NNZ-2566 Program Presented at International Autism Conference

SYDNEY, Australia, 7 August 2012: Dr Michael Snape, Chief Scientific Officer of Autism Therapeutics Ltd, gave a presentation on NNZ-2566 and the rationale for its use in autism spectrum disorders at the ICare4Autism 2012 International Autism Conference in Jerusalem. Autism Therapeutics Ltd is supporting preparations for the clinical trials in Rett Syndrome and development of NNZ-2566 in autism spectrum disorders under contract to Neuren Pharmaceuticals Limited (ASX: NEU). A copy of the presentation is attached to this announcement and will be posted on Neuren's website www.neurenpharma.com.

About Rett Syndrome

Rett Syndrome is a post-natal neurological disorder which occurs almost exclusively in females following apparently normal development for the first six months of life. Typically, between 6 to 18 months of age, patients experience a period of rapid decline with loss of purposeful hand use and spoken communication. Many patients have recurrent seizures. They experience a variety of motor problems including increased muscle tone (spasticity) and abnormal movements. They are never able to provide for their own needs. It is a rare disorder and is believed to be second only to Down Syndrome as a cause of chronic neurological problems that include severe communication, motor disabilities and epilepsy. Rett Syndrome is caused by mutations on the X chromosome of a gene called MECP2. There are more than 200 different mutations found on the MECP2 gene. Rett Syndrome strikes all racial and ethnic groups, and occurs worldwide in up to 1 of every 10,000 female births and affects some 15,000 girls and women in the U.S. alone.

About Neuren

Neuren Pharmaceuticals is a biopharmaceutical company developing new therapies for brain injury, neurodevelopmental and neurodegenerative disorders and cancer. Neuren presently has two clinical-stage molecules, NNZ-2566 and Motiva®, in Phase 2 clinical trials largely funded by the US Army and the National Health and Medical Research Council, respectively. Through its subsidiary, Perseis Therapeutics Limited, Neuren is developing monoclonal antibodies against Trefoil Factors 1 and 3, proteins produced by cancer cells that are associated with cancer spread and reduced patient survival.

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autism therapeutics

NNZ-2566

neuren pharmaceuticals

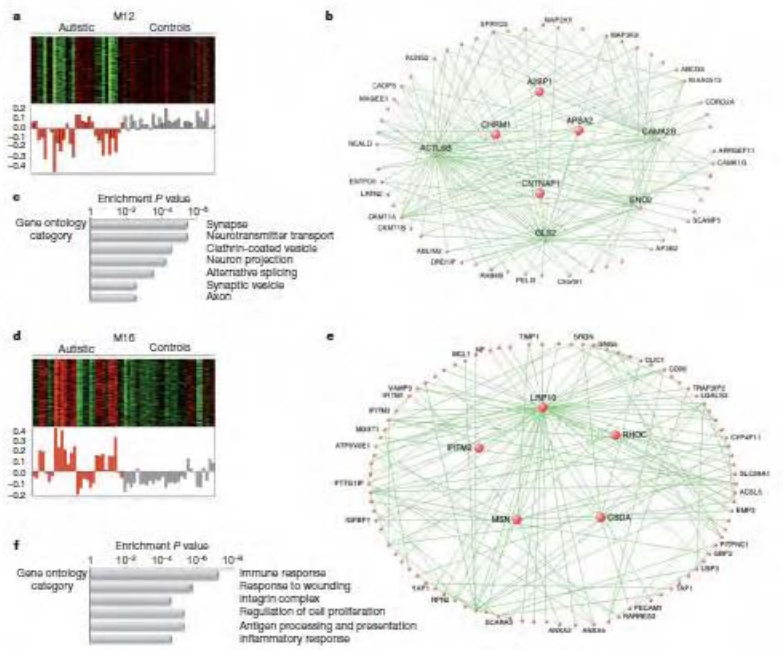
Rationale for use in Autism Spectrum Disorders

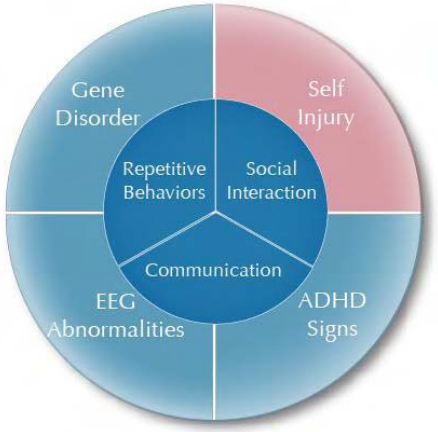
Overview

- Autism: a disorder of synaptic connectivity involving neuroinflammation
- Both synaptic connectivity and neuroinflammatory processes may involve the PI3K-Akt-mToR pathway
- The natural growth factor IGF-1 is broken down in the body to IGF-1[1-3] or Glypromate.
- Glypromate and NNZ-2566 act to reduce neuroinflammation.
- These effects may be mediated by modulation of the PI3K-Akt-mToR pathway.
- NNZ-2566 is an analogue of Glypromate developed by Neuren Pharmaceuticals Ltd .
- NNZ-2566 has enhanced oral availability and a pharmaceutical profile suitable for investigation in autism spectrum disorders.
- Clinical studies are planned by Neuren

Autism

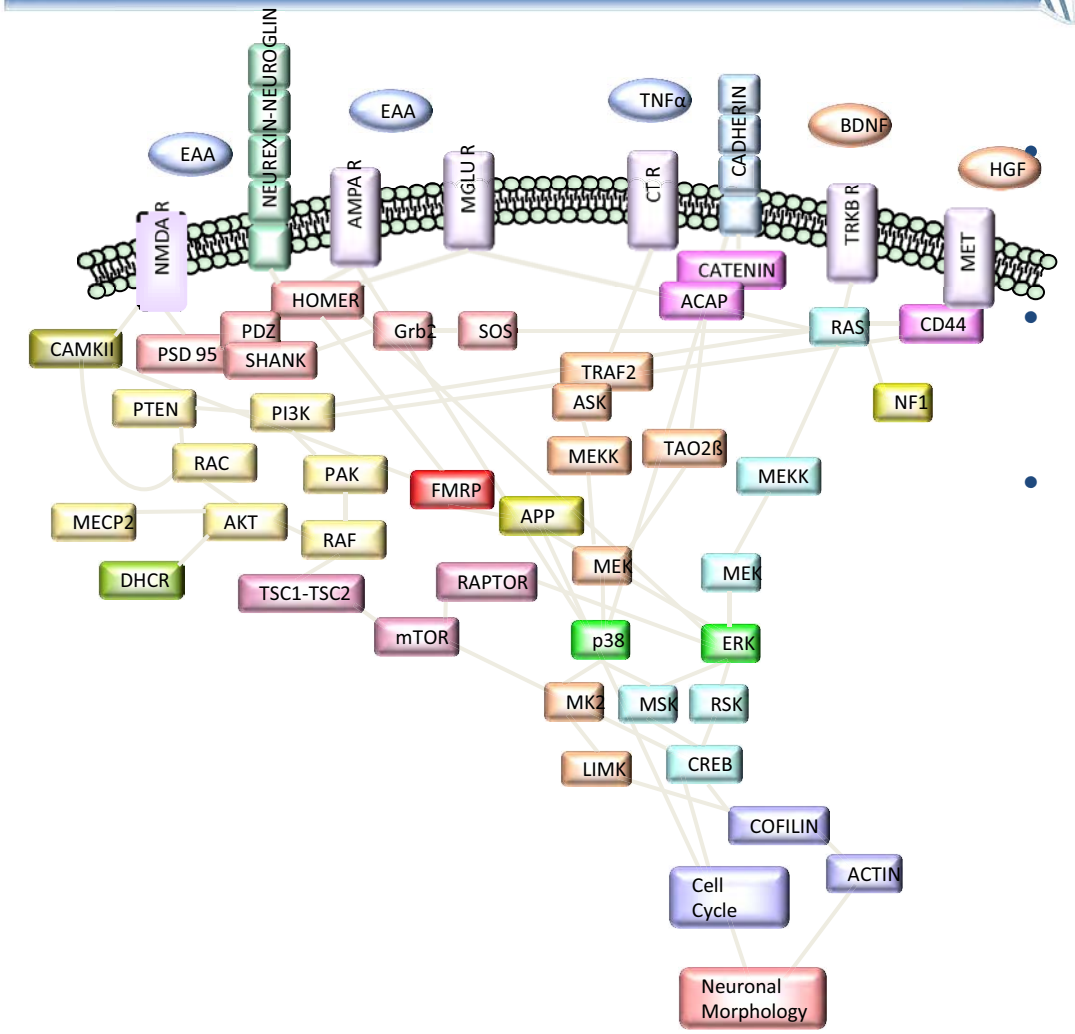
- Heterogeneous disorder
- Heavily genetically influenced
- Genes affected commonly relate to synaptic or immune function[1]





[1] Vioneagu et al (2011) Nature 474:380

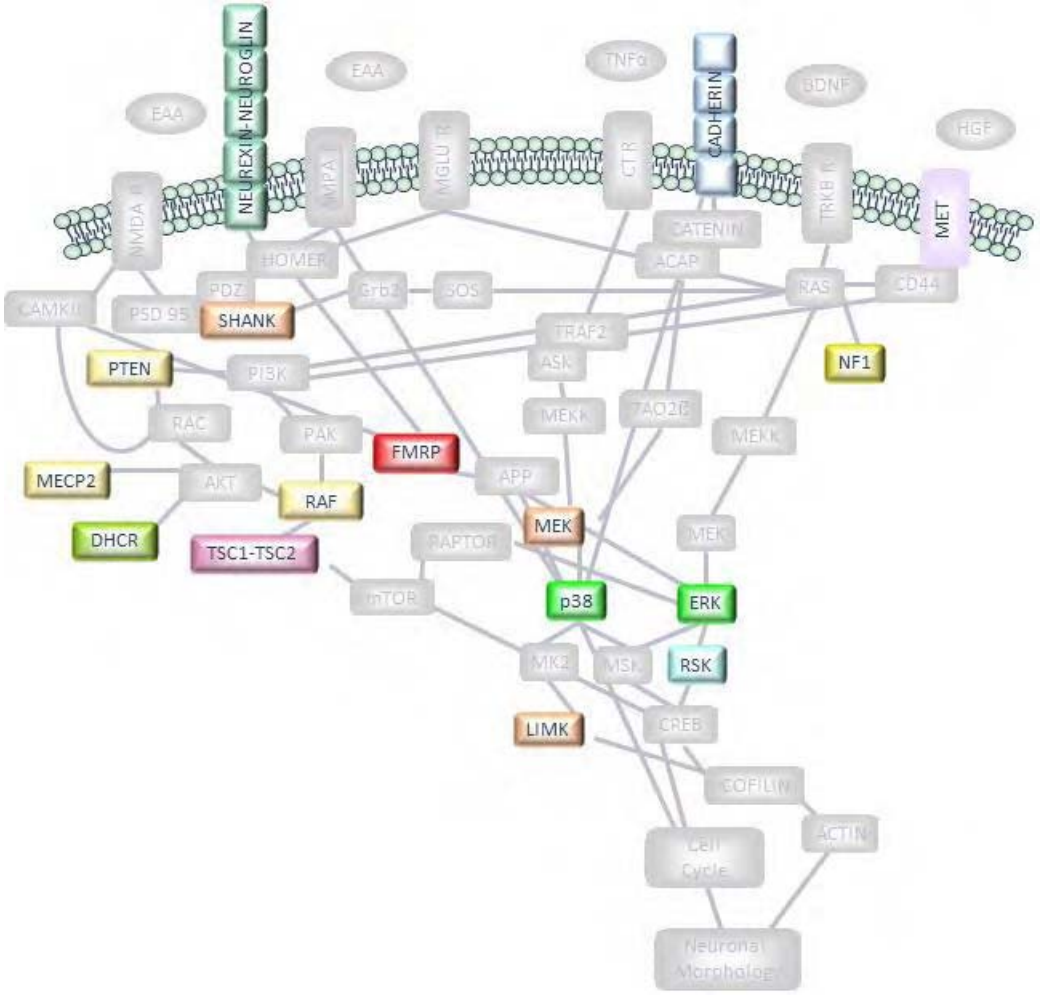
Neuronal Signalling Pathways



- Neural function relies on plasticity of synaptic connections
- Intraneuronal pathways underlying plasticity well understood
- Pathways involve e.g. Ras-MEK-ERK or PTEN-Akt-mToR[2]

[2] Kelleher et al (2004) Neuron 44:59

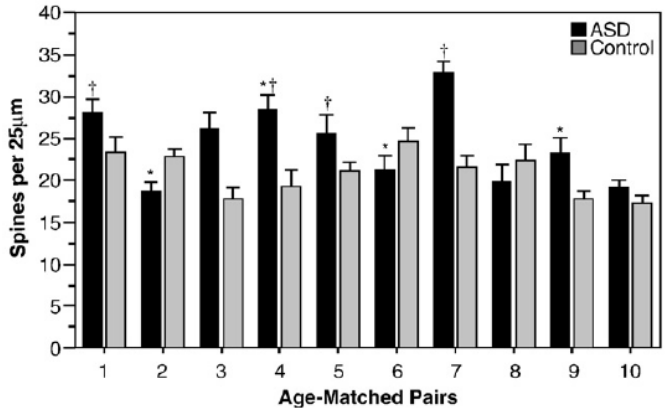
Mapping ASDs onto Signalling Pathways

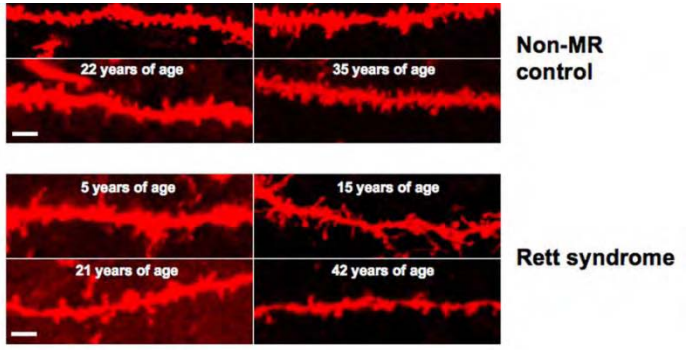


NF1	NEUROFIBROMATOSIS
FMRP	FRAGILE X SYNDROME
TSC1-TSC2	TUBEROUS SCLEROSIS
PTEN	COWDEN SYNDROME
RAF	NOONAN SYNDROME
LIMK	WILLIAMS-BEUREN SYNDROME
DHCR	SMITH LEMLI OPTIZ SYNDROME
MEK	COSTELLO SYNDROME
RSK	COFFIN-LOWRY SYNDROME
SHANK	PHELAN McDERMID SYNDROME
MECP2	RETT SYNDROME
MET	GENE VARIANT ASSOCIATED WITH AUTISM
CADHERIN	GENE VARIANT ASSOCIATED WITH AUTISM
NEUREXIN-NEUROGLIN	GENE VARIANT ASSOCIATED WITH AUTISM
p38	ACTIVATION IN AUTISM
ERK	ACTIVATION IN AUTISM

Synapses in ASDs

- Altered synapses in idiopathic[3] and syndromic autism[4,5]





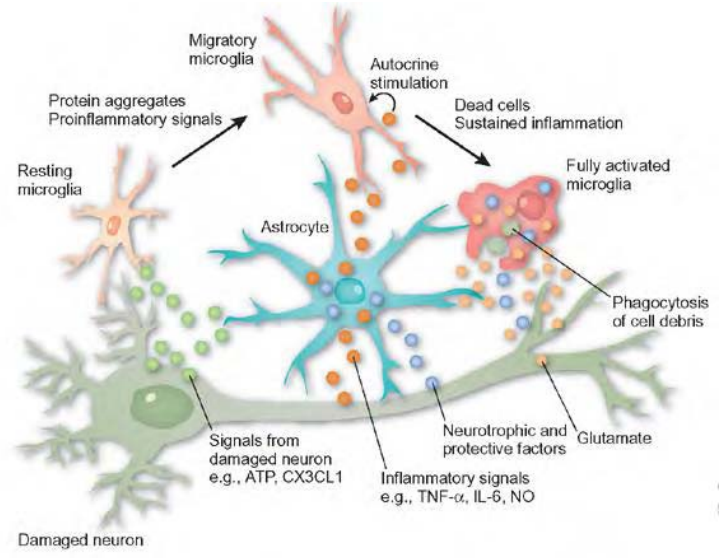
[3] Hutsler and Zhang (2010) Brain Res 1309:83

[4] Irwin et al (2000) Cerebral Cortex 10:1038

[5] Chapleau et al (2009) Neurobiol Dis 35:219

Neuroinflammation

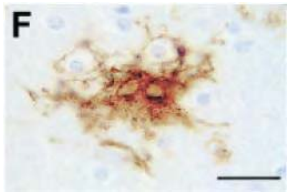
- Neurons supported within the brain by microglia[6]
- Microglia have a diverse range of functions[7] including:
  - Regulation of transmitters e.g. glutamate
  - Removal damaged tissue
  - Regulation of synapses



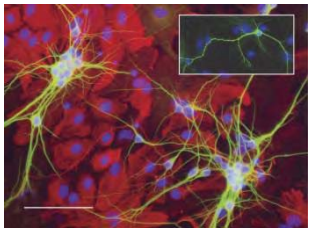
[6] Monk and Shaw (2006) Nat Med 12:885
[7] Hughes (2012) Nature 485:570

Neuroinflammation in ASDs

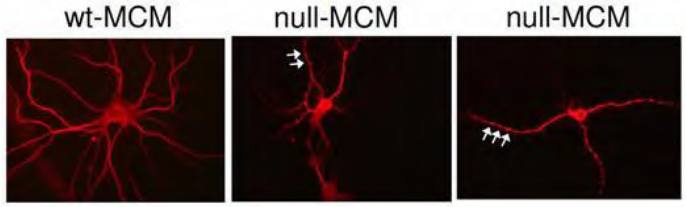
- Microglia and astroglia are activated in brain in autism[8]



- Fragile X Syndrome astrocytes can institute neuronal phenotype[9]



- Microglia in Rett Syndrome[10]



[8] Vargas et al (2005) Ann Neurol. 57:67
[9] Jacobs et al (2010) BMC Neurosci. 11:132
[10] Maezawa and Jin (2010) J Neurosci. 30:5346

Cytokines in ASDs

- Cytokines are cell signalling molecules produced by immune system cells including microglia
- Interleukin-6 is an example.
- Interleukin-6 may be involved in autism[11], Fragile X Syndrome[12] and Rett Syndrome[13]
- Interleukin-6 can activate microglia[14]
- IL-6 induces changes in dendritic spine density and reduces social interaction in an animal model of autism[15]

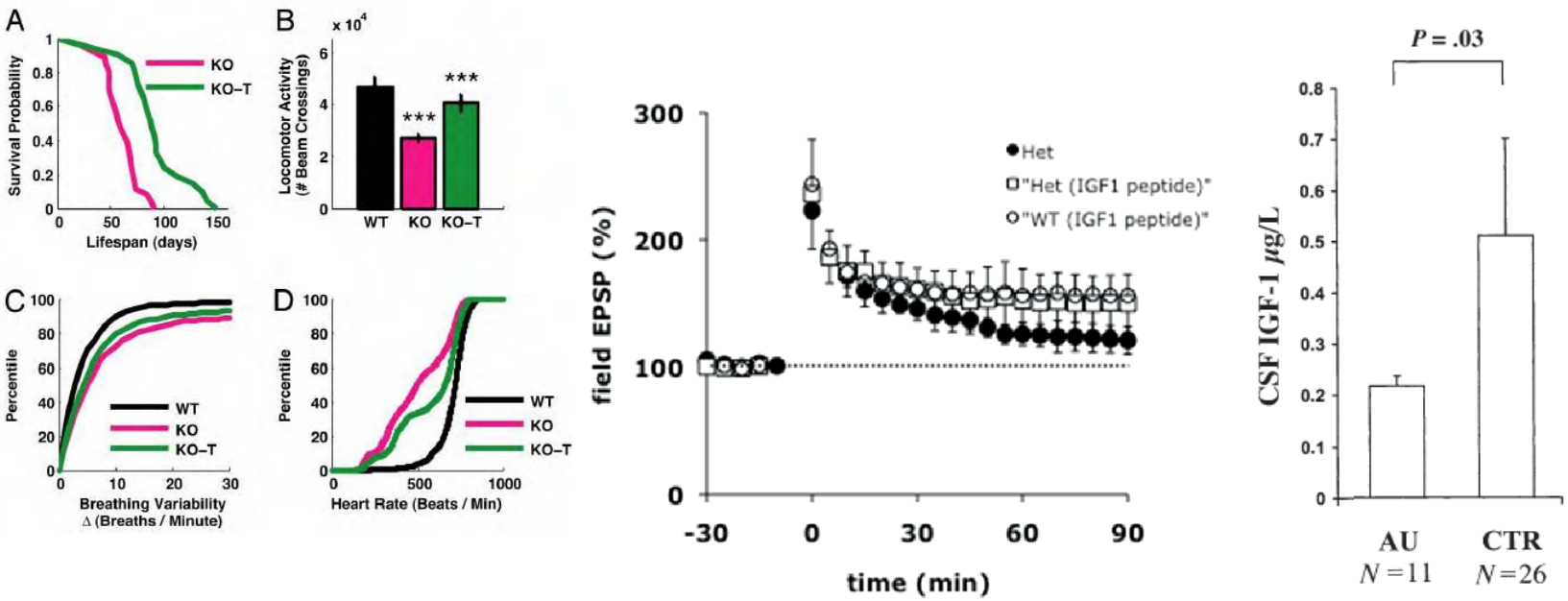
[11] Ashwood et al (2011) Brain Behav Immun. 25:40
[12] Ashwood et al (2010) Brain Behav Immun. 24:898
[13] De Filippis et al (2012) Neuropsychopharmacology 37:1152
[14] Krady et al (2008) J Neurosci Res. 86:1538
[15] Wei et al (2012) Biochim Biophys Acta. 1822:831

Summary

- Idiopathic and syndromic ASDs involve:
  - Neuroinflammation
  - Changes in cytokines such as IL-6
  - Altered microglial function
  - Aberrant control of synapse formation
  - Potentially via the Akt-mToR pathway
- Interventions that address these issues may have therapeutic utility

IGF-1

- Insulin like growth factor 1 (IGF-1) is a natural growth factor that has many functions in controlling growth, including neurons and synapses.
- IGF-1 is altered in autism[16], may rescue function in Rett Syndrome[17] and in ASD caused by changes in the shank3 gene[18]:



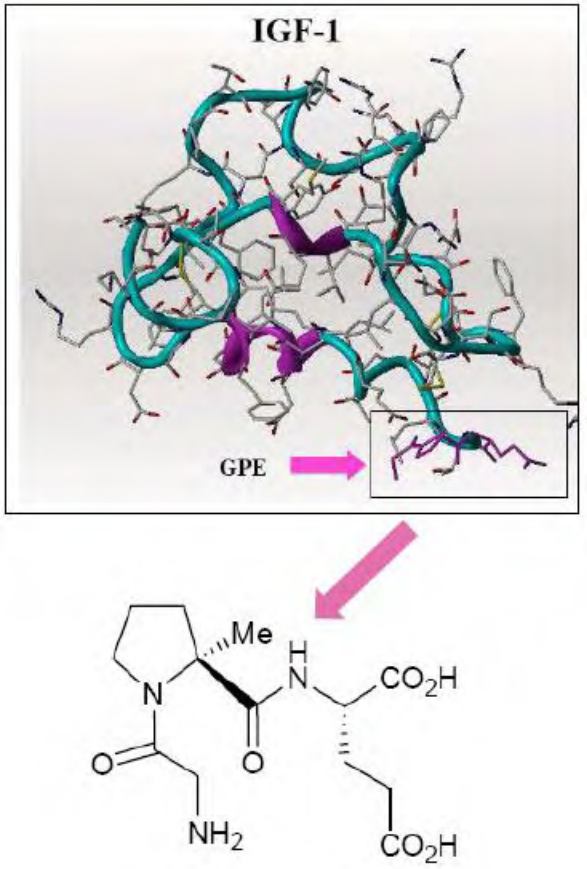
[16] Riikonen (2003) J Child Neurol 18 693

[17] Tropea et al. 2009, PNAS 106 2029

[18] Buxbaum et al http://sfari.org/news-and-opinion/conference-news/2011/international-congress-of-human-genetics-2011/growth-factor-improves-autism-symptoms-in-mice

IGF-1[1-3]

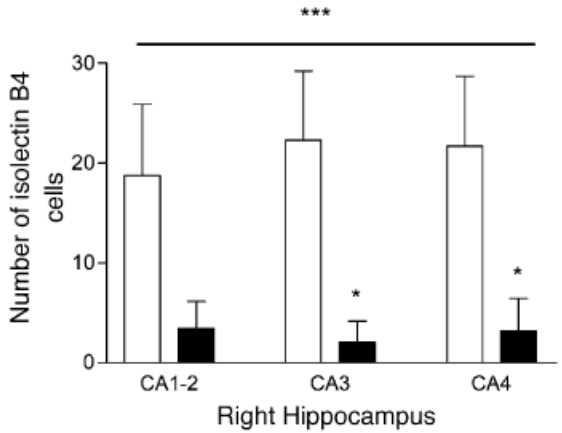
- IGF-1 is metabolized in the body
- Endogenous peptidase enzymes cleave IGF-1, separating the terminal tripeptide
- The terminal tripeptide known as IGF-1[1-3] or Glypromate rescues function in the *mecp2* mouse model of Rett Syndrome[19]



[19] Tropea et al. (2009) PNAS 106:2029

IGF-1[1-3] Mechanism of Action

- IGF-1[1-3] (Glypromate):
  - Reduces cytokines[20] and neuroinflammatory markers in brain[21]
  - Activates Akt-mToR pathway in microglia[22]
  - Increases markers of presynaptic and postsynaptic synapses[23]
  - Activates Akt-mToR pathway in *mecp2* knockout mouse model of Rett Syndrome[22]



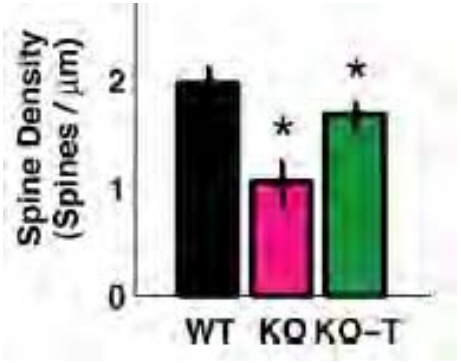
IGF[1-3] reduces number of microglia in hippocampus following hypoxia ischemia in rat brain[22]

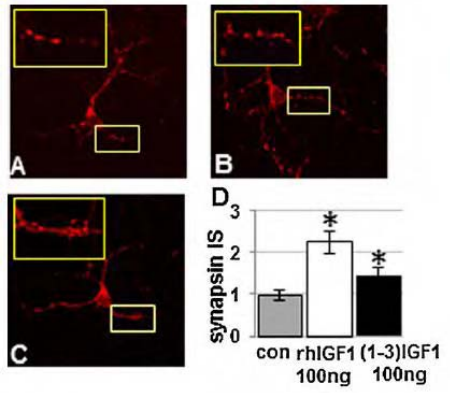
[20] Casandra et al (2011) http://www.conference-services.net/reports/template/onetextabstract.xml?xsl=template/onetextabstract.xsl&abstractID=529747
[21] Guan et al (2004) Neuropharmacology 47:892
[22] Tropea et al. (2009) PNAS 106:2029
[23] Corvin et (2012) Neurosci Lett. 520:51

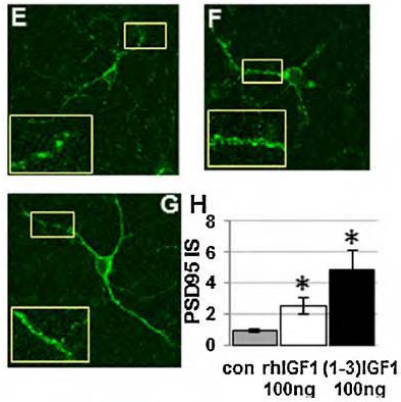
IGF-1[1-3] Mechanism of Action

- IGF-1[1-3] (Glypromate) increases dendritic spine density in *mecp2* mouse model of Rett Syndrome[24]

- IGF-1[1-3] (Glypromate) increases pre- and post- synaptic markers[25]





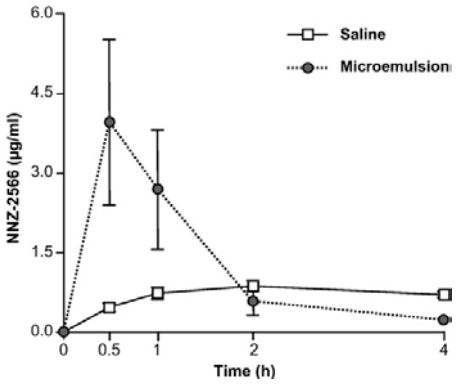


[24] Corvin et (2012) Neurosci Lett. 520:51

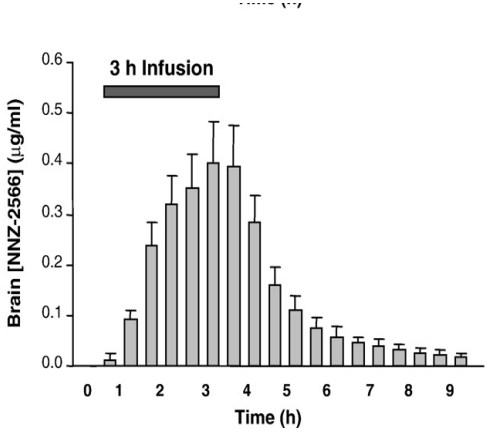
[25] Tropea et al. (2009) PNAS 106:2029

NNZ-2566

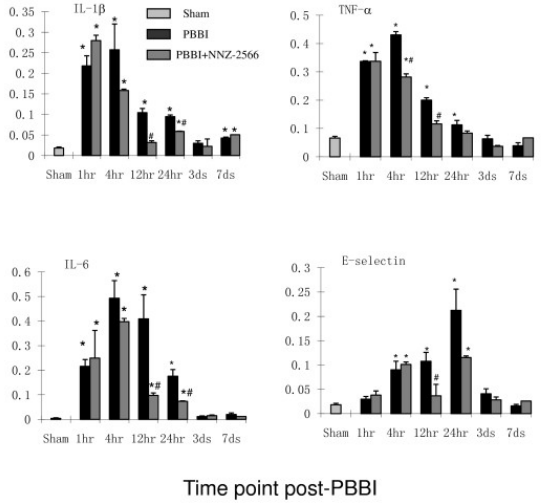
- Clinical study of IGF-1 (InCrelex™) underway[26]
- IGF-1 (InCrelex™) not orally available and may not penetrate into brain[27]
- NNZ-2566 is IGF-1[1-3] modified to be orally available and penetrate the brain[28]
- NNZ-2566 may act on cytokines such as IL-6[29]



Orally available



Brain penetrant



[26] http://clinicaltrials.gov/ct2/show/NCT01253317?term=increlex+rett+syndrome&rank=1

[27] EMEA Scientific Discussion Increlex

[28] Bickerdike et al (2009) J Neurol Sci. 278:85

[29] Casandra et al (2011) http://www.conference-services.net/reports/template/onetextabstract.xml?xsl=template/onetextabstract.xsl&abstractID=529747

Summary

- ASDs may involve alterations in:
  - Synaptic function
  - Neuroinflammation
  - the Akt-mToR pathway
- IGF-1 and Glypromate is a natural growth factor that:
  - May act via the Akt-mToR pathway
  - Reduces neuroinflammation
  - Rescues deficits in the synapse
  - Acts in transgenic models of ASDs
- NNZ-2566
  - Modified form of IGF-1[1-3] suited to medicinal use
  - Currently planned for clinical investigation in Rett Syndrome