Individual Medicine

Back ground

- **Birgitte Søgaard, Divisional Director, H. Lundbeck A/S**
- **27 years within industry**
  - Therapeutic areas, autoimmune diseases, cancer, diabetes and CNS
- **Worked with sales and marketing**
- **Assay development**
- **Clinical research phase 1-4**
- **Translational Medicine**

Personalised medicine - perspective for mental disorders

- **Personalised medicine**
  - General concept and background
  - Within mental disorders
  - Exemplified with treatment of major depressive disorder
    - Diagnosis and clinical treatments
    - Various approaches to improve through personalisation
    - Results
    - Future perspectives

3

Definition

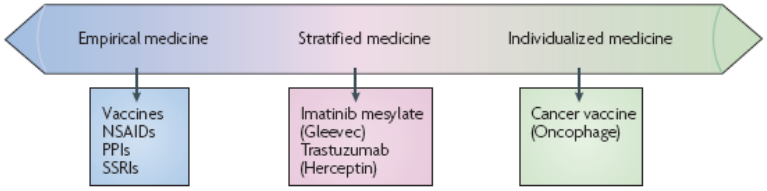
Biological Marker (Biomarker):

A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention

Biomarkers Definition Working Group: Clin Pharmacol Ther 2001; 69: 89-95

4

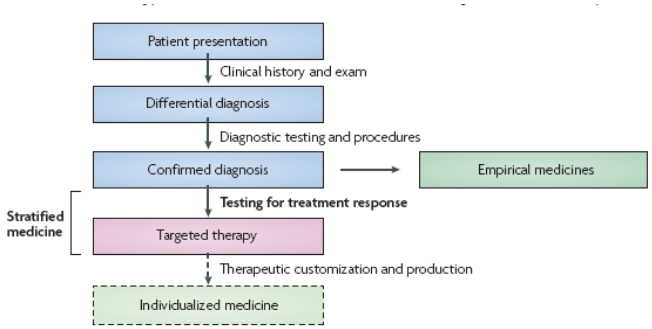
Treatment paradigms



Source: Mark R. Trusheim *et. al.*, Nature Reviews, Volume 6, April 2007

5

Decision Flow



Source: Mark R. Trusheim *et. al., Nature Reviews, Volume 6, April 2007*

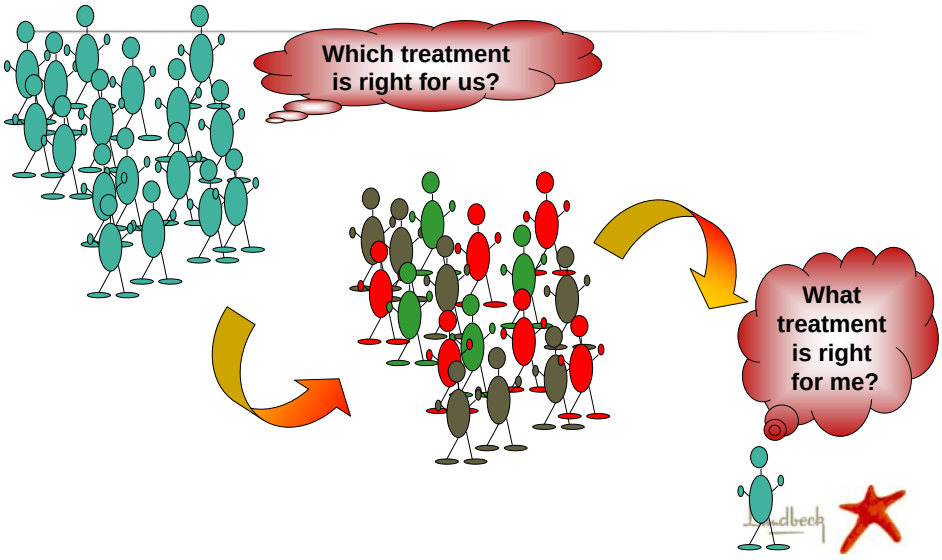
6

Diseases biological undefined

- **Most diseases are multifactorial diseases**
- **Most diseases are not phenotypical well described**
  - Clinical description is based on subjectivity

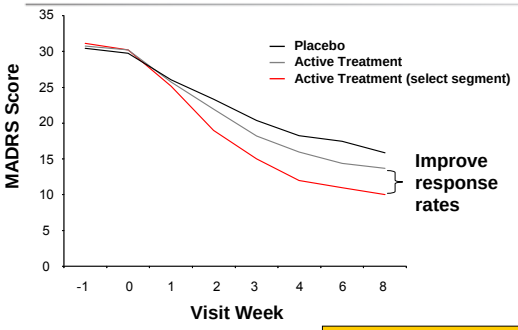
7

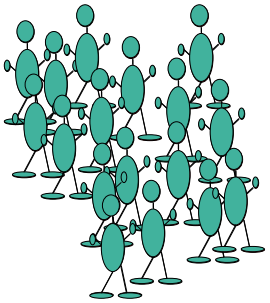
Predicting Treatment Response



8

Expected Benefits





Expected Benefits

- **Enriched groups**
- **Improved efficacy**
- **Enlarge therapeutic window?**

9

Perspectives for treatment of mental disorders

- **Personalised treatment**
  - Relevant for treatments where
    - Underlying disease variability reflecting multiple aetiology or
    - Indistinguishable clinical presentation for biologically distinct conditions
    - Multiple relevant targets for intervention
    - Different ADME characteristics, toxicity or tolerability of therapeutic regimens
    - Adaptiveness of disease leading to treatment resistance
    - Multiple treatment options with heterogenous responses
    - A logistically and medically acceptable clinical biomarker (to be identified)
  - Extent of individualisation
    - Per individual
    - Per (sub) population sharing a feature in common
    - Per diagnosis + one or more specific marker (e.g. genotype)

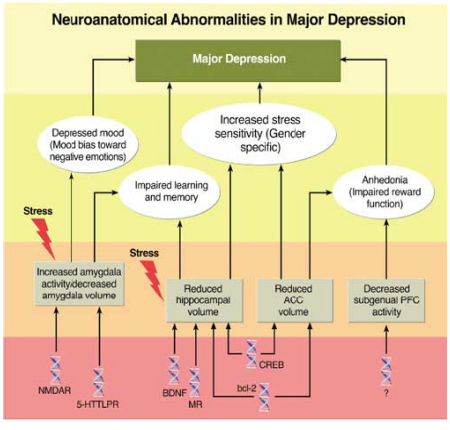
10

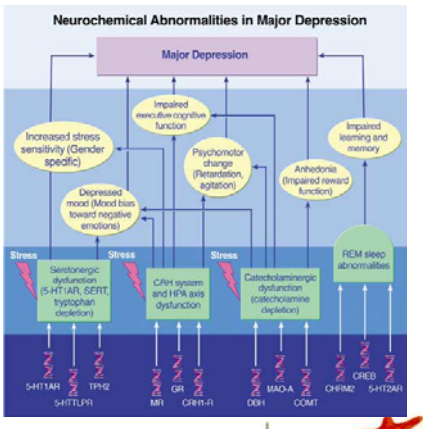
Depression as an example

- **Diagnosed based on the following symptoms**
  - Depression is a common mental disorder:
    - Sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy and poor concentration.
  - May be chronic or recurrent
    - Substantially impairing an individual's ability to cope with daily life
    - At its most severe, depression can lead to suicide (DSM IV)
- **Social consequences**
  - Disability
    - Leading cause measured by YLDs
    - The 4th leading contributor to the global burden of disease (DALYs) in 2000
    - By the year 2020, projected to reach 2nd place of the ranking of DALYs calculated for all ages, both sexes
  - Treatment
    - Antidepressant medications and some forms of psychotherapy are effective for approx. 60 %
    - Side effects relatively common
    - Relapse common

11

Endophenotypes for Major Depression





Hasler, Neuropsychopharmacol 2004

12

Potential biomarkers within depression

- **Genotype**
  - 5HT* transporter, 5HT1A
- **Gene expression**
  - CREB, IL1, IL6, arrestine…..
- **Neuro-endocrine markers/responses**
  - Cortisol, CRH, …
- **Metabonomics**
  - Neurotransmitter pattern
- **Neuronal**
  - Imaging: PET, fMRI, MRI-volumetric (hippocampus)
  - EEG

*** 5HT= serotonin**

13

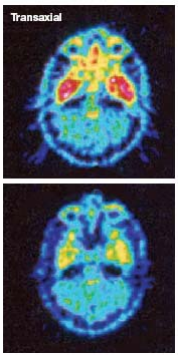
Perspectives for depression

- **Diagnostic**
  - Identify patient population that is more homogeneous
  - Identify patient population that obtain better response with specific treatment
  - No one biomarker believed to be sufficient, but set of markers supplemented with clinical observations
- **Treatment optimisation**
  - Predict which pharmacological treatment optimal for individual / subsegment of depressed population
  - Predict alternative and better treatment if first line not optimal
- **Translational medicine**
  - Use identified markers to identify new drug target or predictive animal models

14

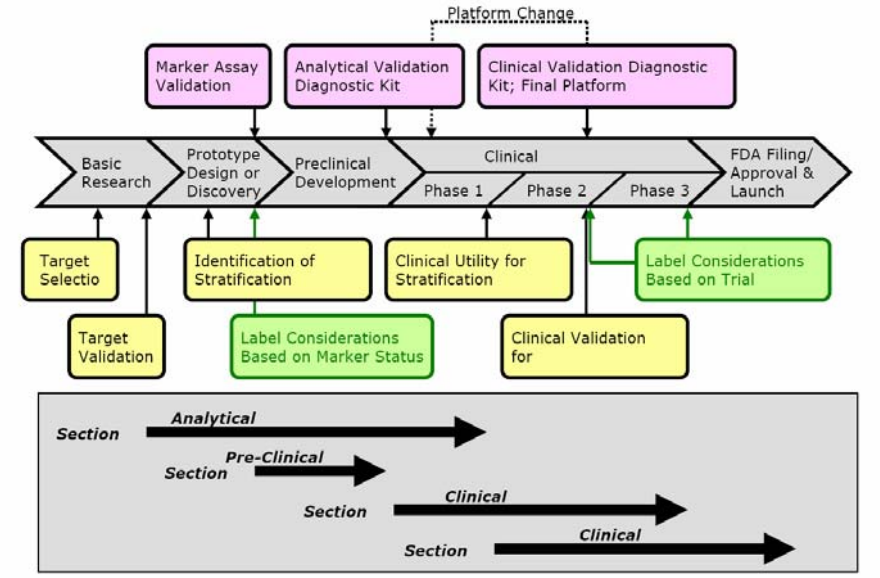
Research and Development at Lundbeck

- **Several approaches across various studies**
  - PET, fMRI
  - QEEG
  - Genotyping
  - Mapping endophenotype (patient history)
  - Gene expression



15

Drug-Device Co-Development Process (FDA Concept Paper)



Example from Lundbeck's own research

- **Focus on gene expression**
  - Assessment of mRNA in peripheral leukocytes
  - Methodology development (qPCR*)
  - Sampling from healthy volunteers and patients diagnosed with MDD
    - "Diagnostic" approach
  - Sub-segmentation of patients based on
    - Baseline characteristics (biomarkers and/or clinical symptoms)
    - Treatment response (according to treatment?)
    - Risk of relapses
  - Identify new treatment approaches / targets
    - Based on gene expression pattern representing various (new) pathways
    - Generate new hypothesis for novel drug treatments

* quantitative Polymere Chain Reaction

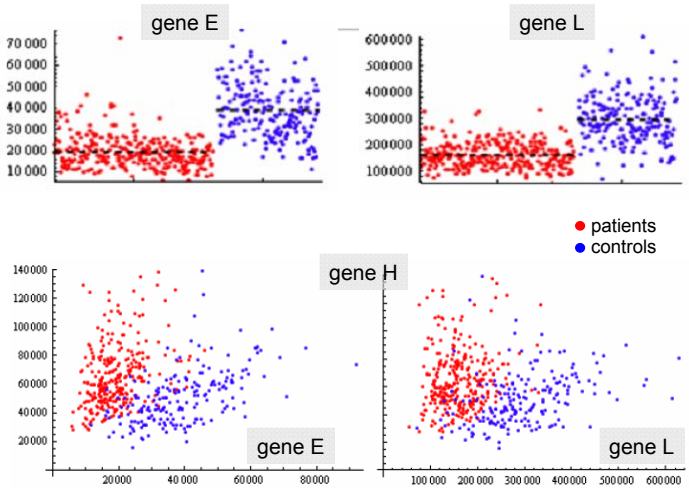
17

Focused Gene Panel as Blood Biomarkers

- **Selection of core genes**
  - Related to therapeutic area
  - Reliably measurable by qPCR in human blood leukocytes

Gene	Pathway	In house	Literature vs in house
gene A	transmitter-related	up	✓
gene B	transmitter-related	up	✓
gene C	transmitter-related	down	∅
gene D	signaling	down	✓
gene E	signaling	down	✓
gene F	signaling	up	—
gene G	signaling	up	✓
gene H	signaling	up	✓
gene I	signaling	up	✓
gene J	signaling	down	✓
gene K	signaling	no change	✓
gene L	signaling	down	✓
gene M	signaling	down	∅
gene N	signaling	down	✓
gene O	signaling	up	✓
gene P	signaling	up	∅
gene Q	signaling	down	✓
gene R	signaling	up	—
gene S	signaling	up	✓
gene T	signaling	down	✓
gene U	metabolism	up	∅
gene V	metabolism	up	∅
gene W	metabolism	up	✓
gene X	metabolism	up	✓
gene Y	signaling	down	✓
gene Z	signaling	no change	∅
gene ZA	signaling	up	✓
gene ZB	signaling	up	✓
gene ZC	signaling	up	✓

Transcription classifying Depression Segment



Core candidate genes can classify patients with 81-86% accuracy

Several two-gene combinations (of core genes) reach accuracies of 92%

Three-gene combinations to reach accuracies of 93%

19

Next steps

- **Extended pool of genes included**
- **Look for subsegmentation of patients**
  - Clinical symptomatology
  - Pathways involved
  - Treatment response
- **Back translation to animal models**
  - New targets identification
- **Translation – biomarker development**
  - Co-diagnostic
  - Surrogate marker?

20

Reading

- **ICH guidance no 17**
- **ICH Topic M 3 (R2)**
  Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
- **FDA Critical Path Documents**
- **FDA and EMEA homepages**

21