Preisverleihung 2026

STIFTUNG
PROFESSOR DR. MAX CLOËTTA

Heft Nr. 54

Prof. Dr. Martin Jinek
«From Bacterial Immunity to Genome Surgery –
The Past, Present and Future of CRISPR Genome Editing»

Prof. Dr. Mirjam Christ-Crain
«From Vasopressin Deficiency to Excess: New Diagnostic and Therapeutic Pathways in Disorders of Water Balance»

STIFTUNG
PROFESSOR DR. MAX CLOËTTA

dreiundfünfzigste Preisverleihung

30. Oktober 2026
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Heft Nr. 54 der Schriftenreihe

Stiftung Professor Dr. Max Cloëtta
Leimbachstrasse 225, 8041 Zürich
Telefon 044 508 10 82
E-Mail info@cloetta-foundation.ch
www.cloetta-foundation.ch

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VORWORT

Prof. Dr. Fritjof Helmchen
Stiftungsratspräsident

Die Stiftung Professor Dr. Max Cloëtta freut sich ausserordentlich, die Verleihung der diesjährigen Cloëtta-Preise erneut in Basel feiern zu dürfen – in einer Stadt, die für ihre lange Tradition in Medizin und Lebenswissenschaften steht und damit einen würdigen Rahmen für die Auszeichnung zweier aussergewöhnlicher Forscherpersönlichkeiten bietet. Im letzten Jahrzehnt fand die Preisverleihung bereits 2016, 2019 und 2023 in Basel statt.

In diesem Jahr zeichnet die Stiftung **Prof. Dr. Martin Jinek** von der Universität Zürich und **Prof. Dr. Mirjam Christ-Crain** vom Universitätsspital Basel aus. Beide haben in ihren jeweiligen Forschungsfeldern Massstäbe gesetzt und mit ihren Arbeiten nicht nur die Grundlagenforschung geprägt, sondern auch Wege zu konkreten medizinischen Anwendungen eröffnet und diese vorangebracht.

Prof. Dr. Martin Jinek ist einer der führenden Forscher im Bereich der CRISPR Genom-Editierung. Er hat mit seinen bahnbrechenden Arbeiten 2012/2013 massgeblich dazu beigetragen, die molekularen Mechanismen des oft als «Genschere» bezeichneten CRISPR-Cas9-Systems zu entschlüsseln, welches die Biologie in den letzten Jahren revolutioniert hat. Seine Arbeiten zur Struktur und Funktionsweise von Cas9 und verwandten Enzymen haben unser Verständnis grundlegend verändert, wie RNA-geführte Nukleasen ihre Zielsequenzen erkennen und schneiden. Diese Erkenntnisse sind nicht nur wissenschaftlich bedeutsam, sondern bilden auch die Grundlage für die Entwicklung präziserer und sicherer molekularer Werkzeuge zur Behandlung genetischer Erkrankungen. Prof. Jineks Forschungsgruppe hat darüber hinaus neue CRISPR-assoziierte Systeme entdeckt und charakterisiert, die das therapeutische Potenzial dieser Technologien erheblich erweitern.

Prof. Dr. Mirjam Christ-Crain ist Professorin für klinische Forschung und Endokrinologie an der Universität Basel sowie Chefärztin für Endokrinologie, Diabetes und Metabolismus am Universitätsspital Basel und international eine der renommiertesten Expertinnen auf dem Gebiet der Hyponatriämie und des Diabetes insipidus. Ihre klinisch-translationale Forschung hat die Diagnostik und Therapie dieser häufigen, aber komplex zu behandelnden Störungen des Wasserhaushalts grundlegend verbessert. Insbesondere hat sie mit der Etablierung des Kopeptin-Tests eine diagnostische Methode etabliert, die in der klinischen Praxis weltweit eingesetzt wird und Patientinnen und Patienten eine belastende und fehleranfällige Diagnostik erspart. Ihre randomisierten klinischen Studien zu Themen wie der Behandlung chronischer inadäquater Antidiurese (der ungenügenden Ausscheidung von Wasser) und der Rolle von verschiedenen Rezeptoren bei krankhaft gesteigertem Durst (primäre Polydipsie) stehen beispielhaft für klinische Forschung von höchster methodischer Qualität mit unmittelbarer Relevanz für die Patientenversorgung.

So unterschiedlich die Forschungsfelder der beiden Preistragenden auf den ersten Blick erscheinen mögen, verbindet sie doch ein gemeinsamer Anspruch: die Präzision. Prof. Jinek strebt präzise molekulare Eingriffe ins Genom an, während Prof. Christ-Crain sich die präzise Diagnose und gezielte Korrektur physiologischer Dysregulationen zum Ziel gesetzt hat. In beiden Fällen ist es die konsequente Verbindung von grundlagenwissenschaftlichem Verständnis und klinischer Wirksamkeit, die ihre Arbeit auszeichnet.

Die Cloëtta Stiftung ist stolz, mit diesen beiden Preisen Forschung zu würdigen, die exemplarisch zeigt, wie wissenschaftliche Neugier und methodische Strenge den Weg zu besseren Therapien ebnen können. Wir freuen uns auf eine festliche Preisverleihung in Basel und danken herzlich allen, die zu ihrer Vorbereitung beigetragen haben.

Stella Vondra
Geschäftsführerin

Im Jahr 2026 blickt die Stiftung Professor Dr. Max Cloëtta auf ein weiteres Jahr zurück, in dem die Förderung herausragender medizinischer und naturwissenschaftlicher Forschung im Zentrum ihrer Tätigkeit stand. Seit ihrer Gründung verfolgt die Stiftung das Ziel, wissenschaftliche Exzellenz sichtbar zu machen, vielversprechende Forschende in entscheidenden Phasen ihrer Laufbahn zu unterstützen und den Austausch zwischen Grundlagenforschung und klinischer Medizin zu stärken.

Diesen Auftrag erfüllt die Stiftung mit drei bewährten Instrumenten: dem jährlich verliehenen Cloëtta-Preis, den seit 1983 vergebenen Forschungsstellen sowie dem 2010 eingeführten Programm «Klinische Medizin Plus». Gemeinsam ermöglichen diese Förderinstrumente Unterstützung in unterschiedlichen Phasen einer wissenschaftlichen und klinischen Laufbahn und leisten damit einen nachhaltigen Beitrag zur medizinischen Forschung in der Schweiz.

Mit der 53. Verleihung des Cloëtta-Preises am 30. Oktober 2026 in Basel setzt die Stiftung diese Tradition fort und würdigt erneut zwei Persönlichkeiten, deren Arbeiten die biomedizinische Forschung in besonderer Weise geprägt haben.

Stiftungsrat

Der Stiftungsrat besteht aus neun Mitgliedern und vereint wissenschaftliche Expertise mit Fachkompetenz in den Bereichen Finanzen und Recht. Sechs Professorinnen und Professoren der Medizin und Naturwissenschaften von führenden Schweizer Universitäten bilden zugleich den Wissenschaftlichen Ausschuss. Drei weitere Mitglieder mit ausgewiesener Expertise in Finanzen und Recht bilden den Vermögensausschuss.

Diese Zusammensetzung gewährleistet eine fundierte Beurteilung und gezielte Förderung, die sich an den aktuellen Entwicklungen und

Bedürfnissen der medizinischen und naturwissenschaftlichen Forschungspraxis orientiert. Gleichzeitig stellt die Expertise des Vermögensausschusses eine professionelle und nachhaltige Führung des Stiftungsvermögens sicher.

Unser besonderer Dank gilt allen Mitgliedern des Stiftungsrats und seiner beiden Ausschüsse, die ihr Fachwissen und ihre Erfahrung mit grossem Engagement einbringen. Ebenso danken wir den externen Expertinnen und Experten, deren unabhängige Gutachten eine wichtige Grundlage für die sorgfältige Auswahl der Preistragenden bilden.

Cloëtta-Preis

Seit der Gründung der Stiftung am 27. September 1973 ist der Cloëtta-Preis fest in ihrem Zweck verankert. Die Statuten sehen seine Schaffung und jährliche Verleihung zur Auszeichnung von Persönlichkeiten vor, die sich in besonderer Weise um bestimmte Gebiete der medizinischen Forschung verdient gemacht haben.

Seit seiner ersten Verleihung im Jahr 1974 prägt der Cloëtta-Preis die Geschichte der Stiftung und ihr Wirken für die medizinische Forschung in der Schweiz.

Die 53. Preisverleihung findet am 30. Oktober 2026 in Basel statt. Gastgeberin ist Stiftungsrätin Prof. Dr. Daniela Finke. Die feierliche Veranstaltung verbindet die Ehrung der Preistragenden mit Musik, persönlicher Begegnung und dem Austausch zwischen Menschen aus Forschung, Medizin und dem Umfeld der Stiftung. Damit schafft die Preisverleihung zugleich Raum für Vernetzung und Begegnung über Institutionen und Fachgebiete hinweg.

Forschungsstellen

Seit 1983 vergibt die Stiftung Professor Dr. Max Cloëtta Forschungsstellen an Schweizer Universitäten, Kliniken und Institute. Das Programm richtet sich an vollständig ausgebildete und unabhängige Forschende mit klinischer und/oder experimenteller Erfahrung, die sich durch herausra-

gende wissenschaftliche Leistungen ausgezeichnet haben und sich auf dem Weg zu einer dauerhaften akademischen Position befinden.

Die Förderung wird für maximal fünf Jahre gewährt und finanziert das Gehalt der geförderten Personen auf dem Niveau einer lokalen Assistenzprofessur oder einer vergleichbaren Position. Grundlagenforschende widmen ihre Arbeitszeit grundsätzlich vollständig der Forschung; klinisch Forschende mindestens 70 Prozent. Zusätzliche Projektkosten werden nicht finanziert.

2026 wurden die Rahmenbedingungen des Programms weiterentwickelt. An die Stelle einer starren Altersgrenze trat das akademische Alter: Bewerberinnen und Bewerber dürfen zum Zeitpunkt der Bewerbungsfrist in der Regel höchstens acht Jahre nach dem zuletzt erworbenen Doktorat stehen, wobei definierte Anrechnungen berücksichtigt werden können. Damit trägt die Stiftung unterschiedlichen wissenschaftlichen und klinischen Karriereverläufen besser Rechnung.

Im Jahr 2026 fördert die Stiftung Professor Dr. Max Cloëtta folgende Forschende mit laufenden Forschungsstellen:

Stephan Hirschi, PhD
Universität Bern, Institut für Biochemie und Molekulare Medizin
Projekt: «Unravelling the molecular mechanisms of cholesterol and lipid transport in Plasmodium falciparum: towards discovery of new antimaterials.»
Unterstützungsdauer: 1.1.2026 – 31.12.2030

Mathias Wenes, MD
University of Geneva, Faculty of Medicine
Projekt: «The metabolic-genetic link in CD8 T cells»
Unterstützungsdauer: 1.6.2025 – 31.5.2030

Raphael Morscher, MD
Universitäts-Kinderspital Zürich, Pädiatrische Onkologie, Hämatologie und Stammzellentransplantation
Projekt: «Personalized Targeting of Metabolism in Children with Cancer (PeTaMe-ta).»
Unterstützungsdauer: 1.7.2025 – 30.6.2030

Lucas Boeck, MD
University of Basel & University Hospital Basel, Biomedicine, Pulmonary Infection Biology
Projekt: «Designing sterilising antibiotic treatments through Antimicrobial Single-Cell Testing»
Unterstützungsdauer: 1.10.2023 – 30.9.2028

Die Ausschreibung 2026 befindet sich derzeit im Auswahlverfahren. Die Interviews mit den ausgewählten Kandidatinnen und Kandidaten finden im Januar 2027 statt; neue Forschungsstellen können frühestens im Juni 2027 beginnen.

Klinische Medizin Plus

Seit 2010 vergibt die Stiftung Professor Dr. Max Cloëtta Stipendien «Klinische Medizin Plus». Das Programm richtet sich an klinisch tätige Ärztinnen und Ärzte während oder unmittelbar nach Abschluss ihrer fachärztlichen Weiterbildung und ermöglicht einen drei- bis zwölfmonatigen Weiterbildungsaufenthalt an einer renommierten Institution im Ausland.

Im Zentrum steht das praxisnahe Erlernen neuer Methoden und die Vertiefung spezialisierter Techniken oder Kompetenzen, die nach der Rückkehr in die Schweiz in die klinische Tätigkeit und in das institutionelle Umfeld eingebracht werden können. Die Förderung leistet einen Beitrag an Reise- und Lebenshaltungskosten während des Aufenthalts.

Die Ausschreibung 2026 ist zum Zeitpunkt der Erstellung dieser Broschüre noch nicht abgeschlossen; der Entscheid über die neuen Stipendien erfolgt im Oktober 2026. Nachfolgend sind deshalb die

Stipendiatinnen und Stipendiaten aufgeführt, deren Förderperiode im Jahr 2026 läuft:

Valentin Loser, MD
CHUV, Universitätsklinikum Lausanne, Abteilung für klinische Neurowissenschaften
Projekt: «Advanced Training in Clinical Neuro-physiology and Peripheral Nerve Disorders»
Gastinstitution: Service de Neurology, CHU du Saint-Étienne, St-Étienne, Frankreich
Unterstützungsdauer: 11.5.2026 – 30.4.2027

Michaël Huguenin, MD
Inselspital Bern, Visceral Surgery and Medicine
Projekt: «Fellowship in Robotic Colorectal Surgery: Innovative Approaches to Cancer, Inflammatory Bowel Disease, and Pelvic Floor Disorders»
Gastinstitution: Département de chirurgie digestive, Centre hospitalier de l'Université de Montréal (CHUM), Kanada
Unterstützungsdauer: 1.12.2025 – 30.11.2026

Maurine Dujardin, MD
CHUV, Centre Hospitalier Universitaire Vaudois, Maternité
Projekt: «Identification of biomarkers predictive of uterine graft functionality after ischaemia-reperfusion»
Gastinstitution: LabTAU, INSERM U1032 and Hôpital Femme Mère Enfant, Lyon, Frankreich
Unterstützungsdauer: 15.12.2025 – 14.12.2026

Samanta Buchholzer, MD
Geneva University Hospital, Oral and Maxillofacial Surgery
Projekt: «Clinical and Academic Training in Oral and Maxillofacial Surgery»
Gastinstitution: Hospices Civils de Lyon – Hôpital Lyon Sud, Lyon, Frankreich
Unterstützungsdauer: 1.12.2025 – 31.10.2026

Victor Staartjes, MD
Zurich University Hospital, Neurosurgery
Projekt: «Clinical Fellowship in neurosurgical / minimally invasive spine surgery, incl. training in advanced intraoperative imaging and navigated surgery, augmented reality-guided surgery; research in artificial intelligence in spinal neurosurgery»
Gastinstitution: Capio Stockholm Spine Center, Löwenströmska Hospital, Stockholm, Schweden
Unterstützungsdauer: 1.7.2025 – 30.6.2026

Basile Pache, MD
Lausanne University Hospital, Gynaecology oncological surgery and Obstetrics
Projekt: «Fellowship in gynecological oncological surgery»
Gastinstitution: Montréal University Hospital Center (CHUM), Québec, Kanada
Unterstützungsdauer: 1.7.2025 – 30.6.2026

Isabella Bielicki, MD
University Children's Hospital beider Basel (UKBB), Pediatric Surgery
Projekt: «Fellowship; gain experience in advanced surgical techniques in pediatric colorectal surgery, including minimally invasive approaches, complex reconstructions, and innovative procedures»
Gastinstitution: Children's Hospital Colorado, Aurora, USA
Unterstützungsdauer: 1.7.2025 – 30.6.2026

Geschäftsstelle

Ein besonderer Dank gilt dem Stiftungsrat und seinem Präsidenten für ihr grosses Engagement und die professionelle Zusammenarbeit. Ebenso schätzen wir die enge und vertrauensvolle Zusammenarbeit mit den Universitäten, Kliniken und Forschungsinstitutionen in der ganzen Schweiz.

Diese Zusammenarbeit trägt wesentlich dazu bei, die Stiftung weiter zu vernetzen und ihre Sichtbarkeit zu stärken. Der wachsende Kontakt zu ehemaligen Preistragenden und Geförderten ist dabei ebenso wichtig wie die fortschreitende Digitalisierung, die neue Möglichkeiten für einen zeitgemässen und direkten Austausch schafft.

Stella Vondra
Geschäftsführerin

THE CLOËTTA PRIZE 2026
IS AWARDED TO

PROFESSOR

MARTIN JINEK

BORN IN 1979 IN TŘINEC, CZECH REPUBLIC,

FULL PROFESSOR OF BIOCHEMISTRY
AT THE UNIVERSITY OF ZURICH,

FOR HIS PIONEERING BASIC RESEARCH AND METHODOLOGICAL INNOVATION, REVEALING THE MOLECULAR PRINCIPLES AND MECHANISMS OF RNA-GUIDED CRISPR-CAS SYSTEMS AND ADVANCING THE SCIENTIFIC FOUNDATIONS OF GENOME-EDITING TECHNOLOGIES THAT ARE TRANSFORMING BIOMEDICAL RESEARCH.

BASEL, 30TH OCTOBER, 2026

IN THE NAME OF THE FOUNDATION BOARD:

THE PRESIDENT **THE VICE PRESIDENT**

MARTIN JINEK

CURRICULUM VITAE

Martin Jinek
Born: 31 May 1979, Třinec, Czech Republic
Nationality: Czech Republic
ORCID: 0000-0002-7601-210X
Department of Biochemistry, University of Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland

Academic positions

2024 – present	**Professor**, Department of Biochemistry, University of Zurich (Faculties of Science and Medicine)
2018 – 2024	**Associate Professor** (tenured), Department of Biochemistry, University of Zurich
2013 – 2018	**Assistant Professor** (tenure track), Department of Biochemistry, University of Zurich
2007 – 2012	**Postdoctoral Fellow**, University of California, Berkeley, USA. Advisor: Prof. Jennifer A. Doudna

Education

2002 – 2006	**PhD** (*Dr. rer. nat.*, *summa cum laude*), University of Heidelberg; research at EMBL Heidelberg, Germany. Supervisor: Dr. Elena Conti
1998 – 2002	**MSci** Chemistry (Class I); **BA (Hons)** Natural Sciences (Class I), Trinity College, University of Cambridge, UK

Awards, honours and fellowships

2026	**Cloëtta Prize**, Professor Dr. Max Cloëtta Foundation
2026	**Marcel Benoist Swiss Science Prize**
2024	**Elected Member, EMBO**
2017 – 2023	**International Research Scholar**, Howard Hughes Medical Institute
2017	**Georg Friedrich Götz Prize**

2015	**EMBO Young Investigator Award**
2015	**Vallee Scholar Award**, Bert L. and N. Kuggie Vallee Foundation
2015	**Friedrich Miescher Award**, Swiss Society for Molecular and Cellular Biosciences
2014	**Dr. Ernst Th. Jucker Prize**
2014	**John Kendrew Young Scientist Award**, EMBL
2007–2010	**HFSP Long-Term Fellowship**
2007	**EMBO Fellowship**

Research leadership and supervision

Supervised a total of 9 postdoctoral researchers, 16 PhD students (11 graduated) and 24 master's students. Group members have held competitive personal fellowships from EMBO, HFSP, Marie Skłodowska-Curie, FEBS and the SNSF. Former group members with independent faculty positions:

Prof. Daan Swarts	Associate Professor, Wageningen University, NL — postdoc 2015–2018
Prof. Luuk Loeff	Assistant Professor, Leiden University Medical Center, NL — postdoc 2018–2025
Prof. Irma Querques	Assistant Professor, Max Perutz Labs, University of Vienna, AT — postdoc 2019–2023
Prof. Martin Pacesa	Assistant Professor, Dept. of Pharmacology, University of Zurich, CH — PhD student 2016–2021
Dr. Migle Kazlauskiene	Group Leader, University of Vilnius Medical School, LT — postdoc 2018–2024

Institutional responsibilities and teaching

2020 – present	Director, PhD Program in Biomolecular Structure and Mechanism (BSM), Life Science Zurich Graduate School (University of Zurich / ETH Zurich)
2013 – present	Member, Molecular Life Sciences and RNA Biology PhD Programs, Life Science Zurich Graduate School; Faculty member, Faculties of Science and Medicine, University of Zurich
2014 – present	BCH252 *Post-transcriptional regulation of gene expression* – Organizer and lecturer (28 h/yr); BCH310 *Biochemistry III* — co-organizer and lecturer (14 h/yr); lecturer in BIO708/BME263 *Gene Therapy: From Bench to Bedside* and BCH100; Examiner, Practical Course in Biochemistry, Faculty of Medicine (~30 h/yr); lecturer, RNA Biology Block Course, ETH Zurich

Commissions of trust and service to the research community

- Peer review for *Nature, Science, Cell, Molecular Cell, PNAS, Nature Biotechnology, Nature Structural & Molecular Biology, Nature Communications, The EMBO Journal, eLife, Nucleic Acids Research* and others
- Evaluator, ERC Starting and Advanced Grants; EMBO and SNSF Postdoctoral Fellowships
- 2022 – Consultant, Swiss National Advisory Commission on Biomedical Ethics (BAG)
- 2016 – Consultations for the Federal Ethics Committee on Non-Human Biotechnology and the Swiss Expert Committee for Biosafety (BAFU); reviewer of genome editing policy documents for the European Academies Science Advisory Council (EASAC)
- 2015 – Co-author of *A prudent path forward for genomic engineering and germline gene modification*, *Science* 348:36–38. A key position statement framing international governance of human germline editing

Knowledge transfer and intellectual property

2012 – present	Caribou Biosciences, Inc. (Berkeley, USA) — co-founder; member of the Scientific Advisory Board
2013 – present	Co-inventor, *Methods and Compositions for RNA-Directed Site-Specific DNA Modification and for RNA-Directed Modulation of Transcription* (US 13/842,859 and >25 issued US patents and derivatives)
2022	Co-inventor, *S15 as a factor of CRISPR-transposon activity* (EP22178728.6)

Publication record

100 peer-reviewed publications (84 original research articles; 16 reviews, commentaries and book chapters); h-index 52; 30,845 citations (Scopus, July 2026). 80 publications as principal investigator, of which 34 original research articles as corresponding or co-corresponding author.

Selected publications

1. Pelea O, Tálas A, Carrera JF, Mathis N, van de Venn L, Yeh CD, Kulcsár PI, Marquart KF, Weber Y, Gerecke SE, Harvey-Seutcheu IF, Mailänder D, Pfleiderer MM, Chanez C, Corn JE, Schwank G, **Jinek M**. Programmable genome editing in human cells using RNA-guided bridge recombinases. ***Science*** (2026); eadz1884. doi: 10.1126/science.adz1884

2. Pacesa M, Lin CH, Cléry A, Saha A, Arantes PR, Bargsten K, Irby MJ, Allain FH, Palermo G, Cameron P, Donohoue PD, **Jinek M**. Structural basis for Cas9 off-target activity. ***Cell*** (2022); 185:4067–4081.e21. doi: 10.1016/j.cell.2022.09.026

3. Schmitz M*, Querques I*, Oberli S, Chanez C, **Jinek M**. Structural basis for the assembly of the type V CRISPR-associated transposon complex. ***Cell*** (2022); 185:4999–5010.e17. doi: 10.1016/j.cell.2022.11.009 **Equal contribution*

4. Pacesa M, Loeff L, Querques I, Muckenfuss LM, Sawicka M, **Jinek M**. R-loop formation and conformational activation mechanisms of Cas9. ***Nature*** (2022); 609:191–196. doi: 10.1038/s41586-022-05114-0. Epub 2022 Aug 24

5. Querques I*, Schmitz M*, Oberli S, Chanez C, **Jinek M**. Target site selection and remodelling by type V CRISPR-transposon systems. ***Nature*** (2021); 599:497–502. doi: 10.1038/s41586-021-04030-z. Epub 2021 Nov 10. **Equal contribution*

6. Donohoue PD*, Pacesa M*, Lau E, Vidal B, Irby MJ, Nyer DB, Rotstein T, Banh L, Toh MS, Gibson J, Kohrs B, Baek K, Owen ALG, Slorach EM, van Overbeek M, Fuller CK, May AP, **Jinek M**†, Cameron P. Conformational control of Cas9 by CRISPR hybrid RNA-DNA guides mitigates off-target activity in T cells. ***Mol Cell*** (2021);81:3637–3649.e5. doi: 10.1016/j.molcel.2021.07.035 **Equal contribution*. †*Co-corresponding author*

7. Niewoehner O*, Garcia-Doval C*, Rostøl JT, Berk C, Schwede F, Bigler L, Hall J, Marraffini LA, **Jinek M**. Type III CRISPR-Cas systems produce cyclic oligoadenylate second messengers. ***Nature*** (2017); 548:543–548. doi: 10.1038/nature23467 **Equal contribution*

8. Anders C, Niewoehner O, Duerst A, **Jinek M**. Structural basis of PAM-dependent target DNA recognition by the Cas9 endonuclease. ***Nature*** (2014); 513:569–73. doi: 10.1038/nature13579

9. **Jinek M**, East A, Cheng A, Lin S, Ma E, Doudna J. RNA-programmed genome editing in human cells. ***Elife*** (2013); 2:e00471. doi: 10.7554/eLife.00471

10. **Jinek M**, Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentier E. A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. ***Science*** (2012); 337:816–21. doi: 10.1126/science.1225829

FROM BACTERIAL IMMUNITY TO GENOME SURGERY – THE PAST, PRESENT AND FUTURE OF CRISPR GENOME EDITING

Martin Jinek

Introduction

Genome editing, the precise and targeted modification of the genetic material of living organisms, is one of the most transformative advances in modern molecular biology. The discovery and development of CRISPR-based genome editing tools have revolutionized our capabilities, from unravelling fundamental biological processes to driving breakthrough progress in medicine, agriculture and biotechnology. With the approval of the first CRISPR-based human therapy at the end of 2023, and with the first customized, patient-specific in vivo editing treatment administered in 2025, CRISPR genome editing has ushered in a new era of genomic medicine.

I came to this field as someone who is passionate about biological molecules. Ever since my undergraduate studies, I have had a long-standing interest in RNA. My doctoral work at the European Molecular Biology Laboratory in Heidelberg, under the supervision of Dr. Elena Conti, provided me with thorough training in structural biology and a deep appreciation of molecular mechanisms. These combined interests and experiences shaped my postdoctoral research, taking me to the laboratory of Prof. Jennifer Doudna at the University of California, Berkeley. Here, I became fascinated by CRISPR, a recently discovered molecular system in which bacteria use small RNAs to defend their genomes against viruses and other genetic parasites. My work identified the CRISPR-associated protein Cas9 as an RNA-programmable DNA endonuclease in 2012, making the fundamental mechanistic discovery that led to the development of CRISPR genome editing. Since establishing my own research group at the University of Zurich in 2013, I have continued to study how RNA-guided enzymes and related prokaryotic

defence systems recognise and manipulate nucleic acids, and how those mechanisms can be harnessed for genome engineering.

This essay aims to provide a broad view of the CRISPR genome editing landscape, including the discoveries from which it arose, the technologies that define its present applications, and the developments likely to shape its future. I also outline the limitations that continue to constrain genome editing technologies, since much of the innovation of the past decade is best understood as a continued effort to address them. The essay draws on a recent review of the field that I wrote together with Martin Pacesa and Oana Pelea (Pacesa, Pelea and Jinek, 2024), updated to reflect latest developments and illustrated by the studies that my laboratory has pursued in this context. I apologize to those whose work could not be cited due to space constraints.

The past: development and limitations of CRISPR genome editors

Historical background

Genome editing has its origin in the study of eukaryotic DNA repair. Pioneering work in the early 1990s showed that induction of a targeted double-strand break (DSB) in mammalian cells using the homing endonuclease I-SceI stimulated homologous recombination at the target site (Rouet et al., 1994), establishing the concept of genome modification using DSB-generating nucleases. Targeting specific, i.e. unique, genomic sites however requires nucleases with appropriately long recognition sites. The technologies aiming to address this were initially entirely protein-based and involved fusions of non-specific DNA endonucleases with tandem arrays of sequence-specific DNA-binding modules – first zinc-finger nucleases (ZFNs), introduced in the early 2000s, and later transcription activator-like effector nucleases (TALENs) in 2010–2011 (Wood et al., 2011; Joung and Sander, 2013). These developments set the stage for genome editing, but the laborious design and generation of ZFNs and TALENs limited their use. The discovery and development of RNA-guided, CRISPR-associated (Cas) nucleases marked a revolutionary shift, due to the ease with which the specificity could be programmed (Doudna and Charpentier, 2014).

That programmability emerged from an unrelated line of research. In 2007, the CRISPR loci of bacteria were shown to operate as an adaptive immune system directed against bacteriophages and other mobile genetic elements (Barrangou et al., 2007). CRISPR systems contain sequences derived from an invading genome integrated into a repetitive array (crRNAs), each corresponding to a previously encountered invader. Their transcription and processing yield CRISPR RNAs that function as molecular guides that program molecular machineries composed of Cas proteins to recognize the invading nucleic acids and target them for destruction (Nussenzweig and Marraffini, 2020). Subsequent work on so-called type II systems established that cleavage of phage DNA occurs at defined positions and requires the protein Cas9 (Garneau et al., 2010; Sapranauskas et al., 2011), and that maturation of the crRNA depends on a second RNA molecule, the trans-activating crRNA (tracrRNA) (Deltcheva et al., 2011). The minimal set of components sufficient for DNA cleavage nonetheless remained undefined.

My own involvement in this research began at this point. Working as a postdoctoral fellow in Jennifer Doudna's laboratory, in collaboration with Emmanuelle Charpentier and her group, we showed in 2012 that Cas9 functions as a DNA-cleaving endonuclease whose specificity is determined by a dual-RNA guide structure composed of crRNA and tracrRNA, and that the two RNAs could be fused into a single guide RNA (sgRNA), providing a fully programmable one-nuclease–one-guide-RNA design (Jinek et al., 2012). Targeting Cas9 to a specific genomic site could thereby be achieved simply by designing an sgRNA with a matching sequence. This set off a race to repurpose the enzyme for genome editing, which culminated in several studies published in early 2013, including one resulting from our own work (Jinek et al., 2013), reporting that expression of Cas9 and specific sgRNAs in eukaryotic cells led to the introduction of genetic modifications at target genomic loci.

CRISPR nuclease-based genome editing

The programmability of CRISPR-Cas nucleases to recognize and cleave DNA in a site-specific manner enabled their rapid adaptation for genome editing technologies (Mali et al., 2013; Cong et al., 2013; Jinek

et al., 2013). The archetypal Cas9 protein from *Streptococcus pyogenes* (SpCas9) remains the most widely used gene editor owing to its intrinsically high activity and specificity. To direct the SpCas9 to a genomic locus of interest, a 20-nucleotide guide sequence at the 5′ end of the sgRNA is designed to match the sequence of the DNA target by canonical base pairing. Target binding additionally depends on the presence of a short protospacer adjacent motif (PAM) located on the non-target strand (NTS) of the DNA, immediately downstream of the target site (Anders et al., 2014). Initial recognition of the PAM results in local unwinding of the target DNA at the PAM-proximal end of the target site to enable the seed sequence of the guide RNA to base pair with the target strand (TS) (Sternberg et al., 2014). Formation of the guide-TS heteroduplex drives conformational changes that ultimately lead to nuclease activation (Pacesa et al., 2022a). DNA cleavage is catalyzed by the HNH and RuvC domains, which cleave the TS and NTS, respectively, three nucleotides upstream of the PAM sequence, generating DSBs with either blunt ends or single-nucleotide 5' overhangs (Jinek et al., 2012; Gasiunas et al., 2012). Selective inactivation of either nuclease domain converts Cas9 into an RNA-guided nickase, whereas inactivation of both converts it into an RNA-guided DNA-binding protein, capable of delivering a fused effector domain to a chosen genomic position. This has been leveraged to redeploy Cas9 for transcriptional or epigenetic regulation of the genome, as opposed to its direct modification.

Much of my laboratory's work over the past decade has been devoted to understanding how the target DNA recognition process occurs at the molecular level and how it results in targeted cleavage. The motivation was not purely academic since almost every limitation that constrains CRISPR genome editing is a direct consequence of molecular features of the enzymes, which evolved to function as effectors of a bacterial immune system rather than as precision genome editing tools. Each of them had to be understood before it could be addressed by rational engineering. The engineering efforts described later in this essay are built on a mechanistic foundation that was laid, in large part, by structural biology and biochemistry.

Our crystallographic analysis of apo and RNA-bound Cas9 demonstrated that guide RNA loading triggers a large conformational rearrangement that activates the nuclease (Jinek et al., 2014). Subsequent structures of Cas9 bound to a guide RNA and a target DNA revealed that the PAM is read out in a base-paired duplex through major-groove contacts with conserved arginine residues, and that interactions with the PAM duplex promote local strand separation immediately upstream of it (Anders et al., 2014). Since the PAM is recognised by a discrete, structurally defined domain, this immediately indicated how PAM specificity might be redesigned. Single-molecule and biochemical experiments showed that Cas9 interrogates DNA by PAM-dependent sampling, with strand separation and heteroduplex formation initiating at the PAM and proceeding directionally towards the distal end of the target (Sternberg et al., 2014). More recently, a series of cryo-electron microscopy structures allowed us to visualise R-loop formation directly. Partial guide-target hybridisation initially relocates the HNH nuclease domain into a catalytically incompetent checkpoint conformation. Completion of the guide-target heteroduplex, accompanied by its distortion and by concomitant structural rearrangements of the Cas9 REC2 and REC3 domains, triggers conformational activation (Pacesa et al., 2022a). The structural snapshots provide a static overview of the functional states. Our long-standing collaboration with Prof. Giulia Palermo has mapped the conformational dynamics of Cas9 using multi-microsecond and enhanced-sampling molecular dynamics simulations (Palermo et al., 2016, 2017b). These showed that PAM binding acts as an allosteric effector coupling the two spatially separated catalytic sites (Palermo et al., 2017a), that the REC lobe senses the guide–target heteroduplex and either licenses or locks the HNH domain in an inactive conformational checkpoint (Palermo et al., 2018), and that cleavage itself proceeds by a two-metal-ion mechanism whose chemistry is tightly dependent on catalytic magnesium ions (Casalino et al., 2020; Nierzwicki et al., 2022).

Collectively, our studies have established a mechanistic model of Cas9 in which its activity is governed by molecular checkpoints that prevent nuclease activation until the target DNA is engaged. This has direct technological consequences as it explains why high-fidelity variants, described later in this essay, gain specificity but incur a kinetic penalty,

why chemical modification of the guide RNA can finetune specificity to eliminate off-target recognition, and which parts of the enzyme are amenable for structure-guided rational engineering.

Cas12a, a nuclease originating from type V CRISPR-Cas systems, was discovered a few years after Cas9 and likewise repurposed for genome editing (Zetsche et al., 2015). In contrast to Cas9, Cas12a does not require a tracrRNA and instead catalyses nucleolytic processing of its own guides by recognising a conserved pseudoknot structure in the repeat-derived segment of the crRNA (Fonfara et al., 2016), a feature that has been exploited for multiplexed editing in vivo. Cas12a targets DNAs containing a 5′-terminal TTTV PAM and cleaves both strands within the PAM-distal part of the target site using a single RuvC catalytic site. Cas12a is a highly efficient nuclease capable of precise gene editing, with properties complementary to those of Cas9, while its slower cleavage kinetics contribute to its comparatively high specificity in cells.

Our initial crystal structures of Cas12a bound to a guide RNA precursor and to a complete R-loop revealed the mechanisms underpinning the guide processing activity and target DNA recognition, showing that Cas12a guides contain a pre-ordered seed sequence that primes target binding (Swarts et al., 2017). We subsequently showed that Cas12a makes a DSB sequentially by cleaving the NTS first and TS second. The enzyme then releases the PAM-distal cleavage product while remaining bound to the PAM-proximal product in a catalytically competent, transactive state, able to cleave additional single-stranded DNA substrates indiscriminately (Swarts and Jinek, 2019). How the two strands reach one active site in turn was again addressed computationally with the Palermo group (Saha et al., 2020; Saha et al., 2024).

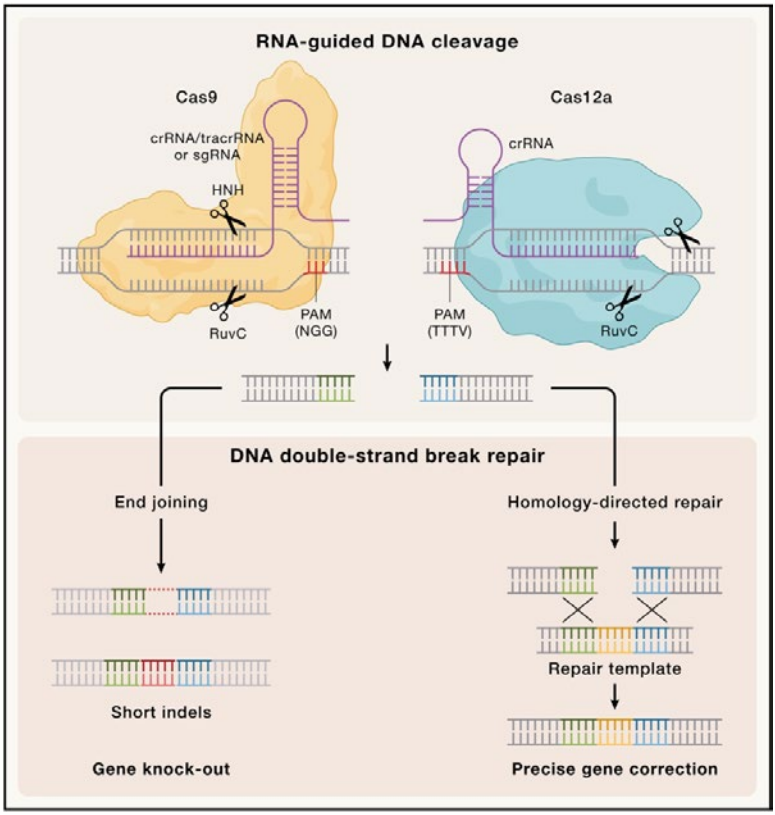

Figure 1 | Molecular principles of CRISPR nuclease-based genome editing. *CRISPR genome editing relies on RNA-guided nucleases such as Cas9 and Cas12a for site-specific target DNA recognition and cleavage. Cas9 utilizes a dual guide RNA composed of a crRNA/tracrRNA pair or a single-guide RNA (sgRNA), whereas Cas12a is programmed with a crRNA only. Target DNA recognition is dependent on complementarity with the spacer sequence of the guide RNA as well as the presence of a protospacer adjacent motif (PAM). Cas9 recognizes an NGG PAM, while Cas12a requires a TTTV PAM. Upon target binding, the nucleases catalyze DNA cleavage, generating a DNA double-strand break. DSB repair by cellular DNA repair pathways leads to the introduction of genetic modifications (edits). The end joining pathways result in short insertions or deletions (indels), while homology-directed repair (HDR) using an exogenous DNA repair template can be used to engineer precise modifications. Image and caption reproduced from Pacesa, Pelea and Jinek, 2024 under CC BY 4.0 licence.*

In first-generation CRISPR genome editing based CRISPR-associated nucleases, the editor generates a double-strand DNA break and the edit is determined and installed by the DNA repair pathway that resolves it ***(Figure 1)***. Two pathways compete to repair DSBs produced by Cas9 or Cas12a. The first, and by a considerable margin more active in mammalian cells, religates the two ends directly, either by non-homologous end joining (NHEJ) or by microhomology-mediated end joining (MMEJ). Because the exposed termini of the DSB are processed before ligation, the junction is frequently imprecise, resulting in the formation of short insertions or deletions (collectively termed indels) at the cleavage site. This is most commonly used to selectively disrupt gene sequences to achieve gene knockouts, or gene deletions, by the simultaneous introduction of two DSBs in close proximity. Conversely, homology-directed repair (HDR) is a precise pathway that relies on a homologous DNA molecule to guide the outcome of repair. By exogenously providing an artificial repair template, either a double-stranded DNA delivered via plasmids or viral vectors, or a synthetic single-stranded oligonucleotide carrying the desired mutation flanked by homology arms, HDR can be exploited to introduce mutations, insertions or deletions precisely within the targeted locus. Although this approach in principle enables editing with single-nucleotide precision, HDR is mostly active only in dividing cells, as it requires repair factors commonly expressed only in the S and G2 phases of the cell cycle. Furthermore, its efficiency depends on the type of repair template, the delivery method, the cell type and the local chromatin context. The interface between the CRISPR nuclease editor at the DSB site and the DNA repair pathways affects the editing outcome. A collaborative project with the research group of Prof. Petr Cejka revealed that Cas9 remains bound to the DSB following cleavage and holds the two ends in proximity, and that the translocase HLTF must displace it before resection or religation can proceed, which accounts for the divergent editing behaviour of the two Cas9 nickase variants in cells (Reginato et al., 2024).

Limitations of CRISPR genome editors

The adaptation of CRISPR-Cas systems as programmable editing tools has advanced numerous areas of basic and applied research. However, the activity, and consequently the application potential, of first-generation

CRISPR-based editors is limited by several key factors including specificity, targeting scope, the need to rely on endogenous DSB repair mechanisms to achieve genomic edits, and the constraints of their cellular delivery ***(Figure 2)***.

Off-target activity

Natural CRISPR-Cas systems tolerate, to a certain degree, mismatches between the guide RNA and the target as an evolutionary consequence of the need to counter the high mutational rate of phages. This property is undesirable for genome engineering, as it may result in editing of partially complementary off-target sites elsewhere in the genome. Numerous studies have shown that Cas9 tolerates a considerable number and variety of nucleotide mismatches between the guide and the target sequence, ranging from single mismatches to multiple consecutive mismatches or even nucleotide insertions and deletions (Pattanayak et al., 2013; Tsai et al., 2015; Pacesa et al., 2022b). Simultaneous off-target cleavage at multiple sites can result in genomic rearrangements such as deletions, inversions or chromosomal translocations and trigger DNA damage and stress response pathways (Kosicki et al., 2018; Tsuchida et al., 2023). Off-target editing remains a critical concern for therapeutic applications and has prompted major efforts to predict and detect off-target edits, a goal to which our structural work has contributed through improved off-target prediction algorithms and guide RNA design, and to improve the specificity of genome editors by molecular engineering.

Our contribution to this aspect of genome editing has addressed the molecular basis underpinning the off-target activity of Cas9. To this end, we determined a series of crystallographic structures of Cas9 off-target complexes containing various mismatches at varying positions of the guide RNA-DNA heteroduplex (Pacesa et al., 2022b). These revealed that off-target binding is enabled by the formation of non-canonical base pairs and structural distortions and preservation of base stacking within the guide-off-target heteroduplex, which is highly dependent on the type and position of the nucleotide mismatches. We observed that off-targets containing single-nucleotide deletions are accommodated by base skipping rather than by formation of an RNA bulge. Finally, mismatches distal to the PAM were observed to unpair the duplex and induce a rearrangement of the

REC lobe that interferes with conformational activation. This finding explains data from a number of off-target profiling studies showing that Cas9 binds far more genomic sites than it cleaves. The conformational activation of Cas9 thus functions as a kinetic proofreading checkpoint between binding and catalysis.

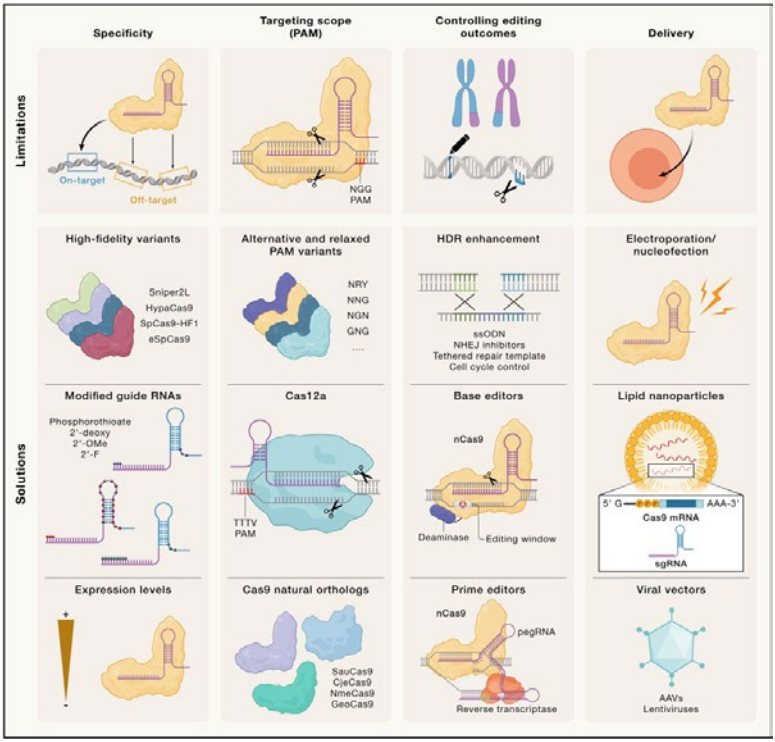

Figure 2 | Limitations of CRISPR Genome Editing. *CRISPR genome editing faces four principal limitations, each addressed by specific technological solutions. Specificity: Off-target activities of genome editors have been addressed by the development of high-fidelity nuclease variants, chemically modified guide RNAs and controlled expression of genome editor nucleases. Targeting scope: The NGG PAM sequence requirement of SpCas9 restricts the scope of targetable genomic sites. This is addressed using engineered variants of Cas9 with alternative or relaxed PAM requirements, other naturally derived Cas9 orthologs with alternative PAM requirements, and Cas12a enzymes. Control of Editing Outcomes: Various*

approaches, including asymmetric or tethered HDR repair templates, cell cycle synchronization and NHEJ inhibitors, have been developed to enhance the efficiency of HDR and suppress the formation of indels by end-joining pathways. Second-generation technologies such as base or prime editing enable the introduction of precise modifications independently of HDR. Delivery: Cellular delivery of genome editor components is facilitated by electroporation/nucleofection, lipid nanoparticles and viral vectors. Image and caption reproduced from Pacesa, Pelea and Jinek, 2024.

Targeting scope constraints due to PAM requirements

The DNA-binding mechanism of CRISPR nucleases restricts their targeting scope to genomic sites flanked by a PAM sequence. Although the NGG PAM of SpCas9 theoretically permits finding a suitable target site every eight nucleotides on average, some genomic regions are not easily targetable owing to high A/T content. Naturally occurring Cas9 orthologues with alternative PAM specificities have been identified and adopted for genome editing, but many have even more restrictive PAM requirements (Esvelt et al., 2013; Ran et al., 2015; Kim et al., 2017). Although this provides greater targeting specificity and reduces off-target activity, it often results in suboptimal cleavage and editing efficiencies. Cas12a nucleases are highly complementary to Cas9 in that they recognise T-rich PAM sequences. However, their targeting scope is likewise restricted. To address these constraints, engineered variants of Cas9 with altered or relaxed PAM requirements have been developed, as described later in this essay.

Controlling editing outcomes

Although the generation of DSBs significantly enhances the rate of HDR in mammalian cells, HDR remains restricted to dividing cells and often yields heteroallelic outcomes because of simultaneous edits installed by end-joining pathways. The precision of editing is further limited by other adverse outcomes, including large deletions, chromosomal rearrangements and even chromosome loss, as well as by activation of the p53-mediated DNA damage response (Haapaniemi et al., 2018). These risks are compounded at loci with nearby homologous sequences, as illustrated by our collaborative work with the group of Prof. Janine Reichenbach that aimed to achieve therapeutic correction of a mutation in the pseudogene-associated *NCF1* locus that causes chronic granulomatous disease. Here, concurrent targeting of

the gene and its two adjacent pseudogenes resulted in chromosome rearrangements including megabase-size copy-number changes (Raimondi et al., 2024). These findings indicate that local genomic context strongly affects editing outcomes, with important implications for the safety of potential therapeutic applications.

Delivery

The targeted delivery of gene editors remains the limiting factor for most *in vivo* and *ex vivo* applications. Moreover, the immunogenicity of the editors and their delivery vectors is another concern, since pre-existing anti-Cas9 antibodies and reactive T cells are present in humans (Charlesworth et al., 2019). In cultured cells, electroporation and lipid-mediated transfection are presently the standard delivery modalities. Transient delivery of reconstituted ribonucleoprotein complexes has become the preferred choice for *ex vivo* therapeutic editing, since prolonged expression from a plasmid increases off-target editing and risks random integration. *In vivo* delivery has relied mainly on adeno-associated viruses, whose favourable immunogenicity and tropism are offset by a limited cargo capacity (approximately 4.7 kb), or on lipid nanoparticles carrying editor mRNA together with synthetic guide RNAs.

The present: current CRISPR technologies and their applications

Since the first demonstration of CRISPR-based editing in 2013, the field has advanced at an exceptional pace. The capabilities of the first-generation, DSB-dependent editors have been extended by innovations that increased their efficiency and versatility or refined their precision by reducing off-target activity. Concerns over safety nevertheless persist, arising both from unintended off-target editing and from the genotoxicity of on-target breaks. Together with the low efficiency of HDR, these concerns have motivated the development of second-generation technologies such as base and prime editors that edit without generating DSBs or needing a repair template.

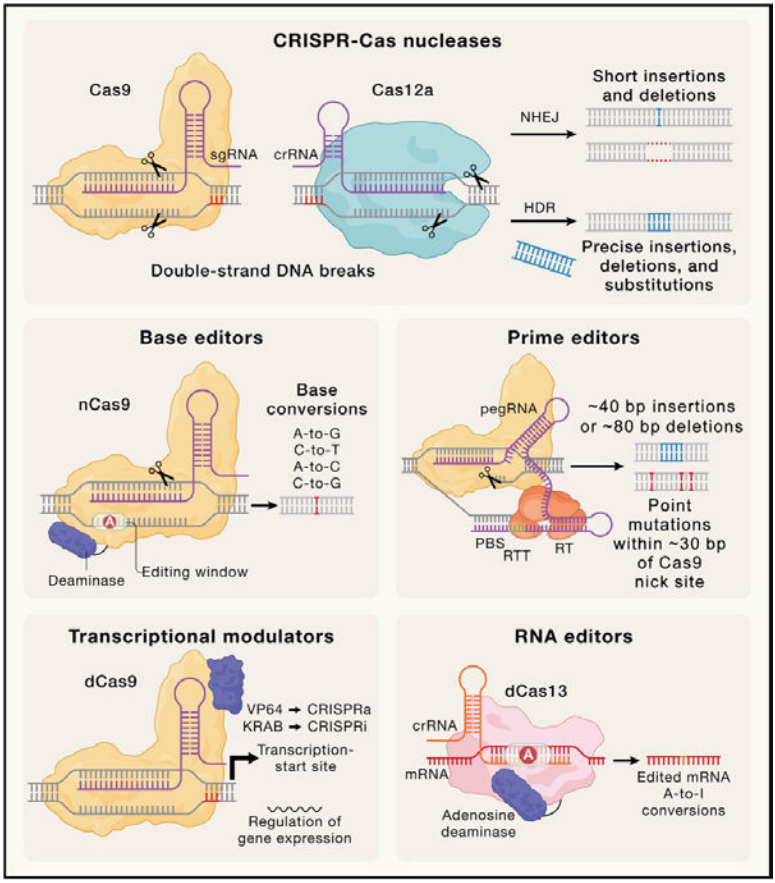

Figure 3 | Current CRISPR-based genome editing technologies. *An overview of currently utilized genome editor technologies based on CRISPR-associated nucleases and their derivatives. DSB-based genome editing: Nucleases Cas9 and Cas12a enable efficient gene knock-outs and provide limited capability to generate HDR-mediated knock-in edits. Base Editing: This approach employs a fusion of a Cas9 nickase (nCas9) with nucleobase modifying enzymes. Base editors enable the direct conversion of a single nucleotide base into another without the need for double-strand breaks. This approach is particularly effective for introducing specific point mutations (A-to-G or C-to-T, and also A-to-C or C-to-G), enabling precise gene correction or the introduction of stop codons for precise gene knock-outs. Prime Editing: This technology combines a Cas9 nickase with a reverse transcriptase (RT)*

and uses a prime editing guide RNA (pegRNA) consisting of a Cas9 sgRNA fused to a RT template (RTT) and a primer-binding site (PBS). Nicking the non-target DNA strand enables its extension by RT upon hybridization to the PBS in the pegRNA, thereby copying the RTT sequence into the target locus. Prime editing enables the insertion, deletion, and replacement of short DNA sequences up to several tens of nucleotides. Transcriptional Modulators: These tools enable RNA-guided control of gene transcription by targeting a deactivated Cas9 (dCas9) fused with transcriptional modulation domains (such as VP64, or KRAB) to gene promoters. RNA Editors: Diverging from genome editing, RNA editors utilize RNA-targeting Cas13 nucleases, either for targeted transcript degradation (when catalytically active) or for transcript editing (when rendered catalytically inactive and fused to adenosine deaminases). Image and caption reproduced from Pacesa, Pelea and Jinek, 2024.

Nucleases beyond Cas9

The establishment of Cas9 as a genome editor prompted the search for other naturally occurring RNA-guided nucleases, starting with Cas12a identified in 2015 (Zetsche et al., 2015). Bioinformatic surveys have since yielded a wide array of type V Cas12 effectors (Yan et al., 2019). These offer distinct PAM requirements, guide RNA formats and cleavage patterns and often exhibit higher specificity in cells, attributable in part to slower cleavage kinetics (Strohkendl et al., 2018). Compact Cas12-family enzymes are of particular interest for applications where packaging into viral vectors is required. In turn, the discovery of RNA-targeting nucleases such as Cas13 has facilitated applications based on targeted degradation or editing of RNA transcripts and underpinned nucleic acid detection technologies (Shmakov et al., 2015; Cox et al., 2017). Although each enzyme carries its own constraints that shape its *in vivo* activities and off-target profiles, the availability of several orthogonal systems has permitted a more tailored approach to a given editing problem as well as enabled multiplexed editing.

High-fidelity Cas9 variants and guide RNA modifications

To address off-target activity, engineered variants of SpCas9 with improved specificity have been developed using two complementary approaches. The first involves structure-based rational design of fidelity-enhancing mutations, based on the concept that eliminating specific contacts between the Cas9 protein and the bound DNA target makes the complex more sensitive to mismatches and thus reduces the probability

of off-target binding and cleavage (Kleinstiver et al., 2016). Biophysical and biochemical studies of these variants revealed that the mutations substantially slow the rate of DNA cleavage, thereby promoting off-target release (Chen et al., 2017). The second approach uses directed evolution to select for mutations that reduce off-target editing (Casini et al., 2018; Vakulskas et al., 2018). Although the high-fidelity variants developed to date offer considerably increased specificity over wild-type enzymes, their efficiencies vary across DNA targets and applications. As each target is associated with a unique set of genomic off-targets with variable editing frequencies, none of the currently available high-fidelity variants is likely to be universally applicable.

Engineering the guide RNA offers a compelling alternative to high-fidelity Cas9 enzymes. Truncating the guide segment from 20 to 17–18 nucleotides has been shown to significantly reduce off-target activity at a variety of sites (Fu et al., 2014), although it can also decrease efficiency or trigger editing at new off-target sites. Modifications at the 5′ end of the guide, either through introduced secondary structures or unpaired nucleotides, likewise mitigate off-target recognition. CRISPR hybrid RNA-DNA (chRDNA) guides are particularly effective at mitigating off-target activity. Developed by Caribou Biosciences, a leading CRISPR therapeutics company, chRDNAs contain 2′-deoxynucleotide substitutions placed at defined positions within the guide segment that substantially increase the specificity of editing in primary human T cells while preserving on-target activity. In a collaborative work, our crystal structures of the chRDNA complexes revealed that these substitutions distort the guide–target duplex geometry and allosterically modulate Cas9 activation kinetics, disfavouring the binding and cleavage of off-target substrates (Donohoue et al., 2021). Other chemical modifications, such as 2′-O-methyl or 2′-fluoro nucleotides and phosphorothioate linkages, also increase specificity and enhance guide stability, while retaining robust in vivo activity (Hendel et al., 2015; Yin et al., 2017), although the effects of modified nucleotides are highly position-dependent.

Alternative PAM genome editors

To overcome targeting constraints imposed by the PAM requirement, several studies have expanded the targeting scope of SpCas9 by structure-

based rational engineering or directed evolution of the PAM-interacting domain. This initially led to the VQR, EQR and VRER variants, capable of targeting NGAN, NGNG and NGCG PAMs, respectively (Kleinstiver et al., 2015). Our crystallographic analysis of these enzymes showed that the non-canonical PAMs are recognised by an induced-fit mechanism in which the introduced substitutions facilitate conformational remodelling of the PAM region of the bound DNA (Anders et al., 2016). Subsequent efforts relaxed PAM selectivity further, yielding variants capable of NRN PAM targeting and nearly "PAM-less" designs, as exemplified by the development of the SpRYc Cas9 variant in a collaborative project that our group contributed to. Compact Cas9 orthologues have been broadened in the same way. A recent study by the research group of Prof. Gerald Schwank, to which our group also contributed, used phage-assisted continuous evolution to generate evoCjCas9, a variant of the smallest Cas9 characterised to date, whose relaxed PAM preference enables a tenfold increase in the number of targetable sites, while its compact size enables base and prime editing using single-AAV vector delivery (Schmidheini et al., 2024). Although the in vivo editing activity of engineered or evolved variants is highly variable, and relaxed PAM targeting is generally associated with a decrease in specificity, they have significantly expanded the targeting potential of Cas9.

Base editing

Base editors (BEs) generate targeted point mutations without a DSB and without a homology template, and therefore function in cells in which HDR is unavailable. They are modular fusions of a Cas9 nickase with a nucleotide deaminase (Anzalone et al., 2020). Cytosine base editors combine a cytidine deaminase such as APOBEC1 with a uracil glycosylase inhibitor domain and mediate C-to-T conversion (Komor et al., 2016), whereas adenine base editors achieve A-to-G conversion using a TadA-derived adenosine deaminase evolved to act on single-stranded DNA (Gaudelli et al., 2017). The deaminase acts within an editing window in the displaced non-target strand, and the resulting uracil or inosine is read during replication as thymine or guanine. Successive design iterations have improved activity, reduced deaminase-dependent off-target editing and extended the repertoire to several transversions. The predictability of the outcome has made BEs powerful instruments for genetic

variant screening and for the correction of point mutations. Their principal limitations concern bystander editing within the window, residual off-target activity and the generation of nicks and rearrangements at the on-target site, albeit less frequently than Cas9 nucleases.

Prime editing

Prime editors (PEs) combine a Cas9 nickase bearing an inactivated HNH domain with an engineered reverse transcriptase enzyme and are programmed by a prime editing guide RNA (pegRNA) whose 3′ extension encodes both a primer-binding site and the intended edit (Anzalone et al., 2019). The Cas9 component nicks the non-target strand, the exposed 3′ end anneals to the pegRNA and is extended by the reverse transcriptase, and the resulting 5′ flap is excised and ligated. Prime editing enables insertions of up to approximately 40 bp, deletions of up to approximately 80 bp and point mutations as far as 30 bp from the nick. Successive PE generations have improved efficiency through thermostable reverse transcriptases, a second nick on the non-edited strand, inhibition of mismatch repair, better expression and nuclear localisation, and stabilised pegRNAs. The editor protein itself has also been subjected to directed evolution. Aiming to further improve the performance of prime editors, we recently contributed to a collaborative project with the Schwank group that used a yeast-based continuous evolution platform to identify substitutions in both the nickase and the reverse transcriptase which, in combination, raised prime editing rates several-fold in mammalian cells and supported higher efficiencies in the liver and brain in vivo (Weber et al., 2024). Prime editor efficiencies nonetheless remain variable and frequently low, depending on the intended edit, target site sequence and the cell type. Furthermore, on-target breaks are not entirely avoided by PE use.

Transcriptional modulation and RNA targeting

CRISPR systems have also been adapted for transient control of gene expression. A catalytically inactive Cas9 fused to a repressor such as the KRAB domain and directed to a promoter permits efficient transcriptional downregulation (CRISPRi) (Qi et al., 2013; Gilbert et al., 2013), while fusions with transactivation domains or histone-modifying enzymes activate expression (CRISPRa) (Maeder et al., 2013; Konermann et al.,

2015), and both formats have been widely used for genome-wide screening. Because DNA binding by Cas9 is considerably more promiscuous than cleavage, off-target modulation is a frequent problem. In an alternative approach, RNA-targeting Cas13 enzymes have been deployed for transcript silencing and editing, most usefully as fusions with adenosine deaminase acting on RNA (ADAR), which convert adenosine to inosine within a target transcript and so achieve the equivalent of an A-to-G change (Cox et al., 2017). Since RNA edits are transient, such approaches are attractive wherever a temporary effect is preferable to a permanent alteration of the genome.

Current applications in basic research and human medicine

CRISPR genome editing technologies have enabled a wide range of applications across biology and medicine. In basic research, editing has become the standard means of generating isogenic cell lines, engineered organoids and genetically modified model organisms in which candidate pathogenic variants can be validated. Multiplexed CRISPR editing has made a considerable impact on plant breeding and on metabolic engineering in microorganisms. Pooled functional genomic screens using guide RNA libraries, combined with nucleases, CRISPRi, CRISPRa or the second-generation editors, permit systematic perturbation of thousands of genes and regulatory elements (Bock et al., 2022). Notably, the combination of CRISPR screens with single-cell transcriptomics is providing unprecedented insights into biological processes. CRISPR systems have further been repurposed as molecular diagnostics and as gene drives directed against disease-transmitting insects (Kaminski et al., 2021; Bier, 2022). Most consequentially, the decade has yielded a multitude of candidate treatments for inherited diseases, several of which have progressed from preclinical models into clinical trials.

Ex vivo therapeutic applications

CRISPR-based genome editing of patient-derived cells ex vivo, followed by their expansion and re-transplantation, is a powerful strategy for treating genetic disorders manifested in blood cells. The haemoglobinopathies provide the clearest example, and the first such treatment is now approved in Europe, the UK and the USA. Sickle cell disease and transfusion-dependent β-thalassaemia both arise from mutations in the

β-globin gene, yet the approved therapy does not correct them. Electroporation of Cas9 ribonucleoprotein into CD34+ haematopoietic stem cells instead disrupts an erythroid-specific enhancer of BCL11A, relieving the repression that silences fetal γ-globin after birth and restoring a functional substitute for the defective adult subunit (Frangoul et al., 2021).

Cellular immunotherapy represents a second powerful ex vivo application of CRISPR genome editing. In the currently approved autologous chimeric antigen receptor (CAR) T cell therapies, the receptor gene is introduced by lentiviral transduction and integrates at essentially random positions, within a manufacturing process that is complex and liable to failure. Editing permits equivalent cells to be prepared from healthy donors, since targeted insertion of the CAR at the T cell receptor α constant locus simultaneously removes the endogenous receptor responsible for graft-versus-host disease, while simultaneous knock-out of genes encoding regulatory factors limits exhaustion and extends persistence. In a notable example of this approach, base-edited CAR-T cells carrying several simultaneous modifications have been used to induce remission in children with relapsed T cell leukaemia (Chiesa et al., 2023). In this context, our collaborative work with Caribou Biosciences on chRDNA guides (Donohoue, Pacesa et al., 2021) has helped to support clinical programs that use CRISPR-generated CAR-T cells for treating B cell lymphoma and multiple myeloma.

In vivo therapeutic applications

In vivo editing relies on direct administration of the editor to the affected tissue. Here, proof of principle studies in animal models have notably achieved restoration of dystrophin expression in Duchenne muscular dystrophy by muscle-directed AAV delivery, rescue of spinal muscular atrophy by delivery of a cytosine base editor to the brain, and by sub-retinal injection for retinal diseases (Amoasii et al., 2018; Arbab et al., 2023). The liver is currently the most accessible organ due to its efficient uptake of systemically administered lipid nanoparticles. In transthyretin amyloidosis, where the misfolded protein is produced predominantly in the liver, LNP-mediated delivery of Cas9 mRNA and synthetic sgRNAs achieved a substantial reduction of serum transthyretin in a clinical trial, the first systemically delivered in vivo CRISPR therapy (Gillmore et al., 2021).

A similar strategy directed at PCSK9 using an adenine base editor, pursued by the Schwank laboratory in collaboration with our group, reduced serum LDL cholesterol in cynomolgus macaques by more than half without detectable off-target mutations (Rothgangl et al., 2021). In a recent clinical trial that showcases the power of in vivo genome editing, an individually designed base editing therapy could be rapidly designed, manufactured and administered to successfully treat a single infant with a genetic urea cycle disorder within several months from diagnosis. Demonstrating that patient-specific editing medicines are technically feasible for rare genetic disorders, this development represents a critical breakthrough in personalized medicine (Musunuru et al., 2025).

The future: emerging technologies for genome writing

As the limitations of current CRISPR technologies have become clear over the past decade, new approaches continue to be developed to address these constraints and improve the efficacy and versatility of genome editing. Some of these efforts have aimed to diversify the existing molecular toolbox through the discovery of new classes of compact RNA-guided nucleases or development of alternative enzymatic activities for writing DNA. Other tools now function by modulating the epigenome or the transcriptome instead of modifying the genome itself. The development of new editor tools continues to go hand in hand with advances in their delivery, which remains a challenge for therapeutic applications. A major unmet need in the field, however, is the insertion of long, gene-sized DNA sequences, particularly in post-mitotic cells lacking HDR. Emerging, third-generation systems aim to close these technology gaps. In this context, our current work focuses on RNA-guided transposases and recombinases, aiming to provide mechanistic insights to facilitate their technological translation.

Expanding and diversifying the molecular editing toolbox

The ongoing search for novel RNA-guided nucleases is largely motivated by the need for alternative enzymes with orthogonal guide RNA scaffolds and targeting capabilities. Minimal protein size is a major factor, as it facilitates the construction of fusion proteins (such as BEs and PEs) and their efficient delivery using viral vectors. This is exemplified by the

ultracompact Cas12f nuclease (422 amino acids), whose in vivo editing activity has been enhanced by deep mutational scanning and structure-guided design (Hino et al., 2023). The molecular genome editing toolkit has also been expanded with the evolutionary ancestors of Cas9 and Cas12, namely IscB/IsrB and TnpB nucleases, which are encoded within prokaryotic transposable elements where they contribute to the transposition mechanism and promote transposon retention. Both systems have now been demonstrated to mediate programmable genome editing in human cells (Altae-Tran et al., 2021). The compact size of these enzymes should facilitate their delivery; however, further engineering will be needed to increase their currently low efficiency and limited targeting scope.

Other efforts focus on developing alternative enzymatic activities for the installation of genome edits. Unlike prime editors, in which a reverse transcriptase copies part of the guide RNA into the target site, DNA polymerase editors use a phage-derived polymerase provided in trans to extend a Cas9-generated nick from a tethered linear DNA template, enabling insertions of over 100 nucleotides, or combine Cas9 with DNA-dependent polymerases and HUH endonucleases that covalently attach DNA templates to the editor. Retroelement-based editing exploits non-long terminal repeat retrotransposons that mediate DNA insertion by target-primed reverse transcription, nicking the target DNA and using the exposed 3′ end to prime reverse transcription of the element's own RNA. Structural studies of the silkworm R2 element revealed its mechanisms of target recognition and initiation and showed that it can be retargeted to non-native sequences using a Cas9 nickase (Wilkinson et al., 2023), and site-specific retrotransposon activity has since been reprogrammed to new DNA sites directly. These technologies could in principle deliver gene-sized payloads, but the precision of insertion and the control of off-target effects require further validation.

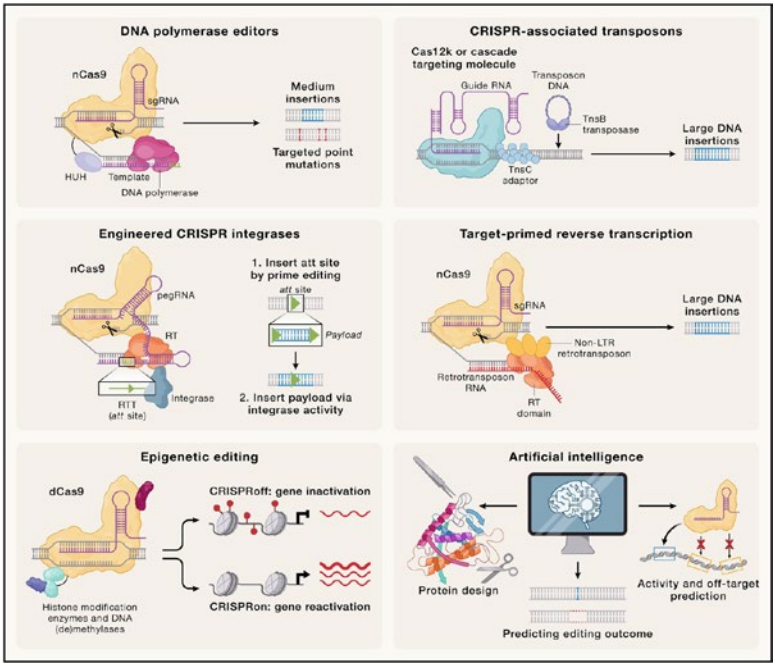

Figure 4 | Emerging technologies in genome editing. *A summary of emerging technologies in the genome editing field. DNA Polymerase Editors: This technology combines Cas9 nickases with DNA polymerases and tethering of a single-stranded DNA template, for example using an HUH endonuclease. A key difference from prime editing lies in its use of DNA polymerase rather than reverse transcriptase and the delivery of the DNA template in trans. CRISPR-Associated Transposons: These naturally occurring mobile genetic elements utilize CRISPR effector complexes in conjunction with transposase proteins for RNA-guided transposition to insert long DNA sequences into specific genomic sites. Engineered CRISPR integrases: These technologies are based on combining prime editors with site-specific serine recombinases. The prime editing initially introduces a recombinase att site at the target DNA location, subsequently enabling recombinase-catalyzed insertion of large DNA payloads. Target-primed reverse transcription: This process involves fusing nickase Cas9 with non-LTR retrotransposon-derived reverse transcriptases and RNAs. It operates by nicking the target DNA to generate a free 3' end to prime reverse transcription of the retrotransposon-associated RNA, resulting in targeted DNA insertion. Epigenetic Editors: Fusions of deactivated dCas9 with DNA methylases and histone-modification enzymes enable targeted chromatin modifications at specific genomic locations, leading to the heritable repression of gene expression (CRISPRoff) without altering the underlying*

DNA sequence. Gene reactivation (CRISPRon) involves targeting repressed genes using Cas9 fusions with DNA demethylases and transcriptional activator domains. Artificial Intelligence in Gene Editing: AI is making significant inroads in de novo protein and guide design, as well as in computational prediction of off-target sites and editing outcomes. Image and caption reproduced from Pacesa, Pelea and Jinek, 2024.

Finally, an emerging set of technologies dispenses completely with changing the DNA sequence. CRISPR-based epigenome editing introduces targeted epigenetic modifications that can nonetheless persist through many cell generations. By fusing DNA- and histone-modifying enzymes to nuclease-dead Cas9, chromatin can be restructured at a specific locus to induce or repress target gene expression. The CRISPRoff approach exploits DNA methyltransferases together with KRAB repressor domains to silence gene expression efficiently and heritably in proliferating cells, and silencing can be reversed by CRISPRon, which combines Cas9 with the DNA demethylase TET1 and transcriptional activation domains (Nuñez et al., 2021). Editing the transcriptome offers a similarly reversible alternative, owing to the limited lifetime of mRNAs within the cell. Recent advances include the Cas7-11 system, a single-protein CRISPR-Cas effector re-engineered to knock down transcripts with minimal off-target and no apparent collateral activity in mammalian cells, and CRISPR-mediated trans-splicing, which uses RNA-targeting Cas13 enzymes together with a trans-splicing RNA to replace or insert large segments of mammalian transcripts. Together with the RNA base editors described above, these technologies expand the potential for treatments requiring transient or reversible genetic modulation.

Novel delivery methods

Efficient and precise delivery of editor complexes into target cells or organs remains the most significant limiting factor for genome editing. New LNP formulations enable tissue-specific targeting, offering a versatile approach for delivering CRISPR components with enhanced cellular uptake and reduced off-target editing (Cheng et al., 2020). Cell-penetrating peptides have shown considerable potential, particularly for editing primary human cells (Foss et al., 2023). Engineered virus-like particles (VLPs) devoid of viral genetic material have emerged as a powerful alternative to viral vectors for in vivo applications (Banskota et al., 2022).

However, the cytotoxicity, off-target and immunogenicity profiles of these technologies will need rigorous assessment across cell types and tissues, and their scalability and manufacturing cost continue to pose a significant challenge for clinical translation.

Artificial intelligence

The rapid adoption of artificial intelligence and deep learning in the biological sciences has also reached genome editing. Machine-learning models that predict editing outcomes, efficiency and off-target activity now routinely guide the selection of guide RNAs for CRISPR nucleases, base editors and prime editors (Xiang et al., 2021; Marquart et al., 2021). AI-based methods are increasingly being applied to the computational design of novel nucleases. The limitations of these approaches lie in the underlying training data, which are often sparse and heterogeneous, and in model interpretability. These challenges notwithstanding, AI-assisted approaches are likely to become indispensable both for designing editors and for anticipating the consequences of their use in the future.

Programmable insertion of large DNA payloads

Genome editing that relies on template-directed repair of double-strand breaks is largely restricted to proliferating cells in which HDR is active, and the efficiency of HDR-mediated insertion scales inversely with insert size, severely limiting the ability to insert long DNA fragments or entire genes. Although prime editing facilitates insertions without relying on HDR, the inserts are currently restricted to a few tens of nucleotides. However, many monogenic disorders, exemplified by cystic fibrosis, retinitis pigmentosa or Duchenne muscular dystrophy, are multiallelic, i.e. caused by multiple distinct mutations scattered across the gene sequence. For such diseases, insertion of a complete, functional copy of the coding sequence at the endogenous locus would provide a single, mutation-agnostic treatment approach. The capabilities of prime editors have been extended by combining them with serine recombinases and integrases, whereby prime editor-mediated installation of a recombinase recognition site enables subsequent insertion of multi-kilobase DNA sequences by the recombinase (Yarnall et al., 2023). They nevertheless require the sequential action of two systems, leave a recombinase landing pad as a genomic scar, and present a considerable coding payload for delivery. These constraints have

motivated the discovery and development of natural systems that insert DNA in an autonomous manner.

CRISPR-associated transposases

CRISPR-associated transposase (CAST) systems are naturally occurring Tn7-like transposable elements that have co-opted CRISPR-Cas effectors as targeting modules to mediate RNA-guided DNA transposition (Klompe et al., 2019). As the transposase enzymes encoded in these systems insert DNA autonomously, without generating double-strand breaks and without any requirement for HDR, CASTs are in principle highly suited for programmable gene-sized insertion in human cells. Understanding how these elaborate molecular machines function has been a major focus of my laboratory's research in recent years. Type V CAST systems use the RNA-guided pseudonuclease Cas12k as the targeting module. Our structural work showed that target recognition by Cas12k primes ATP-dependent polymerisation of the AAA+ ATPase TnsC into a helical filament that remodels the bound target DNA, generating a recruitment platform for the transposase TnsB. The assembly of the targeting complex additionally depends on the zinc-finger protein TniQ and, unexpectedly, on the ribosomal protein S15 (Querques et al., 2021; Schmitz et al., 2022). Type I CAST systems follow the same logic but use a multisubunit Cascade complex for targeting. Target recognition by Cascade triggers oligomerisation of TnsC into a heptameric ring, which in turn recruits the TnsAB transposase through conserved interactions with its C-terminal tail (Finocchio et al., 2025). Most recently, our structures of the TnsAB paired-end complexes and the complete 1.2 MDa transpososome holocomplex defined molecular determinants of transposon end recognition and excision, and revealed the mechanism that underpins target DNA-dependent activation of the transposase (Walter et al., 2026; Finocchio et al., 2026). Together these studies establish a unified structural and mechanistic blueprint for RNA-guided DNA integration.

Translating this blueprint into a genome editing technology has proved challenging. Type V CASTs remain poorly active in human cells, and natural type I systems were initially only minimally active. The decisive advance has come from laboratory evolution. Phage-assisted continuous evolution of the transposase, combined with structure-guided engineering

of the DNA-targeting module, yielded an evolved system that achieves integration efficiencies of roughly 10–30 % for kilobase-sized cargoes (Witte et al., 2025). This represents an improvement of more than two orders of magnitude over the natural starting system and brings CASTs to efficiencies relevant for therapeutic gene insertion. Our structural framework should facilitate further rational optimisation. However, the principal remaining challenges are the multicomponent architecture and large coding size of these systems, which complicate delivery, and the need for rigorous assessment of insertion fidelity *in vivo*.

RNA-guided bridge recombinases

A conceptually distinct solution for programmable DNA integration emerged in 2024 with the discovery that IS110 insertion sequences, a family of minimal prokaryotic mobile genetic elements, encode a recombinase that is programmed by a non-coding RNA (Durrant et al., 2024). This bridge RNA guide, also described as a seekRNA, is bipartite, folding into target-binding (TBL) and donor-binding (DBL) loops, each containing variable segments that base pair with both strands of 14-nucleotide target and donor sites defined by an invariant CT core dinucleotide. Depending on the relative orientation of the donor and target sites, the recombinase mediates programmable deletions, inversions or insertions. Because a single short RNA specifies both partners of the recombination reaction, the system is fully reprogrammable, unlike canonical serine and tyrosine recombinases, which recognise fixed sequences. Structural and biochemical studies have established the underlying mechanism, in which initial nicking of the target and donor top strands is followed by strand exchange and ligation to generate a Holliday junction intermediate, which is then resolved through bottom-strand cleavage. The reaction is carried out by a tetrameric synaptic complex of target- and donor-loop-bound recombinase dimers, in which composite active sites combine a RuvC-like DEDD motif with a conserved catalytic serine (Hiraizumi et al., 2024).

Although the prototypical IS621 recombinase can be reprogrammed to efficiently mediate genetic rearrangements in bacteria, its activity in human cells is very low. Screening the natural diversity of the IS110 family, we identified ISCro4, from *Citrobacter rodentium*, as a highly

active recombinase capable of mediating RNA-guided recombination in human-derived cells. Our cryo-EM structure of its synaptic complex showed that its enhanced activity, as compared to IS621, arises partly from additional contacts with the bound nucleic acids, as well as from substitutions in the hydrophobic core and on the molecular surface that likely improve its solubility and stability in cells. Splitting the bridge RNA into independently expressed TBL and DBL RNAs nearly doubled its activity. Delivered either from plasmids or as an all-RNA formulation combining recombinase mRNA with chemically modified synthetic guides, ISCro4 mediates chromosomal deletions and inversions, as well as insertion of multi-kilobase donor DNA at endogenous sites at efficiencies above 6 %, including corrective editing at disease-relevant loci (Pelea et al., 2026). This work, a collaboration with the groups of Profs. Gerald Schwank and Jacob Corn, was published alongside an independent study in which protein and guide RNA engineering pushed insertion efficiencies towards 20 % and demonstrated megabase-scale chromosomal rearrangements (Perry et al., 2025). The system has since been shown to function across kingdoms, with engineered variants supporting scarless large-fragment editing in plant cells.

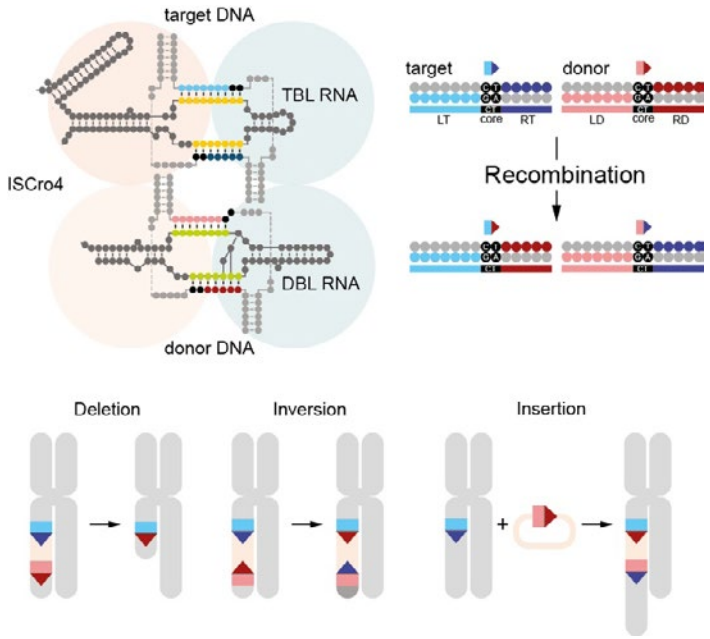

Figure 5 | RNA-programmed DNA recombination by bridge recombinase ISCro4. *ISCro4 is directed by a bridge RNA with two corresponding loops: a target-binding loop (TBL) and a donor-binding loop (DBL) that guide recombination between 14-nt target and donor DNA sites. This mechanism enables the introduction of genomic deletions, inversions, and targeted insertions.*

The major advantage of RNA-guided bridge recombinases lies in the combination of precise, scarless editing without generating double-strand breaks and independently of HDR, all achieved by a single compact protein and a short RNA that can be readily delivered. Their principal drawback is specificity, intrinsically limited by the 14-nucleotide length of the target and donor sites. In the first instance, this can be addressed by restricting the edits to unique sites in the genome. Of all possible core-containing 14-mer sequences, approximately 1.5 million occur exactly once in the human genome, and 94 % of protein-coding genes, as well as around 90 % of pathogenic variants listed in ClinVar, contain at least one unique site. A comparable number of sequences are

completely absent from the human genome and can therefore serve as genome-orthogonal donor sites. Beyond this, continued molecular engineering of the recombinases and their guide RNA scaffolds, along with high-throughput guide RNA profiling and computational prediction, will be needed to deliver the precision required for therapeutic applications.

Outlook

The past decade has seen genome editing transition from an emerging scientific question to a transformative technological solution. First-generation CRISPR technologies, based on site-specific double-strand breaks and endogenous repair, have been complemented by second-generation technologies such as base editing and prime editing that modify target DNA directly without DSB generation. Emerging third-generation technologies address the two major unmet needs in the field, namely precise insertion of large, gene-sized payloads and reversible control of gene expression without altering the genome at all. Their advancement is enabled by two complementary approaches, metagenome mining to discover novel molecular systems and, in parallel, molecular engineering of existing ones, increasingly supported by machine learning. The current trajectory suggests that these technologies will continue to be refined, with gradual improvements in specificity, efficiency and delivery. Nucleic acid-guided systems are likely to remain central to genome editing, owing to their simple programmability and adaptability as compared with purely protein-based technologies. However, the mode of their application may evolve, with potential shifts towards more transient editing approaches, and towards transient delivery, to minimise genomic disruption and immune responses.

It is worth emphasising how much of this progress has come from discovery rather than design. Cas9, Cas12a, CRISPR-associated transposases and bridge recombinases were all identified as components of naturally occurring prokaryotic defence systems or mobile genetic elements. This is one of the reasons why my laboratory has continued to explore other prokaryotic genome defence systems, aiming to provide molecular insights that inform our understanding of their biological functions but that could also be useful for technological adaptation. In type

III CRISPR-Cas systems we found that target RNA recognition triggers the synthesis of cyclic oligoadenylate second messengers that activate downstream effector proteins, a signalling logic strikingly reminiscent of oligoadenylate signalling in mammalian innate immunity (Niewoehner et al., 2017; Garcia-Doval et al., 2020; Jungfer et al., 2024; Jungfer et al., 2025). Beyond CRISPR, we have revealed the molecular mechanism of the plasmid-eliminating DdmDE system of pandemic *Vibrio cholerae*, in which the prokaryotic Argonaute protein DdmE recruits the helicase-nuclease DdmD onto invading DNA (Loeff et al., 2024). We have collaborated with the laboratory of former group member Daan Swarts on the SPARTA system (Finocchio et al., 2024). We also defined the mechanism of the anti-phage nuclease Shedu, which recognises free DNA ends and nicks at a fixed distance from them (Loeff et al., 2025). None of these studies were taken up with a technology in mind, yet the cyclic-nucleotide and Argonaute systems have already begun to find diagnostic and biotechnological uses. We continue to investigate the hitherto unexplored diversity of prokaryotic immune systems and mobile genetic elements. Understanding how these systems work at the molecular level will be critical for their technological exploitation.

With first-generation CRISPR genome editing technologies already approved for ex vivo clinical use and in vivo therapies demonstrated in the clinic, the bottleneck constraining future genome-directed therapeutics will no longer necessarily be the lack of safe, efficient or precise genome editors. The primary challenges will lie in delivery, especially to organs other than the blood and liver and to certain cell types ex vivo. Advances in in vivo delivery, such as those seen in mRNA vaccine development, are likely to catalyse the application of these technologies significantly, and even in the tissues that are currently editable, more basic research will be needed to identify safe editing targets. The range of treatable diseases will thus expand with the development of new delivery vectors and with the continued characterisation of disease-causing genetic variants and their corrective strategies.

Ethical and societal implications, particularly concerning human germline modification, will remain at the forefront of discussions about genome editing. As research studies in human embryos have shown,

current technologies are not sufficiently safe or efficacious for germline editing for reproductive purposes, and its therapeutic utility is in any case limited, likely to benefit only a small number of individuals. Nevertheless, the urgency of international consensus on the governance and responsible stewardship of these technologies cannot be overstated, in light of their rapid development, continuous improvement and potentially widespread adoption. Despite the challenges that remain, the future of genome editing is bright. It has the potential not only to drive research breakthroughs and transform human medicine, but also to improve agriculture and address ecological challenges, thereby laying the foundation for a healthier and more sustainable future.

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THE CLOËTTA PRIZE 2026
IS AWARDED TO

PROFESSOR

MIRJAM CHRIST-CRAIN

BORN IN 1974 IN BASEL, SWITZERLAND,

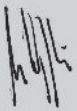
PROFESSOR OF ENDOCRINOLOGY AND CLINICAL RESEARCH AT THE UNIVERSITY OF BASEL AND HEAD OF THE CLINIC FOR ENDOCRINOLOGY, DIABETES AND METABOLISM AT UNIVERSITY HOSPITAL BASEL,

FOR HER PIONEERING PATIENT-ORIENTED RESEARCH ON VASOPRESSIN-DEPENDENT FLUID DISORDERS, TRANSFORMING THEIR DIAGNOSIS THROUGH COPEPTIN-BASED TESTING AND DEVELOPING INNOVATIVE THERAPEUTIC APPROACHES FOR SIAD, HYPONATREMIA AND ARGININE VASOPRESSIN DEFICIENCY (AVP-D).

BASEL, 30TH OCTOBER, 2026

IN THE NAME OF THE FOUNDATION BOARD:

THE PRESIDENT **THE VICE PRESIDENT**



MIRJAM CHRIST-CRAIN

CURRICULUM VITAE

Mirjam Christ-Crain

Business Address

University Hospital Basel
Div. of Endocrinology, Diabetes and Metabolism
Petersgraben 4, CH-4031 Basel, Switzerland
Email: mirjam.christ-crain@unibas.ch

Personalia

Date of birth: September 14th, 1974
Citizenship: Basel-Stadt, Switzerland
Marital Status: Married, 3 children
Address: Passwangstrasse 4, 4059 Basel
ORCID: https://orcid.org/0000-0002-6336-0965

Research Highlights

- 1st-highest ranked expert in Diabetes insipidus and 6th-highest ranked expert in hyponatremia worldwide based on articles published since 2011 (https://expertscape.com/ex/diabetes+insipidus); https://expertscape.com/ex/hyponatremia
- H-Index (google scholar 18.9.2026): 98
- ORCID: https://orcid.org/0000-0002-6336-0965

1. Education

2008	PhD thesis, University of London
2007	Habilitation University of Basel
2006	Acceptance of FMH (specialty exam) Endocrinology
2000	MD thesis
Nov. 1999	Swiss Federal Medical Examination
1996 – 1997	Visiting semesters in Vienna, Austria

1993 – 1999	Medical school, University of Basel, Switzerland
1985 – 1993	High school and College Basel-Stadt, Matura Typus A,

2. Current position

2025 – present	Head of Clinic, Div. of Endocrinology, Diabetes and Metabolism, University Hospital Basel, Switzerland, full professor of Endocrinology, University of Basel

3. Previous positions

2013 – 2025	Deputy Head of Clinic, Div. of Endocrinology, Diabetes and Metabolism, University Hospital Basel, Switzerland
2014 – 2023	Head of Department of Clinical Research, University of Basel
2009 – 2014	SNF-Professorship
2009 – 2013	Consultant, Div of Endocrinology, University Hospital Basel, Switzerland
2007 – 2009	Senior physician, Div of Endocrinology, University Hospital Basel, Switzerland
2005 – 2007	Postdoctoral Research fellow, PhD student, Lab of molecular Endocrinology, St.Bartholomews Hospital, London
2004 – 2005	Resident, Div. of Endocrinology, Diabetes and Clinical Nutrition, Dept. of Internal Medicine, University Hospitals, Basel, Switzerland
2003 – 2004	Resident Emergency Division, University Hospital Basel, Switzerland
2001 – 2003	Resident, Clinic of Internal Medicine, University Hospital, Basel, Switzerland
2000 – 2001	Resident, Internal Medicine, Gemeindespital Riehen

4. Teaching experience and teaching awards

- Examiner of FMH exams in endocrinology/diabetology, (since 2007)
- Regular group lecturing for medical students 3rd, 4th, and 6th year (since 2004)
- Lecturer for medical students in endocrinology 3rd, 4th and 6th year (since 2002)
- Best teaching awards (University of Basel, Medical faculty) in 2016, 2017, 2019, 2020, 2021, 2022, 2024, 2025.
- Nominated for best teaching awards of University of Basel (all faculties) in 2021, 2022, 2024.

5. Editorial and Journal Review activities

2021	Associate Editor of the *European Journal of Endocrinology*
2020	Member of the editorial Board of the *Journal of Endocrinology and Metabolism*
2020	Guest Editor of *Best practice in Endocrinology* Ad hoc reviewer of several Journal including *the Lancet, Clinical Endocrinology, Journal of Internal Medicine, Science translational medicine*

6. Grant review activities

Since 2020	Member of the research council of the Swiss National Science Foundation
2024	Member of the Grant evaluation of the Italian Ministry of Research
2016 – 2022	Member of the scientific Council (“wissenschaftlicher Beirat”) of the ProPatient Foundation Basel

7. Membership in Panels, Scientific and Professional Organizations, Expert Activities

- President elect of the European Society of Endocrinology, 2025–2027
- Chair of the Education Committee of the European Society of Endocrinology, 2020–2024
- Member of the Council of the Swiss National Science Foundation, 2020–
- Schweizerischer Wissenschafts- & Innovationsrat (SWIR) 2016–2019
- Schweizerische Akademie der Med. Wissenschaften (SAMW) single membership 2015–
- Member of the PhD Commission University of Basel (2014 – 2020)
- Member of the council (Vorstand) of the Swiss Society of Endocrinology and Diabetes (SGED) 2009 – 2019
- International guidelines group "Corticosteroids in critical illness" (Head: D.Annane, S. Pastores)
- European Endocrine Society 2006 –
- British Endocrine Society 2005 –
- Endocrine Society 2003 –
- Swiss Society of Endocrinology & Diabetology (SGED) 2002 –
- Swiss Association for Medicine (FMH) 2000–

8. Conference Organization

- Member of the POC of ENEA (European Neuroendocrine Association) conference September 2024, Sevilla.
- Member of the POC International Society of Endocrinology (ISE) Buenos Aires, October 2020
- Main organizer of the Swiss Annual Endocrinology Congress in Bern, 2014–2019

9. Major Awards and Honors

- Outstanding clinical Investigator Award of the American Endocrine Society 2026
- Cloetta Prize 2026
- Otto Naegeli Prize for Medical Research 2024
- Taft Lecturer at the Endocrine Society of Australia's Annual Scientific Meeting, November 2021
- Trust visiting professor, British Endocrine Society, November 2020
- Award of the European Society of Endocrinology for young investigators (below 45 years of age) 2019, Annual European Endocrine Conference in Lyon, May 2019
- Bebbi Award 2012 of the city of Basel
- National Latsis Award 2009
- SULM (Swiss Union for Laboratory Medicine) presidential Award 2008
- Amerbach Award 2007 for best habilitation of medical faculty (University of Basel)
- Servier Award Clinical Endocrinology 2007
- Swiss Society of Internal Medicine (SGIM) Award 2007
- GlaxoSmithKline Pneumo-Award 2006
- Prix de la Fondation Endocrinology, Switzerland, 2005
- Servier Award Clinical Endocrinology 2005
- Viollier Award 2005
- Pfizer Award 2005 for best clinical research paper in infectious diseases
- Award of the Swiss Diabetes Foundation 2004
- Matura-Preis (Bachelor's Award) Humanistisches Gymnasium Basel 1993

10. Major Grants

2024	IICT Grant SNSF (OxyTution Trial)
2022	SNSF Project grant (Empower trial)
2020	IICT Grant SNSF (HIT trial)
2018 – 2022	SNSF Project grant (CARGOx trial)
2015 – 2019	SNSF Project grant (CODDI trial)
2009 – 2015	SNSF Professorship

11. Mentoring and supervision of young researchers

Number of supervised master students:	25
Number of supervised MD theses:	26, 14 of those chose Endocrinology as specialty

Supervised MD PhD students:	*Current position*
Clara Sailer (2016 – 2020)	Registrar Endocrinology, Brigham and the Women's hospital, Boston, USA
Milica Popovic (2017 – 2021)	Senior Manager Medical Affairs, Scientific Communication GmbH
Laura Potasso (2018 – 2022)	Postdoctoral researcher, Endocrinology, University Hospital Basel, Switzerland
Cihan Atila (2020 – 2023)	Postdoctoral researcher, Endocrinology, University Hospital Basel, Switzerland
Sophie Monnerat (2020 – 2023)	Postdoctoral researcher, University hospital Basel, Switzerland
Sven Lustenberger (2023 – 2026)	Registrar, Cantonal hospital of Biel, Switzerland
Julia Beck (2021 – ongoing)	
Andi Nikaj (2024 – ongoing)	
Michelle Müller (2024 – ongoing)	
Talitha Hildebranth (2026 – ongoing)	
Cyril Vogel (2026 – ongoing)	

12. Invited lectures at international meetings

Approx. 20 invitations per year

13. Publication List

H-Index (google scholar 18.9.2026): 98
ORCID: https://orcid.org/0000-0002-6336-0965

10 most important publications Mirjam Christ-Crain

10. Refardt J, Potasso L, Pelouto A, Trappe M, Gregoriano C, Koster M, Vodanociv D, Norello D, Ravioli S, Cukoski S, Boesing M, Ryser B, Sambula L, Rapsch N, Monnerat S, Beck J, Werlen L, Santos de Jesus J, Bontognali M, Schuetz P, Zandbergen A, Peri A, Kastelan D, Lindner G, Leuppi J, Bilz S, Mueller B, Burst V, Hoorn E, **and Christ-Crain M.** Targeted hyponatremia correction in hospitalized patients. ***NEJM Evid. 2026 Mar;5(3):EVIDoa2500086.*** PMID: 41733398 DOI: 10.1056/EVIDoa2500086.

9. Atila C, Chifu I, Drummond B, Vogt D, Nahum U, Fassnacht M, Winzeler B, Refardt J **and Christ-Crain M**. A novel diagnostic score for diagnosing arginine vasopressin deficiency (central diabetes insipidus) or primary polydipsia with basal laboratory and clinical parameters: results from two international multicentre prospective diagnostic studies. ***Lancet Diabetes Endocrinol.*** **2025** Jun 13 (6): 505–515. DOI: 10.1016/ S2213-8587(25)00053-1

8. Refardt J, A Cihan , Chifu I, Ferrante E, Erlic Z, Drummond JB, Indirli R, Drexhage, Sailer CO, WidmerA, Felder S,Powlson AS, Hutter N, Vogt D, Gurnell M, Soares Rocha B, Hofland J, Beuschlein F, Fassnacht M, Winzeler B, **and Christ-Crain M.** Arginine vs. Hypertonic Saline-Stimulated Copeptin to Diagnose AVP Deficiency. ***N Engl J Med.*** **2023** Nov 16;389(20):1877–1887. DOI: 10.1056/NEJMoa2306263.

7. Atila C, Holze F, Murugesu R, Rommers N, Hutter N, Varghese N, Sailer CO, Eckert A, Heinrichs M, Liechti ME, **and Christ-Crain M.** Oxytocin in response to MDMA provocation test in patients with arginine vasopressin deficiency (central diabetes insipidus): a single-centre, case-control study with nested, randomised, double-blind, placebo-controlled crossover trial. ***Lancet Diabetes Endocrinol.*** **2023** May 12:S2213-8587(23)00120-1. DOI: 10.1016/S2213-8587(23)00120-1.

6. Refardt J, Imber C, Nobbenhuis R, Sailer C, Haslbauer A, Monnerat S, Bathelt C, Vogt D, Berres M, Winzeler B, Bridenbough S, **and Christ-Crain M.** Treatment Effect of the SGLT2-inhibitor Empagliflozin on chronic SIAD –results of a double-blind, randomized, crossover, placebo-controlled trial. ***J Am Soc Nephrol.*** **2022** Nov 17:ASN.2022050623. DOI: 10.1681/ ASN. 2022050623

5. Atila C, Loughrey PM, Garrahy A, Winzeler B, Refardt J, Gildroy P, Hamza M, Pal A, Verbalis JG, Thompson CJ, Hemkens LG, Hunter SJ, Sherlock M, Levy MJ, Karavitaki N, Newell-Price J, Wass JA, **and Christ-Crain M.** Central diabetes insipidus from a patients' perspective: management, psychological co-morbidities, and re-naming of the condition – results from an international web-based survey. ***Lancet Diabetes Endocrinol.*** **2022** Oct;10(10):700–709. DOI: 10.1016/S2213-8587(22)00219-4. Epub 2022 Aug 22.

4. Winzeler B, Sailer C, Coynel D, Zanchi D, Vogt D, Urwyler S, Refardt J, **and Christ-Crain M.** A randomized controlled trial of the GLP-1 receptor agonist dulaglutide in primary polydipsia. ***J Clin Invest*** **2021** Oct 15;131(20) e151800. DOI: 10.1172/JCI151800.

3. Winzeler B, Nicole Cesana-Nigro N, Refardt J, Vogt D, Imber C, Morin M, Popovic M, Steinmetz M, Sailer C, Szinnai G, Chifu I, Fassnacht M, **and Christ-Crain M.** Arginine-Stimulated Copeptin Measurements – A new Test for Diabetes Insipidus: A prospective diagnostic Study. ***Lancet. 2019*** Jul 11. pii: S0140-6736(19)31255-3. DOI: 10.1016/S0140-6736(19)31255-3.

2. **Christ-Crain M,** Bichet DG, Fenske WK, Goldman MB, Rittig S, Verbalis JG, Verkman AS. Diabetes insipidus. ***Nat Rev Dis Primers.*** **2019** Aug 8;5(1):54. DOI: 10.1038/s41572-019-0103-2.

1. Fenske W*, Refardt J*, Chifu I, Schnyder I, Winzeler B, Drummond J, Ribeiro-Oliveira Jr A, Drescher T, Bilz S, Vogt DR, Kroiss M, Christ E, Henzen C, Fischli S, Tönjes A, Mueller B, Schopohl J, Flitsch J, Brabant G, Fassnacht M, **and Christ-Crain M.** A Copeptin-based Approach in the Differential Diagnosis of Diabetes Insipidus. ***N Engl J Med.*** **2018** Aug 2;379(5):428–439. DOI: 10.1056/NEJMoa1803760 PMID: 30067922.

FROM VASOPRESSIN DEFICIENCY TO EXCESS: NEW DIAGNOSTIC AND THERAPEUTIC PATHWAYS IN DISORDERS OF WATER BALANCE

Mirjam Christ-Crain[1,2]
[1]*Department of Endocrinology, Diabetology and Metabolism, University Hospital Basel, Basel, Switzerland*
[2]*Department of Clinical Research, University of Basel, University Hospital Basel, Basel, Switzerland*

1. Introduction

Water is the major constituent of the human body, and extracellular water concentration is regulated within remarkably narrow limits. Even modest deviations can have important clinical consequences. A deficit of water relative to body solute results in hypernatraemia and cellular dehydration, whereas an excess of water causes hyponatraemia and cellular swelling. The brain is particularly vulnerable to both disturbances. Precise regulation of water balance is therefore a fundamental requirement of human physiology.

At the centre of this regulatory system is arginine vasopressin (AVP), a nine-amino-acid peptide hormone synthesized in magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus. AVP is transported along axons to the posterior pituitary and released into the circulation primarily in response to increases in plasma osmolality and, at higher stimulus intensities, reductions in effective circulating volume. In the kidney, AVP binds to vasopressin V2 receptors on collecting-duct cells and promotes insertion of aquaporin-2 water channels into the apical membrane, thereby increasing renal water reabsorption and limiting urinary water loss.

Disorders of the AVP system occur at opposite ends of this physiological spectrum. Insufficient AVP secretion impairs renal water conservation, resulting in hypotonic polyuria and compensatory polydipsia. This disorder, historically termed central diabetes insipidus, is now designated

arginine vasopressin deficiency (AVP deficiency). Conversely, persistent antidiuretic activity despite hypotonicity impairs free-water excretion and may result in hyponatraemia, most characteristically in the syndrome of inappropriate antidiuresis (SIAD).

Despite their apparently straightforward physiology, these disorders have long posed substantial diagnostic and therapeutic challenges. At the outset of this research programme, differentiation of AVP deficiency from primary polydipsia still relied largely on the indirect water deprivation test, a burdensome procedure whose diagnostic criteria had not undergone rigorous prospective validation. Direct measurement of AVP was a conceptually attractive alternative but remained technically unreliable because of the peptide's instability in plasma and the limitations of available assays. Similarly, although hyponatraemia is the most common electrolyte disorder in clinical practice, treatment recommendations were supported by limited interventional evidence, and it remained uncertain whether correction of chronic hyponatraemia improves clinically meaningful outcomes.

These unresolved clinical questions have shaped our research programme over almost two decades. The overarching objective has been to define the information required for accurate diagnosis, identify physiological mechanisms that can provide this information, and determine whether improved pathophysiological understanding can translate into safer and more effective treatment.

This approach initially focused on copeptin, a stable surrogate marker of AVP secretion, and subsequently enabled a fundamental reassessment of the diagnostic pathway for the polyuria–polydipsia syndrome, replacing indirect assessment of renal concentrating capacity with direct functional assessment of the AVP system. Clinical studies then identified important unresolved issues relating to treatment safety, quality of life and disease nomenclature. Persistent psychological and socio-emotional symptoms in patients with AVP deficiency further led to the hypothesis that hypothalamic-pituitary injury may also result in clinically relevant oxytocin deficiency.

At the opposite end of the water-balance spectrum, our work on hyponatraemia and SIAD has followed the same physiology-based approach. We investigated whether sodium-glucose cotransporter 2 (SGLT2) inhibitors, developed for other indications, could promote electrolyte-free water excretion and thereby provide a novel therapeutic strategy for SIAD. We also examined whether increased dietary protein intake could enhance water excretion through increased endogenous urea generation. Finally, the Hyponatremia Intervention Trial (HIT) addressed the broader clinical question of whether more intensive correction of chronic hyponatraemia reduces death or rehospitalisation.

Collectively, these studies define a continuum of disordered water balance rather than a series of unrelated conditions: insufficient AVP activity at one end and excessive antidiuresis at the other. Investigation of this continuum has generated new biomarkers, diagnostic strategies and therapeutic approaches, while also identifying important areas of persistent uncertainty.

Figure 1 summarises the synthesis, secretion and principal target pathways of arginine vasopressin and oxytocin.

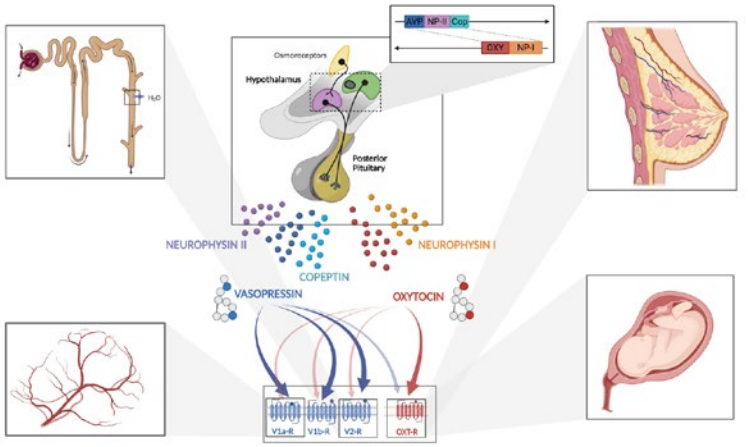


Figure 1. *The hypothalamic–posterior pituitary axis. AVP is generated from pre-pro-vasopressin together with neurophysin II and copeptin, whereas oxytocin is generated with neurophysin*

1. Magnocellular hypothalamic neurons project to the posterior pituitary and to central targets; AVP acts through V1A, V1B and V2 receptors, whereas oxytocin signals through OXTR. Reproduced from: Atila C, Refardt J, Christ-Crain M. J Clin Endocrinol Metab. 2026;111:922–937.

2. Making vasopressin measurable: the emergence of copeptin

Accurate assessment of a hormonal disorder requires reliable measurement of the relevant hormone. For AVP, this fundamental requirement has historically represented a major analytical challenge.

AVP has a short half-life, a substantial proportion of circulating peptide binds to platelets, pre-analytical handling is demanding, and conventional assays are technically challenging. Consequently, direct AVP measurement, although physiologically intuitive, did not become a sufficiently robust routine tool for the differential diagnosis of disorders of water balance.

Measurement of copeptin provided a solution to this analytical problem[1]. Copeptin is the C-terminal component of the AVP precursor peptide, pre-pro-vasopressin. AVP, neurophysin II and copeptin are generated from the same precursor and stored together in neurosecretory vesicles. They are released in parallel, but in contrast to AVP, copeptin is highly stable in plasma and serum and can be measured reproducibly using immunoassays.

The clinical utility of copeptin depends on the extent to which it reflects physiological AVP secretion. Early studies demonstrated appropriate changes in circulating copeptin concentrations during water deprivation and water loading[2]. Direct comparisons of copeptin and AVP across hypo-osmolar, iso-osmolar and hyperosmolar conditions subsequently confirmed their close relationship[3], and studies of release and decay kinetics under controlled osmotic conditions further established copeptin as a robust surrogate marker of the vasopressin system[4].

Importantly, copeptin is not exclusively a marker of osmolality. Like AVP, its secretion is strongly influenced by non-osmotic stimuli, including haemodynamic stress, nausea, and severe somatic or psychological

stress. Some of our early studies therefore also examined copeptin as a stress biomarker in acute illness. These properties are relevant to interpretation: copeptin concentrations must always be considered within the corresponding physiological and clinical context.

The greatest diagnostic utility of copeptin emerged in the polyuria–polydipsia syndrome. Patients present with excessive production of dilute urine and compensatory fluid intake. After exclusion of common secondary causes, including uncontrolled diabetes mellitus, hypercalcaemia and hypokalaemia, the principal diagnostic challenge is to distinguish AVP deficiency, AVP resistance and primary polydipsia.

In AVP deficiency, hypothalamic-pituitary AVP secretion is insufficient. In AVP resistance, AVP secretion is preserved or increased, but renal responsiveness is impaired. Primary polydipsia, by contrast, results from excessive fluid intake, which suppresses AVP secretion and, when sustained, reduces the renal medullary concentration gradient. Despite their distinct pathophysiology, all three conditions may present with closely overlapping clinical features.

Diagnostic misclassification has important clinical consequences. Administration of desmopressin to a patient with primary polydipsia may cause excessive water retention and potentially severe hyponatraemia, whereas failure to provide desmopressin to a patient with marked AVP deficiency may result in severe polyuria, dehydration and hypernatraemia. Diagnostic accuracy is therefore directly relevant to patient safety.

Our early prospective studies demonstrated that a markedly elevated basal copeptin concentration can identify AVP resistance without water deprivation. A basal concentration above 21.4 pmol/L identified all patients with AVP resistance in these cohorts[5,6], providing an important first simplification of the diagnostic pathway.

The more challenging distinction is between AVP deficiency and primary polydipsia, because basal copeptin concentrations overlap substantially between these conditions. This overlap is physiologically plausible:

chronic excessive fluid intake suppresses the vasopressin system in primary polydipsia, whereas partial AVP deficiency retains some secretory capacity. Basal measurements alone may therefore be insufficient for diagnostic discrimination.

Accordingly, reliable differentiation requires controlled and physiologically appropriate stimulation of the AVP system.

3. Replacing the water deprivation test

Limitations of the indirect water deprivation test

For decades, the indirect water deprivation test was considered the standard diagnostic procedure for the polyuria–polydipsia syndrome. In conventional protocols, patients undergo prolonged water deprivation, often for approximately 17 hours, with serial measurements of body weight, plasma sodium and urine osmolality. The underlying principle is that dehydration should stimulate endogenous AVP secretion and urine concentration in healthy individuals and patients with primary polydipsia, but not in patients with AVP deficiency. Subsequent administration of desmopressin is used to distinguish AVP deficiency from AVP resistance.

Several physiological factors, however, limit the discriminatory capacity of this approach. Chronic excessive fluid intake reduces the renal medullary concentration gradient and thereby impairs urinary concentrating capacity even when AVP secretion is intact. Conversely, renal compensatory mechanisms may permit greater-than-expected urine concentration in some patients with AVP deficiency. Consequently, partial AVP deficiency and primary polydipsia show substantial diagnostic overlap.

Moreover, the diagnostic cut-offs used for decades were derived from very small patient populations and had not been adequately validated in prospective studies.

The overall diagnostic accuracy of the indirect water deprivation test for differentiating AVP deficiency from primary polydipsia is therefore only approximately 70–77 %[5,7], which is insufficient for a test that may determine lifelong treatment with desmopressin.

Hypertonic saline-stimulated copeptin
Because increased plasma osmolality is the principal physiological stimulus for AVP secretion, we hypothesised that a defined osmotic challenge could provide a more reproducible stimulus than prolonged dehydration and allow direct assessment of the hormonal response by measuring copeptin.

This rationale led to the development of hypertonic saline-stimulated copeptin testing.

In this protocol, 3 % saline is administered under close supervision, with frequent rapid measurements of plasma sodium. Once the target sodium concentration is reached, copeptin is measured and plasma sodium is promptly re-lowered by oral and intravenous rehydration. The diagnostic principle is that patients with primary polydipsia retain an intact AVP secretory response and therefore show an appropriate increase in copeptin, whereas patients with AVP deficiency fail to mount an adequate response.

In 2018, we reported a prospective multicentre study in the New England Journal of Medicine directly comparing hypertonic saline-stimulated copeptin with the classical water deprivation test[7]. Using a stimulated copeptin cut-off of 4.9 pmol/L, hypertonic saline-stimulated copeptin distinguished AVP deficiency from primary polydipsia with an overall diagnostic accuracy of 97 %, compared with 77 % for the indirect water deprivation test.

A similarly substantial improvement was observed in the particularly challenging distinction between partial AVP deficiency and primary polydipsia, the subgroup in which the traditional test performs least reliably.

These findings shifted the diagnostic strategy from indirect assessment of the renal response to prolonged, incompletely standardised dehydration towards direct functional interrogation of the AVP system. Hypertonic saline-stimulated copeptin testing was also considerably shorter than prolonged water deprivation and, despite transient symptoms related to hypertonic saline, was preferred by most patients.

On the basis of these data, hypertonic saline-stimulated copeptin became the reference standard for differentiating AVP deficiency from primary polydipsia.

However, the gain in diagnostic accuracy is accompanied by important procedural requirements. Hypertonic saline testing requires experienced supervision, frequent sodium measurements to avoid excessive hypernatraemia, and prompt rehydration after the target sodium concentration has been reached. The test is therefore unsuitable for selected patients, including those with heart failure or epilepsy.

Arginine stimulation as a simpler alternative
To develop a simpler stimulation test that does not require induction of hypernatraemia, we investigated non-osmotic stimulation of copeptin with arginine.

Arginine is an established stimulus of anterior pituitary hormone secretion. In a prospective study published in The Lancet in 2019, arginine infusion also induced a clear rise in copeptin in healthy individuals and in patients with primary polydipsia[8]. A copeptin concentration of 3.8 pmol/L measured 60 minutes after initiation of arginine infusion yielded an initial diagnostic accuracy of 93 %.

The arginine stimulation test can be completed within one hour, does not require continuous sodium monitoring, and is generally well tolerated.

Because diagnostic cut-offs require prospective validation, we subsequently conducted a multicentre head-to-head study in which patients underwent hypertonic saline and arginine stimulation in randomised order[9]. Published in the New England Journal of Medicine in 2023, the study confirmed the high diagnostic performance of hypertonic saline-stimulated copeptin, with an accuracy of 95.6 %, sensitivity of 91.3 % and specificity of 98.9 %. By contrast, the previously proposed single arginine cut-off of 3.8 pmol/L achieved a diagnostic accuracy of only 74.4 %.

Arginine nevertheless remains clinically useful when interpreted using high-specificity lower and upper decision thresholds. Stimulated copeptin

concentrations of ≤3.0 pmol/L and >5.2 pmol/L identify a substantial proportion of patients with high specificity. In addition, 72 % of participants preferred arginine to hypertonic saline because adverse effects were less pronounced. These findings support a tiered diagnostic strategy: hypertonic saline provides the highest diagnostic certainty when appropriate infrastructure is available and no contraindication is present, whereas arginine offers a simpler alternative in selected patients.

Continuing to simplify diagnosis

Subsequent work has pursued two complementary strategies to further simplify diagnosis.

First, we evaluated alternative stimuli for copeptin secretion. Glucagon increased copeptin in healthy controls and patients with primary polydipsia, but not in patients with AVP deficiency, providing proof of concept for another non-osmotic stimulation test[10]. More recently, oral urea was investigated as an osmotic stimulus; in a proof-of-concept study, a standardised oral urea load elicited a measurable copeptin response in primary polydipsia, whereas concentrations remained low in AVP deficiency[11]. We have also evaluated mannitol as an osmotic stimulus that does not require induction or monitoring of hypernatraemia. Mannitol was well tolerated and produced a robust osmotic stimulus, but external validation in a multicentre study is required before clinical implementation.

Second, we examined whether dynamic testing is necessary in all patients. By combining data from two large international prospective cohorts, we developed a diagnostic score integrating basal laboratory measurements with clinical characteristics, including symptom onset, nocturia and relevant pituitary history[12] (***Figure 2***). The objective is not to replace high-quality dynamic testing when diagnostic uncertainty persists, but to identify patients in whom sufficiently high or low pre-test probability may permit a simplified diagnostic pathway.

Figure 2 summarises the diagnostic algorithm for the polyuria–polydipsia syndrome developed from these studies.

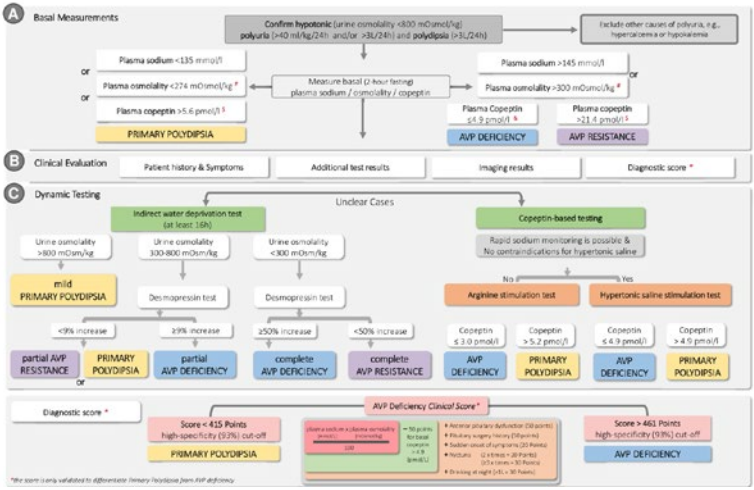


Figure 2. *Diagnostic algorithm for AVP deficiency. The algorithm integrates basal laboratory measurements, clinical features and imaging findings and reserves dynamic testing for diagnostically uncertain cases. Hypertonic saline-stimulated copeptin provides the highest diagnostic accuracy, whereas arginine stimulation offers a simpler alternative using high-specificity lower and upper decision thresholds. Reproduced from: Atila C, Refardt J, Christ-Crain M. J Clin Endocrinol Metab. 2026;111:922–937.*

4. AVP deficiency beyond diagnosis: treatment, safety and the patient's perspective

Advances in diagnostic accuracy are clinically meaningful only if they translate into safer and more effective patient management.

AVP deficiency is treated with desmopressin, a synthetic AVP analogue with strong selectivity for the V2 receptor and a substantially longer duration of action than endogenous AVP[13]. Appropriate desmopressin replacement rapidly reduces polyuria, polydipsia and nocturia and can substantially restore sleep and day-to-day functioning.

However, pharmacological replacement also bypasses an important physiological safety mechanism.

In healthy individuals, water intake lowers plasma osmolality and suppresses endogenous AVP secretion, thereby permitting excretion of dilute urine and preventing excessive water retention. Desmopressin is not subject to this endogenous osmoregulatory feedback. Consequently, fluid intake in excess of physiological requirements during ongoing desmopressin action may lead to water retention, a fall in plasma sodium and dilutional hyponatraemia.

Although this adverse effect had long been recognised, its real-world frequency and patients' understanding of preventive strategies had not been adequately characterised.

To characterise the real-world burden and management of AVP deficiency, we conducted a large international web-based survey involving 1,034 patients[14].

Hyponatraemia was frequently reported. Approximately 22 % of participants reported outpatient hyponatraemia, and approximately one quarter reported an episode severe enough to require hospitalisation. Other cohorts have similarly identified biochemical hyponatraemia in approximately one third of patients receiving desmopressin.

The same dataset identified a simple preventive strategy: periodic 'desmopressin escape'. Rather than administering desmopressin rigidly at fixed intervals, patients may periodically delay or omit a dose until breakthrough polyuria occurs. This transient aquaretic period permits excretion of retained free water before the next dose is administered. Patients who regularly used this strategy reported fewer episodes of hyponatraemia than those who were unaware of it or who were aware of the strategy but did not use it.

The survey also identified a separate patient-safety issue during hospitalisation. Patients reported confusion between diabetes insipidus, as the disorder was then termed, and diabetes mellitus, sometimes resulting in

omission of desmopressin and adverse clinical consequences. In patients with AVP deficiency who are fasting, unable to access water, acutely ill or have impaired consciousness, interruption of desmopressin can rapidly cause severe dehydration and hypernatraemia.

These observations indicated that the traditional disease terminology itself represented a clinically relevant patient-safety concern.

Figure 3 shows the frequency of hyponatraemia during desmopressin treatment and illustrates the principle of the desmopressin escape strategy.

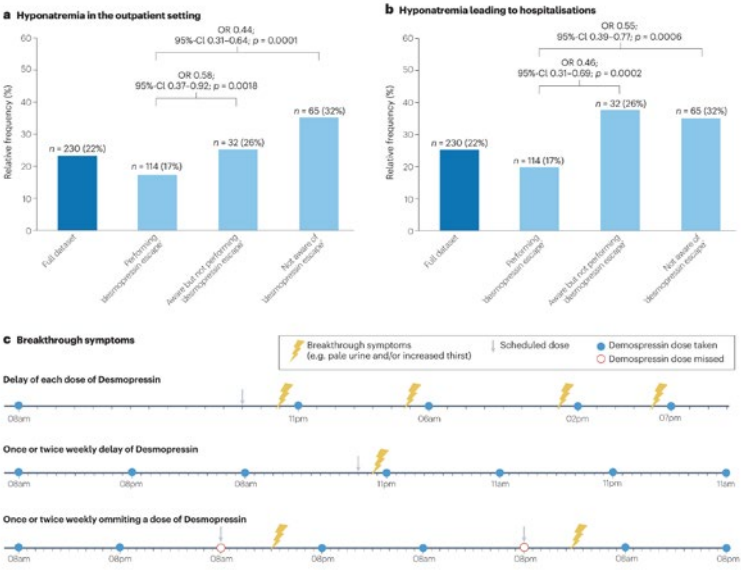


Figure 3. *Hyponatraemia during desmopressin treatment and the 'desmopressin escape' strategy. Panels a and b show the frequency of outpatient hyponatraemia and hyponatraemia requiring hospitalisation according to awareness and use of desmopressin escape. Panel c illustrates strategies in which desmopressin doses are delayed or periodically omitted until breakthrough polyuria occurs. Reproduced from: Atila C, Refardt J, Christ-Crain M. Nat Rev Endocrinol. 2024;20:487–500.*

Rationale for renaming the disease
The term diabetes insipidus has been used for centuries. Historically, 'diabetes' referred to the passage of large volumes of urine, whereas the descriptors 'mellitus' and 'insipidus' distinguished sweet-tasting from tasteless urine. From a contemporary pathophysiological perspective, however, diabetes mellitus and diabetes insipidus are entirely distinct disorders.

Our international survey quantified the clinical consequences of this shared terminology[14]. Eighty per cent of respondents reported that healthcare professionals had confused their condition with diabetes mellitus on at least one occasion. Most participants considered general knowledge of the disorder among healthcare professionals to be insufficient, and 85 % favoured a name that no longer contained the term 'diabetes'.

Importantly, these data demonstrated that the rationale for changing nomenclature was not solely pathophysiological precision, but also the prevention of concrete patient-safety events identified by affected individuals.

An international working group that I led, involving major endocrine societies worldwide, subsequently recommended replacing central diabetes insipidus with arginine vasopressin deficiency and nephrogenic diabetes insipidus with arginine vasopressin resistance[15].

The revised terminology directly reflects pathophysiology: AVP deficiency denotes insufficient hormone synthesis or secretion, whereas AVP resistance denotes impaired renal responsiveness despite preserved or increased AVP availability. Primary polydipsia remains the principal differential diagnosis.

5. Beyond vasopressin: is oxytocin deficiency a human disease?

The patient survey also raised the possibility of an additional, previously under-recognised component of posterior pituitary dysfunction.

Despite effective control of polyuria and polydipsia with desmopressin, substantial residual morbidity was reported. Twenty-five per cent of par-

ticipants reported increased anxiety, 25% sleep disturbances and 23% depressed mood; disturbances of stress management and perceived personality changes were also reported. Overall, 64% described impaired quality of life[14].

These findings could potentially reflect the underlying hypothalamic-pituitary disease, previous neurosurgery, tumour-related morbidity or additional anterior pituitary hormone deficiencies. However, psychological symptoms were also observed in patients without major anterior pituitary deficits, suggesting that additional neuroendocrine mechanisms might contribute.

AVP and oxytocin (OXT) are synthesised by closely neighbouring and partly overlapping neuronal populations within the supraoptic and paraventricular hypothalamic nuclei. Their genes are located in close proximity, their precursor proteins share organisational similarities, and both hormones are transported to and released from the posterior pituitary. Hypothalamic injury sufficient to impair vasopressinergic neurons may therefore also affect oxytocinergic pathways.

Although oxytocin is best known for its peripheral roles in parturition and lactation, the oxytocinergic system has much broader central functions. Oxytocinergic neurons project widely throughout the central nervous system, and experimental studies implicate oxytocin signalling in social recognition, attachment, emotional processing, anxiety, stress regulation and aspects of metabolism.

These observations led to the hypothesis that oxytocin deficiency could contribute to the persistent socio-emotional phenotype observed in a subset of patients with AVP deficiency.

As with AVP, however, basal oxytocin concentrations are difficult to interpret. Assay performance varies, pre-analytical conditions influence measurements, and peripheral concentrations do not necessarily reflect central oxytocinergic activity. Studies in patients with hypothalamic-pituitary disease have consequently reported conflicting basal concentrations, including reduced, unchanged and increased values.

Accordingly, assessment of a potential oxytocin deficiency is likely to require a dynamic stimulation test rather than reliance on basal hormone concentrations.

Using MDMA as a physiological probe

Conventional pituitary stimuli have not provided sufficiently robust oxytocin responses for diagnostic use. Hypertonic saline induces only a modest increase in oxytocin, and responses to exercise and hypoglycaemia are similarly small or inconsistent.

3,4-Methylenedioxymethamphetamine (MDMA) is a potent activator of the human oxytocin system. In addition to increasing peripheral oxytocin concentrations, MDMA produces characteristic prosocial and emotional effects, including increased feelings of closeness and trust and altered processing of negative social cues. In a controlled experimental setting, MDMA therefore provides an opportunity to assess both biochemical oxytocin release and associated functional responses.

In our 2023 study, basal plasma oxytocin concentrations were comparable in patients with AVP deficiency and matched healthy controls[16]. Following MDMA administration, healthy controls exhibited an approximately eight-fold increase in circulating oxytocin, whereas no comparable increase was observed in patients with AVP deficiency.

The divergent biochemical response was accompanied by corresponding behavioural differences. In healthy controls, MDMA produced the expected subjective effects and reduced state anxiety around the time of peak oxytocin release. These effects were markedly attenuated or absent in patients with AVP deficiency. Changes in the recognition of negative facial emotions were likewise observed in controls but not in patients.

Figure 4 summarises the principal biochemical and socio-emotional findings of the MDMA stimulation study in patients with AVP deficiency and healthy controls.

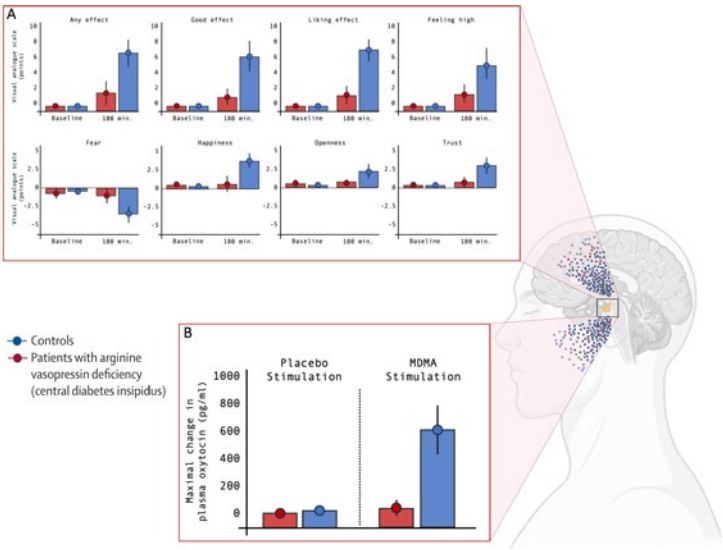


Figure 4. *Oxytocin and socio-emotional responses to MDMA in patients with AVP deficiency and healthy controls. Healthy controls exhibited the expected subjective effects of MDMA and a pronounced increase in plasma oxytocin, whereas both behavioural responses and stimulated oxytocin release were markedly attenuated in patients with AVP deficiency. Reproduced from: Atila C, Refardt J, Christ-Crain M. Nat Rev Endocrinol. 2024;20:487–500.*

These findings do not imply that all patients with AVP deficiency have complete oxytocin deficiency, nor does MDMA represent a practical routine diagnostic stimulus. Rather, the study provided proof of concept that a subgroup of patients with AVP deficiency may have impaired stimulated oxytocin release that is not detectable from basal measurements alone.

Subsequent work has further characterised the associated clinical phenotype, including anxiety, depression, alexithymia and other psychopathological features in patients with AVP deficiency and primary polydipsia[17].

In parallel, we returned to the biomarker challenge. Analogous to the co-secretion of copeptin with AVP, neurophysin I is released together with oxytocin from its precursor system. We recently demonstrated that neurophysin I has properties that make it a promising and potentially more robust biomarker of the oxytocin system[18]. Whether neurophysin I can assume a diagnostic role analogous to copeptin for AVP requires systematic clinical validation.

The remaining key question is therapeutic: whether oxytocin replacement can improve socio-emotional outcomes in patients with evidence of oxytocin deficiency. Small studies in hypothalamic disease have suggested potential benefits of intranasal oxytocin on social interaction or emotion recognition, but controlled interventional evidence remains lacking. Supported by the Swiss National Science Foundation with a large grant, we are currently evaluating this therapeutic question in a multicentre randomised controlled trial.

Classical hypopituitarism is defined by deficiencies of anterior pituitary hormones and AVP. Oxytocin has largely been absent from this framework because a non-obstetric oxytocin deficiency syndrome has not been established. Our findings suggest that posterior pituitary dysfunction may be broader than previously recognised and that some symptoms historically attributed non-specifically to impaired quality of life after hypothalamic disease may have a specific neuroendocrine component.

6. The other side of vasopressin: hyponatraemia and SIAD

The preceding sections address insufficient AVP secretion. Hyponatraemia represents the opposite disturbance of water balance, in which impaired free-water excretion results from persistent antidiuretic activity or other mechanisms that favour water retention.

Hyponatraemia is the most common electrolyte disorder encountered in hospital practice, affecting more than 15 % of hospitalised patients and substantially higher proportions in selected acutely or chronically ill populations. Although defined by a reduced plasma sodium concentration,

hyponatraemia is fundamentally a disorder of water relative to body solute rather than simply a state of sodium deficiency[19].

Plasma sodium concentration is determined by the relationship between exchangeable body sodium and potassium and total body water. Hyponatraemia therefore develops when water accumulates disproportionately to solute. Relevant mechanisms include non-osmotic AVP release during true volume depletion; reduced effective arterial blood volume in heart failure or cirrhosis despite extracellular fluid expansion; glucocorticoid deficiency; excessive water intake in combination with insufficient solute intake; and impaired water excretion associated with diuretics, particularly thiazides.

Among these aetiologies, SIAD is particularly important and accounts for approximately 35–40 % of cases in several hospital cohorts.

In SIAD, antidiuretic activity persists despite hypotonicity and in the absence of an appropriate haemodynamic stimulus. Continued AVP-dependent water reabsorption produces hypotonic hyponatraemia. SIAD may be associated with a broad range of conditions, including malignancy, pulmonary and central nervous system disorders, pain, nausea and medications.

Accurate diagnosis is more complex than application of isolated laboratory criteria. Classification requires confirmation of hypotonicity; assessment of urine osmolality and urine sodium in the appropriate clinical context; exclusion of adrenal insufficiency and relevant renal or thyroid dysfunction; and careful evaluation of medication exposure and volume status[20].

In contrast to its diagnostic utility in the polyuria–polydipsia syndrome, copeptin has limited discriminatory value in hyponatraemia. Concentrations overlap extensively across different aetiologies because AVP secretion may be appropriately increased in hypovolaemia and heart failure as well as inappropriately increased in SIAD. An absolute copeptin concentration therefore does not establish whether AVP secretion is appropriate for the prevailing haemodynamic and osmotic context[21].

7. New therapeutic approaches to SIAD

Fluid restriction remains the traditional first-line treatment for chronic SIAD. Its physiological rationale is to reduce water intake below the kidney's impaired capacity for free-water excretion[20].

In clinical practice, fluid restriction has important limitations, particularly poor tolerability and adherence. Restriction to 500 – 1,000 mL/day may be burdensome, and the increase in plasma sodium is often modest, especially in patients with high urine osmolality. Additional treatment is therefore frequently required.

Alternative strategies include increasing osmotic solute excretion with oral urea and antagonising AVP signalling with vasopressin receptor antagonists such as tolvaptan. Both approaches can increase plasma sodium, but each has limitations. Urea is inexpensive and physiologically attractive, although palatability and variable availability have constrained its use. Tolvaptan is highly effective but may cause brisk aquaresis and overcorrection, requires close monitoring, and is costly in many healthcare systems.

We therefore investigated whether established pharmacological or nutritional interventions could be repurposed to exploit renal physiology through mechanisms distinct from direct AVP receptor antagonism.

SGLT2 inhibition: glucosuria-induced osmotic diuresis
SGLT2 inhibitors were developed as glucose-lowering agents. By inhibiting sodium-glucose cotransport in the proximal tubule, they induce glucosuria. Their clinical indications subsequently expanded because of substantial cardiovascular and renal benefits.

For the treatment of SIAD, the relevant pharmacological consequence is glucosuria-induced osmotic diuresis.

Because impaired electrolyte-free water excretion is central to SIAD, we hypothesised that increasing urinary glucose excretion could provide an

additional osmotic load, increase urine volume and promote water excretion despite persistent antidiuretic activity.

We first tested this hypothesis in a randomised, double-blind, placebo-controlled trial involving 87 hospitalised patients with SIAD[22]. All participants received standard fluid restriction of < 1,000 mL/day and were randomised to empagliflozin 25 mg or placebo for four days.

Plasma sodium increased in both groups, but the increase was significantly greater with empagliflozin, approximately 10 mmol/L compared with 7 mmol/L with placebo. These findings provided proof of principle that SGLT2 inhibition can enhance correction of SIAD-associated hyponatraemia.

We subsequently assessed whether this strategy was also effective in the outpatient setting, which is particularly relevant for patients with chronic SIAD requiring sustained therapy.

In a randomised, double-blind, placebo-controlled crossover trial in outpatients with chronic SIAD, four weeks of empagliflozin increased plasma sodium by approximately 4.1 mmol/L compared with placebo[23]. Although numerically modest, an increase of this magnitude is clinically relevant in chronic SIAD, in which plasma sodium is often only several millimoles per litre below the normal range and may therefore shift patients towards normonatraemia without severe fluid restriction.

Together, these trials established glucosuria-induced osmotic diuresis as a novel physiological strategy to increase water excretion in SIAD.

Appropriate patient selection and established safety precautions for SGLT2 inhibitors remain essential. A larger, longer-term trial has now been completed, and analysis is pending.

Protein supplementation: increasing endogenous osmotic solute
A second therapeutic strategy was based on the fundamental dependence of renal water excretion on daily solute intake.

Dietary protein is metabolised to nitrogenous compounds that are converted to urea in the liver and subsequently excreted by the kidney. Because urea contributes substantially to daily osmotic load, increased protein intake should enhance endogenous urea generation and thereby increase renal water-excretory capacity.

In the TREASURE proof-of-concept study, we investigated 17 outpatients with chronic SIAD[24]. Participants received high-protein supplementation (90 g/day for seven days) and, in a separate treatment period, oral urea (30 g/day). Protein supplementation increased plasma sodium together with plasma and urinary urea concentrations, and the magnitude of the sodium increase was similar to that observed with oral urea.

These findings have two principal implications. First, they confirm that solute availability is an important determinant of water homeostasis; AVP activity alone does not determine renal water excretion, because the amount of osmoles available for urinary excretion is also critical. Second, protein supplementation may be particularly relevant for patients with concomitantly low protein intake or loss of muscle mass, in whom a nutritional intervention could simultaneously improve protein intake and enhance renal water clearance.

Figure 5 summarises the sites of action of established and emerging treatments for hyponatraemia.

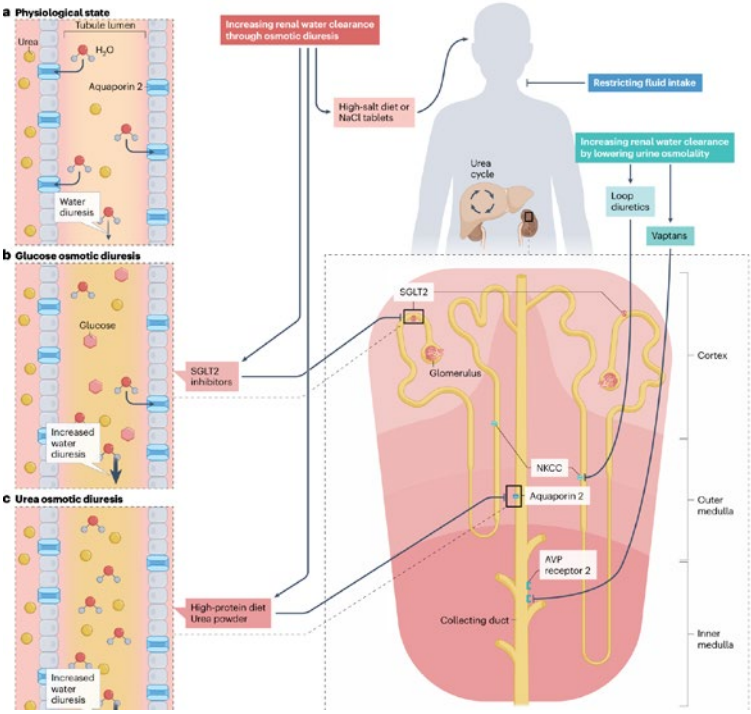


Figure 5. *Sites of action of established and emerging treatments for hyponatraemia. Fluid restriction reduces water intake; loop diuretics and vaptans reduce urinary concentrating capacity; SGLT2 inhibitors induce glucosuria and osmotic diuresis; and urea or high-protein intake increase osmotic solute excretion and thereby enhance renal water clearance. Reproduced from: Monnerat S, Christ-Crain M, Refardt J. Nat Rev Endocrinol. 2025;21:564–579.*

8. Does correcting hyponatraemia improve clinical outcomes?

Historically, mild chronic hyponatraemia was often regarded primarily as a biochemical abnormality, in contrast to acute severe hyponatraemia, in which rapid osmotic water shifts into the brain may cause cerebral oedema, seizures, impaired consciousness and death. During chronic hypotonicity, cerebral adaptation through loss of electrolytes and organic osmolytes limits cellular swelling and contributed to the concept of 'asymptomatic hyponatraemia'.

Over the past two decades, however, chronic hyponatraemia has increasingly been recognised as a clinically relevant condition. It is associated with impaired attention and neurocognitive performance, gait instability, falls, osteoporosis, fractures and reduced quality of life, as well as increased mortality and rehospitalisation across a broad range of underlying diseases[19].

Our prospective work contributed to the characterisation of neurocognitive and neuromuscular abnormalities in chronic hyponatraemia[25]. Other studies have suggested that some of these abnormalities improve following correction of plasma sodium. Bone metabolism may also be affected: in patients with chronic SIAD, an increase in plasma sodium was associated with increased osteoblast activity[26], providing a potential biological link between correction of hyponatraemia and bone health.

A central challenge in interpreting these associations is confounding by underlying disease. Patients with hyponatraemia are frequently older, have greater comorbidity and are more severely ill than normonatraemic patients. Hyponatraemia may therefore contribute causally to adverse outcomes, but it may also function predominantly as a marker of disease severity.

This distinction has major therapeutic implications. If chronic hyponatraemia is a causal mediator of mortality and rehospitalisation, effective correction should improve these outcomes. If it is primarily a marker of underlying disease, normalisation of plasma sodium alone may not alter prognosis. This uncertainty provided the rationale for the Hyponatremia Intervention Trial (HIT).

Observational studies consistently reported higher rates of falls, fractures, neurocognitive impairment, prolonged hospitalisation, rehospitalisation and mortality in patients with hyponatraemia than in those with normal plasma sodium. Meta-analyses further suggested lower mortality among patients in whom hyponatraemia improved.

However, observational associations cannot establish causality. Patients whose plasma sodium corrects may have more reversible disease, fewer comorbidities or a more favourable overall prognosis, whereas persistent hyponatraemia may identify patients with advanced cardiac, hepatic, malignant or pulmonary disease.

A randomised intervention trial was therefore required to determine whether targeted correction of hyponatraemia itself improves major clinical outcomes.

The Hyponatremia Intervention Trial
HIT was a pragmatic, randomised, controlled, multicentre trial conducted at nine European centres. We enrolled 2,173 hospitalised adults with chronic hypotonic hyponatraemia and plasma sodium < 130 mmol/L[27]. Participants were randomised to either a structured targeted strategy for correction of hyponatraemia or routine care.

The intervention was deliberately pragmatic and was not restricted to a single pharmacological treatment. The underlying aetiology of hyponatraemia was assessed and therapy was selected according to a predefined diagnostic and therapeutic algorithm. In SIAD, for example, treatment could be escalated from fluid restriction to oral urea and, when required, to tolvaptan. Treatment response was reviewed daily, with escalation when plasma sodium failed to increase adequately.

The primary endpoint was the clinically relevant composite of death or rehospitalisation within 30 days.

Targeted treatment increased the rate of biochemical correction. Normonatraemia was achieved in 60.4 % of participants in the targeted-treatment group compared with 46.2 % receiving routine care, and the mean

maximal absolute increase in plasma sodium was also greater with targeted treatment.

However, the greater degree of biochemical correction did not translate into a statistically significant reduction in the primary clinical endpoint. Death or rehospitalisation occurred in 20.5% of the targeted-treatment group and 21.8% of the routine-care group, corresponding to an estimated absolute difference of –1.3 percentage points (95% confidence interval, –4.9 to 2.2 percentage points).

Thirty-day mortality was 8.0% in both groups, and rehospitalisation rates were likewise similar. Overcorrection was uncommon (2.3% with targeted treatment versus 1.4% with routine care), and no cases of osmotic demyelination syndrome occurred.

Figure 6 summarises the principal results of the Hyponatremia Intervention Trial.

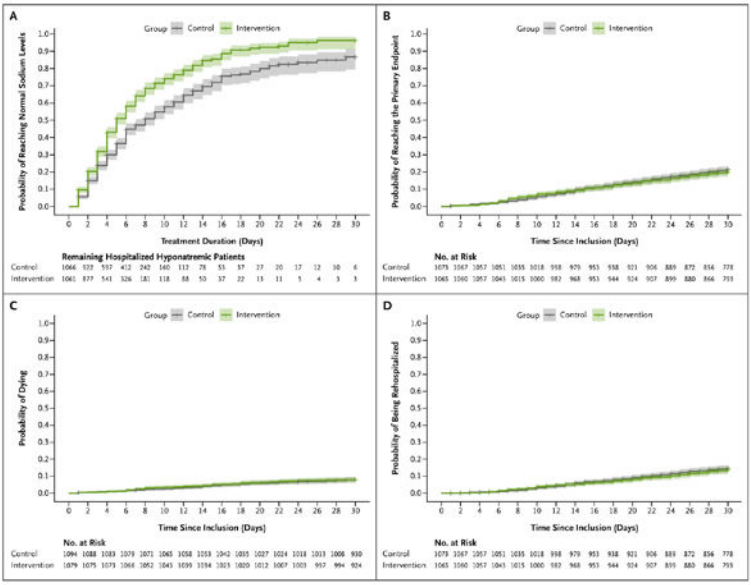


Figure 6. *Time-to-event analyses from the Hyponatremia Intervention Trial. Targeted treatment increased the probability of achieving normonatraemia during treatment (panel A), whereas death or rehospitalisation, death alone and rehospitalisation alone within 30 days were similar between the targeted-treatment and routine-care groups (panels B–D). Reproduced from: Refardt J, Potasso L, Pelouto A, et al.; HIT Study Investigators. NEJM Evidence. 2026;5(3):EVIDoa2500086.*

Although targeted treatment improved biochemical correction, the primary hypothesis that more consistent correction of hyponatraemia would reduce major short-term clinical events was not supported.

HIT demonstrates that, in a heterogeneous population of hospitalised patients with chronic hyponatraemia, increasing the proportion of patients who achieve normonatraemia beyond that achieved with routine care does not, by itself, reduce 30-day mortality or rehospitalisation.

These findings should not be interpreted as evidence that chronic hyponatraemia should remain untreated. The control group received routine clinical care rather than no treatment, and almost half achieved normonatraemia.

9. Perspectives

This research programme originated from a clinical problem: the differential diagnosis of the polyuria–polydipsia syndrome was both insufficiently accurate and burdensome for patients.

The resulting studies have substantially changed the diagnostic approach to the polyuria–polydipsia syndrome. Hypertonic saline-stimulated copeptin replaced an indirect assessment with direct functional interrogation of the AVP system, increasing diagnostic accuracy from approximately 70–77 % to more than 95 % while shortening the diagnostic procedure and improving patient acceptability[7,9].

Improved diagnosis also revealed important challenges in long-term management. Despite the efficacy of desmopressin, patients remained at risk of hyponatraemia and hospital-related treatment errors. Systematic assessment of patient-reported experience identified a practical preventive strategy, demonstrated substantial quality-of-life impairment and ultimately contributed to an international change in disease nomenclature[14,15].

These patient observations also generated a new biological hypothesis. Persistent anxiety and socio-emotional difficulties could not always be explained by conventional pituitary hormone deficiencies, while the anatomical proximity of vasopressinergic and oxytocinergic neurons suggested concomitant impairment of the oxytocin system. Dynamic testing with MDMA demonstrated markedly impaired stimulated oxytocin release in patients with AVP deficiency[16]. Current work is evaluating both the therapeutic potential of oxytocin replacement and the diagnostic utility of neurophysin I as a more practical biomarker[18].

At the opposite end of water-balance physiology, studies in SIAD applied the same mechanistic approach to treatment development. SGLT2 inhibition promotes electrolyte-free water excretion through glucosuria-induced osmotic diuresis, whereas protein supplementation increases endogenous urea generation and osmotic solute excretion.

HIT subsequently extended this research from biochemical efficacy to patient-relevant outcomes. Targeted correction increased the probability of achieving normonatraemia but did not reduce 30-day mortality or rehospitalisation. These findings indicate that future treatment strategies for hyponatraemia should become more precisely aligned with underlying pathophysiology, clinical phenotype and patient-relevant outcomes.

Future directions:

First, diagnostic strategies should continue to become simpler without compromising accuracy. Hypertonic saline-stimulated copeptin has excellent diagnostic performance but requires specialised infrastructure. Future work will evaluate simpler stimulation tests, including mannitol, in international multicentre studies designed to further streamline the diagnostic pathway.

Second, posterior pituitary medicine should extend beyond AVP. The possibility of clinically relevant oxytocin deficiency raises fundamental questions regarding the effects of hypothalamic disease on emotion, behaviour, metabolism and quality of life. Ongoing randomised trials are evaluating oxytocin replacement different populations and patient groups.

Third, the management of hyponatraemia should move from a predominantly sodium-centred approach towards patient-centred treatment. Biochemical normalisation alone is insufficient as an outcome. Future trials should identify phenotypes in which chronic hypotonicity contributes causally to specific complications, including cognitive impairment, gait disturbance, fracture risk and impaired quality of life, and determine whether safe correction reverses these outcomes.

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