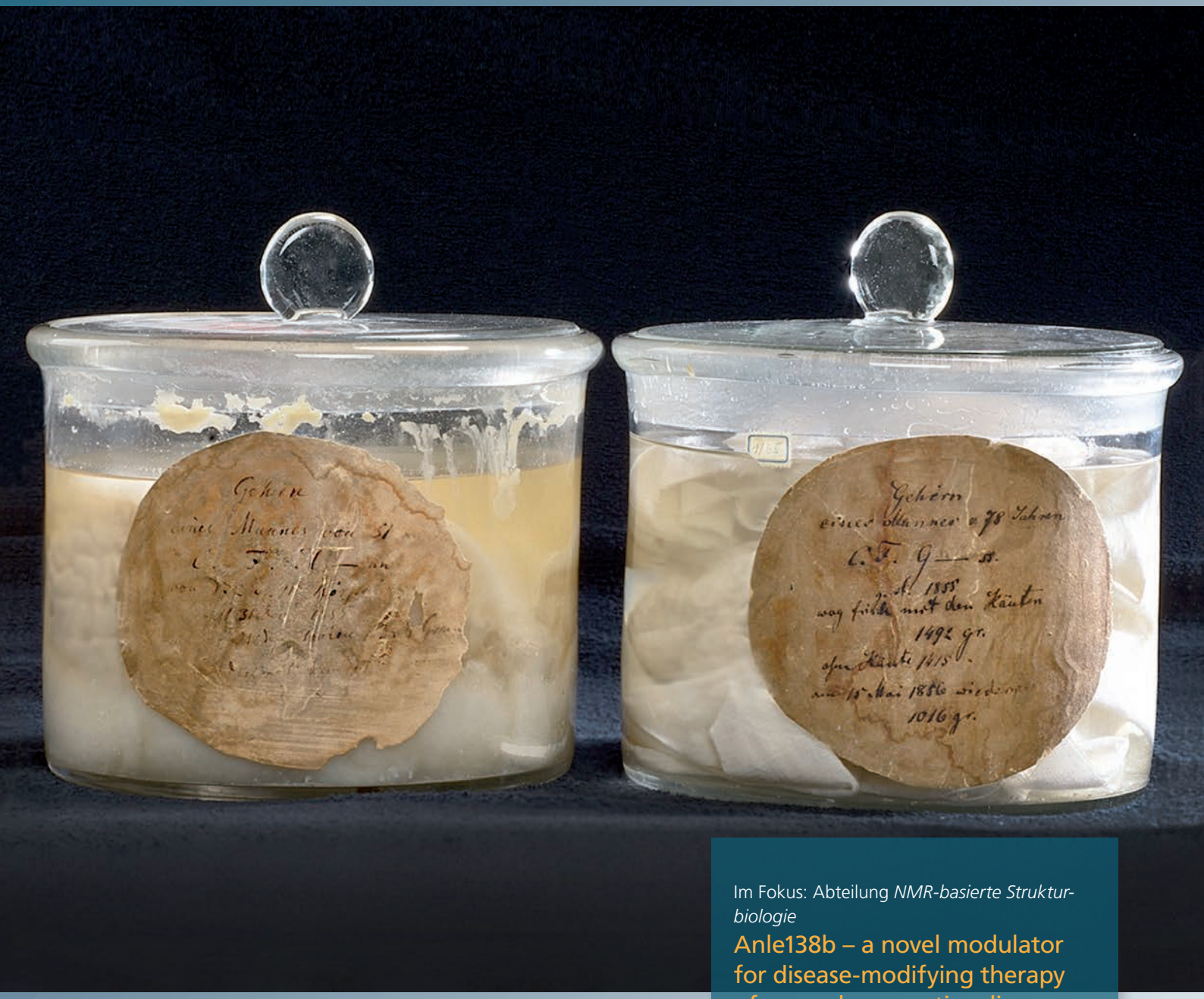
Max-Planck-Institut für biophysikalische Chemie

MPIbpc NEWS

19. Jahrgang | Dezember 2013



Im Fokus: Abteilung *NMR-basierte Strukturbiologie*

Anle138b – a novel modulator for disease-modifying therapy of neurodegenerative diseases

Aktuelle Pressemitteilungen

Wahre Identität des Gauß-Gehirns aufgeklärt

Rezension

Manfred Eigens neuestes Buch

INHALT

Anle138b – a novel oligomer modulator for disease-modifying therapy of neurodegenerative diseases and tool compound for neuronal cell biology

Sergey Ryazanov, Andrei Leonov, and Christian Griesinger

Department of *NMR-based Structural Biology*

The recent review by Eliezer Masliah[1] starts with the statement: "The lack of disease-modifying treatments for neurodegenerative diseases explains the need for developing new therapies that target the molecular origins of the pathology." Disease modifying is a type of therapy which delays and ideally stops neurodegeneration, i.e. loss of functionality of the neurons and eventually loss of the neurons themselves rather than ameliorating the symptoms resulting from neurodegeneration. Neurodegenerative diseases include the most prevalent types such as Alzheimer's disease (AD) and Parkinson's disease (PD), amyotrophic lateral sclerosis as well as Creutzfeldt-Jacob disease (CJD) and Huntington's disease (HD). An overview of the present and of the future expected number of patients with the respective diseases is given in Figure 1.

In all these diseases, at least one type of protein aggregates in the brain and at the same time neuronal functionality declines and neurons die. While until a few years ago, the plaques found in the brains of patients that had deceased from neurodegenerative disorders were held responsible for the disease, it is now well accepted that intermediate forms, so-called oligomers, are the more likely cause for neurodegeneration. Previously, we also contributed to this work in a collaboration with Markus Zweckstetter within the Department of *NMR-based Structural Biology* and other groups at the *Center for Nanoscale Microscopy and Molecular Physiology of the Brain* (CNMPB)[2]. Still, the molecular mechanisms, specifically how these oligomeric forms of protein aggregates deteriorate the function of neurons and finally kill them, are elusive despite worldwide intensive research. At the very least the proteins which aggregate are identified for the different neurodegenerative diseases, i.e. Abeta and tau for AD, α-Synuclein for PD, prion protein for CJD, polyglutamine for HD and several muscular dystrophies, and islet amyloid polypeptide (IAPP) for diabetes mellitus type 2.

In order to investigate the underlying molecular mechanisms of neurodegeneration but also to find therapeutic approaches, we started a program in 2005 with the goal to develop aggregation inhibitors. These inhibitors would not only stop or reduce fibril formation but also formation of oligomeric species. For therapeutic reasons, our interest also aimed at optimizing bioavailability. The hope was that compounds able to prevent oligomer formation would also be neuroprotective. This would also substantiate the idea that removal of oligomers would indeed be neuroprotective. This research project was implemented in collaboration with Armin Giese at the *Center for Neuropathology and Prion Research* at the LMU Munich[3]. When we started the collaboration, Armin Giese had already performed a library screen of 20,000 compounds with the SIFT assay which he had developed earlier at our institute with contributions from the Eigen Department. The SIFT assay is based on single molecule detection of dye labeled proteins and works at nanomolar concentration of both the protein as well as the small molecule inhibitor. Due to the different intensity of the fluorescence of a monomer (one dye) or an oligomer (several dyes) it is possible to count the number of monomers and oligomers in a sample. Thus, with this screen, small molecules which decrease the number of oligomers can be identified[4]. As will become apparent, the low possible concentrations of both molecules was essential for making progress. The simultaneous screening of aggregation inhibition for prion protein and α-Synuclein

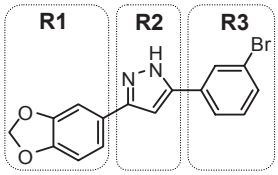
Total prevalent cases of Parkinson´s disease by region (2007-2017)

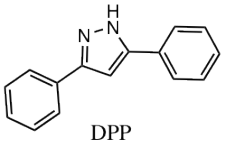
Region	2007	2012	2017
Europe	1 406 900	1 531 300	1 647 400
United States	1 011 900	1 099 100	1 218 800
Japan	673 900	779 000	867 700
Total	3 092 700	3 409 400	3 733 900

Total prevalent cases of Alzheimer´s disease by region (2007-2017)

Region	2007	2012	2017
Europe	2 507 300	2 814 700	3 125 500
United States	2 478 400	2 705 700	2 938 200
Japan	1 147 900	1 433 000	1 753 300
Total	6 133 600	6 953 400	7 817 000

Fig. 1. Observed and expected prevalence of Parkinson's- and Alzheimer's disease according to *Decision Resources, Inc.* 2008. Numbers are brought up to a round figure. Estimates include people aged 40 years or older.





DPP

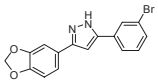
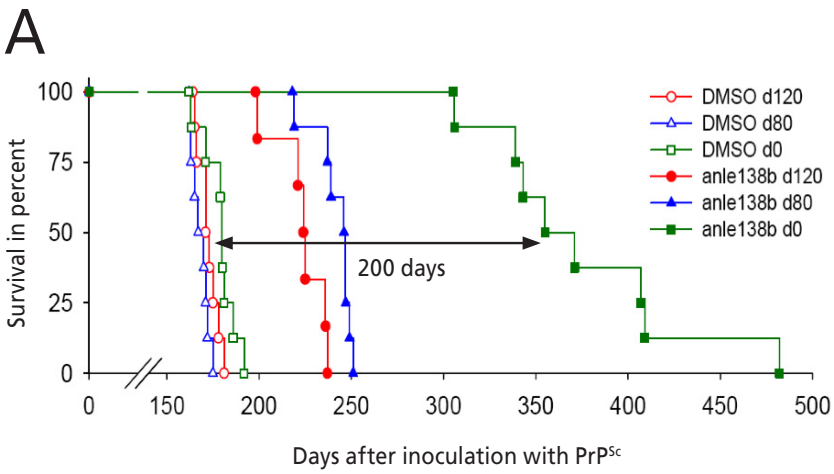
compound	R1	R2	R3	% inhibition α-syn SIFT$	% inhibition PrP^{Sc} PMCA#	% inhibition PrP^{Sc} *in vivo**	conc. brain [nmol/g]
anle138b				77	84	78[a]; 57[b], 108[c]	34.1
sery312b				<10	42	13[a]	3,6
anle253b				50	80	59[a]	2.1
sery384				99	55	<10	13,9
sery417				<10	51	<10[a]	0
anle138c				99	19	<10[a]	n.d.
sery338b				<10	46	35[a]	30.3
sery345				57	<10	<10[a]	16.6
sery378b				74	34	39[a]	26
anle234b				<10	<10	<10[a]	32.1
anle186b				<10	48	30[c]	31.1
sery335b				90	52	68[a]; 46[b]	29.6
anle197b				<10	16	<10[b]	n.d.
anle236b				<10	<10	12[a]	39.3
anle232b				<10	26	23[a]	n.d.

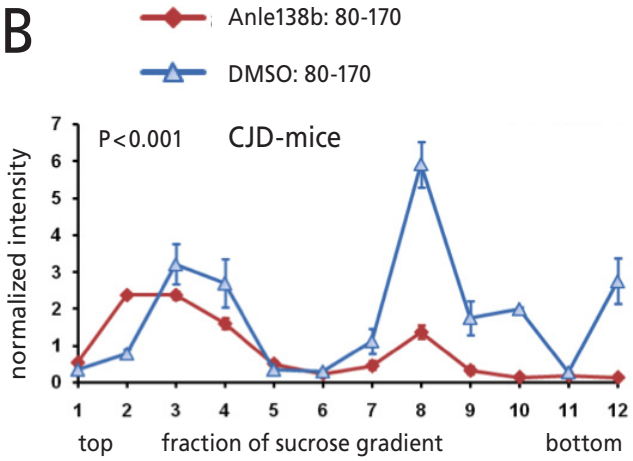
Table 1. Structure-activity relationship of diphenylpyrazoles (DPP; mother compound top right). The table quantifies efficacy to inhibit α-Synuclein oligomer formation and prion protein propagation in vitro (SIFT, PMCA) and in vivo in prion-inoculated mice. The compound concentrations achieved in the brain 4 h after oral application of 1 mg compound in DMSO/peanut butter. The formulae show the deviation of the compound from the mother compound. Figure taken from Ref. 3.

provided diphenylpyrazoles and two other less promising molecular scaffolds (Figure 1) which modulated the aggregation of prion protein and α-Synuclein at the level of oligomers, in other words they prevented the conversion of monomers to oligomers that are commonly observed in the absence of the compounds. Diphenylpyrazoles and related compounds are quite easy to synthesize in several steps from commercially available materials. Therefore, a library, such as shown in Table 1, could be quickly made by the two first authors of this article. The library had two distinct classes of molecules: water-soluble molecules such as anle145c or anle138c, whose hydrophilicity was generated by the two or three OH groups, and more lipophilic compounds such as anle138b. The water-soluble molecules are potent aggregation inhibitors similar to compounds such as green tea extract (EGCG), baicalein, or the spice curcumin, a compound present in turmeric. Feeding mice with these compounds leads to micro- or submicromolar concentrations in the brain (EGCG and metabolites: 400 nM[5]; curcumin and metabolites: 1 μM[6]). Similarly, anle138c could not be detected in the mouse brain even if it was seen in the blood of mice.

The second class of more lipophilic molecules was obtained by linking the two vicinal OH groups of anle138c with a methylene group. Their lipophilicity and small size allows them to cross the blood brain barrier at higher concentrations than the mentioned hydrophilic compounds. So far, the most efficient candidate out of approximately 250 compounds synthesized is anle138b, which is a compromise between bioavailability and aggregation inhibition. After oral application, anle138b reaches a concentration of 100 micromolar in the mouse brain and has a half-life of approximately four hours due to the slow cleavage of the methylenedioxo moiety of anle138b in the liver. Metabolites are then too hydrophilic to pass the blood brain barrier and, therefore, cannot be detected in the mouse brain. Application of anle138b in various animal models is reported in the mentioned publication[3].

Here, only two of these models shall be reviewed. The first one is a model for the Creutzfeldt-Jacob disease. In its sporadic form, the disease kills approximately 120 patients per year in Germany within three to six months. There is presently no treatment available. Almost 30 years ago, its juvenile variant form, thought to be caused by food consumption, had a sharp increase due to people eating beef that was infected with BSE. To date, CJD is the only disease that is infectious, i.e. intake of prion particles into the gut or blood stream can trigger the disease. Current mouse models for most neurodegenerative diseases do not reproduce all the features of progression and of symptoms in humans. In contrast, the CJD mouse model used in our studies reproduces the main features of the human disorder, namely fast death with little variation, prion deposits in the brain, neurodegeneration, and wasting of the animal. In the CJD





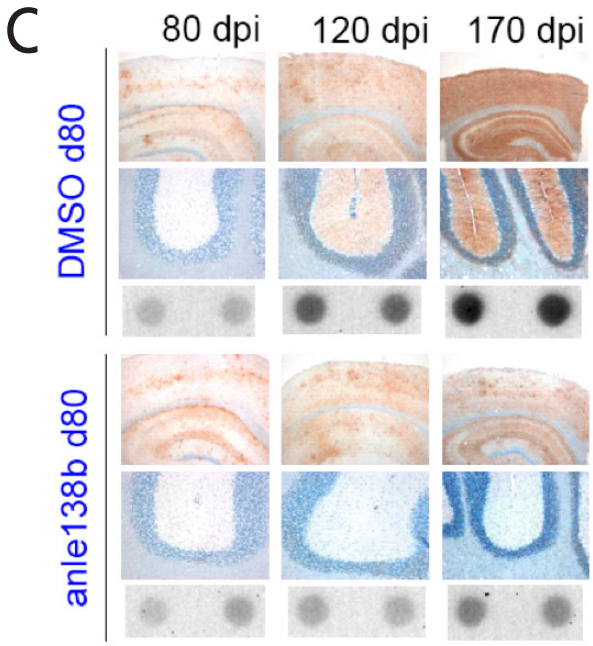


Fig. 2. Influence of daily anle138b treatment on PrP^{Sc} accumulation and prion pathology of mice infected with Rocky Moutain Laboratory (RML) scrapie. **(A)** Survival curves of mice treated orally with anle138b beginning at day 0 as well as 80 or 120 days after inoculation (dpi) of prion protein into the mouse brain. The anle138b application prolonged life maximally (by 200 days) when started at day 0. Even when started at an advanced disease stage 120 days after scrapie prion inoculation, life extension is considerable. **(B)** Size distribution of PrP^{Sc} aggregates was analyzed by sucrose-gradient centrifugation. Mice treated with anle138b show a strong reduction of high molecular weight species (fractions 7–12). Also small molecular weight oligomers (fractions 3–4) are reduced and show a shift towards smaller size (fraction 2) indicating that anle138b blocks aggregation at the level of small oligomers. DMSO-treated mice are indistinguishable from terminally ill untreated mice. **(C)** Immunohistochemistry (*upper row* cortex/hippocampus, *middle row* cerebellum) and dot blot analysis (*lower row*) showed that anle138b treatment inhibits PrP^{Sc} accumulation in comparison to DMSO treated control animals. Treatment started at day 80 after inoculation (dpi). Figures taken from Ref. 3.

mouse model, infection is achieved by intracerebral inoculation of prion protein in the scrapie form obtained from mice that had suffered from CJD. After intracerebral inoculation, the mice die within 180 days. Oral feeding with 6 mg of anle138b directly after inoculation delays death of these mice by 200 days (measured when half of the mice have died). This is the longest life extension observed so far in this model. Brain histology demonstrates that considerably less prion aggregates are formed compared to untreated animals. If anle138b application is started only 80 or 120 days after inoculation, then life extension is reduced – as expected for a neuroprotective molecule in an animal model, where neurodegeneration starts after inoculation. Still, even starting the application at day 120, when mice have clinical symptoms, extends their life span. The observation that anle138b is an aggregation inhibitor in vitro and that aggregates are reduced in treated animals suggests that this is indeed the mode of action. In vitro, not only fibrillar aggregates but also oligomers were reduced. Indeed, ultracentrifugation in a sucrose gradient shows that larger oligomeric species are reduced (Figure 2B, fraction 8), and for smaller oligomers the size distribution is shifted towards smaller ones (Figure 2B, fractions 2,3,4). These results are nicely in line with the in vivo observation. Thus, these experiments suggest that the modulation of the oligomer size distribution with anle138b is responsible for the life span increase of treated mice versus untreated ones (Figure 2).

Anle138b was also tested on several PD mouse models. The hallmark of Parkinson's disease is the aggregation of α-Synuclein that forms so-called Lewy bodies. One of the tested mouse models introduced by Francisco Pan-Montojo shall be described in more detail here since it works with wild type mice and recapitulates the prion like spreading of α-Synuclein aggregates between neurons[7]. This prion like spreading between neurons was observed by Heiko Braak in 2006 from human autopsies. With this observation the pathologist deduced the hypothesis that α-Synuclein aggregates are first observed in peripheral neurons, such as gut neurons or olfactory neurons, and then spreading

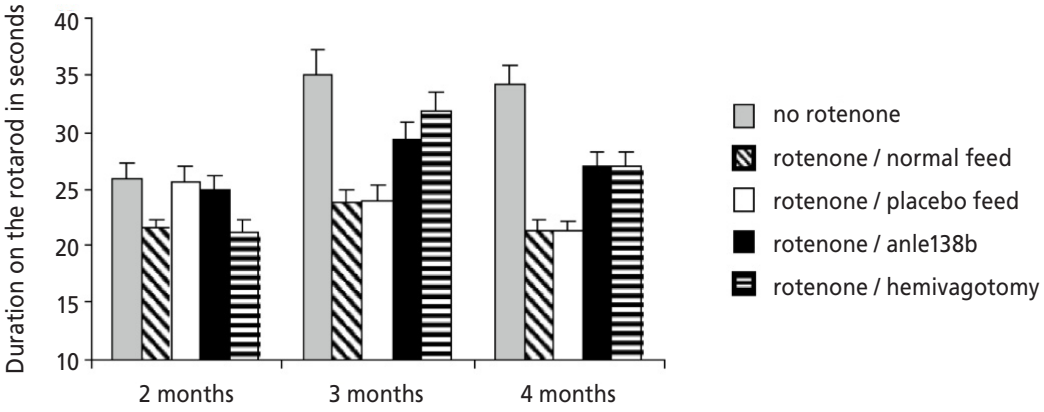


Fig. 3. Quantitative locomotion performance of mice in the topic rotenone model described in the text. Mice not treated with rotenone have the best performance since they stay on the rotating rod for the longest time. Topical application of rotenone to the gut leads to a reduction of locomotion performance that is rescued by application of anle138b. Almost similar rescue is observed for 4 month-old mice by cutting the vagus. Figure taken from Ref. 3.

occurs to an extent that α-Synuclein aggregates reach the brain. There, it specifically affects the substantia nigra, which causes neurodegeneration and dopamine depletion leading to the diagnostic PD symptoms of locomotion impairment[8]. The spreading was recently also observed in vitro as well as in animal models in vivo[9]. Indeed, physicians specializing in the treatment of Parkinson's disease observe that a considerable number of PD patients lose their smell up to ten to 15 years before observation of locomotion problems. The other pathway from the gut to the brain was recently corroborated in a longitudinal study. This study, however, is not yet statistically significant due to the small number of patients[10]. In this study, individuals with α-Synuclein deposits in the gut developed PD symptoms three to five years later, while those individuals that did not have such deposits in the gut neurons were asymptomatic after these three to five years. Apart from the interesting possibility to screen the population for risk groups of PD much earlier than diagnosis of PD is possible, these observations on humans are the basis of the mouse model developed by Pan-Montojo. Daily application of the complex I inhibitor rotenone topically in the gut of a wild type mouse induces α-Synuclein aggregation in the gut that then spreads to the mouse brain and leads to α-Synuclein aggregation in the substantia nigra. This results in locomotion performance decline as observed by putting the mice on a rotating rod (rotarod test) and measuring the time until they fall from the rotatorod. The authors describe in their publication[7] that there is no systemic effect of the topically applied rotenone. Feeding of the mice with anle138b in addition to the topical rotenone application improves the locomotion performance compared to the mice that were treated with only rotenone but did not obtain anle138b (Figure 3). In order to better judge the efficacy of anle138b treated mice, the α-Synuclein spreading pathway (vagus or sympathicus) was cut which led to better locomotion performance of these mice compared to rotenone treated ones and similar performance with those mice treated with both rotenone and anle138b. Thus, treatment with anle138b has a similar efficacy as interrupting the spreading pathway by cutting the vagus or sympathicus.

In another mouse model[3] the familiar mutant A30P-α-Synuclein was overexpressed. Here, anle138b treatment prolonged life of the mice by approximately ten weeks irrespective of whether treatment was started immediately or in week 50. As a result, the number of Lewy bodies was reduced and, as expected from the in vitro experiments, the oligomeric species of α-Synuclein analyzed by sucrose-gradient ultracentrifugation of mouse brain homogenate was shifted to smaller molecular weights. This is very similar to the observation made in the prion mouse model. The similarity of the observations regarding oligomer modulation in the PD and CJD animal model and in vitro suggest that anle138b is effective due to removal of those oligomers that have been linked to neuronal toxicity.

The inhibition of aggregate formation of two proteins with very different primary structures by the same compound is on the one hand surprising since small molecules normally interact specifically with side chains, which induce selectivity. On the other hand, in the amyloid field, dyes such as thioflavin T or congo red stain fibrils of Abeta, tau, α-Synuclein or prion protein do not recognize the amino acid sequence but secondary structures. Therefore, we hypothesize that anle138b binds to conformational features that are constant between different oligomers in a hitherto not understood way and disassembles these oligomers into smaller less toxic ones. For structural biologists this opens up new opportunities to study highly relevant structures of a protein assembly with and without anle138b. From the chemical biology perspective, anle138b can be used as a tool compound in order to investigate the biological changes from a cellular standpoint that lead to neurodegeneration in the absence of the compound and delayed neurodegeneration in the presence of the compound. We expect that these investigations will keep us busy for the coming years. These studies are even more interesting, since anle138b does not only modulate aggregation of prion protein and α-Synuclein in vivo but also Abeta and tau, in addition to IAPP and poly-Q. Concomitantly, anle138b application to mouse models

of AD improves learning and memory compared to the wild type behavior. Furthermore, locomotion is improved in poly-Q mouse models. Therapeutic applications shall therefore be pursued by the company MODAG that will become operational at the end of the year based on the patent on the compounds[11]. Further opinions on the therapeutic value of various approaches can be found in the very interesting blog: *www.cureffi.org/*

Finally, the diphenylpyrazol compounds shall be developed into PET tracers, which is presently funded as part of the EU consortium *MultiSyn*.

References

1. Valera E, Masliah E: Immunotherapy for neurodegenerative diseases: Focus on α-synucleinopathies. *Pharmacology & Therapeutics* **138**, 311-322 (2013).

2. Karpinar DP, Balija MBG, Kügler S, Opazo F, Rezaei-Ghaleh N, Wender N, Kim H-Y, Taschenberger G, Falkenburger BH, Heise H, Kumar A, Riedel D, Fichtner L, Voigt A, Braus GH, Giller K, Becker S, Herzig A, Baldus M, Jäckle H, Eimer S, Schulz JB, Griesinger C, Zweckstetter M: Pre-fibrillar α-synuclein variants with impaired β-structure increase neurotoxicity in Parkinson's disease models. *EMBO J* **28**, 3256-3268 (2009).

3. Wagner J, Ryazanov S, Leonov A, Levin J, Shi S, Schmidt F, Prix C, Pan-Montojo F, Bertsch U, Mitteregger-Kretzschmar G, Geissen M, Eiden M, Leidel F, Hirschberger T, Deeg AA, Krauth JJ, Zinth W, Tavan P, Pilger J, Zweckstetter M, Frank T, Bähr M, Weishaupt JH, Uhr M, Urlaub H, Teichmann U, Samwer M, Bötzel K, Groschup M, Kretzschmar H, Griesinger C, Giese A: Anle138b: a novel oligomer modulator for disease-modifying therapy of neurodegenerative diseases such as prion and Parkinson's disease. *Acta Neuropathol* **125**, 795-813 (2013).

4. Bieschke J, Giese A, Schulz-Schaeffer W, Zerr I, Poser S, Eigen M, Kretzschmar H: Ultrasensitive detection of pathological prion protein aggregates by dual-color scanning for intensely fluorescent targets. *Proc Natl Acad Sci USA* **97**, 5468-5473 (2000).

5. Abd El Mohsen MM, Kuhnle G, Rechner AR, Schroeter H, Rose S, Jenner P, Rice-Evans CA: Uptake and metabolism of epicatechin and its access to the brain after oral ingestion. *Free Radical Biol Med* **33**,1693-1702 (2002).

6. Pan MH, Huang TM, Lin JK: Biotransformation of curcumin through reduction and glucoronidation in mice. *Drug Metab Dispos* **27**, 486-494 (1999).

7. Pan-Montojo F, Anichtchik O, Dening Y, Knels L, Pursche S, Jung R, Jackson S, Gille G, Spillantini MG, Reichmann H, Funk RHW: Progression of Parkinson's disease pathology is reproduced by intragastric administration of rotenone in mice. *PLoS One* **5**, e8762 (2010);
Pan-Montojo F, Schwarz M, Winkler C, Arnhold M, O'Sullivan GA, Pal A, Said J, Marsico G, Verbavatz JM, Rodrigo-Angulo M, Gille G, Funk RH, Reichmann H: Environmental toxins trigger PD-like progression via increased alpha-synuclein release from enteric neurons in mice. *Sci Rep* **2**, 898 (2012).

8. Braak H, de Vos RA, Bohl J, Del Tredici K: Gastric alpha-synuclein immunoreactive inclusions in Meissner's and Auerbach's plexuses in cases staged for Parkinson's disease-related brain pathology. *Neurosci Lett* **396**, 67-72 (2006).

9. Desplats P, Lee HJ, Bae EJ, Patrick C, Rockenstein E, Crews L, Spencer B, Masliah E, Lee SJ: Inclusion formation and neuronal cell death through neuron-to-neuron transmission of alpha-synuclein. *Proc Natl Acad Sci USA* **106**, 13010-13015 (2009).

10. Shannon KM, Keshavarzian A, Dodiya HB, Jakate S, Kordower JH: Is alpha-synuclein in the colon a biomarker for premotor Parkinson's disease? Evidence from 3 cases. *Mov Disord* **27**, 716-719 (2012).

11. Giese A, Bertsch U, Kretzschmar H, Habeck M, Hirschberger T, Tavan P, Griesinger C, Leonov A, Ryazanov S, Weber P, Geissen M, Groschup MH, Wagner J: New drug for inhibiting aggregation of proteins involved in diseases linked to protein aggregation and/or neurodegenerative diseases. *WO/2010/000372 (2010)*

In unserem Artikel haben wir die Ergebnisse einer Publikation auszugsweise vorgestellt, die zusammen mit der Gruppe von Armin Giese am *Zentrum für Neuropathologie und Prionforschung* der LMU München entstanden sind (siehe Ref. 3). Es geht um die Nutzung der Substanz anle138b, die aus einem Hochdurchsatz-Screening von 20 000 Verbindungen und nachfolgender medizinalchemischer Optimierung entstanden ist. Die Eigenschaften von anle138b als Modulator toxischer Proteinverklumpungen, die typisch für neurodegenerative Erkrankungen sind, werden ebenso beschrieben wie die Wirkung der Substanz in Tiermodellen der Creutzfeldt-Jakob-Erkrankung und der Parkinson-Erkrankung.

Hierbei ergibt sich als wahrscheinliches Szenario, dass anle138b die Verklumpung mehrerer Proteine derart beeinflusst, dass sich toxische Oligomere nicht mehr in der üblichen Menge bilden. Dadurch verbesserte sich das Krankheitsbild in verschiedenen Mausmodellen erheblich. Dieser Prozess deckt sich mit den in vitro-Eigenschaften von anle138b und verwandter Verbindungen aus der Diphenylpyrazolreihe, deren wirksamster Vertreter bisher anle138b ist. Anle138b eröffnet jetzt die Möglichkeit, den Einfluss der Substanz auf die atomare Struktur von Proteinaggregaten zu untersuchen. Außerdem kann anle138b als Werkzeug genutzt werden, um dem Toxizitätsmechanismus bei der Neurodegeneration auf die Spur zu kommen.

Sergey Ryazanov
studied organic chemistry at Saint Petersburg State University (Russia) and joined the *NMR-based Structural Biology Department* at the MPIbpc in 2006. Enrolled in the *GAUSS* doctoral program he is working on the development of novel therapeutic approaches for neurodegenerative diseases.

Andrei Leonov
studied chemistry at Saint Petersburg State University (Russia) and received his PhD in chemistry in 2000 at the University of Göttingen. He joined the *NMR-based Structural Biology* Department in 2003 as head of the Project Group *Organic Synthesis*.

Christian Griesinger
studied chemistry and physics at the University of Frankfurt/Main, where he received his PhD in 1986. After a postdoctoral stay at the École Polytechnique Fédérale in Zurich (Switzerland), he accepted a professorship for Organic Chemistry at Frankfurt University in 1990. Since 1999, he has headed the Department of *NMR-based Structural Biology.*

Wahre Identität des Gauß-Gehirns aufgeklärt

Die über 150 Jahre alten Gehirnpräparate des Mathematikers Carl Friedrich Gauß und des Göttinger Mediziners Conrad Heinrich Fuchs sind vertauscht worden, und das vermutlich bereits bald nach beider Tod im Jahr 1855: Zu diesem überraschenden Schluss ist Renate Schweizer, Neurowissenschaftlerin an der *Biomedizinischen NMR Forschungs GmbH*, gekommen. Die zu Forschungszwecken in einer Sammlung der Universitätsmedizin Göttingen archivierten Gehirne hat sie jetzt korrekt identifiziert und im Magnetresonanz-Tomografen mit Experten anderer Fachdisziplinen umfassend dokumentiert. *(Brain, 26. Oktober 2013)*

Walnussartige Strukturen erscheinen auf dem Computermonitor. Sie offenbaren, was sich im Inneren des Magnetresonanz-Tomografen in der *Biomedizinischen NMR Forschungs GmbH* verbirgt: Es ist das über 150 Jahre alte Gehirnpräparat des Mathematikers Carl Friedrich Gauß. Renate Schweizer überwacht die Messungen, die Schicht für Schicht das innenliegende Gewebe sichtbar machen. Danach platziert sie vorsichtig ein weiteres Gehirn auf den Untersuchungstisch, mit dem normalerweise Probanden in die „Röhre" gefahren werden. Es stammt von dem Mediziner und Begründer der pathologisch-anatomischen Sammlung der Universität Göttingen, Conrad Heinrich Fuchs – verstorben wie Gauß im Jahr 1855. Die aktuelle Untersuchung der historischen Gehirne, die aus der Sammlung im Institut für Ethik und Geschichte der Medizin der Universitätsmedizin Göttingen stammen, haben einen konkreten Anlass: „Was Forscher bisher als Gauß-Gehirn untersucht hatten, war gar nicht sein Gehirn – es gehörte dem Mediziner Fuchs. Die Gehirne der beiden Wissenschaftler sind vor vielen Jahren vertauscht worden und müssen daher neu dokumentiert werden", schildert die Biologin und Psychologin die überraschende Erkenntnis aus ihren Nachforschungen.

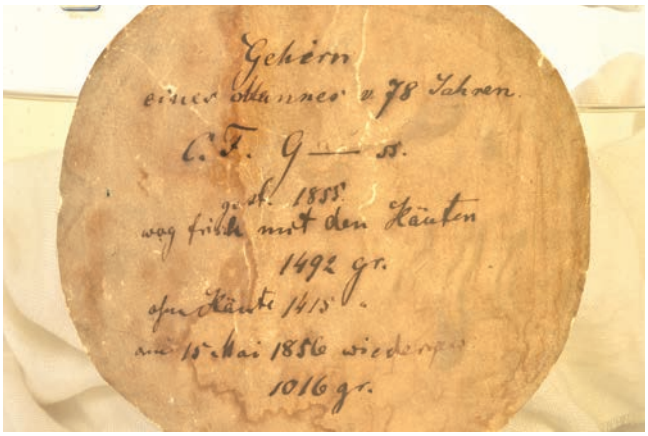
Diese unerwartete Entdeckung machte die Wissenschaftlerin während Recherchen zu ihrem Forschungsgebiet – der Gehirnregion um die sogenannte

Zentralfurche. In den Windungen entlang der Zentralfurche verarbeitet das Gehirn Reize wie Berührungen, Wärme oder Schmerz und steuert Bewegungen. Am Gauß-Gehirn vermutete Renate Schweizer eine seltene anatomische Variation: eine sichtbare Zweiteilung der Zentralfurche. Sie tritt bei weniger als einem Prozent der Menschen auf. Für die betroffenen Personen ist sie normalerweise unbedeutend, in Einzelfällen kann sie zu minimalen Veränderungen der Motorik und Sensorik führen.

Bilder nicht deckungsgleich

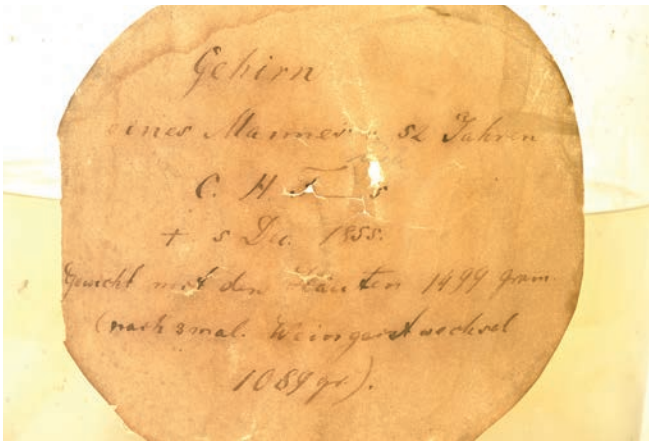
Auf Magnetresonanztomografie (MRT)-Bildern des vermeintlichen Gauß-Gehirns aus der Universitätssammlung, die 1998 von Jens Frahm und seinem Team an der *Biomedizinischen NMR Forschungs GmbH* aufgenommen wurden, hatte Renate Schweizer eine solche Zweiteilung der Zentralfurche entdeckt. Um ihren Befund zu überprüfen, forscht sie in der Primärliteratur nach. Rudolf Wagner, ein Göttinger Anatom und Freund von Gauß, hatte seinerzeit die Gehirne von Gauß und Fuchs präpariert, untersucht und in Veröffentlichungen von 1860 und 1862 bildlich dokumentiert. Doch auf seinen Abbildungen findet sie die zweigeteilte Zentralfurche – anders als erwartet – nicht etwa am Gauß-Gehirn wieder. Stattdessen passen die MRT-Bilder haargenau auf Wagners Abbildung von Fuchs' Gehirn.

Renate Schweizers Besuch in der Sammlung im Institut für Ethik und Geschichte der Medizin bestätigt ihren ersten Verdacht: Das Originalgehirn von Gauß befindet sich tatsächlich im Glasgefäß mit der Aufschrift „C. H. Fuchs". Das Fuchs-Gehirn wiederum ist etikettiert mit „C. F. Gauss". „Meine These nach den momentan vorliegenden Informationen ist, dass die Gehirne wahrscheinlich schon relativ bald nach Wagners Untersuchungen in die falschen Gefäße gelangten, als die Oberfläche der Hirnrinde nochmals vermessen wurde", so die Neurowissenschaftlerin. Weitere vergleichende Arbeiten zu den Gehirnen von Gauß und Fuchs gab es nicht. Und so fiel die Verwechslung später niemandem auf. Dass die Gehirne von Gauß und Fuchs jetzt korrekt zugeordnet sind, ist auch eine wichtige Information für die Göttinger Gauß-Gesellschaft. „Ihr Geschäftsführer Axel Wittmann hat das Projekt von Anfang an aktiv unterstützt und begleitet, sein umfangreiches Wissen war extrem hilfreich, um die Verwechslung aufzudecken", berichtet Renate Schweizer.



Historisches Etikett für das Gehirn von Carl Friedrich Gauss: „Gehirn eines Mannes v. 78 Jahren. C.F. Gauss. Gestorben 1855, wog frisch mit den Häuten 1492 gr., ohne Häute 1415 gr., am 15. Mai 1856 wiedergewogen 1016 gr.".

Historical label for the brain of Carl Friedrich Gauss: "Brain of a man aged 78 years. C.F. Gauss. Died 1855, weight with fresh celebral membranes 1492 gr., without celebral membranes 1415 gr., weighed again on May 15th, 1856: 1016 gr.".



Historisches Etikett für das Gehirn von Conrad Heinrich Fuchs: „Gehirn eines Mannes v. 52 Jahren. C.H. Fuchs, gestorben 5. Dec. 1855, Gewicht mit den Häuten 1499 Gramm, (nach 3mal. Weingeistwechsel 1089 gr.)".

Historical label for the brain of Conrad Heinrich Fuchs: "Brain of a man aged 52 years. C.H. Fuchs. Died on December 5th, 1855, weight with celebral membranes 1499 gr. (after three times change of alcohol 1089 gr.)".

Schätze für die Forschung

Ihre Entdeckung zeigt, wie wichtig historische Sammlungen für die aktuelle Forschung sind. Renate Schweizer bekräftigt: „Es ist ein Glücksfall für uns Forscher, dass die Gehirne in der Sammlung auch nach über 150 Jahren in einem einwandfreien Zustand der Wissenschaft zugänglich sind." So konnte sie die Verwechslung eindeutig feststellen und die historischen Gehirne im Magnetresonanz-Tomografen untersuchen. Dafür arbeitete die Neurowissenschaftlerin eng mit ihrem ehemaligen Teamkollegen Gunther Helms zusammen, der sich in der *Serviceeinheit MR-Forschung* der Abteilung *Kognitive Neurologie* an der Universitätsmedizin Göttingen mit der MRT von Hirnpräparaten befasst. Der Leiter der *Biomedizinischen NMR Forschungs GmbH* Jens Frahm betont: „Wir suchen nicht nach dem Genie in den Hirnwindungen. Für uns steht die langfristige Dokumentation im Vordergrund, um eine Basis für weitergehende Grundlagenforschung zu schaffen." Alle MRT-Bilder und Fotografien der historischen Gehirne werden daher digital archiviert und so langfristig für die Wissenschaft gesichert. Für neue Forschungsprojekte sind diese ein wichtiger Impuls. So untersucht Renate Schweizer derzeit anhand der MRT-Bilder die zweigeteilte Zentralfurche in Fuchs' Gehirn auch unter der Oberfläche der Hirnrinde.

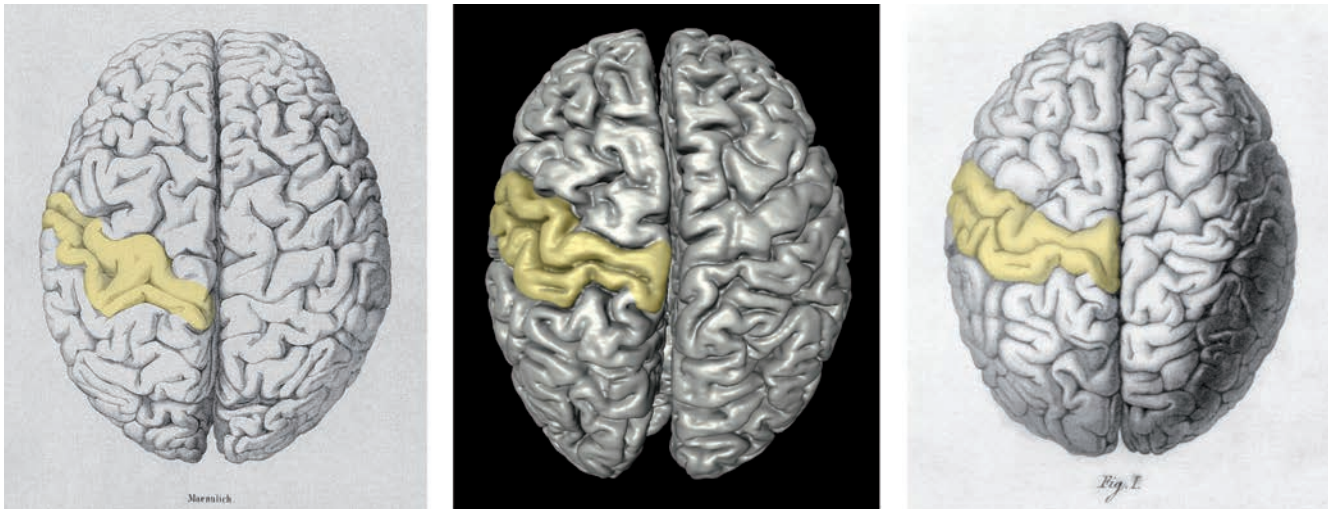
Mithilfe der MRT-Bilder konnten die Forscher auch nachweisen, dass frühere Veröffentlichungen über das vermeintliche Gauß-Gehirn keine falschen Informationen lieferten. In diesen wurde das Denkorgan des Mathematikers als normal beschrieben. Walter Schulz-Schaeffer, Leiter des Schwerpunkts *Prion- und Demenzforschung* des Instituts für Neuropathologie an der Universitätsmedizin Göttingen, bestätigt nach einer ersten Begutachtung der aktuellen MRT-Bilder:

Das Gehirn des genialen Mathematikers und Astronomen Gauß ist ebenso wie das des Mediziners Fuchs anatomisch weitgehend unauffällig. Beide ähneln sich zudem in Größe und Gewicht. „Die altersbedingten Veränderungen an Gauß' Gehirn sind für einen 78-jährigen Mann normal. Veränderungen in den Basalganglien lassen auf einen Bluthochdruck schließen", so der Neuropathologe.

Nicht jede MRT-Untersuchung eines historischen Präparats lässt eine solch klare Aussage zu. Neuropathologen und MRT-Wissenschaftler erforschen daher derzeit gemeinsam, wie sich Gewebe und Organe bei jahrzehnte- oder jahrhundertelanger Aufbewahrung in Alkohol verändern und wie sich mit angepassten MRT-Methoden die Interpretation der erhaltenen Bilder verbessern lässt.

Die historischen Gehirne haben indes nach den Untersuchungen wieder ihre wohlverdiente Ruhe in der Universitätssammlung gefunden. Eine Verwechslung ist künftig ausgeschlossen. (cr/es)

Hören Sie in einem Podcast, wie Renate Schweizer die Vertauschung der Gehirnpräparate von Gauss und Fuchs aufdeckte: *http://eu.www.mpg.de/de/institute/mpibpc/gaussgehirn.mp3*



Die Gehirne von Carl Friedrich Gauß und Conrad Heinrich Fuchs im Vergleich. Rudolf Wagners Lithografie des Fuchs-Gehirns aus dem Jahr 1862 (links) und sein Kupferstich des Gauß-Gehirns von 1860 (rechts) zeigen deutliche Unterschiede. Das mittlere Bild ist eine aktuelle MRT-Oberflächenrekonstruktion von Gauß' Gehirn. Die Zentralfurche ist in der linken Gehirnhälfte jeweils gelb eingefärbt.

The brains of Carl Friedrich Gauss and Conrad Heinrich Fuchs side by side. Rudolf Wagner's lithograph of Fuchs' brain from 1862 (left) and his copperplate of Gauss' brain from 1860 (right) show clear differences. The middle image is a recent MRI surface reconstruction of Gauss' brain. The central sulcus in the left half of each brain is colored yellow. *(MRT image: Jens Frahm and Sabine Hofer / Biomedizinische NMR Forschungs GmbH 2013)*

Unraveling the true identity of the brain of Carl Friedrich Gauss

Historical brain specimens of mathematician Carl Friedrich Gauss and Göttingen physician Conrad Heinrich Fuchs, preserved over 150 years ago, were mixed up – and this probably happened soon after their death in 1855. This is the surprising conclusion reached by Renate Schweizer, neuroscientist at the *Biomedizinische NMR Forschungs GmbH*. She has now correctly identified the two brains, which are kept in a collection at the University Medical Center Göttingen. Working together with experts from various disciplines, she documented the brains using modern magnetic resonance imaging (MRI).

Walnut-like structures appear on the computer screen. They reveal what is inside the MRI scanner at the *Biomedizinische NMR Forschungs GmbH*: the 150-year-old brain of mathematician Carl Friedrich Gauss. Renate Schweizer monitors the MRI measurements as the images of the brain come into view section by section. Then she carefully places another brain on the examination table, where usually subjects are prepared for their MRI scans. It is the brain of Conrad Heinrich Fuchs – who was a medical scholar and founder of the University

of Göttingen's collection of pathological specimens and, like Gauss, died in 1855. This unusual examination of historical brains from the collection at the Institute of Ethics and History of Medicine at the University Medical Center Göttingen has a specific purpose: "What scientists have recently been examining as Gauss' brain was not his brain at all, but actually originated from Fuchs. The two scientists' brains have been mixed up many years ago, and now need to be properly documented again," explains Renate Schweizer, biologist and psychologist, the surprising results of her investigations.

Renate Schweizer made this unexpected discovery during extended anatomical studies in her own research field – the region of the brain around the so-called central sulcus. The gyrus on one side along the central sulcus processes somatosensory stimuli like touch, temperature, or pain, the gyrus on the other side controls muscular movements. She suspected that Gauss' brain featured a very rare anatomical variation: a divided central sulcus. This variation is found in less than one percent of the population and remains without consequences to the people affected. If at all, it can cause minimal changes in motor and somatosensory function.

Images were not congruent

In the MRI surface reconstruction of the alleged Gauss brain, taken in 1998 by Jens Frahm's team at the *Biomedizinische NMR Forschungs GmbH*, Renate Schweizer had spotted this division of the central sulcus. To confirm her findings, she checked the original literature. Rudolf Wagner, a Göttingen anatomist and friend of Gauss, had not only preserved and studied the brains of both Gauss and Fuchs, but has also meticulously depicted the brain surfaces in his publications dating back to 1860 and 1862. But contrary to what she expected to see, Renate Schweizer did not find the divided central sulcus in the images of Gauss' brain. Instead, the MRI surface reconstruction perfectly matched Wagner's picture of Fuchs' brain.

When Renate Schweizer went to the collection at the Institute of Ethics and History of Medicine, her initial suspicion was convincingly confirmed: The jar marked "C. F. Gauss" contained the brain taken from C. H. Fuchs, while the original brain taken from Gauss was in a jar marked "C. H. Fuchs". "My theory, according to the information I currently have, is that the brains were probably put into the wrong jars soon after Wagner's studies, at the time when the surface of the cerebral cortex was being re-evaluated by other scholars in 1864," the neuroscientist states. No further comparative studies of the brains of Gauss and Fuchs are known to have been undertaken afterwards and so no one noticed the mix-up.

That the brains of Gauss and Fuchs are now properly assigned is also a significant finding for the Göttingen-based Gauss Society. "Its secretary, Axel Wittmann, provided excellent support right from the start of the project, and his extensive knowledge was extremely helpful in uncovering the – probably unintentional – mistake made so many years ago," Renate Schweizer reports.

Invaluable treasure trove for science

The discovery also shows how important historical collections are for modern-day research. The neuroscientist states, "It is a stroke of luck that the brains in the collection are in very good condition and still accessible to researchers more than 150 years later." For the MRI measurements she closely collaborated with former team colleague Gunther Helms, an expert for investigations of brain specimens in the *MR Research Unit* at the Department of *Cognitive Neurology* at the University Medical Center Göttingen.

As Jens Frahm, head of the *Biomedizinische NMR Forschungs GmbH*, emphasizes: "We are not looking for the genius in the gyri of the brain. Our aim is to fully document the historical specimens to preserve them for future research." All MRI scans, surface reconstructions, and photographs of the historic brains are now digitally archived, saving them as long-term scientific assets. But the MRI scans are already significant for present day research projects: Renate Schweizer herself is currently using the images to gain novel insights into the divided central sulcus in Fuchs' brain below the surface of the cerebral cortex.

The new MRI results also demonstrate that earlier publications on the alleged Gauss brain did not provide false information. There, the mathematician's brain was described as normal. Walter Schulz-Schaeffer, head of the *Prion and Dementia Research Unit* of the Institute of Neuropathology at the University Medical Center Göttingen, inspected the recent images. He confirms that the brain of the brilliant mathematician and astronomer Gauss, like that of the physician Fuchs, is largely anatomically inconspicuous. The two brains are also similar in size and weight. "The age-related changes in Gauss' brain are normal for a 78-year-old man. Changes in the basal ganglia could be indicative of high blood pressure," the neuropathologist comments.

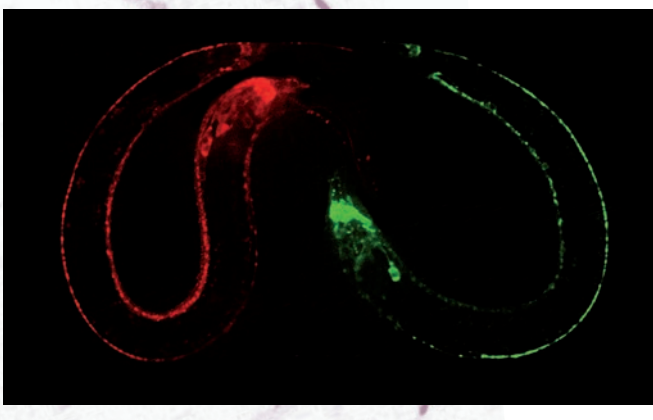
Not every MRI scan of a historical specimen allows for such clear statements. That is why neuropathologists and MRI scientists are now cooperating to study how tissue and organs change if stored in alcohol for decades or centuries, and how MRI methods can be adapted to improve the interpretation of the images obtained – to make even better use of all the information stored in the historical specimens.

Neuroscientist Renate Schweizer

In the meantime the historical brains have again found their well-earned rest in the university collection – with no chance of a mix-up ever again.

cr/Renate Schweizer

Listen in a podcast how Renate Schweizer discovered the mix-up of the brains of Gauss and Fuchs (*in German*): *http://eu.www.mpg.de/de/institute/mpibpc/gaussgehirn.mp3*



Die Aktivität der Nervenzellen des Fadenwurms *Caenorhabditis elegans* im Wachzustand (rot) und im Schlaf (grün). *(Bild: Henrik Bringmann / MPIbpc)*

Was den Fadenwurm müde macht

Warum schlafen Menschen und auch viele Tiere? Unser Wissen ist noch immer lückenhaft, wenn es um den Ursprung und die Funktion des Schlafes geht. Doch so viel ist klar: Alle Lebewesen, die über ein Nervensystem verfügen, müssen schlafen, um zu überleben. Dies gilt auch für den Fadenwurm *Caenorhabditis elegans*. Forscher um Henrik Bringmann vom MPIbpc haben jetzt einen Faktor entdeckt, der die Fadenwurm-Larve vom wachen in einen schlafähnlichen Zustand versetzt. Da auch in Wirbeltieren ähnliche Mechanismen wirksam sind, könnten die Forschungsergebnisse zu wichtigen neuen Erkenntnissen in der Schlafforschung führen. *(Current Biology, 29. Oktober 2013)*

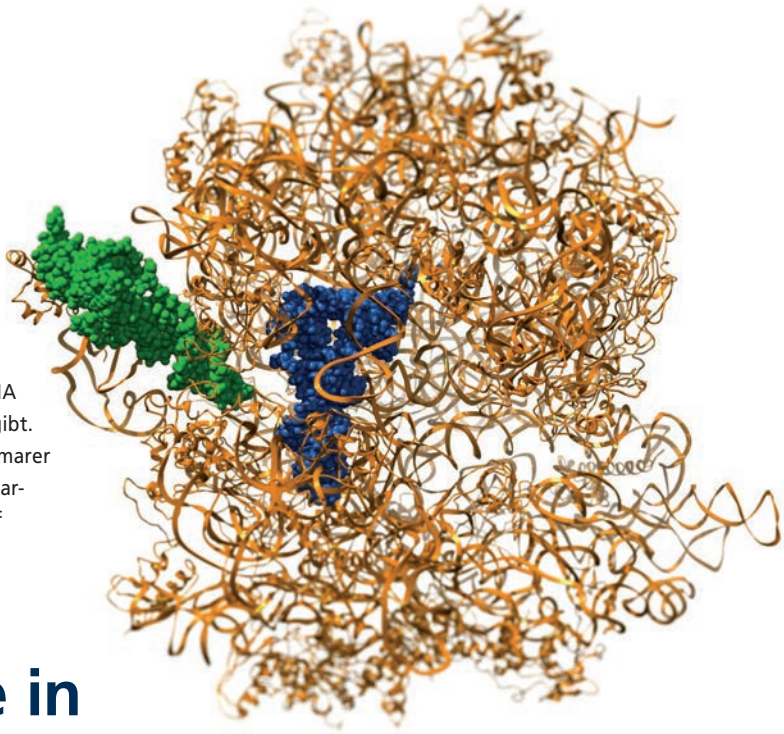
Eine durchwachte Nacht rächt sich: Am nächsten Tag können wir uns schlecht konzentrieren, fühlen uns gereizt und abgeschlagen und unser Stoffwechsel gerät aus dem Gleichgewicht. Die teils gravierenden Folgen von zu wenig Schlaf machen deutlich, wie wichtig dieser Ruhezustand für unseren Körper ist. Unser Wissen über die Ursache und Funktion des Schlafes ist allerdings noch immer äußerst bruchstückhaft.

Wichtige neue Erkenntnisse zum Schlaf verspricht ausgerechnet ein kleiner Fadenwurm namens *Caenorhabditis elegans*, den sich auch Schlafforscher Henrik Bringmann vom MPIbpc für seine Forschung zunutze macht. Denn auch der ein Millimeter kleine Wurm durchlebt während seiner Entwicklung vier schlafähnliche Zustände. Nach jeder dieser Ruhephasen häutet sich das Tier. Ähnlich wie ein schlafender Mensch ist die Larve dabei entspannter und reagiert weniger sensibel auf äußere Reize. Zudem nimmt die Aktivität ihrer Nervenzellen deutlich ab. Anders als bei den meisten Tieren und uns Menschen wird der Schlaf-Wach-Rhythmus der Wurmlarve aber nicht durch den äußeren Tag-Nacht-Zyklus gesteuert, sondern durch seinen Häutungsrhythmus. Stört man den Wurm während seiner Ruhephasen, können auch hier die Folgen schwerwiegend sein: Das Tier leidet unter Schlafstörungen, es kommt zu Defekten beim Häuten und die fehlende Ruhe kann schließlich zum Tod der Larve führen.

Auf Schlaf programmiert

Das Forscherteam um Henrik Bringmann hat jetzt in einem aufwendigen Genscreen einen wichtigen molekularen Schalter namens aptf-1 identifiziert, der den Wurm vom wachen in den schlafähnlichen Zustand versetzt. „Dieser Schalter kommt nur in fünf der insgesamt rund 300 Nervenzellen des Fadenwurms vor", erklärt Henrik Bringmann. Wie sein Team herausfand, wirkt aptf-1 aber nur in einer einzigen Nervenzelle – RIS genannt – tatsächlich schlaffördernd. Aktiviert das aptf-1 die RIS-Nervenzelle, „programmiert" diese die Larve auf „Schlaf". Gestörte Ruhephasen sind die Folge, wenn man dem Fadenwurm die RIS-Nervenzelle entfernt.

Vergleichbare schlaffördernde Mechanismen kommen auch bei Wirbeltieren vor. „Uns interessiert daher, ob diese auch bei höheren Tieren für den Übergang von Wachsein zu Schlaf sorgen", so der Forschungsgruppenleiter. Ein Indiz hierfür ist das Char-Syndrom beim Menschen. Betroffene weisen eine Genmutation des AP2ß-Proteins auf, das mit dem aptf-1 verwandt ist. Als Symptome dieser seltenen Erkrankung treten unter anderem Schlafstörungen wie Schlafwandeln und eine deutlich reduzierte Schlafdauer auf. „Ob der schlafähnliche Zustand des Fadenwurms und der Schlaf des Menschen tatsächlich einen gemeinsamen Ursprung in der Evolution haben, müssen weitere Untersuchungen der genauen Steuerung der Schlafkontrollmechanismen zeigen", sagt Schlafforscher Henrik Bringmann. (ms/cr)



Transfer-RNA (tRNA)-Moleküle am Ende ihrer Wanderung durch das Ribosom (oranges Bändermodell). Die grüne tRNA befindet sich bereits am Ausgang des Ribosoms, die blaue tRNA sitzt in der mittleren Position, an der es seine Aminosäure abgibt. In der Arbeit wurden insgesamt 25 solcher Strukturen mit atomarer Genauigkeit bestimmt und anschließend mithilfe von Molekulardynamiksimulationen zu einem kompletten Bewegungsablauf zusammengesetzt. *(Bild: Forschungszentrum Jülich)*

Faszinierende Einblicke in den „Maschinenraum" der Proteinfabrik

Wer treibt bei komplexen Arbeitsabläufen eigentlich wen an? Diese Frage stellt sich auch in den Proteinfabriken der Zelle – den Ribosomen. Computersimulationen eines Forscherteams aus Göttingen, Jülich und Düsseldorf haben erstmals mit atomarer Genauigkeit gezeigt, welche Mechanismen und Kräfte im Ribosom am Werk sind. Ihre Experimente machten das „Hebel- und Räderwerk" sichtbar, das die Bewegungen des Ribosoms kontrolliert und koordiniert. *(Nature Structural & Molecular Biology, 3. November 2013)*

Ribosomen sind molekulare Hochleistungsmaschinen. Sie fertigen nach den in der DNA codierten Bauplänen Proteine – die universellen Werkzeuge aller Zellen. Proteine empfangen und übermitteln Signale, transportieren zelluläre Fracht oder sorgen für Wachstum und Bewegung. Für die Proteinproduktion muss zunächst eine Arbeitskopie der DNA erzeugt werden – die sogenannte Boten-RNA. Wie ein Fließband wird die Boten-RNA durch das Ribosom hindurchgeschleust. Dabei wird es in Schritten von jeweils drei Nukleinsäurebasen abgetastet. Die Tripletts werden wiederum von den passenden Aminosäure-Transportern – sogenannten Transfer-RNAs oder kurz tRNAs – abgelesen, die eine bestimmte Aminosäure binden. Die Aminosäuren werden nacheinander zu einer Kette zusammengesetzt und ergeben schließlich ein neues Proteinmolekül.

Wissenschaftlern vom MPIbpc war es vor Kurzem gelungen, hoch aufgelöste Momentaufnahmen dieses Prozesses mit einem Elektronenmikroskop aufzunehmen. Ihre 50 Strukturen des Ribosoms in verschiedenen Zuständen der Proteinsynthese zeigen, welchen Weg die tRNAs während der Proteinproduktion durch das Ribosom nehmen und wo sie andocken. Ein Forscherteam aus Göttingen, Jülich und Düsseldorf hat mit Computersimulationen die einzelnen Schnappschüsse jetzt in eine zeitliche Reihenfolge gebracht und untersucht, wie sich die tRNA-Moleküle auf ihrem Weg durch das Ribosom bewegen und welche molekularen Kräfte dabei wirken.

Gunnar Schröder, Leiter einer Nachwuchsgruppe am Forschungszentrum Jülich und Juniorprofessor an der Heinrich-Heine-Universität Düsseldorf, erklärt: „Damit haben wir es erstmals geschafft, aus einzelnen Elektronenmikroskopie-Aufnahmen mithilfe von Computersimulationen einen vollständigen Bewegungsablauf im Ribosom zusammenzusetzen." Gunnar Schröder hat aus den früheren elektronenmikroskopischen Aufnahmen die atomaren Modelle erstellt, auf denen die aktuellen Computersimulationen basieren. Helmut Grubmüller, Direktor am MPIbpc, betont: „Nun sehen wir nicht nur, welche Prozesse im Inneren der Proteinfabrik ablaufen, sondern auch, durch welche Kräfte diese Prozesse angetrieben werden." Das Ergebnis dieser Arbeit ist eine „Filmsequenz" – direkt aus dem „Maschinenraum" der Proteinfabrik.

Die neuen detaillierten Einblicke des Forscherteams in den „Maschinenraum" der Ribosomen sind auch für die Medizin von Bedeutung. Bestimmte Antibiotika bekämpfen Krankheitserreger deshalb so wirksam, weil sich Ribosomen von Bakterien und höheren Organismen in wichtigen Details unterscheiden. Solche Antibiotika hemmen nur die bakterielle Proteinfabrik; die Ribosomen höherer Zellen dagegen bleiben verschont. Um zukünftig neue Antibiotika entwickeln zu können, ist ein genaues Verständnis der Struktur und Funktion des Ribosoms eine unerlässliche Grundlage.

Gemeinsame Pressemitteilung des Forschungszentrums Jülich, der Heinrich-Heine-Universität Düsseldorf und des MPIbpc

Oxford University Press (May 23, 2013)

Bild: Ruthild Winkler-Oswatitsch

Review of Manfred Eigen's newest book:

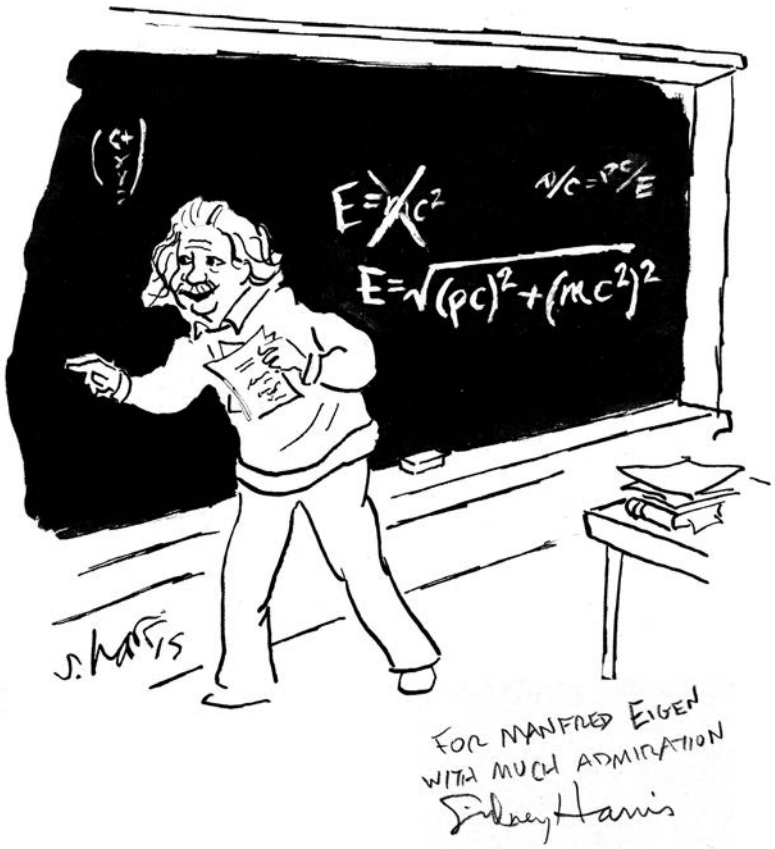
From strange simplicity to complex familiarity

His musical home drew Manfred Eigen's zeal towards the arts, and had it not been for Hitler's war he might have started a career as piano virtuoso. But when the war ended, a day before his 18th birthday, he had been forced to serve as anti-aircraft auxiliary for more than two years and found himself detained in an American prisoner-of-war camp near Salzburg. Returning home after a two-month walk on foot, he decided to seize the first opportunity to attend a university, and chose to study physics and chemistry in Göttingen. But in spite of his brilliant achievements in the natural sciences and his manifold duties in the scientific community, he never neglected his love for music, literature, and the fine arts. With this book, almost seventy years later, he presents the summa of his life's work and interests:

From strange simplicity to complex familiarity – A treatise on matter, information, life and thought.

Neither a textbook nor a piece of popular science, and also not an autobiography – it is a combination of science and reflection, of subtle arguing and casual talk; a meticulously composed work of art in itself. Manfred Eigen outlines in his personal manner the world-view which is no doubt the prevailing view of the majority of scientists at our time. He describes how the universe is built, how it functions, and how it evolves: from simple constituents and laws that we perceive as *strange*, to structures of unimaginable complexity with which we are nevertheless *familiar* in everyday life; from quarks, atoms, and molecules to living beings and their brains. Embedded in this all-embracing presentation is Eigen's own theory of biological evolution, conceived in the late sixties, after he had won the Nobel Prize of Chemistry, and refined in the course of the last forty years: a theory which describes Darwinian evolution on a molecular level and formulates it with the rigor of physical laws.

The book encompasses virtually all the natural sciences plus mathematics. Hence it reaches out beyond the expertise of almost any single person. The reading is by no means easy; we are drawn deep down into the subtleties of the author's arguments and high up onto the summits of his visions. It takes time and dedicated participation to digest all this, but every now and then the hard stuff is interrupted by digressions of many kinds: recollections of encounters with colleagues from all fields, historical annotations, anecdotes, or charming plays on words.



The treatise is a succession of fifty essays, ten each in five chapters whose titles shake hands as they proceed from "strange" elementary simplicity to "familiar" complex organization: 1. Matter and energy, 2. Energy and entropy, 3. Entropy and information, 4. Information and complexity, 5. Complexity and self-organisation. The individual essays are headed by provoking questions, some tongue-in-cheek like "How far is it from Shannon to Darwin?" (playing with the names of towns and theories), others rather stern like "How is entropy related to order?". Even though each essay is a fitting piece in the design of the grand opus, it may be read (almost) independently of the others, just as one may listen to individual movements of a symphony. Yet they are artfully arranged, and the very last section – 5.10. "It from bit" or "Bit from it" – comes full circle back to the beginning when it muses about the evolution of the entire universe.

Theory for the origin of life

Every single essay would deserve a thorough discussion, both for its own line of thought and for its role as building block in the overall reasoning. Lack of space prevents this here, so let us focus on the central theme: the foundation of a theory for the origin of life, following the tradition of physics, but extending it from the physics of matter to "the physics of information".

The first two chapters deal with the physics of non-living matter – simple in its composition and elementary in the theories developed for an understanding, such as quantum mechanics and relativity theory. Since much of it could only be unveiled with ever more sophisticated instruments which extend our sensual perception, and with highly abstract thinking, the *simplicity* of this aspect of the world appears indeed *strange*. It characterizes the laws that govern the most fundamental phenomena like quarks inside nuclei, electrons in atoms, or the interaction of radiation and matter. But it also applies to the macro world of composite but inanimate matter such as solids, liquids, or stars, where thermodynamics and statistical mechanics provide appropriate tools. Entropy has served here well as the key concept relating microstates to macrostates, with the crucial assumption that all possible microstates have equal a priori probability; the entropy is then the logarithm of the number of microstates compatible with a given macrostate. The same number can be interpreted as the *information* needed to specify a microstate: Shannon used this purely quantitative concept as a measure of the information content of a message transmitted along a communication line.

At this point Manfred Eigen argues that there must be more to information than this number because it completely ignores the *meaning* of a message. He turns his attention to the *semantic* aspect of information and uses this as the fundamental concept when it comes to an understanding of life. The distance between Shannon airport in Ireland and the seaport Darwin in Australia, almost antipodes on our globe, is taken as a metaphor for the different nature of Shannon's communication theory and Darwin's theory of evolution, both dealing with information. The book's third chapter is devoted to an explication of this difference.

The stage is then set for a new *physics of information* – of information with meaning generated in the course of evolution. The forth chapter, where this theory unfolds, is the longest of

the book and undoubtedly its central part; the corresponding mathematics is provided in an elaborate appendix by Peter Schuster. The chapter starts with the questions "How complex is chemistry?" and "How does nature tame chemical complexity?". Considering any conceivable chemical compound as a possible microstate, their shear number ridicules the basic assumption of statistical physics that they should all be equally probable: The vast majority of them cannot even exist because the number of compounds exceeds by far the number of atoms in the universe. The real complexity of the living world could only emerge "by first reducing chemical complexity", and that is what happened some four billion years ago, when molecules of tRNA type appeared, which had the combined abilities to perform catalytic functions and to reproduce themselves, with certain probabilities for errors/mutations on which selection could operate – in short, when Darwinian evolution started on the level of molecules.

Natural selection as a physical law

Manfred Eigen constructs, as an appropriate framework for the dynamics of Darwinian evolution, a 4^N-dimensional *information space*, where N is the total length of the sequences of four nucleic acids that have so far come in existence. Genes are points in this space, and their kinship is expressed in terms of the geometry defined by Hamming distances as a metric. On this basis, and drawing on his seminal paper of 1971, Eigen describes "natural selection as a physical law" (section 4.7.). An important feature of the governing equations is that they do not select for single points in information space but for distributions of such points which come as eigenstates of a dynamical matrix – called *quasispecies* in analogy to the quasiparticles of physics.

The clone "Eminent" of *Paphiopedilum* MANFRED EIGEN, registered in 1983 by Motoo Kimura

Underlying and corroborating this reasoning is a rich body of "Darwinian experiments" with phage RNA. They were inspired by Sol Spiegelman's work on "serial transfer" in the 1960s and carried out under the guidance of the late Christof Biebricher in Eigen's institute. The importance of empirical guidance as a prerequisite of theoretical thinking is strongly advocated in the closing section of chapter 4 whose heading "pure thought = poor thought?", if taken without question mark, expresses Eigen's credo as a scientist. "Poor thinking" may not be lacking sophistication, elegance, or intellect, he says, but as long as it has not been checked by observation, it remains speculation. As an amusing case in point he tells the story of the wrong prediction of the genetic code by Francis Crick and others.

The origin of life – on a molecular level – is the topic of the last chapter. It goes into more detail of both experiments and their theoretical description. Exponential growth is demonstrated to characterize normal Darwinian evolution where new quasispecies get a chance to compete with the old, but the selection of the basic design of life – coupling of genotype (information) and phenotype (function) with cyclic feedback – followed a hyperbolic growth law where newcomers are suppressed even if they might have won the original race had they happened to be there. The key feature of such design is its *hypercyclic organization* as proposed in Eigen's original work of 1971, and elaborated on in his book with Peter Schuster *The hypercycle* of 1979. The chapter goes on to compare these ideas with those of others, friends in spirit and critics. Section 5.9. reports on the development of "evolution machines" based on experience and ideas acquired in Eigen's lab at the Göttingen Max Planck Institute for Biophysical Chemistry, and used to start a biotechnological company. The last section, as mentioned before, connects back to the beginning with reflections on *The life of the cosmos* (Smolin 1977).

Several times, notably at the end of the conclusions, it is mentioned that the full path from "strange simplicity" to "complex familiarity" has not yet been completed. The "Treatise on matter, information, life and thought" has come so far as to cover the early stages of life on earth. A second volume is planned, with main emphasis on even more complex and familiar topics: "Life, thought, and human culture". At his age of 86 Manfred Eigen is not sure he will be able to complete this task. Let us be grateful for the present book which took a long time to mature: a masterpiece of scientific literature, an authoritative compendium of what the natural sciences have achieved up to the turn of the millennium, a magnum opus of a unique kind, unmatched in character and scope.

Peter Richter

Peter Richter

studied theoretical physics in Göttingen and received his PhD in 1971 from the University of Marburg. In 1973, he returned to Göttingen and worked as a research associate with Manfred Eigen at the MPIbpc until 1977. After research stays at MIT in Cambridge (USA) and Stanford University (USA) Peter Richter was appointed as professor of theoretical physics at the University of Bremen in 1980. His research interests are nonlinear systems and structure formation, mathematics of dynamical systems, chaos, fractals, integrable problems of classical mechanics, as well as regular and chaotic spinning tops. From 2003 to 2005, he was also Vice President for teaching affairs at the University of Bremen. Since his retirement in 2011, he is engaged in physics teacher education as *Wilhelm und Else Heraeus Seniorprofessor*.

Azubis waren in Heidelberg auf Tour

24 Auszubildende und zwei Ausbilder aus unserem Institut waren während der diesjährigen Azubifahrt drei Tage in Heidelberg unterwegs. In einem abwechslungsreichen Programm konnte sich die Gruppe aktiv als Team finden. Gemeinsam besuchten die Azubis das MPI für Kernphysik und besichtigten bei einem Stadtrundgang die Heidelberger Innenstadt samt Schloss. Im Hochseilgarten schließlich wagten sie sich in luftige Höhen.

Dort kam es beim Klettern nicht nur auf die Leistung des Einzelnen an, sondern es ging darum, als Gruppe zu bestehen. Die größte Herausforderung war der wackelige, acht Meter hohe Pfahl. Ihn zu erklimmen und oben zu stehen, ohne sich irgendwo festhalten zu können, gelang oft nur durch die Motivation und Tipps der Gruppe. Auch der folgende Sprung in die Tiefe war nur durch die Sicherung der anderen möglich.

Die lobenden Worte von allen Seiten über die *tolle Truppe* war wohl die schönste Auszeichnung für die Teilnehmer.

Peter Böttcher

Max-Planck-Gesellschaft erhält Prinz-von-Asturien-Preis

Am 25. Oktober wurde die Max-Planck-Gesellschaft (MPG) mit dem *Prinz-von-Asturien-Preis* in Oviedo (Spanien) für ihre internationale Zusammenarbeit geehrt. Der spanische Kronprinz verlieh die Auszeichnung auf einer feierlichen Festgala. Die MPG hat das Preisgeld von 50 000 Euro aus eigenen Mitteln noch einmal verdoppelt, um damit spanischen Nachwuchsforschern Gastaufenthalte an einem Max-Planck-Institut (MPI) zu ermöglichen.

Max-Planck-Präsident Peter Gruss, Soojin Ryu, Ali Shahmoradi, Matthias Weißenbacher und Damian Refojo (von links) auf dem Weg zur feierlichen Preisverleihung in Oviedo.

Max Planck President Peter Gruss, Soojin Ryu, Ali Shahmoradi, Matthias Weißenbacher and Damian Refojo (from left) on their way to the official awards ceremony in Oviedo.
(Copyright: Fundación Príncipe de Asturias)

Einmal im Jahr blickt die Welt auf Oviedo – die Hauptstadt Asturiens. Ende Oktober wird dort vor dem altehrwürdigen Hotel De La Reconquista ein Teppich ausgerollt, der nicht rot sondern blau ist – die Farbe der *Prinz-von-Asturien-Stiftung*. Diese Ehre gilt den Gewinnern der *Prinz-von-Asturien-Preise* – und die MPG ist in diesem Jahr einer von ihnen.

Die MPG erhält den Preis in der Kategorie *Internationale Zusammenarbeit*. Sie folgt damit Einrichtungen wie dem *Internationalen Roten Kreuz*, dem *Roten Halbmond*, der *Weltgesundheitsorganisation* oder der *Bill & Melinda Gates-Stiftung*. Die Jury lobte die europäische Ausrichtung der MPG, den interdisziplinären Ansatz und die enge Zusammenarbeit zwischen MPIs und Forschungseinrichtungen sowie Universitäten in der ganzen Welt. Dabei hob sie neben der wissenschaftlichen Exzellenz auch die internationale Nachwuchsförderung in Form der mehr als 40 Partnergruppen weltweit hervor, durch die hochqualifizierte junge Wissenschaftler beim Aufbau einer eigenen Arbeitsgruppe in ihren Heimatländern unterstützt werden.

4000 MPG-Forscher aus über 100 Ländern

Vier junge Max-Planck-Wissenschaftler, Ali Shahmoradi, Damian Refojo, Soojin Ryu und Matthias Weißenbacher, begleiteten Max-Planck-Präsident Peter Gruss nach Oviedo – stellvertretend für die rund 4 000 MPG-Nachwuchsforscher aus mehr als 100 Ländern. Die Verleihung des „spanischen Nobelpreises“ vor 2 000 Gästen schaffte es schließlich sogar auf die Titelseite der größten spanischen Tageszeitung: El País.

Der Preis sei eine wunderbare Auszeichnung und Würdigung für die Arbeit aller Max-Planck-Forscher und ihrer Partner weltweit, sagte Peter Gruss. Er betonte: „Wissenschaft ist immer auch ein Brückenbauer. Durch den Austausch junger Nachwuchsforscher stärken wir das Verständnis für die Belange im jeweils anderen Land. Und wir legen die Grundlage für eine grenzüberschreitende wissenschaftliche Zusammenarbeit, ohne die wir die großen Probleme der Menschheit nicht werden bewältigen können.“

Die MPG wird das verliehene Preisgeld von 50 000 Euro aus eigenen Mitteln noch einmal um denselben Betrag aufstocken und daraus ein Förderprogramm für spanische Nachwuchswissenschaftler finanzieren. Insgesamt 15 Doktoranden und Postdoktoranden können damit für maximal zwei Monate an einem MPI forschen. Die MPG setzt damit angesichts der Sparmaßnahmen ein Zeichen für die Wissenschaft. Denn vor dem Hintergrund der Finanz- und Wirtschaftskrise wurden die Zuschüsse für die staatlichen Universitäten und Fördermittel für Auslandsaufenthalte in Spanien gekürzt. „Investitionen in Bildung und Forschung sind immer auch Investitionen in unsere wissenschaftliche, ökonomische und gesellschaftliche Wettbewerbsfähigkeit“, so der Max-Planck-Präsident. Er ermutigte die europäischen Staaten, ihr Engagement für Wissenschaft und Forschung auszubauen. (cr, *mit Material aus Pressemitteilungen der MPG*)

Max Planck Society receives Prince of Asturias Prize

On October 25, 2013, the Max Planck Society (MPS) was conferred the *Prince of Asturias Award* for International Cooperation in Oviedo (Spain) by the Spanish crown prince. The MPS will double the prize money of 50,000 euros from its own resources to provide Spanish junior scientists with the opportunity to carry out research at a Max Planck Institute (MPI) in Germany.

Once a year the world looks at Oviedo – the capital of Asturias. At the end of October, a blue carpet – in the color of the *Prince of Asturias Foundation* – is rolled out in front of the renowned Hotel De La Reconquista to honor the awardees of the *Prince of Asturias Prize*. This year again the foundation honored awardees in eight categories and the Max Planck Society is one of the prize winners.

The research organization receives the award in the category *International cooperation*, following in the footsteps of institutions such as the *International Red Cross* and the *Red Crescent Movement*, the *World Health Organization*, or the *Bill and Melinda Gates Foundation*. In its statement the jury emphasized the interdisciplinary approach of the MPS and the close cooperation among research centers and universities around the world. Alongside the Max Planck Society's scientific excellence, the foundation's jury also praised the organization's international advancement of young researchers through its more than 40 Partner Groups worldwide.

Four young Max Planck researchers, Ali Shahmoradi, Damian Refojo, Soojin Ryu, and Matthias Weißenbacher, accompanied Max Planck President Peter Gruss to Oviedo – as representatives for the 4 000 young researchers in the MPS from more than 100 countries. The award ceremony of the "Spanish Nobel Prize" with 2 000 guests finally made it even on the front page of Spain's biggest daily newspaper: El País.

"This prestigious prize was a wonderful recognition of the work of all Max Planck researchers and their partners worldwide," President Peter Gruss said. "Science always builds bridges. Through the exchange of young researchers and scientists, we aim to foster understanding for the culture and concerns of other countries. And we lay the foundations for a scientific collaboration across borders, without which the major problems of humanity cannot be resolved."

The MPS will double the prize money awarded by the *Prince of Asturias Foundation* by 50,000 euros from its own resources to finance a grant program for young Spanish researchers. A total of 15 doctoral and postdoctoral students can now be invited for a research stay at an MPI for up to two months.

Due to the financial and economic crisis, the Spanish government has cut funding for state universities and funds for research stays abroad. "Investments in education and research are at the same time always investments into our scientific and economic competitiveness, and the competitive ability of our society," said the Max Planck President. He encouraged the European states to further strengthen their commitment to science and research. (cr, *with material from MPS press releases*)

Der *Prinz-von-Asturien-Preis* wird in acht Kategorien verliehen. Die Max-Planck-Gesellschaft erhält den *Prinz von Asturien-Preis* in der Kategorie *Internationale Zusammenarbeit*. Mit dem Preisgeld wird auch eine Skulptur überreicht, die auf einen Entwurf des Künstlers Joan Miró zurückgeht.

The *Prince of Asturias Prize* is awarded in eight categories. The Max Planck Society receives the award in the category *International Cooperation*. It is conferred together with a sculpture going back to a design by the artist Joan Miró.

IMPRESSUM

Redaktionsleitung
Carmen Rotte (cr), Tel. 1304

Redaktion
Carmen Rotte, Tel. 1304
Elisa Schubert (es), Tel. 1308
Marianne Steinke (ms), Tel. 1310

Mitarbeit
Ulrich Kuhnt, Tel. 1646

Layout
Claus-Peter Adam, Tel. 1474
Hartmut Sebesse, Tel. 1580

Fotos
Irene Böttcher-Gajewski, Tel. 1135
Peter Goldmann, Tel. 1423

Intranet
Claus-Peter Adam, Tel. 1474
www.mpibpc.intern/intern/de/aktuell

Druck
PR Druckerei Göttingen

Max-Planck-Institut für biophysikalische Chemie
Am Faßberg 11, 37077 Göttingen
Tel. +49 551 201-0
Fax +49 551 201-1222
www.mpibpc.mpg.de