Editorial

Dear Biozentrum Alumni,

We are pleased to introduce you, once again, to two Biozentrum Alumni; Tobias Pauli, a specialist in ophthalmology and eye surgery, who already looked deeply into other’s eyes during his Biozentrum days – back than it was flies’ eyes – and Kathrin Thedieck, Professor of Metabolic Signaling, who is working across the Dutch-German border.

Alumninews also talked to Richard Neher, who recently joined the Biozentrum as a new Professor of Computational Modeling of Biological Processes. He gives us an insight into his online tool “nextstrain.org” for which he has just been awarded the Open Science Prize, his research on influenza and other viruses and his new joint project investigating the spread of hospital germs together with Adrian Egli, from the University Hospital Basel, who himself reports on his investigations.

We wish you enjoyable and interesting reading.

Prof. emeritus Hans-Peter Hauri,
President of the Biozentrum Alumni Board

Prof. Erich Nigg,
Director of the Biozentrum and Member of the Alumni Board
Alumninews You studied medicine in Basel. What brought you to ophthalmology?

Tobias Pauli This resulted from my time at the Biozentrum. My PhD project in Walter Gehring’s lab was on eye development. At the time, he had the idea to study a human eye disease, macular degeneration, using the fly model. There were also ophthalmologists involved in this project and this attracted my interest in this profession. After completing my dissertation, I soon found a position at the Eye Clinic of the University Hospital in Basel.

An Why did you decide to do a PhD?

TP After finishing my studies, I didn’t want to immediately start working in the hospital. Through the practical courses, I realized that I was interested in research and so I looked around for interesting projects. I had already read many things about Walter Gehring’s work and ectopic eyes. And so one thing led to the other and after a meeting with Walter Gehring the matter was settled.

An How did you experience Walter Gehring and his research at that time?

TP I can still vividly remember my first meeting with him. Walter Gehring stood before me with chalk in his hand, describing the eye project and explaining this with drawings of interactions and some diagrams on the blackboard. His enthusiasm for research and how he inspired others fascinated me totally. And he seemed to just bubble over with ideas.

An And which idea finally developed into your PhD project?

TP In the first project, I wanted to examine the human gene which was responsible for the hereditary form of macular degeneration, using the fly as a model. Unfortunately, the fly was unsuitable for this. And so I carried out my dissertation on a classical eye development project. At the beginning, it was totally exciting for me, when my colleagues introduced me to crossing flies and then how to select them. As a medical doctor, I had no idea about this. How to identify the males and the females and how to pick out the virgins among the female flies... I remember thinking, wow, they are amazing being able to do that. But after two or three years, I could also almost tell which were males or females while in flight.

An Do you still profit from your research today in your work as an eye specialist?

TP I think that the fine motor skills of the fingers, that were trained through my work in the lab, for example, when removing the imaginal disc from fly larvae, helped me at the beginning to perform eye surgery.

An How difficult was it to start working as a doctor at the Eye Clinic after four years at the bench?

TP That was a big transition. I was pretty stressed for the first three months. We...
Alumni portraits

Tobias Pauli has been working as a specialist in ophthalmology and eye surgery at the Eye Center (Augenzentrum) at Basel SBB station since 2009. After studying medicine, he undertook his PhD as part of the MD-PhD Program at the Biozentrum in Walter Gehring’s research group. Pauli then commenced his four-year clinical training as an ophthalmologist and, in 2008, completed the specialist exams.

did not have much contact with patients during our medical studies and after four years in the lab I had forgotten a number of things. Especially at the beginning I sometimes wished to go back to the lab and my work with the flies. I still enjoy thinking about those days. And even though at the practice I don’t always do something as exciting as in my lab time, it is good to see that my patients do need me. Today, the small things I do are very important, in contrast to earlier, where in the global research arena, what I achieved was extremely tiny.

An Wasn’t it strange at first to look so deeply into the eyes of so many people?
TP There is always the examination device between me and the patient. Every day, I see so many eyes, you might think this is boring. But that’s not the case. I find every eye unique and beautiful to look at. It is also the interpersonal contact when speaking with the patient that I greatly value in my profession and that with many simple means, such as glasses, drops and ointments, we can enormously improve the eyesight and consequently the quality of life of people.

An How can we look after our eyes?
TP What applies to the rest of the body, also applies to the eye. So by doing some sport, eating healthy food, not smoking and not looking with unprotected eyes in the sun, you are already doing much for eye health. In any case, from about the age of 40, you should have your eye pressure checked regularly.

An Did you learn your skills directly on the patient?
TP Yes, all non-surgical procedures, such as laser treatments or removing foreign bodies from the cornea, are learned one by one on the patient. Surgery requires more fine motor skills. These I learned step-by-step from my boss, an accomplished surgeon. Initially, one operates in twos. Should something not be so optimal, the more experienced surgeon can take over. So that the final result is still perfect in the end.

An Do you remember your first surgery?
TP Oh, that was pretty nerve wracking. But you keep on practicing until you no longer shake. In order to achieve the recognition as an eye surgeon, one has to have carried out a surgical procedure, such as replacing the clouded lens in cataract surgery, at least 200 times. By now, I must have performed operations on around a thousand eyes.

An What do you do in a regular day at the practice?
TP In most cases, I do routine work such as controls of eyesight, eye pressure or the retina, or deal with complaints such as conjunctivitis. Among the most common diseases are age-related macular degeneration. It is diagnosed more frequently, as we are getting older and older. And this takes us back to Walter Gehring.

An Why?
TP When I started working with him, his mother was suffering from macular degeneration and that was his motivation to investigate what actually happens at the molecular level in the disease, using flies. When he told his mother that he was now doing research in this area, she said, “Now you are finally doing something sensible”. 
The cross-border commuter.

Borders are not an obstacle for her, they exist to be crossed. Kathrin Thedieck has lived at open borders since her childhood. This has shaped her self-image as a European. The fact that the Biozentrum alumna now commutes between the Netherlands and Germany seems to be a logical consequence. As a Professor of Metabolic Signaling she also enthusiastically crosses the border between the fields of metabolism and kinase signaling.

Since 2013, Kathrin Thedieck has been Associate Professor at the University Medical Center Groningen (UMCG) and at the European Medical School (EMS), a cooperation project of the Dutch University of Groningen and the Carl von Ossietzky University of Oldenburg in Germany. Kathrin Thedieck received her PhD at the Helmholtz Center for Infection Research (HZI) in Braunschweig. From 2006 to 2008, she was a postdoc at the Biozentrum and subsequently a research group leader at the Albert Ludwig University of Freiburg in Germany.
Alumninews  What attracts you to transnational research?
Kathrin Thiedieck  This is my first professorship and it is incredibly exciting. I have great freedom in conducting my research and developing new projects, and in doing so, I learn a lot about what constitutes a faculty and how the committees and institutions work on both sides of the border. In contrast to the trinational Upper Rhine region, where cross-border exchange has been cultivated for decades, we are still at the very beginning. In many ways the border is still a real border and there are many practical hurdles for my employees on both sides of it. So, if my science should not succeed, I’ll set up a support office for cross-border commuters here in the north (she laughs).

An  Do the challenges reach beyond practical hurdles?
KT  Definitely. Take the cultural differences as an example. As a Basler or a Lörracher, one knows quite well that the other side communicates differently, even though we speak more or less the same language. It is similar in the north, but people are sometimes less aware of it. Hence, I not only need to speak the language of each country, but I often also need to act as an intercultural mediator. My time spent in the region of Basel has prepared me well for this challenge.

“With children you need flexibility because a family does not fit into any scheme.”

An  You have been working on mTOR since your time as a postdoc in the group of Mike Hall...
KT  Yes, Mike and the Biozentrum have strongly influenced my further scientific career. Currently, my research focuses on stress networks converging on mTOR. More specifically, we investigate which stress inputs activate or inhibit the network, how they interact, and the impact of this interplay on drug response. Furthermore, we are investigating the cross-talk between different signaling networks as well as the interaction between metabolism and signaling. This was also one of my main reasons for joining the EMS.

An  To what extent?
KT  In Groningen, my group is embedded in pediatrics where we have a strong focus on inborn errors of metabolism. Hence, my department has great expertise in metabolically characterizing children with rare diseases in detail. I am particularly interested in how we can link our computer-based signaling models to models of metabolism in order to develop new therapy concepts. Already when looking at the mathematical models it becomes obvious that signaling researchers think quite differently to those in the metabolism field. Combining this is an exciting challenge. In the neurosciences at the University of Oldenburg, I am very close to the application of our research results because disturbances of the mTOR pathway, such as in the rare genetic disease tuberous sclerosis complex (TSC), can have severe neurological consequences including epilepsy. The neurological effects of mTOR are, so far, comparatively poorly investigated – thus a new and interesting research field lies ahead.

An  What is important to you as a research group leader?
KT  Team spirit is central to me. I would like my coworkers to feel and act like a team and to stand together to cope with challenges. This is essential to me as I work best in an environment where I feel appreciated and valued. By the way, I noticed that for a long time I had more female job applicants. I guess, this is because of being a female role model. Interestingly, since we are publishing in high ranked scientific journals, the male applicants have outnumbered the females. This suggests that men and women base their career decisions on different criteria.

An  You have a son. How difficult is it to reconcile a family and a scientific career?
KT  This has often been quite challenging. At the beginning, when my son was still very young, I was sometimes close to my stress limit. Therefore, one must carefully consider if this is the most sensible way. For my coworkers, of course, I try to offer the best possible working conditions, but I also tell them quite frankly what an academic research career can mean and that it is absolutely legitimate to take a different decision. In my opinion, the most important thing one needs with children is flexibility at work because a family does not simply fit into any scheme.

An  Was biology already your vocation from the beginning?
KT  Not entirely. After school, I was faced with the decision to study art or biology. At the time, I thought I would rather study a natural science, which I couldn't just learn by myself, and that I could still follow my interest in the arts. This turned out to be only partly true. However, I find many aspects of art in science. A creative moment exists in both. Nowadays, the arts are still an important aspect of my life, but at the moment I am following this more passively, which works well in Groningen as we have a thriving art scene.

An  Do you still have time to dare to do something new?
KT  Yes, for example just last year, I was invited to give a lecture in Montreal and there I did dog sledding for the first time. And since only recently I have a new hobby – motorcycling. It actually came about as I wanted to learn Dutch in a fun way. So, I learned how to ride motorbikes with a Dutch instructor. It was hard work for my teacher, as I had no idea of the language nor the bike. I did not expect it beforehand but motorcycling has become a big passion. And in the meantime I think I speak Dutch rather well, yet still with a slight German accent.
New Professor

Richard Neher, the new professor of Computational Modeling of Biological Processes, recently moved to the Biozentrum. Easygoing and successful describes him well. He has just been awarded the Open Science Prize for his online tool “nextstrain.org”. And with canoe polo he has made it to the German Premier League.

Alumninews You are investigating influenza and various other viruses. How did you get into this?

Richard Neher My education is actually that of a theoretical physicist. Over the years, however, I became more and more interested in biological questions. This started during my time as a PhD student in Munich with the modeling of single molecule experiments. In the USA, I then drifted in the direction of evolution and designed theoretical models. From there on it was only a small step to start to investigate the evolution of viruses.

An And then HIV came into play...

RN Correct. In recent years we have been investigating HIV. We wanted to understand how it changed over the years in a single individual and in which parts of its structure. Currently, however, we are mostly working with influenza viruses. We analyze their spread and the emergence of new virus variants to describe and predict which of these will prevail in the coming season.

An On what do you base your predictions?

RN We take genome sequences of the viruses, which we obtain from international influenza data bases. Influenza

Richard Neher studied physics at the universities of Göttingen and Munich, where in 2007, he received his PhD with a thesis on dynamic aspects of DNA. He then pursued postdoctoral studies at the Kavli Institute for Theoretical Physics at the University of California, Santa Barbara. Most recently, Richard Neher was a research group leader at the Max Planck Institute for Developmental Biology in Tübingen, where he began his research on the evolution and spread of viruses.
sequencing data is immediately shared and available online. With these data, we can create a phylogeny of the viruses that shows their evolution.

**An** How can these results be used?
**RN** The predictions are relevant for the composition of new influenza vaccines. We cooperate with health authorities in the USA. Our results then contribute towards the recommendation for the vaccine composition for the coming year.

**An** So, you predict the type of vaccine for the next flu season?
**RN** Not quite. Many different aspects influence this decision. It can happen, for example, that a virus variant is predicted for which there is no virus representative available. In short, it is not always technically possible to produce what the prediction recommends. In addition, you have to be very cautious in the preparation, because a vaccine with a virus variant that changes during production, or does not illicit a good response, can actually do more harm than good.

**An** What makes the influenza virus so successful?
**RN** The flu virus’ strategy is to change every year so that people are no longer immune to this new strain, and the virus can then repeatedly infect them. Currently, intensive research is being carried out on a flu vaccine aimed at the invariable regions of the virus in order to permanently cripple the pathogen. That would be the optimal vaccine.

**An** Why is the development of such a sustainable vaccine so difficult?
**RN** To persuade the immune system to actually attack the non-variable parts of the virus, instead of those that change easily, is difficult. The virus constantly changes its surface molecules; a similar strategy to that of HIV.

**An** Why is it possible to develop an annual vaccine against the flu virus, but not against HIV?
**RN** What you have to keep in mind with HIV is that our immune system does not manage per se to get rid of the virus – unlike the flu virus. In addition, HIV is much more diverse, in other words, there are many more genetic variants globally, so it is almost impossible to cover all variants with a single vaccine.

**An** Would it be theoretically possible, to at least develop a vaccine for one of these HIV variants?
**RN** That would be possible theoretically, but since one does not know with which virus variant one could come into contact, such a vaccine would not really be helpful.

**An** You use open access data for your computer analyses. What does Open Science mean to you?
**RN** For me, it means the open sharing of genetic data, raw data or methods to maximize the benefits to society, reproducibility and data reuse.

**nextstrain.org**
With “nextstrain.org”, Richard Neher has developed an open access online tool that predicts the spread of viruses and the course of epidemics. In addition to influenza, HIV and Zika, he also investigated the spread of Ebola. Matthew Cotton (photo center) from the Wellcome Trust Sanger Institute in Cambridge, UK, was in Sierra Leone/Liberia in 2014 and analyzed the data for the affected region directly on the computer with colleagues.
An But does this work in practice?

RN A conflict naturally arises. An individual researcher wants to turn his data into as many good publications as possible and therefore withhold the data for a relatively long period of time. For science as a whole, it would be much better to share results as early as possible. In the past years this issue has once again moved into the spotlight due to the Ebola epidemic in West Africa in 2014, or the Zika epidemic in South America. During this Public Health Crisis all the relevant journals and funding institutions had signed a memorandum saying that all relevant data should be made immediately accessible to the public, and that the prior publication would not be a hindrance to publish a paper at a later date.

An Did this agreement help?

RN Yes and no. With open access to the data we were able to reconstruct the distribution routes of Ebola and Zika. But despite of this exceptional situation, there have unfortunately been research groups who have withheld their results until their articles were published.

An To what extent could you use your online tool “nextstrain.org” in the case of Ebola?

RN Within one day, we set up the analysis pipeline for the Ebola virus and all the raw data that was available to us was integrated and analyzed immediately. We were able to track the spread of the virus and, for example, recognize whether and how Ebola infected people were travelling. For example, new virus sequences, which had so far only existed in Liberia, suddenly appeared in Sierra Leone. Such information helps to initiate appropriate preventive measures as well as precautions.

An What would be possible future projects?

RN We started to develop a tool for the spread of pathogenic bacteria. We would like to follow this up at the Biozentrum. For this project I am also in contact with Adrian Egli of the University Hospital. Together, we want to develop a software that can be used to investigate the spread of hospital germs. But there are also many possibilities to network with the infection biologists at the Biozentrum or computational biologists such as Erik van Nimwegen, who is working on E. coli bacteria.

An You were also offered a position at the LMU Munich. Why did you decide in the end to come to the Biozentrum?

RN To be honest, the decision was not easy. I knew Munich already very well. One of the main reasons for my decision was that the Biozentrum is a much bigger, more diverse institution, with a lot of potential points for cooperation that were not really being offered in Munich.

An By your lab are still some moving boxes and a paddle...

RN Since my school days, I have kayaked a lot and have also played canoe polo. In fact, quite intensively. In 1998 we even made it to the German Premier League – which sounds a bit bigger than it really is, in this rather unknown sport. Whilst I was studying in Munich, I did mostly whitewater kayaking. And I know that there is a polo team here in Basel. At some point I will take my paddle and pass by there.

> home
Infection routes in Basel.

This last winter brought an influenza wave to Europe, unrivaled by many others. Adrian Egli, Head of the Division of Clinical Microbiology at the University of Basel, investigated the spread in Basel and explains why this year’s flu outbreak was one of the worst ever measured. Now he is planning a new project together with Richard Neher – this time not on influenza, but on multi-resistant hospital pathogens.

“If you think: ‘Hmm, maybe I have caught the flu,’ then you can be sure that it is not the case,” says Adrian Egli. “Having the flu makes you feel so ill with high fever within a few hours. You don’t even wonder if it could be the flu; you know it immediately.” Together with scientists from the ETH Zürich and the Department of Environmental Sciences of the University of Basel, Egli has investigated the spread of the flu virus in Basel. They distributed about 30,000 questionnaires to hospital patients and patients of local doctors to find out where the infected people live, where they work or which tramlines they use in order to create a transfer model for the entire city.

This winter’s wave of flu was one of the worst flu outbreaks ever measured. Almost five times as many cases were counted as in the previous year. As it was extremely cold, even before Christmas, the spread of the flu began two months earlier than usual. “Temperature has a strong impact as the viruses survive mainly on cold surfaces – on automatic doors, at the ticket machine, at the traffic lights or on door handles,” explains Egli. Additional factors that influence the spread are the virus itself and how the immune system of the population responds to it. “Most probably this year’s virus was a new variant and therefore difficult for our defense system to recognize.” The most effective way to avoid an infection is to have the flu vaccination. But to entirely prevent the annual flu wave, a vaccination rate of 50 to 60 percent of the population would be necessary. “At the moment we are miles away from that,” Egli comments.

In Switzerland about 30 percent of the over 65 year olds are vaccinated, of people below the age of 65, less than 15 percent. There is no mandatory vaccination. Even doctors are not obliged to be vaccinated. “Nevertheless, I get vaccinated every year. Not just for my own health but also not to be a carrier who might infect other patients.” That’s why Adrian Egli recommends that all people who are in contact with chronically ill, immunocompromised or elderly people should be vaccinated annually.

About a quarter of a million people in Switzerland succumb to the flu each year. About 1,500 of them die. Apart from these sad individual outcomes, "With next-strain.org we want to analyze the spread of multi-resistant bacteria.”
the economic impact is enormous. “If one imagines that about half of the 250 000 infected people are unable to work for one week, then the cost of absenteeism due to sickness over the year is expected to be in the billions,” emphasizes Egli. The resulting costs for medication, doctor’s visits or hospital stays are not even taken into account in this calculation. Hence, consistent vaccination against influenza would not only be a health measure but also a very cost-effective preventive measure.

A simple way to prevent an infection is by regular handwashing and disinfection – and avoiding large crowds of people. "Maybe one should cancel the Basel Carnival. But of course no one would do that!" Egli says with a smile.

Currently he is planning a project together with Richard Neher – not on influenza, but on another, equally present-day microbe: a multi-resistant variant of the bacterium Staphylococcus aureus (MRSA), the so-called “hospital bacterium”. As there is a worldwide problem with the increase in multi-resistant organisms, they would like to use the tool “nextstrain.org” to analyze the spread of multi-resistant bacteria in Swiss hospitals. “Within the framework of the National Research Program for the Study of Antibiotic Resistance, we will investigate the epidemiology of infections and resistance in order to better understand the dynamics of the bacteria transmitted in the hospital or from the environment,” he points out.

Another example is the normal intestinal microbe E. coli. Nowadays, in Swiss hospitals, about 12 percent of the bacterial population is already multi-resistant to the common antibiotics. Each year this increases by one percent. E. coli is found in all bodies of water and colonizes 80 to 90 percent of the surface of fresh chicken meat. It is found on cutting boards in the kitchen, it is in our environment, in our food chain – simply everywhere. People are constantly in contact with multi-resistant pathogens. But this does not mean that they will get sick. "Our own bacteria provide a natural protective barrier. Even if we come into contact, we do not remain carriers," so Egli.

Antibiotic resistance itself is something natural. It doesn’t exist just because antibiotics are used in the clinic. Antibiotic resistance has been around since bacteria first existed. Bacteria themselves produce antibiotics in the fight against competitors. So, the bacteria themselves are naturally resistant to their own antibiotics. “The problem is rather in how we deal with antibiotics and that there is no commercial interest to actively look for new ones as not much money can be made with antibiotics. One can only hope that a rethinking takes place and that pharmaceutical companies invest more in this area,” concludes Egli. ❍

> home
Honors.

Richard Neher wins the Open Science Prize.
Prof. Richard Neher is the joint winner of the Open Science Prize, together with Prof. Trevor Bedford of the Fred Hutchinson Cancer Research Center in Seattle. The two scientists have been awarded the prize, endowed with about $230,000, for their open access online tool “nextstrain.org”, which allows the real-time tracking of the evolution and spread of viral pathogens, such as HIV or Ebola. This provides public health authorities and medical personnel with a tool to better control the outbreak and course of epidemics and enables them to initiate appropriate measures. The Open Science Prize was founded by the American National Institutes of Health (NIH), the Howard Hughes Medical Institute and the British Wellcome Trust.  >more

Silvia Arber receives the 2017 Louis-Jeantet Prize for Medicine.
The 2017 Louis-Jeantet Prize for Medicine was awarded to Prof. Silvia Arber and to the immunologist Prof. Caetano Reis e Sousa, senior group leader at The Francis Crick Institute, United Kingdom. Arber received this award for her contributions to our understanding of how movement is controlled in mammals. The Louis-Jeantet Prize for Medicine refers to one of the best-endowed awards in Europe, fosters scientific excellence and finances the continuation of innovative research projects with high added value and of more or less immediate practical significance in the treatment of diseases.  >more

Research.

Store and supply – how the brain saves time. Prof. Peter Scheiffele
Our brain is the most complex and flexible organ of the human body. But how do neurons in the brain adapt their function in response to stimuli within a very short time frame? The research group of Prof. Peter Scheiffele has demonstrated that neurons store a reserve stock of RNA molecules in the cell’s nucleus. After a neuronal stimulus the stored RNA molecules are mobilized in order to adjust the function of the neuron. Thus, this newly uncovered mechanism provides new insights regarding the fast adaptation of the brain during learning processes.  >more
Not necessarily harmful: Protein aggregates in the brain.
Prof. Martin Spiess

Protein aggregates in neurons are characteristic for Alzheimer’s, Parkinson’s and other neurodegenerative diseases. These so-called amyloids arise from misfolded proteins and lead to cell death. The team headed by Prof. Martin Spiess has demonstrated using the hormone vasopressin as an example, that such amyloids in the cell can also have an important physiological function. Vasopressin is stored in the nerve cells in the form of amyloid-like granules. Upon stimulation these tiny granules are secreted into the blood, where they dissolve and release the hormone. Harmful protein aggregates produced by defective proteins appear to be an adverse result of the ability to form granules. >more

Immune defense without collateral damage. Prof. Dirk Bumann

The immune cells of the human body identify and ingest invading pathogens and render them harmless using highly toxic substances. It is important that these substances only destroy bacteria while causing as little collateral damage as possible to the surrounding tissue. The research groups headed by Prof. Dirk Bumann of the Biozentrum and Dr. Nina Khanna, Department of Biomedicine, discovered how white blood cells solve this difficult task. They produce an enzyme, myeloperoxidase (MPO), which produces an aggressive acid which burns a hole into the bacterial cell envelope and kills the bacterium without causing damage to its surroundings. The findings may provide new approaches for immunity strengthening therapies. >more

Relocation of proteins with a new nanobody tool.
Prof. Markus Affolter

Proteins control central vital processes such as organ development and growth. In this context, not only the composition of the proteins is important but also their position which can influence their function. The research group led by Prof. Markus Affolter has now developed a novel nanobody tool that allows the relocation of proteins and thus to study their function in a position-dependent manner. In the future, the new nanobody tool can be applied for a wide variety of studies on organ growth and may contribute to a better understanding of how organ growth is regulated. >more

Treating cancer with drugs for diabetes and hypertension.
Prof. Michael Hall

A combination of a diabetes medication and an antihypertensive drug can effectively combat cancer cells. The team of researchers led by Prof. Michael Hall reported that the antihypertensive drug syrosingopine potentiates the anti-cancer efficacy of the anti-diabetic drug metformin. This drug cocktail drives cancer cells to programmed “suicide” and is effective in a wide range of cancers. The scientists could demonstrate that the inhibition of the respiratory chain in the mitochondria is a key mechanism. This study may have implications for future clinical application of combination scenarios targeting the energy needs of tumor cells. >more