Universität Rostock Traditio et Innovatio

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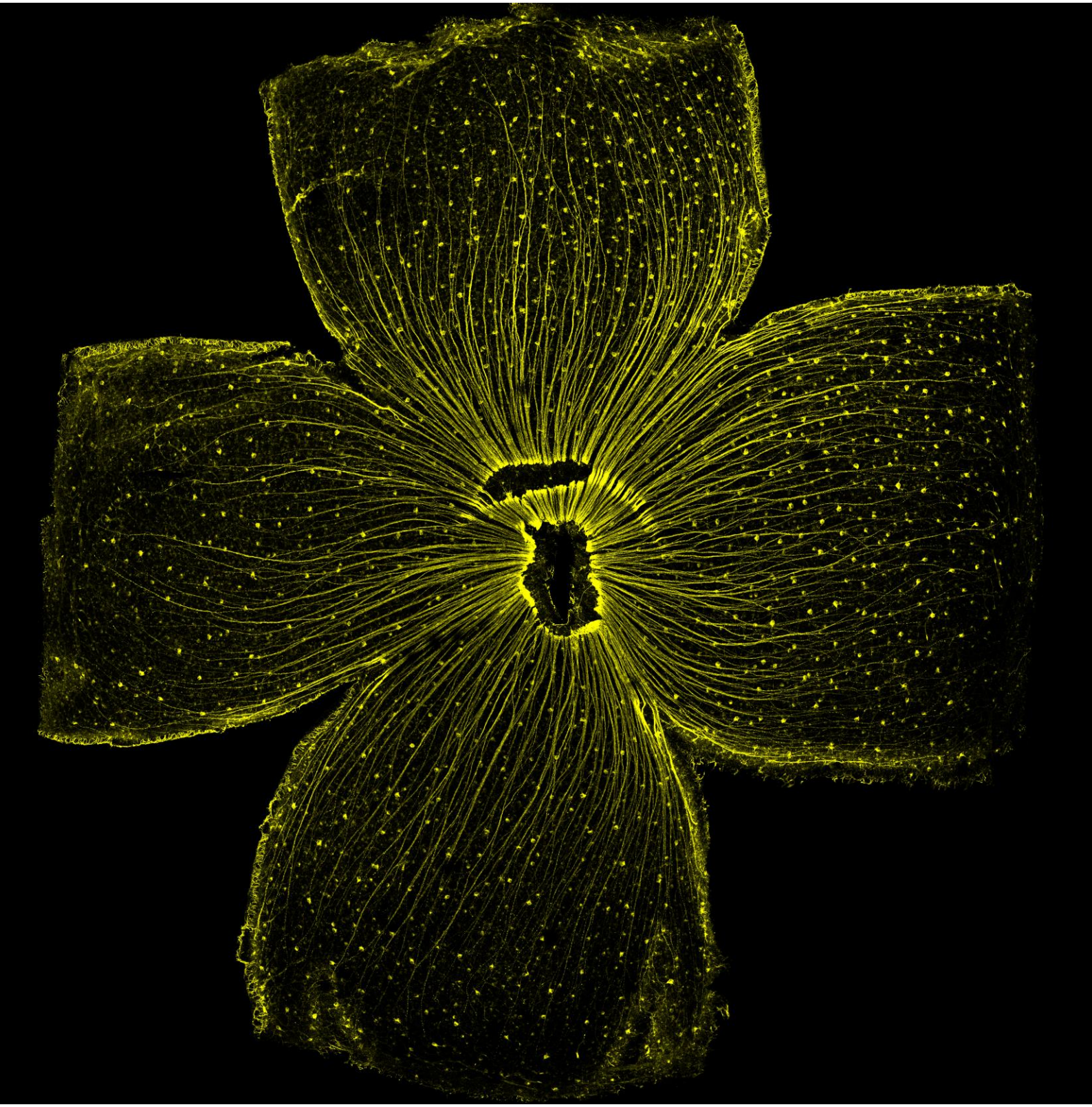
Universitätsmedizin Rostock



3. Rostock Summer School of Neurodegenerative Diseases

29 & 30 September 2025

Program & Abstracts

3. Rostock Summer School of Neurodegenerative Diseases

Dear Madam or Sir,

I cordially welcome you to the 3rd Rostock Summer School on Neurodegenerative Diseases, which consists of the Schilling Symposium and the Clinician Scientist day. The central topic is the connection from basic science to clinical translation in neurodegeneration with special focus on motor neuron diseases. I am honored to welcome so many well-known researchers in the field for this day, together with many young scientists which promises us a varied program with hopefully stimulating discussions. I also feel privileged that my colleagues from Rostock are once more willing to give insights in their clinical work on neurodegeneration, sharing with us state-of-the-art knowledge and technologies in the respective topic of neurodegenerative diseases.

I wish you all unique days in Rostock.

Yours sincerely,

Prof. Dr. Dr. Andreas Hermann
Schilling Professor for Translational Neurodegeneration
Head of Translational Neurodegeneration Section “Albrecht Kossel”

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Program

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29th September 2025
Clinician Scientist Day

08:45 Welcome

09:00 Anatomy of Neurodegeneration
Dr. Sarah Joost

09:30 Neuropathology of neurodegenerative diseases
Prof. Dr. Dr. Andreas Hermann

10:00 Syndromatology I: Dementia – cognitive disorders in neurodegeneration
Prof. Dr. Stefan Teipel

- Coffee break –

11:00 Sleep in neurodegenerative diseases
Dr. Wiebke Hermann

11:30 Structural imaging of neurodegeneration
PD Dr. Ebba Beller

12:00 Neuroimaging: the clinical perspective
Prof. Dr. Dr. Andreas Hermann

12:30 Syndromatology II: Movement disorders
Prof. Dr. Alexander Storch

- Lunch –

14:00 Ultrasound imaging neurodegeneration
Prof. Dr. Uwe Walter

14:30 Drug treatment for movement disorders
Dr. Matthias Löhle

15:00 Deep brain stimulation for movement disorders
PD Dr. René Reese

15:30 Syndromatology III: Other neurodegenerative diseases
Prof. Dr. Dr. Andreas Hermann

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Universitätsmedizin Rostock

29th September 2025
Clinician Scientist Day

Speakers

PD Dr. Ebba Beller
Institute of Radiology, University Medical Center Rostock

Prof. Dr. Dr. Andreas Hermann
Department of Neurology, Translational Neurodegeneration Section „Albrecht Kossel“, University Medical Center Rostock
Center & German Center for Neurodegenerative Diseases (DZNE)

Dr. Wiebke Hermann
Department of Neurology, University Medical Center Rostock

Dr. Sarah Joost
Institute of Anatomy, University Medical Center Rostock

Dr. Matthias Löhle
Department of Neurology, University Medical Center Rostock

PD Dr. René Reese
Department of Neurology, University Medical Center Rostock

Prof. Dr. Alexander Storch
Department of Neurology, University Medical Center Rostock & German Center for Neurodegenerative Diseases (DZNE)

Prof. Dr. Sefan Teipel
University Medical Center Rostock Center & German Center for Neurodegenerative Diseases (DZNE)

Prof. Dr. Uwe Walter
Department of Neurology, University Medical Center Rostock

30th September 2025
Schilling-Symposium

09:00 Welcome

Chair: Prof. Dr. Alexander Storch

09:30 Neurodegeneration and aging: common traits or individualized medicine?
Prof. Dr. Dr. Andreas Hermann, University Medical Center Rostock

10:00 From mitochondria to metabolome: Metabolic adaptations in stress-tolerant marine mollusks
Prof. Dr. Inna Sokolova, University of Rostock

10:30 Exploring diagnostic and prognostic biomarkers for ALS in japanese and swedish cohorts
Kazuki Obara, Lund University (**Data Blizz)**

10:45 "Raisin bread sign" as a radiological feature in patients with pontine autosomal dominant microangiopathy and leukoencephalopathy
Mai Kikumoto, MD, Ph.D, Hiroshima University (**Data Blizz)**

– 11:00-11:30 Coffee break –

Chair: Prof. Dr. Michael Sendtner

11:30 TDP-43 gains are losses
Carlo Scialò, MD, PhD, University of Zurich

12:00 Short tandem repeats as genetic modifiers of brain function in health and diseases
Ahmad Aziz, MD, PhD, DZNE Bonn

12:30 Social interactions of people with dementia
Hanna Knecht, DZNE Greifswald (**Data Blizz)**

12:45 The Cornea – a Window into Neurodegeneration?
Dr. Karsten Sperlich, University Medical Center Rostock (**Data Blizz)**

– 13.00-14.00 Lunch & Posters –

Chair: Prof. Dr. Dr. Andreas Hermann

14:00 A song of light and power – Using light as an energy replacement for longevity
Dr. Shahaf Peleg, FBN Dummerstorf

14:30 The possible role of telomere position effects in neuronal development and neurodegenerative diseases
Prof. Dr. Michael Walter, University Medical Center Rostock

15:00 Frontotemporal dementia – diagnostic biomarkers and neurodevelopmental reserve
Alexander Santillo, MD, PhD, Lund University

15:30 Impact of norepinephrine on adult neurogenesis
Svenja Koch **(Data Blizz)**

15:45 Pulsed electromagnetic field (PEMF) stimulation rescues deficient axonal organelle motility through repair of damaged, underlying microtubule tracks in amyotrophic lateral sclerosis (ALS)
Dr. Arun Pal **(Data Blizz)**

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Universitätsmedizin Rostock

30th September 2025
Schilling-Symposium

Speakers

Ahmad Aziz, MD, PhD
Population & Clinical Neuroepidemiology, DZNE Bonn

Prof. Dr. Dr. Andreas Hermann
Department of Neurology, Translational Neurodegeneration Section „Albrecht Kossel“, University Medical Center Rostock & German Center for Neurodegenerative Diseases (DZNE)

Mai Kikumoto, MD, Ph.D., Assistant Professor
Department of Clinical Neuroscience and Therapeutics, Hiroshima University Graduate School of Biomedical and Health Sciences, Hiroshima, Japan

Hanna Knecht
Psychosocial Epidemiology and Public Health, DZNE Greifswald

Svenja Koch
Department of Neurology, University Medical Center Rostock, Germany

Prof. Dr. Bernd Krause
Dean and Scientific Board of the University Medical Center Rostock

Kazuki Obara
Lund University

Dr. Arun Pal
Dresden High Magnetic Field Laboratory (HLD), Helmholtz-Zentrum Dresden-Rossendorf, Germany & Division for Neurodegenerative Disease, Dept. Neurology, Technische Universität Dresden, Dresden, Germany

Dr. Shahaf Peleg
Research Institute for Farm Animal Biology (FBN), Dummerstorf

Prof. Dr. Michael Sendtner
Universitätsklinikum Würzburg, Director Institute of Clinical Neurobiology

Prof. Dr. Inna Sokolova
Institute of Biological Sciences, Chair of Marine Biology, University of Rostock

Alexander Santillo, MD, PhD, Associate Professor
Clinical Memory Research Unit, Lund University

Carlo Scialò, MD, PhD
Department of Quantitative Biomedicine, University of Zurich

Dr. Karsten Sperlich
Department of Ophthalmology, University Medical Center Rostock

Prof. Dr. Alexander Storch
Director, Department of Neurology, University Medical Center Rostock & German Center for Neurodegenerative Diseases (DZNE)

Prof. Dr. Michael Walter
Director, Institute of Clinical Chemistry and Laboratory Medicine, University Medical Center Rostock

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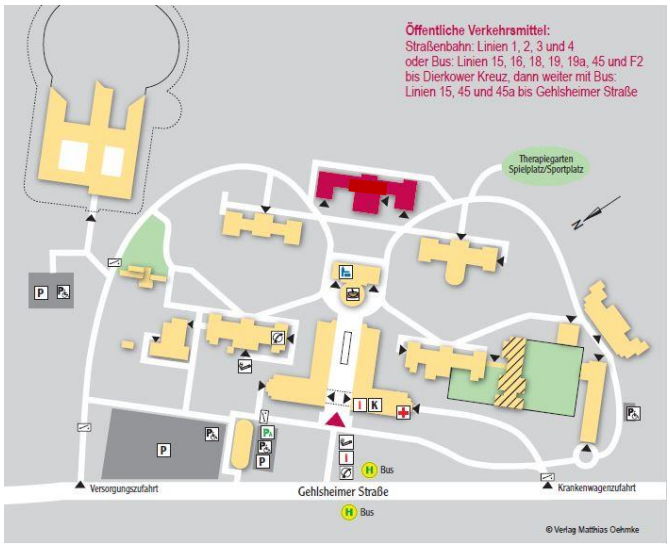
General informations

Locations

29th September 2025 - Campus Gehlsdorf

University Medical Center Rostock
Department of Neurology
Department of Head- and Neuromedicine
Translational Neurodegeneration Section „Albrecht Kossel"

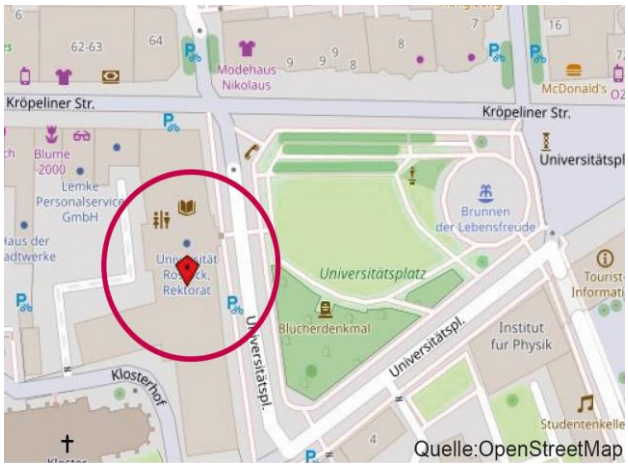
Gehlsheimer Straße 20, 18147 Rostock



30th September 2025 – Main building

University of Rostock, Rectorate
Aula, 1. OG

Universitätsplatz 1, 18055 Rostock



Contact & Organisation

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Universitätsmedizin Rostock

Hermann und Lilly Schilling-Stiftung

Hermann und Lilly Schilling-Stiftung

The foundation was established in 1970 by Aloysia Schilling. She was the wife of Hermann Schilling, former State Finance Councillor of the Prussian State Bank and member of the Board of Directors of Vereinigte Elektrizitäts- und Bergwerks-Gesellschaft (VEBA), who died in 1961.

Areas of Support

As part of its “Neuroscience in the Clinic” program (1997 to 2021), the foundation financed a total of seven departments/institutes for basic clinical research at neurological university clinics. These new establishments enable scientists working in the field of basic clinical research to take up questions from the clinic and transfer the results of their research into clinical application.
The following departments were established as part of the program:

- Institut für Klinische Neuroimmunologie, Klinikum Großhadern der Ludwig-Maximilians-Universität München
- Abteilung für Experimentelle Neurologie, Neurologische Klinik der Charité
- Abteilung Kognitive Neurologie, Eberhard-Karls-Universität Tübingen
- Abteilung Klinische Neurobiologie, Neurologische Universitätsklinik Heidelberg
- Institut für Klinische Neurobiologie, Neurologische Klinik und Poliklinik der Universität Würzburg
- Sektion für Klinische und Molekulare Neurogenetik, Klinik für Neurologie der Universität und des UK S-H, Campus Lübeck
- Abteilung für Kognitive Neurobiologie, Zentrum für Neurologische Medizin, Universitätsmedizin Göttingen

As part of the “Schilling Professorship and Translational Neuroscience Research Group” program launched in 2015, the following institutions are being funded:

- Schilling-Professur "Vaskuläre Neuroimmunologie" und Forschungsgruppe "Translationale Neurowissenschaften", Universitätsklinikum Hamburg-Eppendorf
- Schilling-Professur und Forschungsgruppe "Translationale Neurodegeneration", Universitätsmedizin Rostock
- Schilling-Professur "Neurologie und Translationale Neurowissenschaften" und "Translationale Schilling Forschungsgruppe für immunvermittelte Synaptopathien", Universitätsklinikum Jena.
- Schilling-Professur und Forschungsgruppe für Translationale Neurowissenschaften, Universitätsklinikum Mainz

The foundation launched a special programme in 2023: the Schilling Professorship and Research Group for Computational Neurology, which funds two endowed professorships at the University of Cologne and Charité Berlin.

Furthermore, every two years the foundation awards the ‘Schilling Research Prize of the Neuroscience Society’ in the amount of €20,000.

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Albrecht Kossel

CHEMIE IN UNSERER ZEIT

DOI: 10.1002/ciuz.202010003

Ein Nobelpreisträger aus Mecklenburg

Albrecht Kossel und die Nukleinbasen

EDITH FRAMM | JOACHIM FRAMM

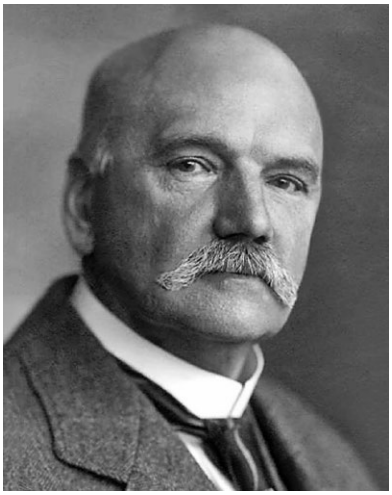

Abb. 1 ***Kossel um 1913.*** *(Archiv der Universität Heidelberg)*

Nobelpreisträger – und trotzdem kaum bekannt: Albrecht Kossel schuf mit seinen Arbeiten wesentliche Voraussetzungen für das Verständnis des Aufbaus von Nukleinsäuren und wurde 1910 mit dem Nobelpreis für Physiologie oder Medizin ausgezeichnet. Eine Spurensuche.

Am 16. September 2003 fand an der Universität Rostock ein akademischer Festakt zum 150. Geburtstag des Nobelpreisträgers Albrecht Kossel (1853–1927) statt. Im Anschluss wurde ein großer öffentlicher Platz in Rostock nach ihm benannt. Auch ein Institut der Universität trägt seinen Namen. Seit 2014 wird auch von der Gesellschaft Deutscher Chemiker alle zwei Jahre der „Albrecht-Kossel-Preis" für Biochemie verliehen. Doch weder in seiner Heimat Mecklenburg noch in den Fachkreisen ist Kossel ausreichend bekannt.

Sein Name ist mit der bedeutungsvollen Entdeckung der Nukleinbasen Adenin, Guanin, Thymin und Cytosin verbunden, deren Abfolge im Molekülfaden der DNA die Erbinformation bildet. Für die Arzneimitteltherapie haben die genetischen Grundlagen eine ganz besondere Bedeutung gewonnen [1].

Nachfolgend sollen Leben und Wirken Albrecht Kossels in Erinnerung gebracht werden.

Albrecht Kossels Lebensweg

Albrecht Kossel (Abbildung 1) wurde 1853 in Rostock geboren und wuchs dort auch auf. Der Vater war Kaufmann und Reeder, später preußischer Konsul und Bankdirektor. Erwähnenswert ist, dass der Großvater mütterlicherseits in Rostock einen Samenhandel betrieb und damit auch international großen Erfolg hatte. Albrechts Begabung und Begeisterung für die Botanik, mit der er schon in seiner Gymnasialzeit auffiel, mag er von diesem Großvater geerbt haben. Gern hätte Albrecht Botanik studiert, aber der Vater riet zu Medizin oder Pharmazie. Die Wahl fiel auf die Medizin.

Eine große Anziehungskraft ging von Straßburg aus. Dort wurde nach dem Deutsch-Französischen Krieg eine Elite-Universität gegründet. Die finanzielle Situation des Vaters war jedoch schwierig geworden, und auch die fünf jüngeren Brüder sollten eine Ausbildung bekommen. Nur ein in Rostock gestiftetes Stipendium ermöglichte das Studium in Straßburg. Die Auflagen dieses Stipendiums führten dazu, dass Kossel abwechselnd zwei Jahre auch in Rostock studierte, dort seine Examina ableistete und 1878 promoviert wurde.

Kossel begann am Pharmakologischen Institut der Universität Rostock bei Prof. Gaethgens (1839–1915) zu arbeiten, aber wenig später wurde eine Assistentenstelle bei Prof. Hoppe-Seyler (1825–1895) frei, dem Direktor des Straßburger Physiologisch-Chemischen Instituts. Kossel fühlte sich sehr zu dieser Persönlichkeit hingezogen, schon während des Studiums hatte er bei Hoppe-Seyler kleinere Untersuchungen durchgeführt. Niemand konnte ahnen, dass die Tätigkeit in Straßburg der Anfang bahnbrechender Forschungen bilden würde. Intensive, gewissenhafte Arbeiten führten 1881 zur Habilitation für die Fachgebiete Physiologische Chemie und Hygiene.

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Als dann Emil du Bois-Reymond, der Direktor des Physiologischen Instituts in Berlin, einen Leiter seiner chemischen Abteilung suchte, empfahl Hoppe-Seyler Albrecht Kossel. Dieser übernahm die Stelle im Oktober 1883. Dort gelangen ihm trotz der umfangreichen Lehraufgaben bedeutende Entdeckungen (Abbildung 2). Als er 1885 an einer Versammlung der deutschen Naturforscher und Ärzte in Straßburg teilnahm, lernte er Luise Holtzmann, seine spätere Frau, kennen. Drei Kinder wurden geboren, der Sohn Walther, der ein herausragender Physiker wurde, die Tochter Hedwig, die leider sehr früh verstarb und die Tochter Gertrud.

In Berlin wurde er 1887 zum außerordentlichen Professor berufen. Aber ein eigener Lehrstuhl blieb ihm zunächst versagt. 1895 fügte es sich, dass er in Marburg Ordinarius für Physiologie wurde. Kossel konnte dort seine Forschungen unvermindert fortsetzen. Doch noch einmal sollte er sich verändern: Er nahm den Ruf auf den Lehrstuhl für Physiologie in Heidelberg an. Die Forschung mit zahlreichen Schülern und Mitarbeitern ging weiter. Auszeichnungen, vor allem sechs Ehrendoktorate (in den Jahren 1904–1923) sowie Mitgliedschaften in wissenschaftlichen Akademien des In- und Auslands, häuften sich.

Albrecht Kossel wurde die Leitung des 7. Internationalen Physiologenkongresses übertragen, der 1907 in Heidelberg stattfand. 1908 wurde er Prorektor in Heidelberg. 1910 erhielt er den Nobelpreis. 1913 ereilte Kossel ein schwerer Schicksalsschlag, denn seine Frau verstarb mit 49 Jahren an einer Bauchspeicheldrüsenentzündung. Dann folgte die Katastrophe des Ersten Weltkrieges. Kossel pflegte eine weltweite Zusammenarbeit mit bedeutenden Forschern. Sie brach nun zu seinem großen Bedauern ab. Nach dem Krieg waren die Deutschen nicht erwünscht, nur langsam normalisierte sich der wissenschaftliche Austausch. 1924 wurde Kossel emeritiert. Albrecht Kossel konnte weiterhin eigene wissenschaftliche Untersuchungen durchführen. Bis 1927 forschend tätig, wurde Kossel wie einst Hoppe-Seyler erst durch den Tod das Handwerkzeug aus der Hand genommen.

Die Entdeckung der Nukleinbasen

1878 begann Albrecht Kossel in Straßburg, die Arbeiten von Friedrich Miescher (1844–1895) fortzusetzen. Miescher hatte 1869 im Laboratorium von Felix Hoppe-Seyler in Tübingen aus den isolierten Zellkernen der Leukozyten des Eiters eine bisher unbekannte, phosphorhaltige Substanz gewonnen, die er Nuklein nannte [3]. Kossel konnte zunächst 1883 nachweisen, dass zellkernreiche Gewebe und Organe auch mehr Nuklein-Phosphorsäure enthalten. Gezielte Hungerversuche an Hühnern und Tauben zeigten, dass das Nuklein kein Reservestoff ist: Die Menge an Nuklein veränderte sich nur wenig, unabhängig davon, ob ein Organismus hungerte oder nicht. Daraus folgerte Kossel, dass die Funktion des Nukleins eher bei der Neubildung des Gewebes zu suchen sei. Außerdem konnte er beweisen, dass Guanin ein Spaltprodukt des aus Gänseblut gewonnenen Nukleins ist [4]. Guanin war seit 1844 als eine stickstoffreiche Base bekannt, die sich in den Exkrementen von Säugetieren und Vögeln anreichert. Erste Erkenntnisse zum Vorkommen des Guanins im Nuklein gab es schon seit 1874. Sie gingen auf den Schweizer Chemiker Jules Piccard (1840–1933) zurück, der Mieschers „Nuclein des Lachsspermas“ (Nukleinsäure) untersucht hatte [5].

Abb. 2 ***Das ehemalige Physiologische Institut in Berlin, Dorotheenstraße 96 (Teilansicht). Hier gelang es Albrecht Kossel und seinen Mitarbeitern in den Jahren 1890–1894, die Nukleinbasen Adenin, Guanin, Thymin und Cytosin als Spaltprodukte der Nukleinsäure nachzuweisen.*** *(Foto Framm, 2018)*

Am 12. Januar 1885 berichtete Kossel vor der Berliner Chemischen Gesellschaft über eine bedeutende Entdeckung. Er konnte aus einer größeren Menge Rinder-Bauchspeicheldrüse, die in der Berliner Firma C. A. F. Kahlbaum von dem Chemiker Adolph Bannow (1844–1919) aufbereitet worden war, eine stickstoffreiche Base mit der Summenformel $C_5H_5N_5$ isolieren, für die er, abgeleitet von dem griechischen Wort „aden“ für Drüse, den Namen Adenin vorschlug. Kossel wies sie wenig später auch als Spaltprodukt des Hefenukleins nach [6, 7].

Richard Altmann (1852–1900) in Leipzig war es 1889 gelungen, aus dem Nuklein der Hefe den Eiweißanteil abzutrennen und eine phosphorhaltige organische Säure zu isolieren. Er gab ihr den Namen Nukleinsäure [8]. Kossel konnte nach Altmanns Verfahren diese Nukleinsäure herstellen und dann Adenin und Guanin als Spaltprodukte nachweisen. Es stellte sich dabei heraus, dass auch ein Kohlenhydrat Bestandteil der Nukleinsäure sein musste. Kossel wählte für die basischen Substanzen Adenin, Guanin und seine Derivate den zusammenfassenden Namen Nukleinbasen [9].

Im November 1893 berichtete Kossel von weiteren Entdeckungen. Aus den Thymusdrüsen des Kalbes hatte er mit dem Assistenten Albert Neumann Nukleinsäure gewonnen und mit Schwefelsäure behandelt. Es bildete sich ein gut kristallisiertes Spaltprodukt, für das der Name Thymin vorgeschlagen wurde. 1894 konnten sie aus den Thymusdrüsen noch eine weitere Substanz isolieren. Sie gaben ihr den Namen Cytosin [10].

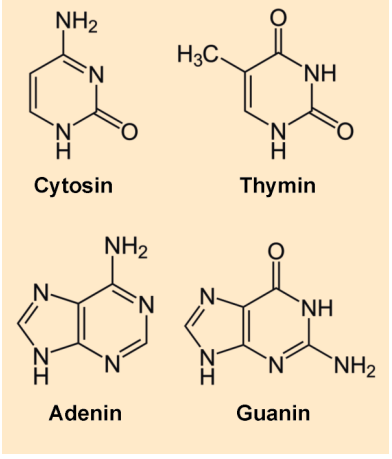
Nachdem am Ende des 19. Jahrhunderts – im Wesentlichen durch die Synthesen Emil Fischers (1852–1919) – die Strukturformeln des Guanins und Adenins als Purinkörper

und die des Thymins als Pyrimidinkörper endgültig aufgeklärt worden waren, konnte Kossel mit seinem Mitarbeiter Hermann Steudel (1871–1969) auch die Strukturformel der Nukleinbase Cytosin als Pyrimidinkörper zweifelsfrei feststellen [11].

Es hatte sich inzwischen erwiesen, dass Guanin, Adenin sowie Thymin und Cytosin (Abbildung 3) in allen entwicklungsfähigen Zellen zu finden sind. Die Erkenntnisse über diese vier Nukleinbasen sollten für die weiteren Forschungen einen unerschütterlichen Grundstein legen. Albrecht Kossel konnte sie eindeutig als Bausteine der Nukleinsäure charakterisieren. In seinem Nobelvortrag am 12. Dezember 1910 hob er hervor: *„Es gelang mir, eine Reihe von Bruchstücken zu erhalten … welche durch eine ganz eigentümliche Ansammlung von Stickstoffatomen gekennzeichnet sind. Es sind hier nebeneinander … das Cytosin, das Thymin, das Adenin und das Guanin.“* [12]

Mit diesen Erkenntnissen schuf Kossel wesentliche Voraussetzungen für das berühmte Doppel-Helix-Modell der Desoxyribonukleinsäure, das 1953 von James D. Watson und Francis Crick entwickelt wurde. Die Entdeckung der fünften primären Nukleinbase im Jahr 1900 in Marburg geht auf Alberto Ascoli (1877–1957) zurück. Kossel war jedoch offenbar (s. u.) maßgebend daran beteiligt [13].

ABB. 3 | DIE VIER NUKLEINBASEN



Weitere Arbeiten

Ende Oktober 1888 teilte Albrecht Kossel in Berlin eine andere Entdeckung mit. In einem Tee-Extrakt, der ihm vom Rostocker Apotheker und Fabrikant Friedrich Witte (1829–1893) zugeleitet worden war, wurde außer dem Adenin eine weitere, bisher unbekannte Substanz gefunden. Es erwies sich, dass diese mit Theobromin und Coffein verwandt war. Beide Stoffe hatte Emil Fischer hinreichend charakterisiert. Aufbauend auf Fischers Erkenntnissen stellte Kossel nicht nur die Summenformel, sondern auch die Strukturformel auf. Er schlug für die neue Substanz den Namen Theophyllin vor [14]. Sieben Jahre später gelang Emil Fischer die synthetische Darstellung. Nachdem es ab 1970 möglich geworden war, Theophyllin in retardierter Arzneiform herzustellen, wurde es für einige Jahrzehnte das weltweit bevorzugte Mittel für die Dauertherapie bei Asthma.

Schwerpunkt der Arbeiten Kossels blieb jedoch die Erforschung der Chemie des Zellkerns. Schon 1884 gelang ihm der Nachweis eines eiweißartigen Körpers im Nuklein des Gänseblutes. Damit war die bereits in seiner Habilitationsschrift geäußerte Vermutung, dass die Nukleine aus einem Eiweißkörper und der phosphorhaltigen Substanz bestehen, bestätigt worden. Für diesen Eiweißkörper schlug Kossel den Namen Histon vor [15].

In den Samenzellen des Lachses hatte Friedrich Mieschers eine basische Substanz gefunden, die mit dem Nuklein salzartig verbunden war, und sie Protamin genannt. Kossel wies deren Eiweißnatur nach. Im Protamin der Samenzellen des Störs, das den Namen Sturin erhielt, entdeckte er zeitgleich mit Sven Gustav Hedin (1859–1933) eine neue basische Substanz, das Histidin [16]. Außerdem wies er die bereits bekannten basischen Aminosäuren Arginin und Lysin nach. Auch die Protamine des Lachses (Salmin) und des Herings (Clupein) dienten Kossel als Ausgangsstoffe.

Protamine und Histone waren Eiweiße, die vergleichsweise weniger Aminosäuren enthielten. Sie bildeten den Gegenstand vielfältiger weiterer Untersuchungen. Gemeinsam mit seinem Mitarbeiter Friedrich Kutscher entwickelte Kossel eine neue Analysenmethode für Eiweiße [17]. Dieses Silberbarytverfahren blieb viele Jahre die beste Analysenmethode für Histidin, Arginin und Lysin: Die Eiweiße wurden hydrolysiert und die drei basischen Aminosäuren abgetrennt. Wieder in Lösung gebracht wurde das Gemisch mit Silbersulfat oder Silbernitrat bei bestimmter Alkalität (Bariumhydroxidlösung) gefällt. Bei ganz schwacher alkalischer Reaktion fällt Histidinsilber, bei stark alkalischer fällt Argininsilber aus. Im Filtrat dieser Fällungen lässt sich dann das Lysin nach Entfernung des Silbers als Pikrat isolieren. Mit dieser Methode konnte der Anteil der drei basischen Aminosäuren in verschiedensten Eiweißen quantitativ bestimmt werden, und sie war der Ausgangspunkt für Kossels intensive Suche nach einem Ordnungsprinzip für die Eiweiße. Später verwendete er für die Analysen Flaviansäure, die mit Arginin ein fast unlösliches Salz bildet [18]. Es zeigte sich, dass der Guanidinteil des Arginins, der Imidazolteil des Histidins und die endständige Aminogruppe im Lysin nicht an der Peptidbindung der Eiweiße beteiligt sind. Kossel vermutete, dass diese ungebundenen stickstoffhaltigen Teilstrukturen eine bestimmte biologische Bedeutung haben [19]:

„Ich stelle mir das Eiweißmolekül so vor, dass es jederzeit auf einen chemischen Angriff mit irgendeiner seiner charakteristischen Gruppen antworten kann. So, wie an einem Weinstock die Trauben hängen, so verfügt das Eiweißmolekül über eine große Anzahl charakteristischer Gruppen … Werden irgendwelche speziellen Kombinationen benötigt, so liegen sie in angreifbarer Form schon da.“

Kossel vermutete außerdem, dass die Funktionen der Eiweiße von ihrer chemischen Struktur abgeleitet werden müssen. Von besonderer Bedeutung für die Entwicklung und das Grundverständnis der Biochemie sollte sich die

Baustein-Hypothese Kossels erweisen, die er bei Amtsantritt als Prorektor in der Aula der Universität Heidelberg vortrug [20] und nach der Kohlenhydrate und Eiweiße oft aus lauter gleichartigen, kleineren Teilstücken bestehen. Als Beispiel führte er Stärke und Glykogen an, die aus der einfachen Substanz Traubenzucker gebildet werden. Auch die Eiweiße seien aus Teilstücken zusammengesetzt, den Aminosäuren: *„Einzelne dieser Stücke oder Segmente, zum Beispiel das Leucin, können sich zwar vielfach wiederholen, aber dann sind andere dazwischen gefügt. … Die Art der Zusammenfügung … ist eine gesetzmäßige.“ „Die Proteinstoffe, welche dem Hühnchen als Nahrung dienen, müssen gewissermaßen umrangiert werden, um später in den Horngebilden der Haut oder im Blut oder im Knorpel als neue Eiweißart zu erscheinen.“* Aus den pflanzlichen Proteinmolekülen, die dem tierischen Organismus zugeführt werden, entstünden durch Verdauungsvorgänge die Aminosäuren. Aus diesen Bausteinen würden dann im Organismus die körpereigenen Proteine aufgebaut.

Diese Bausteinhypothese bezog Kossel nicht nur auf die Eiweiße, sondern auch auf Fette, Kohlenhydrate und Nukleinsäuren. Um zu beweisen, dass die Bausteine in allen Lebewesen identisch sind, untersuchte er mit seinen Mitarbeitern viele Organismen. Kossel fand sie in den Schuppen der Ostseefische, in den Heidelberger Glühwürmchen, in der Bäckerhefe, in mecklenburgischen Gänsen und Rindern, in Schmetterlingen und Löwenmäulchen und in indischen Teeblättern.

KOSSEL SCHUF WESENTLICHE VORAUSSETZUNGEN FÜR DAS DOPPEL-HELIX-MODELL DER DNA VON WATSON UND CRICK

Gemeinsam mit Henry Drysdale Dakin (1880–1952) entdeckte Kossel das Enzym Arginase, das Arginin in Ornithin und Harnstoff spaltet [21].

Überlegungen zu den Erbvorgängen finden sich in seinem Nobelvortrag am 12.12.1910 [12]. Dort betonte er, dass die an die Nukleinsäure locker gebundenen Proteine des Zellkerns einen ungewöhnlich hohen Anteil an stickstoffreichen Aminosäuren haben. Der hohe Stickstoffanteil gelte auch für die Nukleinsäuren selbst und grenzt beide Gruppen scharf von den übrigen Bestandteilen der Zelle ab. *„Diese stickstoffreichen und phosphorhaltigen Atomgruppen sind es, deren Ablagerungsstätten … bei der Zellteilung zuerst in Bewegung gebracht werden und deren Übertragung auf andere Zellen einen wesentlichen Teil des Befruchtungsvorgangs ausmacht.“*

In einer Rede bei der Jahresfeier der Heidelberger Akademie formulierte er 1921 [22]: *„… Erbfaktoren werden bei der Befruchtung übertragen und müssen also in dem befruchteten Ei in kleinster Dimension niedergelegt sein. Wir können uns heute kaum eine andere Vorstellung von der Festlegung so vieler Form und Stoff bestimmender Anlagen auf engstem Raum machen, als dadurch, dass wir sie auf die Lagerung der Moleküle und Atome beziehen.“ … „Denkt man sich an Stelle eines jeden Eiweißbausteins einen Buchstaben, so kann durch geeignete Zusammenstellung derselben schon eine genaue Aufzählung der Eigenschaften eines Organismus geliefert werden. … Neben ihnen finden wir andere Stoffe, welche die Möglichkeiten der Kombination erhöhen können!“*

Noch in seinen letzten Lebensjahren konnte Kossel wichtige Befunde, auch zur Natur der Eiweiße im Allgemeinen, gewinnen. Kurz vor seinem Tod vollendete er eine größere Monographie mit dem Titel „Protamine und Histone“ [23].

Herausgeber der Zeitschrift für physiologische Chemie

1877 hatte Felix Hoppe-Seyler für sein neues Fachgebiet die „Zeitschrift für physiologische Chemie“ gegründet. Kossel wurde 1895 Mitglied des Redaktionskollegiums. Als Hoppe-Seyler im gleichen Jahr verstarb, übernahm Kossel gemeinsam mit Eugen Baumann (1846–1896) die Herausgabe der Zeitschrift, die zu Ehren ihres Lehrers nun „Hoppe-Seylers Zeitschrift für physiologische Chemie“ genannt wurde. Kossel blieb auch nach Baumanns Tod 1896 der Herausgeber.

Diese Zeitschrift hatte für die Entwicklung der Physiologischen Chemie eine besondere Bedeutung, denn sie war viele Jahre die einzige Zeitschrift, die ausschließlich der Biochemie gewidmet war. Namhafte Wissenschaftler aus dem In- und Ausland waren Mitglieder der Redaktion. 1914 erreichte der Jahrgang einen Umfang von 3000 Seiten. In den Kriegsjahren ging der Umfang stark zurück, weil nur noch Biochemiker aus dem Deutschen Reich und Österreich-Ungarn sowie dem neutralen Ausland Beiträge einreichten. Die russischen Gelehrten Wladimir Gulewitsch (1867–1933) und Ivan Pavlov (1849–1936), die Mitglieder der Redaktion waren, schieden jedoch während des Ersten Weltkriegs nicht aus. Es blieb eine Verbindung erhalten, die diese Repräsentanten der internationalen Wissenschaft geschaffen hatten. Bereits 1920 traf bei Kossel wieder ein Beitrag aus St. Petersburg (Petrograd) für die Zeitschrift ein. Als 1923 der 130. Band aus Anlass seines 70. Geburtstages Kossel gewidmet wurde, gab es auch Beiträge eines englischen und eines US-amerikanischen Schülers. Seit 1996 erscheint die Zeitschrift unter dem Namen „Biological Chemistry“.

Werk und Persönlichkeit

Albrecht Kossel entwickelte sein Lebenswerk in der Epoche der aufblühenden deutschen Naturwissenschaften, aus der viele Nobelpreisträger hervorgingen. 1954 schrieb der Biologe Fritz Kaudewitz (1921–2001) über Kossel [24]: *„Mit ihm ging nicht nur ein großer Wissenschaftler dahin. Ein Mensch, dessen Güte und innere Ausgeglichenheit, dessen Wahrhaftigkeit und Pflichtgefühl schlechthin vollkommen waren, hatte sein Leben vollendet. Denen, die nach*

ihm kamen und sein Werk weiterführten, mag er als ein leuchtendes Beispiel dafür erschienen sein, wie sehr echte wissenschaftliche Leistung von der seelischen Kraft einer in sich ausgeglichenen großen Persönlichkeit getragen wird."

Schon früh entdeckte Kossel seine Neigung für die Botanik. Doch verankert hat er sich im neuen Fachgebiet der Physiologischen Chemie. Instinktsicher drang er in unerforschte Bereiche vor, arbeitete mit Zielstrebigkeit und Genauigkeit. Nicht plötzliche geniale Eingebungen waren es, sondern gewissenhafte Glied an Glied anfügende Einzelforschungen, die ihn auszeichneten. Angriffen anderer Forscher trat er entschieden und selbstbewusst mit Beweisführung entgegen. Kossel wurde sich immer sicherer über die Bedeutung der Biochemie und sprach 1908 [20]: *„Die Biochemie ist leer ausgegangen, als man an den deutschen Hochschulen die Welt des Geistes in Professuren verteilte, und doch suchen wir die Lösung der wichtigsten und tiefsten Probleme des Lebens in ihrer Werkstätte."*

AUCH AN DER DER ENTDECKUNG DER FÜNFTEN PRIMÄREN NUKLEINBASE URACIL WAR KOSSEL BETEILIGT

Albrecht Kossel hatte großen Anteil daran, dass sich die Biochemie noch zu seinen Lebzeiten als selbständiges Fachgebiet an den deutschen Universitäten durchsetzen konnte.

Kossel neigte nicht dazu, Hypothesen aufzustellen; nur was bewiesen werden konnte, hatte Bedeutung. Aber man darf davon ausgehen, dass er etwas ahnte von dem sich entwickelnden Gewaltigen, das in diesen Anfängen lag. 50 Jahre hat er ununterbrochen geforscht, eine tiefe Freude an der experimentellen Arbeit blieb ihm ein Leben lang erhalten. Sie fand in 120 Veröffentlichungen ihren Niederschlag. Kossel lehnte es ab, dass sein Name bei Publikationen erschien, die zwar ihren Ursprung in seinem Institut hatten sowie von ihm gefördert und begleitet wurden, wenn er nicht selbst bei den Experimenten mit tätig geworden war. So kam es dazu, dass Alberto Ascoli diese bedeutsame Veröffentlichung über die Entdeckung des Uracils lediglich mit einem „innigsten Dank" an seinen Lehrer abschließen konnte. Dieser habe ein nie versiegendes Interesse an den Forschungen gehabt, so schrieb er, und eine unerschöpfliche Bereitwilligkeit, jederzeit mit Rat und Tat zu helfen. Ascoli fügte noch an: *„ ... wie oft wäre ich sonst entmutigt den sich vor mir auftürmenden Schwierigkeiten machtlos gegenübergestanden!"* [13]

Kossel pflegte weitverzweigte internationale Kontakte, viele Reisen führten ihn ins Ausland. Scheinbar unpolitisch zeigte er im Ersten Weltkrieg beachtenswerte Haltungen. Er verweigerte die Unterschrift unter das propagandische Manifest des Deutschen Reiches „An die Kulturwelt". Viele berühmte Persönlichkeiten, unter ihnen die meisten deutschen Nobelpreisträger, unterzeichneten sie. Als er im Hungerwinter als Ernährungsexperte bedrängt wurde, ließ er wissen [25]: *„Auf Ersuchen der Reichsregierung soll ich der Bevölkerung klarmachen, dass die Lebensmittelrationen ausreichend sind? Diese Anstiftung zur Lüge weise ich mit Empörung und Entrüstung weit von mir."*

Biographen erwähnen Kossels Bescheidenheit und verbinden sie mit seinem norddeutschen Charakter. Siegfried Edlbacher schrieb über sein Wesen [19]: *„Nachdenklich und ernst, ja manchmal melancholisch, doch stets getragen von einem leisen Humor."*

Besonders eindrucksvoll würdigte ihn Ulf Lagerkvist [29]: *„ ... his elucidation of the chemical nature of some building blocks that make up nucleic acids and chromatine has secured immortality for this exceedingly modest and almost shy man."*

Viele Jahre glaubte man, dass die Nukleinsäure bei allen Lebewesen uniform sei und deshalb nicht Träger der Erbinformation sein konnte. Außerdem verlagerte sich die biochemische Forschung nach den beiden Weltkriegen ins Ausland. So geschah es, dass Werk und Persönlichkeit Albrecht Kossels zum großen Teil in Vergessenheit geraten sind. Thomas Müller-Bohn schrieb jetzt [26]: Es *„... drängt sich der Gedanke auf, dass Albrecht Kossel als Mensch und Forscher nachträglich mehr Würdigung verdient. Da die DNA-Bestandteile Adenin, Cytosin, Guanin und Thymin von ihm beschrieben wurden, läge es nahe, sie als Kosselsche Nukleinbasen zu bezeichnen."*

Zusammenfassung

Das 21. Jahrhundert wird bereits als das Zeitalter der Genetik bezeichnet. Tiefgreifende gesellschaftliche Veränderungen sind zu erwarten. Mit dieser Entwicklung sind viele berühmte Namen verbunden. Doch Albrecht Kossel, der die bedeutungsvollen Bausteine der Nukleinsäure entdeckt und erstmalig charakterisiert hat, ist wenig bekannt. Er erhielt 1910 den Nobelpreis, geriet später in Vergessenheit. Mehr als vier Jahrzehnte vergingen, bis man verstand, dass es die Kosselschen Nukleinbasen Adenin, Guanin, Thymin und Cytosin sind, die in der DNA die Erbinformation kodieren. Es ist das Anliegen, Leben und Werk Albrecht Kossels zu beschreiben und die Erinnerung an diesen herausragenden Biochemiker zu fördern. Seine große Persönlichkeit ragt vorbildhaft in die Gegenwart hinein.

Summary

The 21st century has already been described as the age of genetics. Far-reaching social changes are to be expected. Many famous names are associated with this development. However, little is known about Albrecht Kossel, who discovered the important building blocks of nucleic acids and characterised them for the first time. He was awarded the Nobel Prize in 1910 and later fell into oblivion. More than four decades passed before it was understood that it is the Kossel's

WAS MAN WISSEN MUSS

Albrecht Kossel (1853–1927) entdeckte die Basen Adenin, Guanin, Thymin und Cytosin als Bausteine der Nukleinsäure.

Kossel wurde zum Pionier der Genetik, denn diese Kosselschen Nukleinbasen codieren in der DNA die Erbinformation.

1910 wurde Albrecht Kossel für seine herausragenden Leistungen auf dem Gebiet der Biochemie mit dem Nobelpreis geehrt.

Albrecht Kossel (1853–1927) discovered the bases adenine, guanine, thymine and cytosine as building blocks of nucleic acid.

Kossel became a pioneer in genetics, because these Kossel's nucleic bases encode the genetic information in the DNA.

In 1910 Albrecht Kossel was honoured with the Nobel Prize for his outstanding achievements in the field of biochemistry.

nucleic bases adenine, guanine, thymine and cytosine that encode the genetic information in DNA. It is our aim to describe the life and work of Albrecht Kossel and to promote the memory of this outstanding biochemist. His great personality projects exemplarily into the present.

Schlagwörter

Albrecht Kossel, Nobelpreis, Proteinforschung, Nukleinbasen, DNA.

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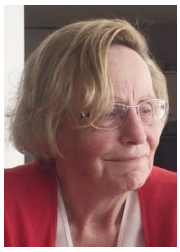

Dr. Edith Framm, geboren 1944 in Wismar. Medizinstudium in Berlin, Rostock und Halle. 1969 erfolgte die Promotion und danach die Ausbildung zur Fachärztin für Allgemeinmedizin. Sie war zunächst in einer Poliklinik in Wismar tätig, bis sie sich in eigener Praxis als Landärztin in Blowatz bei Wismar niederließ. Seit 2003 wurden von ihr mehrere Romanbiografien verfasst, darunter „Albrecht Kossel und die DNA – ein Nobelpreisträger aus Mecklenburg", Koch und Raum, Wismar 2019.

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Abstracts

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Speakers

Short tandem repeats as genetic modifiers of brain function in health and disease

Ahmad Aziz

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Dementia and other neurodegenerative diseases are among the leading causes of disability worldwide and have an immense societal impact due to lack of effective treatments. For developing better preventive and therapeutic strategies, it is essential to clarify their still largely elusive genetic basis and pathophysiology. Emerging insights from the study of rare hereditary repeat expansion disorders, like Huntington disease and many spinocerebellar ataxias, caused by elongations of repetitive DNA sequences (‘short tandem repeats’ (STRs)) indicate that STRs could induce instability of neuronal DNA (‘neurogenomic somatic instability’), and thereby instigate molecular changes that lead to neuronal degeneration. However, the role of highly prevalent STR variations or their somatic instability in the pathogenesis of common age-associated neurodegenerative diseases is unknown. In my presentation I will provide an overview of our recent work in this area which focuses on the assessment of the role of STRs and their somatic instability in the pathogenesis of neuronal degeneration, the defining hallmark of all neurodegenerative diseases.

Neurodegeneration and aging: common traits or individualized medicine?

Andreas Hermann

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Most neurodegenerative diseases arise during aging and are currently not curable. Currently disease mechanisms are often solely investigated from the side of the degenerative insults, despite aging is the largest risc factor for the development of those diseases. A major need is to combine this view with the understanding how the organisms or the brain can escape such insults (resilience). We aim to develop novel strategies to cure neurodegenerative diseases by combining research on pathological and healthy aging and research on neurodegenerative pathophysiology. We comparatively analyse mechanisms of physiological and pathological aging, (ii) to understand their role on the development of resilience factors against neurodegeneration, (iii) unravel the pathophysiological cascade of neurodegenerative diseases and (iv) to translate these approaches in innovative therapeutic interventions in clinical application. The combination of these two principles is a novel and very promising concept for the therapy of neurodegenerative diseases.

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“Raisin bread sign” as a radiological feature in patients with pontine autosomal dominant microangiopathy and leukoencephalopathy

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Introduction

Pontine autosomal dominant microangiopathy and leukoencephalopathy (PADMAL) is a hereditary cerebral small vessel disease (cSVD) caused by pathogenic variants in the *COL4A1* 3′ untranslated region (UTR). *COL4A1* encodes a collagen type IV alpha 1 chain, one of the components of the brain vascular basement membrane. The recurrent ischemic episodes in PADMAL are likely to start from mid-thirties to mid-forties, and the neuroimaging feature is characterized by pontine multiple small infarctions and leukoencephalopathy. However, since no definitive radiological signs for PADMAL have been established during life, the decision to perform genetic testing for *COL4A1* can be difficult in some cases. In this study, we attempted to detect a significant feature of patients with PADMAL by analyzing the radiological features. Methods

We genetically examined two patients (F1-IV-2 and F1-IV-6) from Family 1 (F1) with undiagnosed familial cSVD, along with five unaffected relatives by performing whole exome sequencing and Sanger sequencing. Subsequently, we clarified the radiological feature shared by F1-IV-2 and F1-IV-6 by assessing their findings on magnetic resonance imaging (MRI). The diagnosis for the deceased patient (F1-IV-2) was confirmed pathologically by a postmortem examination. Subsequently, we screened clinicoradiological features of patients in the cohort of juvenile cerebral vessel disease (CVD) at Hiroshima University Hospital (n = 40; age of the onset between age 31 and 50 years). Sanger sequencing was performed to confirm the variants of the same gene as those in F1.

Results

We identified the pathogenic variant in the *COL4A1* 3′ UTR within the same locus in F1-IV-2 and F1-IV-6 but not in the unaffected family members. The variants in *COL4A1* 3′ UTR have been reported to be causative of PADMAL, and these patients were diagnosed with PADMAL. Multiple small infarctions and white matter hyperintensities were observed on MRI in both patients. As the appearance of the pons that contained these characteristic small oval infarctions resembled raisin bread, we coined the name ‘raisin bread sign’ for this unique radiological feature. In the postmortem examination of F1-IV-2, oval ischemic lesions in the pons were observed at the locations identical to that of the raisin bread sign observed on the MRI. Among the CVD cohort, we identified two patients (F2-II-3 and F3-II-2) with the same radiological findings as genetically confirmed PADMAL patients in F1. Both patients harbored the variant in the *COL4A1* 3′ UTR within the same locus as patients in F1. This indicates the high positive predictive value of this radiological feature in the diagnosis of PADMAL.

Conclusion

We evaluated radiological features in the pons of PADMAL patients. The neuroimaging feature characterized by oval ischemic infarctions in pons, for which we coined the name “raisin bread sign”, is quite important in screening the patients with PADMAL. Since our study was conducted in a small number of patients at a single hospital, further accumulation of cases is needed. However, this sign enables us to make the decision in identifying candidates for *COL4A1* 3′ UTR genetic testing in patients with CVD more accurately, including sporadic cases.

Social interactions of people with dementia

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Background: We lack information about the social interactions of people with dementia, which would be valuable for social interventions because of their positive impact. With this research, we therefore aimed to explore these interactions in detail, including their characteristics, their importance, how they might be scaled up and which of them are of importance for people with dementia.

Methods: Descriptive analyses were based on responses of 501 people in dementia care (mainly family and professional caregivers; over three-quarters female; average age 53.5 years) to a structured, quantitative survey.

Results: The study population mentioned social interactions to be important and valuable for people with dementia, especially simple ones that most often take place in the home environment such as laughing or singing together, hugging, experiencing touch, and taking part in meaningful everyday activities. Particularly non-verbal social interactions such as smiling were highlighted. Social interactions were connected to several beneficial effects (e.g., feeling of safety, positive emotions) and were considered generally important for dementia symptoms. Simply showing an understanding for dementia symptoms and community organized activities were among the actions seen as crucial to improving social interactions of people with dementia.

Conclusions: With this research, we provide a first insight into the social interactions of people with dementia and highlight the importance of increasing simple social interactions in primary care and beyond.

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Impact of norepinephrine on adult neurogenesis

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The adult mammalian brain retains the capacity for regeneration through the generation of new neurons from neural stem or progenitor cells, a process known as adult neurogenesis. This process is probably regulated by norepinephrine (NE), a neurotransmitter which is particularly produced in the locus coeruleus (LC).

To investigate the dedicated role of cerebral noradrenaline in adult neurogenesis, we employed a novel inducible and conditional genetic knockout mouse model based on a floxed dopamine-β-hydroxylase (DbH) gene and the inducible CreERT2 driven by Camk2a Promotor. After knockout induction with tamoxifen for three weeks as well as after additional six weeks of observation, a successful reduction of DbH neurons was confirmed by immunohistochemically staining for tyrosine hydroxylase (TH) and DbH in the LC. To assess neurogenic activity, we performed immunostainings for Pax6, EdU, and BrdU. Initial experimental data show differences in proliferation between the two tested groups. Tamoxifen-treated animals displayed a significantly elevated body temperature and feed consumption. In addition, a behavioral test battery (light-dark box, open field, sucrose preference and novel object recognition) revealed no changes in exploratory behavior or hedonia, however, the tamoxifen-treated animals showed signs of increased anxiety as they spend more time in zones considered as safe.

These findings provide initial experimental evidence for the involvement of NE in regulating emotional behavior possibly by affecting adult neurogenesis, and establish a robust model for future mechanistic investigations.

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Exploring Prognostic Biomarkers for ALS in a Japanese cohort

Kazuki Obara

Lund University

Background:

Neurofilament light chain (NfL) is the most established cerebrospinal fluid (CSF) biomarker for amyotrophic lateral sclerosis (ALS), showing robust prognostic performance. However, it remains unclear to what extent other biomarkers complement NfL and improve predictive accuracy beyond established clinical predictors.

Methods:

We included 264 patients fulfilling the revised El Escorial criteria for ALS. Baseline CSF samples were analyzed for NfL, pTau181, pTau217, GFAP, and Aβ42/40, together with blood tests including creatinine and CK. The patients underwent baseline ALSFRS-R and pulmonary function testing and were followed every six months until death.

Prognostic evaluation was performed using (1) linear mixed-effects models to estimate individual ALSFRS-R slopes, and (2) Cox proportional hazards models. For the slope analysis, the generalized linear models (GLMs) and machine learning (ML) models were applied to assess both linear and non-linear associations. The prediction of ML models was evaluated through nested 5×5 cross-validation and interpreted using SHAP values.

Results:

NfL explained more variance in ALSFRS-R slope than any other single CSF biomarker, although less than core clinical predictors (e.g., % vital capacity). Adding NfL to the core clinical predictors improved prognostic performance, but simply adding other CSF biomarkers as covariates did not provide further benefit. In contrast, GLMs incorporating interactions between NfL and Aβ status improved prediction, approaching the levels of ML models that integrated all CSF biomarkers. In Cox models, a similar saturating effect with NfL and core predictors was observed.

Conclusions:

NfL is the dominant CSF biomarker for prognosis in ALS. While additional CSF biomarkers added little in linear models, interactions with Aβ status and non-linear ML approaches revealed potential prognostic contributions. This framework warrants validation in external cohorts, and future studies should clarify to what extent biomarker signals may derive from background co-pathologies.

Pulsed electromagnetic field (PEMF) stimulation rescues deficient axonal organelle motility through repair of damaged, underlying microtubule tracks in amyotrophic lateral sclerosis (ALS)

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Repetitive pulsed electromagnetic fields (PEMFs) can have a beneficial impact on cellular events and serve as an alternative to magnetic stimulations (MS) driven by continuously oscillating alternating currents (ACMS). In our *ThaXonian M2M* project, we develop a prototype of a patient stretcher with multiple arrayed built-in magnetic-field coils that allow to expose all body parts to vectorized electromagnetic fields of any spatiotemporal modulation for the treatment of neurodegenerative diseases. The coils can be operated either in a continuous ACMS mode or with repetitive PEMFs by charging-discharging a bank of capacitors (PEMF). Through our accompanying *in vitro* PEMF experiments on cultured iPSC-derived spinal motor neurons from familiar ALS patients, we empirically establish the optimal magnetic field configuration with respect to the amplitude, shape, length and repetition rate of the pulses. Moreover, the specific architecture of our compartmentalized neuron cultures enables us to test different orientations of the magnetic-field lines to the axonal plane. Following PEMF, we analyze its impact on axonal organelle trafficking, underlying microtubule integrity, regeneration after axotomy and DNA damage response (DDR) in the nucleus by live-cell imaging. All four readout assays are clinically relevant for neurodegeneration and revealed clear defects in our untreated ALS neurons. So far, we found a sustained rescue of the motility of axonal mitochondria and lysosomes after PEMF at perpendicular field orientation that was accomplished through the preceding repair of the underlying microtubule tracks that are otherwise fragmentated in late-stage spinal motor neurons from ALS patients with carboxyterminal FUS mutations. Presumably, PEMF triggers these phenotypic rescues similar to our previous ACMS experiments through systemic transcriptomic alterations involving diverse transmembrane neurotransmitter receptors and ion channels and triggered kinase signaling cascades that eventually alter transcription and other DNA binding factors in the nucleus. In essence, PEMF at peak-field strength several of tens higher than used for ACMS is faster and more efficient than ACMS in mediating these phenotypic rescues. Our results point to a powerful non-invasive and non-pharmacological novel treatment of neurodegenerative diseases.

A song of light and power – Using light as an energy replacement for longevity

Shahaf Peleg

Research Institute for Farm Animal Biology (FBN), Head of Working group Energy Metabolism and Epigenetics

Mitochondria are the powerhouse of the cell and their activity is essential for energy production to maintain homeostasis. During aging, mitochondrial function is thought to become dysregulated, which might result in an impaired ability to meet cellular energy demand. For example, the mitochondrial membrane potential, the protonmotive force (PMF), is thought to decrease in old age.

Recently, we exploited a novel approach that allows the conversion of light energy to mitochondrial chemical energy by using a light-activated proton pump. Essentially, such an approach offers an alternative pathway to maintain healthy PMF by pumping protons independent of the mitochondrial electron transport chain. We have recently shown that such approach rescues age-associated decrease of the PMF and increases the lifespan of the worms.

The potential of utilizing light activated proton pumps for increasing lifespan and health span in other organisms is still not assessed. I will discuss our current efforts to translate our technology into mammalian cells and tissues.

From mitochondria to metabolome: Metabolic adaptations in stress-tolerant marine mollusks

Inna Sokolova

Institute of Biological Sciences, Chair of Marine Biology, University of Rostock

Metabolism is a fundamental property of life, driven by a complex network of biochemical reactions that extract energy from molecules and generate essential structural components. Energy metabolism—encompassing assimilation, conversion, and utilization—links physiology, behavior, and ecology and is highly sensitive to environmental fluctuations. Dynamic regulation of ATP production ensures organisms maintain homeostasis and adapt to changing conditions, making metabolic flexibility key to resilience. Mitochondria play a central role in ATP production, redox balance, Ca^{2+} homeostasis, and stress responses in aerobic organisms. They are highly sensitive to changes in oxygen, temperature, salinity, and pollution, which can cause energy deficiency, mitochondrial damage, and metabolic disruption. However, stress-tolerant marine organisms, such as intertidal mollusks, exhibit remarkable metabolic flexibility, maintaining homeostasis under stress and rapidly restoring function during recovery. This talk explores the mechanisms underlying adaptive metabolic responses to intermittent hypoxia and reoxygenation in intertidal mollusks. Emphasis will be placed on mitochondrial functional and proteomic adaptations and their integration with cellular metabolism and stress protection pathways. Finally, I will highlight key knowledge gaps and future research directions to better understand metabolic adaptations in highly variable environments like the intertidal zone.

Frontotemporal dementia - diagnostic biomarkers and neurodevelopmental reserve

Alexander Santillo

Clinical Memory Research Unit, Lund University

This talk will cover exiting developments in the field of frontemporal dementia (FTD). First, we will discuss how biomarkers (CSF and blood fluid biomarkers) can assist in differentiating FTD from psychiatric disorders. Secondly, we will cover how new biomarkers (PET and blood biomarkers) can help us differentiate between FTD and Alzheimer´s disease. Lastly, we will present new findings how FTD bridges intrauterine neurodevelopment and adult neurodegeneration.

TDP-43 gains are losses

Carlo Scialò

University of Zurich, Department of Quantitative Biomedicine

Neurodegeneration in ALS and FTD results from both gain of toxicity and loss of normal function of the RNA-binding protein TDP-43, but their mechanistic connection remains unclear. Increasing evidence suggests that TDP-43 aggregates act as self-templating seeds, propagating pathology through the central nervous system via a prion-like cascade. We developed a robust TDP-43 seeding platform for quantitative assessment of TDP-43 aggregate uptake, cell-to-cell spreading and loss of function within living cells, while they progress towards pathology. We show that both patient-derived and recombinant TDP-43 pathological aggregates were abundantly internalized by human neuron-like cells, efficiently recruited endogenous TDP-43 and formed cytoplasmic inclusions reminiscent of ALS/FTD pathology. Combining a fluorescent reporter of TDP-43 function with RNA-sequencing and proteomics we demonstrated aberrant cryptic splicing and a loss of function profile resulting from TDP-43-templated aggregation. Our data highlight known and novel pathological signatures in the context of seed-induced TDP-43 loss of function.

The Cornea — a Window into Neurodegeneration?

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Neurodegeneration can remain subclinical for years before crossing clinical thresholds. The non-invasive detection of early small-fiber and neuroimmune changes remains a central unmet need. The cornea provides a unique, living “biopsy” of peripheral small fibers and immune surveillance: its subbasal nerve plexus (SNP) is composed of unmyelinated C-fibers and can be visualized at cellular resolution with in vivo corneal confocal microscopy (IVCCM). Modern IVCCM is repeatable and quantitative, enabling longitudinal assessment of the same microanatomy—an advantage rarely offered by conventional neurodiagnostics.

Technological advances now extend corneal imaging from single frames to large-area mosaics, time-lapse/dynamic imaging, and 3D reconstructions, paired with automated and AI-assisted analytics. This toolkit allows robust measurement of corneal nerve architecture (e.g., fiber length/density, branching, tortuosity, fractal descriptors) and dynamic phenomena (e.g., nerve migration, dendritic cell motility), at scale and with improved reproducibility. These capabilities reframe the cornea from an ophthalmic niche into a systems-level sensor of neuroimmune health.

Critically, corneal nerve alterations detected by IVCCM mirror systemic small-fiber pathology in multiple conditions and correlate with clinical severity or progression—most prominently in diabetic neuropathy where SNP metrics predict neuropathy development and track regeneration, but also in HIV-associated neuropathy, Parkinson’s disease, and chemotherapy-induced neurotoxicity. Such evidence supports the concept that corneal neuroanatomy carries signatures of systemic neurodegeneration, potentially preceding or complementing conventional nerve tests. In parallel, IVCCM visualizes corneal immune cells (notably dendritic cells) and their in vivo dynamics, offering an integrated view of neuro-immune crosstalk that is difficult to access elsewhere in the human body.

We will present the current state of corneal confocal microscopy as a translational tool in neurodegeneration, outlining how recent advances in large-area, longitudinal IVCCM, dynamic imaging, and AI-assisted analytics unlock a new level of precision in capturing corneal nerve and immune architecture. We will showcase our own unique platform and methodology, currently the only setup worldwide that combines large-scale mosaics, longitudinal registration, and quantification. This integrated approach not only overcomes the limitations of conventional small-frame IVCCM but also establishes the cornea as a globally unparalleled window into neurodegenerative and neuroimmune processes.

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The possible role of telomere position effects in neuronal development and neurodegenerative diseases

Michael Walter

Rostock University Medical Center

Telomeres are repetitive nucleotide sequences at the ends of each chromosome. Long telomeres can silence genes millions of bases away through a looping mechanism called telomere position effect over long distances (TPE-OLD). There is some evidence that TPE-OLD supports the tumor-suppressive effect of replicative senescence and but may also cause problems when mutations, insertions or other telomeric modifications occur.

Using a comprehensive computational framework aimed at suggesting genes whose transcriptional regulation is likely to be influenced by their chromosomal position we noticed that affected genes in repeat expansion disorders (REDs) usually have high TPE-OLD scores, i.e., they are probably TPE-OLD genes. REDs are a heterogeneous group of conditions that mainly affect the nervous system and are caused by the expansion of short repetitive DNA sequences (1–6 bp) within their respective genes. All these diseases are characterized by a strongly age-dependent onset. We therefore plan to investigate the possibility that abnormal TPE-OLD effects may lead to abnormal expression and function of TPE-OLD genes at short telomeres in ALS, M. Huntington or Spinocerebellar ataxia type, as it has similarly been shown for facioscapulohumeral muscular dystrophy (FSHD) and the TPE-OLD gene *SORBS2.*

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Posters

Investigating the effects of Parkinson's disease associated mutations in *RHOT1* on lipid transfer and α-synuclein distribution

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Background: Parkinson's disease is the second most common neurodegenerative disorder, affecting about 10 million people worldwide. At the cellular level, Parkinson's disease is characterized by dysfunction of multiple organelles e.g. mitochondria, the endoplasmic reticulum (ER), peroxisomes, or lysosomes. These alterations are accompanied by disturbances in essential processes such as lipid homeostasis and the pathological aggregation of proteins like α-synuclein. Disrupted lipid homeostasis and transfer, particularly at organelle contact sites such as mitochondria-ER contract sites (MERCS), is closely linked to the aggregation of α-synuclein. Growing evidence points to a mutual relationship between lipid metabolism and protein aggregation in Parkinson´s disease: Altered lipid composition influences α-synuclein structure, membrane binding, and aggregation propensity. Miro1 regulates mitochondrial and peroxisomal dynamics and serves as a calcium sensor. Furthermore, Miro1 is involved in the regulation of MERCS, which are essential, amongst others, for lipid transfer. We recently identified heterozygous mutations in the *RHOT1* gene (encoding Miro1) in four individuals with Parkinson´s disease, but their impact on MERCS integrity, organelle function, lipid metabolism and α-synuclein aggregation remains poorly understood.

Methods: To investigate the interplay of altered lipid homeostasis and protein aggregation, we generated neurons from induced pluripotent stem cells with CRISPR/Cas9-engineered *RHOT1* mutations. These included a patient-derived variant and mutations designed to disrupt Miro1's interaction with the PINK1/Parkin pathway, key regulators of mitochondrial quality control. Live-cell imaging, western blotting, and dot blotting were utilized to investigate lipid droplet formation and protein aggregation in neurons. Neuronal cultures were maintained for up to 80 days, with samples collected every 10 days.

Results: Analysis revealed a progressive increase in the intracellular α-synuclein level up to day 50, followed by a subsequent decline. In contrast, analysis of the corresponding culture supernatants revealed a slight decrease of extracellular α-synuclein beginning on day 10. Furthermore, a significant increase in aggregation was observed in neurons at 40 days compared to neurons at 24 days in culture. Finally, analysis of lipid droplet formation demonstrated an increase of lipid droplets after oleic acid treatment in control neurons, while Miro1 mutant neurons exhibited an impaired lipid droplet formation.

Conclusion: These results highlight Miro1's pivotal role in lipid homeostasis and α-synuclein aggregation in PD pathogenesis.

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Unraveling Mutation-Specific Nucleocytoplasmic Transport Dysfunction in Patient-derived Motor Neurons

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Amyotrophic lateral sclerosis (ALS) is a fatal age-associated neurodegenerative disorder characterized by the progressive degeneration of upper and lower motor neurons, leading to muscle weakness, paralysis, and death. Monogenetic subtypes represent ~10 % of ALS cases, with the particularly relevant genetic alterations for this study including *FUSED IN SARCOMA* (FUS), *TRANSACTIVE RESPONSE DNA BINDING PROTEIN 43* (TDP-43, TARDBP), and *CHROMOSOME 9 OPEN READING FRAME 72* (C9orf72). Notably, FUS mutations provide a compelling model for NCT dysfunction, since most disease-associated FUS mutations occur within the nuclear localization signal (NLS), thereby directly impairing nuclear import and causing pathological cytoplasmic mislocalization of FUS. Nucleocytoplasmic transport (NCT), a key cellular pathway increasingly implicated in ALS pathogenesis, mediates nuclear import and export of protein and RNA cargoes through nuclear pore complexes (NPCs) composed of multiple nucleoporins (Nups). These exhibit alterations in various ALS models alongside several transport-associated proteins, highlighting a broader role for NCT dysfunction beyond specific mutations. This study investigates NCT dysfunction in induced pluripotent stem cell (iPSC)-derived spinal motor neurons from patients with FUS-, C9orf72-, and TARDBP-associated ALS, focusing on subtype-specific alterations of NCT disruption. Protein localization and expression of Nups and transport-associated proteins will be assessed by immunofluorescence and western blot, while functional transport integrity will be evaluated using a viral transduction-based reporter assay encoding fluorescently labeled shuttle proteins to monitor nucleocytoplasmic trafficking. The aim of this study is to define subtype-specific contributions to ALS pathogenesis and evaluate their potential for targeted therapeutic approaches versus generalized treatment strategies.

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Establishing Neuronal Models to Investigate MERCS Dysfunction in *PRKN*-Associated Parkinson's Disease

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Background: Mitochondria–ER contact sites (MERCS) are essential for calcium signalling, lipid exchange and mtDNA maintenance. Their dysfunction has been proposed as an upstream contributor to mitochondrial impairment in Parkinson's disease, particularly in *PRKN*-linked forms of Parkinson´s disease. Parkin, encoded by the *PRKN* gene, regulates mitophagy and MERCS-associated proteins such as MFN2. The R275W mutation leads to loss of Parkin protein and function, mirroring knockout-like phenotypes.

Objective: This project investigates how Parkin deficiency impacts MERCS structure and function, aiming to clarify their role in mitochondrial dysfunction in *PRKN*-associated Parkinson´s Disease.

Methods: We are generating *PRKN* knockout induced pluripotent stem cells (iPSC) using CRISPR-Trap, which disrupts gene expression via cassette insertion without relying on frameshift mutations or protein truncation. These lines are being differentiated into small molecule neural precursor cells (smNPCs) as a foundation for subsequent studies in neurons. In parallel, iPSC lines harboring homozygous Parkin R275W mutations and the respective isogenic control are also being differentiated into smNPCs. These models will be applied in downstream MERCS analyses.

Outlook: The established models will serve as tools to dissect MERCS-related phenotypes in Parkin deficiency. They will enable future imaging and proteomic studies to explore how MERCS alterations contribute to neurodegeneration in Parkinson´s Disease.

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Mitochondria are aggregation hubs in neurons

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Insoluble aggregates are a hallmark of many neurodegenerative diseases. Mutations in fused in sarcoma (FUS) cause amyotrophic lateral sclerosis, with FUS aggregates being the hallmark pathology. The exact mechanism of FUS aggregation remains elusive, however. Cytoplasmic mislocalization of nuclear FUS and subsequent sequestration into stress granules, which can serve as aggregation seeds, are currently in the focus in understanding the origin of FUS aggregates. Mitochondria are intracellular organelles with extreme environmental conditions. Strong pH fluctuations, increased temperature, high production of reactive oxygen and nitrogen species together with limited options for chaperone activity are a challenge for mitochondrial protein homeostasis.

By using a split-GFP approach with β-sheets 1-10 targeted to either outer mitochondira membrane, inner mitochondria membrane or the matrix, we confirmed that FUS can be present in all of these locations. We were then wondering whether mitochondrial FUS is prone to aggregation and indeed we show that FUS associated with mitochondria is indeed more prone to aggregation compared to nuclear localized FUS. Specifically FUS visualized with the matrix targeted GFP undergoes rapid morphological changes akin to aggresome formation.

To analyze whether other proteins are affected as well, we probed for the mitochondrial antiviral signalling protein MAVS, which is residing on the surface of mitochondria and is a signal transducer of the cytoplasmic RNA sensors RIG1 and MDA5 and induces the expresison of proinflammatory cytokines and interferones upon aggregration. We show that MAVS is more aggregated in the mitochondrial fractions of iPSC derived motoneurons carrying the FUS-p.P525L mutation. This is shown bothas well by co-immunostaining of MAVS with the amyloid stain Congo Red and by qPCR analysis of interfone stimulated genes.

Lastly we wondered whether mitochondrial impairment is sufficient to cause protein aggregation. After 1h treatment with either 25 µM CCCP (electron transport chain uncoupler), 10 µM OligomycinA (ATP synthase inhibitor) or MG132 (inhibition of MAVS degradation) we found a significant increase in interfore stimulated genes’ expression, indicating that mitochondrial dysfunction can be sufficient for mitrochondrial protein aggreagtion and downstream signalling cascades.

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Molecular mechanisms of hyperoxia-induced accelerated embryonic neurogenesis

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Oxygen is a critical factor influencing embryonic development, particularly in the brain. In support of this, it has been shown that exposing pregnant mice to elevated oxygen levels for 48 h accelerates neurogenesis in their embryos. However, the underlying mechanisms remain unclear. In this study, we exposed pregnant dams to 75% oxygen at embryonic day 14.5 for 4 h, 8 h, or 24 h, and analyzed embryonic brains via immunofluorescence to assess cell cycle progression by BrdU/EdU staining, cell division orientation by γ-tubulin staining, and primary cilium formation by pericentrin and Arl13b staining. As an initial effect, we observed a prominent accumulation of $BrdU^+$ cells direct at the ventricular surface after 4 h of hyperoxia treatement whereas there were less EdU^+ cells in the subventricular zone (SVZ). Furthermore, it induces a shift towards more flat mitotic spindle angles, associated with symmetric cell divisions, and an increase in centrosomal structures lacking cilia formation. Whereas this lack and the $BrdU^+$ cell accumulation were still observable after 8 h of treatment, there were no longer alterations regarding the mitotic spindle angle. In contrast, there were less $BrdU^+$ cells in the SVZ at this time point. Upon extending towards 24 h, the previous accumulation of $BrdU^+$ cells in hyperoxia-treated animals was gone, and there was no difference regarding the BrdU/EdU-labeled cells detectable between both groups. Of note, neither the S phase length, nor the number of mitotic cells were changed at any time point. Ongoing studies aim to determine whether hyperoxia accelerates the entire cell cycle, potentially explaining these observed changes. In conclusion, our study suggests that multiple mechanisms contribute to the effects of hyperoxia. However, each appears to represent only a small piece of the puzzle, and none alone seems to account for a predominant oxygen-related signaling pathway.

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Microglial *Npc1* Deficiency Affects Brain Development and Neurodegeneration in Niemann–Pick Disease Type C

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Abstract

Niemann-Pick disease Type C (NPC) is a neurodegenerative disorder primarily caused by mutations in the *NPC1* gene, resulting in the massive accumulation of unesterified cholesterol in late endosomes/lysosomes. Dysfunction of microglia is a hallmark in *Npc1* mutant mice (*Npc1*$^{-/-}$ mice), however, the mechanisms by which Npc1 regulates microglial function remain unclear. In this study, we employed a *Cx3cr1*-Cre; *Npc1*$^{flox/flox}$ mouse model and human *NPC1* mutated microglia-like cells (iMGs) derived from human induced PSCs to investigate the effects of microglia-specific *Npc1* deletion. Our findings demonstrated that *Npc1* knockout in microglia reduces the lifespan and influences other types of cells in the mutated mice. Furthermore, iMGs exhibites similar molecular signatures as observed microglia in the mouse model. Taken together, our results help understand the underlying mechanisms of microglial dysfunction in NPC.

Prematurely Aged Human Microglia Exhibit Impaired Stress Response and Defective Nucleocytoplasmic Shuttling of ALS associated FUS

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Abstract

Microglia, the brain's resident immune cells, are crucial for maintaining healthy brain homeostasis. However, as the brain ages, microglia can shift from a neuroprotective towards a neurotoxic phenotype, contributing to chronic inflammation and promoting neurodegenerative processes. Despite the importance of understanding microglial aging, there are currently few human *in vitro* models to study these processes. To address this gap, we have developed a model in which human microglia undergo accelerated aging through inducible progerin expression. HMC3-Progerin cells display key age-related markers such as activation of the senescence-associated secretory phenotype (SASP) as well as an increase in DNA damage. These prematurely aged HMC3 cells show a reduced response to LPS activation, exhibit impairments in essential microglial functions including decreased migration and phagocytosis as well as transcriptomic alterations including a shift observed in aging and neurodegeneration. Additionally, we observed an impaired stress response and a defect in nucleocytoplasmic transport, especially affecting the Amyotrophic lateral sclerosis (ALS) associated protein FUS. This suggests that microglia play a contributory role in driving neurodegenerative processes in the aging brain. Our microglia aging model offers a valuable tool for exploring how aged microglia affect brain function, enhancing our understanding of their role in brain aging.

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Mitochondrial Ca^{2+} Overload via MCU triggers ferroptosis in FUS-ALS

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Mutations in the fused in sarcoma (FUS) gene, which cause familial amyotrophic lateral sclerosis (ALS), increase cellular susceptibility to ferroptosis by impairing antioxidant defenses. However, the upstream mechanisms that drive this vulnerability remain largely unknown. Mitochondrial calcium overload is a key regulator of cell death, and the mitochondrial calcium uniporter (MCU) is a central pathway for calcium entry. In this study, we investigated whether MCU-mediated calcium entry drives ferroptosis in FUS-ALS. Using small molecule neural progenitor cells (smNPCs) and derived spinal motor neurons with both wild-type or mutant (P525L) FUS, we assessed mitochondrial calcium dynamics, lipid peroxidation, and cell viability following ferroptosis induction. Our findings show that P525L cells exhibit elevated baseline mitochondrial reactive oxygen species (ROS) levels, which are further exacerbated by RSL3 and erastin treatment. Notably, inhibiting the MCU with Ru360 significantly reduced ROS accumulation, lipid peroxidation, and ferroptotic cell death. Our findings demonstrate that mitochondrial calcium overload via the MCU is a novel driver of ferroptosis in FUS-ALS. This establishes a mechanistic link between mitochondrial dysfunction and iron-dependent neurodegeneration, and it identifies the MCU as a potential therapeutic target.

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Disrupted nucleocytoplasmic transport and RNA-binding protein homeostasis: mechanisms linking aging and ALS pathogenesis

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The nuclear pore complex (NPC) orchestrates nucleocytoplasmic transport (NCT), maintaining homeostasis through precise regulation of gene expression, RNA processing, and cellular stress responses. NCT disruption represents a central pathogenic mechanism in amyotrophic lateral sclerosis (ALS) and emerges as a hallmark of the aging, revealing a convergent pathological pathway between physiological aging and age-associated neurodegeneration. These transport deficits coincide with compromised nuclear envelope integrity and redistributed NPC protein localization, though the underlying molecular mechanisms driving NCT failure may differ between aging-related processes and neurodegenerative disease contexts.

Previous proteomic and clustering studies revealed age-associated nucleocytoplasmic redistribution of RNA-binding proteins (RBPs) linked to RNA metabolism, protein homeostasis, and neurodegenerative disease pathways, particularly ALS. These findings prompted further investigations into NCT disruption patterns across aging and distinct ALS subtypes by using patient-derived fibroblasts from healthy young, mid-age and old donors, patients with the premature aging disorder Hutchinson Gilford-Progeria syndrome (HGPS), and ALS patients carrying either *FUS* mutations or *C9orf72* repeat expansions. A viral transduction-based reporter assay directly monitoring nucleocytoplasmic trafficking demonstrated age-associated NCT impairment, with significantly reduced transport efficiency in old donor fibroblasts. Notably, HGPS and both ALS subtypes exhibited disrupted NCT, revealing a generalized shuttle dysfunction beyond protein-specific defects. NPC protein analysis showed reduced Nup50 and Nup153 expression in old and FUS-ALS fibroblasts, with Nup50 cytoplasmic redistribution occurring specifically during aging. Analyses of additional NPC proteins and transport receptors are ongoing.

These findings establish impaired NCT and aberrant RBP localization as shared features of aging and neurodegeneration, reinforcing NCT dysfunction as a central mechanism in age-related neurogenerative disorders and a promising therapeutic target for future interventions.

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Retrotransposable elements are activated in FUS-ALS

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Retrotransposable elements (RTEs) constitute a substantial fraction of the human genome and encompass multiple classes, including long interspersed nuclear elements (LINEs), short interspersed nuclear elements (SINEs), and endogenous retroviruses (ERVs). Among them, LINE1 and ERVK elements are of particular interest due to their potential to mobilize and disrupt genomic integrity. Aberrant activation of RTEs has been implicated in neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS). Mutations in FUS, an RNA-binding protein essential for RNA metabolism and genome stability, are amongst the most common familiar forms in Europe and particularly prevalent in young patients. Recent studies suggest that TDP-43 dysfunction leads to the derepression of RTEs, which contributes to genomic instability and neurotoxicity. The effect of FUS dysfunction on RTE expression remains unclear. Understanding this interaction may uncover novel mechanisms of ALS pathogenesis.

To investigate RTE activity in FUS-ALS, we used hiPSC-derived motor neurons carrying FUS mutation. We first analyzed publicly available bulk RNA-seq data (GEO: GSE272827) from isogenic KG25 FUS-WT/P525L_eGFP cells. Repetative elements expression was quantified using SQuIRE, which performs genome alignment and generates count matrices. Differential expression of LINE1 and ERVK elements was assessed at the locus and subfamily levels. For gene expression analysis, we applied the nf-core/rnaseq pipeline (FastQC, trimming, STAR alignment), followed by featureCounts quantification. The RNA-seq data indicate upregulation of LINE1 and ERVK at both the locus and subfamily levels, consistent with derepression of RTEs in FUS-ALS.

To validate the RNA-seq findings, we examined the LINE1 ORF1p and the ERVK integrase domain at the protein level. Elevated levels of both LINE-1 ORF1p and ERVK-IN were observed in FUS-p.P525L iPSC-derived MNs, indicating the translation of RTEs, which may contribute to activation of downstream pathawys. However, further mechanistic analysis is needed to investigate these activations, such as neuroinflammation.

Next, we will assess the impact of DNA damage with topoisomerase II inhibitor etoposide treatment on LINE1/ERVK RNA and protein levels. In parallel, we will evaluate changes in histone methylation and colocalization of γH2A.X with RTEs. Finally, we will interfere with FUS expression and reverse transcriptase inhibitors to evaluate putative ttherapeutical interventions.

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Hypoxia inducible factor 2 α does not affect cortical brain development

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Dynamic changes in physiological oxygen levels are crucial for proper cortical brain development. In this context, oxygen is important not only for its role in energy-metabolism but also as a signaling factor. While a lot is already known about its most prominent signaling factor hypoxia inducible factor (Hif) 1α, not much is known about its functional similar subunit Hif2α during cortical development. Therefore, we utilized Hif2α knockout mice (Emx1 and Nestin driven), which were kept under maternal hypoxia (10% pO_2), physioxia (21% pO_2) or hyperoxia (75% pO_2) for 48 h and analyzed their cortical development by immunohistochemistry at E16.5. The analysis of newborn neurons (BrdU) and cortical layer IV (Tbr1), V (Ctip2) and upper layer neurons (Satb2) revealed a clear effect of oxygen, where especially hyperoxia is able to increase the number of layer V neurons in E16.5 fetuses. However, neither the number of newborn neurons, nor the number of layer specific neurons were affected by Hif2α knockout. Similar, oxygen related effects on neural stem and progenitor cells seems to be not mediated via Hif2α in E16.5 fetuses

Additionally we established an *in vitro* model of embryonic neural stem cells (NSCs) and compared the expression of Hif2α-associated genes via qPCR with *in vivo* data. A significant, Hif2α-specific reduction of the target gene *Slc2a1* was observed *in vitro*, but not *in vivo*. However, we performed additional *in vitro* analyses, including immunohistochemistry and qPCR, to investigate the impact of Hif2α and varying oxygen conditions on the expansion and differentiation of NSCs. These experiments did not reveal any significant Hif2α-dependent effects, but rather demonstrated an influence of oxygen.

In conclusion, while oxygen clearly modulates cortical development, Hif2α is dispensable for these processes. Oxygen-dependent changes in neurogenesis and cortical development appear to be mediated through Hif2α-independent mechanisms.

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Argonaute2 knockout in glutamatergic neurons impairs retina development

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Abstract

During development, the mammalian retina originates from the diencephalon and shares both anatomical and functional similarities with the central nervous system (CNS). Retinal ganglion cells (RGCs), which are Vglut2-positive (Vglut2$^+$) glutamatergic neurons, exhibit typical properties of CNS neurons. In present study, we demonstrated that the conditional deletion of Argonaute2 (Ago2), an RNA-binding protein crucial for microRNA (miRNA)-mediated gene silencing, in Vglut2$^+$ neurons led to impaired development of RGCs. Moreover, Ago2-deficient mice exhibited morphological defects of horizontal and amacrine cells, as well as increased glial activation in the retina. These findings highlight the critical role of Ago2 in retinal development, where it regulates neuron-blood vessel interactions through the microRNA signaling pathway.

Establishment of a HepG2 cell model of hepatic Wilson disease with knocked-in p.His1069Gln mutation in the ATP7B gene

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Wilson's disease (WD) is an autosomal recessive disorder of copper (Cu) metabolism caused by mutations in the *ATP7B* gene, which encodes a copper-transporting P-type ATPase. WD occurs in approximately 1 in 30,000 to 50,000 people. Cu is an important cofactor of many enzymes in the Golgi apparatus, but is strictly regulated due to its toxicity. ATP7B plays a central role in Cu distribution and excretion. Cu is taken up into liver cells and either incorporated into Cu-dependent enzymes or the blood protein ceruloplasmin (CP) or excreted into the bile if there is an excess in an ATP7B-dependent manner. Defective ATP7B function leads to harmful Cu accumulation, which causes oxidative stress, cell damage and inflammation. WD patients usually show liver or neuropsychiatric symptoms. Treatment involves Cu chelators or zinc, the latter being recommended especially in the early stages. New therapeutic approaches are being explored, including gene therapy and modulation of autophagy. There is a considerable need for research into obtaining specific cell models for investigating the molecular and cellular pathomechanisms of WD.

The WD cell model presented here was obtained *via* genomic manipulation of the *ATP7B* gene in wild type HepG2 (HepG2-WT) cells using a CRISPR-Cas9 approach. Targeting of exon 14 to obtain a HepG2 cell line homozygous for the ATP7B c.3207C>A (p.His1069Gln) mutation (HepG2$^{H1069Q/hom}$) was done using gRNA sequence 5'-GGCCAGCAGTGAACACCCCT(TGG)-3' and a single stranded oligonucleotide donor to facilitate homology directed repair. Genetic validation of the cells was carried out using the Ion Torrent chip technology.

The established isogenic hepatocyte-like cell model demonstrates extended defects in ATP7B protein transport, mitochondrial morphology, Cu tolerance, CP maturation and differential gene expression suggestive of oxidative stress, which are central features of WD.

The HepG2$^{H1069Q/hom}$ cell model represents a significant contribution to cellular models for WD and can provide a cellular platform for targeted research into novel molecular therapies in the future.

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Metal on the mind: neurotoxic effects of orthopedic materials

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Cobalt and chromium-based alloys, widely used in metal joint replacements, have been associated with elevated systemic metal levels and neurological symptoms including depression, cognitive decline, and, in rare cases, parkinsonism. Cobalt ions can cross the blood–brain barrier, where they may interfere with neuronal function by mimicking hypoxic stress and promoting mitochondrial damage. Despite increasing clinical concern, molecular mechanisms driving cobalt-induced neurotoxicity, remain largely unexplored.

The primary aim of this project is to investigate the long-term neurodegenerative effects of chronic exposure to metallic wear products on the peripheral and central nervous systems. A key aspect is to identify the direct neurotoxic effects of metal ions and nanoparticles, which can cross the blood-brain barrier (BBB). In addition, the indirect effects mediated through systemic inflammation and microglial activation will be identified.

We investigated the direct effects of metal ions ($CoCl_2$, $CrCl_3$, $NiCl_2$) and cobalt alloy particles ($CoCr_{28}Mo_6$, ~450 nm) on human iPSC-derived motor neurons *in vitro*, focusing on oxidative stress, mitochondrial dysfunction, and programmed cell death pathways. Neurons are differentiated and matured over 30 days before exposure to metal ions and particles. Cell viability and cytotoxicity are assessed via LDH release and viability assays, while flow cytometry is used to evaluate cell death, mitochondrial stress, and oxidative damage using markers NeuO, propidium iodide (PI), and MitoSOX. Particle uptake is examined by Dark Field Microscopy (DFM) in both motor neurons and microglial cells.

Motor neuron and microglial cell viability was assessed following exposure to $CoCr_{28}Mo_6$ particles, revealing dose-dependent toxicity, with microglial cells exhibiting greater sensitivity. Among metal ions tested, $NiCl_2$ showed the highest cytotoxicity across both cell types, while $CrCl_3$ was least toxic. DFM demonstrated rapid particle accumulation in both neurons and microglia. Flow cytometry after 7 days of exposure showed a reduction in viable neuronal populations and an increase in stressed or fragmented cells, particularly at higher doses of cobalt particles and ions, indicating progressive neurotoxicity.

This study shows that cobalt ions and CoCr28Mo6 particles cause dose-dependent toxicity in motor neurons and microglia, with microglia being more sensitive. Nickel was the most toxic ion, while chromium showed minimal effects. Rapid particle uptake, especially in microglia, suggests a role in indirect neurotoxicity.

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Long-term deep brain stimulation modulates non-motor symptoms and associated neurogenesis in an alpha-synuclein rat model of Parkinson's disease

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Background:

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a well-established treatment for motor symptoms in Parkinson's disease (PD). However, mechanisms behind effects on non-motor domains and associated neurogenic processes remain insufficiently understood. This study investigates behavioral and neurogenic outcomes of long-term STN-DBS in an alpha-synuclein-overexpressing (SNCA) PD rat model.

Methods:

Nine-month-old SNCA rats underwent either active bilateral STN-DBS (STIM) or sham stimulation (SHAM) for six weeks. Wild-type (WT) littermates served as additional controls. Behavioral assessments included the Sucrose Preference Test (SPT), Buried Pellet Test (BPT), and Light-Dark Box Test (LDB), conducted before and at the end of the DBS period. Adult neurogenesis was examined in the olfactory bulb, third ventricle, and dentate gyrus via thymidine analogue labeling.

Results:

STIM rats exhibited reduced anxiety-like behavior and improved olfaction during long-term DBS, compared to SHAM animals. STN-DBS normalized sucrose consumption and altered locomotor and exploratory activity in the LDB. Dopaminergic neuron counts confirmed the expected nigral degeneration in SNCA rats, with partial restoration in STIM animals. In the olfactory bulb, no significant differences in newborn neurons or correlations with behavioral improvements were observed. In contrast, stem cell proliferation around the third ventricle was modulated by DBS, suggesting a potential, though not yet behaviorally linked, neurogenic response.

Conclusion:

Long-term STN-DBS ameliorates non-motor symptoms in a genetic PD rat model. While these effects were not mediated by associated neurogenesis in the olfactory bulb, stimulation-induced changes in other neurogenic niches warrant further investigation.

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Innate immune signaling in a FUS-ALS iPSC-derived microglia

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Background: Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease and the most prevalent form of motor neuron disease. Mutations in the Fused in Sarcoma (*FUS*) gene are found in 4% of genetic ALS and up to 1% of sporadic ALS cases and result in mislocalisation of the FUS protein from the nucleus to the cytoplasm, where it forms toxic aggregates. In recent years, abundant innate immune signaling has been implicated in the ALS pathophysiology.

In detail, cellular sensors like cGAS, RIG-I, and MDA5 detect endogenous or exogenous nucleic acids and trigger downstream signaling, including the phosphorylation of TBK1 and IRF3, resulting in the production of interferons and pro-inflammatory cytokines that influence neighboring cells and may contribute to ALS pathology. However, it is not known if microglia, as the main primary immune cells in the CNS, are implicated in these signaling abnormalities or not.

Methods: Microglia were generated from iPSCs using the Haenseler et al. (2017) protocol, including a CRISPR/Cas9-engineered FUS-P525L mutant and an isogenic control line. To stimulate immune signaling, cells were treated with LPS and the double-stranded RNA analogue poly(I:C). IMT1 was used to block mitochondrial transcription and etoposide to induced DNA damage. The STING antagonist H-151 was used to inhibit the signaling STING-TBK1-IRF3 pathway, both alone and in combination with etoposide. Vehicle controls included water and DMSO. Pathway activation and downstream effects were assessed via immunofluorescence, qPCR, and Western blotting, targeting key markers and inflammatory cytokines.

Results: Preliminary analyses demonstrate treatment-dependent variations in the expression of interferon-stimulated genes and corresponding protein levels in *FUS*-mutant microglia. In general, microglial cells exhibit a generally higher basal activation of innate immune pathways compared to motor neurons. In FUS-mutant microglia, a mild baseline increase in innate immune-related gene expression, along with TBK1 phosphorylation (pTBK1), was observed. Intriguingly, this was even more pronounced after stimulation with poly(I:C) and etoposide. Additionally, combined treatment with the STING inhibitor H-151 and etoposide led to a reduction in pTBK1 levels and a dampened expression of interferon-stimulated genes, suggesting a potential suppressive effect of STING inhibition under inflammatory conditions. These results remain preliminary and require further validation through additional experiments and replicates.

Conclusion: The activation of innate immune pathways in microglial cells harboring *FUS* mutations may constitute a significant contributing factor in the pathogenesis of ALS. However, a more comprehensive understanding of the underlying mechanisms necessitates further investigation, particularly into the direct effects of *FUS*-mutant microglia on motor neurons and the immunological homeostasis within the brain.

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Lipid peroxidation and Ferroptosis in iPSC-derived neurons with loss of VPS13A

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Introduction: Chorea-Acanthocytosis is a rare autosomal-recessive neurodegenerative disease, which is caused by mutations in the *VPS13A* gene, typically leading to a loss of the VPS13A protein. VPS13A is located at membrane contact sites and takes part in transporting lipids between organelles. Previous studies suggest alterations of cellular calcium handling in VPS13A-deficient cells. Impaired calcium homeostasis is involved in the formation of reactive oxygen species, which in turn can trigger lipid peroxidation and membrane damage, ultimately causing ferroptosis, a form of programmed cell death.

Methods: We used iPSC-derived neurons from patients with Chorea-Acanthocytosis and compared those to cells from age- and gender matched healthy donors. Lipid peroxidation was induced by RSL3, a GPX-4 inhibitor. Different calcium-channel specific inhibitors were used in order to investigate a possible involvement of calcium dyshomeostasis in lipid peroxidation and ferroptosis. Liproxstatin-1 was applied to specifically inhibit ferroptosis. We analysed oxidative membrane damage using the lipid peroxidation sensor Bodipy665/676. Images were acquired on an inverted LSM 900 microscope (Zeiss). Further, cell viability was assessed under increasing concentrations of RSL3 using the AquaBluer assay on a plate reader. Co-staining with propidium iodide and Hoechst 33342 served as independent method to assess cell viability.

Results: Our results show that lipid peroxidation was significantly elevated in VPS13A-deficient neurons compared to healthy control neurons. None of the applied calcium-channel inhibitors had a significant impact on lipid peroxidation. Preliminary results of the AquaBluer assay and the co-staining of propidium iodide and Hoechst 33342 suggest that VPS13A deficient neurons might be more prone to RSL3-induced ferroptosis.

Discussion: Our results suggest that deficiency of the lipid transfer protein VPS13A is associated with increased lipid peroxidation, likely increasing the vulnerability against ferroptosis. Since the AquaBluer assay is based on mitochondrial activity, comparison with the mitochondria-independent PI/Hoechst assay point to impaired mitochondrial function in VPS13A-deficient neurons. However, our study does not yet answer the question of the extent to which the previously observed disruption of cellular calcium homeostasis contributes to increased lipid peroxidation in VPS13A deficient neurons and therefore highlights the need for further research.

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