About OMICS International

OMICS International through its Open Access Initiative is committed to make genuine and reliable contributions to the scientific community. OMICS International hosts over 700 leading-edge peer-reviewed Open Access Journals and organizes over 1000+ International Conferences annually all over the world. OMICS International journals have over 3 million readers and the fame and success of the same can be attributed to the strong editorial board which contains over 50000 About OMICS International eminent personalities that ensure a rapid, quality and quick review process. OMICS International signed an agreement with more than 1000 International Societies to make healthcare information Open Access. OMICS International Conferences make the perfect platform for global networking as it brings together renowned speakers and scientists across the globe to a most exciting and memorable scientific event filled with much enlightening interactive sessions, world class exhibitions and poster presentations.

www.conferenceseries.com
Biomarker Discovery and Validation for Major Depressive Disorder (MDD)

Alexander M. Buko PhD
VP Business and Product Development
Over 12 years of growth and discovery

- Over 12 years of growth
- ~ 3 years in USA (Boston)
- Unique metabolic data based upon CE-MS platform
- Proprietary data analysis software
- Large metabolomic data library of over 1600 compounds
- Accurate quantitation profiling on over 400 metabolites
- Over 500 projects a year (2014)

One of the largest metabolomics research center (>50 MS systems)
Pipeline to Discovery/Validation

The Process
- SOP
- Validation
- QC
- Quantitative
- Internal standards
- Documentation
- Algorithm generation
- Statistical analysis
- PCA, OPLS-DA, HCA
- Diagnostic plan

Samples
- Documentation
- SOP
- Sufficient group size
- Proper control groups
- Clinical data
HMT Biomarker Process

- **Profiling** – Significant changes within limited number of samples and controls using high performance platform
- **Metabolite Identification** – Validated reference material
- **Validation** – Using larger number of samples to account for natural and biological variation to validate previously identified metabolites – working with other omic and phenotype data...
- **Biology** – Connection between the validated metabolite biomarkers and their biological processes or pathways
- **Clinical plan** – How such biomarker would be used in field
  - Type 0: disease progression, history, outcome
  - Type 1: therapeutic effect or intervention
  - Type 2: Surrogate: clinical end point
HMT Biomarker Pipeline

Target Disease

DISCOVERY
Select candidate BMs in small-scale study

VERIFICATION
Begin to assess specificity of candidates

VALIDATION
Establish sensitivity and specificity

CLINICAL ASSAY DEVELOPMENT
Assay optimization

Central Nervous System disease (CNS)

Depression
2008-
PCT/JP2010/063713

Enzyme Assay (on going) etc.

Chronic pain
2010-

Metabolic disease

Non-alcoholic steatohepatitis (NASH)
2009-
PCT/JP2011/059813

Diabetic nephropathy
2008-
PCT/JP2011/060178

Cancer

Colorectal cancer
2009-
特開2011-106994

Target Disease

Depression
2008-
PCT/JP2010/063713

Enzyme Assay (on going) etc.

Chronic pain
2010-

Non-alcoholic steatohepatitis (NASH)
2009-
PCT/JP2011/059813

Diabetic nephropathy
2008-
PCT/JP2011/060178

Colorectal cancer
2009-
特開2011-106994

Central Nervous System disease (CNS)

Depression
2008-
PCT/JP2010/063713

Enzyme Assay (on going) etc.

Chronic pain
2010-

Metabolic disease

Non-alcoholic steatohepatitis (NASH)
2009-
PCT/JP2011/059813

Diabetic nephropathy
2008-
PCT/JP2011/060178

Cancer

Colorectal cancer
2009-
特開2011-106994

Target Disease

Depression
2008-
PCT/JP2010/063713

Enzyme Assay (on going) etc.

Chronic pain
2010-

Non-alcoholic steatohepatitis (NASH)
2009-
PCT/JP2011/059813

Diabetic nephropathy
2008-
PCT/JP2011/060178

Colorectal cancer
2009-
特開2011-106994
EDTA-treated plasma was collected by vacuum blood tubes.

Plasma was prepared within 2 hours, and stored at -80 degree Celsius.

Metabolites were extracted using (H₂O:MeOH:CHCl₃).

Metabolites in the aqueous layer were analyzed by capillary electrophoresis-time-of-flight mass spectrometry system (CE-TOFMS: Agilent) by anion (negative) and cation (positive) modes.

Yielded plasma metabolome data include 538 metabolites.

Metabolite levels were compared across patient cohorts.
Early Discovery

- Hospital/IRB: National Center of Neurology and Psychiatry, JAPAN (NCNP)
- Diagnosis: DSM-IV-TR. SCID. Depression scale was estimated by the CES-D.
- Non-MDD group: Subjects answered a newspaper advertisement.
- All subjects are Asians living in Japan (mainly in Tokyo).
- CES-D: Center for Epidemiologic Studies Depression Scale (a simple questionnaire, 18>MDD for Japanese). This score is used to be reference to diagnose MDD.

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>Adjustment Disorder</th>
<th>MDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>31</td>
<td>7</td>
<td>34</td>
</tr>
<tr>
<td>Age</td>
<td>37.8 (20-63)</td>
<td>49.4 (27-78)</td>
<td>38.9 (20-70)</td>
</tr>
<tr>
<td>Gender</td>
<td>M 15, F 16</td>
<td>M 2, F 5</td>
<td>M 14, F 20</td>
</tr>
<tr>
<td>BMI</td>
<td>21.8 (16.6-30.4)</td>
<td>23.7 (18.7-33.3)</td>
<td>22.9 (18.6-31.2)</td>
</tr>
<tr>
<td>CES-D (Score)</td>
<td>7.7 (0-17)</td>
<td>21.6 (13-34)</td>
<td>31.6 (8-50)</td>
</tr>
</tbody>
</table>
Promising Results

Plasma Biomarker Concentration (µM)

P = 4.6 \times 10^{-8}

Not significant

Non-MDD control (n=31)

MDD (n=34)

Adjustment disorder (n=7)

Phosphoethanolamine (PEA)

Reduction (57%) in median value

No significant difference b/w AD & Ctrl

“Outliers” in whisker plot are “out of season” patients
Phosphoethanolamine (PEA)
Molecular formula: $\text{C}_2\text{H}_8\text{NO}_4\text{P}$
Exact mass: 141.019097

Receiver operator characteristic (ROC) curve for biomarkers observed in 72 plasma samples
(34 MDD, 38 non-MDD individuals)

Sensitivity: 82%, Specificity: 95%

AUC = 0.87 ($P < 0.0001$)
95% CI: (0.78, 0.96)
Plasma PEA level correlates significantly with the popular depression rating scale.

Subjects >18 in CES-D are depressed in Japanese population

$R = -0.433 \ (P = 0.0001)$
Correlates with HAMD-17 Score

The 17-item Hamilton Rating Scale for Depression (HAMD-17)
Correlates with Remission

Plasma EAP is strikingly decreased in MDD patients.
Clinical Features

- Correlation with HAMD-17 and CES-D good
- PEA levels restored with remission
  - Medication can be reduced when levels rebound over 1.8 uM
- Depression with high PEA suggests other diagnoses
- In Bipolar Disease, PEA is low when depressed, high when manic
Assay Transfer

- Initial Discovery and early validation
- CE-MS advance scan – relative data
- CE-MS QQQ – quantitative data
- IC-FLD
In Clinical Validation (> 1,100 tests)

- Expand comparisons to other disorders (PTSD)
- Exercise
- Circadian Rhythm
- Alcohol
- Eating, Smoking
- Drug use
- Other nationalities
ROC Improves – Onto Larger Studies

**Large Scale Validation studies (2015-)**

- Toyoko-Keiai Hospital of St. Marianna Assoc.
- Shinjuku Mental Clinic

Initial Large scale validation study was done in the Dr. Kawamura’s clinic (formally designated as “Kawamura Clinic for General Practice, Gyokikai Medical Corporation”).

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI-II &gt; 10</td>
<td>73.3</td>
<td>84.4</td>
</tr>
<tr>
<td>BDI-II &gt; 18</td>
<td>40</td>
<td>100</td>
</tr>
<tr>
<td>PHQ-9</td>
<td>76</td>
<td>81</td>
</tr>
<tr>
<td>PHQ-2</td>
<td>76</td>
<td>82</td>
</tr>
<tr>
<td>CED-D &gt; 16</td>
<td>86.7</td>
<td>76.6</td>
</tr>
<tr>
<td>CES-D &gt; 21</td>
<td>73</td>
<td>96.1</td>
</tr>
<tr>
<td>PEA &lt; 1.50 uM</td>
<td><strong>94.4</strong></td>
<td><strong>92.8</strong></td>
</tr>
</tbody>
</table>

% finds MDD | % Hit is MDD
Diagnostics Plan

Patients with Depressive Episode

- Schizophrenia
- Bipolar (manic)
- Bipolar (depressive)
- Major depressive disorder (drug-effective)
- Major depressive disorder (remission)
- Schizoaffective disorder
- Healthy
- Anxiety disorder
- Adjustment disorder
- Dysthymic disorder
- PTSD
- Developmental disorder
- Personality disorder

1.5μM < PEA

1.5μM > PEA

1.43-1.57 μM
Effect of SSRI and SNRI Treatment

- Studies showed imbalances in dopamine, norepinephrine, and serotonin in patients with depression. An SSRI and an SNRI both affect absorption of serotonin, but an SNRI also affects noradrenaline levels in the brain.
- SSRI: Selective Serotonin Reuptake Inhibitors (Paxil, Prozac, Zoloft)
- SNRI: Serotonin Noradrenaline Reuptake Inhibitors (Effexor, Pristiq)

Observations

- With **SSRI treatment**, PEA decreases. Perhaps **anxiety** is an excited brain, SSRI is effective with anxiety. Lower PEA may be calming down brain.

- With **SNRI treatment**, PEA increases. Perhaps **depression** due to decline in noradrenaline function. SNRI activates brain, stimulates dopamine and PEA increases.
Depression is Not Solely a Brain Disorder- It has a Complex Systemic Impact

Depression can be assessed by measuring multiple biological mediators within the Neuroendocrine, Hypothalamic, Pituitary, Adrenal, Metabolic and Immune Systems.
What is PEA?

- A phosphomonoester metabolite of phospholipid metabolism

- In developing brain, phosphomonoesters are normally elevated during the period of neuritic proliferation

- Role of phosphomonoesters in membrane biosynthesis

- It is NOT beta-phenylethylamine (PEA); a naturally occurring trace amine neurotransmitter and neuroregulator that is normally synthesized in the brain from the amino acid phenylalanine.
Biosimilars to PEA

[Chemical structures of PEA, 3-aminopropylphosphonic, and GABA]

PEA

3-aminopropylphosphonic

GABA
PEA bioactivity

- PEA showed little activity at any of the GABA binding sites.
- PEA was most potent at GABAB sites.
- The GABAB receptor 1 gene is mapped to chromosome 6p21.3 within the HLA class I region close to the HLA-F gene. Susceptibility loci for multiplesclerosis, epilepsy, and schizophrenia have also been mapped in this region.
- The efficient exclusion of PEA from GABA binding sites may be an important physiologic mechanism in the control of inhibitory neurotransmission.


Inactivity of phosphoethanolamine, an endogenous GABA analog decreased in Alzheimer’s disease, at GABA binding sites. Klunk WE¹, Debnath ML, McClure RJ, Pettegrew JW.
Tissue specific accumulation of free PEA (rabbit)

NOTE: Anandamide is an endogenous cannabinoid neurotransmitter. It was isolated in 1992. It is important in the regulation of feeding behavior, and the neural generation of motivation and pleasure. In addition, anandamide injected directly into the forebrain reward-related brain structure nucleus accumbens enhances the pleasurable responses of rats to a rewarding sucrose taste, and enhances food intake as well.
PEA and Alzheimer’s Disease

- PEA stable post mortem brain
- 5–10 samples, umol/g PEA:
- Phospholipid turnover
- Precursor to phosphatidylcholine
- Released during some depolarizing events
- Often followed by taurine release

Phosphoethanolamine and ethanolamine are decreased in Alzheimer’s disease and Huntington’s disease.
Ellison DW, Beal MF, Martin JB.
Other Pipeline Developments

- Diabetic Nephropathy
Biomarkers Diabetic Nephropathy (DN)

- 78 Type 2 DM patients
  - Without nephropathy and albuminuria (non-DN) – 20 patients
    - UACR* 12.1 +/- 6.7 mg/g    eGFR 81.9 +/- 24.0
  - Early DN with micro-albuminuria (Micro-DN) – 32 patients
    - UACR 103.9 +/- 77.8 mg/g    eGFR 70.5 +/- 21.9
  - Overt DN with macro-albuminuria (Macro-DN) – 26 patients
    - UACR 1055.3 +/- 741.3 mg/g    eGFR 47.2 +/- 25.6

*Urine Albumin-to-Creatinine Ratio (UACR).

Metabolic profiling reveals new serum biomarkers for differentiating diabetic nephropathy.
Hirayama A¹, Nakashima E, Sugimoto M, Akiyama S, Sato W, Maruyama S, Matsuo S, Tomita M, Yuzawa Y, Soga T.
Discovery

- CE-TOFMS analysis of serum
- Relative metabolite ratios
- Spearman’s rank correlation to UACR, eGFR
- Multiple logistic regression
- PCA analysis
OPLS-DA* (0.95 range)

*Orthogonal Projections to Latent Structures - discriminant analysis
19 candidates separate DN stages

<table>
<thead>
<tr>
<th>MID</th>
<th>Mode</th>
<th>m/z</th>
<th>Non-DN</th>
<th>Micro-DN</th>
<th>Macro-DN</th>
<th>p value</th>
<th>Formula</th>
<th>Metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>C</td>
<td>114.067</td>
<td>0.501±0.153</td>
<td>0.612±0.209</td>
<td>1.052±0.506</td>
<td>&lt;0.0001</td>
<td>C₄H₅N₃O</td>
<td>Creatine</td>
</tr>
<tr>
<td>17</td>
<td>C</td>
<td>129.067</td>
<td>0.046±0.035</td>
<td>0.065±0.049</td>
<td>0.125±0.079</td>
<td>&lt;0.0001</td>
<td>C₄H₆N₂O₂</td>
<td>Aspartic acid</td>
</tr>
<tr>
<td>29</td>
<td>C</td>
<td>134.046</td>
<td>0.126±0.025</td>
<td>0.141±0.041</td>
<td>0.170±0.036</td>
<td>&lt;0.0001</td>
<td>C₄H₇NO₄</td>
<td>γ-Butyrobetaine</td>
</tr>
<tr>
<td>39</td>
<td>C</td>
<td>146.118</td>
<td>0.028±0.007</td>
<td>0.032±0.008</td>
<td>0.039±0.010</td>
<td>&lt;0.0001</td>
<td>C₇H₁₀NO₂</td>
<td>Citruline</td>
</tr>
<tr>
<td>51</td>
<td>C</td>
<td>156.139</td>
<td>0.006±0.005</td>
<td>0.005±0.004</td>
<td>0.001±0.003</td>
<td>&lt;0.0005</td>
<td>C₇H₁¹NO</td>
<td>SDMA</td>
</tr>
<tr>
<td>52</td>
<td>C</td>
<td>158.154</td>
<td>0.063±0.020</td>
<td>0.055±0.022</td>
<td>0.040±0.012</td>
<td>&lt;0.0007</td>
<td>C₉H₁₈NO</td>
<td>Kynurenine</td>
</tr>
<tr>
<td>69</td>
<td>C</td>
<td>176.104</td>
<td>0.194±0.053</td>
<td>0.190±0.060</td>
<td>0.275±0.081</td>
<td>&lt;0.0005</td>
<td>C₉H₁₃N₃O₃</td>
<td></td>
</tr>
<tr>
<td>78</td>
<td>C</td>
<td>203.150</td>
<td>0.006±0.002</td>
<td>0.007±0.002</td>
<td>0.010±0.005</td>
<td>&lt;0.0004</td>
<td>C₈H₁₈N₄O₂</td>
<td></td>
</tr>
<tr>
<td>82</td>
<td>C</td>
<td>209.093</td>
<td>0.010±0.004</td>
<td>0.011±0.005</td>
<td>0.016±0.005</td>
<td>&lt;0.0005</td>
<td>C₁₀H₁₁NO</td>
<td></td>
</tr>
<tr>
<td>96</td>
<td>C</td>
<td>243.184</td>
<td>0.026±0.013</td>
<td>0.019±0.012</td>
<td>0.015±0.007</td>
<td>&lt;0.0002</td>
<td>C₁₃H₁₆N₃O₃</td>
<td></td>
</tr>
<tr>
<td>97</td>
<td>C</td>
<td>244.106</td>
<td>0.000±0.001</td>
<td>0.000±0.001</td>
<td>0.002±0.002</td>
<td>&lt;0.0003</td>
<td>C₁₀H₁₈N₄O₂</td>
<td></td>
</tr>
<tr>
<td>114</td>
<td>C</td>
<td>276.128</td>
<td>0.008±0.006</td>
<td>0.006±0.004</td>
<td>0.003±0.003</td>
<td>&lt;0.0004</td>
<td>C₁₂H₁₉N₄O₃</td>
<td></td>
</tr>
<tr>
<td>127</td>
<td>C</td>
<td>302.197</td>
<td>0.106±0.050</td>
<td>0.079±0.047</td>
<td>0.062±0.028</td>
<td>&lt;0.0002</td>
<td>C₁₅H₂₀N₃O₅</td>
<td></td>
</tr>
<tr>
<td>134</td>
<td>C</td>
<td>316.213</td>
<td>0.010±0.009</td>
<td>0.006±0.007</td>
<td>0.003±0.002</td>
<td>&lt;0.0001</td>
<td>C₁₆H₂₁N₄O₃</td>
<td></td>
</tr>
<tr>
<td>152</td>
<td>A</td>
<td>96.960</td>
<td>0.216±0.063</td>
<td>0.243±0.063</td>
<td>0.341±0.103</td>
<td>&lt;0.001</td>
<td>C₈H₁₂N₃O</td>
<td></td>
</tr>
<tr>
<td>158</td>
<td>A</td>
<td>103.014</td>
<td>0.003±0.002</td>
<td>0.004±0.002</td>
<td>0.005±0.002</td>
<td>&lt;0.0001</td>
<td>C₉H₁₃N₂O</td>
<td></td>
</tr>
<tr>
<td>202</td>
<td>A</td>
<td>149.049</td>
<td>0.030±0.006</td>
<td>0.034±0.009</td>
<td>0.051±0.019</td>
<td>&lt;0.0001</td>
<td>C₉H₁₃NO</td>
<td></td>
</tr>
<tr>
<td>232</td>
<td>A</td>
<td>187.098</td>
<td>0.020±0.013</td>
<td>0.017±0.011</td>
<td>0.009±0.004</td>
<td>&lt;0.0001</td>
<td>C₉H₁₈O₄</td>
<td></td>
</tr>
<tr>
<td>246</td>
<td>A</td>
<td>209.031</td>
<td>0.029±0.012</td>
<td>0.024±0.009</td>
<td>0.016±0.013</td>
<td>&lt;0.0001</td>
<td>C₉H₁₈O₆</td>
<td></td>
</tr>
</tbody>
</table>
Correlation to clinical measurements

<table>
<thead>
<tr>
<th>MID</th>
<th>Metabolite</th>
<th>UACR Coefficients</th>
<th>UACR p value</th>
<th>eGFR Coefficients</th>
<th>eGFR p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Creatinine</td>
<td>0.5701</td>
<td>&lt;0.0001*</td>
<td>-0.8832</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>17</td>
<td></td>
<td>0.4968</td>
<td>&lt;0.0001*</td>
<td>-0.5808</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>29</td>
<td>Aspartic acid</td>
<td>0.4993</td>
<td>&lt;0.0001*</td>
<td>-0.3912</td>
<td>0.0004*</td>
</tr>
<tr>
<td>39</td>
<td>γ-Butyrobetaine</td>
<td>0.4942</td>
<td>&lt;0.0001*</td>
<td>-0.6492</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>51</td>
<td></td>
<td>0.4728</td>
<td>&lt;0.0001*</td>
<td>0.2204</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>52</td>
<td></td>
<td>-0.4871</td>
<td>&lt;0.0001*</td>
<td>-0.0678</td>
<td>0.053</td>
</tr>
<tr>
<td>69</td>
<td>Citrulline</td>
<td>0.4300</td>
<td>&lt;0.0001*</td>
<td>-0.6531</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>78</td>
<td>SDMA</td>
<td>0.4820</td>
<td>&lt;0.0001*</td>
<td>-0.7111</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>82</td>
<td>Kynurenine</td>
<td>0.5351</td>
<td>&lt;0.0001*</td>
<td>-0.5627</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>96</td>
<td>Kynurenone</td>
<td>-0.3085</td>
<td>0.006b</td>
<td>0.1975</td>
<td>0.083</td>
</tr>
<tr>
<td>97</td>
<td>Kynurenone</td>
<td>0.5223</td>
<td>&lt;0.0001*</td>
<td>-0.7651</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>114</td>
<td>Kynurenone</td>
<td>-0.3638</td>
<td>0.001b</td>
<td>0.1392</td>
<td>0.224</td>
</tr>
<tr>
<td>127</td>
<td>Kynurenone</td>
<td>-0.2961</td>
<td>0.009b</td>
<td>0.2035</td>
<td>0.074</td>
</tr>
<tr>
<td>134</td>
<td>Kynurenone</td>
<td>-0.3669</td>
<td>0.001a</td>
<td>0.2397</td>
<td>0.0355</td>
</tr>
<tr>
<td>152</td>
<td>Kynurenone</td>
<td>0.5336</td>
<td>&lt;0.0001*</td>
<td>-0.7687</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>158</td>
<td>Kynurenone</td>
<td>0.4980</td>
<td>&lt;0.0001*</td>
<td>-0.6302</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>202</td>
<td>Kynurenone</td>
<td>0.6352</td>
<td>&lt;0.0001*</td>
<td>-0.7455</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>232</td>
<td>Azelaic acid</td>
<td>-0.5210</td>
<td>&lt;0.0001*</td>
<td>0.3739</td>
<td>0.00075</td>
</tr>
<tr>
<td>246</td>
<td>Galactaric acid</td>
<td>-0.4596</td>
<td>&lt;0.0001*</td>
<td>0.4152</td>
<td>0.0002</td>
</tr>
</tbody>
</table>
ROC analysis – non-DN / DN patients

- \(\gamma\)-butyrobetaine, SDMA, azelaic acid, **MID 114, MID 127**
- Best Panel, highest AUC

- Aspartic acid, SDMA, azelaic acid, galactaric acid
- Best panel, only known metabolites

AUC values: 0.927 and 0.844
Conclusions

- Biomarker discovery and validation is a pipeline
- Starts with accurate, quantitative data
- Builds increasing group size, additional controls
- Assay development
- Single (PEA) or multiple analyte panel (DN)
- Biological / pathway analysis
- Clinical plan (Type 0, 1, 2)
  - Algorithm based (combination clinical / blood metabolites)
  - Classifier, scoring
Quantitative
High value metabolic space
Unique resolution CE-MS
Experienced

Noriyuki Kawamura
MD, Ph.D.
Director- General
Gyokikai Medical Corporation
Kawamura Clinic for General Practice
Clinical Institute of Molecular Psychiatry

Human Metabolome Technologies America, Inc.

Boston Office:
24 Denby Road, Suite 217, Boston, MA 02134, USA
617-987-0554
Let Us Meet Again in Baltimore, USA

Team Biomarkers welcomes you all to the next chapter – 7th International Conference on Biomarkers & Clinical Research scheduled for Nov 28-30, 2016 in Baltimore, USA

Please Visit:
www.conferenceseries.com
http://www.omicsonline.org/
http://biomarkers.conferenceseries.com/