The New Face of Pathology in Precision Medicine

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Outline

• Traditional “Old Face” Pathology
• 4P Medicine – Precision Medicine
• Translational “New Face” Pathology
• Stratified Medicine Programme
• NUSOM
Joseph Coats (1846-1899)
Chair in Pathology, Glasgow (1894)
“Old Face” of Pathology

- **Rudolf Virchow** (1821-1902)
- Chair of Pathological Anatomy (1849)
- **Father of “Cellular Pathology”**
- Diseases originated within the cells rather than from imbalance of fluids
- Understanding disease mechanisms at cellular level
Robin Warren, Nobel laureate in Medicine (2005) – Discovery of Helicobacter pylori and its role in peptic ulcer

“There were numerous lymphocytes and plasma cells in the stroma. A thin blue line was visible on the surface, which on high power I thought consisted of numerous bacteria. My colleagues could not (or did not want to) see them, so I stained them.....”
The Impact of “Traditional” Pathology

- Morphological observation
- High quality tissue samples
- Intellectual curiosity

There is nothing more deceptive than an obvious fact!

Mechanistic/collaborative approach (with B Marshall, Junior Gastroenterologist, CS Godwin, Microbiologist, JA Armstrong, Electromicroscopist)
Pathological Grade and Prognosis

Good

Bad
Traditional Role of the Pathologist

Pattern recognition!!

- Morphological evaluation of tissues and cells (can be subjective!)
- Unequivocal Diagnosis (not always possible!)
- Pathological stage and grade (needs to be standardised!) on which to base prognosis and therapy → Molecular biomarkers
Cell Communication and Adhesion
Molecular Morphology

Communication via Cellular Continuities

INTEGRINS
- Fn Fibrils
- \( \alpha \) and \( \beta \)
- Actin
- Vinculin

CADHERINS
- \( \alpha \) and \( \beta \)
- Actin

Ig CAMs
- Eph-Ligand
- TK domain

SELECTINS
- PSGL-1
- CRD repeats

Abnormal $\beta$-catenin cellular localisation (nuclei) occurs in aggressive tumours.

Beta-catenin is preserved at the cell-cell junctions.

Beta-catenin nuclear localisation.
Fascin expression in cancer

Poor prognostic marker:

- Colon cancer
- Prostate cancer
- Lung cancer
- Ovarian cancer
- Bladder cancer
Translational Pathology
Accelerating discoveries at the bench to understand and eradicate disease at the bedside

Molecular biomarkers to predict prognosis and response to treatment: Precision medicine

Her-2 neu
4P(5P) of Modern Medicine

- Preventive
- Predictive
- Partnership (Participatory, health literacy)
- Precision (Personalised healthcare)
- Pathology
Role of Pathology and Pathologists in Precision Medicine

- **Customisation** of Healthcare
- **Targeting drugs** for each unique genetic profile

**Key requirements:**
- Molecular diagnostics
- Drug development programme
- High quality Pathology including good tissue sample history (rubbish in…rubbish out: **TISSUE IS THE ISSUE!**)
Role of the Pathologist/1

- Provision of high quality tissue samples
- Evaluation and integration of morphology and molecular analysis
- Clinical context and interpretation of results
Role of the Pathologist/2

- **Pattern recognition still very important**
- Morphological evaluation of tissues and cells *(less subjective!)*
- Unequivocal Diagnosis *(is possible!)*
- Prognosis and Therapy is based on molecular signatures as well as pathological staging
- **Molecular biomarkers**
The Path to Personalized Medicine
Margaret A. Hamburg, M.D., and Francis S. Collins, M.D., Ph.D.

Another important step will be expanding efforts to develop tissue banks containing specimens along with information linking them to clinical outcomes. Such a resource will allow for a much broader assessment of the clinical importance of genetic variation across a range of conditions. For example, a patient with a rare inherited disease could be matched to volunteers with similar genetic profiles, thereby enabling a more precise understanding of the disease's biology and the potential efficacy of different treatments.
Basic Science
Translational Science
Regulatory Science

For example:
- Gleevec (TK inhibitor) in GIST
- Herceptin (HER2) in breast cancer (approved companion tissue-based diagnostic tests)
SYLLABUS FOR RESEARCH MODULE (Royal College of Pathologists 2010)

- Fundamentals of the scientific process and evidence-based medicine.
- The role of research in the modern NHS
- **The ethical background of research on people and human tissue**
- The ethical background to research on animals
- **Tissue banking**
- Study design
- Statistics
- **Working in a research laboratory**
- The scope of pathology techniques
- **The pathologists role in the research team**
- The pathologist as educator, advisor, facilitator and supervisor of research
- Managing research grants and people employed on research grants
- The importance of probity in research
- Evaluation of the impact and cost of introducing research based discoveries into clinical practice
- Critical assessment of own and other people’s data
- Applying for grant funding
- Writing a paper, preparing a paper, and/or writing a chapter or book
- Reviewing publications, theses and grants
Biorepository

- Infrastructure to streamline the process of tissue acquisition and distribution
- Tissues, blood, urines, cytological preparations (normal and diseased)
- Ensuring researchers are compliant with both legal and ethical principles of storing and using human tissues in research
Pre-analytical phase in Pathology

- Tissue handling, preservation, storage and transport
- Fixation (time, type) and paraffin embedding
- Storage of frozen specimens (when possible)
- Dissection and block selection for microscopic and molecular analysis
Analytical phase in Pathology

- Image-based procedure (cutting, microdissection, TMA, conventional staining techniques, immunohistochemistry)
- Molecular analysis (nucleic acid extraction, PCR based technologies, next generation sequencing)
- Evaluation and integration of results
This mouse could be the key to a cure for baldness (but there’s a risk it may make your feet grow as well)
Over-expression of oncogenic beta-catenin is associated with increased cell proliferation

- De novo hair follicle morphogenesis and hair tumour formation (pilomatricoma)
- Intestinal dysplasia and adenoma
- Liver cell hyperplasia and hepatomegaly
- Polycystic kidney disease
Personalised Cancer Care

“The new face of oncology stresses the importance of a multidisciplinary approach to cancer care and requires a close collaboration with Pathology”
Our vision is to establish a national molecular diagnostics service delivering high quality, cost effective tests for patients, with routine consent for the collection, storage and research use of genetic, treatment and outcomes data.
Phase One of the CR-UK Stratified Medicine Programme (2011-13) is a mixture of service delivery...
...and research infrastructure

Research Database

Genetic and Clinical Data

Anonymised Data

Clinical Hubs (hospitals)

1 2 3 4 5 6 7

Genetic Data

Samples

Technology Hubs (labs)

Researchers Partners NHS

9,000 Cancer Patients

Research infrastructure

Service delivery
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Phase One of the programme will deliver on five core aims that enable stratified medicine delivery and research

1. **Significant scale across many sites**
   - 9,000 samples collected from 6 hospitals and analysed for c.20 markers in 3 labs with associated data available for research.

2. **Proven service model**
   - Detailed costs, protocols and service models for adoption across the NHS of a genetic testing service, delivered within clinical turnaround times.

3. **Routine consent for research**
   - All patients consented for DNA, diagnostic, treatment and outcome data to be linked and stored in a secure research database

4. **Bioinformatics database**
   - Detailed specifications for an information system that can link and extract anonymised diagnostic, treatment and outcome data

5. **New cancer assays**
   - Development of a standardised and validated £300 panel of genetic tests for the important clinical and research markers in the major solid tumours
Lessons to learn from Phase One: to improve molecular diagnostic testing service in order for it to be successfully rolled out nationally

Phase Two

- Integrate lessons learnt from Phase One into broader practise in clinics
- Adoption of new technologies such as next generation sequencing.
- Focus on specific cancer types.
- Application in other disease areas.
- Broaden the scope and utility of datasets captured

Phase Three

- National consolidated molecular diagnostics service delivering quality assured, continuously improving and cost effective tests for patients.
- Network will ensure that consent remains routine practice for molecular diagnostics.
NU Medicine

- Integrated Academic Health System
- National Medical Holding was established in 2008. Six specialist hospitals in Astana (four are already JCI accredited) 3000 beds
- New National Oncology Research Center (To open in 2016-17) in partnership with UPMC
- Center of Life Sciences – precision medicine, regenerative medicine, global health, genomic medicine
- School of Medicine (NUSOM) opened in 2014
Vision - NUSOM

World class center of excellence in

• Health Care Education
• Biomedical research
• Patient care

To improve health and well-being of Republic of Kazakhstan, Central Asia and beyond
Mission - NUSOM

• To educate science-based, compassionate and skilled clinicians to practice medicine in the 21st Century

• To do cutting edge research to advance the understanding of medical science and improve human health
What makes a great doctor?

A great doctor should be: Intelligent, Science-based, Skilled, Compassionate, Caring, Listener, Confident, Approachable, Decisive

“The good physician treats the disease; the great physician treats the patient who has the disease.”

~William Osler
• Biomedical Sciences (already established) 23 faculty members

• Medicine (to be established in 2015-2016)

• Surgery (to be established in 2015-2016)

• Research Priorities – cancer, cardiovascular, neuroscience, population health, infection and immunity
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