

**POLYGLUTAMINE ELONGATION ASSAY FOR
DRUG SCREENING**

CAG Repeat disorders

Disorder	Protein	Normal No of Repeats	No of Repeats in mutant protein	Chromosome involved/ mode of transmission
Huntington's disease	Huntingtin	11-34	37-120	4p / autosomal dominant
Spinal and bulbar muscular atrophy	Androgen receptor	11-33	40-62	X /X linked
Spinocerebellar ataxia				
Type 1	Ataxin 1	25-36	41-81	6p /autosomal dominant
Type 2	Ataxin 2	15-24	35-59	12q /autosomal dominant
Type 3	Ataxin 3	13-36	68-82	14q /autosomal dominant
Type 6	Ataxin 6	4-16	21-27	19p /autosomal dominant
Type 7	Ataxin 7	7-35	37-130	3p /autosomal dominant
Dentatorubropallidoluysian atrophy	Atrophin 1	7-25	49-85	12p /autosomal dominant

Progressive neuronal loss

(Different pattern → Different symptoms)

Severity of the disease is function of age and size of CAG expansion

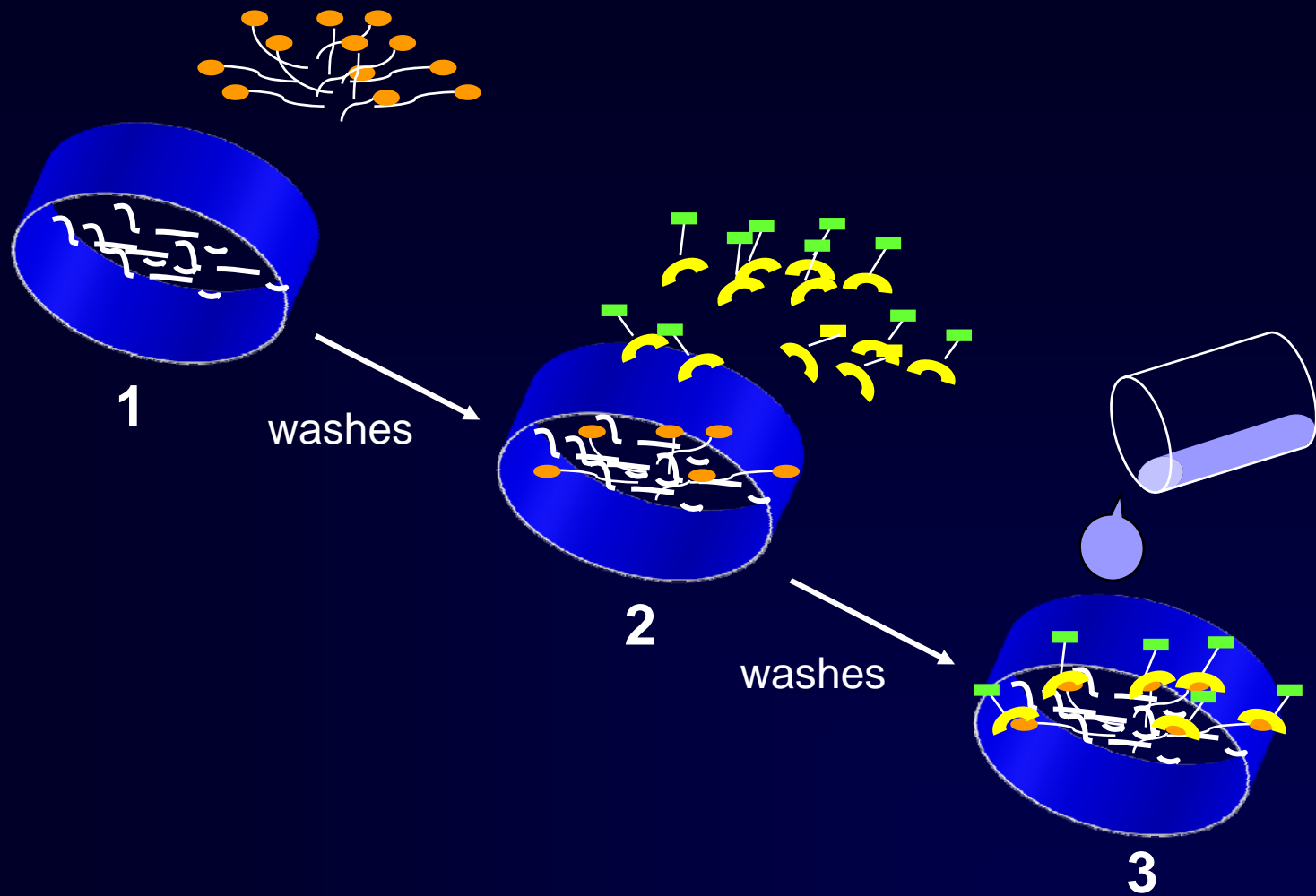
Formation and accumulation of polyGln containing protein into insoluble aggregates in the nucleus and/or cytoplasm of the affected neurons

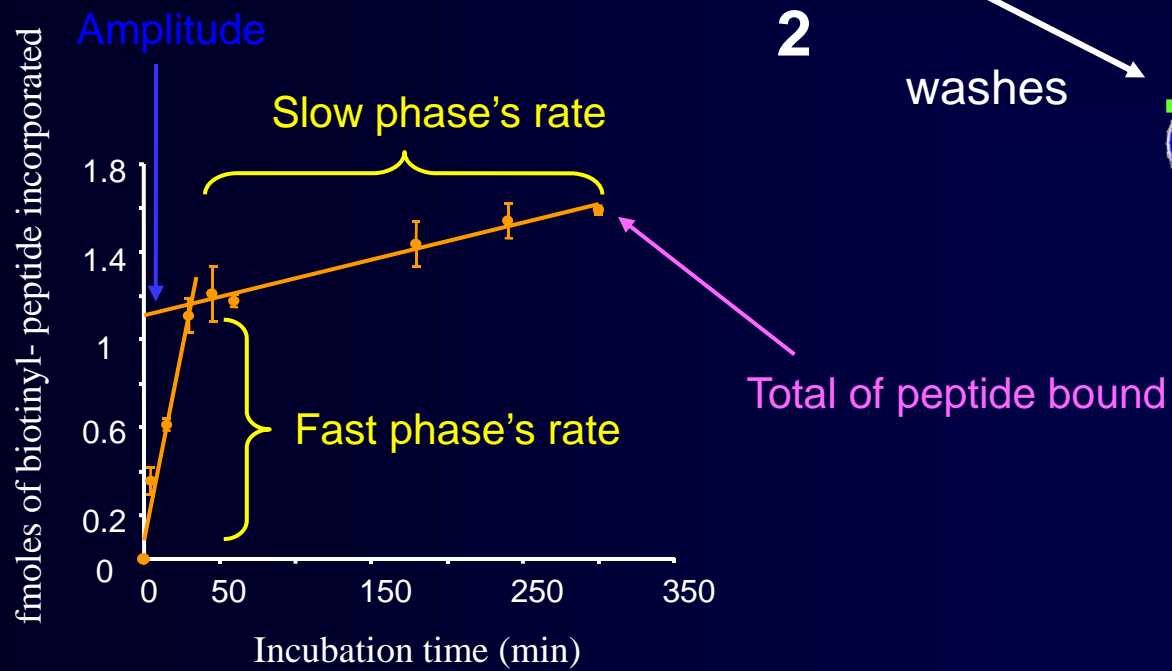
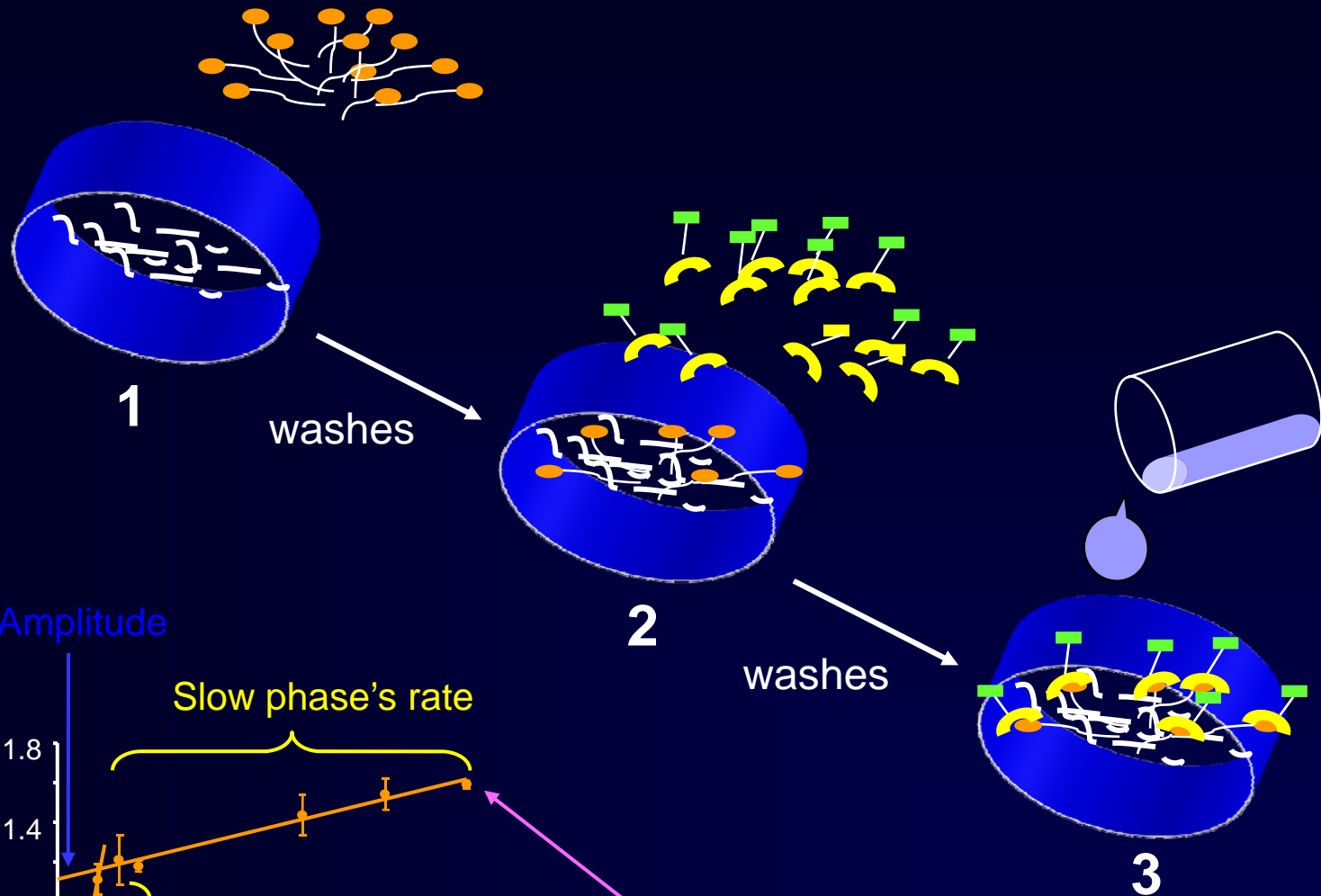


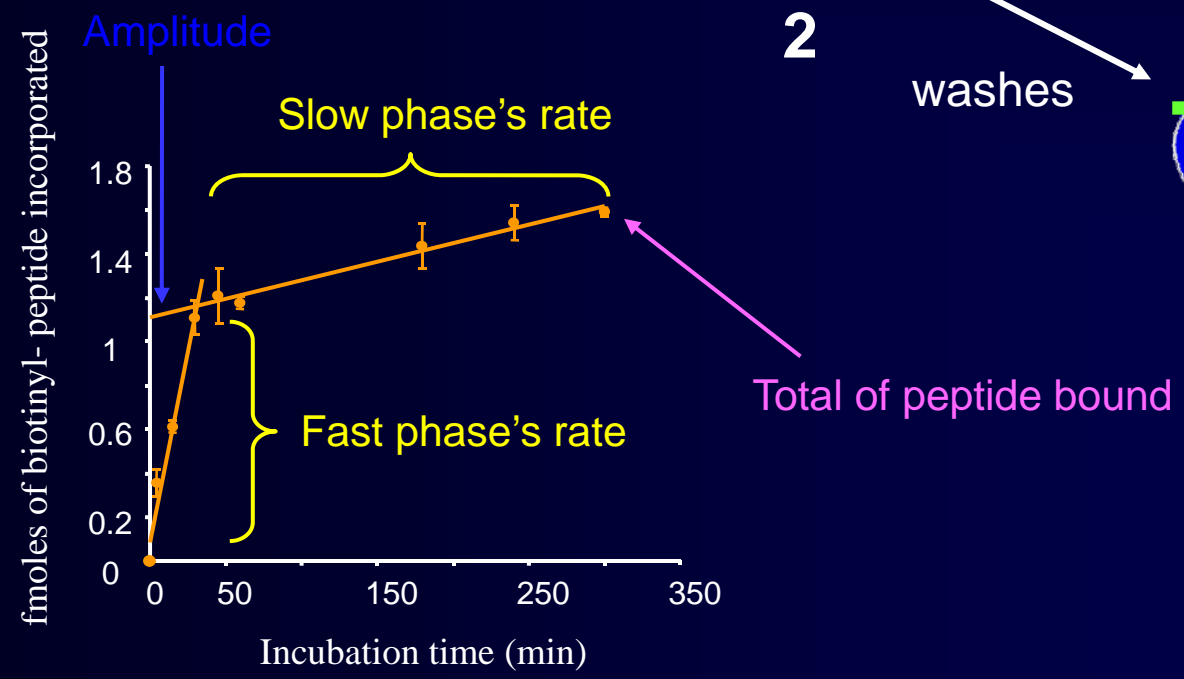
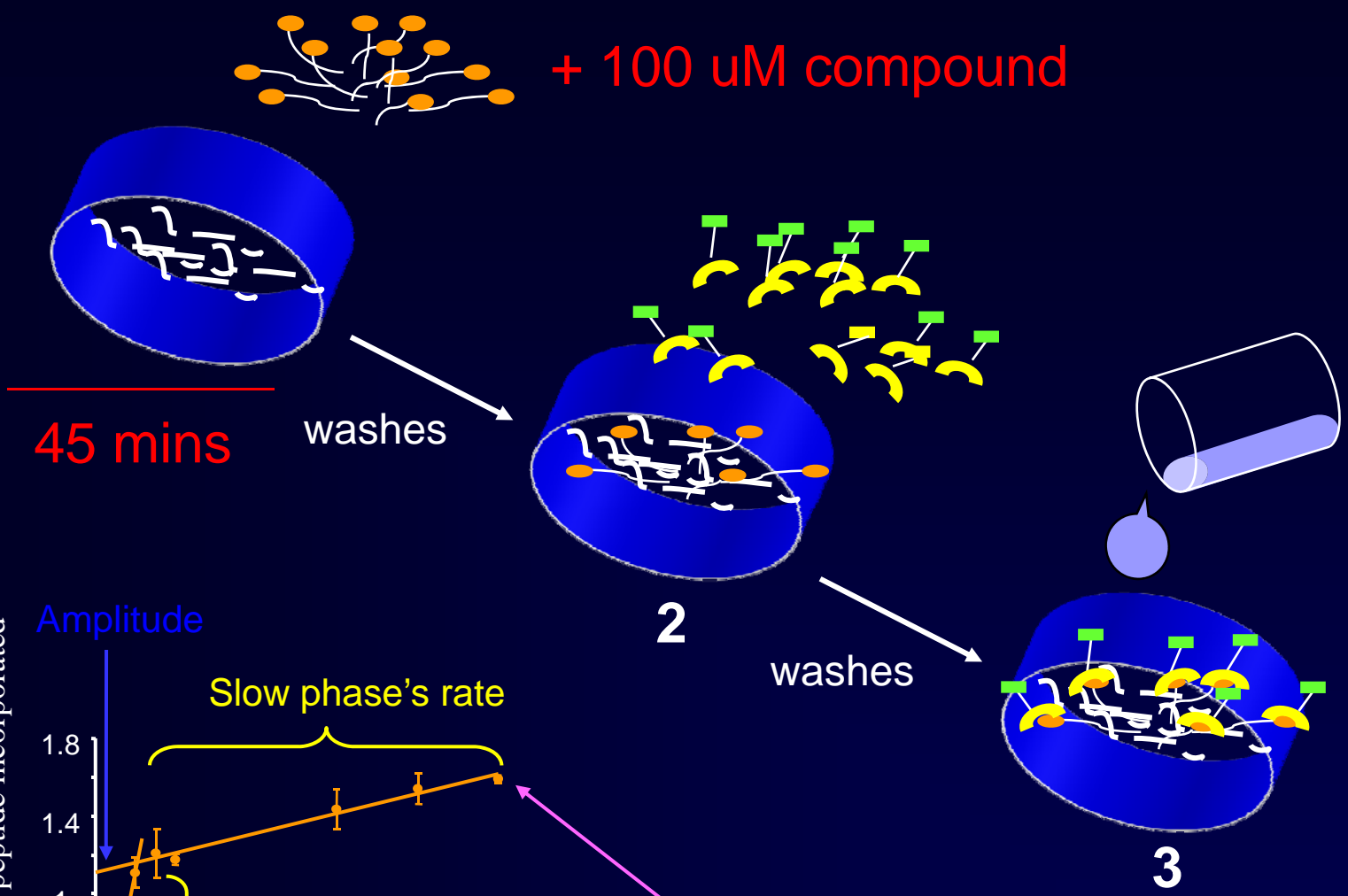
Expanded polyGln sequence itself responsible for pathogenesis

POLYGLN ELONGATION ASSAY

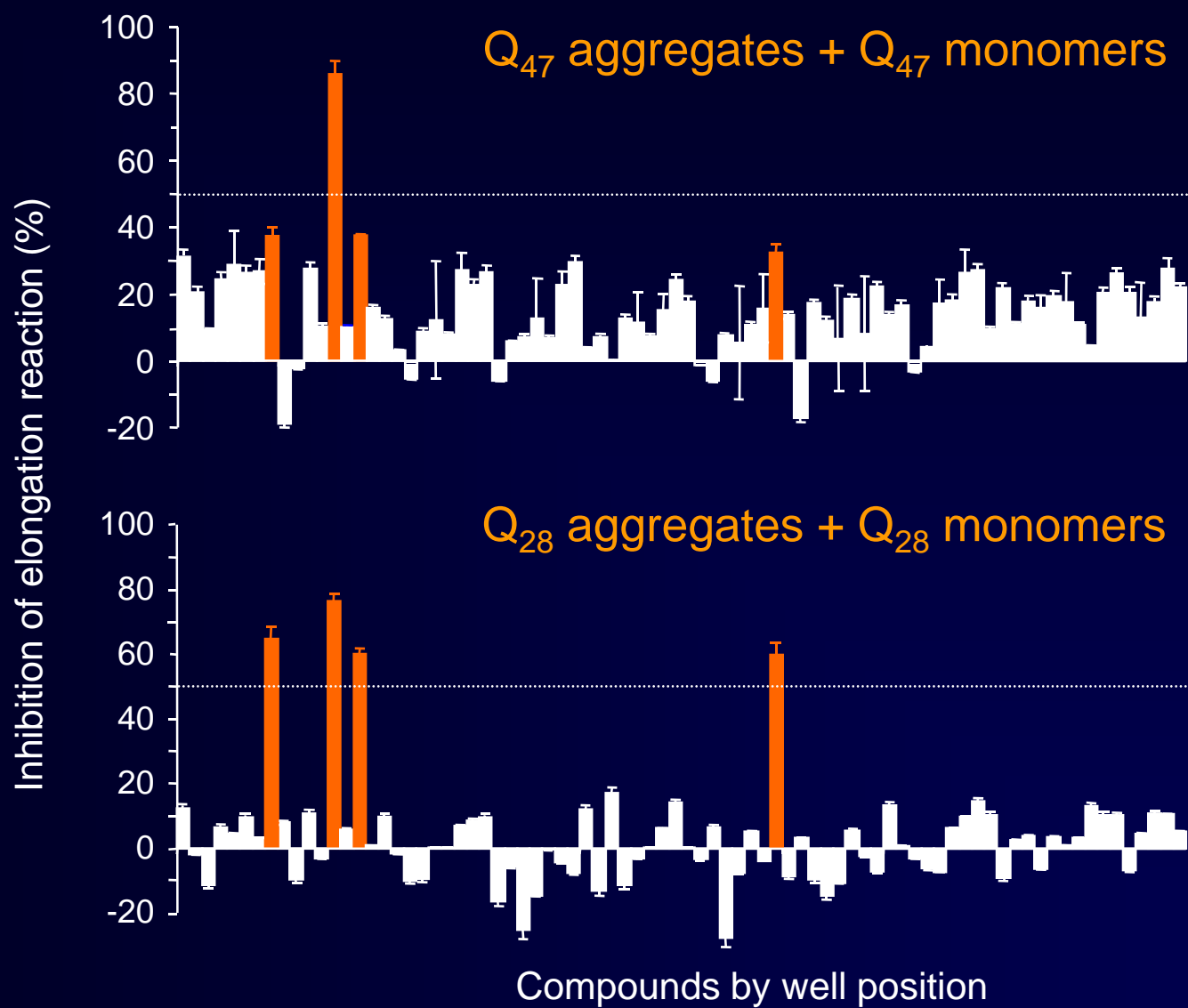
- ☞ Aggregation behavior of polyGln sequences
- ☞ Effects of the polyGln repeat length on the aggregation process
- ☞ Detection of elongation-competent polyGln aggregates in tissue
- ☞ Screen for aggregation inhibitors



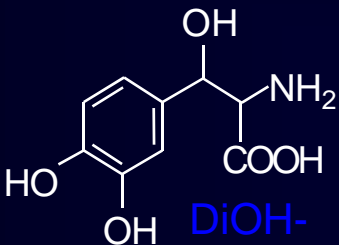
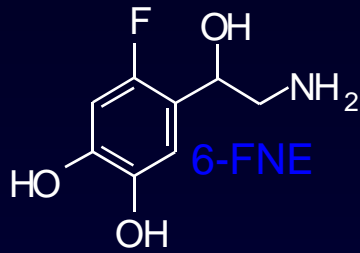

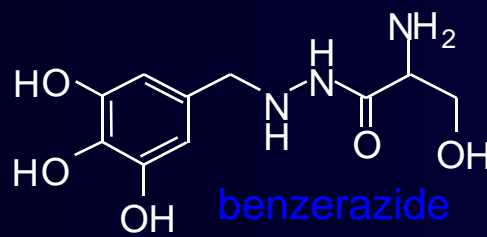
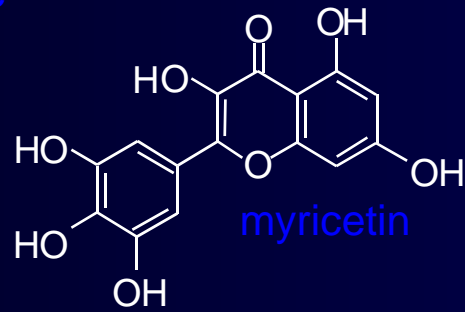



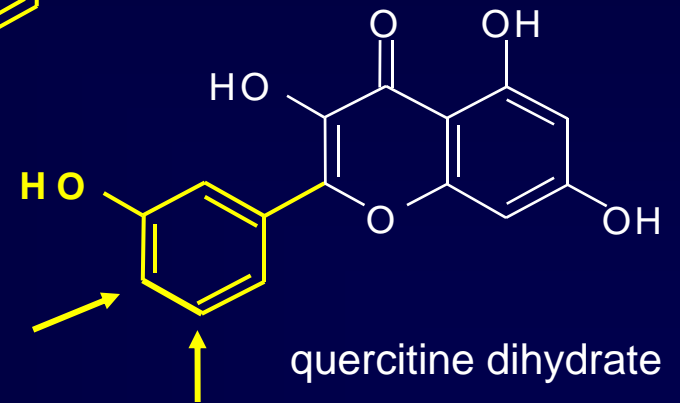
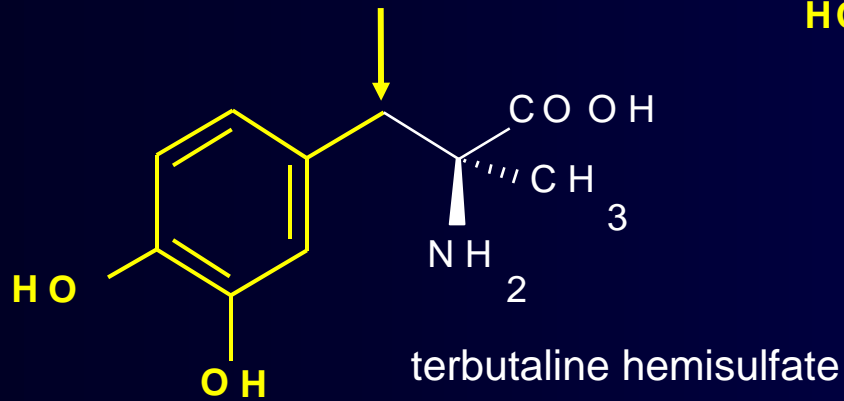
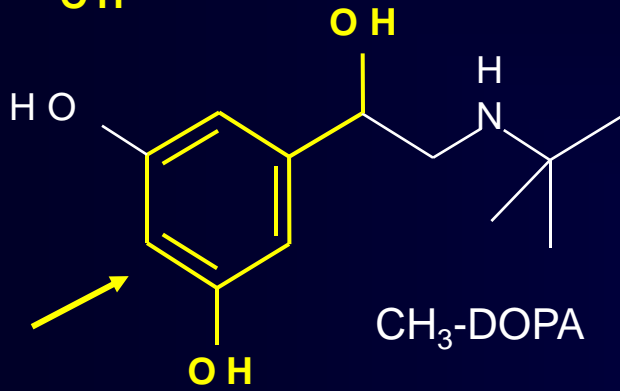
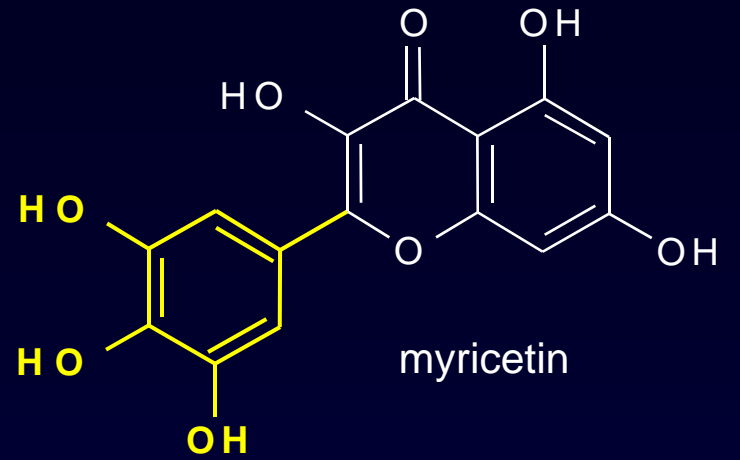
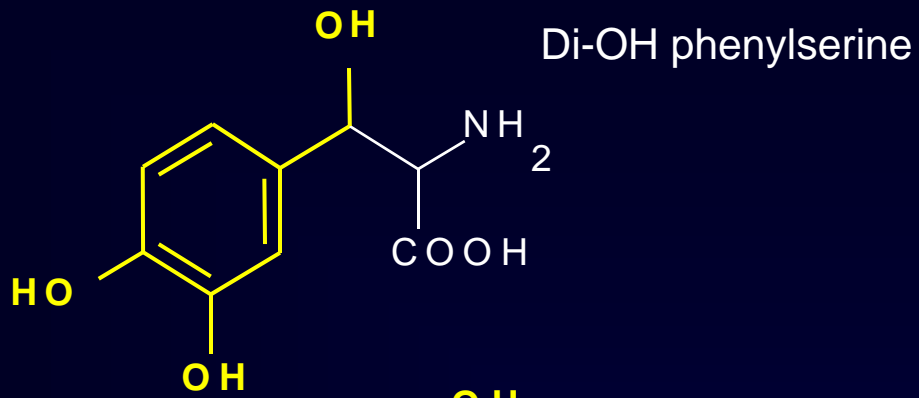


Enhancement of the HIT-rate by using short sequences



IC₅₀ values

	+ biotinyl-Q28		+ biotinyl-Q47
	Q28	Q47	Q47
 <p>DiOH-phenylserine</p>	43	19	17
 <p>6-FNE</p>	71	1000	1000
 <p>CH₃-NE</p>	200	1000	1000
 <p>benzerazide</p>	92	234	214
 <p>myricetin</p>	9	22	17
 <p>2-OH-apomorphine</p>	74	360	341



The age of the compound affects the dose-response curve

