抗衰老多糖及其应用

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研究重点与策略：衰老及相关疾病

衰老与抗衰老

衰老相关疾病

- 神经退行性疾病
- 恶性肿瘤

药物种类

- 多糖、寡糖、糖缀合物
- 蛋白、多肽、肽缀合物
- 天然与合成小分子
- 中药复方

疾病模型

- 酵母（单细胞）
- 秀丽线虫（无脊椎动物）
- 斑马鱼（脊椎动物）
- 哺乳动物及人细胞

相信进化论…

岭南生物资源

岭南特色中药

南海海洋生物

Making the Case for Aging and Neurodegeneration

Background overview

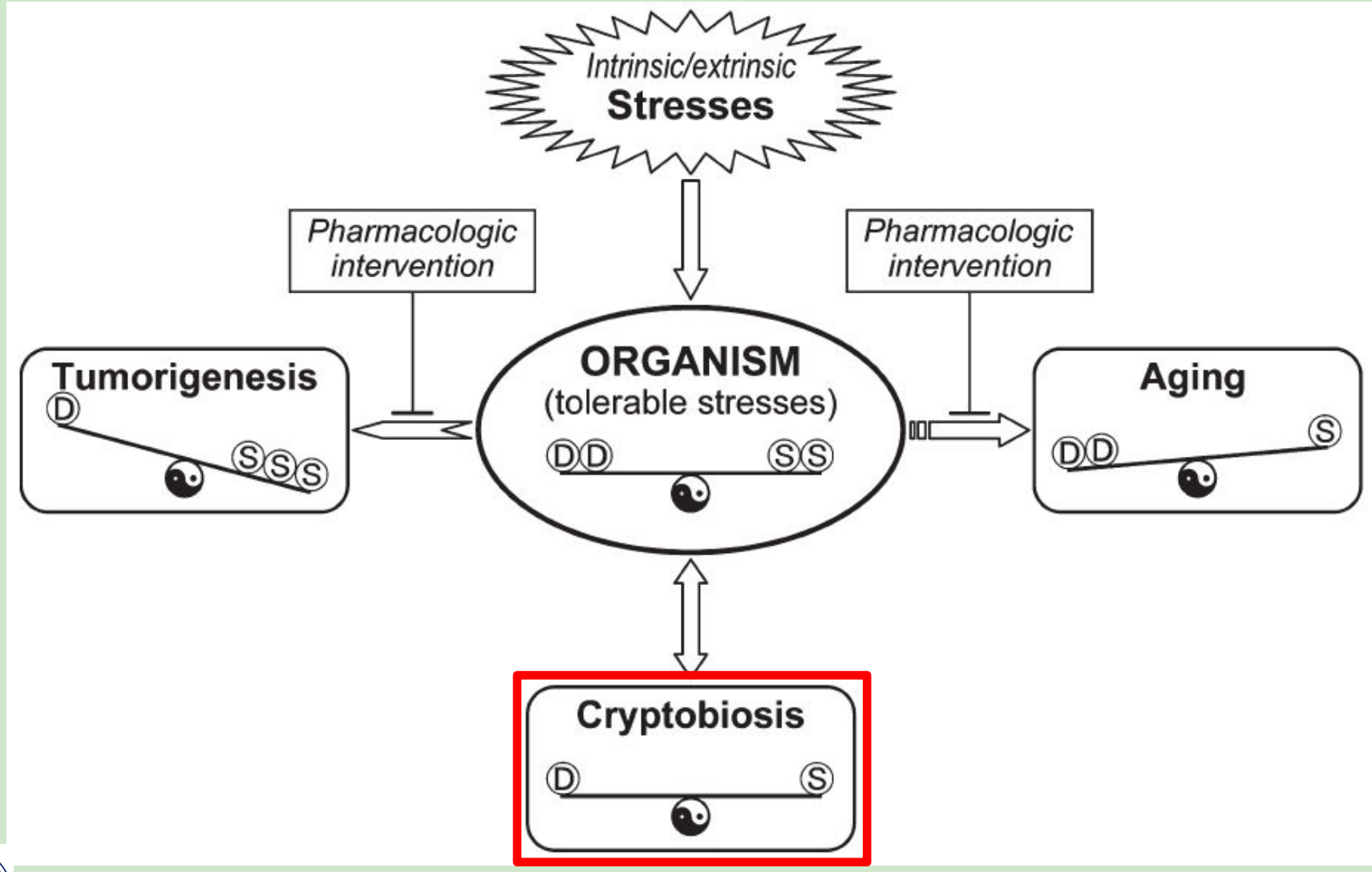
- Laboratory background
- *Caenorhabditis elegans*

Recent work

- Glycotherapeutics
- Biopharmaceuticals
- Small molecules
- Herbal formulae

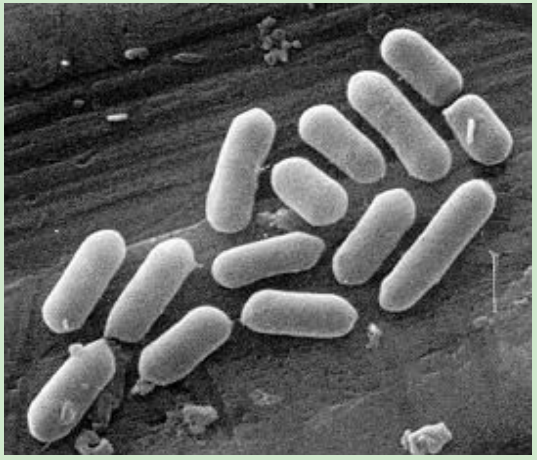
Cryptobiosis, Aging and Cancer:

Yin-Yang Balancing of Signaling Networks

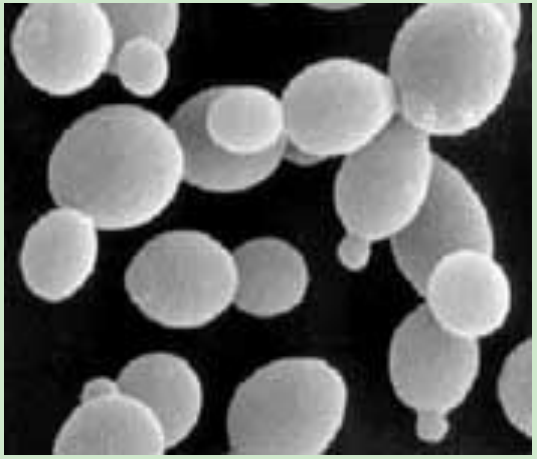


Huang Z & Tunnacliffe A (2006) *Rejuvenation Res* 9: 292–296.

Anhydrobiotes



Bacteria



Yeast

Resurrection plant
Selaginella lepydophylla

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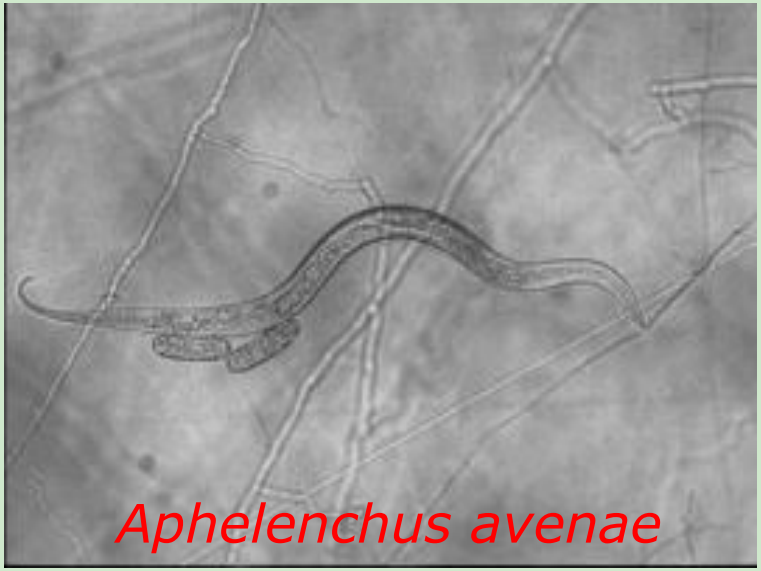
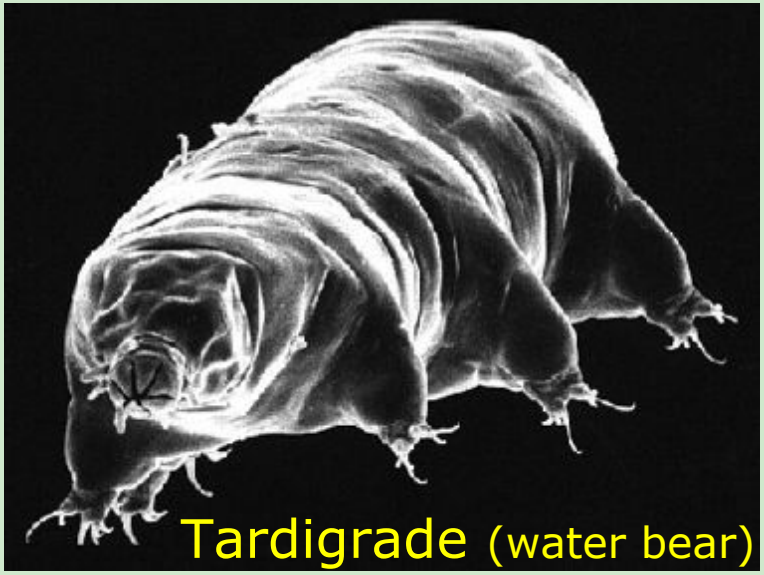
Anhydrobiotes



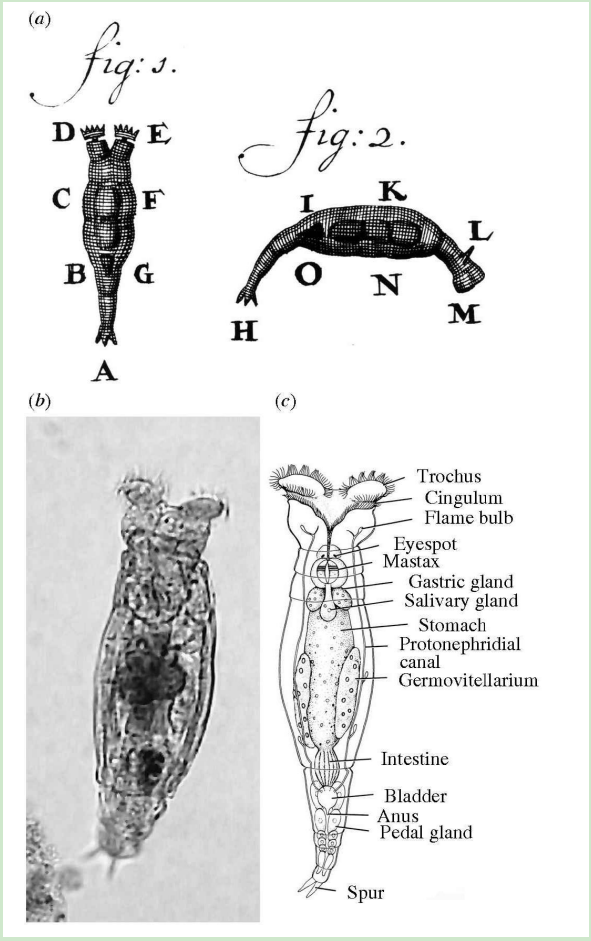


Antony van Leeuwenhoek 1702: animalcules (微小动物)

Anhydrobiosis

= life without water

"suspended animation"



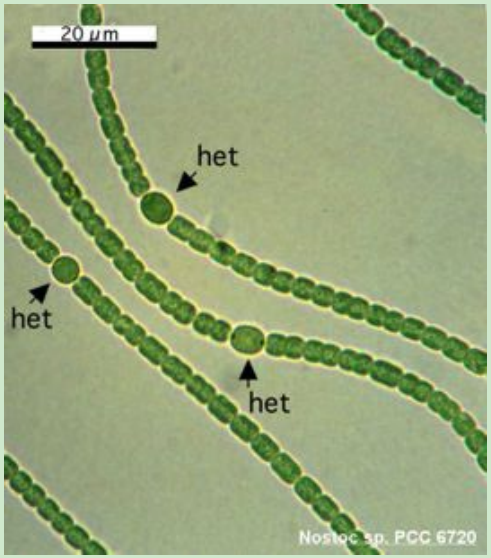
Tunnacliffe A & Lapinski J (2003) *Phil Trans R Soc Lond B* 358: 1755–1771.

Anhydrobiotes

Nostoc flagelliforme

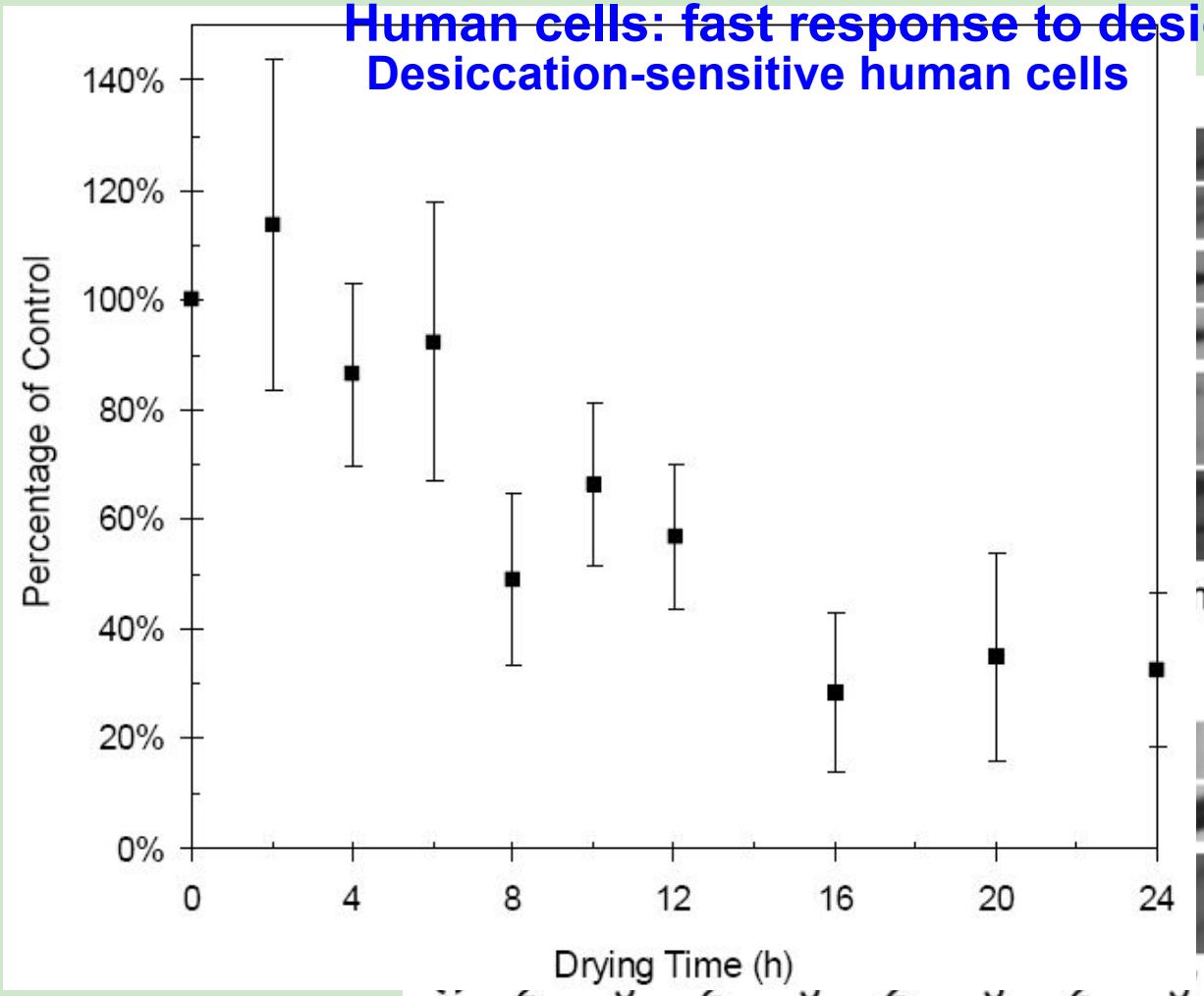
Nostoc sphaeroides

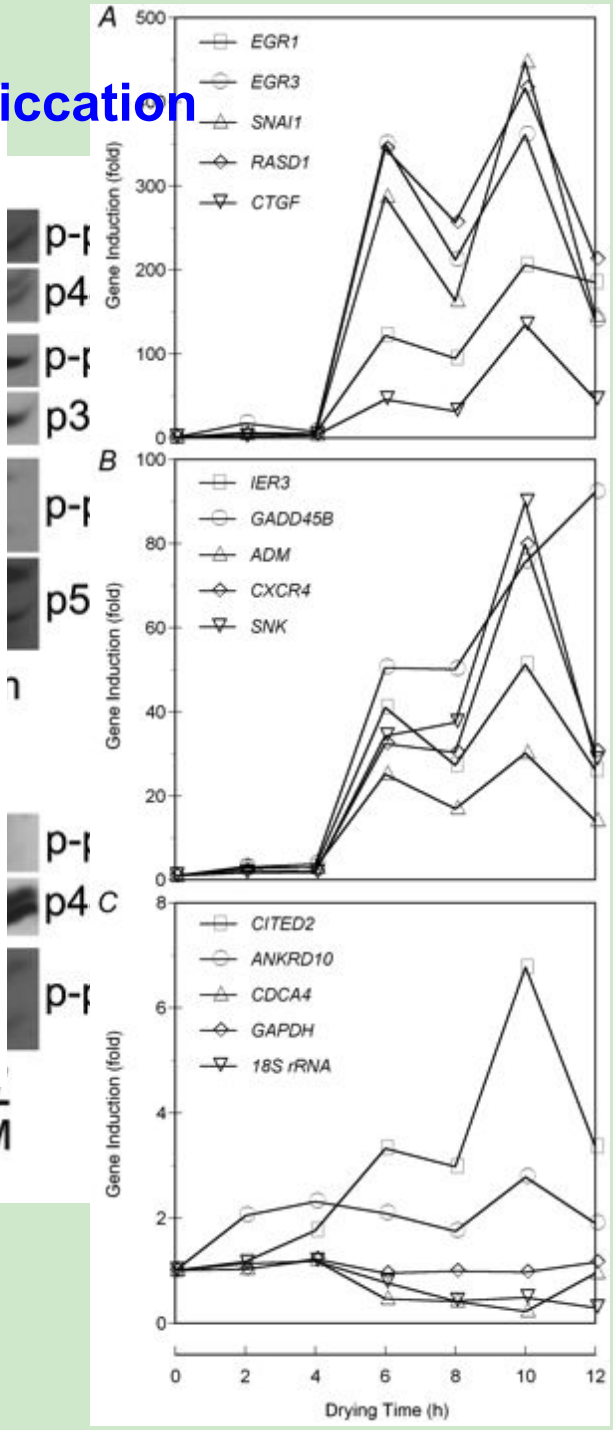
Nostoc commune



Human cells: fast response to desiccation

Desiccation-sensitive human cells

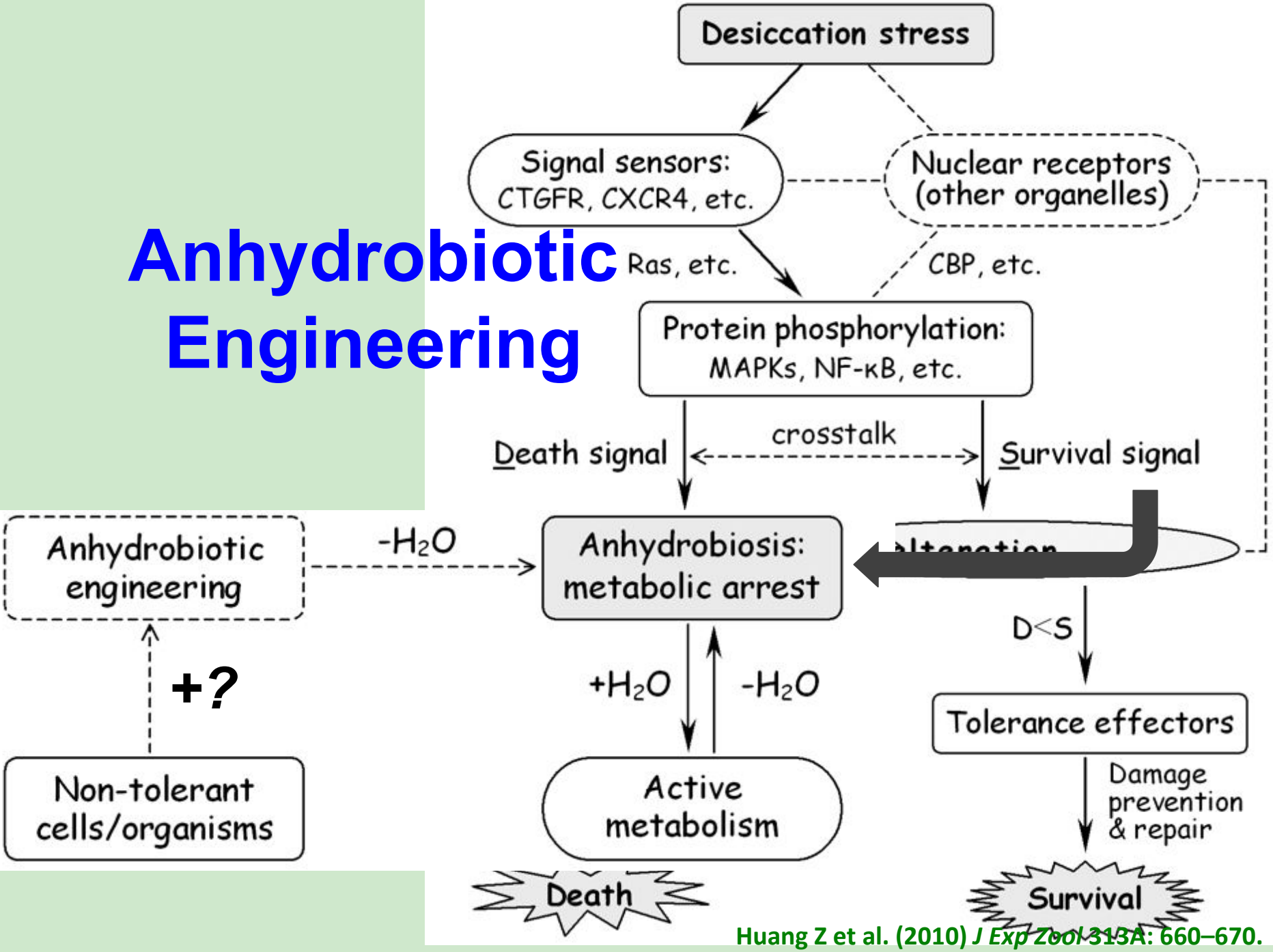




Survival of T-REx 293 cells at 98% relative humidity

Huang Z & Tunnacliffe A (2004) *J Physiol* 558: 181–191.
Huang Z & Tunnacliffe A (2005) *FEBS Lett* 579: 4973–4977.
Huang Z & Tunnacliffe A (2007) *Methods Enzymol* 428: 269–277.

Anhydrobiotic Engineering



Huang Z et al. (2010) *J Exp Zool* 313A: 660–670.

Anhydrobiosis and ageing

PreAP + AP + PostAP >> normal lifespan,
for both true and "partial" anhydrobiosis

PreAP + PostAP ≈ normal lifespan,
for true anhydrobiosis

PreAP + PostAP ≤ normal lifespan,
for "partial" anhydrobiosis

Huang Z & Tunnacliffe A (2006) *Rejuvenation Res* 9: 292–296.

A quest for longevity…

500 years ago, the Spanish explorer Ponce de León drank his way around the Florida coast during his expedition to find the legendary fountain of youth.

Finkel T (2003) *Nature* 425: 132–133.

阿凡达

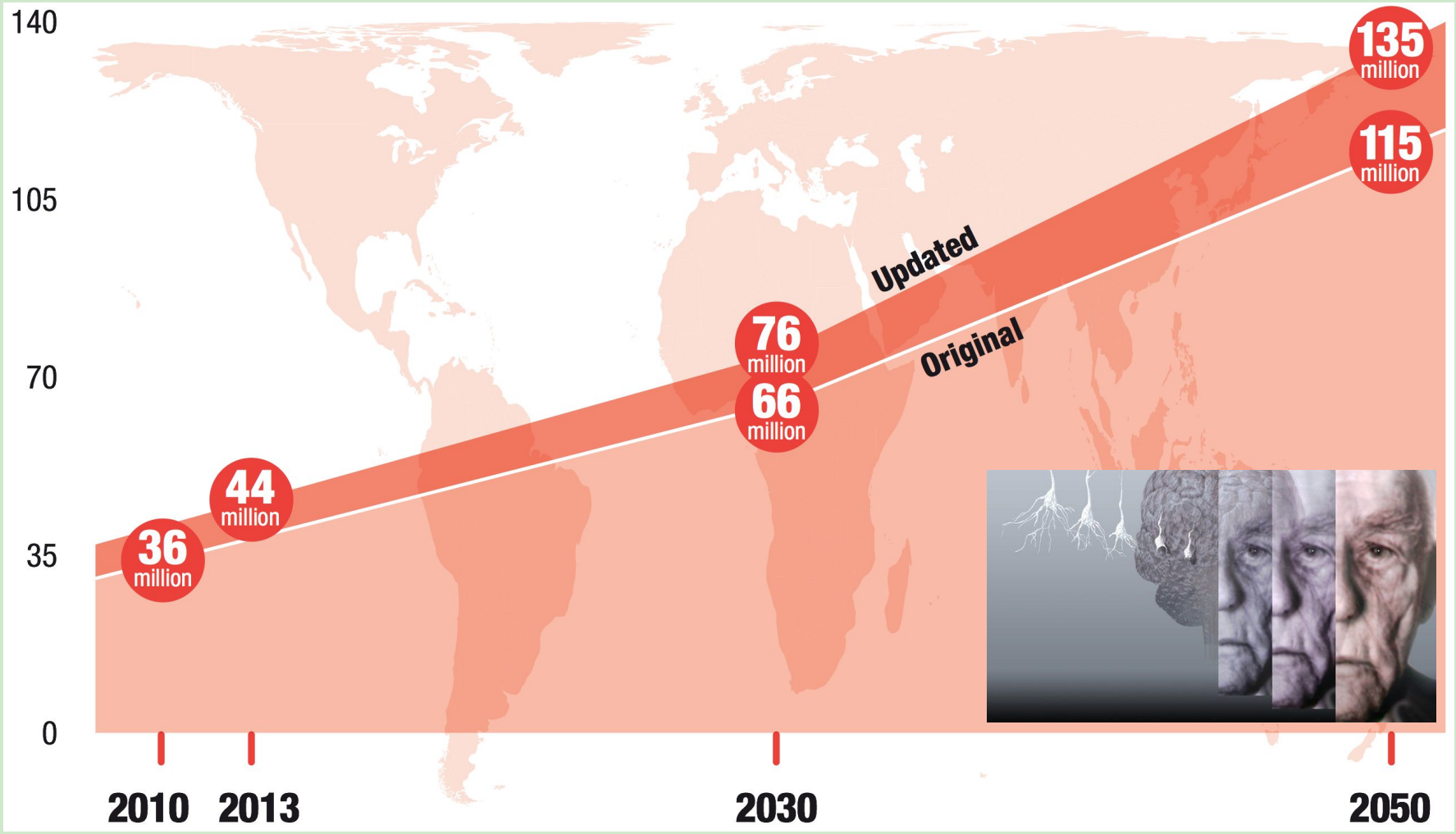
Neurodegenerative diseases: Alzheimer's disease as an example

- **Worldwide:** (Williams M. *Curr Opin Investig Drugs* 10: 23–34, 2009)
  - **25-34 million AD patients currently**

>40 millions now

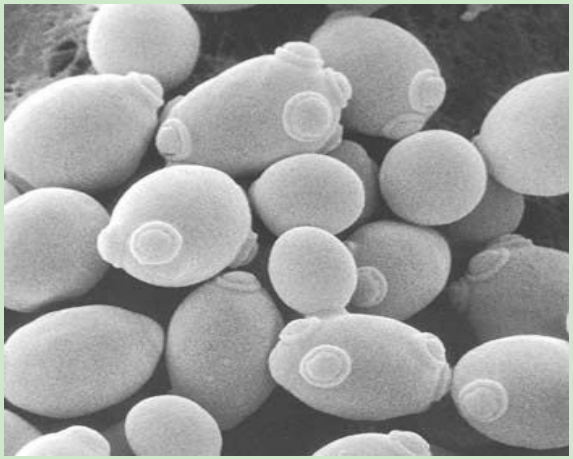
  - ●AD incidence at age 60: > 5% (higher for older population)广东省（2014）
  - ●Relevant cost: >1 000 000 000 000 yuan
  - **25% population >60 years old by 2030**

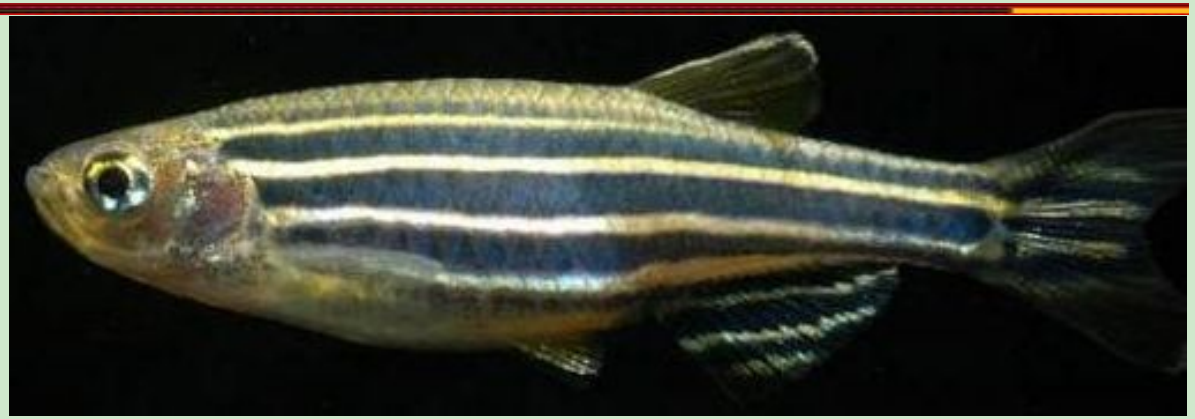
People with dementia worldwide

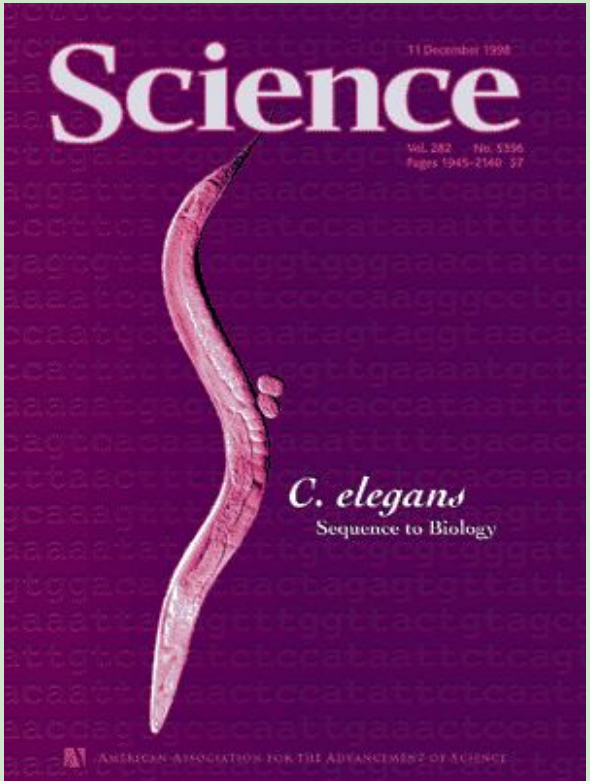


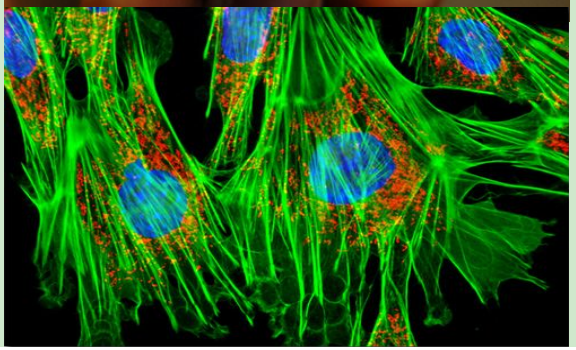
Prince M et al. (2013). *Policy Brief for Heads of Government: The Global Impact of Dementia 2013–2050*.

Well-characterised models



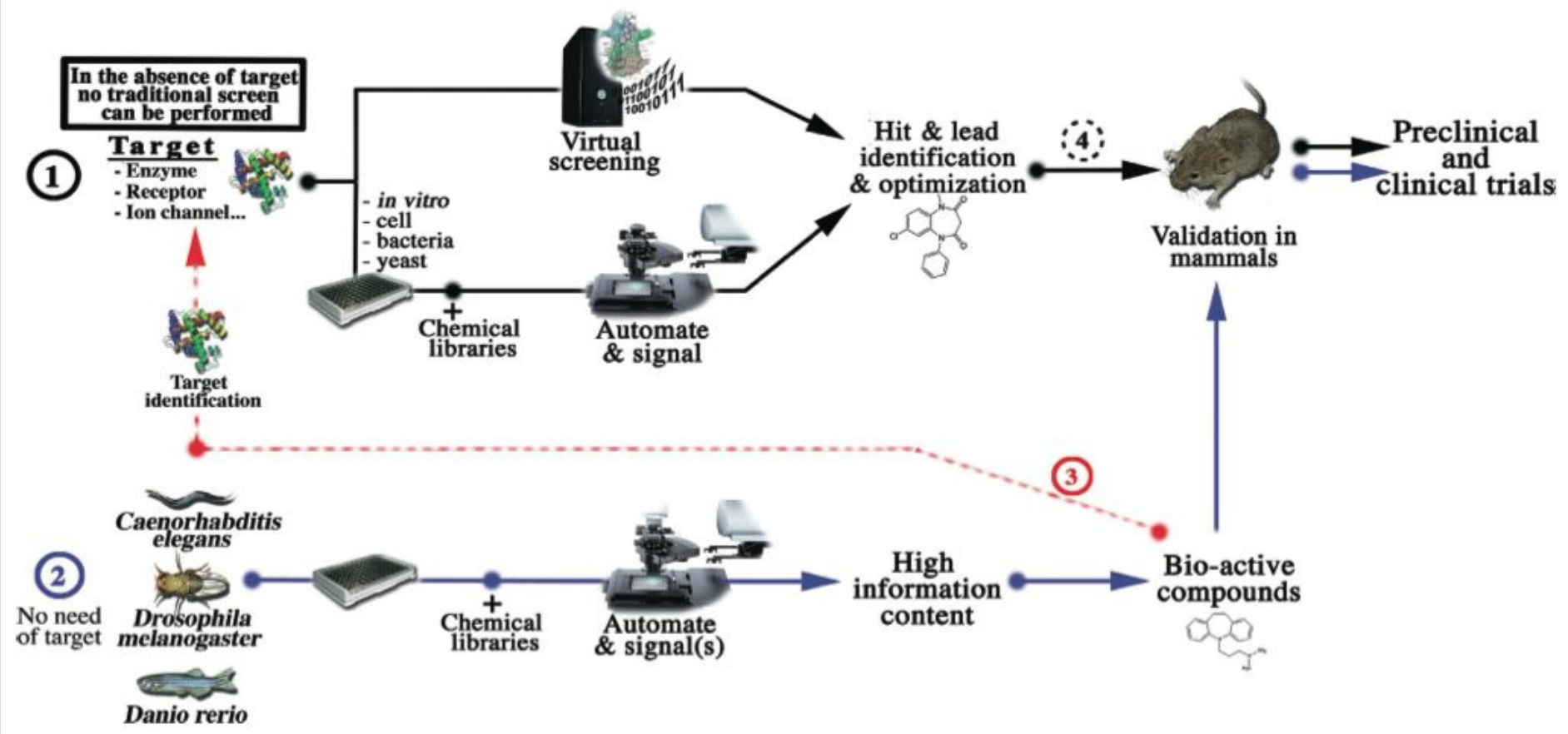






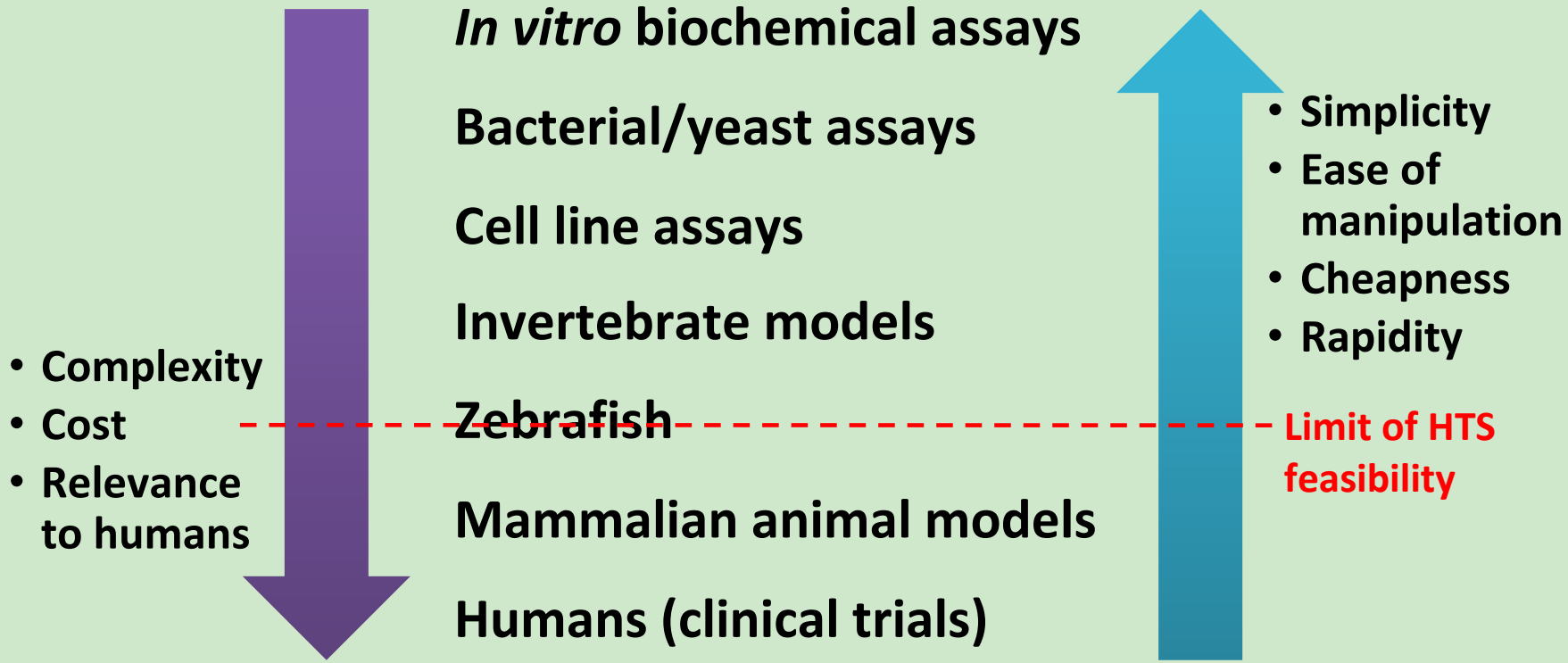
***In vivo* screening**

Whole-animal screening & drug discovery



Giacomotto J & Ségalat L (2010) *Br J Pharmacol* 160: 204–216.

High throughput screening: relevance/efficiency trade-off



- **The selected option is always a trade-off between relevance to humans and screening efficiency.**
- **Note the position of invertebrate models with respect to the limit of HTS feasibility and relevance to humans.**

Ségalat L (2007) *ACS Chem Biol* 2: 231–236.

Making the Case for Aging and Neurodegeneration

Background overview

- Laboratory background
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Recent work

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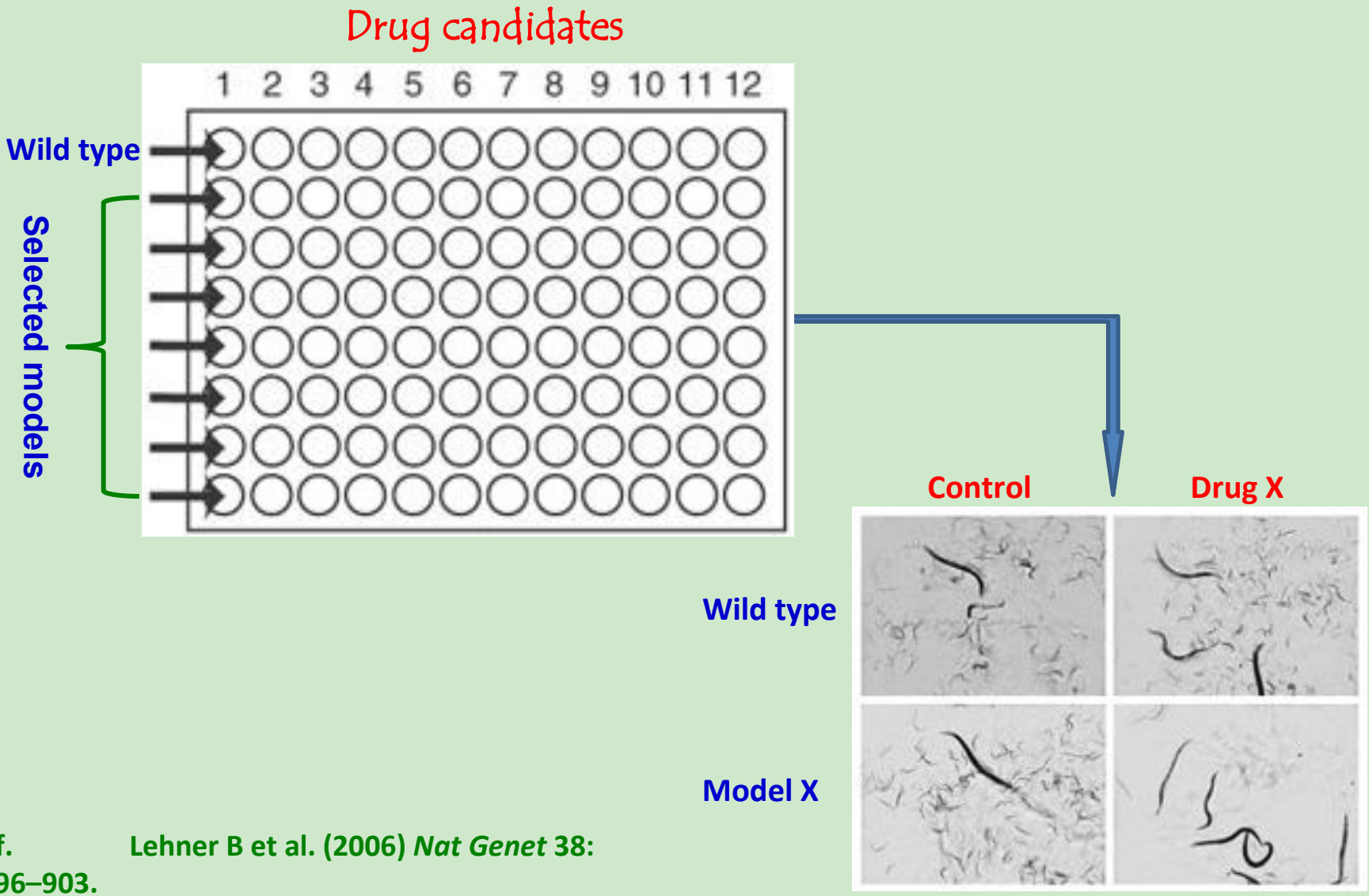
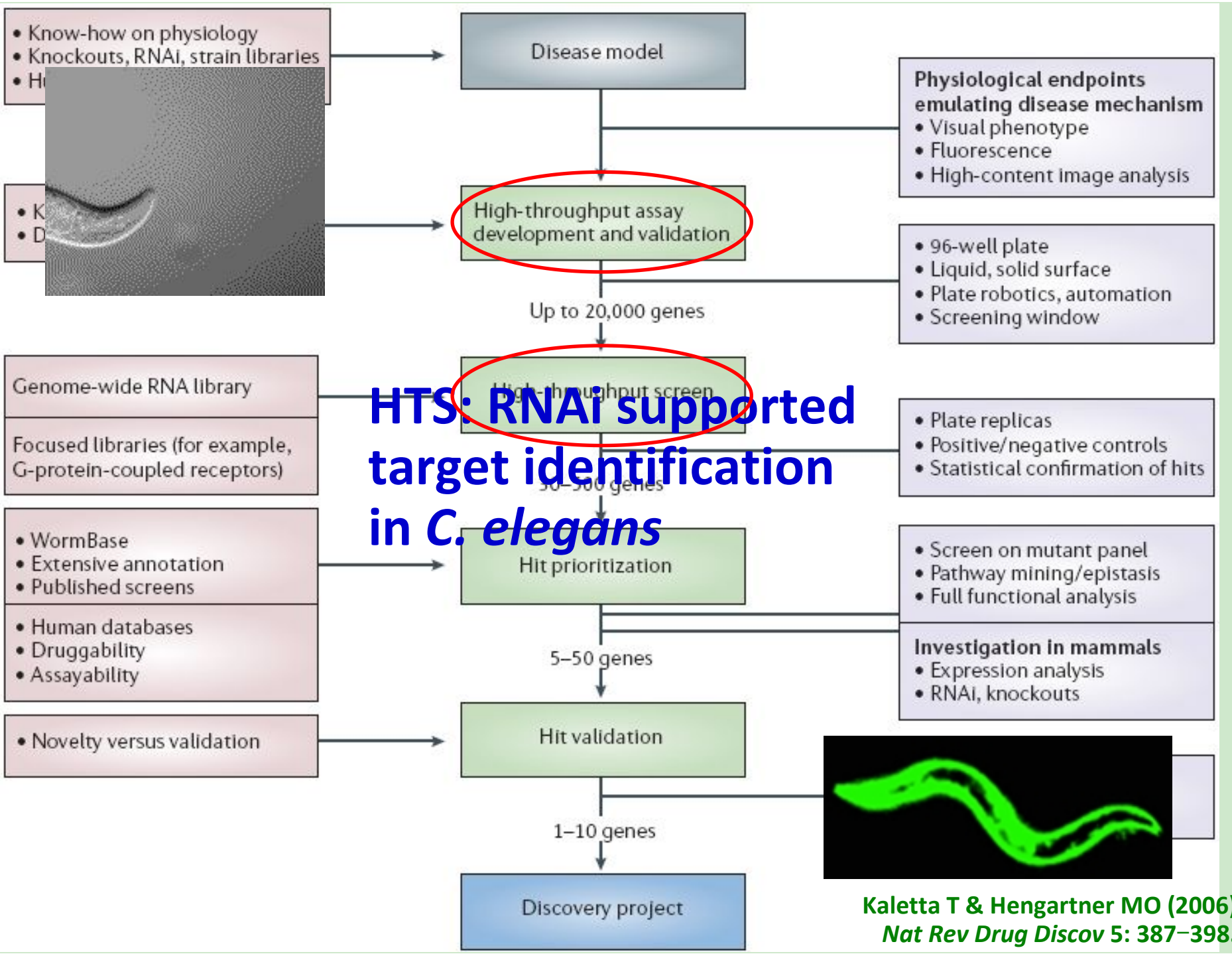
- Biopharmaceuticals
- Small molecules
- Herbal formulae

Drugging the worms…



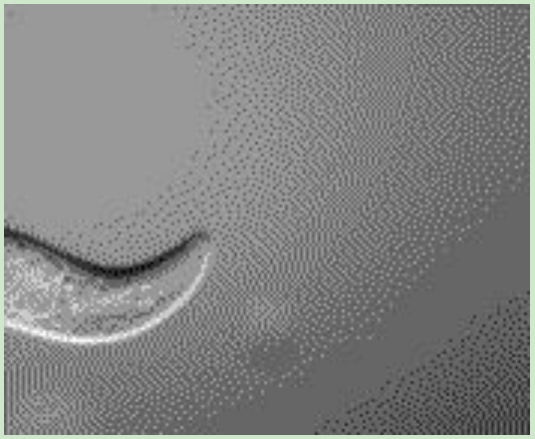
Cf. Lehner B et al. (2006) *Nat Genet* 38: 896–903.

HTS: RNAi supported target identification in *C. elegans*



Kaletta T & Hengartner MO (2006)
Nat Rev Drug Discov 5: 387–398.

Caenorhabditis elegans as a model



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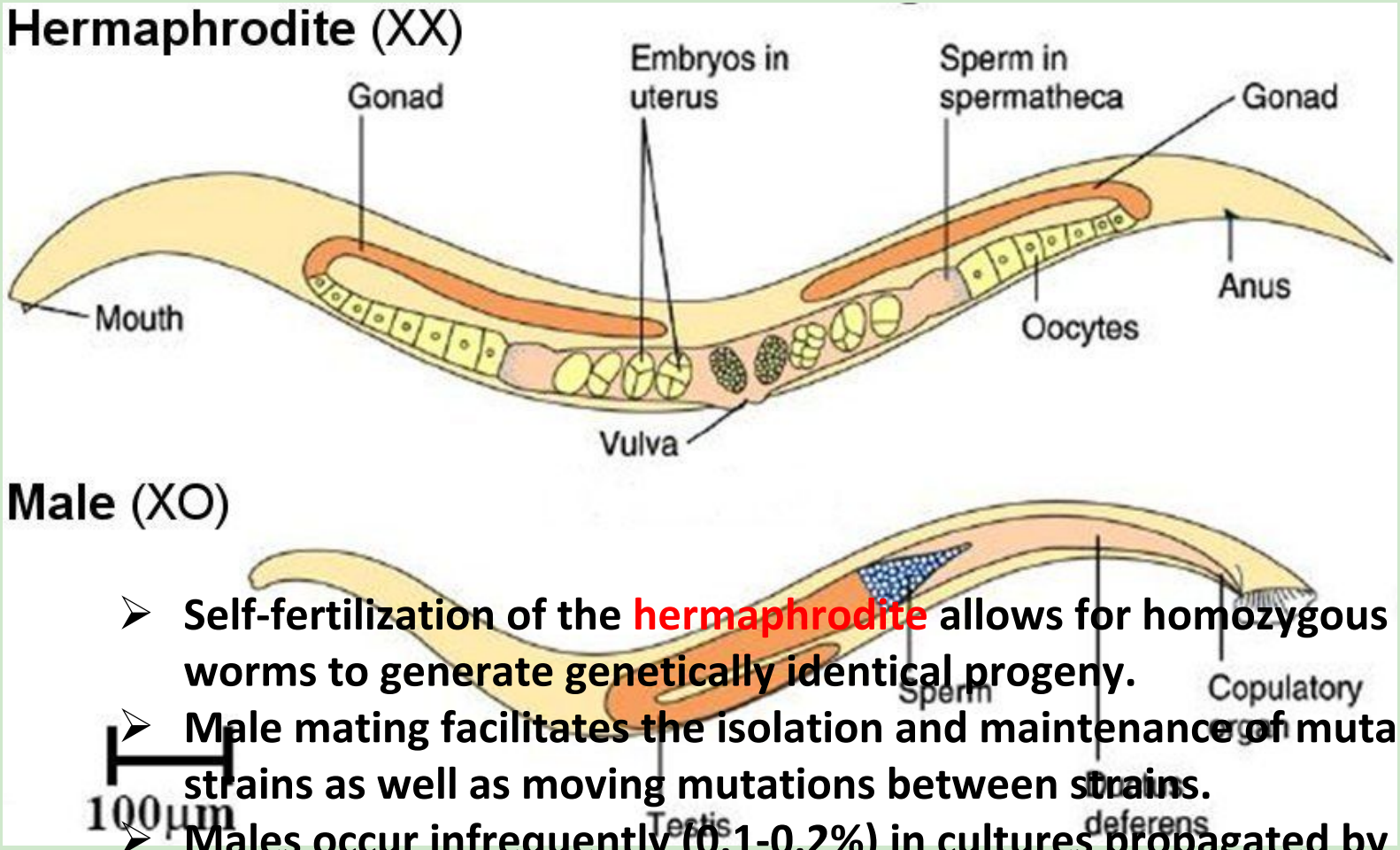
Drug the wor

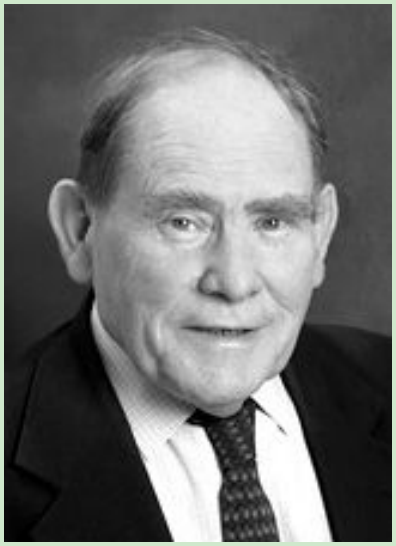
秀丽线虫



- Self-fertilization of the hermaphrodite allows for homozygous worms to generate genetically identical progeny.
- Male mating facilitates the isolation and maintenance of mutant strains as well as moving mutations between strains.
- Males occur infrequently (0.1-0.2%) in cultures propagated by hermaphrodite self-fertilization.

C. elegans and Nobel Prize

The Nobel Prize in Physiology or Medicine 2002



Sydney Brenner

H. Robert Horvitz

John E. Sulston

…for their discoveries concerning 'genetic regulation of organ development and programmed cell death'

C. elegans and Nobel Prize

The Nobel Prize in Physiology or Medicine 2006

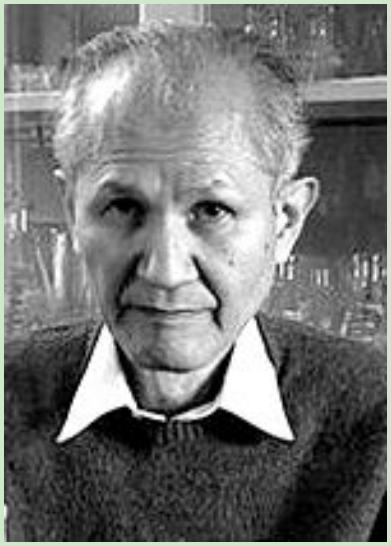
Andrew Z. Fire

Craig C. Mello

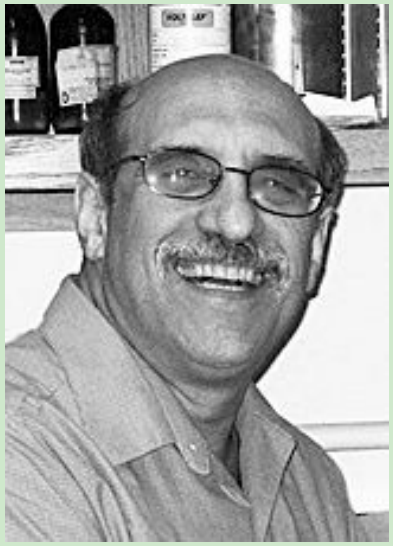
…for their discovery of RNA interference – gene silencing by double-stranded RNA

C. elegans and Nobel Prize

The Nobel Prize in Chemistry 2008



Osamu Shimomura



Martin Chalfie

Roger Y. Tsien

… for the discovery and development of the green fluorescent protein, GFP

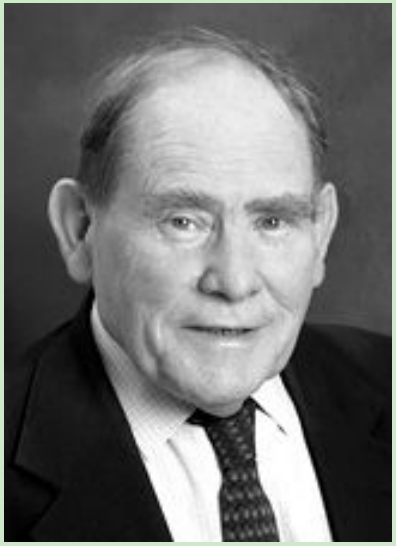
C. elegans: who's who

MIT

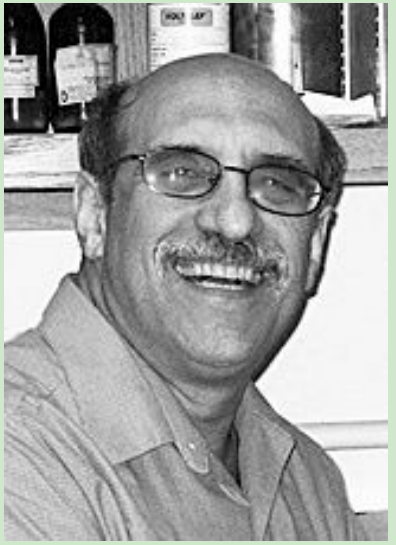
- **Bachelors, math & economics**
- **PhD, biology**

high school friends

***C. elegans* postdocs**
Cambridge



Supervisor
(*C. elegans* originator)



Harvard

- **Bachelor, biochemistry (though intending to study math)**
- **PhD, physiology**

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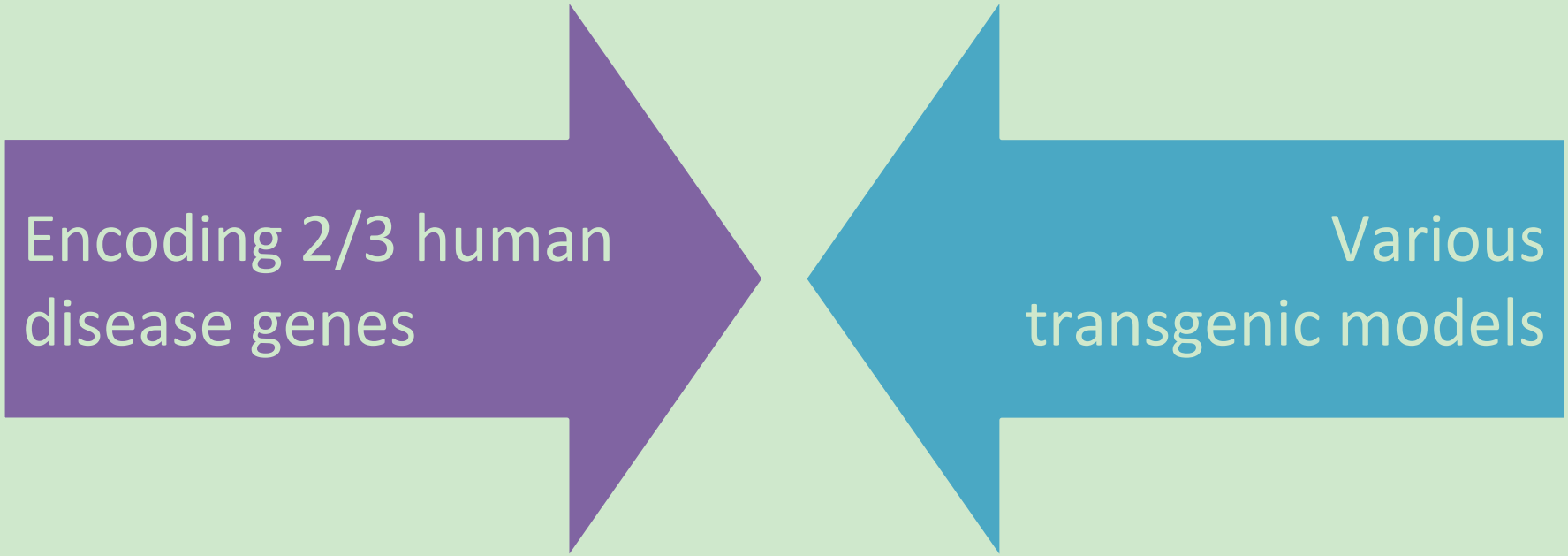
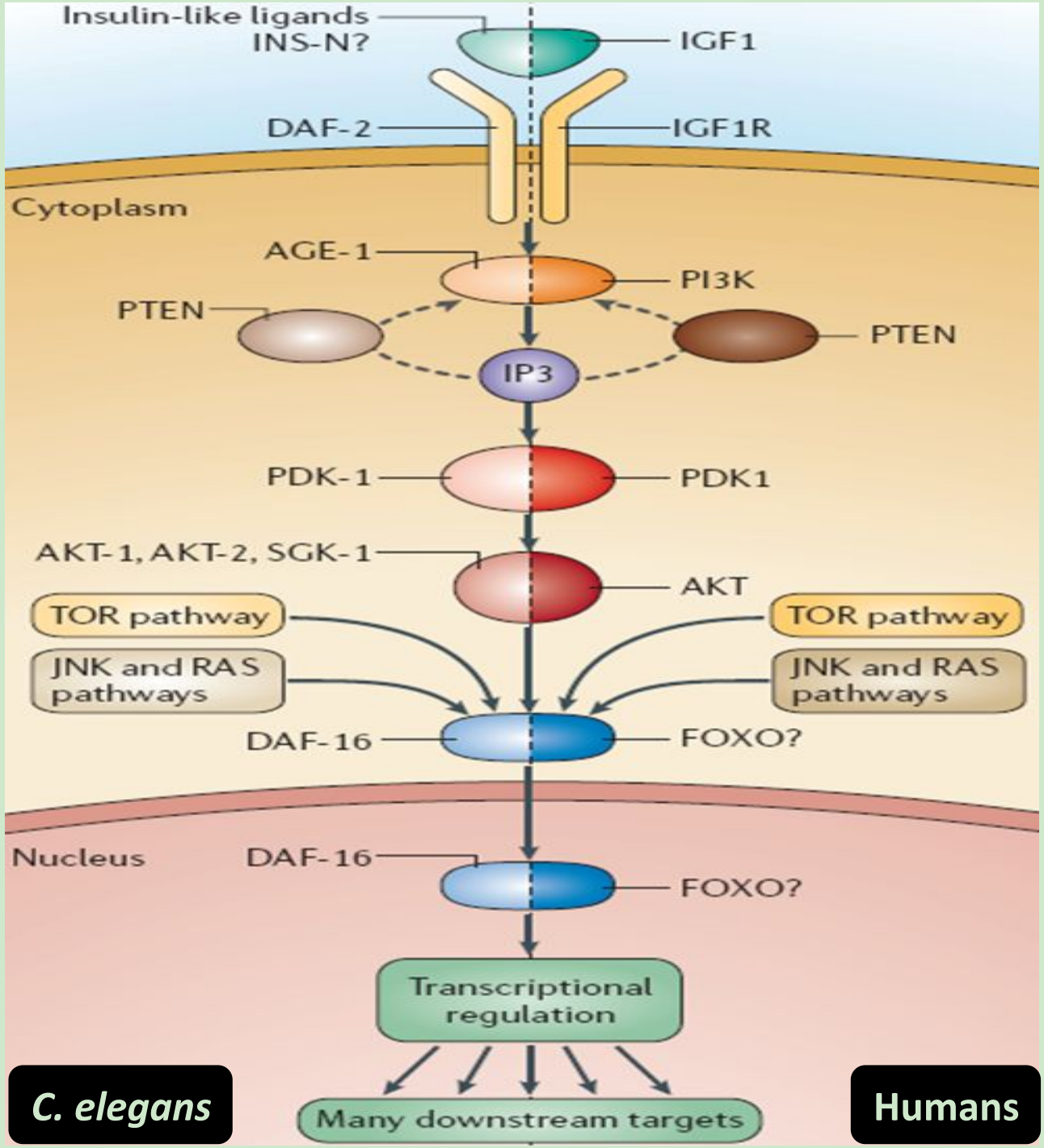
C. elegans: clinical relevance



Pharmacological agents can affect cellular phenotypes similarly in both humans and *C. elegans*, demonstrating the utility of the model for pharmaceutical target validation.

Sluder AE & Baumeister R (2004) *Drug Discov Today Technol* 1: 171–177.



Molecular pathways that lengthen lifespan in *C. elegans* and the corresponding components in humans.

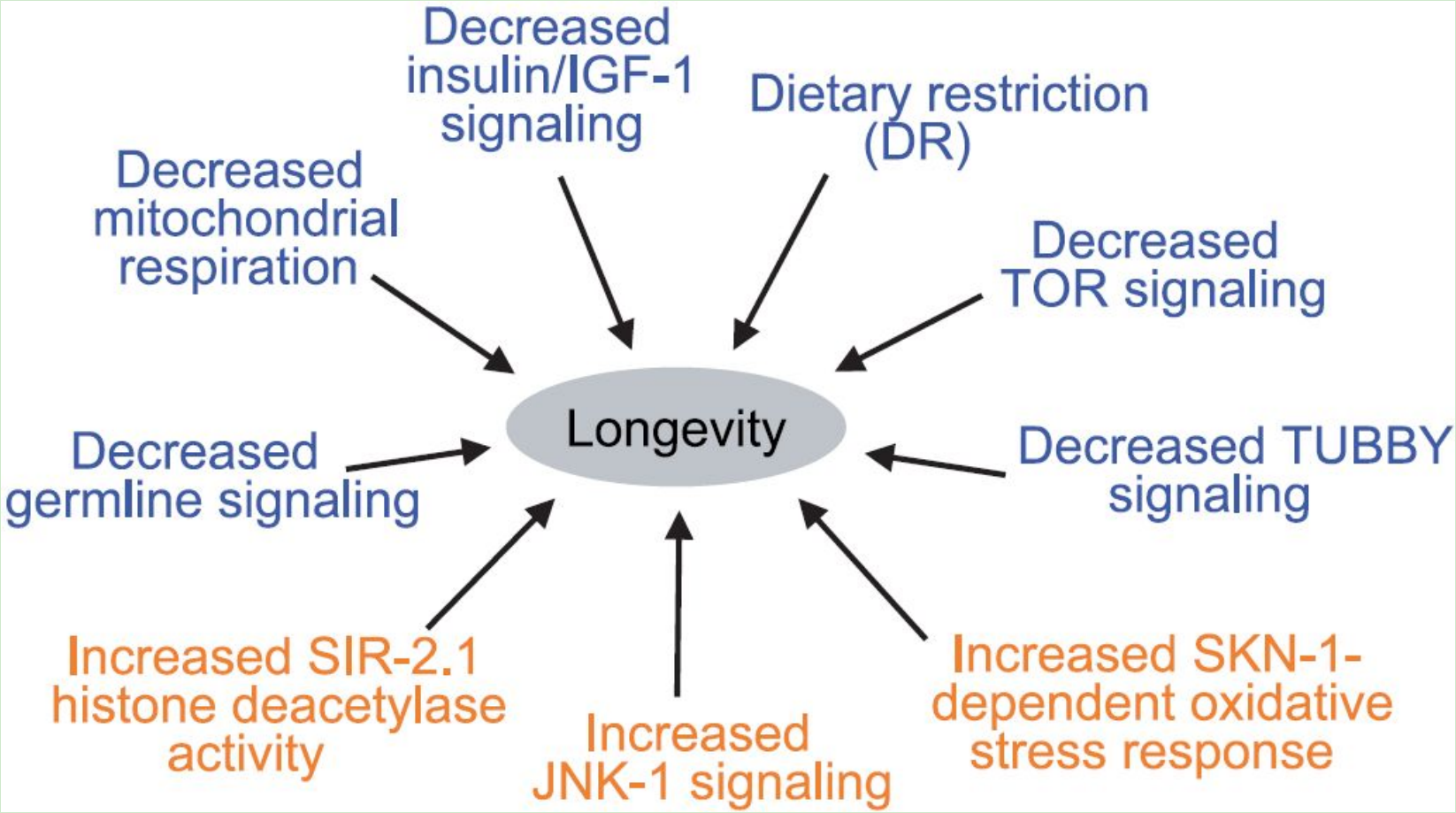
DAF-2: IGF1R

AGE-1: PI3K

DAF-16: FOXO

Christensen et al. (2006)
Nat Rev Genet 7: 436–448.

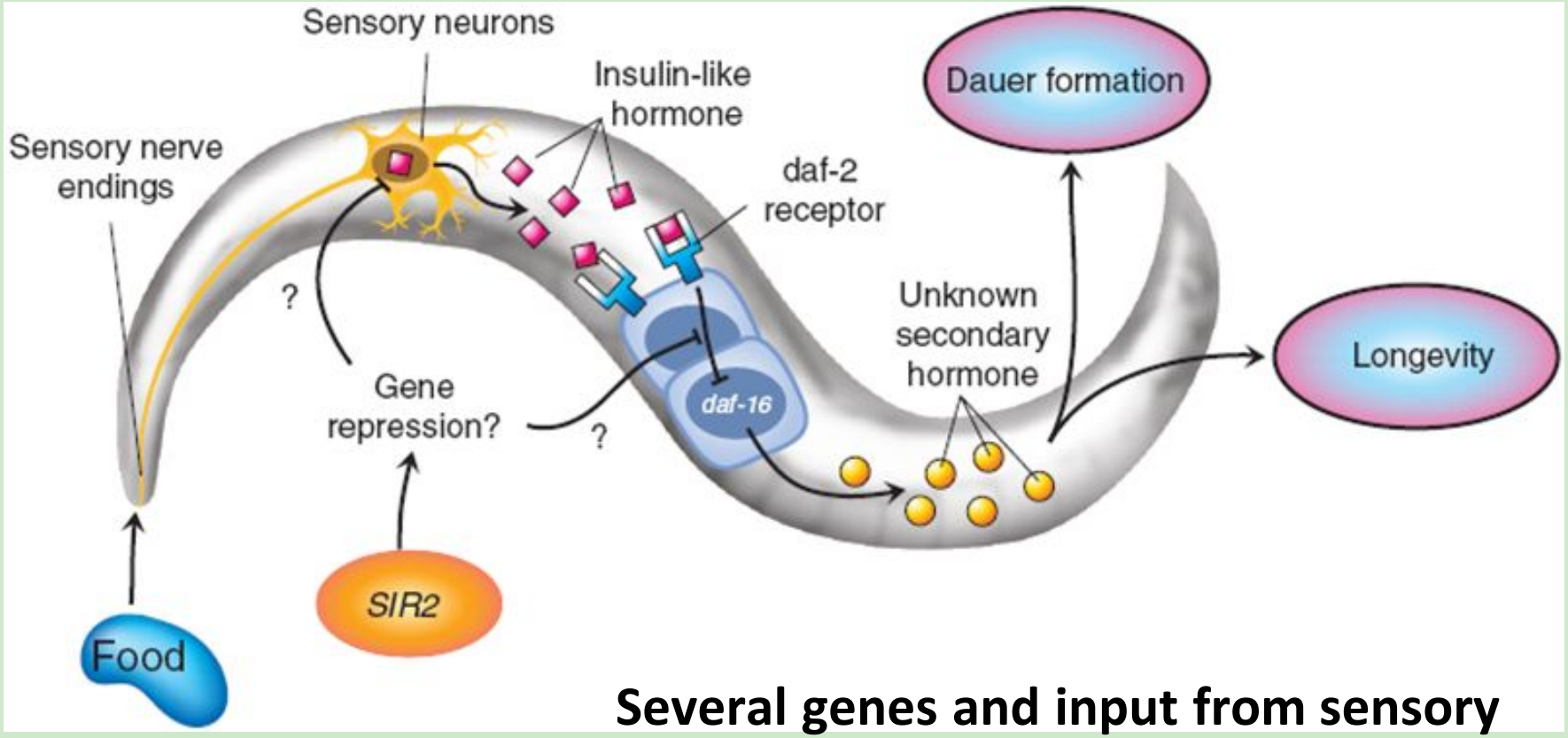
Evolutionarily conserved mechanisms: complex regulation of life span in *C. elegans*



Decreased activity (in blue) and increased activity (in orange) of the signaling pathways and processes lead to longevity in the animal.

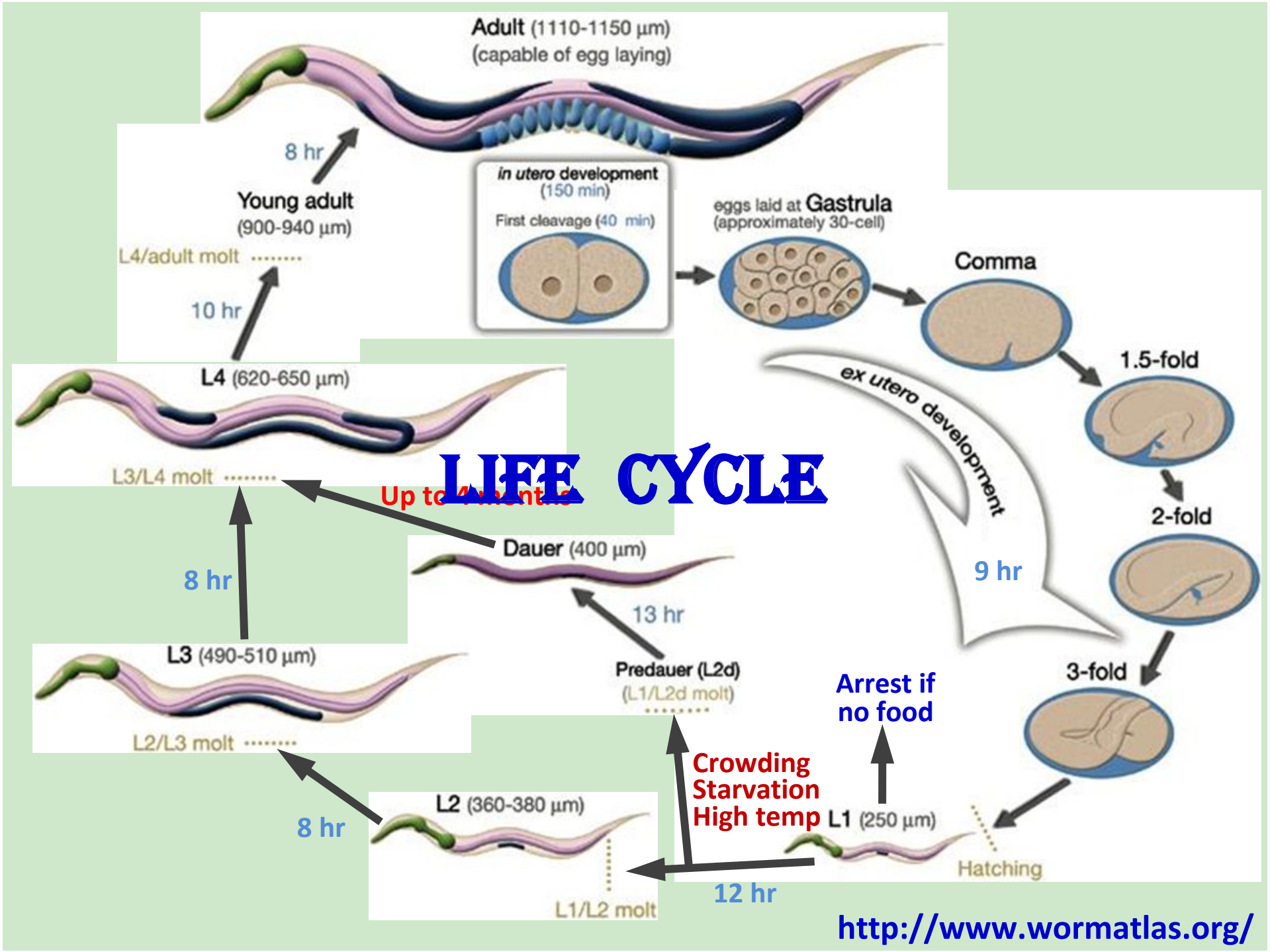
Schaffitzel E & Hertweck M (2006) *Exp Gerontol* 41: 557–563.

C. elegans: ageing signalling

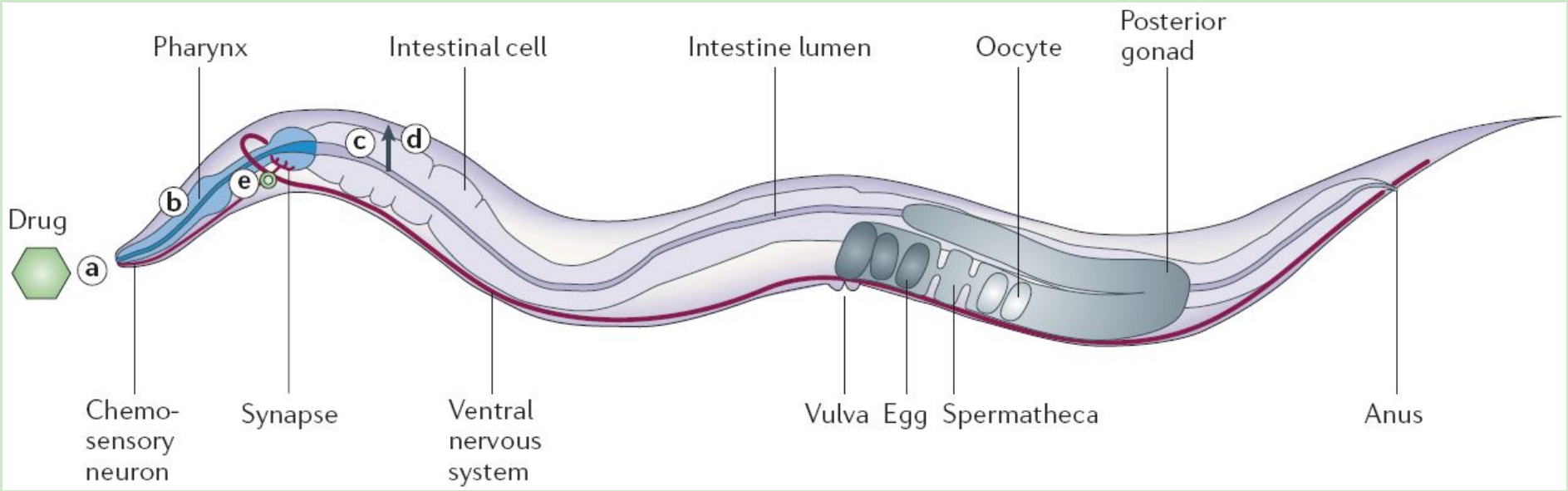


Several genes and input from sensory organs and the reproductive system influence the pace of ageing.

Leslie M (2001) *Science Aging Knowledge Environment* (1): oa1.


Adult (1110-1150 µm)
(capable of egg laying)
8 hr
Young adult
(900-940 µm)
L4/adult molt
10 hr
L4 (620-650 µm)
L3/L4 molt
Up to 4 months
Dauer (400 µm)
13 hr
Predauer (L2d)
(L1/L2d molt)
8 hr
L3 (490-510 µm)
L2/L3 molt
8 hr
L2 (360-380 µm)
L1/L2 molt
Crowding
Starvation
High temp
12 hr
L1 (250 µm)
Hatching
Arrest if
no food
in utero development
(150 min)
First cleavage (40 min)
eggs laid at Gastrula
(approximately 30-cell)
Comma
1.5-fold
2-fold
3-fold
ex utero development
9 hr
LIFE CYCLE
http://www.wormatlas.org/

Drugging the worms…



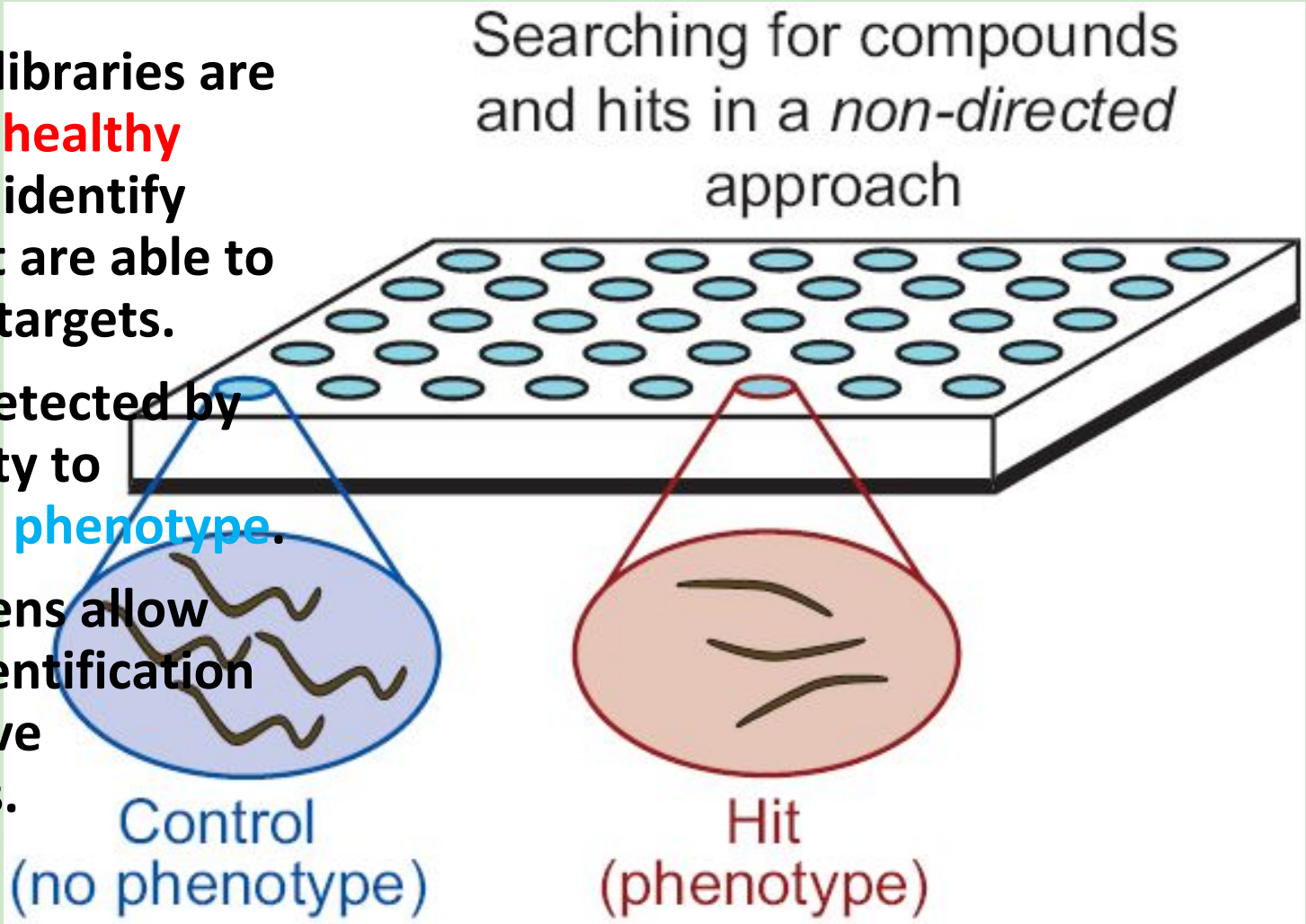
Drug entry route into *C. elegans*:

- **ingestion;**
- **uptake through the skin; and**
- **uptake via exposed sensory neuronal endings.**

Kaletta T & Hengartner MO (2006) *Nat Rev Drug Discov* 5: 387–398.

C. elegans in high-throughput screening

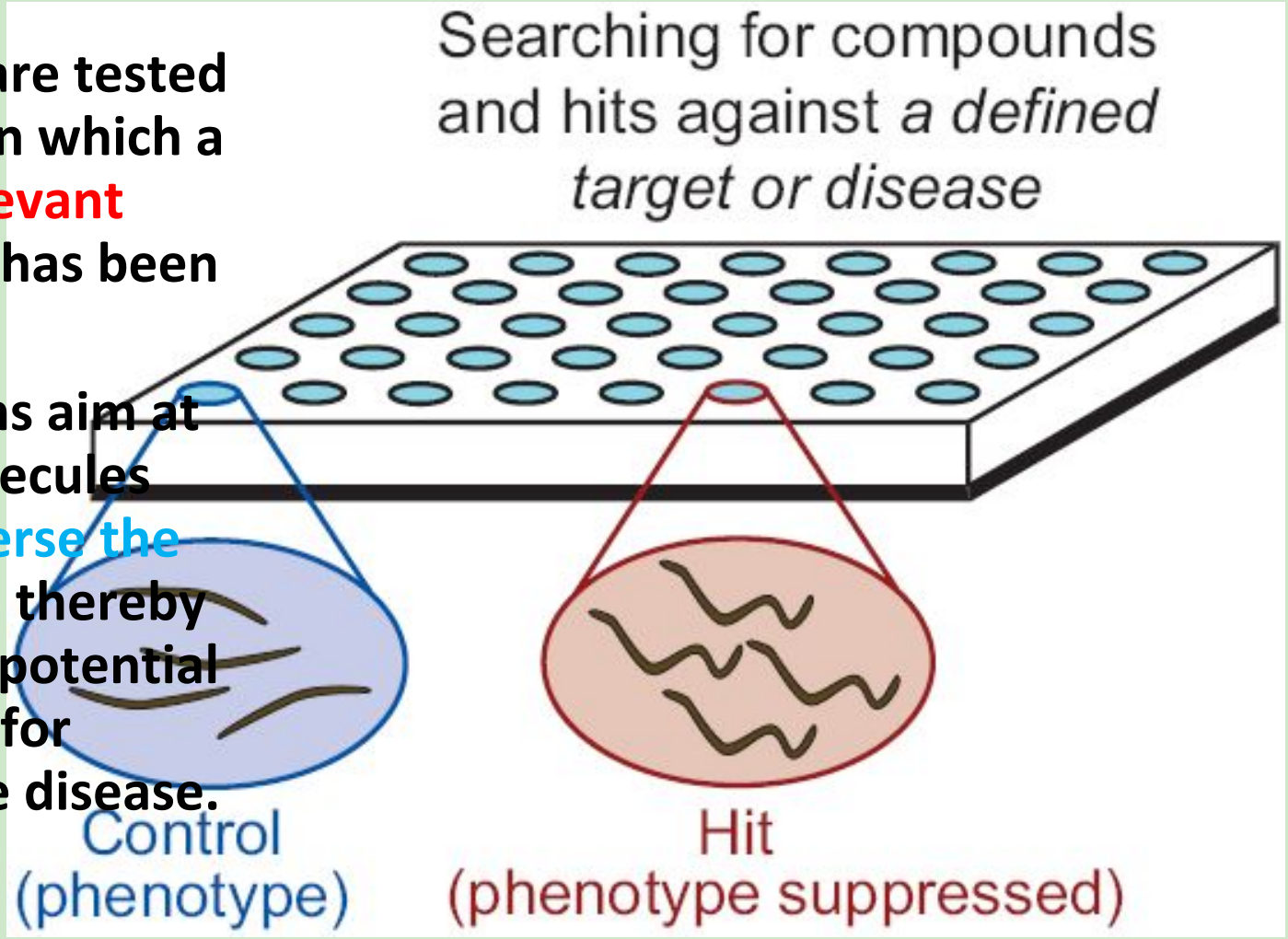
- **Chemical libraries are tested on healthy worms to identify drugs that are able to hit worm targets.**
- **Hits are detected by their ability to produce a phenotype.**
- **Such screens allow for the identification of bioactive molecules.**



Ségalat L (2007) *ACS Chem Biol* 2: 231–236.

C. elegans in high-throughput screening

- **Chemicals are tested on worms in which a disease-relevant phenotype has been created.**
- **Such screens aim at finding molecules able to reverse the phenotype, thereby identifying potential candidates for treating the disease.**



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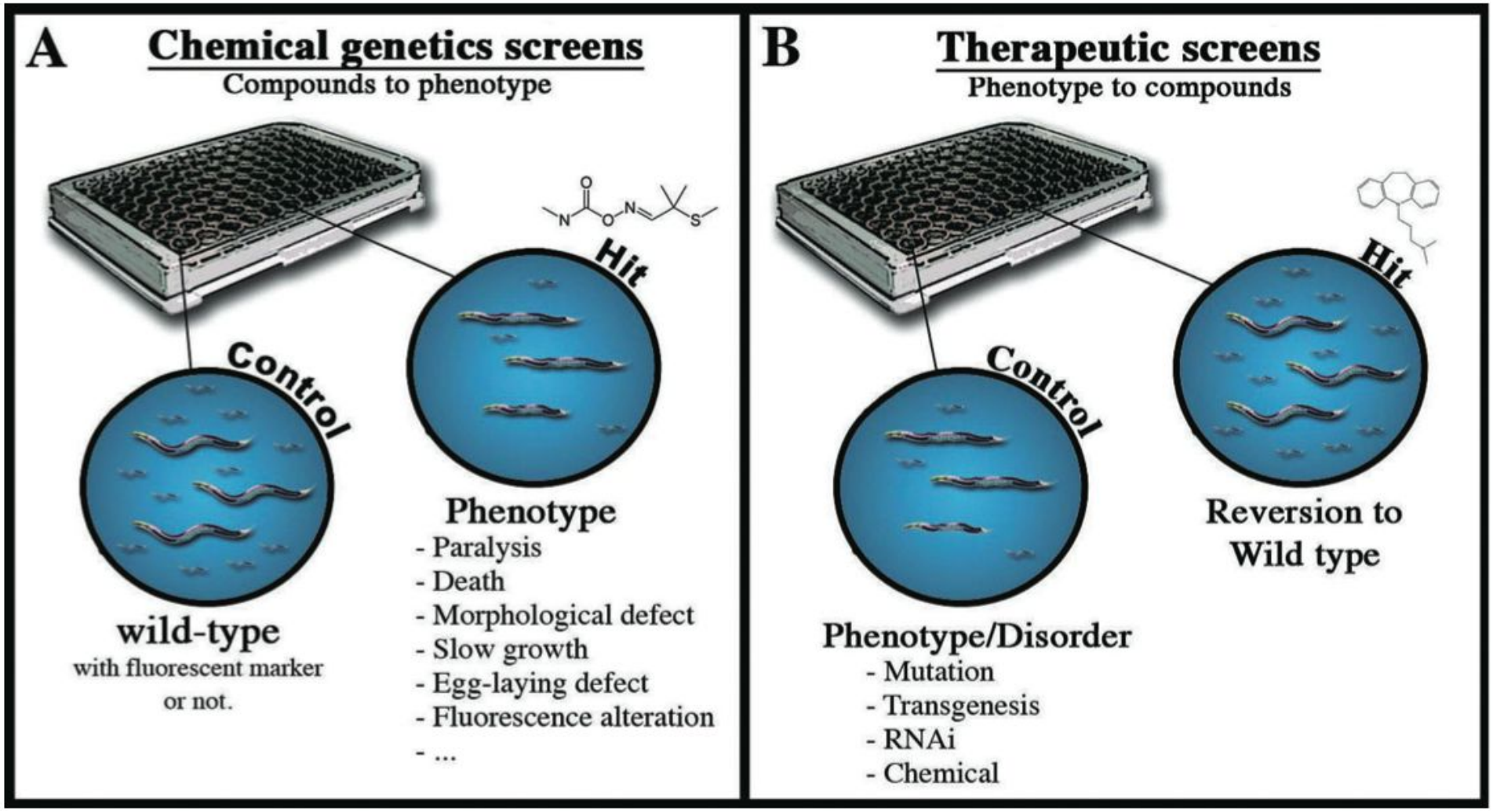
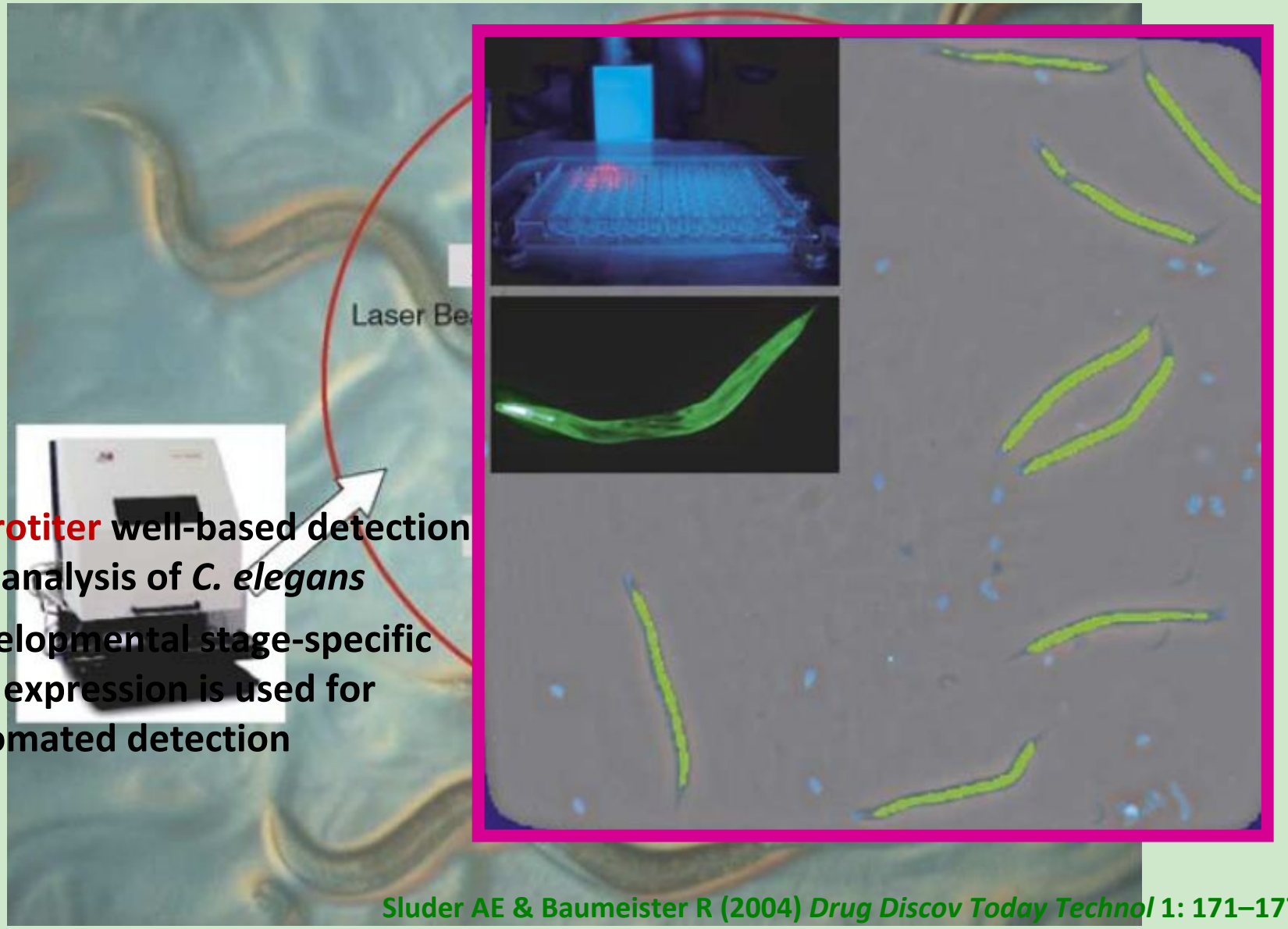
Ségalat L (2007) *ACS Chem Biol* 2: 231–236.



Giacomotto J & Ségalat L (2010) *Br J Pharmacol* 160: 204–216.

COPAS Biosorter: automated sorting of *C. elegans*

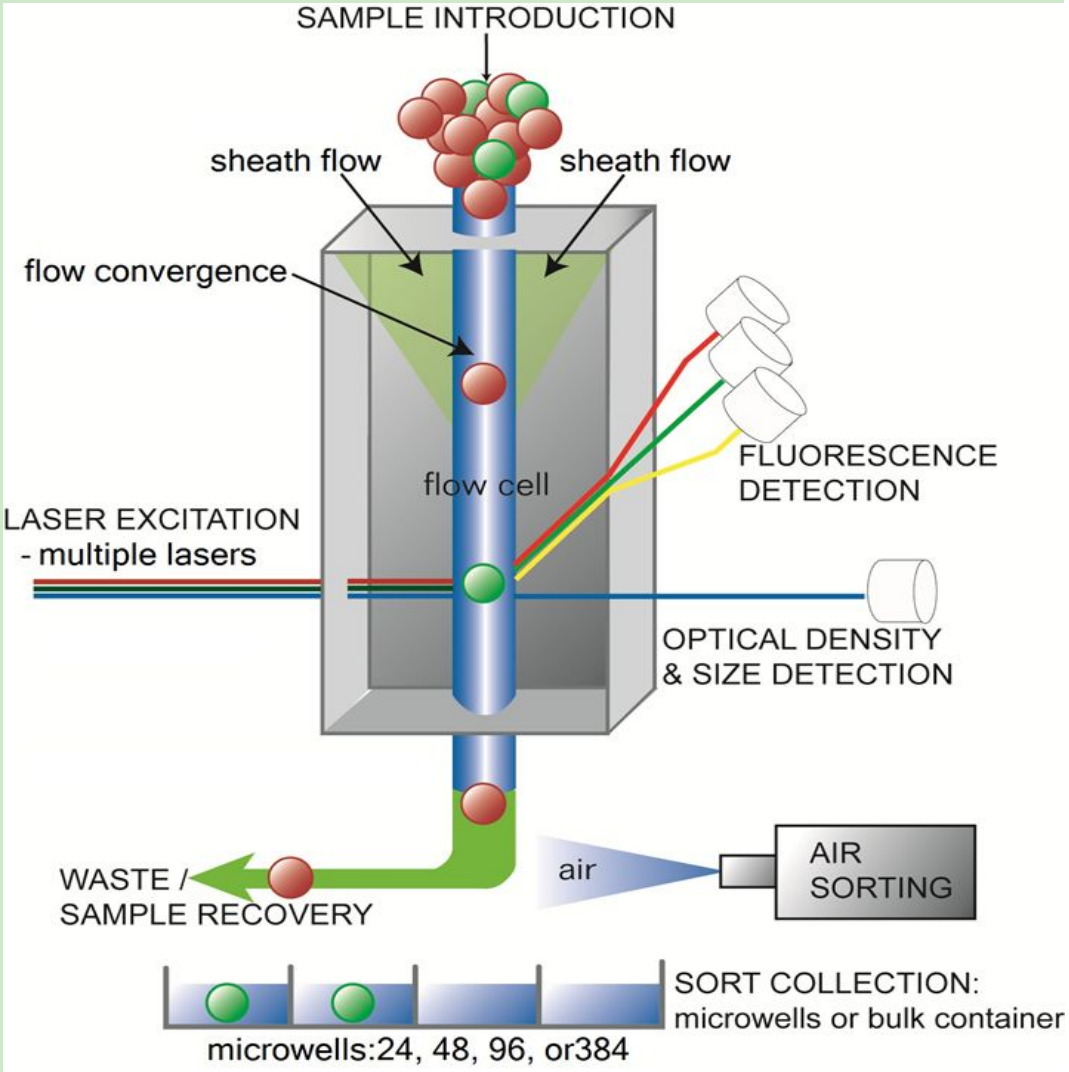


- **Microtiter** well-based detection and analysis of *C. elegans*
- Developmental stage-specific **GFP** expression is used for automated detection

Sluder AE & Baumeister R (2004) *Drug Discov Today Technol* 1: 171–177.

优势：

- 秀丽线虫无损分选
- 全自动、高通量、高精度



用途：

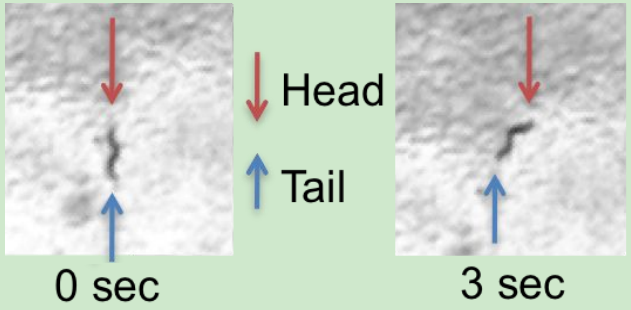
- 线虫寿命
- 神经毒性
- 神经保护
- 生殖发育
- ……

COPAS

Behaviorial analysis

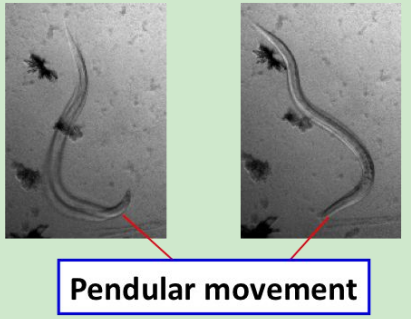
Movement on solid

- Measure “Head to Head” and “Tail to Tail” distances



Pendular movement frequency

- Record the number of pendular movement per min

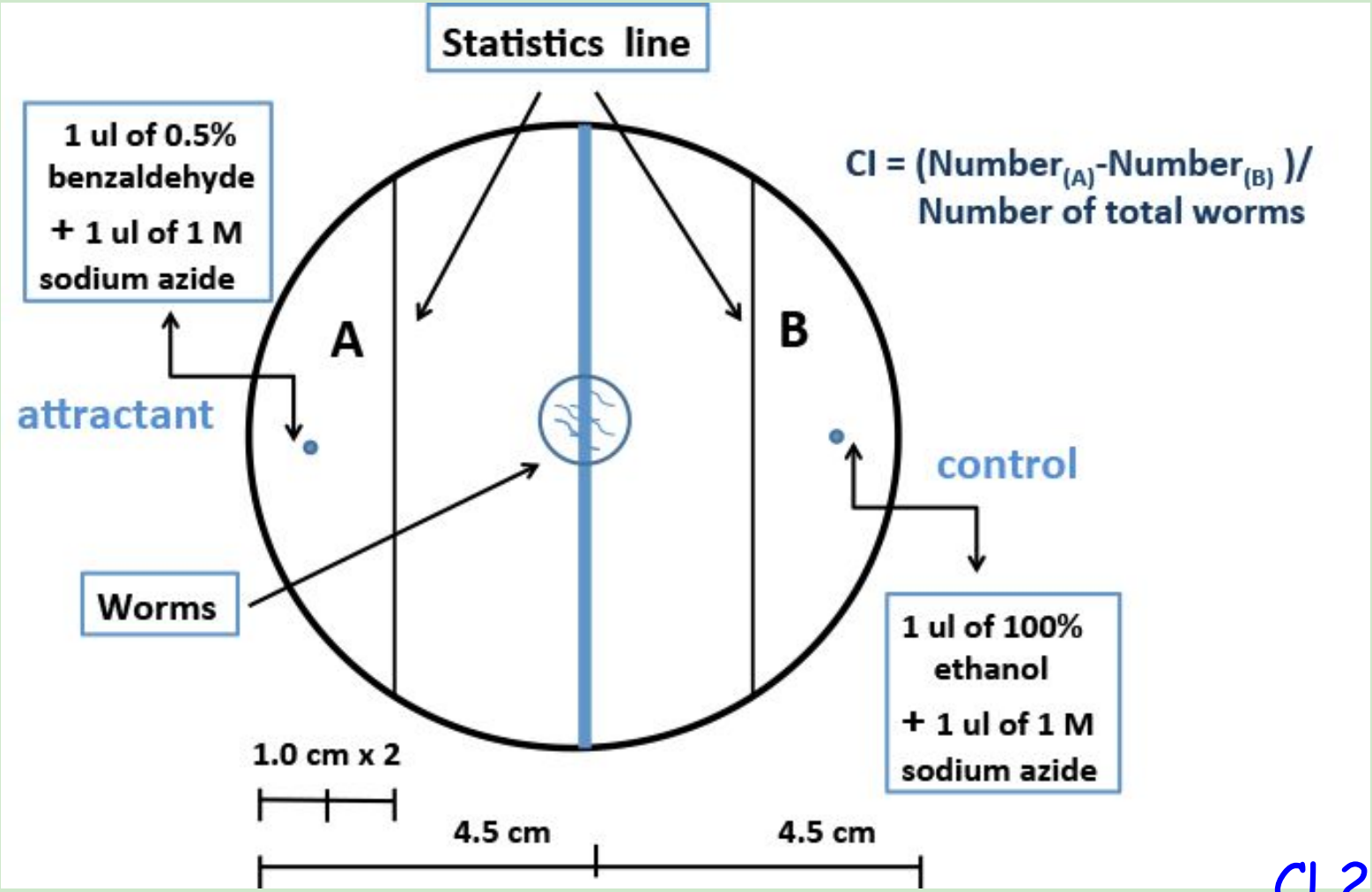


Coiling frequency

- Record the number of coiling per min

Guo W et al. (unpublished).

Chemotaxis assay



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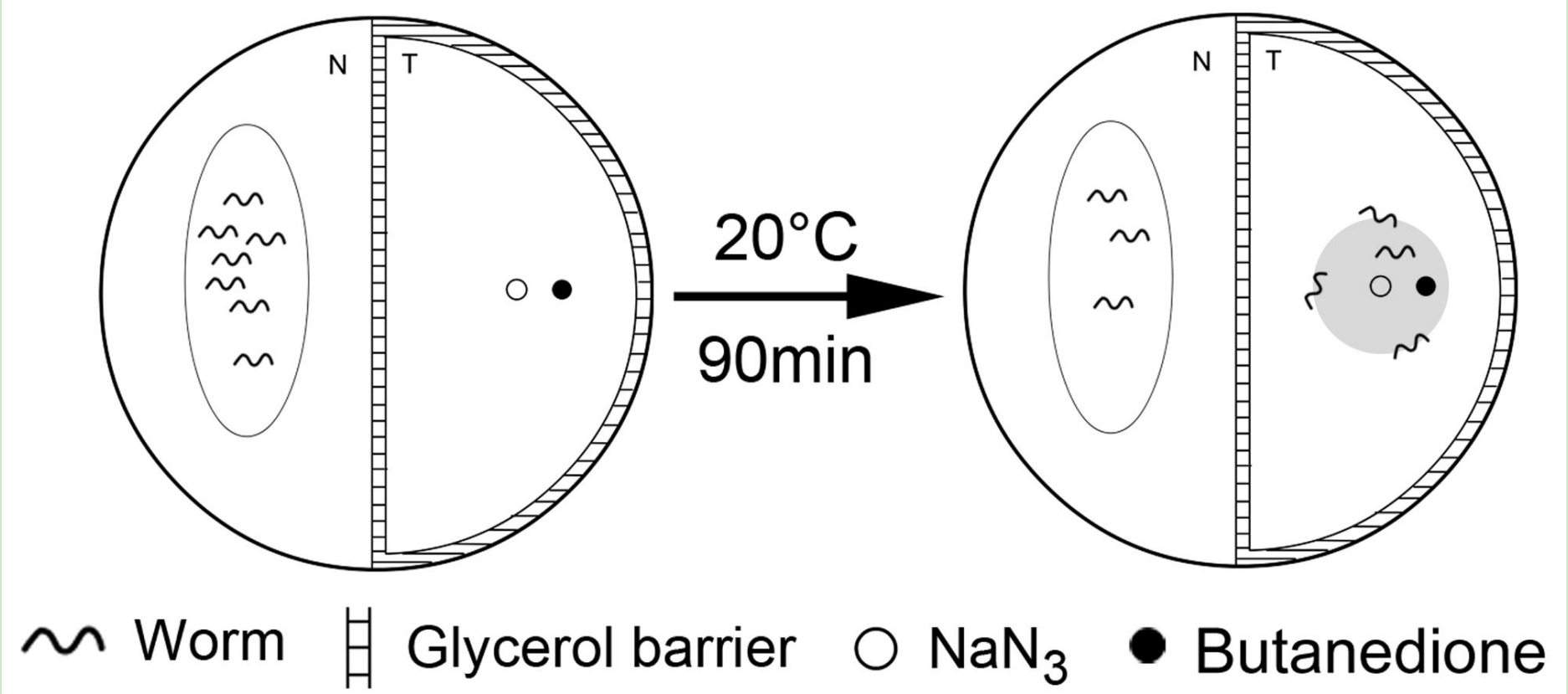
Xiao L et al. (in preparation).

Osmotic avoidance behavior assay system



Xiong S et al. (in preparation).

秀丽线虫

- 作为模式生物，秀丽线虫具有以下突出优点：
  - 生活周期短：受精卵到成虫～3天，寿命2-3周；
  - 遗传资源丰富：大量转基因和突变模型；
  - 易于人工培养：固液培养均可；
  - 高通量筛选：如96/384孔微板培养、COPAS；
  - 基因组序列已知：首个完成测序的多细胞生物；
  - RNA干扰：全基因组RNA干扰饲喂文库。

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Caenorhabditis elegans in Chinese Medicinal Studies: Making the Case for Aging and Neurodegeneration

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[2]School of Pharmaceutical Sciences, Wuhan University, Wuhan, China.

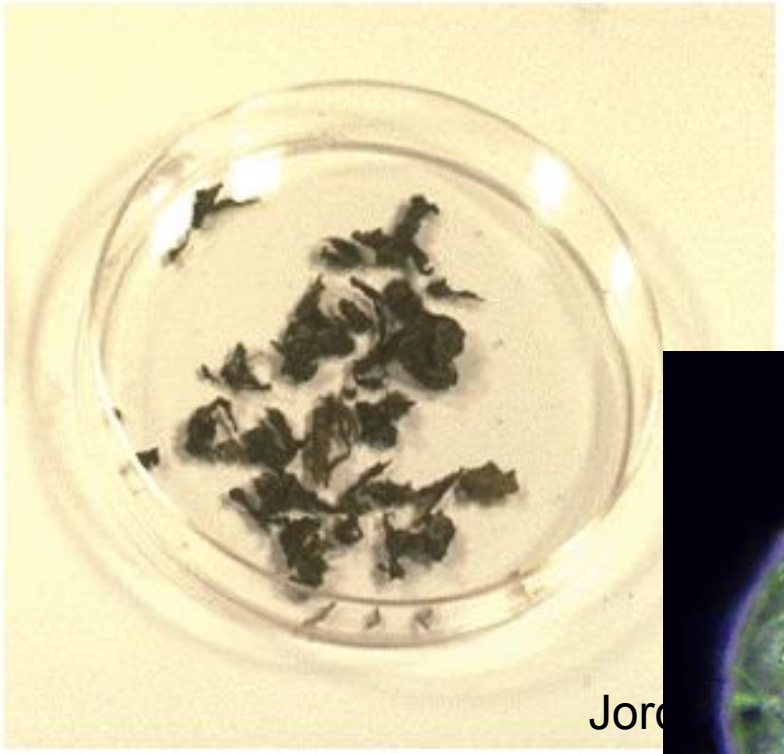
Making the Case for Aging and Neurodegeneration

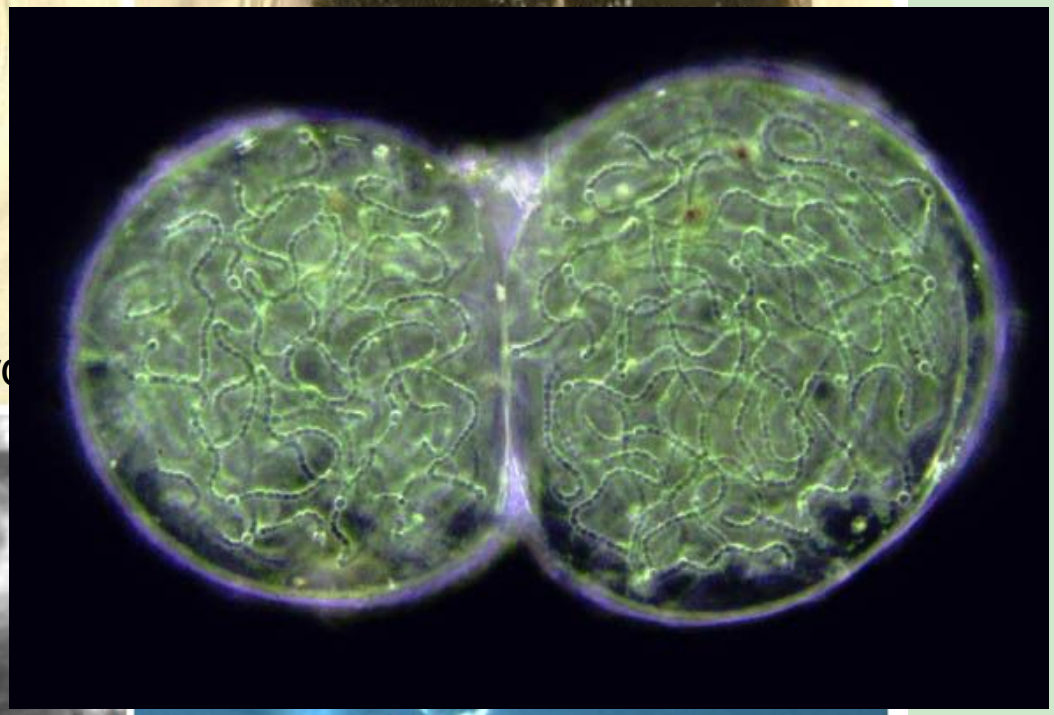
Background overview

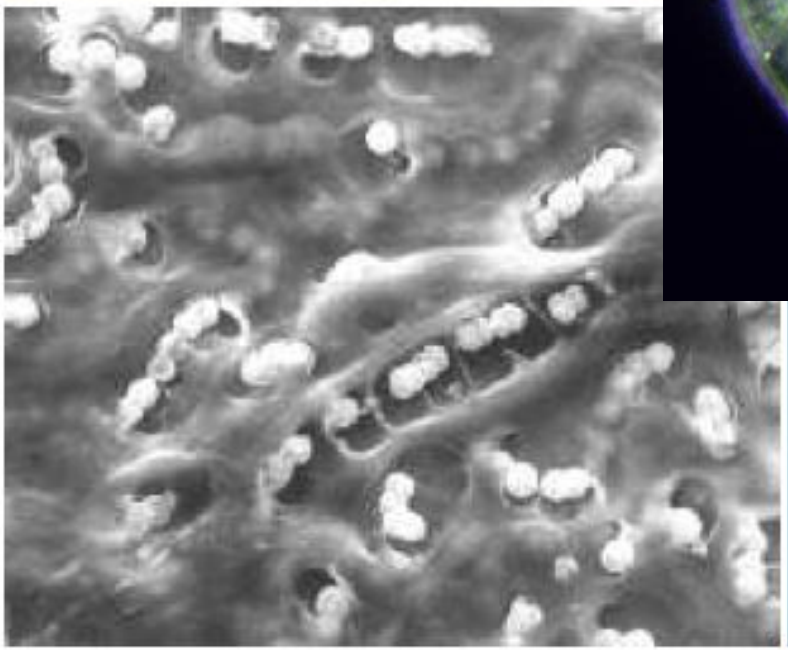
- Laboratory background
- *Caenorhabditis elegans*

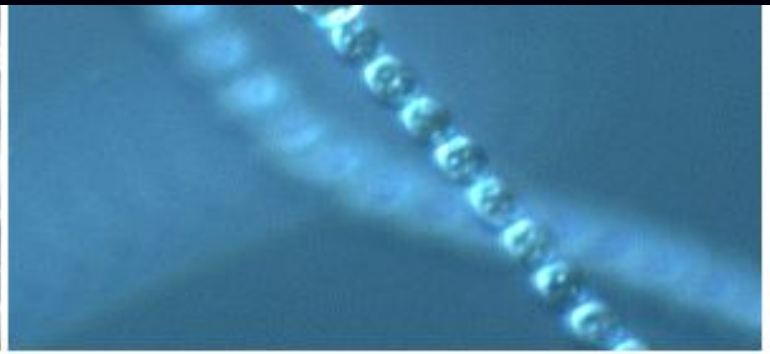
Recent work

- Glycotherapeutics
- Biopharmaceuticals
- Small molecules
- Herbal formulae



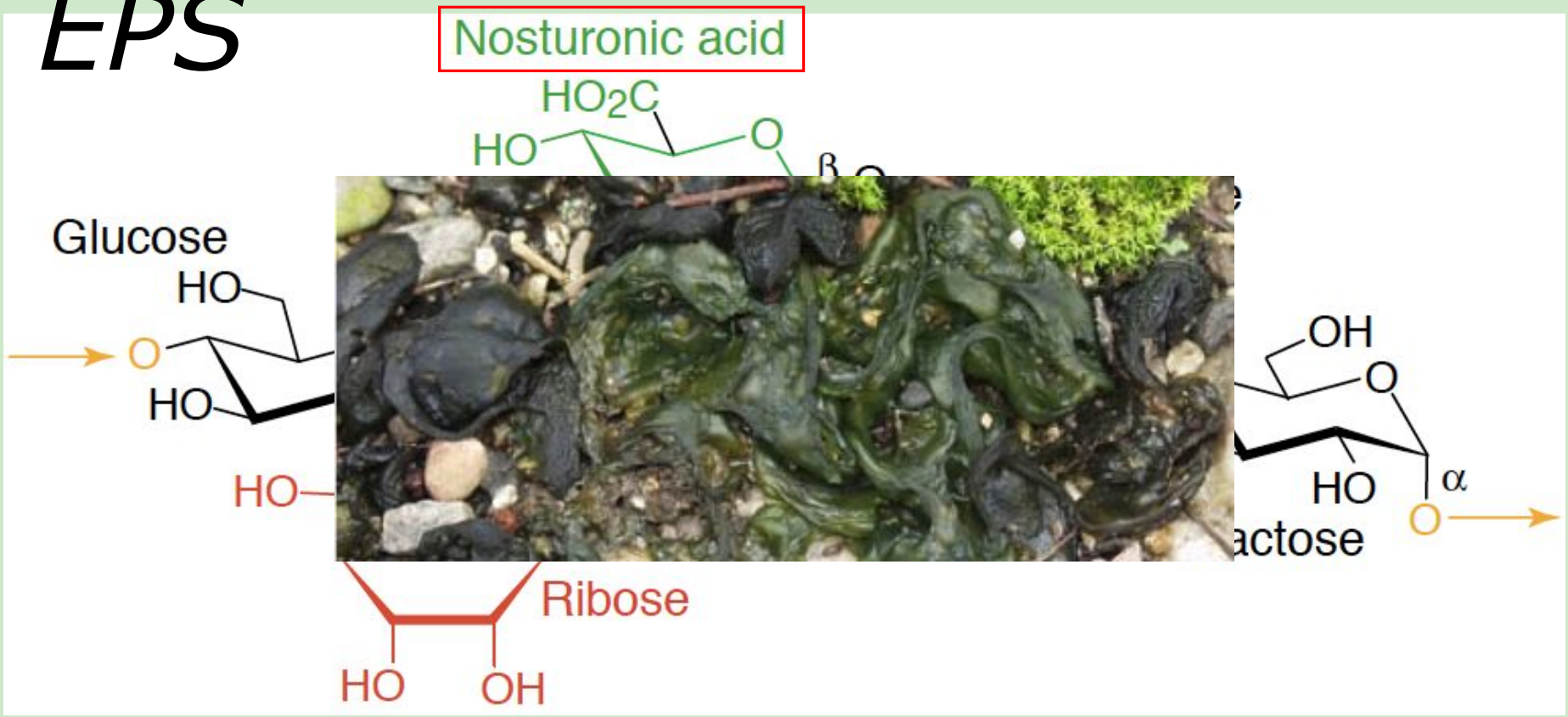






Nostoc commune polysaccharide

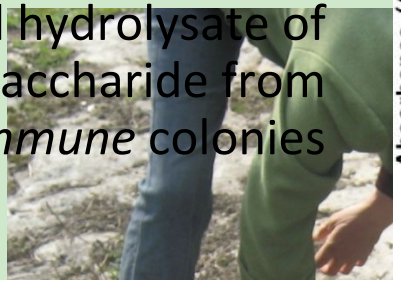
EPS

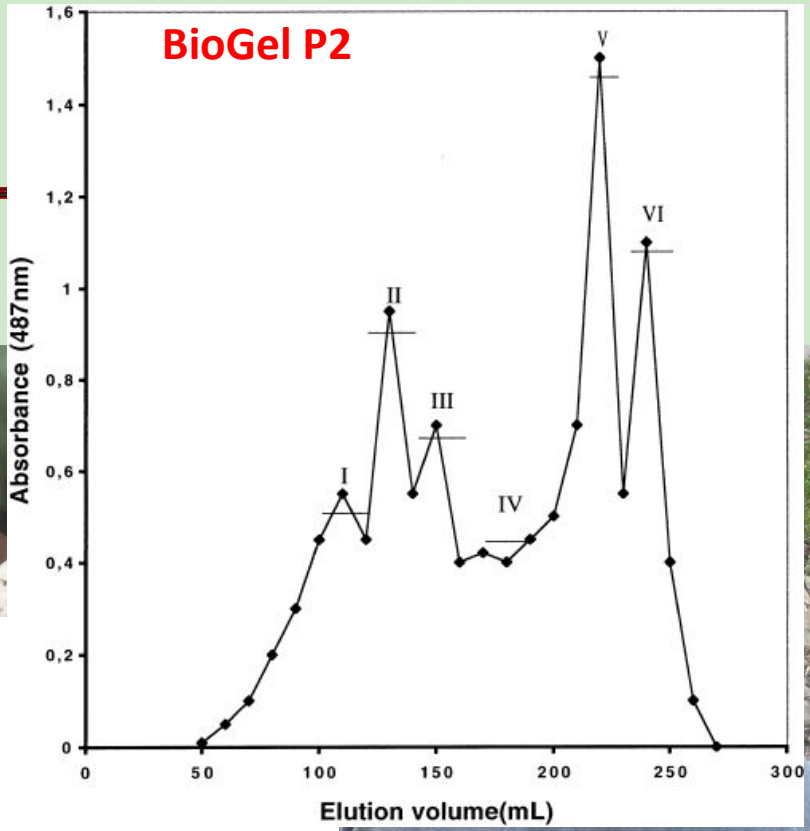


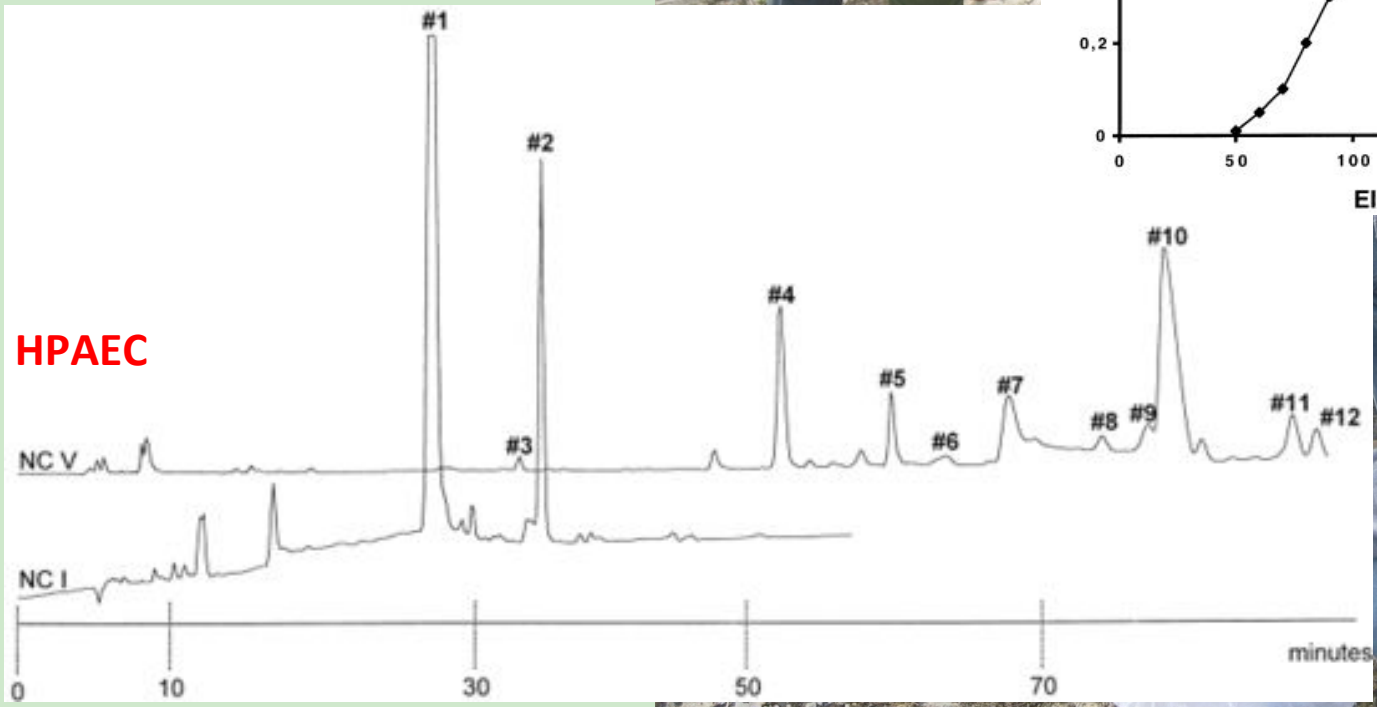
Huang Z et al. (1998) *J Phycol* 34: 962–968.
Helm RF et al. (2000) *J Bacteriol* 182: 974–982.
Huang Z et al. (2000) *Carbohydr Res* 328: 77–83.
Brüll LP et al. (2000) *J Phycol* 36: 871–881.

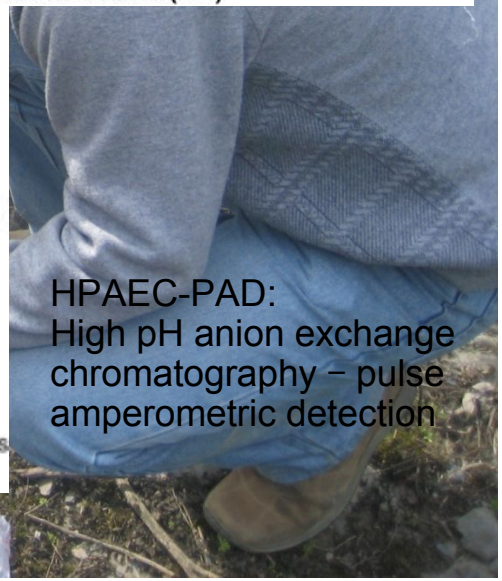
Nostoc polysaccharides

Weak acid hydrolysate of the polysaccharide from field *N. commune* colonies

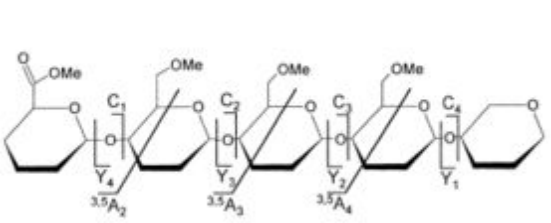




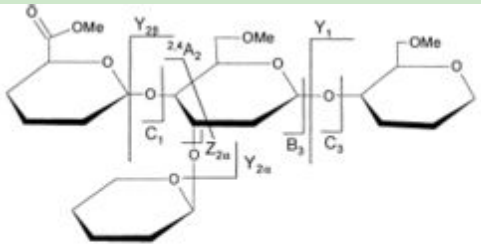




Nostoc polysaccharides



HPAEC #11



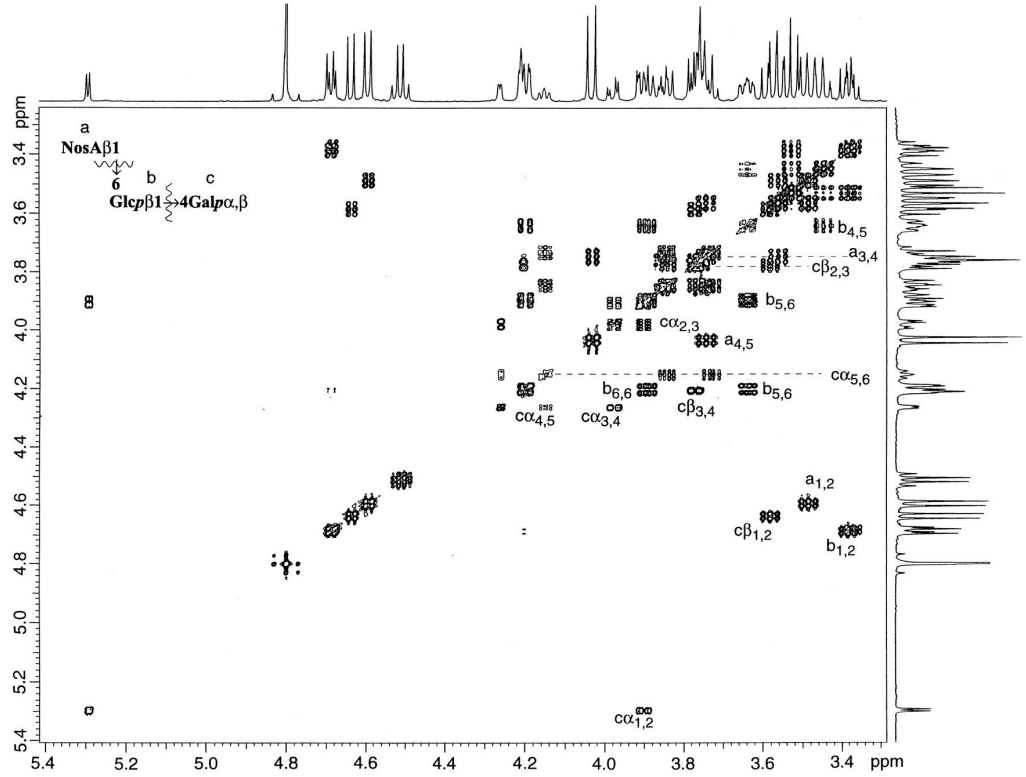
HPAEC #9

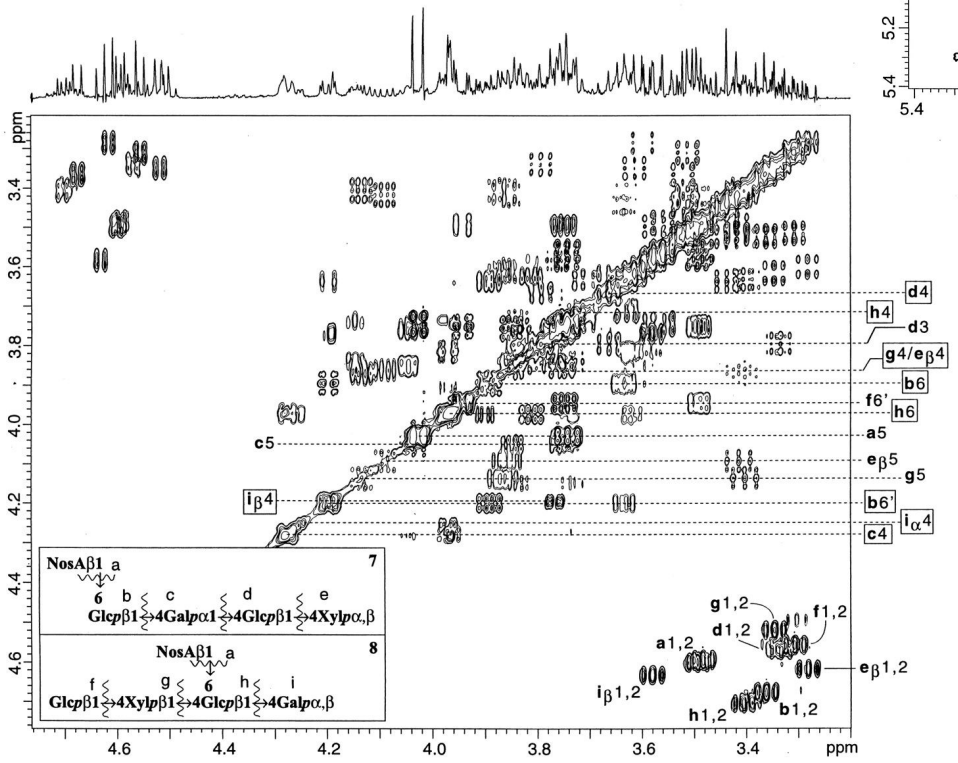
Positive ion mode nanoES CID tandem mass spectrum of per-O-methylated *N. commune* oligosaccharides

Brüll LP et al. (2000) *J Phycol* 36: 871–881.

Nostoc polysaccharides

COSY spectrum of
***N. commune* oligosaccharides**



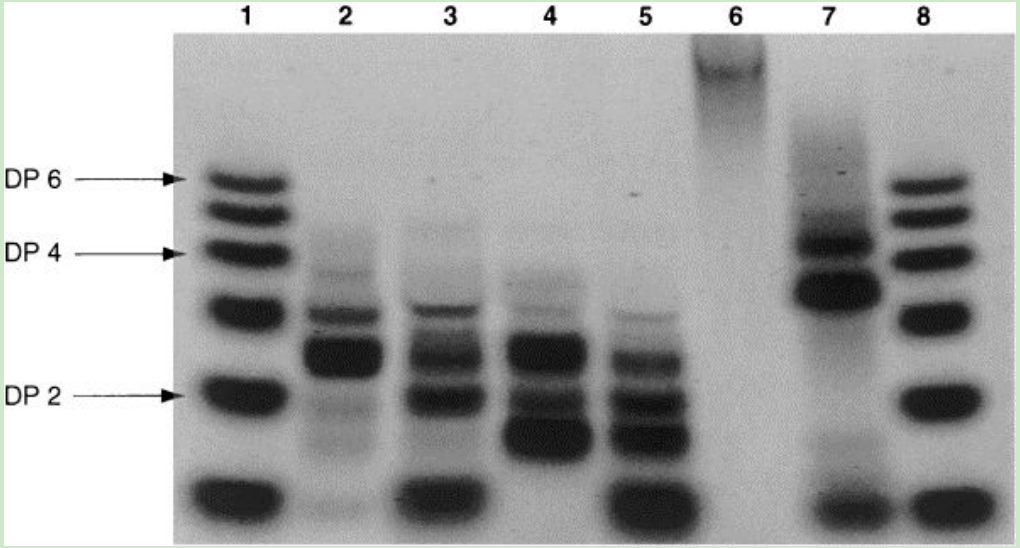


A trisaccharide

Mixture of two pentasaccharides

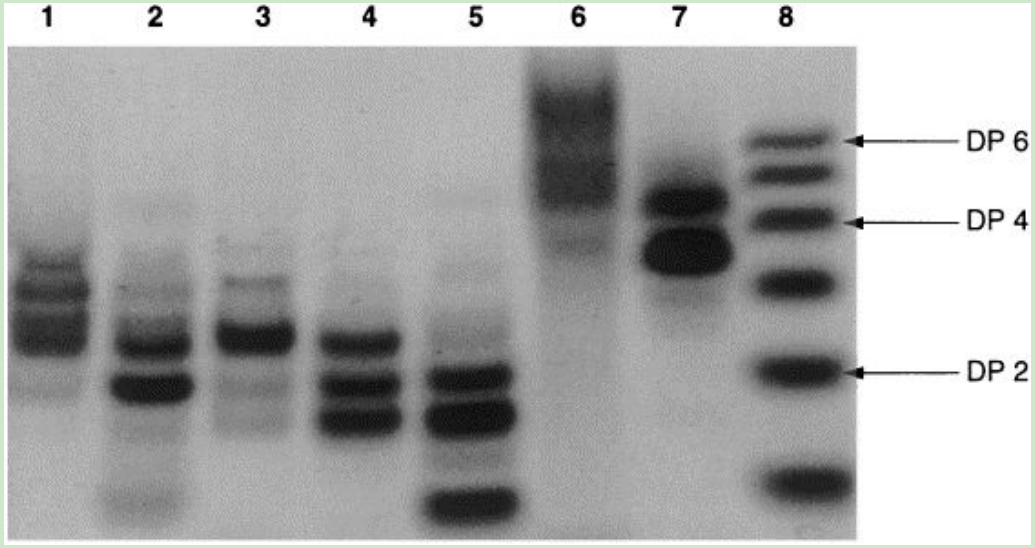
Helm RF et al. (2000) *J Bacteriol* 182: 974–982.

Nostoc polysaccharides: Protective functionality of nosturonic acid & D-ribofuranose in native EPS



Lane 6: lithium – ethylenediamine treated *Nostoc* EPS after BioGel P2 purification and AA-labeling; **Lane 7**: oligosaccharides after the Driselase digestion and AA-labeling of the Li – EDA-treated glycan of Lane 6

Lane 6 and 7: Li – EDA-treated glycan after Driselase digestion, followed by Bio-Gel P2 purification into high (Lane 6) and low (Lane 7) molecular weight fractions.



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Huang Z et al. (2000) *Carbohydr Res* 328: 77–83.

Nostoc polysaccharides

Oligosaccharide strucutres

1 β-D-Glc*p*-(1→4)-D-Xyl*p*

β-D-NosA
1
↓
6

2 β-D-Glc*p*-(1→4)-D-Gal*p*

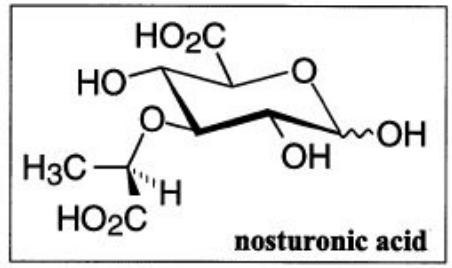
β-D-NosA
1
↓
6

3 β-D-Glc*p*-(1→4)-α-D-Gal*p*-(1→4)-β-D-Glc*p*-(1→4)-D-Xyl*p*

β-D-NosA
1
↓
6

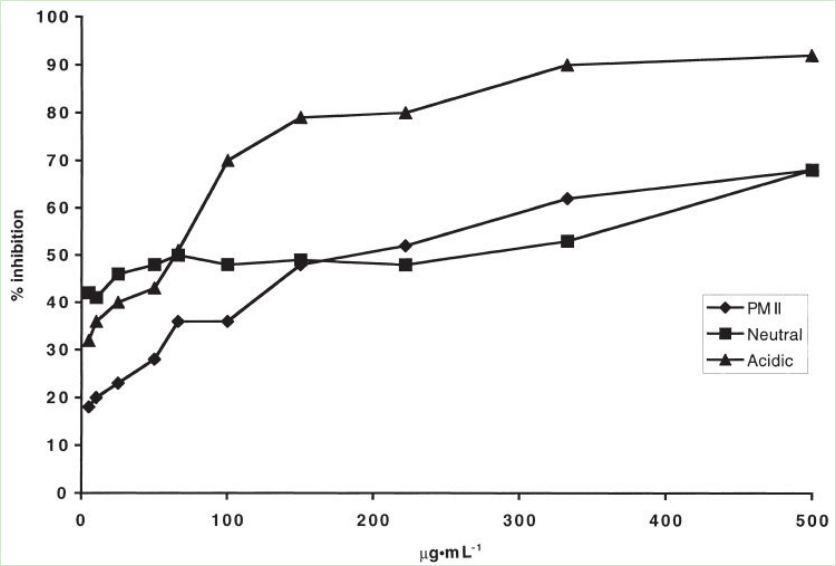
4 β-D-Glc*p*-(1→4)-β-D-Xyl*p*-(1→4)-β-D-Glc*p*-(1→4)-D-Gal*p*

5 [β-D-NosA
1
↓
6
β-D-Glc*p*-(1→4)-α-D-Gal*p*-(1→4)-β-D-Glc*p*-(1→4)-D-Xyl*p*
3
↑
1
α-D-Rib*f*]



nosturonic acid

Complement inhibition



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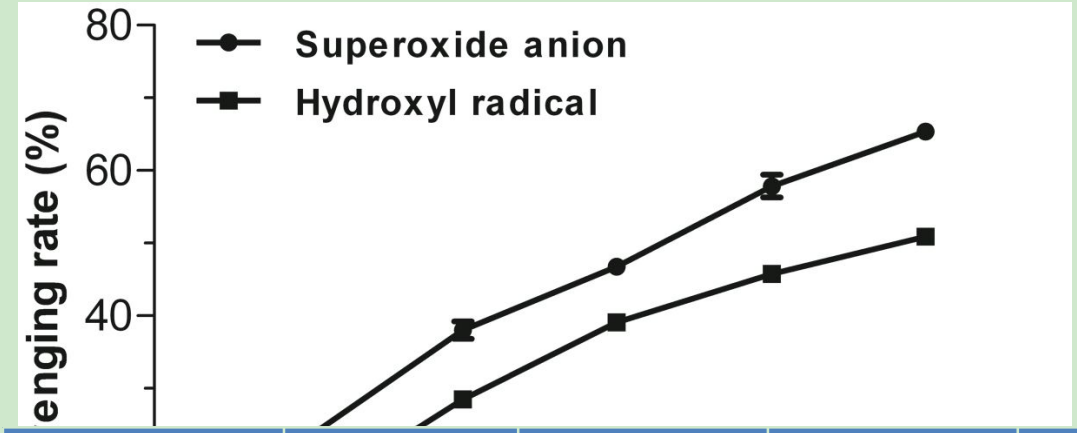
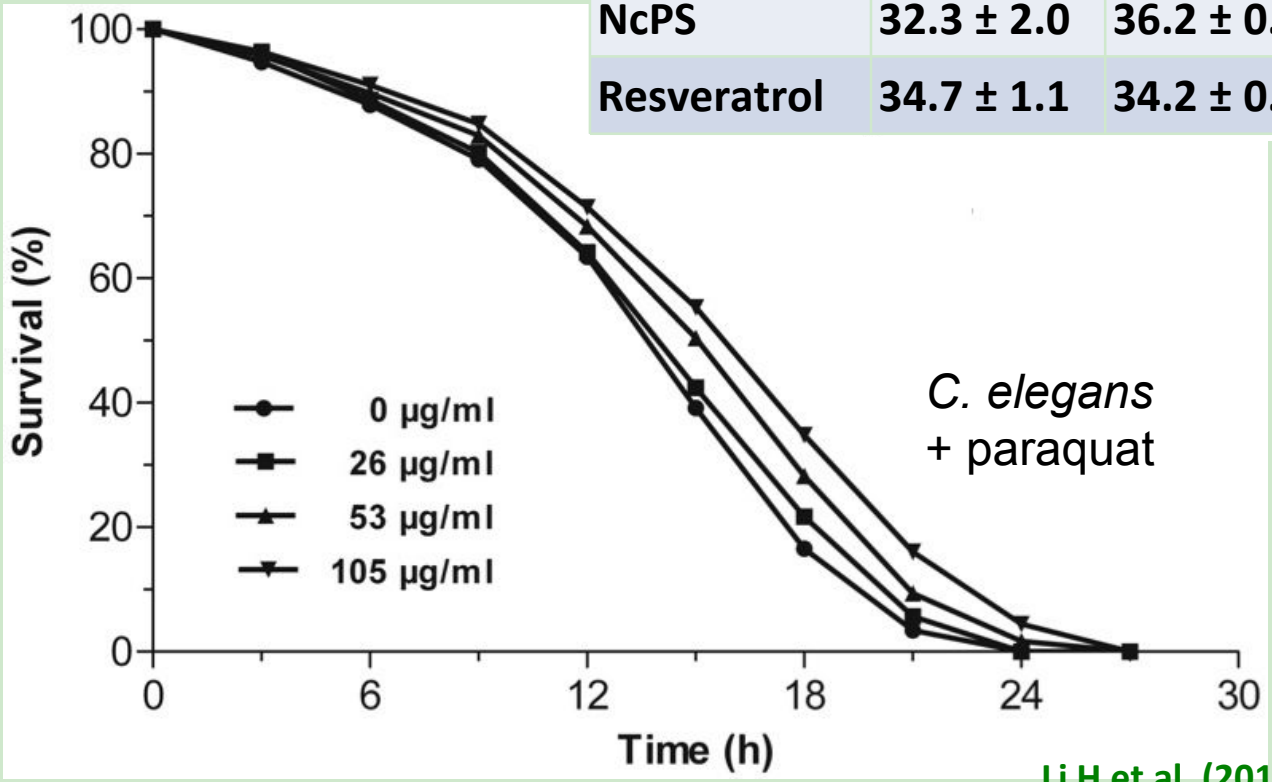
Huang Z et al. (2000) *Carbohydr Res* 328: 77–83.
Helm RF et al. (2000) *J Bacteriol* 182: 974–982.
Brüll LP et al. (2000) *J Phycol* 36: 871–881.

Nostoc polysaccharide

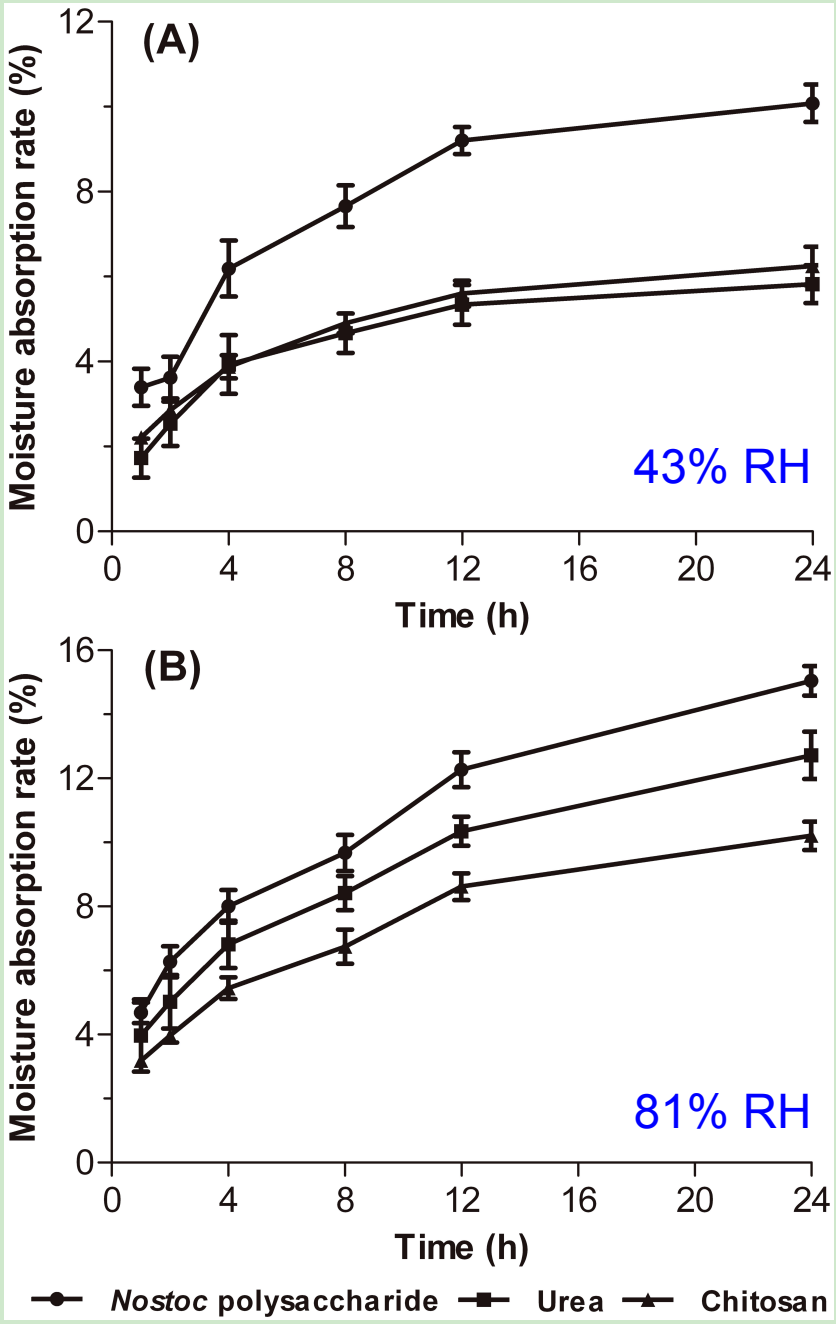


C. elegans	SOD	CAT	GPX	MDA
Control	24.5 ± 1.8	31.9 ± 0.8	14.7 ± 0.5	2.1 ± 0.2
NcPS	32.3 ± 2.0	36.2 ± 0.7	16.5 ± 0.4	1.9 ± 0.1
Resveratrol	34.7 ± 1.1	34.2 ± 0.9	16.8 ± 0.5	1.9 ± 0.1



C. elegans
+ paraquat

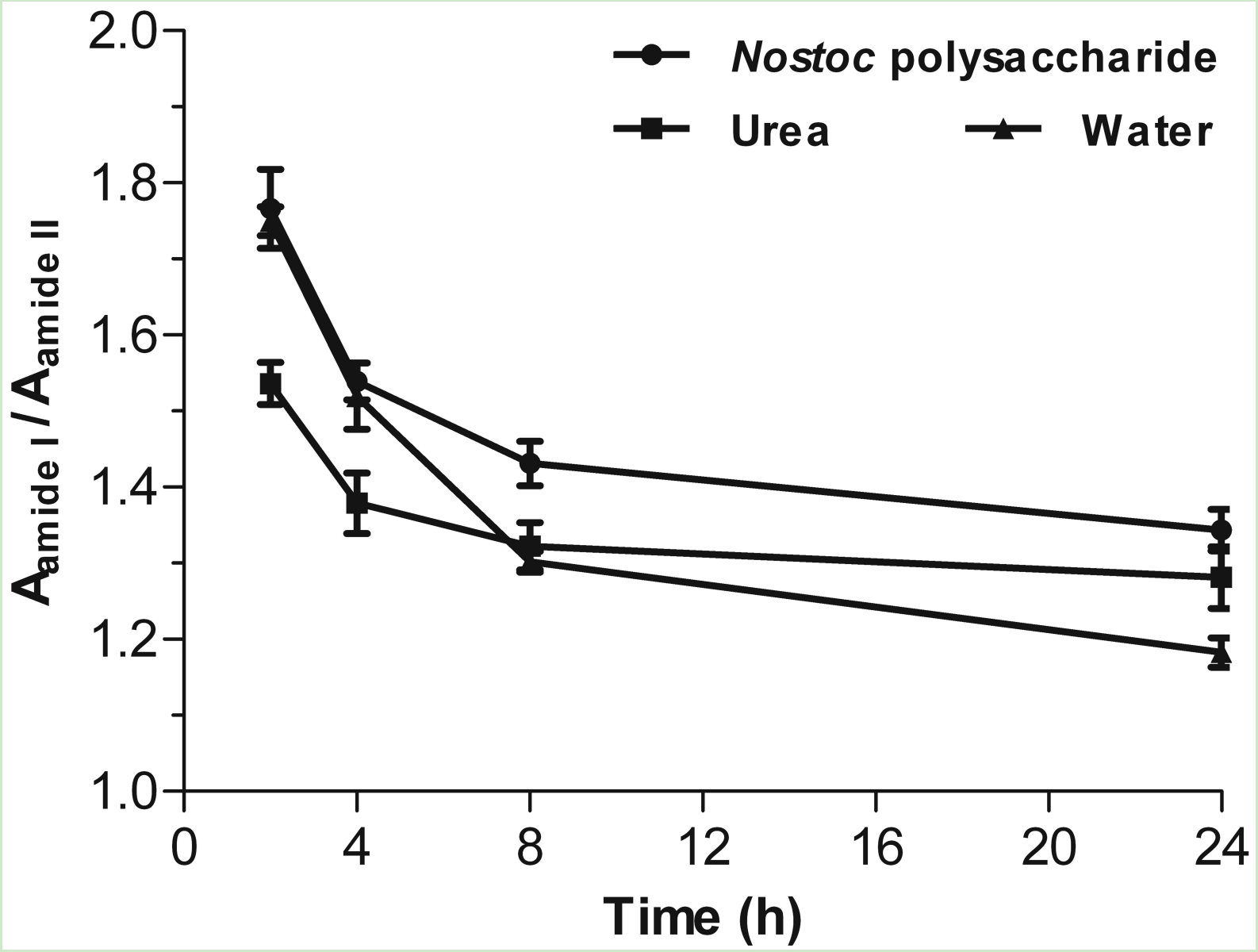
Li H et al. (2011) *Carbohydr Polym* 83: 1821–1827.



43% RH

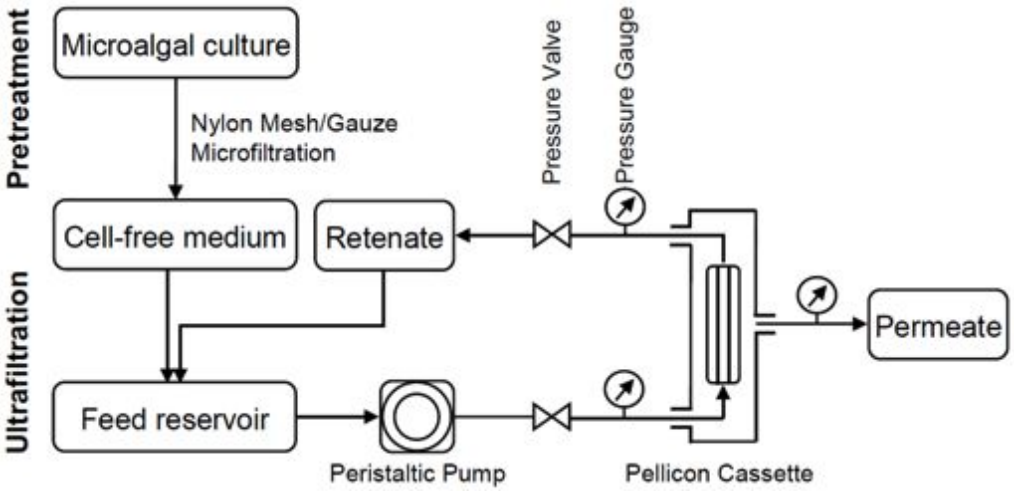
Silica gel

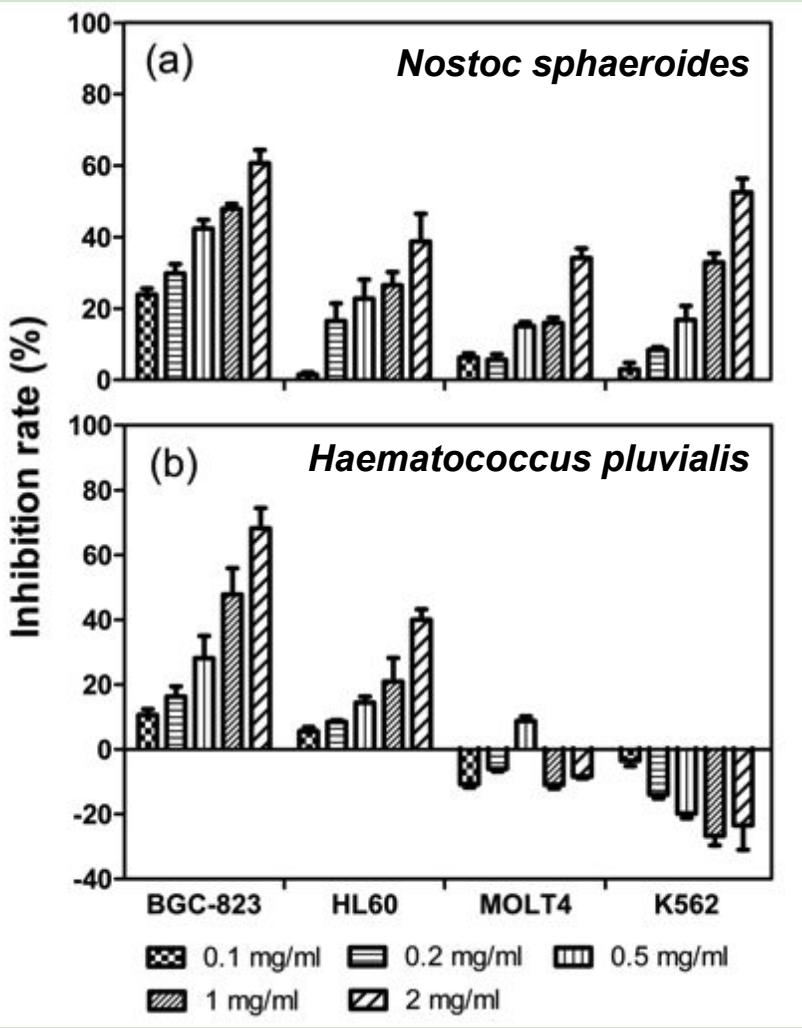
Li H et al. (2011) *Carbohydr Polym* 83: 1821–1827.



Li H et al. (2011) *Carbohydr Polym* 83: 1821–1827.

Antitumor: microalgal polysaccharides





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Li H et al. (2011) *Proc Biochem* 46: 1104–1109.

Pilot-scale EPS isolation from algal cultures



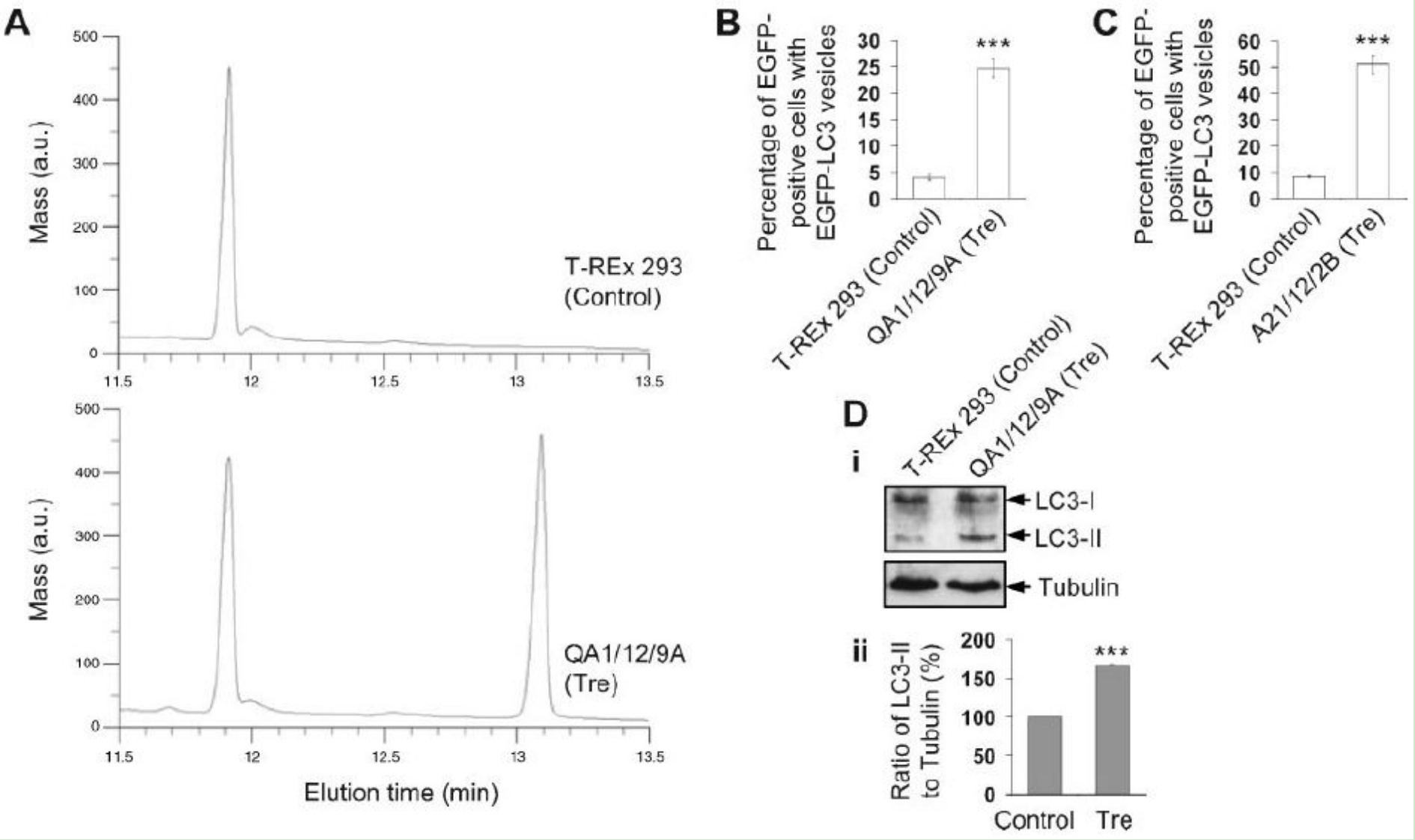



Li H et al. (2011) *Proc Biochem* 46: 1104–1109.

Ultrafiltration of cell-free media for EPS isolation

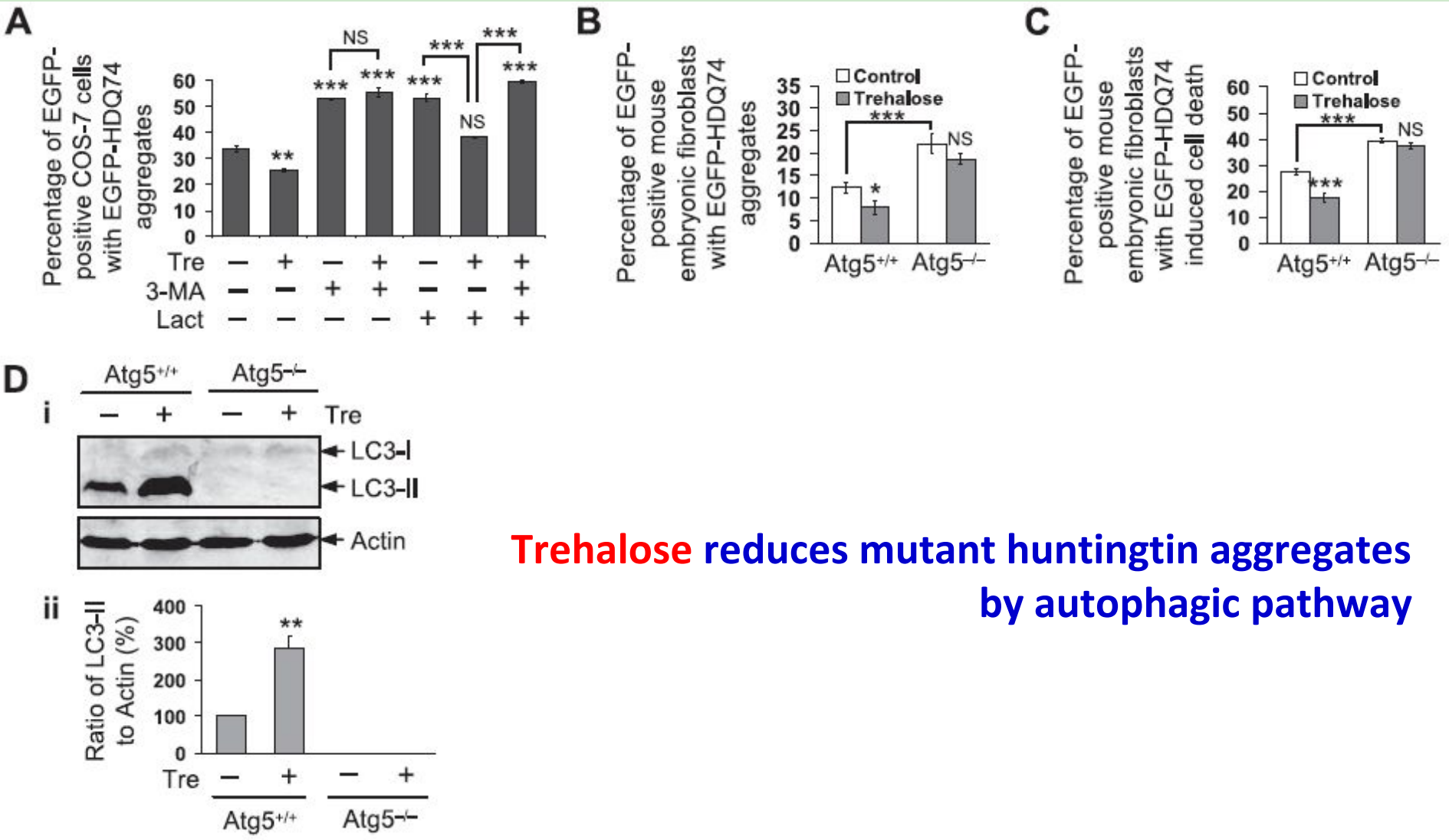
Microalgae	Culture time (d)	Feed volume (L)	Ultrafiltration time (h)	Average permeate flux [L/(m²⋖h)]	EPS yield (mg/L)
Nostoc commune	30	10	0.5	36.8	26.7
Nostoc sphaeroides	30	10	0.5	36.6	22.4
Spirulina platensis	15	460	24.4	36.8	77.2
	30	90	4.6	37.5	204.7
	36	110	5.6	37.2	231.3
Haematoccocus pluvialis	28	450	24.2	36.3	33.2
	42	35	1.8	37.5	41.5
	70	10	0.5	37.8	73.8
Chlorella pyrenoidosa	10	145	7.4	38.3	3.5
Chaetoceros muelleri	15	90	4.8	35.7	188.2

Li H et al. (2011) *Proc Biochem* 46: 1104–1109.



Cells synthesizing intracellular trehalose have increased autophagy

Sarkar S et al. (2007) *J Biol Chem* 282: 5841–5652.



Trehalose reduces mutant huntingtin aggregates by autophagic pathway

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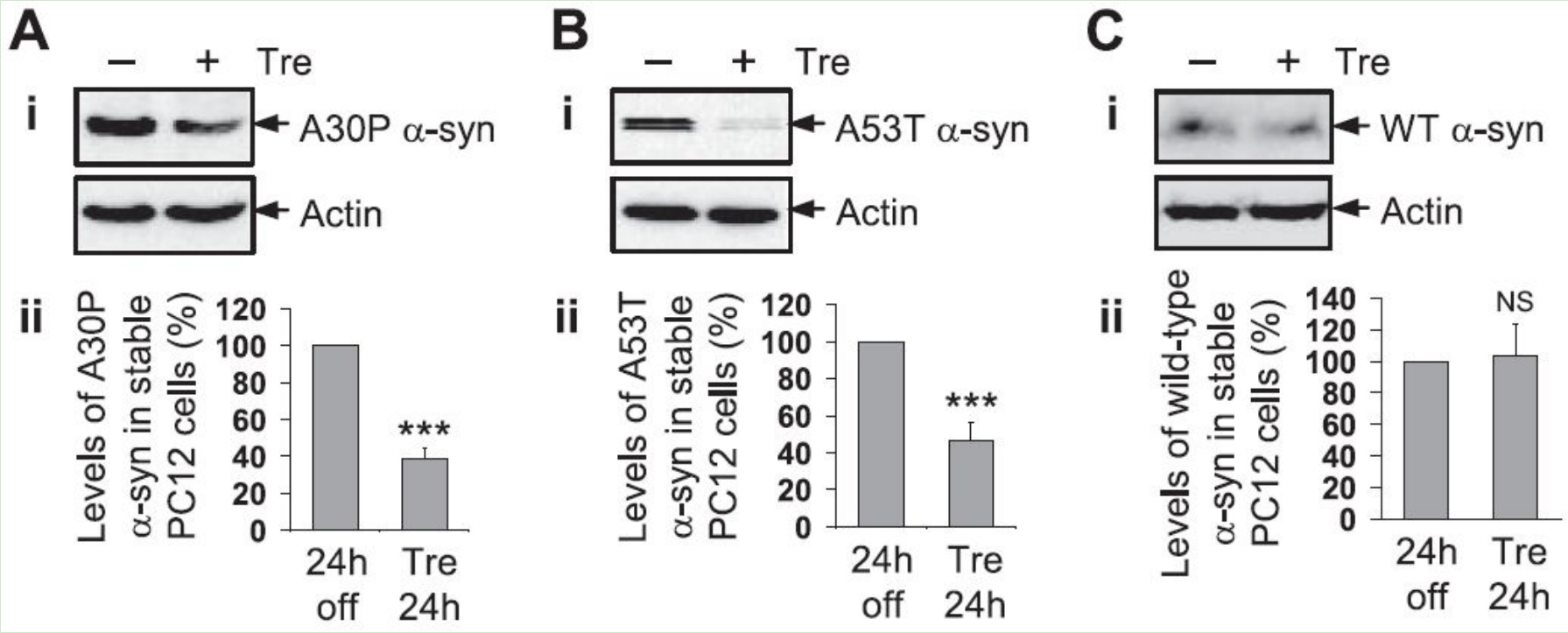
Sarkar S et al. (2007) *J Biol Chem* 282: 5841–5652.



Trehalose enhances the clearance of α-synuclein mutants

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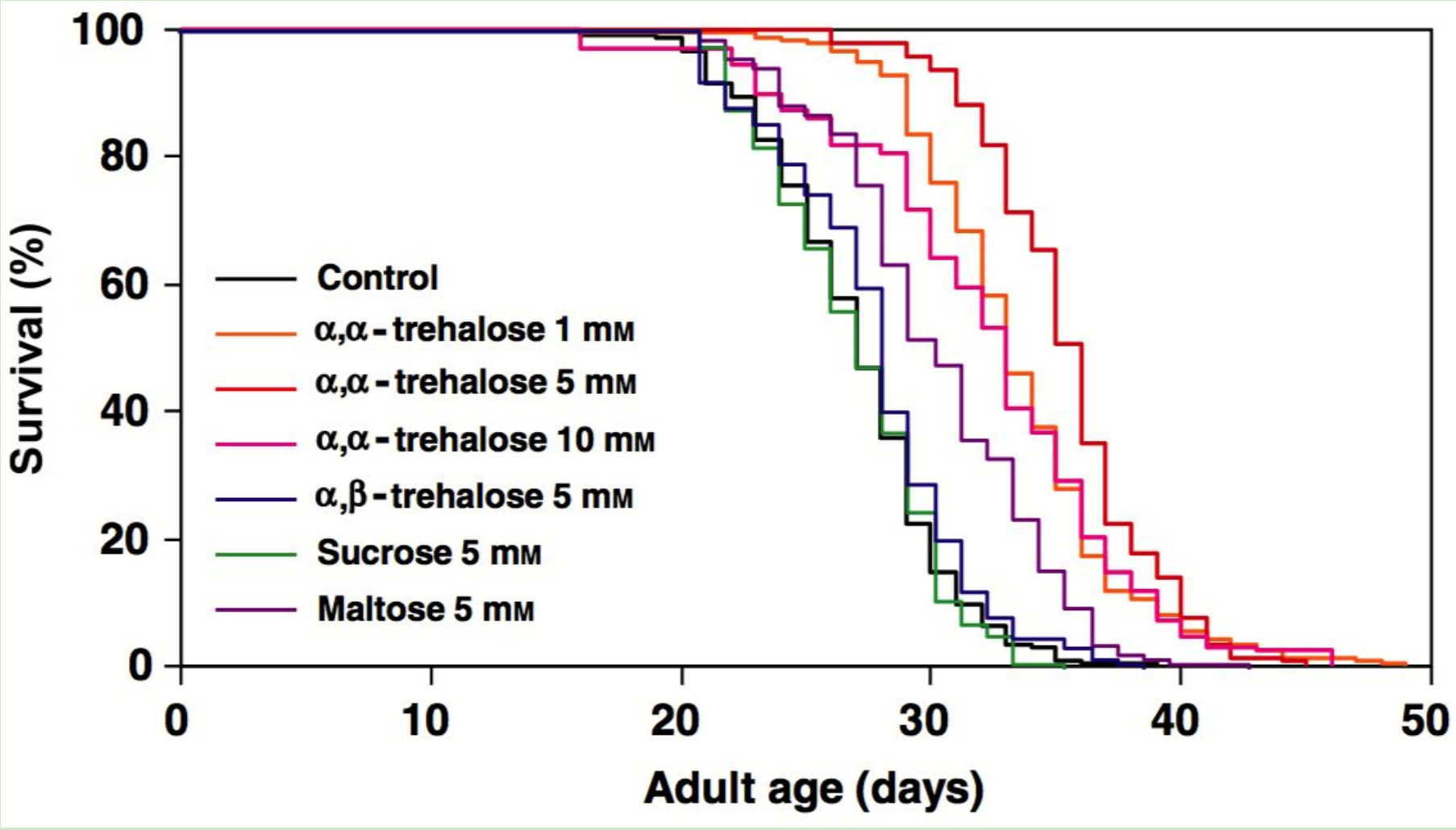
Sarkar S et al. (2007) *J Biol Chem* 282: 5841–5652.

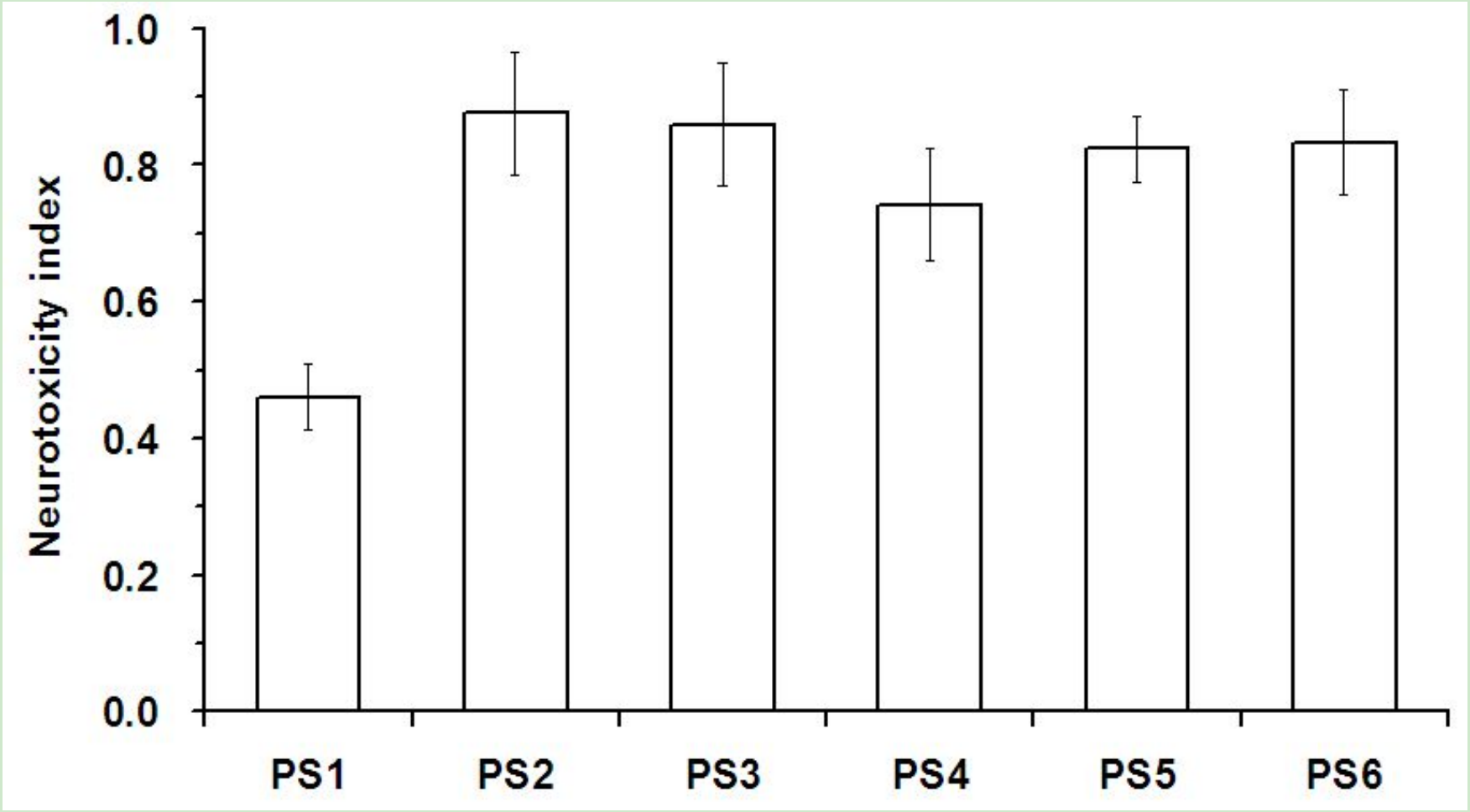


Honda Y et al. (2010) *Aging Cell* 9: 558–569.

抗衰老与神经保护类传统中药

- 轻身延年:枸杞、灵芝、首乌、红景天、绞股蓝、 ……
- 安神定志:天麻、茯苓、龙骨、远志、丹参、麦冬、……
- 益智开窍:人参、党参、石菖蒲、刺五加、柏子仁、……

Polysaccharides from anti-aging herbs: neuroprotective screening



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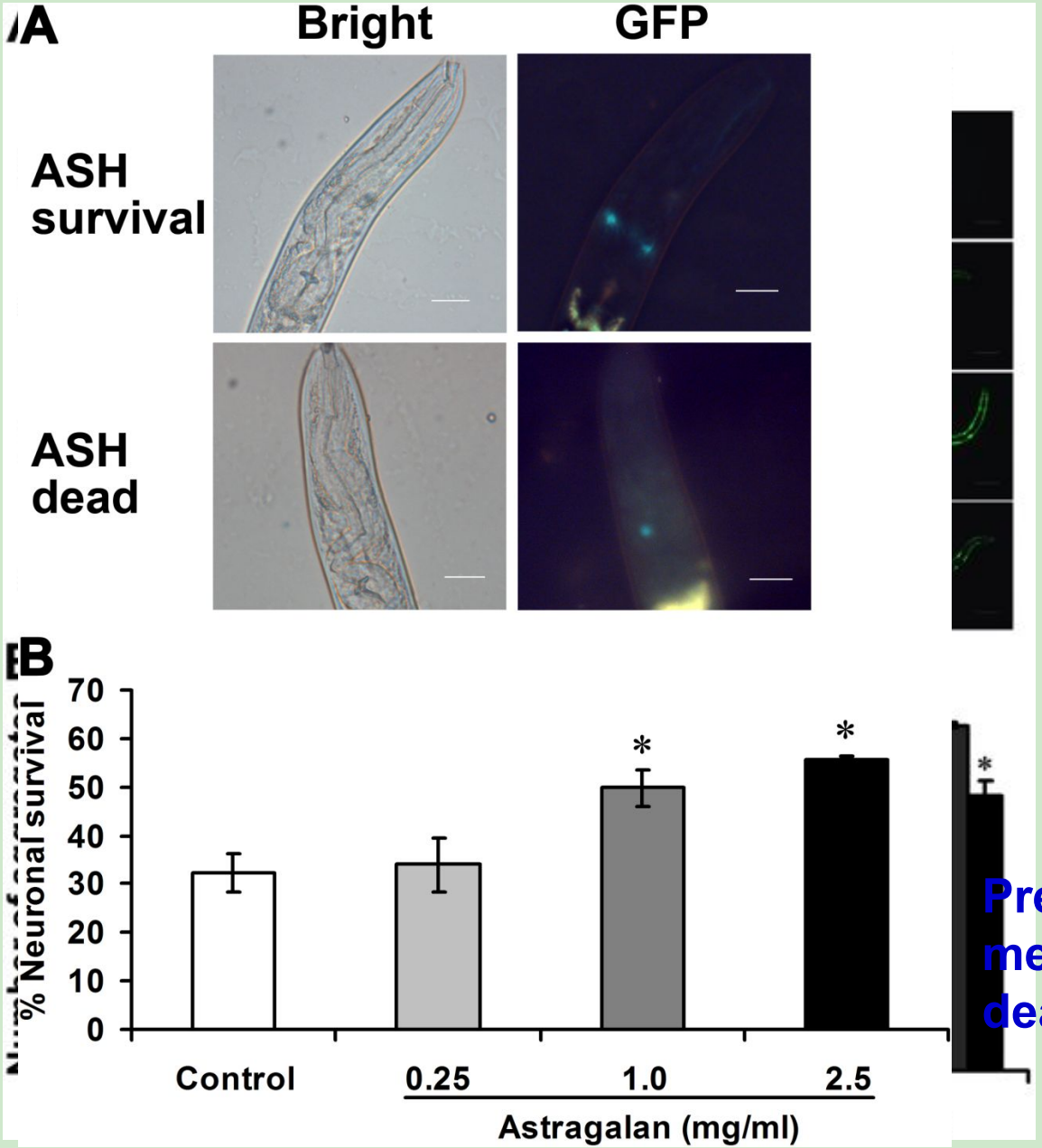
Zhang H et al. (2012) *Biochem J* 441: 417–424.



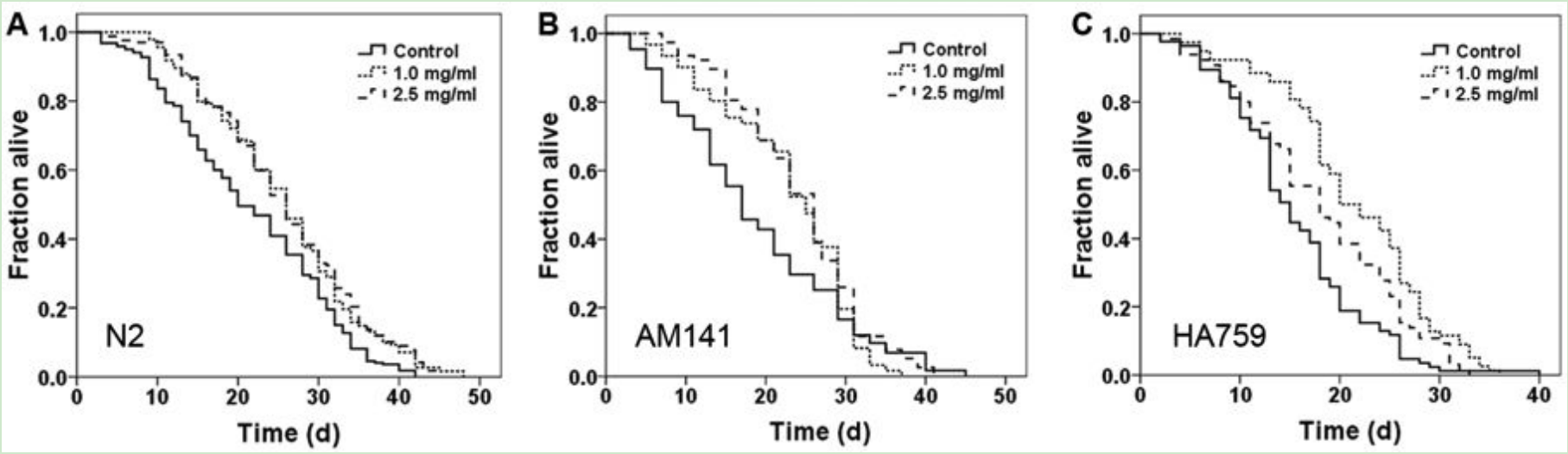
Reduction of polyQ40 aggregation in *C. elegans* AM141

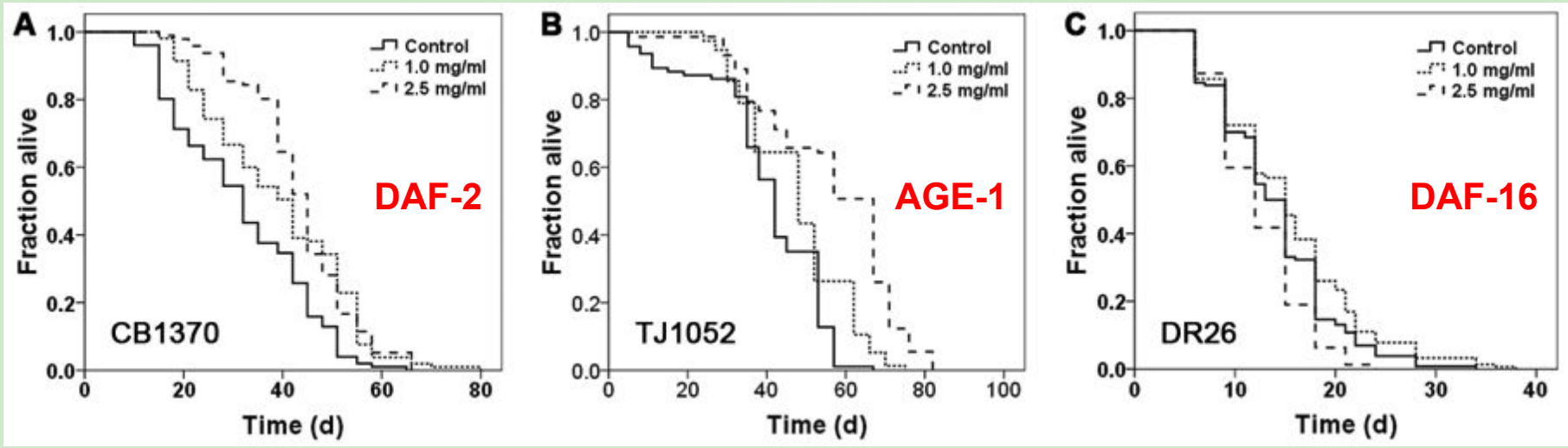
Polysaccharide from *Astragalus membranaceus*

Prevention of polyQ150-mediated ASH neuronal death in *C. elegans* HA759

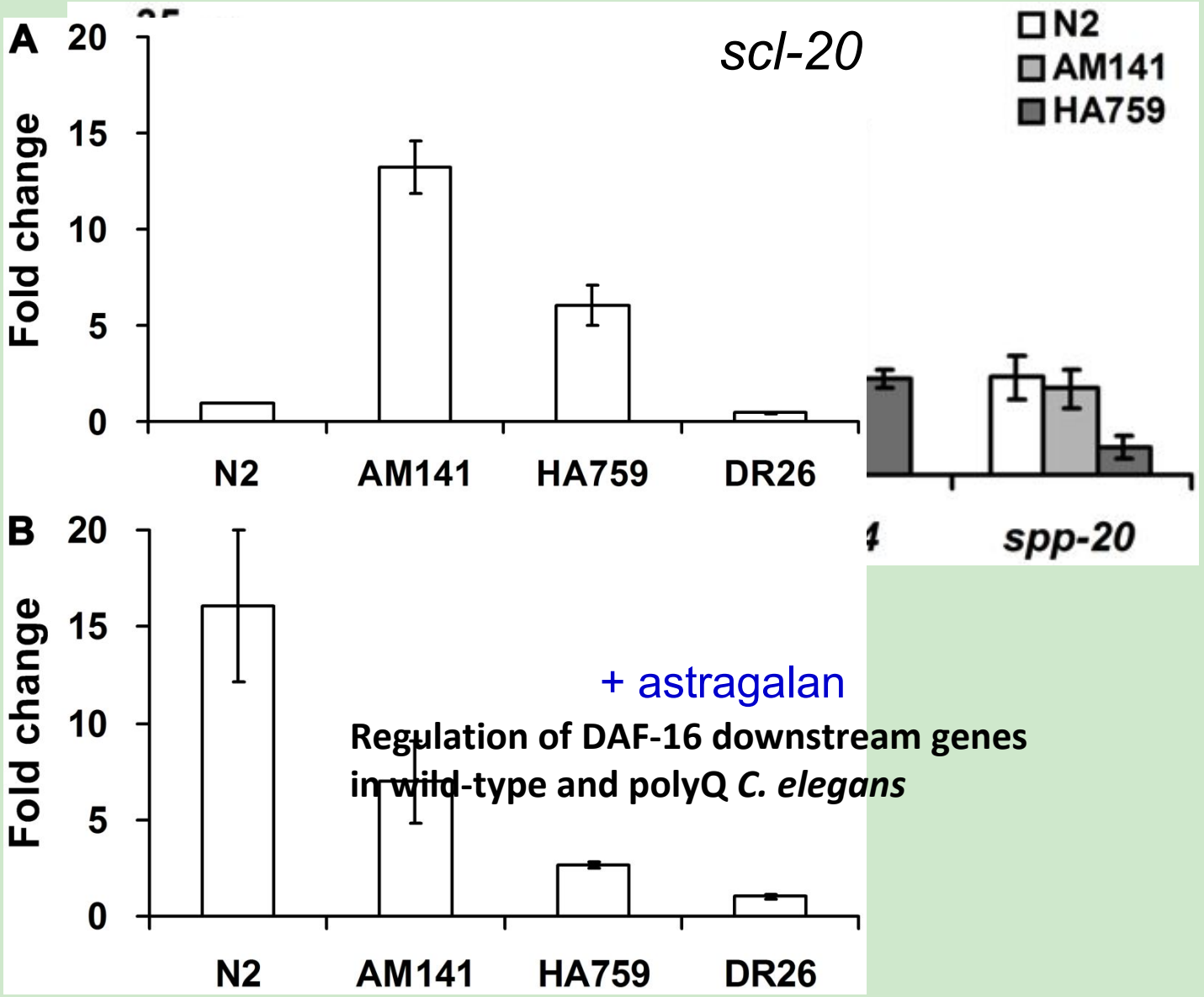
Zhang H et al. (2012) *Biochem J* 441: 417–424.

Lifespan-extending effect of astragalan in *C. elegans*





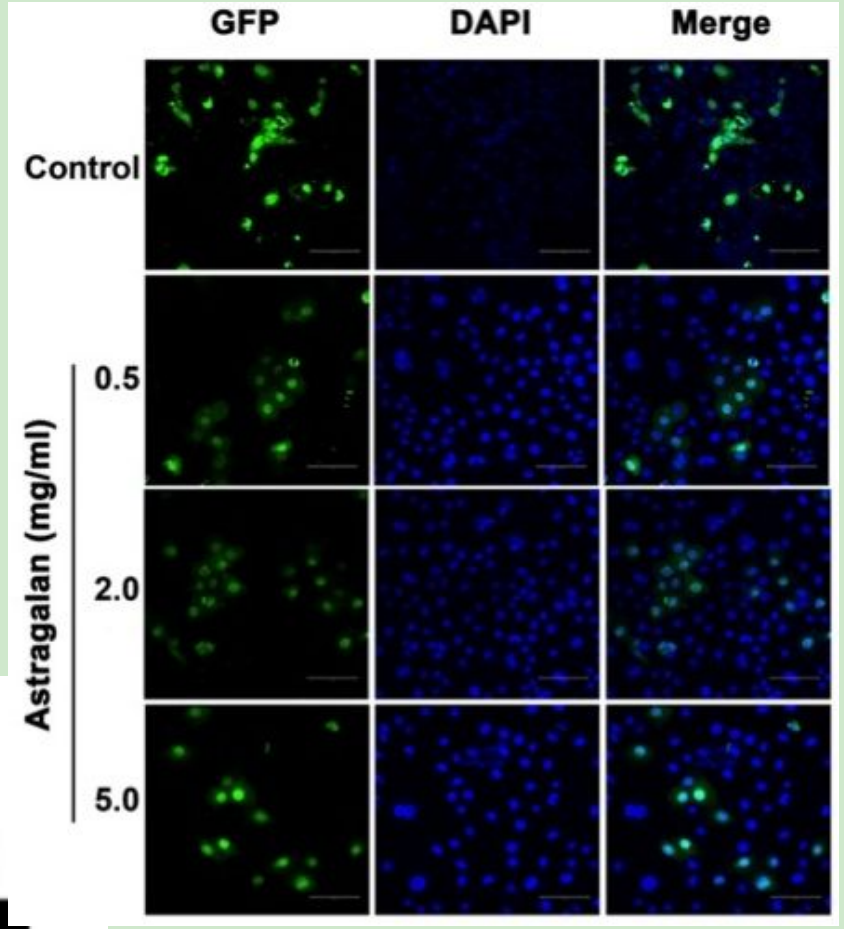
Zhang H et al. (2012) *Biochem J* 441: 417–424.

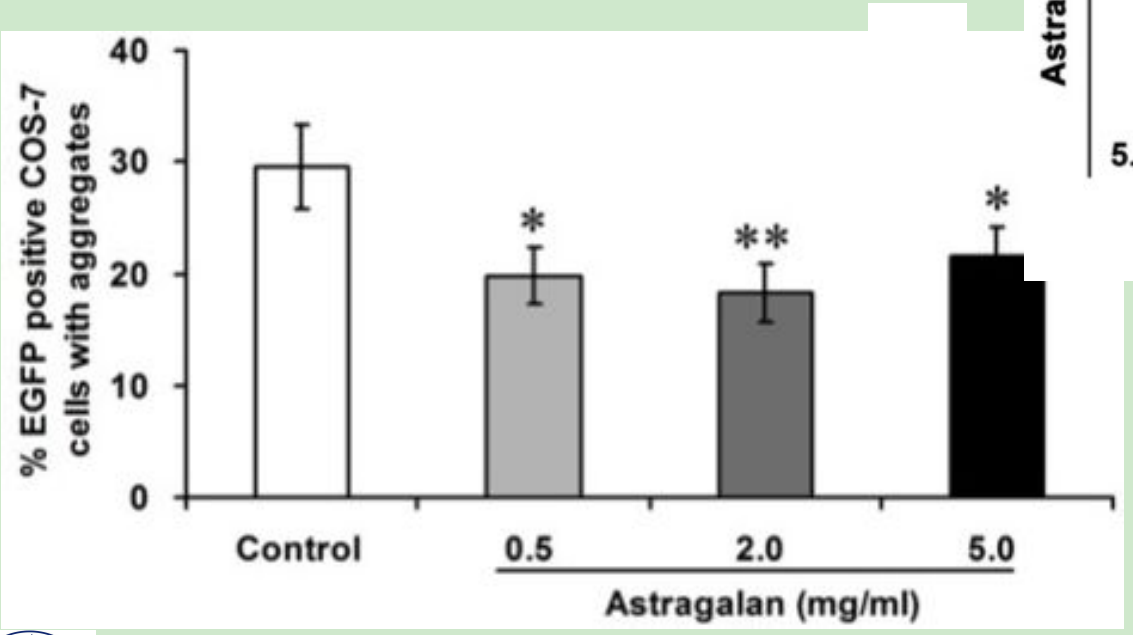


scl-20 (*dct-2*) encodes a predicted SCP-like extracellular protein homologous to mammalian GliPR1 and functions to regulate both lifespan and tumor cell proliferation.

Zhang H et al. (2012) *Biochem J* 441: 417–424.

Reduction of HDQ74 aggregation by astragalan in COS-7 cells





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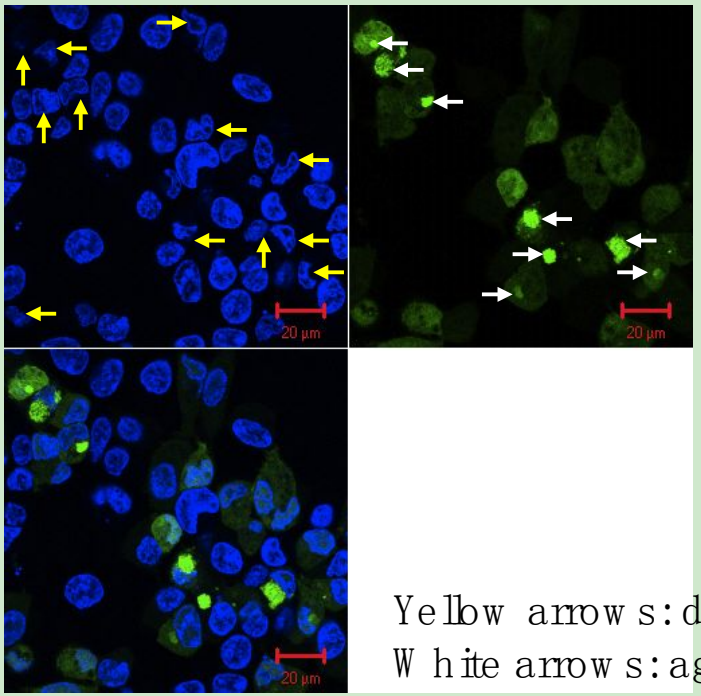
Zhang H et al. (unpublished data).

Polysaccharides for effect on intracellular $A\beta_{42}$-EGFP aggregation

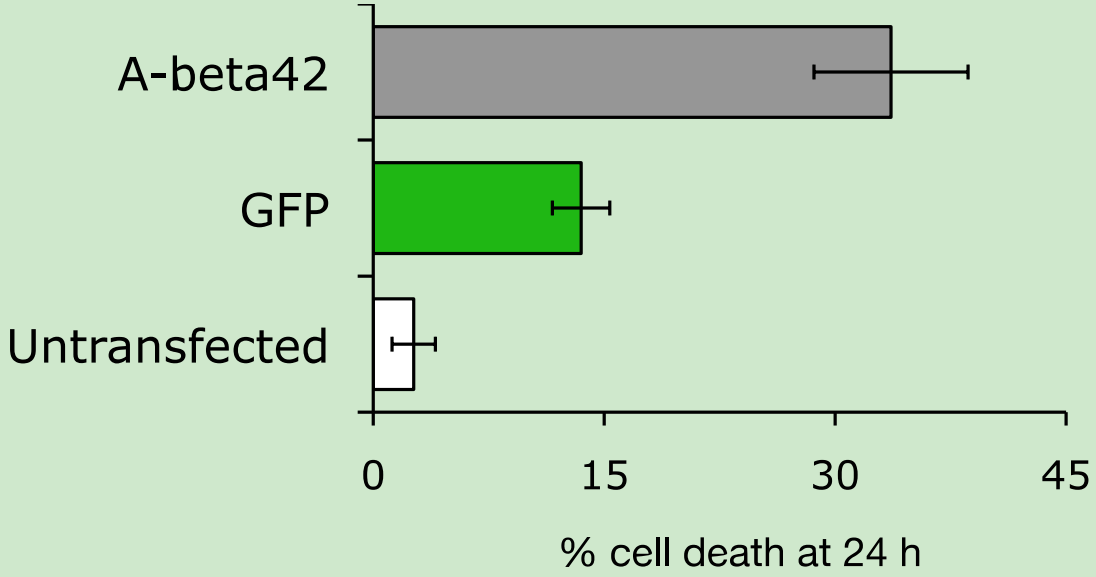
sample	source of polysaccharide (Latin name)	source of polysaccharide (Chinese name)	% aggregation relative to untreated cells	standard deviation
	none (control: $A\beta_{42}$-EGFP only)		100	2
PS1	*Astragalus membranaceus* (Fisch.) Bge.	Huang Qi	112	3
PS2	*Achyranthes bidentata* Bl.	Niu Xi	89	1
PS4	*Cuscuta chinensis* Lam.	Tu Si Zi	131	3
PS5	*Rubia cordifolia* L.	Qian Cao	79	2
PS8	*Viscum coloratum* (Komar.) Nakai	Hu Ji Sheng	107	2
PS9	*Poria cocos* (Schw.) Wolf	Fu Ling	93	2
PS10	*Salvia miltiorrhiza* Bge.	Dan Shen	86	3
PS12	*Adenophora tetraphylla* (Thunb.) Fisch.	Nan Sha Shen	106	5
PS13	*Schisandra chinensis* (Turcz.) Baill.	Wu Wei Zi	101	2
PS14	*Rheum palmatum* L.	Da Huang	90	6
PS15	*Polygonum multiflorum* Thunb.	He Shou Wu	115	6

Chakrabortee S et al. (2012) *Biochem J* 442: 507–515.

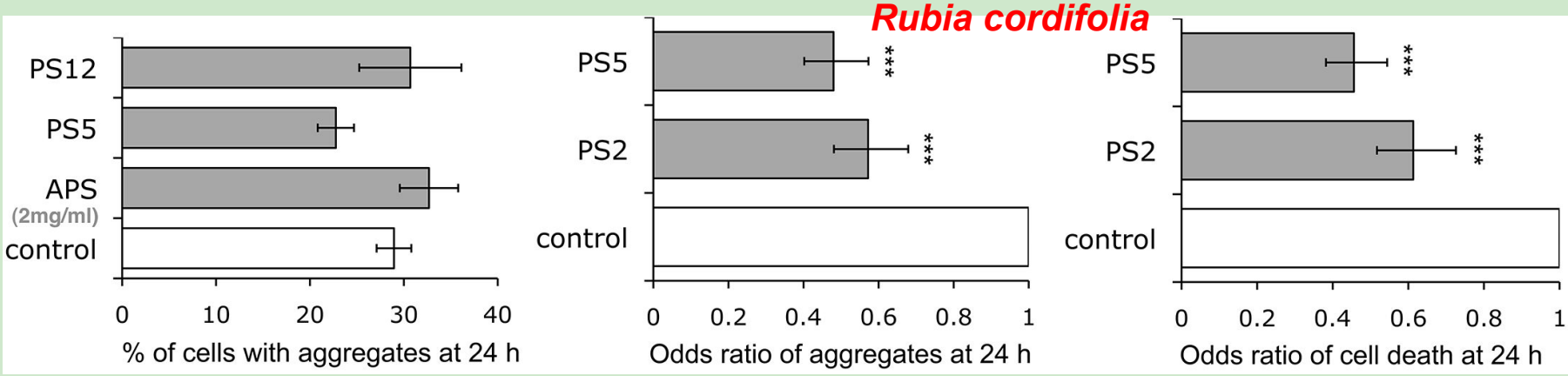
Mammalian cells expressing A β 42-GFP



Yellow arrows: dead cells
White arrows: aggregates



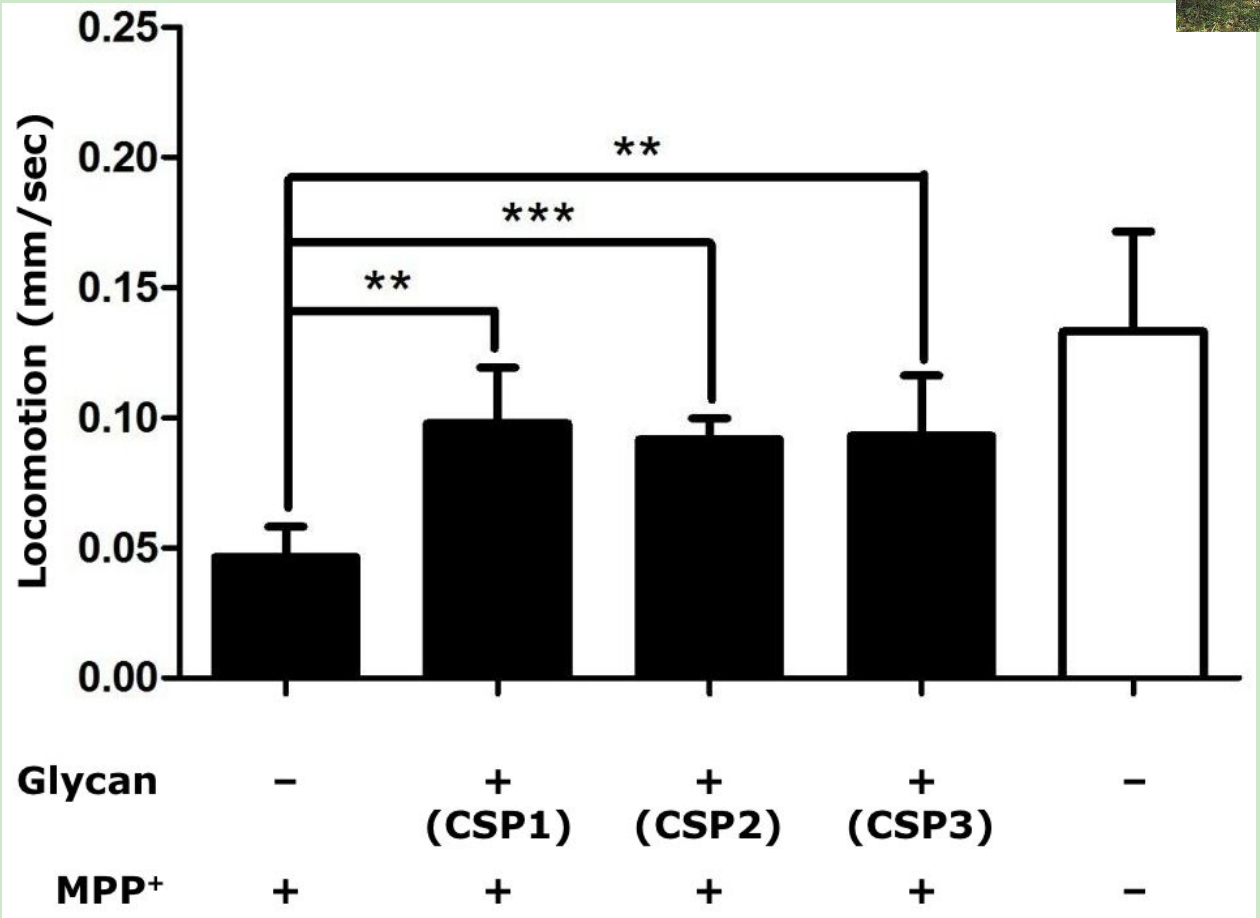
Rubia cordifolia



Chakrabortee S et al. (2012) *Biochem J* 442: 507–515.

Chaenomeles speciosa polysaccharides

皱皮木瓜



Pharmacologic suppression of MPP$^+$-induced locomotion defect in *C. elegans*

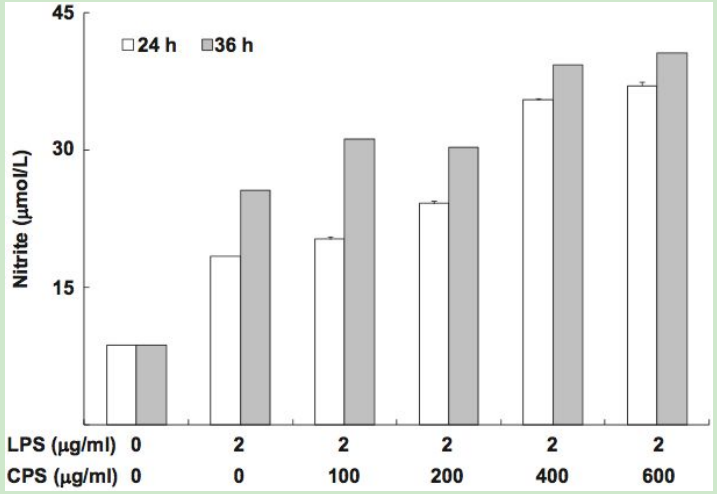
School of Biosciences and Biopharmaceutics

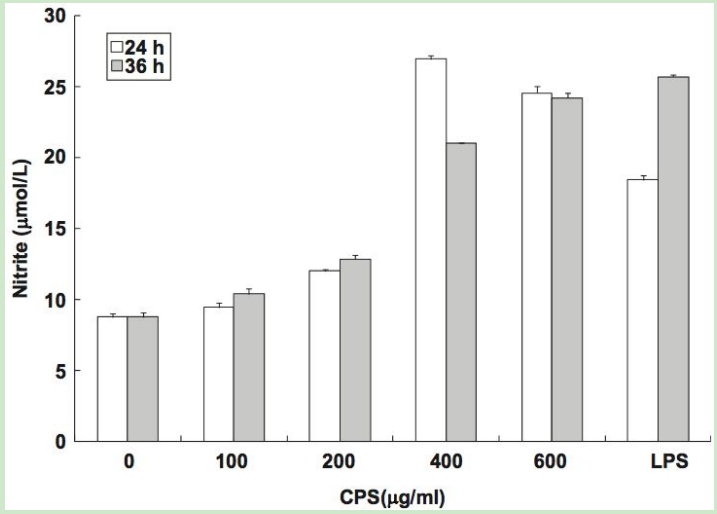
Wang Q et al. (2014) *Rejuvenation Res* 17: 205–208.

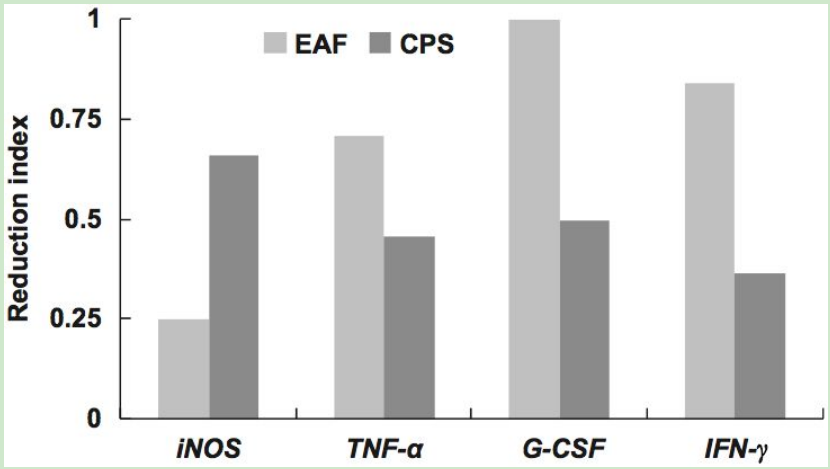
Chaenomeles speciosa polysaccharide

皱皮木瓜

NO production in RAW264.7 cells







Effect on LPS-induced expression of inflammation-related genes

Modulation of nitric oxide production in macrophage cells

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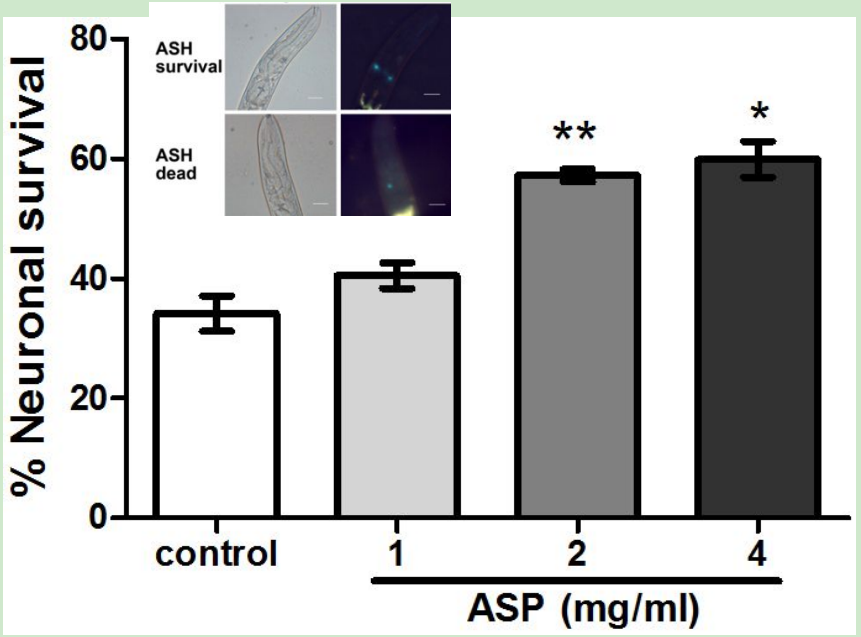
Zhu Q et al. (2012) *J Ethnopharmacol* 144: 441–447.

Acanthopanax senticosus polysaccharide

刺五加



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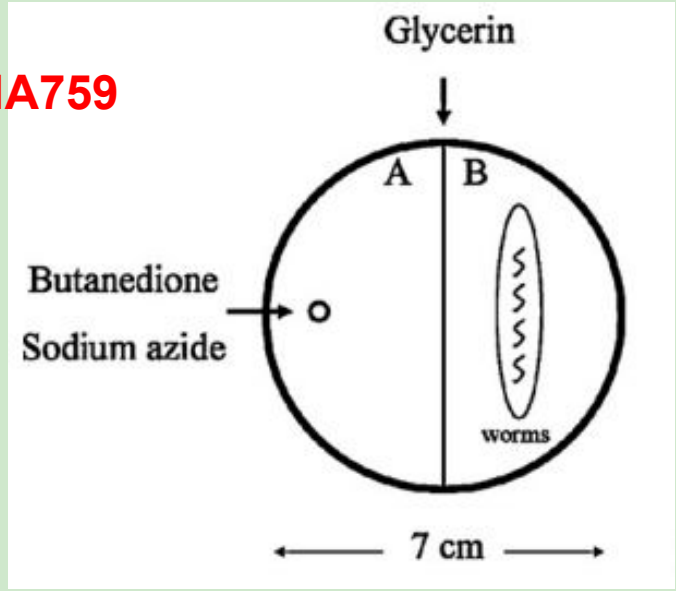
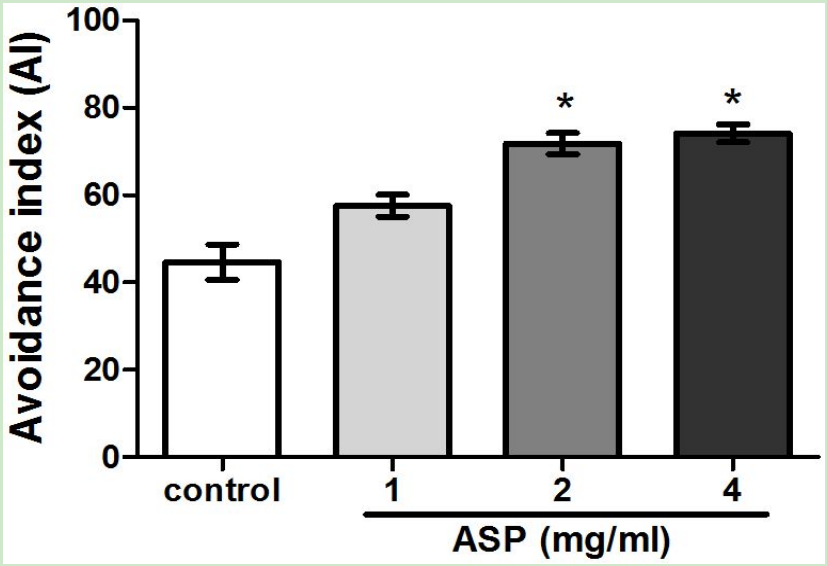
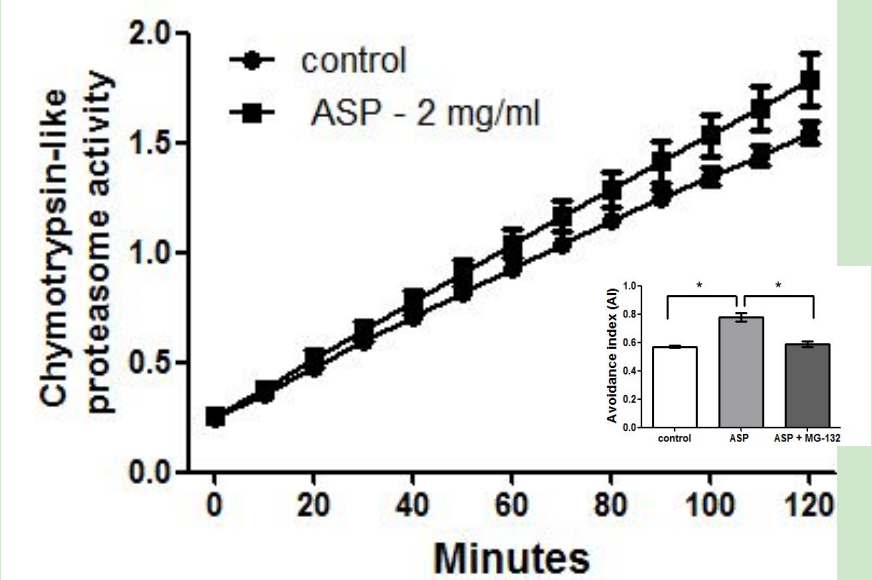
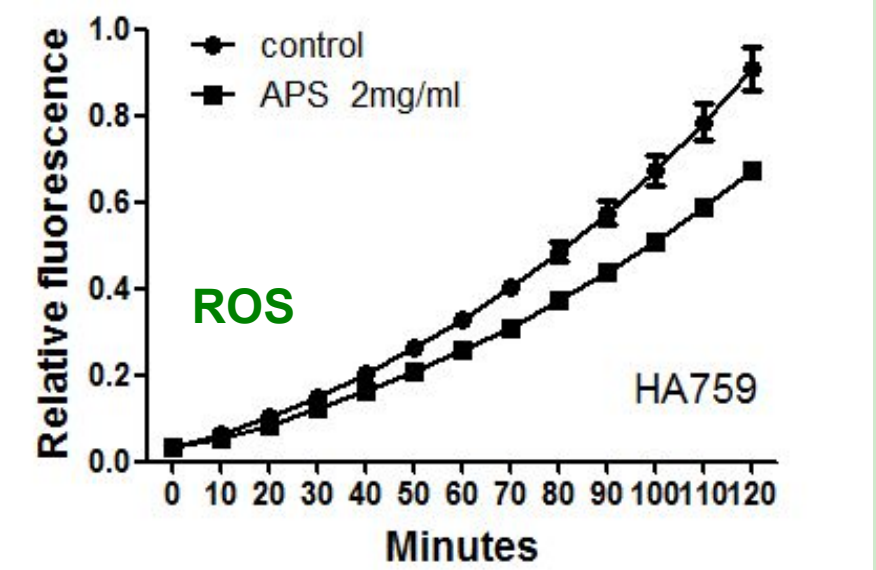
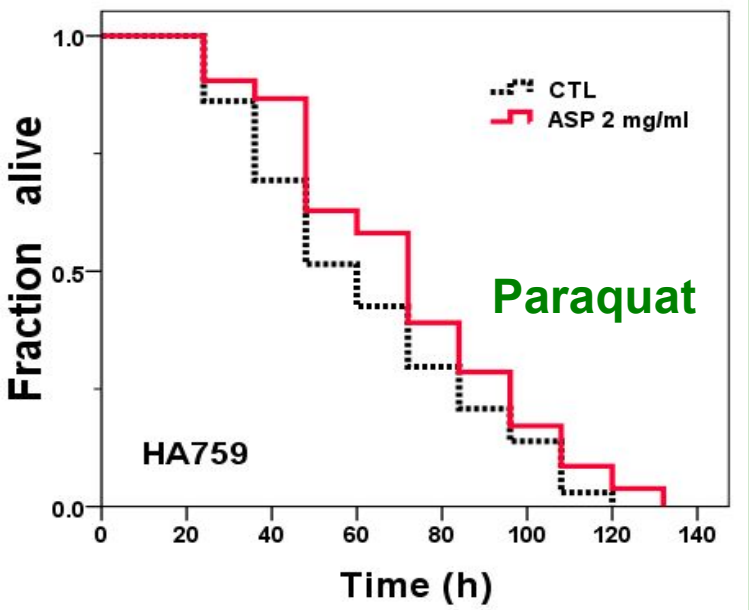


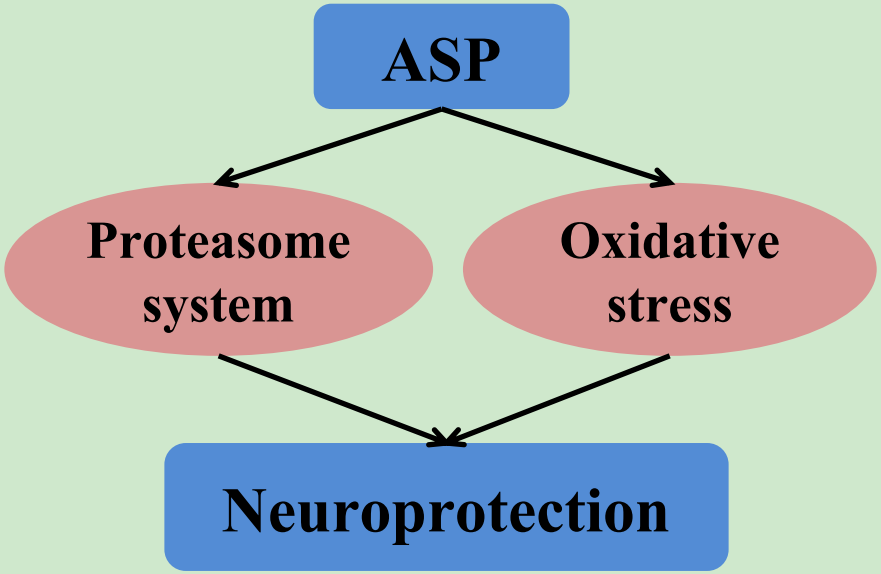


Acanthopanax senticosus polysaccharide

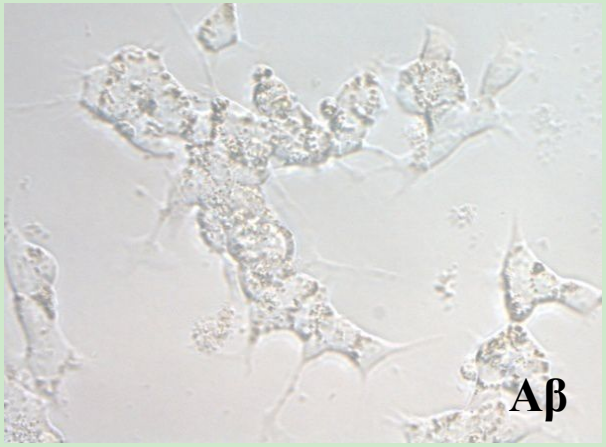


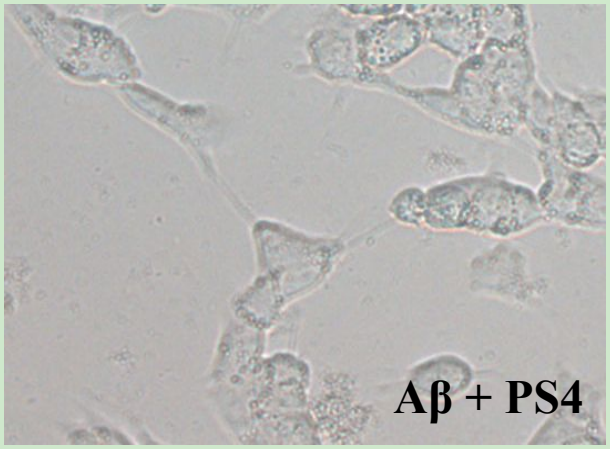


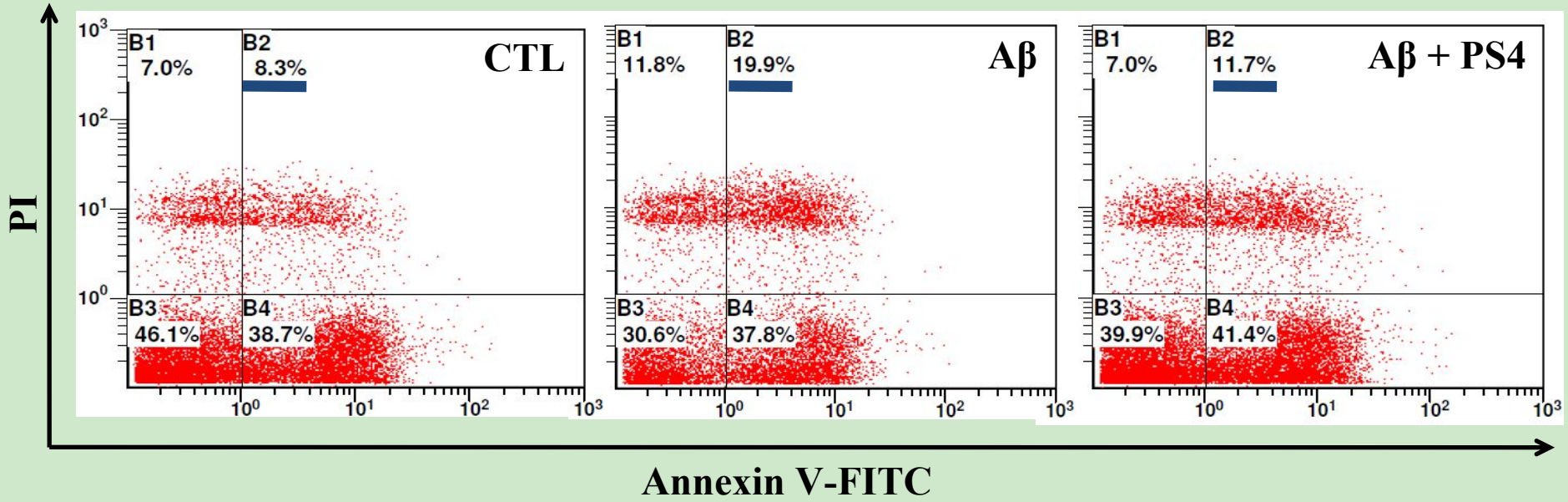




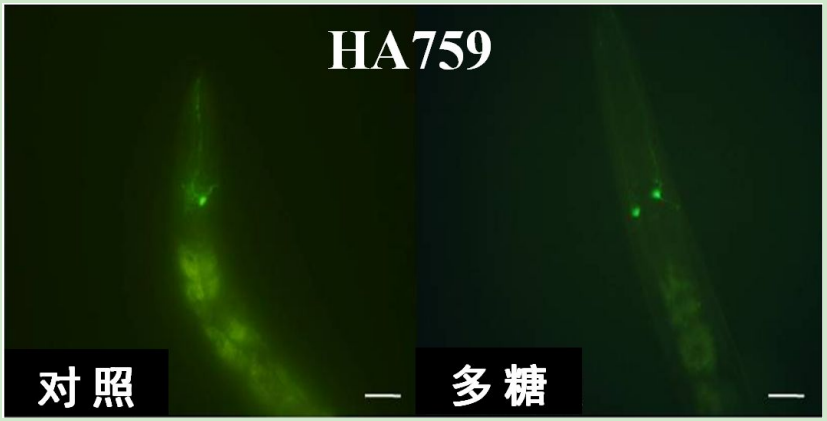
Rubia cordifolia polysaccharide reduces Aβ-induced apoptosis

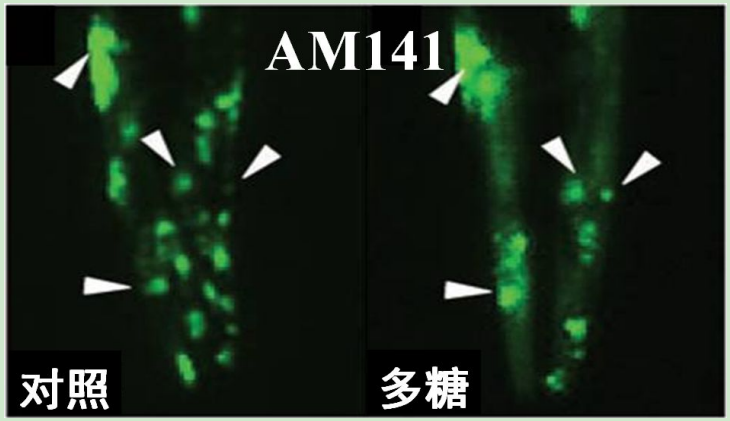


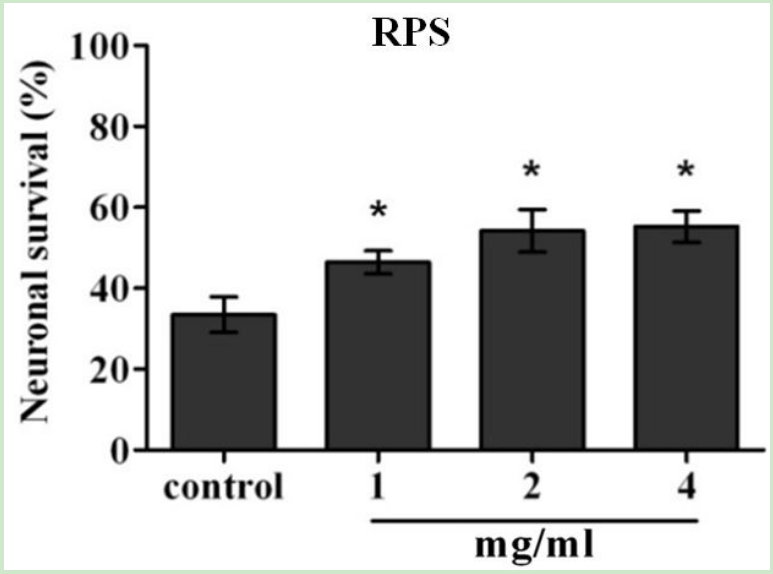


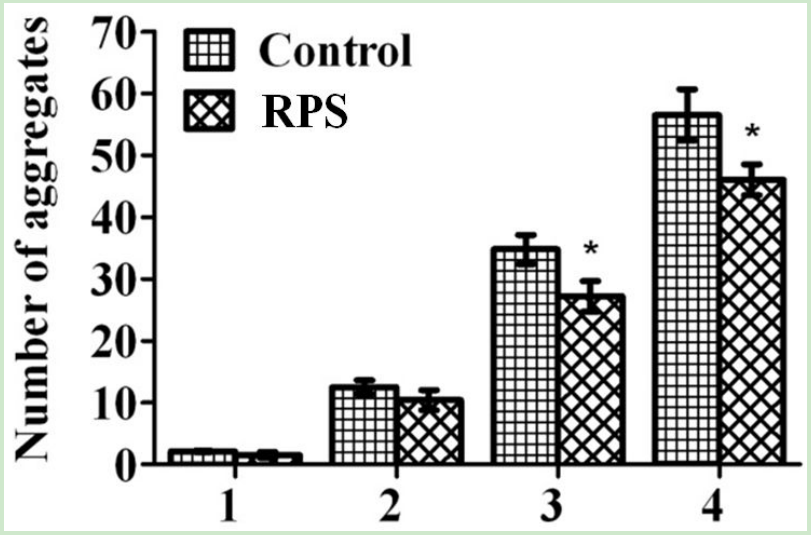


Rubia cordifolia polysaccharide



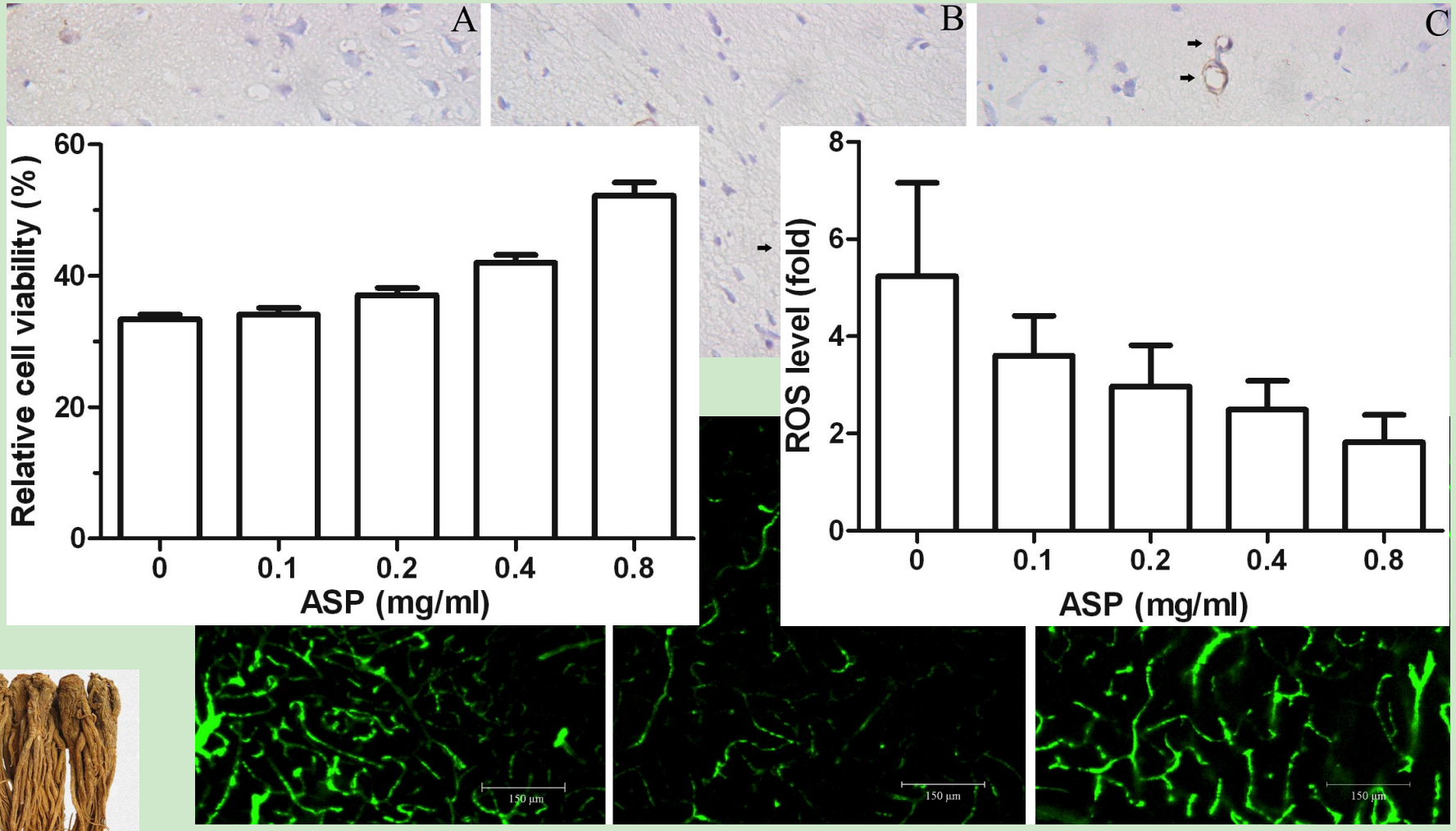






Angelica sinensis polysaccharides:

Ameliorating oxidative stress in PC12 cells & ischemic brain injury in rats



Lei T et al. (2013) *Neural Regen Res* 9: 260–267.

Making the Case for Aging and Neurodegeneration

Background overview

- Laboratory background
- *Caenorhabditis elegans*

Recent work

- Glycotherapeutics
- Biopharmaceuticals
- Small molecules
- Herbal formulae

Anti-aging medicinal herbs…




Noticeably,

most Chinese herbs are dried products

no matter whatever the reasons are !





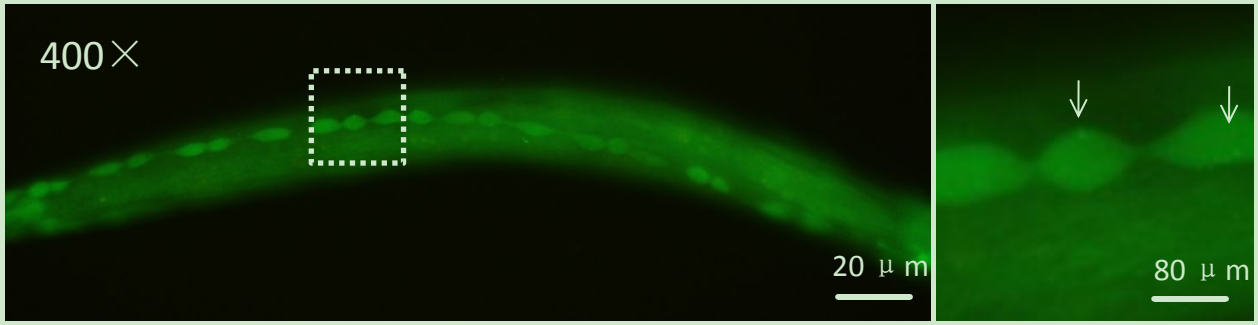

new proteins…

Long-live animals

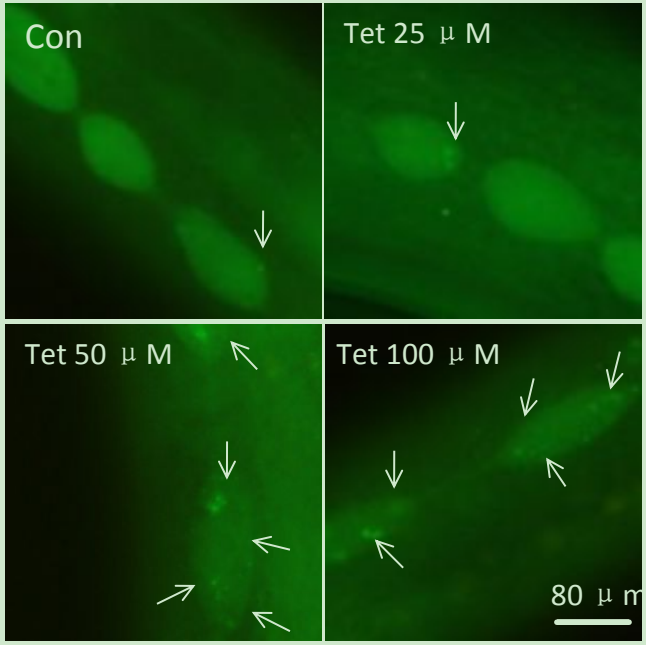
Regenerative animals

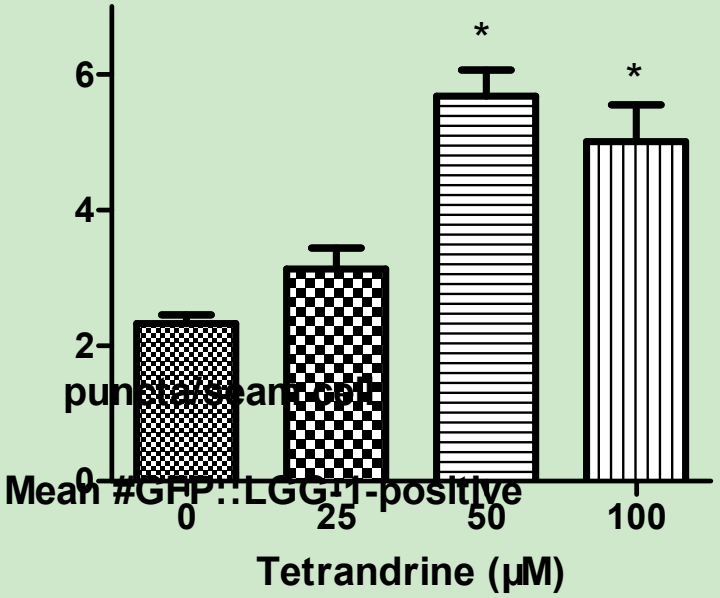
Small molecules: autophagy inducer

汉防己



Tetrandrine
DA2123





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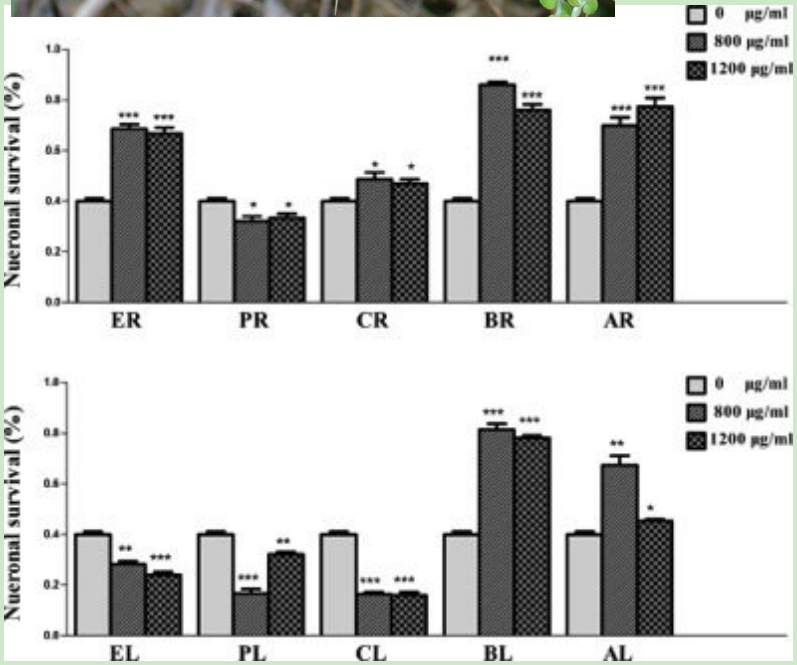
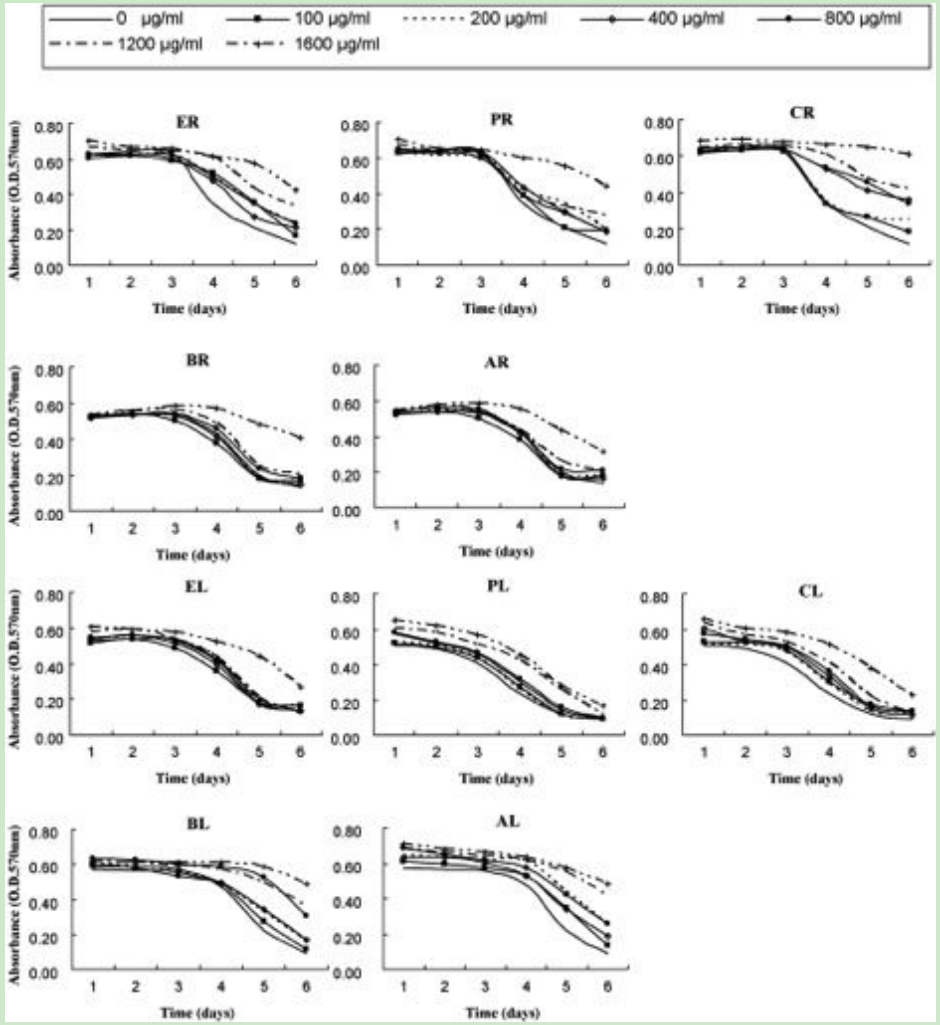
Gong K et al. (2012) *J Biol Chem* 287: 35576–35588.

Damnacanthus officinarum extracts: neuroprotection & lifespan extension in *C. elegans*

恩施巴戟（四川虎刺）





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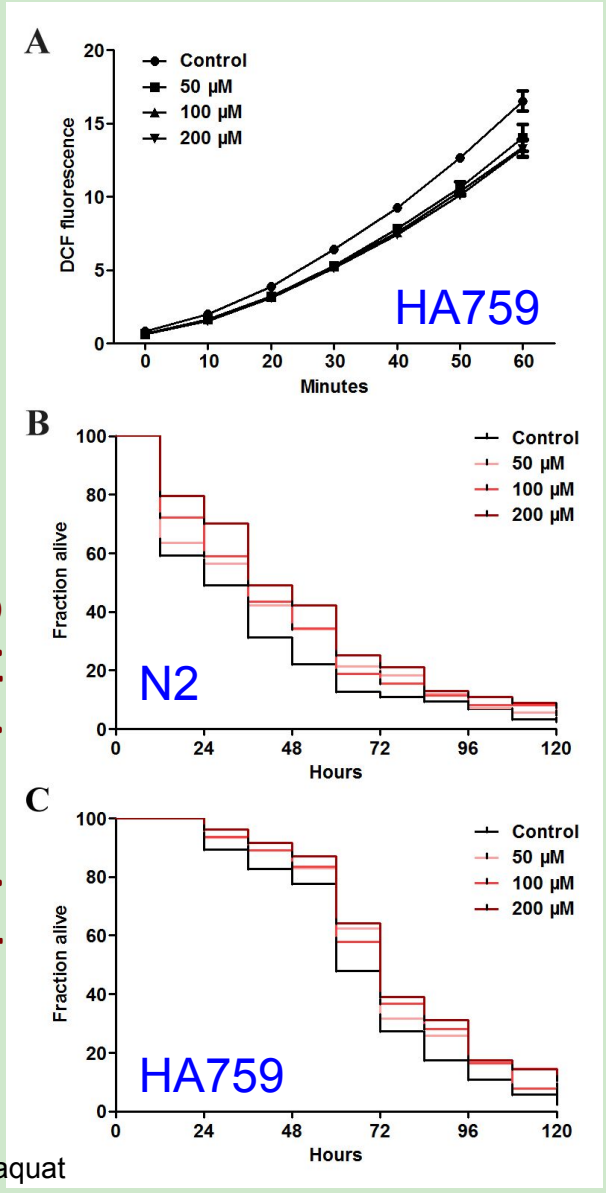
Yang X et al. (2012) *J Ethnopharmacol* 141: 41–47.

Salidroside protects C. elegans neurons from polyQ-mediated toxicity

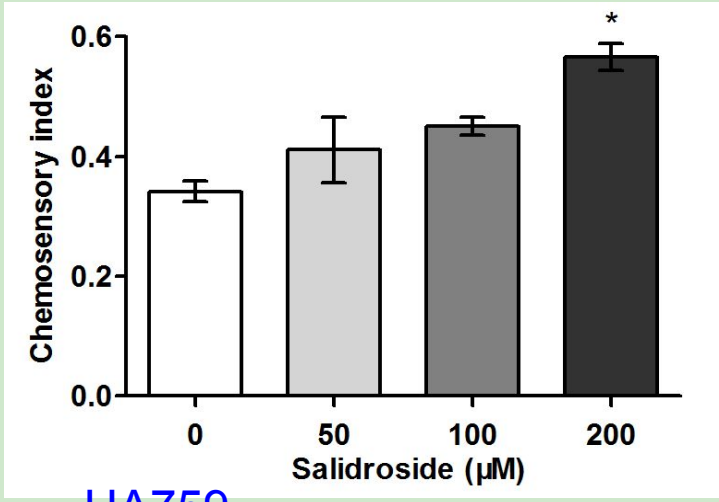
ROS level

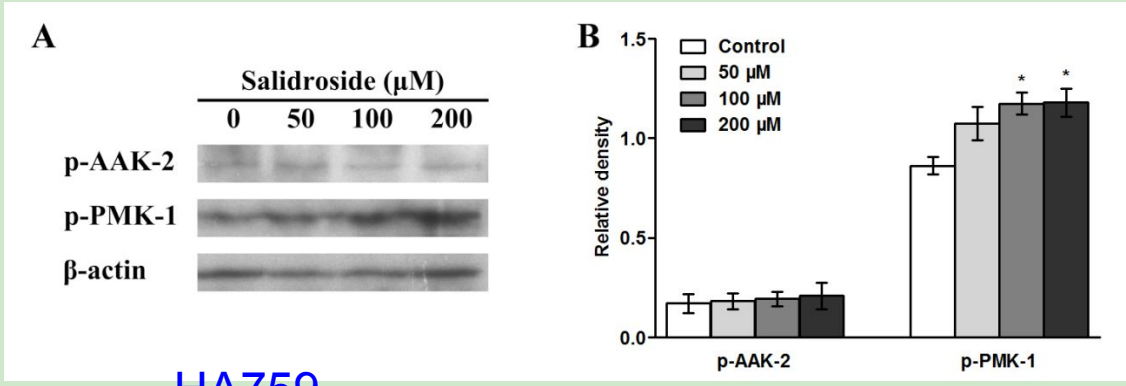
Oxidative survival



paraquat

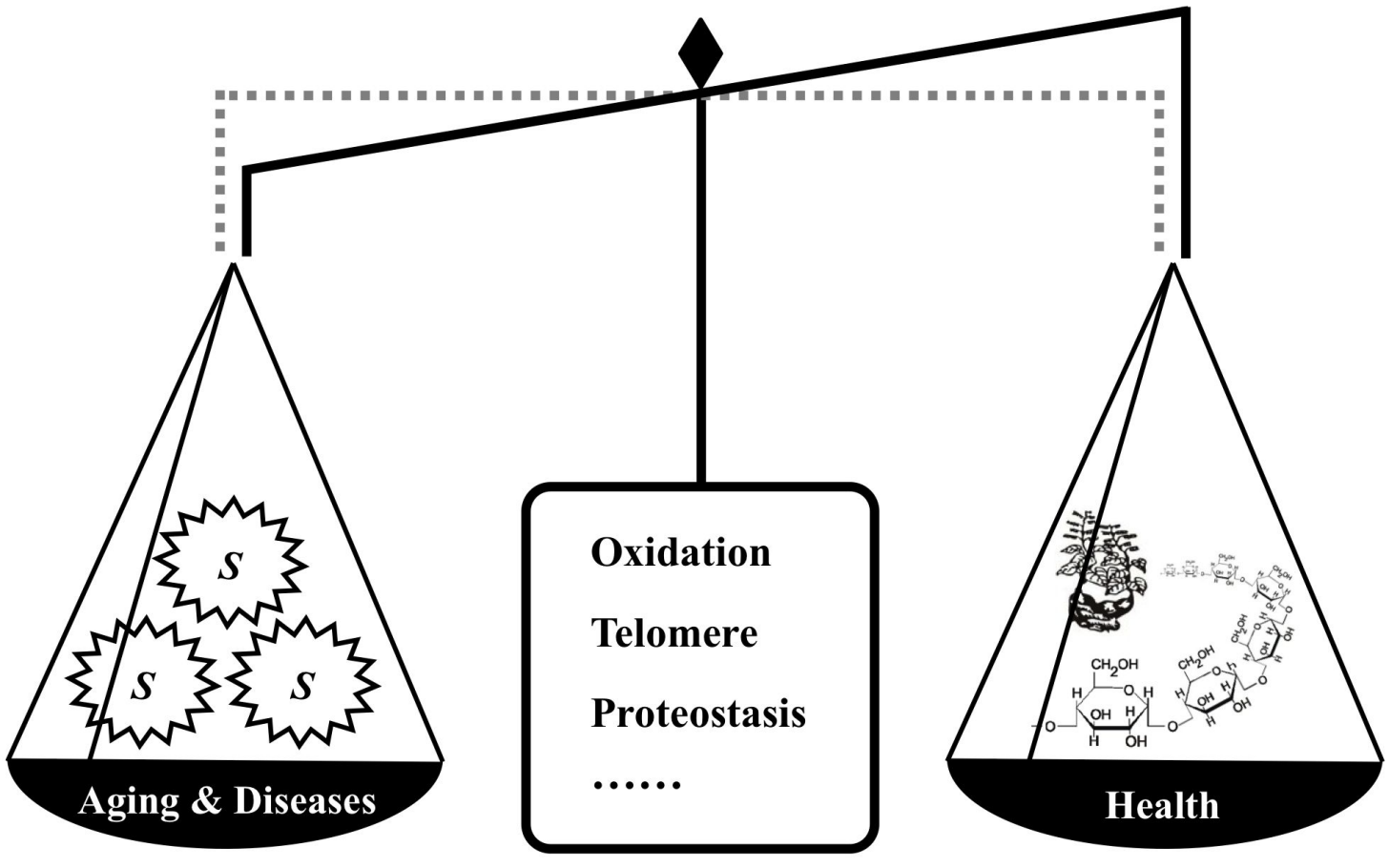
红景天





Xiao L et al. (2014) *Molecules* 19: 7757–7769.

Bioactive polysaccharides: mechanisms of action



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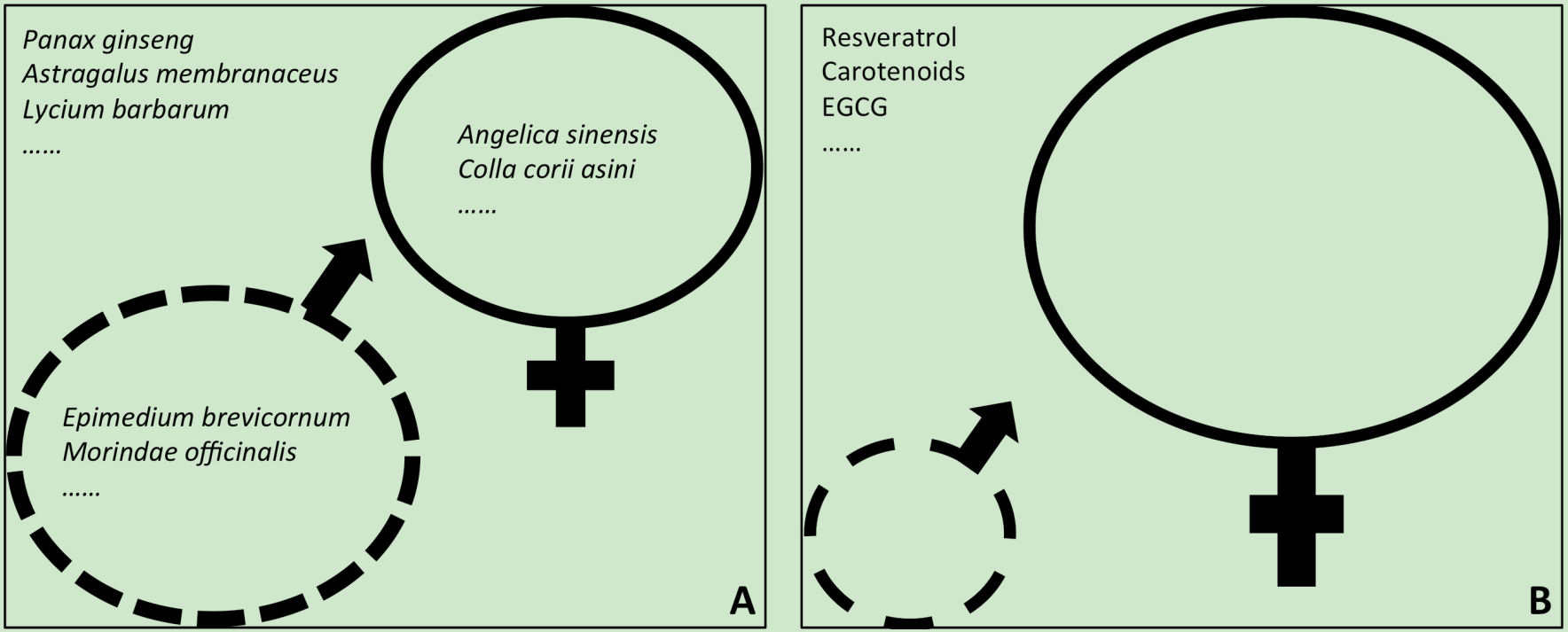
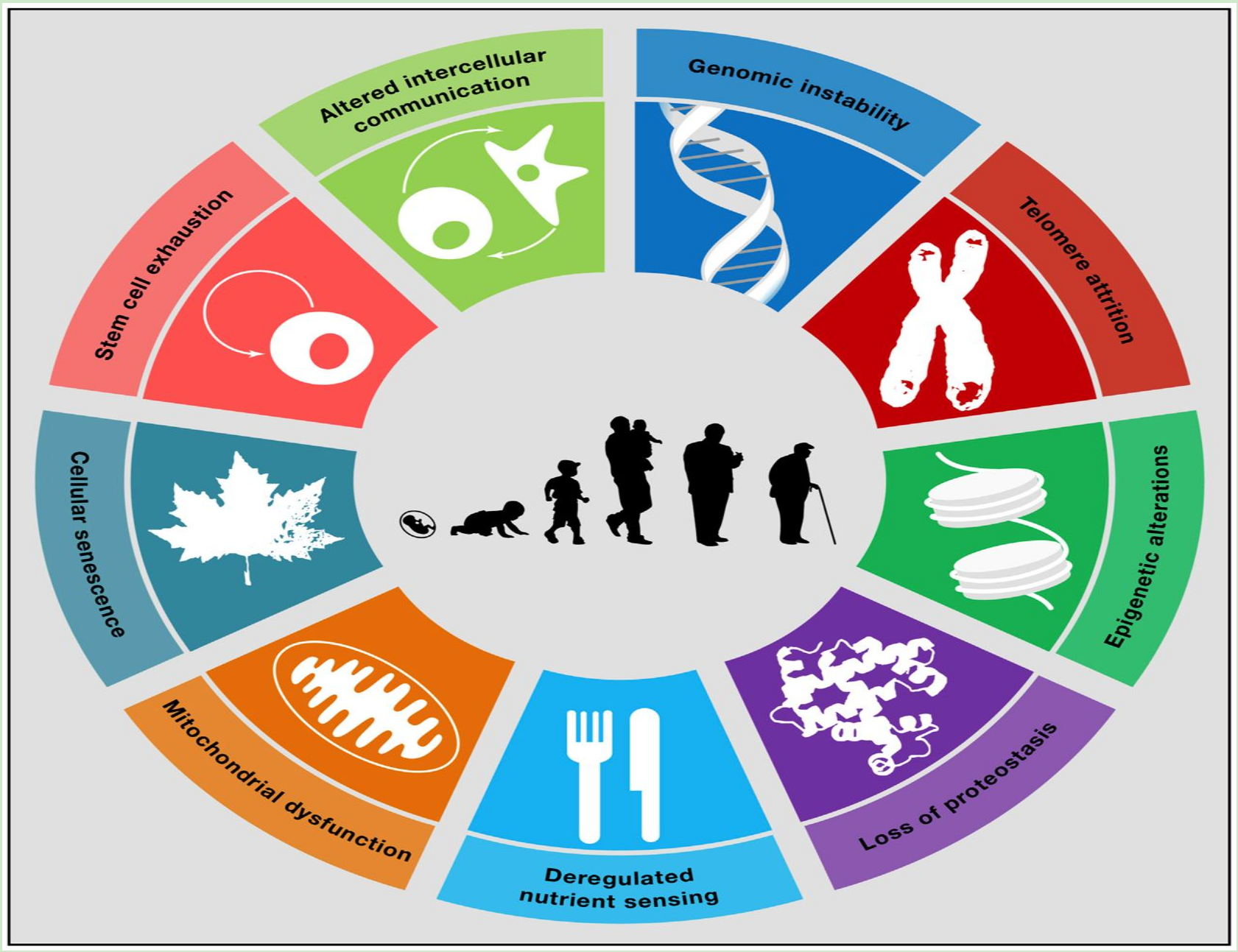
Li H et al. (2014) *Rejuvenation Res* 17: (in press).

Other anti-aging products



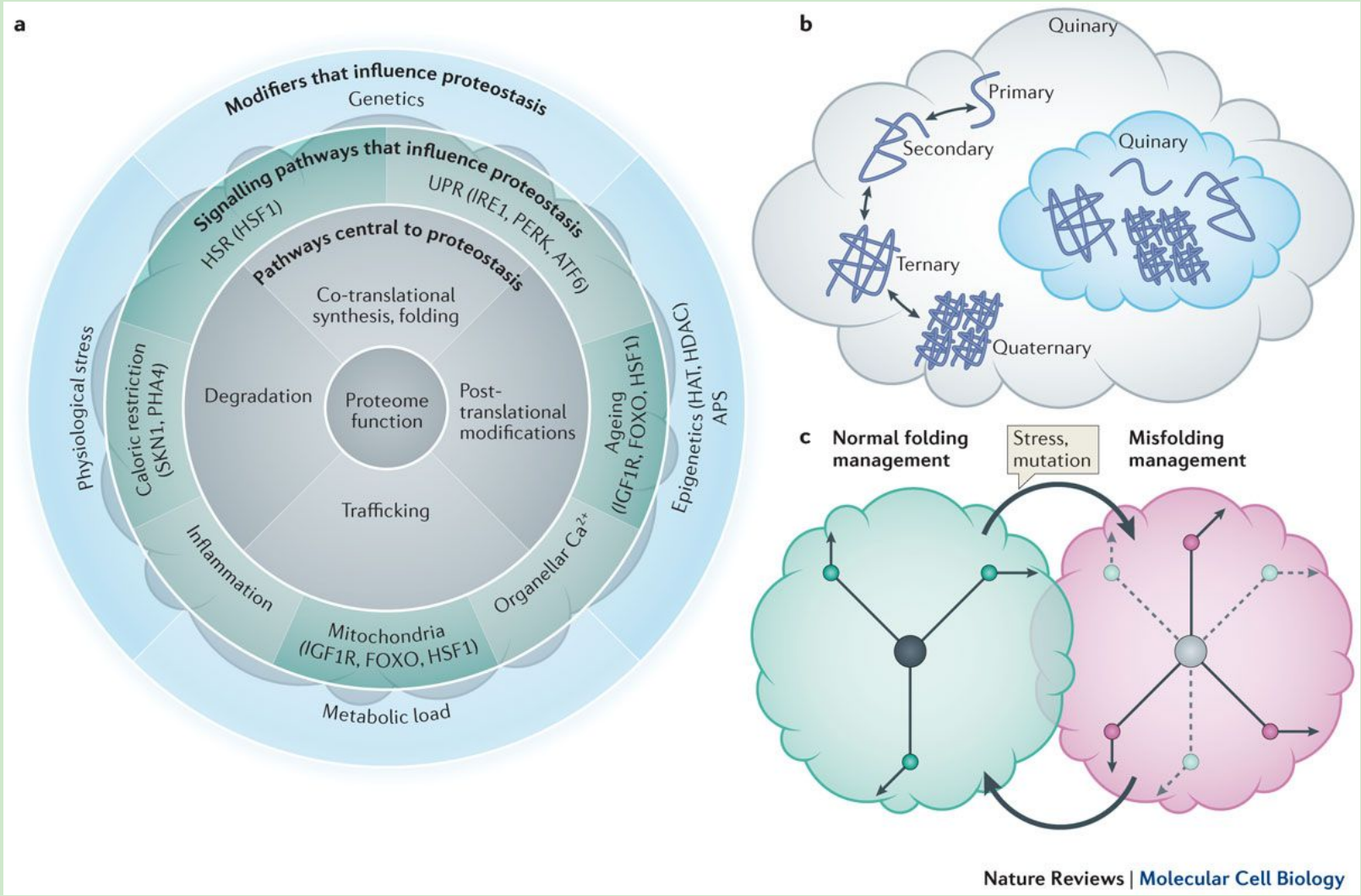
Anti-aging functional beverages sold online in China

Yang F et al. (2014) *Rejuvenation Res* 17: (in press).



López-Otín C et al. (2013) *Cell* 153:1194–217.

Proteostasis network functioning as a cloud

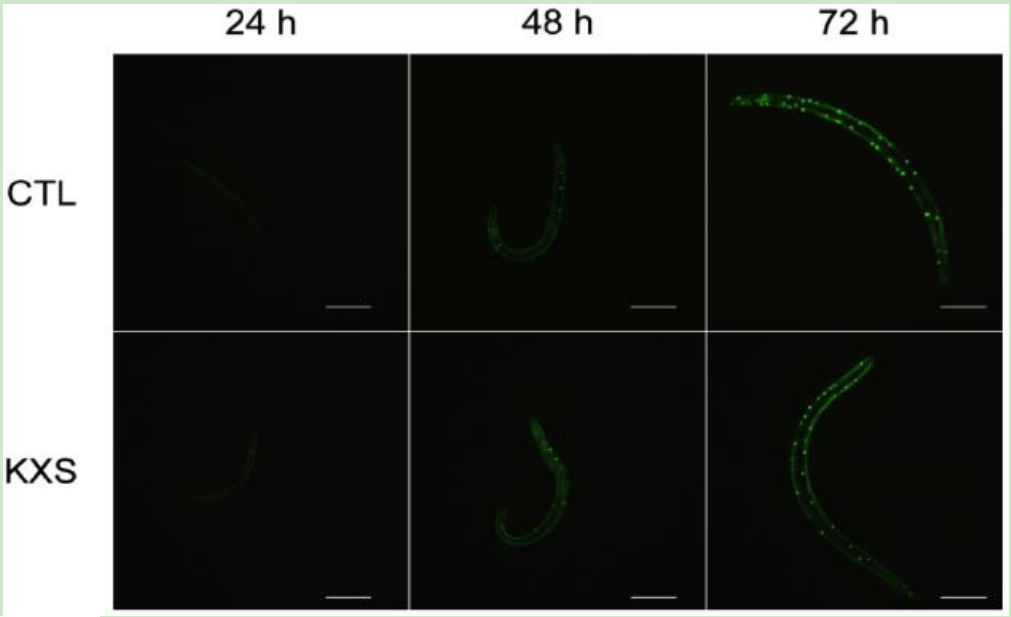


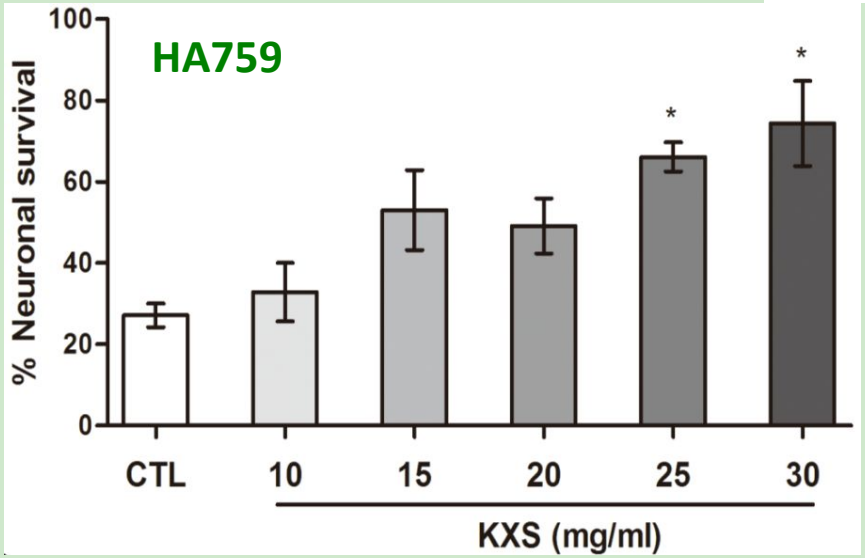
Powers ET & Balch WE (2013) *Nat Rev Mol Cell Biol* 14: 237-248.

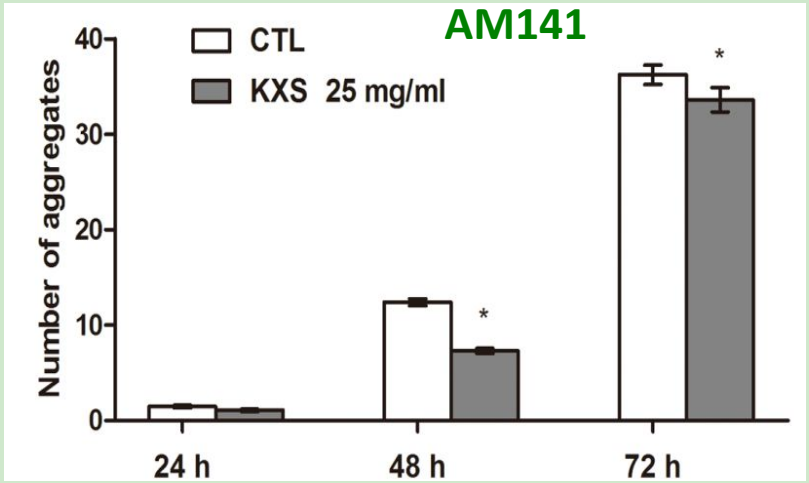
Kai-Xin-San:

Neuronal protection in *C. elegans* HD models

唐菖蒲、远志、人参、茯苓



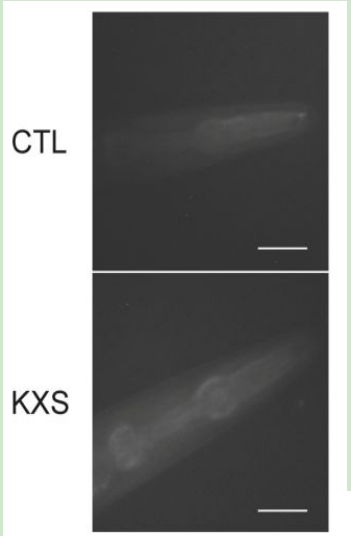


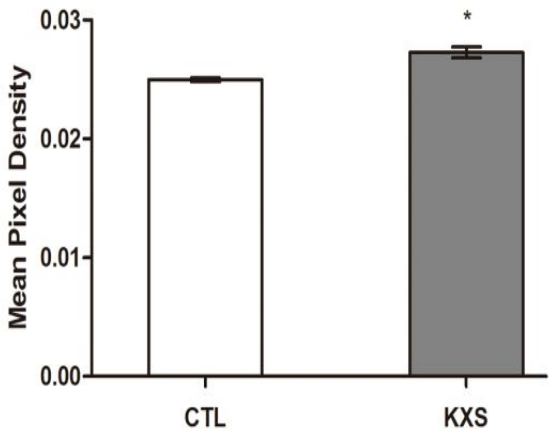


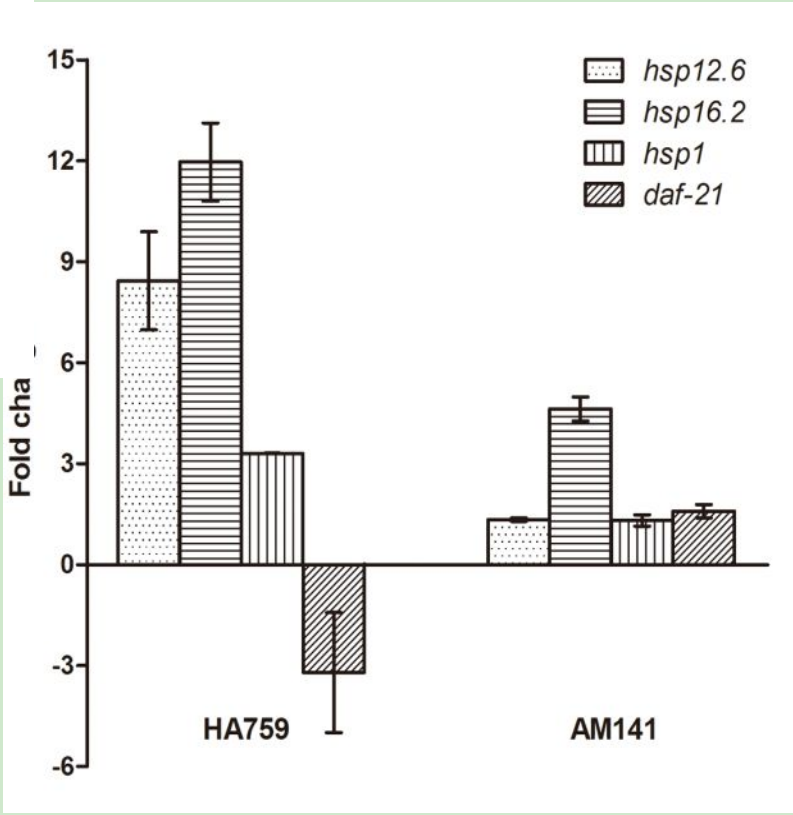
Xaio LY et al. (to be submitted).

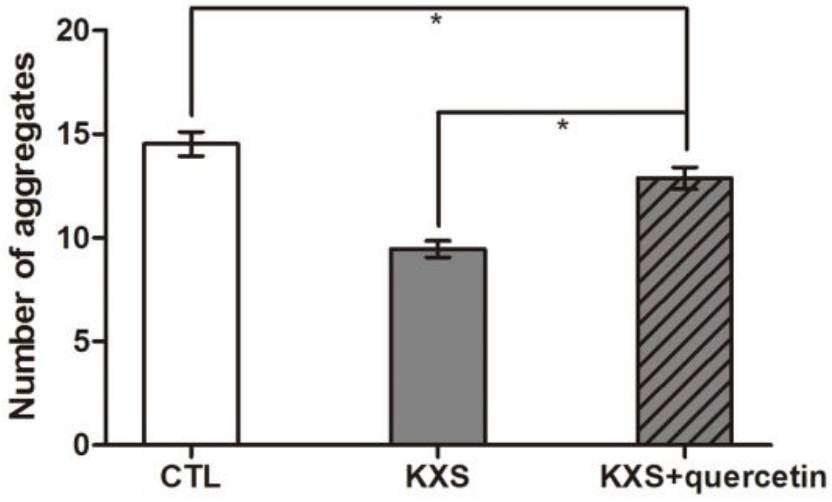
Kai-Xin-San:

Neuronal protection in *C. elegans* HD models









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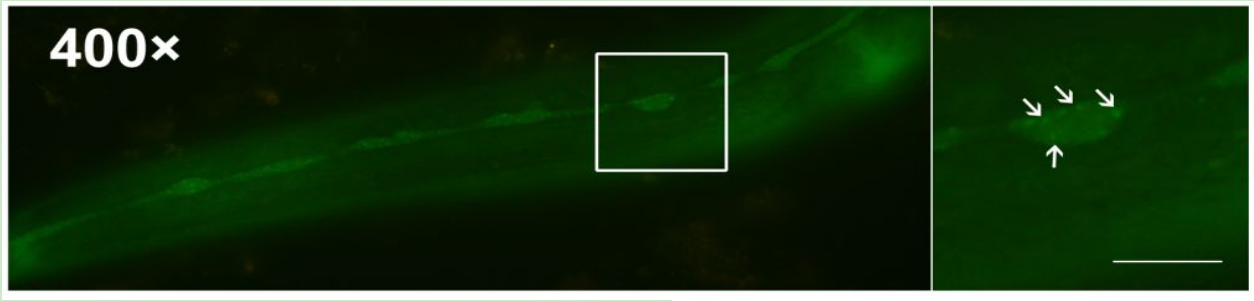
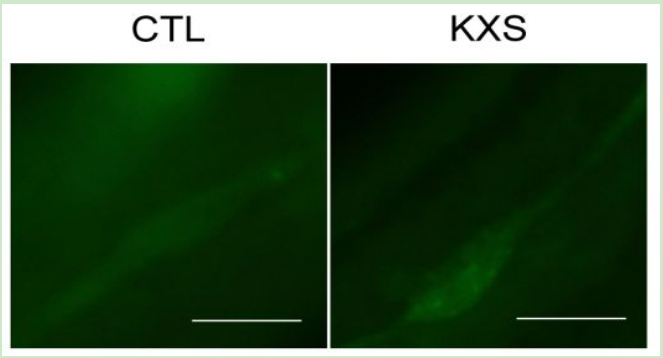
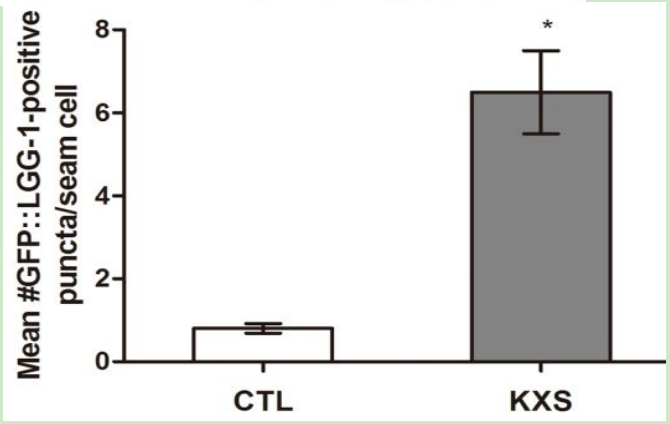
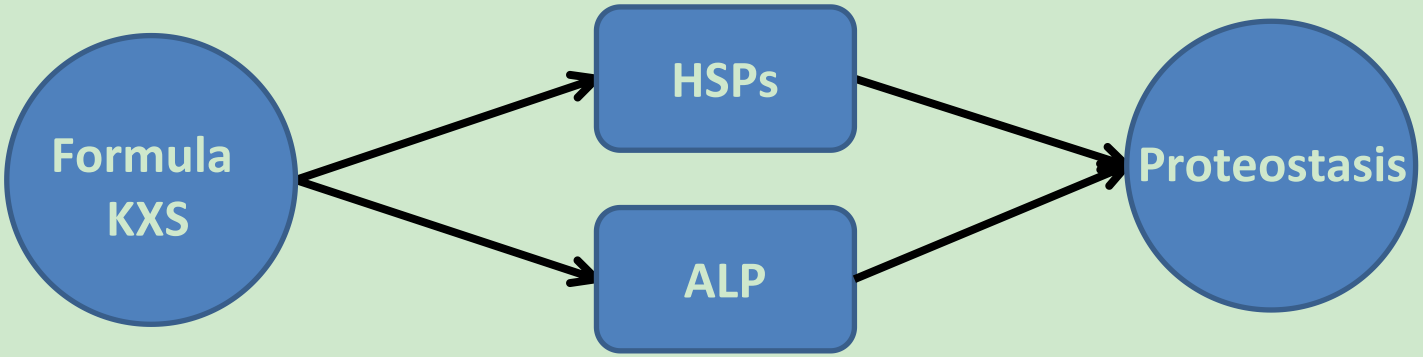
Neuronal protection in *C. elegans* HD models







Increased autophagy



Xaio LY et al. (to be submitted).


早安美丽
Morn Belle
清莹保湿洁面乳
3.5 fl.oz 100ml
早安美丽
Morn Belle
水润滋养保湿乳
早安美丽
Morn Belle
均衡润泽爽肤水


早安美丽
Morn Belle
均衡润泽爽肤水
早安美丽
Morn Belle
清莹保湿洁面乳
3.5 fl.oz 100ml

Acknowledgments