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Pathological Society
Understanding Disease

# Nottingham Pathology 2016
# Invited Speaker Abstracts

9th Joint Meeting of the British Division of the International Academy of Pathology and the Pathological Society of Great Britain & Ireland

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**Companion Sessions**
AIDPATH · British Lymphoma Pathology Group
Association of Clinical Electron Microscopists
UK Cardiac Pathology Network · Renal EQA

## KEY

Ⓟ = Presenter

## PRESENTER'S INDEX

To be found at the end of this document, after the abstract listings.

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# S1

## Early Detection Biomarkers and Risk Estimation Models for Ovarian Cancer

MR Russell[1]; A D'Amato[1]; A Gentry-Maharaj[2]; A Ryan[2]; J Kalsi[2]; U Menon[2]; I Jacobs[3];Ⓟ RLJ Graham[1]

*[1]University of Manchester, Manchester, UK; [2]University College London, London, UK; [3]University of New South Wales, Sydney, Australia*

**Purpose of Study:** There are many issue within the field of biomarker discovery, we will focus on our experience of working with clinical serum samples from biobanks. We will present a recent study we carried out on the identification of early detection ovarian cancer (OC) biomarkers. OC has the highest mortality of all gynaecological cancers. Early diagnosis offers an approach to achieving better outcomes for patients.
**Methods:** Using mass spectrometry and immunoassays we conducted a blinded-evaluation of prospectively collected preclinical serum from participants in the multimodal group of the UK Collaborative Trial of Ovarian Cancer Screening.
**Summary of Results:** Using isobaric tags (iTRAQ) we identified proteins differentially expressed between OC cases and controls. A second targeted mass spectrometry analysis of twenty of these candidates using SWATH identified Protein Z as a potential early detection biomarker for OC. This was further validated by ELISA analysis in 482 serial serum samples, from 80 individuals, 49 OC cases and 31 controls, spanning up to 7 years prior to diagnosis.
**Conclusion:** Our work demonstrated that Protein Z is a novel independent early detection biomarker for Type I and Type II ovarian cancer; which can discriminate between both types. Protein Z also adds to CA125 and potentially the Risk of ovarian Cancer algorithm in the detection of both subtypes. We will also discuss some of our preliminary work on building risk estimation models for early detection of OC.

# S2

## Molecular Stratification of Vulval Cancer and its Precursors

Ⓟ CS Herrington

*University of Edinburgh, Edinburgh, UK*

There are two distinct forms of vulval intraepithelial neoplasia (VIN). Usual-type VIN (uVIN) occurs in younger women, and is associated with infection with high-risk human papillomavirus (HPV) types and hence with neoplasia at other anogenital sites. The terms low-grade and high—grade squamous intraepithelial lesion (LSIL and HSIL respectively) are recommended for these HPV-associated lesions. Associated squamous cell carcinomas (SCCs) are generally of warty or basaloid type. Differentiated type VIN (dVIN), by contrast, occurs in older women, is not typically associated with HPV infection but rather shows a clinico-pathological association with lichen sclerosus and HPV-negative keratinizing SCC. The HPV-related biology of uVIN/SIL is relatively well understood, and there is good evidence for the diagnostic use of p16 immunohistochemistry (a surrogate marker of high-risk HPV infection when used in the correct context) to identify these lesions. However, dVIN is a more problematic diagnosis and its biology is much less clear. The reported association with *TP53* mutation is inconsistent: *TP53* mutations are neither unique to dVIN nor found in all dVINs. Moreover, a large worldwide study found that, although HPV was more prevalent in basaloid vulval SCC, keratinising SCCs were not infrequently HPV-positive. In addition, whilst the vast majority of uVIN/SIL contained HPV, viral DNA was also found in almost half of 'dVINs'. The relationship between HPV infection and the two morphological categories of VIN/SIL and SCC is therefore not absolute, and it may be more appropriate to classify VIN/SIL and SCC primarily according to HPV status. However, even if the two pathways are identified on the basis of the presence or absence of HPV, there is still a need for specific markers of the non-HPV-associated pathway (true dVIN) in order to distinguish it from non-neoplastic squamous mimics.

# S3

## Cervical Neoplasia: Mechanisms of Disease Progression, Biomarkers and Therapeutic Targets

Ⓟ J Doorbar

*University of Cambridge, Cambridge, UK*

In most cases, cervical neoplasia results from infection by 'high-risk' (hr) human papillomaviruses (HPV) , with these viruses being responsible for the vast majority of cervical cancers. Despite this association, hr HPV types are in fact extremely prevalent in the general population, and in most individuals, cause only asymptomatic lesions that regress after a period of months or years. The development of neoplasia is influenced by the epithelial site of infection, with cancer pdeveloping over time in lesions where viral gene expression is deregulated. Deregulation is influenced by the cellular microenvironment, and occurs at different frequencies depending on whether the site of infection is the ectocervix, the cervical transformation zone, or the columnar/reserve cells of the endocervix. Current thinking suggests that aberrant viral gene expression occurs at other sites where hr HPV infections cause cancer, such as the anal transformation zone and the tonsillar crypts, with cancer progression depending ultimately on the accumulation of genetic changes in the host cell chromosome. A general unifying general principle therefore, is that deregulated viral gene expression causes neoplasia, and that this predisposes to cancer progression in individuals who are persistently infected. Advances in our understanding of HPV-associated neoplasia have impacted disease management, thorough the introduction of prophylactic vaccines and through advances in cervical screening. Cervical screening is an important intervention strategy, that will be used alongside vaccination for the foreseeable future, although we expect that standard pathology analysis will be replaced by molecular pathology analysis based on our growing understanding of HPV biology. Although we still lack therapeutic agents that can cure HPV in both low and high-grade lesions, our increasing understanding of the molecular processes affected by these viruses is now suggesting new approaches for treatment.

# S4

## Molecular Pathology of Endometrial Cancer

Ⓟ MJ Arends

*University of Edinburgh, Edinburgh, UK*

A new molecular pathology-based classification system for endometrial cancer was proposed by The Cancer Genome Atlas (TCGA) research network (2013), using an integrated genomic, transcriptomic and proteomic characterisation of >370 endometrial adenocarcinomas. They were classified into 4 groups: (1) ultramutated cancers with DNA polymerase epsilon (POLE) proofreading mutations; (2) hypermutated cancers with defective mismatch repair (dMMR) and microsatellite instability (MSI); (3) endometrial cancers with a low frequency of DNA somatic copy number alterations (SCNA); (4) endometrial cancers with a high frequency of SCNA, but a low mutation rate, with frequent TP53 mutations and low ER and PR levels. The fourth SCNA-high group (26%) included the uterine serous and serous-related carcinomas, and ~25% of the endometrioid carcinomas that were originally morphologically classified as high-grade endometrioid adenocarcinomas. The cancers in the first three groups were almost all endometrioid carcinomas, with TCGA group (1) ultramutated cancers (7%) having a very high DNA mutation rate due to proofreading mutations in the POLE enzyme resulting in misincorporation of incorrect nucleotides during DNA replication, particularly C-to-A base changes. TCGA group (2) hypermutated cancers (28%) had a high DNA mutation rate due to defective DNA mismatch repair from acquired silencing of MLH1 expression due to promoter methylation, and these tumours were characterised by microsatellite instability. TCGA group (3) cancers (39%) had a low frequency of SCNAs and a low mutation rate, but mutations in a range of cancer genes including PTEN, CTNNB1, PIK3CA, PIK3R1, KRAS, ARID1A and ARID5B. This molecular pathology-based classification system was recommended for future clinical trials and post-surgical adjuvant treatment discussions, particularly for patients with aggressive tumours or group (2) dMMR/MSI tumours potentially responsive to immune checkpoint blockade.

# S5

## Immunotherapy, Lung Cancer and Pathology

Ⓟ KM Kerr

*Aberdeen University Medical School, Aberdeen, UK*

PD-1:PD-L1 interaction are one of the main ways in which lung cancer cells down-regulate the immune response to tumour cell antigens, thus avoiding tumour immune elimination. The introduction of immune checkpoint inhibitors which prevent the negative regulatory effects of PD-1:PD-L1 binding has been a step-change in lung cancer therapeutics. Therapeutic trials of at least five such agents (monoclonal antibodies directed against either PD-1 or PD-L1) have consistently shown response rates (ORR) of approximately 10 – 30% when used in second or greater line, and these ORR are now translating into survival benefit for patients. With one exception, these trials have also shown better outcomes for patients whose tumours express, to varying degrees, PD-L1 protein assessed by immunohistochemistry (IHC). It is important to note that, whilst the PD-L1 positive groups show ORR of approx. 20-50% depending on drug and expression level, responses are still seen in patients deemed PD-L1 negative by IHC testing. This has called into question the validity of PD-L1 IHC as a biomarker. Nonetheless, pathologists now face the prospect of reading anti-PD-L1 IHC as a selective biomarker for immune checkpoint inhibitor therapy in lung cancer. Our problem is that in the clinical trials for each drug so far studied, a different PD-L1 IHC assay has been used, requiring different staining platforms. Furthermore, definitions of a 'positive' test vary between the drug-assay combinations. Little is known about how comparable, or different, these assays are, and even less about the adequacy, in this predictive setting, of any laboratory developed lest (LDT) that might use alternative anti-PD-L1 IHC clones and detection chemistry. It remains to be seen whether or not it is safe to select a patient for a particular treatment, based upon either an alternative assay or an LDT, none of which were validated in the original clinical trial. Or indeed, whether alternative biomarkers can be identified.

# S6

## Diagnostic Pathology of Lung Cancer in 2016: Managing the Challenge and Getting the Answers

Ⓟ JR Gosney

*Royal Liverpool University Hospital, Liverpool, UK*

The approach to the diagnosis, classification and analysis of lung cancer has changed beyond all recognition in the last decade. This revolution, which is still gathering momentum, is being driven by the continuing development of drugs that are active against particular sub-groups of lung cancer defined more by their genetic pathology or their protein expression than by their morphology. It began with the development of small molecule tyrosine kinase inhibitors active against mutations in the EGFR gene and rearrangement of the ALK gene; the third generation of these agents is already here and more are in the pipeline. A new, separate and rapidly-developing challenge concerns the detection and assessment of expression of the PD-L1 ligand as a guide to the rational and cost-effective use of new immune modulating agents directed against either the PD-L1 ligand itself or its companion receptor, PD-1. The rapid, accurate and integrated analysis of diagnostic histology or cytology specimens which is now crucial to the management of patients with lung cancer poses major challenges for pathologists handling specimens of pulmonary tumours.

# S7

## The LungPath Study: Variation in Lung Cancer Pathological Diagnostic Practice in England and How Quality May be Improved

Ⓟ PJ Cane

*Guy's and St Thomas' Hospital, London, UK*

The LungPath Study was multi-centre audit aiming to investigate the variation in the standard of pathological diagnosis of lung cancer across England. Advances in lung cancer care mean it is now usually necessary to obtain a tissue diagnosis, histological subtype and the results of predictive marker studies in order to determine optimum treatment. Data from the UK National Lung Cancer Audit, such as the histological confirmation rate and the proportion of lung cancers classified as non-small cell not otherwise specified, show that there is wide variation between centres in the quality of the pathological diagnosis of lung cancer. The study involved twenty-two randomly selected lung cancer units from across England. Each centre collected data on every new lung cancer patient seen during the study period of January to June 2012. For each patient, clinical and radiology data was collected along with copies of all pathology reports from diagnostic and staging investigations. The quality of pathological diagnosis was assessed according to guidelines from the National Institute of Health and Clinical Excellence, the International Association for the Study of Lung Cancer and the Royal College of Pathologists. We received complete or near complete data from 19 of the 22 units covering 1500 patients. Analysis shows marked variation between centres in the proportion of tumours for which a pathological diagnosis was obtained, the procedures used to obtain tissue and the locations sampled. There is also variation in histological sub-typing, whether cytological or histological samples were obtained, use of immunohistochemistry and the proportion of cases tested for EGFR mutation. In addition to presenting these findings and attempting to explain the differences in practice and current guidelines, recommendations for improved care will be discussed.

# S8

## Trainees' Symposium: The Pathologist in the MDT

D Dodwell[1]; K Horgan[1]; N Sharma[1];Ⓟ AM Hanby[2]

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The Multidisciplinary Team Meeting (MDTM) is at the core of the management of those presenting with breast symptoms and ensures safe practice through the 'triple assessment'. In the main the work of the MDTM revolves around the diagnosis or exclusion of breast cancer. A good breast cancer pathologist needs to be an integral part of a team and craft and present their pathology analysis and reports not only to make a diagnosis, but also assist as much as possible in the detailed management of individual patients. Not only does this extend to things like correlation of what might be in a core biopsy to the radiology, but to an awareness of relevant trials for which certain pathology features may represent entry criteria. In our symposium we will illustrate 'dos and don't', 'best practice' and illustrations of where the future may take us in a series of mock cases- designed to bring out importance of multidisciplinary working in breast cancer management.

# S9

## The Undergraduate Strategy for the Pathological Society of Great Britain & Ireland

Ⓟ P Quirke

*Leeds University, Leeds, UK*

The Pathological Society places great importance in exposing students to the excitement and the opportunities that arise from a career in academic pathology. Our strategy is composed of national and local elements. Nationally, together with sister organisations, we will run two *'Introduction to Pathology'* undergraduate immersion courses taking place in London and Leeds in the summer. It is our hope that these activities amongst others will spark interest in pathology, leading students to take advantage of free undergraduate membership of the College which brings with it undergraduate membership of the Society. Our Undergraduate Society membership includes benefits such as eligibility to apply for financial support for intercalated degrees and summer research projects. Additionally student-led societies are supported financially through the undergraduate committee of the Pathological Society. This committee generates liaison between the undergraduate membership through the Undergraduate Network and delivers the Undergraduate Forum for the summer meeting which we hope many of our members will attend.
Within each University we wish to ensure that students are introduced to research in their first years and gain an understanding of the importance of research within their local curriculum. Locally we will help student-led pathology/research societies to carry out these aims and encourage students to explore pathology/research careers through MRes/iBSc's programmes or even iPhD's in Pathology. Embedded within these societies will be Pathology Ambassadors who will act as a contact point to for students, generating opportunities for engagement in pathology, answering questions and stimulating local interest. These Societies are encouraged to engage with the local Academy of Medical Sciences Inspire lead. To understand more please come to the talk! The undergraduate strategy will be critical for the success of the Society in coming years so please let us know how we can improve this.

# S10

## A Research Career in Pathology

Ⓟ NP West

*University of Leeds, Leeds, UK*

The number of trainee histopathologists actively engaging in research has risen over recent years following the introduction of a defined academic training pathway and the support of bodies like the Pathological Society. A research career is exceptionally rewarding and offers the chance to undertake potentially ground breaking research alongside clinical training.
An interest in histopathology research can begin as an undergraduate and a number of opportunities exist to allow students to explore a research career and embed themselves within academic histopathology groups at an early stage. Most medical schools offer special study modules where students can apply to do a piece of research in an area of interest. Several students also opt to undertake research placements during the summer holidays. This can be taken further with a full year out from a medical degree to intercalate a BSc/MRes, or even undertake a three year Doctoral degree.Following university, academic foundation placements allow for a four month period of research and lead into specialist training pathways where further experience can be gained as an academic clinical fellow (ACF), with up to 25% of time spent in research. This is usually followed by three years out of clinical training to complete a higher degree and leads into a clinical lectureship (CL) where 50% of time is spent undertaking research at an increasingly independent level. ACF and CL opportunities are advertised across the UK in centres of academic excellence. On completion of clinical training, a senior lectureship allows continuation of academic activities at a senior level alongside working as an NHS consultant.
A research career is stimulating and varied, and offers the chance to undertake research in a world class environment. You get the opportunity to travel widely and experience pathology practice across the world as well as present your work to the scientific community. It is a career path highly recommended by the speaker!

# S11

## Molecular Pathology: From Discovery to Test

Ⓟ AJ Freemont; DC Mangham; K Boylan

*University of Manchester, Manchester, UK*

Molecular Biology/Molecular Pathology, in their broadest sense, have given a massive insight into the functioning of normal and diseased tissues. However, it is estimated that less than 1% of newly discovered biomolecules have been translated into tests to help patients and doctors. This could be because there is no clinical value in these tests, but the truth is that there are no easy routes for translating these newly discovered molecules into the clinic. Where there are barriers progress is slow. The fundamental problem has been that no one has sought the input of pathologists (the gatekeepers of test roll out into the NHS) in this translational pathway and pathologists themselves have been too pre-occupied with service delivery, and the organisations they work for too busy trying to balance budgets, to promote the development of suitable pathways and pipelines for translation. In 2015 MRC and EPSRC, working together funded, 6 "Molecular Pathology Nodes" to assist in Translation. One node works in "Breathomics", 4 in early "Discovery/Validation", and one, that in Manchester (The Manchester MRC/EPSRC Molecular Pathology Node or the Manchester Molecular Pathology Innovation Centre [MMPathIC]) works on the full translational pathway. This talk will focus on the latter as an exemplar to the issues around translation from "Discovery to Test". It will cover; decision pathways around adoption of biomarkers for clinical translation; support for translation; regulatory pathways; successes and barriers; working with industry; and rewards for researchers patients, doctors and the NHS. This is one of the main areas for the future of pathology. It is the basis of future careers in all branches of pathology and ideally suited to intelligent, technically able and even entrepeneurial young doctors. We would argue, it is the only career someone with those three skills would wish to enter, but we am biased and you must judge.

# S12

## Evolution of Classifications in Lung Pathology

Ⓟ AG Nicholson

*Royal Brompton and Harefield NHS Foundation Trust, London, UK*

The aim of this lecture is to highlight the importance of disease classification. Nearly every diagnosis that we make relies on ordered divisions, primarily diseases themselves, but also categorisations such as staging. We rarely have time to think of the reasoning behind these classifications, but they should be thorough, reproducible, globally applicable and dynamic. As an example, the 2015 WHO classification of lung tumours has undergone a variety of changes since 2004, reflecting advances in tumour genetics and therapy over the past decade. A classification system for small biopsies and cytology is now provided and adenocarcinoma classification has been refined significantly to increase its clinical relevance, whilst other major tumour groups have been simplified. New tumours within the lungs have also been recognised in the past decade, overall with increased reliance not just on immunohistochemistry but also molecular categorisation emphasising its dynamic nature. Changes in one classification system may also affect another – the updated classification of adenocarcinomas will likely impact on the 8$^{th}$ TNM staging system in terms of multiple tumour nodules and measurement of tumour invasive size. However, classifications should not undergo change just because time passes. Whilst the 2002 classification of idiopathic interstitial pneumonias was a major revision that led to an ordered system of seven histological patterns associated with seven clinicopathological entities (and even demoted histopathology from being the "gold standard" to be replaced by multidisciplinary review), its 10 year review led to minimal changes, as the system was shown to be both clinically relevant and reproducible in terms of making diagnoses. What is both exciting and worrying at the same time is that this is not the trend as most classifications systems are becoming increasingly complex and updates ever more frequently demanded.

# S13

## Models of Endometriosis

C Barbara; C King; A Prentice; J Brenton;Ⓟ DS Charnock-Jones

*University of Cambridge, Cambridge, UK*

Endometriosis is a benign condition affecting approximately 10% of women of child bearing age and is associated with significant morbidity, a principle feature of which is pain which is frequently depilating. Along with the impact in women's lives it is also associated with substantial economic burden (approximately $50 billion a year in the USA alone). In order to develop treatments for this condition several different animal models have been developed and each with advantages and disadvantages. The most commonly accepted cause of endometriosis is retrograde menstruation in which endometrial fragments seeded in the peritoneal cavity implant and develop inflammatory lesions. The various models which set out to mimic this commonly use surgical implantation of uterine or endometrial fragments and these have been developed in a variety of species (rat, rabbit, mouse and primate). More recent models have sought to use menstrual-like endometrial tissue. The availability of models which more faithfully recapitulate the human condition should lead to increased understanding of the molecular mechanisms underlying the disease and hence to more effective treatments. In addition, there is good epidemiological evidence that endometriosis is a plausible precursor to clear cell and endometrial ovarian cancer. Hence, there is also a need to understand the molecular basis of this and models are now well enough developed to allow this to take place. I will describe several of the models in and give examples of their use and. I will also describe a novel method of ex-vivo genetic modification of human tissue which can be used in a xenograft model.

# S14

## Engineering Large Animal Models of Human Disease

Ⓟ CBA Whitelaw

*University of Edinburgh, Edinburgh, UK*

The recent development of gene editing tools and methodology for use in livestock enables the production of new animal disease models. These tools facilitate site-specific mutation of the genome allowing animals carrying known human disease mutations to be produced. There are various gene editing tools, each differing subtly from the other, and all can be used to produce a range of large animals models of diseases. This genomic technology is in its infancy but the expectation is that through the use of gene editing tools we will see a dramatic increase in animal model resources available for both the study of human disease and the translation of this knowledge into the clinic. Comparative pathology will be central to the productive use of these animal models and the successful translation of new therapeutic strategies.

# S15

## Models of Human Papillomavirus-Associated Disease

Ⓟ J Doorbar

*University of Cambridge, Cambridge, UK*

Human Papillomaviruses cause a range of serious disease, including the vast majority of cervical cancers, most anal cancers and around half of all head and neck cancers. They are also responsible for troublesome benign epithelial lesions, including genital warts and laryngeal papillomas, and in some individuals these viruses can lead to recurrent respiratory papillomatosis and other difficult to manage diseases. As a result, there is a great need for model systems that accurately mimic papillomavirus infections in humans. This is complicated by the diverse variety of HPVs, which now number over 200 types, and the different strategies they have evolved to persist in the population. The most well developed models involve the culture of HPV-containing keratinocytes in organotypic raft culture, an approach which appears to accurately mimic the life cycle of several of the high risk cancer associated HPV types. Included amongst these are HPV16 and 18, which cause the majority of cervical cancers. The low-risk HPV types persist less well in tissue culture models, and our ability to study the productive life cycle of these viruses is more limited. Although ongoing research is likely to improve this situation, animal models of papillomavirus disease can provide considerable basic information as to how lesions form, regress, and can be controlled by the immune system. The best studied are Cottontail Rabbit Papillomavirus, Rabbit Oral Papillomavirus, and more recently, Mouse Papillomavirus (MmuPV), the latter of which is providing exciting new insights viral tropisms and immune control. In addition, transgenic models of disease have helped us to understand the consequences of persistent viral gene expression and the importance of cofactors such as hormones and UV irradiation in the development of neoplasia and cancer. It is hoped that such disease models will eventually lead us to a better understanding and better treatments for human disease.

# S16

## Cross-Species Models of Human Melanoma

Ⓟ DJ Adams

*Wellcome Trust Sanger Institute, Hinxton, UK*

Although transformation of melanocytes to melanoma is rare, the rapid growth, systemic spread, as well as the chemoresistance of melanoma present significant challenges for patient care. Here we review animal models of melanoma, including murine, canine, equine, and zebrafish models, and detail the immense contribution these models have made to our knowledge of human melanoma development, and to melanocyte biology. We also highlight the opportunities for cross-species comparative genomic studies of melanoma to identify the key molecular events that drive this complex disease.

# S17

## Genetic Factors and Mechanism Underlying Drug Induced Liver Injury

Ⓟ GP Aithal

*Nottingham University Hospitals and University of Nottingham, Nottingham, UK*

Concordance between hepatotoxic potential of drugs detected in animal models and humans is poor; investigations performed in the pre-clinical phase have largely failed so far to detect serious hepatic adverse reactions leading to the attrition of drugs during their development and post-marketing withdrawals. The hypothesis that inter-individual variation in response to a drug including the development of 'idiosyncratic' drug-induced liver injury (DILI) is determined primarily by the genetic susceptibility of an individual has been investigated in a number of candidate gene case-control studies as well as genome wide association studies (GWAS) over the past decade. Variations in the metabolism and excretion of a drug would lead to accumulation of reactive intermediates which in turn can bind to cellular or circulating proteins resulting in the formation of covalent adducts. According to 'hapten hypothesis', the presentation of particular drug-peptide complex to T cells is influenced by the characteristics of specific peptide binding groves of Human leucocyte antigen (HLA) molecules which in turn are determined by HLA genotypes; this interaction results in an immune mechanism mediated liver injury. Interestingly, a relatively small number of HLA alleles have overlapping associations with a variety of adverse reactions including DILI, cutaneous hypersensitivity and drug-induced pancreatitis. These observations have stimulated renewed interest in 'pharmacological interaction (p-i) concept' which proposes that some drugs are able to initiate an immune response through a non-covalent binding with the MHC-T cell receptor complex. In addition, 'altered peptide repertoire model' is another potential mechanism underlying certain examples of drug induced hypersensitivity.

# S18

## Patterns of Drug-Induced Liver Injury

Ⓟ SG Hubscher

*University of Birmingham, Birmingham, UK*

The majority of commonly prescribed drugs are potentially hepatotoxic and most of the common patterns of liver injury are potentially drug-induced. It therefore follows that the possibility of a drug reaction should be considered in the differential diagnosis of anyone presenting with liver injury. The diagnosis of drug-induced liver injury is generally based on an appropriate clinical history (including time course) and the exclusion of other relevant causes of liver injury. Liver biopsy is not routinely required to establish a diagnosis of drug toxicity, but may still be obtained in cases where there is diagnostic uncertainty or if there is a possibility of a dual pathology. It is worth remembering that a number of potentially hepatotoxic agents may not be identified by routine history taking – examples include herbal remedies, over the counter non-prescribed drugs, illicit drugs and recently administered drugs, no longer being taken (e.g. antibiotics). This presentation will discuss a practical diagnostic approach to the histological assessment of drug-induced liver injury (DILI), focusing on the main histological patterns seen in DILI and highlighting features that should increase the index of suspicion for a drug reaction as a likely cause of liver injury. Examples of the latter include "pure" cholestasis, zonal necrosis, acute hepatitis with disproportionately severe necrosis or cholestasis and inflammatory infiltrates rich in eosinophils or granulomas. The final diagnosis depends on clinico-pathological correlation, including exclusion of other diseases which may produce a similar pattern of liver injury.

# S19

## Liver Disease in the Immunocompromised Patient

Ⓟ SE Davies

*Cambridge UH NHSFT, Cambridge, UK*

The success of anti-retroviral agents in HIV infection has altered the pattern and presentation of earlier AIDS defining diseases, liver disease now being the second cause of mortality, frequently with chronic viral hepatitis co-infection. Patients are also rendered immunodeficient following transplantation, either bone marrow or of solid organs, following chemotherapy for various malignancies or with anti-inflammatory agents for autoimmune conditions. Several rare conditions can lead to impaired immunity, often presenting in childhood. Immunocompromised individuals are at risk of infections and malignancy, in particular lymphoma and several immunosuppressant drugs can lead to liver enzyme abnormalities and hepatotoxicity in some individuals. Common community-acquired or opportunistic organisms may infect patients, including fungi, protozoa, bacteria, viruses with also reactivation of some viruses and tuberculosis. Patients often present with atypical symptoms and disseminated disease, frequently involving the liver. Certain drugs used to treat complicating infections or to treat HIV, may in turn be associated with liver injury. The development of non-alcoholic fatty liver disease with steroid immunosuppression is common. A spectrum of hepatic vascular changes, some causing portal hypertension, are evident with varying immunodeficient states, including combined variable immunodeficiency disease. With immunosuppression the natural history of chronic HCV is accelerated, with more rapid development of fibrosis, and this includes following liver transplantation when graft recurrence is near universal. A rare and severe manifestation is Fibrosing Cholestatic Hepatitis, initially identified with hepatitis B virus post liver transplantation. The role of chronic hepatitis E virus infection in causing progressive chronic hepatitis in solid organ transplant recipients has also become apparent recently.

# S20

## PREDICTR Study: Biomarkers in Oro-Pharyngeal Squamous Cell Carcinoma

Ⓟ M Robinson

*Newcastle University, Newcastle upon Tyne, UK*

The incidence of oro-pharyngeal squamous cell carcinoma (SCC) has more than doubled in the UK over the last two decades. Around a half of the cases are human papillomavirus (HPV)-related SCCs, which are known to have a favorable prognosis when compared to HPV negative cases at the same site. Laboratory tests used to determine HPV status, namely, p16 immunohistochemistry and HPV specific tests (polymerase chain reaction or in situ hybridization-based tests) are being used in clinical practice for diagnosis and prognostication and have been incorporated into clinical trial protocols for patients with oro-pharyngeal SCC. It is also known that clinical parameters such as disease stage, tobacco consumption and co-morbidities influence the prognosis of oro-pharyngeal SCC, however, accurate assessment of these factors is often problematic. Consequently, there is a search for other biomarkers that may refine the molecular classification of the disease and improve selection of patients for the most appropriate treatments. This presentation will provide an overview of recent work in the field and describe the progress of a UK-based, multi-centre observational study examining biomarker expression in formalin-fixed paraffin-embedded tissue from patients with oro-pharyngeal SCC (PREDICTR-OPC UKCRN 11317 Chief Investigator Professor Mehanna, University of Birmingham).

# S21

## Is it Worth Vaccinating Boys Against HPV? — A Pathologist's Perspective

Ⓟ CJL Meijer

*Dept of Pathology, VUMC, Amsterdam, Netherlands*

High Risk HPV (hrHPV) is the causative agent of cervical cancer and is associated with a proportion of vulvar, vaginal, anal, penile and oro-pharyngeal carcinomas; low risk HPV is associated with genital warts. In the last decade 3 prophylactic HPV vaccines based on HPV L1 virus-like particles have been developed: A bivalent vaccine (Cervarix®, GSK) directed against HPV 16 and 18, a quadrivalent vaccine against HPV 6,11,16 and 18, (Gardasil4®, SPMSD) and in recent year a nonavalent vaccine against HPV6,11,16,18, 31,33, 45,52 and 58, (Gardasil9®, SPMSD). The vaccines, given in three doses (0,1/2,6 months) show the best results in HPV negative (naïve) women and boys (9-12 years), have high seroconversion rates and protect against vaccine type associated (pre) neoplasms. Immunity for the bivalent and quadrivalent vaccines has been shown to last over 10 years. From serum equivalence studies similar results are expected for the nonavalent vaccine. Original cost-effectiveness (CE) studies based only on prevention of cervical cancer, a 3 dose scheme and prices per dose over € 100,- showed that vaccinating only girls was most cost-effective, provided that the vaccine uptake was at least over 70%. However prevention of anal carcinomas in MSM is not effective in such a policy and gender specific vaccination does not promote vaccination uptake. New developments in recent years have major effects on the original CE studies and argue for reconsideration of the only girl vaccination policy. In the original CE studies non-cervical HPV-associated carcinomas in particular the proportion of hrHPV in non-cervical oro-pharyngeal carcinomas were not taken into account. 2 dose schemes appear to be as effective as the 3 dose schemes, and prices per vaccine dose given in country-wide vaccination programmes have dropped under € 25,-. In the lecture it will be discussed why gender neutral vaccination may be the way forward for preventing HPV-associated neoplasms

# S22

## Dermatopathology

Ⓟ W Merchant

*St James's Hospital Leeds, Leeds, UK*

My part of this talk will cover new insights and problem areas in cutaneous mesenchymal neoplasms, adnexal tumours and Melanocytic neoplasms. It will cover how to make the diagnosis of Atypical Fibroxanthoma [AFX] and pleomorphic dermal sarcoma. New sights into the behaviour of cutaneous smooth muscle tumours will be covered and their familial setting. The recent entities of PEComa and epithelioid angiomatous nodule will be discussed. In addition genetic insights into cutaneous fibrohistiocytic neoplasms and their diagnostic value will be reviewed. The entities of post irradiation atypical vascular lesion and its distinction from angiosarcoma will be discussed with new molecular diagnostic insights. In the field of adnexal tumours, the problem of primary versus metastatic disease will be reviewed. In addition, cutaneous neoplasms which may indicate a possible syndrome will be highlighted, including how to spot epidermodysplasia verruciformis and incontinentia pigmenti. In the field of melanocytic tumours , pitfalls in diagnosis will be covered, including special site naevi and lentiginous melanoma. Within the area of Spitz Naevi, new genetic insights including BAP1 and Alk mutations will be discussed.

# S23

## Cutaneous Lymphomas

Ⓟ A Robson

*IPOLFG, Lisbon, Portugal*

Mycosis fungoides (MF) is the most common primary cutaneous lymphoma, and CD30(+) lymphoproliferative diseases are encountered reasonably frequently. Primary skin lymphomas differ clinically & histopathologically from the more nodal counterparts, & a good clinical history is paramount in securing the correct diagnosis, a tenet that seems counterintuitive to pathologists and continues to lead to misdiagnoses. MF is characterised clinically by patches, plaques and tumours. It is essential to establish the presence of these lesions to secure this diagnosis. Similarly, this staging is clinically defined, although histopathology does broadly reflect the stage. Lesions may have a psoriasiform or lichenoid pattern. Typically, a patch of MF has a light lymphoid infiltrate extending into a non-spongiotic epidermis. Features that can assist diagnosis include: lining up of the mononuclear cells in the basal epidermis, cytological atypia & Pautrier microabscess formation. A plaque or tumour of MF exhibits these features in more florid fashion, but also a heavier dermal involvement. There may be loss of the epidermal component.The majority of cases have a CD4(+) T-cell phenotype. Immunophenotyping is not usually helpful in differentiating MF from non-neoplastic infiltrates. An unusual phenotype (eg CD4/8-) does not alter the diagnosis /prognosis. CD30(+) lymphoproliferative disease embraces a spectrum of diseases characterised by neoplastic expression of CD30. These vary from lymphomatoid papulosis (LyP), which has a widely variable histopathology but an indolent clinical course, to anaplastic large cell lymphoma (ALCL), which may be fatal. LyP subtypes A-F are recognised with a further variant associated with 6p25.3 translocation. A typical clinical history of relapsing papules and nodules is necessary for a diagnosis of LyP. "Overlap" cases between LyP and ALCL, complete a complex relationship. CD30 is also expressed by sundry reactive conditions, sometimes in striking numbers.

# S24

## Neutral Evolution in Colorectal Cancer: How Can We Distinguish Functional from Non-functional Variation?

Ⓟ A Sottoriva[1]; TA Graham[2]; B Werner[1]; M Williams[2]; C Barnes[3]

[1]*The Institute of Cancer Research, London, UK;*
[2]*Queen Mary University of London, London, UK;* [3]*UCL, London, UK*

Despite extraordinary efforts to profile cancer genomes, interpreting the vast amount of genomic data in the light of cancer evolution remains challenging. In particular, although genomic intra-tumour heterogeneity (ITH) has become a hot topic in cancer, determining what variation is actually functional and clinically relevant remains an open question. Here we propose a "null model" of genomic ITH based on neutral evolution that can be applied to both single biopsies and multi-region next-generation sequencing data from human malignancies. We will present evidence of functional and non-functional variation in colorectal cancer, with some tumours characterized by complex evolutionary dynamics and on-going clonal selection, and others in which all tumour-driving alterations were already present in the first transformed cell that subsequently grew neutrally. Importantly, reanalysing cancer genomic data within the neutral framework allows the measurement, in each individual patient, of both the in vivo mutation rate and the timing of mutations. This result provides a new way to interpret existing cancer genomic data and to discriminate between functional and non-functional ITH.

# S25

## The Consensus Molecular Subtypes of Colorectal Cancer

Ⓟ L Vermeulen

*Academic Medical Center, Amsterdam, UK*

Colorectal cancer (CRC) is an often lethal disease with heterogeneous outcomes and drug responses. We recently reported on a gene expression-based classification scheme. We detected four consensus molecular subtypes (CMSs) with distinguishing features: CMS1 (microsatellite instability immune, 14%), hypermutated, microsatellite unstable and strong immune activation; CMS2 (canonical, 37%), epithelial, marked WNT and MYC signaling activation; CMS3 (metabolic, 13%), epithelial and evident metabolic dysregulation; and CMS4 (mesenchymal, 23%), prominent TGF-β activation, stromal invasion and angiogenesis. Samples with mixed features (13%) possibly represent a transition phenotype or intratumoral heterogeneity. We consider the CMS groups a robust classification system and the basis for future clinical stratification and subtype-based targeted interventions.

Our current work focusses on resolving the underlying biology of the subtypes. In this respect we have identified a epigenetic regulatory network that characterizes the poor prognosis mesenchymal subtype (CMS4). Epigenetic marks associated with this network, including methylation of the promoter regions of microRNA200 (miR200) family members, identify patients belonging to this subtype and associate with poor disease outcome.

Another strategy we explore in order to classify patients into CMSs without the need of full-transcriptome analysis is an immunohistochemical classifier. Using a panel of 5 markers (CDX2, FRMD6, HTR2B, ZEB1 and KER) as well as microsatellite instability status we obtained high concordance with transcriptome based classifications. Using this approach we further validated the poor prognosis of CMS4 cancers. In addition we corroborate earlier observations that patients that present with mesenchymal cancers (CMS4) do not benefit from anti-EGFR therapy independent of RAS mutation status. This finding highlights the potential of the molecular subtypes in informing treatment decisions in the future.

# S26

## Somatic Evolution of Barrett's/Oesophageal Cancer

Ⓟ SA McDonald

*Queen Mary, University of London, London, UK*

Barrett's oesophagus confers an increased risk for the development of oesophageal adenocarcinoma. While the conversion to cancer risk is low for the individual patient, the large numbers of patients being diagnosed means oesophageal adenocarcinoma is an increasing problem, particularly in the UK. There are no effective biomarkers for predicting which Barrett's patients will progress and this is because we do not fully understand the evolution of the disease. Barrett's is characterized as the erosive replacement of the normal oesophageal squamous epithelium with a metaplastic glandular phenotype. The Barrett's epithelium consists of a broad range of gland phenotype that contain a distribution of gastric and intestinal cell lineages and each is a clonal unit. Barrett's glands are likely to be protean therefore they represent an evolving ecosystem. Many studies have investigated the diversity of Barrett's genotype and how this progresses to cancer, but Darwinian selection acts on the phenotype not the genotype. It is therefore important to understand that the unit of selection in Barrett's is the gland. Here, we propose that the significance of the evolution of Barrett's gland phenotype and its diversity have not been fully appreciated and that this is an important omission when we consider that all current diagnoses are based on histopathological analysis. In this presentation I discuss our latest findings suggesting that Barrett's evolves from the gastric mucosa and that the progression to cancer can occur from a diverse range of gland phenotypes.

# S27

## Molecular Heterogeneity of Gastric Cancer

Ⓟ HI Grabsch

*Maastricht University Medical Center, Maastricht, Netherlands*

Gastric cancer is the fifth most common cancer in the world and the third leading cause of cancer death worldwide. The past decade has seen the development of multimodal treatment strategies combining surgery, chemotherapy and/or radiotherapy for patients with locally advanced resectable disease. Whereas targeted therapies have proven to be very effective in lung cancer, colorectal cancer and melanoma, targeted therapy has been much less successful in metastatic gastric cancer. Gastric cancer show extraordinary high inter- and intra-tumour heterogeneity which is only partly reflected in the histological classifications currently used such as WHO and/or Lauren classification. Recently, several new classifications have been proposed using comprehensive molecular data suggesting that there is also substantial molecular heterogeneity in this disease. Interestingly, molecular gastric cancer subtypes seem to be related to anatomic location, histological phenotype, metastatic spread as well as survival in some of the classifications. This lecture will provide a summary of the recently proposed molecular gastric cancer classifiers and discuss their clinical utility e.g. whether and how they might be able to guide clinical decision making in the near future and ultimately improve patient outcome.

# S28

## Gastric Adenocarcinoma of Fundic Gland Type – A New Entity

Ⓟ T Yao[1]; H Ueyama[2]

[1]*Juntendo University Graduate School of Medicine, Tokyo, Japan;*
[2]*Juntendo University School of Medicine, Tokyo, Japan*

We proposed gastric adenocarcinoma of fundic gland type (GA-FG) as a new entity having distinct clinicopathological characteristics, which is defined by positive immunohistochemical stain with pepeinogen I (a marker for chief cell) and/or H+-K+-ATPase (a marker for parietal cell) (Am J Surg Pathol 34: 609-619, 2010).

GA-FG tended to occur in upper third of the stomach (fundus) of senior. GA-FG usually generates at the deep portion of almost normal fundic gland mucosa and grows in a flat or polypoid configuration initially. Even a small lesion invades submucosa. With regard to biological behavior, GA-FG was considered to be less aggressive because of low cellular atypia, no lymphovascular invasion, low proliferating activity, lack of p53 protein overexpression and good prognosis. After the first report, further research revealed that GA-FG was not associated with H. pylori infection basically.

We also analyzed the molecular events of GA-FG, and suggested that a progression of GA-FG, at least in part, might be associated with GNAS mutation and Wnt/β-catenin signaling pathway. Recently, many cases of an aggressive variant of GA-FG with high cellular atypia, lymphovascular invasion and metastasis have been discovered, many of which had a differentiation toward the gastric foveolar epithelium in addition to fundic gland differentiation. GA-FG should be paid more attention to even in the country, in which the incidence of H. pylori infection is low. Although original GA-FG is less aggressive and has a good indication for the curative endoscopic resection, GA-FG with a foveolar differentiation should be carefully treated. 'Adenocarcinoma of fundic gland mucosal type' may be an appropriate nomenclature for an aggressive variant of GA-FG with a foveolar differentiation.

# S29

## The Role of Immunohistochemistry in Diagnosis in Breast Pathology

Ⓟ AHS Lee

*Nottingham University Hospitals, Nottingham, UK*

Most diagnoses in breast pathology can be made using the simple morphology provided by haematoxylin and eosin sections. Immunohistochemistry can be helpful in less straightforward cases, but must be interpreted in the light of the morphology. Myoepithelial markers help to distinguish invasive carcinoma from in situ carcinoma and sclerosing lesions, and in the assessment of papillary lesions. The myoepithelial layer may be attenuated around carcinoma in situ and in sclerosing lesions. Basal cytokeratins (CK14 and CK5/6) and oestrogen receptor help classify intra-acinar proliferations. Epithelial hyperplasia of usual type shows patchy expression of these markers, whereas clonal proliferations such low and intermediate grade ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS) are usually negative. DCIS with a solid growth pattern can be difficult to distinguish from LCIS. E-cadherin usually shows membrane expression in DCIS and is usually negative in LCIS. Antibodies to catenins can help in difficult cases. Cytokeratins are useful for identifying spindle cell carcinoma and small nodal metastases of carcinoma. Metastases to the breast can resemble mammary carcinoma, but immunohistochemistry is helpful in identifying metastases. Different antibodies are useful for different tumours: TTF-1 for lung cancer, WT1 and PAX8 for ovarian carcinoma, S100, melan-A and HMB45 for melanomas and lymphoid markers for lymphomas. It is important to be aware of the strengths and weaknesses of individual antibodies. Smooth muscle actin is a sensitive myoepithelial marker, but also stains fibroblasts and blood vessels. Smooth muscle myosin heavy chain and p63 are more specific, but do not work well in poorly fixed tissue. S100 is expressed by about 40% of breast cancers as well as by melanomas. Often it is best to use a panel of antibodies. It is also important that internal and external controls stain appropriately.

# S30

## An Update on the Biology, Pathology and Implications of Breast Cancer Risk Lesions

Ⓟ SE Pinder

*King's College London, London, UK*

The term 'risk lesions' is used for entities that confer an increased risk of subsequent development of ductal carcinoma in situ (DCIS) or invasive cancer in either breast. However, the phrase is also used for lesions of uncertain malignant potential (B3) on core biopsy, which are known to be associated with the presence of DCIS or invasive carcinoma in that same area of the breast at the time of diagnosis (better termed 'upgrade'). Many are the same lesions, including atypical ductal hyperplasia/atypical intraductal epithelial proliferation (AIDEP), lobular neoplasia and flat epithelial atypia (FEA). These have a significant upgrade rate; that for AIDEP varies from 18%-87% for 14g needles compared to 10-39% with 11g or 9g samples. For lobular neoplasia the upgrade rate is 27%, even if detected co-incidentally. The upgrade for the newer entity of FEA is less clear, but lower, and in the range 10-20%. Until recently, surgical excision has been the diagnostic procedure of choice but new approaches are recommended, such as thorough sampling/excision by vacuum-assisted techniques. The risk of development of breast cancer in women with FEA is low. Patients with other atypical epithelial proliferations on biopsy have approximately a 4x increased risk of subsequent breast cancer. Some, but not all, series suggest that this is higher in women with a family history of breast cancer, and if there are multiple foci of atypia, particularly atypical lobular hyperplasia. The risk is also higher in younger, pre-menopausal women. Cancers that develop in women with a previous diagnosis of atypia are essentially similar to those without, regarding histological grade, lymph node stage and tumour subtype, but subsequent carcinomas are even more likely to be ER positive (91% vs 85%).

# S31

## An Update on the Molecular Classification of Breast Cancer

Ⓟ EA Rakha

*University of Nottingham, Nottingham, UK*

Breast cancer (BC) is a heterogeneous disease with a diverse spectrum of diseases featuring distinct histological, biological, and clinical phenotypes. Tumours of similar clinicopathological features show different behaviour and response to specific therapy. Advancements in high-throughput molecular techniques and bioinformatics have contributed to the improved understanding of BC biology, refinement of molecular taxonomies and the development of novel prognostic and predictive molecular assays. Molecular testing has become increasingly important in the prevention, diagnosis, and treatment of BC. Although molecular taxonomies of BC have attracted great deal of attention in the past decade, currently there is more interest in the application of multiparameter gene assays to prognostically stratify certain BC classes into distinct groups to guide decisions on adjuvant systemic therapy. Applications of next generation sequencing to BC research are expanding and may change the way we understand and treat BC in the near future. Despite the enormous amount of work that has been carried out to develop and refine BC molecular prognostic and predictive assays, it is still in evolution. With the increasing use of more sophisticated molecular techniques, large amounts of data will continue to emerge, which could potentially lead to identification of novel therapeutic targets and allow more precise classification systems that can accurately predict outcome and response to therapy.

# S32

## Atypical Large Glandular Proliferations of the Prostate

Ⓟ M Varma

*University Hospital of Wales, Cardiff, UK*

The differential diagnosis of atypical large glandular proliferations of the prostate includes benign conditions such as seminal vesicle type epithelium, normal central zone histology and clear cell cribriform hyperplasia; high-grade PIN (HG-PIN) and malignant lesions such as pseudohyperplastic prostatic acinar carcinoma (PAC), cribriform PAC, prostatic ductal adenocarcinoma (PDC), PIN-like PDC and intraductal carcinoma of the prostate (IDC-P).

HG-PIN is a surrogate marker for missed cancer in negative prostate biopsies (PBx) so it is not necessary to report HG-PIN in radical prostatectomies or in PBx with prostate cancer. The incidence of missed cancer is significantly lower with extended biopsy protocols so routine re-biopsy may not be necessary following identification of isolated HG-PIN in this scenario.

PDC is characterised by a papillary fronds lined by pseudostratified epithelium with oval pleomorphic nuclei unlike single layered glands of PAC lined by cuboidal cells with more uniform round nuclei. PDCs are often located centrally in the prostate with patients often presenting with haematuria or obstruction and the tumour identified on TURP. However, these tumours may be located entirely in the peripheral zone and identified by PBx.

Some prostatic adenocarcinomas lined by pseudostratified epithelium closely resemble HG-PIN with flat or tufted growth pattern and have been referred to as "PIN-like ductal carcinoma". However, PIN-like PDCs are not as aggressive as the usual PDC and are graded as Gleason pattern 3.

IDC-P usually represents intraductal spread of high-grade, high-stage invasive PAC. However, distinction from HG-PIN and invasive carcinoma may be difficult or even impossible in some cases. When IDC-P is identified in PBx in the absence of invasive cancer, some experts recommend immediate re-biopsy while others recommend radical therapy. There is significant variation in the diagnosis and reporting of IDC-P even among expert uropathologists.

# S33

## An Introduction to the New Grading System for Prostate Cancer

Ⓟ DM Berney

*Queen Mary University of London, London, UK*

The Gleason grading system has been in use for over 40 years and has undergone many revisions. After the 2005 ISUP revisions, one might have expected a period of stability, however it became clear that certain patterns wer being interpreted differently by different centres, and that there was increasing evidence that some patterns, such as rounded cribriform glands, although traditionally assigned Gleason pattern 3, had a worse prognosis. A second concern was the clinican and patient interpretation of a grading system which ran from 2-10, when 6 was the lowest score seen on prostate biopsy. A third concern was evidence that Gleason score 3+4=7 showed highly significant separation from Gleason score 4+3=7, in a number of large cohorts, and that this information was underutilised by some of the tools used to predict prognosis in prostate cancer. In 2014, over 50 pathologists and clinicians met at a meeting in Chicago organised by ISUP to reach consensus on these issues. There was consensus about the removal of both rounded cribriform glands and glomeruloid glands into pattern 4. There was also consensus that a system of grade groups, originally devised by Dr J Epstein be introduced. The grade groups from 1-5 allows both separation of Gleason 3+4=7 (Grade group 2) from Gleason 4+3=7 (Grade group 3) and also is a system easily interpretable by patients and clinicians. The system has been included in the 2016 WHO classification of genito-urinary malignancies. Evidence will be presented from both radical prostatectomy and biopsy data, validating the strength of grade groups in terms of both PSA relapse and death from disease. Other current issues in grading include the role of including the percentage of high grade disease seen, and also whether to give overall grade and percentage assessments for each case or whether information from individual prostate cores should be used, taking the 'worst' grade and percentage seen. These differences may lead to great changes in individual patient management. These changes will have many practical implications in terms of pathologist workload, but may lead to greater clarity and accuracy of prognostic information for clinicians, especially when dealing with diagnostic prostate biopsies.

# S34

## What the Clinician Wants in Prostatic Biopsy and Prostatectomy Reporting

Ⓟ TJ Walton

*Nottingham University Hospitals NHS Trust, Nottingham, UK*

Good decision-making underpins good surgical care and outcomes. Nowhere is this more true than in prostate cancer management. In this regard the histopathologist plays a key role informing routine decision-making in multidisciplinary team meetings, in theatre and in outpatients. In this lecture Mr Tom Walton, Consultant Urological Surgeon and Urology Cancer Lead at Nottingham University Hospitals NHS Trust, uses clinical scenarios and intraoperative video footage to give a personal perspective on how pathology reporting impacts upon clinical practice.

# S35

## Pathology and Imaging in Prostate Cancer

Ⓟ HU Ahmed

*University College London, London, UK*

The current diagnostic pathway is inaccurate as it relies on sampling the prostate without a visible lesion. Ultrasound simply allows the user to see the prostate but not a malignant phenotype. As a result, multi-parametric MRI is increasingly used prior to biopsy to determine what might reside in the gland so that the operator can make a decision about whether to biopsy and if a biopsy is considered to more accurately deploy the needles. As a result, key questions have arisen which the speaker will delve into. Can we avoid a biopsy in men with a negative MRI? Can we target alone or are systematic biopsies required? Are MRI - invisible malignant areas important since they have not declared a clinically visible phenotype? Can we apply our current risk stratification systems on targeted biopsies? Is the new prognostic grouping for Gleason scores the right way to go? Can we selectively treat areas of the prostate rather than the entire prostate? The new imaging based paradigm has given rise to many critical questions for which we do not yet have all the answers.

# S36

## Prostate Cancer: Molecular and IHC Approaches

Ⓟ C Magi-Galluzzi

*Cleveland Clinic, Cleveland, Ohio, USA*

Immunohistochemistry (IHC) has become an essential tool in the evaluation of prostate needle biopsies (NBx) to help establishing an initial diagnosis of limited prostate cancer (PCA). ERG protein expression and PTEN protein loss have been proposed as potentially useful markers to distinguish intraductal carcinoma from high-grade prostatic intraepithelial neoplasia. Another diagnostic role of IHC is to confirm or exclude the prostatic origin of a high-grade tumour in primary or metastatic setting, where PCA may be confused with nonprostatic carcinomas. PTEN loss is infrequent in clinically insignificant PCA; accordingly PTEN loss in Gleason score 6 PCA on NBx indicate a higher likelihood of clinical significant PCA and of upgrading at radical prostatectomy, with important implications for patients who are potential candidates for active surveillance (AS). Tumour volume in a discontinuous NBx core may also impact AS eligibility. A recent study has shown that ~25% of discontinuously involved NBx cores showed tumour foci with discordant ERG/SPINK1 status, consistent with multiclonal disease. Clonal assessment may have a potential clinical impact in candidates for AS. Over the past several years, a multitude of tissue-based molecular tests and algorithms has been developed to enhance diagnostic accuracy, improve pre-treatment and post-treatment patient risk stratification, and identify aggressive versus indolent PCA to facilitate therapeutic decision-making. Some of the tests currently available are useful to decide who to rebiopsy and to reduce the number of unnecessary biopsies; others are useful to distinguish aggressive from indolent tumours and decide who to surveil or treat. Each test assesses the presence or absence of a differing but specific set of genes known to be associated with PCA risk and provide patient and treating clinicians with a "risk score" that may be helpful in deciding whether a patient can confidently choose AS or require early treatment.

# S37

## Cancer Immunotherapy

Ⓟ LG Durrant

*University of Nottingham, Nottingham, UK*

Checkpoint inhibitors have validated the concept that T cells can be an effective therapy for cancer, giving durable responses in metastatic disease. One of the reasons that some cancers are more sensitive to this type of therapy is because they have a high mutational load. This includes chemically induced tumours such as melanoma, lung, renal and bladder but can also includes MSI colorectal cancer. However, many mutated-epitopes do not bind to MHC and/or are not recognized by the T cells. Such patients may t require a cancer vaccine that stimulates de novo T cell responses prior to checkpoint blockade. As T cells cloned from spontaneously regressing patients recognize tumour-associated epitopes, it seems logical to stimulate responses to these epitopes. They also have the advantage of being useful in a wide range of patients rather than requiring personalized vaccines. SCIB1 is a human IgG1 DNA vaccine encoding epitopes from gp100 and TRP-2. A phase I trial in metastatic melanoma patients showed that SCIB1 induced T cell responses and disease regression. Of particular interest were the patients with fully resected disease, all of whom remain alive 42 months (range 36-55) after their initial immunisation. Furthermore, preclinical studies have shown that SCIB1 synergises with anti-PD.1 therapy and a combination trial is planned. Alternative antigens may be post-translational modified proteins such as self-antigens modified by citrullination, which converts arginine residues in proteins to citrulline. Focusing on the intermediate filament protein vimentin, which is frequently expressed in tumour cells during epithelial-to-mesenchymal transition, we immunized mice with citrullinated vimentin peptides. Remarkably, a single immunization with modified peptide, up to 14 days after tumour implant, resulted in long term survival in 60-90% of animals with no associated toxicity. These results show how citrullinated proteins may offer attractive cancer vaccine targets.

# S38

## Viral Oncogenesis and Hepatocellular Carcinoma

Ⓟ WL Irving

*University of Nottingham, Nottingham, UK*

Around 75% of all hepatocellular carcinomas (HCC) arise in patients chronically infected with either hepatitis B or hepatitis C viruses. This review will discuss host, virological and environmental factors associated with the development of HCC, and how an understanding of disease pathogenesis may lead to improvements in the prognosis for patients diagnosed with HCC.

# S39

## GIST: An Expanding Molecular Landscape Driving a Molecular Diagnostic Service – What is New and Relevant

Ⓟ P Taniere; B O'Sullivan; M Smith; F Hughes; C Swift; O Cain; N Deshmukh

*Queen Elizabeth Hospital, Birmingham, UK*

Over 80% of GISTs carry a mutation in either KIT or PDGFR alpha; mutation testing is not mandatory prior to tyrosine kinase inhibitor prescription, but it is now current practice to test any GISTs, at the time of diagnosis on surgical resection specimen or diagnostic biopsy/fine needle aspiration. Tumours are tested for exons 9, 11, 13 and 17 of KIT and exons 12, 14 and 18 of PDGFR alpha. Very rare mutations have been identified in exons 8 and 14 of KIT. Testing is performed by Sanger sequencing or Next Generation Sequencing; the clinically relevant hot spot D842V mutation within exon 18 of PDGFR alpha can also be specifically targeted allowing quicker turn around time, using homebrew assay or commercial kits (Qiagen pyrosequencing kit). Mutation testing could also be performed on plasma; this represents an interesting approach to screen for secondary mutations in tumours progressing under therapy. GISTs which are wild type for KIT and PDGFR alpha represent a heterogeneous group of tumours; some of them are part of clinical syndromes (Neurofibromatosis type 1, Carney's triad, Carney-Stratakis syndrome) but most are sporadic. Any KIT/PDGFR alpha wild-type GIST requires SDHB expression assessment by immunohistochemistry. Loss of SDHB expression can be secondary to methylation of SDHC promoter or to a mutation within one of the SDH genes (mainly SDHA); mutation can be sporadic or germline. SDH competent wild type GISTs frequently have mutation within genes usually altered in cancers such as BRAF (Boikos et al. Jama Oncol 2016). It remains a group of 5% of GISTs lack abnormalities of KIT, PDGFRA, SDH, or RAS signalling pathways (quadruple wild-type GISTs).

# S40

## Is There a Role for Genetics in the Diagnosis of Undifferentiated Sarcomas?

Ⓟ N Pillay

*UCL Cancer Institute, London, UK*

Cancers are classified primarily on the basis of their tissue of origin. This classification system is used to inform diagnosis, prognosis and treatment. The recent large sequencing endeavours such as The Cancer Genome Atlas (TCGA) and International Cancer Genome Consortium (ICGC) have generated molecular (genomic, transcriptomic and methylation) profiles of tens of thousands of different cancer samples. The 100,000 Genomes project in the UK is also likely to contribute significantly to this emerging molecular classification of disease and would underpin the design of biologically relevant clinical trials enabling personalised medicine. Pan-cancer analyses of big data is in it's infancy but has already shown that one in ten cancer patients could be classified differently and therefore be eligible for different therapeutic options. This has major implications for sarcoma patients, up to 25% of whom cannot be classified into defined classes and are categorised as undifferentiated sarcoma or pleomorphic sarcoma NOS (not otherwise specified). This talk will focus on the promise of pan cancer analysis for the pathological classification of sarcoma and the utility of genomics and epigenomics in the understanding of the biology of tumours of mesenchymal origin.

# S41

## Molecular Pathology of Bone Tumours – Getting More Accurate Diagnostic, Prognostic and Predictive Information

Ⓟ MF Amary

*RNOH, London, UK*

With rare exceptions, until recently, bone tumours were classically diagnosed on morphological grounds with the aid of clinical / radiological correlation. Molecular genetics is increasingly paying an important role not only in the diagnoses of unusual cases but also in stratifying patient for different treatment modalities. Data generated from different studies, including large scale DNA and RNA sequencing has shown recurrent alterations associated with specific tumour types. Some of these alterations have been included in clinical practice. Benign and malignant central cartilaginous tumours are associated with IDH1 or IDH2 gene mutation. High-grade central chondrosarcomas may show loss o CDKN2A and /or TP53 alterations. Dedifferentiated chondrosarcoma, with or without osteosarcomatous differentiation, may be diagnosed even in the absence of a well-differentiated cartilaginous component via the detection of IDH1 or IDH2 gene mutation. Mesenchymal chondrosarcomas are associated with HEY1-NCOA2 fusion transcript. Identifying this transcript helps to differentiate these tumours from other round cell or chondroblastic sarcomas. Epiphyseal osteoclast-rich tumours: giant cell tumour (GCT) and chondroblastoma are associated with alterations in H3F3A or H3F3B genes. Although the diagnoses of these lesions is not challenging in the majority of the clinical cases, in unusual cases or small biopsies, the detection of these alterations may lead to the correct choice of treatment. In GCT, treatment with Denosumab is now an option to precede surgery in large tumour volume cases or sites in which the surgical procedure would be difficult. FGFR1 gene amplification, found in 20% of HG osteosarcomas that respond poorly to chemotherapy, is currently used as a tool to stratify patients for inclusion into clinical trials. Molecular genetics studies have also defined a new subtype of bone sarcoma associated with BCOR-CCNB3 fusion transcript.

# S42

## Stem Cells and Lineage Commitment in Bone Tumours

Ⓟ AE Grigoriadis

*King's College London, London, UK*

Primary bone tumours represent a large heterogenous group of malignancies that originate in bone, and are distinct from bone tumours that arise as a result of metastasis from carcinomas such as breast, lung and prostate. Primary bone tumours range from benign lesions, such as osteoblastomas and osteochondromas, to highly aggressive malignant tumours that include osteosarcoma and chondrosarcoma to name but a few. Each of those are characterised by marked inter- as well as intra-tumour heterogeneity. Regardless of the bone tumour type, the general molecular and cellular mechanisms that result in transformation of normal bone tissue to cancerous tissue are largely unknown. There are large-scale efforts that are ongoing in many laboratories, that are aimed at understanding the genetic basis of bone tumour pathogenesis through high-throughput genomic and sequencing approaches with a view to identify germline and/or somatic mutations that drive tumour formation. Alternative and complementary approaches involve gaining a better understanding of the cell biology of bone cell transformation, to identify the specific cell population(s) that are targets for mutations and transformation, as these cells are likely to be responsible for not only tumour initiation, but propagation, recurrence and chemoresistance, as well as metastasis. Significant advances have been made in recent years in identifying so-called cancer stem cells and/or tumour-initiating cells in haematopoietic malignancies and carcinomas, however, the identification of such cells in bone tumours are only beginning to be elucidated, and represent an exciting future area of discovery. This presentation will discuss the rationale behind identifying cancer stem cells in bone, and will describe the cellular, molecular and animal model systems being used by many laboratories to identify the specific mesenchymal lineage and/or osteogenic stem/progenitor cells that drive bone tumour formation.

# S43

## The Expanding Family of Ewing's and Related Tumours

Ⓟ F Puls

*Sahlgrenska University Hospital, Gothenburg, Sweden*

Ewing's sarcoma is the prototypical sarcoma with "small round blue cell tumour" (SRBCT) morphology arising in soft tissue and bone. Classical Ewing's sarcoma is molecularly characterized by gene fusions between EWSR1/FUS and a member of the ETS family of transcription factors. As FISH and RT-PCR analyses now complement almost every newly diagnosed case of Ewing's sarcoma, there is increasing interest in SRBCT sarcomas lacking the typical EWS/FUS-ETS rearrangements, tentatively labelled "Ewing's-like sarcomas". In recent years, other recurrent gene-fusions have been identified in this group. The two largest subsets are primitive sarcomas harbouring CIC-DUX4 and BCOR-CCNB3 gene fusion as well as few variants, in which CIC or BCOR have different fusion partners. Morphological and clinical overlap with classical Ewing's sarcoma is broad. However there is increasing knowledge about what separates CIC-DUX4 and BCOR-CCNB3 sarcomas on morphological, clinical and genetic level from classical Ewing's sarcoma. CIC-DUX4 sarcomas arise in variable anatomic regions predominantly within the soft tissues in a wide age-range and show a primitive, but variable morphology. BCOR-CCNB3 sarcomas arise preferentially in bone in young males. Morphologically, BCOR-CCNB3 sarcoma overlaps with Ewing's sarcoma, but some cases show a plump spindle cell morphology. It remains a matter of debate, if these groups represent separate tumour categories or should remain integrated within the family of Ewing's sarcoma. Morphological and clinical features are discussed as well as diagnostic strategies for correct classification and identification of genetic aberrations.

# S45

## The Pathologist and the 100K Genome Project

Ⓟ M Jimenez-Linan

*Cambridge University Hospital, Cambridge, UK*

The 100,000 Genomes Project was launched in 2012. The aim is to sequence 100,000 whole genomes from NHS patients with cancer and rare diseases by 2017. The purpose of the project is to create a new genomic medicine service for the NHS with the potential to improve the prevention and treatment of these conditions. The project will be delivered in thirteen Genomic Medicine Centres (GMCs) across the NHS in England. The quality of the genomic sequence data relies on the quality of DNA extracted. Pathologists play a vital role in the rapid collection, handling and processing of the tumour samples and are critical in the selection of high quality, well-characterised tissue for DNA extraction and in the assessment of tumour cell content within the sample. This project is a prime opportunity for the improvement and integration of laboratory processes across the NHS and for the incorporation of genomic analysis as an integral part of diagnostic histopathology.

# S46

## Principles of Next Generation Sequencing

Ⓟ A Sharif

*East Midlands Regional Molecular Genetics Laboratory, Nottingham, UK*

Next generation sequencing or massive parallel DNA sequencing has brought significant changes in the laboratory workflow and has allowed molecular diagnostic laboratories to test for increasing number of hereditary disorders. This same technology has applications in many areas of pathology. This talk will give an overview of the principles of next generation sequencing with reference to some of the commonly used sequencing platforms and discuss the relative advantages and disadvantages of these platforms. Issues related to data analysis, interpretation and storage of data will also be discussed.

# S47

## Next Generation Sequencing — Applications

Ⓟ XM Fernandez

*Thermo Fisher Scientific, Paisley, UK*

We are witnessing a paradigm shift in contemporary medicine, as genomic tools become pervasive in clinical research. Technological advances in the analysis of DNA and related molecules are bringing an increase in our understanding of disease in what is called precision medicine, the analysis of genetic variation is helping to redefine disease at the molecular level. Resources for -omics data are growing at an unprecedented pace following the wide-uptake of high throughput sequencing by life scientists. The challenge in harnessing all this genomic data is matched by the need to educate the key stakeholders. Biomedical researchers are being outpaced by the amount of data generated and struggle to interpret it. Thus, automated workflows and new algorithms are being developed to overcome the primary bottleneck (not data acquisition): interpretation. Voluminous genomic and biological data collections are being integrated into new tools.

# S48

## SMRT® Technology – A Paradigm Shift in Sequencing

Ⓟ S Picton

*Pacific Biosciences, Menlo Park, USA*

In an effort to overcome inherent challenges in the field of genomics, we sought to develop novel technology that pushed the boundaries of sequencing. The result, SMRT Sequencing, harnesses the natural process of DNA replication and enables real-time observation of DNA synthesis. With this unique technology, we equip innovative scientists and deliver the results needed to drive genetic discovery. As the field of genomics evolves, there is a growing awareness in the scientific community of the importance of long-read data. Long sequence reads improve mappability for resequencing and simplify de novo assembly. PacBio Systems allow you to directly sequence DNA and achieve long sequencing reads with uniform coverage. Our Single Molecule, Real-Time (SMRT) Sequencing technology consistently produces some of the longest average read lengths available in the industry (average > 10,000 bp, some reads > 60,000 bp). These long reads give you the ability to assemble high-quality de novo genomes, catalogue full-length isoforms, unambiguously align sequences, observe fully phased alleles, span repetitive elements and complex regions and resolve structural variants. An overview of the technology and applications will be presented.

# S49

## The Use of Proteomics in Diagnostics: Liver Fibrosis Biomarkers

Ⓟ B Gangadharan; A Kumar; E Barnes; P Klenerman; RA Dwek; N Zitzmann

*University of Oxford, Oxford, UK*

Proteomics can help to discover and quantify novel biomarkers and we show how this is achieved using liver fibrosis as an example. Liver biopsy is the reference standard for assessing liver fibrosis and serum biomarkers are less invasive. The severity of liver fibrosis can be determined using immunoassays. However biomarkers may be degraded due to sample storage conditions and therefore may not be detected using these antibody-based assays. Detection of biomarkers by mass spectrometry overcomes this disadvantage and the approach can be applied to all diseases.Two dimensional gel electrophoresis (2DE) was used to find differences in proteins in plasma samples from patients with varying liver fibrosis stages. The identified proteins were potential liver fibrosis biomarkers. Mass spectrometry can assay for biomarkers by detecting their tryptic peptides and fragments and was used to develop an antibody-free assay. We are the first and only lab in the UK to use a novel absolute quantitation method which is the only biomarker assay using a universal calibration mix.Using 2DE, we identified several potential biomarkers for liver fibrosis which were analysed by Western blotting using plasma samples from patients with varying stages of liver fibrosis. Our novel biomarkers were promising when compared to the markers used in current liver fibrosis tests. A mass spectrometry assay was developed for the best novel liver fibrosis biomarker.We are working towards the first ever antibody-free biomarker assay for liver fibrosis. Our assay is nine times faster than conventional quantitation by mass spectrometry making our approach for absolute biomarker quantitation applicable for clinical use. This is also the only assay which can analyse all points of the calibration curve and determine the absolute concentration of the biomarker in a single acquisition. Our assay may help reduce the need for invasive liver biopsies and the approach could be used for any other disease.

# S50

## Metabolomics: Shedding Light on Human Health and Diseases

J Wood[1]; A Lourdusamy[1]; J Ward[1]; D Barrett[2]; R Rahman[1];Ⓟ D Kim[2]

*[1]Children's Brain Tumour Research Centre, School of Medicine, University of Nottingham, Nottingham, UK; [2]Centre for Analytical Bioscience, School of Pharmacy, University of Nottingham, Nottingham, UK*

Metabolomics has built a rich history for the analysis of small biomolecules which represent 'metabolite profiles' in biofluids, cell and tissue extracts. Since metabolites provide the phenotypic outcome of gene expression or metabolomic activities of a cell, global metabolite profiling can give a rapid snapshot of the cell physiology and provide insight into relationships between genotype and phenotype. Therefore, these profiles have been increasingly used in applications for human health and diseases including biomarker and drug discovery, and disease onset and progress monitoring. Here in Nottingham, we apply advanced analytical approaches to investigate complex biological and pharmaceutical problems in human and mammalian samples. A major area of investigation is the role of biological metabolites in important biological processes and disease states, particularly using liquid chromatography-mass spectrometry (LC-MS)-based metabolomics. I will present published and unpublished examples of metabolomics applications to illustrate how these techniques can be used for biomarker discovery of disease, disease diagnosis and drug discovery as a complementary method to current pathology techniques. For example, we investigated intra-tumour heterogeneity (ITH) in multiple glioblastoma (GBM) regions using LC-MS-based metabolite profiling and confirmed key metabolites that are biologically significant at invasive margin from which secondary tumours are most likely to arise. This is the first to address ITH with multi-region biopsies using advanced LC-MS-based metabolite profiling.

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