Pathological Society

Understanding Disease

Invited Speaker Abstracts

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S1

Grading Cancer Evolution for Prognostication

Ⓟ TA Graham

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The question "what is the prognosis of this tumour?" is the same question as "how will this tumour evolve next?". Consequently, it seems logical that efficacious prognostic and treatment-predictive biomarkers can be found by *measuring the evolutionary process of cancer development itself*. But current biomarkers, including state-of-the-art in molecular diagnostics, measure only the *outputs* of the evolutionary process: factors including the organisation, spread, shape and expression profiles of tumour cells. I will describe our (and others') development of evolutionary biomarkers that quantify the underlying dynamics of tumour evolution and are also mindful of the tumour microenvironment that imposes selective pressures on the tumour cells. Intra-tumour heterogeneity is one such biomarker. The level of diversity within a population largely determines how evolvable that population is: if there is no diversity natural selection cannot operate, whereas diverse populations are likely to contain well-adapted individuals that can prosper in changing environments. Consequently worse prognosis is expected to correlate with increased within-tumour diversity. I will describe how we have measured within-tumour diversity, both genetically and phenotypically, and used these measures to successfully determine prognosis in both established cancers and in premalignant lesions.

S2

'Born to be Bad' – How Evolutionary Dynamics Determine Prognosis

Ⓟ DSS Shibata

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Multi-regional sequencing studies, particularly comparing mutations from opposite tumour sides, reveal that most human colorectal tumors are single expansions. Many of the mutations detectable by conventional exome sequencing appear to originate from the first few growth divisions. Therefore, one can analyze the genetic and spatial information encoded in a present-day tumour to reconstruct (or coalesce) back to its start, when the tumour first started growing. The distributions of mutations in colorectal tumours are consistent with star-like phylogenies and neutral evolution during growth, where selection is primarily conferred by the public drivers present in the final first tumour cell rather than from private mutations acquired stepwise during growth. Therefore, the malignant potential of the final tumour is essentially determined by phenotype of its first tumour cell (i.e. "born to be bad or born to be good"). From a practical standpoint, sampling from opposite tumour sides more readily distinguishes between public mutations, present in all tumour cells, and private mutations acquired during growth. In addition, events that occur early during such "Big Bang" tumour expansions largely determine the intratumoural heterogeneity in the final tumour. For example, in cancers, the abnormal cell mobility or intermixing eventually needed for invasion or metastasis can be expressed in its first tumour gland, resulting in the same private mutation on opposite sides of the final tumour. Moreover, neutral evolution during tumour growth may help explain subsequent therapeutic resistance because it maximizes the numbers of potentially resistant variants within a tumour population. Like the start of the real universe, it may be possible to reconstruct in great detail the starts of individual human tumours by sampling from its different parts.

S3

TRACERx Renal (TRAcking Renal Cell Carcinoma Evolution Through Therapy (Rx))

Ⓟ S Turajlic

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Identifying and understanding the genomic events that drive cancer is fundamental for delivering precision medicine. In addition to identifying recurrent genomic driver aberrations across multiple tumour types next-generation sequencing (NGS) studies have revealed extensive intra-tumour heterogeneity (ITH) evidenced by genetically distinct subclones existing within a single tumour. ITH is a significant hurdle for precision medicine, not least through the effect of tumour sampling bias on prognostic and predictive biomarker development. ITH is an emerging theme in ccRCC. Our group has demonstrated profound ITH in a cohort of ccRCCs revealing branched tumour evolution. Critically, the majority of known driver events and potential therapeutic targets are found to be subclonal suggesting that they are under-represented in single biopsies. The impact of ITH on the course and treatment of ccRCC is an area of unmet scientific and clinical need. Multi-disciplinary approaches to decipher evolution in ccRCC, allow us to examine: (1) the association of ITH with disease progression (informing the management of small renal masses); (2) the relationship between the clonal architecture of the primary tumour and its metastases (helping to define the role of nephrectomy, lymph node clearance, metastasectomy and thrombectomy in the setting of early or advanced disease); and (3) the routes to treatment resistance (potentially informing systemic therapy combinatorial approaches). To this end we have set up TRACERx Renal (TRAcking Renal Cell Carcinoma Evolution Through Therapy (Rx)), a multi-site, multi-disciplinary study which aims to collect and analyse a large number of cases which reflect a range of ccRCC stages and metastatic patterns.

S4

Clonal Evolution in Lymphoma and Leukaemia

Ⓟ J Fitzgibbon

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The Centre of Haemato-Oncology at Barts in London maintains one of the largest collections of sequential lymphoma and leukaemia tumour tissue repositories in the UK and this has provided us with a unique opportunity to trace the genetic changes in these cancers over time. In Follicular lymphoma (FL), the t(14;18) is considered the earliest molecular lesion resulting in the upregulation of the pro survival factor Bcl2 creating a pool of long lived B cells that give rise to indolent lymphoma. We have uncovered a highly complex pattern of tumour evolution in these lymphomas, consistent with the existence of a common progenitor B cell (CPC) population which we now believe is critical for propagating new episodes of disease and which is responsible for the tell tail relapsing remitting course associated with this indolent disease. The clonal relationship between this CPC population and the corresponding mature tumour can follow either a 'rich' or 'sparse' evolutionary pattern, dependent on the genetic semblance between progenitor and lymphoma populations and is enriched for mutations in components of the epigenome, including histone methyl (KMT2D) and acetyl-transferases (CREBBP). A knowledge of the stability of mutations throughout the course of the disease has informed the creation of a translational pipeline suitable for precision medicine where our group in conjunction with the PMAL (precision medicine in aggressive lymphoma consortium) is concentrating on testing the efficacy of targeting activating mutations in EZH2 and the mTOR pathway. Altogether, our experiments suggest that a diagnostic sample in isolation is not sufficient to capture all the information needed in order to optimise and manage patient care most effectively. Spatial and temporal variations in the genetic architecture of these tumours must be considered in biomarker led investigation.

S5

Biological Therapies and Gastrointestinal Pathology

Ⓟ AC Bateman

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The advent of novel monoclonal antibody treatments designed to target specific cellular messaging pathways ('biological therapies') impact on the gastrointestinal (GI) tract in two main ways – (1) biological therapies for the treatment of inflammatory bowel disease (IBD); and (2) GI side effects of biological therapies for cancer treatment. Anti-TNF alpha monoclonal antibodies (e.g. infliximab, adalimumab) are the most commonly used biological therapies for IBD and may be very effective in ulcerative colitis (UC) and Crohn's Disease (CD) refractory to 'conventional' medical treatments. Specimens resected after these treatments often show features less characteristic of IBD than those after no biological therapy. Infliximab use has also rarely been associated with fulminant hepatic failure. Other 'general' side effects of this treatment include opportunistic infections (e.g. tuberculosis, histoplasmosis), cardiac failure, demyelinating disorders and neoplasia (e.g. lymphoma). Anti-integrin therapies (e.g. vedolizumab, etrolizumab) and a JAK inhibitor (tofacitinib) have also shown promising early results in severe IBD. Biological anti-cancer therapies are now increasingly used for a range of advanced stage tumours. These include anti CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4) antibodies (e.g. ipilimumab) anti-PD-1 (programmed death 1 and programmed death ligand 1) receptor antibodies (e.g. pembrolizumab) used for malignant melanoma and several other tumours. These agents may prolong survival but side effects include colitis. The latter shows a spectrum of histological features; from changes resembling graft-versus-host disease, to severe colitis with cryptitis and crypt abscess formation. Interestingly, one biological therapy (infliximab) has been used successfully to treat steroid-resistant colitis caused by another (ipilimumab). However, colectomy has been required in severe cases.

S6

Biological Therapies and Dermatopathology

Ⓟ MJD Goodfield

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Biological therapies have had a dramatic effect on patient care in Dermatology, particularly psoriasis. Since the introduction of the anti-TNF agents, understanding of pathways of inflammation relevant to skin disease has increased dramatically, and the range of target molecules and diseases, expanded. Even eczema, neglected for so long, may now have targeted biologics within the next few years. The use of these targeted agents has usually been predictable, both in terms of effectiveness and side effects, with infection, particularly TB, being the most common adverse events. One agent, targeting CD11a, has been withdrawn because of the high rate of PML, but in general, registry data has shown that infection risk is similar to standard systemic agents. Similarly, there appears to be no additional risk of skin cancer, solid tumours or lymphoma. However, there have been unsuspected occurrences – psoriasis appearing de-novo in patients with inflammatory bowel disease, pustular relapse in patients with psoriasis of chronic plaque pattern, eczema occurring de-novo in patients whose psoriasis or arthritis or bowel disease has successfully responded – as well as other unusual patterns of response. Coupled with the ability of biologics, particularly anti-TNFs, to stimulate auto-antibody production and sometimes frank auto-immune disease, the assessment of patients on biologics with cutaneous reactions can be complex, and involves close clinico-pathological correlation. New biologics targeting new molecules are appearing very quickly, and the ability of these agents to modify cutaneous physiology, sometimes pathologically, is an on-going clinical challenge. Tyrosine kinase inhibitors and Janus kinase inhibitors can produce an array of cutaneous effects in patients treated for non-cutaneous disease including cancer: recognising macro- and micro-scopic patterns requires close observation of many patients.

S7

Biological Therapies and Renal Pathology

Ⓟ MM Yaqoob

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The biologics used in renal clinical practice include several monoclonal and polyclonal antibodies aimed at specific cellular receptors and or signalling proteins. The effect of their mechanisms of action includes depleting or blocking specific cell subpopulations, complement system, or removing circulating preformed antibodies and blocking their production. They are used commonly but not exclusively in transplantation for induction, desensitization ABO-incompatible renal, and rescue therapy of steroid-resistant acute rejection. Biologics are increasingly used also in lupus nephritis, renal vasculitis and thrombotic microangiopathy (TMA) secondary to atypical hemolytic – uremic Syndrome. However, biologics used for rheumatogical (anti-TNF) and oncological (anti VEGF and Immune check inhibitors) conditions have been associated with both specific and non-specific renal lesions. It is important to be aware of these unwanted renal consequences to guide clinicians in withdrawing culprit biological agent to protect kidneys from further damage.

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