



DEVELOPING DRUGS TO TREAT DISEASES

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OF AMYLOID TOXICITY.....**

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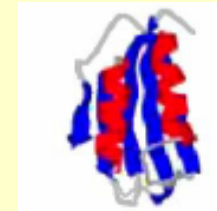
**CNS and Ageing Conference
Clare College, Cambridge
26th January, 2012**

AMYLOID TOXICITY AND DISEASE



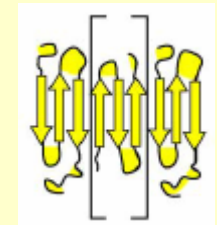
Amyloid toxicity underlies over 20 diseases

AMYLOID PROTEIN	CLINICAL SYNDROME
β -amyloid	Alzheimer's disease
Amylin	Type 2 diabetes
β 2-Microglobulin	Dialysis-related amyloidosis (DRA)
α -Synuclein	Parkinson's disease
Prion protein	Creutzfeldt-Jakob Disease (CJD)
Tau	Fronto-temporal dementias
Huntingtin (poly Q expansion)	Huntington disease
Superoxide dismutase	Amyotrophic lateral sclerosis
Transthyretin	Senile systemic amyloidosis
	Familial amyloidotic polyneuropathy
γ -Crystallin	Cataract
Lysozyme	Lysozyme systemic amyloidosis
Ig light chains	Primary systemic amyloidosis
Serum amyloid A	Secondary systemic amyloidosis



Normal folded proteins

↓ *misfolding*



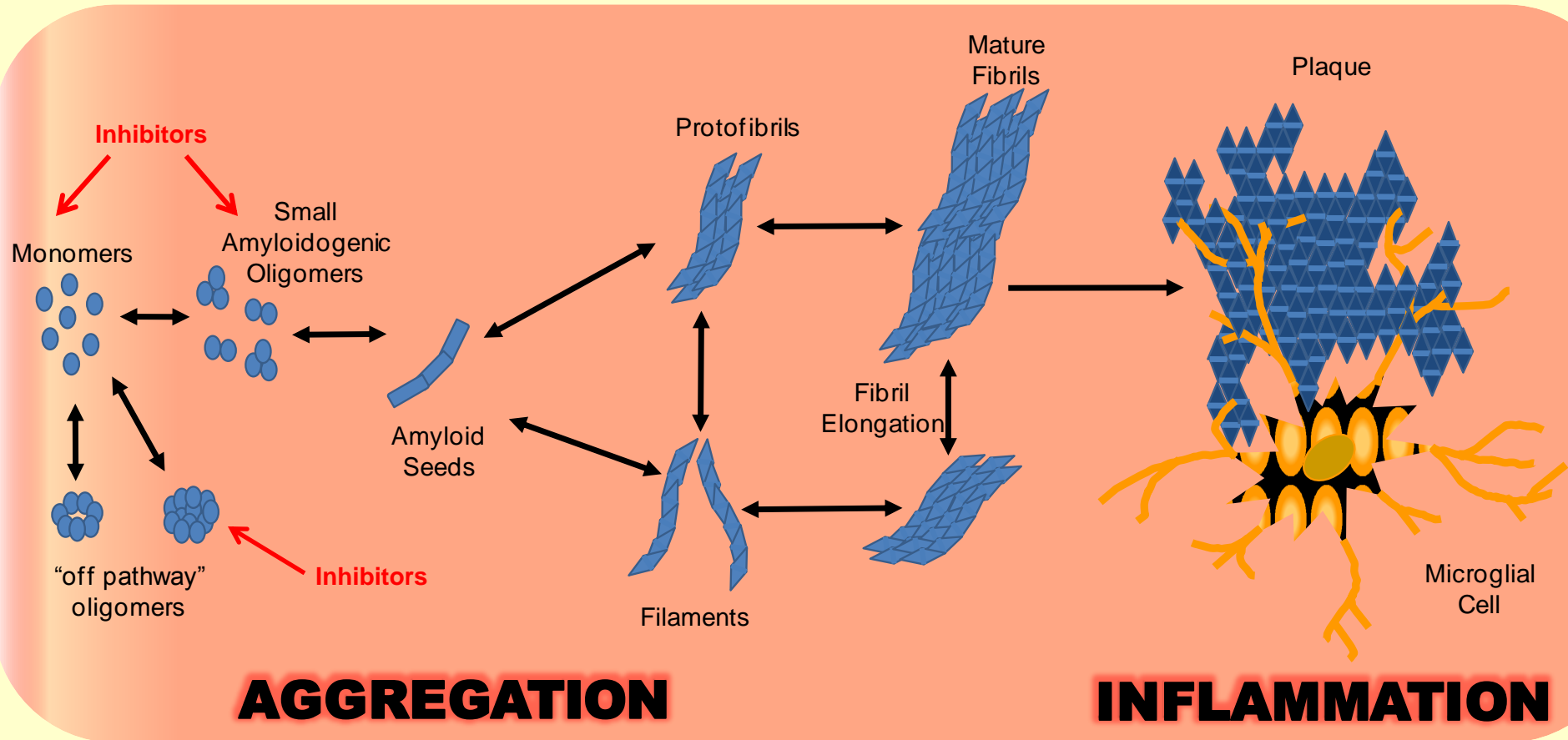
Toxic soluble oligomers

↓

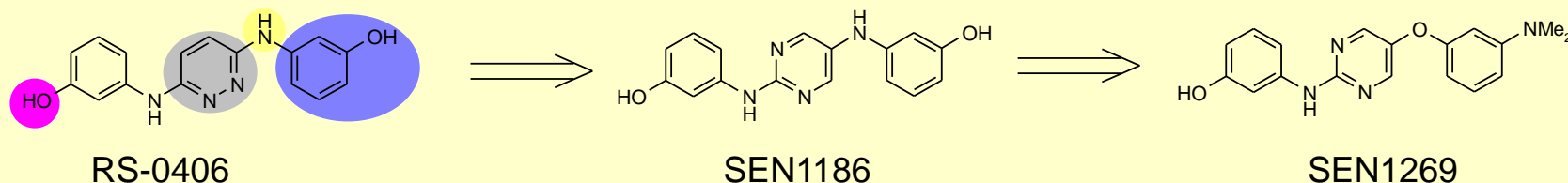


Amyloid plaques

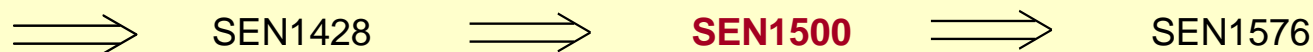
THE PATHOLOGY OF AMYLOID AGGREGATION



EVOLUTION OF LEAD COMPOUNDS

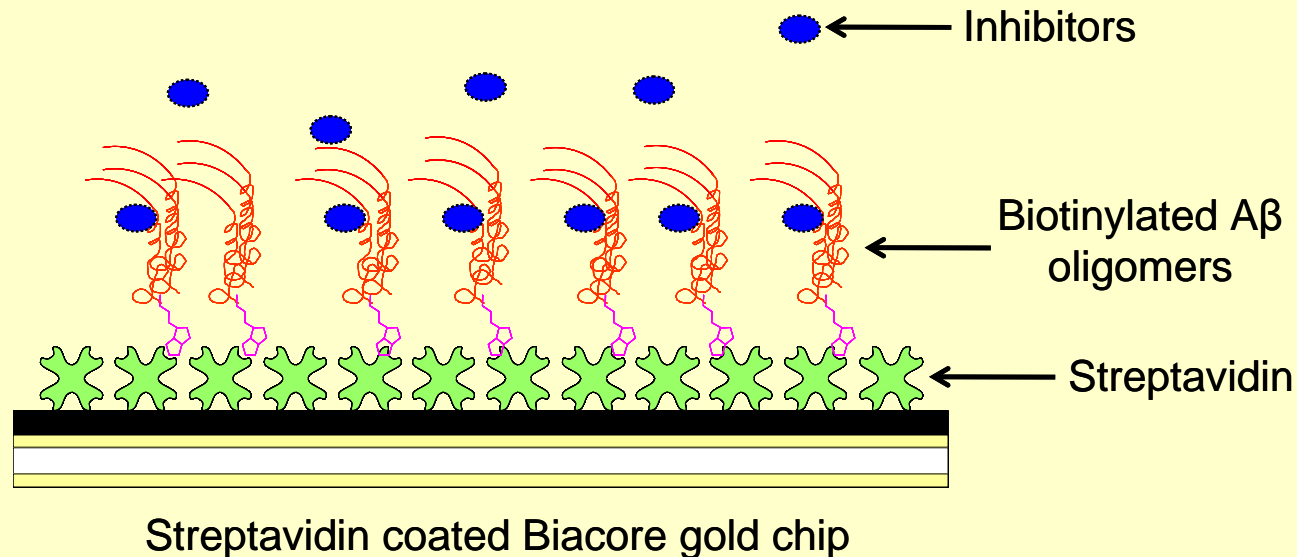


- Changes to heterocyclic nucleus advantageous and link from NH to O advantageous
- One phenolic OH can be replaced by a more acceptable group with retention of activity
- Improvement to potency, understanding of SAR
- Unacceptable *in vitro* ADME, poor pharmacokinetics

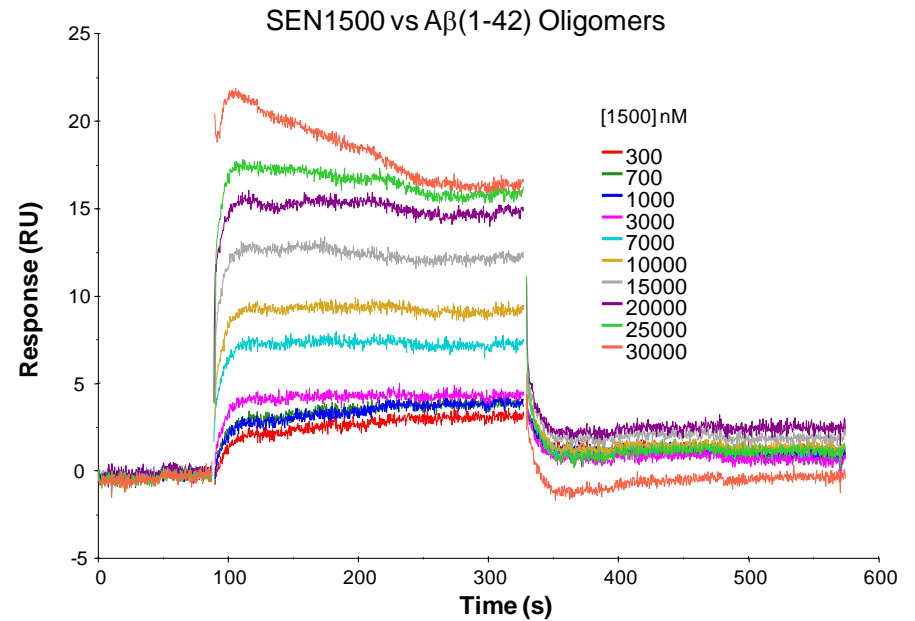
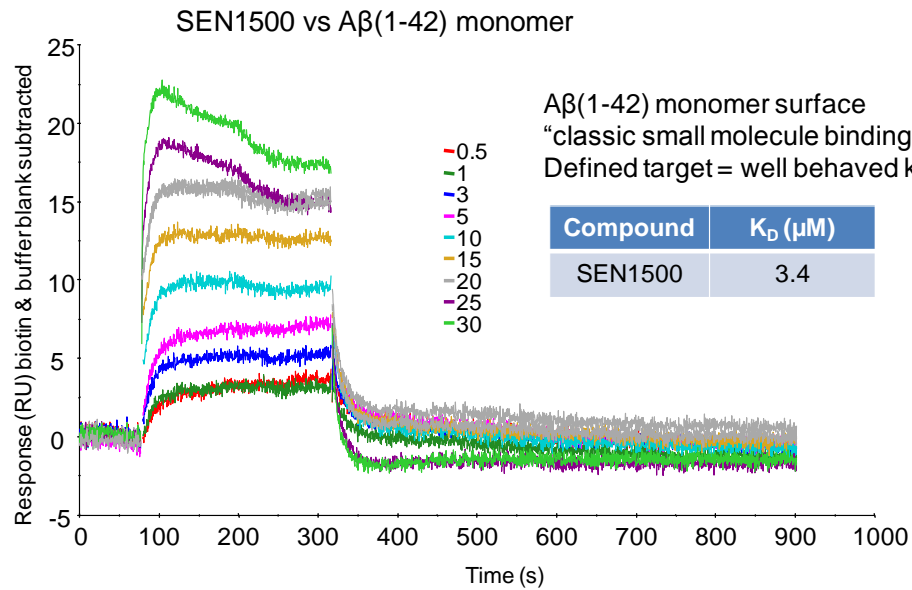


- Non-phenolic
- Acceptable *in vitro* ADME profile, oral bioavailability, CNS penetration
- Good potency
- Oral activity in an acute model of cognitive function

- Experiments with using A β monomer and oligomers [BiacoreT100]
- A β (1-42) monomer prepared from N-terminus biotinyl-A β (1-42) [50% DMSO/buffer loading]
- A β (1-42) oligomers prepared from N-terminus biotinyl-A β (1-42): A β (1-42) [1:10] according to the method of Maezawa *et al.* and Kaye *et al.* and immobilised on streptavidin chip surface
- Evaluated binding of SEN1500, SEN1576 and other inhibitors



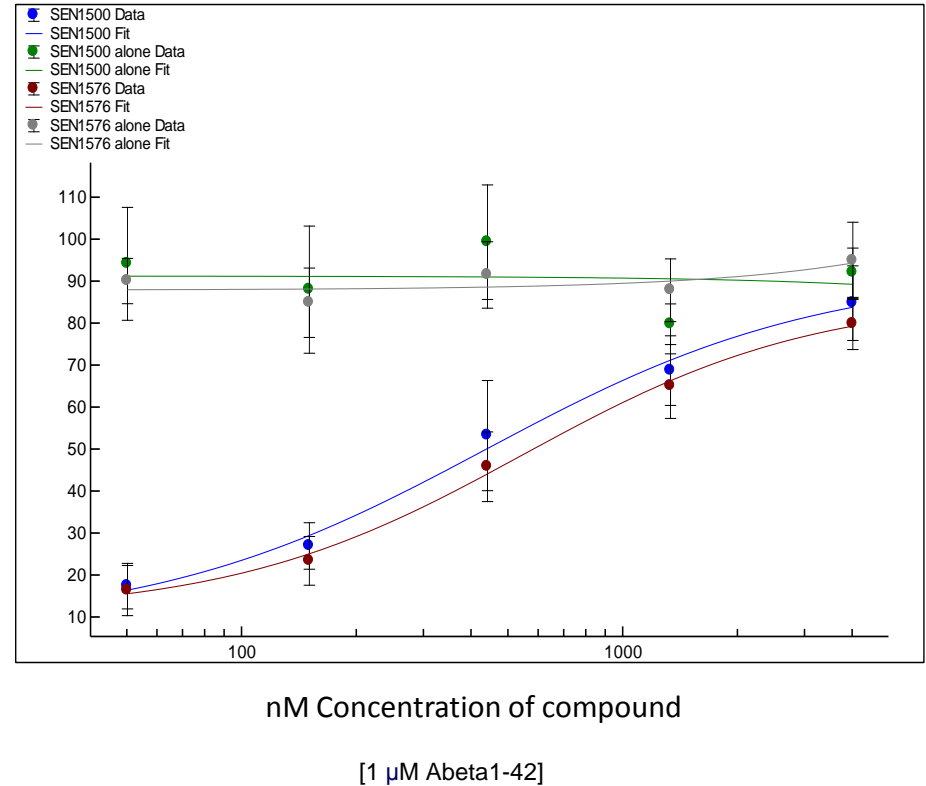
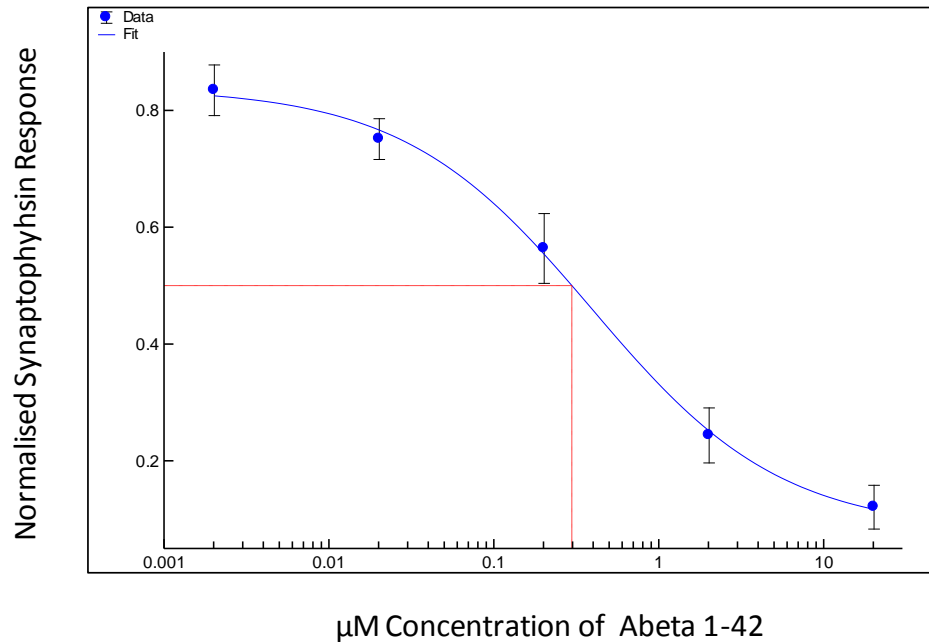
BINDING OF SEN1500 TO A β (1-42) MONOMER AND OLIGOMERS



A β 1-42 TOXICITY/SYNAPTOPHYSIN ASSAY



Concentration Response Curve For Abeta 1-42 using a Synaptophysin ELISA Readout in Mouse Primary Cortical Cells



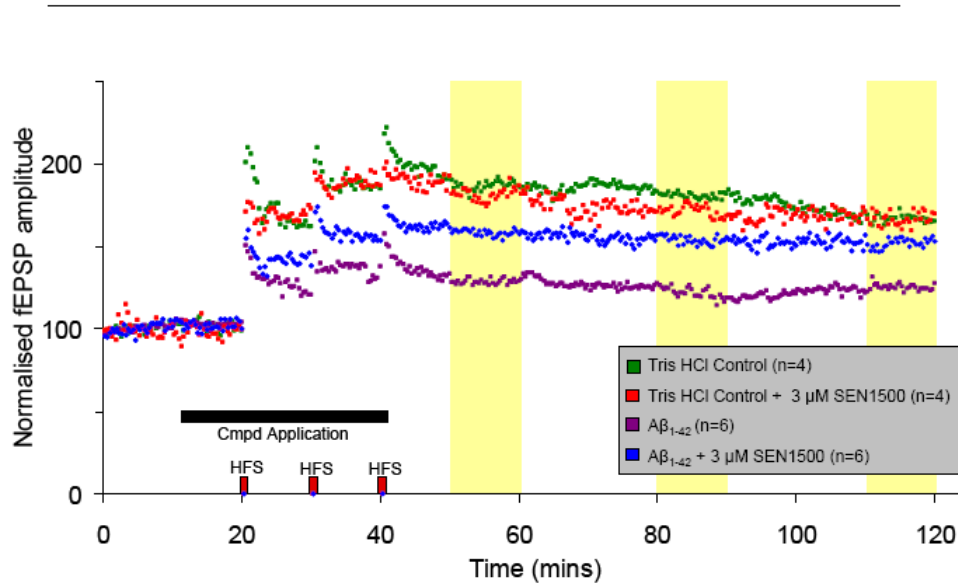
[1 μ M Abeta1-42]

IN VITRO LTP: SEN1500

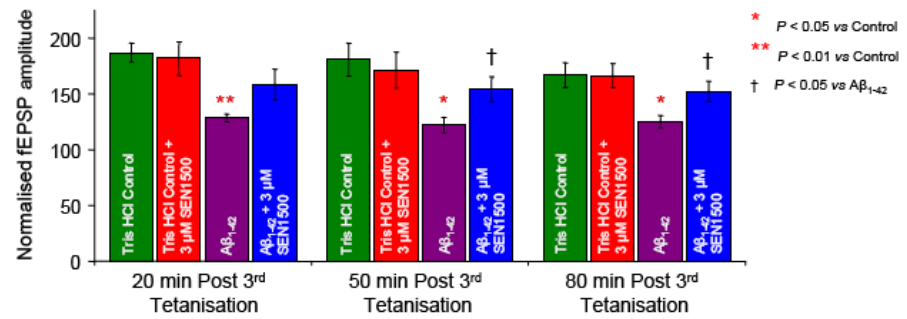


SEN1500 vs Aβ1-42

Summary fEPSP Amplitude Plots

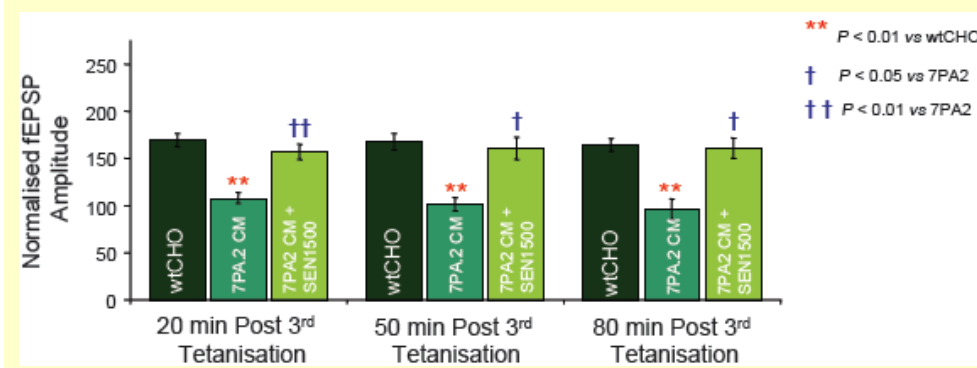
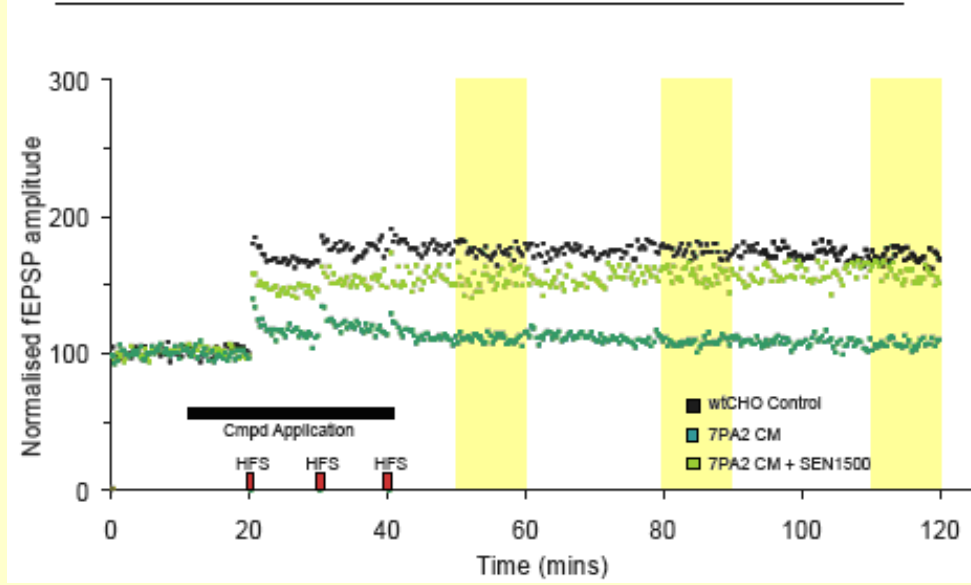


Summary Graph



SEN1500 vs 7PA2 CM

Summary fEPSP Amplitude Plots (n=4)



SEN1500: PHARMACOKINETIC PARAMETERS

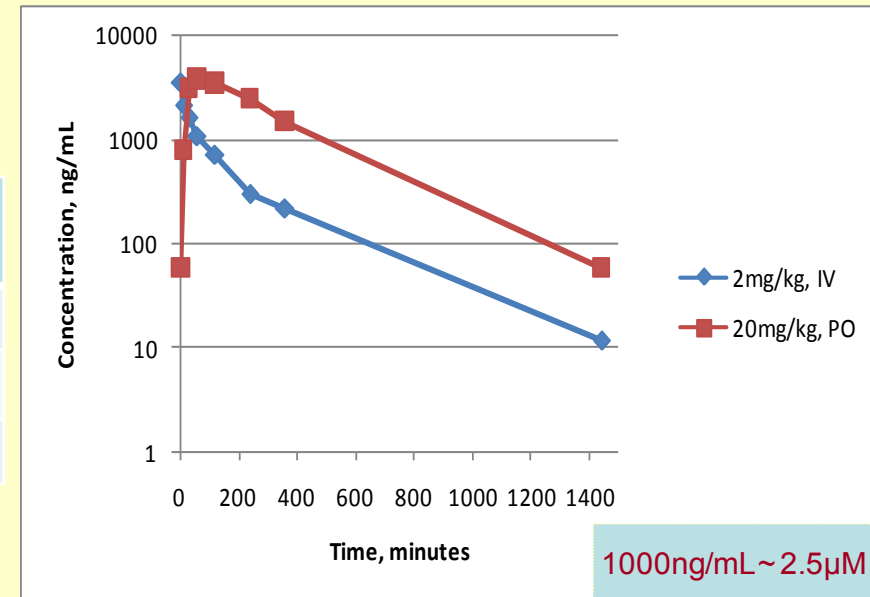


Dose	t _{1/2} (min)	CL (mL/min/kg)	V _{ss} (mL/kg)
2mg/kg, IV	254	6	1468

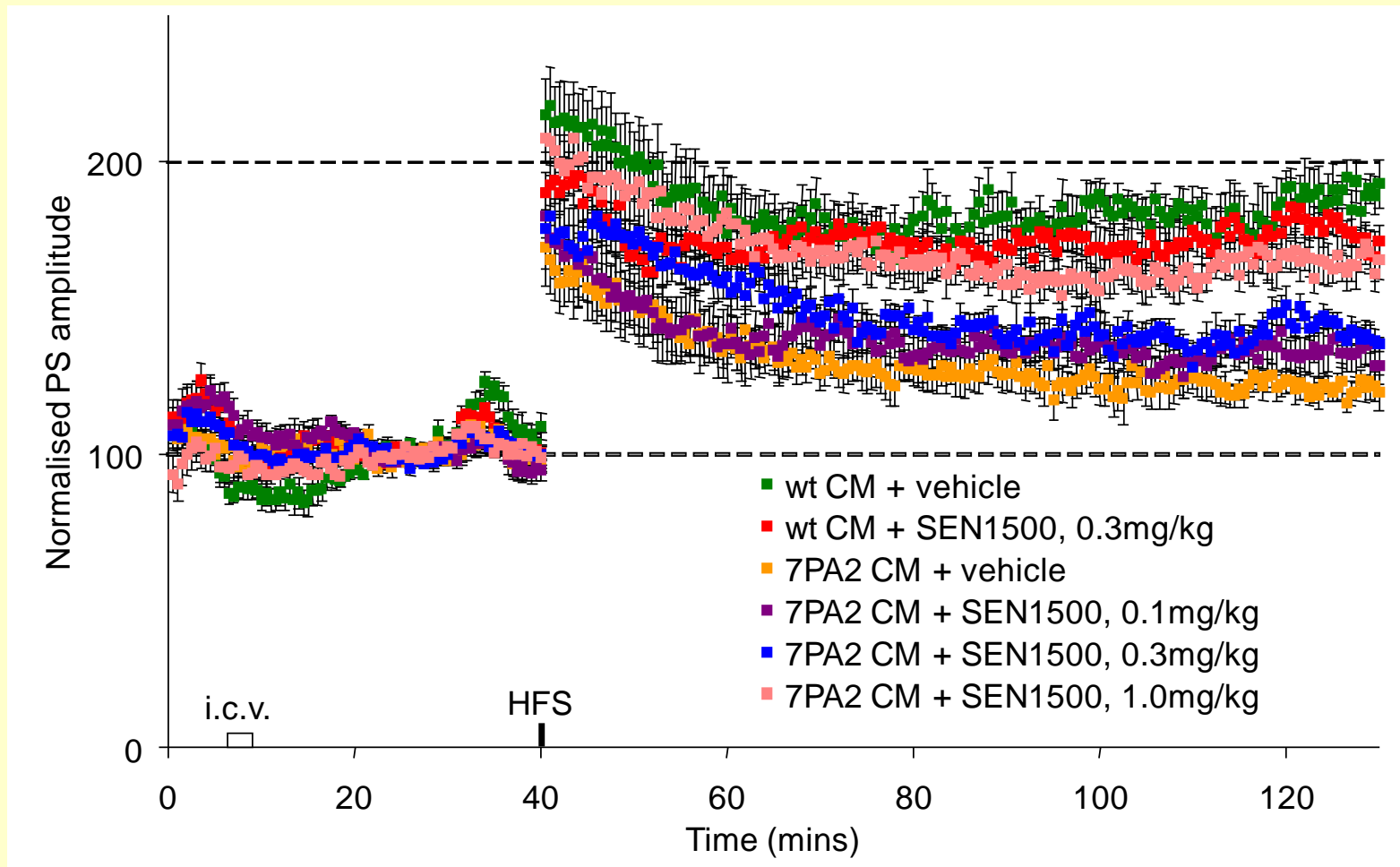
Dose	t _{1/2} (min)	C _{max} (ng/mL)	T _{max} (min)	Bioavailability (%)
20mg/kg, PO	221	3864	80	42

Brain and plasma concentrations (2mg/kg, IV dose)

Time (min)	Brain (ng/g)	Plasma (ng/mL)	Brain/Plasma
30	830	1272	0.64
60	685	850	0.79
180	247	284	0.88



IN VIVO LTP IV DATA FOR SEN1500: 7PA2 CM INSULT DOSE RANGING STUDY

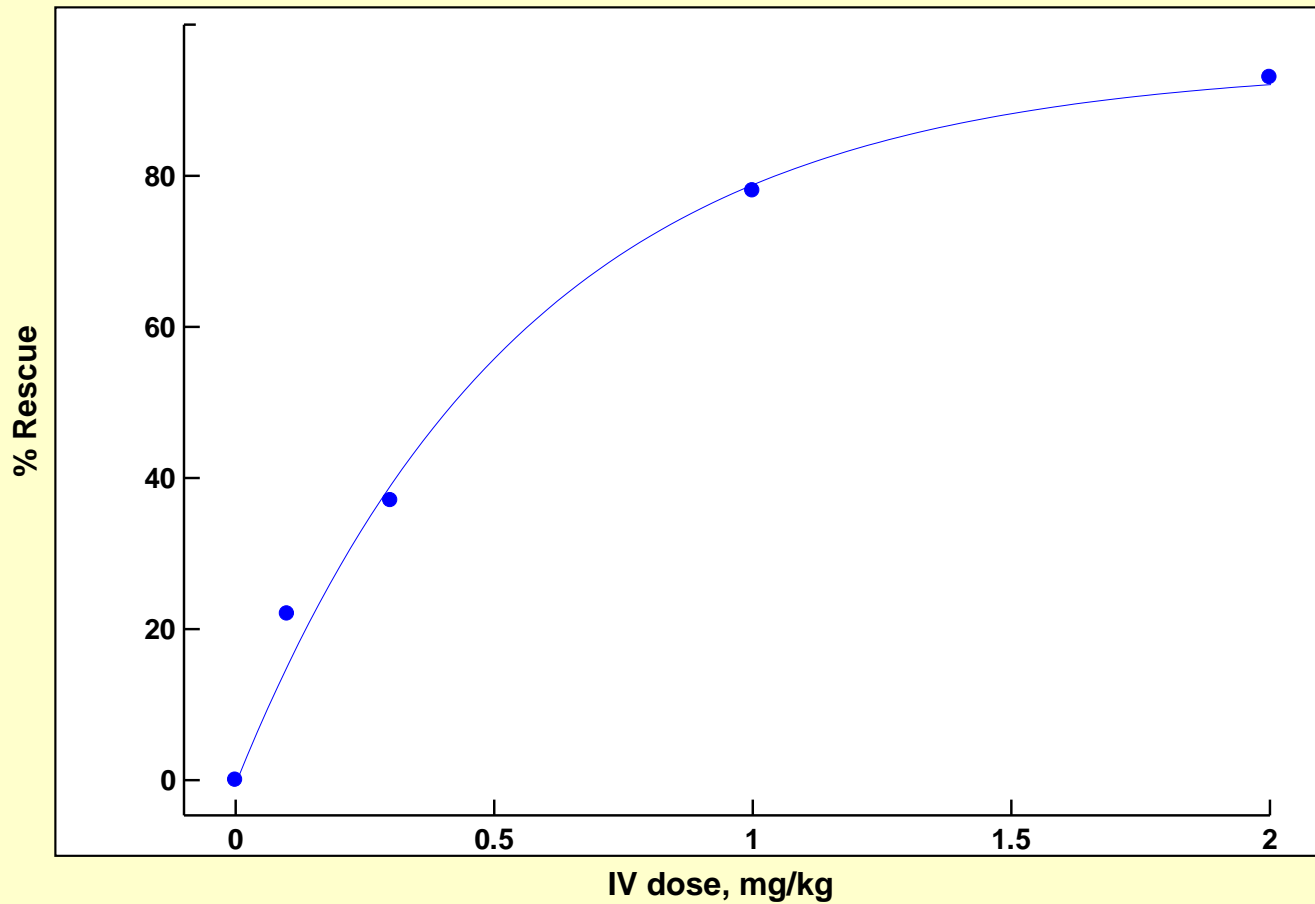


- (i) Inhibition by 7PA2 CM of long-term potentiation of population spike amplitude
- (ii) Attenuation of this effect by SEN1500; $N=6$ all groups

DOSE RESPONSE CURVE FOR *IN VIVO* LTP

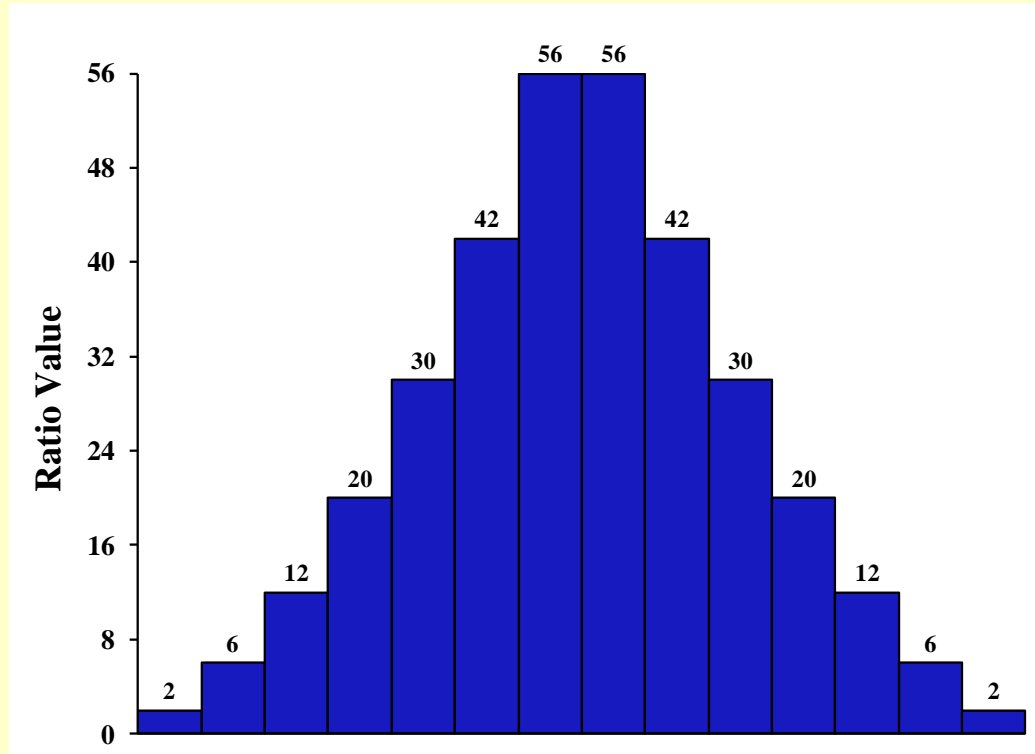


Normalised % Rescue



Includes 2mg/kg data from previous experiment

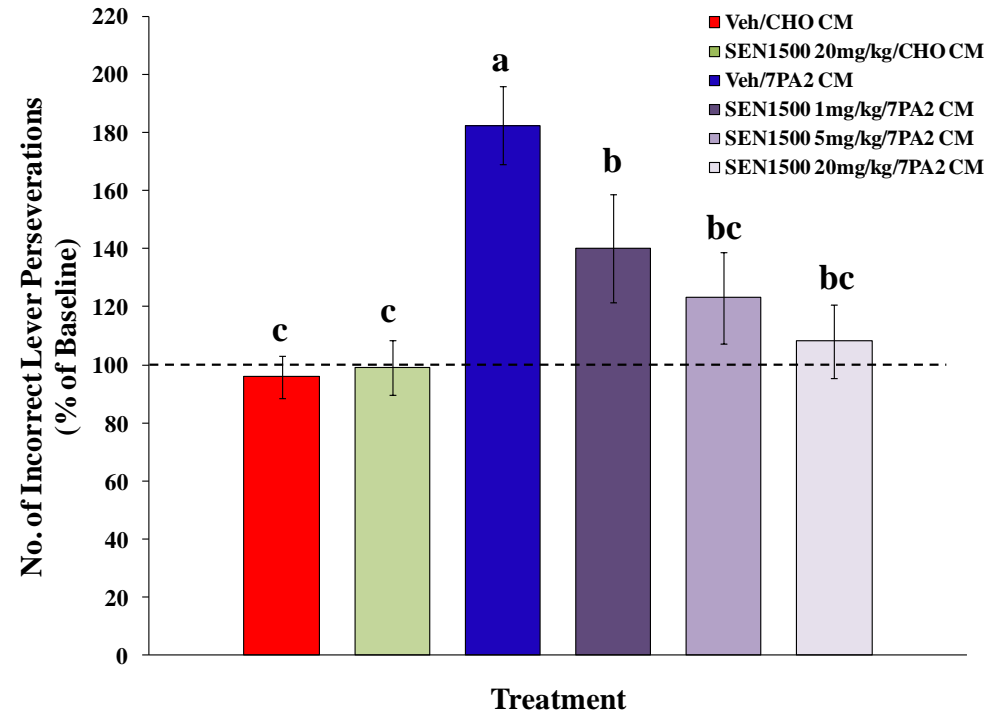
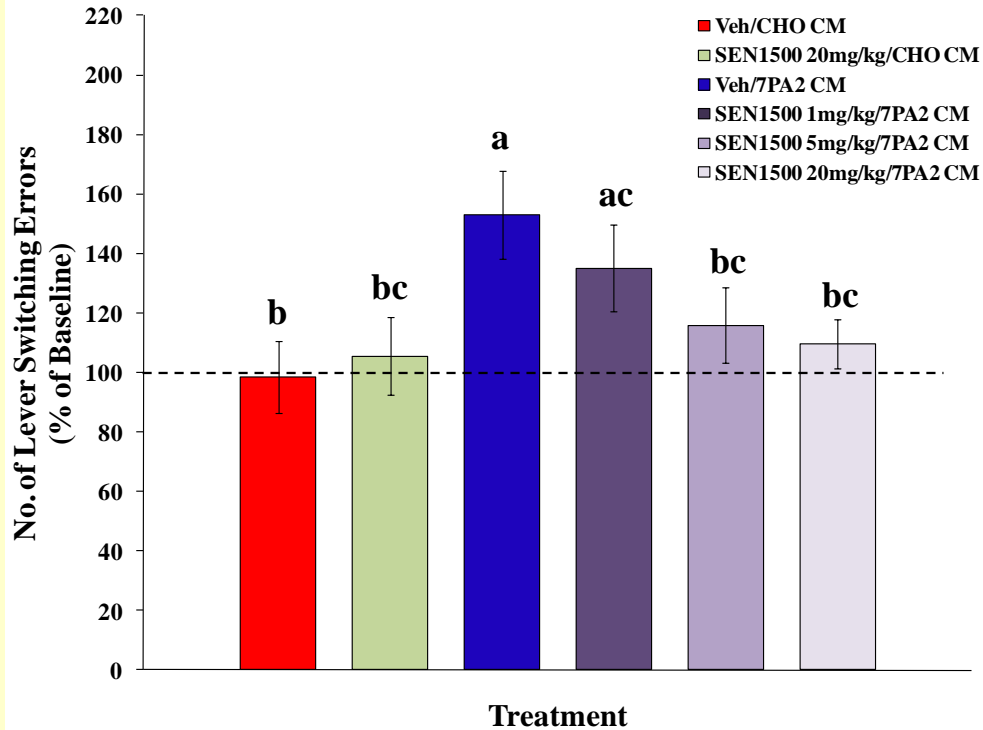
ALCR MODEL: PROTOCOL



6 Cycles:



EFFECT OF ORALLY ADMINISTERED SEN1500 IN ALCR MODEL (RAT)



Effect of SEN1500 (1mg/kg, 5mg/kg and 20mg/kg, PO) treatment on ICV 7PA2 CM-induced lever switching errors.

Data presented as % baseline mean \pm SEM; N = 14

a,b,c Non-overlap superscripts indicate significant differences between groups.

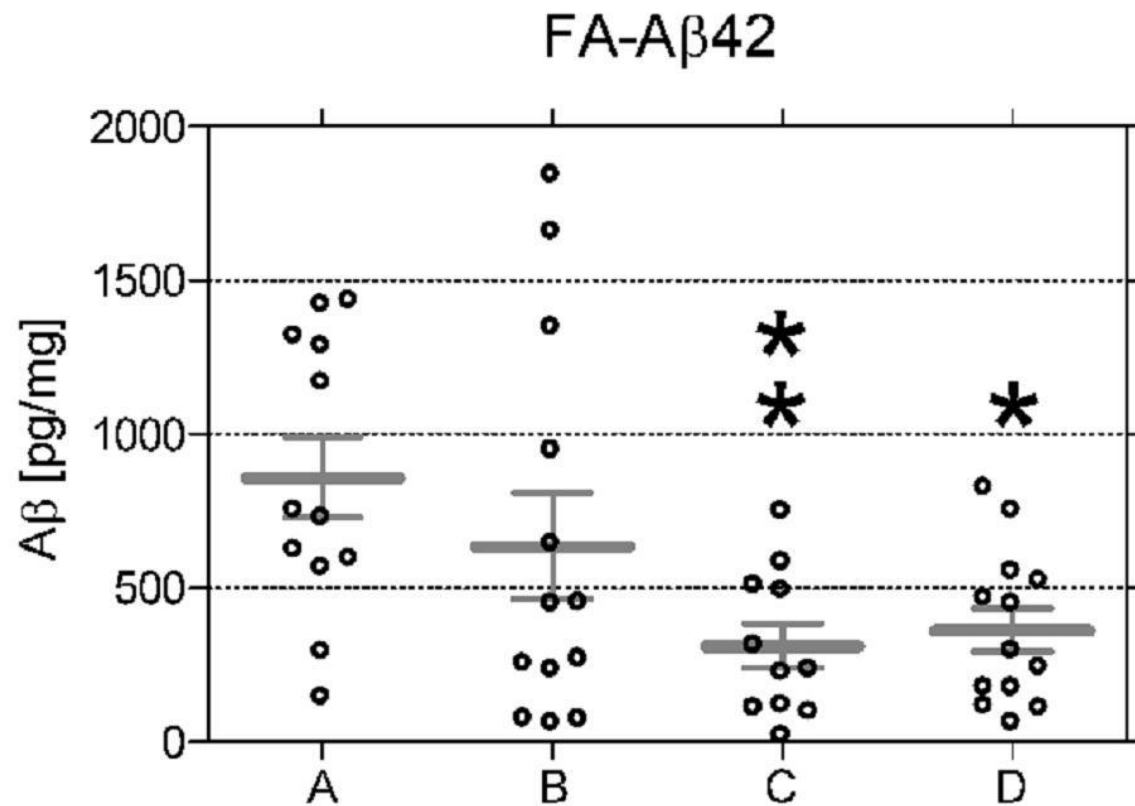
Effect of SEN1500 (1mg/kg, 5mg/kg and 20mg/kg, PO) treatment on ICV 7PA2 CM-induced incorrect lever perseverations

Data presented as % baseline mean \pm SEM; N = 14

a,b,c Non-overlap superscripts indicate significant differences between groups

Acute oral dose of drug providing protection against an ICV administered insult of A β

CHRONIC EFFECT OF ORALLY ADMINISTERED SEN1500 IN APP_{SL} TRANSGENIC MICE (JSW)



- A - Placebo
- B - 5mg/kg SEN1500
- C - 20mg/kg SEN1500
- D - 80mg/kg SEN1500



Senexis has discovered inhibitors of A β toxicity which are:

- Active in primary assays
- Bind to A β monomer and oligomers
- Active in rescuing deficit in LTP caused by A β
- Protective in an acute model of mild cognitive impairment
- Biomarker data in chronic transgenic models
- Acceptable ADME-tox profiles
- Orally bioavailable and CNS penetrating

A large, blue-outlined arrow pointing downwards, containing the text "Mechanistically consistent" written vertically.

Mechanistically consistent



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