Preisverleihung 2024

STIFTUNG
PROFESSOR DR. MAX CLOËTTA

Heft Nr. 52

Prof. Dr. Andrea Alimonti
«Role of cellular senescence in cancer and cancer therapy»

Prof. Dr. Andrea Ablasser
«Immune sensing DNA as a danger signal»

STIFTUNG
PROFESSOR DR. MAX CLOËTTA

einundfünfzigste Preisverleihung

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INHALT

VORWORT

Prof. Dr. Fritjof Helmchen

Wir freuen uns, die diesjährige Verleihung der Cloëtta-Preise am 29. November 2024 wieder in Lausanne feiern zu dürfen, nachdem wir dort zuletzt 2018 gefeiert haben. In diesem Jahr würdigen die Preise die herausragenden wissenschaftlichen Leistungen zweier Forschender, Prof. Dr. Andrea Ablasser und Prof. Dr. Andrea Alimonti, die grundlegende Erkenntnisse über molekulare Signalwege gewonnen haben, welche Immunreaktionen und Tumorprozessen zugrunde liegen. Interessanterweise gibt es dabei zum Teil thematische Überschneidungen, etwa im Hinblick auf molekulare Veränderungen, die mit der Alterung von Zellen einhergehen und die sich auf Nachbarzellen im umgebenden Gewebe auswirken können. Solch tiefgreifende Erkenntnisse über die Funktion spezieller Moleküle und ihrer molekularen Interaktionen innerhalb der Zelle sowie über die Gewebe-Beeinträchtigungen, die Fehlfunktionen dieser Signalwege verursachen, bergen auch immer neue Chancen in sich, krankhafte Veränderungen quasi an der Wurzel zu packen. Dies kann zum Beispiel durch die Identifizierung oder Entwicklung von Substanzen geschehen, die gezielt hemmend oder aktivierend eingreifen können. Insofern eröffnen die Arbeiten beider Preistragenden spannende Möglichkeiten, neue Therapien für verschiedene Krankheiten zu entwickeln, um letztlich betroffenen Personen besser helfen zu können.

Prof. Dr. Andrea Ablasser von der École Polytechnique Fédérale de Lausanne (EPFL) hat in ihrer Forschung eine fundamentale Signalkaskade unseres angeborenen Immunsystems aufgedeckt. Diese Signalkaskade dient der Detektion pathogener DNA eindringender Viren und Mikroben und muss präzise reguliert werden, um eigene von fremder DNA zu unterscheiden. Da dieser Signalweg bei verschiedenen Immunreaktionen und Entzündungsprozessen eine wesentliche Rolle spielt (unter anderem auch bei COVID-19), eröffnen sich durch die mechanistischen Einsichten vielseitige neue Möglichkeiten für therapeutische Ansätze.

Prof. Dr. Andrea Alimonti leitet das Institut für Krebsforschung (IOR) in Bellinzona und ist Professor für experimentelle Onkologie an der Università della Svizzera Italiana (USI) und der ETH Zürich. Seine Forschung zu molekularen Prozessen der Zellalterung und ihrer Auswirkungen auf die Hemmung bzw. Förderung des Wachstums von Krebszellen und auf Metastasierung hat wichtige Erkenntnisse erbracht, die insbesondere auch Grundlage von mehreren laufenden klinischen Studien sind, z.B. zu neuen Therapieansätzen bei Prostatakrebs.

Wir freuen uns, diese beiden Forschungspersönlichkeiten für ihre exzellenten wissenschaftlichen Arbeiten von hoher Relevanz mit dem Cloëtta-Preis 2024 auszuzeichnen. Ebenso freuen wir uns, dass die Cloëtta Stiftung 2024 wieder mehrere junge Medizinerinnen und Mediziner mit Stipendien im Rahmen des Programms «Klinische Medizin Plus» fördern konnte.

Ich bedanke mich beim gesamten Stiftungsrat für die hervorragende Zusammenarbeit, bei Anja Witte und neu auch Stella Vondra für die ausgezeichnete Geschäftsführung, und ich wünsche Ihnen eine anregende Lektüre dieser Broschüre und viel Freude bei der diesjährigen Feier.

Anja Witte
Geschäftsführerin

Stiftungsrat

Im Jahr 2024 gab es keine Veränderungen in der Zusammensetzung des Stiftungsrates. Dem Gremium gehören, wie bereits langjährig bewährt, sechs hochkarätige Medizinprofessorinnen und -professoren sowie drei anerkannte Experten auf dem Gebiet der Finanzen und des Rechts an.

Im August erreichte uns die traurige Nachricht vom Hinschied unseres Cloëtta-Preisträgers von 1982 und ehemaligen Stiftungsratsmitglieds Prof. Dr. Jürgen Johann Leopold Zapf. Von 1993 bis 2008 hat er die Geschicke der Stiftung Prof. Dr. Max Cloëtta massgeblich geprägt und sich unentwegt für den wissenschaftlichen Nachwuchs in der medizinischen Forschung eingesetzt. Sein Engagement für die Wissenschaft, sein enormes Fachwissen, sein unerschöpflicher Einsatz, seine Weitsicht und sein Interesse für den einzelnen Menschen werden uns in bester Erinnerung bleiben, und wir sind ihm dafür von Herzen dankbar.

Einmal mehr bedanken wir uns ausdrücklich bei den Mitgliedern des Stiftungsrates, die engagiert ihr Fachwissen und ihre Erfahrung einbringen, sowie bei den externen Expertinnen und Experten, deren Gutachten die Entscheidungsfindung auch bei der Auswahl der Cloëtta-Preistragenden unterstützen. Erst diese breit abgestützte Kompetenz ermöglicht es der Stiftung, ihren Zweck wirkungsvoll umzusetzen und die medizinische Forschung sowie die damit verbundenen naturwissenschaftlichen Hilfsdisziplinen in der Schweiz und im Ausland zu fördern und zu unterstützen.

Cloëtta-Preis

Zum 51. Mal wird 2024 der Cloëtta-Preis verliehen. 96 exzellente Forscherinnen und Forscher haben den mit je CHF 50 000 dotierten Preis seit der ersten Preisverleihung 1974 erhalten. Zum 50-jährigen Bestehen der Stiftung erhielten 2023 zudem zwei brillante Forscherinnen den Cloëtta-Jubilee-Preis. 2024 freuen sich der Stiftungsrat und die Geschäftsstelle,

eine Forscherin aus dem Bereich der Immunologie und einen Forscher aus dem Bereich der Onkologie mit dem Cloëtta-Preis auszuzeichnen: Der erste Preis geht an Herrn **Prof. Dr. Andrea Alimonti**, Direktor des Instituts für Krebsforschung (IOR) in Bellinzona und Professor für experimentelle Onkologie an der Università della Svizzera Italiana (USI) und der ETH Zürich. Mit Frau **Prof. Dr. Andrea Ablasser** wird die leitende Forscherin für angeborene Immunsysteme der École Polytechnique Fédérale de Lausanne (EPFL), School of Life Sciences, geehrt. Unser herzlicher Dank gilt den Verantwortlichen der EPFL, wo wir erneut zu Gast sein dürfen, und ihrem Vertreter in unserem Stiftungsrat, Prof. Dr. Bernard Thorens, für die Unterstützung bei der Organisation der diesjährigen Preisverleihung.

Forschungsstellen

Die Forschungsstellen der Stiftung Prof. Dr. Max Cloëtta sind für den akademischen Mittelbau in der Schweiz von grosser Bedeutung. Finanziert werden Stellen an schweizerischen Hochschulen, Kliniken oder Instituten für bereits ausgebildete und selbstständig arbeitende Forscherinnen und Forscher bis max. 40 Jahre. Mit diesem Programm will die Stiftung den Forschungsnachwuchs in der Schweiz fördern und den Stelleninhabenden helfen, die manchmal nicht einfache Phase bis zur Berufung auf eine ordentliche Professur zu überbrücken. Die Stipendien werden alle zwei Jahre vergeben, im Jahr 2024 erfolgte die nächste Ausschreibung mit einer Vergabe von voraussichtlich zwei Stellen im Jahr 2025.

2024 förderte die Stiftung Prof. Dr. Max Cloëtta die folgenden Forschenden an Schweizer Universitäten mit Unterstützungsperioden von dreieinhalb bis fünf Jahren:

Dr. Sophie Croizier, 1984, Universität Lausanne,
Center for Integrative Genomics.
Projekt: «Stress regulation of energy metabolism»
Unterstützungsdauer: 1.9.2021–31.7.2024
(ursprünglich bis 31.08.2026 – erhielt Berufung auf Tenure Track Assistant Professor Position an der Universität Lausanne)

Dr. András Jakab, 1985, Universitäts-Kinderspital Zürich,
Center for MR-Research.
Projekt: «From axons to therapy: Characterizing the connectivity
of the human thalamus with 3D multi-scale imaging»
Unterstützungsdauer: 1.10.2020–31.12.2025 (ursprünglich bis
31.12.2024 – erhielt Verlängerung)

Dr. Paula Nunes-Hasler, 1980, Universität Genf,
Institut für Pathologie und Immunologie.
Projekt: «Exploring the ER-phagosome connection during
antigen cross-presentation»
Unterstützungsdauer: 1.10.2019–30.9.2024

Dr. Joel Zindel, 1986, Universitätsspital Bern,
Departement für Viszerale Chirurgie und Medizin.
Projekt: «Mesothelial cell recruitment in injury repair and
post-surgical adhesion formation»
Unterstützungsdauer: 1.5.2023–30.04.2028

Dr. Lucas Boeck, 1980, Universitätsspital Basel,
Departement für Biomedizin.
Projekt: «Designing sterilising antibiotic treatments through
Antimicrobial Single-Cell Testing (ASCT)»
Unterstützungsdauer: 1.10.2023–30.09.2028

Dr. Salvatore Piscuoglio, 1982, erhielt eine Berufung als Associate
Professor in Genetics an die Humanitas Universität in Italien
und beendete seine Cloëtta-Forschungsstelle an der Universität Basel,
Departement Biomedizin, am 31.12.2023 (ursprüngliche Unter-
stützungsdauer: 1.7.2021–30.6.2026).
Projekt: «Biomarker identification to guide surgical intervention after
neoadjuvant chemoradiotherapy in rectal cancer»

Klinische Medizin Plus

Seit 2010 vergibt die Stiftung Prof. Dr. Max Cloëtta Stipendien «Klinische Medizin Plus». Medizinerinnen und Medizinern werden während oder unmittelbar nach Abschluss ihrer Facharztausbildung Stipendien von drei bis maximal zwölf Monaten für die Absolvierung einer Spezialausbildung an einer renommierten, vornehmlich ausländischen Institution ausgerichtet.

2024 unterstützte die Stiftung Prof. Dr. Max Cloëtta folgende Medizinerinnen und Mediziner mit einem Stipendium:

Dr. med. Oliver Bichsel, 1994, Oberarzt i.V.,
Klinik für Neurochirurgie, Universitätsspital Zürich.
Projekt: «Fellowship in Stereotactic and Functional Neurosurgery»
Guest Institution: Division of Neurosurgery,
University of Toronto, Toronto Western Hospital in Toronto, Canada,
1.7.2024–30.6.2025

Dr. med. Beat Moeckli, 1989, Senior Resident Surgery,
Universitätsspital Genf.
Projekt: «Use of AI to predict outcomes after
liver transplantation for hepatocellular carcinoma
using multimodal data input»
Guest Institution: University of California in Los Angeles,
USA & University Health Network in Toronto, Canada,
1.10.2023–31.1.2024

Dr. med. dent. Clemens Raabe, 1990, Dentalchirurg,
Faculty Member, Klinik für Dentalchirurgie und Stomatologie,
zmk Bern, Universität Bern.
Projekt: «Clinical training in patients with peri-implant
inflammatory diseases»
Guest Institution: Poliklinik für Zahnärztliche Chirurgie &
Implantologie, Zentrum für Zahn-, Mund- und Kieferheilkunde,
Goethe Universität, Frankfurt am Main, Deutschland,
1.4.2024–31.3.2025

Dr. med. Tabea Sutter, 1991, Resident, Universitätsspital Zürich.
Projekt: «Training in the field of fetomaternal hematology with a specific focus on improvement of peripartal care of patients with hemoglobinopathies»
Guest Institution: University of Toronto, Pricess Margret Cancer Center and Mount Sinai Hospital, Toronto, Canada,
1.7.2024–30.6.2025

Dr. med. Manon Vouga, 1989, Senior Registrar «Cheffe de Clinique», Universitätsspital CHUV.
Projekt: «Foetal therapy & Management of Placenta Accreta Spectrum (PAS) disorders»
Guest Institution: Saint George's University Hospital, NHS Trust, Tooting, London, United Kingdom,
1.5.2024–30.4.2025

Wechsel der Geschäftsstelle

Während 2023 ganz im Zeichen des 50-jährigen Stiftungsjubiläums stand, hat die Stiftung Prof. Dr. Max Cloëtta sich 2024 intensiv um die Stärkung ihrer internen Prozesse bemüht, um sicherzustellen, dass wir gut aufgestellt sind für die kommenden 50 Jahre. Im Zuge dessen hat unsere Geschäftsstelle zu einem neuen Dienstleister gewechselt, wobei Anja Witte der Stiftung als Geschäftsführerin zumindest vorübergehend erhalten bleibt. Der Wechsel bringt frischen Wind und wird dafür sorgen, dass die Arbeitsabläufe noch effizienter werden, damit die Stiftung Prof. Dr. Max Cloëtta mittels ihrer Förderprogramme auch weiterhin einen entscheidenden Beitrag im Bereich der medizinischen Forschung in der Schweiz leisten kann, indem sie aussergewöhnliche Talente anerkennt und fördert.

THE CLOËTTA PRIZE 2024
IS AWARDED TO

PROFESSOR

ANDREA ALIMONTI

BORN IN 1975 IN MENDRISIO, SWITZERLAND

FULL PROFESSOR OF EXPERIMENTAL ONCOLOGY AT THE UNIVERSITÀ DELLA SVIZZERA ITALIANA (USI) AND ETH ZURICH, AND DIRECTOR OF THE INSTITUTE OF ONCOLOGY RESEARCH (IOR) IN BELLINZONA,

FOR HIS GROUND-BREAKING WORK IN PROSTATE CANCER BIOLOGY, WHICH LED TO NOVEL THERAPEUTIC APPROACHES FOR THIS COMMON MALIGNANCY

LAUSANNE, 29TH NOVEMBER 2024

IN THE NAME OF THE FOUNDATION BOARD:

THE PRESIDENT

THE VICE PRESIDENT

A MEMBER

ANDREA ALIMONTI

CURRICULUM VITAE

Name

Andrea Alimonti

Researcher ID

https://scholar.google.nl/citations?hl=en&user=1QwnL9YAAAAJ

Date of birth

07/09/1975

Actual Position

2010 **Head, Molecular Oncology**
Institute of Oncology Research
Oncology Institute of Southern Switzerland, Bellinzona, Switzerland
2017 **Full Professor of Pharmacology,**
University of Padova, Italy
2017 **Full Professor of Oncology**
Università della Svizzera Italiana, Lugano, Switzerland
2020 **Full Professor of Experimental Oncology and Translational Cancer Medicine**
ETH Zurich, Switzerland
2024 **Director**
Institute of Oncology Research, Bellinzona, Switzerland

Education

2000 **MD degree, Magna Cum Laude (GPA: 110/110)**
University of Rome «La Sapienza» Rome, Italy
2001 **State examination for MD**
University of Rome «La Sapienza» Rome, Italy

2004 **Residency in Clinical Oncology, Magna Cum Laude**
Regina Elena National Cancer Institute, Rome, Italy
2013 **PD, University of Lausanne (UNIL), Faculty of Biology and Medicine**
Lausanne, Switzerland

Postdoctoral Training

2007–2009 **BIDMC-Harvard Medical School** – Boston, United States
Division of Cancer Genetics, Lab.: Pier Paolo Pandolfi, MD PhD
Position: Postdoctoral Clinical/Research Fellow
2004–2007 **Memorial Sloan-Kettering Cancer Center** – New York, United States
Division of Human Pathology, Lab.: Pier Paolo Pandolfi, MD PhD
Position: Postdoctoral Clinical/Research Fellow
2000–2004 **Regina Elena National Cancer Institute of Rome** – Rome, Italy
Division of Medical Oncology: Prof. Francesco Cognetti
Position: Resident in Clinical Oncology

Prizes and Awards

2022 **Benioff Initiative for Prostate Cancer Research Award**
2020 **PCF Challenge Award**
2019 **PCF Challenge Award**
2019 **Prix Robert Wenner, Ligue Suisse contre le Cancer**
2019 **Pfizer Research Prize in Oncology**
2015 **J. Steiner Foundation Award**
2010 **Swiss Bridge Award**

Grants and Fellowships

2024–2027 Fond'Action contre le cancer
2024–2026 Helmut Horten Foundation

2024–2026 **SNSF BRIDGE Discovery grant (#218607)**
2024–2026 Swiss Cancer League grant (#KFS-5777-02-2023)
2023–2028 **SNSF Advanced Grant (#216062)**
2023–2025 MIUR PRIN 2022 (2022BMY7X2)
2023–2025 NATL INST OF HLTH NCI (#R21CA277064)
2022–2024 Innosuisse Innovation Project (#103.496 IP-LS)
2022–2025 **SNSF grant (#207978)**
2022–2024 ETH Zurich Lymphoma Challenge (#LC-2-21)
2022–2023 Benioff Initiative for Prostate Cancer Research
2021–2024 PHRT grant (#2021-355)
2021–2024 Swiss Cancer League grant (#5262)
2021–2024 **SNSF Sinergia grant (202302)**
2021–2024 **SNSF Excellence grant (#201274)**
2021–2024 Dept. of the Army – USAMRAA – DoD, FY20 Translational Science Award – Partnering PI Option (#W81XWH2110076, sub-awardee)
2021–2024 Fondazione Leonardo
2021–2022 Novartis Foundation (#21A009)
2021–2022 Innosuisse Innovation Project (#46608.1 IP-LS)
2020–2022 **PCF Challenge Award (#20CHAL04)**
2020–2022 ISREC Foundation
2020–2021 Fondazione San Salvatore
2020–2021 Fondazione Cariparo
2019–2024 AIRC IG 2018 (#22030)
2019–2023 MIUR PRIN2017 (2017237P5X)
2019–2021 **PCF Challenge Award (#19CHAL08)**
2019–2020 **Prix Robert Wenner, Ligue Suisse contre le Cancer (#RWP-4813-06-2019)**
2018–2021 **SNSF grant (#176045)**
2018–2020 Swiss Cancer League grant (#4267)
2017–2018 Horten Foundation
2016–2021 **European Research Council (ERC) consolidator grant (#683136)**
2015–2019 J. Steiner Foundation
2015–2018 Swiss Card-Onco-Grant of Alfred and Annemarie von Sick
2015–2017 Swiss Cancer League grant (#3505)
2015–2016 Horten Foundation

2015 EMBO Young Investigator Program (YIP)
2013–2014 Novartis Foundation
2012–2016 IIR Pfizer grant
2012–2015 **SNSF Ambizione grant (#136612)**
2011–2014 Swiss Cancer League grant (#2721)
2010–2016 **European Research Council (ERC) starting grant (#261342)**
2010–2013 Swiss Bridge Award
2010–2011 My First AIRC Grant (#MFAG 10805)
2009–2010 European Society of Medical Oncology (ESMO) Research Grant
2008–2012 Marie Curie International Reintegration Grant
2007–2008 Department of Cancer Genetics, BIDMC Harvard Medical School, «Co-clinical trial project»
2006–2007 Department of Medicine, Prostate Cancer Division, «MSKCC fellowship and career support»
2005–2006 Susan G. Komen foundation fellowship
2004–2005 Italian Association of Medical Oncologist (AIOM) fellowship

Institutional responsabilities

2020 Decano of Pharmacology (BIO/14), University of Padova
The Pharmacology sector of the University of Padova includes 60 scientists (3 Full Professors, 8 Associate Professors, 9 Assistant Professors, and 40 junior scientists)
2017 Member of the PhD Graduate Studies Committee of the PhD program in Pharmacological Sciences, Department of Pharmaceutical and Pharmacological Sciences, University of Padova
2017 Organizer of the IOR International Lecture Series for the PhD Program in Cancer Biology and Oncology
2017 Member of the PhD Graduate Studies Committee of the PhD Program in Cancer Biology and Oncology, Faculty of Biomedical Sciences, USI, Lugano

Laboratory

Molecular Oncology, Institute of Oncology Research, Bellinzona, Switzerland
Research team: 12 postdocs, 5 PhD students, 3 visiting clinical fellows, 2 lab manager, 1 technician, 3 bioinformaticians, 1 master student
Budget/year: 1.500.000 CHF

Supervisions of junior researchers at graduate and postgraduate level

From 2010, I have supervised 40 researchers, 26 graduates (Jingjing Chen, Ajinkya Revandkar, Manuel Colucci, Mariantonietta D'Ambrosio, Clarissa Spataro, Jelena Vassileska, Maria Luna Perciato, Madhuri Kalathur, Tiziano Bernasconi, Emiliano Pasquini, Giuseppe Attanasio, Martina Troiani, Nicolò Pernigoni, Nicolò Bancaro, Miriam Saponaro, Ping Lai, Silvia Bressan, Saman Sharifi, Federico Gianfanti, Luisa Maraccani, Anna Kohl, Aurora Valdata, Yungrui Li, Miles Sarill, Yuxin Li, Du Yingxi) and 14 postgraduates (Alberto Toso, Arianna Calcinotto, Ilaria Guccini, Diletta Di Mitri, Daniela Brina, Abdullah Alajati, Elena Zagato, Sara Zumerle, Maria Andrea Desbats, Bianca Calì, Liu Lei, Martino Maddalena, Sabrina Naud, Qingzhu Shi). All the PhD students have obtained postdoctoral fellow positions in Switzerland and abroad. Seven postdoctoral fellows have obtained independent PI positions in Switzerland and abroad.

PI in ongoing clinical studies

Combination Study of AZD5069 and Enzalutamide (ACE, NCT03177187, EudraCT 2016-003141-28)

Valid Biomarkers in Blood to Predict the Response to Therapy in Prostate Cancer Patients (NCT03408964)

Phase I/II Trial of Abiraterone Acetate in Combination with Tildrakizumab (anti-IL23 targeting monoclonal antibody) in Men with Metastatic Castration-Resistant Prostate Cancer (mCRPC) (ACTIon: NCT04458311, EudraCT 2019-003485-40)

Phase I/II Study to Assess the Safety, Tolerability and Preliminary Anti-Tumour Activity of Oral Combination Antibiotic Therapy to Modulate the Microbiome in Combination with Enzalutamide in Patients With Metastatic Castration Resistant Prostate Cancer (mCRPC) (PROMIZE, NCT06126731)

A prospective observational study to assess the association between gut microbiome/use of antibiotics and response to treatments for metastatic castration resistant prostate cancer (mCRPC) (FLORA, Rif CE TI 3831)

Evaluation of Safety and Tolerability of Salvia Haenkei Extract as a Dietary Supplement Ingredient (NCT05936346)

Memberships in panels

2023 Actual member of the Scientific Advisory Board, ISREC Foundation
2019 Member of the Gustav & Ruth Jacob Foundation
2018 Member of the GU panel of ESMO
2018 Actual member of the Expert Selection Committee (Oncology) «La Caixa Foundation»
2017 Actual member of the Scientific Commission (Wiko) of the Swiss Cancer League
2014 Actual member of the Scientific Advisory Board, IBSA Foundation

Memberships of scientific societies

2020 European Association for Cancer Research (EACR)
2015 Società Italiana di Farmacologia (SIF)
2014 American Association for Cancer Research (AACR)
2013 Member of the Young Academy of Europe
2012 Member of the urogenital cancer board of SAKK
2005 Full Member of the European Society of Medical Oncology (ESMO)
2004 Full Member of the Italian Association of Clinical Oncology (AIOM)

Organization of scientific meetings

2024 IBSA Foundation Forum «New Frontiers in cancer and healthy aging» (organizer), Napoli, Italy
2023 IBSA Foundation Forum «Culture and Longevity» (organizer), Zurich, Switzerland
2023 IBSA Foundation Forum «New Frontiers in biological and environmental determinants of aging» (organizer), Bellinzona, Switzerland
2023 IBSA Foundation Forum «Personalized therapy in oncology» (organizer), ICML, Lugano, Switzerland
2021 IBSA Foundation Forum «Vaccines and monoclonals to regain our freedom» (organizer), ICML, Lugano, Switzerland
2019 IBSA Foundation Forum «Revolutionary Therapies for Cancer» (organizer), ICML, Lugano, Switzerland
2018 European Society of Medical Oncology Annual Meeting (scientific committee), Madrid, Spain
2017 IBSA Foundation Forum «Basic mechanisms of cancer immunotherapy» (organizer), ICML, Lugano, Switzerland
2015 VIII IBSA Foundation Forum «Cancer immunology makes it to clinic» (organizer), Lugano, Switzerland
2014 European Society of Medical Oncology Symposium (scientific committee), Barcelona, Spain
2012 IMPAKT Breast Cancer Conference (scientific committee), Brussels, Belgium

Editorial Boards:

Reviewer for Nature, Nature Genetics, Journal of Clinical Oncology (JCO), Clinical Cancer Research, Cancer Research, Carcinogenesis, European Journal of Cancer and Cancer Chemotherapy and Pharmacology, PNAS

RESEARCH OUTPUT LIST

Publications in international peer-reviewed scientific journals (short selection of the most relevant publications)

Please see the full list of publications here:
https://scholar.google.nl/citations?hl=en & user=1QwnL9YAAAAJ

1. Calì B, Troiani M, Bressan S, Attanasio G, Merler S, Moscarda V, Mosole S, Ricci E, Guo C, Yuan W, Gallagher L, Lundberg A, Bernett I, Figueiredo I, Arzola RA, Abreut EB, D'Ambrosio M, Bancaro N, Brina D, Zumerle S, Pasquini E, y M, Lai P, Colucci M, Pernigoni N, Rinaldi A, Minardi D, Morlacco A, Moro FD, Sabbadin M, Galuppini F, Fassan M, Rüschoff JH, Moch H, Rescigno P, Francini E, Saieva C, Modesti M, Theurillat JP, Gillessen S, Wilgenbus P, Graf C, Ruf W, de Bono J, **Alimonti A**. Coagulation factor X promotes resistance to androgen-deprivation therapy in prostate cancer. **Cancer Cell**. **2024** Sep 16:S1535-6108(24)00317-9. doi: 10.1016/j.ccell.2024.08.018

2. Colucci M, Zumerle S, Bressan S, Gianfanti F, Troiani M, Valdata A, D'Ambrosio M, Pasquini E, Varesi A, Cogo F, Mosole S, Dongilli C, Desbats MA, Contu L, Revankdar A, Chen J, Kalathur M, Perciato ML, Basilotta R, Endre L, Schauer S, Othman A, Guccini I, Saponaro M, Maraccani L, Bancaro N, Lai P, Liu L, Pernigoni N, Mele F, Merler S, Trotman LC, Guarda G, Calì B, Montopoli M, **Alimonti A**. Retinoic acid receptor activation reprograms senescence response and enhances anti-tumor activity of natural killer cells. **Cancer Cell**. **2024** Feb 27:S1535-6108(24)00048-5. doi: 10.1016/j.ccell.2024.02.004

   Commentaries *in **Cancer Cell**: Unleashing a safe and potent pro-senescence anti-tumor strategy*
   *in **Cancer Discov**: Retinoids Induce Senescence and NK Cell Activity in Prostate Cancer*

3. Guo C, Sharp A, Gurel B, Crespo M, Figueiredo I, Jain S, Vogl U, Rekowski J, Rouhifard M, Gallagher L, Yuan W, Carreira S, Chandran K, Paschalis A, Colombo I, Stathis A, Bertan C, Seed G, Goodall J, Raynaud F, Ruddle R, Swales KE, Malia J, Bogdan D, Tiu C, Caldwell R, Aversa C, Ferreira A, Neeb A, Tunariu N, Westaby D, Carmichael J, Fenor de la Maza MLD, Yap C, Matthews R, Badham H, Prout T, Turner A, Parmar M, Tovey H, Riisnaes R, Flohr P, Gil J, Waugh D, Decordova S, Schlag A, Calì B, **Alimonti A**, de Bono JS. Targeting myeloid chemotaxis to reverse prostate cancer therapy resistance. **Nature**. **2023** Oct 16. doi: 10.1038/s41586-023-06696-z

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ROLE OF CELLULAR SENESCENCE IN CANCER AND CANCER THERAPY

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1. Introduction

Cellular senescence is a stable cell cycle arrest that occurs in diploid cells and limits their proliferative life span. The first description of this phenomenon dates back to 1960s, when Hayflick and Moorhead observed that human diploid fibroblasts in culture could reach a maximum number of cell divisions before arresting their growth[1]. This biological clock, known as the «Hayflick limit», is caused by a progressive shortening of telomeres upon each cell division and represents a physiological response to prevent genomic instability and, therefore, accumulation of DNA damage[2]. This phenomenon is currently defined as replicative senescence. Senescent cells can accumulate with age and at sites of age-related pathologies[3], and can have an impact on the normal physiology of the tissues, causing a progressive functional deterioration. However, diploid cells can also experience an accelerated senescence response, independent from the telomere shortening, known as premature senescence[4, 5]. This senescence response occurs immediately after certain insults, such as genotoxic stress induced by anti-cancer therapies and metabolic shock. Oncogenic stress triggered by the overexpression of certain oncogenes or loss of tumor suppressor genes (TSGs) in primary and tumor cells also induces senescence[6, 7]. Contrary to apoptotic cells, senescent cells remain permanently arrested in the tissues and metabolically active. One of the key hallmarks of these cells is the production of several secreted factors known as the SASP that render senescent cells capable of communicating with the surrounding tissue microenvironment. It has been demonstrated that senescence occurs *in vivo* in different tumors, where it arrests tumor development and progression. Thus, because of its anti-proliferative effects, senescence also appears to be a potent antitumor mechanism. This tumor-suppressive function of senescence has paved the way for

treatments that enhance senescence for cancer therapy, a process termed pro-senescence therapy for cancer. However, senescence in cancer works as a double-edged sword. Indeed, in tumors of certain genetic backgrounds, senescent cells through the SASP can push the proliferation of neighboring tumor cells, drive tumor invasiveness and metastasis, or subvert the anti-tumor function of immune cells, leading to cancer progression. In this context, the elimination of senescent tumor cells through senolytics or the use of compounds that reprogram the SASP has emerged as a promising avenue to treat different types of cancers. In this review, I outline my laboratory's contributions to advancing the understanding of senescent tumor cell biology, uncovering the interaction between these cells and the tumor immune response, and identifying several effective treatments targeting senescent tumor cells that have been proven effective in treating cancer patients.

2. Hallmarks of cellular senescence

Senescent cells are not characterized by universal or specific biomarkers but rather by a number of nonexclusive markers. Cell cycle arrest is a crucial characteristic for the identification of all types of senescence. Still, it cannot be considered a unique marker because multiple cellular mechanisms can drive a stable replicative arrest. However, the inability to express genes required for proliferation, even in a pro-mitogenic environment, allows distinguishing senescence from quiescence, a non-proliferative state of the cells that are readily reversed in response to mitogens.- Senescent cells are characterized by a higher activity of senescence-associated β-galactosidase (SA-β-gal) at pH 6 and can be identified by flow cytometry using fluorescein di-D-galactopyranoside, a substrate that can be cleaved by galactosidase. In senescent cells, cell cycle arrest correlates with an augmented level of cell cycle inhibitors, including p16INK4a, p21CIP1, and p27. Moreover, elevated expression of p19ARF, p53, and PAI-1 are observed in senescent cells and used as miscellaneous senescence biomarkers[8] ***(Figure 1)***. In addition, senescent cells are commonly characterized by an altered cell size with a more smoothed shape compared with proliferating cells and exhibit senescence-associated heterochromatin foci formation, accumulation of lipofuscin, DNA damage foci, loss of lamin B1, senescence-associated distension of satellites, expression of

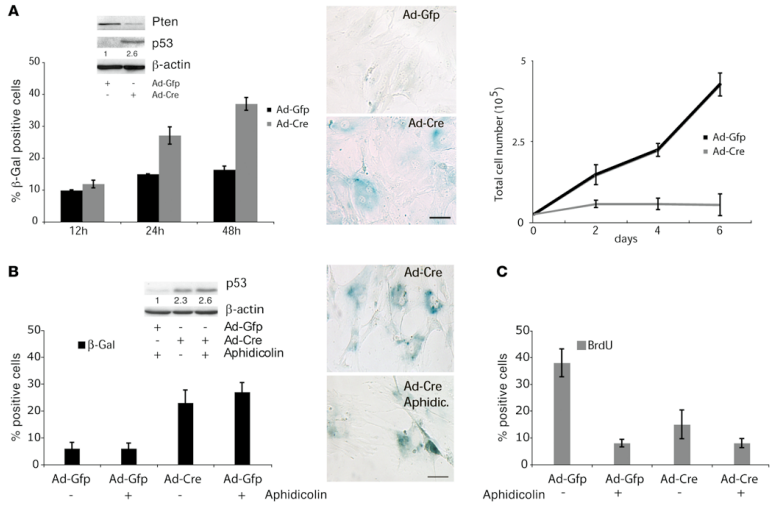

Figure 1. Senescence driven by Pten loss occurs in the absence of cellular proliferation. *(A) Western blot analysis of Ptenlx/lx MEFs infected with Ad-GFP or Ad-Cre. SA-β-Gal staining and its quantification. Scale bar: 10 μm. Growth curve of Ptenlx/lx MEFs after infection with Ad-GFP or Ad-Cre. (B) Quantification of SA-β-Gal staining and Western blot analysis for p53 in Ptenlx/lx treated MEFs (C) Quantification of BrdU incorporation in Ptenlx/lx MEFs infected as in B.*

From Alimonti A et al. «A novel type of cellular senescence that can be enhanced in mouse models and human tumor xenografts to suppress prostate tumorigenesis.» The Journal of Clinical Investigation, 2010.

embryonic chondrocyte-expressed 1 (DEC1) and decoy death receptor 2 (DCR2), upregulation of some microRNAs (miRNAs) and secretion of a large number of factors, including growth factors, cytokines, chemokines, and proteases, known as the senescence-associated secretory phenotype (SASP) or senescence-messaging secretome[9]. All the above-mentioned features define the gold-standard markers to identify senescent cells and represent the actual hallmarks of senescence[10, 11]. Nonetheless, there is growing interest in finding novel markers of senescence that could also have a prognostic potential in aging and cancer. One of the characteristics of senescent cells is that they remain metabolically active and able to produce and secrete a plethora of factors that can affect the tissue mi-

croenvironment in different modalities[12, 13]. A key feature of the senescence phenotype is the acquisition of this altered cell metabolism, which is indispensable for the accomplishment of the senescence program. Depletion of the catabolic enzyme glycogen phosphorylase in cells results in glycogen accumulation, which is associated with reduced proliferation and a corresponding induction of senescence[14]. Growing literature on the metabolism of cellular senescence reports that both glucose consumption and lactate production are elevated during senescence[15–17].

3. Cellular senescence in cancer

Oncogene activation in mammalian cells results in proliferative stress and senescence induction that limits tumor growth. Thus, senescence is a physiological tumor-suppressive mechanism that inhibits the progression from benign tumor lesions to malignant tumors. The induction of senescence by oncogene activation is termed OIS. The first experimental evidence of OIS came from overexpression experiments of oncogenic $HRAS^{G12V}$ in human fibroblasts resulting in a permanent cell cycle arrest[2]. Mutations in the RAS oncogene are common in many human cancers. However, its sole activation is not sufficient to drive transformation and requires cooperation with other oncogenes and tumor suppressors[18]. RAS overexpression in the absence of additional hits drives cells into senescence, and this mechanism works as a barrier to block tumor growth *in vivo*[19]. Interestingly, $HRAS^{G12V}$overexpression is accompanied by the concomitant upregulation of $p19^{ARF}$, Pml, p53, retinoblastoma, and $p16^{INK4a, 5, 20}$, and inactivation of these genes results in evasion of $HRAS^{G12V}$-induced cellular senescence. Similarly, co-expression of oncogenes such as c-MYC, E1A, or DRIL1 bypasses RAS^{G12V}-induced senescence[21]. Overexpression of additional oncogenes such as HER2, EGFR, and PI3K can also drive senescence in primary and tumor cells, and their signaling alters the SASP[22, 23]. Mutations in BRAF are a common feature in human melanoma patients. However, mutations that lead to constitutive activation of BRAF promote OIS *in vitro* and result in the formation of melanocytic nevi *in vivo*, a form of benign skin tumor with senescent cells. In particular, mutated BRAF overexpression initially drives hyperproliferation in melanocytes and then induces $p16^{INK4a}$ expression, which drives the arrest of the cell cycle and establishment of senescence[24]. As discussed above for RAS,

BRAF-induced senescence is also the result of interaction between BRAF itself and other oncogenes and tumor-suppressor genes. In this case, the expression of IGFBP7 is necessary for senescence establishment, and loss of this protein is a critical step in the progression to melanoma[25]. Loss of the tumor suppressor PTEN in a BRAF-mutated context promotes tumor progression and metastatic melanoma *in vivo*[26]. On the other hand, inactivation of oncogenes can also induce senescence. MYC inactivation induces cellular senescence and regression in different tumoral specimens such as lymphoma, osteosarcoma, and hepatocellular carcinoma (HCC)[27]. These effects are driven by multiple mechanisms, reflecting the implication of MYC in different elements of the tumor microenvironment. Importantly, the presence of a proficient immune system is a prerequisite for senescence resulting from MYC inactivation[28]. Another mechanism by which senescence is induced is represented by the loss or inactivation of TSGs. One of the first descriptions of this phenomenon *in vivo* is related to the tumor suppressor PTEN, whose loss induces a senescence response named PICS[26]. Unlike OIS, PICS occurs in the absence of DNA damage response (DDR). In PICS, PTEN loss drives p53 activation through activation of mTOR and ARF-mediated inhibition of MDM2. In addition, PTEN loss can induce $p16^{INK4A}$ through upregulation of the transcription factor Ets2[29] and involves APC/CDH1[30]. In murine models of prostate cancer, ablation of PTEN leads to a benign prostate tumor lesion called prostatic intraepithelial neoplasia, which is characterized by a number of senescent tumor cells[26]. However, when combined with p53 inactivation, these lesions progress to invasive prostate cancer because of evasion of PICS[26,31]. Interestingly, in recent years, several PICS regulators have been identified. For instance, the inhibition of S-phase kinase-associated protein 2 (Skp2) restores senescence in PTEN- and p53-deficient tumors through the upregulation of p27[32] SMAD4 inactivation or overexpression of COUP-TFII, a SMAD4 inhibitor, also promotes the bypass of PICS by allowing the transcription of cyclin D1 in Pten-null tumors[33]. Similarly, because PTEN-deficient prostate cancer cells rely on NOTCH signaling for proliferation, pharmacological inhibition of γ-secretases or inhibition of NOTCH1 enhances senescence in both Pten- and Pten;p53-deficient prostate cancers through induction of p27 expression[34]. Casein kinase 2 (CK2) also regulates senescence driven by loss of PTEN through STAT3 activation[35]. Preclinical and clinical studies

have also shown that HER2 activation in Pten-null tumors leads to PICS escape, causing aggressive prostate cancer[36]. Finally, inactivation of the tumor-suppressor inositol polyphosphate-4-phosphatase (INPP4B) in a PTEN-deficient context leads to an increase in cellular senescence driven by p53 upregulation[37]. Mutations or loss of function in the gene neurofibromin 1 (NF1) drive a human disorder called type I neurofibromatosis, characterized by the development of benign tumors in both the peripheral and central nervous system. In these lesions, mutations or inactivation of NF1 lead to activation of the N-RAS pathway and to the induction of senescence characterized by high expression of SA-β-Gal and $p16^{INK4a}$[38, 39]. In addition to this, the inactivation of NF-1 has been shown to drive senescence establishment in human melanocytes, too[40]. Inactivating mutations of TSC2 gene in primary murine embryo fibroblast displayed early senescence associated with overexpression of $p21^{CIP1/WAF1}$ that is rescued by loss of p53[41]. Mutations in von Hippel–Lindau TSG, an E3-ubiquitine ligase, are frequent in human renal cell carcinomas and hemangioblastomas. Studies in murine models clarified that von Hippel–Lindau inactivation induced cellular senescence and benign renal tumors through the upregulation of pRB and p27 in a process dependent on functional p53 and HIF[42]. The absence of RB1 in thyroid cells leads to cellular senescence driven by N-RAS, resulting in the formation of benign adenomas, and only upon inactivation of the RAS pathway is there progression to carcinoma[43]. Restoration of the TSG p53 *in vivo* in p53-deficient tumors drives tumor regression in lymphoma and sarcoma models by enhancing senescence[31]. Additional studies in a liver cancer model show that p53 reactivation leads to senescence induction and tumor regression through the activation of the innate immune system[44].

4. Exploiting senescence for cancer therapy

4.1 Pro-senescence therapy for cancer

Compounds that target cellular senescence hold significant potential for use in pro-senescent therapy for cancer. By specifically inducing or enhancing senescence in cancer cells, these therapies can halt tumor growth and proliferation. Pro-senescent strategies can also make tumor cells more susceptible to the immune system and other treatments, potentially leading to better clinical outcomes[45]. These approaches represent a prom-

ising avenue in cancer therapy, offering a novel way to control and eliminate malignant cells by exploiting their natural aging processes. My research has demonstrated that compounds that selectively target genes regulating cellular senescence can be used to enhance senescence in cancer[28].

To identify compounds that enhance senescence in cancer cells, we developed an innovative chemogenomic screening approach[35]. This technique combines the strengths of chemical biology and genomics, allowing scientists to systematically explore the interactions between various small molecules and genetic targets. By integrating these disciplines, we identified compounds that trigger the senescence process in different cancer cells. This method not only helped us discover potential pro-senescent therapies but also provided insights into the underlying mechanisms of action, paving the way for more targeted and effective cancer treatments. This screening led to the identification of CK2 as a key player in the survival of these cancer cells[35]. CK2, a serine/threonine kinase, was found to be essential for the survival and proliferation of PTEN-deficient cancer cells. Mechanistically, we show that *Pten* loss increases CK2 levels by activating STAT3. CK2 upregulation in *Pten* null tumors affects the stability of Pml, an essential regulator of senescence. However, CK2 inhibition through available compounds stabilizes Pml levels, enhancing senescence in prostate tumors. By using this approach, we also found that inhibiting the Notch signaling pathway in PTEN-deficient prostate cancer models leads to a significant arrest in tumor growth and upregulation of cellular senescence[34]. Using prostate conditional inactivation of both Pten and Notch1 along with preclinical trials carried out in Pten-null prostate conditional mouse models, we demonstrated that Pten-deficient prostate tumors are addicted to the NOTCH signaling. Importantly, we found that pharmacological inhibition of γ-secretase promotes a p27-dependent growth arrest in both Pten-null and Pten/Trp53-null prostate tumors by triggering cellular senescence[34].

Cellular senescence can exert dual effects on tumors, either suppressing or promoting tumor progression. The senescence-associated secretory phenotype, released by senescent cells, plays a crucial role in this dichotomy. Consequently, the clinical challenge lies in developing compounds that safely enhance senescence in cancer, favoring tumor-suppressive

SASP factors over tumor-promoting ones. Recently, we explored the role of retinoic acid receptor (RAR) activation in cancer therapy, discovering that RAR agonists can induce senescence in prostate cancer ***(Figure 2)***[46].

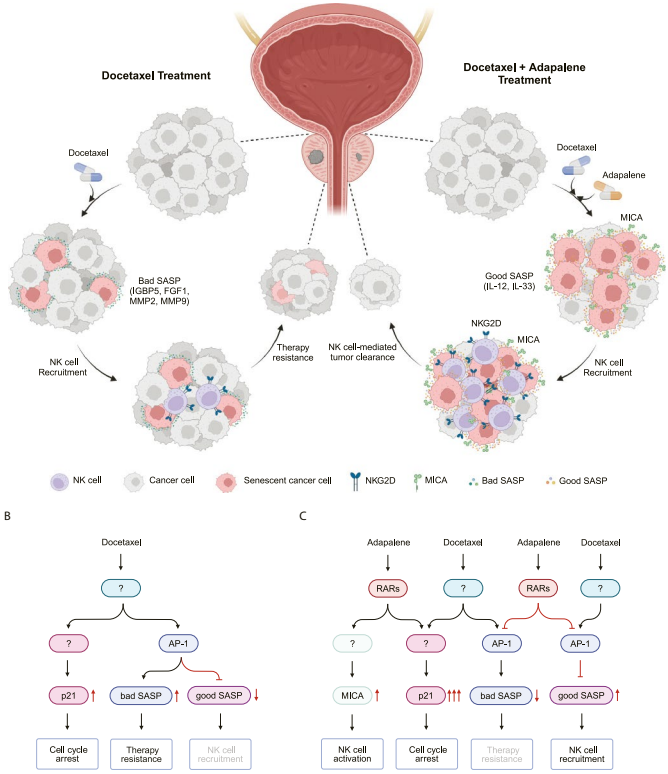

Figure 2. Three birds with one stone: Reaping the benefits of RAR agonist. *(A–C) Inducing cancer cell senescence by p21; reprogramming SASP by antagonizing AP-1 activation; activating NK cell-mediated tumor surveillance by upregulation of NKG2D ligands and recruitment of NK cells to tumor lesion. SASP, senescence-associated secretory phenotype; bad SASP: tumor-promoting SASP; good SASP, tumor-inhibiting SASP; AP-1, activating protein-1.*

From Chen S et al. «Unleashing a safe and potent pro-senescence anti-tumor strategy.» Cancer Cell, 2024.

Activation of the retinoic acid receptor was found to reprogram the cellular senescence response in cancer cells. This reprogramming alters the secretory phenotype of senescent cells, making them less supportive of tumor growth and more visible to the immune system. We demonstrated that RAR activation in cancer cells promotes senescence and that the SASP of these cells enhances the anti-tumor activity of natural killer (NK) cells. In preclinical mouse models of PCa, the combination of the RAR agonist adapalene and docetaxel promotes a tumor-suppressive SASP that enhances natural killer (NK) cell-mediated tumor clearance more effectively than either agent alone. These findings suggest that targeting RAR enhances the immune system's ability to fight cancer by reprogramming the tumor microenvironment. It provides a novel insight into how manipulating the senescence response can be used to boost anti-tumor immunity, potentially improving the efficacy of existing cancer therapies and offering a new avenue for treatment development.

4.2 Drawbacks of pro-senescence therapy and development of senolytics

Traditional cytotoxic chemotherapy, despite having been designed to induce tumor-cell killing, has the potential to induce senescence in some tumors and at certain particular conditions. Although initially this was seen as a beneficial response, evidence gathered at various laboratories raised the concern of potential detrimental secondary effects derived from the induction of senescence in cancer cells[47]. The complex mixture of pro-inflammatory cytokines, growth-factor molecules, and matrix-remodeling enzymes (collectively known as SASP, senescence-associated secretory phenotype) released by senescent cells to the tumor microenvironment represents a potential pro-tumorigenic cocktail. Indeed, recent evidence demonstrates that chemotherapy-induced senescence can promote metastasis through the SASP by stimulating the survival and migration of tumor cells[47]. Understanding the relative contribution of cell senescence to cancer restriction or metastatic growth is fundamental to developing more effective and safer anti-cancer therapies. Metastatic tumor growth is the most devastating form of cancer, and for which, in most cases, we lack effective means of control. Prostate cancer is the most frequent cancer in men, with more than 160 000 new cases each year in

the United States alone. Fortunately, in localized and advanced prostate tumors, surgery and radiation are curative treatments. For metastatic disease, however, despite advances in chemotherapeutic drugs and the use of androgen deprivation, acquired resistance ultimately leads to the death of patients. Understanding the molecular basis of metastatic prostate tumor growth would allow the development of more effective treatments and to identify those patients at higher risk of suffering from the deadly form of the disease. My team has explored the role of senescence in prostate cancer metastases using a mouse model with conditional ablation of the tumor suppressor Pten, which leads to the development of indolent tumors exhibiting senescent characteristics. I hypothesized that the SASP produced by Pten-deficient tumors either lacks pro-metastatic activity or contains a factor that inhibits metastatic progression. To test this, my team profiled the secretome of senescent prostatic tumors lacking Pten and compared it to that of non-senescent tumors developed in mice deficient in both Pten and Trp53 (the latter being crucial for senescence induction). Among the factors identified, Timp1 – a matrix metalloprotease inhibitor known to regulate cell invasion and migration in cancer – was the most significantly upregulated, independent of senescence induction[48]. To further investigate Timp1's role in restricting metastasis in senescent prostate tumors, my team generated mice deficient in both Pten and Timp1. We found that genetic inactivation of Timp1 led to metastatic growth in senescent tumors, but not in non-senescent tumors lacking Trp53[48]. This suggests that Timp1 may inhibit a SASP factor released by senescent cells within the tumor microenvironment. To confirm whether senescent cells were driving the metastatic growth observed in Pten/Timp1-deficient animals, my team used a senolytic agent that selectively targets and kills senescent cells. Removing senescent cells from these double-null mice impaired metastatic potential without affecting the growth of non-senescent tumors[48]. These findings suggest that while senescent tumors can promote metastasis, Timp1 produced by senescent cells acts as a protective factor, blocking this metastatic activity. The implications for prostate cancer therapy are significant, particularly since some current treatments may induce cancer cell senescence. For instance, the chemotherapeutic drug Docetaxel causes tumor regression in Timp1-proficient tumors but accelerates metastasis in the absence of Timp1. Similar results were observed in experiments using human prostate cancer cells, where

Timp1-deficient cells implanted into recipient mice and treated with Docetaxel showed increased metastatic growth. However, when these mice were concurrently treated with the senolytic drug Navitoclax, the accumulation of senescent tumor cells was prevented, thereby inhibiting metastasis in TIMP1-deficient tumors[48]. This critical finding indicates that the genetic context of tumors significantly influences their response to chemotherapy, either suppressing tumor growth or facilitating metastatic progression ***(Figure 3)***. Understanding these dynamics could inform more effective and personalized treatment strategies for prostate cancer patients.

From a mechanistic perspective, my team investigated the effects of the senescent secretome in the absence of Timp1. We found that cell culture media from senescent cells lacking Timp1 promoted invasion and migration in other cells that typically lack these abilities, suggesting that a paracrine effect is at play. Proteome profiling of the secretome from these Timp1-deficient senescent cells treated with Docetaxel identified several potential factors responsible for the enhanced cell migration, including GDF15, FGF1, and IGFBP5 – three known regulators of cell migration[49].

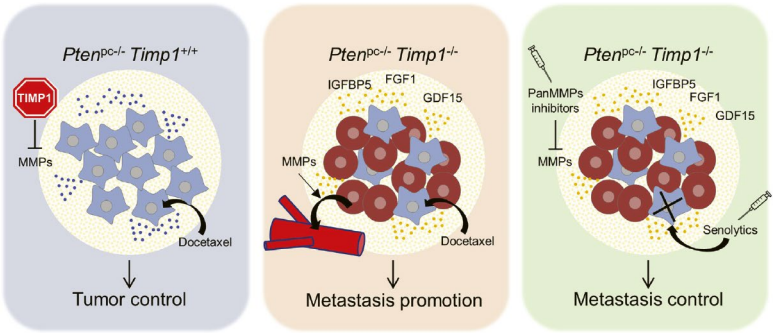

Figure 3. TIMP1 controls the pro-metastatic activity of secreted factors from senescent cells.

From Da Silva-Álvarez S, Collado M. «The Jekyll and Hyde of Senescence in Cancer: TIMP1 Controls the Switch from Tumor-Controlling to Tumor-Promoting Senescence.» Cancer Cell, 2021.

These findings offer a clear explanation for how the senescence response can shift from being tumor-suppressive to promoting metastasis, thereby helping to reconcile seemingly contradictory results in the field.

Overall, the interplay between TIMP1 and senescence also highlights the potential of senolytic therapies in cancer treatment, particularly in fine-tuning the balance between the beneficial and harmful effects of cellular senescence. Understanding this relationship further could lead to more effective strategies for targeting senescent cells in cancer, improving both patient outcomes and longevity. In an effort to develop better senolytics for cancer therapy that could prevent metastasis formation in patients treated with therapy-induced senescence, we used single-cell transcriptomics to analyze cancer cells from the Pten null Timp null metastatic mouse model and found different populations of senescent tumor cells.50 We found that these senescent clusters are heterogeneous in the expression of genes regulating their secretory phenotypes and survival[51]. Senescent tumor cells are known to be resistant to programmed cell death due to the upregulation of BCL2 and BCL-XL10,52. However, an extensive analysis of the pro-survival pathways upregulated in senescent prostate tumor cells was lacking. We, therefore, took advantage of a novel bioinformatic tool named SIT to annotate pro-survival gene pathways deregulated in senescent prostate tumor cells in order to identify a common vulnerability. We found that senescent tumor cells upregulate pathways involved in necroptosis and apoptosis. By separating genes involved in pro-apoptotic and anti-apoptotic pathways, we found that the latter were significantly upregulated in senescent tumor cells[51]. Among the identified pro-survival genes ($n=47$) we found 12 genes that positively correlated (Pearson's coefficient >0.4) with the senescence. Among these, *Mcl-1*, a member of the BCL2 gene family, was the most correlated gene. Of note, *Mcl-1* was more upregulated than *Bcl2*, a well-known target of senolytic therapy. We next classified senescent tumor cells in two subpopulations based on *Bcl2* expression ($Bcl2^+$ and $Bcl2^-$). Surprisingly, we found that roughly 50 % of senescent tumor cells were not expressing *Bcl2* at high levels. On the contrary, *Mcl-1* was expressed both in the $Bcl2^+$ and $Bcl2^-$ clusters, and it was the most upregulated gene in these clusters when compared to additional pro-survival genes[51]. Altogether, these data suggest that the majority of senescent tumor cells rely

on *Mcl-1* over-expression and that this cell population upregulates gene pathways that may contribute to tumor progression through different mechanisms. While treatment with the Bcl-2 inhibitor Navitoclax results in the reduction of metastases in PTEN_shTIP1 null senescent tumor-bearing mice, treatment with the Mcl-1 inhibitor S63845 leads to the complete elimination of senescent tumor cells and metastases[51]. The study suggests that Mcl-1 inhibitors could be used in combination with other treatments to improve outcomes by eliminating therapy-resistant senescent cells and preventing metastases.

4.3 The interplay between senescence and myeloid inflammation

The interplay between senescent tumor cells and immune cells is a dynamic and complex relationship that can influence tumor progression and therapy outcomes. Senescent tumor cells can impact the TME through the SASP. On the one hand, the SASP can recruit immune cells such as macrophages, natural killer (NK) cells, and T cells to the tumor site[53]. These immune cells can recognize and eliminate senescent tumor cells, thereby exerting an anti-tumor effect. This process is known as senescence surveillance and is crucial in preventing the progression of early-stage tumors.

However, the relationship between senescent tumor cells and immune cells is not always straightforward. In some cases, the SASP can create a pro-tumorigenic environment by attracting immunosuppressive cells, such as myeloid-derived suppressor cells (MDSCs), which can inhibit the anti-tumor immune response and drive tumor proliferation and treatment resistance. In this regard, my team was the first to uncover the critical interplay between senescent tumor cells and myeloid cells, revealing a previously unrecognized mechanism of tumor progression.

Our research demonstrated that senescent tumor cells actively recruit polymorphonuclear MDSCs (PMN-MDSCs) in the tumor microenvironment through the SASP, which includes a range of chemokines and cytokines, such as Cxcl2,3,5[52]. Once recruited, myeloid cells play a pivotal role in modulating the tumor's response to therapy. In this respect, my team has contributed to several key discoveries on the biology of myeloid cells by

demonstrating that these cells can not only block anti-tumor immunity but also directly support tumor progression through different mechanisms.

5. Role of inflammatory myeloid cells in prostate cancer

My team has significantly expanded our understanding of how the tumor microenvironment, particularly the immune cells within it, influences cancer progression and resistance to therapy. We first discovered that PMN-MDSCs are critical paracrine drivers of prostate cancer progression, particularly in the context of castration-resistant prostate cancer (CRPC)[54]. We demonstrated that myeloid cells within the prostate tumor of CRPC mouse models and patients express high levels of the inflammatory cytokine IL-23 levels, and this is associated with resistance to androgen-deprivation therapy (ADT), which is a standard treatment for prostate cancer[54].

We discovered that IL-23 promotes the survival and proliferation of prostate cancer cells, even in the context of ADT, by activating the androgen receptor (AR) signaling pathway in prostate cancer cells, thereby bypassing the need for androgens ***(Figure 4)***. Specifically, IL-23 activates the JAK2-STAT5 pathway in prostate cancer cells, leading to increased expression of the androgen receptor and its target genes[54]. The study further explored the potential of targeting IL-23 as a therapeutic strategy to combat CRPC, providing evidence that IL-23 blockade could be an effective therapeutic approach to prevent or treat castration-resistant prostate cancer[54]. The research opens up new avenues for the development of IL-23 inhibitors or therapies that target the IL-23 signaling pathway, which could be combined with existing treatments to improve outcomes for patients with advanced prostate cancer.

Of note, my team also demonstrated that the CXCR2 receptor is a key regulator of PMN-MDSCs recruitment in the tumor microenvironment and that its inhibition could block tumor-infiltration of PMN-MDSCs, thus enhancing the efficacy of androgen-deprivation therapy in prostate cancer[52, 54, 55].

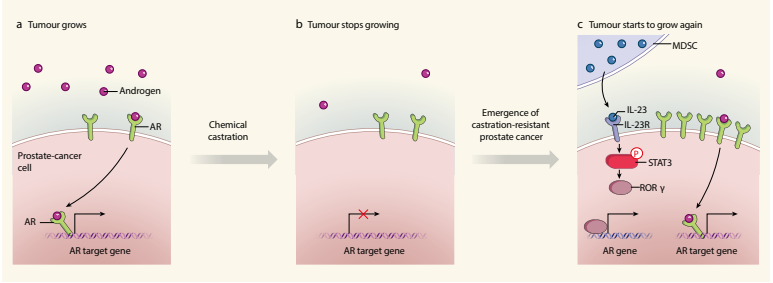

Figure 4. An immune cell drives treatment resistance in prostate cancer. a, *When androgens binds to AR, this drive the expression of genes that promote PCa growth.* ***b****, ADT slows tumor progression in a transient manner.* ***c****, When PCa resume its proliferation, the condition is called CRPCa, which is infiltrated by MDSCs, that can drive treatment failure. MDSC cell secretes a protein called IL-23, that will bind to the IL-23 receptor (IL-23R) on tumour cells. This binding triggers a pathway in the tumour cell mediated by the proteins RORγ and STAT3 (the latter is phosphorylated; P is a phosphate group), which can drive AR expression that boosts prostate-cancer growth.*

From Galsky MD. «Resistance to prostate-cancer treatment is driven by immune cells.» Nature, 2018.

In a follow-up study, by exploiting multiple mouse models and scRNAseq approaches, we performed a more comprehensive characterization of the whole secretome of PMN-MDSCs and demonstrate that PMN-MDSCs from CRPC tumors are also a key extrahepatic source of F10 in the TME of tumors resistant to multiple androgen-deprivation therapies, including those with anti-IL-23 antibody and CXCR2 inhibitors (Calì et al, Cancer Cell, in press).

FX is a vitamin K-dependent coagulation factor of the blood coagulation cascade[56], synthesized as a zymogen in the liver and secreted into the bloodstream.[57] FX occupies a central position in the coagulation system, as both the intrinsic and extrinsic pathways of the coagulation cascade converge on its activation.[58] The relationship between venous thromboembolism (VTE) and cancer was first described in 1865 by Armand Trousseau, who found that tumors promoted coagulation and platelet activation in patients.[59] Although several clinical studies in cancer patients

with or without VTE have suggested that LMWH prolongs the overall survival of different cancer patients, whether coagulation factors directly cause tumor growth remains poorly understood.[60]

We found that FX derived from PMN-MDSCs supported androgen-independent prostate tumor growth by paracrine activation of PAR2 expressed on prostate tumor cells, leading to the emergence of therapy resistance in different mouse models of PCa (Calì et al, Cancer Cell, in press). Differently from IL-23, which drives the transcription of AR and downstream target genes via the pSTAT3-RORγ axis, PMN-derived FX triggers tumor growth by activating the ERK pathway in epithelial cancer cells through PAR2. These results indicate a direct role of FX on PCa cell biology, other than the indirect FXa pro-angiogenic and pro-metastatic effects already described for other malignancies. Intriguingly, we also identified CD84 as a key marker of this oncogenic myeloid subset expressing high levels of *F10* in both preclinical and clinical PCa cancer settings (Calì et al, Cancer Cell, in press). Further bioinformatic analysis unveiled that these *Cd84*$^{+}$, *F10*^{high} PMNs were also characterized by low expression levels of *Cxcr2*, suggesting the existence of an aggressive PMN subset in CRPC with lower sensitivity to CXCR2 inhibitors. We also provided evidence that direct FXa inhibitors can antagonize resistance to ADT and enhance the efficacy of enzalutamide in PCa. (Calì et al, Cancer Cell, in press). Notwithstanding, we have also shown that compounds impacting the prostate cancer secretome at the translational level can ameliorate response to therapy. We, in fact, recently discovered that prostate cancer cells activate the Akt/mTOR and MNK/eIF4E signaling pathways to reprogram their translatome, which is the set of mRNAs translated into proteins[61]. This reprogramming leads to the increased production and secretion of three key proteins: hepatocyte growth factor (HGF), secreted phosphoprotein 1 (SPP1 or osteopontin), and biglycan (BGN). These proteins are implicated in enhancing tumor cell survival, proliferation, and invasion. Of note, these secreted proteins also recruit MDSCs and tumor-associated macrophages (TAMs) to the tumor microenvironment. The findings suggest that targeting the Akt/mTOR and MNK/eIF4E pathways could disrupt this process, potentially leading to new therapeutic strategies that could both inhibit tumor growth and enhance the effectiveness of immunotherapies.

These research studies underscored the importance of the tumor microenvironment in cancer progression and resistance to therapy and paved the way for the design and exploitation of novel combinatorial strategies for CRPC treatment. It also highlights the potential of targeting non-cancerous cells, such as myeloid cells, within the tumor microenvironment to disrupt the support systems that enable tumor growth and survival.

5.1 Impact of myeloid cells on cellular senescence in cancer

Once recruited in the prostate TME, myeloid cells can also significantly impact tumor cell senescence in response to chemotherapy. My team has provided relevant contributions in this context by demonstrating that myeloid cells can interfere with the senescence process in the prostate TME[52]. On one hand, we showed that PMN-MDSCs can suppress the senescence induced by treatments such as chemotherapy or radiation. By doing so, MDSCs allow tumor cells to escape tumor-induced senescence, enabling them to resume proliferation. Of note, this escape not only supports continued tumor growth but also creates a dangerous environment for further genetic evolution. The tumor cells that bypass senescence under the influence of MDSCs are prone to acquiring additional genetic alterations, which can lead to more aggressive and treatment-resistant cancer phenotypes[52]. Mechanistically, we demonstrated that PMN-MDSCs exert their anti-senescence effects through the secretion of interleukin-1 receptor antagonist (IL-1RA), which inhibits the SASP ***(Figure 5)***[52]. This discovery has significant implications for cancer therapy, as it suggests that targeting the interaction between senescent tumor cells and MDSCs can enhance the efficacy of current therapies and prevent the development of more aggressive tumor forms. Inhibiting MDSCs by blocking the CXCR2 receptor with a small molecule inhibitor could enhance the effectiveness of therapy-induced senescence and restore the function of the adaptive immune response in prostate cancer. While these findings are focused on prostate cancer, the mechanism involving MDSCs and CXCR2 is relevant to many types of cancers. Indeed, similar therapeutic strategies could be applied to other malignancies where MDSCs play a role in immune suppression.

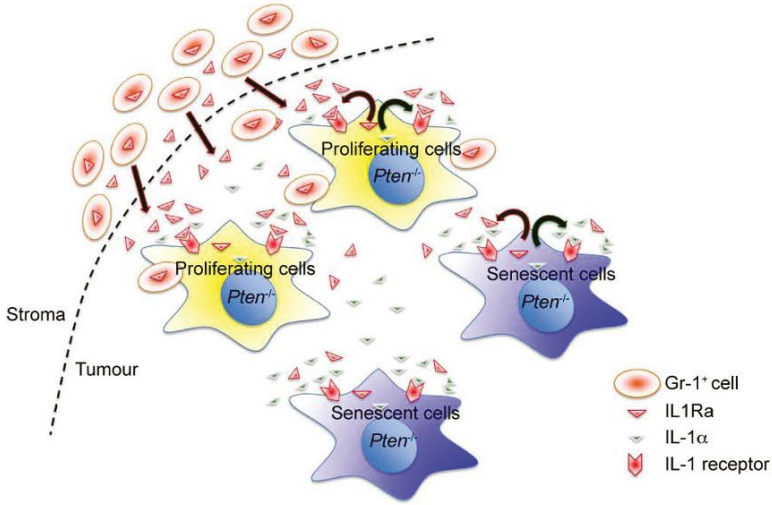

Figure 5. *Gr-1$^+$ myeloid cells recruited to the tumor site oppose Pten-loss-induced cellular senescence by secreting IL-1RA in the tumor microenvironment.*

From Di Mitri D et al. «Tumour-infiltrating Gr-1$^+$ myeloid cells antagonize senescence in cancer». Nature, 2014.

On the other hand, we discovered that tumor-associated macrophages (TAMs) can be successfully repolarized[62] to induce tumor cellular senescence[62]. By exploiting a CXCR2 inhibitor, we highlighted how TAMs, typically known for their tumor-promoting activities, can be reprogrammed to adopt an anti-tumorigenic role[62]. This transformation is achieved through the strategic inhibition of the CXCR2 pathway, leading to a shift in the macrophages' behavior. One of the most striking findings of this study is that re-educated macrophages begin to secrete tumor necrosis factor-alpha (TNFα), a cytokine with potent pro-inflammatory and anti-tumor properties[62]. The secretion of TNFα plays a crucial role in driving cellular senescence in cancer cells. By inducing senescence, TNFα contributes to the suppression of tumor growth and the stabilization of the cancerous state, preventing further progression. Targeting TAMs to induce the secretion of TNFα and drive senescence could represent a novel approach to cancer therapy, particularly in cancers where senescence has been shown to play a protective role against tumor progression.

Thus, inhibiting CXCR2 in myeloid cells serves a dual purpose in combating advanced prostate cancer. Firstly, it blocks the recruitment of myeloid-derived suppressor cells (MDSCs) to the tumor microenvironment (TME), reducing their immunosuppressive and anti-senescent effects. Secondly, CXCR2 inhibition promotes the reprogramming of tumor-associated macrophages (TAMs). These reprogrammed TAMs begin to secrete tumor necrosis factor-alpha (TNFα) within the TME, promoting cellular senescence cellular senescence. This senescence-inducing activity contributes to halting the proliferation of cancer cells, thereby exerting a therapeutic effect in mice with advanced prostate cancer.

5.2 Targeting senescence in the immune system

Senescence in immune cells, also known as immunosenescence, refers to the process by which immune cells undergo aging, leading to a decline in their function. This can impact various aspects of the immune response, contributing to reduced immunity and increased susceptibility to infections, cancer, and chronic diseases, particularly in the elderly. Most studies on immune senescence focus on the role of T cells. Exhaustion and senescence of T cells were reported in different types of cancers[63]. Senescent T cells in the TME have altered phenotypes, including high expression of senescence-associated-β-galactosidase (SA-β-Gal), downregulated expression of the costimulatory molecules CD27 and CD28, and high expression of additional senescence-associated markers, including Tim-3, CD57, CD45RA, and killer cell lectin-like receptor subfamily G member 1 (KLRG-1)[63]. In addition, senescent T cells have reduced expression of the effector molecules perforin and granzyme B (GzmB) and possess strong suppressive activity that potently amplifies the immune suppression within the TME[63.]

Besides that, whether myeloid cells can undergo senescence has remained largely unknown for many years[64]. In this regard, a recent study from my team has made a significant breakthrough in this area. We discovered that PMN-MDSCs can undergo cellular senescence while still maintaining their functional activity within the tumor microenvironment of prostate cancer[55]. The study demonstrates that Apolipoprotein E (ApoE) produced by tumor cells can induce a senescent-like state in

PMN-MDSCs within the prostate cancer microenvironment by binding to TREM2[55]. This induction is evidenced by the upregulation of classical senescence markers such as p21, $p16^{INK4a}$, and the presence of senescence-associated β-galactosidase (SA-β-gal) activity in these immune cells. The research finds that these senescent-like PMN-MDSCs persist in the tumor microenvironment over time, contributing to the chronic inflammation and immunosuppressive milieu that facilitates tumor growth and resistance to therapy[55]. The research also highlights that these cells secrete a specific set of cytokines and pro-inflammatory factors, contributing to a tumor-promoting environment.

The persistence and functional activity of senescent-like PMN-MDSCs in the tumor microenvironment pose a significant challenge for immunotherapy. Since these cells suppress T cell activity, they can diminish the efficacy of therapies aimed at boosting the immune response against cancer. Therapeutically, this study demonstrated that compounds that can eliminate senescent PMN-MDSCs can enhance the efficacy of Enzalutamide treatment in different mouse models.

A screening of 500 compounds in this cell population identified an HDAC inhibitor as a powerful immunosenolytic agent[55]. This inhibitor was able to selectively eliminate senescent-like myeloid cells from the tumor microenvironment, effectively reducing their tumor-promoting effects ***(Figure 6)***.

6. Clinical translation of the findings

Our discoveries on myeloid cell biology and senescence in prostate cancer have inspired the design and execution of a clinical trial assessing the role of the MDSCs inhibitor AZD5069 in combination with androgen receptor signaling inhibitors in metastatic CRPC (mCRPC) patients. We conducted an international phase 1, multi-centre, single-arm, open-label trial (ClinicalTrials.gov identifier: NCT03177187, EudraCT: 2016-003141-28) at three centres in Europe (RMH (UK), Belfast City Hospital (UK), Oncology Institute of Southern Switzerland (Switzerland) (***Figure7)***, to test a CXCR2 inhibitor in patients with mCRPC progressing after at least one androgen-receptor inhibitor[65].

By enrolling 23 patients, we showed that combining CXCR2 inhibitors with drugs blocking androgen receptors, such as enzalutamide, imparted durable clinical benefit with biochemical and radiological responses in a subset of metastatic CRPC patients (~25 %), without dose-limiting

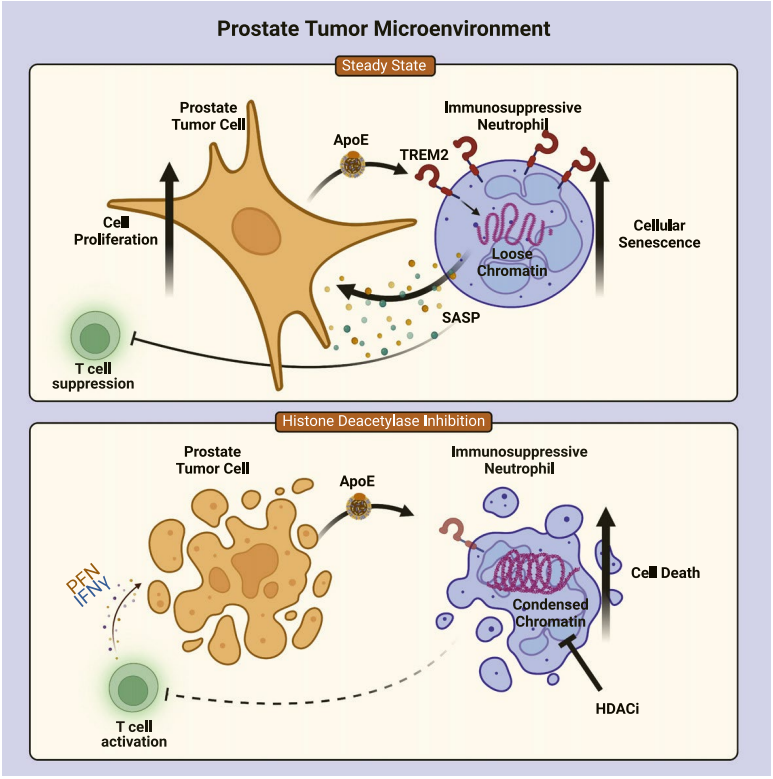

Figure 6. *Immunosuppressive neutrophils express markers of senescence in the prostate tumor microenvironment. Tumor-derived ApoE induces senescence in TREM2+ neutrophils. TREM2+ neutrophils correlate with poor prognosis in prostate cancer patients. HDAC inhibition eliminates senescent neutrophils, improving cancer therapy efficacy.*

From Bancaro N et al. «Apolipoprotein E induces pathogenic senescent-like myeloid cells in prostate cancer». Cancer Cell, 2023.

toxicity. We further demonstrated at clinical level that in patients with mCRPC, neutrophilia associated with tumor cell expression of senescence-related transcripts and that elevated levels of CXCR2 ligands were associated with increased infiltration of myeloid cells and were prognostic of worse disease. Consistently, inhibition of myeloid cell infiltration into tumors through CXCR2 inhibitors reduced the immunosuppressive and pro-tumorigenic signaling within the tumor microenvironment, restoring the effectiveness of therapies like androgen-deprivation therapy[65].

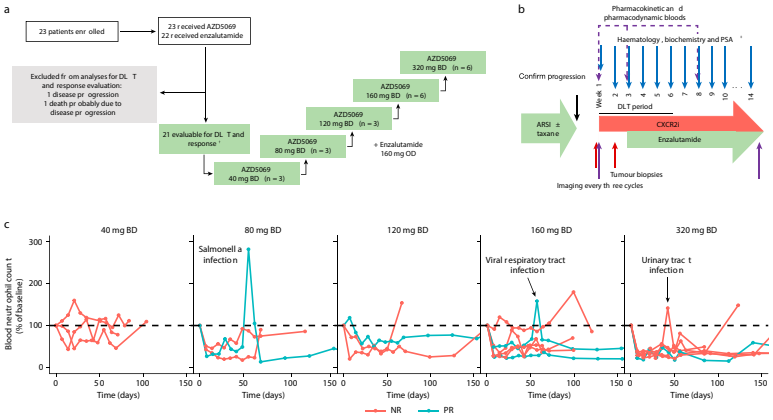

Figure 7. a. *Patient disposition per Consolidated Standards of Reporting Trials guidelines. †Two patients were replaced per protocol after coming off study before completing the DLT period for a reason other than a DLT, and therefore were not evaluable for the primary endpoint or response.* ***b****, Clinical trial schema. Patients had confirmed disease progression on androgen deprivation therapy and at least one ARSI. Week count relative to the commencement of AZD5069 administration is shown. Cohorts 1–4 started AZD5069 2 weeks before enzalutamide; cohort 5 started drugs concurrently. ‡PSA test was carried out on day 1 of each cycle.* ***c****, By-patient, serial, peripheral blood neutrophil counts for each dose level of AZD5069. All available data points up to day 150 are shown. NR, patient classed as a non-responder; PR, patient classed as a partial responder.*

From Guo C et al. «Targeting myeloid chemotaxis to reverse prostate cancer therapy resistance». Nature, 2023.

Moreover, the combination therapy also enhanced the infiltration and activity of cytotoxic T cells within the tumor, suggesting that blocking myeloid chemotaxis not only prevents the formation of a supportive microenvironment but also reinvigorates anti-tumor immune responses.

The study provides a strong rationale for the clinical development of CXCR2 inhibitors as adjunct therapies in prostate cancer treatment, particularly for patients with advanced or therapy-resistant forms of the disease. By disrupting the myeloid cell-mediated resistance mechanisms, these inhibitors could enhance the efficacy of existing therapies and potentially overcome resistance in patients who have limited treatment options.

These findings also encourage the exploration of similar strategies in other cancers where myeloid cells play a role in therapy resistance. This research also highlighted the dynamic nature of the tumor microenvironment and its role in shaping cancer's response to therapy. The translational data from the clinical study described above indicate that CXCR2 blockade upregulates the expression of the chemotactic cytokines CXCL1, CXCL2 and CXCL8. Of note, we have also found co-expression of CXCR1 with CXCR2 on intratumor MDSCs of mCRPC, indicating that CXCR1 redundant signaling may limit the biological impact of selective CXCR2 inhibition[65]. Overall, these data suggest that combined CXCR1 and CXCR2 inhibition is required to maximize clinical benefit from this therapeutic strategy. We are therefore now starting a new proof-of-mechanism and proof-of-concept clinical trial evaluating the safety, tolerability, biological and antitumor activity of dual CXCR1 and CXCR2 blockade in combination with apalutamide for men suffering from metastatic castration-resistant prostate cancer (mCRPC).

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ANDREA ABLASSER

BORN IN 1983 IN AACHEN, GERMANY

FULL PROFESSOR OF LIFE SCIENCES AT THE ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE (EPFL),

FOR HER GROUND-BREAKING WORK ON THE CGAS-STING PATHWAY, FOR ELUCIDATING ITS ROLE IN INNATE IMMUNITY AND IDENTIFYING IT AS A TARGET FOR THE TREATMENT OF INFLAMMATORY DISEASES

LAUSANNE, 29TH NOVEMBER 2024

IN THE NAME OF THE FOUNDATION BOARD:

THE PRESIDENT

THE VICE PRESIDENT

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ANDREA ABLASSER

CURRICULUM VITAE

Contact/Personal

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Date of birth: 13th July 1983
Martial status: married; two children: Maximilian (*2021), Felix (*2024)

Education

2010	Dissertation in Medicine, Ludwig-Maximilians-University, Munich *(Summa cum laude)*
2008	Approbation in Medicine National German Medical Exam (grade: 1.0; top 0.2 % of all students in GER)
2001–2008	Medical School, Ludwig-Maximilians-University, Munich, GER, with clinical rotations at Harvard Medical School, Boston, USA, and at the University of Oxford, UK

Professional Experience

Since 2021	Full Professor, Swiss Federal Institute of Technology Lausanne, CH
2019–2021	Associate Professor, Swiss Federal Institute of Technology Lausanne, CH
2014–2019	Tenure Track Assistant Professor, Swiss Federal Institute of Technology Lausanne, CH
2008–2014	Post-doctoral research fellow, University of Bonn, GER

Distinctions and Fellowships

2024 NOMIS distinguished Scientist Award
2020/2022/2023 Named *«Highly Cited Reseacher»* by the Clarivate Analytics
2023 SNSF Consolidator Grant
2022 Elected member, German Academy of Sciences Leopoldina
2020 Prix Leenards for Translational Medical Research
2019 Elected member, European Molecular Biology Organization (EMBO)
2018 ERC Starting Grant
2014 SNSF Starting Grant
2007 Fellow of the Munich-Harvard-Alliance and German Academic Exchange Service (DAAD)
2005 Fellow of the German National Merit Foundation (Studienstiftung des Deutschen Volkes)

Awards

2025 Paul Ehrlich and Ludwig Darmstaedter Prize
2024 Cloëtta Prize
2023 Paul-Martini-Prize
2021 EMBO Gold Medal
2021 Pezcoller Foundation-EACR Translational Cancer Researcher Award
2021 Dr. Josef Steiner Cancer Award
2021 German Cancer Award
2021 Friedrich Miescher Award
2020 William B. Coley Award
2019 Sanofi-Institut Pasteur International Junior Award
2019 Prix Zonta
2018 National Latsis Prize
2018 ACTERIA Early Career Research Prize in Immunology
2018 Eppendorf Award for Young European Investigators
2014 GlaxoSmithKline Award for Basic Medical Research

2014 Paul Ehrlich und Ludwig Darmstaedter Prize for Young Researchers
2013 Max von Pettenkofer Prize
2013 Jürgen Wehland Prize
2010 Dissertation Prize of the University of Munich

Field of Research

The innate immune system is critical for maintaining health but it also contributes to a range of human diseases. My research focuses on understanding how cells sense DNA as a danger signal and how this translates into the regulation of innate immunity. With my scientific efforts I aim at elucidating fundamental principles of our immune system and at inspiring new therapeutic approaches for the treatment of inflammatory conditions and cancer (Ablasser A. and Chen Z., Science 2019).

Selected Publications

- The CRL5-SPSB3 ubiquitin ligase targets nuclear cGAS for degradation.

Xu, P., Liu, Y., Liu, C. *et al.* The CRL5–SPSB3 ubiquitin ligase targets nuclear cGAS for degradation. *Nature* **627**, 873–879 (2024). https://doi.org/10.1038/s41586-024-07112-w

- cGAS/STING drives ageing-related inflammation and neurodegeneration.

Gulen, M.F., Samson, N., Keller, A. *et al.* cGAS–STING drives ageing-related inflammation and neurodegeneration. *Nature* **620**, 374–380 (2023). https://doi.org/10.1038/s41586-023-06373-1

- Clathrin-associated AP-1 controls termination of STING signalling.

Liu, Y., Xu, P., Rivara, S. *et al.* Clathrin-associated AP-1 controls termination of STING signalling. *Nature* **610**, 761–767 (2022). https://doi.org/10.1038/s41586-022-05354-0

- The cGAS-STING pathway drives type I IFN immunopathology in COVID-19.

Domizio, J.D., Gulen, M.F., Saidoune, F. *et al.* The cGAS–STING pathway drives type I IFN immunopathology in COVID-19. *Nature* **603**, 145–151 (2022). https://doi.org/10.1038/s41586-022-04421-w

- Structural mechanism of cGAS inhibition by nucleosomes.

Pathare, G.R., Decout, A., Glück, S. *et al.* Structural mechanism of cGAS inhibition by the nucleosome. *Nature* **587**, 668–672 (2020). https://doi.org/10.1038/s41586-020-2750-6

- BAF restricts cGAS on nuclear DNA to prevent innate immune activation

B. Guey; M. Wischnewski; A. Decout; K. Makasheva; M. Kaynak *et al. Science*. 2020-08-14. Vol. 369, num. 6505, p. 823–828. DOI: 10.1126/science.aaw6421.

- Targeting STING with small-molecule covalent inhibitors

Haag, S.M., Gulen, M.F., Reymond, L. *et al.* Targeting STING with covalent small-molecule inhibitors. *Nature* **559**, 269–273 (2018). https://doi.org/10.1038/s41586-018-0287-8

- cGAS produces a 2'-5'-linked cyclic dinucleotide second messenger that activates STING.

Ablasser*, … , Hornung*; *co-corresponding author
Ablasser, A., Goldeck, M., Cavlar, T. et al. cGAS produces a 2'-5'-linked cyclic dinucleotide second messenger that activates STING. *Nature* **498**, 380–384 (2013). https://doi.org/10.1038/nature12306

- Cell intrinsic immunity spreads to bystander cells via the intercellular transfer of cGAMP. Ablasser,…, Hornung.

Ablasser, A., Schmid-Burgk, J., Hemmerling, I. *et al.* Cell intrinsic immunity spreads to bystander cells via the intercellular transfer of cGAMP. *Nature* **503**, 530–534 (2013). https://doi.org/10.1038/nature12640

Innovation & Technology Transfer

The discovery of cGAMP (Ablasser et al., Nature 2013 (a)) led to the development of a novel class of immunotherapy. Several major pharmaceutical companies (GSK, Merck, BMS) and various start-ups are conducting or preparing clinical trials with cGAMP derivatives for cancer immunotherapy.
Following my discovery of STING inhibitors (Haag et al., Nature 2018), I have co-founded IFM Due, Boston, US, which has developed next generation STING inhibitors for the treatment of autoimmune and inflammatory diseases. In 2019, IFM Due started a collaboration with Novartis for the development of first-in-class, first-in-human STING antagonists. In 2024, IFM Due's program was accepted for clinical testing and acquired by Novartis.

Patents

- «STING inhibitors» (WO 2019/122202); Authors: Ablasser A, Reymond L, Haag S, Roush W, Venkatraman S. «cGAS super-enzymes for cancer immunotherapy» (WO 2023/161178 AI); Authors: Ablasser A, Samson N, Keller A.
- «The CRL5SPSB3 ubiquitin ligase targets nuclear cGAS for degradation» (EU Provisional Patent Application EP23180944); Authors: Ablasser A, Li L, Xu P.
- «Compounds for the treatment of inflammatory diseases» (EU Provisional Patent Application EP24178191); Authors: Ablasser A, Hooftman A, Reymond L.

Professional Service & Teaching

- Co-organizer Keystone Symposium «Resolution of Inflammation and Inflammaging» (to be held 2025/6)
- Member working group «RNA-based medicines»of the German National Academy of Sciences Leopoldina (2022–)
- Co-organizer International Conference on Nucleic Acid Immunity, Dresden, GER (2023)

- Co-organizer Keystone Symposium «Innate Immunity: From Innate Sensing to Adaptive Immunity» Snowbird, USA (2023)
- Member of the Scientific Steering Committee of the Dubochet Center for Imaging, EPFL (2021–)
- Member and chair of the steering committee of the Biomolecular Screening Facility, EPFL (2021–)
- Editorial board member Cell (2021–)
- Member of the Interdisciplinary Seed Fund committee, EPFL (2020)
- Editorial board member Immunity (2019–)
- Main organizer CSF Monte Verrat Workshop «Nucleic Acid Immunity» (2018)
- Co-organizer of EPFL Life Science Faculty Retreats (2017, 2018)
- Member of the EPFL summer research program (SRP) committee (2018–)
- Member of the EDMS doctoral program committee (2015–)
- Main instructor «Immunology – advances and therapeutic implications»; Master level; EPFL (2014–)
- Instructor «Landmark Papers in Cancer and Infection»; PhD level, EPFL (2016–)
- Instructor «Physiology II (Immunology)»; Bachelor level; EPFL (2016–2022)

Research Funding

I have managed more than 20 research grants that were awarded by different national and international funding agencies, foundations, or biopharmaceutical companies, including ERC, SNSF Starting and Consolidator grants, SNSF Project grants, EMBO, Else Kröner-Fresenius-Stiftung, Novartis Foundation for Medical Research, BRIDGE Discovery, Swiss Life, UCB Pharma, IFM Therapeutics, Fondation Acteria, Gebert Rüf Stiftung, NCCR Chemical Biology, Dr. Josef Steiner Cancer Grant, Fondation Leenards, NOMIS foundation.

DISCOVERY AND THERAPEUTIC TARGETING OF CGAMP – AN ANCIENT SIGNAL OF INNATE IMMUNITY

Viruses are the most abundant and diverse pathogens on earth. Every organism must defend itself against viral infection – antiviral immunity is essential for life. Across the tree of life, from bacteria and plants to animals and humans, distinct antiviral defense systems have evolved that sense infection and, in turn, initiate cellular responses to block viruses from replication and further spread. Our research focuses on one of nature's most fundamental mechanism of antiviral immunity, which is governed by so-called cyclic dinucleotides and conserved over billions of years. Understanding the molecular basis of this ancient mechanism of antiviral immunity made possible entirely new therapeutic approaches for treating cancer and inflammatory diseases by engaging or suppressing, respectively, cyclic dinucleotide-mediated immune responses.

The recognition of DNA from incoming viruses is a highly conserved strategy to detect invading microbes. Utilizing the «building blocks» of life itself to sense infection allows the immune system to respond to virtually all classes of pathogens with the only exception being RNA viruses. Knowledge about the existence of an innate immune defense system, which is directed by (viral DNA) dates back to the middle of the last century. By then it was shown that the presence of viral DNA in the interior of a cell can trigger potent type I interferon (IFN) responses (Isaacs et al., 1963). Despite these early insights, it has only been over the last 15 years that the mechanism behind this mysterious DNA sensing and signaling machinery has been revealed. First studies have identified that a gene termed *STING1* encoding for STING was crucial for mediating a cellular immune response to DNA (Ishikawa et al., 2009). In separate work, STING was then found to act as receptor that mediates immune responses towards bacterial cyclic dinucleotides – molecules that at the time were only known as bacterial, but not metazoan, second messenger signals (Burdette et al., 2011; Woodward et al., 2010). Further work then discovered that an enzyme, termed cyclic GMP-AMP synthase (cGAS), is positioned upstream of STING and activated by DNA to produce an endogenous cyclic dinucleotide, which akin to bacterial cyclic dinucleotide

signals, stimulates STING to produce antiviral mediators (Sun et al., 2013). Work by us then established that the cGAS-derived cyclic dinucleotide, cGAMP, is composed of an entirely novel linkage chemistry associated with outsized immuno-stimulatory properties in human cells (Ablasser, Goldeck, et al., 2013). Additional early work from us revealed that cGAMP acts as an immune signaling molecule that operates between cells, revealing an entirely novel principle by which innate immunity can be propagated at the tissue level (Ablasser, Schmid-Burgk, et al., 2013). Today, we know that this cyclic dinucleotide-based defense mechanism – the cGAS- STING pathway – originated in bacteria over billions of years ago to protect from phage infection (Cohen et al., 2019; Morehouse et al., 2020). Meanwhile, numerous studies have highlighted the importance of the cGAS-STING pathway as a central intracellular innate immune sensing system, and shown that intrinsically produced cGAMP is pivotal for mounting an antimicrobial responses against a diverse range of medically relevant pathogens (Ablasser & Chen, 2019) ***(Fig. 1).***

Apart from protecting from infection, the innate immune system is also essential in fending off tumors. We and others have independently shown that cGAMP produced by activated cGAS can provoke a STING-dependent inflammatory response in transforming cells and cells exposed to genotoxic agents to promote senescence, a hallmark mechanism of tumor suppression (Gluck et al., 2017; Yang et al., 2017). Together with other

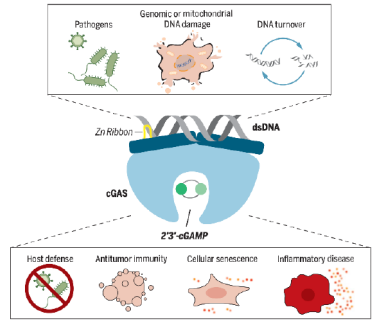

Fig. 1 | cGAS in action: Expanding roles in immunity and inflammation *(Ablasser & Chen, 2019).*

studies, understanding the involvement of cyclic dinucleotides in natural and therapy-induced antitumor immunity has provided a new framework for the treatment of cancer (Samson & Ablasser, 2022). Accordingly, many studies in preclinical models have shown that cyclic dinucleotides can have profound anti-tumor effects through engaging STING, and the stimulation of antitumor immunity (Corrales et al., 2016). As a results of this line of investigation, cGAMP-based molecules and next-generation STING agonists are being tested in various settings for the treatment of solid cancers and lymphoma.

While innate immunity can be beneficial in the context of cancer, many most prevalent human diseases will benefit from interventions that block aberrant inflammation. Notably, the past decade has revealed that aberrant cGAMP production and STING signaling is relevant for the pathogenesis of many common inflammatory diseases, including myocardial infarction, metabolic liver disease, cancer and metastases, autoimmune disorders, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and many more (Decout et al., 2021). As detailed below, we have contributed to this line of research by showing the detrimental effects of excessive and chronic STING signaling in COVID-19 and even in the natural degenerative process of aging (Di Domizio et al., 2022; Gulen et al., 2023). With the advanced understanding of the broad pathogenic roles of the cGAS-STING pathway, the idea emerged that inhibition of this mechanism might be a powerful strategy for many human diseases. Yet, attempts to define inhibitors of the pathway proved immensely difficult. Back in 2018, we described first small-molecule inhibitors of STING and demonstrated for the first time that STING blockade could ameliorate detrimental immune activation in a preclinical model of autoinflammation (Haag et al., 2018). As of today, numerous studies have further evidenced that blocking cGAMP- mediated activation of STING in autoimmune and inflammatory disease contexts can have substantial clinical benefits. Consequently, many world-leading pharmaceutical companies and biotech start-ups have initiated programs aimed at diminishing the pathological effects of cGAMP-induced immunity by targeting cGAS or STING. It is anticipated that cGAS or STING blocking medicines can profoundly impact the way inflammatory diseases will be managed in the future.

The mechanism of innate immune activation in general and the cGAS-STING pathway in particular are by now fairly well documented. By contrast, host strategies to prevent, regulate and terminate DNA-dependent immunity are still poorly understood. Yet, innate immunity demands precision and control. This paradigm applies even more so for DNA sensing. An essential element of life, DNA is common to both microbes and the host and it has all the potential to serve as potent ligand for cGAS. The risk of self recognition makes the use of DNA sensors a curious strategy with potentially adverse consequences for the host – as illustrated above. Hence, at the foundation of any discussion on activation of DNA-induced immunity is a discussion of its regulation. Over the past years, we have elucidated several molecular «checkpoints» that together direct cGAS-STING preferentially towards sensing of infection, while tolerating host nucleic acids (Guey & Ablasser, 2022; Wischnewski & Ablasser, 2021). In the following sections, I will put more context to the scientific achievements we have made over the past years, and I will conclude with offering a glimpse into some unresolved mysteries of innate immunity that we seek to tackle in ongoing and future research.

The cGAS-STING pathway regulates cellular senescence

Senescence is a cellular program in which cells stop dividing and undergo profound transcriptional changes. Initially discovered in human fibroblasts upon extensive *in vitro* culture, it has now become clear that senescence is highly relevant for various distinct biological processes including tumour suppression, wound healing, embryonic development, tissue repair and also, paradoxically, tumorigenesis (Campisi, 2013). Moreover, senescence has a fundamental role in organismal ageing (Childs et al., 2015). A hallmark of senescent cells is the production of a diverse set of cytokines and chemokines, collectively referred to as the senescence-associated secretory phenotype (SASP) (Coppe et al., 2008). Of importance, through the SASP senescence can be transmitted to bystander cells and, thus, the SASP is critically involved in the reinforcement and propagation of senescence in cell cultures *in vitro* and also in tissues and organs *in vivo*. But despite the central role of the SASP in senescence the mechanism of its regulation remained for long unclear.

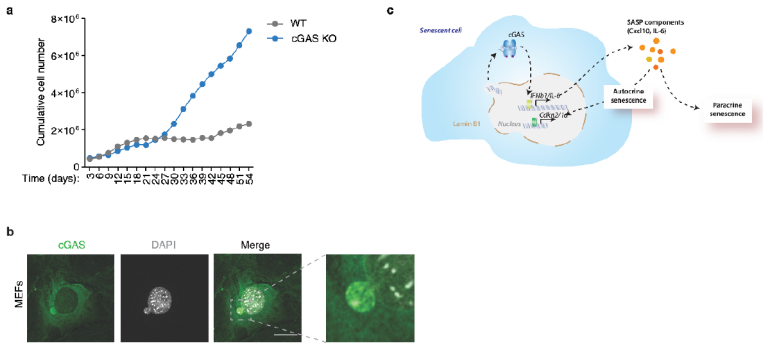

Fig. 2 | Regulation of senescence by the cGAS-STING signalling pathway. *(a) Proliferation curves of wild-type (WT) and cGAS KO mouse embryonic fibroblast (MEFs) in culture. (b) In senescent MEFs cGAS (green) enriches at chromatin (grey), which protrudes into the cytosol. (c) Model of the mechanism underlying cGAS-dependent regulation of cellular senescence.*

Studying cellular functions of cGAS, we repeatedly observed that cells deficient for cGAS showed a markedly reduced senescence response upon extensive culturing *in vitro* ***(Fig. 2a)***. Similar to cells deficient for cGAS, cells derived from STING knockout (KO) mice exhibited a reduced senescence response, as did human fibroblast that were depleted of cGAS. Together, these data indicated that the cGAS-STING pathways participates in the regulation of cellular senescence. Given its core function in the regulation of cytokine secretion during infection, we next probed whether cGAS may influence senescence in a paracrine manner. Indeed, we found that cGAS KO cells were severely compromised in the production of SASP factors and, consequently, failed to propagate the senescence response. We then focused to understand the mechanism of cGAS activation in senescent cells. We postulated that aberrant DNA fragments, as accumulating during senescence, can act as cell-intrinsic activators of cGAS ***(Fig. 2b)***. Finally, we tested the physiological relevance of cGAS by assessing its involvement in oncogene-induced senescence *in vivo*. To this end, we delivered an oncogene *(Nras G12V)* into wild-type and cGAS KO mice and examined the senescence response in the liver. Remarkably, we found that the livers of mice deficient for cGAS

showed a markedly reduced senescence response as indicated by decreased expression of senescence markers (e.g., p21 expression, SA-β-Gal activity) and SASP production. Together, these findings established endogenous DNA sensing through the cGAS-STING pathway as an important regulator of senescence and the SASP (Gluck et al., 2017) ***(Fig. 2c).***

Description of first-in-class small molecule inhibitors of STING

Today the role of cGAS and STING as drivers of disease-associated inflammation is well established (Decout et al., 2021). As a result, extensive research efforts both from academia and the pharmacology industry aim at blocking the cGAS-STING pathway in a number of human diseases. In 2018, with the broad involvement of cGAS/STING in inflammatory disease awaiting discovery, we set out to identify small-molecule compounds capable of manipulating STING-driven type I IFN responses (Haag et al., 2018). By performing high-throughput chemical screens, we identified two compound classes, both of which specifically blocked STING at nanomolar concentrations. In a series of subsequent experiments, we were able to reveal an unexpected mechanism of inhibition in its very detail. We found that the compounds act on STING by covalent binding to a cysteine residue, which is located at the transition between a cytosolic loop and a transmembrane region of STING. This binding impairs the palmitoylation of STING and, thereby, retains STING in a signaling incompetent state. Remarkably, administration of the identified compounds to mice suffering from an auto inflammatory disease resulted in a significant amelioration of several disease-associated features ***(Fig. 3)***. Our work therefore presented for the very first time compelling experimental evidence that drug-mediated suppression of STING is effective in the setting of inflammatory disease. Apart from rare autoin-

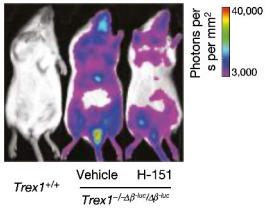

Fig. 3 | Targeting STING with small- molecule inhibitors. *Trex1 KO mice expressing a IFN-b inducible luciferase contstruct (Trex1-/-Δβluc/Δβluc) were treated or not with H1-51 and overall luciferase activity was assessed. WT mice severed as control.*

flammatory diseases, aberrant cGAS/STING activity turned out to be relevant in the broader category of autoimmune and inflammatory diseases, and it is reasonable that additional medical indications will be defined as the field keeps progressing. The STING antagonists described by my group immensely aided the exploration of relevant disease indication. Beyond offering an invaluable new research tool to advance insight into the biology of STING, new pharmacological agents – based on this discovery – have transitioned into clinical development and testing. It is expected that pharmacological blockade of the cGAS-STING pathway will have enormous impact on the clinical management of diverse inflammatory conditions with huge unmet medical need.

The cGAS-STING pathway is a driver of immunopathology in COVID-19

Coronavirus disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected hundreds of millions people worldwide. A salient feature of the disease is that it can result in a large spectrum of clinical outcomes: whereas some individuals develop mild upper respiratory tract symptoms or even remain asymptomatic, others progress to severe pulmonary disease, multi-organ failure, and death. Several correlative and descriptive clinical studies have established that hyper-activation of the innate immune system is an essential contributor to the development of severe disease (Blanco-Melo et al., 2020). Despite this progress, mechanistic insight into the underlying immunopathology remained scarce early into the pandemic. Moreover, most immune profiling in living patients had initially been conducted in samples obtained from blood. While these approaches have yielded valuable information about COVID-19, they have failed to accurately reflect cellular and molecular events at the tissue level, where disease manifests. Together, these limitations left a big gap in our understanding of COVID-19 pathogenesis.

To gain insight into the immuno-pathological processes at the tissue level, we profiled skin manifestations of ten COVID-19 patients. This led us to uncover a macrophage-dependent type I IFN signature with prominent signs of endotheliopathy, a hallmark feature of COVID-19 ***(Fig. 4a)***.

Based on the strong correlation between the accumulation of dying cells and the levels of type I IFNs, we hypothesized that cell damage-mediated activation of the cGAS-STING pathway is at the origin of hyper-inflammatory responses in COVID-19. In support of this idea, we detected selective biomarkers of cGAS-STING activity in skin biopsies and lung autopsies from COVID-19 patients ***(Fig. 4b)***. To further dissect the mechanism of cGAS-STING activation in the lung, we devised a vascularized lung-on-chip model to recreate *in vitro* the dynamic interaction of macrophages, endothelial, and alveolar cells. Unexpectedly, besides eliciting a STING-dependent type I IFN response in macrophages, airway infection with SARS-CoV-2 also promoted *in trans* activation and cell death of endothelial cells in a STING-dependent manner ***(Fig. 4c)***. Lastly, in a mouse model of SARS-CoV-2 infection, administration of a STING inhibitor reduced lung pathology and cytokine responses resulting in improved overall outcomes (***Fig. 4d)***. In summary, our comprehensive work identified the cGAS-STING pathway as a central driver of immunopathology in COVID-19 (Di Domizio et al., 2022). In doing so, our study revealed the mechanistic basis for the opposing type I IFN responses in COVID-19, which despite its importance, remained poorly understood: in contrast to the direct recognition of viral RNA by Toll-like receptors and RIG-I-like receptors, which promote rapid host-protective type I IFN activities, the cGAS-STING pathway is at the apex of a maladapted innate immune signalling program, which aberrantly responds to tissue

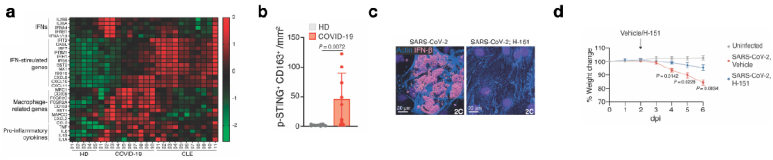

Fig. 4 | cGAS-STING promotes immunopathology in COVID-19. *(a) Immune gene expression profiles of COVID-19 skin lesions, Cutaneous lupus erythematosus, and skin of healthy donors (HD). (b) Quantification of p-STING+ macrophages in COVID-19 skin lesions and healthy skin. (c) Representative 3D images of the vascular face of uninfected or SARS-CoV2-infected LoCs with or without vascular H-151 perfusion. (d) Relative weight loss in mice after SARS-CoV-2 infection with post-infection regimen.*

damage, and, thereby potentiates deleterious inflammation. An important implication of our work is that targeting upstream innate immune sensing machinery in COVID-19 could be more efficacious and safer than currently available immunosuppressive drugs or anti-cytokine therapies.

Discovery of cGAS-STING as a driver of ageing-associated inflammation and neurodegeneration

Aging has been fascinating humankind ever since. A complex process promoted by the confluence of multiple genetic and environmental variables, ageing perturbs physiological integrity and predisposes to the development of several illnesses. A salient feature of ageing – highly conserved in mammals – is the presence of a low-grade inflammatory phenotype, sometimes popularly referred to as «inflammaging», which affects every organ of the body (Franceschi et al., 2018). Critically, age-related inflammation is not merely one out of many parameters that silently accompany the ageing process. Instead, over the last decade of research, strong evidence has built up to implicate inflammation as a pivotal cause of age-related dysfunction and a crucial accelerator of age-related diseases. Supporting this notion, interventions into maladaptive processes during ageing commonly involve a reduction in inflammatory signals. Yet, despite its essential role in ageing, understanding the molecular origins of age-associated inflammation remains incomplete. Prior to our work, no innate immune signalling mechanism has been mapped out clearly to regulate age-dependent inflammation *in vivo*. Further, whether pharmacological targeting of innate immune signalling could ameliorate age- related pathologies, such as neurodegeneration, was originally not known. If revealed, such insight has the potential to pinpoint a strategy to improve human healthspan.

Our discovery on the links between cGAS-STING pathway engagement and cellular senescence – a well-known aging hallmark – prompted us to explore the role of cGAS/STING in ageing *in vivo*. To this end, we administered a small-molecule STING inhibitor, as previously characterized in our laboratory (Haag et al., 2018), to old mice to selectively interfere with cGAS-STING signalling at the end of life. We observed that inhibition of STING in aged mice confers broad suppression against sev-

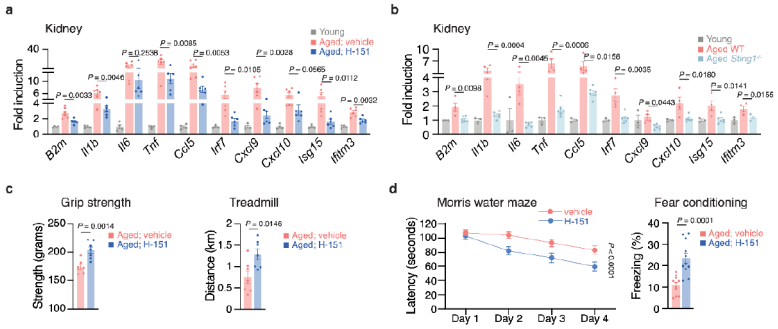

Fig. 5 | STING promotes inflammation and dysfunction in ageing. *(a, b) Kidney mRNA expression levels of proinflammatory and interferon- stimulated genes in young (n = 4) and aged mice treated or not with H-151 (n = 6) (a) and of young (n = 3), aged WT (n = 4) and Sting1-/-mice (n = 6). (b) Relative expression measured to the average of aged vehicle-treated (a) or aged WT (b) mice. (c) Physical condition of aged mice treated or not with H-151 (n = 7), evaluated by grip strength and treadmill running distance. (d) Cognitive function tests (n = 11 mice) evaluated by Morris water maze test (left, latency to reach the platform over multiple days) and fear conditioning (right, % time spent freezing).*

eral inflammatory hallmarks of ageing, both in several peripheral organs and the brain (***Fig. 5a)***. Critically, analysis of tissues from aged *Sting1*-deficient mice revealed similar STING-dependent changes, validating the power of pharmacologically inhibiting STING to interrogate effects of STING during ageing *in vivo* ***(Fig. 5b)***. Remarkably, this decline in inflammation upon STING blockade was accompanied by improved physical and cognitive capability ***(Fig. 5c)***. Similar to the effects in mice, we ascertained that inhibition of STING suppresses age- associated inflammation in senescent models of human cells and human tissue explants.

Intrigued by the observation that STING inhibition restores brain function of old mice, we decided to investigate the upstream molecular events that activate STING in the ageing brain. Combining single-nuclei and bulk transcriptional profiling, biomarker assessment, and functional cellular assays, we uncovered a brain-intrinsic cGAS-STING response originating in microglia to direct pro-inflammatory cytokine expression, tissue inflammation, and neuronal loss in the hippocampus – the central

region of memory processes. In search of an endogenous DNA ligand, we unexpectedly revealed that mitochondrial DNA acts as a trigger of cGAS in aged microglia ***(Fig. 6a)***. Thus, in addition to aberrant genomic DNA, this finding expanded the repertoire of endogenous ligands that promote aberrant immunity in senescence. Finally, to further understand the impact of microglial cGAS activity on brain inflammation and function, we generated a tamoxifen-inducible microglia restrictive cGAS gain-of-function mouse – *the first* ever reported in vivo model enabling the selective engagement of cGAS. Strikingly, we found that unleashing cGAS in microglia phenocopies to a large part their transcriptional profiles in ageing and neurodegenerative diseases resulting in neuronal loss and cognitive impairment ***(Fig. 6b, c)***. Thus, this finding demonstrated that absent any other trigger, microglia-selective activation of the cGAS-STING pathway is sufficient to direct the development of neurodegener-

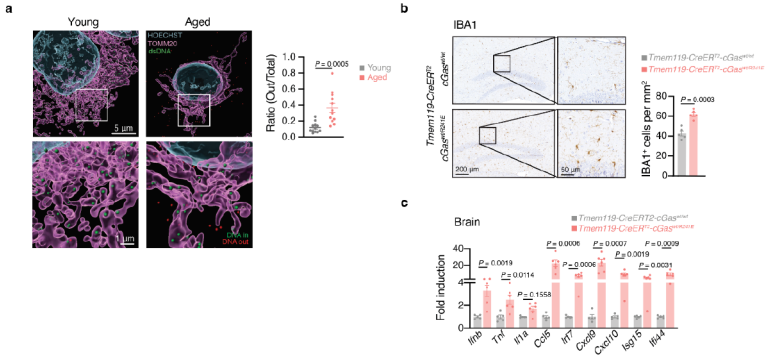

Fig. 6 | DNA-induced cGAS activation promotes microglial activation and neuroinflammation. *(a) Representative 3D reconstructions from Airyscan images and quantification of cytosolic DNA foci outside of mitochondria in microglia isolated from young and aged mice. The ratio of DNA foci outside mitochondria was measured for each cell relative to total counts of cytosolic foci (inside, green, and outside, red) (n = 12 cells, from 3 mice). Scale bars, 5 µm (top), 1 µm (bottom). (b) Representative images and quantification of hippocampal IBA1 staining of Tmem119- creERT2-cGaswt/wt and Tmem119-creERT2-cGaswt/R241E mice (n = 5). Scale bars, 200 µm (left), 50 µm (right). (c) Brain mRNA expression levels of proinflammatory genes and interferon-stimulated genes from Tmem119-creERT2-cGaswt/wt (n = 5) and Tmem119-creERT2-cGas (wt/ R241E)(n = 6) mice.*

ation. In summary, our comprehensive work revealed the cGAS-STING pathway as a critical driver of inflammatory responses during ageing. Further, in establishing a connection between microglia-intrinsic engagement of cGAS/STING and neurodegeneration our work provided insight into a key, but missing aspect in understanding degenerative brain processes. **«One big mystery is how exactly immune cells – […] – talk to the brain»** (Diana Kown, *Nature* June 2022).

Neurodegenerative diseases manifest in a variety of ways. Although each disorder is linked to different hallmark changes, recent evidence points to a core set of microglial transcriptional responses common to a spectrum of distinct conditions (Deczkowska et al., 2018). Crucially, the transcriptional changes elicited by cGAS/STING in microglia that we revealed using our cGAS gain-of-function mouse model are known to be associated with Alzheimer's Disease and other neurodegenerative pathologies. Thus, based on our work, we propose that aberrant cGAS-STING activity could be a common feature of other neurodegenerative conditions.

Molecular mechanism of STING signaling termination

STING is a central mediator of innate immunity and has been exciting a lot of interest as a drug target for novel immunotherapeutics. Since the discovery of STING in 2008, cellular, molecular, and structural studies have provided a detailed understanding of the mechanism by which STING *activates* immune responses (Barber, 2015). But signal transduction cascades in biology demand precise negative-feedback regulation to shape transient responses and ensure homeostasis – the (cGAS-) STING pathway is no exception to this rule. Indeed, it has long been appreciated that inside cells, STING function is strictly controlled by intracellular trafficking events and compartmentalized signal transduction to balance immune outcomes. Upon activation, STING leaves its steady-state location at the endoplasmic reticulum and transits through the Golgi – the site of signal transduction – to finally reach lysosomes, where activated STING is efficiently degraded. Failure in the swift lysosomal degradation of STING or its abnormal retention at the Golgi have been associated with severe autoinflammatory conditions. Despite its critical importance, little was known about negative-feedback regulation of STING,

and no mechanism was described that could explain how signalling at the Golgi is timed and terminated. Together, these aspects left behind an important gap in understanding the fundamental biology of STING. We have identified and structurally characterized the adaptor-protein complex (AP)-1 in the negative regulation of STING, revealing in essence the «beginning of the end» of STING-dependent innate immune activation (Liu et al., 2022).

To elucidate cellular mechanisms of STING regulation, we visualized the trafficking of activated STING inside cells.

Intriguingly, we detected activated STING contained in clathrin-coated vesicles (CCVs), small intracellular vesicles best-known for their function to transport cargos in between distinct cellular compartments ***(Fig. 7a, b)***. Inspired by this observation, we focused on understanding the mechanism by which STING is loaded into CCVs and on characterising the functional consequences of this phenomenon. This led us to discover that

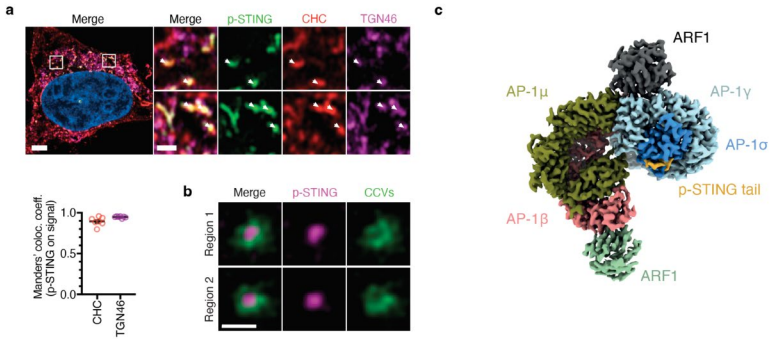

Fig. 7 | Clathrin-associated AP-1 terminates STING signaling*. (a) Airyscan imaging of HeLaSTING cells stimulated with diABZI. One representative cell of n = 7 cells. White arrows point at occurrences of p-STING. Scale bars, 4 μm (left) or 1 μm (zoomed-in squares). Colocalization of p-STING with CHC is quantified by Manders' colocalization coefficients. Mean ± s.e.m. of n = 7 cells. (b) STED images showing p-STING enclosed in CCVs from cells transfected with mCherry-clathrin and Flag-STING and stimulated with diABZI. (c) Cryo-EM reconstruction of the core AP-1 subunits in complex with the phosphorylated C terminal tail of STING.*

the adaptor protein-complex (AP)-1 is recruited onto activated STING, mediating its sorting into CCVs destined for lysosomal degradation. Interfering into this process abolishes lysosomal degradation of STING and leads to exaggerated type I IFN responses. Unexpectedly, we found that STING phosphorylation by the protein kinase TBK1 – the molecular event that launches signalling activation – is required for the recognition of STING by AP-1. A 2.3 Å cryo-electron microscopy structure of phosphorylated STING in complex with AP-1 defined how a single phosphate moiety on STING enables selective recruitment of activated STING ***(Fig. 7c)***. In sum, our results explained the structural basis of negative-regulation of STING and establish that signal initiation is inextricably associated with its termination,

Restricting cGAS from responding to nuclear self DNA

The physical separation between nuclear DNA and cytoplasmic cGAS by the nuclear envelope (NE) has long been viewed as a key cellular safeguard to avoid aberrant innate immune activation. However, transient loss of nuclear integrity can occur during normal physiological processes. It has remained unclear how cGAS is controlled during transient loss of nuclear compartmentalization.

In an effort to interrogate the response of cGAS to perturbation in nuclear compartmentalization, we discovered that the down-regulation of barrier-to-autointegration factor 1 *(BAF)* resulted in robust cGAS-dependent type I IFN responses ***(Fig. 8a)***. We could correlate the cGAS-dependent cellular response with the occurrence of spontaneous nuclear envelope rupture events that were a direct consequence of BAF depletion and resulted in prominent intranuclear cGAS translocation ***(Fig. 8b)***. Notably, several other experimental means to disrupt nucleo-cytoplasmic compartmentalization did not result in cGAS activation, indicating that BAF serves a unique function in the regulation of cGAS. Further study into the mechanism of BAF-dependent control over cGAS uncovered that through its ability to bind dsDNA, BAF effectively compromises cGAS catalytic activity on DNA. Using single-molecule TIRF microscopy, we revealed that rather than passively blocking accessible DNA binding sites, BAF dynamically outcompetes cGAS on DNA and, thereby, prevents the

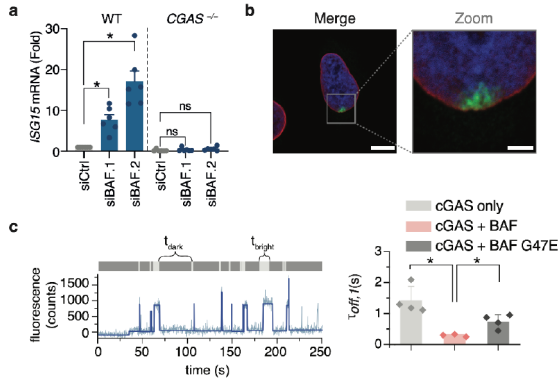

Fig. 8 | BAF restricts cGAS on nuclear DNA to prevent innate immune activation.

(a) A knockdown of BAF induces ISG15 expression in wild- type (WT) but not in CGAS knockout (-/-) HeLa cells. (b) Confocal fluorescence images of BAF KD cells, revealing intranuclear cGAS (green) accumulation. DAPI is shown in blue and lamin A marking the nuclear border in red. (c) Single- molecule analysis of cGAS binding to dsDNA (left) and off- rates of cGAS interactions with DNA in the absence or presence of BAF or DNA-binding defective BAF G47E mutant, respectively.

formation of stable DNA-cGAS interactions ***(Fig. 8c)***. At the cellular level, we validated that on exposed nuclear DNA, cGAS can only accumulate in significant amounts in the absence of BAF, explaining why BAF is a critical checkpoint in innate DNA regulation. Compared to several other chromatin architectural proteins, BAF stood out in its potency to counteract aberrant self-recognition events of cGAS. In sum, our study revealed a critical cellular safeguard strategy, distinct form physical sequestration, that is utilized by cells to protect themselves against the potentially damaging consequences of aberrant recognition of nuclear self-DNA (Guey et al., 2020).

Structural mechanism of cGAS inhibition by nucleosomes

While the function and regulation of cytosolic cGAS dominated most research over the past years, a growing body of evidence found cGAS present inside the cellular nucleus where it strongly associates with chroma-

tin (Zierhut et al., 2019). The chromatinized state of genomic DNA has been reported to limit cGAS activity and the presence of nucleosomes markedly reduces dsDNA-induced cGAMP synthesis. However, how cGAS can be juxtaposed to nucleosomal DNA without undergoing activation, has so far remained unknown.

In an effort to elucidate the regulation of cGAS inside the nucleus, we made the notable observation that chemotherapeutic drugs (e.g., doxorubicin, aclarubicin) known to evict histones, the building blocks of nucleosomes, led to a robust mobilization of the intranuclear cGAS pool ***(Fig. 9a)***. Moreover, we found that nucleosomes and chromatin arrays potently inhibited dsDNA-induced cGAS catalytic activity in vitro. Based on these findings, we reasoned that nucleosomes directly engage cGAS. We next used Cryo-electron microscopy (Cryo-EM) to elucidate the structural basis of cGAS nucleosome interactions. We found that a

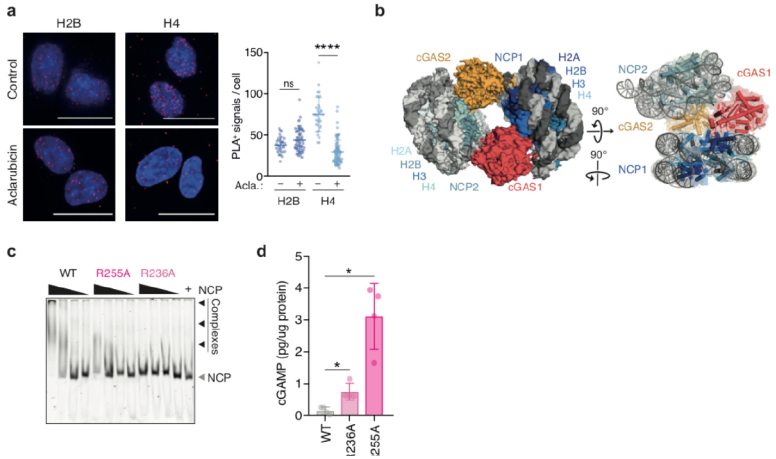

Fig. 9 | Structural mechanism of cGAS inhibition by nucleosomes. *(a) cGAS dynamically engages nucleosomes upon treatment with anthracyclines in HeLa cells as revealed by proximity-ligation assay. (b) Structural overview of the 2:2 cGAS-nucleosome complex. (c) Mutations on the cGAS interface that engages the nucleosome acidic patch (cGAS R255A/R236A) abrogate nucleosome tethering in vitro. d, In living cells, expression of cGAS R236A and R255A triggers spontaneous catalytic activity.*

2:2 cGAS:nucleosome complex is formed *in vitro* and we obtained the structure of the sub-complex comprising one cGAS molecule engaging one nucleosome core particle (NCP) at 3.1 Å resolution ***(Fig. 9b)***. Interestingly, the structure revealed that two independent contact sites are the basis for this core cGAS NCP interaction: one is based on contacts between three cGAS loops and the nucleosome acidic patch, and another one is based on contacts between the dimer interface of cGAS and nucleosomal DNA, respectively. We validated our structural model in several *in vitro* binding and enzymatic activity assays, which confirmed that interaction between cGAS and the acidic patch of the nucleosome are critical to confer inhibition over cGAS disabling an engagement of cGAS with naked dsDNA ***(Fig. 9c)***. An unexpected observation that emerged from our work was that cGAS interacts with a second nucleosome in an *in trans* configuration leading to the formation of multimeric cGAS-nucleosomal complexes ***(Fig. 9b)***. To what extent such *in trans* interaction are relevant in living cells will require future studies. For this study, the relevance of the cGAS interaction with the nucleosome in living cells has turned out to be critical: cGAS mutants unable to engage to the acidic patch showed spontaneous catalytic activity *in vivo* ***(Fig. 9d)***. In sum, our work provided a long sought explanation for how cells can differentiate between self and non-self DNA: nucleosomes serve as inbuilt identifiers of host genomic DNA, which, if present, restrict cGAS activity by tightly engaging the receptor and, thus, rendering cGAS incapable of binding to juxtaposed naked DNA (Pathare et al., 2020). We speculate that this safeguard mechanisms likely has been important for the evolution of the cGAS- dependent innate DNA recognition system.

Discovery of proteasomal degradation to balance nuclear cGAS levels

The somehow unexpected finding that cGAS – a universal DNA sensor equipped with the capacity to induce powerful innate immune response – resides inside the nucleus of cells afforded profound adaptation of our model of cGAS regulation and associated function. Still very little is known about the biological role of nuclear cGAS and the means by which cells control nuclear cGAS to maintain cellular homeostasis was unclear.

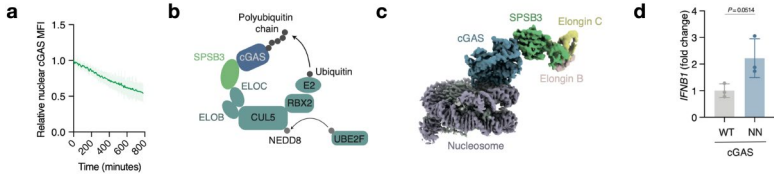

Fig. 10 | Nuclear cGAS degradation by the CRL5-SPSB3 complex. *(a) Relative nuclear cGAS-GFP MFI in post-mitotic HeLa cells. (b) Schematic model of CRL5-directed substrate ubiquitylation via the ELOBC adaptor complex and SPSB3. (c) A composite cryo-EM density map of the nucleosome-cGAS-SPSB3-ELOBC complex, assembled from two focused-refinement maps (nucleosome-cGAS and cGAS-SPSB3-ELOBC). (d) Expression of type I IFN gene expression in cells expressing wild-type (WT) cGAS or a cGAS mutant defective in SPSB3 binding (NN).*

To start exploring the fate of nuclear cGAS, we tracked a GFP-fused version of cGAS by live-cell imaging ***(Fig. 10a)***. From these microscopy studies and follow-up cell biology experiments, we gathered evidence for nuclear cGAS being subject to proteasomal degradation. A focused RNAi screen led us to identify all core components of the cullin 5-RING E3 ubiquitin ligase (CRL5) complex and a previously uncharacterised substrate receptor called SPSB3 as essential in dictating nuclear cGAS protein stability ***(Fig. 10b)***. Intrigued by these findings, we hypothesized that cGAS might be subject to ubiquitylation by the SPSB3-CRL5 complex. Indeed, combining cell biology and biochemistry allowed us to confirm this idea and to uncover a conserved lysine pair on cGAS that CRL5 targets for ubiquitin ligation. To understand how the ubiquitin ligase machinery is recruited to cGAS, we then determined a 3.5 Å cryo-electron microscopy structure of nucleosome-bound cGAS engaging SPSB3 ***(Fig. 10c)***. Remarkably, the structure revealed a highly conserved minimal cGAS degron motif comprising two asparagine residues as the key contact to SPSB3. Mutagenesis of the «NN degron» or the «KK ubiquitin site» on cGAS completely abolishes cGAS destruction by the SPSB3-CRL5 complex both *in vitro* and in living cells. Finally, interference with SPSB3-directed cGAS degradation elevates baseline type I IFN levels in cells providing enhanced protection from viral infection ***(Fig. 10d)***. Along with previously defined interactions with nucleosomes as defined

by us (Pathare et al., 2020), our results provided a complete structural model of nuclear regulation of cGAS, establish a hitherto unknown function for SPSB3-CRL5 in immunity, and demonstrate a role for innate sensing of genomic DNA in priming cell autonomous type I IFN signalling (Xu et al., 2024).

Understanding the molecular and structural rules that dictate the turnover of proteins essential for life has enormously impacted the therapeutic design of innovative medicines. Examples include VHL-mediated degradation HIFa, which governs oxygen sensing, or MDM2-dependent destruction p53, which regulates DNA repair. Likewise, we envision that SPSB3-mediated degradation of cGAS, as revealed in our work, will lay the foundation for a new modality of innate immunotherapy.

Perspective

All living beings need to defend themselves against infection by pathogens. To perceive and respond to pathogens, the cells of the innate immune system are equipped with receptors that recognize specific pathogen-derived features (Takeuchi & Akira, 2010). Following ligand binding, these receptors transduce activity through a series of interactions to specify an immune response, ultimately promoting protection against pathogens. Representing one of the earliest events of an immune response, innate immune signaling continues to be an overwhelmingly important area of biomedical research, and much has been learned about the fundamental mechanisms of immune activation. However, innate immunity demands regulation and signaling activity must be coordinated with environmental cues and cell state for accurate function. As highlighted in the examples above, errors in controlling innate immunity can lead to disease: In fact, inflammation caused by the aberrant activity of innate immune receptors is now being viewed as a major driver of numerous human pathologies as well as natural aging (Furman et al., 2019). Hence, inactivity, negative control and termination are central ingredients of innate immunity. Deciphering the regulatory network of innate immunity is paramount to truly understand innate immunity. It is this core idea that underlies major current and near-future efforts of our research program. We apply a wide range of methods, including structural biology, biochemis-

try, cellular assays, and *in vivo* work, to establish a mechanistic understanding of innate immune control and its impact on cell state and tissue inflammation. We believe that this research can reward us with rich knowledge of the fascinating complexity of the innate immune response, including the discovery of new elements of immune signaling cascades as well as insight into the (re)programmability of immune cell function. Equally exciting, our work can shed new light on the evolution of innate immunity: Did nature differentially utilize regulatory components to adjust innate immune function and potentiate or dampen, respectively, the inflammatory tone in certain species? Last, identifying «innate immune» checkpoints has all the potential to advance the understanding of dysfunctional immune responses in diverse disease contexts.

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Die Stiftung Professor Dr. Max Cloëtta

Die Stiftung Professor Dr. Max Cloëtta wurde am 27. September 1973 in Zürich von Dr. Antoine Cloëtta zu Ehren seines Vaters Prof. Dr. Max Cloëtta errichtet.

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«Die Stiftung bezweckt:
a) die Unterstützung und Förderung der medizinischen Forschung sowie der damit verbundenen naturwissenschaftlichen Hilfsdisziplinen in der Schweiz;
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