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Understanding Disease — Guiding Therapy

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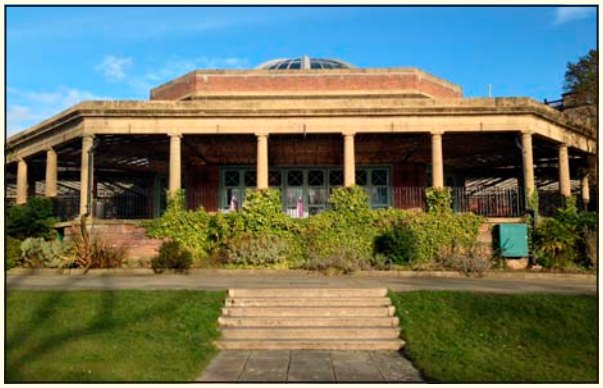

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PHOTOGRAPHS

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S1

Exploring the Junk in Our Genomes: The Blurred Boundary Between Coding and Non-Coding RNAs

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Only ~4% of the human genome encodes protein, whilst ~85% is transcribed into RNA. These transcribed regions give rise to non-coding RNAs, many of which are >200nt in length, and termed long non-coding RNAs (lncRNAs). Mutations in protein-coding genes have been thoroughly mapped and their contribution to human disease dissected. Yet we have limited understanding of how mutations in the other parts of the genome impact human health. It is therefore important to understand lncRNA functions and their potential contribution to human disease. LncRNAs exhibit more tissue and developmental-stage specific expression than mRNAs. They are enriched in the nervous system and testes. Several lncRNAs regulate neuronal differentiation and lncRNA mis-regulation has been implicated in neurological disorders (e.g. BACE-AS1 in Alzheimer's Disease). The molecular function of lncRNAs is highly dependent on their nucleotide sequence and the proteins they interact with, in a sequence specific manner. In fact, many lncRNAs have been shown to interact with ribosomes and a small proportion show evidence of translation, resulting in the synthesis of small peptides. However, these translation events remain controversial and their medical importance poorly understood. To determine the biological importance of neuronal lncRNA-ribosome interactions, we have characterized lncRNAs during neuronal differentiation (SH5Y5Y cells). qRT-PCR of translation complexes indicates that many neuronal lncRNAs are associated with ribosomes. To globally detect lncRNA-translation machinery interactions we have performed Poly-Ribo-Seq. We have found ~180 lncRNAs upregulated during differentiation, ~70% of which are associated with ribosomal complexes e.g. LINC01116. ~150 lncRNAs show evidence of translation. Many of these lncRNA translation events are regulated during neuronal differentiation. We are currently investigating the potential function of these lncRNAs-ribosome interactions, in neuronal differentiation.

S2

How will the 100,000 Genomes Project Affect Histopathologists?

Ⓟ JL Jones

Barts Cancer Institute, QMUL, London, UK

Pathology and Pathologists have been central to the delivery of the 100,000 Genomes Project, and will continue to be key in translating the promise of Genomic Medicine into patient benefit. Appropriate tissue sampling is the cornerstone of diagnostic pathology and is of the same importance to all genomic testing: tumour content, in-situ versus invasive elements, mixed tumour morphology – all might impact on the interpretation of a test performed on homogenized samples. The handling of tissues and its optimal fixation also underpins accurate diagnosis, but the deleterious effect of formalin fixation on whole genome sequencing (WGS) required the implementation of fresh tissue pathways for which the logistical challenges are not inconsiderable. A number of laboratories have employed innovative solutions, such as vacuum packing, but this is not without its own challenges. As WGS results are returned from the 100,000 Genomes Project, Pathologists are joining Genomic Tumour Advisory Boards, to integrate these genomic results with the histopathology – for many there is a knowledge gap and the profession needs to be proactive in filling this. The legacy of the 100,000 Genomes Project is the NHSE Genomic Medicine Service. Again, Pathology is at the core of this, being primarily responsible for requesting appropriate tests and providing appropriate samples. The service is in its infancy and Pathology has a role in shaping it, which we should embrace. Genomic analysis will not replace histopathology, it will enhance it – in diagnostic, prognostic and therapeutic evidence. We are all Molecular Pathologists now.

S3

Latest Developments in Lynch Syndrome and the Reproductive Tract

Ⓟ IM Frayling

Institute of Medical Genetics, University Hospital of Wales, Cardiff, UK

Remarkably, from the Prospective Lynch Syndrome Database (www.PLSD.eu) we now understand that Lynch syndrome (LS) is a sex-limited condition characterised by a predisposition to endometrial cancer in females who have pathogenic variants affecting one of the four DNA mismatch repair (MMR) protein genes: *MLH1, MSH2, MSH6* and *PMS2*. Additional predisposition to ovarian cancer is seen in females, as well as to colorectal cancer in both males and females, who harbour such variants affecting *MLH1, MSH2* and *MSH6*. We also realise from the PLSD that survival of both endometrial and ovarian cancer in LS is good compared to the general population. In addition, ovarian cancer survival in LS is especially good compared to those predisposed by pathogenic variants in *BRCA1/2*, because the biology is different: ovarian LS tumours are generally of non-serous type. Compared to large bowel tumours, we understand rather less about how and why gynaecological cancers arise and develop in LS, but parallels are emerging in the critical importance of the immune system and non-dysplastic premalignant changes. The reasons why different propensities to cancers are seen with the different genes has up to now been obscure, but some clues are perhaps becoming apparent. LS is *not* a rare disease, and this increased understanding is important in improving the diagnosis and care of all cancer patients, not just those with LS.

S4

Molecular Pathology of Diagnostic Evaluation in Lynch Syndrome

Ⓟ MJ Arends

University of Edinburgh, Edinburgh, UK

Lynch Syndrome (LS) is an inherited autosomal dominant disorder predisposing individuals to a range of cancers, most commonly endometrial and ovarian cancer in the female reproductive tract, and colorectal cancer in the gastrointestinal tract. It is caused by pathogenic mutations of the DNA mismatch repair (MMR) pathway genes, MLH1, MSH2, MSH6 and PMS2, which prevent the detection and repair of DNA replication errors, mismatches and insertion/deletion loops, and some other nucleotide abnormalities. Gynaecological cancers may occur as sentinel events for Lynch syndrome in women. Hence, there is an opportunity to screen for and diagnose LS in women before other cancers occur, permitting cancer surveillance programmes, preventative measures, cascade testing of at-risk relatives and influencing treatment options, such as immune checkpoint blockade. Screening of cancer samples for LS usually involves MMR IHC and/or MSI testing, with MLH1 promoter methylation testing to distinguish sporadic MLH1-negative cancers, with subsequent germline sequencing. MMR IHC analysis can identify the specific protein that is lost or abnormal, indicating the likely mutated gene. MMR proteins form heterodimers, MLH1 – PMS2 and MSH2 – MSH6, that are stable. However, MMR proteins are unstable in the unpaired state. Although MLH1 and MSH2 can form stable heterodimers with other proteins, PMS2 and MSH6 only dimerise with MLH1 and MSH2 respectively, affecting interpretation of the patterns of loss or abnormality, with this interpretation best performed by an experienced pathologist and with high quality MMR IHC staining requiring participation in a NEQAS scheme.

S5

Case Presentation: Spectrum of MMR Deficient Cases in Routine Practice

Ⓟ AD Attygalle

Royal Marsden Hospital, London, UK

Immunohistochemical expression of mismatch repair proteins is a reliable screening test for Lynch Syndrome and also in the detection of sporadic cases of mismatch repair deficiency and is therefore used routinely as part of the histological work-up of all cases of endometrial carcinomas and endometriosis associated ovarian carcinomas. It is also pivotal in the algorithmic approach used in the clinical application of the TCGA integrated genomic classification of endometrial carcinomas, identifying the hypermutated MSI high subgroup. Accurate interpretation of immunohistochemistry is crucial and is dependent not only on good technical optimisation but also the awareness of pitfalls related to fixation and background/non-specific staining. The cases presented will illustrate the spectrum of mismatch repair deficiency in practice and also highlight difficulties associated with interpretation.

S6

A Day in the Life of a Histopathologist

Ⓟ SC Lishman

North West Anglia NHS Foundation Trust, Peterborough, UK

Pathology is made up of numerous different specialties, the largest of which is histopathology. As a histopathologist, no two days are ever the same. My day might include performing a post mortem examination for the Coroner to find out why someone has died, giving evidence at an inquest, dissecting entire organs that have been removed in the operating theatre, presenting cancer cases at a multi-disciplinary team meeting or, the bulk of my work, examining slides under the microscope to make a diagnosis. I request and interpret immunohistochemical and molecular tests, teach biomedical and medical students and doctors in training, and contribute to research and quality improvement processes. I also give talks to schools and the public about pathology, represent the specialty on national committees and attempt to influence policy makers to ensure that there is appropriate investment in pathology services. My talk will concentrate on the diagnostic work of a histopathologist but you will get a glimpse of the other fascinating roles that exist in the specialty and beyond.

S7

Stromal Tumours of the Bladder

Ⓟ JH Shanks

The Christie NHS Foundation Trust, Manchester, UK

A large variety of mesenchymal tumours occur in the bladder. An area of particular diagnostic difficulty is interpretation of spindle cell lesions and distinction of sarcomatoid carcinoma and sarcoma from the group of lesions referred to as pseudosarcomatous myofibroblastic proliferation (PMP). The presentation will focus on distinction of PMP/IMT from sarcomatoid carcinoma and spindle cell sarcomas. Look for areas of nuclear hyperchromasia with pleomorphism, often with high cellularity. If possible, use wide sampling to seek any typical carcinoma merging with the lesion or carcinoma in situ. Mitotic figures may be present in bladder IMT/PMP, but not atypical mitoses. Necrosis is common on the ulcerated surface but is not specific. Deep necrosis away from the surface is rare in bladder IMT/PMP but if present in isolation, with otherwise typical features, is insufficient for malignancy. Sarcomatoid carcinomas of bladder frequently show minimal/focal cytokeratin positivity. Blocks with the most 'epithelioid' areas should be selected for work-up. Broad spectrum cytokeratins such as MNF116 and AE1/3 are not specific, and paradoxically are more likely to be extensively positive in IMT/PMP of bladder, in contrast to often very limited staining in sarcomatoid carcinoma. p40 and high molecular weight cytokeratins (CK5/6 and/or 34betaE12) are more specific for sarcomatoid carcinoma, if positive. Positive ALK-1 immunohistochemistry in the context of a bladder spindle cell lesion is strong supportive evidence of IMT/PMP, providing rhabdomyosarcoma is excluded by an appropriate panel. Approximately 50% of bladder IMT/PMPs are ALK-1 positive by immunohistochemistry, so a negative does not exclude IMT/PMP. FISH with breakapart probes demonstrates a signal pattern consistent with ALK-1 gene rearrangement (at 2p23) in a similar proportion. Rhabdomyosarcoma should be considered for a mesenchymal bladder lesion in children; myogenin and MyoD1 should be included in in the panel.

S8

Colorectal Cancer: Phenotype vs. Genotype

Ⓟ NP West

University of Leeds, Leeds, UK

Colorectal cancer is the fourth most common cancer in the UK and the second most common cause of cancer-related mortality. Patient outcomes have significantly improved year on year due to screening and advances in treatment to include better imaging, surgery and oncology. Pathologists have played a major role in improving outcomes over many years through describing the tumour phenotype from macroscopic and microscopic interpretation of the resection specimen. In recent years, advances in molecular pathology have led to additional tests including genotyping being introduced into routine clinical practice to facilitate stratified medicine. Many molecular markers proposed in the literature never make it into routine practice due to a failure to validate in larger prospective studies or providing only limited additional clinical value. It is critical when evaluating any new potential biomarker that it gives significant added value to the current gold standard and is economically viable. This talk will summarise the important phenotypic and genotypic markers available to pathologists reporting colorectal cancer specimens and suggest which ones are the most valuable.

S9

Tools You Need to Analyse Genomics

Ⓟ HM Wood

University of Leeds, Leeds, UK

Background: Genomic data, and similar high throughput information, are increasingly being used in a pathological setting, both for research and as a diagnostic tool. The volumes of data produced makes analysis using standard office software impossible. Whilst there is a plethora of specialist tools available, it can be difficult to decide which is the best tool for each step, and daunting to learn some of the steps for people with little or no coding or command line experience.
Rationale behind pipelines: All sequence data goes through a number of similar steps, such as adapter trimming and alignment before more specialised steps such as variant calling or read counting. Similarly, array-based methods have some steps in common with all tools, and some which are specific. It is important to understand the rationale behind these steps individually so that an informed decision can be made as to how to construct an analysis pipeline.
Available resources: A number of bioinformatic solutions are available, which are designed for a variety of methodologies and require different levels of informatic experience. Some, such as the Agilent Surecall, are designed around one or a few specific assays. Others, such as the proprietary Illumina Basespace, or the open source Galaxy platform are more modular in nature and allow users to build pipelines in a familiar mouse-based computing environment. Other pipelines can be built from individual packages assembled in a command line environment, which are harder to learn, but allow for greater flexibility and automation. Most pipelines can be run on local machines or in a cloud computing infrastructure. Once data has been processed, high level analysis can be carried out using standard software such as excel or SPSS, or more specialised tools such as R or MATLAB. Through understanding the processes needed to analyse their data and the available tools, users can build analysis pipelines which best suit their particular situation.

S10

TILs: The Next Morphological Biomarker in Breast Cancer for Daily Practice Use?

Ⓟ R Salgado

Peter MacCallum Cancer Centre, Mebourne, Australia

The assessment of Tumour Infiltrating Lymphocytes (TILs) is gaining importance as a prognostic marker in breast cancer. Recently, the 2019 St Gallen Breast Cancer Conference as concluded that TILs should be routinely reported in TNBC and TILs will be included also in the 2019 WHO/IARC Blue Book edition on Breast Tumour classification. High TILs are associated with a better outcome and a better response to neoadjuvant therapy in Triple-negative and HER2 positive breast carcinomas, as well as having strong prognostic value in improving estimates of distant recurrence-free survival , disease-free and overall survival in early-stage TNBC treated with standard adjuvant/neoadjuvant chemotherapy (Level 1B evidence). This is based on an evaluation by pathologists using H&E stained glass slides at time of diagnosis (pre-treatment and in the residual disease post neoadjuvant chemotherapy). Their quantification is done on H&E tissue sections during diagnosis procedure and follows international recommendations (www.tilsinbreastcancer.org). Development of computational pathology and machine learning methods in this area is very promising. Clinical utility using TILs as a biomarker for selection of patients for treatment with immune-checkpoint-inhibition is ongoing. TILs evaluated on an HE as an alternative to classical biomarkers such as PDL1 is promising based on phase I and II trial data. TILs are used as a stratification factor in clinical trials and should be included in all studies involving or evaluating prognosis. At the current lecture the international consensus scoring recommendations, pitfalls on TIL-assessment and how to mitigate these pitfalls, will be elaborated on (see www.tilsinbreastcancer.org). Evidence will be presented that the current recommendations can be extrapolated to other tumour settings, such as lung cancer.

S11

Breast Digital Pathology in Day-to-Day Practice

Ⓟ RA Millican-Slater

Leeds Teaching Hospitals Trust, Leeds, UK

As described by the Royal College of Pathologists, "digital pathology has the potential to improve patient care and support the pathology workforce by making the diagnosis and monitoring of disease much more efficient." At Leeds Teaching Hospitals NHS Trust we have been scanning almost all the glass slides for breast specimens since January 2017, and since May 2017, I have been reporting the vast majority of my workload using scanned images and using a digital microscope rather than glass slides and the traditional light microscope. This shift in practice brings huge benefits and opens up the potential for exciting developments, though is not without its challenges. I will describe my personal experience in moving to using digital pathology for day-to-day diagnostic practice, including the validation process, the advantages of using a digital system, the difficulties in adopting a digital workflow, key lessons learned and future opportunities.

S12

Combining Clinical and Academic Training in Pathology

Ⓟ JL Griffin

Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

Histopathology training is an ideal environment in which to pursue a combined clinical academic career: A focus on applied science, daily use of techniques used in research and civilised working hours all contribute to histopathologists being well placed to work in basic, translational and clinical research. As personalised medicine becomes an established part of clinical care, the need for research-active histopathologists is greater than ever, as are the opportunities to get involved in this interesting and demanding career. In this talk I will discuss the routes into academic pathology, the broad range of opportunities that are available and how to balance research with clinical training.

S13

The Role of Molecular Pathology in Cancer Care

Ⓟ RJ Byers

University of Manchester, Manchester, UK

Pathology is a constantly evolving field and clinical discipline due to advances in understanding of disease, technology platforms and requirements for improved patient care. This is well illustrated by the increasing role of molecular pathology in cancer care. Haematopathology, which deals with diagnosis of lymphoma and leukaemia has led the field in application of molecular pathology, resulting in significant advances in our understanding of the disease processes underlying these cancers, the development of targeted treatment and improved patient outcomes. More recently similar advances have been made in lung, breast and colorectal caner. I will give an overview of the above themes in the clinical role of molecular pathology in patient care.

S14

IgG4-Related Disease in the Pancreatobiliary System: How Good is Histopathology as the Gold Standard of Diagnosis?

Ⓟ BH Haugk

Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

IgG4-related disease (IgG4-RD) is a rare, multiorgan, fibroinflammatory condition that most commonly affects the pancreatobiliary system and responds well to corticosteroid treatment. It clinically presents with tumefactive lesions that can mimic neoplasms on imaging and therefore its correct diagnosis is vital in preventing unnecessary, potentially life changing surgery. Type 1 autoimmune pancreatitis is the commonest presentation of IgG4-RD affecting approximately 60% of patients. It can be associated with IgG4-related sclerosing cholangitis, IgG4-related hepatopathy and/or IgG4-related cholecystitis but isolated hepatobiliary presentations are rarely seen. IgG4-RD is an organ-destructive disease with characteristic histopathological features: 1. Dense lymphoplasmacytic inflammatory infiltrate, often with eosinophils, 2. Fibrosis, at least focally with a storiform pattern, 3. Obliterative phlebitis, as well as immunohistochemical evidence of tissue specific levels of increased IgG4 positive plasma cells with an IgG4+/ IgG+ plasma cell ratio >40%. Confident pathological diagnosis may be possible on resection specimens but confirming IgG4-RD in small biopsies poses a great challenge and mere IgG4 staining is neither diagnostic nor predictive of IgG4-RD. Histopathology remains nevertheless an important component in the diagnosis of IgG4-RD in this setting. Reaching a diagnosis requires striking a balance between strict application of diagnostic histological criteria of IgG4-RD in biopsies and close correlation with pre-treatment clinical features including specific imaging findings, multiple organ involvement and elevated serum IgG4. The crucial role of the histopathologist will often lie in the thorough exclusion of malignant neoplasms in biopsy material but also reviewing potential previous archival histopathological specimens for presence of IgG4-RD. A multidisciplinary team approach is critical in facilitating best patient care.

S15

Recent Advances in Hepatocellular Carcinoma

Ⓟ DG Tiniakos

Institute of Cellular Medicine, Newcastle upon Tyne, UK

Recent classification of hepatocellular carcinoma (HCC) is based on morphology and underlying molecular alterations recognising two main HCC subgroups, the proliferative with worse prognosis (expression of stem cell markers, *TP53* mutations, *FGF19* amplification) and the non-proliferative (activation of *JAK/STAT* pathway, *CTNNB1* activating mutations). New subtypes of HCC have been introduced: massive macrotrabecular HCC (5-10% of HCC, high serum AFP, large size, trabeculae >6-cell thick in >50% of the tumour, predictor of HCC recurrence, *TP53* mutations and *FGF19* amplification); steatohepatitic (steatosis, ballooning or Mallory–Denk bodies, fibrosis and inflammatory foci, JAK/STAT pathway activation, more common in patients with the metabolic syndrome and steatohepatitis in the background liver); chromophobe HCC (5% of HCC, related to HBV infection, alternative lengthening of telomere -ALT phenotype by telomere flurorescent *in situ* hybridsation (FISH); other less common entities. A specific fusion transcript, DNAJB1-PRKACA, has been identified in fibrolamellar carcinoma (FLC). The resulting chimeric kinase functions as a driver of carcinogenesis in FLC and FISH for the PRKACA rearrangement is useful for confirming diagnosis. An international multidisciplinary group has proposed a consensus terminology for primary liver carcinomas with both hepatocytic and cholangiocytic differentiation. The diagnosis of combined hepatocellular carcinoma-cholangiocarcinoma (cHCC-CCA) should be based on morphology using routine haematoxylin and eosin and not on immunophenotype. The morphology of intermediate cell carcinoma is distinct and immunohistochemistry for hepatocytic (i.e. HepPar1) and cholangiocytic markers (i.e. keratin 19) is required to highlight its mixed HCC-CCA differentiation. Cholangiolocellular carcinoma is a distinct molecular entity that is now classified within cholangiocarcinoma.

S16

The Role of Liver Biopsy in an Era of Expanding Non-Invasive Assessment

Ⓟ SE Davies

Cambridge University Hospitals NHS FT, Cambridge, UK

The role of liver biopsy has undergone a major shift from the original indications some 50 years ago, when it would have been primarily used for diagnosis. It is now infrequent that clinicians don't have a good idea of the diagnosis based on serology of autoantibodies, including the expanding catalogue of 2nd order antibodies in autoimmune processes with atypical presentations, of viral antibodies (hepatitis A to E being routinely available) and genetic studies. The commonest risk factors are environmental, Fatty Liver Disease either related to alcohol or otherwise, primarily Insulin Resistance and may be relatively easily ascertained. And so the role of biopsy has evolved to one of attempting to Grade the severity of the process and Stage the extent, usually by the amount of fibrosis, with a view to prognosis and patient management. We are also in an era where non-invasive methods of assessing the stage of disease are becoming readily available and reliable, some based on blood tests and complex algorithms, others with assessment of liver stiffness as an indication of fibrosis. In reality, there is often MORE than 1 aetiology possible and the role of biopsy is to establish which may be the dominant factor. Partly this reflects the number of people in society at risk of Fatty Liver Disease increasingly being picked up with abnormal liver biochemistry or who have this as a second pathology within the biopsy. There are often multiple possible causal agents for acute derangement of liver function, particularly with the use of drugs in oncology patients or on immunosuppression. The overall incidence of dual pathology present in biopsies has increased, making the assessment more complex and challenging to the pathologist. Awareness of the clinical scenario and question being asked is essential to interpretation of a liver biopsy.

S17

Autoimmune Hepatitis: The Role of Histopathology in Clinical Diagnosis and Management

Ⓟ SG Hubscher

University of Birmingham, Birmingham, UK

Liver biopsy continues to play an important role in the diagnosis and management of patients with autoimmune hepatitis (AIH). The histological assessment of liver biopsies from patients known or suspected to have AIH involves two main components:
1: Establishing a diagnosis of AIH. In the absence of a specific diagnostic test for AIH, liver biopsies are frequently obtained at the time of first presentation. Histological assessments include identifying the presence of typical or compatible features that would support a diagnosis of AIH and the absence of features that might suggest an additional or alternative diagnosis (e.g. biliary disease or fatty liver disease). Typical features include lymphoplasmacytic inflammation of portal tracts, interface hepatitis, hepatocyte rosettes and emperipolesis. These features may be helpful in distinguishing AIH from other diseases associated with portal/periportal hepatitis. Cases with an acute presentation typically have prominent lobular inflammation and may be difficult to distinguish from other causes of acute lobular hepatitis (e.g. viral agents and drugs).
2: Assessment of disease severity. This includes the assessment of inflammatory activity and fibrosis, both of which have implications for treatment and prognosis. The severity of interface hepatitis in baseline biopsies predicts the subsequent development of fibrosis. In patients who have achieved biochemical remission following treatment with immunosuppressive agents, the presence of persistent interface hepatitis is associated with an increased risk of relapse if immunosuppression is withdrawn. In patients with an acute presentation, the presence of extensive bridging or panacinar necrosis is associated with an increased risk of acute liver failure. Between 25% and 33% of patients have cirrhosis at presentation, including some patients with an acute presentation. Such cases may be less responsive to immunosuppression and are at risk of developing HCC.

S18

Hypoxia

Ⓟ CW Pugh

University of Oxford, Oxford, UK

The variable levels of oxygen encountered in different tissues in health and disease will be described, including a discussion of the association between tumour hypoxia and outcomes. The hypoxia-inducible factor signalling pathway will be reviewed, including a brief discussion of the roles of different components in physiological and pathological responses. Effects of hypoxia and hypoxia-signalling on the immune system in both human tumours and model systems will be outlined. Some suggestions will be made on how this information might be used both in the classification and therapy of diseases.

S19

The Interplay Between Cell Stress, Cell Death and Inflammation

Ⓟ SJ Martin

Trinity College Dublin, Dublin, Ireland

Inflammation is initiated in response to Infection, Injury or Cell Stress, that all share the ability to elicit the production of an array of cytokines, chemokines and other factors that recruit cells of the innate immune system and also initiate wound repair. While it is very well established that conserved components of infectious agents, called PAMPs (pathogen-associated molecular patterns), and molecules released by necrotic cells, called DAMPs (damage-associated molecular patterns), promote inflammatory responses, it is less well appreciated that conditions which provoke Cell Stress (such as misfolded protein-induced ER stress, mitochondrial depolarization, heat shock, DNA damage) can also instigate inflammatory cytokine production in a manner that is poorly understood at present. Receptors for TRAIL and FasL have been dubbed 'death receptors' as these receptors can act as potent initiators of apoptosis in many cell types. As a consequence, 'death receptor' signaling has been studied almost exclusively in the context of cell death outcomes. However, TRAIL and FasL can also induce NFκB-dependent expression of pro-inflammatory cytokines, which can engage multiple facets of the immune system (Cullen et al., 2013; Cullen and Martin, 2015). We have recently shown that TRAIL and Fas receptor engagement leads to the assembly of an NFκB-activating 'FADDosome' complex where caspase-8 unexpectedly plays a critical scaffold role in the process leading to inflammatory cytokine production (Henry and Martin, 2017). Thus, in addition to their well-known roles as a 'death ligands', TRAIL and FasL can promote inflammation in certain settings. Here, I will discuss recent data from our laboratory that suggest that cell stress leads to inflammation via death receptor upregulation and activation.

S20

Robotic Surgery in Head and Neck Cancer: Implication for Pathologists

Ⓟ M Robinson

Newcastle University, Newcastle upon Tyne, UK

Trans-Oral Robotic Surgery (TORS) was approved by the FDA in 2009. Over the past decade surgical robotic systems have been acquired by the NHS, mainly for urological surgery, however, UK head and neck surgeons have taken the opportunity to utilize the technology for the benefit of their patients. There are currently around 15 units providing a TORS service in England. Whilst the surgical methods have evolved, there has been little consideration about the pathological assessment of the surgical specimens and a lack of understanding around the oncological principles that underpin minimally invasive surgical techniques in the head and neck region. This presentation will address the pathological issues encountered during the handling of TORS specimens. The challenges include identifying anatomical boundaries, appropriate block selection, assessment and interpretation of resection margins, the use of intra-operative frozen sections, the assessment of the tongue base mucosectomy for patients with head and neck cancer of unknown primary, and TORS for recurrent disease. The presentation will conclude with emerging innovations, such as the intelligent-Knife (i-Knife) to guide surgical excision and the potential of step serial sections to identify sub-clinical HPV-related oro-pharyngeal squamous cell carcinomas.

S21

Update in Salivary Gland Pathology: New Terminology and Molecular Diagnostics

Ⓟ RHW Simpson

University of Calgary, Calgary, Canada

Several primary salivary neoplasms have been shown to have characteristic molecular genetic abnormalities. These are increasingly important in diagnosis and probably soon as the basis for specific therapy. There is also a strictly limited role as prognostic markers in some cases. The best established neoplasms with specific molecular signatures are mucoepidermoid, adenoid cystic, (mammary analogue) secretory and hyalinising clear cell carcinomas, with rearrangements of MAML2, MYB, ETV6 and EWSR1 respectively. There are usual gene partners and for example, in mucoepidermoid, most show a CRTC1-MAML2 fusion, but in a minority, this is CRTC3-MAML2. Analogous genetic variants have been described in the other carcinomas. In addition to the malignancies, about 70% of pleomorphic adenomas show abnormalities of PLAG1 or HMGA2 genes, although this is of limited value in everyday practice. A second group of other carcinomas also have genetic abnormalities, although the value of these findings is yet to be established; in polymorphous (low grade) adenocarcinoma, most display a recurrent E710D hotspot somatic mutation within the catalytic loop of the kinase domain of PRKD1, and in cribriform adenocarcinoma (CATS or CASG) 80% of cases were found to have rearrangements of the PRKD1-3 genes. Recently, a HTN3-MSANTD3 fusion was demonstrated in a subset of acinic cell carcinomas. A third group is that of neoplasms that have well established molecular signatures, and arise in the salivary glands only exceptionally rarely – these include NUT carcinoma, desmoplastic small round cell tumour and adamantinoma-like Ewing's sarcoma. All these genetic rearrangements have allowed us better to define various entities morphologically and for example, hyalinising clear cell carcinoma is no longer a diagnosis of exclusion. The 2017 WHO Classification recognises some of these developments, but this is a fast developing field and the classification will require updating again fairly soon.

S22

CTCF Maintains Regulatory Homeostasis of Cancer Pathways

Ⓟ SJ Aitken[1]; X Ibarra-Soria[1]; E Kentepozidou[2]; P Flicek[2]; C Feig[1]; JC Marioni[2]; DT Odom[1]

[1]Cancer Research UK Cambridge Institute, Cambridge, UK; [2]European Bioinformatics Institute, Hinxton, UK

CTCF binding to DNA helps partition the mammalian genome into discrete structural and regulatory domains. Complete removal of CTCF from mammalian cells causes catastrophic genome dysregulation, likely due to widespread collapse of 3D chromatin looping and alterations to inter- and intra-TAD interactions within the nucleus. In contrast, *Ctcf* hemizygous mice with lifelong reduction of CTCF expression are viable, albeit with increased cancer incidence. Here, we exploit chronic *Ctcf* hemizygosity to reveal its homeostatic roles in maintaining genome function and integrity. We find that *Ctcf* hemizygous cells show modest but robust changes in almost a thousand sites of genomic CTCF occupancy; these are enriched for lower affinity binding events with weaker evolutionary conservation across the mouse lineage. Furthermore, we observe dysregulation of the expression of several hundred genes, which are concentrated in cancer-related pathways, and are caused by changes in transcriptional regulation. Chromatin structure is preserved but some loop interactions are destabilised; these are often found around differentially expressed genes and their enhancers. Importantly, the transcriptional alterations identified *in vitro* are recapitulated in mouse tumours and also in human cancers. This multi-dimensional genomic and epigenomic profiling of a *Ctcf* hemizygous mouse model system shows that chronic depletion of CTCF dysregulates steady-state gene expression by subtly altering transcriptional regulation, changes which can also be observed in primary tumours.

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S23

Colorectal Cancer Biomarkers: From Molecular Modelling to Immunohistochemistry

Ⓟ GI Murray

University of Aberdeen, Aberdeen, UK

Colorectal cancer is one of the commonest types of cancer and it has been recognised for many years that there is a requirement to identify biomarkers of this type of tumour which can provide prognostic information additional that obtained by careful histopathologic assessment. This lecture will describe the discovery and validation of colorectal cancer biomarkers based on the development of monoclonal antibodies to tumour associated proteins. Initial studies used small patient cohorts now much larger patient cohorts are available. The sophistication of the molecular approach has evolved embracing a range of molecular tools and technologies for studying proteins. Early studies developed monoclonal antibodies to invasion associated proteins in particular matrix metalloproteinases. Amino acid sequence alignment combined with low resolution 3D protein molecular modelling was used to identify likely antigenic regions that could be targeted for the development of sequence specific monoclonal antibodies. Through this approach matrix metalloproteinase-1 was as identified as a marker of poor prognosis in colorectal cancer. Current studies now utilise a range of sophisticated molecular tools to identify potential protein targets. Amino acid sequence homology, antigenic prediction, protein modelling have all contributed to developing a robust approach to identify tumour associated proteins for which monoclonal antibodies can be developed. These studies have identified the brown fat associated proteins as a novel pathway in colorectal cancer and uncoupling protein 1 as a prognostic biomarker in both discovery and validation cohorts of colorectal cancer.

S24

Update on Lung Cancer Staging

Ⓟ AG Nicholson

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There have been several changes in the eighth TNM that impact on the pathological staging of lung cancer.

1: In relation to the T category, from 1 to 5 cm, each centimetre increase in cancer diameter is associated with worsening survival (T1a-c, 2a,b). Cancers greater than 5 cm but less than or equal to 7 cm are now staged as T3, and those greater than 7 cm as T4. T2 classification is also used for tumors, breaching the visceral pleura, involving the main bronchus and tumors associated with atelectasis or obstructive pneumonitis that extends to the hilar region, either involving either part of the lung or the whole lung. Involvement of the diaphragm has a T4 prognosis. Invasion of the mediastinal pleura was seldom used and is has been discontinued.

2: For sub-solid nodules, 2011, new entities of adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and lepidic predominant adenocarcinoma were defined. leading to recognition of introduction of a Tis(AIS) classification for adenocarcinoma in situ (Tis(AIS)) and T1mi for minimally invasive adenocarcinoma. For tumours with lepidic growth, only the invasive size of the tumour should be used for the T size. As the amount of lepidic tumour may potentially be underestimated grossly, evaluation of cancer size may require re-examination of the specimen and careful correlation with microscopic and radiographic findings.

3: For multiple tumours, staging overall has not changed, but there is additional notation that recognizes (a) separate primary lung cancers presenting as predominantly ground-glass opacities on imaging with typically non-mucinous adenocarcinoma showing lepidic predominant morphology, and (b) pneumonic presentation on imaging that typically correlates with invasive mucinous adenocarcinoma.

4: Other areas (R category (e.g. R1(cy+) , subdivision of N) also have proposed changes for data collection in relation to the 9th TNM, and the impact of these on pathological staging will be discussed

S25

Molecular Biology of Mesothelioma-Implications for Diagnosis and Management

Ⓟ F Galateau Salle

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Malignant mesothelioma is a rare cancer less than 0,3% of all cancers, highly lethal, histologically extremely heterogeneous cancer, resistant to the majority of conventional chemotherapies. This disease is largely linked to asbestos exposure in more than 80% of the cases in men, occurring with a long delay of latency (30-40 years after initial exposure). The major direct damage of asbestos fibers on mesothelial cells and the chronic inflammatory response (macrophages and other immune cells) with release of oxygen species may be an important factor in the carcinogenesis of malignant mesothelioma. More recently, mesothelioma was reported to be associated with inherited genetic mutations in less than 5% and can occurs in family being part of the BAP1 cancer associated syndrome. The last WHO classification in 2015 of malignant diffuse or localized mesothelioma reported that the most prevalent type was subdivided in epithelioid (80%) sarcomatoid (up to 10%) and biphasic (in 10-15%) composed of epithelioid and biphasic morphologies with at least 10% of each component suggesting a role for epithelial to mesenchymal transition at the molecular level. All these characteristics make this tumour extremely original molecularly compared to other cancers. However, since recently there was a very limited use of molecular testing in malignant mesothelioma compared to lung cancer explaining the weaknesses of knowledge on molecular biology for diagnosis and treatment of this dramatic disease. Then, analysis based on NGS or Sanger sequencing were reported by Bueno et al, identifying recurrent somatic alterations in BAP1, Nf2 and CDKN2A(p16), CUL1, TP53, SETDB1 with additionnal findings reported by Hmeljak et al from TCGA analysis showing a strong expression of the immune checkpoint gene VISTA with implications for immune response to immunotherapy. Alcala et al, found that the molecular profile of MPM was better explained by a continuous spectrum based on an immune an vascular pathway.

S26

Diagnosing Interstitial Lung Disease Is No Longer "Business as Usual": A Contemporary Diagnostic Approach to Fibrosing Interstitial Pneumonias

Ⓟ BT Larsen

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Purpose: Idiopathic pulmonary fibrosis (IPF) is a syndrome characterized by progressive lung scarring, manifest as the usual interstitial pneumonia (UIP) pattern. Recent therapeutic advances have made distinction of IPF from all other fibrosing interstitial pneumonias essential. Per consensus criteria, diagnosis of IPF no longer requires a biopsy in an appropriate context if a UIP pattern is seen radiologically. In current practice, lung biopsies are typically reserved for patients having indeterminate clinical or imaging findings. Consequently, the frequency of encountering biopsies with other fibrotic patterns may have increased in recent years.
Methods: To update pathologists on fibrotic interstitial pneumonias, IPF and its common mimics will be reviewed, including connective tissue disease-associated interstitial lung disease, chronic hypersensitivity pneumonitis, and other less common causes of diffuse lung fibrosis.
Results: It is incumbent on pathologists to be aware of the shifting landscape in pulmonary pathology and the clinical implications of histological diagnoses in the current era. In addition, pathologists must recognize the critical role of multidisciplinary discussion in the diagnostic process. For IPF and each of its mimics, histological characteristics will be reviewed and clinical and radiological findings will be discussed, emphasizing findings that can be used to increase diagnostic certainty and enable distinction of IPF from other entities. Throughout this review, the clinical implications of histological diagnoses will be emphasized, and current treatment approaches will be reviewed.
Conclusion: Often, clues in the lung biopsy may offer the first suggestion of a non-IPF diagnosis when lung fibrosis is encountered, but clinical and radiological information must also be incorporated to arrive at the best diagnosis. Accurate classification of fibrosing interstitial pneumonias is essential for proper treatment selection.

S27

The Human Protein Atlas: Implications for Human Biology and Precision Medicine

Ⓟ C Lindskog

Uppsala University, Uppsala, Sweden

In the evolving era of "big data", integration of datasets from different omics technologies, such as genomics, transcriptomics and proteomics have received increased attention. The Human Protein Atlas database (www.proteinatlas.org) with >200.000 visits per month, constitutes a comprehensive open-access knowledge resource for spatial localisation of proteins in organs, tissues, cells and organelles. The mapping is based on genome-wide mRNA expression data, which is summarised on the interactive webpage and used for categorisation of all human genes based on expression level and tissue distribution. The analysis is combined with tissue microarray-based immunohistochemistry covering all major normal human organs and cancer types, and a large effort is put into enhanced antibody validation strategies. In 2017, a new Pathology Atlas was released, based on genome-wide expression data from the Cancer Genome Atlas. RNA-Seq data and clinical metadata from 8,000 individual patients corresponding to 17 major cancer types was used for determining the correlation between RNA expression levels and overall survival time for each gene in each cancer type. The new data, together with antibody-based protein expression data from the corresponding cancer types, opens up for pursuing better diagnostic schemes and designing personalised cancer treatment regimes.

S28

Next Generation Immunohistochemistry: Considerations for the Practising Pathologist

Ⓟ JM Ziai

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Highly multiplexed methods to profile tissues' protein and RNA content are becoming increasingly common. While not currently part of routine practice, the "next generation" of immunohistochemical (IHC) methods will increasingly impact basic and translational research as well as diagnostic practice in the coming years. The surgical pathologist – whether a diagnostician, research collaborator or primary investigator – must therefore develop a sophisticated understanding of the chemistry, function, and composition of various multiplexing methods as well as their respective strengths and limitations to continue to serve as an effective consultant to both researchers and clinicians. Multiple methods that enable both "low" (<6) and "high" (>6) level multiplexed IHC are currently available for use. However, use is often limited to technology access programs and can be cost-prohibitive even for small studies. The initiation, design, sample selection, and data interpretation of a multiplexed IHC study must therefore be carefully considered. This lecture will provide an overview of multiplexed IHC methods that are available today with focus on both "low" level methods (e.g. tyramide signal amplification) as well as "high" level methods, particularly mass spectrometry-based methods (imaging mass cytometry (IMC), multiplex ion beam imaging (MIBI)) and NanoString Digital Spatial Profiling (DSP). Learnings from pilot studies with both DSP and MIBI/IMC on such issues as method chemistry, sensitivity, and reproducibility will be shared and recommendations for application, experimental design and interpretation of highly multiplexed IHC from these platforms will be summarized.

S29

Receptor Tyrosine Kinase Signalling in the Absence of Kinase Activity and Cancer of Non-Genetic Origin

Ⓟ JE Ladbury

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FGFR2-expressing cancer cells with low concentrations of the adaptor protein Grb2 show high prevalence for metastatic outcome. In non-stimulated cells the SH3 domain (and not the SH2 domain(s)) of Plcγ1 directly competes for a proline-rich binding site at the very C-terminus of FGFR2 with the C-terminal SH3 domain of Grb2. Reduction of Grb2 concentration permits access of Plcγ1 to the receptor. Recruitment of Plcγ1 in this way is sufficient to up-regulate phospholipase activity. This results in increased cell motility and promotion of cell invasive behaviour in the absence of extracellular receptor stimulation. Therefore metastatic outcome can be dictated by the constitutive competition between Grb2 and Plcγ1 for the phosphorylation-independent binding site on FGFR2. Since the majority of receptor tyrosine kinases have proline-rich sequences in their C-termini, the possibility of a second tier of signal transduction in the absence of growth factor stimulation, or kinase-activating mutations emerges – leading to cancer of non-genetic origin.

S30

The Fourth Edition of the WHO Classification of Skin Tumours: Classification of Melanoma

Ⓟ DM Massi

University of Florence, Florence, Italy

The recent WHO Classification of Skin Tumors published in 2018 (1) has introduced a novel multidimensional approach to the classification of melanoma defining nine biologically distinct pathways to melanoma development. These pathways take origin from the integrated taxonomy of melanocytic neoplasms which encompasses the cell of origin (epithelium and non-epithelium associated melanocytes), the pathogenetic role of ultraviolet radiation and skin pigmentation, and the complex genomic and molecular alterations whose knowledge and mechanisms have been deeply and remarkably enriched over the past years. On a molecular basis, melanoma can be considered as a group of biologically distinct lesions that develop through different mutational pathways. Considering the integrated taxonomy further developed for the WHO Classification of Skin Tumors, fourth edition, published in 2018 (1), the following pathways have been defined:

Pathway I: Low-Cumulative Solar Damage (CSD) Melanoma (including Superficial Spreading Melanoma and low-CSD Nodular Melanoma)
Pathway II: High-Cumulative Solar Damage (CSD) Melanoma (including Lentigo Maligna Melanoma and high-CSD Nodular Melanoma)
Pathway III: Desmoplastic Melanoma
Pathway IV: Malignant Spitz Tumor
Pathway V: Acral Melanoma
Pathway VI: Mucosal Melanoma
Pathway VII: Melanoma arising in Congenital Nevus
Pathway VIII: Melanoma arising in Blue Nevus
Pathway IX: Uveal Melanoma

Each pathway is characterized by specific epidemiology, clinical and histopathological features, pattern of metastasis, etiopathogenetic role of UV radiation, predisposing germ-line alterations, somatic mutations, and mutator mechanisms. The main molecular and histopathological features of the different pathways will be critically discussed.

References: 1. Elder DE, Massi D, Scolyer RA, Willemze R, Editors. WHO Classification of Skin Tumours. Fourth Edition, Lyon: IARC; 2018.

S31

Determining Risk Status from Pathology, Genetics and Outcome Data in Cutaneous Squamous Cell Carcinoma: A National Project

Ⓟ PJ Craig

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Primary cutaneous squamous cell carcinoma (cSCC) has been studied little compared to other cancers perhaps due to a lack of good epidemiological and outcome data, and a lack of effective treatment options for those with advanced disease. Recently, in collaboration with Public Health England (PHE), incidence data for primary cutaneous SCC per year incorporating data from histopathology reports has shown an incidence of over 25500 per annum (Venables ZC et al. Nationwide Incidence of Metastatic Cutaneous Squamous Cell Carcinoma in England. JAMA Dermatol. 2018 Nov 28). Furthermore they were able to assess the incidence of metastatic cSCC by matching primary and secondary cancers in the same patient. Metastatic disease occurred in 2.4% of cSCC in males and 1.1% of females with an increased risk on the lip, ear, age >90 and immunosuppression, and 70% occurred within the first 2 years of diagnosis of the primary cSCC. A further study from the same group has shown an increase in incidence of 5% per annum for both cSCC and basal cell carcinoma. Indeed, some have predicted a doubling in incidence for cSCC in the next 25 years, due to an ageing population and increased UV exposure. Given this disease and management burden, cSCC has been identified as a research priority by the British Association of Dermatologists (BAD). Using this data in conjunction with PHE, a research group (UK Kertatinocyte Collaborative) has been set up including histopathologists to create a virtual tissue bank of these cases to produce an extensive, valuable research resource so the research community including pathologists can apply to use this material. The project will aim to use pathology, genetics and outcome data to determine risk status and guide management and new therapies.This will require collaboration from pathologists in confirming the diagnosis and sourcing the paraffin blocks. This lecture will discuss the project and epidemiology, pathology, genetics and current therapies for cSCC.

S32

Newer and Unusual Forms of Oesophagitis and Gastritis

Ⓟ K Sheahan

St Vincent's University Hospital, Dublin, Ireland

There has been a greater understanding of established inflammatory conditions of the oesophagus and the stomach in recent years. There have also been descriptions of newer entities. Some of these entities are novel however many are related to newer treatment modalities and medications including biologicals and immunotherapy. Diagnosis of drug-induced injury in the upper gastrointestinal tract is difficult. Some compounds are associated with characteristic patterns of injury, however, many are not. Patterns of injury generally are not specific and mimic other gastrointestinal conditions. In addition, these therapies and other immunosuppressive conditions predispose to infection. One proposed new entity is lymphocytic oesophagitis. There is recent evidence that this histological pattern is associated with primary oesophageal motility disorders. Lymphocytic and collagenous gastritis may be part of a pan-enteric inflammatory disorder, while isolated forms have also been seen secondary to Olmesartan therapy. While eosinophilic oesophagitis is now widely recognised both clinically and pathologically, eosinophilic gastritis remains rare and enigmatic. Finally, Crohn's disease affects the oesophagus and stomach not uncommonly and is often overlooked.

S33

Appendiceal Neoplasia and Pseudomyxoma Peritonei

Ⓟ NJ Carr

Peritoneal Malignancy Institute, Basingstoke, UK

Mucinous appendiceal neoplasms are not uncommon. Correct diagnosis is important because some are managed with prolonged follow-up or radical surgery. Mucinous appendiceal neoplasms may be low grade or high grade, and are distinguished from mucinous adenocarcinoma by a lack of infiltrative invasion. The latest edition of the WHO Classification will be based on the consensus classification of the Peritoneal Surface Oncology Group International (PSOGI). A fairly common problem is the differential diagnosis of mucinous neoplasm from ruptured appendiceal diverticulum. Both can show crypt disarray, epithelial serration and extravasation of mucin outside the appendix. Favouring a diverticulum are hyperplastic features confined to the luminal portion of the mucosa, preservation of essential mucosal architecture and intramucosal neuromas. Pseudomyxoma peritonei is a rare and distinctive syndrome that is due to an appendiceal primary in the vast majority of cases, although occasionally other primary sites may be responsible. The presence of signet ring cells confers a worse prognosis, and such lesions are now identified separately. When a low grade ovarian mucinous neoplasm is associated with true pseudomyxoma peritonei the appendix is usually the primary site. The exception is a low grade mucinous neoplasm arising in a mature teratoma of the ovary; such lesions not only behave identically to appendiceal lesions but also show the same genetic abnormalities. There are histological features that can point to an ovarian mucinous tumour being metastatic rather than primary, and SATB2 expression is a promising new marker in this respect. Goblet cell carcinoid tumours are an unusual type of neoplasm that almost invariably arise in the appendix. The term "carcinoid" is confusing in this context because they are actually a type of adenocarcinoma and are not related to neuroendocrine tumours. The latest edition of the WHO Classification will eliminate "carcinoid" from its nomenclature.

S34

Tumour Testing and Developments in the Understanding of Carcinogenesis in Lynch Syndrome

Ⓟ IM Frayling

Institute of Medical Genetics, University Hospital of Wales, Cardiff, UK

Recent work is showing that there is more than one way that colorectal cancers develop in Lynch syndrome (LS), and that the immune system plays a critical role in determining which pathway an individual cancer follows. Moreover, this may help to explain the differing propensities to cancer associated with inherited pathogenic variants in the different genes. This has important implications for the tumour tests already carried out, and opens up other possible tests that may be worthwhile. It is now realised that there are at least three pathways to a large bowel cancer in LS. Firstly, LS patients can and do develop sporadic adenomas, initiated by mutations in the *APC* gene, like anyone in the general population. These then acquire a sporadic somatic mutation in the normal allele of the respective MMR gene, to become a cancer with DNA mismatch repair deficiency (dMMR). Secondly, one of the ~10,000 dMMR crypts that a LS patient has in their colorectal mucosa undergoes a mutation in beta-catenin, resulting in a flat intra-mucosal lesion which is not polypoid, but is immediately invasive. Thirdly, some of these lesions acquire secondary *APC* mutations, thence to become adenomatous, polypoid and eventually a cancer. Because dMMR leads to the production of highly antigenic frameshift peptides (FSP), LS patients have increasing titres of antibodies to such antigens and also have strong specific T-cell responses. This keeps their propensity to develop tumours in check, to some extent, but also reveals a variety of mechanisms of immune escape, relevant clinically. It is important to note that there is no evidence that tumours in LS develop any quicker than any others, and that the raised mutation rate in LS (and other) tumours is not in itself a driver in carcinogenesis. Rather, it is derangement of cell-cycle control and apoptosis by mutations in MMR proteins that is the driver, with implications for the functional tests used to interpret possibly pathogenic MMR gene variants.

S35

TNM8 and RCPath 2017: Updates and Controversies

Ⓟ NP West

University of Leeds, Leeds, UK

The eighth edition of TNM staging was published in 2016 and has been in routine use since the 1st January 2018 in the UK. Prior to TNM8 going live, the Royal College of Pathologists published the fourth edition of the guidelines for reporting colorectal cancer to ensure consistency with TNM8. The serial changes in TNM staging, often based on limited evidence, have caused significant controversy internationally over recent years. Subsequently several countries, including the UK, resisted the change from TNM5 to TNM6 and TNM7. Reporting requirements have therefore markedly changed for UK pathologists from a staging system that has been in routine use since 1997. This talk will summarise the reasons why the UK has now finally opted to adopt the latest guidance, the changes introduced in TNM8 when compared to TNM5 for colorectal cancer reporting, and will highlight where UK practice continues to deviate from the UICC guidance. It will also attempt to give practical guidance in difficult areas such as tumour deposits and regression grading, and show some examples of cases where staging is changed depending on the version of TNM used.

S36

Industrial Centre for AI Research in Digital Diagnostics (iCAIRD)

Ⓟ G Bryson

Queen Elizabeth University Hospital, Glasgow, UK

The industrial Centre for Artificial Intelligence in Digital Diagnostics (iCAIRD) is an Innovate UK funded innovation centre based in Glasgow but with links and academic and industry partners across Scotland and the UK. The centre includes digital pathology (with main partner Philips) and radiology (main partner Canon). We are building on an existing integrated programme of pathology digitisation across NHS Scotland, academic expertise in image analysis and AI in digital pathology, and strong industrial partnerships.

For digital pathology, there are three main focuses:

1. The first step required for development and adoption of AI in pathology is the widespread implementation of primary diagnostic digital pathology. We will fully digitise the Pathology Department at the Queen Elizabeth University Hospital – currently the largest in the UK (over 110,000 requests p.a.; 47 Consultant Pathologists). As part of this deployment, we are co-developing and implementing a reporting solution to enable a distributed digital pathology deployment.
2. The current cellular pathology workforce crisis requires new efficient ways of working. As an exemplar project, we aim to increase capacity by developing AI algorithms to assist in the efficient reporting of endometrial and cervical biopsies.
3. We will capture high volumes of images and linked data in a EPCC/HDRUK database to act as a resource for the development of future precision digital diagnostics.

S37

The Use of Light Sheet Microscopy to Develop Novel Approaches to Define Vascular Structure in Health and Disease

Ⓟ KJ Griffin

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Purpose of the study: This presentation will introduce light sheet microscopy and will discuss the associated tissue processing protocols and imaging workflow. This will be approached in the context of using light sheet microscopy to develop novel approaches to define vascular networks in health and disease (Pathological Society Career Development Fellowship).
Methods: Tissue clearing; immunolabelling; light sheet imaging; post-processing workflows.
Summary of results: Diabetes mellitus (DM) is a global health burden which will affect ~500 million people by 2035. In DM, healthy tissue (be that brain, myocardium or skeletal muscle) is lost because of a failure of adequate tissue perfusion. Our group studies the factors influencing neovascularisation in a murine model of critical limb ischaemia (CLI). The ability to quantitatively analyse vessel development within tissue samples is a crucial part of this work, which, to date, has only been possible in 2-dimensions. Moreover, when studying murine and human skeletal muscle vasculature, it is routine practice to rely on immunofluorescent labelling of cryosections, imaged with confocal microscopy. These approaches focus on small tissue regions, meaning we could neglect important spatial differences in pathology, and fail to appreciate the interplay between the vascular, nervous, and immune systems in recovery from ischaemia.
Conclusions: Using light sheet microscopy of optically cleared murine tissues we create topological 3-dimensional maps of our pre-clinical samples, thus offering a greater scope to understand and quantify vascular remodelling. Once optimised, we will extend these developments to the study of limb ischaemia and ulceration in patients with DM. In the future these technologies could potentially be translated into clinical practice, for example in the assessment of the micro-circulation to individualise patient treatment in CLI and better predict functional outcome following lower limb revascularisation.

S38

Changing Landscape in the Management of Advanced Bladder Cancer

Ⓟ SA Hussain

University of Sheffield, Weston Park Cancer Centre, Sheffield, UK

Several new drugs have emerged in the management of advanced metastatic bladder cancer that have shown exciting results in randomised clinical trials. The clinical trials of immune check point inhibitors in advanced bladder cancer has shown promising results. Proportion of patients with metastatic bladder cancer treated with immune check point inhibitors in second line setting and achieving long term durable responses has increased. Their use in first line setting and neo-adjuvant and adjuvant settings are being tried in clinical trials. Improvements in our understanding of tumour biology of bladder cancer and further sub classification of bladder cancer is helping to provide more insights into choices of treatments and new drugs are being developed for targeted therapies in bladder cancer. Clinical trials in second line/third line have also shown promise. Trial of Docetaxel plus Ramicurimab versus Docetaxel and Placebo met its primary end point with imporvement in progression free survival. Role of Erdafitinib in biomarker positive patients has recently received FDA approval and is the first biomarker driven drug to get approval in advanced bladder cancer. Amongst the myriad of promising drugs there will undoubtedly be some that would fail to meet current hopes, but we can be optimistic that using this approach of robust molecular profiling and preselecting patients within clinical trials with matched treatments, more and more drugs will find a useful place in keeping advanced cancer at bay for longer than can be achieved at present. This will also help to move some of these exciting targeted therapies to earlier stages of cancer as single agents or in combination with established therapies within clinical trials.

S39

The Management of Gynaecological Cancers in Lynch Syndrome: The Manchester International Consensus Meeting

Ⓟ EJ Crosbie; NAJ Ryan; Manchester International Consensus Group; DG Evans

University of Manchester, Manchester, UK

Purpose: There are no internationally agreed clinical guidelines as to how best to manage the risk, prevention and treatment of gynaecological cancers in women with Lynch Syndrome. The Manchester International Consensus Group was convened in April 2017 to develop clear and comprehensive clinical guidance regarding the management of the gynaecological sequelae of Lynch Syndrome based on existing evidence and expert opinion from medical professionals and patients.
Methods: Stakeholders from Europe and North America worked together over a two-day workshop to achieve consensus on best practice. Stakeholders included patients, patient support groups, gynaecologists, clinical geneticists, medical oncologists, colorectal surgeons, gastroenterologists, histopathologists, genetic pathologists, health economists, epidemiologists, gynaecology nurse specialists and genetic counsellors.
Results: Guidance was developed in four key areas: (1) whether women with gynaecological cancer should be screened for Lynch Syndrome and (2) how this should be done; (3) whether gynaecological surveillance was of value for women with Lynch Syndrome; and (4) what preventive measures should be recommended for women with Lynch Syndrome to reduce their gynaecological cancer risk.
Conclusion: The Manchester International Consensus Guideline provides comprehensive clinical guidance that can be referenced by both patients and clinicians so that women with Lynch Syndrome can expect and receive appropriate standards of care.

S40

Molecular DCIS Update

Ⓟ EJ Sawyer

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Existing methods for accurately predicting the behaviour of DCIS are poor and the management of patients with established DCIS is very varied, including complete surgical excision with or without additional radiotherapy and/or hormone therapy. The development of biomarkers that can predict recurrence/progression of DCIS would dramatically impact on the clinical care of women with DCIS. There is concern regarding over-treatment and this is reflected in new clinical trials of DCIS offering observation alone following biopsy for low and intermediate grade DCIS (LORIS trial in UK and LORD trial in the Netherlands). However, for some women omitting radiotherapy after BCS is associated with a high risk of development of invasive disease and for observation-only to be a viable treatment option, it is imperative that biomarkers are identified in order to avoid under treatment of those most at risk. The Sloane Project is a UK-wide prospective audit of screen-detected, non-invasive and atypical hyperplasias of the breast. The Project started in 2003 and now has data on 10,500 cases of DCIS diagnosed in the UK between 1/4/03 – 31/3/12. From this cohort, we have a identified a series of DCIS cases that have developed an ipsilateral recurrence after breast-conserving surgery and a series of DCIS that have not recurred. Molecular analyses of the primary DCIS tissue has been performed including copy number analysis, targeted sequencing and RNA seq in collaboration with the DCIS_PRECISION team. The preliminary analysis of this data will be presented.

S41

Tricky Topics for Trainees on Soft Tissue Pathology

Ⓟ K Thway

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Soft tissue tumors are a group of rare childhood and adult neoplasms with differentiation towards mesenchymal tissue, which can originate anywhere in the body. There are over 150 sub-types of benign and malignant soft tissue tumors. They are pathologically diverse and complex, but often show highly overlapping morphological and immunophenotypic characteristics, and benign soft tissue tumors can be close morphological mimics of highly aggressive malignant neoplasms. Soft tissue tumors frequently exhibit similar clinical and radiologic presentations, and histology therefore remains the cornerstone of diagnosis. Due to their rarity and the often infrequent exposure to soft tissue tumors outside of tertiary centers, soft tissue pathology can present a real challenge in training. This session will focus on some key diagnostic challenges in soft tissue pathology, and aims to demonstrate a basic, safe approach to dealing with soft tissue tumors, correlating clinical features with morphology, immunohistochemistry and molecular diagnostic approaches.

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