Manuel Salto-Tellez, MD (LMS), FRCPth, FRCPI
Professor and Chair of Molecular Pathology
Clinical Consultant Pathologist
Deputy Director, Centre for Cancer Research and Cell Biology
Why do we need to change the training of (Histo)pathology?

&

What is the Belfast Model?

&

Who is ultimately responsible?
Why do we need to change the training of (Histo)pathology?

&

What is the Belfast Model?

&

Who is ultimately responsible?
A Case for Integrated Morphomolecular Diagnostic Pathologists


Time for diagnostic molecular histopathology and cytology at the College

It seems that histopathology is getting involved with more and more molecular diagnostic techniques. How can the average laboratory keep up with these developments? Manuel Salto-Tellez makes an impassioned plea for molecular pathology to be put on a sound basis at the core of the routine diagnostic process.
ANATOMICAL DIMENSION OF PATHOLOGY

ANATOMICAL / CLINICAL DIMENSION OF PATHOLOGY (HISTOLOGY AND CYTOLOGY)

“... transforming pathology of the dead into pathology of the living.”

Lauren V. Ackerman

Gordon Signy

K Shanmugaratnam
ANATOMICAL-CLINICAL DIMENSION OF PATHOLOGY

TREATMENT AND/OR PROGNOSIS

Paediatric Sarcomas
Colorectal Cancer
Lympho–proliferative Disorders
Lung Cancer
Breast Cancer
Gastrointestinal Stromal Tumours

ANATOMICAL-CLINICAL DIMENSION OF PATHOLOGY

TREATMENT AND/OR PROGNOSIS

SURG PATH Diagnosis of Paediatric Sarcomas
SURG PATH Diagnosis of Colorectal Cancer
SURG PATH Diagnosis of Lympho - proliferative Disorders
SURG PATH Diagnosis of Lung Cancer
SURG PATH Diagnosis of Breast Cancer
SURG PATH Diagnosis of Gastrointestinal Stromal Tumours

ANATOMICAL-CLINICAL DIMENSION OF PATHOLOGY

TREATMENT AND/OR PROGNOSIS

SURG PATH
Diagnosis of Paediatric Sarcomas

SURG PATH
Diagnosis of Colorectal Cancer

SURG PATH
Diagnosis of Lympho - proliferative Disorders

SURG PATH
Diagnosis of Lung Cancer

SURG PATH
Diagnosis of Breast Cancer

SURG PATH
Diagnosis of Gastrointestinal Stromal Tumours

ANATOMICAL - CLINICAL - MOLECULAR DIMENSION OF PATHOLOGY

TREATMENT AND/OR PROGNOSIS

Molecular Detection of Translocations
KRAS/BRAF Mutation Analysis
Microsatellite Instability Analysis
Specific translocations
B & T cell rearrangements
Analysis of EGFR Mutations
HER2-neu Status
Analysis of C-kit Mutations

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The Value of traditional Pathology has not diminished. It is simply no longer sufficient.
Jared Schwartz, CAP President
TREATMENT AND/OR PROGNOSIS

Multiple Biomarker Analysis

- Molecular Detection of Translocations
- KRAS/BRAF Mutation Analysis
- Microsatellite Instability Analysis
- Specific translocations
- B & T cell rearrangements
- Analysis of EGFR Mutations
- Analysis of C-kit Mutations

Surgeon Pathology:

- Diagnosis of Paediatric Sarcomas
- Diagnosis of Colorectal Cancer
- Diagnosis of Lympho-proliferative Disorders
- Diagnosis of Lung Cancer
- Diagnosis of Breast Cancer
- Diagnosis of Gastrointestinal Stromal Tumours

Pharmacogenomics

ANATOMICAL - CLINICAL - MOLECULAR DIMENSION OF PATHOLOGY

TREATMENT AND/OR PROGNOSIS

Pharmacogenomics

Multiple Biomarker Analysis

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Pharmacogenomics

Multiple Biomarker Analysis

TREATMENT AND/OR PROGNOSIS

ANATOMICAL - CLINICAL - MOLECULAR DIMENSION OF PATHOLOGY

### Table 1. Recurrent molecular genetic abnormalities associated with specific sarcomas.

<table>
<thead>
<tr>
<th>Small round cell pattern</th>
<th>Translocation</th>
<th>Fusion protein</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNET/Ewing sarcoma</td>
<td>t(11;22)(q24;q12)</td>
<td>EWSR1-FLI1</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>t(12;22)(q13;q12)</td>
<td>EWSR1-ERG</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>t(11;22)(q22;q12)</td>
<td>EWSR1-ETV1</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>t(11;22)(q33;q12)</td>
<td>EWSR1-FLI1</td>
<td>90</td>
</tr>
<tr>
<td>Desmoplastic small round cell tumor</td>
<td>t(11;22)(p13;q12)</td>
<td>EWSR1-WT1</td>
<td>&gt; 95</td>
</tr>
<tr>
<td>Alveolar rhabdomyosarcoma</td>
<td>t(2;13)(q35;q14)</td>
<td>PAX3-FKBX10a</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>t(11;13)(p13;q14)</td>
<td>PAX7-FKBX10a</td>
<td>60</td>
</tr>
<tr>
<td>Myxoid lipid sarcoma</td>
<td>t(12;16)(p13;q11)</td>
<td>FUS-MYH11</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>t(12;23)(q11;q11)</td>
<td>EWSR1-COPA</td>
<td>95</td>
</tr>
<tr>
<td>Poorly differentiated synovial sarcoma</td>
<td>t(X;18)(p11.2;q11.2)</td>
<td>SYT-SSX1</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>SYT-SSX2</td>
<td>35</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Recurrent molecular genetic abnormalities associated with specific non-Hodgkin's lymphomas.

<table>
<thead>
<tr>
<th>Lymphoma type</th>
<th>Chromosomal abnormalities</th>
<th>Frequency (%)</th>
<th>Mechanism of oncogene deregulation</th>
<th>Preferred detection method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular lymphoma (FL)</td>
<td>t(14;18)(q32,q21)</td>
<td>85</td>
<td>BCL2/BCL11 fusion → upregulated expression of BCL2 (transcriptional deregulation)</td>
<td>PCR, FISH</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma (DLBCL)</td>
<td>t(14;18)(q32,q21)</td>
<td>20</td>
<td>BCL2/BCL11 fusion → upregulated expression of BCL2 (transcriptional deregulation)</td>
<td>PCR, FISH</td>
</tr>
<tr>
<td>Burkitt's lymphoma</td>
<td>t(3;14)(q27;5)</td>
<td>35</td>
<td>Translocation of bcl-6 → overexpression of BCL-6 (transcriptional deregulation)</td>
<td>FISH</td>
</tr>
<tr>
<td>Mantle cell lymphoma (MCL)</td>
<td>t(11;14)(q13;q32)</td>
<td>70–90</td>
<td>CyclinD1/IGH fusion → upregulated expression of BCL1 (transcriptional deregulation)</td>
<td>PCR, RT-PCR, CC</td>
</tr>
<tr>
<td>Extramedullary marginal zone lymphoma (MALT)</td>
<td>t(11;18)(q21;q21)</td>
<td>35*</td>
<td>AP2A/MALT1 fusion → chimeric fusion protein → NFAT activation</td>
<td>FISH, RT-PCR, IHC</td>
</tr>
<tr>
<td>Low-grade fibromyxoid sarcoma</td>
<td>t(7;16)(q33;p11.2)</td>
<td>FUS-CREB11</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Angiomatoid fibrous hystiocytoma</td>
<td>t(12;22)(q13;q12)</td>
<td>EWSR1-CREB1</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Inflammatory myofibroblastic tumor</td>
<td>t with 2p23</td>
<td>AKT fusions</td>
<td>&gt; 50</td>
<td></td>
</tr>
</tbody>
</table>

### The relevance of molecular diagnostics in the practice of surgical pathology

Siok-Bian Ng, Victor Lee, Kukodi Das & Manuel Salto-Tellez

1 National University of Singapore, National University Hospital, Yong Loo Lin Medical School, Department of Pathology; 5 Lower Kent Ridge Road, 119076, Singapore

**Expert Opinion**

*Many translocation partners with bcl-6 described [60].
*Percentage of occurrence in gastric and lung MALT, with which this is most commonly associated.
*Percentage of occurrence in extranodal MALT but not GIT, lung, thyroid and breast.
*Aberrant nuclear expression of BCL-10 associated with t(1;14) and t(1;11) [68] in MALT.
*Subcellular location of chimeric fusion protein provides information with regards to the type of translocation.
**Several genes implicated, for example, IKB, mRN145, mRN164 (40:44).

General references to this table: [40,43,44,49,60].

PCR: Polymerase chain reaction; FISH: Fluorescent in situ hybridization; CC: Conventional cytogenetics; SR: Southern blot; IHC: Immunohistochemistry; SHM: Somatic hypermutation.
# Selected target therapeutics in clinical oncology practice

<table>
<thead>
<tr>
<th>Targeted Therapeutics</th>
<th>Target</th>
<th>Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibodies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>VEGF</td>
<td>Breast Ca/CRC/NSCLC</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>EGFR/KRAS</td>
<td>CRC and HN Ca</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>EGFR</td>
<td>CRC</td>
</tr>
<tr>
<td>Rituximab</td>
<td>CD20</td>
<td>B-cell lymphoma</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Her-2</td>
<td>Breast Ca/Gastric cancer</td>
</tr>
<tr>
<td>Small molecule inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Proteasome</td>
<td>MM and MCL</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>ALK</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>EGFR</td>
<td>NSCLC/pancreatic cancer</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>EGFR</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Imatinib</td>
<td>c-kit/BCR-ABL</td>
<td>GIST/CML</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Her-2 and EGFR</td>
<td>Breast Ca</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>VEGFR/PDGFR/RAF</td>
<td>HCC and RCC</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>VEGFR/PDGFR/RET</td>
<td>GIST and RCC</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>mTOR</td>
<td>RCC</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>BRAF</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Vorinostat/Bortezomib</td>
<td>HDAC</td>
<td>Cutaneous TCL</td>
</tr>
</tbody>
</table>
Molecular biomarkers used in clinical standard-of-care decision making in colorectal cancer

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Diagnostic</th>
<th>Prognostic/Predictive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>APC</strong> mutation detection</td>
<td><strong>MMR</strong> protein expression (MSH2, MLH1, MSH6, PMS2)</td>
<td><strong>KRAS</strong> mutation analysis</td>
</tr>
<tr>
<td><strong>MMR</strong> mutation detection</td>
<td><strong>MSI</strong> (microsatellite instability) analysis</td>
<td><strong>BRAF</strong> mutation analysis</td>
</tr>
<tr>
<td><strong>BRAF</strong> mutation detection</td>
<td><strong>MYH</strong> mutation detection</td>
<td><strong>Thymidylate synthase protein expression</strong></td>
</tr>
<tr>
<td><strong>LKB1, SMAD4, BMPR1A, PTEN</strong> mutation detection</td>
<td><strong>MSI</strong> gene expression signature</td>
<td><strong>MSI</strong></td>
</tr>
</tbody>
</table>

Molecular testing in breast cancer


<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Detection</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER</td>
<td>IHC</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>PR</td>
<td>IHC</td>
<td></td>
</tr>
<tr>
<td>HER2/ERBB2</td>
<td>IHC; ISH</td>
<td>Trastuzumab; lapatinib</td>
</tr>
<tr>
<td>CD44</td>
<td>IHC</td>
<td>Lapatinib</td>
</tr>
<tr>
<td>VEGF</td>
<td>IHC</td>
<td>Bevacizumab; vandetanib</td>
</tr>
<tr>
<td>PTEN</td>
<td>IHC</td>
<td>Olaparib</td>
</tr>
<tr>
<td>PI3K</td>
<td>PCR</td>
<td>NVP-BEZ235</td>
</tr>
<tr>
<td>mTOR</td>
<td>IHC</td>
<td>Temsirolimus; everolimus</td>
</tr>
<tr>
<td>IGF-1R</td>
<td>IHC</td>
<td>Dalotuzumab</td>
</tr>
<tr>
<td>TOP2a</td>
<td>IHC</td>
<td>Anthracyclins</td>
</tr>
<tr>
<td>EGFR</td>
<td>IHC</td>
<td>Gefitinib; lapatinib</td>
</tr>
</tbody>
</table>

Comprehensive molecular characterization of gastric adenocarcinoma

1. Tumours positive for Epstein–Barr virus
   - PIK3CA mutations
   - extreme DNA hypermethylation
   - amplification of JAK2, CD274 (also known as PD-L1) and PDCD1LG2 (PD-L2)
2. Microsatellite unstable tumours,
   - Elevated mutation rates, including mutations of genes encoding targetable oncogenic signalling proteins
3. Genomically stable tumours,
   - diffuse histological variant
   - mutations of RHOA or fusions involving RHO-family GTPase-activating proteins
4. Tumours with chromosomal instability
   - marked aneuploidy and
   - focal amplification of receptor tyrosine kinases
Identification and Validation of an Anthracycline/Cyclophosphamide–Based Chemotherapy Response Assay in Breast Cancer


Figure 2. Kaplan–Meier time to recurrence curves stratified by the DNA damage response deficiency (DDRD) assay. Kaplan–Meier time to recurrence curves censored at 5 years for 191 breast cancer patients treated with adjuvant 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) (A) and 664 early breast cancer patients from 3 studies (14–16) in which patients did not receive DNA-damaging chemotherapy (B). $P$ values are derived from the two-sided Wald test. The number of events/patients at risk at various time intervals are noted in the tables below the curves. CI = confidence interval; HR = hazard ratio.
As comprehensive (high-throughput) as possible

- Plasma-free DNA (PB)

As sensitive as possible, blood-based
Figure 2 Cancer immunotherapy. Immunological approaches to cancer therapy are based on use of cytotoxic immunocytes (cytokine induced killer cells, tumor infiltration cells, tumor antigen loaded dendritic cells), cancer vaccines, monoclonal antibodies. Therapeutic vaccines enhance pre-existing immunity and lead to a more robust antitumor immune response whereas monoclonal antibodies are used to inhibit critical molecules for tumor growth and survival. PD: Programmed death.
Validation of Next Generation Sequencing Technologies in Comparison to Current Diagnostic Gold Standards for 
BRAF, EGFR and KRAS Mutational Analysis

Clare M. McCourt¹, Darragh G. McArt¹, Ken Mills², Mark A. Catherwood², Mark A. Catherwood², Perry Maxwell¹,⁴, 
David J. Waugh³, Peter Hamilton¹, Joe M. O’Sullivan³,⁴, Manuel Salto-Téllez¹,³,⁴,⁵

¹Molecular Pathology Programme, Centre for Cancer Research and Cell Biology, Queen’s University Belfast, Belfast, United Kingdom, ²Haematology Programme, Centre for Cancer Research and Cell Biology, Queen’s University Belfast, Belfast, United Kingdom, ³Prostate Cancer Programme, Centre for Cancer Research and Cell Biology, Queen’s University Belfast, Belfast, United Kingdom, ⁴Belfast Trust, Belfast City Hospital, Belfast, United Kingdom, ⁵Cancer Science Institute Singapore, National University Health System & National University, Singapore, Singapore
1. Technological Advancement

Table 1. NGS list of considerations prior to diagnostic validation

<table>
<thead>
<tr>
<th>Before NGS is validated for molecular diagnostic purposes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Should every target be validated?</td>
</tr>
<tr>
<td>Should we calculate sensitivity/specificity/precision/accuracy for every target? And for every sample type?</td>
</tr>
<tr>
<td>How do we validate the bioinformatics curation of the results?</td>
</tr>
<tr>
<td>Is the turnaround time (TAT) competitive?</td>
</tr>
<tr>
<td>What is the minimum number of targets to make NGS cost-efficient in diagnostics?</td>
</tr>
<tr>
<td>How does NGS perform with routine clinical sample material?</td>
</tr>
</tbody>
</table>

Journal of Pathology

J Pathol 2014; 234: 5-10
Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/path.4365

Next-generation sequencing: a change of paradigm in molecular diagnostic validation#

Manuel Salto-Tellez1 and David Gonzalez de Castro2

1 Northern Ireland Molecular Pathology Laboratory, Centre for Cancer Research and Cell Biology, Queen’s University Belfast, UK
2 Molecular Diagnostics Department, Centre for Molecular Pathology, Royal Marsden NHS Foundation Trust, London, UK
KRAS
NRAS
BRAF
PI3KCA
p53

= £200 per sample

Dr David González de Castro
SOLID TUMOURS - LEVELS OF TESTING

- HUMAN CANCER COMPREHENSIVE: 160
- Tumour COMPREHENSIVE: 38
- CLINICALLY RELEVANT: 32
- ACTIONABLE MUTATIONS: 8 (3-4)
Molecular Pathology in Contemporary Diagnostic Pathology Laboratory
An Opinion for the Active Role of Surgical Pathologists

Gregory Y Lauwers, Stephen Black-Schaffer, and Manuel Salto-Tellez

To maintain its central role in the evaluation of patients, surgical pathology will need completely to incorporate the molecular diagnostic for the understanding and characterization of diseases.

If surgical pathologists attempt, even passively, to resist this change, it could have 3 hugely significant consequences:

1) inviting others to perform molecular testing of surgical pathology samples, moving the central role of tissue-based diagnosis out of the field of pathology

2) compromising the strategic position of our discipline at the crossroads between the clinical practice of medicine and the scientific understanding of diseases

3) Loosing on revenue: molecular diagnostics is the fastest growing area of medicine, moving a budget of many billions of dollars, and a share of it should justifiably find it way to divisions of anatomic pathology, where it has the potential best to be understood and most appropriately integrated.
INTEGRATION LEADING TO FULL DIAGNOSTIC, PROGNOSTIC AND THERAPEUTIC OPINION

CLINICO-PATHOLOGICAL INTEGRATION

MORPHO-MOLECULAR INTEGRATION

TRADITIONAL INTEGRATION

Pulmonary pathology
- Multiple translocations
- Her-2/neu amplification (GC)

Gastrointestinal Pathology
- KRAS/BRAF mutations (CRC)
- MSI analysis
- c-kit mutation (GIST)
- Her-2/neu amplification (GC)

Gynaecological Pathology
- HPV Subtype Identification

Lymphoreticular Pathology
- B- and T-cell receptor gene rearrangements
- Multiple translocations

CNS Pathology
- 1p 19q LOH (Gliomas)

Urological Pathology
- Various Chromosomal Abnormalities (BC)

Soft Tissue Pathology
- Her-2/neu amplification
- TOP 2A amplification
- Multiple gene amplification

Breast Pathology
- EGFR Mutations

Clinical History and Clinical Presentation
- Other Laboratory Investigations
- Diagnostic Imaging

FINAL PATHOLOGICAL DIAGNOSTIC OPINION

Lauwers, Black-Schaffer, Salto-Tellez
Am J Surg Pathol 2010;34:115-117
Why do we need to change the training of (Histo)pathology?

&

What is the Belfast Model?

&

Who is ultimately responsible?
What is the Belfast Model?

1. **Training during training - FRCPath**

2. **Training outside training – Fellowship / MSc**
<table>
<thead>
<tr>
<th>Test with a Predominant Diagnostic Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcoma Translocation Detection</td>
</tr>
<tr>
<td>Lymphoma Translocation Detection</td>
</tr>
<tr>
<td>Clonality Testing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test with a Predominant Genetic Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microsatellite Instability Testing</td>
</tr>
<tr>
<td>Mismatch Repair Protein Expression</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tests with a Predominant Therapeutic Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS/NRAS Mutation Testing</td>
</tr>
<tr>
<td>BRAF Mutation Testing</td>
</tr>
<tr>
<td>EGFR Mutation Testing</td>
</tr>
<tr>
<td>ALK Protein Expression</td>
</tr>
<tr>
<td>EML4-ALK Translocation Detection</td>
</tr>
<tr>
<td>Multiple Central Nervous System Molecular Testing</td>
</tr>
<tr>
<td>ER, PR and Her2 Protein Expression</td>
</tr>
<tr>
<td>Her2 Amplification</td>
</tr>
<tr>
<td>c-KIT Mutation Analysis</td>
</tr>
<tr>
<td>PDGFRA Mutation Analysis</td>
</tr>
</tbody>
</table>
**Molecular Pathology**

<table>
<thead>
<tr>
<th>Stage A (0-12 months)</th>
<th>Stage B (12-18 months)</th>
<th>Stage C (24-30 months)</th>
<th>Stage D (33 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introductory lectures on molecular diagnostics</td>
<td>Compulsory 2-8 month attachment in molecular diagnostics (See Table 1)</td>
<td>OPTION 1: 1 year full-time tissue molecular diagnostics (see Table 2) OPTIONAL 2: 1 year “sustaions” attachment with part-time practice in a subspecialty and part-time reporting the related molecular tests</td>
<td></td>
</tr>
</tbody>
</table>

**General Training Framework**

<table>
<thead>
<tr>
<th>Year 1 assessment at end of year to exit stage</th>
<th>Exit stage with FRCPath part 1 examination</th>
<th>Exit Stage with FRCPath part 2 examination with/without extra modules in Autopsy and Cytological cytology (additional 3 months each)</th>
<th>End of Training</th>
</tr>
</thead>
</table>

Table 1  Topics to be covered during the 2–3-month attachment

<table>
<thead>
<tr>
<th>Outline of topic</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA</td>
<td>Overview, structure, replication</td>
</tr>
<tr>
<td>RNA</td>
<td>Transcription, types/structures, RNA polymerases, regulation of transcription, microRNAases</td>
</tr>
<tr>
<td>Proteins</td>
<td>Amino acids, genes and genetic code, translation</td>
</tr>
<tr>
<td>NA extraction methods</td>
<td>Isolation of DNA and RNA, assessment of quality and quantity of nucleic acids</td>
</tr>
<tr>
<td>PCR</td>
<td>History of PCR, advanced PCR and PCR optimisation, PCR detection and evaluation techniques, limitations of PCR and troubleshooting</td>
</tr>
<tr>
<td>Analysis and characterisation of NA</td>
<td>Hybridisation technologies, detection systems, results interpretation</td>
</tr>
<tr>
<td>Nucleic acid amplification</td>
<td>Target, probe and signal amplification</td>
</tr>
<tr>
<td>Gene mutations</td>
<td>Types, detection and nomenclature of gene mutations</td>
</tr>
<tr>
<td>DNA sequencing</td>
<td>Direct sequencing, bioinformatics</td>
</tr>
<tr>
<td>Molecular oncology</td>
<td>Analytic targets of molecular testing, gene rearrangements</td>
</tr>
<tr>
<td>High-throughput technologies</td>
<td>DNA/RNA microarrays, NGS and TGS, whole genome sequencing</td>
</tr>
<tr>
<td>Validation and optimisation procedures</td>
<td>R&amp;D within molecular diagnostics present and future</td>
</tr>
<tr>
<td>Quality control and quality assurance</td>
<td>Discussion of QA and QC in molecular diagnostics</td>
</tr>
<tr>
<td>Regulation in the use of human tissues for research</td>
<td>Introduction to biobanking, research ethics and research governance within academia and the healthcare setting</td>
</tr>
<tr>
<td>Core skills in slide annotation</td>
<td>Be able to identify and annotate areas for macrodissection relevant to downstream testing, Be able to assign percentage tumour content</td>
</tr>
<tr>
<td>Core skills in macrodissection</td>
<td>Taught how to perform tissue macrodissection procedures</td>
</tr>
<tr>
<td>Core skills in DNA extraction</td>
<td>Taught how to perform DNA extraction procedures</td>
</tr>
</tbody>
</table>

QA, quality assurance; QC, quality control; NA, nucleic acid; NGS, Next Generation Sequencing; TGS, Third Generation Sequencing.
Box 2  Content of training for molecular diagnostics
1-year fellowship (Option 1, Stage C)

**Principles**

Knowledge and skills in core molecular technologies and techniques
Expertise in the molecular pathology of breast cancer
Expertise in the molecular pathology of colorectal cancer
Expertise in the molecular pathology of lung cancer
Expertise in the molecular pathology of malignant melanoma
Expertise in the molecular pathology of gastrointestinal stromal tumours (GISTs)
Expertise in the molecular pathology of sarcomas
Expertise in the molecular pathology of paediatric cancers, thyroid cancer, central nervous system neoplasias and others
Research, development and innovation in molecular pathology
Leadership and management of a molecular diagnostic laboratory
Training and education

What is the Belfast Model?

1. Training during training - FRCPath

2. Training outside training – Fellowship / MSc
CRUK Accelerator

CRUK DIGITAL MOLECULAR PATHOLOGY & TRAINING NETWORK

BELFAST

SOUTHAMPTON

Manchester

Newcastle

Leicester

MARSDEN

UCL Neuro

£3.7M
**Figure 1**

Targets of antibody immune modulators. (a) Targetable members of the CD28/CTLA-4 immunoglobulin superfamily include cytotoxic T lymphocyte antigen 4 (CTLA-4) (1), programmed cell death protein 1 (PD-1) (5, 7), B and T cell attenuator (BTLA) (84), lymphocyte activation gene 3 (LAG3) (85), and inducible T cell costimulator (ICOS) (86). (b) Targetable members of the tumor necrosis factor (TNF) superfamily include CD40 (87, 88), OX40 (89), CD137/4-1BB (90), glucocorticoid-induced TNFR-related protein (GITR) (91), and CD27. (c) Programmed cell death 1 ligand 1 (PD-L1). Mel: melanoma. (d) Killer inhibitory receptor (KIR). (e) T cell Ig and mucin-containing domain 3 (TIM3).
Hamilton P (Salto-Tellez M). Oncotarget 2015 (accepted)
Comparative Expression Analysis Reveals Lineage Relationships between Human and Murine Gliomas and a Dominance of Glial Signatures during Tumor Propagation In Vitro

Nico V. Henriquez¹, Tim Forshew², Ruth Tatevossian², Matthew Ellis¹, Angela Richard-Loendt¹, Hazel Rogers⁵, Thomas S. Jacques³, Pablo Garcia Reitboeck¹, Kerra Pearce⁴, Denise Sheer², Richard G. Grundy⁵, and Sebastian Brandner¹
**Table 1 — Pathology-centred activities in the research endeavour.**

- Molecular diagnostics in the context of clinical trials
- Analysis of tissues ahead of molecular analyses
- Tissue biobanking
- Digital pathology
- Pathology informatics
- Data manager
- Biomarker validation
- Integration of validated biomarkers into routine diagnostics

**Table 2 — Digital pathology.**

- Automated digitalization of images for storage and multi-site discussion
- Automated scoring of IHC
- Automated counting of hybridization signals
- Automated identification of tumour in sections for subsequent microdissection

**Table 3 — Pathology bioinformatics.**

- Digital imaging
- Pathology integration of pathological data, clinical data and biomarker analytical results
- Translation of high-throughput analysis to biomarkers with meaningful diagnostic/clinical relevance
- Translation of high-throughput analysis to pathology reports

**Review**

**Molecular pathology — The value of an integrative approach**

*Manuel Saito-Tellez*\(^a,b,\), *Jacqueline A. James*\(^a,b,\), *Peter W. Hamilton*\(^a\)

\(^a\)Northern Ireland Molecular Pathology Laboratory, Centre for Cancer Research and Cell Biology, Queen's University, Belfast, Northern Ireland, UK

\(^b\)Tissue Pathology, Belfast Health and Social Care Trust, Belfast, Northern Ireland, UK
### Taught Components – Weeks 1-14

<table>
<thead>
<tr>
<th>Week</th>
<th>Topic</th>
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<tbody>
<tr>
<td>Wk1</td>
<td>Induction</td>
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<tr>
<td>Wk2</td>
<td>Molecular Diagnostics</td>
</tr>
<tr>
<td>Wk3</td>
<td>Digital Pathology</td>
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<tr>
<td>Wk4</td>
<td>Low-throughput Technologies</td>
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<tr>
<td>Wk5</td>
<td>High-throughput Technologies</td>
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<td>Wk6</td>
<td>Bioinformatics</td>
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<td>Wk7</td>
<td>First Assessment</td>
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<td>Wk8</td>
<td>Test Validation</td>
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<td>Wk9</td>
<td>Accreditation procedures</td>
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<td>Laboratory QA &amp; QC</td>
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<td>Biobanking</td>
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<td>Industrial Collaborations</td>
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<tr>
<td>Wk13</td>
<td>Clinical Trials</td>
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<tr>
<td>Wk14</td>
<td>Second Assessment</td>
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### Sub-specialty Projects Weeks 15-40

<table>
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<tr>
<th>Institution</th>
<th>Project</th>
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<tbody>
<tr>
<td>UCL</td>
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<td>Southampton</td>
<td>Cancer Immunology</td>
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<tr>
<td>Manchester</td>
<td>Liquid Biopsy Pathology</td>
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<tr>
<td>Belfast</td>
<td>Biomarker Discovery &amp; Validation</td>
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<tr>
<td>Newcastle</td>
<td>Clinical Trials</td>
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<td>Translational Bioinformatics</td>
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<td>Leicester</td>
<td>Molecular Pathology of Lung Cancer</td>
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<td>ICR/Belfast</td>
<td>Digital Molecular Pathology</td>
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<tr>
<td>Belfast</td>
<td>High-throughput Technologies</td>
</tr>
</tbody>
</table>
CRUK DIGITAL MOLECULAR PATHOLOGY & TRAINING NETWORK

- BELFAST: Manpower, IT, Instrumentation, EPITHELIAL INTERROGATION Training
- UCL: Neuro Manpower Training
- SOUTHAMPTON: Manpower, IT Instrumentation, CANCER IMMUNE INTERROGATION Training
- MARSDEN: Manpower, WGS QA/QC Training
- Leicester: Lung Ca Training
- Newcastle: Clin Trials Training
- Manchester: Liq Bx Training
Why do we need to change the training of (Histo)pathology?

&

What is the Belfast Model?

&

Who is ultimately responsible?
WE ARE NOT TEACHING THE HISTOPATHOLOGISTS OF THE FUTURE

THERE IS NO CONFIDENCE THAT HISTOPATHOLOGISTS WILL LEAD THE FUTURE OF DIAGNOSTICS, OR THE FUTURE OF CLINICAL/APPLIED RESEARCH

The College needs to lead an urgent review of the histopathology curriculum