ISB[M]

Alzheimer's disease: to find out optimal design of clinical trials

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Alzheimer's disease (AD) is the most common form of dementia. AD is associated with **senile plaques** (extracellular deposits of amyloid) and **neurofibrillary tangles** (intracellular aggregates of hyperphosphorylated tau protein) in the brain.

The effect of Abeta production/clearance modulators have been tested clinically with **no observed cognitive benefit**.

A possible reasons are :

- The **potency** of the compounds tested was **not sufficient** to have an effect
- The **exposure** of the compounds was **not sufficient** to test the potency in the clinical trial for the duration necessary.

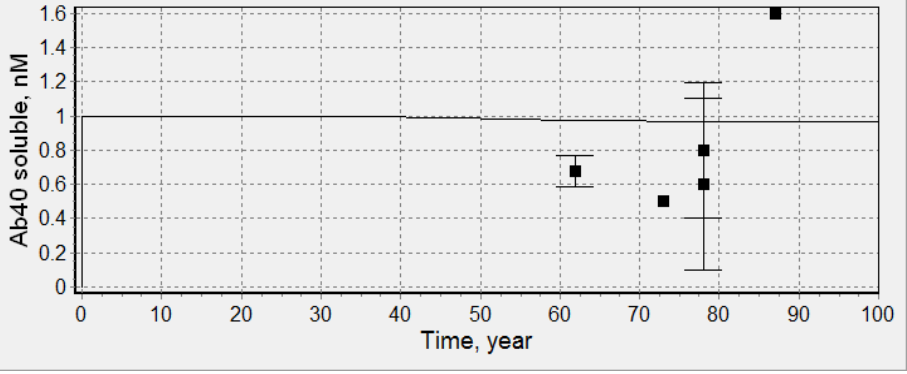
QUESTION: **How to find out optimal potency/exposure of the modulators for Abeta production/clearance in clinical trials?**

ANSWER: **To develop SP model of Abeta aggregation in human in vivo.**

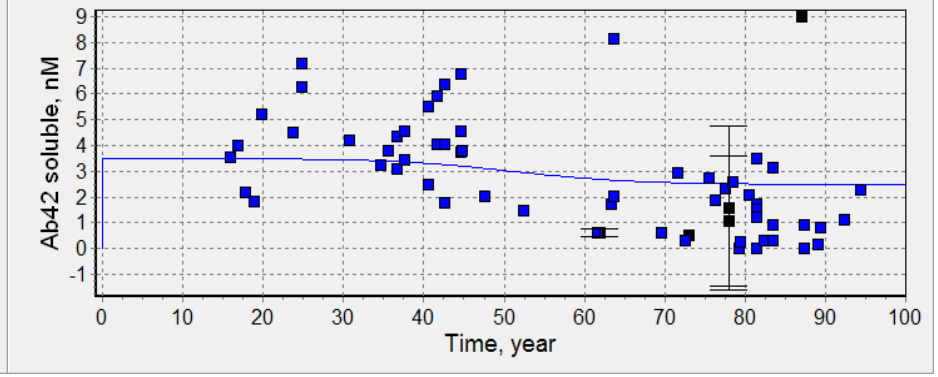
Human model verification and validation

- Human data obtained by **post-mortem** autopsy for healthy subjects.
- Parameters responsible for fibril formation have been identified

Soluble Ab40 and Ab42



Exp Neurol. 1999 Aug;158(2):328-37 ***[10]***
Arch Neurol. 2009 Feb;66(2):190-9 ***[7]***
Arch Neurol. 2008 Jul;65(7):906-12 ***[13]***



Black points: *Exp Neurol. 1999 Aug;158(2):328-37* ***[10]***
Arch Neurol. 2009 Feb;66(2):190-9 ***[7]***
Arch Neurol. 2008 Jul;65(7):906-12 ***[13]***
Blue points: *Brain Pathol. 2010 Jul;20(4):787-93* ***[individual]***

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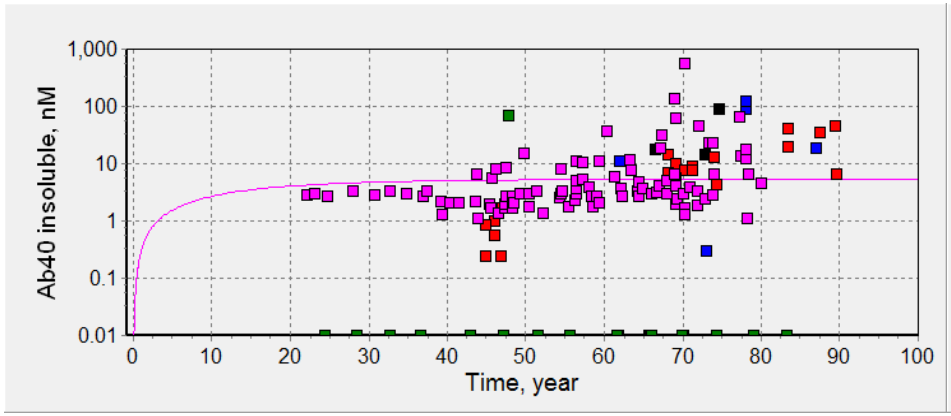
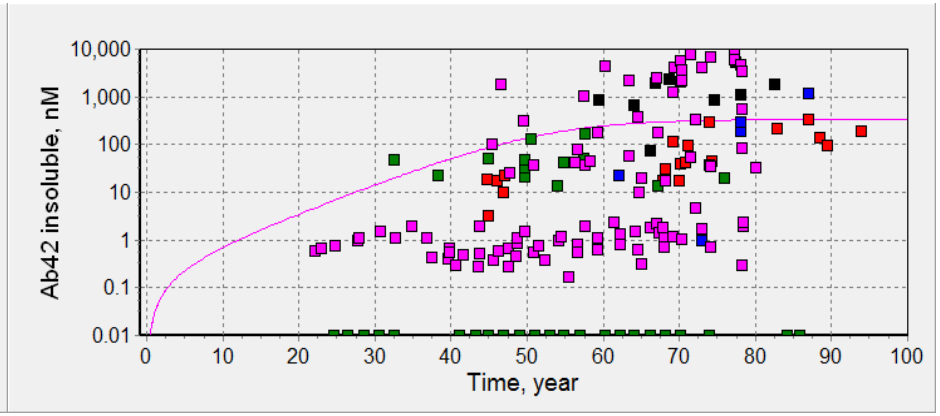
Insoluble Ab40 and Ab42





Black point: *Am J Pathol. 1998 Jun;152(6):1633-40* ***[individual]***
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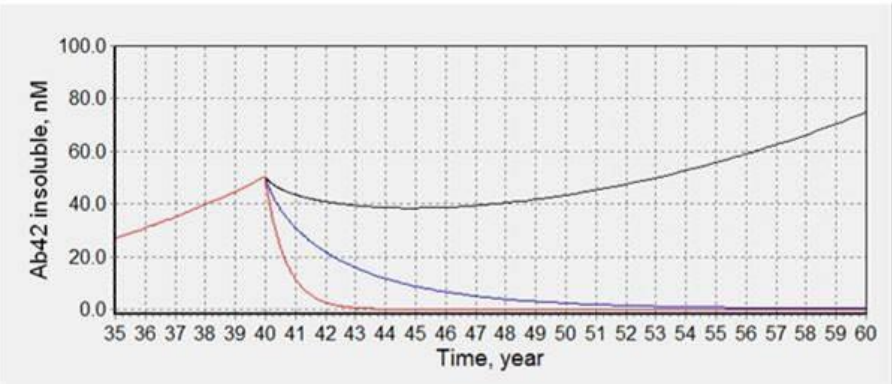
Red point: *Neurobiol Aging. 2008 Feb;29(2):210-21* ***[individual]***
Green point: *Am J Pathol. 1998 Jun;152(6):1633-40* ***[individual]***
Pink point: *Am J Pathol. 2000 Dec;157(6):2093-9* ***[individual]***

Drug treatment simulations (Ab42 insoluble)

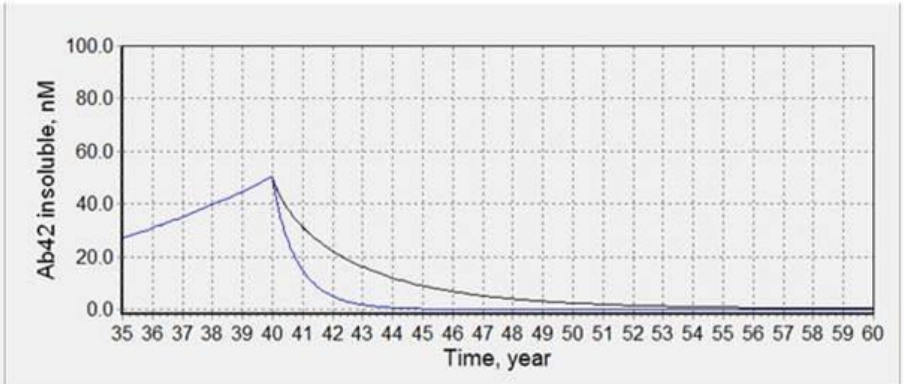
We simulate treatment of AD patient by decreasing of synthesis or increasing of degradation. For this simulation we take AD patient model where we change degradation constants of soluble Ab after 40 years.

Start of treatment: 40 years

Synthesis inhibition: Black – 25% Blue – 50% Red – 100%



Degradation increase: Black – x2 Blue – x10



Conclusions

- A model describing Abeta aggregation in healthy human subjects and AD patients has been developed.
- Insoluble plaque acts as an additional source of Abeta for multiple years with 50% inhibition.
- Amyloid cascade hypothesis **has not been tested** given **recent and current clinical trials** due to insufficient duration of treatment and/or too little potency.
- In order to test the amyloid cascade hypothesis in a clinically reasonable amount of time (**2-3 years**) a compound will need to have the ability to reduce Abeta production by **>>50%** (**75-95%** would be preferable).

Acknowledgements

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