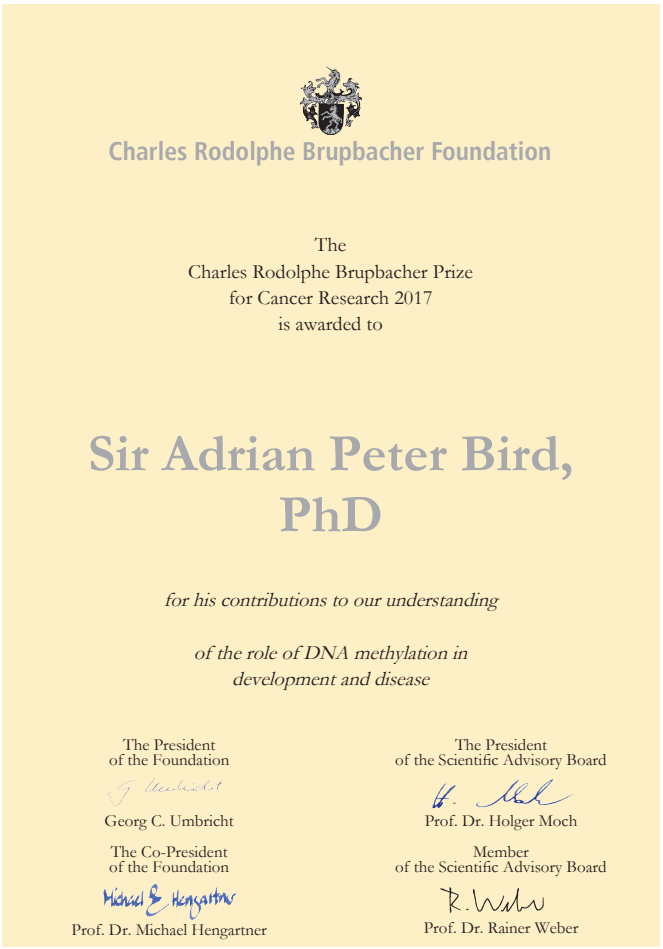

Laudatio

Josef Jiricny

The Watson-Crick model of DNA consists of two anti-parallel sugar-phosphate chains that are held together in the double helix by pairs of complementary bases: adenine/thymine and guanine/cytosine. But DNA of most organisms contains also a fifth base, 5-methylcytosine, first described in 1925 by Johnson and Coghill as a constituent of nucleic acid isolated from Mycobacterium tuberculosis. The biological roles of 5-methylcytosine have remained enigmatic for many years until the demonstration that it is a key component of the bacterial restriction/modification system, which brought Werner Arber, Daniel Nathans and Hamilton Smith the 1978 Nobel Prize in Physiology or Medicine, and made restriction enzymes the primary tools of molecular biology. Four decades have passed since then, but the role of 5-methylcytosine in eukaryotic DNA metabolism is still shrouded in mystery. We know that the sperm methylation pattern is largely erased after fertilization and that methylation is gradually reintroduced during embryogenesis and differentiation, but the processes that regulate the cell type- and tissue-specific methylation patterns remain to be elucidated. We have also learned that DNA can be not only methylated, but also demethylated, and that aberrant methylation can lead to disease - including cancer. Again, how these processes are regulated remains to be discovered. However, we have learnt a great deal about 5-methylcytosine metabolism during the past three decades and much of our knowledge came from the laboratory of Adrian Bird.

Adrian spent his doctoral and postdoctoral time in Max Birnstiel's laboratory, first in Edinburgh and then in Zurich, studying the amplification of ribosomal DNA in Xenopus laevis. In this organism, genomic rDNA in somatic tissues is highly methylated, while the extrachromosomal amplicons are unmethylated. When he returned to Edinburgh to establish his own group, Adrian set out to study the methylation pattern of these loci using the newly-available methylation-sensitive restriction enzymes. Moving from frog to sea urchin to mice, he noted that while genomic DNA was largely resistant to cleavage with HpaII, a restriction enzyme inhibited by methylation, a small fraction was cut into very small fragments, which he called HpaII tiny fragments, or HTF islands. These genomic features, later renamed CpG islands, were subsequently shown to be frequently associated with active housekeeping genes and to be generally unmethylated. Their aberrant methylation, for example in cancer cells, resulted in transcriptional silencing and Adrian was able to show that the latter phenomenon was linked to the binding of factors displaying high affinity for densely-methylated DNA. These polypeptides share a conserved "methylated-CpG binding domain", and have many interesting biological roles. Thus, MBD2 and 4 have been shown to suppress intestinal tumourigenesis. However, one member of this protein family, MeCP2, stands out from the rest. Adrian's laboratory established a knock-out mouse model and noted that its pathology was reminiscent of that seen in individuals affected with a severe neurological disorder, Rett Syndrome (RTT), which affects around one

person (predominantly female) in 10'000. Indeed, RTT patients could be shown to carry mutations in the MeCP2 gene. Importantly, the Bird laboratory showed that the resulting severe neurological phenotype is reversible when the protein is re-expressed, which promises that the Rett Syndrome might be curable in the future.

Adrian has unquestionably made a major contribution not only to our understanding of DNA methylation, but also to the entire field of epigenetics, which plays a key role in development and in disease. But his influence is much broader that that. He is a role model for young scientists as a teacher, as a tutor and as a member of numerous advisory boards. He is also a member of key strategic bodies that decide on the future of scientific research. With people like Adrian at the helm, the ship of science need not fear even the stormiest seas.

Sir Adrian Peter Bird

Summary Curriculum vitae

Appointment Buchanan Professor of Genetics

Address University of Edinburgh
The Wellcome Trust Centre of Cell Biology
The King's Buildings, Mayfield Road
Edinburgh EH9 3JR
United Kingdom

Date of Birth July 3, 1947

Education

1968-71 PhD, University of Edinburgh
Supervisor: Dr. Max L. Birnstiel
Thesis title: "The Cytology and Biochemistry of Ribosomal DNA amplification in Xenopus laevis oocytes."

1965-68 BSc.(Hons.) Biochemistry 2(1)
University of Sussex

Post-Doctoral Positions

1974-75 Swiss National Fund Fellowship
University of Zürich, Switzerland
Laboratory of Prof Max L Birnstiel

1971-73 Damon Runyan Memorial Fellowship
Yale University, USA, Laboratory of Dr. J.G. Gall

Positions held

2011– Associate Faculty at The Sanger Institute, Cambridge
1999–11 Director, Wellcome Trust Centre for Cell Biology, University of Edinburgh
1990– Buchanan Chair of Genetics, University of Edinburgh
1987–90 Senior Scientist, Research Institute for Molecular Pathology, Vienna, Austria
1987 Head of Structural Studies Section, MRC Clinical and Population Cytogenetics Unit Western General Hospital, Edinburgh, U.K.
1975–86 Research Group Leader, MRC Mammalian Genome Unit, Edinburgh, U.K.

Awards & Honors

2016 Harold Ackroyd Lecture, Caius College, Cambridge
2016 Francis Crick Lecture, MRC Laboratory of Molecular Biology, Cambridge
2016 Shaw Prize in Life Science and Medicine, Hong Kong
2015 Jordan Translational Medicine Lecture, University of Oxford
2014 BBVA Frontiers of Knowledge Award, Madrid
2014 Jacob's Ladder Norman Saunders International Research Prize, Toronto
2014 Knighthood New Year's Honours list
2014 Rosalind Franklin Lecture, King's College London
2013 GlaxoSmithKline Prize Lecture, Royal Society, London
2012 Royal Society GlaxoSmithKline Prize Lecture and Medal
2012 Jean Shanks Lecture, Academy of Medical Sciences, London
2011 Gairdner International Award, Toronto
2010 Honorary Doctorate, Sussex University
2008 Charles-Léopold Mayer Prize, French Academy of Sciences, Paris
2007 Novartis Medal of The Biochemical Society
2005 Commander of the Order of the British Empire
2002 Almroth Wright Lecturer, Imperial College London
2002 34th Bruce-Preller Prize Lectureship, Royal Society of Edinburgh
1999 Louis-Jeantet Prize for Medicine, Geneva
1999 Gabor Medal of the Royal Society, London
1986 Federation of European Biochemical Societies Anniversary Prize of the Gesellschaft für Biologische Chemie

Learned Societies

- Elected Foreign Associate, US National Academy of Sciences (2016)
- Elected Member of EMBO Council (2016)
- Honorary membership of the Biochemical Society (2012)
- Elected Fellow of the Academy of Medical Sciences (2001)
- Elected Fellow of the Royal Society, Edinburgh (1994)
- Howard Hughes International Fellow (1993-98)
- Elected Fellow of the Royal Society, London (1989)
- Elected to European Molecular Biology Organisation (1987)

External Committees

- International jury for the Start and Wittgenstein Prize of the Austrian Science Fund (2016-2021)
- Governing Body, Lister Institute for Preventive Medicine (2015)
- Adviser to the National Autism Project, The Shirley Foundation, UK (2015)
- Trustee and Chair of Research Strategy Committee at Cancer Research UK (2010-present)
- Scientific Advisory Boards: Gurdon Institute, Cambridge; Friedrich Miescher Institute, Basel; Stratified Medicine Scotland, Glasgow; Crick Institute, London
- Trustee of the Kirkhouse Trust, Scotland (2001-present)
- Trustee of the Rett Syndrome Research Trust, USA (2008-present)
- Editorial Boards: PeerJ
- Governor of the Wellcome Trust (2000-2010)

Public Engagement

- Rett Syndrome Anniversary family weekend, Northampton (2015)
- Abcam Scientist of the month (July 2015)
- HowTheLightGetsIn Philosophy Festival, Hay on the Wye, Wales (2013)
- Café Scientifique, Cockermouth, UK (2012)

Keynote Lectures

- London Chromatin Club Meeting, University College London (2016)
- SyBoSS Conference, Oberstdorf (2015)
- Edinburgh University Alumni weekend (2015)
- Keystone Symposia on DNA methylation/epigenetics, Keystone, Colorado (2015)
- Newlife Foundation Brighter Minds Symposium, London, UK (2014)
- Chromatin & Epigenetics Conference Cold Spring Harbor, New York (2012)
- EMBO Dynamic Genome Meeting, Nice (2013)
- 12th International Workshop of Developmental Nephrology, Edinburgh (2013)
- Plenary speaker Killam lecture series, Dalhousie University, Halifax, Nova Scotia (2013)
- Glasgow University Wellcome Trust 4yr PhD Scientific Retreat (2013 Guest Lecturer)
- Chromatin, Replication and Chromosomal Stability Conference, University of Copenhagen (2013)
- Epigenesys Meeting, University of Cambridge (2013)
- Epigenetics & Chromatin Meeting, Cold Spring Harbor (2012)

Teaching

PhD training

- Supervised 30 post-graduate students; 24 as 1st supervisor and 6 as 2nd supervisor (all competed successfully)

Undergraduate training

- Lectures to 4th year students in "Gene Expression", "Molecular Biology of Disease" and "Medical Biology

Patents/commercialisation

- CXXC Patent: Identification of CpG islands licenced to New England Biolabs, Oncomethylome Sciences, Sigma Aldridge, Qiagen and Active Motif.
- Monoclonal antibody against hydroxymethylcytosine (collaboration with Babraham Institute). Licensed to Diagenode.
- MBD reagents: antibodies licensed to Millipore (Upstate)
- pET Expression vector expressing MBD2b. Licensed to Applied Biosystems

Current Research Funding

Rett Syndrome Research Trust
"A research consortium to define the function of MeCP2: A step towards the development of therapeutics for treating Rett Syndrome"
Amount awarded: £673,484
Dates: 14 Jan 2014 - 15 Jan 2017

Sylvia Aitken Charitable Trust
Understanding Rett Syndrome by generating animal models with altered versions of the MeCP2 gene
Amount awarded: £181,924
Dates: 1 Sept 2014 - 30 Aug 2017

Wellcome Trust Studentship
Grant ref: 100469
"Genetic manipulation of MeCP2 in the human neuronal LUHMES cell line with a view to gene therapy of Rett Syndrome
Amount awarded: £151,134
Dates: 1 Oct 2012 - 30 Sept 2016

Wellcome Trust Investigator Award
Grant ref: 107930
"Towards understanding and treatment of MeCP2-related disorders"
Amount awarded: £2,814,000
Dates: 1 Jan 2016 – 31 Dec 2020

European Research Council Advanced Grant
Grant ref: EC 694295 Gen-Epix (ERC-AdG)
"Genetic determinants of the epigenome"
Amount awarded: €2,499,717
Dates: 1 Jun 2016 – 31 May 2021

DNA methylation patterns and cancer

Sir Adrian Peter Bird

The instructions for constructing the human body are stored by the genome as a sequence of DNA bases. This chemical code directs the synthesis of thousands of different proteins needed for life. To facilitate the controlled release of the information, the genome acquires chemical marks in the form of methyl groups that are added to genomic DNA as an extra layer of "epigenetic" regulation. The human genome has high DNA methylation levels throughout, but this "sea" of methylation is interrupted by short "islands" that are methylation-free. These so-called CpG islands coincide with many gene control regions and they serve as platforms for binding of enzymes that modify chromosome structure, thereby facilitating gene regulation. In cancer cells, CpG island control regions often acquire DNA methylation, leading to aberrant shutdown of the associated gene. In fact altered methylation patterns in tumours usually affect large domains that include many genes and also inter-genic DNA, but the underlying cause for this epigenomic de-regulation is unknown. Our recent research implicates proteins that recognize short DNA sequence motifs in modulating DNA methylation and other features of the "epigenome". The results suggest that the epigenome, which is often thought to respond to the external environment, is greatly influenced by the "hard-wired" sequence of the genome. Proteins that appear to link the genome with the epigenome are frequently mis-expressed in cancer and are likely to be important contributors to oncogenesis.