GAGNA A. & CH. VAN HECK
Prize 2015

18 November 2015

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GAGNA A. & CH. VAN HECK PRIZE

The triennial and international « Gagna A. & Ch. Van Heck Prize », amounting to 75,000 €, rewards a scientist or a Medical Doctor, in recognition of a research work which has contributed to the treatment of a disease currently incurable, or which has raised hopes for curing the disease.

This Prize was first granted in 2003 and constitutes one of the most prestigious Belgian Prize in biomedical science.

The Prize is awarded to:

Stephen P. JACKSON

Ph.D. in Molecular Biology, University of Edinburgh (UK)
Head of Cancer Research UK Laboratories, The Gurdon Institute, University of Cambridge (UK)
Professor of Biology, University of Cambridge (UK)

Identification of key mechanisms for the detection, signaling and repair of DNA damages.

Professor Stephen Jackson’s pioneering academic research has provided us with many of the key principles by which cells detect DNA damage, signal its presence and mediate its repair. His discoveries have had particularly major impacts on our understanding of how human cells deal with the most toxic of all DNA damages: the DNA double-strand break (DSB). In addition to establishing some of the most important foundations of present-day DNA repair research, Jackson’s work has also shown us how cellular dysfunction and disease arise when DNA repair or DNA-damage signaling goes awry. Additionally, his work has led to the development of an innovative new approach to cancer therapy that kills cancer cells whose ability to repair DNA damage has been compromised.
MEMBERS OF THE JURY

GAGNA A. & CH. VAN HECK PRIZE 2015

Mr COLIGE Alain           Senior Research Associate of the F.R.S. - FNRS at Université de Liège

Mr LEO Oberdan           Professor at Université Libre de Bruxelles
                        President of the Jury

Mr LETESSON Jean-Jacques   Professor at Université de Namur

Mr OCTAVE Jean-Noël       Professor at Université Catholique de Louvain

Mr PARMENTIER Marc        Professor at Université Libre de Bruxelles

Mrs VAN LINT Carine      Research Director of the F.R.S. - FNRS at Université Libre de Bruxelles

Mr VIKKULA Miikka        Professor at Université Catholique de Louvain
Stephen P. JACKSON

Cancer Research UK Laboratories
The Gurdon Institute
University of Cambridge, UK

“Identification of key mechanisms for the detection, signaling and repair of DNA damages”
Summary

**Background**

Professor Stephen Jackson’s transformational academic achievements relate to cellular events that detect, signal the presence of and repair DNA damage; events whose defects contribute to many age-related human diseases. Prior to Jackson becoming an independent researcher, it had been established that DNA damage occurs in cells. It was also known that there are certain ways of repairing different forms of DNA damage. However, at that time it was not known that DNA damage in fact triggers a much wider array of intracellular events. Also, nothing was known about the molecular nature of the major DNA repair system that responds to the most toxic of all forms of DNA damage: double-strand breaks (DSBs).

**The beginning: a DNA-damage activated protein kinase (DNA-PK)**

Jackson entered the DNA repair field through studying the DNA-dependent protein kinase (DNA-PK). After defining the DNA-PK target consensus (subsequently found to be similar to those of the related kinases ATM and ATR), he showed DNA-PK to comprise a catalytic subunit (DNA-PKcs) and a DNA-targeting protein (Ku). Jackson’s subsequent findings relating to DNA repair all emanated from his ensuing, seminal discovery in 1993 that DNA-PK enzyme activity is triggered by DSBs through the ability of Ku to bind to broken DNA ends. This provided a key conceptual basis for cellular DNA-damage detection, repair and signaling, and paved the way for Jackson’s many subsequent transformational impacts on our understanding of such medically important processes.

**DNA-PK forms the basis for the NHEJ system of DSB repair**

Soon after showing that DSBs activate DNA-PK, Jackson and colleagues established that Ku and DNA-PKcs are crucial for the pathway called non-homologous end-joining (NHEJ) that repairs most DSBs in all complex organisms, including humans. In addition to showing how Ku or DNA-PKcs loss causes cells to become hypersensitive to DNA damage triggered by agents such as ionizing radiation, Jackson’s work also showed that NHEJ proteins are needed for immune system development through mediating immune-receptor gene rearrangements by V(D)J recombination.

Jackson and colleagues subsequently identified and/or helped determine the functions of all other core human NHEJ proteins, including the DNA ligase IV-XRCC4 complex and the XRCC4-related proteins XLF and PAXX. He also established – contrary to dogma at the time – that related NHEJ components and processes are conserved in yeast and in
certain bacteria. More recently, Jackson and colleagues showed how DSB repair by NHEJ and another pathway, homologous recombination, are affected by chromatin structure, and how they are reciprocally regulated by cell-cycle status via factors such as yeast Sae2 and its human counterpart CtIP.

**Other DNA-damage activated kinases, pathways and processes**

By showing how DNA damage detection can induce protein post-translational modifications (PTMs), Jackson’s work on DNA-PK provided a paradigm for how DNA-damage triggers intracellular signaling events whose amplification and diversification subsequently influence myriad aspects of cellular physiology. In this regard, another landmark in DNA repair and DNA-damage signaling was Jackson’s cloning of the cDNA for DNA-PKcs. His ensuing work established that DNA-PK is a bona fide protein kinase, despite its catalytic domain being most related to those of inositol phospholipid kinases. Furthermore, his work revealed that the DNA-PKcs kinase domain has homology with those of the proteins ATM and ATR, which Jackson and others then showed work through related DNA-damage induction mechanisms. Jackson’s many contributions to this area included purifying ATM and ATR, providing assays for their enzymatic activities, identifying targets, and identifying protein partners that function to recruit/activate ATM or ATR by mechanisms analogous to the Ku-DNA-PKcs paradigm. Jackson also established that ATM- and ATR-mediated signaling events are connected to one another and cell-cycle regulated.

During his work on ATM and ATR, Jackson showed how these and additional factors are targeted to DNA-damage sites, and interact in regulated ways by phosphorylation-dependent recognition mechanisms via specialized protein structures such as FHA domains and BRCT domains. In this regard, it is noteworthy that Jackson defined the first function for a chromatin modification in cellular DSB responses by demonstrating that phosphorylation of histone H2A(X) affects cellular sensitivity to DNA damage and promotes DNA repair. He also provided a mechanism for this function in mammalian cells by establishing that it serves as a binding site for the protein MDC1, which then mediates the recruitment of many other proteins to DNA-damage sites.

Jackson’s work also provided us with insights into how DNA repair is affected by diverse other cellular factors and, conversely how DNA repair and DNA-damage signaling impinge on various aspects of cellular biology. For example, he showed that DSB-repair proteins control normal telomere functions. He also discovered that mammalian cell replicative senescence – the arrest of cell proliferation upon repeated passage of primary human cells in culture – reflects an ATM/ATR based DNA-damage response triggered by shortened telomeres. More recently, Jackson’s research established how other PTMs, such as ubiquitylation, sumoylation, poly-ADP ribosylation, acetylation and methylation play key roles in cellular responses to DSBs.

**A new therapeutic approach: killing cancer cells by “synthetic lethality”**

By working in yeast, Jackson found that defects in some DNA-repair components only
cause marked DNA-damage hypersensitivity in the absence of other DNA repair factors, a phenomenon based on the genetic principle termed “synthetic lethality”. Recognizing that some cancer cells lack certain DNA repair factors and would thus likely be particularly reliant on other DNA-repair pathways, Jackson realized that “synthetic lethal” relationships between pathways might also be exploited pharmacologically and clinically.

Through refining biochemical assays for enzymes such as DNA-PK, ATM and ATR and the DNA-damage activated DNA-repair enzyme PARP in his academic laboratory in the mid-1990s, Jackson found that it was possible to identify small-molecule compounds that could inhibit such enzymes. Based on this and his prior yeast and mammalian cell findings, Jackson founded the company, KuDOS Pharmaceuticals, and as part-time Chief Scientific Officer (CSO), he steered KuDOS to become an integrated drug-discovery and development company. KuDOS was acquired in 2006 by AstraZeneca but functioned as an AstraZeneca subsidiary, with Jackson as CSO until 2010. Based on his work showing how other PTMs such as ubiquitylation and sumoylation control key DNA repair processes, in mid-2011 Jackson founded the company MISSION Therapeutics to develop drugs targeting enzymes of the ubiquitin PTM system to treat cancer via synthetic-lethality and other mechanisms.

The programmes Jackson established and steered within KuDOS produced compounds such as ATM, DNA-PK and PARP inhibitors that are now widely used as research tools. Moreover, the KuDOS-generated compounds olaparib (a PARP1/2, inhibitor), AZD8055 (an mTOR inhibitor) and AZ20 (an ATR inhibitor) are now in clinical trials. Most notably, Jackson and colleagues showed that olaparib and related PARP inhibitors exhibit striking cytotoxicity towards cancer cells impaired in homologous-recombination through them possessing mutations in BRCA1 or BRCA2, thus validating the “synthetic-lethal pharmacology concept” that Jackson had outlined in his original 1997 KuDOS Business Plan. This nurtured the development of olaparib as the first of a new class of anti-cancer agents working via synthetic lethality: killing cancer cells by targeting their genetic dependency on particular DNA repair systems (their “Achilles’ heels”) but having little effect on normal cells and therefore having few toxic side-effects.

Olaparib (marketed by AstraZeneca as Lynparza™) recently received approval by the US FDA (Food and Drug Administration) and the EMA (European Medicines Agency) for treating ovarian cancers with BRCA1/2 mutations. There is now much excitement that olaparib and other PARP inhibitors may soon become approved for treating various other cancers.
Curriculum Vitae

Stephen Philip JACKSON, FRS, FMedSci

Frederick James Quick and Cancer Research UK Professor of Biology,
Head of Cancer Research UK Laboratories,
The Gurdon Institute, University of Cambridge, UK

PERSONAL DETAILS

Date of Birth: July 17, 1962 (age 52)
Place of Birth: Nottingham, UK
Nationality: British

Work Address: The Gurdon Institute
University of Cambridge
Tennis Court Road
Cambridge, CB2 1QN, UK

Telephone: (01223) 334102 or 331725
Fax: (01223) 334089
E-mail: s.jackson@gurdon.cam.ac.uk

PROFESSIONAL EXPERIENCE

2012-present  Associate Faculty Member, The Sanger Institute, Hinxton, Cambridge, UK
2011-present  Founding Scientist and Chief Scientific Officer (part-time), MISSION Therapeutics Ltd., Babraham, Cambridge, UK.
2010-present  Recipient of salary supplement from Cancer Research UK
2009-present  Frederick James Quick and Cancer Research UK Professor of Biology, Department of Biochemistry, University of Cambridge, UK.
2004-present  Head, Cancer Research UK Laboratories, The Wellcome Trust and Cancer Research UK Gurdon Institute, University of Cambridge, UK.
1995-present  Senior Group Leader, The Gurdon Institute, University of Cambridge, UK.
1995-present  Fellow of St John’s College, University of Cambridge, UK.
1995-2009 Frederick James Quick Professor of Biology, Department of Zoology, University of Cambridge, UK.

1997-2008 Chief Scientific Officer (part time), KuDOS Pharmaceuticals Ltd., Cambridge, UK.

1997 Sole Founding Scientist, KuDOS Pharmaceuticals Ltd., Cambridge, UK.

2001-2004 Deputy Director, The Gurdon Institute, University of Cambridge, UK.


1987-1991 Postdoctoral research in the laboratory of Prof. R. Tjian, University of California at Berkeley, USA.

1985-1987 Graduate research in laboratory of Prof. J. D. Beggs, University of Edinburgh, UK.

1983-1985 Graduate research in the laboratory of Prof. J. D. Beggs, Department of Biochemistry, Imperial College of Science and Technology, London, UK.

EDUCATION

1983-1987 University of Edinburgh, Scotland, UK; Ph.D. in Molecular Biology

1980-1983 University of Leeds, UK; B.Sc. Honours (1st Class) in Biochemistry

1978-1980 High Pavement Sixth-Form College, Nottingham, UK.

1973-1978 Haywood Comprehensive School, Nottingham, UK.

AWARDS AND MEMBERSHIPS OF SCIENTIFIC ORGANIZATIONS

2015 The Gagna A. & Ch. Van Heck Prize “For determining how cells recognize and repair DNA damage and translating this knowledge towards new cancer therapies”

2015 The Sackler Lecture (delivered in Cambridge and at the Academy of Medical Sciences, London)

2014 Thomson Reuters Highly Cited Researcher

2014 Fellowship of the European Academy of Cancer Sciences

2014 Fellowship of Imperial College Faculty of Medicine

2012 Member of the UK BioIndustry Association
Among the most highly cited European cancer researchers, 1998-2009
[http://www.labtimes.org/labtimes/issues/lt2012/lt01/lt_2012_01_40_42.pdf]

Royal Society Buchanan Medal for distinguished contributions to the medical sciences

Medical Research Council Keynote Prize Lecture; Society of Toxicology Anniversary Annual Meeting, Washington, USA. March 9th, 2011.

Among the most highly cited European molecular biologists, 1997-2008

BBSRC Innovator of the Year

Elected to the Fellowship of the Royal Society

Biochemical Society GlaxoSmithKline Award

Honorary degree of Doctor of Science; University of Nottingham

Degree of Doctor of Science; University of Cambridge

ISI Highly Cited Researchers in ISIHighlyCited.com

Member of the British Association for Cancer Research

Member of the European Association for Cancer Research

Anthony Dipple Carcinogenesis Young Investigator award

Elected to the Academy of Medical Sciences

Elected to the European Molecular Biology Organisation

Biochemical Society Colworth Medal

Tenovus Medal for Cancer Research

Eppendorf-Nature European Young Investigator Award

Member of the Biochemical Society

Member of the Cambridge Philosophical Society

COMMITTEE MEMBERSHIPS

Sept 2015- Wellcome Trust Collaborative Awards Committee

2013-present International Scientific Advisory Board; Netherlands Cancer Institute

2013-present Scientific Advisory Board; MRC Clinical Sciences Centre
2012-present  Chair, Gurdon Institute Biological Safety Committee
2012-present  Scientific Advisory Board: MRC Protein Phosphorylation and Ubiquitylation Unit, Dundee
2012-present  Cancer Research UK Science Committee
2012-2013  Scientific Advisory Group; Cancer Research UK London Research Institute
2011-present  Scientific Advisory Board; MRC Toxicology Unit, Leicester
2011-present  Steering Committee, Cambridge Cancer Centre
2010-2012  Cancer Research UK Drug Discovery Advisory Group
2009-2013  Chairman of the Board, Scottish Centre for Cell Signalling (SCILLS), Dundee, Scotland
2008-present  Scientific Advisory Board; Beatson Institute, Glasgow, Scotland
2005-present  Scientific Advisory Board; Radiation Oncology & Biology Institute, Oxford
2003-present  Gurdon Institute Management Committee
2009-2011  Strategic Board of the Drug Discovery Program, IFOM-IEO, Milan, Italy

STATEMENT OF RESEARCH INTERESTS

The aim of my academic research is to better understand how cells detect DNA damage and signal its presence to the DNA repair and cell cycle machineries. Towards this end, my laboratory is using a broad range of techniques and approaches, in both mammalian and yeast cells. It is my belief that a deeper knowledge of these pathways will yield a better understanding of the diseases that can arise when such pathways are lost – such as hereditary and sporadic cancer, neurodegeneration, developmental defects, immune deficiencies, infertility and premature ageing – and will suggest new strategies for treating such diseases. Much research in my lab has arisen from the paradigm of DNA damage detection and signalling that I established for the DNA-PK protein kinase a number of years ago. Although a considerable amount of my lab’s current work is still focused on pathways controlled by DNA-PK and the related kinases ATM and ATR, our research is increasingly determining how other post-translational modifications, such as protein acetylation, poly(ADP)-ribosylation, ubiquitylation and sumoylation, also control key DDR events. Further details about my academic laboratory can be found at: http://www2.gurdon.cam.ac.uk/~jacksonlab/

KUDOS PHARMACEUTICALS LTD. AND MISSION THERAPEUTICS LTD

I founded KuDOS in 1997 to translate knowledge of DNA repair and DNA-damage response (DDR) pathways into new treatments for cancer. The overall concept was to
develop drugs for use as stand-alone agents (acting via synthetic-lethality and related mechanisms) and/or to enhance the efficacy of DNA-damaging anti-cancer treatments such as chemotherapies and radiotherapy. Acting as Chief Scientific Officer (CSO) I with help from my many colleagues, took the company through three rounds of venture-capital financing, raising ~£43 million. This allowed KuDOS to develop into a fully integrated drug-discovery and drug-development company. Having generated several drug candidates and taken these to various stages of development, KuDOS was acquired in 2005/6 by AstraZeneca for $210 million; and until 2010, KuDOS functioned as a Cambridge-based subsidiary of AstraZeneca with me as CSO. The programmes that I established and steered within KuDOS produced compounds such as ATM, DNA-PK and PARP inhibitors that are now widely used as research tools. Moreover, the KuDOS-generated compound Lynparza™/olaparib (a PARP1/2, inhibitor) is a registered drug (see below), while AZD8055 (an mTOR inhibitor) and AZ20 (an ATR inhibitor) are in clinical trials (DNA-PK and ATM inhibitors are in preclinical development).

In 2002, I initiated a collaboration between KuDOS and the laboratory of Professor Alan Ashworth (Institute for Cancer Research, London, UK) to explore the impact of DNA repair inhibitors on cells mutated in the breast and ovarian cancer predisposition genes, BRCA1 and BRCA2. This and ensuing preclinical and clinical findings revealed olaparib and related PARP inhibitors to exhibit striking cytotoxicity towards cells with BRCA1 or BRCA2 deficiencies, thus validating the “synthetic-lethal pharmacology concept” that I had in my 1997 KuDOS Business Plan: killing cancer cells by targeting their genetic dependency on particular DNA repair systems (their “Achilles’ heels”) but having little effect on normal cells and therefore having few toxic side-effects. In addition to extending lives (in some cases for many years) of cancer-trial patients, clinical data have highlighted olaparib’s potential in BRCA1/2 hereditary and non-hereditary cancers, including breast, pancreatic, prostate and ovarian. Lynparza™/olaparib recently received FDA and EMA approval for use in ovarian cancers with BRCA1/2 mutations. Lynparza™/olaparib is thus the first-in-class drug targeting PARP, and is the first drug to exploit the synthetic-lethality concept. It is currently being evaluated in seven Phase III trials.

Realizing that therapeutic opportunities arising from my research were not being adequately exploited, I conceived MISSION Therapeutics. MISSION has received strong venture-capital backing and set up its operations on the Babraham Science Campus near Cambridge, with me serving as its part-time Chief Scientific Officer [http://www.missiontherapeutics.com/].

SEMINARS

Over 310 invited seminars since 1992.
EDITORIAL BOARDS

- **2015-present**  Oncotarget
- **2012-present**  Science Signaling (Board of Reviewing Editors)
- **2010-present**  Biomolecules
- **2008-present**  Aging
- **2003-present**  Genes and Development
- **2001-present**  DNA Repair
- **1999-present**  EMBO Journal
- **1999-present**  Carcinogenesis
- **2005-present**  The Scientist
- **2004-2014**  Current Biology
- **2011-2014**  PLoS Biology
- **2000-2011**  Nature Reviews
- **2001-2010**  Science
- **2000-2010**  EMBO Reports
- **2001-2009**  Faculty of 1000
- **2000-2005**  British Journal of Cancer

PATENTS

Granted patent applications in various territories relating to: DNA damage response (DDR) proteins as targets for anti-cancer therapies; assays for identifying small-molecule inhibitors of DDR proteins; the development and use of specific DDR inhibitors; and the demonstration of synthetic-lethality as an anti-cancer strategy based on the use of DDR inhibitors such as PARP inhibitors to selectively kill cancer cells deficient in homologous recombination mediated DNA repair (US2005227919).

MEETINGS AND CONFERENCES ORGANIZED OR CO-ORGANIZED

- **2016**  Abcam conference “Maintenance of Genome Stability”, Panama
- **2015**  EMBO conference “The DNA Damage Response in Cell Physiology and Disease”, Greece
2014 Abcam conference “Maintenance of Genome Stability”, St. Kitts
2013 EMBO conference “The DNA Damage Response in Cell Physiology and Disease”, Greece
2013 Keystone Symposium “Genomic Instability and DNA Repair”, Banff Canada
2012 Abcam conference “Maintenance of Genome Stability”, The Bahamas
2011 Chromosome Structure, Damage and Repair, Anavissos, Greece
2010 A-T Workshop “Molecular Basis of A-T”, California, USA
2010 “Telomeres and Genome Stability” Conference, Marseilles, France
2010 Abcam conference “Maintenance of Genome Stability”, Antigua
2009 DNA Repair Integrated Project Symposium, Crete
2008 “Telomeres and Genome Stability” Conference, Villars-sur-Ollon, Switzerland
2006 “Telomeres and Genome Stability” Conference, Villars-sur-Ollon, Switzerland
2004 EMBO/58th Harden Conference “Telomeres and Genome Stability” Cambridge, UK. This has evolved to a regular meeting, occurring every two years
2002 International symposium “Signalling the Future” Liverpool, UK
1997 Biochemical Society Annual Symposium “Cellular Responses to Stress” Dundee, UK
1996-2005 Annual Molecular Biology and Cancer Network Conference “Genes and Cancer”, University of Warwick, UK
1995 UK-RSA Symposium “Cell Growth Control” Cape Town, South Africa
1994 The first “EMBL Conference on Gene Transcription”, Heidelberg, Germany
1993 Biochemical Society Meeting “Signalling from the plasma membrane to the Nucleus” Sheffield, UK
TEACHING (University of Cambridge)

Lecturer and examiner (2002-2013): Part IB ‘Cell and Developmental Biology’
Organizer, lecturer and examiner: Part II course ‘Cell growth and genome stability’

RESEARCH TRAINEES

Predoctoral: 19 Pre-doctoral students including:

1993-1994  Peter Baumann  Investigator, Stowers Institute for Medical Research, Kansas, USA.
1994-1997  David Gell  Menzies Research Institute, Australia
1997-2001  Andrew McAinsh  Centre for Mechanochemical Cell Biology, Warwick Medical School, University of Warwick
1997-2001  Damien D’Amours  Group Leader, Institute for Research in Immunology and Cancer, University of Montreal, Canada
1999-2003  Rajat Roy  Research Associate, Imperial College
1999-2003  Ali Jazayeri  Head of Protein Engineering, Heptares Therapeutics, Hertfordshire
2000-2004  Philip Reaper  Research Scientist with Vertex Pharmaceuticals Inc., Oxfordshire
2002-2006  Peter Ahnesorg  Medical Manager, Oncology Department, Roche Switzerland
2005-2008  Robert Driscoll  Postdoctoral Fellow, K. Cimprich Laboratory, Stanford, California, USA.
2006-2010  J. Ross Chapman  Group Leader, University of Oxford
2006-2011  Jorrit Tjeertes  Postdoctoral Fellow, Novartis, Switzerland
2010-2014  Jessica Brown  SpR in Medical Oncology, Addenbrooke’s Hospital, Cambridge.
Postdoctoral: 22 Post-doctoral fellows including:

1991-1995  Robert White  Professor of Biochemistry, University of York
1994-1997  Susan Critchlow  Senior Staff Scientist Astra Zeneca, UK.
1994-1999  Graeme Smith  Director of Research, Astra Zeneca, UK
1995-1998  Ugur Yavuzer  Associate Professor, Istanbul Technical University, Istanbul, Turkey.
1996-1997  Tonya Bliss  Research Scientist, Stanford University, California, USA.
1996-2002  Jessica Downs  Reader in Genome Stability, MRC Genome Damage and Stability Centre, Sussex University
1996-1999  Raimundo Freire  Staff Scientist, Hospital Universitario de Canarias, Tenerife, Spain
1997-2001  Steve Bell  Professor of Microbiology, Sir William Dunn School of Pathology, Oxford
1997-2001  Daniel Durocher  Group Leader, Samuel Lunenfeld Research Institute Toronto, Canada
1997-2002  John Rouse  Professor of Chromosome Biology and Post-Graduate Programme Coordinator, MRC Protein Phosphorylation Unit, University of Dundee, UK.
1997-2003  Fabrizio d'Adda di Fagagna  Group leader, FIRC Institute for Molecular Oncology in Milan, Italy
1998-2001  Nick Lakin  Lecturer, Biochemistry Department, University of Oxford, UK.
1999-2001  Brandi Williams  Center for Translation Medicine at the Moran Eye Center, University of Utah, USA.
1998-2003  Soo-Hwang Teo  Chief Executive, Cancer Research Initiatives Foundation, University Malaya Medical Centre, Malaysia
1999-2004  Michal Goldberg  Lecturer, The Hebrew University, Jerusalem, Israel
2000-2004  Muriel Grenon  Postdoctoral fellow, National University of Ireland, Galway, Ireland
2001-2004  Veronique Smits  Hospital Universitario de Canarias, Tenerife, Spain
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<tr>
<th>Year</th>
<th>Name</th>
<th>Position and Institution</th>
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<tr>
<td>2001-2005</td>
<td>Manuel Stucki</td>
<td>Group Leader, University of Zurich, Switzerland</td>
</tr>
<tr>
<td>2003-2005</td>
<td>Jacob Falck</td>
<td>Novo Nordisk Biotech Fund, Denmark</td>
</tr>
<tr>
<td>2001-2006</td>
<td>Abdel Moumen</td>
<td>Head Biotechnology R&amp;D Projects, MAScIR Medical Biotechnology, Morocco</td>
</tr>
<tr>
<td>2003-2007</td>
<td>Alessandro Sartori</td>
<td>Institute of Molecular Cancer Research, University of Zurich</td>
</tr>
<tr>
<td>2002-2008</td>
<td>Serge Gravel</td>
<td>Sherbrooke University, Quebec, Canada</td>
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<tr>
<td>2004-2010</td>
<td>Pablo Huertas</td>
<td>Group Leader in the Andalusian Center for Molecular Biology and Regenerative Medicine, University of Seville</td>
</tr>
<tr>
<td>2006-2010</td>
<td>Sophie Polo</td>
<td>Group Leader, Institut Curie, Paris, France.</td>
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<tr>
<td>2006-2011</td>
<td>Kyle Miller</td>
<td>Assistant Professor, University of Texas at Austin, USA</td>
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<tr>
<td>2011-2014</td>
<td>Jon Travers</td>
<td>MedImmune, Cambridge, UK.</td>
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**Additional Mentoring (current):**

- Shikang Liang (Department of Biochemistry): PhD Mentoring Scheme
- Felipe Cortes Ledesma (CSIC, Spain): EMBO Mentor
- Andrej Alendar (Gurdon Institute): Postdoctoral Mentoring Scheme
- Tanay Ghosh (Gurdon Institute): Postdoctoral Mentoring Scheme
- Marta Teperek-Tkacz (Gurdon Institute): Postdoctoral Mentoring Scheme
- Ka Hing Che (Gurdon Institute): Postdoctoral Mentoring Scheme
- Joanna Loizou (CeMM, Austria): Advisor/Mentor
- Saskia Suijkerbuijk (Gurdon Institute): Postdoctoral Mentoring Scheme
- Claudia Wurzenberger (Gurdon Institute): Postdoctoral Mentoring Scheme
- Nina Oberbeck (MRC LMB): PhD Second Supervisor
- Sam Behjati (Sanger Institute): Wellcome Trust Clinical PhD External Advisor
- Charlotte Sutherell (Department of Chemistry): PhD Mentoring Scheme
Therese Anderson (Gurdon Institute): Postdoctoral Mentoring Scheme
Mark Jackman (Gurdon Institute): Postdoctoral Mentoring Scheme
Alejandra Gariol (Gurdon Institute): Postdoctoral Mentoring Scheme
Bernhard Strauss (Gurdon Institute): Postdoctoral Mentoring Scheme
Antonio Campos Caro (Gurdon Institute): Postdoctoral Mentoring Scheme
Johanna Rees (Gurdon Institute): Postdoctoral Mentoring Scheme
Kei Miyamoto (Gurdon Institute): Postdoctoral Mentoring Scheme
Qiang Wu (Gurdon Institute): Postdoctoral Mentoring Scheme
Mikkel Christensen (Gurdon Institute): Postdoctoral Mentoring Scheme

PUBLICATIONS

- 180 peer-reviewed research publications plus 39 peer-reviewed review articles and 24 other review articles and book chapters.
- 16 first author publications.
- 159 corresponding/co-corresponding author publications.
- h-index: 114 (Google Scholar)
- Total citations: >51,000
- i10 index: 244

Research Articles:


**Review articles:**


APPENDIX: From Ku to KuDOS and the clinical concept of synthetic lethality

Two major factors led me to establish KuDOS Pharmaceuticals Ltd. and the drug discovery programmes within it. First, during the mid 1990’s, my group developed biochemical screening methods for DNA-PK and other DDR enzymes, leading us to identify initial small-molecule compounds that could inhibit these enzymes and enhance cancer cell killing by DNA damaging agents. Second, also during the mid 1990’s, our work in yeast led us to realize that defects in some DDR pathways only cause marked DNA-damage hypersensitivity in the absence of another DDR pathway. As explained below, such “synthetic lethal” relationships between DDR pathways can be exploited to striking clinical effect.

As outlined in the original KuDOS Business Plan that I wrote in 1997, because they lack particular DDR pathways, one might expect cancer cells to be more susceptible than normal cells to inhibition of certain other DDR pathways:

Although there are many examples of DDR impairment in cancer cells, a prime example is the loss of BRCA1 or BRCA2 function in hereditary breast and ovarian cancers. Here, the patient inherits one inactive copy of BRCA1/2, meaning that she (or he) has a high risk of developing cancer, particularly breast and ovarian malignancies. Notably, while normal cells in such a cancer patient possess a wild-type copy of the BRCA1/2 gene – rendering them BRCA1/2 proficient – the tumour cells have invariably lost the function of the other BRCA1/2 allele, making them dysfunctional for BRCA1/2. Crucially, work between 1997-2001 revealed that BRCA1/2 defects markedly impair DSB repair by HR. In light of these findings, in mid 2002 I (as KuDOS CSO) approached Alan Ashworth (Breakthrough Breast Cancer Centre, London, UK) with the proposal to assess the impact of DNA-PK, ATM and PARP-1 inhibitors in cells proficient or deficient in BRCA1 or BRCA2. Our ensuing collaborative work quickly revealed that BRCA1/2 cells are strikingly hypersensitive to PARP inhibition, being killed at concentrations that are much, much lower than needed to kill BRCA1+/+ or BRCA1-/- cells. Parallel work by Thomas Helleday (University
of Sheffield, UK and University of Stockholm, Sweden) and Nicola Curtin (University of Newcastle-Upon-Tyne, UK) reached similar conclusions. These and subsequent findings thus established PARP inhibitors as the first of a new category of anti-cancer agents that operates on the principle of synthetic-lethality: targeting a pathway that is not essential to normal cells because they possess a compensatory pathway, but which is essential to cancer cells because they lack the compensatory pathway.

On the basis of the above findings and subsequent data generated with mouse cancer models, the orally-active KuDOS PARP inhibitor Lynparza™/olaparib (formerly KU-0059436/AZD2281), was selected by AstraZeneca for a clinical development. While trial-design and formulation issues slowed olaparib’s progress, recently received FDA and EMA approval for use in ovarian cancers with BRCA1/2 mutations. Lynparza™ is thus the first-in-class drug targeting PARP, and is the first drug to exploit the synthetic-lethality concept. It is currently being evaluated in seven Phase III trials.
LAUREATES OF THE
GAGNA A. & CH. VAN HECK PRIZE

2003:
► Michael L. J. APUZZO, University of Southern California, Los Angeles, USA
► Anne DEJEAN-ASSEMAT, Institut Pasteur, Paris, France and
  Laurent DEGOS, Hôpital St-Louis, Paris, France

2006:
► Alexander J. VARSHAVSKY, California Institute of Technology, Pasadena, USA

2009:
► Agnès RÖTIG, Hôpital Necker-Enfants Malades, Paris, France and
  Arnold MUNNICH, Hôpital Necker-Enfants Malades, Paris, France

2012:
► Yehezkel BEN-ARI, InMed - INSERM, Marseille, France

2015:
► Stephen P. JACKSON, The Gurdon Institute, University of Cambridge, UK