DR. JOSEF STEINER KREBSFORSCHUNGSPREIS 2023

DR. JOSEF STEINER
KREBSFORSCHUNGSPREIS 2023

Der 23. Dr. Josef Steiner Krebsforschungspreis
geht an Herrn Dr. Inigo Martincorena.

Herr Dr. Martincorena ist Forschungsgruppenleiter am Wellcome Sanger Institut in Cambridge, UK

Die Preissumme beträgt gesamthaft CHF 1‘000‘000.

Dr. Josef Steiner Krebsforschungspreis 2023

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 Cerrutti, 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 2023 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 Minisymposium am Institut für Physiologie eingeladen, welches im Februar 2023 im Beisein der Preiskommission und des Vorstandes der Stiftung stattfand. Anlässlich dieses Symposiums konnten die Forscherinnen und Forscher ihre Projekte vorstellen. Aus dem gesamten Auswahlverfahren ist Hr. Dr. Martincorena als Gewinner hervorgegangen.

Laudatio für Herrn Dr. Martincorena

Die Dr. Josef Steiner Stiftung verleiht den Josef Steiner Krebsforschungspreis 2023 an Herrn Dr. Inigo Martincorena in Anerkennung seiner bahnbrechenden Forschung zum Verständnis somatischer Mutationen in normalen Geweben und deren Auswirkungen auf die Krebsentstehung. Durch eine elegante Kombination von Technologie-Entwicklung und funktionellen Studien konnte er zeigen, dass mutierte Klone mit mehreren krebsfördernden Driver-Mutationen in menschlichen Geweben über die Jahre akkumulieren, was grosse Auswirkungen auf Alterungsprozesse und verschiedene Erkrankungen hat. Die Studien liefern auch wichtige Hinweise auf die molekularen Mechanismen, die den ersten Schritten der Krebsentstehung zugrunde liegen, woraus sich neue Strategien zur Krebsprävention ergeben könnten.

Curriculum Vitae: Inigo Martincorena

Group Leader
Wellcome Sanger Institute
Genome Campus
Hinxton CB10 1SA
United Kingdom

Phone: +44 1223 494818
email: im3@sanger.ac.uk
website:
https://www.sanger.ac.uk/person/martincorena-inigo/

Present Position

2016 - **Group Leader. Wellcome Sanger Institute, Cambridge, UK.**

Education

2002-2007	MSc in Biology and MSc in Biochemistry. University of Navarra, Spain.
2008-2012	PhD (Evolutionary genomics). University of Cambridge and EBI–EMBL, UK.

Postdoctoral Career

2013-2016	Postdoctoral Fellow. Wellcome Sanger Institute, Cambridge, UK.

Fellowships, Grants and Awards

2023	Dr. Josef Steiner Cancer Research Foundation Award
2021 and 2022	Clarivate Highly Cited Researcher
2016-2022	CRUK Career Development Fellowship
2019-present	Fellow Commoner, Queens' College, University of Cambridge
2016-2017	EMBO Advanced Fellowship
2013-2018	Research Fellow, Queens' College, University of Cambridge
2013-2014	EMBO Long-Term Postdoctoral Fellowship
2010-2011	EIOI Fellowship. Ministry of Science. Spanish Government
2008 and 2011	Caja Madrid Foundation Fellowships, presented by HRH Prince of Asturias
2008	Marie Curie Fellowship for Early Stages. European Commission. EBI-EMBL
2007	National Award for Excellence in Academic Performance. Top final grade in a Biochemistry degree in Spain

Most significant publications

ORIGINAL ARTICLES

Cagan A*, Baez-Ortega A, (…), Martincorena I*. 2022. Somatic mutation rates scale with lifespan across mammals.
Nature. 604(7906):517-524.

- *This paper provided an unprecedented description of the somatic mutation rates and signatures across 16 mammalian species, revealing a strong inverse relationship between somatic mutation rates and lifespan across species.*

Abascal F, (…), Osborne JR*, Martincorena I*. 2021. Somatic mutation landscapes at single-molecule resolution.
Nature. 593(7859):405-410.

- *This paper introduced a new sequencing method (NanoSeq) that enables the accurate detection of somatic mutations in single molecules of DNA and the study of somatic mutagenesis in any human tissue, providing novel results for blood, muscle and brain.*

Lawson ARJ, (...), Martincorena I*. 2020. Extensive heterogeneity in somatic mutation and selection in the human bladder.
Science. 370(6512):75-82.

- *This paper described the mutational landscape of normal bladder, reporting high heterogeneity across donors, new signatures and insights into bladder cancer origin.*

Rheinbay E, (…), Martincorena I*, Pedersen JS*, Getz G*. 2020. *Analyses of Non-Coding Somatic Drivers in 2,658 Cancer Whole Genomes.*
Nature. 578(7793):102-111.

- *Analysing the largest collection of cancer whole-genomes available to date, this paper found that non-coding cancer driver mutations are much rarer than anticipated.*

Martincorena I*, Fowler JC, (…), Jones PH*. 2018. *Somatic mutant clones colonize the human esophagus with age.*
Science. 362(6417):911-917.

- *This paper revealed that mutant clones with somatic mutations in key driver genes colonise the human oesophageal epithelium during life, generalising the scope of our previous findings in skin.*

Martincorena I*, (…), Campbell PJ*. 2017. *Universal patterns of selection in cancer and somatic tissues.*
Cell. 171(5):1029-1041.e21.

- *In this study, I adapted methods from evolutionary biology to cancer genomics and applied them to data from 7,600 patients of 29 different cancer types to answer long-standing questions about cancer evolution.*

Martincorena I, (…), Campbell PJ. 2015. *High burden and pervasive positive selection of somatic mutations in normal human skin.*
Science. 348(6237):880-6.

- *This paper provided the first comprehensive description of somatic mutation and selection in a healthy solid tissue, revealing that human skin is a patchwork of thousands of competing clones carrying cancer-driver mutations.*

Martincorena I*, Seshasayee A, Luscombe NM*. 2012. *Evidence of non-random mutation rates suggests an evolutionary risk management strategy.*
Nature. (485):95-98.

REVIEW ARTICLES

Martincorena I, Campbell PJ. 2015. *Somatic mutation in cancer and normal cells.* **Science**. 349(6255):1483-9. Review.

BIOINFORMATICS

dNdScv: R package containing a suite of maximum-likelihood dN/dS methods designed to quantify selection in cancer and somatic evolution. *https://github.com/im3sanger/dndscv*. Commonly used by the cancer genomics community for driver gene discovery.

PATENTS

Methods for the accurate detection of mutations in single molecules of DNA. International Filling Date: 24.11.2021. WO/2022/112751.

Dr. Inigo Martincorena beschreibt sein preisgekröntes Projekt wie folgt:

Understanding and changing cancer risk: Somatic mutation landscapes at population scale

Somatic mutations accumulate in all cells throughout life. By middle age, most human cells have acquired around 1,000 to 2,000 somatic mutations, at a rate of around 20 to 40 mutations per cell per year (Abascal et al., Nature, 2021). Occasionally, a mutation affects a key gene and confers on the mutant cell a growth advantage within the tissue, leading to the expansion of the cell into a clone. Through a continuous process of somatic mutation and selection, normal cells can progressively acquire the hallmarks of cancer cells and develop into tumours. Due to the central role of DNA mutations in cancer development, the ability to sequence cancer genomes in the past decade has transformed cancer research. This has revealed new cancer genes, known and novel mutational processes, shed light on the evolution of cancer, metastases, and resistance, and helped refine diagnosis, stratification, and therapy.

Far less is known about somatic mutations in normal cells and about the earliest steps in the development of many cancers. Studying this has remained extremely difficult, due to the challenge of detecting mutations present in single cells or in microscopic mutant clones in healthy tissues. For the past 10 years, my colleagues and I have focused most of our research on the study of somatic mutation in normal tissues, which has required the development of increasingly sophisticated sequencing methods. Our first studies revealed that, throughout life, the linings of normal skin and oesophagus become colonised by mutant clones carrying mutations in cancer genes, to the extent that by middle age around a third of all cells in these tissues have already acquired one driver mutation in a cancer gene (Martincorena *et al.*, Science, 2015 and 2018). In several subsequent studies, which required the development of new methods, we described the same phenomenon in normal bladder (Lawson et al., Science, 2020), endometrium (Moore et al., Nature, 2020), lung (Yoshida et al., Nature, 2020), liver (Brunner et al., Nature, 2020) and chronic liver disease (Ng et al., Nature, 2021), among others (Moore et al., Nature, 2021). These studies have unveiled an unexpectedly rich and varied landscape of somatic mutations and clonal expansions in normal tissues, providing a window into the earliest changes in the evolution of cancer and have begun to shed new light on the role of somatic mutations in ageing and disease. The somatic mutation landscape of a given individual is expected to be shaped by both their underlying genetics and a lifetime of environmental exposures and lifestyle habits. Mutagenic carcinogens cause mutations in normal cells, often leaving a characteristic mutational signature that provides a record of previous exposures. Non-mutagenic carcinogens may not alter the genome, but they are likely to alter the clonal composition of a tissue, increasing cancer risk through changes on cellular growth or the tissue microenvironment, and leaving a mark in the frequency, type or size of clonal expansions. Thus, genetics, exposures and lifestyle are all likely to modify our somatic mutation landscape, in turn influencing our individual risk of cancer.

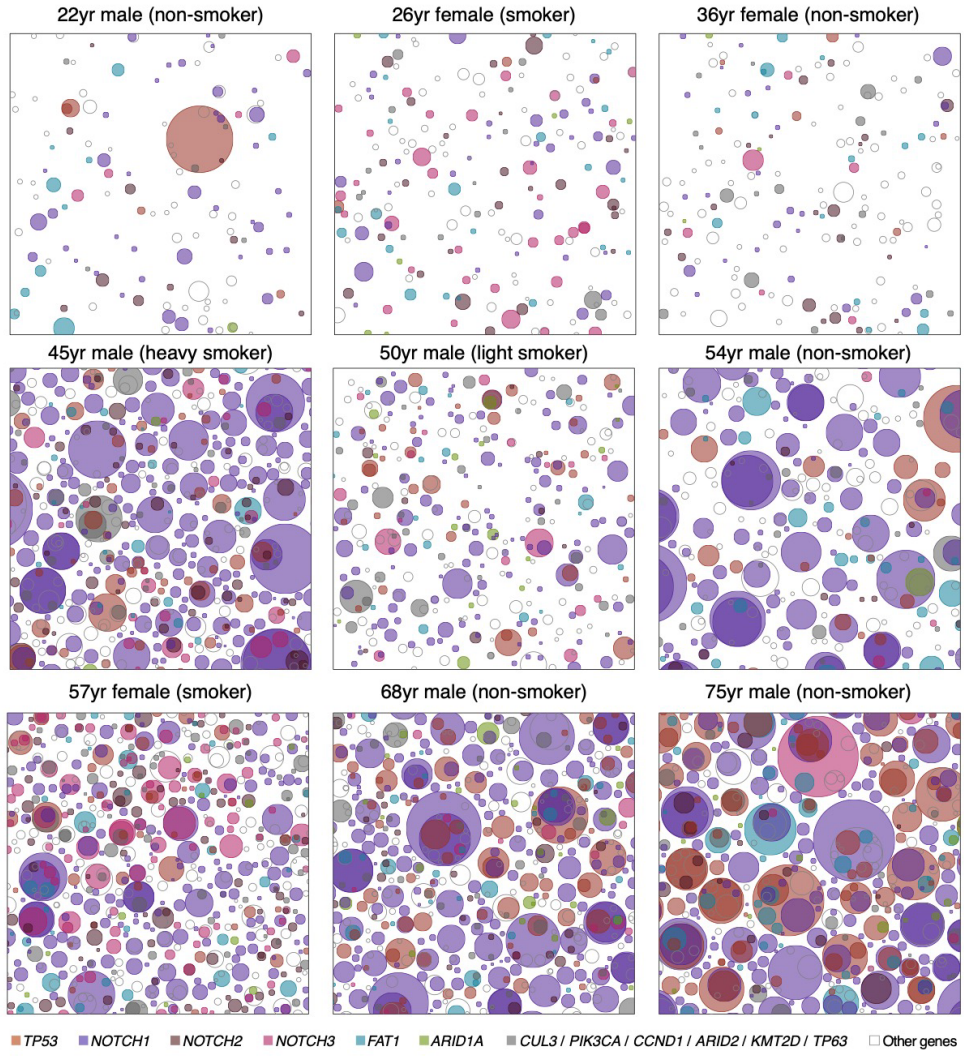

***Figure: Variation of the somatic mutation landscape of normal oesophagus in 9 individuals**. Representation of the clonal composition of oesophageal epithelium in 9 cancer-free individuals (figure from Martincorena et al., Science, 2018). Each square represents 1 cm² of normal oesophageal epithelium from a cancer-free individual, with each circle representing a clone carrying a mutation in a driver gene. The sizes of the clones, their frequency and their density are inferred from DNA sequencing data. The figure summarises the extent to which some normal tissues in healthy individuals become a patchwork of mutant cells carrying cancer-driving mutations as we age.*

Despite the exciting progress of the last few years, so far somatic mutation studies on normal solid tissues have been limited to small numbers of individuals for technical reasons, preventing in-depth studies on how genetics, lifestyle and exposures shape the mutational and clonal composition of a tissue. To address this problem, we have recently developed a new sequencing method (NanoSeq) capable of accurately detecting somatic mutations in single DNA molecules from any tissue, opening the door to somatic mutation studies in large cohorts of individuals using non-invasive samples (Abascal et al., Nature, 2021). Exploiting this new technology, and thanks to the generous support of the Dr. Josef Steiner Cancer

Research Foundation Award, we have launched an ambitious study of the mutational landscape of oral epithelium in 1,000 individuals using buccal swabs collected by post from healthy volunteers. To determine to what extent the variation in mutation rates and clonal expansions is due to exposures or genetics, samples will be obtained from twins in collaboration with the TwinsUK registry. The collection will include samples from hundreds of identical and non-identical twin pairs, with genome-wide genotyping and detailed questionnaires on lifestyle habits and medical histories.

In addition, we will carry out two complementary studies to explore the extent to which external interventions can modify the mutational landscape. In the first study we will obtain buccal swabs from individuals exposed to a diversity of treatments, such as metformin for diabetes, aspirin for heart disease, a range of cancer therapies or immune suppression. When possible, we will collect samples from the same individuals before and after starting these treatments. In a second study, we will use in-vitro epithelial cultures made up of different mutant clones to study a broader range of interventions. We hope that these studies will pave the way to begin to understand how new treatments could be used to reduce the frequency of cancer-causing clones in still healthy individuals, opening the door to new strategies for cancer prevention.

Together, we hope that these studies will provide an unprecedented view into the variation of the somatic mutation landscape across the population, provide new insights into the origins of cancer and the mechanisms behind mutagenic and non-mutagenic risk factors, and open new avenues for cancer prevention.

References

- Abascal F, Harvey LMR, Mitchell E, Lawson ARJ, Lensing SV, Ellis P, […], Martincorena I. (2021). Somatic mutation landscapes at single-molecule resolution. Nature. 593(7859):405-410.
- Brunner SF, Roberts ND, Wylie LA, Moore L, Aitken SJ, Davies SE, […], Campbell PJ. (2019). Somatic mutations and clonal dynamics in healthy and cirrhotic human liver. Nature. 574(7779):538-542.
- Lawson ARJ, Abascal F, Coorens THH, Hooks Y, O'Neill L, Latimer C, […], Martincorena I. (2020). Extensive heterogeneity in somatic mutation and selection in the human bladder. Science. 370(6512):75-82.
- Martincorena I, Roshan A, Gerstung M, Ellis P, Van Loo P, McLaren S, […], Campbell PJ. (2015). High burden and pervasive positive selection of somatic mutations in normal human skin. Science. 348(6237):880-6.
- Martincorena I, Fowler JC, Wabik A, Lawson ARJ, Abascal F, Hall MWJ, […], Jones PH. (2018). Somatic mutant clones colonize the human esophagus with age. Science. 362(6417):911-917.
- Moore L, Leongamornlert D, Coorens THH, Sanders MA, Ellis P, Dentro SC, […], Stratton MR. (2020). The mutational landscape of normal human endometrial epithelium. Nature. 580(7805):640-646.
- Moore L, Cagan A, Coorens THH, Neville MDC, Sanghvi R, Sanders MA, […], Rahbari R. (2021). The mutational landscape of human somatic and germline cells. Nature. 597(7876):381-386.
- Ng SWK, Rouhani FJ, Brunner SF, Brzozowska N, Aitken SJ, Yang M, […], Campbell PJ. (2021). Convergent somatic mutations in metabolism genes in chronic liver disease. Nature. 598(7881):473-478.
- Yoshida K, Gowers KHC, Lee-Six H, Chandrasekharan DP, Coorens T, Maughan EF, […], Campbell PJ. (2020). Tobacco smoking and somatic mutations in human bronchial epithelium. Nature. 78(7794):266-272.