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Science at the Chemistry Biology Interface, some Personal Thoughts

Andreas Marx[a]

Abstract: In this essay, I depict some personal thoughts and experience related to Chemical Biology. A particular emphasis is put on education and training of the new talents in the field and in consequence, I give the youngest generation the opportunity to express their opinion on Chemical Biology.

Keywords: Chemical Biology · Emil Fischer · Graduate Education · Chemistry Biology Interface

1. Prelude: Defining Chemical Biology and some Personal Experiences

I very well remember my first days starting my independent career at the beginning of the new millennium: Discussions boomed on how to coin Chemical Biology and how to define its scope, particularly in comparison to Biological Chemistry and Biochemistry (as well as other disciplines). One of my favourite arguments along these lines was how a discipline that carries one of the drivers, namely Chemistry, as an adjective only in its naming, can be an appealing subject for a chemist: "Doesn't this downgrade Chemistry to nothing else but an auxiliary science for Biology?" Well, these wordings still leave me puzzled. My motivation to start research at the interface of Chemistry and Biology was the interest in gaining insight into processes that determine Life and the aim to understand them in molecular and even atomic details, thus in chemical terms. This fascinating, yet challenging task requires that multiple scientific disciplines are brought together to create new synergistic interdisciplinary approaches with Chemistry being one of the main drivers.

My perception thus, intrinsically subjective is, that several years ago, Chemical Biology was mainly understood as a discipline that discovers and explores new "small" molecules as probes to scrutinize biological processes. Without any doubt, this is an extremely important, timely and lively subject. However, in my eyes Chemistry is much more and I agree with Emil Fischer who put this idea into words:[1] "Chemistry is the land of the unlimited possibilities". Chemistry offers and advances a cornucopia of crucial concepts, approaches, methods and technologies at the Chemistry Biology interface. As an example, inputs from (Bio)Physical, (Bio)Analytical, and Computational Chemistry significantly spur progress in imaging and the omics sciences and at the same time approach the grand challenge to mine the obtained overwhelming data in these areas. It is marvellous to witness the traditional separation of science into different disciplines losing more and more its justification and the respective expertise of the different areas of research in Chemistry and Biology merging into synergistic interdisciplinary and mutually illuminating approaches.

During recent years, the field of Chemical Biology has undergone a continuous maturation process driven by the advent of new technologies and increasing awareness that insights into complex biological systems require interdisciplinary efforts. In consequence, Chemical Biology evolved into a multidisciplinary research area where novel tools and methods are developed to make profound scientific discoveries. This has become possible by impressive advancements made in the Chemical Biology repertoire, generating sophisticated probes that allow to analyse, modulate, and monitor biomolecules and complex biological processes at an atomic and molecular level, respectively. The conceptual transition from a single edge discipline to an integrated research field, where key scientific questions are addressed by multiple, interdisciplinary and complementing approaches, puts Chemical Biology into a prime position to make significant contributions to the understanding of the intricate network of cellular pathways and how they are regulated and fine tuned in a concerted manner.

2. Chemical Biology – A Temporary Hype or Long-lasting Adventure?

One question that I often encounter in discussions with friends is whether Chemical Biology is a "trendy (=fundable)" discipline and if the "current hype", as all "hyped" trends, will vanish over the years? One should keep in mind that in history of civilization several trends have been come back after decades. But is the (prospective) impact on progress in science and its impact on society of research at the interface of

[a] A. Marx
Department of Chemistry, Konstanz Research School Chemical Biology, University of Konstanz, Germany
E mail: andreas.marx@uni konstanz.de

Chemistry and Biology something that has been recognized only recently during the last 25 years? Again, I would like to quote one of the biggest Chemistry giants, Emil Fischer.[1] Already in 1911, on the occasion of an experimental lecture addressing the German emperor, he said:

"…der ganze Stoffwechsel im lebenden Organismus ist eine Aufeinanderfolge chemischer Verwandlungen, die sich an diesen Stoffen vollziehen. Infolgedessen ist die Chemie berufen, mitzuarbeiten an der Lösung der großen Rätsel des Lebens…"

(my translation: "…the whole metabolism in the living organism is a succession of chemical transformations that take place in these substances. As a result, chemistry is called to participate in solving the great riddles of life…")

For me most remarkable was his lecture on "Chemie und Biologie", given at the end of 1915 and especially his following words:

"…So sehe ich, halb im Traum, eine chemisch syntheti sche Biologie entstehen, die der Lebewelt […] gründlich ins Handwerk pfuscht…"

(my translation: "…So I see, half in a dream, a Chemical Synthetic Biology arise that interferes with the living world…")

He concludes with

„…Das Gesagte wird genügen, die großen Linien erkennen zu lassen, auf denen Chemie und Biologie als Bundesgenossen den hartnäckigen […] Kampf mit den Geheimnissen der Lebewelt führen…"

(my translation: "…All that has been said will suffice to reveal the great lines on which Chemistry and Biology as allies lead their persistent struggle with the secrets of the living world…")

Thus, more than a century ago Emil Fischer described the tremendous prospects of an alliance between Chemistry and Biology. Since then, Chemistry on all levels has generated invaluable insights into matter, its constitution, formation and manipulations and provides a plethora of opportunities. Biology has developed from an almost merely descriptive science to a field that also harbours disciplines focussing on molecular insights into Life, such as Biochemistry and Molecular Biology e.g., featuring aspects of diverse but intertwined subjects such as Cell Biology, Genetics, Immunol ogy, Structural Biology, or Microbiology. This provides an excellent basis for future breakthroughs towards understanding of Life. Due to the refinement of tools like mass spectrometry, the picture we get on the complexity of Life increases in a breath taking fashion. To give an example: nowadays, more than 150 posttranslational modifications in proteins[2] are known to modulate the function and life of proteins after translation ranging from being as "simple" as methylation to "more complex" e.g., built of chains of proteins such as ubiquitin[3] or the nucleic acid type polymer poly(ADP ribose)[4] (Figure 1).

The "more complex" protein modifications are of partic ular research interest to me. For instance, the protein modification by ubiquitin, called ubiquitylation comes in different flavors. As ubiquitin also serves as its own substrate, ubiquitin chains are formed, in which the individual moieties are linked via one or several of the seven lysines of ubiquitin. Homogeneous ubiquitin chains, in which the moieties are sequentially linked via the same residue, have been most extensively studied. However, there is a lack of tools that allow to image the formation and degradation of these chains e.g., depending on environmental conditions or in disease states, which would also provide first hand insights into the origins of diseases that stem from the malfunction of these processes. By pushing the limits of protein chemistry, Chemical Biologists have just recently addressed these short comings. They now provide a plethora of tools for new concepts to explore these processes by novel approaches that could not be achieved before.[3] This includes the synthesis of linkage defined ubiquitin chains as well as site specifically modified proteins of particular interest. We are only at the beginning to leverage the options arising from these possibil ities, for example ranging from the elucidation of modifica tion depending interaction networks[5] to a more specific biochemical unknown assembly[6], e.g., in chromosomes to name only two areas that I am actively doing research in.

Andreas Marx, born 1968 in Lübeck (Germany), studied chemistry at the Universities of Freiburg (Germany), Sussex (UK), and Bochum (Germany) 1988 to 1993. He graduated from Professor Bernd Giese's group at the University of Basel (Switzerland) in 1997 in the field of organic chemistry. Afterwards, he joined Professor Hisashi Yamamoto's group at Nagoya University (Japan) as a JSPS/EU postdoctoral fellow in working on organometallic catalysis. At the end of 1999 he started his Habilitation at the University of Bonn with the mentorship of Professor Michael Famulok and obtained the venia legendi in organic chemistry and biochemistry in 2003. January 2004 he followed a call of the University of Konstanz (Germany) for the chair of organic chemistry / cellular chemistry at the Department of Chemistry. Andreas Marx was the Department Head form 2005 2008, Vice Rector of the University of Konstanz for Research and Junior Researchers from 2010 13 and is the coordinator of the "Konstanz Research School Chemical Biology" that was award within the Excellence Initiative of the German federal and state governments in 2007. He is currently a member of the Study Section Chemistry at the German Science Foundation (DFG). The aim of his research is to gain insights into mechanisms of complex biological processes through application of synthetic molecules with tailored functions and properties. The current research comprises the targeted synthesis of functional (bio)molecules (e.g., (oligo)nucleotides, proteins), and their subsequent applications in order to explore complex biological processes. Additionally, he develops biotechnological approaches by combinatorial and rational enzyme design and directed evolution in order to tailor DNA polymerases with new or improved functions. In 2013, he was awarded an ERC Advanced Grant and in 2014 the Karl Heinz Beckurts Prize.

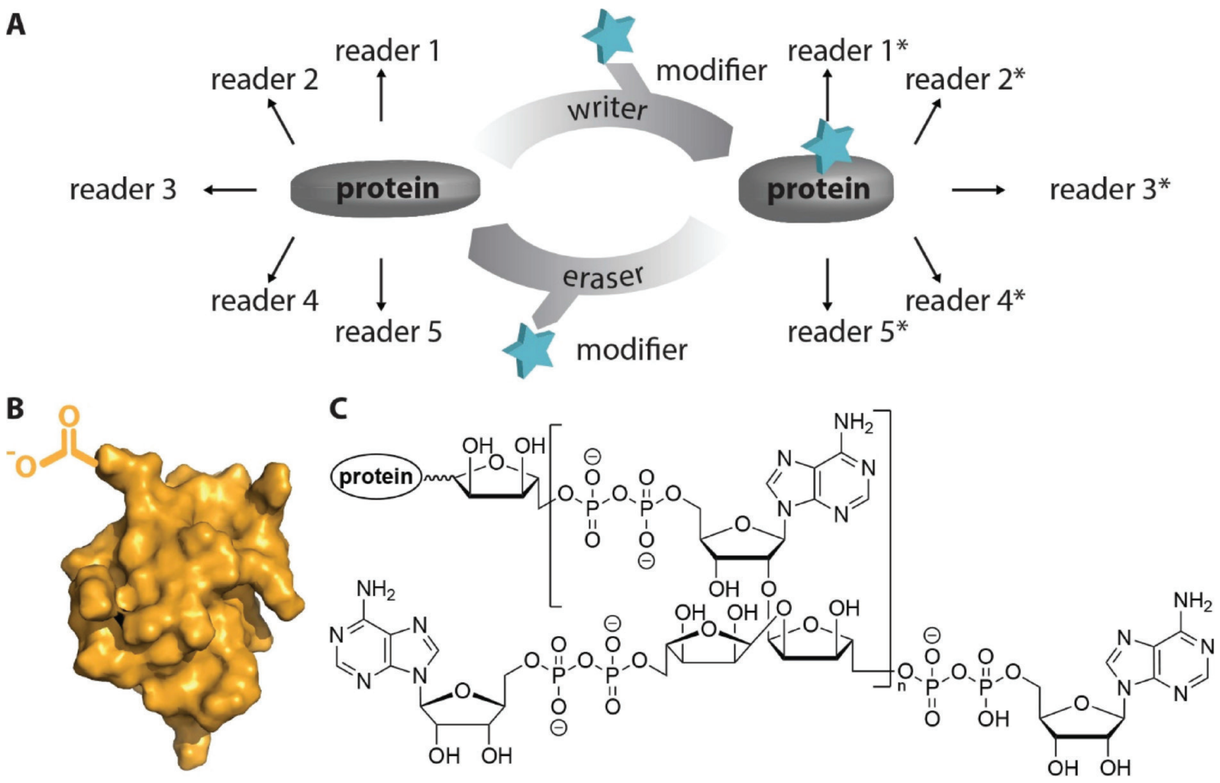

Figure 1. A) Schematic depiction of the writing, reading, and erasure of protein posttranslational modifications. Posttranslational modifications may alter the properties and function of an protein (e.g., switching a protein on or off) and/or its interaction network with other proteins ('readers'). B) Depiction of ubiquitin highlighting its C terminal. C) Structure of poly(ADP ribose).

The "biological machinery" that orchestrates ubiquitylation is built on a three step protein cascade for specific connection of ubiquitin to a target and proteins that reverse the connection. They make up more than 700 proteins (Figure 2).[3]

Malfunction of this machinery is often related to diseases. One example that strikes me is E6AP, an ubiquitin ligase

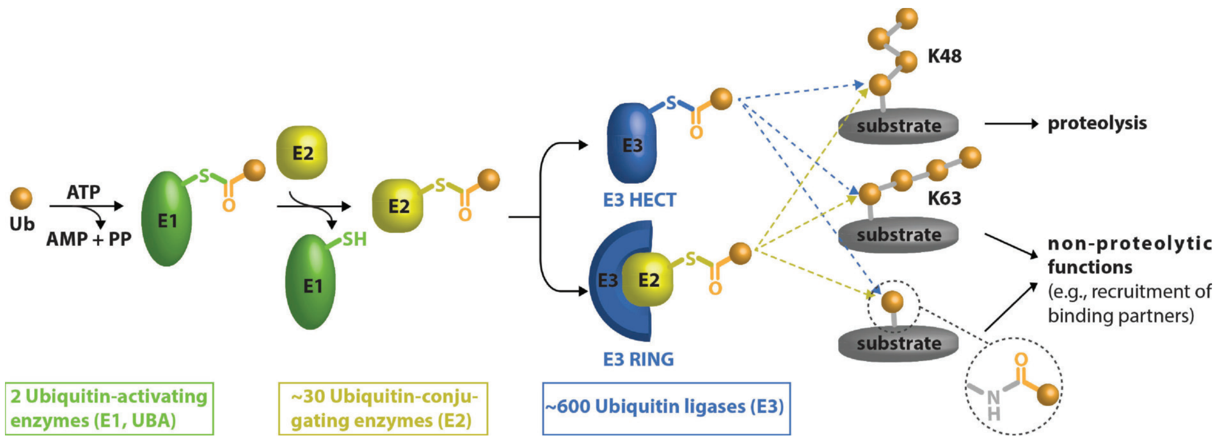

Figure 2. The ubiquitylation cascade. Ubiquitin is activated by ubiquitin activating E1 enzymes (two are known in humans) by the expense of ATP to form thioester with the E1. Ubiquitin it afterwards transferred to ubiquitin conjugating E2 enzymes (more than 30 are known in humans) again to form thioesters. Afterwards the ubiquitin ligase E3 enzymes (about 600 are suspected to be in humans) transfer the ubiquitin to its designated substrate. Ubiquitylation comes in different flavours (e.g., different chain types, mono ubiquitylation, etc.) with different biological consequences.

responsible to connect ubiquitin to specific target proteins. Unscheduled activation of E6AP function contributes to the development of cervical cancer, while loss of its function affects the nervous system leading to the Angelman Syndrome which is characterized by developmental delay and intellectual disability.[7]

The ubiquitin ligases like E6AP are very difficult to target with drug like molecules. I am convinced that in future Chemical Biology will open up opportunities that will allow for medicinal chemists to develop specific inhibitors or activators of dysfunctional ubiquitin ligases ultimately leading to new therapeutic approaches.

Not only proteins get modified after their genesis, also nucleic acids are modified. The number of known posttranscriptional modifications in RNA has risen also to be larger than 150 in recent years and the modifications are very diverse (some examples see Figure 3).[8]

In DNA, the importance of nucleobase modifications for cellular processes was also further delineated and corroborated.[9] Albeit being only in its infancy, studies prove the importance of these natural albeit chemical modifications in homeostasis and emergence of diseases and therapy. Along these lines already some surprises struck me. One of the most remarkable incidents was the finding of the enzymatic function of the Fat mass and obesity associated protein (FTO). Its malfunction is correlated with increase in body weight and obesity. Only recently it was found that its main function was to erase the *N*6 methyl of *N*6 methyladenosine, an abundant nucleobase modification in RNA![10] I am convinced that we will witness many more important and surprising discoveries that are directly related to health and the onset of diseases in future. Chemical Biologists are spurring the field by pushing nucleic acids chemistry and analytics (i.e., by mass spectrometry). However, in order to device valuable therapies, robust and affordable diagnostic means need to be in place. Current approaches for the site specific detection and quantification of RNA and DNA modifications are mostly cumbersome and labour intensive and thus, very error prone.[11] In my eyes, along with the exploration of the Chemical and Molecular Biology of these modifications, practical approaches for the site specific analysis and quantification need to and will be developed.

Despite all the advances and increases in knowledge, we are still far from understanding the impact of these modifications on biological processes even on a molecular or cellular, not to mention organismal level. Moreover, the intricate network of e.g., protein protein, protein nucleic acid, and nucleic acid nucleic acid modifications, is mostly elusive. The elucidation of these pivotal biological processes that are controlled by chemical modifications can only be mastered by close collaboration from Chemistry and Biology. The modifications are diverse and structurally often very complex and thus, very attractive for daring chemists to synthesize and investigate. Often these modifications can only be investigated by chemical synthesis or new (bio)physical means. The impact of many (if not all) modifications and their (mal)function on the onset of diseases is without doubt. Elucidating their biological role and functions will provide new avenues for therapy. Therefore, I am convinced that there are many, yet unforeseeable, opportunities for generations of scientists to discover, reveal and explore in order to advance science and serve the society. Science at the interface of Chemistry and Biology will become even more vivid in the future!

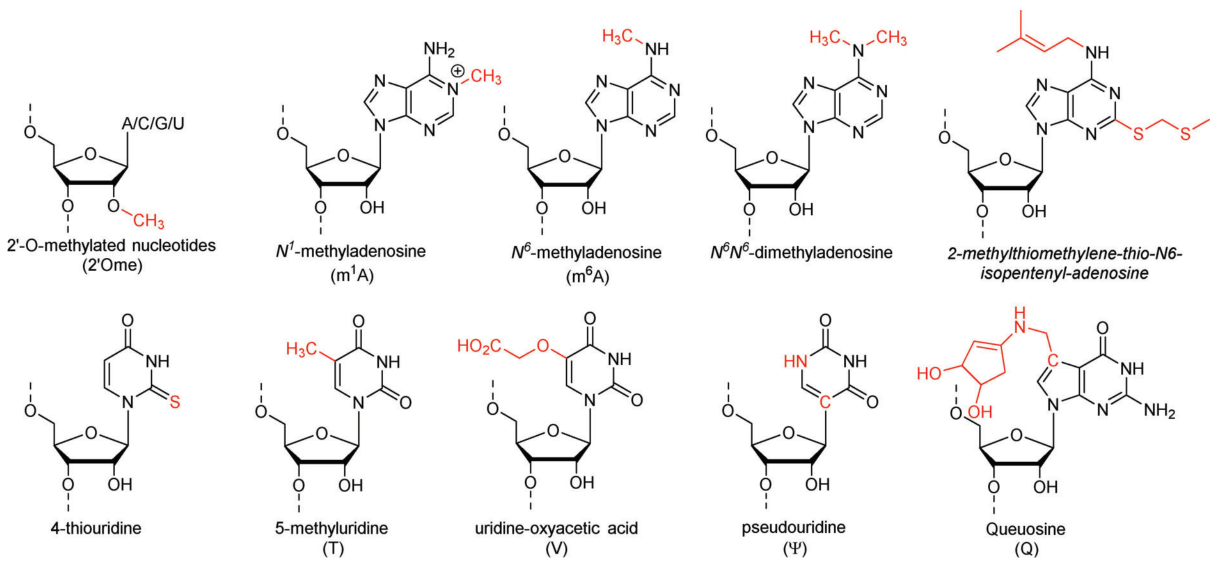

Figure 3. Selected examples of RNA modifications.

3. Teaching and Training of Talents – some Local Experiences

Since approaches in Chemical Biology require interrelated advances on both sides, chemistry and biology, the novel concept of Chemical Biology also involves that the two disciplines and their associated research fields move closer together; a development that puts specific demands on the education and training of the next generations of chemical biologists. Having this in mind, we, at the University of Konstanz, founded a cross departmental graduate programme (i.e., *Konstanz Research School Chemical Biology, KoRS CB*) that was funded in the German Excellence Initiative from 2007 2019.

Our experience is, that graduates trained in Chemistry and Biology work and will continue to work in a wide range of institutions including universities, industrial and business establishments, and government institutions where they advance scientific progress and play important roles in evolving future industrial strategies and enterprises. Due to the speed of technical progress accompanied by the accumulation of scientific data and knowledge, both chemists and biologists are increasingly confronted with interdisciplinary topics and, thus, are facing the challenge of collaborating with professionals from other disciplines to tackle and resolve the foremost questions of basic and applied research. To meet this challenging task, the *KoRS CB* strives to offer (1) an internationally competitive and collaborative research environment that allows its doctoral researchers to address their research projects with state of the art methods and (2) a research training programme that takes account of the different academic backgrounds of the doctoral candidates to provide them with the best possible education and preparation for their career. Perhaps the most challenging task is to keep doctoral fellows interested in broadening their scientific horizon beyond to what may appear to them as essential for their thesis. To achieve this, the *KoRS CB* training programme aims at sensitizing its doctoral researchers to the notion that it takes interdisciplinary collaborative efforts to successfully approach actual and future research problems and that this requires mutual scientific understanding and appreciation, i.e. to learn the language of other disciplines. More details can be found online.

An important basis for the implementation of a graduate programme in Chemical Biology was an interdisciplinary study course at the University of Konstanz. The study course "Life Science" was founded in 2002 and supported by the Departments of Chemistry and Biology with an equal teaching load and with virtually all research groups participating in *KoRS CB* being involved in this programme. With the establishment of the graduate programme in 2007, this interdisciplinary education at the interface of Chemistry and Biology has become a permanent offer starting forthe Bachelor students up to the doctoral level.

4. Two Questions Answered by several Current and Former Konstanz Fellows in Chemical Biology

To finish, I would like to give the floor to younger generations of Chemical Biologists. I asked several of my former and current group members to reply to two questions: Why they are interested in Chemical Biology and what their expectations are regarding the future of this discipline. Responses are depicted in the following.

4.1 Why are you interested in Chemical Biology?

Karin Betz: I'm fascinated by the complex molecular mechanisms that are the basis of living organisms. Further understanding these mechanism is the reason why I am working in the field of Chemical Biology.

Susanne Ermert: Chemical biology is the basis of our life.

Matthias Frese: It's fascinating how the multitude of so little (bio)chemical and biological processes provide the functional basis of a cell and beyond, the proper development of an entire multicellular organism. Understanding the sheer complexity of these systems is quite a challenge as well as a motivation.

Alexander Finke: Chemical techniques or chemically synthesized molecules can facilitate the solving of biological questions and are sometimes even the vital prerequisite.

Simon Geigges: It's fascinating how chemical methods and tools can help to mimic, study and understand biological processes and systems.

Kathrin Götz: During school days I was interested in medicinal topics, however I decided deliberately against a medicinal training, since I not only wanted to treat diseases but wanted to understand their molecular mechanisms. For me doing research in the field of chemical biology is since then the perfect path do this.

Stephan Hacker: It has always fascinated me that Chemical Biology allows us to create novel chemical molecules and immediately use them to understand biologically important systems in the same research group.

Doreen Herzog: For me, Chemical Biology combines the experimental with the intellectual part in science. It's a broad field with different opportunities that's why research in this field never gets boring.

Ramon Kranaster: I like it, because it combines the understanding of biological systems with the chemical capabilities of a chemist.

Samra Ludmann: Coming from chemical synthesis to the Chemical Biology "world" was an important and really satisfying step for me. I was able to use my synthesized compounds to elucidate and understand biological processes. Using chemistry as a toolbox to understand biology is a very powerful tool and both disciplines can benefit from that.

Joachim Lutz: I'm interested in Chemical Biology as it allows the application of innovative methods which are in many cases based on chemistry, in order to address complex biochemical questions that would be hard or even impossible to answer by pure biochemical means.

Maite Missun: The combination of chemical and biological tools and methods to get a better understanding of complex biological processes and systems, makes the field particularly interesting.

Vanessa Radtke: For me, Chemical Biology is a fascinating topic, because I find it impressing how nature can produce such a broad spectrum of biopolymers that differ extremely in their functions although they are built from the same limited number of building blocks. Furthermore, working in this field brings together people who look at the same scientific questions with different perspectives, and this creates an inspiring work atmosphere.

Philip Saumer: I am very interested in applying chemical tools and overall chemical knowledge to complex biological systems in order to gain valuable insights that would have been impossible to gain otherwise. For me this is the essence of Chemical Biology.

Janina von Watzdorf: Chemical Biology is a very broad and multidisciplinary field that is fast growing and expanding as it offers numerous possibilities to gain insight into biological problems at a mechanistic level. Therefore, Chem ical Biology acts as example of how multidisciplinary thinking can really push things along.

Xiaohui Zhao: I think there is a gap between Bio(in) organic Chemistry and Biochemistry which is perfectly filled by Chemical Biology.

4.2 What are your Visions for the Field in the Future?

Karin Betz: People will more and more understand the basic principles in living systems which will help to develop new therapeutics. I assume that also artificial systems mimicking the natural ones will be pushed further. The possibility to sequence whole genomes relatively fast and cheap will change the field of diagnostics. Gained knowledge, however, also comes along with ethical questions which we will also have to handle in the future.

Susanne Ermert: Better understanding of how life, fitness, environment and diseases are connected to each other.

Matthias Frese: Of course, unveiling the complex processes to understand life is the ultimate goal. Thus, once, hereditary diseases will be easily tackled and deathly plagues eradicated.

Alex Finke: As the field is expanding very fast and is already being employed broadly for biotech & biopharmaceut icals, it will have a major impact on our daily life.

Simon Geigges: Chemical Biology research provides the basic knowledge for future developments in biotechnology, diagnostics and health care.

Kathrin Götz: My vison for the field in the future is, that new tools are developed allowing us to study even more complex systems. With the data gathered from these studies it will be possible to tackle diverse problems mankind is facing (e. g. development of new antibiotics).

Stephan Hacker: I think in the future the field will become even more interdisciplinary and have a very important function in bringing together researchers from many disciplines, including Chemistry, Biology, Physics and Computer Scien ces, to tackle important challenges of society.

Doreen Herzog: I would like to see, that Chemical Biology becomes more accepted as an autonomous field in the broad spectra of science. We are not belonging to the chemists and not to the biologists although we combine the knowledge of both parts in our field.

Ramon Kranaster: The interdisciplinary approach will enrich and strengthen multiple frontiers of human research such as the origin of life or the creation of new nanomachines.

Samra Ludmann: The fast progress in Chemical Biolo gy enables to lower the costs for sequencing the whole human genome from 100 mio$ to 1000$ in less than twenty years. Pointing to the future personal diagnostic might be soon feasible and economically efficient. In line with this progress more and more the ethic aspect gains in importance. Do you really want to know, if you e. g. have a mutation that is associated with a not curable disease   for instance, if you do not have any symptoms yet?

Joachim Lutz: In the future I hope that tools established by chemical biologists will allow a deeper understanding of so fare unknown processes that lead to severe phenotypes observed in neurodegenerative diseases, cardiovascular dis eases or cancer.

Maite Missun: Chemical Biology is a relatively new field, which is why my visions for the field in the future would be the application of the gained knowledge and methods, to treat and prevent a variety of diseases, for which traditional pharmaceutical substances and methods fail.

Vanessa Radtke: I hope that in future all the small pieces of knowledge gained by chemical biological research can be combined, giving rise to a big picture   on a molecular level   of how the human body works when healthy and when ill. This knowledge can be used not only to treat the common but also the rare diseases.

Philip Saumer: A great success would be the development of a large toolbox of chemical methods that can be applied to a wide range of biological questions hopefully enabling breakthrough discoveries.

Janina von Watzdorf: Chemical biologists are driven to dissect chemical and biological complexity until new insights emerge. Therefore, there are countless possibilities where scientists in this field can focus on. My vision for Chemical Biology is to keep focusing on solving major health problems that are part of our worldwide society.

Xiaohui Zhao: The field has been and will be further subdivided, such as chemical therapy, chemical imaging, chemical proteomics, chemical immunology, chemical neurol ogy, chemical microbiology, and more.

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