COLOSTRININ/COGNISURE
COGNASE™
THE WHOLE STORY

Tim Shilton, Development Director
ReGen Therapeutics Plc
www.regentherapeutics.com
tim.shilton@regentherapeutics.com

CONTENTS

- Commercial Summary
- What is Colostrinin?
- The pathology of Alzheimer's Disease
- In-vitro data
- In-vivo data
- Safety
- Clinical data
- Mode of action
- Q and A

COMMERCIALISATION

- Metagenics:
  - Nutraceutical 'professional' channel in N. America (Oct.2007 launch) and Australia (June 2007)
  - Expansion to 'retail' sector intended
  - Tablets/capsules : 'Support for healthy cognition'
- Other:
  - Cyprus !
  - Discussions ongoing for all other regions
  - Finished formulation/active ingredient
  - Ingredient supply

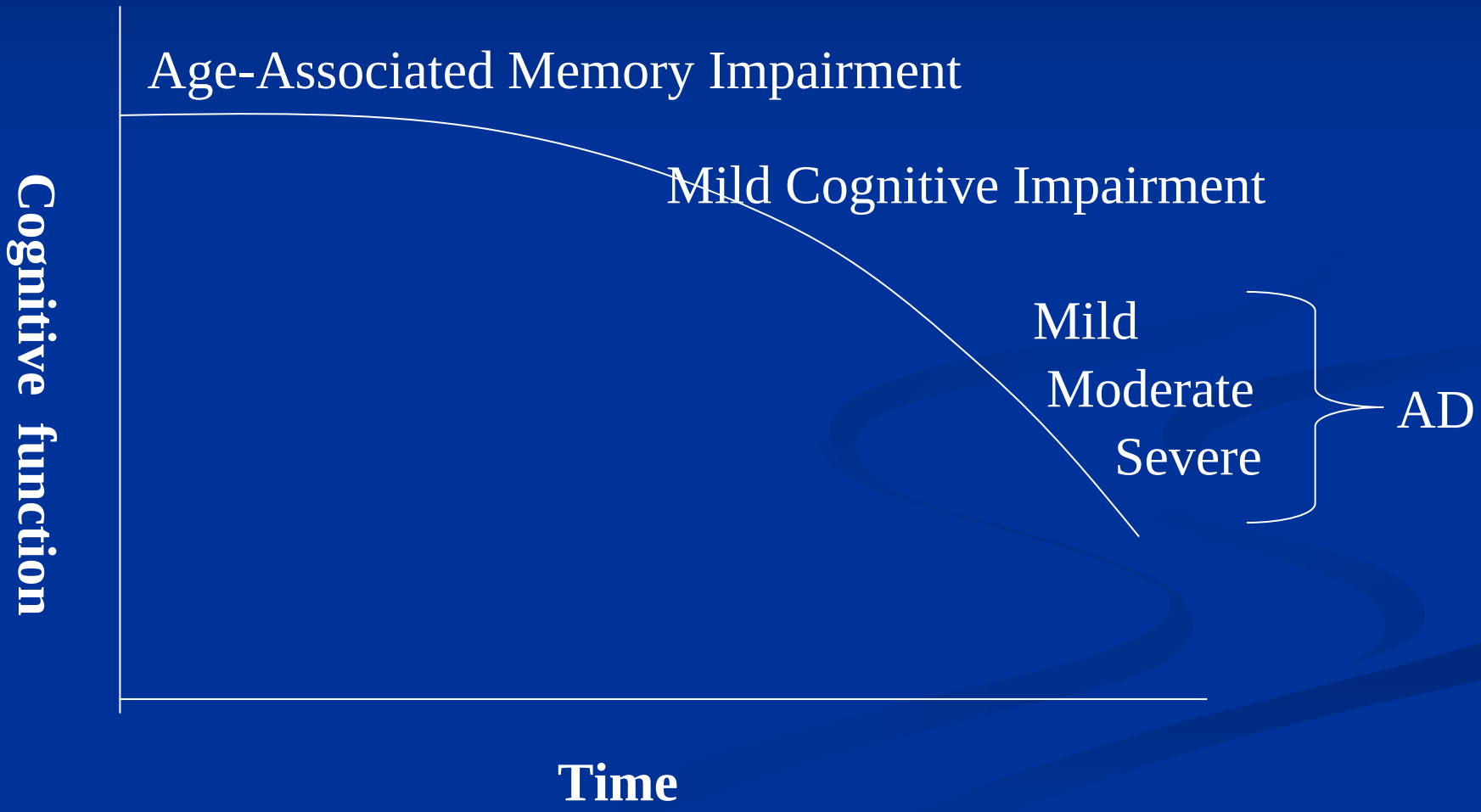
FEATURES/BENEFITS

- Small, low-dose, chewable, chocolate tablet
- Made to high quality standards
- Active from safe natural source
- Significant body of scientific/clinical evidence
- Multifaceted activity

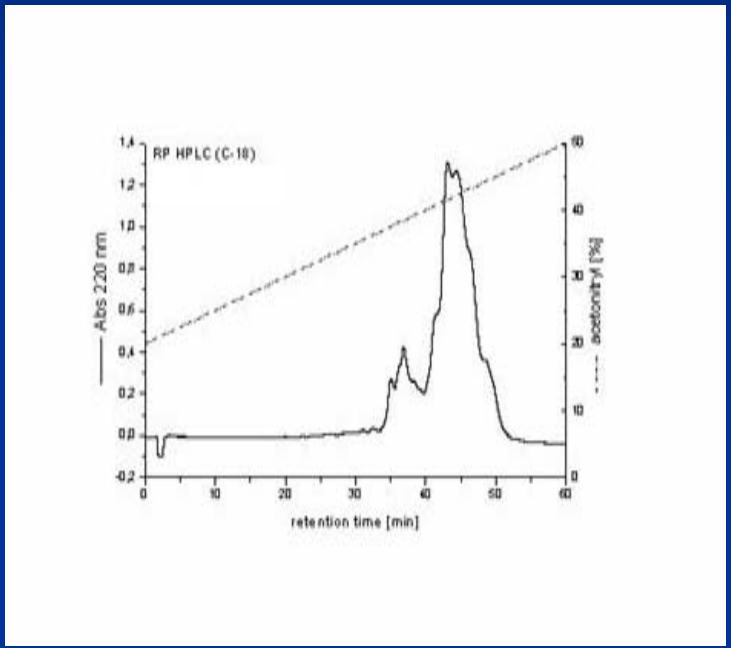
Support for Healthy Brain Aging and Cognition

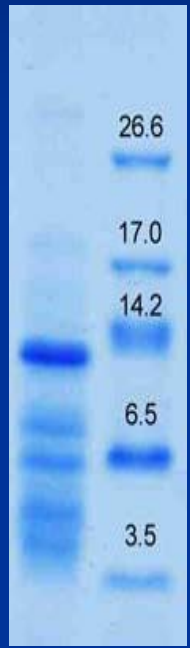
The ‘cornerstone’ of managing age-related cognition problems

CONTINUUM of COGNITIVE DECLINE



CLN MOLECULAR PROFILE





Amino Acid	CLN		
	Ovine Original Method*	Ovine MeOH Method**	Bovine MeOH Method**
Asp/Asn	3.42	2.80	5.13
Ser	5.66	5.05	6.94
Glu/Gln	15.48	15.77	17.99
Gly	3.15	3.03	2.95
His	2.54	2.14	3.28
Arg	2.32	3.34	1.62
Thr	5.73	5.30	4.32
Ala	2.78	2.13	3.06
Pro	21.07	22.50	20.79
Tyr	1.36	1.54	0.47
Val	9.27	11.10	8.15
Met	3.33	1.70	0.70
Lys	5.30	4.93	8.15
Ile	3.17	3.42	3.21
Leu	11.04	10.47	10.33
Phe	4.38	4.77	5.41

*according to M. Janusz et al.1974 (Janusz et al., 1974)
**according to Kruzel *et al*. 2001 protocol (Kruzel et al., 2004) (Kruzel, 2001)

CLN-DERIVED PEPTIDES

##	Sequence	Homology
SEQ #1	RXXXXXXXXXXXXXXXXXXXXXF	casein alpha S-1 homolog
SEQ #2	FXXXXXXXXXXXXV	casein alpha S-1 homolog
SEQ #3	SXXXXXXXXXXXXXXXXXXW	casein alpha S-1 homolog
SEQ #4	GXXXXXXXI	casein beta homolog
SEQ #5	EXXXXXXXXXXXI	casein beta homolog
SEQ #6	VXXXXXXXXXQ	casein beta homolog
SEQ #7	SXXXXXXXXXXXXXXXXXXXXXXXXQ	casein beta homolog
SEQ #8	EXXXXXXR	casein beta homolog
SEQ #9	RXXXXXXV	casein beta homolog
SEQ #10	PXXXXXXXXXXXXXXXP	Fas Ligand homolog
SEQ #11	PXXXXXXXP	Fas Ligand homolog
SEQ #12	FXXXK	casein beta homolog
SEQ #13	MXXXXXP	casein beta homolog
SEQ #14	DXXXXXG	casein beta homolog
SEQ #15	KXXXXXXXXXXXXXT	40% Proline
SEQ #16	QXXXXXXXXXXXXXXXXXXXXXXXQ	48% Proline
SEQ #17	PXXXXXXXXXXXXXXT	37% Proline
SEQ #18	RXXXXXXXXXXXXXXS	31% Proline
SEQ #19	AXXXXXXXXXXXXY	28% Proline
SEQ #20	QXXXXXXXXXXXXXXXXXXXXXXXQ	28% Proline
NP LIS	VESYVPLFP	22% Proline
NP POL	RPKHPIKHQ	22% Proline

MANUFACTURE

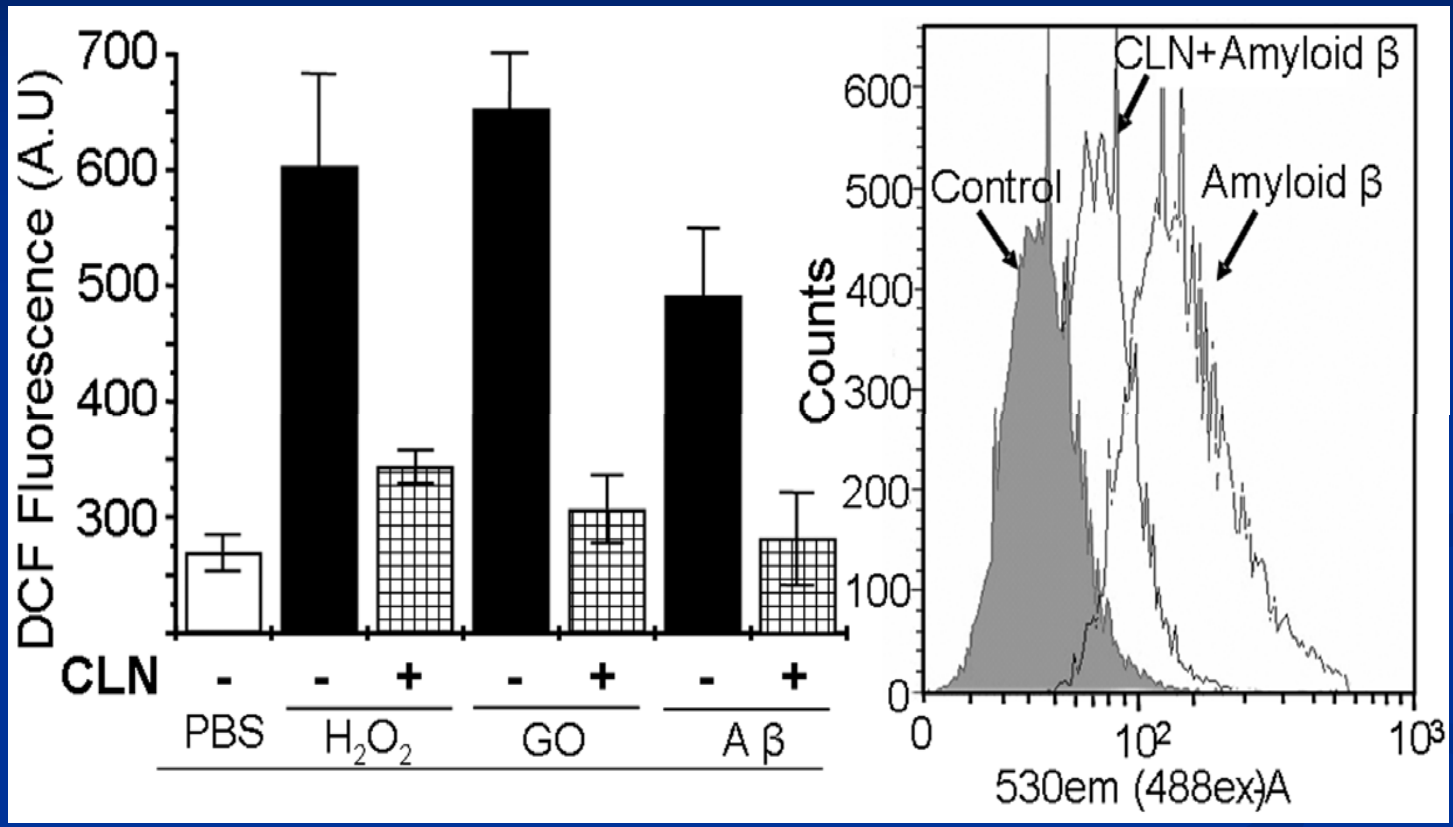
- Industrial scale process defined at US bovine colostrum company (Sterling Technology, SD).
- US by far the largest single market.
- Know-how/facilities and equipment.
- Collection/pooling/standardised raw material.
- Cost/time-effective production of nutraceutical grade 'GMP' material.

AD PATHOLOGY

- Inflammation/oxidative stress (ROS)
- Extracellular beta-amyloid plaque
- Intracellular neuro-fibriliary (tau) tangles

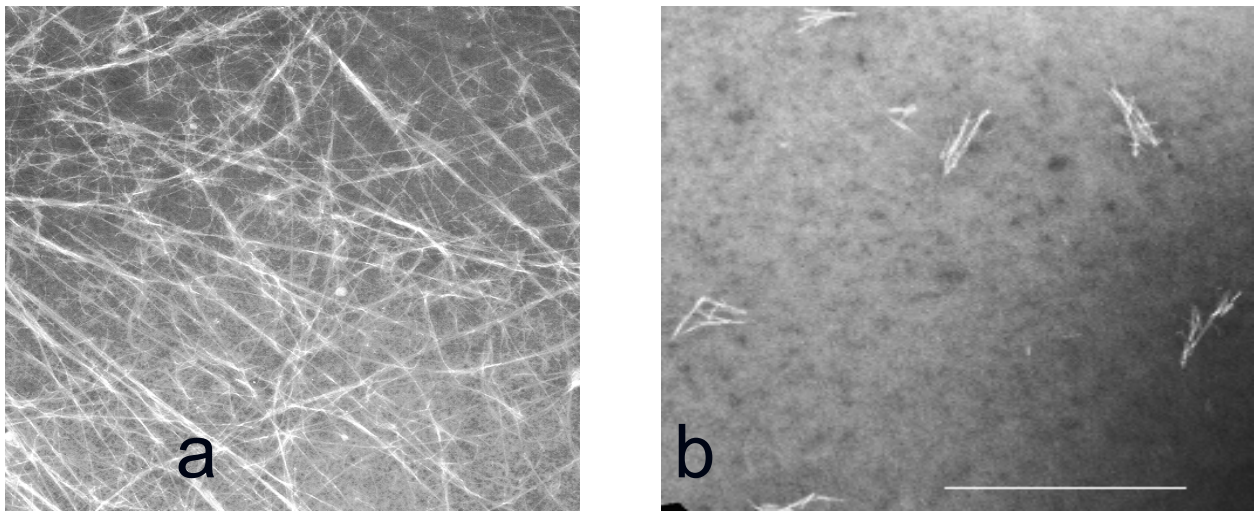
- Neurotoxicity/selective hippocampal (cholinergic) cell death
- Memory/cognition impairment

CLN AND INTRACELLULAR ROS



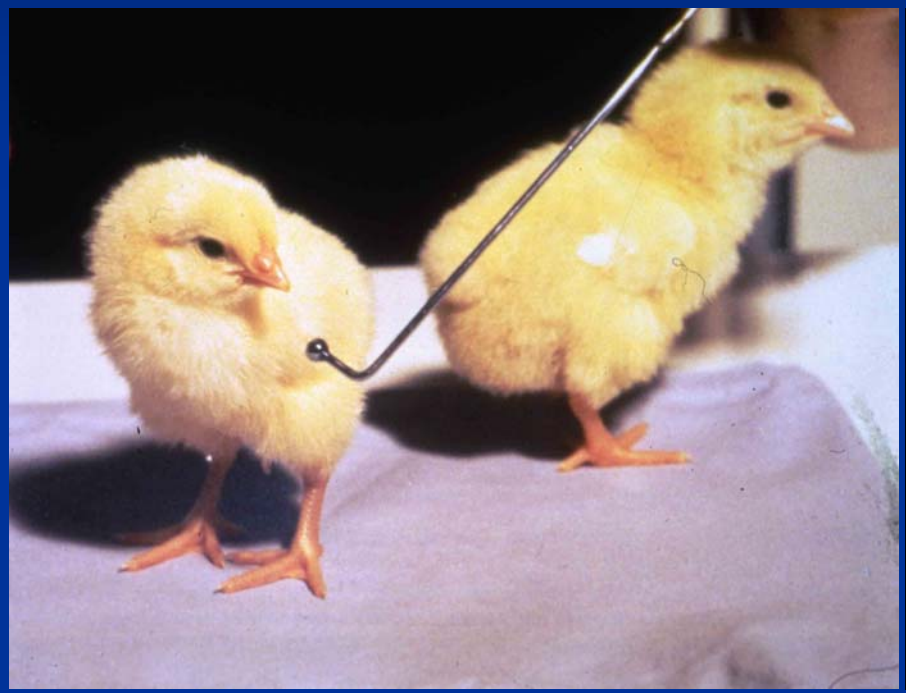
<u>CLN decreases intracellular ROS levels.</u> CLN pre-treatment of cells prevents oxidant-induced increases in ROS levels.

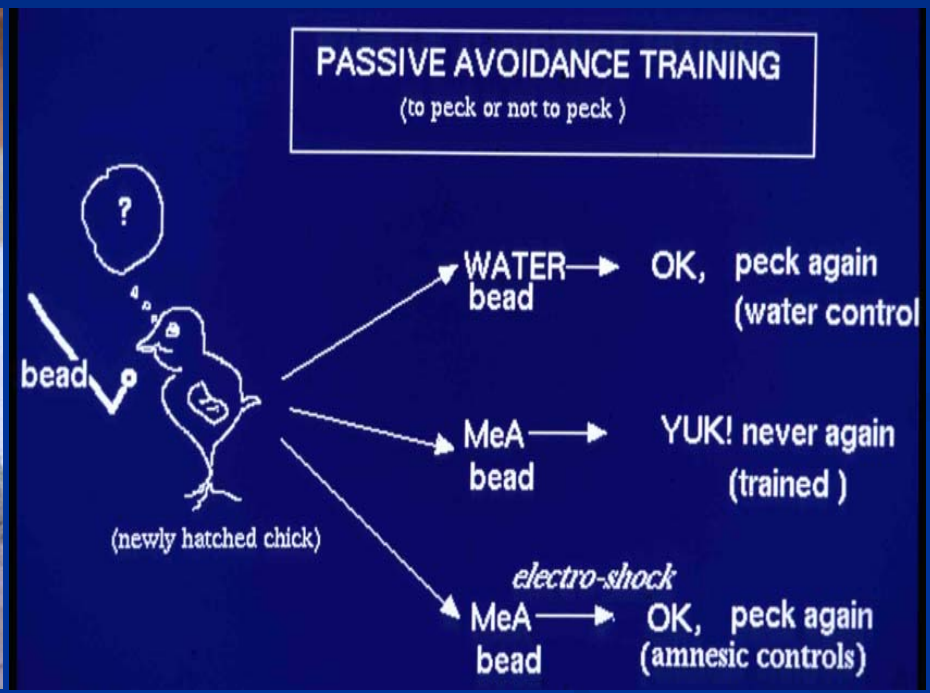
CLN PREVENTS Aβ AGGREGATION



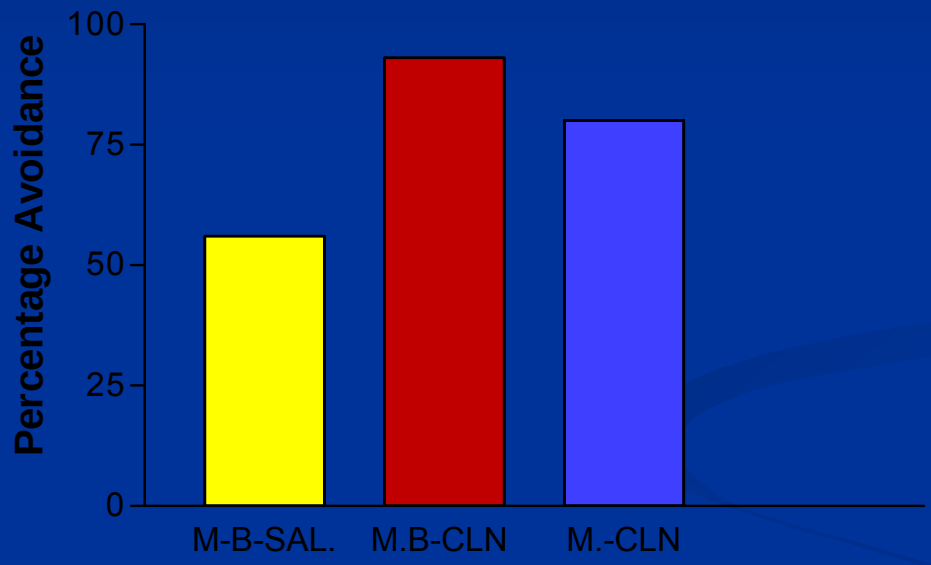
Negative stain electron micrographs of Aβ (1-40) at 0.346 mM concentration (a) in the absence of CLN and (b) with 0.2 mM CLN. Incubation: 20 days at 37 ºC. Bar =1 micrometer

OU-Chick Studies



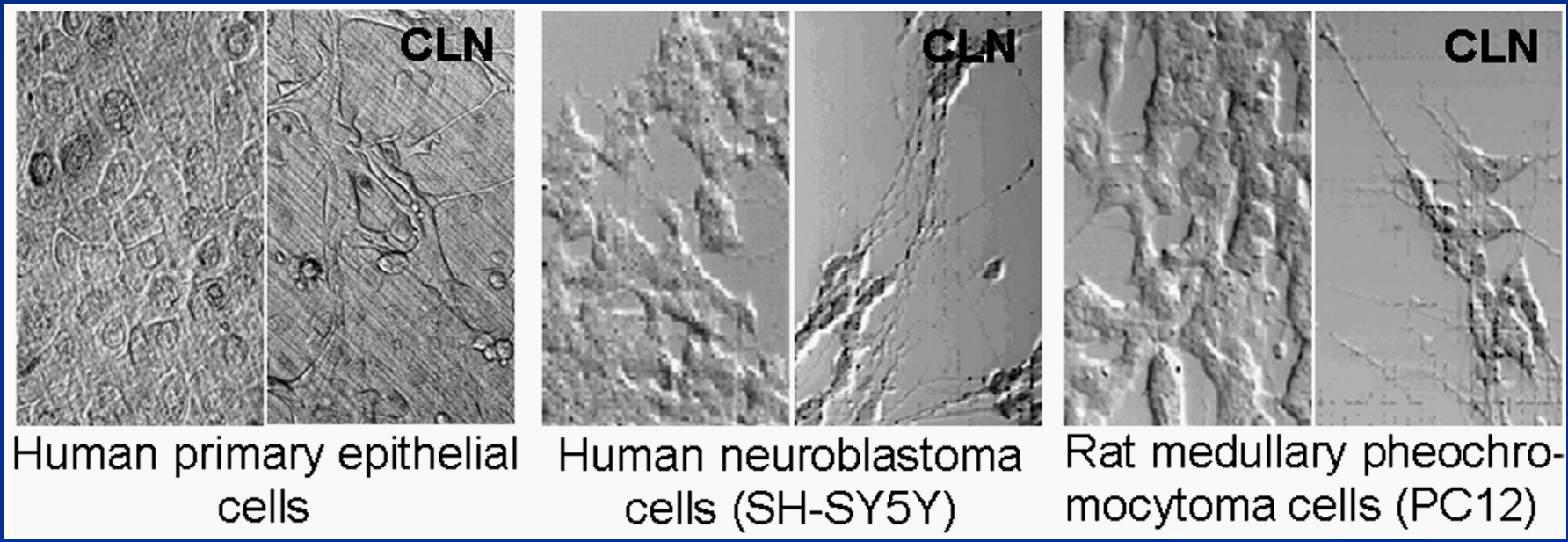


OU – BA DEFICIT MODEL



Neuroprotective effect of Colostrinin: M= Methyl anthranilate, B= β-amyloid, CLN- Colostrinin, SAL = 0.9% saline

CLN INDUCES CELL DIFFERENTIATION

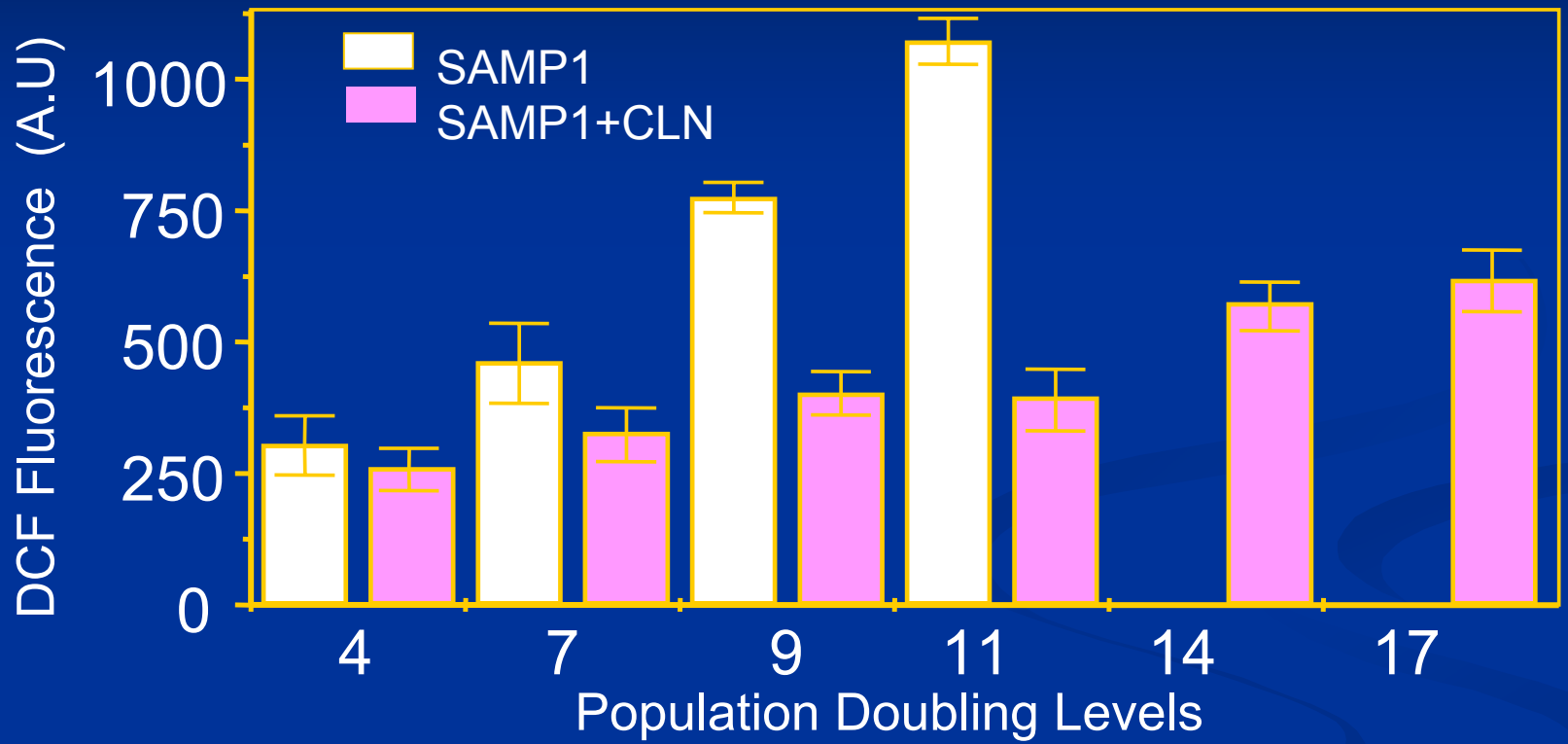


The human primary epithelial cells, human neuroblastoma (SH-SY-5Y) and pheochromocytoma (PC12) cells were cultured in their well-defined culture media and then treated with 100 ng per ml CLN.

CLN AND LIFE SPAN IN SAMP

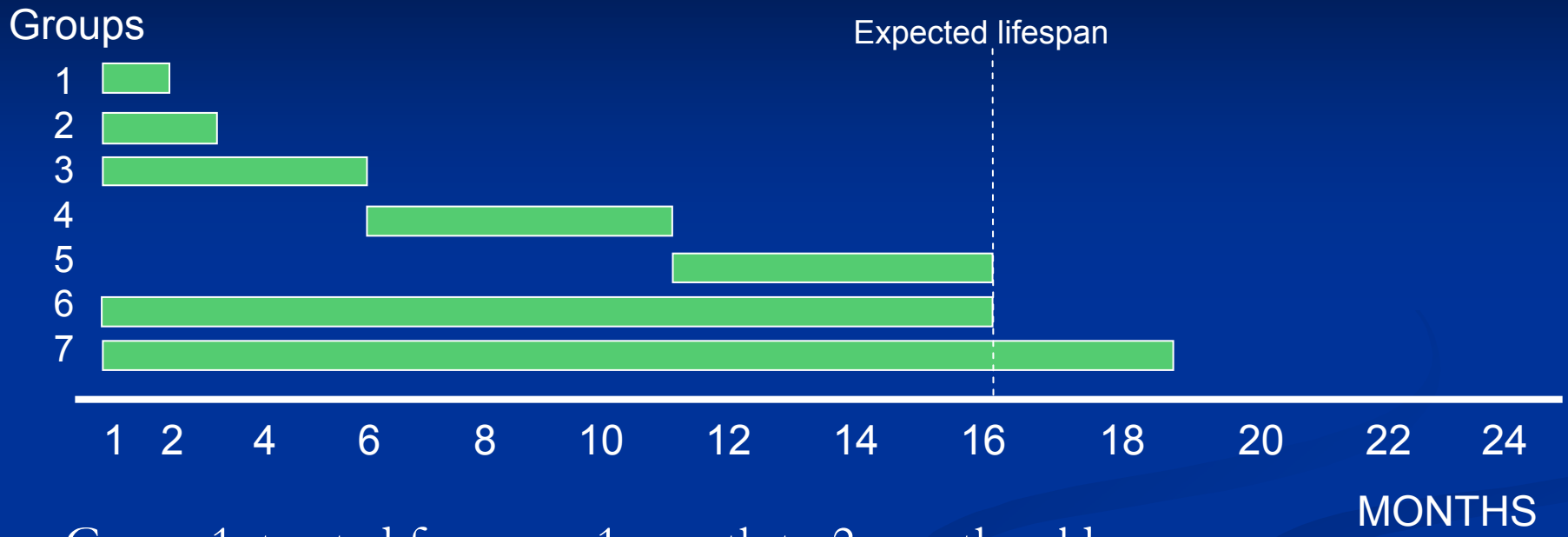
The accelerated senescence strain of mice is a group of related inbred strains consisting of a series of SAMP (accelerated senescence-prone, short-lived) and SAMR (accelerated senescence-resistant, longer-lived) strains. The SAMP strains of mice show an earlier onset of age-associated pathological phenotypes (e.g., age-related deficits in learning and memory) and a shorter lifespan

CLN INCREASES THE LIFE SPAN OF CULTURED CELLS



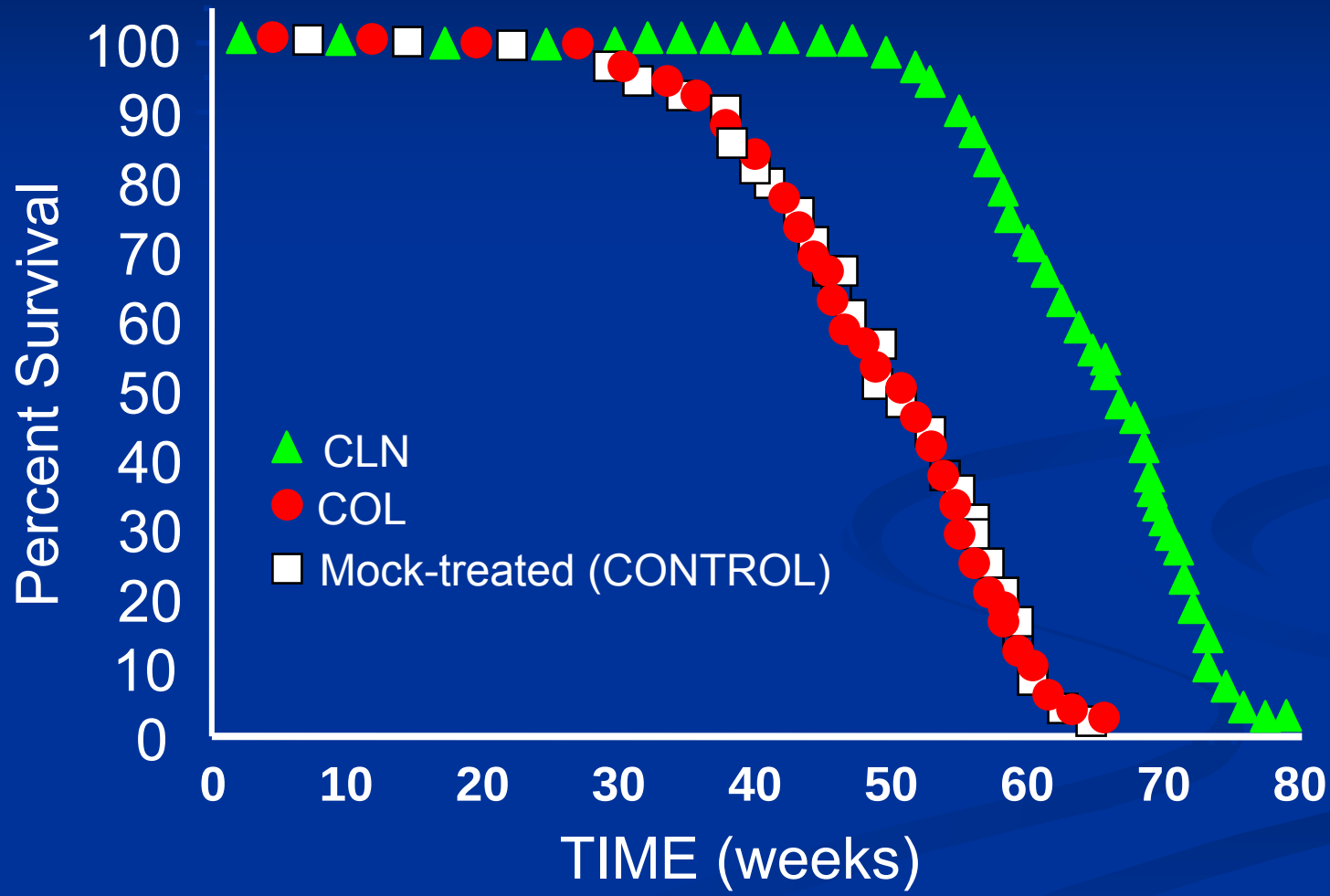
Human and rodent diploid fibroblast exhibit limited proliferative potential (population doublings), and enter a state of permanent growth arrest (cellular aging") in which they remain alive and metabolically active but are completely refractory to mitogenic stimuli

CLN AND LIFE SPAN IN SAMP

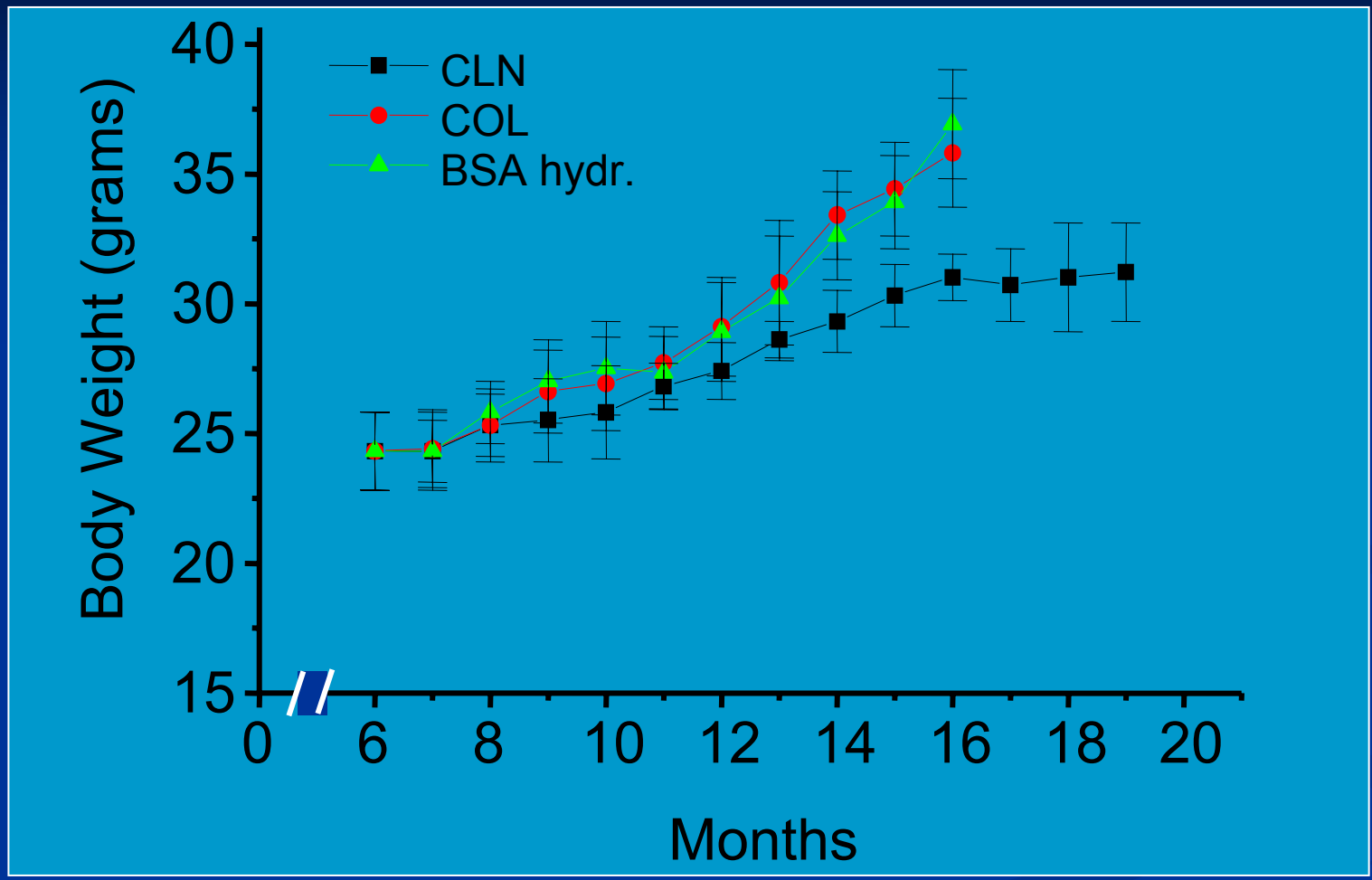


Group 1: treated from age 1 month to 2 months old
Group 2: treated from age 1 months to 3 months old
Group 3: treated from age 1 months to 6 months old
Group 4: treated from age 6 months to 11 months old
Group 5: treated from age 11 months to 16.2 months old
Group 6: treated from age 1 months to 16.2 (expected lifespan)
Group 7: treated from age 1 months to end of their life

CLN AND LIFE SPAN IN SAMP

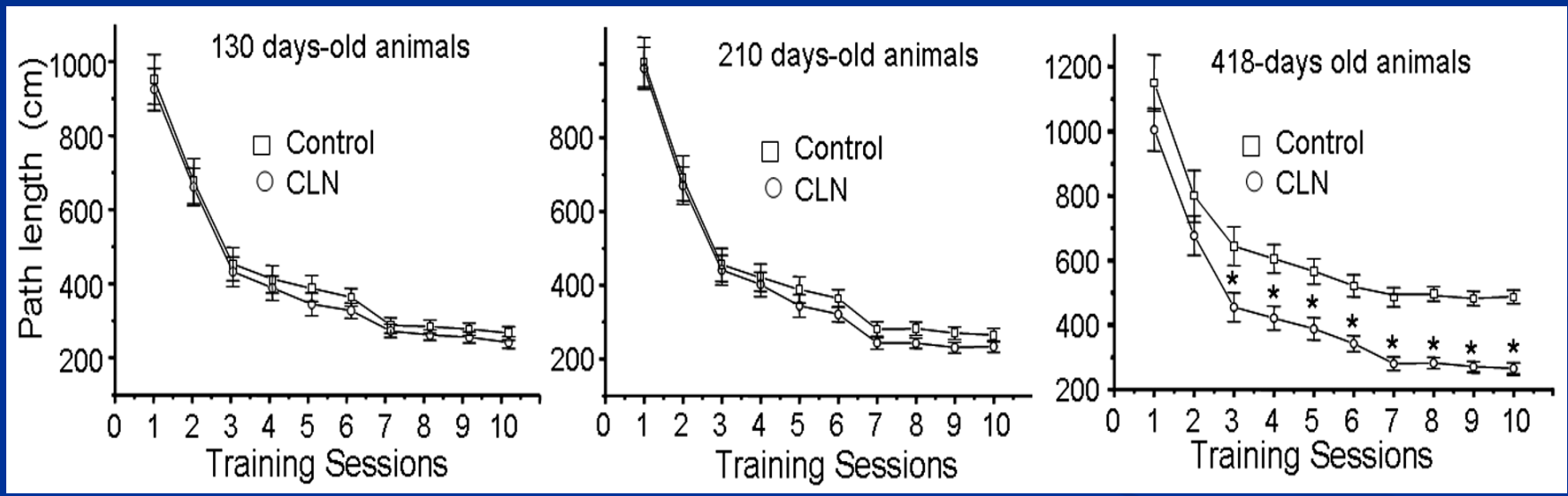


CLN AND BODY WEIGHT IN SAMP



There were no effects of CLN on body weight at young, and middle age, however, older mice were significantly leaner

CLN AND COGNITIVE PERFORMANCE IN SAMP MICE

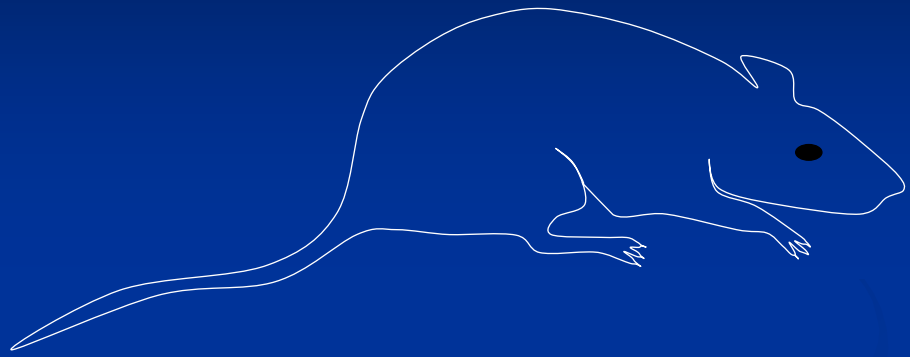


Effect of CLN on learning and memory in young, middle-aged and old animals. The length of the path taken to reach the hidden platform was analyzed to assess the efficiency with which the mice located the platform independently of their speed of swimming.

CLN AND MOTOR SENSORY ACTIVITY IN SAMP MICE

	5 months old		9 months old		14 months old	
	CNTRL	CLN	CNTRL	CLN	CNTRL	CLN
Motor Skills						
Walking Initiation	2.1±0.25	2.2 ±0.2	2.3±0.15	2.2±0.3	3.1±0.2	2.3±0.2
Allay Turning	10.5±1.3	11.2±1.5	10.2±1.0	9.8±0.8	18.4±2.5	12.3±1.5
Negative Geotaxis	9.8±0.5	9.2±0.5	9.6± 1.5	8.8±1.0	14.9±1.0	10.1±0.5
Wire Grip	32.5±2.0	34.6±1.5	31.0±2.0	36.5±0.5	23.0±2.0	30.0±2.0
Bridge Walking	44.4±2.5	46.1±3.0	42.0±2,5	47.2±3.0	26.5±2.5	41.0±2.0
Sensory Activity						
Auditory Startle (force units)	4.7±0.5	4.4±1.0	5.1±2.5	5.3±0.5	2.3±0.5	4.4±1.2
Shock Startle (force units)	24.5±2.2	25.3±1.9	24.2±1.5	26.4±1.2	15.3±2.0	23.6±1.7
Reaction Time (ms)	46.2±2.5	42.1±1.2	45.4±2.0	40.1±.2.5	59.8±2.0	46.1±0.2

SAFETY STUDIES



1. **Genotox Study:**
   - *In vivo* Mammalian Erythrocyte Micronucleus Test (clastogenicity)
   - Bacterial Reverse Mutation Assay (mutagenic potential),
   - *In Vitro* Mammalian Chromosome Aberration Test (clastogenicity)
2. **Animal Toxicology Study:**
   - Short Term, 30-Day Study in Rats
   - Long Term 90-Day Study in Rats

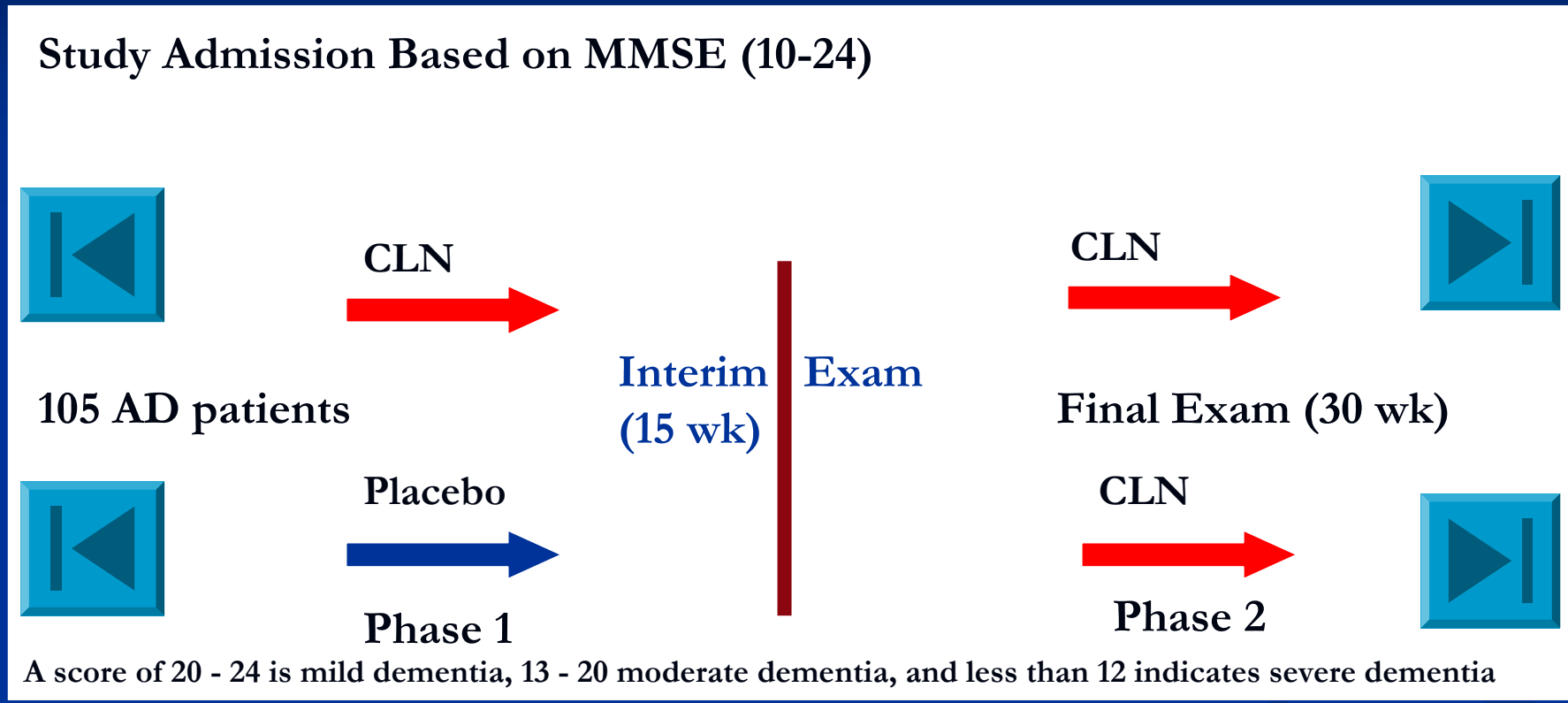
CLN CLINICAL TRIALS

Archivum Immunologiae et Therapiae Experimentalis, (Leszek et al. 1999), *Colostrinin®: a Proline-Rich Polypeptide (PRP) Complex Isolated from Ovine Colostrum for Treatment of Alzheimer's Disease. A Double-Blind, Placebo-Controlled Study (15 CLN subjects).*

Medical Science Monitor, (Leszek et al., 2002): *A long term study – extension of a double blind placebo controlled study (33 CLN subjects with 13 treated for 28 months).*

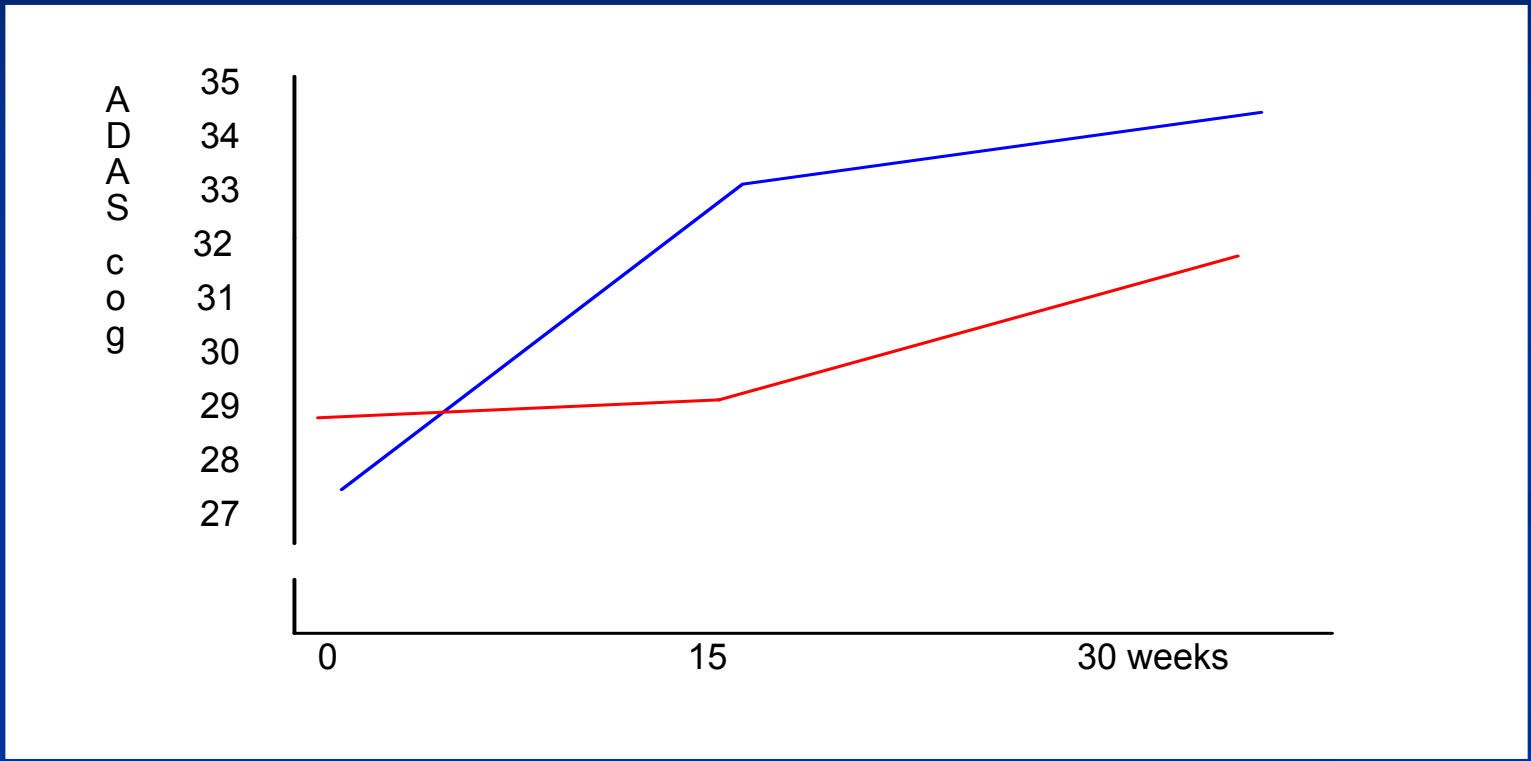
Journal of Alzheimer's Disease, (Bilikiewicz and Gaus, 2004): *30-week trial; Evidence of early beneficial effects on cognitive symptoms and daily functions (106 CLN subjects).*

REGEN CLINICAL TRIAL RG-010



A 15 week double-blind phase comparing CLN with placebo, followed by a second 15 week open labeled phase when all patients received CLN. The dosage: 100 μg on alternate days for three weeks followed by two weeks CLN-free. Three times/phase.

REGEN CLINICAL TRIAL RG-010



ADAS-cog: Alzheimer's Disease Assessment Scale Cognitive Subscale is scored by errors (with a total error score range of 0 to 70). Blue, placebo/active; Red, active/active

RG-010 CLINICAL TRIAL SUMMARY

Safety:

No adverse side effects or safety issues arose from the 30 week trial in 106 Alzheimer's disease sufferers.

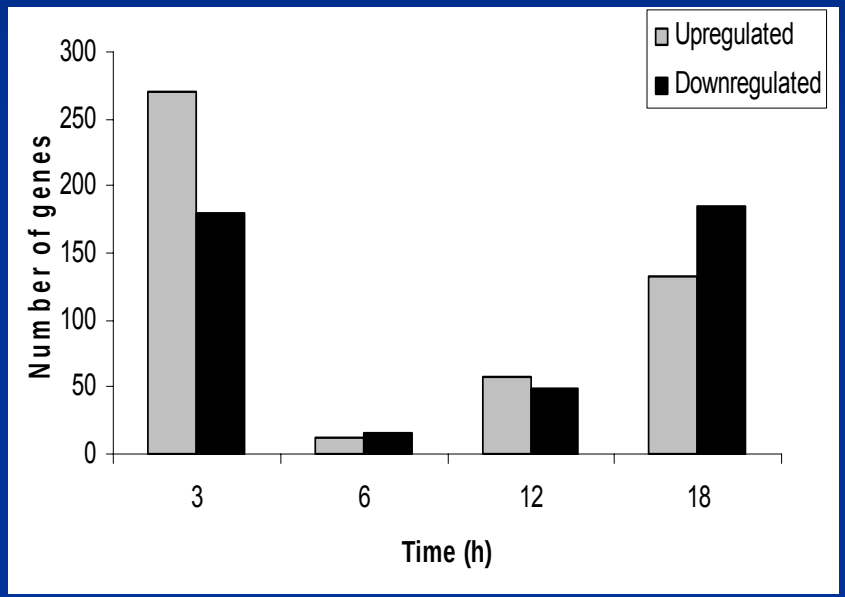
Efficacy:

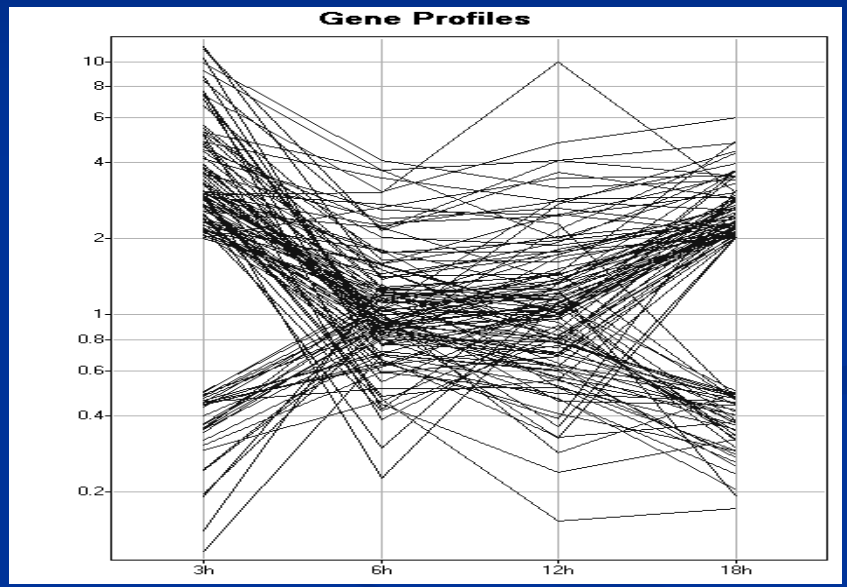
Evidence of early beneficial effects on cognitive symptoms and daily functions. Statistically significant difference: ADAS-cog ($p=0.02$) and Instrumental Activities of Daily Living (IADL; $p=0.02$).

CLN MODE OF ACTION

How can Low oral Dose of CLN be clinically beneficial ?

MUCOSAL ABSORPTION AND SIGNAL TRANSDUCTION



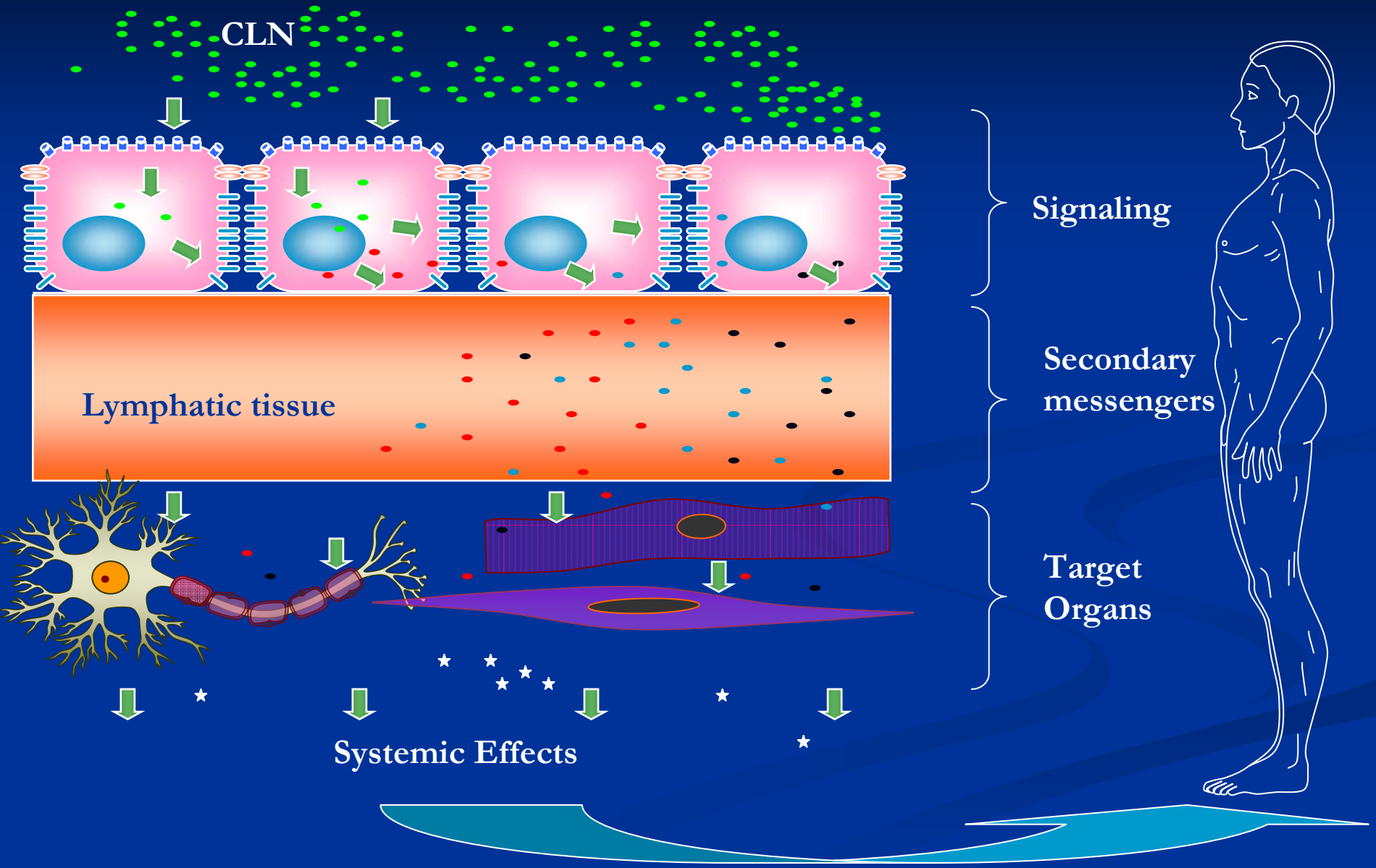


Gene expression levels in TR146, buccal mucosal cell line, were analyzed using Affymetrix GeneChip® Human Genome Focus Array containing over 8,500 verified human sequences from the NCBI RefSeq database.

CLN/PEPTIDE UPDATE

- NPlis - +ve in Water Maze
- NPpol – neuroprotective in in-vitro PD model
- A/B – Modulates molecules of pathways involved in AD pathology (bleomycin hydrolase, APP, Tau)
- C – Modulates molecules of pathways involved in diabetes
- D – Modulates molecules involved in pathways of allergy/inflammation
- In-vivo AD (Tau/BA) and obesity studies ongoing; asthma model being set-up

CLN MOA: SIGNAL TRANSDUCTION



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- Small, low-dose, chewable, chocolate tablet
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The ‘cornerstone’ of managing age-related cognition problems

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(ReGen Chief Scientific Advisor)

Thanks for your Attention

Q and A