autism therapeutics

NNZ-2566

neuren pharmaceuticals

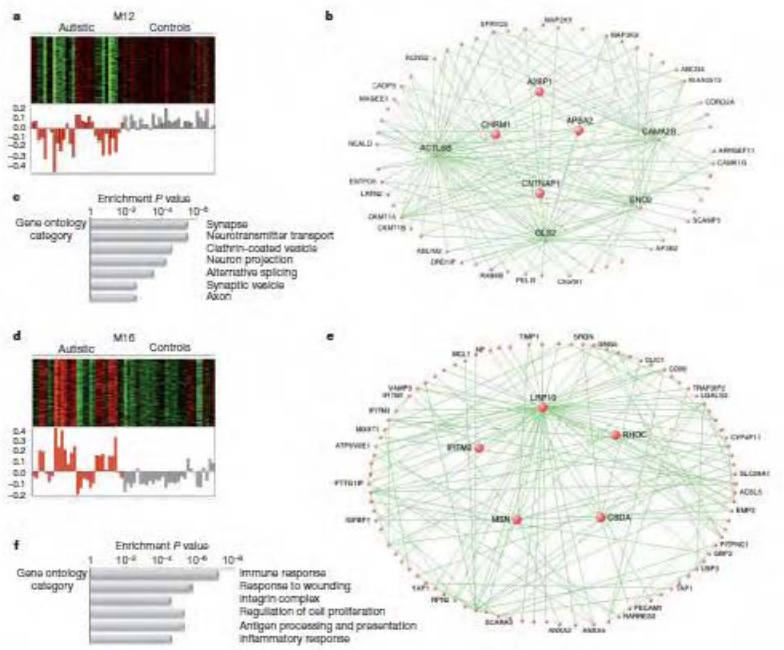
Rationale for use in Autism Spectrum Disorders

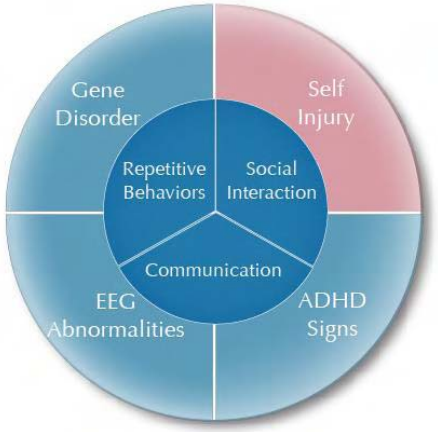
Overview

- 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

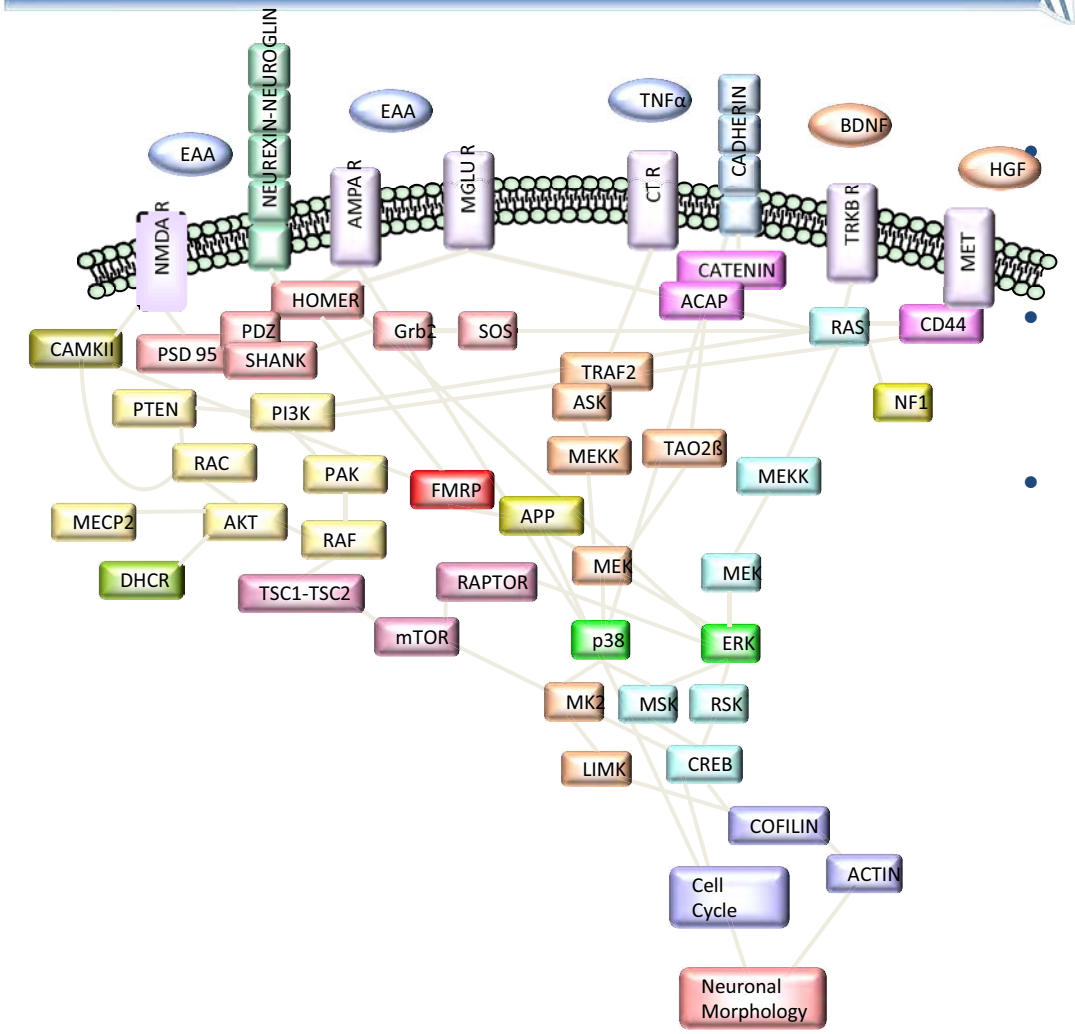
- Heterogeneous disorder
- Heavily genetically influenced
- Genes affected commonly relate to synaptic or immune function[1]





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

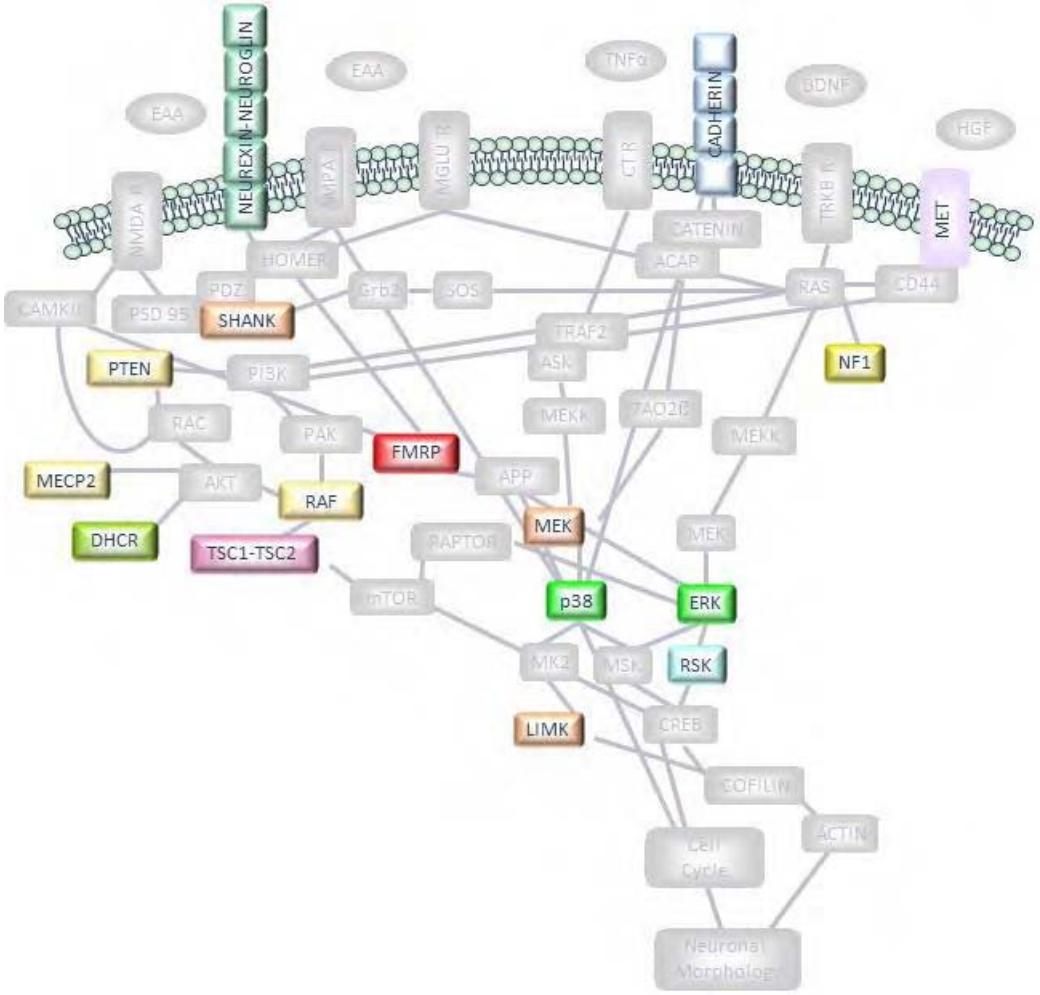
Neuronal Signalling Pathways



- 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

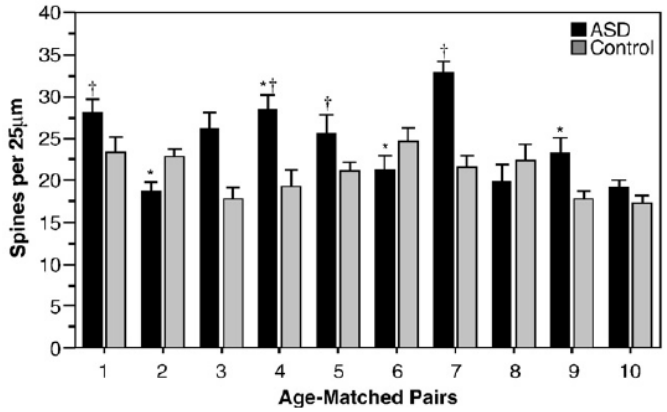
Mapping ASDs onto Signalling Pathways

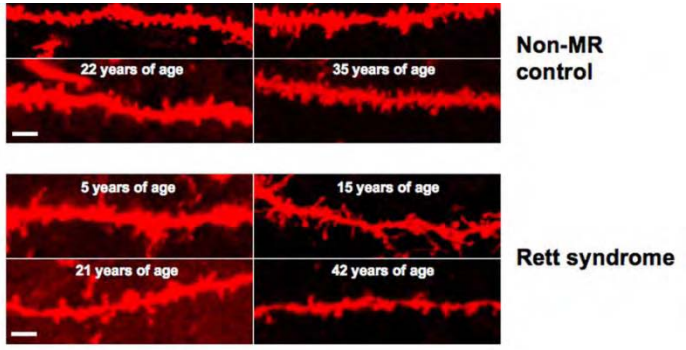


NF1	NEUROFIBROMATOSIS
FMRP	FRAGILE X SYNDROME
TSC1-TSC2	TUBEROUS SCLEROSIS
PTEN	COWDEN SYNDROME
RAF	NOONAN SYNDROME
LIMK	WILLIAMS-BEUREN SYNDROME
DHCR	SMITH LEMLI OPTIZ SYNDROME
MEK	COSTELLO SYNDROME
RSK	COFFIN-LOWRY SYNDROME
SHANK	PHELAN McDERMID SYNDROME
MECP2	RETT SYNDROME
MET	GENE VARIANT ASSOCIATED 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]





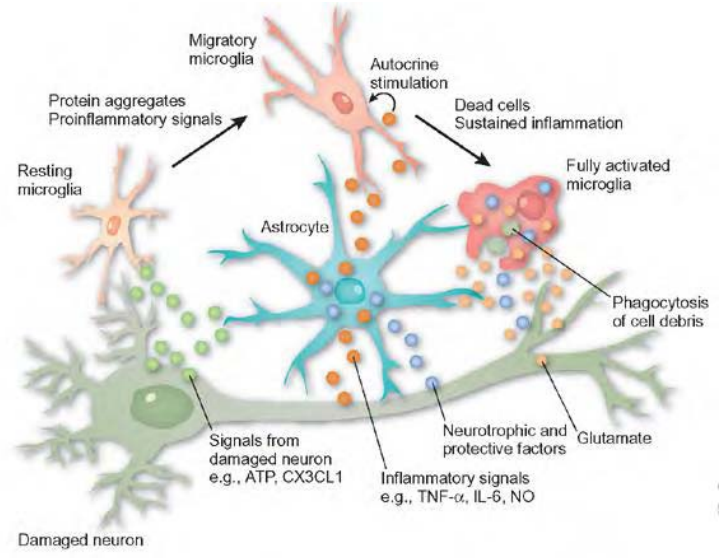
[3] Hutsler and Zhang (2010) Brain Res 1309:83

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

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

Neuroinflammation

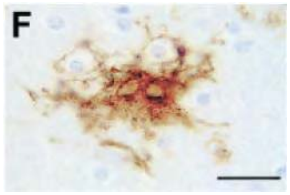
- Neurons supported within the brain by microglia[6]
- Microglia have a diverse range of functions[7] including:
  - Regulation of transmitters e.g. glutamate
  - Removal damaged tissue
  - Regulation of synapses



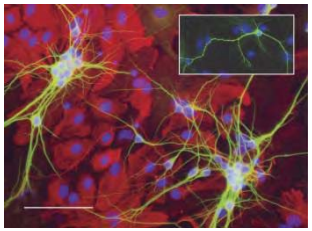
[6] Monk and Shaw (2006) Nat Med 12:885
[7] Hughes (2012) Nature 485:570

Neuroinflammation in ASDs

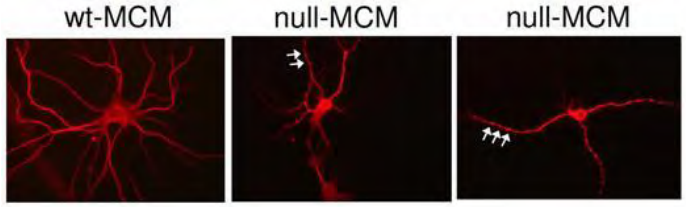
- Microglia and astroglia are activated in brain in autism[8]



- 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]

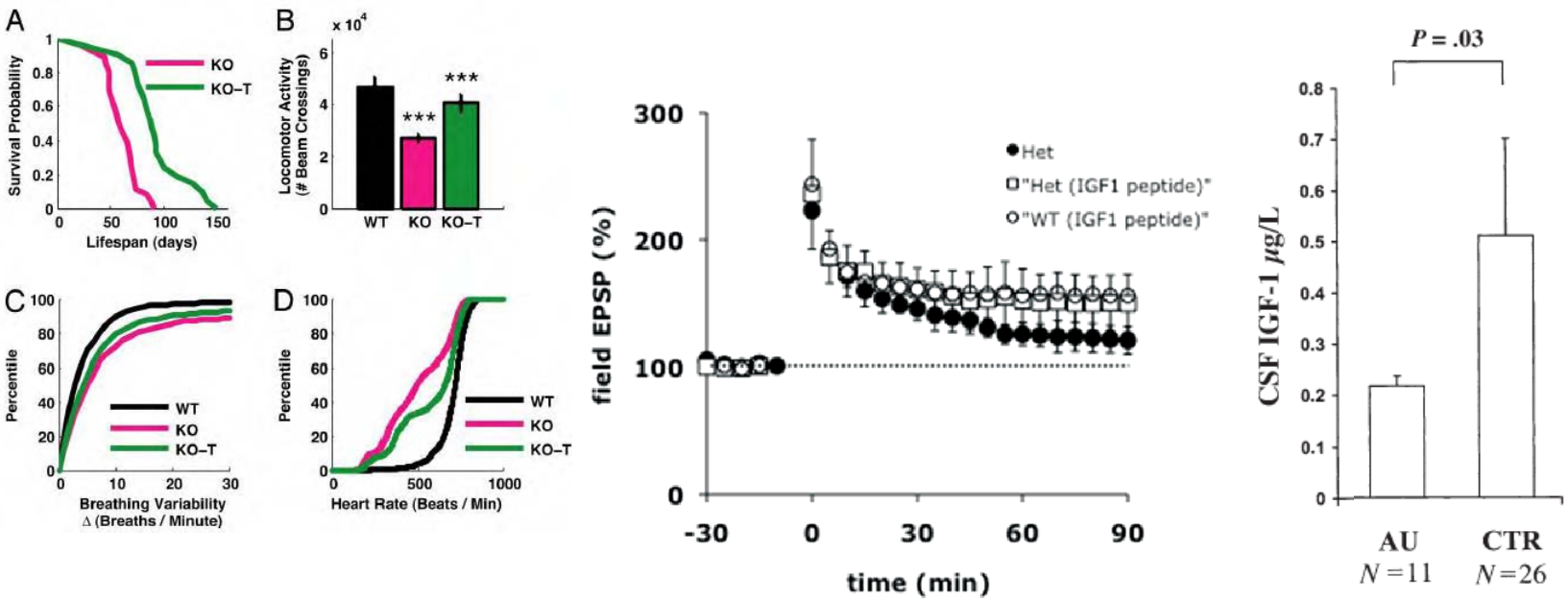
[11] Ashwood et al (2011) Brain Behav Immun. 25:40
[12] Ashwood et al (2010) Brain Behav Immun. 24:898
[13] De Filippis et al (2012) Neuropsychopharmacology 37:1152
[14] Krady et al (2008) J Neurosci Res. 86:1538
[15] Wei et al (2012) Biochim Biophys Acta. 1822:831

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]:



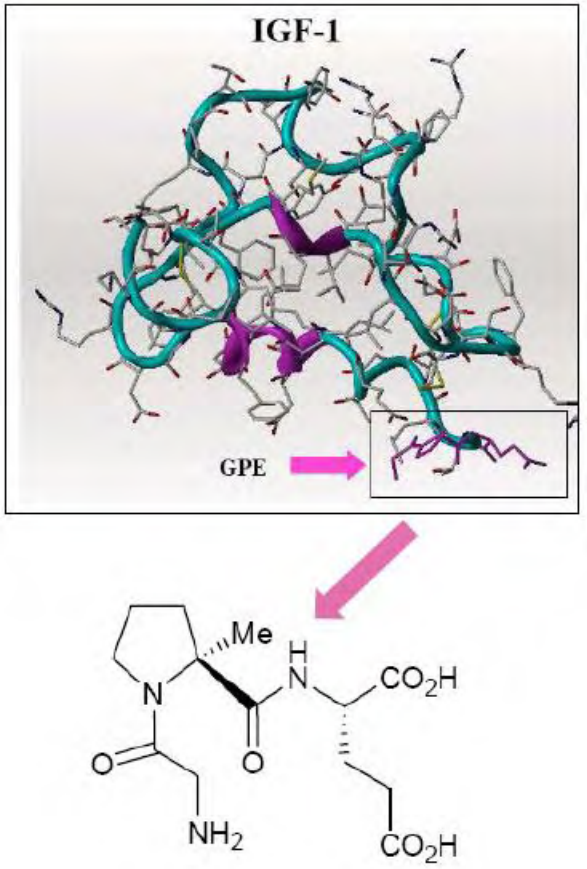
[16] Riikonen (2003) J Child Neurol 18 693

[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]

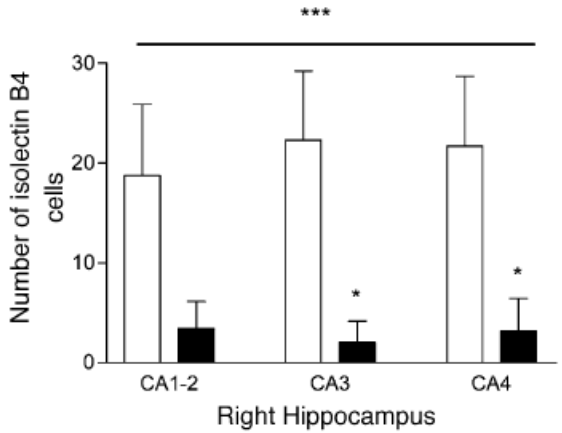
- IGF-1 is metabolized in the body
- Endogenous peptidase enzymes cleave IGF-1, separating the terminal tripeptide
- The terminal tripeptide known as IGF-1[1-3] or Glypromate rescues function in the *mecp2* mouse model of Rett Syndrome[19]



[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]



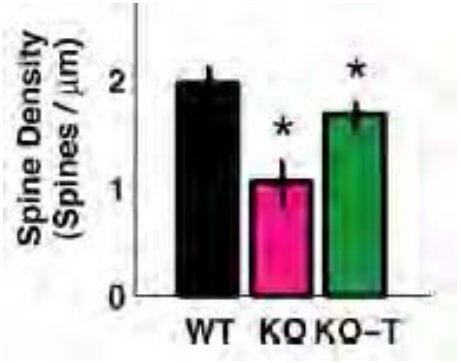
IGF[1-3] reduces number of microglia in hippocampus following hypoxia ischemia in rat brain[22]

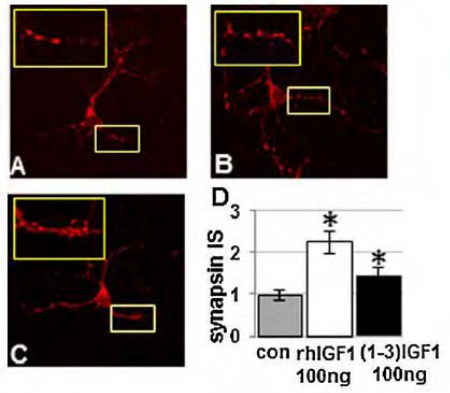
[20] Casandra et al (2011) http://www.conference-services.net/reports/template/onetextabstract.xml?xsl=template/onetextabstract.xsl&abstractID=529747
[21] Guan et al (2004) Neuropharmacology 47:892
[22] Tropea et al. (2009) PNAS 106:2029
[23] Corvin et (2012) Neurosci Lett. 520:51

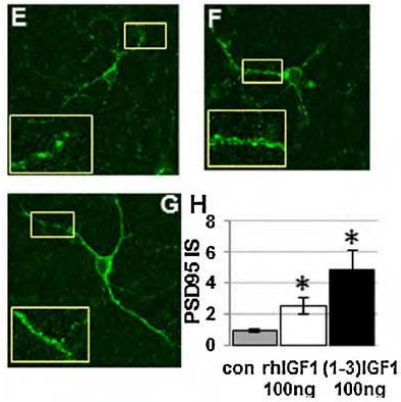
IGF-1[1-3] Mechanism of Action

- 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]





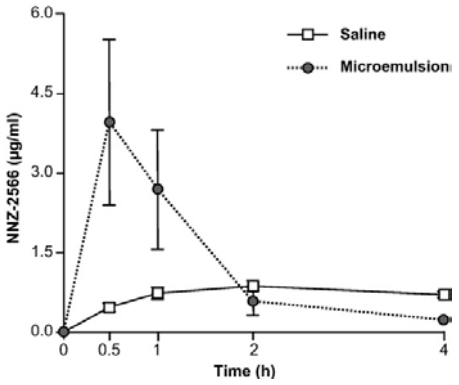


[24] Corvin et (2012) Neurosci Lett. 520:51

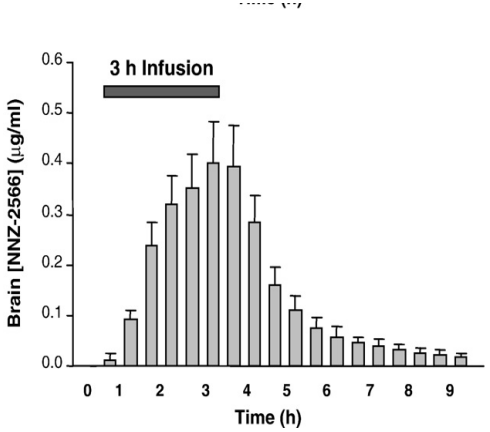
[25] Tropea et al. (2009) PNAS 106:2029

NNZ-2566

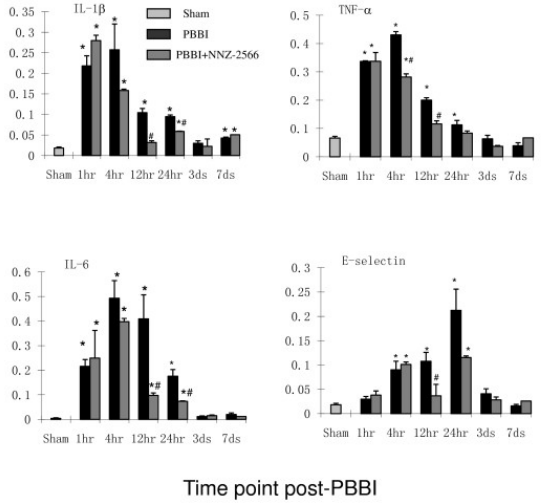
- Clinical study of IGF-1 (InCrelex™) underway[26]
- IGF-1 (InCrelex™) not orally available and may not penetrate into brain[27]
- NNZ-2566 is IGF-1[1-3] modified to be orally available and penetrate the brain[28]
- NNZ-2566 may act on cytokines such as IL-6[29]



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