
Edinburgh-St Andrews Consortium for Molecular Pathology, Informatics and Genome Sciences
International Molecular Pathology Symposium
Tuesday 31st May 2016
09.00 - 18.00
IGMM Lecture Theatre
University of Edinburgh
KEYNOTE SPEAKERS
Professor Panpras Hogendoorn
University of Leiden
Professor Joakim Lundeberg
SciLifeLab, Stockholm
Dr David Bentley
Illumina, Inc
Professor Sue Hill
Chief Scientific Officer England
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NHS England
Integrating Genomics
- the future of medicine
Professor Sue Hill OBE
@CSOsue
Chief Scientific Officer for England
May 2016
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Over the next 10 years this will be seen
Genomic laboratory infrastructure an
100,000 Genomes Project informing
WGS applied routinely and in other c
Functional genomic pathway fully dep
for monitoring)
Medicines and other therapeutic inter
Closer alignment between clinical pra
benefit and improved outcomes for pa
New partnerships with industry
Greater public understanding of the i


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AND VETERINARY MEDICINE
Medical Sciences
Molecular Pathology
MMedSci by Research
www.ed.ac.uk/medicine-vet-medicine/medical-sciences
THE UNIVERSITY of EDINBURGH
Masters in Molecular Pathology
Contact Professor Simon Herrington
for further details
simon.herrington@ed.ac.uk


CM-Path:
Where we should see activity in 5 years
Skills and Capacity
Discovery
Beyond Pathology
Middle-ground
Centres of excellence
Clinical Trials
Technology and information
Cross-cutting themes
• Launch and legacy
CM-Path
Cellular Molecular Pathology Initiative
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Scottish Genomes Partnerships
Scottish Genomes Partnership – Phase 1
• Purchase of Illumina HiSeq X with University of Glasgow, Dec '14
Scottish Genomes Partnership – Phase 2
• Award from MRC/CSO, £6 Million
Scottish Genomes Partnership – Phase 3
• Implementation of WGS into routine NHSS healthcare
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Rachel Dakin


Kenco


Transcription factor vs Kinase
Transcription factor activation is more frequently identified (till now…)
10
31/5/16
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TET Protein Family


The Molecular Pathology
of
Colorectal Cancer Risk
Malcolm Dunlop
igmm
INSTITUTE OF GENETICS & MOLECULAR MEDICINE
MRC
CANCER RESEARCH UK
EPSRC
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Opportunities to advance genomic medicine/research in cancer the NHS
Genomics
• Develop structures for routine consent in NHS for clinical and research
• Develop structures for collection in NHS of high-quality tissue samples
• Routinely process each sample for both molecular pathology and histopathology
• Store molecular data (with clinical data) centrally in (quasi-) real-time
NHS England
Public Health England
NHS
National Institute for Health Research
CANCER RESEARCH UK
EPSRC
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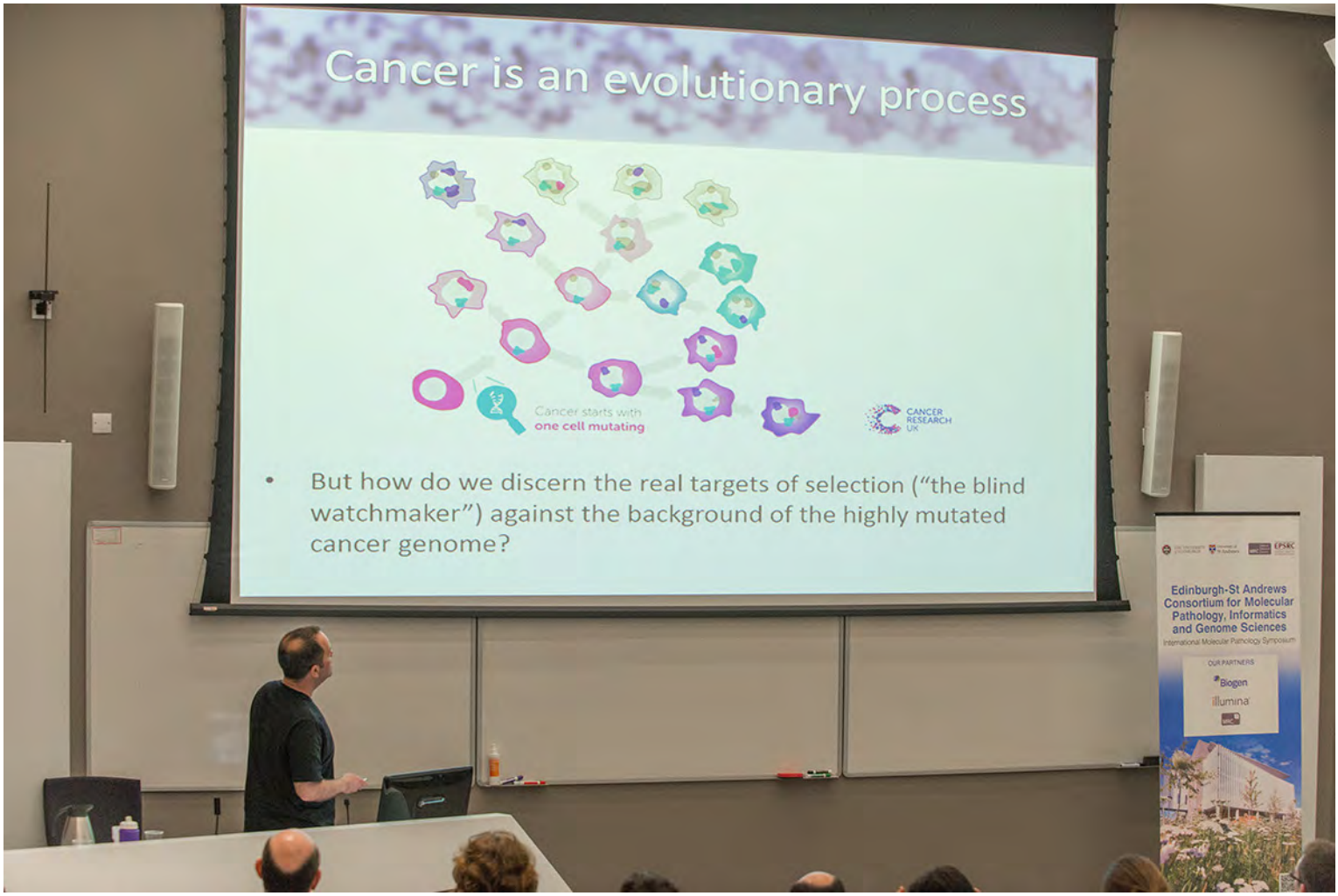
Cancer is an evolutionary process
Cancer starts with one cell mutating
CANCER RESEARCH UK
• But how do we discern the real targets of selection ("the blind watchmaker") against the background of the highly mutated cancer genome?
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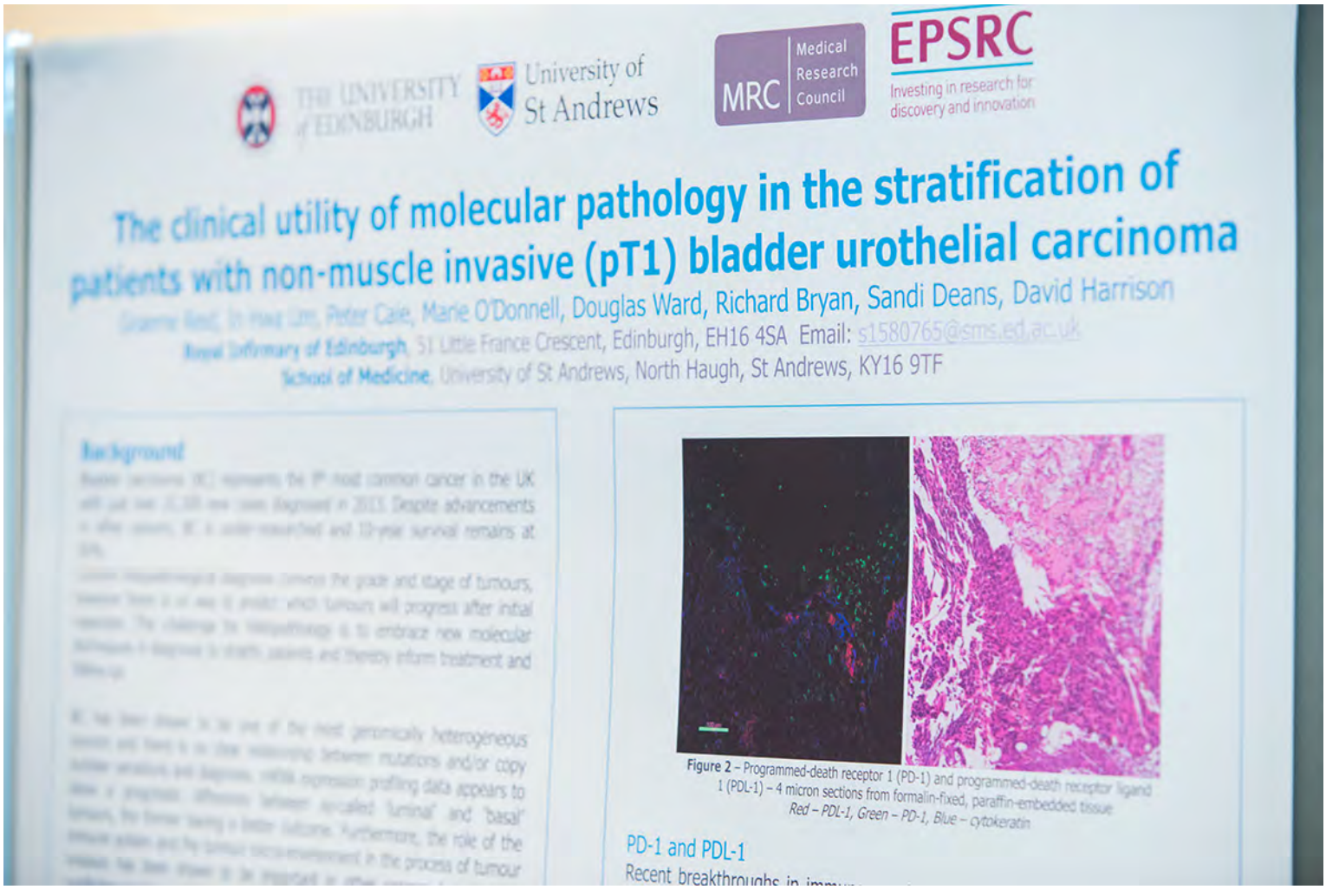
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Investing in research for discovery and innovation
The clinical utility of molecular pathology in the stratification of patients with non-muscle invasive (pT1) bladder urothelial carcinoma
Peter Cale, Marie O'Donnell, Douglas Ward, Richard Bryan, Sandi Deans, David Harrison
Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh, EH16 4SA Email: s1580765@sms.ed.ac.uk
School of Medicine, University of St Andrews, North Haugh, St Andrews, KY16 9TF
Figure 2 – Programmed-death receptor 1 (PD-1) and programmed-death receptor ligand 1 (PDL-1) – 4 micron sections from formalin-fixed, paraffin-embedded tissue
Red – PDL-1, Green – PD-1, Blue – cytokeratin
PD-1 and PDL-1

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What is the role of Viral and Genetic Factors in Human Papillomavirus (HPV) related Vulvar Neoplasia?

Etherton, M., Cuschieri, K., Wakeham, K., Bhatia, R., Howie, S.E., Haas, J.

HPV Research Group, University of Edinburgh, Little France Crescent, Edinburgh EH16 4TJ

email: s1579868@sms.ed.ac.uk www.igmm.ac.uk

Results

HPV 16 Variant Analysis

- HPV positivity within Scottish Vulvar disease is similar to Worldwide data (Table 1)
- European lineages predominated and no excess of 350G polymorphism observed in cases compared to controls (Table 2).

Table 1

	VIN Cases	VSCC Cases
Total Number	166	66
% HPV Positive	78.3% (130)	34.8% (23)

Table 2

Group										
Reference										

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The impact of genotype at the Xp22.2 colorectal cancer risk locus on *SHROOM2* mRNA expression in human colorectal crypt

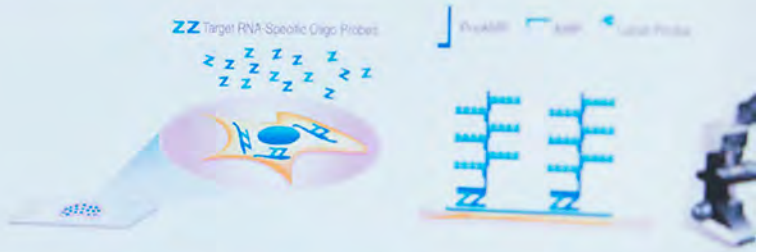
Dr Alice Hardwick. Supervisors: Professor Malcolm Dunlop and Professor Mark Arends

Institute of Genetic and Molecular Medicine, University of Edinburgh, Western General Hospital, Crewe Road South, Edinburgh EH4 2XU

email: alice.hardwick@igmm.ed.ac.uk www.igmm.ac.uk

Background

Colorectal cancer (CRC) is a significant public health burden, with 41,000 new cases and 16,000 deaths in United Kingdom annually.[1] The contribution of multiple socio-demographic, environmental and genetic risk factors have been well characterised in relation to the aetiology of CRC.[2] The heritable contribution to CRC risk is estimated to be up to 35%[3]; rare, high penetrance mutations such as APC in FAP only account for 5% of cases of CRC. Some of the missing heritability has been identified by GWAS. A meta-analysis of GWAS identified SNP rs5934683 at Xp22.2 locus demonstrating genome wide significant association with CRC (OR=1.07, 95% CI = 1.04-1.10, p=2.8x10^{-8}).[4] The risk allele, T (MAF = 0.37) is associated with a marked reduction in expression of nearby gene *SHROOM2* in normal colonic tissue compared to the alternate allele, C (p=1.2x10^{-5}),[5] with genotype at this locus explaining 55% of the variation in expression, providing strong evidence that SNP rs5934683 is either acting as, or tagging, an expression quantitative trait loci.



Schematic diagram displaying RNAscope protocol for FFPE sections[6]

Methodology

We have been unable to identify a suitably reliable and specific antibody for Shroo
As such, we have chosen to employ an RNA in-situ method. RNAscope (Advanced Cell Diagnostics), RNAscope can be

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...re-invasive stage (vulvar intraepithelial neoplasia/VIN) ...ble in one of the carcinogenic pathways. Worldwide, ...PV in VIN is 80% and 40% in VSCC with HPV16 ...V types and variants differ in risk. The T350G ...ropean variants has been associated with increased ... disease. The prevalence of HPV types and variants ...e currently unknown. Determining this is very important ...ation and prophylactic vaccination strategies. Genetic ...ble. Our group has shown an association of a Single ... (SNP) within the CXCR1(Interleukin 8-receptor A) gene ...al disease. IL-8 and CXCR1 are increased in different cancer ...key roles in tumorigenesis. This SNP was studied in vulvar disease. ...non-synonymous SNP is functional or not was also investigated. The ... was to identify viral and host genetic factors associated with vulvar ...utcome to allow patient stratification to improve clinical management.

... prevalence of HPV genotypes and HPV 16 variants in VIN and VSCC ... influence disease progression?

... associated with VIN and VSCC development and it's ...onal?

...ped

...infection selected for HPV 16 variant analysis

...ssful PCR amplification of 2 regions of HPV16 E6

...e alignment to identify variants

Results

HPV 16 Variant Analysis

- HPV positivity within Scottish Vulvar disease is similar to Worldwide data (Table 1).
- European lineages predominated and no excess of 350G polymorphism w... observed in cases compared to controls (Table 2).

Table 1

	VIN Cases	VSCC Cases
Total Number	166	66
% HPV Positive	78.3% (130)	34.8% (23)
% HPV 16 Mono-Infection	81.5% (106)	91.3% (21)
% Other or Mixed Infection	18.5%	8.7%

Table 2

Group	Nucleotide Position - Substitution								No of VIN Cases	No VSC... cases
	109	131	132	135	143	145	178	350		
Reference	T	A	G	A	C	G	T	T	43	10
E350G	.	.	.	.	.	.	.	G	28	4
E135C	.	.	.	C	.	.	.	.	1	0
E131G	.	G	.	.	.	.	.	G	3	0
E131G.2	.	G	.	.	.	.	.	.	1	0
E109C	C	.	.	.	.	.	.	G	2	1
A1-178G	.	.	.	.	.	.	G	.	2	1
AF-2	C	.	T	.	G	T	.	.	0	1

Table 1: HPV positivity in VIN and VSCC.
Table 2: HPV16 Variants observed and nucleotide substitution and position compared to reference genome.

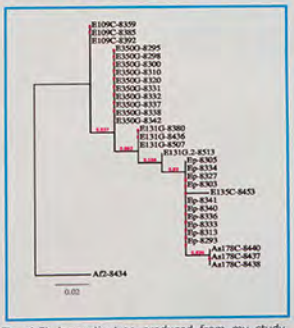

Fig. 4 Phylogenetic tree produced from my study sequences. Horizontal distance represents amount of


and Genetic Factors in Human
related Vulvar Neoplasia?


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e impact of genotype at the Xp22.2 colorectal cancer risk
on SHROOM2 mRNA expression in human colorectal crypts
Hardwick. Supervisors: Professor Malcolm
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