Targeting microglia activation in schizophrenia by minocycline treatment

S.15.02
Susanne A. Wolf
Max-Delbrück-Center in the Helmholtz Association
Berlin, Germany

Disclosure: There is no conflict of interest.
**Microglia phenotypes**

- **Blood CSF Barrier**
- **Blood vessel**
- **TCR**
- **T cell**
- **Monocyte**

**Epithelial cell**

- **CSF**
- **a** Self renewal
- **b** Ramified microglia
- **b** BDNF
- **b** NGF
- **b** NT
- **e** Neural progenitor cells

**Blood Parenchyma**

- **c** Synapse
- **c** Neuron

**Stroma**

- **Mannose receptor**
- **k** Monocyte-derived macrophage

**Activated microglia**

- **MHC II**
- **Intensive acute or chronic activation**
- **Short and moderate activation**
- **Arg1**

**Pathological/injurious conditions**

- **IL-1**
- **IL-6**
- **TNF-α**
- **ROS**
- **NO**

**Immune-resolving**

- **Anti-inflammatory**
- **Neuroprotective**
- **Support cell renewal**

**Daily maintenance**

- **Activation**

**Minocycline targets**

- **Cytokine production in microglia**

- **Giovanoli et al. Transl. Psych. 2016**
- **Mattei et al. Brain Behavior Immunity 2014**


**Cytokines**

- **Phagocytosis**

- **Actuation**
### Minocycline profile

<table>
<thead>
<tr>
<th>Description</th>
<th>Broad spectrum, second generation, lipophilic, tetracycline antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA indications</td>
<td>Acne, chlamydia, gonorrhea, meningitis, prosthetic joint infection, syphilis</td>
</tr>
<tr>
<td>Unlabeled uses</td>
<td>Rheumatoid arthritis, cellulitis</td>
</tr>
<tr>
<td>Research</td>
<td>Huntington’s disease, Parkinson’s disease, <strong>schizophrenia</strong>, amyotrophic lateral sclerosis</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td><strong>Inhibits 30s ribosomal protein synthesis in susceptible bacteria</strong></td>
</tr>
<tr>
<td>Adult Dose</td>
<td>100-200mg/day depending on indication</td>
</tr>
<tr>
<td></td>
<td>Max dose=400mg/day</td>
</tr>
<tr>
<td>Absorption</td>
<td>Well absorbed orally</td>
</tr>
<tr>
<td>Protein binding</td>
<td>70-75%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic to inactive metabolites</td>
</tr>
<tr>
<td>Half-life</td>
<td>Oral ranges from 11-22 hours</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urine, feces</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>CrCl &lt;80 ml/min dose not to exceed <strong>200mg/day</strong></td>
</tr>
<tr>
<td>Hepatic impairment</td>
<td>Use with caution- no specific dose recommendations</td>
</tr>
<tr>
<td>Pregnancy category</td>
<td>D</td>
</tr>
<tr>
<td>Safety</td>
<td>Tooth discoloration, hepatic effects, autoimmune syndromes, CNS effects, tissue hyperpigmentation, hypersensitivity reactions</td>
</tr>
<tr>
<td>Study</td>
<td>Treatment Details</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Liu et al. 2014</td>
<td>Adjunct to risperidone in patients in the first 5 years of illness</td>
</tr>
<tr>
<td>Kelly et al. 2015</td>
<td>Adjunct to CLZ and chronic population positive and cognitive symptoms</td>
</tr>
<tr>
<td>Chaves et al. 2015</td>
<td>Adjunct to CLZ and chronic population MRI (1.5T) and [(99m)Tc]-ECD SPECT population</td>
</tr>
</tbody>
</table>
Microglia associated with schizophrenia

**Post mortem studies:**
Microgliosis in the brain of Schizophrenic patients
- Steiner *et al* 2008, J Psychiatr Res
- Bussen *et al* 2012, Brain Behav Immun

**In vivo studies:**
Microglial activation in the brain of Schizophrenic patients using PET
- van Berckel BN *et al* 2008, Biol Psychiatry
- Doorduin *et al* 2009, J Nucl Med

  Microglial Activity in People at Ultra High Risk of Psychosis and in Schizophrenia: An [11C]PBR28 PET Brain Imaging Study

- Juckel *et al* 2011, Schizophr Res
  microglial dysregulation shown in PolyIC mouse model
- Mattei *et al*. 2014, Brain Behavior Immun
Pathogenesis of Schizophrenia in a mouse model

Causes of Schizophrenia
– Genetics
– Social environment as a trigger for outbreak
– Pathogen-induced
  – Prenatal: Increased risk of schizophrenia for children of mothers suffered from viral infection during pregnancy (2-20 fold, depending on the type of virus)

Process
– possible prenatal trigger
  – progresses until it reaches a critical threshold, typically in the second or third decade;

Functional impairments
– Hallucinations
– Delusions
– Disordered speech
– Disorganized behaviour
– Neurocognitive deficits
– Sensorimotor gating

Morphological manifestations
– Increased volume of ventricles
– Decreased volume of
  • Grey matter
  • Frontal lobe
  • Temporal lobe
  • Hippocampus

Experimental design

PolyI:C → Injection in utero → PPI - human / mouse → Cellular read out
Mouse model of In utero „infection“ with PolyI:C

**Model**

- **ctl.**
- **Poly**

**Treatment**

- **ctrl.**
- **Poly**
- **Poly/Min**

**Neuroinflammation**
- Autoradiography
- Immunohistochemistry

**Microglia preparation**
- Isolation of CD11b cells positive by MACS

**Behavior**
- Prepulse-inhibition (sensori-motor-gating)
- Object recognition
- Sociability test

Mattei et al. submitted

polyinosinic:polycytidylic acid (Poly I:C): Synthetic ligand of TLR3 (mimicks viral encounter)
Adult PolyI:C mice show correlates of positive, negative and cognitive symptoms which are rescued by chronic minocycline treatment.
Mouse model of In utero „infection“ with PolyI:C

**Model**

a) ctrl.

- Poly

**Treatment**

- Minocycline treatment
- 3 mg/kg/day
- Behavior testing

- Poly

- Poly/Mino

**Behavior**

- Prepulse-inhibition (sensori-motor-gating)
- Object recognition
- Sociability test

**Microglia preparation**

- Isolation of CD11b cells positive by MACS

**Neuroinflammation**

- Autoradiography
- Immunohistochemistry

polyinosinic:polycytidylic acid (Poly I:C): Synthetic ligand of TLR3 (mimicks viral encounter)

Mattei et al. submitted
Hippocampal microglial cells from PolyI:C mice show a profoundly altered transcriptome signature.

.... that is normalized by minocycline.
Mouse model of In utero „infection“ with PolyI:C

**Model**
- **a)**
  - **ctl.**
  - **Poly**

**Treatment**
- Minocycline treatment 3 mg/kg/day
- Behavior testing
- Poly
- Poly/Mino

**Neuroinflammation**
- Autoradiography
- Immunohistochemistry

**Behavior**
- Prepulse-inhibition (sensori-motor-gating)
- Object recognition
- Sociability test

**Microglia preparation**
- Isolation of CD11b cells positive by MACS

**Mattei et al. submitted**

**Polyinosinic:polycytidylic acid (Poly I:C):** Synthetic ligand of TLR3 (mimicks viral encounter)
Classical markers of neuroinflammation in PolyI:C mice are normalized by chronic minocycline treatment

$[^{18}\text{F}]\text{GE180}$ Hippocampal binding autoradiography

$[^{11}\text{C}]\text{PBR28}$ PET

Bloomfield et al. 2014

Immunohistochemistry for Iba1

Mattei et al. submitted

Both radiotracers bind to Translocator Protein (TSPO) peripheral benzodiazepine receptor – highly expressed by microglia.
Phagocytosis is impaired and associated genes are downregulated

Mattei et al. submitted
Minocycline normalizes the following aspects

- Behavior
- Transcriptome
- PET ligand binding/Iba 1
- Functional Phagocytosis

Microglia phenotype associated with schizophrenia endophenotype „burn out“
Impaired phagocytosis – a sign of microglia „burn out“ in Alzheimer‘s disease

Heppner et al. Nature Reviews Neuroscience 2015

Krabbe et al. Plos One 2013
Common microglia profile in psychiatric neurodegenerative disorders?

Holtman et al. Acta Neuropathologica Communications 2015

**Figure 6**: Summary figure describing the main findings of the current paper. Survelling microglia are activated either acutely by a ligand such as LPS or by a neurodegenerative and aging brain environment.
Common microglia profile in PolyI:C and APP/PS1 model

Mattei et al. submitted
Common microglia profile in psychiatric and neurodegenerative disorders

Figure 6: Summary figure describing the main findings of the current paper. Survelling microglia are activated either acutely by a ligand such as LPS or by a neurodegenerative and aging brain environment.

Schizophrenia was named “dementia praecox” by Benedict Augustin Morel in 1860.

Holtman et al. Acta Neuropathologica Communications 2015
Mattei et al. submitted
Acknowledgements

MDC Berlin
Dr. Daniele Mattei

University of Leipzig
Dr. Winnie Deuter Conrad
Prof. Peter Brust
Prof. Osama Sabri
Prof. Swen Hesse
Prof. Marianne Pratt

University of Hannover
Prof. Tobias L. Ross

University Hospital Charite Berlin
Prof. Andreas Heinz

University of Groningen
Prof. Eric Boddeke
Dr. Bart Eggen
Dr. Inge Holtmann
Dr. Wandert Schaafsma

BIH
Dr. Andranik Ivanov

Dr. Dieter Beule

Philipp Jordan
Dilansu Güneykaya
Alice Buonfiglioli
Prof. Helmut Kettenmann

Funding
DFG SFB TR43
DFG WO 1418/3-1

MDC/BIMSB
Dr. Carmelo Ferrai
Prof. Ana Pombo

Nencki Institute Warszawa
Prof. Bozena Kaminska
Dr. Piotr Przanowski