrative and Prehistoric Archaeological Science (IPNA) is widely considered to be at the forefront of wetland research. Francesco Menotti

It all began in the middle of the 19th century: Following the harsh winter of 1853/54, the level of Lake Zurich fell dramatically, revealing part of the remains of a prehistoric settlement near Ober-Meilen. Wooden piles jutting out of the water were spotted by village teacher Johannes Aeppli, who contacted the Zurich Antiquarian Society, no doubt failing to realize the full significance of his discovery. The president of the society, Ferdinand Keller, immediately investigated the site. Later that year, he published a paper entitled "Die keltischen Pfahlbauten in den Schweizerseen" ("The Celtic Pile Dwellings in the Swiss Lakes") – the first ever description of the lake settlements.

Creation of a national myth

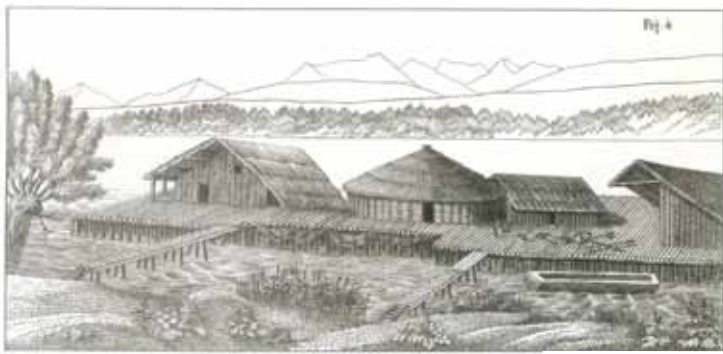
Vestiges of lake settlements also began to be found in other places. The Swiss pile dwellings caused a furor among not only archaeologists but also the general public, both in Europe and elsewhere. Initially, however, the interest taken in them was anything but academic – no systematic effort was made to discover similar archaeological sites; instead, the lake shores were plundered, and the precious finds sold to collectors and museums all over the world. Moreover, the lack of archaeological knowledge at the time meant that inaccurate conclusions were drawn about the structure and purpose of the prehistoric lake villages, which were thought to have consisted of isolated platforms mounted on piles and surrounded on all sides by water. This idea was appropriated – and abused – by nationalist groups, who were seeking to define a unified sociopolitical identity for Switzerland. With memories of the Civil War of 1847 all too fresh, the young nation was still deeply divided.

Against this backdrop, the lake-dwellers were hailed as national heroes in the young federal state. Almost overnight, the powerful image of a proud lakeside village found its way into all areas of Swiss life, including the worlds of business, education, art, literature and even music. The myth created around the lake-dwellers lasted several decades, until archaeological research discovered facts that cast doubt on the notion of idyllic, self-contained lake villages built on stilts. Finds included not only stone, clay and bronze artefacts, but also implements made from wood, deer antlers and bones as well as some fabric. Also found in the archaeological layers were large amounts of animal bones and remains of cultivated or foraged plants, i.e. surplus produce and food scraps. Ironically, it was these beautifully preserved millennia-old finds that put an end to the myth.

Wetland archaeology and the natural sciences

The eventual rejection of the long-perpetuated notions about the lake settlements marked the beginning of wetland research, and in fact the entire discipline of archaeology. It was found that organic material was far better preserved in waterlogged soil than in dry soil. While not always pleasant to look at, the finds greatly contributed to a better understanding of the prehistoric lake settlements. New sub-disciplines such as archaeobotany, archaeozoology and geoarchaeology came into existence and shaped the very foundations of archaeology, with wetland research becoming one of the most successful strands of mainstream archaeology.

Today, major archaeological research projects routinely follow a multidisciplinary approach like that embodied by the IPNA. A recent example is the archaeological excavations



Ferdinand Keller's initial reconstruction of the Ober-Meilen lake settlement (Image: from Keller, 1854: Table I, Fig. 4).



Modern reconstruction based on archaeological research at Cortaillod-Est, a Late Bronze Age pile dwelling on Lake Neuchâtel (Image: Laténium Museum, drawing: K. Bosserdet).

carried out on the construction site for the Opera parking garage in Zurich.

Returning to the lake settlements: As early as the 19th century, a number of researchers conjectured that the villages would originally have been built not as pile-supported platforms above the water, but on dry land near the lakes. An academic controversy ensued over the lake settlements which was to last decades and, in fact, was not fully settled until recently. There is now a consensus among researchers that there were various types of lake settlements. As the controversy subsided, researchers began to focus on issues of chronology.

Mysterious demise

Modern scientific dating methods – C14 (radiocarbon dating) and dendrochronology (tree-ring dating) – have since made it possible to determine with reasonable precision the period in which the lake settlements of the northern Prealps were built, namely between the late 5th millennium and the 7th century BC. However, settlement patterns were far from uniform or linear. Periods of settlement alternated with periods when lake settlements were abandoned. Some of these interruptions were probably the result of environmental changes such as climate variations, while others were due to cultural factors.

What remains a puzzle is why, in the late 7th century BC, these lake settlements disappeared from the Swiss Prealps. An international research project ("The end of the lake-dwelling phenomenon: cultural vs. environmental change") at the IPNA is trying to arrive at an answer by investigating ecological and socioeconomic factors that might have caused the lake settlements to be abandoned. Comparable villages continued to be built and inhabited in other parts of Europe (for instance in the Baltic region and in Scotland) until the first century BC (i.e. Late Iron Age) and even later. The Basel research project will, among other things, compare lake settlements in the Prealps and those in northern Europe, taking into account climatic, economic and cultural aspects.

Professor Francesco Menotti holds an SNF professorship at the University of Basel's Centre for Integrative and Prehistoric Archaeological Science (IPNA, Department of Environmental Sciences). He is the author of *Wetland Archaeology and Beyond: Theory and Practice* (2012), and has co-edited *The Oxford Handbook of Wetland Archaeology* (Menotti and O'Sullivan, 2013), both published by Oxford University Press.

Web 2.0 and the Humanities

Digital media are changing our lives, our thinking and our communication – and therefore also the way we treat cultural phenomena such as literature, art, history, religion and politics. On the challenges of new media for the humanities.

Roberto Simanowski

There is a cartoon in which a father sits next to a boy of about twelve and says, “You do my website ... and I’ll do your homework.” The cartoon accurately depicts the imbalance in media competency of today’s generations, which are described in the vague and paradoxical terms: “digital natives” (for the young) and “digital immigrants” (for the over thirties). This constellation is by no means new, as historical research into reading has shown: 250 years ago, when children started to be sent to school, it was not uncommon for twelve year olds to write the maid’s love letters – an example that also demonstrates that conflicts between media access and youth protection were already in existence in earlier times. Is the father in the cartoon the maid of those far-off times? Has nothing else changed other than the medium and the year?

Demand for media education

What has changed above all is the speed and the extent of the development of new media. Few would have imagined 20 years ago, how profoundly the Internet would one day radically change our entire daily life, and fewer still could have predicted ten years ago how radically Web 2.0 (blogs, YouTube, Wikipedia, Facebook) would change the Internet. Since then, traditional ideas about identity, communication, knowledge, privacy, friendship, copyright, advertising, democracy, and political engagement have fundamentally changed. The neologisms that the new media have generated already testify to this: They blend former opposites (producer, slacktivism, viral marketing), turn traditional concepts upside-down (copyleft, crowdfunding, distant reading) and express the assertion of new principles (citizen journalism, filter bubble, numerical narratives). Those who don’t understand these terms need a lesson in media education

rather than English. Becoming “media educated” is, however, not at all easy. All that seems to be offered are practical skills through “media literacy”.

Media studies is not on the school curriculum either here in Switzerland or in our neighboring country Germany. New media are therefore subtly bringing about a radical reconstruction of core social values with hardly a trace of any discussion in society. In Germany in 2009, this situation caused key institutions of media education to create a “media education manifesto” calling for the development of a “reflective use of media in leisure time, school and work” to be integrated firmly into all areas of education. In Switzerland at the end of 2012, the “Jugendsession” (a political platform for young people in Switzerland) in Bern called upon the Swiss federation to integrate the teaching of media competency into its educational mandate. Both cases deal primarily with the issue of how to use media in a knowledgeable and responsible way – the risks and opportunities of using the Internet from a pragmatic point of view. You have to know how to read Google’s ranking list, when downloads and uploads violate copyright laws, and how to announce private parties on Facebook, so that a whole army does not suddenly turn up on your doorstep. Some of the first initiatives have titles such as “media pass”, “media license” or “surf certificate”.

“Our tools shape us”

This traffic law metaphor may seem fitting, but only as long as it addresses efforts to achieve efficient, smooth running traffic on the information highway and if the question “What sorts of things can I do with the new media and how do I do that correctly?” is not followed by the question “What is this media doing to me?” The endeavor to achieve media compe-

tency is only halfhearted if not accompanied by the ability to reflect *upon* media. For according to the founding thesis of media studies, media create culture and therefore have their own message independent of content, as Marshall McLuhan, Spiritus Rector of Media Studies in Toronto, expressed it: “For any medium has the power of imposing its own assumption on the unwary.” This technologically-based perspective is rightly contradicted by the anthropological point of view with the reference that social practices are always also expressed in the media. This is all the more true of the principle of participation that comes with Web 2.0: It is powerless without its users and only becomes what it is through its mass daily use. At the same time, Web 2.0 is an example of McLuhan’s second thesis: “We shape our tools, and thereafter our tools shape us.” It was when it had a billion users that Facebook became a broad platform of communication and self-presentation, from which, however, neither the individual nor institutions such as museums or universities can subsequently escape unscathed.

Against this background, it would be disastrous if the very society that defines itself as a media society were to not explore the issue of which cultural values and social norms its new key media creates or negates, and how we should view this. It would be disastrous to not also conduct this discussion in the very place where socialization plays a decisive role as a supplement to the family and mass media: at school and initially rather than ultimately at university.

We can rightfully assume the first point of contact for such a discussion is the very discipline that has declared the history, functioning and effect of the media to be its very subject. The fact that an Institute for Media Studies was founded at the university of Basel at the beginning of the century reflects the necessity to provide our media society with reflective knowledge about itself. Meanwhile, the Faculty of Humanities has identified digital studies as the focal area of the Faculty, and the Department of Media Studies has made digital media studies the centerpiece of its profile development. Both of these initiatives testify to the will to make dig-ital media not only a tool but also a subject of research – two approaches that are each indispensable for the future of the humanities, but which have entirely different perspectives.

Digital Humanities

Digital media have been a tool of research in the humanities for some time in the field of digital humanities, which after its life in the shadows of library science in the USA is now treated as an institutional means to secure the future of the humanities and, in this country, is also meanwhile considered a guarantor for third-party funded projects. Its central aims are the application of digital processes and resources for text and image analysis, large data mining and data visualization. In this regard, the University of Basel is already active, for ex-

ample with the English Department’s HyperHamlet database of variations on quotes taken from Shakespeare’s Hamlet (www.hyperhamlet.unibas.ch) and the Art History Department’s SALSAH project on image annotations (www.salsah.org).

Digital Humanities is first of all what the name suggests: computer-supported humanities. This leads to some excited talk about an empirical change; others are concerned about an onslaught of positivism and a rise to power of the nerds in the humanities. The debate about the role algorithmic processes of analysis should play within the humanities is ultimately a debate about the role of the humanities in society. Do we expect objectivizable knowledge of them or does their function within a social system consist of correcting the positivistic paradigm of the natural and engineering sciences with the principle of ambiguity – as the philosopher Odo Marquard postulated 30 years ago in his essay “On the inevitability of the humanities”?

More recent views within digital humanities emphasize that “distant reading” (the reading of large quantities of data using algorithms) does not necessarily mean the end of interpretation. It might even indeed have a synergetic effect if recognized frequencies (for example, of words, topoi, images) and structural characteristics can generate new questions, which in turn can be treated in different ways. The next few years will show whether the humanities’ “Quantitative Turn” can be moderated in its tradition of hermeneutic interpretation, or whether the humanities will be reformed into a pragmatic “Mercantile Knowledge Regime” which abstains from criticism – as feared by the panel on “The Dark Side of the Digital Humanities” at the Modern Language Association conference at the beginning of 2013.

Digital Media Studies

As an instrument of research in the humanities, digital media have not yet been exposed to the particular kind of reflective treatment that was emphasized as a necessity at the beginning of this article. The key question and formulation for this is: “Digital thinking: How is the digital revolution changing our lives?” – which was the title of a conference held by the German Association of University Professors and Lecturers (Deutscher Hochschulverband – DHV) at the end of 2012 and testifies to the increasingly academic topicality of the subject. The question quite naturally addresses all disciplines in the humanities, because digital media are not only changing our way of thinking and methods of communication but also the way in which we deal with literature, art, history, religion and politics. Accordingly, all departments of the Faculty of Humanities are essentially confronted with new aspects of research.

The topics in *Sociology* are evident and have been explored for some time in a variety of ways: The altered concept of friendship due to online social networks; Facebook as a place of (self-)presentation and (of) assessment; the permanent

and ephemeral nature of communication; cyber-bullying, data protection, remix and participation culture etc. *Linguists* have also known for a long time about innovations brought about by media in their field: writing into being, communication using 160 characters or less, written orality, emoticons. *Literary studies* scholars can connect current new media text formats and features – interactive, multimedia, hypertextual, computer-generated – with historical experiments and will have to discuss the future of literature under the conditions of multi-tasking, self-publishing and “social reading”.

New key words for *Art History* alongside aesthetic participation are surely bio- and information art, and the trend of obscuring the difference between applied engineering, sociology and art. For *historians*, the Internet and Web 2.0 are appealing as a mega archive(s) and source(s) of crowd historiography. In *Religious Studies*, topics of interest are on-line confessions, the cult of Apple, cybermystics, the Google “eye” and, of course, the tweeting Pope. Research in *Political Science* will examine how democratic the new media are in light of online petitions, shit storms and slacktivism. Finally, *philosophers* will be able to extend the data protection debate beyond the economic and political focus and, from a cultural studies perspective, link Mark Zuckerberg’s utopia of a transparent society with the tyranny of intimacy in Jean-Jacques Rousseau’s “Confessions” – as Byung-Chun Han, postdoctoral researcher at the Philosophy Department at the University of Basel until 2010, recently presented in his book “The transparent society”.

Interdisciplinary cooperation in practice

It is understandable that media studies, as a subject area, has neither the methodological nor the personnel resources to be able to discuss all of the noted and also unmentioned social, political, aesthetic etc. implications of the new media independently. Its familiarity with digital media and digital media studies equips it more for a role as faculty-wide inspirer and initiator, helping to identify new aspects of research and organize interdisciplinary cooperation. Thereafter, the expertise and ongoing support of the respective faculty coordinator is required.

Thus, new media present a challenge to the working practices in the humanities: Interdisciplinary discussions are required and joint seminars advisable. It is hoped that this will happen over the next few years. A start has already been made with the establishment of the working group on “digital media studies” at the Faculty of Humanities. Its aim: to explore intersecting areas of interest and initiate joint projects. A series of lectures in Fall Semester 2013 will provide the first such opportunity not only for the Faculty of Humanities, but for all students and employees of the University. These lectures will examine how digital media are changing our lives and the new research questions that arise from the perspective of various disciplines in the humanities.

The intention is also, of course, to make research and discussion beyond the campus useful and essentially – as modules of media reflection competency – to weave it into ethics, art and literature teaching in schools. This is done entirely in the spirit of outreach, another promising concept originating from the USA, which seeks to link the academic world more closely with its surrounding communities. Success will not simply be measured by number of new English words learnt: Anyone who can translate the neologisms listed at the beginning is doing well, but better still are those who are also capable of discussing these concepts from the perspective of cultural studies or the humanities.

Roberto Simanowski is a professor at the Department of Philosophy and Media Studies at the University of Basel and the editor of the online magazine *dichtung-digital.org* and the Mewi blog at the *TagesWoche* (<http://blogs.tageswoche.ch/de/blogs/mewiblog>).



Book about the paper

The turbulent history of a media company: The amalgamation of the Basler Nachrichten and the National-Zeitung at the end of 1976 was Switzerland's first major newspaper merger. For years, this "monopoly paper" was attacked from both left and right, but it was initially a successful business. The group expanded rapidly during the 1990s following the acquisition of a publishing company with its own printing house, but it soon found itself weighed down by its many different involvements. Recession and the crisis in the newspaper industry took their toll on the struggling business, which was sold to a bank before being incorporated into a holding company whose ownership was constantly changing hands. This book provides a detailed account of the ups and downs of a firm that started life as a solid family business, grew too fast and risked its very existence as a result, finally ending up as a political football. The subject is examined from two different angles. First, the historical section of the book describes the challenges that confronted the paper over the course of its history. In the second part, ten guest contributors – media personalities and experts on the Swiss media scene – give a personal view on these events and their background. The volume is edited by Dr Walter Rüegg, the former publisher and director of Swiss Radio's German-language service, who is currently a lecturer at the University of Basel. It also includes contributions by three young researchers from the Institute for Media Studies, Christina Klausener, Rahel Walser and Dominic Wirz.

Walter Rüegg (ed.), *Herausgefordert. Die Geschichte der Basler Zeitung*. 352 pp., 57 ill., paperback (also available as an e-book). Christoph Merian Verlag, Basel 2012, 34.00 CHF.



Oil dependency

The world's oil reserves are limited. People have been debating the issue for decades, and now the global struggle for this "black gold" is intensifying. The Basel historian Daniele Ganser provides a fascinating overview of Europe's dependence on oil and, for the first time, traces the history of the oil industry from its beginnings around 150 years ago up to the present, critical situation. The book sheds light on questions such as the influence of oil on the course of the First and Second World Wars, how cheap energy fuelled the economic growth of the post-war years, the oil crises of the 1970s and the ongoing conflict over oil in the Middle East. The author's finding that worldwide production of conventional oil peaked back in 2005 caused something of a stir, yet oil consumption currently stands at 88 million barrels a day. In Great Britain and Norway, Europe's two most important producers, output has fallen sharply, and it is also declining in Indonesia and Mexico. What course will energy policy take in the future? To what extent can oil be replaced by hydroelectric power and by solar, wind and geothermal energy? Can biofuels plug the gap? The author illustrates the links between oil production, resource planning and military conflicts – including the Iraq war and the Libyan conflict – and poses questions for the future. Ganser, who has been working on this topic for about a decade (cf. UNI NOVA 115/Sept. 2010), is a research fellow at Basel University's Sociology Department.

Daniele Ganser, *Europa im Erdölrausch. Die Folgen einer gefährlichen Abhängigkeit*. 416 pp., paperback. Orell Füssli Verlag, Zürich 2012 (2nd edition), 34.90 CHF.



The circumcision debate

In the spring of 2012, Cologne Regional Court declared the religious circumcision of a 4-year-old Muslim boy a criminal offense, following the development of complications. In accordance with the ruling, the tradition by which parents have hitherto had their sons circumcised, must yield to the inviolability of the child. This ruling sparked off a heated debate in many countries and occupied the attention of the media, the public and politicians for months on end. In the author's opinion, this ruling also puts the current state of peace in European society with its religious minorities on the line. He examines the mechanisms and the problematic nature of this debate from the particular perspective of German society's relationship with the Jews. In his own words, the author claimed that in his publication he set out to appeal against the "thoughtlessness of circumcision opponents" and against the "voicelessness on the part of the Jews". What was noticeable about the public debate was that those concerned, namely the Jews and the Muslims, felt completely cornered. Further to his description of the discourse, which he characterizes with the words "nationalization", "colonization" and "projection", the author provides a brief religious and cultural-historical overview of the Jewish circumcision ritual. In Judaism, circumcision – the removal or shortening of the male foreskin – represents entry into the bond with God; for Muslims, it denotes a person's religious persuasion. Professor Alfred Bodenheimer is Professor of Jewish Studies (religious history and literature) at the University of Basel.

Alfred Bodenheimer, *Haut ab! Die Juden in der Beschneidungsdebatte*. 64 pp., paperback (also available as an e-book). Wallstein Verlag, Göttingen 2012, 17.90 CHF.

Christian Tschudin



Professor Christian Tschudin has been Professor of Computer Science at the Department of Mathematics and Computer Science, University of Basel, since 2002. He currently heads this department and also leads the Strategy Commission for Information Supply and Information Technologies (SIVIT) at the University of Basel. He represents the University at a national level on the council of the Switch Foundation, an organization that provides Internet access (and much more) to Swiss universities. Born in 1961 and raised in Basel, he studied here majoring in Mathematics, Physics and Sociology. He then concentrated on Computer Science and completed further study at the University of Geneva leading to a PhD awarded in 1993. He worked as a Research Associate and Senior Research Associate for Computer Science at the universities of Geneva and Zurich, afterward spending a year as a postdoc fellow at the International Computer Science Institute in Berkeley (USA). From 1998 to 2002, he was a full-time Associate Professor in the Department of Computer Systems at Uppsala University (Sweden). His teaching focuses on computer networks, operating systems and theoretical computer science. In his research, he deals with Internet technologies, above all the use of mobile programs in software-defined networking (SDN), packet dynamics and content-centric networking (CCN).

Wired

<http://wired.com/>

Reports in-depth stories about computer trends, gadgets and personalities in the high-tech industry. Reconstructed cyber attacks, a feature about an old Soviet system to autonomously trigger a retaliatory strike, and the current password crisis are given an exciting spin. The print version stands out due to its graphics. The Wired reading app for the Kindle Fire surprises with its innovative navigation and, despite only having a screen at their disposal, readers can leaf through pages almost as though reading the printed magazine.

Techcrunch

<http://techcrunch.com/>

The rumor mill of Silicon Valley, where even the Neue Zürcher Zeitung (NZZ) gets its scoops for its online digital column – so why not read straight from the source? Start-ups, venture capital and disruptive technologies are all but worshipped, and its Crunchbase is the database for all Facebook wannabes. For some light entertainment, read the gleeful comments on the battle of the titans (Google, Amazon and Apple).

Quartz

<http://qz.com/>

A new online newspaper format that has devoted itself to thematic “obsessions”. Topics are followed over a period of months (current examples include “Energy Shocks”, “Euro Crunch” and “Digital Money”), although perhaps not as incisively and eloquently as in The Economist. Certainly a welcome addition to the Web.

Software-Defined Networking

<http://sdncentral.com/>

If you want to observe the current networking revolution at close quarters, SDN Central will serve you well. This technology has not yet come to Switzerland and won't be available for end customers here for a while yet. However, Google uses SDN to operate its core network, VMware recently bought up SDN start-up Nicira for one billion Swiss francs, and SDN is putting market leader Cisco under pressure: The lines are currently being redrawn in the networking market.

Nerd News

<http://slashdot.org/>
<http://theregister.co.uk/>

The classics for nerd news are always good for keeping your finger on the Internet pulse; but I haven't been to these sites much lately.

UNI NOVA general

Most appealing

While browsing the Internet for information on evolutionary developmental biology, I came across the website of the University of Basel and specifically your issue on “Darwin and Evolution” from March 2009. I really like the UNI NOVA magazine and downloaded a few issues for myself as PDFs. This is a most appealing approach to communications work.

Johannes Windhövel
 (Germering, Germany)

UNI NOVA 120

(September 2012),
 focus on “Teeth”

Creating understanding

This edition is an ideal way to create an understanding of the work and focus of Basel University against the backdrop of the project to bring together university dental medicine with the non-private dental clinics in the area. We will distribute a copy of this issue to every dentist and each dental practice in Basel. At the same time, both dental technology and the general administration of dental services will be able to benefit from the excellently compiled overview.

Dr Peter Wiehl,
 director of non-private dental clinics
 in Basel

**Natural Sciences and Gender
Spring Semester 2013**
Series of interdisciplinary lectures on natural sciences and gender, organized by the Center for Gender Studies.
Wednesdays, 6.15pm–8pm, held in lecture hall 001 of the University Kollegienhaus, Petersplatz 1, Basel.

**Pre- and Early History
March 26**
Pre- and Early History: "Exotic" subject or a medium of regional and European identity policy?
Public inaugural lecture given by Professor Brigitte Roeder, Professor of Pre- and Early History. 6.15pm, Museum auditorium (Aula der Museen), Augustinergasse 2, Basel.

**Aeneas Silvius Lectures
April 2**
On the Spirit of Giving – Philanthropy in the 21st Century
Lecture given by Professor Georg von Schnurbein, director of the Centre for Philanthropy Studies at the University of Basel, as part of the Aeneas Silvius series of interdisciplinary lectures on different facets of spirituality. 6.15pm, Kollegienhaus, lecture hall 115, Petersplatz 1, Basel. Further lectures: April 23, May 14 and 28.

**ECG and Depression
April 8**
ECG during sleep as biomarker of depression
Lecture given by Professor Dr Axel Steiger, endocrinology of sleep, Max Planck Institute of Psychiatry, Munich. Monday colloquia at the University Psychiatric Clinics (UPK Basel). 5pm–6pm, Direktionsgebäude, 1st Floor, lecture hall, Wilhelm-Klein-Strasse 27, Basel.

**Landscape
April 11**
"Ware Landschaft – Wahre Landschaft"
Lecture on commodities and the true landscape given by Hans Weiss (Kultur-Ing.), ETH Zurich, former director of the Swiss Foundation for Landscape Conservation (SL), organized by the Naturforschende Gesellschaft Baselland. 8pm, Cantonal Library (Kantonsbibliothek) Baselland, Emma-Herwegh-Platz 4, Liestal. Further lectures: www.ngbl.ch

**Tomorrow's Campus
April 12**
How do we shape the future? Developing tomorrow's campus. Public event to mark the conclusion of the LearnTechNet Project, ITSi (IT Services Integration in Learning and Teaching) at the University of Basel.
From 1pm–5pm, auditorium of the Kollegienhaus, Petersplatz 1. Basel. More information: <http://itsi.ltn.unibas.ch>

**Gaps and Spaces
April 23**
**Mind the gap!
On the place of space in literature.**
Public Habilitation lecture given by PD Dr Ladina Bezzola Lambert, associate professor in English Linguistics. 6.15pm, Aula der Museen, Augustinergasse 2, Basel.

**Women on Coins
April 24**
**Women in power?
Rulers and saints on coins.**
Lecture given by Dr Michael Matzke, Basel, organized by Circulus Numismaticus Basiliensis. 7.15pm, Haus zum Hohen Dolder, St.-Alban-Vorstadt 35, Basel.

**Politics in Ancient Greece
May 7**
Spatially conceived politics. On political discourse in classical Greece
Public inaugural lecture given by Professor Sebastian Schmidt-Hofner, assistant professor in ancient history. 6.15pm, Aula der Museen, Augustinergasse 2, Basel.

**Joseph Novel
May 29**
"Deep is the well of the past": Thomas Mann's Joseph novel
Evening event held at Basel University Library with Bernd M. Kraske, Eva Kraske and Thomas Held (Reinbek/Hamburg). 6pm–7.15pm (approx.), University Library, meet at the lecture hall, 1st floor, Schönbeinstrasse 18–20, Basel. Future evening events: www.ub.unibas.ch

**BIS
May 30**
Financial stability made in Basel – what are the tasks of the Bank for International Settlements?
Europe colloquium with Dr Ulf Lewrick, Bank for International Settlements (BIS). 6.15pm–8pm, Europainstitut, University of Basel, Gellertstrasse 27, Basel.

**The Spine
until February 2014**
**Spine:
Miracle construction or faulty design?
Twinges and tweaks in your back.**
Special exhibition at the Anatomical Museum, University of Basel, Pestalozzistrasse 20, Basel. Opening hours: Monday to Friday 2pm–5pm, Sunday 10am–4pm. Guided talks and workshops for the public. Admission fees: 5 CHF/3 CHF

Further information on future public events: www.unibas.ch > Events

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