Ludwig-Oxford Symposium on Cancer Early Detection and Epigenetics

Online, April 28–29, 2021

Brought to you by Ludwig Cancer Research, the Oxford Centre for Early Cancer Detection and the Cancer Research UK Oxford Centre

#LudwigOxfordSymposium

50 years | LUDWIG CANCER RESEARCH

UNIVERSITY OF OXFORD

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WELCOME

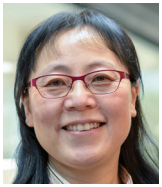
It is our great pleasure to welcome you to this Ludwig-Oxford Symposium on Cancer Early Detection and Epigenetics, brought to you by Ludwig Cancer Research, the Cancer Research UK Oxford Centre and the Oxford Centre for Early Cancer Detection. We are delighted to have organised a programme of engaging talks over the next two days, April 28th and 29th, focusing on the themes of early cancer detection and cancer epigenetics.

Though this is a virtual event, we look forward to many stimulating scientific questions, discussions and exchanges of ideas via the Q&A function. We hope that the talks will inspire new collaborations, enabling multidisciplinary solutions to some of the greatest challenges in cancer research, including the harnessing of recent advances in epigenetics to improve technologies for the early detection of cancer.

Over the next two days you will hear from a variety of leading experts in the fields of cancer early detection and epigenetics from the University of Oxford, Ludwig Cancer Research and beyond. This Symposium is one of many events in 2021 showcasing international research partnerships and the establishment of great scientific institutions as we celebrate the 10-year anniversary of the CRUK Oxford Centre at the University of Oxford, and 50 years of the Ludwig Institute for Cancer Research.

We hope you will enjoy the Symposium, reflecting on what has been achieved in cancer research and the exciting possibilities that lie ahead.

Chi Van Dang
Ludwig Institute for Cancer Research Scientific Director



Xin Lu
Ludwig Oxford Branch Director and Oxford Centre for Early Cancer Detection Director

Mark Middleton
Cancer Research UK Oxford Centre co-Director

Tim Elliott
Cancer Research UK Oxford Centre co-Director

ABOUT THE ORGANISERS

50 years | LUDWIG CANCER RESEARCH

Ludwig Cancer Research is an international collaborative network of acclaimed scientists that has pioneered cancer research and landmark discovery for 50 years. Ludwig combines basic science with the ability to translate its discoveries and conduct clinical trials to accelerate the development of new cancer diagnostics and therapies. Since 1971, Ludwig has invested nearly $3 billion in life-changing science through the not-for-profit Ludwig Institute for Cancer Research and the six U.S.-based Ludwig Centers. To learn more, visit www.ludwigcancerresearch.org

The Ludwig Institute for Cancer Research has had a presence in the UK since 1971 and relocated from London to Oxford in 2007. The Ludwig Oxford Branch is part of the Nuffield Department of Clinical Medicine, within the University of Oxford's Medical Sciences Division. Directed by Xin Lu, the Branch has approximately 120 staff and students investigating all stages of cancer, from the risk of disease through to new treatment opportunities. Ludwig Oxford research groups are interested in the signalling pathways that influence cancer initiation and progression, with a focus on cancer epigenetics, as well as infection, inflammation and gene regulation. The researchers advance cancer prevention, early diagnosis and effective treatment, collaborating closely with many basic and clinical researchers in the Oxford community, as well as the other Ludwig locations.

UNIVERSITY OF OXFORD

The University of Oxford has been placed number 1 in the Times Higher Education World University Rankings for the fifth year running, and at the heart of this success is its ground-breaking research and innovation. Oxford is world-famous for research excellence and home to some of the most talented people from across the globe. The University's work helps the lives of millions, solving real-world problems through a huge network of partnerships and collaborations. The breadth and interdisciplinary nature of Oxford's research sparks imaginative and inventive insights and solutions. To learn more, visit www.ox.ac.uk

ABOUT THE ORGANISERS

The Cancer Research UK Oxford Centre is a network of over 900 members from over 25 different Departments, Units and Institutes of the University of Oxford and Oxford University Hospitals NHS Foundation Trust. This University-NHS Trust partnership provides a cumulative investment of approximately £55 million each year for cancer science in Oxford. By harnessing Oxford's multi-disciplinary world-leading cancer research, we follow the mission of facilitating collaboration on a local, national and international scale to enhance cancer research activity and ensure rapid translation from scientific discovery to save and improve patients' lives. To learn more, visit www.cancercentre.ox.ac.uk

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The Oxford Centre for Early Cancer Detection (OxCODE) launched in June 2019 to build on Oxford's existing momentum and stimulate more early cancer detection research in Oxford. Since its launch, OxCODE members have successfully led funding applications for early detection projects worth over £25 million. With over 220 members from across the University of Oxford and the Oxford University Hospitals NHS Foundation Trust, OxCODE consolidates Oxford's significant expertise to realise the full potential of cross-disciplinary discourse and collaboration for advancing early cancer detection research for patient benefit. To learn more, visit www.oxcode.ox.ac.uk

TECHNICAL INSTRUCTIONS AND ETIQUETTE

The Symposium will be run via the Zoom webinar platform. We strongly recommend downloading the Zoom desktop client for the best attendee experience, but it is also possible to join via a web browser.

JOINING THE MEETING

From the confirmation email or calendar invite you were sent after registering via the Zoom webinar platform, click on *'Click here to join'* or the joining link. ***Please note: The link you have been sent is unique to you—please do not share this with anyone else.***

Dial-in joining is possible if you cannot use the meeting link by searching for a local phone number and entering the Webinar ID. However, please be aware that you may only experience the audio of the meeting.

ATTENDEE EXPERIENCE

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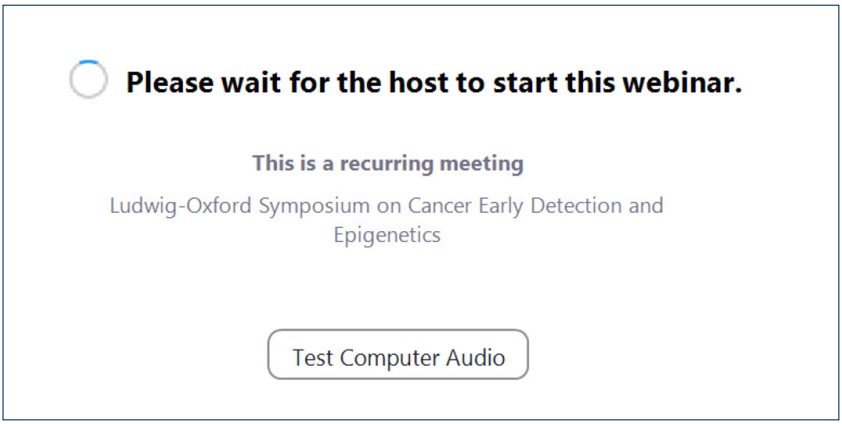

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TECHNICAL INSTRUCTIONS AND ETIQUETTE

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The meeting will be recorded. However, attendees will *not* be included in this cut, and only our speakers will be included in the final video.

HOW TO ASK A QUESTION

Click on the 'Q&A button' at the bottom of the screen, type your question in the Q&A box and select send. Questions will be visible to all panellists and attendees. You have the choice to ask anonymously.

Questions can be upvoted by all attendees by clicking on the 'Thumbs up' icon.

We ask that all questions posted are respectful to the speakers and other participants. Any posts deemed to breach etiquette will be deleted.

Please note: it will not be possible to post questions in the chat as this option has been disabled for attendees of this Symposium.

LEAVE MEETING

While we hope you are able to stay with us throughout the full programme, there may be times when you need to leave the meeting. Simply click 'Leave meeting' to leave the webinar at any time. If you leave, you can re-join using your unique joining link while the webinar is still in progress.

We look forward to welcoming you at Ludwig-Oxford Symposium on Cancer Early Detection and Epigenetics!

TROUBLESHOOTING

If your link doesn't let you enter the event, please try manually joining the webinar by following the instructions here.

If you have a poor connection, try moving to a place with a stronger WiFi signal.

Requests for technical support and any other questions in advance of or during the event can be directed to conference@ludwig.ox.ac.uk. A recording will be available for registered attendees for a limited time period after the event.

For more instructions, please visit the Zoom Help Center pages.

PROGRAMME

WEDNESDAY 28 APRIL

3.00 p.m. UK | 10.00 a.m. U.S. Eastern

Welcome address

Chi Van Dang	Ludwig Institute for Cancer Research Scientific Director
Xin Lu	Ludwig Oxford Branch Director and Oxford Centre for Early Cancer Detection Director
Tim Elliott	Cancer Research UK Oxford Centre co-Director

Session 1

EARLY DETECTION TECHNOLOGIES I
Chair: Bethan Psaila, University of Oxford

UK time	*U.S. Eastern*	
3.20 p.m.	10.20 a.m.	*Cell-free DNA TAPS provides multimodal information for early cancer detection* Chunxiao Song, Ludwig Cancer Research, University of Oxford
3.45 p.m.	10.45 a.m.	*Multi-analyte blood tests for the earlier detection of cancer* Nickolas Papadopoulos, Ludwig Cancer Research, Johns Hopkins University School of Medicine
4:10 p.m.	11:10 a.m.	*10-minute break*
4:20 p.m.	11:20 a.m.	*Computer enhanced endoscopy to improve the early detection of oesophageal cancer* Jens Rittscher, Ludwig Cancer Research, University of Oxford

PROGRAMME

Session 1 *(continued)*

UK time	*U.S. Eastern*	
4:45 p.m.	11:45 a.m.	*Harnessing protease dysregulation to improve disease detection and monitoring* Sangeeta Bhatia, Ludwig Cancer Research, Massachusetts Institute of Technology
5:10 p.m.	12:10 p.m.	*15-minute break*

Session 2

RISK STRATIFICATION FOR EARLY DETECTION
Chair: David Hunter, University of Oxford

UK time	*U.S. Eastern*	
5.25 p.m.	12.25 p.m.	*The early detection of hepatocellular liver cancer (DeLIVER)* Ellie Barnes, University of Oxford
5.50 p.m.	12:50 p.m.	*UK Biobank: a visionary resource for cancer research in the 21st Century* Naomi Allen, University of Oxford
6.15 p.m.	1.15 p.m.	*Risk stratification and early detection of breast cancer* Gillian Reeves, University of Oxford
6.40 p.m.	1.40 p.m.	*Closing remarks (5 minutes)* David Hunter, University of Oxford

PROGRAMME

THURSDAY 29 APRIL

UK time	*U.S. Eastern*	
3.00 p.m.	10.00 a.m.	*Welcome address* Yang Shi, Symposium Co-organiser, Ludwig Cancer Research, University of Oxford

Session 3

CANCER EPIGENETICS I
Chair: Natalia Gromak, University of Oxford

UK time	*U.S. Eastern*	
3.05 p.m.	10.05 a.m.	*Structure and function of mammalian SWI/SNF chromatin remodeling complexes in human cancer* Cigall Kadoch, Ludwig Cancer Research, Dana Farber Cancer Institute
3.30 p.m.	10:30 a.m.	*Modifications of RNA: their function and role in cancer* Tony Kouzarides, University of Cambridge
3.55 p.m.	10.55 a.m.	*The role for DNA methylation and chromatin changes in driving the evolution of tumorigenesis* Stephen B. Baylin, Ludwig Cancer Research, Johns Hopkins University School of Medicine
4.20 p.m.	11.20 a.m.	*10-minute break*

PROGRAMME

Session 4

EARLY DETECTION TECHNOLOGIES II
Chair: Anna Schuh, University of Oxford

UK time	*U.S. Eastern*	
4.30 p.m.	11.30 a.m.	*DNA 5hmC as biomarkers for cancer diagnosis and prognosis* Chuan He, Ludwig Cancer Research, University of Chicago
4.55 p.m.	11.55 a.m.	*ctDNA as a marker for the management of cancer patients* Kenneth W. Kinzler, Ludwig Cancer Research, Johns Hopkins University School of Medicine
5.20 p.m.	12:20 p.m.	*15-minute break*

Session 5

CANCER EPIGENETICS II
Chair: Skirmantas Kriaucionis, Ludwig Cancer Research, University of Oxford

UK time	*U.S. Eastern*	
5.35 p.m.	12.35 p.m.	*Understanding epigenetic mechanisms that control response of tumors to immune checkpoint blockade therapy* Yang Shi, Ludwig Cancer Research, University of Oxford
6.00 p.m.	1.00 p.m.	*Histone H3G34R mutations in gliomas* Nada Jabado, McGill University

PROGRAMME

Session 5 *(continued)*

UK time	*U.S. Eastern*	
6.25 p.m.	1.25 p.m.	*Epigenetic pathways as targets in human disease* Shelley Berger, University of Pennsylvania
6.50 p.m.	1.50 p.m.	*Closing remarks* (10 minutes) Chi Van Dang, Ludwig Institute for Cancer Research Scientific Director

Session 1

EARLY DETECTION TECHNOLOGIES I

Chair:
Bethan Psaila
University of Oxford

Chunxiao Song
Ludwig Cancer Research, University of Oxford

Cell-free DNA TAPS provides multimodal information for early cancer detection

BIOGRAPHY:

Chunxiao Song is a principal investigator at the University of Oxford and leads the Chemical Epigenetics Group at the Oxford Branch of the Ludwig Institute for Cancer Research. His lab develops novel epigenetic sequencing chemistries and applies them to liquid biopsy and other cancer-related studies. He completed his PhD at the University of Chicago and undertook his postdoctoral training at Stanford.

ABSTRACT:

Multimodal, genome-wide characterization of epigenetic and genetic information in circulating cell-free DNA could enable more sensitive early cancer detection. Recently, we developed TAPS as a mild, bisulfite-free method for direct base-resolution DNA methylation sequencing. In this talk, I will present the application of TAPS to cell-free DNA to provide high-quality and high-depth whole-genome cell-free methylomes. We showed that cell-free DNA TAPS provides multimodal information about cell-free DNA characteristics, including DNA methylation, tissue of origin, and DNA fragmentation. Integrated analysis of these epigenetic and genetic features enables accurate identification of early hepatocellular carcinoma and pancreatic adenocarcinoma.

Nickolas Papadopoulos
Ludwig Cancer Research, Johns Hopkins University School of Medicine

Multi-analyte blood tests for the earlier detection of cancer

BIOGRAPHY:

Nickolas Papadopoulos is the co-discoverer of the genetic basis of HNPCC. He was part of the team that was first to sequence all of the protein coding genes of four common human tumor types and later multiple tumor types. Currently, he is focused on the development of clinical applications in early detection, diagnosis and monitoring of cancer. Recently, he co-developed CancerSEEK, a blood test for the early detection of multiple cancers, and co-led the first prospective interventional study utilizing this test.

ABSTRACT:

The earlier a cancer is detected the higher the chance for a successful outcome. For many cancers there are not any screening modalities available. The ability to identify cancers through blood testing is one of the most exciting advances in cancer diagnostics. It also provides the opportunity to detect multiple cancer types with a single test. However, there are many challenges associated with the development of such tests. The presentation will outline such challenges, the biomarkers, technologies and the type of studies required to evaluate the utility of such tests, through the lens of our own experience with CancerSEEK and the DETECT-A prospective interventional study for the detection of cancer in 10,000 individuals without previously detected cancer.

Jens Rittscher
Ludwig Cancer Research, University of Oxford

Computer enhanced endoscopy to improve the early detection of oesophageal cancer

BIOGRAPHY:

Jens Rittscher is a group leader at the Big Data Institute and his appointment is held jointly between the Institute of Biomedical Engineering and the Nuffield Department of Medicine. He is an adjunct member of the Ludwig Institute for Cancer Research and the Wellcome Centre for Human Genetics. His research interests lie in enabling biomedical imaging through AI and medical image analysis, with a current focus to improve understanding of cancer and patient care.

ABSTRACT:

Expert endoscopists can identify areas at risk of developing cancer, but this is challenging and highly operator dependent. Changes in the surface structure of the tissue and other irregularities indicate precancerous and cancer development. We will present a computer-aided video analysis system to automatically assess Barrett's epithelium measurement and to assist less expert endoscopists in identifying areas of risk. By reconstructing the surface of the Barrett's area in 3D from endoscopy video, we propose a novel methodology for measuring the C&M score automatically. This 3D reconstruction provides an extended field of view and also allows us to precisely quantify the Barrett's area including islands. The talk will highlight how our recent advances in assessing video quality will be utilised in training endoscopists. We will outline how our recent work of predicting molecular subtypes of colorectal cancer based on morphology alone will be applied in this setting.

Sangeeta Bhatia
Ludwig Cancer Research, Massachusetts Institute of Technology

Harnessing protease dysregulation to improve disease detection and monitoring

BIOGRAPHY:

Sangeeta Bhatia holds an MD from Harvard Medical School, a PhD from MIT, and a Bachelor's degree from Brown University. At MIT, she is a professor, the inaugural director of the Marble Center for Cancer Nanomedicine and a member of the Ludwig Center for Molecular Oncology. She is a Howard Hughes Medical Institute investigator, on the Board of Directors at Vertex Pharmaceuticals and an elected member of the National Academies of Science, Medicine and Engineering.

ABSTRACT:

Proteolysis has a critical function in normal physiology and disease and proteases are intricately involved in cancer progression and spread. Our understanding of protease function has advanced from non-specific degrading enzymes to a modern appreciation of their diverse roles in post-translational modification and signaling in a complex microenvironment. This new understanding has led to next-generation diagnostics and therapeutics that exploit protease activity in cancer. This talk will include our work on how dysregulation of protease activity may be harnessed with wide-ranging utility from early detection to monitoring therapeutic response.

Session 2

RISK STRATIFICATION FOR EARLY DETECTION

Chair:
David Hunter
University of Oxford

Ellie Barnes
University of Oxford

The early detection of hepatocellular liver cancer (DeLIVER)

BIOGRAPHY:

Ellie Barnes is professor of Hepatology and Experimental Medicine at the University of Oxford and an associate director of OxCODE and leads a research group in applied immunology relevant to liver disease. She led the UK-wide MRC-funded consortium STOP-HCV, developing stratified medicine to optimise clinical outcomes in patients with hepatitis C virus, and is now leading the CRUK-funded DeLIVER programme for earlier hepatocellular carcinoma detection.

ABSTRACT:

Hepatocellular cancer (HCC) is the fastest rising cause of cancer death worldwide, primarily associated with viral infection, alcohol and obesity. Currently, 80% of HCCs are diagnosed at late stage with a 5-year survival < 5%. Current imaging techniques and biomarkers that seek to identify HCC, lack sensitivity, specificity and use outdated modalities. Strategies for the early detection of HCC are urgently required so that curative therapies may be applied. The Cancer Research UK-funded DeLIVER research programme launched in 2020 to better understand the pre-cancerous changes in the liver and use this knowledge to inform new technologies for early HCC detection. We will leverage a unique, genetically characterised cohort of HCV-infected patients with cirrhosis expanded to include additional disease aetiologies to follow prospectively and build a cohort of patients with small HCC. We aim to define the pre-

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cancerous microenvironmental liver landscape through deep phenotyping of cirrhotic tissue in patients with and without HCC and to apply state-of-the-art non-invasive methodologies, including multi-parametric MRI imaging and advanced molecular biomarker technologies for cancer detection. With our multi-disciplinary team, we aim to integrate multi-modal technologies to develop, refine and iterate strategies for translatable HCC detection methods and risk prediction.

Naomi Allen
University of Oxford

UK Biobank: a visionary resource for cancer research in the 21st Century

BIOGRAPHY:

Naomi Allen has been involved in UK Biobank since 2011 and is responsible for co-ordinating the linkage of routine electronic health records into the study for long-term follow-up. She plays a major role in developing the scientific strategy for the introduction of new enhancements into the resource and helps to develop policies that govern access to the data for health research by scientists worldwide.

ABSTRACT:

UK Biobank is a large-scale biomedical database and research resource, containing genomic, lifestyle and health information from half a million UK participants recruited between 2006 and 2010 from across the UK. The aim of this unique resource is to enable scientific discoveries on the prevention, diagnosis and treatment of a wide range of serious and life-threatening illnesses—including cancer. All participants provided consent for their health to be followed-up over time through linkage to routinely collected health records. There are already several thousand incident cases of the most common cancers, which will grow rapidly over the next few years, making research into rarer cancers possible. Researchers from academia and the commercial sector, in the UK and abroad, are using UK Biobank for a wide range of research purposes, including the investigation of genetic and environmental factors in the aetiology and pathophysiology of cancer. This talk will provide an overview of this unique resource, the opportunities for future data collection and how it can be used for groundbreaking cancer research.

Gillian Reeves
University of Oxford

Risk stratification and early detection of breast cancer

BIOGRAPHY:

Gillian Reeves is professor of Statistical Epidemiology and director of the Cancer Epidemiology Unit at the University of Oxford. She originally completed a PhD in statistics before joining the Cancer Epidemiology Unit where she became interested in the aetiology of female cancers. She is PI for the Million Women Study, a large UK study of women's health, which provides the basis for much of her research. Her main interest is in the prevention and early detection of breast and other cancers.

ABSTRACT:

In the UK, mammographic screening is currently offered to all women aged 50-70, with certain "high-risk" groups (eg those with a significant family history) being offered earlier and/or more intensive screening. Many other factors, apart from age and family history, are known to affect breast cancer risk, and there is growing interest in models aimed at predicting a woman's individual risk of breast cancer, with a view to offering more targeted screening interventions. Such models were initially limited to a small number of established risk factors relating to family history, reproductive patterns and prior benign breast disease, but have recently expanded to include other markers of risk such as breast density, genetic risk scores and serum hormone levels, with promising results. In this talk, we compare the performance of existing risk

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prediction models according to the types of risk factors included, and highlight the importance of developing risk stratification tools for specific types of breast cancer, including those associated with a relatively poor prognosis, which are less likely to be detected at routine mammographic screening. In the Million Women Study, we plan to collect digital mammograms and other relevant screening data on ~400,000 participants who have been followed up for breast cancer. These data will be combined with existing data on a wide range of lifestyle and other factors to develop population based risk stratification tools for use in UK women.

Session 3

CANCER EPIGENETICS I

Chair:
Natalia Gromak
University of Oxford

Cigall Kadoch
Ludwig Cancer Research, Dana Farber Cancer Institute

Structure and function of mammalian SWI/SNF chromatin remodeling complexes in human cancer

BIOGRAPHY:

Cigall Kadoch is an associate professor of Pediatric Oncology at the Dana-Farber Cancer Institute, Affiliated Faculty of Biological Chemistry and Molecular Biology at Harvard Medical School, and Institute Member and Epigenomics Program Co-Director at the Broad Institute. The Kadoch laboratory studies the structure and function of chromatin remodeling complexes such as the mammalian SWI/SNF (or BAF) complex, with emphasis on defining the mechanisms underlying cancer-specific perturbations.

ABSTRACT:

Genome-wide sequencing studies in human cancer have unmasked a striking frequency of mutations in the genes encoding subunits of the mammalian SWI/SNF (BAF) family of ATP-dependent chromatin remodeling complexes. Our laboratory uses biochemical, structural and functional genomics-based approaches to study rare, genetically well-defined pediatric cancers including synovial sarcoma, Ewing sarcoma, malignant rhabdoid tumor and others, all of which involve BAF complex perturbations as critical drivers of their oncogenic programs. These studies have informed the mechanistic basis underlying BAF complex targeting and function and have provided new foundations for therapeutic development.

Tony Kouzarides
University of Cambridge

Modifications of RNA: their function and role in cancer

BIOGRAPHY:

Tony Kouzarides did his PhD at the University of Cambridge and postdoctoral work at MRC Laboratory of Molecular Biology and at New York University Medical Center. His research group is focused on epigenetic modifications and their involvement in cancer. He is a founder of Abcam plc, Chroma Therapeutics and STORM Therapeutics, a member of EMBO and a fellow of the British Academy of Medical Sciences, the Royal Society and the American Academy of Arts & Sciences. He is also a CRUK Gibb Fellow.

ABSTRACT:

Many modifications are known to exist on tRNA and rRNA but very few have been detected on mRNA and ncRNA, due to detection issues. Having developed a number of sensitive detection tools for the RNA modifications, we are now in a better position to evaluate their existence and function on mRNAs. We have also carried out numerous numerus CRISPR screens to identify RNA modifying enzymes required for cancer, and specifically for the viability of AML-leukaemia cells.

Using the above tools and approaches we have identified the METTL3 enzyme, that modifies m6A, as a regulator of AML-leukaemia via a chromatin-based pathway. This leukaemic mechanism involves METTL3 being targeted to the promoter of leukaemia genes, via a specific transcription factor, to regulate their

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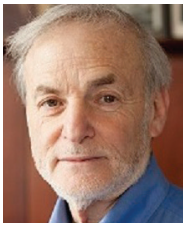
expression. We have now developed a small molecule inhibitor which targets the catalytic activity of METTL3. This molecule is highly specific for METTL3, can phenocopy the cellular consequences of a METTL3 knock out, functions via the mechanism described above, is bioavailable and shows efficacy in mouse models and human PDXs. These results demonstrate that RNA modifying enzymes are druggable, and that other RNA modifying enzymes may be targets for drug discovery. One such target, involving a novel modification of mRNA, will be presented.



Stephen B. Baylin
Ludwig Cancer Research, Johns Hopkins University School of Medicine

The role for DNA methylation and chromatin changes in driving the evolution of tumorigenesis

BIOGRAPHY:

Stephen B. Baylin is Virginia and D.K. Ludwig professor of Oncology and Medicine, and co-director of the Cancer Genetics and Epigenetics Program at The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, USA. He is currently also visiting professor of Cancer Epigenetics at the Ludwig Institute for Cancer Research Branch at the University of Oxford. His work on cancer-specific changes in DNA methylation was foundational for the field of cancer epigenetics.

ABSTRACT:

Abnormalities in patterns of DNA methylation and chromatin assembly are universal in human cancers, but their role in the initiation and progression of these diseases is still being deciphered. This talk will explore our evidence for how these epigenetic alterations play a fundamental role in cellular responses to inflammation and DNA damage, and their association with increased reactive oxygen species (ROS), to drive tumorigenesis from pre-cancerous stages through cancer initiation. A key theme will be that selected, coordinate changes in cancer specific DNA methylation and chromatin affect enhancers and their target gene promoters to repress the inducibility of developmental genes. This allows cells to evolve early in tumorigenesis that possess the stem cell-like properties of maintained

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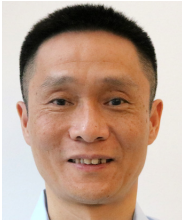
self-renewal and decreased differentiation capacity and an increasing sensitivity to oncogenic addiction to key driver mutations. Understanding these above dynamics, can help dissect the roles of chronic inflammation in underpinning how key factors such as environmental exposures, obesity and aging drive the risk for major cancers. By studying these events in in-vitro and in-vivo model systems, the precise role of the above epigenetic changes can be dissected and key translational implications emerge which can be pivotal for biomarker derivation to achieve early detection of key cancer risk and initiation stages and develop new strategies for cancer prevention and interception.

Session 4

EARLY DETECTION TECHNOLOGIES II

Chair:
Anna Schuh
University of Oxford



Chuan He
Ludwig Cancer Research, University of Chicago

DNA 5hmC as biomarkers for cancer diagnosis and prognosis

BIOGRAPHY:

Chuan He is the John T. Wilson Distinguished Service professor in the Department of Chemistry and Department of Biochemistry and Molecular Biology at the University of Chicago. He is also an investigator of the Howard Hughes Medical Institute and an investigator at the Ludwig Center at the University of Chicago. He's recent research concerns reversible RNA and DNA methylation in biological regulation. His laboratory has spearheaded the development of enabling technologies to study the biology of RNA and DNA modifications.

ABSTRACT:

DNA cytosine methylation (5-methylcytosine or 5mC) is the main epigenetic mechanism in human gene expression regulation. This methylation is oxidized by the human TET family enzymes to 5-hydroxymethylcytosine (5hmC) in an active demethylation process. While 5mC is a mark for gene repression in general, 5hmC tends to mark active loci. We have developed methods to sequence both 5hmC and 5mC genome-wide with low-input DNA samples. We have recently reported the first 5hmC tissue map by characterizing the genomic distributions of 5hmC in 19 human tissues derived from ten organ systems by using 5hmC-Seal, a method that covalently labels and maps 5hmC. Our computational analysis of genome-wide 5hmC distributions confirmed that 5hmC marks active

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regions of the human genome such as activated gene bodies, promoters and active enhancers. Its levels on gene bodies correlate well with corresponding mRNA expression. Importantly, 5hmC is enriched on tissue-specific gene bodies and enhancers. These results provide an extensive 5hmC map across diverse human tissue types and strongly suggest 5hmC as tissue- and cell-specific biomarkers. We have also applied 5hmC-Seal to identify 5hmC markers in cfDNA for cancer early detection with high sensitivity and specificity. We routinely obtain whole-genome, whole-body information using cfDNA from plasma. Our results on cancer early diagnosis, prognosis and treatment stratification will be presented.

Keneth W. Kinzler
Ludwig Cancer Research, Johns Hopkins University School of Medicine

ctDNA as a marker for the management of cancer patients

BIOGRAPHY:

Kenneth Kinzler is professor of Oncology at the Johns Hopkins University School of Medicine and co-director of the Ludwig Center at Johns Hopkins University. He has studied the genetics of human cancer and its clinical utility for more than 35 years. His team has helped define more than a dozen major cancer genes, delineated the APC/CTNNB1 and TP53 pathways, developed novel genetic tools and pioneered the use of released tumor DNA (e.g. liquid biopsies) as a clinical biomarker for cancer.

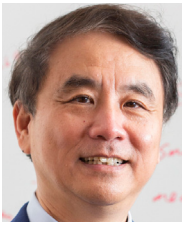
ABSTRACT:

Examples of the utility and limitations of current approaches for the detection of ctDNA will be discussed in the context of managing cancer patients. A new approach optimized for ctDNA detection in the minimal residual disease setting that extends both the sensitivity and specificity of ctDNA detection will be presented.

Session 5

CANCER EPIGENETICS II

Chair:
Skirmantas Kriaucionis
Ludwig Cancer Research,
University of Oxford



Yang Shi
Ludwig Cancer Research, University of Oxford

Understanding epigenetic mechanisms that control response of tumors to immune checkpoint blockade therapy

BIOGRAPHY:

Yang Shi received his PhD and postdoctoral training from NYU and Princeton, respectively. He started his own lab at Harvard where he received tenure professorship in 2004, and was the inaugural C. H. Waddington professor of Pediatrics of Harvard Medical School. He joined the Ludwig Institute Oxford Branch in 2020. He is widely known for the discovery of the first and many histone demethylases, which provided critical novel insights into epigenetic regulation and revealed new drug targets for cancer therapy.

ABSTRACT:

I will discuss our recent efforts towards understanding epigenetic mechanisms that control tumor responses to immune checkpoint blockade (ICB) therapy, and ways to sustain durable responses to ICB.

Nada Jabado
McGill University

Histone H3G34R mutations in gliomas

BIOGRAPHY:

Nada Jabado is a professor of Pediatrics at McGill University, a pediatric neuro-oncologist at the Montreal Children's Hospital and holds a Canada Research Chair in Pediatric Oncology. She completed her residency in pediatrics with a specialization in hemato-oncology and a PhD in Immunology. She pioneered a research program that identified a new molecular mechanism driving pediatric high grade astrocytomas, namely recurrent somatic driver mutations in the tail of histone 3 variants.

BIOGRAPHY:

Histone H3.3 glycine 34 to arginine/valine (G34R/V) mutations drive deadly gliomas and show exquisite regional and temporal specificity, suggesting a developmental context permissive to their effects. Here we show that these tumours also bear activating PDGFRA mutations that display strong selection pressure at recurrence. These mutations arise in interneuron progenitors, where they impair differentiation. The lineage of origin may facilitate PDGFRA co-option through a chromatin loop connecting PDGFRA to the regulatory elements of the core transcription factor specifying this lineage, GSX2, promoting overexpression and mutation of the receptor. At the single-cell level, G34R/V tumors harbor dual neuronal/astroglial identity while they lack oligodendroglial programs, which are actively repressed by GSX2/DLX-mediated cell fate specification.

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Collectively, our results show exquisite lineage dependencies for the exertion of oncogenic potential of a given histone mutation. While traditionally considered as glial malignancies, G34R/V gliomas are in fact neuronal malignancies where interneuron progenitors are stalled in differentiation by G34R/V mutations and malignant gliogenesis is promoted by co-option of a potentially targetable pathway, PDGFRA signaling.

Shelley Berger
University of Pennsylvania

Epigenetic pathways as targets in human disease

BIOGRAPHY:

Shelley Berger is a molecular biologist recognized for research on chromatin biology and epigenetics. Her major research interests are histone and factor post-translational modifications in chromatin regulation and of the tumor suppressor p53. Berger is currently the Daniel S. Och University professor at the University of Pennsylvania. She serves as founding and current director of the Epigenetics Institute in the Penn Perelman School of Medicine.

ABSTRACT:

Chromatin regulatory proteins are frequently mutated in human cancer. Because they are enzymes, chromatin proteins are outstanding targets for drug development. Our work focuses on elucidation of epigenetic pathways that might be cancer drivers, and epigenetic pathways that might augment cancer clinical treatment. Our previous research on the tumor suppressor p53 has revealed that the common p53 mutations utilize epigenetic pathways to drive cancer. In addition, certain cancers retain wild type p53, and we detect repressive p53 protein modifications that restrain its normal activity. Our recent findings reveal new nuclear epigenetic pathways in which wild type p53 functions as a tumor suppressor. We have discovered that p53 as a transcription factor associates with nuclear speckles, which are prominent nuclear bodies that contain proteins and RNA involved in gene expression. While links between

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nuclear speckles and gene activation are emerging, the mechanisms regulating association of genes with speckles are unclear. We find that speckle association of p53 target genes is driven by the p53 transcription factor, and we uncover mechanisms regulating gene-speckle association. Strikingly, speckle-associating p53 targets are more robustly activated and occupy a distinct niche of p53 biology compared to non-speckle-associating p53 targets. Together, our findings illuminate regulated speckle association as a mechanism utilized by a transcription factor to boost gene expression.

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