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Abtrag einer Parylene-Schicht auf einer Edelstahl-Spritzenkanüle mittels Laser-Plasma-Hybrid-Verfahren. mehr

NT4X antibody therapy of Alzheimer's Disease

Scientists at the University of Göttingen developed a novel, proprietary antibody for the therapy and/or diagnosis of Alzheimer's Disease (AD), called "NT4X", directed against specific N-truncated amyloid beta peptide oligomers. *In vivo* therapy showed a completely rescue of memory deficits, a mitigation of neuron loss, reduction of plaque load and advantages to current antibodies in clinical development.

Georg-August-University Göttingen (UMG) and MRC Technology (MRCT)), a UK medical research charity, have signed an exclusive license agreements for the development of a novel therapy of neurodegenerative diseases based on this antibody.

The licence negotiated by MBM ScienceBridge GmbH, will enable UMG to access the world-class antibody humanization expertise of MRCT's Centre for Therapeutics Discovery and the work of its Therapeutic Antibody Group and MRCT to use its renowned capability to take lab tool compounds and turn them into clinical candidates, which will then be licensed to the Pharmaceutical and biotech industry.

Challenge

Alzheimer's Disease (AD) is the main neurodegenerative disease worldwide affecting more than 29 Mill. people. By 2050 the prevalence will quadruple, by this time 1 in 85 persons worldwide will be living with AD. AD still features high growth potential and room for further innovation due to the huge worldwide growth of the number of patients and the lack of efficacious drugs. The AD market is estimated at 2,9 Mrd US$ for 2015, the main countries affected being USA, Japan and Germany.

Our Solution

We developed a new proprietary, monoclonal antibody against Alzheimer's Disease called NT4X. Hallmarks of NT4X:

- **NT4X rescues memory deficits *in vivo*** in two AD mouse models.
- **NT4X reduces neuron loss *in vivo*.**
- **NT4X reduces plaque load *in vivo*.**
- **NT4X shows advantages compared to antibodies in clinical phases.**
- NT4X selectively targets specific Abeta peptide oligomers (from Abeta4-x and pyroglutamate Abeta3-x), but does NOT bind to human monomeric or dimeric Abeta 1-42.
- NT4X is specific for AD, it does not show any cross-reactivity with aggregates from other neurodegenerative diseases.
- NT4X has a very low plaque reactivity.
- NT4X shows a high reactivity with blood vessel pathology (CAA, cerebral amyloid angiopathy) in brain sections from AD patients and in transgenic mouse models.

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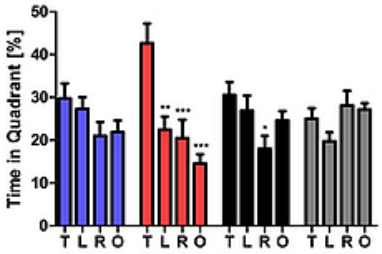
- NT4X could be used for sporadic AD and most familiar AD forms.

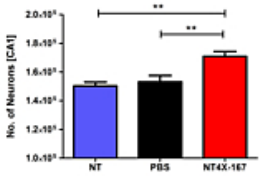
Passive immunization with NT4X rescues learning deficits in 5 month-old Tg4-42hom mice

Spatial reference memory was assessed using the Morris water maze in non-treated mice (blue) and in mice treated (weekly i.p. injection of 10 mg/kg body weight) with NT4X (red), an IgG antibody (grey) and PBS (black).



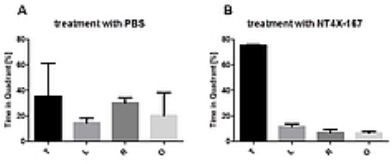
NT4X rescues neuron loss in Tg4-42hom mice

Quantification of neurons in the CA1 of 5 month-old Tg4-42hom mice using unbiased stereology of non-treated mice (blue) or mice treated with weekly i.p. injection of 10 mg/kg body weight of NT4X (red) and PBS (black). NT4x immunized mice displayed 13% more neurons in the hippocampus.



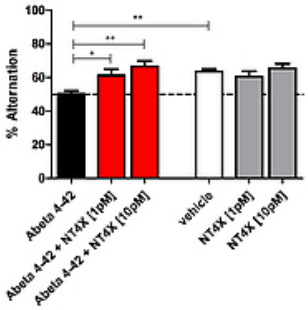
Passive immunization with NT4X rescued memory deficits in aged 5XFAD mice

Assessed with Morris water maze treating 20 week old 5XFAD mice with PBS and NT4X (10 weekly i.p. injections with 10 mg/kg). At 30 weeks of age NT4X treated mice showed significant preference for target quadrant indicating that their spatial reference memory was restored, and a reduced plaque load.



NT4X rescues Abeta4-42 induced working memory deficits in wildtype mice

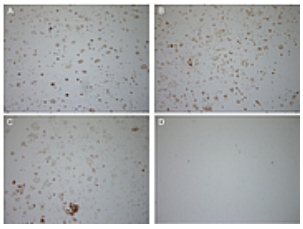
Wildtype mice were intraventricularly injected: Abeta4-42 (black), Abeta4-42 + NT4X (red) or NT4X alone (grey). Working memory was assessed using the Y-maze. The alternation rate in mice treated with Abeta4-42 could be rescued with NT4X (red).



Comparison of NT4X with humanized antibodies in clinical phases

The target engagement of NT4X is an advantage compared to antibodies in clinical phases. Particularly NT4X shows target engagement in the brain of patients with sporadic AD by binding to blood vessels (cerebral amyloid angiopathy, CAA).

NT4X (D) does not bind to precipitated amyloid plaques in brain of AD patients, while Solaneuzumab (B), Bapinezumab (A) and Crenezumab



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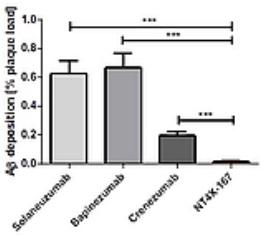
(C) show abundant plaque staining.



Advantages

- Rescue of memory deficits in vivo.
- Reduction of neuron loss in vivo.
- Reduction of plaque load in vivo.
- Very low plaque reactivity.
- High blood vessel amyloid binding.
- Target engagement advantages compared to antibodies in clinical phases.
- NT4X should not be neutralized through binding to plaques, optimizing the therapy compared to other antibodies in clinical phases.
- NT4X should not liberate plaque-bound toxic amyloid peptides from plaques, a likely scenario for other antibodies in clinical phases.

Applications

- Therapy of sporadic Alzheimer's Disease patients.
- Therapy of familial AD.
- Companion diagnostic, for patient recruiting and therapy efficacy test.

Developmental Status

Successful *in vivo* proof-of-principle with several mice models achieved. Favorable comparison to antibodies in clinical phases tested. see more

Patent Status

Patent application in Europe (EP13724769.8) and U.S.A (US14399639) have been filed. Applicant is the Georg-August-University Göttingen.

References

Acta Neuropathologica 2014, 127: 787-801.
Acta Neurophathologica Communications 2013, 1:56.

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