NEWMEDS
Novel methods leading to New medications in Depression and Schizophrenia

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Psychiatry
a continuous burden on Patients, Families, Caregivers and Society

- The global cost of mental health conditions in 2010 was estimated at US$ 2.5 trillion, with the cost projected to surge to US$ 6.0 trillion by 2030.
- Mental Health is one of the top drivers in loss of output
- Schizophrenia and Depression are among the top drivers in Mental Health

Source: The Global Economic Burden of Non-communicable Diseases, 2011
We have had very limited success in psychiatry

Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia

Jeffrey A. Lieberman, M.D., T. Scott Stroup, M.D., M.P.H., Joseph P. McEvoy, M.D., Marvin S. Swartz, M.D., Robert A. Rosenheck, M.D., Diana O. Perkins, M.D., M.P.H., Richard S. E. Keefe, Ph.D., Sonia M. Davis, Dr.P.H., Clarence E. Davis, Ph.D., Barry D. Lebowitz, Ph.D., Joanne Severe, M.S., and John K. Hsiao, M.D., for the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators

In summary, patients with chronic schizophrenia in this study discontinued their antipsychotic study medications at a high rate, indicating substantial limitations in the effectiveness of the drugs. Within this limited range of effectiveness, olanzapine appeared to be more effective than the other drugs studied, and there were no significant differences in effectiveness between the conventional drug perphenazine and the other second-generation drugs.
The Patients are heterogenous

- Mental disorders have been considered "behavioral," implying that an exclusive focus on symptoms could yield a precise diagnosis.

- Research has demonstrated that diagnostic labels such as depression or schizophrenia do not specify the underlying heterogeneity of these disease appropriately.

- Attempts to subdivide these categories by considering additional symptoms, such as anxious depression, have until now failed to give reliably better prediction of treatment response – Tom Insel NIMH.
Key Research Challenges in Psychiatry

Challenge
Why do patients not respond well to current medication?

Question?
Can we identify groups of patients and medications that match better?

Clinical phenotype
Biological phenotype
Animal models
Clinical trials in a meaningful way

We are in desperate need of better tools
The need for a PPP

• The scientific questions that remain unanswered in psychiatry are extremely complex
  – One organisation cannot solve this by themselves
• A number of big pharma have recently pulled out of basic research in psychiatry (GSK, AZ)
  – More will follow due to the costs
• We need a platform where we can join forces
  – IMI has successfully provided that platform
Three major bottlenecks are holding back the progress of the field.

Lack of pathophysiologically relevant animals models to guide the drug discovery efforts.

Lack of tools and tests in healthy volunteers that provide early indications of efficacy.

The reliance of clinical trials on symptom-based DSM-categories which inevitably lead to heterogeneous groups of patients.

Newmeds tries to address this.
Headline achievements of the NEWMEDS program

**Phase 1**
- WP 1, 2, 4: Animal models that truly translate the phenotype of a patient
- WP 4, 5, 6: Experimental Human tools that enable early decision making

**Discovery phase**
- WP 7, 9: Biologically Validated Targets

**Phase IIa**
- WP 3, 7, 8, 9, 10: The way we do clinical trials

**Phase 2b**
- WP 3, 7, 8, 9, 10

**Phase 3**
- WP 3, 7, 8, 9, 10

**Submission**

**WP 1, 2, 4**
Animal models that truly translate the phenotype of a patient

**WP 4, 5, 6**
Experimental Human tools that enable early decision making
Headline achievements of the NEWMEDS program

- Animal-human imaging methodology has been developed and is ready to be used
- Cross site validated cognition assays in rodent

Discovery phase

Phase 1

- Recruitment of more than 1300 subjects, controls and subjects carrying CNVs and MRI scanning of > 300 subjects
- Neuropsychological and anthropometric phenotypes associated with schizophrenia CNVs have been identified
- Links from animal models to humans carriers have been made
- Animal models carrying the CNVs show distinct phenotypes

Phase 2a

Phase 2b

Phase 3

Submission

- The largest database on schizophrenia trials enrolled in EFPIA studies (> 23,000 patients) from where we have collected data to improve clin trials – Shorter and more efficient trials
- The largest database on treated depressed populations generated - no single gene does it.

- Cognitive and electrophysiological batteries have been validated in animal models ready to be used in humans
- 14 animal models of schizophrenia evaluated in a proteomic markers panel

- The largest database on treated depressed populations generated - no single gene does it.

- depressiontools.org, an easy-to-operate web calculator to determine whether a biomarker is meaningful or not
An example from NEWMEDS...

There is clearly a genetic link....

<table>
<thead>
<tr>
<th>If you have a schizophrenic....</th>
<th>Your risk of getting schizophrenia is....</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identical twin</td>
<td>46%</td>
</tr>
<tr>
<td>Both parents</td>
<td>48%</td>
</tr>
<tr>
<td>Sibling or parent</td>
<td>12%</td>
</tr>
<tr>
<td>Aunt, Nephew, grand parent</td>
<td>5%</td>
</tr>
<tr>
<td>First cousin, great aunt</td>
<td>2%</td>
</tr>
<tr>
<td>No relatives</td>
<td>1%</td>
</tr>
</tbody>
</table>
Copy Number Variations (CNVs) could they be the link?

Rare chromosomal deletions and duplications increase risk of schizophrenia

The International Schizophrenia Consortium*

Schizophrenia is a severe mental disorder marked by hallucinations, delusions, cognitive deficits and apathy, with a heritability estimated at 73–90% (ref. 1). Inheritance patterns are complex, and the number and type of genetic variants involved are not understood. Copy number variations (CNVs) have been identified in individual patients with schizophrenia and in neurodevelopmental disorders (2), but large-scale genome-wide surveys have not been performed. Here we report a genome-wide survey of rare CNVs in 3,391 patients with schizophrenia and 3,181 ancestrally matched controls, using high-density microarrays. For CNVs that were observed in less than 1% of the sample and were more than 100 kilobases in length, the total burden is increased up to sixfold with comparisons with control groups. Single occurrences are not as opposed to were found within the frame, which includes x51. Associations with first-degree relatives were not previously been studied genome-wide for a model of schizophrenia of multiple rare hits at specific loci.

Strong association of de novo copy number mutations with sporadic schizophrenia

Bin Xu1,2, J Louw Roos3, Shawn Levy4, E J van Rensburg

Schizophrenia is an etiologically heterogeneous psychiatric disease, which exists in familial and non-familial (sporadic) forms. Here, we examine the possibility that rare de novo copy number (CN) mutations with relatively high penetrance contribute to the genetic component of schizophrenia. We carried out a whole-genome scan and implemented a number of strategies for finding and confirming CN mutations. Conformed de novo mutations were significantly associated with schizophrenia.

Large recurrent microdeletions associated with schizophrenia

Hreinn Stefansson1,4, Dan Rujescu5, Sven Cichon6,7, Ole P. H. Pietiläinen1, Andres Ingason1, Stacy Steinberg1, Ragnheidur Fosdal1, Engelbert Sigurdsson1, Thorurd Sigurdsson1, Cassandra B. V. Brem1,2,3, Thomas Hansen1,2, Klaus D. Jakobsen3, Pia Boods1,2, Stefan Schmidtchen1,2, Hanne Bjerregaard1,2, Jørgen Kjærgaard1,2, Jørgen H. Pedersen1,2, Erik S. Simonsen1,2, Sven Cichon6,7, Heiko W. Schurmann1,2, Pia Bools1,2, Per Olofsson1,2, Mats Gyllensten1,2, Mats Holm1,2, Sten H. K. H. Dorph-Petersen1,2, Martin T. Müller1,2, Sören W. Thomsen1,2, Matthieu Zeller1,2, Andreas Linthorst1,2, Christian J. Helms1,2, Henrik Ullum1,3, Iben M. Mikkelsen1,2, Eicke Andresson1,2, Pia Bølts1,2, Sanne Nijsen1,2, Leena Pettersen1,2, David A. Collier3,4, David St

LETTERS

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What are CNVs and Why are the CNVs so interesting?

CNVs are Chromosomal deletions and duplications containing several genes

<table>
<thead>
<tr>
<th>Genes</th>
<th>Healthy</th>
<th>Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td>22q11</td>
<td>100</td>
<td>30</td>
</tr>
</tbody>
</table>
Pursuing CNV variants as entries into psychiatry

**Basis:** Unrelated CNVs can lead to similar functional outcome (schizophrenia)

**Aim - ultimately:**
Identify drug targets with a strong link to underlying biology

**How:**
Characterize CNV mouse models
Characterise Human carriers of CNVs
Identify schizophrenia relevant phenotypes in the mice

**Outcome:**
Platform to identify targets that may be used across diseases with similar biological dysfunctions
Converging symptoms and disorders

We have made mice models of these syndromes.

We also have access to human carriers of these CNVs.

CNV carriers
Phenotypes seen in both CNV animals and human carriers have been found and might represent a novel platform from which we can start to hunt for novel drugs.
What next?

• Finalise the validation of our tools
  – So that drug hunting can begin!
• Find a way to best leverage what we have achieved so far and secure that work continues and commitment remains high
Will Newmeds develop new drugs??

NO

But we will provide methods and novel entries to go "drughunting"
And when will we have a novel drug?

A novel platform to screen

A novel target to screen on next year

A novel drug candidate in 4 years

A truely novel drug in many years...
What impacts has NEWMEDS had?

Sadly,
• We have not as yet changed the lives of the patients that suffer from schizophrenia and depression

BUT we have
• Gained novel insights into the biology of these diseases
• Standardised the application of cognitive models across several industrial partners
• Developed novel tools for drug discovery [animal models, human imaging]
• Developed new web tools for analysis [image analysis, biomarker significance]
• Provided information for the design of more efficient clinical trials

• A single EFPIA company would not have done this on their own
• EFPIA companies continue to stay committed to Psychiatry
Thank you

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www.newmeds-europe.com
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(tot al of 125)
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Copenhagen, Lundbeck 2010

London, Lilly 2011

Paris, Servier 2012

Ludwigshafen, Abbott 2013