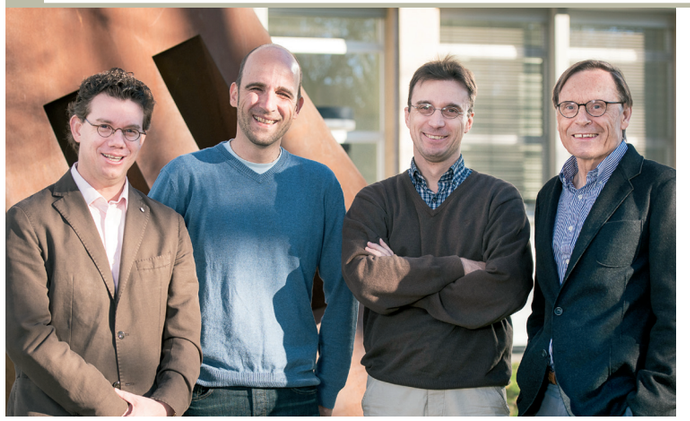
ing and further fuelling the strategic partnership between the universities of Freiburg and Nagoya as represented by FRIAS and the Nagoya Institute for Advanced Research, respectively. What is particularly satisfying about the various formats for group research at FRIAS is the large number of top quality applications from the University of Freiburg and/or its strategic global partner universities. This funding format thus falls on very fertile ground, which is something that was to be expected from excellent research universities competing with the best universities in the world, but it is reassuring to see that this expectation is really borne out. FRIAS thus shows its strategically important role in promoting individual and group research formats, on the one hand, and giving a new quality to research cooperation with international premium-partner institutions of the University of Freiburg, on the other hand.

But FRIAS would not be a proper Institute for Advanced Studies if research collaboration happened only top down. Besides such official funding formats as sketched above, which come with official applications, fixed time schedules and extensive peer-review processes, it is fantastic to see that group research can also emerge bottom-up, quite simply through FRIAS fellows identifying shared thematic and methodological interests and defining interfaces for joint activities. A case in point this academic year is the interdisciplinary research group on the topic of "Inequality" that has emerged at FRIAS, formed by fellows from disciplines as diverse as Criminology, Sociology, Anthropology, History or Cultural Studies (see the article on pp. 12-13). It is activities like these that demonstrate the added value an international research college such as FRIAS has to offer. The fact that the emergence of such bottom-up activities does not have to be left to pure chance can be exemplified by the extremely successful experiment of a joint FRIAS retreat in the Black Forest right at the beginning of the current academic year (the 2nd weekend of October). The primary objective of this joint undertaking was to speed up the community building process between the new fellows and members of the project groups, with a particular focus on bridging the cultural gap between the humanities and social sciences, on the one hand, and the natural and life sciences, medicine, and engineering, on the other. (Some impressions of the retreat can be found on p.34.)
You see: FRIAS is not running out of ideas for innovations and optimizing existing formats and practices!

Bernd Kortmann
Speaker, FRIAS Board of Directors

RESEARCHING CELLULAR CLEANERS
FRIAS PROJECT "MEMBRANE TRAFFICKING IN AGEING AND DISEASE"



v.l.n.r.: Prof. Dr. Tobias Huber; Prof. Dr. Jörn Dengjel; Prof. Dr. Stefan Eimer; Prof. Dr. Klaus Aktories

When complex systems age, defects become more likely – in this respect, cells and technical components are not so very different. But biology has a distinct advantage over technology: Not only do cells make use of a large number of mechanisms to monitor and control the quality of their components, they can also draw upon a broad range of repair processes. It is only when these processes cease to function optimally that diseases appear – in particular, cancer and heart disease, but also diseases that stem from the degeneration of the nervous system, such as Alzheimer's and Parkinson's.

One specific repair process is known as autophagy or autophagocytosis. The word is derived from the Greek, combining the words for "auto" (self) and "phagein" (to eat). Accordingly, autophagy is an intercellular process in which cellular waste is broken down so that it can later be used to create new structures – in other words, it is a form of cellular recycling.

To stick with the technology comparison, someone is needed to collect the rubbish within the cell and someone is needed to dismantle it. Autophagosomes are responsible for collection, using their double membranes to envelop proteins and protein aggregates as well as cell organelles and infectious organisms. In effect, they serve as the cell's rubbish bins. Lysosomes are then introduced to dismantle the material. Lysosomes are cell organelles that contain digestive enzymes, which allow them to enclose the material to be disposed of and then break it down into its individual proteins.

Once the components have been separated in this manner, they are available to build new organelles within the cell. This process is used not only to break down the cell's own ageing functional units, but also to dismantle biogenic foreign bodies, in other words bacteria and viruses.

Unfortunately, this sophisticated system does not always work flawlessly, and over the course of a lifetime, an individual's cellular repair functions begin to weaken. The reasons for this have not yet been conclusively established. Do the control and repair mechanisms lack sufficient capacity, allowing unprocessed materials to accumulate over time? Is there damage in the cell organelles that the repair troops cannot detect? Or do individual actors perhaps send contradictory signals as part of this complex interaction?

The current FRIAS Research Focus, "Membrane Trafficking in Ageing and Disease", is seeking answers to these questions. The group comprises representatives of various faculties at the University of Freiburg: Jörn Dengjel is a dermatologist, Klaus Aktories a pharmacologist and toxicologist, Stefan Eimer a cell biologist

FRIAS Junior Fellow Dr. Manuela Antonioli at work

and Tobias Huber a nephrologist. The group's goal is to develop a better understanding of fundamental biological mechanisms, thereby creating a foundation for new treatment approaches that make healthy ageing possible. FRIAS is funding the project for a year. From 29–31 January 2016, the group organized an international conference on autophagy that drew renowned researchers from around the world to Saigerhöh in the Black Forest in order to discuss the latest developments and results in autophagy research.

The principles of autophagy have been known for forty years, but scientists have only recently begun to understand its full complexity. Today, for example, we know that membrane trafficking plays an important role in the process, because membranes determine whether or not the order to recycle is transmitted to the cellular cleaners in each specific case.

In order to understand membrane trafficking, it is necessary to take a closer look at the tasks that membranes perform. Membranes divide the cell into functional units, so-called compartments, and separate the interior of the cell from the organelles, such as the nucleus or the mitochondrion, the powerhouse of the cell. Membranes also transport molecules within and between cells, so that nutrients can be accumulated, and they trigger signals and transmit these signals between the functional units.

In this way, membranes prevent unwanted substances from infiltrating the various compartments of the cell – that is, if everything goes according to plan. However, now we know that various age-related diseases have one thing in common: They are all triggered by defects in membrane trafficking processes, and they often express themselves through the abnormal accumulation of biomolecules and organelles in the cells. This means that when membrane trafficking processes fail, autophagy no longer functions properly.

"Up until 10 or 15 years ago, scientists still thought that there was no way to influence membrane trafficking, but now we know that it is possible", says Jörn Dengjel. The focus is on the so-called Rab proteins, which control membrane trafficking between specific compartments.

It has since been shown that an active autophagic process contributes to the longevity of cells and thus of the whole organism, and conversely, that reduced autophagic activity leads to faster ageing. In light of this, the idea of stimulating autophagy, in other words the cleaning process within the cell, seems obvious. This would allow scientists to attempt to fundamentally slow down the ageing process, because in some cell types, ageing has a clear effect on functionality. Across the population, for example, the kidney loses an average of roughly one percent of its functionality for every year of life.

If external intervention into the cellular recycling processes were possible, several additional treatment options would open up. For example, the activation of cellular recycling could be used to block tumour growth during an early stage of cancer. An impulse that stimulates recycling processes could also have a therapeutic effect on the degeneration of nerve cells. The critical question is therefore: Which processes are suited to control the recycling of cellular waste? This is particularly important for cells such as nerve cells that no longer divide.

There are three known triggers that prompt cells to initiate recycling. The first are internal cellular maintenance processes. Secondly, a nutrient deficiency may be responsible, because the reduced availability of amino acids prompts increased processing of old cell components. One can think of this as functioning much like a resource-based economy: When a resource becomes scarce, recycling increases in order to recover the resource from waste material. Provided it does not cause any explicit deficiency symptoms, a reduction in nutrient supply can therefore slow cellular ageing.

The third aspect involves infections. When fighting bacteria and viruses, the recycling process is an especially important component of the innate immune system. Today, we are aware of ten different bacterial toxins that can trigger autophagy.

Scientists are therefore also asking how autophagosomes come to be formed. We know that this process is controlled by genes – scientists have identified more than 30 genes that trigger autophagy and can therefore stimulate the breakdown of waste materials within the cell.

However, many questions remain unanswered. For example, which factors determine where cellular rubbish collectors develop? How do they identify the substrates that require disposal? How does the process of autophagy adjust to various stress conditions within the cell, such as a lack of nutrients? Which molecules – known as cellular effectors – determine the capacity of the recycling process? And more generally, which causal relationships exist between age-related changes in the autophagic process and changes in other cellular structures and mechanisms?

We now know that an enzyme known as mTOR, which is present in all mammals, plays a key role in this process. mTOR (the abbreviation for mechanistic target of rapamycin) is a critical enzyme for controlling the survival, growth, multiplication and mortality of cells. Rapamycin is a substance that is obtained from bacteria and indirectly binds to mTOR, inhibiting the enzyme's function. Since mTOR blocks autophagy, it follows that rapamycin promotes cellular recycling.

mTOR functions by adding a phosphate group to several other proteins or enzymes, thereby activating signalling molecules. By removing the marker, mTOR can also deactivate these molecules. The substance is thus the first step in a cascade of signalling pathways and is consequently of particular interest to researchers.

On the basis of individual components such as these, scientists are attempting to generate a complete picture of the autophagic process. It is now known, for example, that a lipid called LC3 is stored in the proteins before the process of autophagy begins. The same mechanism has been observed with the ATG8 protein in yeast. Yet here, too, the exact mechanisms remain unclear.

A complex field, which raises the question of how research should best proceed. The Freiburg scientists are drawing upon various organisms and cell cultures. Yeasts are always practical test objects, but cultivated cervical cancer cells, so-called HeLa cells, have also become a standard research material. In addition, the researchers are conducting experiments on mice and the thread worm Caenorhabditis elegans (the model organism par excellence).

In pursuing its research, the working group is turning to modern methods of analysis. "For example, we're using mass spectroscopy," says Dengjel. Different modelling systems and molecular biological and protein biochemical approaches are available that make it possible to simultaneously identify and measure changes to the molecules in the cell in their entirety. Among these are the so-called omics methods, namely a range of processes which all end in the aforementioned suffix – from genomics to metabolomics to lipidomics.

The first steps toward a medication based on research results have already been taken. According to initial studies, administering the natural substance spermidine, which is found in soy and wheat, can slow age-related memory loss. Though a corresponding medication does not yet exist, researchers believe in the substance's potential. Perhaps it is the first of many that will allow for targeted control of cellular cleaners in the future.

(bj)