DR. JOSEF STEINER KREBSFORSCHUNGSPREIS 2021

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Der Dr. Josef Steiner Krebsforschungspreis 2021
geht an Frau Prof. Dr. Andrea Ablasser.

Frau Ablasser ist Professorin am
Global Health Institute der EPFL in Lausanne.

Die Preissumme beträgt gesamthaft CHF 1‘000‘000.

Dr. Josef Steiner Krebsforschungspreis 2021

Doktor Josef Steiner, Inhaber der „Dr. Steiner Apotheke und Bahnhofdrogerie“ in Biel, hat bei seinem Tode im Jahre 1983 ein grosses Vermögen hinterlassen, welches entsprechend seinem letzten Willen die finanzielle Basis der Dr. Josef Steiner Krebsstiftung bildete. Ziel der Stiftung ist die Förderung der Krebsforschung und die Auszeichnung hochverdienter Wissenschafter auf allen Gebieten der Krebsforschung. Als erster Preisträger konnte 1986 ein Schweizer, Dr. Peter Cerutti, geehrt werden. Seither konnten zahlreiche hervorragende Wissenschafter aus Europa, USA, Australien und der Schweiz mit dem Dr. Josef Steiner Preis ausgezeichnet werden.

Im Bestreben, die Krebsforschung im Sinne des Stifters effizient und nachhaltig zu fördern, wird seit 1998 ein hervorragendes Forschungsprojekt für die Periode von vier Jahren mit einem Betrag von 1’000’000 Schweizerfranken unterstützt. Der Forschungsgruppenleiter oder die Forschungsgruppenleiterin wird zusätzlich mit einem persönlichen Preis in der Höhe von 50'000 Schweizerfranken ausgezeichnet.

Die Auswahl des preisgekrönten Projektes erfolgte nach einem mehrstufigen strengen Auswahlverfahren. Der Dr. Josef Steiner Preis 2021 wurde in renommierten Wissenschafts-zeitschriften ausgeschrieben. Die eingereichten Projektskizzen wurden vom Stiftungsrat und einer aus Fachvertretern zusammengesetzten Preiskommission gesichtet und bewertet. Als Kriterien wurden die wissenschaftliche Qualität und die Originalität der Projektskizzen, die Qualifikation der Projektverfasser, sowie die Beurteilung der Machbarkeit der vorgeschlagenen Projekte in Betracht gezogen. Sechs hervorragende Projektskizzen wurden ausgewählt und die Verfasserinnen und Verfasser aufgefordert, ein überarbeitetes und detailliertes Projekt einzureichen. Für die Projekte wurden 2 vergleichende Beurteilungen von externen Gutachtern eingeholt.

Zusätzlich wurden die sechs Projektverfassenden zu einem aufgrund der Covid-19 Situation virtuell stattfindenden Symposium eingeladen, welches im Januar 2021 im Beisein der Preiskommission und des Vorstandes der Stiftung stattgefunden hat. Anlässlich dieses Symposiums konnten die Forscherinnen und Forscher ihre Projekte vorstellen. Aus diesem strengen Auswahlverfahren ist Fr. Prof. Dr. Andrea Ablasser als Siegerin hervorgegangen.

Laudatio für Frau Prof. Dr. Andrea Ablasser

Die Dr. Josef Steiner Stiftung verleiht den Josef Steiner Krebsforschungspreis 2021 an Frau Prof. Dr. Andrea Ablasser in Anerkennung ihrer bahnbrechenden Forschung im Bereich der Immunerkennung von Viren. Basierend auf ihren Untersuchungen von Mechanismen, mittels welcher das Immunsystem Viren aufgrund derer genetischen Andersartigkeit erkennt, fand sie neue Wege, wie diese Mechanismen auch bei Krebszellen eine Rolle spielen, die sich durch genetische Instabilität und Umgehung der Immunreaktion auszeichnen. Dies eröffnet innovative Aspekte in der Krebs-Immuntherapie, welche zu einer neuen Generation von Immuntherapeutika zur Behandlung von Krebs führen kann.

Curriculum Vitae Andrea Ablasser

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Positions

2021 **Full Professor, Swiss Federal Institute of Technology, Lausanne, CH**

2019 **Associate Professor, Swiss Federal Institute of Technology, Lausanne, CH**

2014 **Tenure Track Assistant Professor, Swiss Federal Institute of Technology, Lausanne, CH**

Education

2010 **Dissertation in Medicine, University of Munich (LMU), Germany**

2008 **Approbation in Medicine, University of Munich (LMU), Germany**

Postdoctoral Training

2008-2014 University of Bonn, Bonn, GER
Institute for Clinical Chemistry and Clinical Pharmacology
Lab. Prof. Dr. Veit Hornung
Position: Postdoctoral Research Fellow and Junior Group leader

Fellowships, Grants and Awards

2021 Pezcoller Foundation-EACR Translational Cancer Researcher Award
2021 Dr. Josef Steiner Cancer Award
2021 German Cancer Award
2021 Friedrich Miescher Award
2020 Named *"Highly Cited Reseacher"* by the Web of Science Group
2020 William B. Coley Award
2020 Prix Leenards for Translational Medical Research
2019 Sanofi-Institut Pasteur International Junior Award
2019 Prix Zonta
2019 Elected EMBO Member
2018 National Latsis Prize
2018 ACTERIA Early Career Research Prize in Immunology
2018 Eppendorf Award for Young European Investigators
2018 ERC Starting Grant
2014 SNSF Starting Grant
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
2007 Fellow of the Munich-Harvard-Alliance
2007 Fellow of the German Academic Exchange Service (DAAD)

2006	Fellow of the Graduate School 1202, German Research Foundation (DFG)
2005	Fellow of the German National Merit Foundation (Studienstiftung des Deutschen Volkes)

Most significant publications

ORIGINAL ARTICLES

1) Pathare G°, Decout A°, Glück S, Cavadini S, Makasheva K, Hovius R, Kempf G, Weiss J, Guey B, Melenec P, Fierz B, Thomä NH*, Ablasser A*. Structural mechanism of cGAS inhibition by nucleosomes. ***Nature*** 2020 Nov;587(7835):668-672. °equal contribution, *corresponding authors

2) Guey B, Wischnewski M, Decout A, Makasheva M, Kaynak M, Sakar MS, Fierz B, Ablasser A. BAF restricts cGAS on nuclear DNA to prevent innate immune activation. ***Science*** 2020 Aug;14;369(6505):823-828.

3) Haag SM, Gulen MF, Reymond L, Gibelin A, Laurence A, Decout A, Heymann M, van der Goot G, Turcatti G, Behrendt R, Ablasser A. Targeting STING with small-molecule covalent inhibitors. ***Nature*** 2018 Jul;559(7713):269-273.

4) Gulen MF, Koch U, Haag SM, Schuler F, Apetoh L, Villunger A, Radtke F, Ablasser A. Signalling strength determines proapoptotic functions of STING. ***Nature Communications*** 2017 Sep 5;8(1):427.

5) Glück S, Guey B, Gulen MF, Wolter K, Kang TW, Schmacke NA, Bridgeman A, Rehwinkel J, Zender L, Ablasser A. Innate immune sensing of cytosolic chromatin fragments through cGAS promotes senescence. ***Nature Cell Biology*** 2017 Sep;19(9):1061-1070.

6) Wassermann R, Gulen MF, Sala C, Garcia Perin S, Lou Y, Rybniker J, Schmid-Burgk JL, Schmidt T, Hornung V, Cole ST*, Ablasser A*. The ESX-1 secretion system of Mycobacterium tuberculosis differentially regulates cGAS- and inflammasome-dependent intracellular immune responses. ***Cell Host & Microbe*** 2015 Jun 10;17(6):799-810. *corresponding authors

7) Ablasser A, Schmid-Burgk JL, Hemmerling I, Horvath G, Schmidt T, Latz E, Hornung V. Cell intrinsic immunity spreads to bystander cells via the intercellular transfer of cGAMP. ***Nature*** 2013 Nov 28;503(7477):530-4.

8) Ablasser A*, Goldeck M, Cavlar T, Deimling T, Witte G, Röhl I, Hopfner K-P, Ludwig J, Hornung V*. cGAS produces a 2´-5´-linked cyclic dinucleotide second messenger that activates STING. ***Nature*** 2013 Jun 20;498(7454):380-4. * corresponding authors

9) Civril F, Deimling T, de Oliveira Mann C. C, Ablasser A, Moldt M, Witte G, Hornung V, Hopfner K-P. Structural mechanism of cytosolic DNA sensing by cGAS. ***Nature*** 2013 Jun 20;498(7454):332-7.

10) Ablasser A, Bauernfeind F, Hartmann G, Latz E, Fitzgerald KA, Hornung V. RIG-I-dependent sensing of poly(dA:dT) through the induction of an RNA polymerase III-transcribed RNA intermediate. ***Nature Immunology*** 2009; 10(10):1065-72.

11) Hornung V, Ablasser A, Charrel-Dennis M, Bauernfeind F, Horvath G, Caffrey DR, Latz E, Fitzgerald KA. AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC. ***Nature*** 2009 Mar 26;458(7237):514-8.

REVIEW ARTICLES

1) Decout A, Katz JD, Venkatraman S, Ablasser A.
The cGAS-STING pathway as a therapeutic target in inflammatory diseases.
Nature Reviews Immunology 2021 Apr 8:1-22.

2) Ablasser A, Hur S.
Regulation of cGAS- and RLR-mediated immunity to nucleic acids.
Nature Immunology 2020 Jan;21(1):17-29.

3) Ablasser A, Chen Z.
cGAS in action: Expanding roles in immunity and inflammation.
Science 2019 Mar 8;363(6431)
4) Glück S, Ablasser A.
Innate immunosensing of DNA in cellular senescence.
Current Opinion in Immunology 2019 Feb;56:31-36.

5) Ablasser A, Gulen MF.
The role of cGAS in innate immunity and beyond.
Journal of Molecular Medicine 2016 Oct;94(10):1085-1093.

6) Hornung V, Hartmann R, Ablasser A, Hopfner K.-P.
OAS and cGAS: unifying concepts in the sensing and signaling in response to cytosolic RNA and DNA.
Nature Reviews Immunology 2014 Aug;14(8):521-8.

Prof. Dr. Andrea Ablasser beschreibt ihr preisgekröntes Projekt wie folgt:

How does a fundamental danger sensing pathway impact on tumor growth and therapy?

The idea to utilize the inherent ability of our immune system to detect and eradicate tumors has been existing for decades. Today, therapies that enhance the functioning of adaptive immune cells can achieve robust tumor regression and, thus, have revolutionized the treatment of several types of cancer. Despite this remarkable success, most patients do not respond to the existing repertoire of immunotherapies or develop therapeutic resistance. This observation highlights the need to explore alternative immune mechanisms that could be a new target in the context of cancer.

In the beginning, the focus of my research had been centered on elucidating how the innate immune system detects viral infection. These efforts led us to contribute to the description of a fundamental signaling pathway, the so-called cGAS-STING pathway, which signals the presence of viral DNA in infected cells (1). In brief, on binding to DNA in the cell cytosol, the enzyme cGAS produces a cyclic dinucleotide molecule called cGAMP. cGAMP functions as a second messenger to activate the adaptor molecule STING, which then initiates a signaling cascade that ultimately triggers the production of numerous innate immune modulators, including secreted cytokines and chemokines. The innate immune response evoked by engaging the cGAS-STING pathway is essential for promoting host defense against various medically relevant pathogens.

Intriguingly, attempts to identify the mechanisms that alert the innate immune system to the presence of growing tumors have uncovered that they are predicated on the same molecular

pathways that also contribute to pathogen recognition. In this regard, it turned out that the recognition of "out-of-context" self-DNA, a hallmark danger signal of damaged cells, through the cGAS-STING pathway constitutes a prime mediator of both natural as well as iatrogenic antitumor immunity (2). For example, cGAMP signaling within immune cells is essential for mounting an effective response against transplanted tumors in mice through generating potent cytotoxic T cell responses (3). In addition, we and others have shown that the cGAS-STING pathway also exerts tumor-suppressive effects from operating within chronically stressed somatic cells en route to malignant transformation (4-6). Finally, the cell and tissue damage inflicted by traditional cancer therapies, including radiotherapy or chemotherapy, has been shown to promote an antitumor immune response involving cGAS-STING pathway activation (7). Together, these and many other reports on the intimate molecular connections between innate immunity and antitumor responses have excited enormous interest in the therapeutic exploitation of the cGAS-STING pathway as a target for the next generation of immunotherapies (Figure 1) (8).

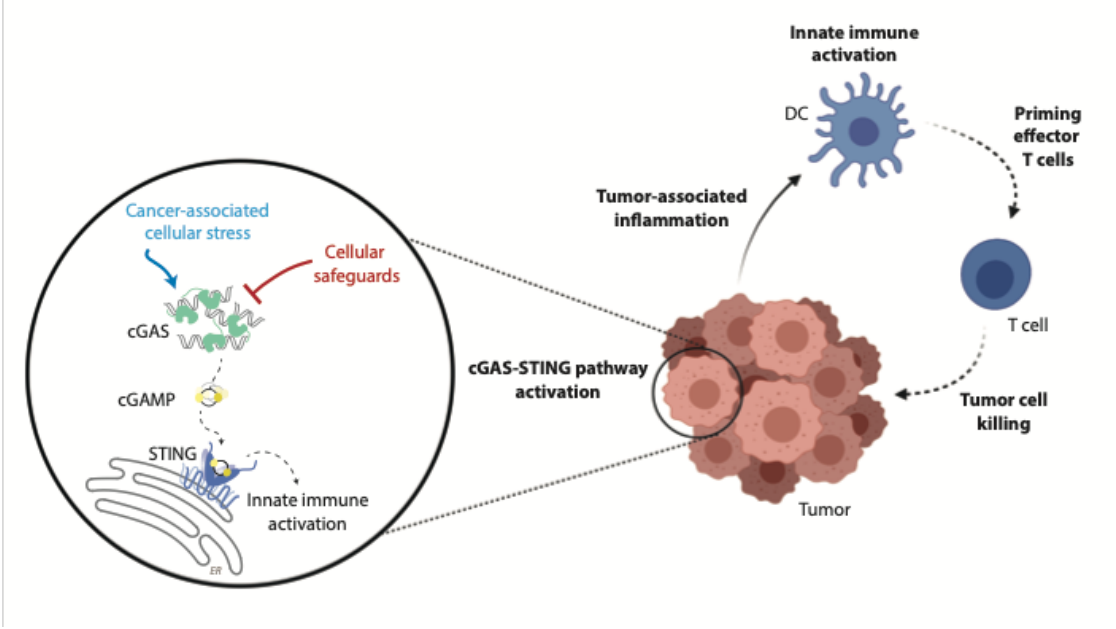

Figure 1 | The cGAS-STING pathway and cancer. On binding out-of-context DNA, cGAS promotes cGAMP synthesis triggering STING and innate immune activation in tumors. At the same time, fundamental cellular safeguard mechanisms inhibit this repsonse. Once engaged in tumors, cGAS-STING signaling can augment tumor-associated inflammation to augment anti-tumor immune responses.

In the lack of a specific, dedicated mechanism to sense cancer, it will be critical to understand how signaling pathways initially evolved to detect pathogens are manipulated or, perhaps, even hijacked by tumors. In this spirit, my laboratory currently seeks to advance our understanding of the biological relevance of the cGAS-STING pathway in the context of antitumor immunity. Toward the realization of this goal, the support from the Dr. Josef Steiner Cancer Award will be of immense importance. In particular, we are interested in providing a more comprehensive insight by focusing on emerging

new features of cGAS-STING pathway regulation, including the mechanisms that limit self-DNA sensing under normal circumstances. For example, we and others have recently shown that inside the nucleus, cGAS is potently suppressed through nucleosomes or chromatin architectural proteins (9-13). In light of these advancements, we will now be able to interrogate to what extend such tolerogenic cellular safeguard strategies contribute to tumor evolution. Next to closing these conceptual gaps in our understanding of cGAS-STING responses in tumors, we also aim to test whether they offer a new means to manipulate cGAS activity to augment the innate immune response for therapeutic purposes. In that respect, synthetic molecules engaging STING have been generated and have yielded promising results in multiple preclinical cancer models (14). Moreover, explorative trials in humans on the efficacy of these treatments are currently ongoing. However, these existing therapies depend on intratumoral application, limiting the usage of these agents for many malignant conditions. The pharmacological targeting of an inhibitor cellular checkpoint of the GAS-STING pathway may represent one strategy to overcome this limitation, and we will address this in the framework of the research project supported by the Dr. Josef Steiner Cancer Award.

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5. Dou Z, Ghosh K, Vizioli MG, Zhu J, Sen P, Wangensteen KJ, et al. Cytoplasmic chromatin triggers inflammation in senescence and cancer. Nature. 2017;550(7676):402-6.
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7. Deng L, Liang H, Xu M, Yang X, Burnette B, Arina A, et al. STING-Dependent Cytosolic DNA Sensing Promotes Radiation-Induced Type I Interferon-Dependent Antitumor Immunity in Immunogenic Tumors. Immunity. 2014;41(5):843-52.
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12. Guey B, Wischnewski M, Decout A, Makasheva K, Kaynak M, Sakar MS, et al. BAF restricts cGAS on nuclear DNA to prevent innate immune activation. Science. 2020;369(6505):823-8.
13. Uggenti C, Lepelley A, Depp M, Badrock AP, Rodero MP, El-Daher M-T, et al. cGAS-mediated induction of type I interferon due to inborn errors of histone pre-mRNA processing. Nature Genetics. 2020;52(12):1364-72.
14. Corrales L, Glickman LH, McWhirter SM, Kanne DB, Sivick KE, Katibah GE, et al. Direct Activation of STING in the Tumor Microenvironment Leads to Potent and Systemic Tumor Regression and Immunity. Cell Rep. 2015;11(7):1018-30.