Breathomics — the new molecular pathology?

Prof. Paul S. Monks
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Molecular pathology is a discipline that seeks to describe and understand the origins and mechanisms of disease at the level of macromolecules (for example DNA, RNA and protein) largely using patient samples.
Molecular Pathology Nodes

Edinburgh-St Andrews Consortium for Molecular Pathology, Informatics and Genome Sciences

Glasgow Molecular Pathology (GMP) Node

The Newcastle Proximity Laboratory

Manchester Molecular Pathology Innovation Centre

Nottingham Molecular Pathology Node (NMPN) for Integrated Multi-platform Biomarker Research and Knowledge Transfer

East Midlands Breathomics Pathology Node (EMBER) - Institutions University of Leicester, Loughborough University and University Hospitals of Leicester NHS Trust
East Midlands Breathomics Pathology Node (EMBER)- Our Vision

- **Multidisciplinary** world-class centre - scientists from pathology, chemistry, physics, medicine, bioinformatics, mathematics, statistics, and health sciences in Academic-Industry Partnerships.
- **Innovation** and development of novel breathomic applications for near-patient testing.
- **Translate** technology in adults and children to enhance the benefits of stratified medicine.
- **National leadership, training, capacity building**
- Partner with industry, NHS, patient groups.
- **Qualification and adoption** of breathomics as novel molecular pathology tests.
LEICESTERSHIRE

Founding Partners

Loughborough University (LU)

University Hospitals NHS Trust & UoL - Glenfield General Hospital (GGH) Cardio-Respiratory-acute (CDU/CCU) and tertiary centre

University Hospitals NHS Trust & UoL - Leicester Royal Infirmary (LRI) A&E - Diagnostic Development Unit (DDU) Cancer Services, Infectious Diseases Children's Hospital

East Midlands Pathology Services - EMPATH

University of Leicester (UoL)

INDUSTRY PARTNERS

EMBER

LEICESTERSHIRE

2 mile radius

12 miles 20min

20m 35min

4 mile radius
What is breathomics and what can we see?
Breath-omics – diagnostic, theranostic & prognostic

Breath contains hundreds to thousands of organic compounds coming from the chemical processes taking place in your body.

Advantages
- Non-invasive procedure
- No risk allowing for repeated use
- Suitable for people of all ages and conditions
- Quick to perform/immediate results

Fingerprint disease
Breath Alcohol (Pharmokinetics)

- Ethanol metabolism – well defined process
- Good ‘proof of principle’ experiment to show monitoring of processes occurring in the body

Monks and Willis, Educ.Chem., 2010
Ovarian Cancer - Pilot Study

Ability to discriminate ovarian cancer from healthy controls as well as benign cysts from cancer.
Clostridium difficile

- Ability to differentiate strains
- Pathogenic and non-pathogenic have different metabolic products

With Martha Clokie, Sharmilah Kuppasami, Andy Ellis

Kuppasami et al, Metabolomics 2015
Sexually Transmitted Infection

Cultures

Clinical Specimens

PCA Biplot of VOCs emitted by Sexually Transmitted Infection (STI) cultures

- Proteolytic compound (nM)
- Chlamydia
- Trichomonas
- Gonorrhea
- Candida

PCA plot of Vaginal Swabs

- Control
- Candida & Bacteria
- Bacterial vaginosis
EMBER

From laboratory scale to clinical scale
EMBER Work Strands

- WS1. Innovation management- management and governance structure comprising of an executive management board, a scientific board, an operations group and an external advisory board.
- WS2: Ex-clinic 'breathomic' systems- knowledge management, bioinformatics and biostatistics
- WS3: In-clinic 'breathomic' technologies- optimisation of sample collection and technical validation
- WS4: Clinical disease cohorts- 'breathomic' discovery and clinical validation
- WS5: Training
- WS6: Dissemination, Exploitation, and implementation
Breathomic Systems and Technologies

Analytical Pathway Key Interfaces

- Methodology and standardisation
- Knowledge management-
  - Bioresource and meta-data
  - Novel visualisation tools
  - Novel biostatistical approaches
Sampling and Measurement of the breath-ome

Standardised and reproducible breath sampling coupled to state of the art analytical tools to provide detailed chemical fingerprinting of the breath volatiles
Real-time measurements of breath composition
a) Acetone – simple marker for diabetes
b) Acetonitrile – marker for smokers
Off-line sampling
Array of Technology

Discovery

Point of Care
Diagnostic Development Unit

Sight, Smell and Feel of a Patient

Multi-spectral imager:
Measures patient's colour changes. Quicker but less detailed than hyper-spectral imager.

High definition infra-red imager:
Measures temperature changes, which can be sign of problems.

Hyper-spectral imager:
Picks up changes in colour of patient that could mean liver or kidney problems.

Mass spectrometer for breath analysis:
Looks at body's metabolism and detects bacteria.

Propac monitor:
Standard NHS machine that measures pulse, blood pressure and electrical activity of heart.

LCD monitors:
Show imaging data

Spirometer:
Measures breath volume, depth and speed, and picks up gases linked to infection.

Gas sampling instrument and capnograph:
Gauges exhaled and inhaled carbon dioxide.

Near infrared spectroscopy monitor:
Measures oxygen in body.

Transcutaneous oximetry monitor:
Measures oxygen and carbon dioxide in blood.

Supra-thoracic Doppler:
Ultrasound, measuring heart function.

Thoracic electrical bioimpedence monitor:
Shows how well heart and circulation working.

Courtesy of Daily Mail

UNIVERSITY OF LEICESTER
Clinical Programme

Two core clinical programs

- Acutely breathless patient
  - Phenotyping, biomarker discovery and replication in undifferentiated breathless patients.
  - Mapping of acute phase biomarkers to stable state disease.
- Lung cancer indicator detection [LUCID]
What are the key metabolites in breath associated with acute exacerbations of breathlessness due to:

- Airways disease (eosinophilic versus non-eosinophilic)
- Heart failure (+ BNP > 500 ng/ml)
- Community acquired pneumonia

How do acute phase metabolites map to stable state disease?
Training

- Capacity building of future experts in breathomics
- PhDs clinical and non-clinical (5 funded applications for others)
- MSc modules
- Intercalated BSc projects
- Courses for clinical, allied health professionals and scientists
WS6: Dissemination, Exploitation, Implementation
BIG Wins- IMPACT

1) **Clinicians**- with improved diagnostics and biomarkers,

2) **Patients**- by improved clinical decision making with near-patient, non-invasive technologies that are widely applicable,

3) **Health care providers**- decision making for optimising allocation of resources,

4) **Pharmaceutical industry**- 'breathomics' as an outcome in early phase development, stratification, companion diagnostic in the clinic,

5) **Platform technology industries**- improvements in the development of novel devices with clinical applications and the embedding this new molecular pathology in health care.
“Whiff of Death”

Exposed cadaver on sand

Buried cadaver in sterile soil
EMBER ---- *The sky is the limit!* : Exhaled Metabolites -> Breath Cloud

- Industry
  - SMEs
  - Pharma

- Analytical Chemistry

- Environmental Data
  - Environment
  - DDU in A&E CDU

- Big Data
  - Loughborough BRISSKit
  - l2b2/tranSMART
  - Biostatistics

- Big Cohorts
  - BRUs x 3
  - Acutely breathless
  - Stable state disease

- Track Record
  - Van Geest facility
  - LUCID NHS-SBRI DDU

- Expertise in Phenotyping

- Training and Development
  - PIs, Post Docs, PhD, MSc programs

- EMPATH
  - Driving national agenda quality pathology services