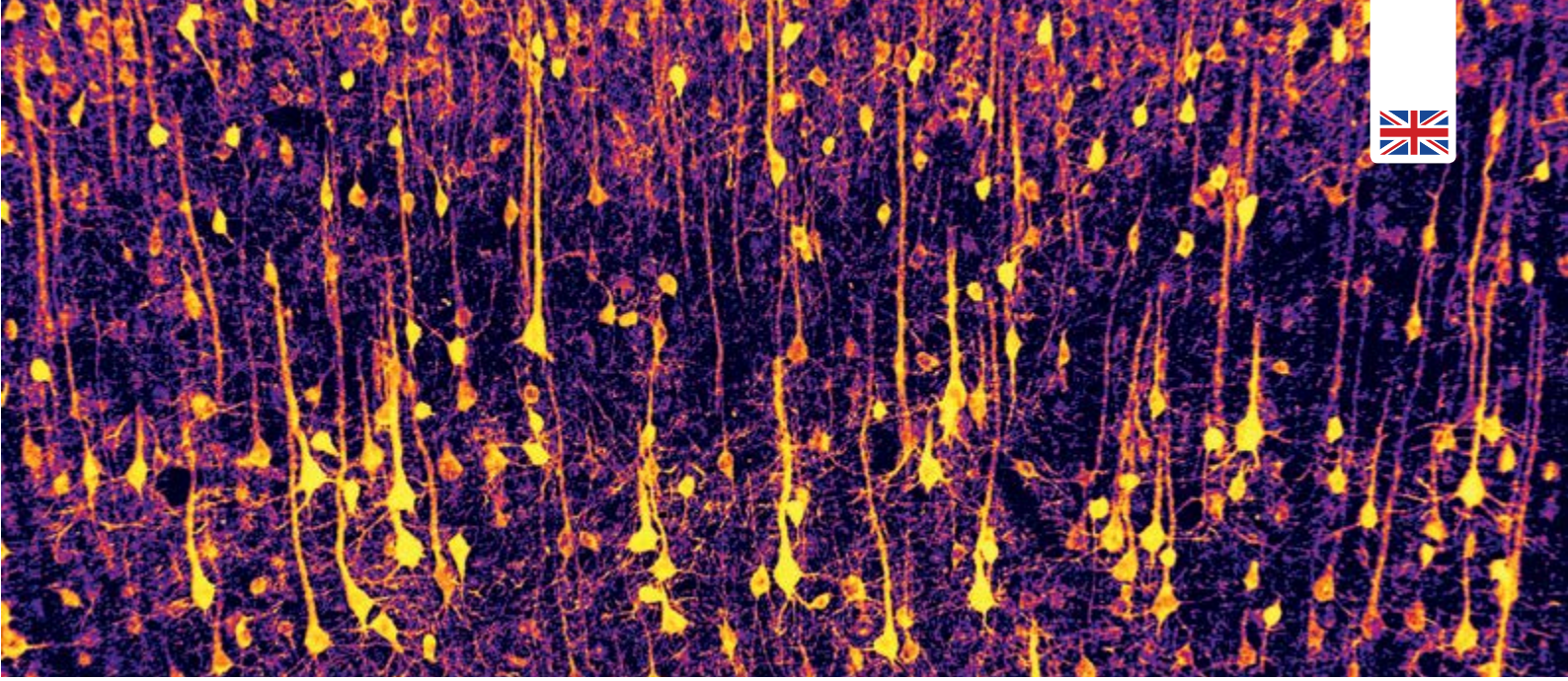

Forschung aus erster Hand | 02

Healthy Ageing

The up- and downside of caloric restriction for ageing and health

Besides improving the functionality of stem cells in mice, a caloric restriction also leads to a fatal weakening of their immune system – counteracting the life-lengthening effect of a diet.

Patients in completely locked-in state communicate

Researchers at the University of Tübingen could break through the silence of completely locked-in patients. Since they are able to hear, the researchers used oxygenation levels of blood in the brain to communicate with the patients.

Drug management of elderly patients with chronic myeloid leukemia

The German CML Study Group investigated the influence of age on the drug treatment on patients with chronic myeloid leukemia (CML). They suggest that the standard dose of 400 mg per day might be too low for elder patients.

Leibniz Healthy Ageing

Dear Readers

Silence – the thing that strikes one most upon walking into the room of a locked-in patient is the silence. But that does not mean that patients suffering from locked-in syndrome have completely lost the will to live. A team of Tübingen-based researchers have discovered a way for patients who are completely paralysed to communicate.

Alongside the University of Tübingen, Jena University Hospital also published an article in this issue of Healthy Ageing – Forschung aus erster Hand magazine. Here researchers examined how older patients suffering from chronic myelogenous leukaemia respond to drug-based treatment. The article reveals whether the elderly patients react differently from younger patients.

Of course, the current edition of the magazine also contains findings straight from the LRA Healthy Ageing: scientists at the FLI were able to prove that a low-calorie diet does not simply increase life expectancy, it can also have negative effects. Research carried out at the LIN investigated how a single protein can influence spatial learning.

Scientists from Japan and Germany will discuss all these topics during a workshop on Healthy Ageing to be held in Tokyo in late June. The two countries are confronted with similar problems relating to demographic change – scientists are determined to provide some answers about health, active participation and age-appropriate living. The current issue will give you insight into the fascinating discussions that we are anticipating in Tokyo.

We wish you a pleasant read!

Astrid van der Wall
Coordinator LRA Healthy Ageing

Imprint

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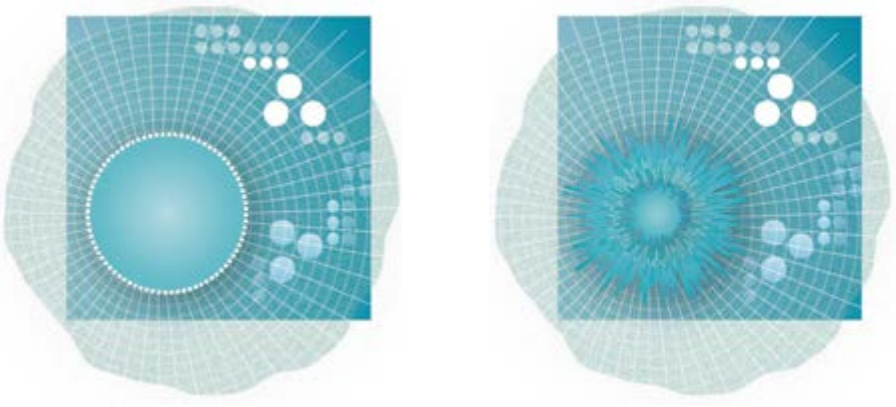
The up- and downside of caloric restriction for ageing and health

It's already well known that a diet may have a life-extending effect. Researchers from the Leibniz Institute on Aging - Fritz Lipmann Institute (FLI) in Jena/Germany, now showed that besides improving the functionality of stem cells in mice, a caloric restriction also leads to a fatal weakening of their immune system - counteracting the life-lengthening effect of a diet.

Only few years ago, researchers succeeded in prolonging the lifespan of worm *C. elegans*, fruit fly *D. melanogaster* and rats by almost 50 % through a simple caloric restriction – which immediately fueled hopes for having found one key to a longer life also for humans. However, transferring these results to long-lived primates shortly after was not equally successful and cooled down the enthusiasm quite quickly. Now, ageing researcher Prof. Dr. Karl Lenhard Rudolph, Scientific Director of the Leibniz Institute on Aging – Fritz Lipmann Institute (FLI) in Jena/Germany, and his team showed that caloric restriction even has a severe downside. In feeding experiments, the stem cells of mice, which were set on a diet, were found to age slower – but the murine immune system was almost completely cut down. Outside of optimal, sterile laboratory conditions, this could lead to severe live-shortening infections.



Compared to young stem cells (left), older ones (right) lose part of their functionality with every cell division. Long term caloric restriction helps to keep stem cells in their resting phase (quiescence) and, thus, slows down stem cell aging. Source: FLI/Maren Blaschke.

Caloric restriction slows down the ageing of blood stem cells

The study focused on the effects of caloric restriction on blood stem cells (so-called hematopoietic stem cells, HSC) that are responsible for building red blood cells or lymphocytes (immune cells). Like for any other adult stem cells, HSC functionality decreases with every single cell division – the stem cells age. This is why they stay in a resting phase (quiescence) most of the time and are only activated when a massive cell reproduction is required (e. g. after acute blood loss). In their study, the researchers in Jena investigated how a 30 % food restriction effects stem cell ageing in mice. One main result was that the HSC stayed in a quiescent state even if simulated stress would have required their activation. This effect was found regardless of how long the diet lasted. Thus, during diet, the blood stem cells did not age at all and their functionality to build new blood cells remained increased even one year after diet.

Caloric restriction weakens the immune system

But the long-term diet had a downside as well: The mice's immune system was almost completely cut down. Although the diet had no strong effect on the overall cell number of blood cells, the production of lymphocytes – needed for immune defense – was decreased by up to 75 %. As a consequence, mice were particularly prone to bacterial infections.

The results are not yet transferable to humans

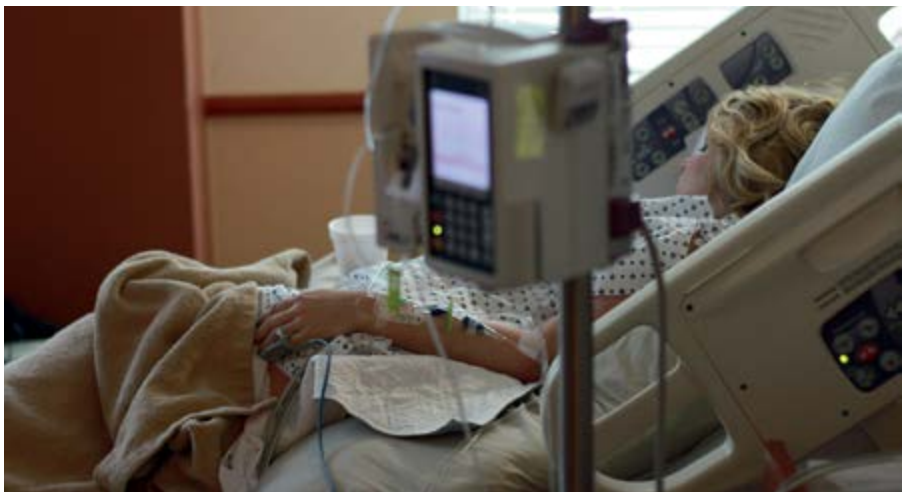
For many years, long term caloric restriction has been understood as an easy intervention to effectively slow down ageing. Results from Jena, however, now elucidate that diet is not only a weapon to fight for a longer life but rather is a double-edged sword.

„The study provides the first experimental evidence, that long term diet increases stem cell functionality, but results in immune defects in the context of prolonged bacterial infection, too. Thus, positive effects of a diet are not transferable to humans one to one", Rudolph sums up the study results. Even if – under laboratory conditions – ageing of single cells or tissues may be slowed down through a diet, the immune suppression may have fatal consequences in real life. To benefit from caloric restriction or medicinal mimetika aiming at increasing health in the elderly, possible risks of such interventions to come down with life-threatening infections remain to be elucidated. „In sepsis patients, we see a higher survival rate for those with a higher body weight than for patients who are very lean", Prof. Dr. Michael Bauer, Director of the Center for Sepsis Control and Care at University Hospital Jena (UKJ), concurs.

Original Publication: Tang D et al. (2016): *Dietary restriction improves repopulation but impairs lymphoid differentiation capacity of hematopoietic stem cells in early aging.* J Exp Med 213(4): 535-37. doi: 10.1084/jem.20151100. **Contact**: presse@leibniz-fli.de.

Patients in completely locked-in state communicate via metabolic brain signals and may end unbearable silence

Until now, it was impossible to communicate with a completely locked-in patient. Niels Birbaumer and some of his colleagues at the University of Tübingen/Germany could break through the silence. Since locked-in patients are able to hear, the researchers used oxygenation levels of blood in the brain to communicate with them. Between 70 and 90% of the answers were correct — and the patients signaled good life quality.



Locked-in patients are not able to use a single muscle. Breathing, eating, drinking - all have to be done by machines. When the locked-in state is comletely, they are not even able to move their eyes. Source: pixabay.com.

Only few things seem to be so unbelievable like the fate of a completely locked-in patient. The brain is totally disconnected from the body since no nerve signal reaches a muscle. The locked-in patient is condemned to absolute motionlessness meaning that he is not able to walk, eat, drink, go to the toilette, or even raise an arm. A locked-in state also means a total loss of communication. Speaking, mimic, gesture, all these things do not work without muscles. A completely locked-in patient cannot even move his eyes to communicate with his surroundings.

Locked-in does not mean valediction from all life

When all muscle activity is lost, the patient lies in his bed, without any motions, with artificial respiration, fed by a stomach tube. The mucous membranes run dry and the eyes are closed. The tactile sense does not work any longer and the patient does not sense any human contact. But in contrast to patients in a comatose state, the ears are still open. Locked-in patients are able to hear. They notice what family members, doctors or other persons are talking about. What a chance for scientists to get into contact with these patients.

Brain machine interfaces

Researchers headed by Niels Birbaumer at the University of Tübingen/Germany found a method to communicate with locked-in patients. Four persons with amyotrophic lateral sclerosis responded to short questions via changing the oxygenation- and deoxygenation-levels of frontal brain areas. Humans are able to feel the flow of blood in their vessels, even in the brain. The changes in oxygenation were registered by near infrared spectroscopy (NIRS). The locked-in state of the tested patients lasted from four months up to eight years. 20 to 60 short questions were asked each session. The patients answered with „yes“ or „no“. In advance, the scientists validated the oxygenation signals by asking questions with known answers. 16 to 60 sessions over several months assured an average correct response rate of more than 70 % to known and 90 % correct answers to open questions. All patients reported good quality of life. Open question answers were validated by stability over time, information of family and care takers. The results suggest that brain machine interfaces using metabolic signals may end the unbearable silence of completely locked-in patients.

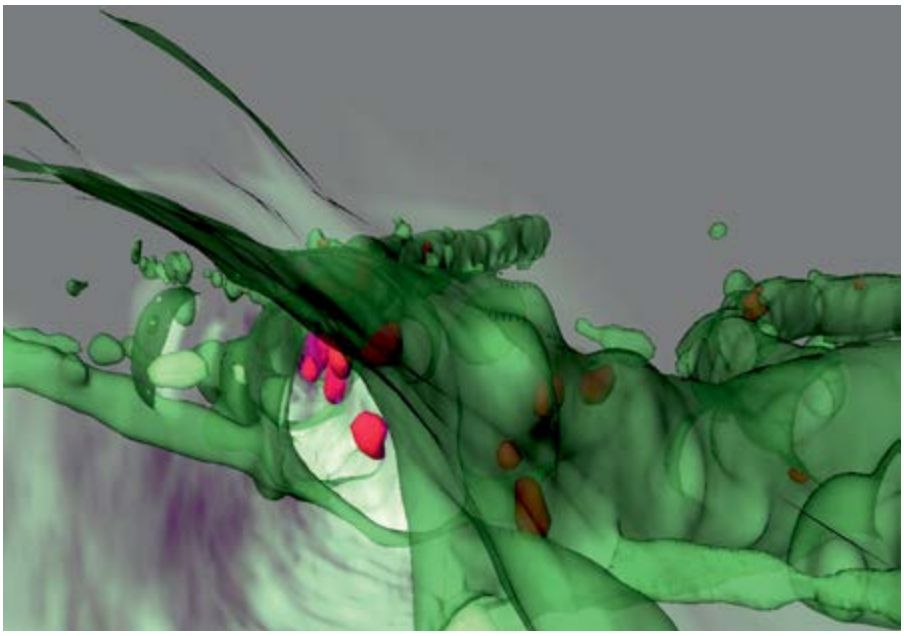
Original Publication: Gallegos-Ayala G, Furdea A, Takano K, Ruf CA, Flor H, Birbaumer N (2014): *Brain communication in a completely locked-in patient using bedside near-infrared spectroscopy.* Neurology 82(21): 1930-32. **Contact:** niels.birbaumer@uni-tuebingen.de.

Silence — the thing that strikes one most upon walking into the room of a locked-in patient is the silence. But that does not mean that patients suffering from locked-in syndrome have completely lost the will to live. It is a slow process in which the patient can get used to the catastrophe. Most patients suffer from illnesses like amyotrophic lateral sclerosis (ALS), multiple sclerosis (SM) or parkinson disease. In the beginning, most of the diseases are not recognized. Later on they become more obvious and get irreversible worse. There are no reliable studies about the number of completely locked-in patients in Germany or Europe. It is difficult to differentiate the completely locked-in patients from patients in a coma vigil. Maybe 3.000 patients in Germany are treated like they do not have any contact with their surroundings while they hear everything.

Neuronal protein influences spatial learning

Jacob is a neuronal protein that plays an important role as a mediator of signals between synapses and the cell nucleus. The Jacob protein was discovered in the late 1990s by Dr. Michael Kreutz at the Leibniz Institute for Neurobiology in Magdeburg/Germany. In a new study researchers from the LIN and the Otto von Guericke University Magdeburg show that Jacob influences hippocampus-dependent learning processes.

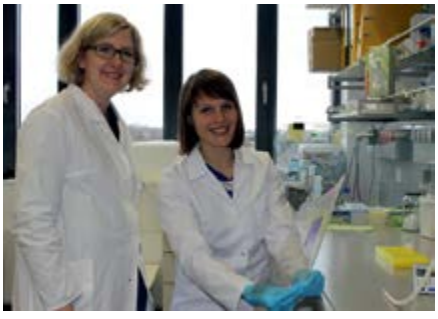
The human brain consists of billions of nerve cells that communicate via contacts called synapses. Within a synapse, around 1.000 different proteins regulate the proper transduction of signals coming from other neurons thereby influencing learning and memory processes. Some neurological and developmental disorders are caused by defective genes that code for synaptic proteins. One of these proteins is Jacob. A research team led by Dr. Michael Kreutz, head of the research group Neuroplasticity at the LIN, and his co-worker Dr. Christina Spilker have now further illuminated the function of Jacob within the brain. In their study the scientists investigated how Jacob regulates neuronal and synaptic plasticity and learning processes in the brain. During learning, and the formation of a memory trace, the activity of brain cells and neuronal networks is increased leading to structural changes and strengthening of the corresponding synapses that last over time. This process is called synaptic plasticity.



The figure shows a three-dimensional neuron (green) with phosphorylated Jacob proteins inside (red-purple). Source: LIN/Anna Karpova.

Spatial learning

The researchers showed that the morphology of the hippocampus, a brain region important for learning processes, is altered in mice deficient for the Jacob protein. Hippocampal neurons of Jacob knockout mice have a less complex anatomy and a reduced number of synapses compared to normal wild type mice and this influences the learning ability of the mice. In behavioural tests, the scientists analysed hippocampus-dependent learning and showed that Jacob knockout mice had deficits like e. g. in spatial learning experiments or in the object recognition test.



Unraveling Jacob's secrets: Dr. Christina Spilker (on the left) and doctoral student Katarzyna Grochowska in the lab.
Source: LIN/Sophie Ehrenberg.

Jacob influences Brain-derived neurotrophic factor (BDNF) signaling in the hippocampus

The growth factor BDNF plays a documented role in hippocampal synapse and dendrite formation during development. The Kreutz-group has shown previously that Jacob influences activity-dependent BDNF gene transcription. In the present study the scientists analysed the BDNF content of nerve cells from Jacob knockout mice during early postnatal development. Interestingly neurons from knockout mice had lower BDNF levels compared to control cells and this could explain the morphological alterations and learning deficits in the knockout mice. Application of BDNF to cultured nerve cells could rescue the morphological deficits in hippocampal pyramidal neurons devoid of Jacob.

Jacob as a candidate gene for a rare developmental disease

For a long time mutations in the Jacob gene were associated with the Kallmann syndrome, a rare developmental disease characterized by absence of puberty and the loss of olfactory sense. With their mouse model the researchers could now show that the absence of the Jacob protein does not result in symptoms related to the Kallmann syndrome but rather leads to hippocampal dysplasia as described above.

Original Publication: Spilker C et al. (2016): *A Jacob/Nsmf Gene Knockout Results in Hippocampal Dysplasia and Impaired BDNF Signaling in Dendritogenesis.* PLoS Genet 12(3): e1005907. doi: 10.1371/journal.pgen.1005907.
Contact: sophie.ehrenberg@lin-magdeburg.de.

Elderly patients with chronic myeloid leukemia might need another drug management than younger ones

The German CML Study Group headed by Prof. Dr. Andreas Hochhaus at Jena University Hospital/Germany investigated the influence of age on the drug treatment on patients with chronic myeloid leukemia (CML). The results suggest that the standard dose of 400 mg per day might be too low for elder patients. Using a double dose, nearly as many patients as in the younger control group survive five years.

Only twenty years ago, chronic myeloid leukemia (CML) could not be treated efficently. CML makes up about 20 % of all leukemia and becomes more frequent with age. The disease of the blood (hemato-poietic) stem cells in the spinal cord is typically diagnosed in a age between 60 and 65 years. The prognosis for the patients has changed dramatically since efficient stem cell transplantation and drug treatment is possible. Currently 83 % of the patients are alive ten years after their first diagnosis.

Efficient drug treatment

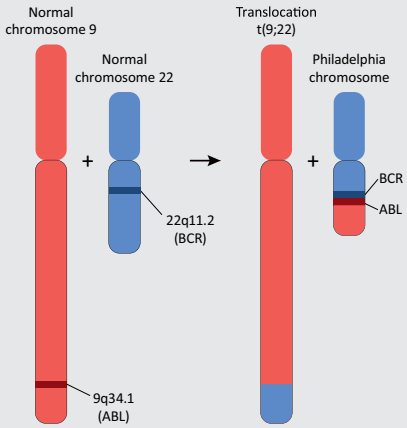
Besides other methods, CML can be treated with a tyrosine kinase inhibitor. In CML cells the tyrosine kinase, a protein which regulates cell divisions as explained in the grey box below, is always activated. That leads to an uncontrolled growth of cancer cells. In the correct dose, the tyrosine kinase inhibitor takes control over the cell divisions. In combination with stem cell transplantation in the spinal cord, CML can be treated efficiently in the early stages of sickness. Prior to these treatment possibilities, the age of the patients played an important role for their prognosis. Since the introduction of drugs, the influence of age decreased dramatically.

At Jena University Hospital patients with chronic myeloid leukemia are treated in the Day Care Clinic Oncology. Source: UKJ/Anna Schroll.

Other diseases are more important for quality of life

But what is the correct drug dose for which age? Older patients are more often affected by additional diseases than younger ones while suffering from CML. Such comorbidities influence the health-related quality of life in elderly patients. For older patients it is even more important to reduce drug doses quickly, to avoid interactions with the treatments of other diseases. Researchers headed by Prof. Dr. Andreas Hochhaus at Jena University Hospital/Germany wanted to know, how the dose of drug treatment influences the disease progression in younger and older patients. Sufferers in different age-groups got imatinib (an efficient tyrosine kinase inhibitor) either in a dose of 400 mg per day or in a dose of 800 mg per day. The allocated dose was then reduced step by step while controlling the cancer cells. The results were encouraging: Older patients with a starting dose of 800 mg per day achieved a good status as fast as younger ones. In contrast to the standard dose with which older patients got a good status much later. „We suggest that the optimal dose for older patients is significantly higher than the standard dose of 400 mg per day“, stated Prof. Hochhaus. „With a higher dose, the survival rate of older patients within five years was similar to that of younger patients.“

Original Publication: Saussele S, Krauss MP, Hehlmann R, Lauseker M, Proetele U, Kalmanti L, et al. (2015): *Impact of comorbidities on overall survival in patients with chronic myeloid leukemia: results of the randomized CML study IV.* Blood 126(1): 42-9. **Contact**: andreas.hochhaus@med.uni-jena.de.



The genetic information of humans is organized in chromosomes. 23 pairs of chromosomes are in every cell of us. The **Philadelphia chromosome** is a specific genetic abnormality in chromosome 22 of leukemia cancer cells. The chromosomal defect in the Philadelphia chromosome is a translocation, in which parts of two chromosomes, 9 and 22, swap places. The result is, that a fusion gene is created by positioning the ABL1 gene on chromosome 9 to a part of the BCR (break point cluster region) gene on chromosome 22. This reciprocal change of small chromosomal pieces creates an elongated chromosome 9 and shortened chromosome 22, the Philadelphia chromosome. The chromosome carries an oncogenic BCR-ABL gene fusion. The intact ABL gene expresses a protein, the tyrosine kinase, which plays an important role in the regulation of cell divisions. In contrast, the BCR-ABL transcript codes for a protein that is „always on“ or continuously activated, which results in unregulated cell divisions – cancer develops.

Leibniz Research Alliance Healthy Ageing starts cooperation with Japan

The population of Japan is ageing – just like that of Germany. Japanese scientists estimate that by 2030, 25.6 % of the country's population will be aged 65 and over. The Federal Statistical Office predicts that 34.6 % of Germany's population will be aged 60 and over by the same year. That means that Germany and Japan will be among the countries with the oldest populations worldwide. They will therefore need to rise to similar challenges: scientists are trying to find solutions to challenges relating to healthcare, pensions, active participation and age-appropriate living.

To this end, scientists from Germany and Japan will participate in a workshop on Healthy Ageing to be held in Tokyo from 20 to 22 June 2016, when they will discuss cognition research, stem cell research and spatial planning, among other topics. The workshop is being organised by the Leibniz Research Alliance (LRA) Healthy Ageing in collaboration with the Japan Science and Technology Agency (JST) and the Japan Agency for Medical Research and Development (AMED). "Through this workshop, the Leibniz Association will be able to further expand its key international collaborations," says Prof. Matthias Kleiner, President of the Leibniz Association. "The Japanese side has been adopting completely different strategies for dealing with certain areas of demographic change than we have here in Germany." To foster scientific collaborations with Japan, Dr. Iris Wieczorek – who is since many years also senior research fellow at the GIGA Institute of Asian Studies – is representing the Leibniz Association in Tokyo and offering advice to its member institutes. "Of course, we are hoping to get plenty of ideas for our own research and for future German-Japanese projects in age research," adds Prof. Dr. Lenhard Rudolph. Together with Prof. Dr. Jean Krutmann (Leibniz Research Institute of Environmental Medicine), Rudolph is speaker of the LRA Healthy Ageing and Director of the Leibniz Institute on Aging in Jena. The German Embassy in Tokyo is to foster budding binational projects in the field by hosting a reception where scientists, scientific organisations and public funding bodies will be able to meet and exchange ideas.

The **Leibniz Association** connects 88 independent research institutions that range in focus from the natural, engineering and environmental sciences via economics, spatial and social sciences to the humanities. Leibniz institutes address issues of social, economic and ecological relevance. They conduct knowledge-driven and applied basic research, maintain scientific infrastructure and provide research-based services. The Leibniz Association identifies focus areas for knowledge transfer to policy-makers, academia, business and the public. Leibniz institutions collaborate intensively with universities – in the form of "Leibniz ScienceCampi" (thematic partnerships between university and non-university research institutes), for example – as well as with industry and other partners at home and abroad. They are subject to an independent evaluation procedure that is unparalleled in its transparency. Due to the importance of the institutions for the country as a whole, they are funded jointly by the Federation and the Länder, employing some 18,500 individuals, including 9,300 researchers. The entire budget of all the institutes is approximately 1.7 billion EUR.

The **Leibniz Research Alliance (LRA) Healthy Ageing** is a network of 21 Leibniz Institutes complemented by renowned institutes in Germany and abroad. It brings together researchers from the fields of biology, medicine, psychology, education, sociology and economics. Their task is to research the factors that underlie the ageing process. They do this in interdisciplinary projects, an approach that allows them to investigate every aspect of healthy ageing, to collaborate on applying for projects, and to share resources and knowledge.

Japan Science and Technology Agency (JST) is one of the core institutions responsible for the implementation of science and technology (S&T) policy in Japan, including the government's S&T Basic Plan. JST takes a leadership role in developing both Japanese and global S&T as an innovation navigator, from knowledge creation – the wellspring of innovation – to ensuring that the fruits of research are shared with society. JST undertakes its mission in a comprehensive manner, also providing a sound infrastructure of S&T information and raise awareness and understanding of S&T-related issues in Japan.

The **Japan Agency for Medical Research and Development (AMED)** engages in research and development in the field of medicine, establishing and maintaining an environment for this R&D, and providing funding, in order to promote integrated medical R&D from basic research to practical applications, to smoothly achieve application of outcomes, and to achieve comprehensive and effective establishment/maintenance of an environment for medical R&D.

Prof. Dr. Bernhard Müller will talk about urban development in ageing societies

Prof. Dr. Bernhard Müller will talk in the Abbe-Zentrum at the Beutenberg in Jena on Thursday, September 1, 2016, 16:00 h. He is director of the Leibniz Institute of Ecological Urban and Regional Development (IOER) in Dresden/Germany. His subject will be the effects of ageing societies on urban and regional development. His presentation is part of the lecture series Science & Society. The talks in this series are organized by the Leibniz Institute on Aging (FLI) and the Leibniz Research Alliance Healthy Ageing twice a year. They widen the biomedical ageing research focus of Jena by social and societal aspects. The event is free and open to the public.

Prof. Dr. Bernhard Müller is a leading German researcher and policy expert in the fields of regional planning and development. Currently, as a member of the Habitat III Policy Unit "Urban Spatial Strategies: Land Market and Segregation", he is preparing the 3rd United Nations Conference on Housing and Sustainable Urban Development in October 2016. Source: IÖR.

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