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OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.
Changes in blood, detected in urine

Youhe Gao

Chinese Academy of Medical Sciences

University of Oxford 2014-4-15
What is biomarker?
My Definition

• Biomarker is the measurable change associated with a physiological or pathophysiological process.
Biomarker = Change
In Blood

Homeostasis mechanisms
= minimal changes
= less biomarkers
In Urine

Accumulate all the changes =
Lots of biomarkers
Change removal

Several organs are important in removing waste from the body.

The **lungs** remove carbon dioxide.

The **skin** provides a surface for small amounts of water and salt to move out of the body.

The **liver** converts excess protein into **urea**.

The **kidneys** remove **unwanted** substances such as urea, excess water and salt.
Changes of proteins induced by anticoagulants can be more sensitively detected in urine rather than plasma.
Changes of protein induced by anticoagulants

**Changes**

- Heparin
- 27 proteins in urine
- 3 proteins in plasma

- Argatrabon
- 61 proteins in urine
- 1 protein in plasma

Clotting times increased

Validation of changes in protein levels
Advantages of Urine Proteome

- Non-invasive
- Simpler than plasma
- Reflects changes of plasma
- Close to kidney and prostate
Urine Proteome is Informative

• Up to published result in 2011, 2300 proteins identified totally
• 4000-5000 with current technology
Low Background

• Actually low protein concentration is better for biomarker discovery

• Low constitutional component is better for revealing the changes
### TABLE III. Frequency of Aberrant Methylation in Urine and Plasma DNA

<table>
<thead>
<tr>
<th></th>
<th>GSTP1</th>
<th>RASSF2</th>
<th>HIST1H4K</th>
<th>TFAP2E</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urine</td>
<td>Plasma</td>
<td>Urine</td>
<td>Plasma</td>
</tr>
<tr>
<td><strong>Positives (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young asymptomatic males</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy negative</td>
<td>6%</td>
<td>20%</td>
<td>37%</td>
<td>2%</td>
</tr>
<tr>
<td>All stages PCa</td>
<td>59%</td>
<td>31%</td>
<td>59%</td>
<td>31%</td>
</tr>
<tr>
<td>T1 (n = 47 U, 46 P)</td>
<td>83%</td>
<td>37%</td>
<td>82%</td>
<td>16%</td>
</tr>
<tr>
<td>T2 (n = 28 U, 25 P)</td>
<td>71%</td>
<td>32%</td>
<td>82%</td>
<td>16%</td>
</tr>
<tr>
<td>T3 (n = 7)</td>
<td>100%</td>
<td>71%</td>
<td>100%</td>
<td>57%</td>
</tr>
<tr>
<td>T4 (n = 2)</td>
<td>100%</td>
<td>50%</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td><strong>Median DNA (range), ng/ml</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young asymptomatic males</td>
<td>0 (0–0.07)</td>
<td>0 (0–0.00)</td>
<td>0 (0–0.09)</td>
<td>0 (0–0.00)</td>
</tr>
<tr>
<td>Biopsy negative</td>
<td>0.001 (0–0.15)</td>
<td>0 (0–0.02)</td>
<td>0.007 (0–0.70)</td>
<td>0 (0–0.04)</td>
</tr>
<tr>
<td>All stages PCa</td>
<td>0.008 (0–91.18)</td>
<td>0 (0–0.27)</td>
<td>0.022 (0–9.91)</td>
<td>0 (0–0.09)</td>
</tr>
<tr>
<td>T1 (n = 47 U, 46 P)</td>
<td>0.006 (0–91.80)</td>
<td>0 (0–0.18)</td>
<td>0 (0–0.05)</td>
<td>0 (0–0.09)</td>
</tr>
<tr>
<td>T2 (n = 28 U, 25 P)</td>
<td>0.008 (0–8.88)</td>
<td>0 (0–0.05)</td>
<td>0 (0–0.05)</td>
<td>0 (0–0.09)</td>
</tr>
<tr>
<td>T3 (n = 7)</td>
<td>0.029 (0.001–14.37)</td>
<td>0.001 (0–0.27)</td>
<td>n.a. (0–0.14)</td>
<td>n.a. (0–0.00)</td>
</tr>
<tr>
<td>T4 (n = 2)</td>
<td>n.a. (0.01–0.14)</td>
<td>n.a. (0–0.14)</td>
<td>n.a. (0–0.14)</td>
<td>n.a. (0–0.14)</td>
</tr>
</tbody>
</table>
Not just within urinary tract

- This is the first study to demonstrate that analysis of urinary MMPs may be useful in determining disease status in a variety of human cancers, both within and outside of the urinary tract.

- MMP:  
  - 72KD  
  - 92KD  
  - >150KD

(CANCER RESEARCH 58, 1395-1399. 1998)
Plasma and Urinary Desmososine as biomarkers for COPD

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Demographic and desmososine data for group 2 consisting of healthy volunteers and patients with an exacerbation of chronic obstructive pulmonary disease (COPD)</th>
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</thead>
<tbody>
<tr>
<td>Sample type</td>
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<tr>
<td></td>
<td>Urine and sputum</td>
</tr>
<tr>
<td></td>
<td>Patients with ‘during an exacerbation’ COPD</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
</tr>
<tr>
<td></td>
<td>Patients with ‘during an exacerbation’ COPD</td>
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<tr>
<td>Group</td>
<td>Healthy volunteers (HV2a)</td>
</tr>
<tr>
<td>Number of participants</td>
<td>62</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>13/41/8/0</td>
</tr>
<tr>
<td>Smoking status (smokers/e-smokers/non-smokers/unknown)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>22 (21—45)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>25±4</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>103±13</td>
</tr>
<tr>
<td>uDES (ng/mg creatinine)</td>
<td>8 (6—10)</td>
</tr>
<tr>
<td>bDES (ng/ml)</td>
<td>—</td>
</tr>
</tbody>
</table>

Thorax 2012 67: 502-508
Urine of brain tumor patients contains significantly higher levels of MMP-2, MMP-9, and MMP-9/NGAL compared with control samples.


©2008 by American Association for Cancer Research
The loss of urinary MMPs after resection of a brain tumor, demonstrating that tumor presence is related to increased urinary MMP activity and removal of that tumor correlates with subsequent clearing of detectable urinary MMP activity.

# Urine/Blood in Biomarker Studies

Up to 2013-5-29

<table>
<thead>
<tr>
<th>Year</th>
<th>Count</th>
<th>Year</th>
<th>Count</th>
<th>Urine/Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>3436</td>
<td>2013</td>
<td>302</td>
<td>8.79%</td>
</tr>
<tr>
<td>2012</td>
<td>20759</td>
<td>2012</td>
<td>1401</td>
<td>6.75%</td>
</tr>
<tr>
<td>2011</td>
<td>19996</td>
<td>2011</td>
<td>1369</td>
<td>6.85%</td>
</tr>
<tr>
<td>2010</td>
<td>19097</td>
<td>2010</td>
<td>1288</td>
<td>6.74%</td>
</tr>
<tr>
<td>2009</td>
<td>17733</td>
<td>2009</td>
<td>1056</td>
<td>5.95%</td>
</tr>
<tr>
<td>2008</td>
<td>16993</td>
<td>2008</td>
<td>1057</td>
<td>6.22%</td>
</tr>
<tr>
<td>2007</td>
<td>16509</td>
<td>2007</td>
<td>952</td>
<td>5.77%</td>
</tr>
<tr>
<td>2006</td>
<td>15186</td>
<td>2006</td>
<td>918</td>
<td>6.05%</td>
</tr>
<tr>
<td>2005</td>
<td>15389</td>
<td>2005</td>
<td>860</td>
<td>5.59%</td>
</tr>
<tr>
<td>2004</td>
<td>14208</td>
<td>2004</td>
<td>767</td>
<td>5.40%</td>
</tr>
<tr>
<td>2003</td>
<td>13417</td>
<td>2003</td>
<td>696</td>
<td>5.19%</td>
</tr>
</tbody>
</table>
Urinary Protein Biomarker Database

- [http://122.70.220.102/biomarker](http://122.70.220.102/biomarker)
- Manually curated in the lab
- Around 450 papers at mid 2013

Mol Cell Proteomics 2011 10: M111.010975
Disadvantages as Biomarker Source

- Big variation
- Need more cases to validate
Way to solve the problem

- More sample
- Higher throughput MS
- More analyzing power
Problem with samples

- Very diluted
- Protein degradation
Possible ways to save

- Precipitate: organic solvent consuming
- Freeze dry: energy and labor consuming
- Extraction: cost
- Not suitable for large numbers of samples
Urimem
Urimem

Urinary proteins
dried on a filter and
stored in vacuum
Urinary Proteins on Membrane
Why is that important?
Changed the face of medicine

- “Hard as it is to believe today, a single concept developed by Dr. Henry Plummer (1874 – 1936) at the beginning of the 20th century changed the face of medicine.”

http://www.mayoclinic.org/tradition-heritage/medical-records.html
Changed the face of medicine

• The concept was a centralized medical record, stored in a single repository, and capable of traveling with the patient. (1907)

• Now
  – paperless
  – filmless
  – chartless

http://www.mayoclinic.org/tradition-heritage/medical-records.html
Biobanking: foundation of personalized medicine

- Blood
- Urine
- Skin cells
- Organ
- Tissue
- other things taken from a body

Hewitt RE. Curr Opin Oncol. 2011 23(1):112-9
Biobanking’s future:
Long-term at room temperature
Can we decode urine proteome?

• Not yet, especially in population
• But having large number of samples will help
• Need more researchers
We need control

- What is the **normal variation** of healthy human urine proteome?
Risk You Don’t Want to Take

You
• Discovery and validation in Blood
• Hard and expensive
• Patent

Others
• Take your clue, validate in urine
• Easy and Cheap
• New patent
Urine smells good!
It tastes even better!
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• Liu Liu

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