Rejuvenation of the Aged Brain

An Example of Drug Delivery in Drug Repurposing

Ludwig Aigner
IntelGenx, Grand Opening, Saint-Laurent, May 10th 2016
YESTERDAY
Age: Risk Factor Number 1

Teresa Niccoli, Linda Partridge, Ageing as a Risk Factor for Disease, Current Biology, Volume 22, Issue 17, 2012, R741 - R752
with the age of 90

every 2nd person suffers of dementia
Massive Increase in the Prevalence of AD
Dome truths and pillar talk
Global population, % of total

Age 65 years

Age 15 years

1970

2015

2060

Source: UN
A HUGE WAVE OF PATIENTS WITH DEMENTIA
A HUGE UNMET NEED

No / Little Efficacy of Dementia Drugs
Non-Genetic

Genetic
Alzheimer Pathology

![Comparison of normal and Alzheimer neurons with neurofibrillary tangles and amyloid plaques.](image)
Are We Targeting the Right Thing?

Rodrigue et al., Neuropsychol Rev. 2009
1001 Reasons for Neuronal Cell Death ???

[Diagram showing various reasons for neuronal cell death, including protein aggregation, protein degradation, mitochondrial toxicity, and signal transduction.]
Our Targets: Pleiotropic Signaling

- Neurotransmission
  eg Calabresi et al. 2007

- Neurogenesis
  eg Regensburger et al. 2014

- Blood Brain Barrier
  eg Zlokovic et al. 2008

- Neuroinflammation
  eg Hirsch et al. 2009

- Neurodegeneration
  eg Schapira et al. 2011

- Demyelination

- Axonal Damage
  eg Franklin et al. 2008
AGING and REJUVENATION
The Aged Brain is a „Diseased“ Brain

Neurotransmission  
*eg Calabresi et al. 2007*

Neurogenesis  
*eg Regensburger et al. 2014*

Blood Brain Barrier  
*eg Zlokovic et al. 2008*

Neuroinflammation  
*eg Hirsch et al. 2009*

Neurodegeneration  
*eg Schapira et al. 2011*

Demyelination  
Axonal Damage  
*eg Franklin et al. 2008*
Live = Aging

Growth  Plasticity  Degeneration  Disease

Disease Risk

Regeneration
Aging and Rejuvenation

Growth  Plasticity  Degeneration  Disease

„Regenerative Pharmacology“
Can We Turn Back the Clock?
Muscle Research, Aging, and Regenerative Medicine?
Young blood helps to heal aging muscles

Rejuvenation of aged progenitor cells by exposure to a young systemic environment

Irina M. Conboy\textsuperscript{1,*†}, Michael J. Conboy\textsuperscript{1,*}, Amy J. Wagers\textsuperscript{2,*†}, Eric R. Girma\textsuperscript{1}, Irving L. Weissman\textsuperscript{2} & Thomas A. Rando\textsuperscript{1,3}

\textsuperscript{1}Department of Neurology and Neurological Sciences and \textsuperscript{2}Department of Pathology, Stanford University School of Medicine, Stanford, California 94305, USA

\textsuperscript{3}GRECC and Neurology Service, VA Palo Alto Health Care System, Palo Alto, California 94304, USA
Modulating the Systemic Milieu: a Valid Approach

The ageing systemic milieu negatively regulates neurogenesis and cognitive function

Saul A. Villeda1,2, Jian Luo1, Kira I. Mosher1,2, Bende Zou3, Markus Britschgi1, Gregor Bieri1,4, Trisha M. Stan1,5, Nina Fainberg4, Zhaoping Ding1,5, Alexander Eggel1, Kurt M. Lucin1, Eva Czirr1, Jeong--Soo Park1, Sebastien Couillard-Despres6, Ludwig Aigner6, Ge Li7, Elaine R. Peskind7,8, Jeffrey A. Kaye9, Joseph F. Quinn9, Douglas R. Galasko10, Xinmin S. Xie1, Thomas A. Rando11,12, & Tony Wyss-Coray12,5,11

inflammation

neurogenesis

cognition
Old Blood Contributes to Brain Aging

Eotaxin Reduces Neurogenesis

Eotaxin Worsens Cognition

- Eotaxin reduces neurogenesis
- Eotaxin worsens cognition
Eotaxin  Leukotrienes

Allergy / Asthma  Brain Aging  Aging / Degeneration
Leukotrienes Impact on Brain Aging

- Neurotransmission
  - e.g. Calabresi et al. 2007

- Neurogenesis
  - e.g. Regensburger et al. 2014

- Blood Brain Barrier
  - e.g. Zlokovic et al. 2008

- Neuroinflammation
  - e.g. Hirsch et al. 2009

- Neurodegeneration
  - e.g. Schapira et al. 2011

- Demyelination

- Axonal Damage
  - e.g. Franklin et al. 2008

Montelukast
Proof of Principle:
Inhibition of Leukotriene Receptors Improves Cognition in Aged Rats
ARTICLE

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OPEN

Structural and functional rejuvenation of the aged brain by an approved anti-asthmatic drug

Julia Marschallinger1,2, Iris Schäffner3, Barbara Klein1,2, Renate Gelfert1,2, Francisco J. Rivera1,2, Sebastian Illes1,2, Lukas Grassner1,2,4, Maximilian Janssen1,2, Peter Rotheneichner1,2,5, Claudia Schmuckermair6, Roland Coras7, Marta Boccazzi8, Mansoor Chishty9, Florian B. Lagler10, Marija Renic11, Hans-Christian Bauer2,12, Nicolas Singewald6, Ingmar Blümcke7, Ulrich Bogdahn13, Sebastien Couillard-Despres2,5, D. Chichung Lie3, Maria P. Abbraccio8 & Ludwig Aigner1,2
Parkinson’s Disease Dementia / Lewy Body Dementia

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<th>symptoms</th>
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<th>therapy</th>
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<td>motoric</td>
<td>dopaminergic cell loss</td>
<td>dopamine replacement</td>
</tr>
<tr>
<td>dementia</td>
<td>???</td>
<td>rivastigmine</td>
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</table>

**Symptoms**

- 60% Parkinson’s Disease Dementia / Lewy Body Dementia

**Pathology**

- Dopaminergic cell loss

**Therapy**

- Dopamine replacement
- Rivastigmine

**Neurotransmission**

- Eg Calabresi et al. 2007

**Neurogenesis**

- Eg Regensburger et al. 2014

**Blood Brain Barrier**

- Eg Zlokovic et al. 2008

**Neuroinflammation**

- Eg Hirsch et al. 2009

**Neurodegeneration**

- Eg Schapira et al. 2011
Montelukast Improves Cognitive Functions in PD / LBD Animals
for what is thought to be best in any relationship.

point of view.

Repurpose

more suited for a different purpose, or use or convert for use.

for what is thought to be best in any relationship.
Annual Counts of Publications “Drug Repurposing”
“All De- and Regenerations are Similar”
Regenerative Medicine

REPAIR
REPLACE
RESTORE
REGENERATE
REJUVENATE

All Organs
Different Diseases
Montelukast as an Anti-Dementia Therapeutic

Before

MMSE 13: moderate to severe dementia

After 2 Months of Montelukast

MMSE 22: mild dementia
Let’s make a better Montelukast