ELSE KRÖNER-FRESENIUS-STIFTUNG

Research Fields for the Medicine of Tomorrow

Are Breakthroughs Foreseeable?

Imprint

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Dear Readers, Friends and Partners of the Else Kröner-Fresenius-Stiftung,

Can we predict groundbreaking scientific discoveries? A look back in time suggests not – and the path to scientific progress is just as unpredictable. Nevertheless, the allocation of finite funding requires decisions that can only be made based on assumptions. Both public and private research funding is an investment in the future. With the Else Kröner Fresenius Preis für Medizinische Forschung 2017, we hope to provide momentum to a particularly promising research field by making resources available to a prominent scientist in this area. EKFS would therefore like to create a framework that will give the prizewinner the opportunity to make substantial progress in their work and inspire talented young scientists to enter the field. A major criteria for selecting a prizewinner is of course our appreciation for the individual's achievements to date. In 2013, immunologist Ruslan Medzhitov from Yale University received the prize.

The first step toward conferring the 2017 prize is to identify a research field for nominations. This has led us to becoming involved in an exciting process of reflection on scientific theory and history in two workshops. Alongside Nobel Prize winners, senior editors of leading scientific journals and young scientists with a fresh perspective took part in animated discussions. We therefore tapped into the driving force behind science and that which forms its beating heart: intelligent minds uniting creativity and passion. In the hope of sparking your interest, we are reporting on the progress of our search in this booklet.

Dr. Susanne Schultz-Hector
Member of the Executive Board
Else Kröner-Fresenius-Stiftung

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Scope for Creativity

How do You Arrive at a Theory in Science?

Wolfgang Leidhold is an artist – as well as Professor of Political Theory and the History of Ideas at the University of Cologne. The role of creativity in the process of theory formation is one of the subjects he teaches to young scientists from different fields. In its quest for a promising field of research for the next Else Kröner Fresenius Preis für Medizinische Forschung in 2017, EKFS is also involved in similar questions.

Professor Leidhold, as a painter, the knot is one of your motifs – not as a simple fastening device but as a complex labyrinth. Is it a symbol for the knowledge-based society?

The knot is a historic symbol for the opaqueness of our world and cosmos. Within itself it is highly regular. But we see only its outer aspect and not what is inside. One can definitely take it as a symbol for the knowledge-based society, devoted to unraveling complex knots.

You hold seminars in creative theory formation. What are you trying to convey to the new generation of medical professionals?

Basically, it is about communicating a clear picture of the research process. Of course, we know the process from scientific practice – but it also helps to get a bird's eye view of the logical and methodical aspects. This is essential in order to identify the exact point in the process where creativity comes into play.

You have developed a simple model that describes how creativity finds its way into the formation of theories. Could you clarify this?

The process develops in a cycle comprising four stations: starting with the theoretical principles (1) to the observations and experiments derived therefrom (2) and further to the analysis of the new findings thus gained (3). Finally, it is down to classification into that which is already known. This process runs smoothly while everything remains inherently self-consistent and as long as no surprises crop up.

If something unexpected should turn up in steps (2) and (3), then a discovery happens. Sometimes it is possible to integrate the unexpected into the accepted theory by introducing minor modifications. When that does not work, the theory has to be changed. We must then risk a new hypothesis, and this is station (4). At this point we have the space for creativity.

How can we initiate creativity?

The primary hindrance here is our own inner resistance. There is a naysayer within all of us who speaks up when we want to accomplish something new. It says: »Oh, just leave it. It is a stupid idea. Better to carry on with what has already been successful so far.« It took me a whole year to get away from the knot theme in my painting.

When my inner inhibition stands in my way – how do I deal with this?

Recognizing our inner inhibition as a merely psychological barrier, and not as a intuitive counter argument, is the first step in overcoming it. Everything unfamiliar provokes unease, resistance. As soon as we realize that this resistance does not constitute a valid argument against a new idea, we will easily defy it. All creative people – whether artists, researchers or mystics – constantly come up against this archetypal inner naysayer. One does well to anticipate it turning up – then pushing it politely to one side.

Are there other things that block creativity?

There are internal and external barriers. Besides the naysayer, there is a corresponding tendency to accept the familiar. As creatures of habit, we love the established, the trusted, the accepted. A third opponent of creativity is the blind spot – we overlook, we ignore deviating observations, things which do not fit our grid pattern. We say: we will attend to that later – or: it is not so important.

A typical external barrier, for instance, is a climate of coformism in the scientific community; just as obstructive are time pressure, publication stress and a lack of leeway – thus a lack of encouragement towards »playful« trial and error.

For his knot paintings, Wolfgang Leidhold used self-made egg tempera and oil paints. He drew his inspiration from the Gordian knot which Alexander the Great once sliced through with his sword. Leidhold also took the Omphalos of Delphi, symbol for the cosmos, as his inspiration.

As both political scientist and artist, how do you yourself come up with ideas?

To begin with, I take each thought seriously. Any idea will be entered in my diary, an artistic thought in a sketchbook or on a sketching sheet. The question of whether it is beneficial and useful comes much later.

In my experience, artistic and intellectual creativity strengthen each other interactively. Whether that be music, painting or poetry: to be productive yourself in any of these areas in a playful way is highly efficient – it strengthens the intellectual area of our psyche and also stimulates creativity. But it is important to become productive yourself. Just looking at pictures or reading history is of no use.

The Greatest Challenge of All

Can We Predict Breakthroughs?

It is a great challenge to find a promising research field for the Else Kröner Fresenius Preis für Medizinische Forschung 2017. We can start by looking back in time. How do breakthroughs come about, and who or what is the driving force behind them? At the same time, this is really only a starting point – because medical research is a fast-moving field. Here is an overview of where we are now.

Individual, spectacular discoveries have shaped our perception of major breakthroughs throughout scientific history. One such example is the tale of how smallpox was eradicated in a daring experiment by the English doctor Edward Jenner. In 1796, he first infected a young boy with »cowpox serum,« then with the human smallpox virus. The boy survived, and Jenner had thus cleared the way for vaccines against numerous infectious diseases.

Meanwhile, the birth of modern antibiotics can be traced back to Scotsman Alexander Fleming, who returned to an experiment on bacteria after a short holiday in 1928. Astonished, he realized that his experiment was completely ruined; a bluish-green mold had spread and inhibited the growth of his bacteria. He eventually decided to breed the strange mold, thus laying the foundation for the production of penicillin – which is still considered one of the world's most effective antibiotics today.

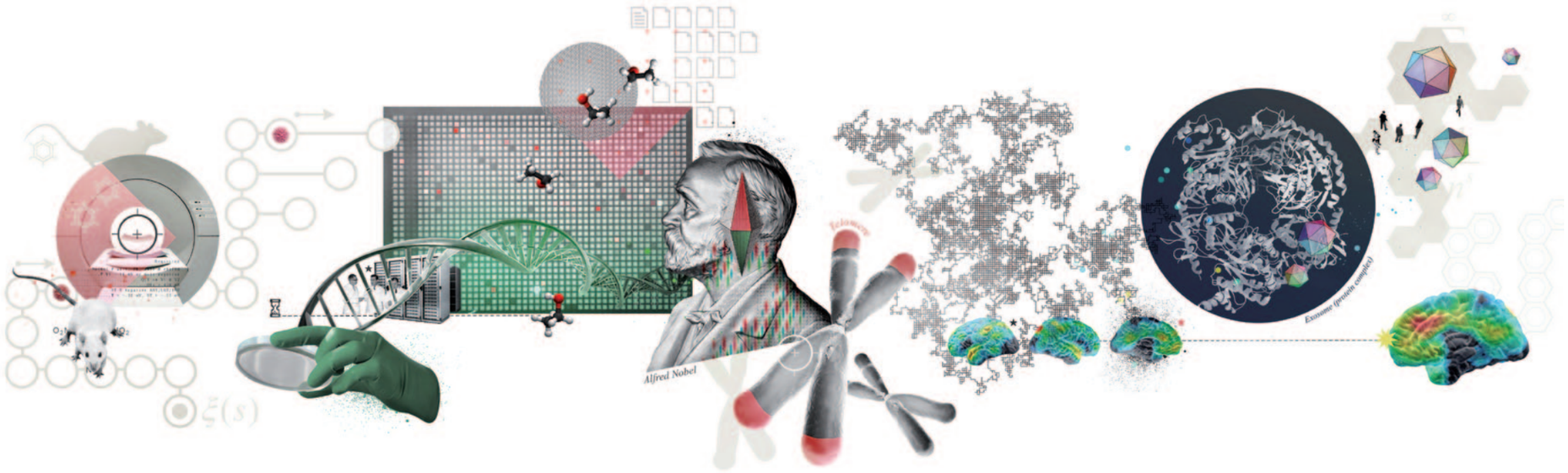
As in the case of penicillin, many scientific discoveries owe a great deal to chance. However, the ability to recognize a chance discovery as a window of opportunity is what defines the mind of a great scientist. »The greatest achievements in science are the consequence of talented and mentally prepared individuals who are able to recognize unexpected results, draw conclusions, and then follow them wherever they lead,« wrote geneticist and chairman of the renowned Lasker Award jury, Joseph Goldstein, in the scientific journal *Nature Medicine.*

Even Peter Agre, a former president of the American Association for the Advancement of Science, only discovered how water is transported in and out of cells by chance – thus solving a long-standing conundrum in the scientific community. The molecular biologist had in fact been researching Rhesus factors, i.e. characteristics found on the surface of red blood cells. In 1988, an unknown protein emerged during his investigations. Instead of disregarding the protein as a distraction or interference, Agre analyzed it and came to understand its significance over a year later: the protein forms aqueous channels in the cell membrane (aquaporins).

The phenomenon is aptly summed up by the word serendipity, which originates from a fairy tale about good luck and opportunity. According to the legend, three princes from Serendip (modern-day Sri Lanka) went on a journey and discovered all manner of things they had not sought out.

Banishing the fear of mistakes

However, serendipity is not everything; mistakes and our treatment of them can play a productive role in scientific breakthroughs, a point emphasized by astrophysicist Mario



A good example of serendipity:
In the 1940s, a researcher discovered that microwaves are suitable for use in the kitchen when he happened to have a candy bar in his pocket in the laboratory. The electromagnetic radiation produced in the lab made his chocolate bar melt. Percy Spencer considered the potential for microwaves to heat food, and the first microwave oven was put on the market not long afterward.

Livio in his article »Don't bristle at blunders«: »Mistakes are not the exclusive province of sloppy or inexperienced scientists. Even the brightest luminaries – including Charles Darwin and Albert Einstein – made serious blunders.«

The 2013 winner of the Else Kröner Fresenius Award, Ruslan Medzhitov, put it this way: »People who are very inventive and creative recognize that they have to form many hypotheses, and that most of these will be proven wrong. […] If you want to be creative, you have to make a lot of mistakes – but if you find you are right, you will have discovered something very important.«

Einstein once said of himself that: »It is not that I am so smart, it is just that I stay with problems longer.« The ability to learn from and accept mistakes is a recurring theme in scientific breakthroughs. This is exemplified by the many years German physician Harald zur Hausen spent pursuing the initially unpopular hypothesis that viruses can cause cervical cancer. His substantiation of this hypothesis using new technologies ultimately earned him a Nobel Prize in 2008.

The competition in research

Yet is the time always ripe for revolutionary discoveries? According to philosopher of science Thomas S. Kuhn (1922–1996), there are long periods in science during which the general acceptance of certain paradigms helps to steadily develop research as scientists expand on and find practical applications for previous discoveries and theories. Kuhn called this the period of »normal science.«

However, there are also periods during which the basic notions of a research area are redefined or rewritten – dubbed »revolutionary science« by T. S. Kuhn. Paradigm-altering breakthroughs are generally preceded by an intensification of research activities: new experimental methods could suddenly allow the analysis of previously inaccessible phenomena, new associations between the disciplines might open the door to new approaches, or accepted theories may come under growing pressure due to increasingly contradictory observations.

Thus, the individual research fields do not move at a constant speed. Instead, they can occasionally sprint ahead, advancing at a tremendous pace, only to later eventually fall behind other research fields again.

Searching for a field where the race is about to start

The development of medical research over the last hundred years has not only been shaped by the emergence and disappearance of individual topics; the field, itself, has also experienced an inconceivable rate of growth. Between 1997 and 2006 alone, the number of medical research publications in the Medline database increased by an average 5.6 percent each year. This indicates a thirteen-year doubling time of research knowledge.[1]

This increase correlates with the growing importance of transdisciplinary research, linking various subjects and research projects. The extensive visual mapping of these connections demonstrates this quite impressively (see image on the next page).

Basic research in physics is dominated by theories that aim to explain the entire universe. These are being tested on a large scale in international experiments such as the Large Hadron Collider at CERN in Switzerland and the ITER fusion reactor in France. In contrast, medical research takes place in a complex network of interactions between individual working groups, which continually exchange hypotheses and their findings. This is reflected in a correspondingly complex network of a multitude of individual, smaller scale theories.

Innovative research results are thus increasingly obtained through intensive networking across disciplines. This is also reflected in the awarding of the Nobel Prize; it is now becoming increasingly difficult to unequivocally attribute any one discovery to an individual or a maximum of three researchers.

Big data in medical research

Besides the growing number of publications and research projects described above, the number of data sets being analyzed per project has also increased. 20 years ago, for instance, a two-week northern blot analysis was required to investigate the expression of a single gene in a specific medical condition.

Today, the expression analysis of thousands of genes can be carried out with significantly less sample material and in a very short time. This enables us to conduct much broader searches when there is no »suspected candidate« for a certain chain of effects, for instance. Such »high throughput« approaches generate data sets which, due to their sheer volume, can only be interpreted through complex bioinformatic analyses.

This incredible computing power does not merely enable us to conduct broad-based search experiments relating to individual questions; it also allows us to mathematically integrate large numbers of individual laboratory findings and build complex models of biological procedures, as is being attempted in the comparatively new discipline of systems biology. Complex computer models have even been used to attempt to predict the future of medical research. However, the creative spark found in talented individuals who transform unexpected results into scientific breakthroughs is virtually impossible to replicate.

The simple-sounding question of what will be the most exciting research fields over the next few years is therefore enormously difficult to answer. In our search for an answer, we will draw on the creativity and knowledge of outstanding researchers, the experience of the most important specialist publications, and the fresh perspectives of young scientists.

Can we predict scientific breakthroughs?
»When research in a given field has failed to yield satisfactory results for a while, the time is ripe for a breakthrough. This means that the probability of a breakthrough increases and the whole field is waiting in anticipation as to when it will occur. We can therefore narrow things down through heightened observation and a greater awareness of prior developments, but we cannot predict who will find the breakthrough or what kind of results to expect. If we could, the observers would be smarter than the discoverers themselves!«
Professor Wolfgang Leidhold
(see interview on pages 4–5).

[1]Source: PO Larsen, M. von Ins: The rate of growth in scientific publication and the decline in coverage provided by Science Citation Index. Scientometrics. Sep 2010; 84(3): 575–603.

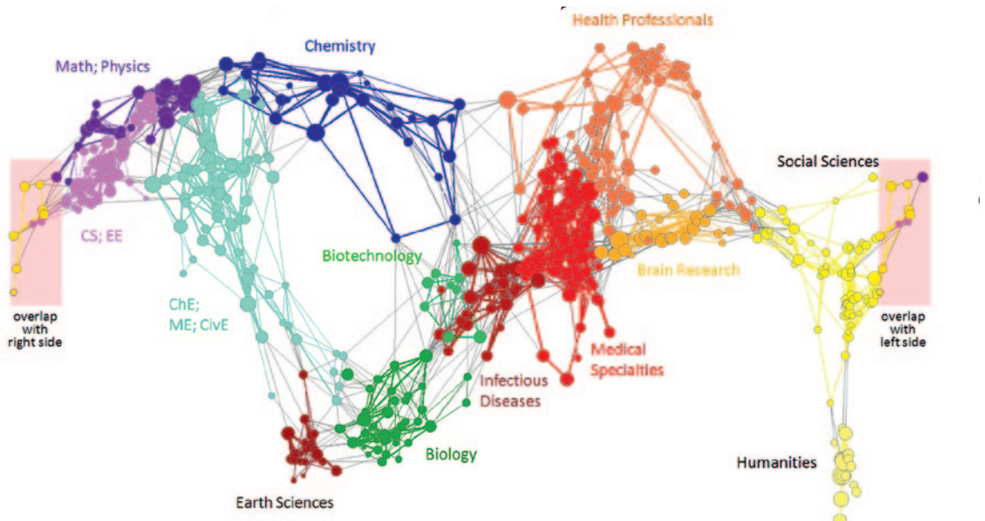


Image: This »Map of Science« from the University of California, San Diego, is based on data from 25,000 specialist journals published between 2001 and 2010. The 25,000 journals were organized into 554 subdisciplines, each in turn belonging to one of thirteen larger scientific fields. The visualization impressively demonstrates the links between the individual disciplines. Börner K, Klavans R, Patek M, Zoss AM, Biberstine JR et al. (2012): Design and Update of a Classification System: The UCSD Map of Science. PLoS ONE 7(7): e39464.

Knowledge Party for Research

Heading for the Next Else Kröner Fresenius Preis für Medizinische Forschung

The view seemed inviting ... just to cast a sweeping glance across the fields of the Taunus and enjoy the sun streaming through the big conference room windows. Instead, close to 20 workshop participants, mainly junior researchers are sitting at three round tables – talking and talking – about the big bang, about obsession and perseverance in research and about the question: What exactly defines a scientific breakthrough?

At the invitation of Else Kröner-Fresenius-Stiftung (EKFS), they met at the foundation's office on the edge of Bad Homburg in the beginning of April. All-encompassing issues were discussed regarding the process of research: What are the decisive framework conditions that make innovative breakthroughs possible? Are such breakthroughs foreseeable? And how can we create an environment in which innovations can unfold?

EKFS is now headed towards identifying and defining a suitable research field for the 2017 award – with postdocs from eight different nations on board for the first steps of the way. The meeting in Bad Homburg is to serve as preparation for a further workshop preceding the opening of the Lindau Nobel Laureates meeting at the end of June.

Yet how can a group of many masterminds from disciplines ranging from bioinformatics to chemistry to neuroscience create an operating framework where an exchange of information is possible in which new ideas can be jointly spun? To build the right structure for this, EKFS has brought in Katharina Janus (see inset). The healthcare management professor from Ulm has developed a concept for the exchange of knowledge – a so-called World Café format – in her »Care Tank« and has already trialed this with a team at several conferences on topics such as evidence-based medicine and incentives in healthcare.

Dare to look at the wider picture

»We all know the conferences where few highly specialized experts expound their knowledge from the podium while the majority of participants just listen,« says Katharina Janus. »As one colleague put it ›We are conferenced out.‹ We need a new concept.« There is often a kind of »silo mentality,« continues the business economist. »Many have their own interests and will say: that is my subject, but not that one so much.« The view of the wider picture is missing.

»Our objective, in contrast, is something akin to facilitating a well-organized party which is relevant in terms of content,« says Katharina Janus. Three things are essential for this: the right guests, good hosts and a relaxed, open atmosphere. »It is a ›knowledge party,‹ so to speak, at which ideas are exchanged and shaped without pursuing minority interests or succumbing to the pressure of justification.«

Ideally participants are open, intellectual people who respect other opinions and who want to enjoy playing a part in a laid-back inquisitive manner. The hosts also have an important role to play: Katharina Janus and her team are there to prevent an accumulation of good discussions and ideas from randomly

fizzling out – as unfortunately often happens. »To stop that happening, we intervene again and again in what's going on in a casual way, helping to abstract and recognize patterns. We extract intermediate positions from the discussion rounds, steer the chain of thoughts anew and let them run free again.«

Included in the team is also artist Mathias Weitbrecht who follows the discussion intently as a so-called visual facilitator and, in real-time dialog with Janus, makes a record on an enormous sheet of paper: using felt pens, a collage of texts, drawings and symbols emerges. The most important perceptions and thoughts swell to a meter-long piece of memorably formed informational architecture. By this means, the progress of the debate is immediately transparent to everyone and its contemplation inspires new ideas in turn. The junior researchers are also accompanied on this day by a Janus team expert: the healthcare scientist Federico Lega from Bocconi University in Milan.

The postdocs in Bad Homburg run through two such rounds of discussion. As starting points, EKFS-board member Susanne Schultz-Hector has selected three scientific breakthroughs each of which will be investigated by a team. For instance, the proof of gravitational waves as evidence for the big bang as well as examples of infectious disease and gene research that have been awarded with Nobel Prizes. How did these breakthroughs come about? How do the concepts and hypotheses of astrophysics differ from those of medical research?

After seven intensive hours, the day in Bad Homburg comes to an end; the postdocs make their way back to their laboratories throughout Europe and as far as Israel. While this first workshop analyzed the role of the individual in research, the discussion in Lindau will focus on research content, announced Susanne Schultz-Hector. »We will be asking in which fields of medical research a particularly rapid increase in findings is to be expected?«

Katharina Janus
The professor of healthcare management and controlling at the University of Ulm also teaches at Columbia University in New York. She is a member of the advisory board of the Allianz Private Krankenversicherungs-AG. She also heads the research network Center for Health Care Management and is director of Care Tank, a platform for innovation in healthcare.

The term *knowledge party*© is a registered trademark of Katharina Janus.

A Concern of the Else Kröner-Fresenius-Stiftung

The Next Generation Takes Center Stage

They come from eight nations spread across the globe and work in five different countries: 14 postdocs take part in the first steps in preparation of the 2017 Else Kröner Fresenius Preis für Medizinische Forschung 2017. They belong to the group of next-generation researchers who have qualified for this year's Nobel Prizewinners gathering in Lindau. Because supporting young talent is a core aim of EKFS, they were invited to take part in the quest for a field of research for the next award. As varied as their research and origins may be, the postdocs are united in their curiosity and the enjoyment of their everyday work in the laboratory.

Imagine you've just celebrated your 100th birthday: Which health problem should humanity have solved?

»When I left Canada after my PhD, it was like stumbling into a forest. How to proceed? Where is my path, where can I keep up my passion? I decided to apply new technology to old biological concepts in immunology and went to the ETH Zürich, as they have state of the art mass spectrometry technologies. The technique we use is much more sensitive than others. I use it to identify all peptides, antigens and so forth which are produced by the pathogen *mycobacterium tuberculosis*, in order to find a better vaccine – I wish for tuberculosis to be eradicated on my 100th birthday.«
(Etienne Caron, *Canada)

Stephan Halle

Marielle Ousset

Konstantinos Grintzalis

Tobias Wagner

Iris Grossman

Tobias Lange

Elzbieta Kowalska

Etienne Caron

What influences you aside from the biomedical sciences?

»I guess research is exactly like a jazz improvisation: You have some ideas, you know some of the structure. Then you are willing to go along and ahead with it and don't get worried about the lack of a script. I think science is very much like a long piece of jazz.« (David Berry, *USA)

»What I learned from playing professional soccer: It is very competitive out there and you learn to deal with frustrations. You can score a goal for your team and everybody is happy, but you can still lose the game. At the same time I learned how to deal with success, I know the exhilarating feeling to score a goal. A feeling you definitely want to experience again, and this applies for science, too. A goal for me would be to build neuroprosthetics which help patients who are paralyzed.«
(David Borton, *USA)

Envisage for us an outcome from the workshop in Bad Homburg.

»Sometimes in research, experts focus too much on details. It might be risky but sensible and worthwhile to give your ideas to people who are not experts in that particular field. They might have a more open mind and see things you don't see.«
(Lianne van de Laar, *Netherlands)


David Berry


David Borton


Joanna Adamczak


Nico Pfeifer


Manuel Koch


Lianne van de Laar

We spoke at length with all the postdocs at the workshop in Bad Homburg. Find out more about the origins, interests and the areas of research of the next-generation scientists on the EKFS website.

www.ekfs.de

A Workshop with Intelligent Minds

Inspiration for the Future

Nobel Prizewinners, young researchers and senior editors of well-known specialist journals: some 40 scientists came together on the June 29, 2014 to discuss seminal fields of medical research. The Else Kröner-Fresenius-Stiftung (EKFS) availed itself of the inspiring environment of the Nobel Laureates meeting in Lindau for the workshop.

The participants

The path of knowledge can neither be planned nor foreseen. And yet, EKFS set out on an experiment in its search for a suitable topic for the 2017 Else Kröner Fresenius Preis für Medizinische Forschung and presented these masterminds with an unanswerable question: Where will the journey in medical research be taking us in the future? Most of the Nobel Laureates approached spontaneously agreed to participate. This indicates that our question remains one of the most tantalizing. And who is better equipped to pursue it than those who have succeeded in overcoming the limits of the hitherto imaginable and who have been distinguished with the Nobel Prize for their pioneering discoveries?

It was also important to us to involve the 2013 Else Kröner Fresenius Award prizewinner. The four million euro award went to Ruslan Medzhitov from the Yale School of Medicine for his past discoveries in immunology as well as in anticipation of his extremely exciting ongoing projects in the field of infectious disease research. From his own experience in implementing the prize grant, he was able to contribute not only to evaluating the scientific potential but also the suitability of a subject worthy of receiving the prize in the future.

Besides the great scientific personages who have themselves produced and experienced research breakthroughs, there are the scouts who aim at recognizing breakthroughs as such: to identify fundamentally significant results from a multitude of submitted manuscripts as well as to recognize emerging trends and potentials of research fields. Acknowledging that the future of research belongs to the young people of today, outstanding junior scientists were the third group of participants. What they lack in knowledge and experience is made up for by enthusiasm and a wealth of ideas. We have already introduced them in the magazine.

Nobel Prize winners

Elizabeth H. Blackburn
Australian-born, she has researched since the 1970s into how chromosomes are protected by their ends, the telomeres. She discovered the enzyme telomerase together with her graduate student Carol Greider, with whom she shared the Nobel Prize in Physiology or Medicine in 2009 (together with collaborator Jack W. Szostak). The molecular biologist is a professor at the University of California, San Francisco and mother to a son.

Aaron Ciechanover
An Israeli biochemist, he received the Nobel Prize in Chemistry for the discovery of ubiquitin-controlled proteolysis (with Avram Hershko and Irwin Rose). He is a professor at the Rappaport Family Institute for Research in Medical Sciences at the Technion in Haifa. In a preliminary discussion he advised that EKFS should follow the example of the Lasker Awards – which enjoy an outstanding reputation. EKFS nevertheless decided to follow its own path – all the more generous is that he took part in our unconventional discussion process.

Edmond H. Fischer
For over 20 years Fischer has belonged to the circle of Nobel Prizewinners in Physiology or Medicine. There is indeed hardly another who has contributed to medical research with so much enthusiasm, overview and knowledge. He and Edwin G. Krebs were distinguished in 1992 for the discovery of the mechanisms that control the metabolic processes in organisms such as reversible protein phosphorylation. The biochemist is a Professor Emeritus of the University of Washington, Seattle.

Klas Kärre,
Chairman of
the Nobel Assembly
for Physiology or
Medicine 2014

Harald zur Hausen
This German medical scientist advanced the initially unpopular hypothesis that viruses can trigger cervical cancer. After many years of intensive research he finally achieved irrefutable proof of his hypothesis, which in 2008 brought him the Nobel Prize in Physiology or Medicine (the other half going to two HIV researchers). The virologist works at the German Cancer Research Center in Heidelberg and is now investigating whether viruses are also involved in the development of bowel cancer.

Ferid Murad
He began his career as a clinician scientist then changed to clinical pharmacology. Murad researched the mechanism of vasoactive substances and was the first to hypothesize and subsequently prove that a small anorganic molecule such as nitrogen monoxide (NO) could act as a powerful signaling molecule. Together with colleagues he unraveled the effect of NO in the dilation of blood vessels. In 1998 he received the Nobel Prize in Physiology or Medicine (with Robert F. Furchgott and Louis J. Ignarro). Murad has five children, is a highly, nearly restlessly active researcher, science speaker and teacher. He currently works at George Washington University in Washington D.C.

Erwin Neher
Up until 2011 the biophysicist was director of the Max-Planck Institute for Biophysical Chemistry in Göttingen. This Leibniz Prize winner closely collaborated with Bert Sakmann for many years, although often not at the same institution. At the center of his work are the discoveries of ion channels in cells, which in 1991 were crowned with the Nobel Prize in Physiology or Medicine. As a Professor Emeritus, the father of five children now researches as an emeritus group leader.

Randy W. Schekman
The molecular biologist was the »youngest« Nobel Laureate among the workshop participants. In 2013 he was awarded the Nobel Prize in Physiology or Medicine (with James Rothman and Thomas Südhof). At the core of his work are the transport mechanisms of proteins within cells. His findings were initially gained using yeast, however the processes could also be verified in higher organisms. Schekman is a professor at the University of California, Berkeley.

Thomas A. Steitz
For his studies on the structure and function of the ribosome, he received the Nobel Prize in Chemistry in 2009 together with Venkatraman Ramakrishnan and Ada Yonath. He presented a tangible crystal structure of ribosomes which are also referred to as »protein factories.« Steitz researches and teaches at Yale University in New Haven and is an investigator at the Howard Hughes Medical Institute. The Steitz Lab is concerned on a broad basis with macromolecules and their internal processes.

Kurt Wüthrich
In 2002 one half of the Nobel Prize in Chemistry went to the Swiss Kurt Wüthrich. He received the distinction for the development of nuclear magnetic resonance spectroscopy (NMR) used for unraveling the three-dimensional structures of macromolecules in solution. Today, Wüthrich divides his time between the ETH Hönggerberg in Zürich and the Scripps Research Institute in La Jolla (California). With dry humor, he submitted that even prize money of a stately four million euros is not much relative to the financial requirements of a fast moving experimental field of research and that the foundation money would perhaps be better invested in the cofinancing of a highly advanced NMR machine.

EKFS is proud and grateful that all the named personages have dedicated their time and above all, their astute minds to our question.

We would particularly like to thank the Foundation Lindauer Nobel Laureate Meetings. The workshop in Lindau would not have been possible without the commitment of both its Chairman Wolfgang Schürer and Managing Director Nikolaus Turner.

Prizes as driving forces

An auspicious signal for the event was an encouraging word of welcome from Klas Kärre, chairman of the Nobel Assembly for Physiology or Medicine 2014: »Research prizes in general are important because they contribute to the recognition of science and motivate talented young people to venture into a science career. Prizes such as the Else Kröner Fresenius Preis für Medizinische Forschung, dedicated to funding future research developments have the potential to initiate new and important discoveries – ultimately to the benefit of mankind.«

Aims and process

The overriding objective of the morning consisted of identifying fields of medical research which

- have far-reaching pathophysiological relevance,
- are ready for a leap in knowledge the coming five to ten years,
- can be expected to generate some 20 to 40 outstanding nominations of prize candidates worldwide.

In-depth discussions: Workshop in the historic Fischerstube at the Bad Schachen Hotel, Lindau am Bodensee

As in Bad Homburg, the highly structured workshop was lead by Katharina Janus and Federico Lega. An artist and a scientific illustrator, Mathias Weitbrecht and Tami Tolpa, recorded the results of the discussion graphically (see center pages).

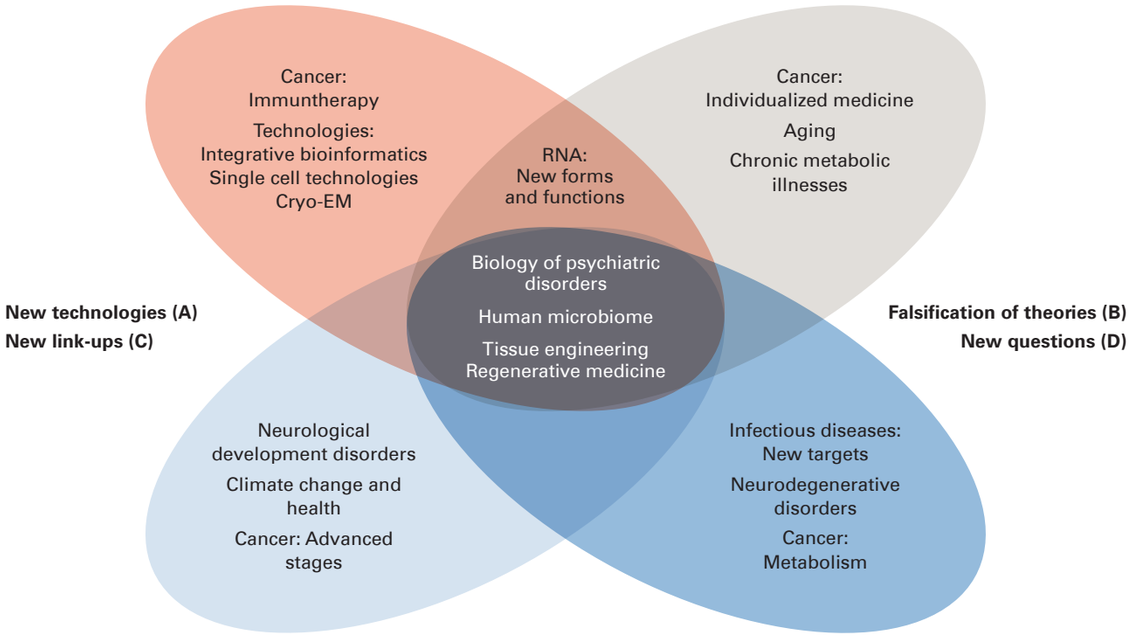
To begin, four groups gathered around separate tables and approached the subject from different jumping-off points:

(A) New technologies that open doors to unanswered questions.
(B) New knowledge challenging accepted theories.
(C) New connections between hitherto unrelated fields.
(D) New fields which have not been studied before.

In the next step, each table named around six forthcoming and promising fields of research. These were further prioritized through a combination of personal rankings of the six identified subjects and intensive discussion. All the participants discussed these fields of research later in a major round and condensed them finally to three favorites.

The goal of the procedure was to generate suggestions in a broad, wide-ranging approach. Our hope was to find converging suggestions from the independently working tables. The approach naturally also carried risks: What if there were no convergence at all? In the preparatory discussion, one of the moderators expressed concern: »You may end up with as many suggestions as there are participants. What will you do then?«

The unfamiliar, highly structured workshop format surprised many participants and was risky for us as hosts of



The image illustrates the results of participants at the four tables, who used the different points and questions (A) to (D) to identify promising research fields (see also page 19). The workshop experiment was a success: there was a strong degree of convergence, with the three research fields in the center of the image appearing several times on the list of results.

the event: Was it to be expected of Nobel Laureates that they would submit to such a highly structured discussion process? Was it acceptable and wise to incorporate »fundamentally democratic« elements into a decision-making process on science? Some participants were critical of this. Erwin Neher, 1991 Nobel Prizewinner in Physiology or Medicine, in the end came to the following conclusion: »I do think that the discussion at individual tables was very interesting (at least at ours) due to a good mix of participants with different perspectives.«

Another question left open was factors that would influence the suggestions and prioritization of subjects. Would participants' own respective fields of research dominate the discussion or would there be room for entirely new ideas? »I thought people would be ›fighting‹ for their favorite field. Indeed, in the beginning there were some personal biases, but these quickly converged on some common themes, and ultimately we had clear consensus,« as Ruslan Medzhitov described the discussions at his table.

Results

One of the most exciting highlights of the morning was the presentation of the suggested research fields. Each of the four tables presented its rankings. Even at first glance, strong overlaps in the most highly prioritized research fields were evident. Many of the participants were surprised: »I was surprised by the convergence of the different groups. The ideas put forward were excellent,« said Orla Smith from *Science Translational Medicine*. Linda Miller named one field on the list which was completely unexpected for her: »One surprise for me was the inclusion of »Climate Change Effects on Health« at one table. Even though I am an immunologist, I think that the biggest science challenge facing society today is climate change. Food production, insect and parasite-borne diseases, tree ranges, bee and other pollinator range changes – so many aspects need hard data upon which to make decisions.« Carsten Könneker from *Spektrum der Wissenschaft*, summarized: »It is remarkable that in groups working independently of each other on different questions, we did indeed to an extent come to the same conclusions in the end. That speaks for the strength of precisely these ideas, but also for the process.«

The three subjects that garnared the strongest support will be very briefly presented in the following. These fields are ripe for acquiring promising new knowledge that has the potential to be pivotal, both for research and clinical implementation.

1. The biology of psychiatric disorders

New functional imaging techniques, as well as the recent development in genomics provide strong stimuli for research. In spite of substantial advances in diagnosis and therapy, the formation of psychiatric disorders is still not understood to a great extent. Furthermore, entirely new possibilities are looming in experimental research into the mechanism of these disorders: new, highly advanced animal models as well as tissue models based on induced stem cells have become available. These new opportunities are flanked by large publicly financed programs dedicated to analyzing the structure, functional integration and metabolism of the brain.

2. The human microbiome

In this field of research, many different specialized disciplines are merging together. There are billions of microorganisms in





Senior editors from the specialist journals:

Alison Abbott
The Briton received her doctorate in pharmacology at the University of Leeds. In 1992 she joined the British science journal *Nature*. She works in Munich where she is now senior European correspondent. She has greatly contributed to the international visibility of German and European research policy-related activities.

Tim Appenzeller
Since 2013 the science editor and author has been head of the news section of the U.S. scientific journal *Science*. For more than 30 years Appenzeller has been making a name for himself in science journalism. He reports, among other things, on environmental topics and was previously chief magazine editor of *Nature*.

Véronique Kiermer
A chemist and molecular biologist, Kiermer is the executive editor and head of Researcher Services for the Nature Publishing Group (NPG) in New York and is deeply involved with the quality of peer review processes. She studied in Brussels and did research on HIV.

Carsten Könneker
Physicist and literary scholar, Könnecker is chief editor with *Spektrum der Wissenschaft* in Heidelberg and is responsible for several magazines. He is head of the National Institute of Science Communication.

Juan Carlos Lopez
A neuroscientist who has worked with amongst others, the Nobel Prizewinner Eric Kandel at Columbia University in New York, Lopez is Mexican by birth. He was chief editor of *Nature Medicine* from 2000 to 2013. Then he switched to industry and is now head of Academic Relations and Collaborations with Roche Pharma Research and Early Development in New York.

Linda J. Miller
An immunologist, Miller was one of the jury members of the Else Kröner Fresenius Award 2013. She advised EKFS in designing the current process of searching for an up-and-coming field of research for the next prize. With a great deal of commitment, she established the contacts with senior editors of specialist journals. Miller founded *Nature Immunology* in 2000.

Esther Schnapp
Since 2008 the scientist has been on the editorial team at *EMBO Reports* in Heidelberg. She received her doctorate at the Max-Planck Institute for Molecular Cell Biology and Genetics in Dresden where she worked on tail regeneration of the Axolotl (salamander). She spent her postdoctorate period in Milan at the San Raffaele Stem Cell Research Institute.

Thomas Schwarz-Romond
During his time as a researcher, Schwarz-Romond investigated the Wnt signaling pathways, i.e. one of the processes with which cells can react to external signals. He has worked at the Max-Delbrück-Centrum in Berlin-Buch, amongst others. Since 2006, Schwarz-Romond has been an editor at the *EMBO Journal* and is now senior editor.

Orla M.Smith
The biochemist studied in London and spent her time as postdoc at the Johns Hopkins Medical Institution in Baltimore. While there, she researched the cell and molecular biology of stem cells. She has worked for various specialist journals like *Cell, Nature Medicine* or *Science*. Smith has in the meantime become managing editor of the journal *Science Translational Medicine.*

our bodies forming various mixed populations and interacting with human host tissues via a multitude of molecules and signals. Increasingly, their role in human health and disease is being recognized – even where previously this had not in the least been suspected. This applies for instance to inflammatory diseases, as well as obesity or cardiovascular disease. »Good bacteria« are in the meantime being clearly distinguished from the bad, pathogenic microbes and researchers are investigating these intensively. An important research objective will be to understand how the human microbiome can be deployed in the service of health and in the prevention of illness. A further pressing question: How can microorganisms be used to overcome resistance to antibiotics? And last but not least: How true is the adage »you are what you eat?«

3. Tissue engineering and regenerative medicine

3D cell structures and tiny organs on a microchip: the regeneration and reconstruction of organs implies an enormous scientific and clinical potential. Both academic and industrial research is at present investing massively in this area. Accordingly, the research field is developing fast, but rapid advancements are also to be reckoned with in the future. Engineering science and stem cell biology merge here. The objective of these efforts is ultimately organ replacement. Closer on the horizon is the utilization of emerging tissue and organ models in research. New possibilities are thus opened up for pathophysiological research into tissues as well as for high-throughput drug screening. The experimental methods will complement and possibly, in part, replace mouse models.

Where do we go from here?

The three subjects are of course already the focus of worldwide research. It is precisely because of the increased activity and availability of major publicly financed resources, however, that enormous opportunities are opening up. The next task for EKFS is to explore these three areas and organize a competitive call for our major research prize. To devise a global, transparent, excellence-orientated nomination and selection process for the next award is a great challenge for which we have to find suitable partners.

»We should try to find new ways to do our science«

How can the individual researcher succeed in maintaining the spark of passion for their work? Young scientist Elzbieta Kowalska has written down her thoughts.

»When the smile on your face is gone, it is a warning sign. If you do not enjoy what you do anymore, you should get up and act. In Western countries, we are used to believing if we study hard, work hard and publish well, we will for sure find our place in science. But it is not that easy anymore. Nowadays, I often see people settle down for something secure and less stressful then what made them smile in the first place because it seems the safer choice. This comes coupled with a disappointment in science, the loss of the scientific spark for new and curious things. The fear of following up an »unsexy« topic and therefore being unfundable (or maybe even considered a little bonkers) is not a friendly companion.

We as scientists have a vocation full of privileges. No, not money-wise, but I have yet to meet persons that based their life on how much they possess and were satisfied with the outcome. In the past years, the degree of anonymity and competition for money in science has increased, and science itself has become more and more a business for »selling a hypothesis« rather than a playground for the mind. As this is our vocation, we should give our utmost, stand up, disagree and try to find new ways to do our science.

We have a lot of freedom: we peer-review ourselves, have regular worldwide meetings, and interact in a cross-disciplinary way as well as across borders. This open dialog is the best way to improve science. Do not take these privileges for granted, do not forget to defend them if necessary. Scrutinize your motives and your way to do science if your smile is fading.

You need to go out on a limb with your idea of how you want to do science. You have to reach out to your fellow scientists if things need to change, hoping that they pick up your spark. And if you all reach a critical mass, you have already succeeded because you planted the seed of doubt that current measures and regulations for doing science are not meeting the requirements of scientists nowadays. And if this critical mass will raise its united voice, engage in moving this train of thoughts forward, then you will have made an impact. You have fulfilled your duty as a scientist: making others think and engage in understanding and solving a problem.

It does not matter where you come from, what university you graduated from or which sex you are as long as you speak up when you think your thoughts will make science a better playground in the future.

This will keep the smile on your face.«

Elzbieta Kowalska
She is one of twelve postdocs who took part in the EKFS workshop in Lindau. The transcription biologist was born in Poland in 1981, grew up in Switzerland and now works at the Max F. Perutz Laboratories in Vienna (Austria). She is investigating which processes control the reading of DNA and RNA. Besides her field of research, she is interested in theories from the sphere of physics – transboundary thinking is her passion.