Biomarkers for Psychiatric Disorders
Max Planck Institute of Psychiatry
from bench to bedside and back ...
<table>
<thead>
<tr>
<th>2004 Disease or injury</th>
<th>2004 As % of total DALYs</th>
<th>2004 Rank</th>
<th>2030 Disease or injury</th>
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<td>Lower respiratory infections</td>
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<td>Diarrhoeal diseases</td>
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<td>2</td>
<td>5.5</td>
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<td>Unipolar depressive disorders</td>
<td>4.3</td>
<td>3</td>
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<td>Ischaemic heart disease</td>
<td>4.1</td>
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<tr>
<td>HIV/AIDS</td>
<td>3.8</td>
<td>5</td>
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<tr>
<td>Cerebrovascular disease</td>
<td>3.1</td>
<td>6</td>
<td>3.2</td>
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<td>Prematurity and low birth weight</td>
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<td>Birth asphyxia and birth trauma</td>
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<td>Road traffic accidents</td>
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<td>Neonatal infections and other*</td>
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<td>10</td>
<td>2.3</td>
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<td>COPD</td>
<td>2.0</td>
<td>13</td>
<td>1.9</td>
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<td>Refractive errors</td>
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<td>14</td>
<td>1.9</td>
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<td>Hearing loss, adult onset</td>
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<td>15</td>
<td>1.9</td>
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<td>Diabetes mellitus</td>
<td>1.3</td>
<td>19</td>
<td>1.6</td>
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</tbody>
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Problem #1
Poor Diagnosis - Artificial Disease Classification

Depression

Bipolar Disorder

Anxiety

Schizophrenia

- Cognitive impairment
- Negative symptoms (for example, deficits of emotional responses)
- Positive symptoms (for example, delusions and disordered thoughts)
- Mood swings

Genes and environment (such as stressful experiences)

Problem #2
Antidepressant Response - Imprecise/Impersonal Medicine

- 2-4 weeks to evaluate response
- switching to alternative antidepressant
  => prolonged suffering
  => suicide risk
  => high healthcare costs
Top Therapeutic Classes by Prescriptions

<table>
<thead>
<tr>
<th>DISPENSED PRESCRIPTIONS MN</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
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<td>Total US Market</td>
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<td>3,866</td>
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<td>1 Antidepressants</td>
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<td>2 Lipid Regulators</td>
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<td>3 Narcotic Analgesics</td>
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<td>5 Ace Inhibitors (Plain &amp; Combo)</td>
<td>159</td>
<td>163</td>
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<td>6 Beta Blockers (Plain &amp; Combo)</td>
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<td>7 Respiratory Agents</td>
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<td>8 Anti-Ulcerants</td>
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<td>104</td>
<td>105</td>
<td>107</td>
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<td>13 Calcium Antagonists (Plain &amp; Combo)</td>
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<td>90</td>
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<td>14 Antirheumatic Non-Steroid</td>
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<td>91</td>
<td>92</td>
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<td>15 Hormonal Contraceptives</td>
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<td>18 Macrolides &amp; Similar Type Antibiotics</td>
<td>63</td>
<td>66</td>
<td>69</td>
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<tr>
<td>19 Hypnotics &amp; Sedatives</td>
<td>58</td>
<td>60</td>
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<td>63</td>
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<tr>
<td>20 Vitamins &amp; Minerals</td>
<td>60</td>
<td>59</td>
<td>58</td>
<td>58</td>
<td>60</td>
</tr>
</tbody>
</table>

IMS Health, National Prescription Audit, Dec 2011

The Use of Medicines in the United States: Review of 2011
Report by the IMS Institute for Healthcare Informatics
Biomarkers
Objectively measured characteristic reflecting physiological, pharmacological, disease processes.

- **Diagnosis**
  - follow disease (stationary, relapsing, etc.)
  - pre-symptomatic detection

- **GWAS dataset query**
  - select a limited list of candidate genes
  - tolerate interrogation of genes with higher p-values

- **Drug development**
  - patient stratification
  - monitor clinical response to treatment

- **Improved understanding of disease processes**
  - pathway analysis
  - target dysfunctional pathways instead of mutant genes
Peripheral vs. Central Biomarkers: Do They Correlate?

- **Discovery**
  - profiling analyses to generate list of biomarkers from relevant tissue (differential expression, turnover, etc.)

- **Qualification**
  - link with biology

- **Verification**
  - screen peripheral fluid for presence

- **Clinical validation**
  - robust, sensitive, specific quantitative method
Biomarker Discovery
Bottom Up vs. Top Down

Mouse Model
- inbred
- homogeneous phenotype
- controlled environment
- primary tissues

Patients
- outbred
- heterogeneous phenotype
- variable environment
- body fluids
- limited cohorts
Criteria for an Animal Model

It is not the aim of animal research to mimic the complexity of human nature, but

... to model selected endophenotypes (face validity)

... to test for the efficacy of pharmacological compounds (predictive validity)

... to study similarities in cellular and molecular processes (construct validity).
Mouse Models for Psychiatric Disease Research

Genetic Risk Factors

- **bottom-up**
  - Genetic Manipulation
    - (ko, transgenic)

- **top-down**
  - Selective Breeding
    - (trait)

Developmental Risk Factors

- Maternal Separation

Aversive Life Events

- Social Stress, Trauma, Repeated Restraint
From Phenotype to Biosignature

homogeneous disease subdimensions biological endophenotype

biosignature

pathways molecular mechanisms

heterogeneous multidimensional phenotype
Post-Traumatic Stress Disorder

Exaggerated implicit fear memory resulting from
- associative fear conditioning
- non-associative sensitization processes/fear components

Symptoms

- Related to memory of trauma
  - Re-experiencing
  - Flashbacks
  - Nightmares
  - Avoidance of and exaggerated response to cues reminding of the trauma

- Unrelated, lack of association
  - Hyperarousal
  - Hypervigilance
  - Increased startle
  - Blunted emotionality
  - Social withdrawal
PTSD Mouse Model
Shock Sensitization and Pharmacological Treatment

Preventive Treatment

Trauma

D0 12h

Symptoms Maturation
D28

Maintenance
D56

Drug Washout

PTSD

Transcriptome
Proteome
Metabolome

Freezing test
Startle test

associative trauma-related
non-associative trauma-unrelated

Chi-Ya Kao
Carsten Wotjak
Philipp Khaitovich
Neurocircuitry of Fear Regulation
Brain Punch -Omics

PrL: prelimbic cortex
ACC: anterior cingulate cortex
NAc: nucleus accumbens
BLA: basolateral amygdala
CeA: central nucleus of amygdala
CA1: cornus ammonis 1 of hippocampus

Chi-Ya Kao
Carsten Wotjak
Judith Reichel
Kathrin Henes
Biosignatures
In-Depth Quantitative Proteomics

Brain Sectioning

Combination and Organellar Fractionation

Protein Fractionation

Proteolytic Digest

Shotgun Mass Spectrometry

Relative Quantitation

Protein Turnover

$^{14}\text{N}$ $^{15}\text{N}$
- One month after shock treatment altered pathways related to:
  - inflammation, synapse, neurotransmitter release
  - energy metabolism, microtubule cytoskeleton, myelination
- Chronic antidepressant drug treatment ameliorates sensitized fear and pathway dysregulation.
- Extracellular fluid metabolome reflects prefrontal molecular alterations.
“The Unpredictable” Antidepressant Treatment Response - delineation of molecular pathway activities
Majority of patients suffering from Major Depression receive Selective Serotonin Reuptake Inhibitor (SSRI) as first-line treatment.

- SSRI efficacy varies to a large extent, 40% of patients do not respond (defined as 50% reduction of symptoms), 60% do not show complete remission of symptoms.

- Delayed onset and side effects.

- SSRI mechanism of action incompletely understood, especially downstream effects (off pathway effects).

- Biomarkers to predict treatment response are needed for clinical trials and to identify affected downstream pathways.
Antidepressant Treatment Response

Christian Webhofer


swimming

floating

28d Vehicle

28d Paroxetine

Christian Webhofer
SSRI Treatment Response
Metabolome Time Course - Pathways

Glycolysis

Citrate Cycle

Energy metabolism

Redox Control

Amino acid metabolism

Hormone signaling
Responder/Non-Responder Inbred (!) Mice

Habituation chronic paroxetine treatment (5 mg/kg, twice a day)

Day -14 Day 0 Day 28 Day 29

Responder

Non-Responder

Vehicle Paroxetine

Time floating (s)

Paroxetine level (ng/ml)

0 100 200 300 400 500 600 700 800 900 1,000

Dongik Park
Marianne Müller
Christiana Labermaier
Carine Dournes
Response/Non-Response
Stratifying Pathways

Hippocampus
Blood plasma

Proteomics
Targeted metabolomics

Computational analysis

Dongik Park
Marianne Müller
Christiana Labermaier
Carine Dournes
Summary – Antidepressant Response

- SSRI and Ketamine affected pathways implicate energy metabolism and oxidative stress.

- Delineation of SSRI response/non-response affected pathways (Purine/Pyrimidine, Glutamatergic, Ubiquitin).

- Several CNS treatment response biomarkers can be detected in the periphery.

- Ketamine
  - several shared biomarkers with SSRI response
  - has opposite effect on glycolysis than SSRI (reason for fast action?)
  - Hydroxynorketamine metabolite with no side effects
Towards clinical translation
Ketamine treatment response case study


Angelika Erhardt
Magdalena Denk
Ketamine response peripheral monitoring

MADRS
BDI
CADSS
BSKE

Ketamine infusion (0.25 mg/kg)

Basal 0min 10min 40min 1h 2h 6h 24h

MADRS
BDI
CADSS
BSKE

MADRS
BDI
CADSS
BSKE

MADRS
BDI
CADSS
BSKE

MADRS
BDI
CADSS
BSKE

Angelika Erhardt
Magdalena Denk
Biomarker Discovery – 100 Years Ago

Writing Balance

Writing Pressure Curves

Emil Kraepelin: Manic-Depressive Insanity and Paranoia (1921) p.42
From Bench to Bedside and Back ...