Stratified, personalised or P4 medicine: a new direction...

Tuesday 12 May 2015
Heartbeat Education Centre, Southampton General Hospital

Session 2

Approaches to the stratification of human disease
Cancer as a model for targeted diagnosis and treatment

Peter Johnson
Professor of Medical Oncology,
University of Southampton

Chief Clinician,
Cancer Research UK
Specific genetic mutations drive initiation and progression of cancers.
Cancer is driven by genetic changes

Frequency of mutations in colorectal cancers

100+ cancers combined show high frequency mutations

Uncommon mutations are probably incidental

Can understanding mutations help with prognosis and treatment?

Wood et al, Science Nov 2007
Some cancers are more mutated than others

The prevalence of mutations varies between tumour types

The mechanisms of transformation are reflected in the molecular footprint

6 possible base substitutions:

- C>A
- C>G
- C>T
- T>A
- T>C
- T>G

Each can have 4 different flanking nucleotides each side, giving 16 different motifs

Patterns of mutation across 96 motifs can be assigned to 21 mutational signatures
Different mutational signatures indicate varying pathogenesis

<table>
<thead>
<tr>
<th>Signature</th>
<th>Presence</th>
<th></th>
<th></th>
<th>Prevalence in cancer samples</th>
<th>Probable association</th>
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</thead>
<tbody>
<tr>
<td>Signature 1A</td>
<td>7</td>
<td></td>
<td></td>
<td>11.7%</td>
<td>Age</td>
</tr>
<tr>
<td>Signature 1B</td>
<td>19</td>
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<td></td>
<td>60.7%</td>
<td>Age</td>
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<tr>
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<tr>
<td>Signature 3</td>
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<td>9.9%</td>
<td>BRCA1/2 mutations</td>
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<tr>
<td>Signature 4</td>
<td>5</td>
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<td>12.1%</td>
<td>Smoking</td>
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<tr>
<td>Signature 5</td>
<td>9</td>
<td></td>
<td></td>
<td>14.4%</td>
<td></td>
</tr>
<tr>
<td>Signature 6</td>
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<td>DNA MMR deficiency</td>
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<td></td>
</tr>
<tr>
<td>Signature 9</td>
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<td></td>
<td>0.6%</td>
<td>Immunoglobulin gene hypermutation</td>
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<td>Pol ε mutations</td>
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<td>Signature 18</td>
<td>1</td>
<td></td>
<td></td>
<td>2.2%</td>
<td></td>
</tr>
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<td>Signature 19</td>
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<td>0.2%</td>
<td></td>
</tr>
<tr>
<td>Signature 20</td>
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<td></td>
</tr>
<tr>
<td>Signature 21</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td></td>
<td></td>
<td>13.6%</td>
<td></td>
</tr>
</tbody>
</table>

- Mutational signature present
- Total validated mutational signatures in a cancer type
- Total cancer types in which a signature is operative
Within histologic types we recognise molecular heterogeneity.
We have had some success in targeting the pathogenetic changes


Stratification shows differential effectiveness

Gefitinib no more effective than placebo overall

Gefitinib more effective than standard treatment if EGFR+

Gefitinib less effective than standard treatment if EGFR-


We are doing the experiments to see how well this approach will work.
Biomarker A: Drug A
Biomarker B: Drug B
Biomarker C: Drug C
Biomarker D: Drug D
Biomarker E: Drug E
Biomarker F: Drug F

NGS sequencing
• Upto 2000 NSCLC patients screened per year
• National screening to national trial
• 28 gene multiplexed NGS panel; detects mutations, deletions, CNV and DNA rearrangement
• Utilising DNA from routine FFPE biopsies

 MATRIX Lung Study
• 6 drugs, 14 stratified arms to begin with
• Phase 2a signal finding study
• Rolling protocol, capable of incorporating new arms
• Sponsored by CRCTU at Birmingham
• PI Professor Gary Middleton
• Recruit across 18 ECMC centres
However, genetic reductionism has its limits
Tumour evolution: immunoediting

Transformed

Tumor antigens

MICA/B
ULBP
(Human)

Rae-1
H60
(Mouse)

Danger*: uric acid,
ECM products

Carcinogens
Radiation
Chronic inflammation
Inherited
Viruses

Normal

Elimination
(Cancer Imnosurveillance)

Equilibrium

Escape

Cancer Immunoediting

Innate & Adaptive Immunity

IFNγ
Perforin
TRAIL

Genetic instability/
immune selection

CD8+

CD4+CD25+
Treg

Galectin-1
IDO

NK

MHC-I

NK

Protection

CD8

NK

CD4+CD25+

NK

Dunn, Old, Schreiber. Immunity Volume 21, Issue 2 2004 137–148
The cycle of cancer immunity

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells/ APCs)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (Immune and cancer cells)
A finely balanced system

- **Priming and activation**
  - CD28/B7.1
  - CD137/CD137L
  - OX40/OX40L
  - CD27/CD70
  - HVEM
  - GITR
  - IL-2
  - IL-12
  - CTLA4/B7.1
  - PD-L1/PD-1
  - PD-L1/B7.1
  - Prostaglandins

- **Cancer antigen presentation**
  - TNF-α
  - IL-1
  - IFN-α
  - CD40L/CD40
  - CDN
  - ATP
  - HMGB1
  - TLR
  - IL-10
  - IL-4
  - IL-13

- **Release of cancer cell antigens**
  - Immunogenic cell death
  - Tolerogenic cell death

- **Trafficking of T cells to tumors**
  - CX3CL1
  - CXCL9
  - CXCL10
  - CCL5

- **Infiltration of T cells into tumors**
  - LFA1/ICAM1
  - Selectins
  - VEGF
  - Endothelin B receptor

- **Recognition of cancer cells by T cells**
  - T cell receptor
  - Reduced pMHC on cancer cells

- **Killing of cancer cells**
  - IFN-γ
  - T cell granule content
    - PD-L1/PD-1
    - PD-L1/B7.1
    - Arginase
    -IDO
    - TGF-β
    - BTLA
    - TIM-3/phospholipids
    - VISTA
CTLA-4 and PD-1/L1 Checkpoint Blockade for Cancer Treatment

Priming phase (lymph node)

Effector phase (peripheral tissue)

T-cell migration

Combined checkpoint blockade

<table>
<thead>
<tr>
<th>Therapy, %</th>
<th>ORR</th>
<th>≥ 80% Tumor Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>7</td>
<td>&lt; 3</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>28</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>Combination (cohort 2)</td>
<td>53</td>
<td>41</td>
</tr>
</tbody>
</table>
Melanoma: Survival after ipilimumab compared to historical controls

Historical controls

- Phase II: 1278 patients in 42 cooperative group trials from 1975 to 2005
- Phase III: 3739 patients in 10 trials from 1999 to 2011
Dissecting cancer immunotherapy

Cancer mutanome

Adaptive immunity

Inflammatory environment
Summary

• Molecular definition of cancer is becoming routine
• Targeted therapy is increasingly effective..
• ..but challenged by heterogeneity and evolution
• Immunotherapy will require a further level of sophistication
• We need to develop the infrastructure to deliver this across our healthcare system
THE INAUGURAL INTERNATIONAL CANCER IMMUNOTHERAPY CONFERENCE
The Reference Meeting for Scientists, Clinicians, Regulators, Drug Developers, and Patient Advocates

TRANSLATING SCIENCE INTO SURVIVAL
September 16-19, 2015
Sheraton New York Times Square Hotel
New York City

Abstract Submission Deadline: June 10, 2015
Advance Registration Deadline: July 27, 2015

The Cancer Research Institute (CRI), the Association for Cancer Immunotherapy (CIMT), the European Academy of Tumor Immunology (EATI), and the American Association for Cancer Research (AACR) are proud to join forces to sponsor the first International Cancer Immunotherapy Conference. This collaborative meeting will be held every year, in lieu of each organization's individual meeting, and will alternate between the United States and Europe. We believe that by combining our efforts we can be more effective and efficient in disseminating the latest cutting-edge information.

To learn more, go to
CancerImmunotherapyConference.org
#icon15

PRESENTED BY

Cancer Research Institute
CIMT
EATI
American Association for Cancer Research

www.southampton.ac.uk/youreit
Adoption of personalised medicine for the therapeutic and diagnostic industries

Jonathan Knowles

Southampton General Hospital    12th May 2015
Precision medicine: New and Old!

The past 1000s of years
Diagnosis and treatment based on what could be seen, smelled, tasted, palpated or intuited (anatomical)

The last 10-100 years (clinical insight)
Diagnosis and treatment based on increasing knowledge about biochemistry and cellular processes (cellular)

Today (generalised guidelines)
Diagnosis and treatment increasingly based on rapidly growing insights into molecular biology, genetics and molecular imaging. (molecules, genes and pathways)

Tomorrow (back to personalised)
Patient management based on individualized computer prediction of optimal therapies for individual patients.
Response to V Raf inhibition in 15 weeks followed by resistance

B = 15 weeks Rx (Zelboraf®)
C = 23 weeks Rx and emergence of MEK1C1215 mutant (Wagle et al. (2011))
Non-responders to Oncology Therapeutics Are Highly Prevalent and Very Costly

Drug Screening on Leukemia Patient samples: FIMM, Helsinki

Drug sensitivity and resistance testing (DSRT ex vivo)

Individual cancer samples & clinical data

Integrated cancer drug sensitivity and molecular profile database

Genomics & Molecular profiling (in vivo)

Genomics & cell signalling

Compendia of responses to drugs

Driver signals and pathways for cancer

Patient-specific treatment recommendations

Patterns of response highlighting MOA, new drugs and biomarkers
Innovating medicine is difficult and often not comfortable!

“the precursor of chemical pharmacology and therapeutics and the most original medical thinker of the sixteenth century.”

Studied alchemy, surgery, and medicine at the University of Basel

Forced to leave the city hurriedly after trouble over his studies in “necromancy”

Returned to Basel to take a professorship of physics, medicine, and surgery offered to him at the insistence of Erasmus.

The medical faculty were infuriated at their authority being undermined and he was forced to leave Basel once again.

Auroleus Phillipus Theostratus Bombastus von Hohenheim 1493-1541
Caris Molecular Intelligence: (CMI) matches patient-specific biomarkers to potential therapies to help doctors individualize cancer treatment

**Sophisticated Tumor Interrogation & Analysis**

- Microdissection of tumor samples by pathologist
- Polymerase chain reaction (PCR) and next-generation sequencing (NGS) - identify mutations
- Fluorescence (FISH) and chromogenic (CISH) in situ hybridization - detect gene rearrangements and gene copy number variations
- Immunohistochemistry (IHC) - determines a biomarker’s level of protein expression
- Sanger Sequencing, Pyro Sequencing, Fragment Analysis

**Extensive Clinical Literature Assessment**

- Maintain an up-to-date repository of the world’s most relevant clinical literature
- Caris has reviewed over 120,000 clinical literature publications
- Creates recommendations based on the strength of clinical evidence supporting associations between biomarkers and treatments
- Performed by disease-specific clinical advisory boards and a team of Ph.D. scientists, oncologists, and pathologists
- Most relevant evidence is assembled into each MI Profile report

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**MI PROFILE**

**FINAL REPORT**

**PATIENT**

- Name: John Doe
- Date of Birth: 12/24/1959
- Sex: Female
- Race: Caucasian

**SPECIMEN INFORMATION**

- Primary Tumor Site: Lung, NSCLC
- Molecular Mass: 120,000
- Inclusion: COL20, OCT-9, 2014
- Completion of Testing: 10/9/2014

**ORDERED BY**

- Test Ordering Physician: Dr. Smith
- Physician’s Office: Texas Lung and Cancer Center
- Location: Dallas, TX 75201
- Phone: 1-800-555-5555

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**THERAPIES WITH POTENTIAL BENEFIT (PAGE 5)**

<table>
<thead>
<tr>
<th>Therapies</th>
<th>Potential Benefit</th>
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<td>ICI therapy</td>
<td>NSCLC</td>
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<tr>
<td>Targeted therapy</td>
<td>ALK</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>ALK</td>
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</tbody>
</table>

**THERAPIES WITH POTENTIAL LACK OF BENEFIT (PAGE 6)**

<table>
<thead>
<tr>
<th>Therapies</th>
<th>Potential Lack of Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>NSCLC</td>
</tr>
</tbody>
</table>

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*Indicates Clinical Trial Opportunity - 12 Chemotherapy Trials + 4 Targeted Therapy Trials (see Order PathConnect℠ program for details)
Caris Molecular intelligence:
Companion diagnostics & NCCN-Guidelines require a multi-technology approach to connect biomarkers to medicines
Caris Clinical Research Activities

Leadership in Oncology Research

Collaboration with Vector Oncology Solutions
- Preparations to launch 6 prospective observational studies over 12 months
- For patients treated with therapies consistent with CMI recommendation
- Track therapeutic response and outcomes for patients with the following tumor types: Sarcoma, Pancreatic, Breast, Lung, Ovarian and Rare tumors

Research Case Study: CMI for Ovarian Cancer
- Median survival was 2.5 years longer after disease recurrence
- Results published at ASCO 2014

Caris Prospective Observational Study
- Multi-center, observational outcomes database
- Launched December 2009
- Collects data on the demographics, presentation, diagnosis, treatment, resource use, and outcomes of eligible patients

<table>
<thead>
<tr>
<th>Year</th>
<th>Abstracts</th>
<th>Presentations</th>
<th>Manuscripts</th>
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<td>2012</td>
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<td>3</td>
</tr>
<tr>
<td>2013</td>
<td>16</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>2014</td>
<td>49</td>
<td>3</td>
<td>14</td>
</tr>
</tbody>
</table>
Tumor profiling market leadership and unmatched utility

- #1 in Actionable FDA approved Drug / Target Associations (56)
- #1 in Patient Profiles Ordered (~70,000)
- #1 in Medical Oncologist Preference (7,000+)
- #1 in Global Distribution (60+ countries)
- #1 in Clinical Revenue
- 4 U.S. and 4 foreign issued patents (China, Singapore, South Africa, South Korea);
  - 71 patent applications pending

First Mover and Industry Leader in Comprehensive Tumor Profiling

5+ Years of Outcome Data Demonstrating Unmatched Clinical Utility

Evidence of clinical utility for CMI drawn from Caris Observational Registry¹

- Retrospectively assigned patients into groups based on whether CMI Followed or Did Not Follow (~500 patients in each group)
- Use of CMI-selected medicines extend life of terminally-ill patients by 274 days (978 vs. 704 days)
- Clinically actionable results found in 95% of MI Profile cases
- Average 25 relevant results per patient
- Inferred reduction in side-effects as CMI Followed patients received 3.2 therapies vs. 4.2 in the Did Not Follow group

¹ Manuscript in preparation
Topological Oligonucleotide Profiling (TOP™)

The complexity of the biological systems driving cells increases by orders of magnitude at each step of transcription and translation.

DNA → mRNA → Proteins

- 2*10⁴ genes
- 10⁵ transcripts
- 10⁶ isoforms

Topology of Protein Complexes

Native State

10⁷ - 10¹⁰ ???

Epigenetic alterations

Transcription factors and promoters

miRs

RISC
Immunocore - engineered T cell receptors

Antibodies target cell surface proteins whilst TCRs access both cell surface and intracellular proteins.
Overview of lead clinical programme - IMCgp100

**Target** - gp100_{280-288} peptide presented by HLA-A2
- IMCgp100 (HLA-A2) addresses ~48% of western market
- ~85% market accessible with additional HLAs (abbreviated development pathway)

**Indications** - Melanoma and glioma, both treatment and adjunct settings

**Manufacturing** - ~1,200 vials from 45L run
- 4 year shelf life so far

**Regulatory status** - CTA/IND approved by MHRA/FDA

**Clinical status**
- Phase 0 complete
- Phase I complete (MTD 600ng/Kg or 50µg)
- Phase IIa started Q4 2013

TCR affinity increased 3,500,000 fold from 85µM to 24 pM

- $K_D \sim 24 \text{ pM}$
- Residence $T_{1/2}$ ~24 hrs at 37°C

Plasma clearance $T_{1/2}$ ~7 hours in humans

- $K_D \text{ nM}$
- Residence $T_{1/2}$ mins
ImmTAC re-directed killing is exquisitely specific

Time-lapse microscopy - 11 hour timeframe

Melanoma targets
“Innocent” bystander cells
T Cells
0.05nM MAGE
specific ImmTAC
Redefinition of Alzheimer’s disease

- Multiple mechanisms may be responsible
- Well characterized patients essential (sleep, activity ...)

- Vascular
- Inflammation
- Synaptic malfunction
- Tau and Amyloid
- Insulin insensitivity (diabetes)
Summary

• Personalised/Precision Health Care is essential for further progress in medicine.

• Strive to redefine human disease in different functional ways.

• Clinical data generation must move on from classical blinded studies to the new/old paradigm of ongoing observational studies with “big data”.

• Change the success metrics of health care to support pilot studies to show Cost Effectiveness and patient benefit.

• Reward effectiveness rather that treatments/procedures
The stratification of human disease across the lifecourse

Cyrus Cooper  FMedSci

Professor of Rheumatology and Director, MRC Lifecourse Epidemiology Unit, University of Southampton; and

Professor of Musculoskeletal Science, University of Oxford; UK
The stratification of human disease across the lifecourse

- MRC Lifecourse Epidemiology Unit
- Development and osteoporotic fracture
  - Growth in utero, adult bone mass, strength and fracture
  - Observational studies of maternal vitamin D status and childhood bone mass
  - Epigenetic mechanisms implicating vitamin D signalling
  - Vitamin D supplementation in pregnancy: towards stratified public health?
- Stratified approaches to treatment in other musculoskeletal disorders

MRC Lifecourse Epidemiology Unit, University of Southampton

Institute of Musculoskeletal Science, University of Oxford
MRC Lifecourse Epidemiology Unit 2015-2020

Observations:
Observational epidemiology
Determinants of health outcomes and health behaviours

Interventions:
Pre-conception, during pregnancy and in adult life
Lifestyle
Behavioural
Pharmacological

Mechanisms:
Systems biology
Health psychology

Lifecourse outcomes:
Musculoskeletal
Metabolic
All cause mortality
Developmental origins of adult disease

Death rates from coronary heart disease among 15,726 men and women in Hertfordshire according to birth weight

David Barker 1936-2013
### Impact of Osteoporosis-Related Fractures in Europe

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<tr>
<th></th>
<th>Hip</th>
<th>Spine</th>
<th>Wrist</th>
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<tbody>
<tr>
<td><strong>Lifetime risk (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>14</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Men</td>
<td>3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td><strong>Cases/yr</strong></td>
<td>615k</td>
<td>516m</td>
<td>560k</td>
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<tr>
<td><strong>Hospitalisation (%)</strong></td>
<td>100</td>
<td>2-5</td>
<td>5</td>
</tr>
<tr>
<td><strong>Relative survival</strong></td>
<td>0.83</td>
<td>0.82</td>
<td>1.00</td>
</tr>
</tbody>
</table>

All sites combined: n=3.5m; cost ~ 39 billion Euros

_Hernlund E et al Arch Osteop 2013; 8(1-2): 136_
The Hertfordshire Cohort Study

<table>
<thead>
<tr>
<th>Weight at Birth</th>
<th>Weight 1st Year</th>
<th>Food</th>
<th>No. of Visits</th>
<th>Condition, and Remarks of Health Visitor</th>
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</thead>
<tbody>
<tr>
<td>8 1/2 lbs</td>
<td>24 1/2 lbs</td>
<td>13</td>
<td>11</td>
<td>Y</td>
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<tr>
<td>Healthy &amp; well developed. Buckland School. Born to S.</td>
<td>7 lbs</td>
<td>18 1/2 lbs</td>
<td>12</td>
<td>Y</td>
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<tr>
<td>Moved to Berry Green, St. Itham. Had measles, pneumonia.</td>
<td>8 1/2 lbs</td>
<td>20 lbs</td>
<td>11</td>
<td>Y</td>
</tr>
<tr>
<td>Healthy &amp; normal. Buckland School. Born.</td>
<td>8 1/2 lbs</td>
<td>22 lbs</td>
<td>9</td>
<td>Y</td>
</tr>
</tbody>
</table>
Birthweight, bone mass (DXA), geometry (HSA), architecture and adult bone strength (HRpQCT)

Bone strength

p=0.01 for trend

Thirds of birth weight in women

M&F<=112oz  M&F-128oz  M&F>128oz

Bone strength

p=0.005 for trend

Thirds of weight at 1yr in women

M<=344;F<=324oz  M-373;F-352oz  M>373;F>352oz

Oliver H et al  Bone 2007; 41: 400-405

Javaid MK et al  J Bone Min Res 2006; 21: 508-12
Javaid MK et al  J Bone Min Res 2011; 26: 1802-7
Tandon N et al  Osteoporosis Int 2012; 23: 2447-59
Birthweight and Adult Bone Mass

Pleiotrophic effect of genes governing birthweight and bone mass?

- 4,008 white, female twins; age 47.5 yrs

- Intra pair differences in birthweight and BMC (adjusted for height/weight)

<table>
<thead>
<tr>
<th>Bone Site</th>
<th>MZ</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Lumbar spine</td>
<td>MZ</td>
<td>0.02</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>MZ</td>
<td>0.04</td>
</tr>
<tr>
<td>Forearm</td>
<td>MZ</td>
<td>0.04</td>
</tr>
</tbody>
</table>

FTO gene SNPs

Antoniades et al. Rheumatol 2003;42:791-796
Southampton Women’s Survey

12,500 non-pregnant Southampton women aged 20-34 years interviewed about diet, body composition, physical activity, social circumstances & lifestyle. Buccal and blood samples taken.

Subsequent pregnancies studied (n=3,160). Ultrasound scans at 11, 19 & 34 weeks. Interviews at 11 & 34 weeks

Maternal blood samples
Paternal buccal & blood samples
Maternal grandparents’ buccal samples

Neonatal anthropometry. Cord bloods

Children followed-up at 6, 12, 24 and 36 months; And at 4, 6, 8 & 10 years
Maternal vitamin D status and childhood bone mass

Princess Anne Hospital Cohort Study, Southampton; Age 9yrs
Southampton Women’s Survey; Age 6yrs

Maternal 25(OH) vitamin D (µg/L)

Javaid MK et al Lancet 2006; 367: 36-43
Moon R et al Osteop Int 2015; 26: 1449-51
Distal femur splaying index = cross-sectional area (cm²) ÷ length (cm)

Mahon P et al  J Bone Miner Res 2010; 25: 14-19
Ioannou C et al  J Clin Endocrinol Metab 2012; 97: 2070-7
Yaqub M et al  Fetal Diag Ther 2013; e-pub
Vitamin D Supplementation in Pregnancy: The MAVIDOS Trial

**Booking (11/40)**

MAVIDOS Sub-studies:
- Bone turnover in mother/cord blood
- Maternal DXA
- Placental/cord epigenetic studies
- Maternal VDR genotyping

**Pregnancies at nuchal US scan**

Check 25D ALP, Ca, Albumin

**Randomisation**

- >100 nmol/l: Not eligible
- 25-100 nmol/l: n=456 each arm

**14/40**

D₃ 1000iu/d

**Placebo**

**36/40**

Repeat 25D ALP, Ca, albumin, glucose

**Birth**

Anthropometry, DXA

**4 years**

Anthropometry, DXA

*World Cong Osteop (2015)*
Epigenetic mechanisms in vitamin D signalling

DNA methylation

The two main components of the epigenetic code

DNA methylation: Methyl marks added to certain DNA bases repress gene activity.

Histone modification: A combination of different molecules can attach to the ‘tails’ of proteins called histones. These alter the activity of the DNA wrapped around them.

Harvey NC et al. J Bone Min Res 2014; 29: 600-7
Free 25(OH)D and RXRA methylation

\[ \beta = -3.29 \]
\[ p = 0.03 \]

Harvey N et al. J Bone Min Res 2014; 29: 600-7
Conclusions

• Stratification can be extended to public health interventions

  • Maternal antenatal vitamin D supplementation with 1000 IU cholecalciferol daily resulted in higher offspring bone mass in winter births

  • Summer to winter decline in maternal vitamin D status abolished with supplementation

  • 1000 IU cholecalciferol daily resulted in vitamin D repletion in over 80% of women

  • Epigenetic profiles may predict responsiveness to vitamin D supplementation during pregnancy

  • A stratified approach to vitamin D supplementation during pregnancy may be warranted

• Stratified approaches to intervention should be considered throughout the lifecourse
With thanks to all at Southampton and Oxford!