DR. JOSEF STEINER KREBSFORSCHUNGSPREIS 2019

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Der Dr. Josef Steiner Krebsforschungspreis 2019
geht an Frau Prof. Dr. Serena Nik-Zainal.

Frau Nik-Zainal ist CRUK Advanced Clinician Scientist am Departement für Medizinische Genetik der Universität Cambridge, England.
Die Preissumme beträgt gesamthaft CHF 1‘000‘000.

Dr. Josef Steiner Krebsforschungspreis 2019

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 2019 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 Symposium eingeladen, welches im Januar 2019 an der Universität Bern stattgefunden hat. Anlässlich dieses Symposiums konnten die Forscherinnen und Forscher ihre Projekte vorstellen. Aus diesem strengen Auswahlverfahren ist Fr. Prof. Dr. Serena Nik-Zainal als Siegerin hervorgegangen.

Laudatio für Frau Prof. Dr. Serena Nik-Zainal

Die Dr. Josef Steiner Stiftung verleiht den Josef Steiner Krebsforschungspreis an Frau Prof. Dr. Serena Nik-Zainal in Anerkennung ihrer bahnbrechenden Forschung im Bereich der Entwicklung neuer Methoden der Bioinformatik zur klinisch-relevanten Klassifizierung von Tumoren. Unter Berücksichtigung der Tatsache, dass jedes Genom einer Krebserkrankung eine unterschiedliche und eigene Signatur an Treiber- und Passagiermutationen aufweist, hat sie die herausfordernde Aufgabe auf sich genommen, diese Mutationen in einer grossen Zahl von Tumoren auf ihre Häufigkeit und Verteilung zu untersuchen, angefangen mit der Verteilung somatischer Mutationen in einer grossen Brustkrebspopulation. Dank der Entwicklung und Anwendung innovativer bioinformatischer Rechensysteme konnte sie genetische Gemeinsamkeiten in den verschiedenen Tumoren nachweisen, die potentiell zur Definition von gezielt therapierbaren Entitäten führt.

Curriculum Vitae von Serena Nik-Zainal

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Honorary Consultant in Clinical Genetics
Group Leader Physiology of Mutagenesis Laboratory
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Actual Positions

2004 **Specialist Registrar in Clinical Genetics**
East Anglian Medical Genetics Service, Cambridge University Hospitals NHS Trust

2009 **Wellcome Clinical Research Training Fellow**
Wellcome Sanger Institute

2013 **Honorary Consultant in Clinical Genetics**
East Anglian Medical Genetics Service, Cambridge University Hospitals NHS Trust

2014 **Career Development Fellow Group Leader**
Wellcome Sanger Institute

2017 **Group leader & CRUK Advanced Clinician Scientist**
MRC Cancer Unit & Department of Medical Genetics
University of Cambridge

Education

2013 **Certificate of Specialist Registration in Clinical Genetics, East Anglia UK**
2012 **PhD degree in Cancer Genomics, Wellcome Sanger Institute**
2003 **MRCP Member of the Royal College of Physicians (London)**
2000 **MBBChir in Clinical Medicine, University of Cambridge**
1998 **BA (First Class Honours) in Medical and Veterinary Science Tripos, University of Cambridge**

Postdoctoral Training

2012-2014 Wellcome Sanger Institute

Fellowships, Grants and Awards

2019 Basser Gray Grant
2019 Dr. Josef Steiner Cancer Research Foundation Award
2018 Early Detection Project Grant
2017 CRUK Advanced Clinician Scientist Award
2017 CRUK Grand Challenge: PRECISION Grant
2016 CRUK Pioneer Award
2014 William Bate Hardy Prize
2014 CRUK Future Leaders Prize
2013 Wellcome Beit Prize
2013 AACR Scholar-In-Training Prize
2013 Wellcome Intermediate Clinical Fellowship
2012 EACR Susan G. Komen Prize
2012 Robin Winter Prize
2009 Wellcome Clinical Research Training Fellowship

Publications

Full bibliography can be found at:
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Top 20 publications:

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10. Davies H, Glodzik D, Morganella S, Yates LR, Staaf J, Zou X, Ramakrishna M, Martin S, Boyault S, Sieuwerts AM, Simpson PT, King TA, Raine K, Eyfjord JE, Kong G, Borg Å, Birney E, Stunnenberg HG, van de Vijver MJ, Børresen-Dale AL, Martens JW, Span PN, Lakhani SR, Vincent-Salomon A, Sotiriou C, Tutt A, Thompson AM, Van Laere S, Richardson AL, Viari A, Campbell PJ, Stratton MR, **Nik-Zainal S.** HRDetect is a predictor of BRCA1 and BRCA2 deficiency based on mutational signatures. ***Nature Medicine***. 2017 Apr;23(4):517-525.
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Prof. Dr. Nik-Zainal beschreibt ihr preisgekröntes Projekt wie folgt:

Accelerating holistic cancer genome interpretation towards the clinic

Today, we can read the entire human genome comprising over 3,000,000,000 DNA base pairs in a single experiment, in less than one day, for less than one thousand US dollars. The speed and scale of reading the genome (or sequencing) has increased extraordinarily in less than a decade. The rate-limiting step in using genomic data today is not sequencing - it is the expertise in the analysis of this deluge of data and in making clinically-useful interpretations for the general population.

Early in my research career, we showed that using all of the mutations present in whole genome sequenced (WGS) tumours could reveal *mutational signatures*, imprints left by mutagenic DNA damage and repair processes that have occurred through cancer development[1,2,3]. Subsequently, we focused on validating these mutation patterns in experimental cellular model systems[4,5,6]. This powerful combination of computational analytics and experimental insights helped to drive the development of clinical computational tools to interpret whole cancer genome data more effectively.

Every tumor is individual. No two cancer genomes have the same set of mutations that are causally implicated in carcinogenesis (called drivers) or passenger mutations that create mutational signatures[7]. At first glance, it may seem a formidable task to dissect this complexity for clinical applications. However, thanks to the principle of not simply doing an experiment and generating data once, but adding, instead, subsequent datasets and performing computational exploration recurrently thus learning and re-learning from available cancer sequencing data, my team has shown that by taking a holistic approach, it is possible to find commonalities across tumors and interpret the whole picture of cancer genomes for the clinical benefit. In this context, we have pioneered the development of bioinformatic tools to classify tumors in clinically-informative ways, for potentially targetable abnormalities[8].

To give an example, we developed an algorithm called HRDetect[8]. Machine-learning methods were used to identify critical mutational signatures that defined tumors which were deficient in a critical repair pathway called Homologous Recombination Repair (HR). We applied HRDetect on a cohort of 560 WGS breast cancers. A surprising 22% of tumors were found to show HR-deficiency. This means that ~ 1 in 5 breast cancer patients has a tumor that could be sensitive to selective therapeutics designed for patients that carry inherited *BRCA1*/*BRCA2* mutation, like poly-ADP ribose polymerase (PARP) inhibitors, and other selective chemotherapeutics such as platinum-based drugs. To translate our research work into clinical application, we are obliged to demonstrate that individual bioinformatic assays such as HRDetect, have prognostic/predictive capabilities. We have indeed done so recently by applying our WGS analysis and interpretation expertise to informative cohorts in a step-wise fashion: first, in small retrospective series[8], second in larger population-wide studies where excellent treatment and clinical outcome data are available (e.g. South of Sweden study (SCAN-B) manuscript in press), and third, in partnership with pharmaceutical companies to demonstrate performance in clinical trials (manuscript in review). The example of how we developed HRDetect from available data and then rapidly applied it demonstrates the impact of the approach.

In the Clinical School at the University of Cambridge, we further enhance translation of our expertise, develop novel, clinically-meaningful algorithms, and share our knowledge through web-based resources. In this context, the Dr. Josef Steiner Award will help to consolidate our current knowledge into infrastructure that is appropriate for the future. We are building a highly-organised data infrastructure based on an improved automated foundation that will permit learning and relearning from ever-growing datasets. The system is also being built with the intention of making genomic data more accessible and user-friendly for biologists and clinicians that are not computational experts, so that the next generation of researchers may be able to explore these data more efficiently. As scientists and clinicians, big data are only useful if we can extract relevant biological/clinical questions from that data. Thus, a strong processing base coupled to improved organization of curated data will prove to be a set-up that is more suitable for advanced data analytics. We will be able to focus on asking novel biological and clinical questions of these large datasets and ultimately, make clinically-relevant progress. Thanks to the help from the Steiner Foundation, we have already been able to accelerate the development of one of our web-based tools, called Signal[9] which serves as a reference resource of mutational signatures. This resource has the largest collection of human mutational signatures derived from cancers and from experimental systems. Users are able to explore data down to the individual patient level. Users are also able to perform their own analyses on our website, by uploading their data and then learning what is in their patient/tumor/experimental datasets.

The Steiner Award will be essential for providing the necessary support for developing a novel data infrastructure for advanced analytics in the Physiology of Mutagenesis Laboratory, thereby allowing us to understand mechanisms of mutagenesis, to develop new clinical algorithms, and to build the model for interpreting whole cancer genomes for the benefit of patients in the future.

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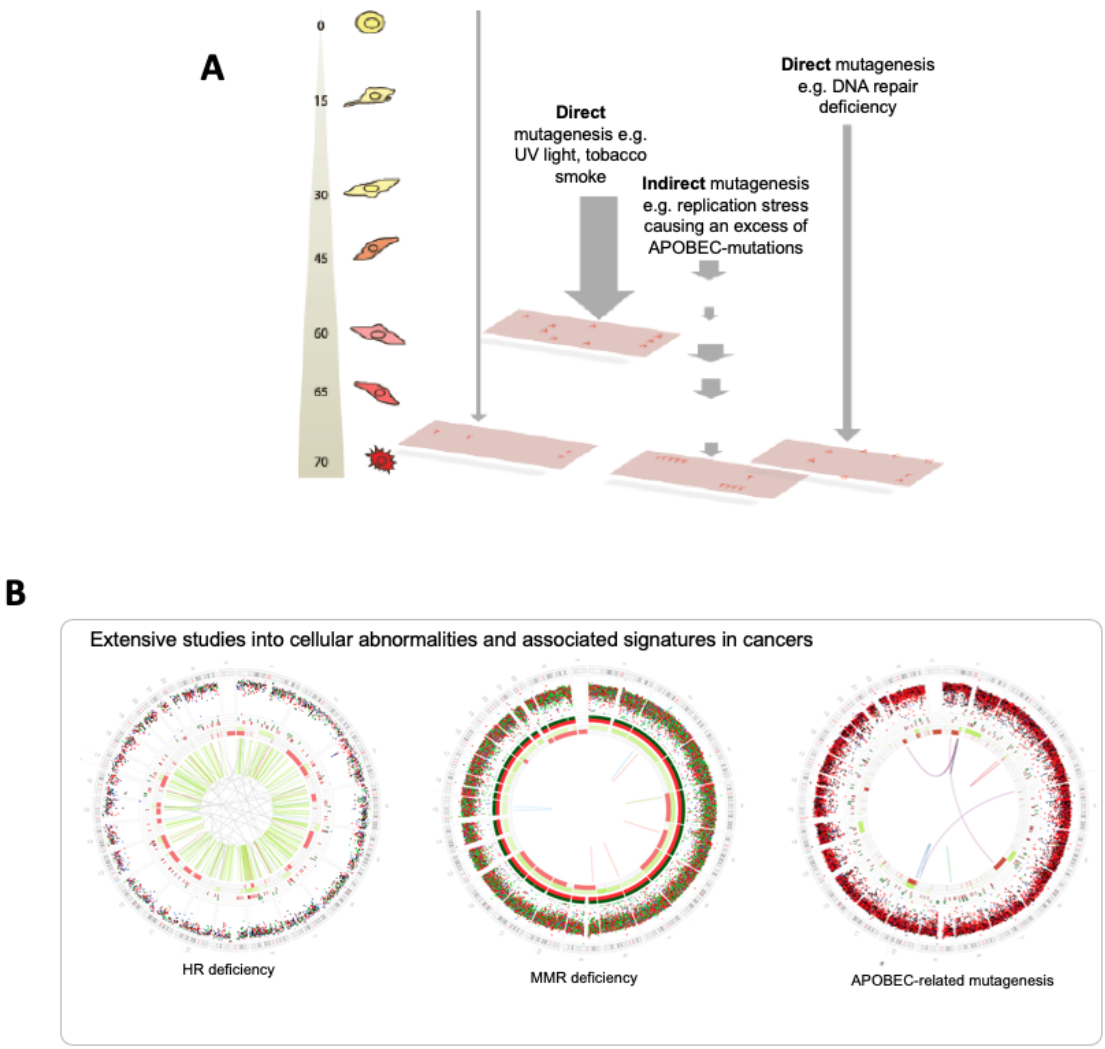

Figure 1: Mutational signatures and whole genome profiles of human cancers: (A) Somatic mutational-signatures can be the outcome of multiple mutational processes. Each mutational process may incur "direct" DNA damage (e.g, UV light causing pyrimidine modifications or DNA repair defects) or "indirect" assaults (e.g. secondary to a disturbance in cellular physiology) and leave a characteristic imprint – or mutational signature – on the cancer genome. The arrows indicate the duration and intensity of exposure to a specific mutational process. The final mutational portrait is a composite of all the mutational processes that have been active over the lifetime of the cancer patient. **(B)** In previous work, we have shown our ability to use machine learning methods to ascertain the multiple mutational-signatures that define tumors with DNA repair deficiencies (first and second circos plots respectively; HR= homologous recombination, MMR = mismatch repair) and tumors with marked abnormalities of cellular physiology (third circos plot) resulting in characteristic appearances. These images are intended to demonstrate the marked differences between tumors with abnormal biologies. Outermost ring = chromosomal ideogram clockwise chr1-chr22,X,Y. Subsequent circles heading inwards: substitutions as dots plotted on log scale of intermutation distance, small insertions/deletions, copy number (pink=losses, green=gains), rearrangements = lines (green=tandem duplications, pink=large deletions, blue=inversions, purple=translocations).