Evidence for homeopathic principles in the basic sciences

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LMHI CONGRESS 2018
5-8 SEPTEMBER CAPE TOWN
Contributing to Sustainable Healthcare

Evidence for homeopathic principles in the basic sciences

1. Introduction
2. Similia
3. Microdose and «potency»
4. Key points

Note: Tables and figures of this presentation are available at:
http://www.paolobellavite.it/news.html

“Art” and “Science” in Medicine

As every field of medicine, homeopathy is characterized by aspects which belong to the “art” of healing and by aspects which are belonging to scientific medicine.

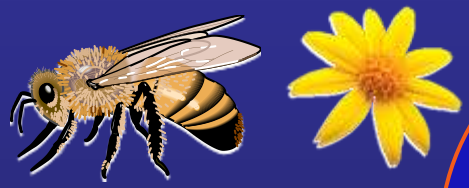
The two “wings” are not in contrast and should be taken into account for a whole evaluation of the medical system.

A rigorous **scientific research** has been carried out in the last 30 years and now we have over 6000 scientific papers in top literature (Pubmed)

SCIENTIFIC INVESTIGATION OF THE HOMEOPATHIC PRINCIPLES

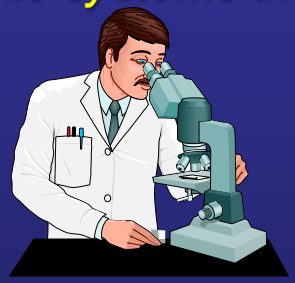
HOW DOES IT WORK?

- Drug **composition**
- Drug **targets** (cells/organs/systems)



Basic sciences

- *In vivo* (animal models)
- *In vitro* (cellular systems)
- Physico-chemistry ("water memory")
- *Dynamic systems theory*



SIMILIA PRINCIPLE

MICRODOSE AND "POTENCY"

TOTALITY OF CURE

DOES IT WORK?

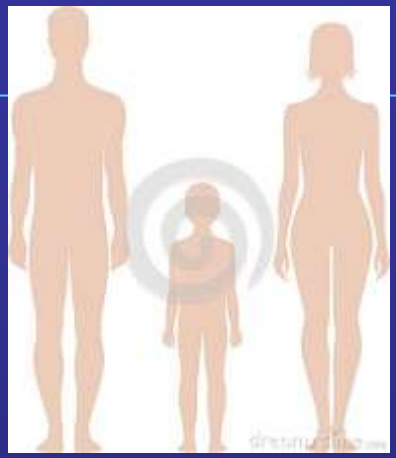
- Adverse effects?
- Is it cost-effective?
- **COULD IT WORK BETTER?**

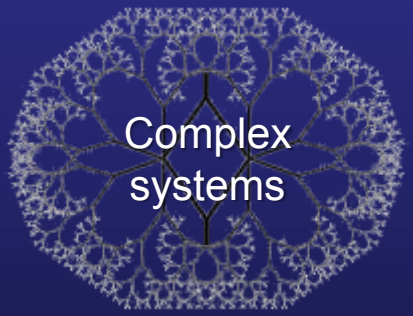
Clinical research

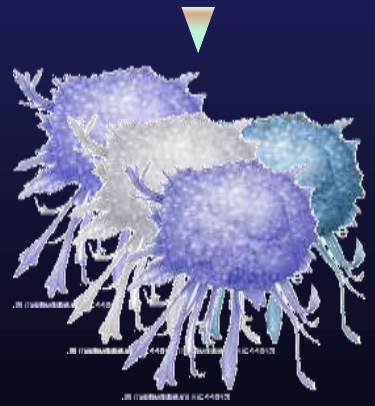
- Provings
- *Observational* studies
- *Prognostic factors* research
- Randomized trials

Laboratory models and homeopathy

- Homeopathy is directed toward the complexity of the whole organism, through mechanisms that are not yet clarified.
- Such action may also appear at the cell level
- Given the holographic fractal nature of all **complex systems**, the fundamental rules of biological responses/pathologies can be unraveled at any level of nature, from the complex organism to the single cells (eg. complete genome in each cell)
- Our working hypothesis (and dr. Benveniste was a pioneer!) is that the biological investigation at the cell level, makes it possible to look at homeopathy in a new and fully rational light





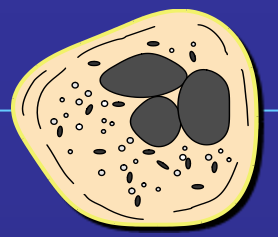


Objects of research:

→ Drug targets (receptors, enzymes, gene expression)

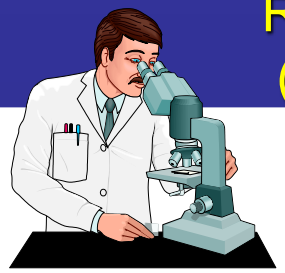
→ Specific mechanisms of action

Basic research in homeopathy
TYPICAL CELLULAR MODELS

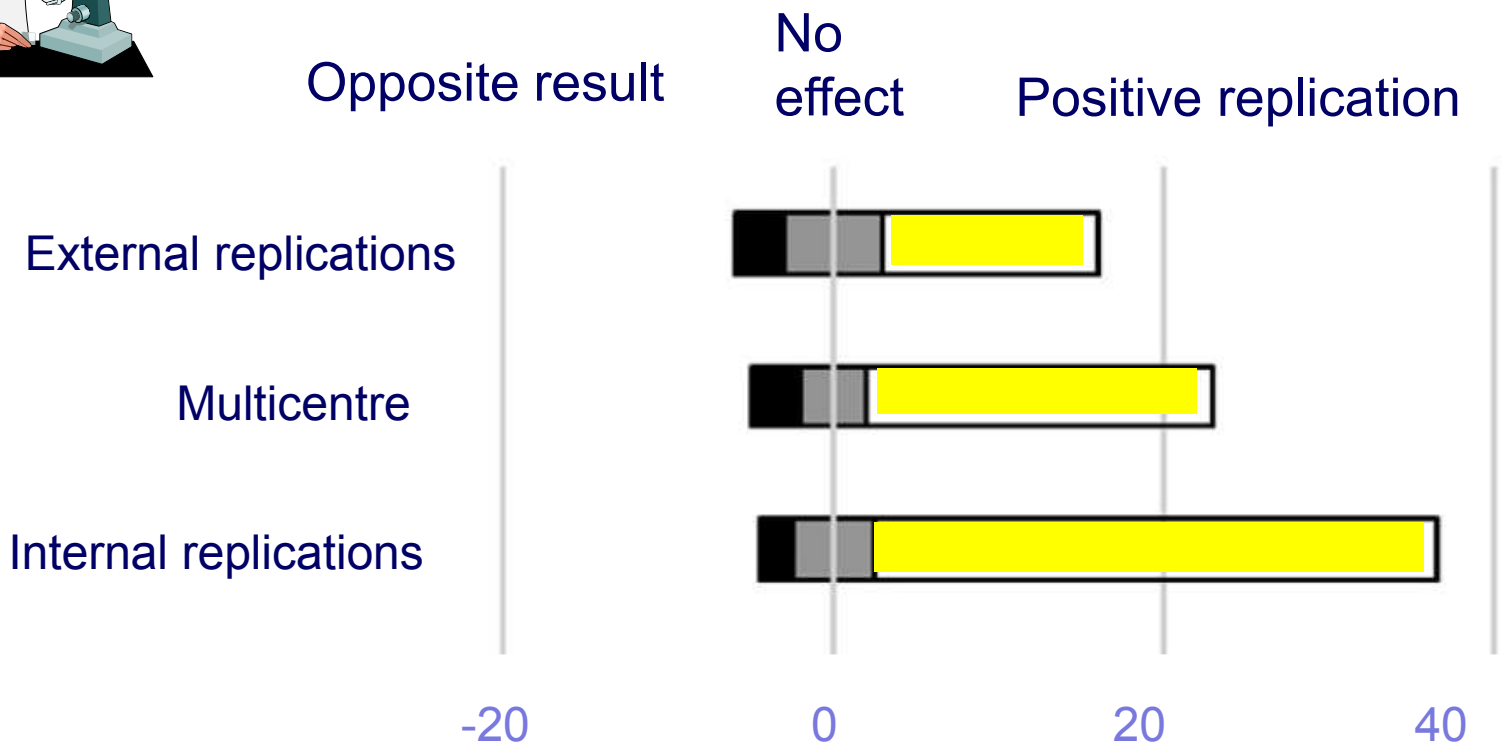


https://www.ncbi.nlm.nih.gov/pubmed/26678723

- Lymphocytes (Colas, Bildet, Bastide, Wagner, Chirila, Fimiani, Seligmann, Toliopulos, Coelho Moreira, Guimarães, Burbano)
- Basophils (Poitevin, Sainte Laudy, Belon, Davenas, Ovelgonne, Hirst, Mannaioni, Ennis, Bellavite, Baumgartner)
- Granulocytes, macrophages (Poitevin, Fletcher, Bellavite)
- Cell lines: Fibroblasts (Boiron, Mansvelt, Fougeray, Valentiner, Saini) Renal cells (Delbancut), Hepatoma (van Wijk, Wiegant), Prostate epitelial (Bigagli) . Neurocytes (Jonas, Bellavite), Macrophages (Bonamin, De Oliveira, Olioso, Marzotto, Siqueira)
- Vegetable cells (Guillemain, Bornoroni, Betti, Sukul, Baumgartner)
- Cancer cells (Jonas, Frenkel, Khuda-Buckhsh, Arora, Saha, Das)



Results of models of basic research *submitted to replication* (total = 98 studies until 2015)



https://www.ncbi.nlm.nih.gov/pubmed/26678723

Replications of fundamental research models in ultra high dilutions 1994 and 2015 e update on a bibliometric study. Peter Christian Endler, Paolo Bellavite, Leoni Bonamin, Tim Jager and Sintia Mazon Homeopathy (2015) 104, 234e245

Some (not all!) players


Jacques Benveniste – F
(Basic research)


Lucietta Betti - I
(Botanical research)


Carla Holandino
- BR (Pharmacology)


Philippe Belon - F
(Basic research)


Louis Rey - F
(Thermoluminescence)


Madeleine Bastide
- F (Immunology)


Christian Endler - A
(Basic research)


Leoni Bonamin – BR
(Basic research)


Vittorio Elia - I
(Chemistry)


A. Khuda Bukhsh
- Ind (Biochemistry)


Nirmal Sukul
- Ind (Basic science)

Thank you Peter!

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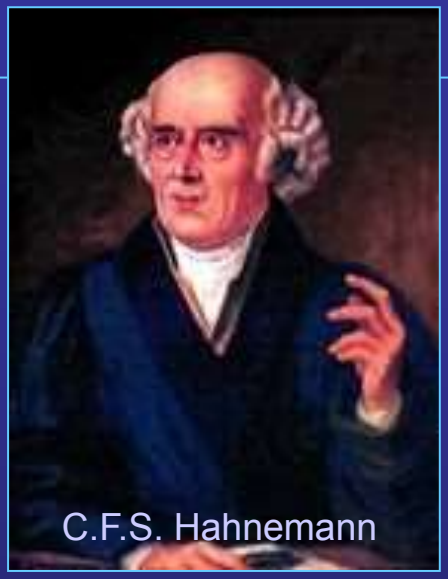
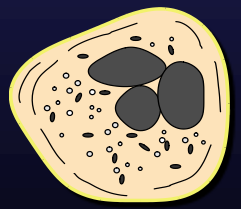

C.F.S. Hahnemann

"The majority of substances have more than one action;
the first is a direct action, which gradually changes into the second,
which I call its indirect secondary action.
The second is generally the opposite of the first"

C.F.S. Hahnemann, 1796



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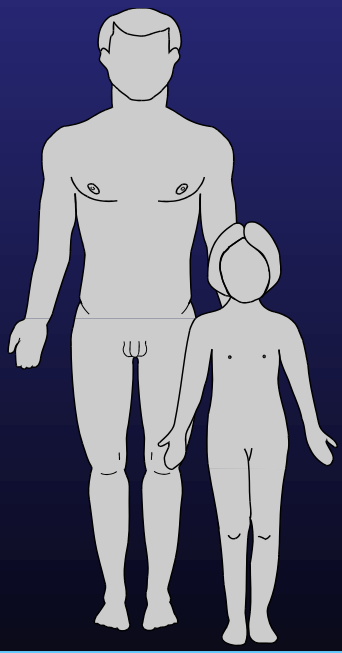
SCIENTIFIC RESEARCH



Janus

Ancient symbol of similitude

ENTRY

PAST

BEGINNING

NEGATIVE

EXIT

FUTURE

ENDING

POSITIVE

Axis (Roman coin)

SCIENTIFIC REEVALUATION OF THE HOMEOPATHIC "SIMILE"

GENERAL HYPOTHESIS:

The "therapeutic similarity" in drug action may be fundamentally based on the widespread phenomenon of inversion of biological effects dependent on the following factors:

1. the dose of the drug,
   and/or
2. the pathophysiological state of the target

Main references in: Bellavite et al .: ECAM Journal 2007 (available online https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1876612/pdf/nel117.pdf)

Experimental studies on APIS M. (1975-2015)

Madeleine Bastide (1935-2007)

1975 ➢Homeopahtic dilutions (7C-9C) of bee venom (*Apis mellifica* and *Apium virus*, have a **protective and curative effect on X-ray induced erythema in albino guinea pig** (Bastide1975, Bildet1989, 1990)

1988 ➢High dilutions of *Apis mellifica* **inhibit basophil degranulation** (histamine release) (Poitevin et al., 1988)

1993 ➢Our group studied the effects of homeopathic preparations of *Apis mellifica* (and *Histamin)* on rat paw edema induced by the injection of inflammatory doses of histamine. High dilutions of up to 30D had a **small but significant inhibitory effect on the development of edema** (Conforti et al.,1993).

2004 ➢We described a **small inhibiting effect of *Apis mellifica*** (4 D, oral drops) in the carrageenan-induced edema in rats .

2014 ➢Bigagli and coworkers (2014) showed with microarray techniques that *Apis mellifica* TM modifies **expression of hundreds of genes** in human prostate epithelial cells; dynamized dilutions (3C, 5C and 7C) still exert significant effects on genes involved in inflammation and oxidative stress

Bernard Poitevin

FIRST «homeopathic» paper in top Journal

Br. J. clin. Pharmac. (1988), **25**, 439–444

In vitro immunological degranulation of human basophils is modulated by Lung histamine and Apis mellifica

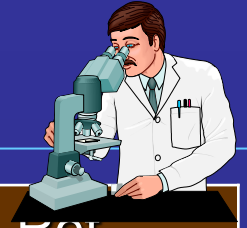
B. POITEVIN, E. DAVENAS & J. BENVENISTE
INSERM U 200, Université Paris-Sud, 32 rue des Carnets, 92140 Clamart, France

1 The effect of high dilutions of two homeopathic drugs Lung histamine (Lung his) and Apis mellifica (Apis mel) used for the treatment of allergic diseases has been assessed on *in vitro* human basophil degranulation. Experiments were conducted blind.

2 Basophil degranulation induced by 1.66×10^{-9} M anti-IgE antibody was significantly inhibited in the presence of 5 Lung his (5th centesimal dilution of Lung his) and 15 Lung his (15th centesimal dilution of Lung his) by 28.8% and 28.6% respectively and by 65.8% in the presence of 9 Apis mel (9th centesimal dilution of Apis mel). Basophil degranulation induced by 1.66×10^{-16} to 1.66×10^{-18} M anti-IgE antibody was also inhibited by high dilutions of Lung his and Apis mel with an inhibition of nearly 100% with 18 Lung his (18th centesimal dilution of Lung his) and 10 Apis mel (10th centesimal dilution of Apis mel). An alternance of inhibition, inactivity and stimulation was observed when basophils were incubated in the presence of serial dilutions of Lung his and Apis mel.

3 The investigation of the clinical efficacy of high dilutions of Lung his and Apis mel should be envisaged in allergic diseases in parallel with *in vitro* and *ex vivo* biological assays.

EXAMPLES OF INVERSE EFFECTS IN LABORATORY SYSTEMS ("conventional" dilutions)



System	Agent	First effect	Inverse effect	Ref.
Yeast	Heavy Metals	**Block growth**	**Low doses increase growth**	Schulz 1988 Martius 1923 Stebbing 1982
Fibroblasts Wheat	Arsenite Cadmium	**Cell toxicity**	**Low doses protect from toxicity or stimulate DNA synthesis**	vanWijk 1995 vanWijk 1997 V.Zglinicki 1992 Betti 1997-2000
Neurons	Naloxone	**Antagonizes morphine**	**Low doses enhance the effect of morphine**	Crain 1995
Neurons	β-amyloid	**Toxic for mature cells**	**Promotes growth of young cells**	Yankner 1990 See also Puzzo 2018
Epithelial cells Tumor cells	Oxidants	**Short-term/high doses decrease viability**	**Long-term/low doses increase viability**	Da Silva 1996 Jenkins 1995
Macrophages	Interfererons Endotoxins	**Activation of resting cells**	**Inhibition of pre-activated cells**	Adams 1992
Platelets	Diclofenac	**Inhibit functions**	**Stimulate platelet adhesion**	Andrioli-Bellavite 1997
Leukocytes	Bacterial peptides	**Stimulate adherence**	**Low doses inhibit adherence**	Bellavite 1993-1997

http://www.paolobellavite.it/files/246_2011SeminarioRomaRey_58wwpoeh.pdf

Inverse effects of Amyloid-β according to the dose

https://www.ncbi.nlm.nih.gov/pubmed/19118188

The Journal of Neuroscience, December 31, 2008 • 28(53):14537–14545 • 14537

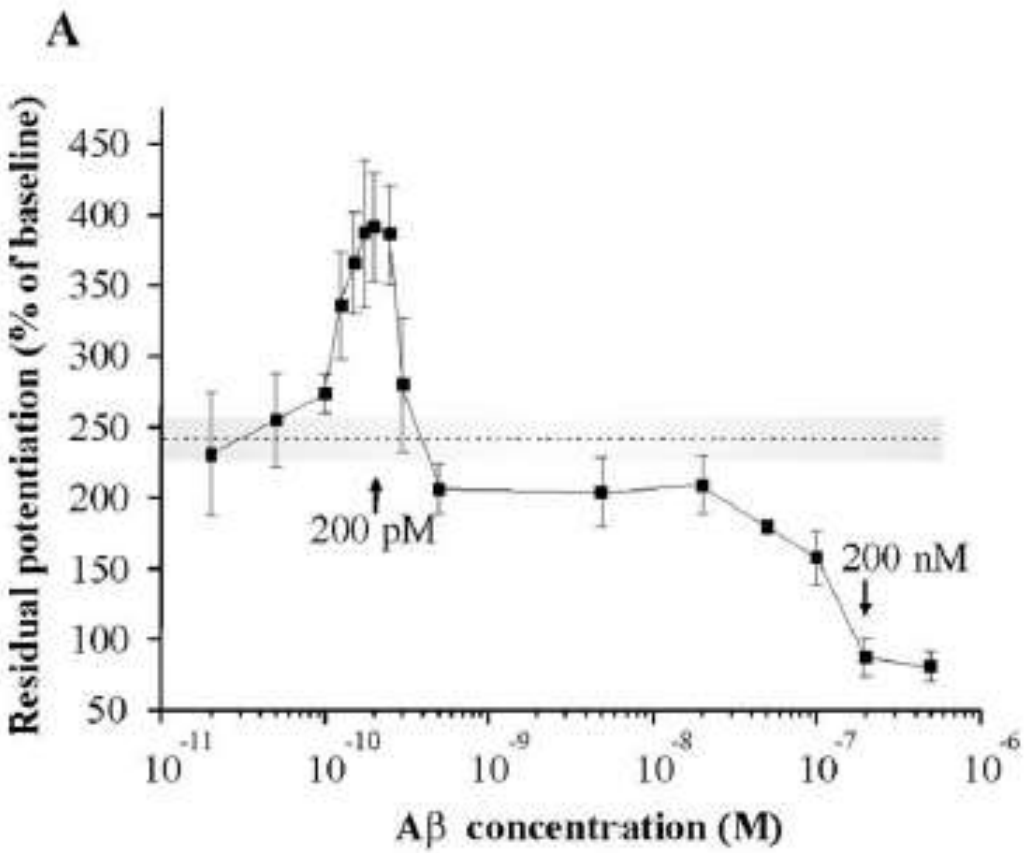
Development/Plasticity/Repair

Picomolar Amyloid-β Positively Modulates Syn Plasticity and Memory in Hippocampus

Daniela Puzzo,[1,2] Lucia Privitera,[1,2] Elena Leznik,[1] Mauro Fà,[1] Agnieszka Staniszewski,[1] Agos Ottavio Arancio[1]
[1]Department of Pathology, Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University
[2]Department of Physiological Sciences, University of Catania, Catania 95125, Italy

Amyloid-β (Aβ) peptides are produced in high amounts during Alzheimer's disease, causing synaptic a ever, they are also released in lower amounts in normal brains throughout life during synaptic activity. H concentrations of a preparation containing both $Aβ_{42}$ monomers and oligomers cause a marked incre potentiation, whereas high nanomolar concentrations lead to the well established reduction of potentiatio produce a pronounced enhancement of both reference and contextual fear memory. The mechanism of ac synaptic plasticity and memory involves α7-containing nicotinic acetylcholine receptors. These findings effects in which low concentrations play a novel positive, modulatory role on neurotransmission and me tions play the well known detrimental effect culminating in dementia.

Key words: amyloid-β; synaptic plasticity; memory; hippocampus; α-7 nicotinic receptors; Alzheimer's dise



THE "SIMILE" IN THE LIFE: EXAMPLES OF "OPPOSITE" or "INVERSE" EFFECTS (Homeopathic dilutions)

Ref: https://www.ncbi.nlm.nih.gov/pubmed/17549232

System	Agent	"Conventional" effect	"Homeopathic" effect	Ref.
Rat, Guinea pig	Histamine Lung Histamine Apis mell.	Pro-inflammatory agent	Histamine (30x), Lung histamine (18c) and Apis mellifica (7c/10c) reduce inflammation symptoms	Bastide 1975,Poitevin 1988, Bildet 1990 Conforti 1993
Rat, Mouse	Arsenic	Whole body and liver toxicity	Ars. high dilutions (7c-30c) protect from intoxication	Lapp 1955; Wurmser 1955; Cazin1987-1991; Banerjee,P, Khuda-Bukhsh 1998-2000
Rat	Nux vomica	Neurohinibition (strychnine)	Reduces alchool-indced sleeping time	Sukul et al., 1999
Rat	Acetylsalycilic acid	Antithrombotic	Acetylsalycilic acid (5c-15c) has pro-thrombotic effects	Beulogne-Malfatti,Doutreme-puich , Eizayag et al. 1998-2012
Rat	Phosphorus	Hepatotoxicity	Phosphorus high dilutions (30x) protects from toxic hepatitis	Bildet 1984, Guillemain 1987 Palmerini 1993
Tadpoles	Thyroxine	Increases the rate of metamorposis	Thyroxine high dilutions (up to 30x) inhibit metamorphosis	Endler 1990-2014, Lingg 2008, Weber 2008, Guedes 2011, Harrer 2013
Rat, Mouse	Gelsemium s.	Toxic and convulsivant	Anxiolytic effect (2c-30c) of Gelsemium s.	Magnani 2010, Venard 2011, Bellavite 2012
Wheat	Arsenic	Cell toxicity	Ars. high dilutions (45x) stimulate vitality	Betti et al. 1997-2014

PARADOXICAL EFFECTS OF ASPIRIN (1990-2013)

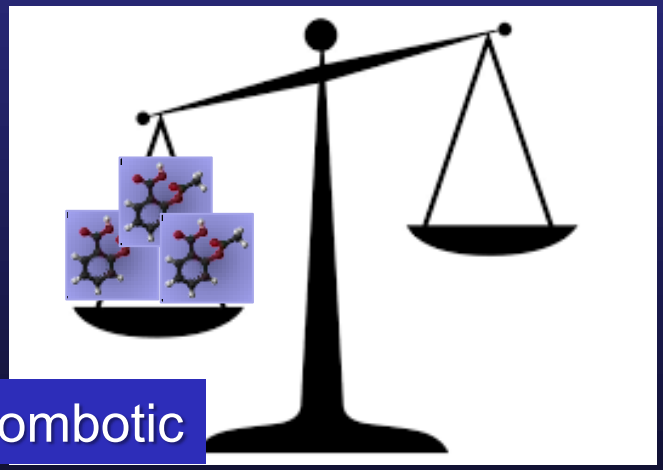
Dr Christian Doutremepuich

Dr Francisco Eizayaga

and Aguejouf,O.; Belougne-Malfatti,E.; Doutremepuich,F.; Belon,P.; Desplat, V;

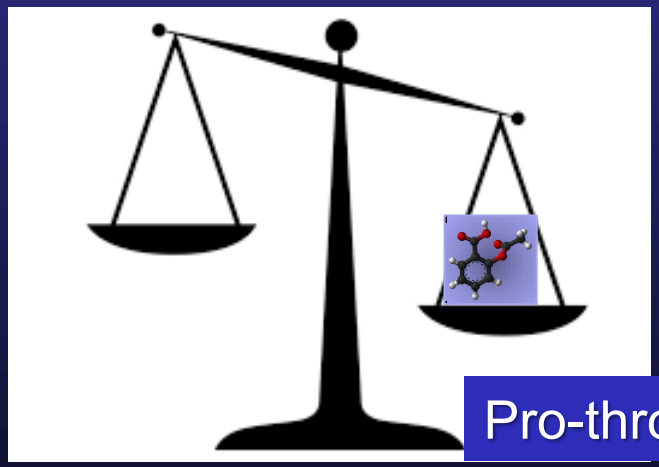
Ref: https://www.ncbi.nlm.nih.gov/pubmed/22292117

High dose (500 mg)
Low dose (50-100 mg)



Anti-thrombotic

«Rebound» effects and
High dilutions (9-15-30CH)



Pro-thrombotic

(Pro-haemorragic) → Adverse effect

«Homeopathic» use? ← (Anti-haemorragic)

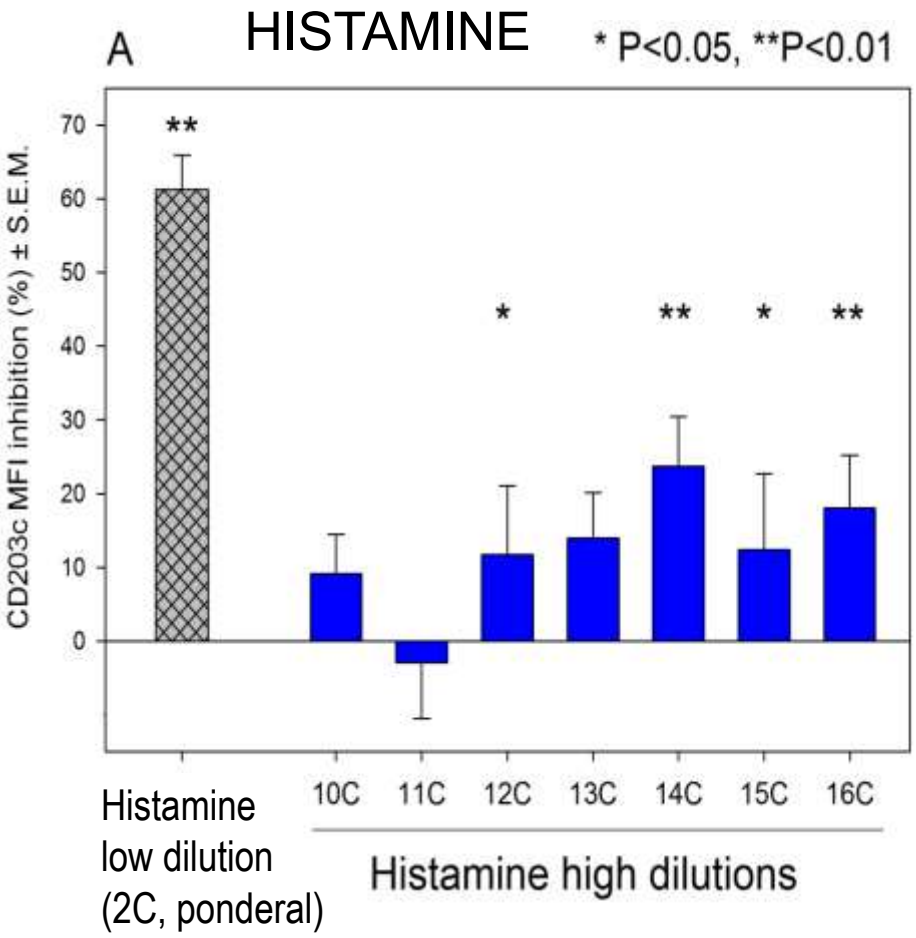
IMPORTANT NOTE

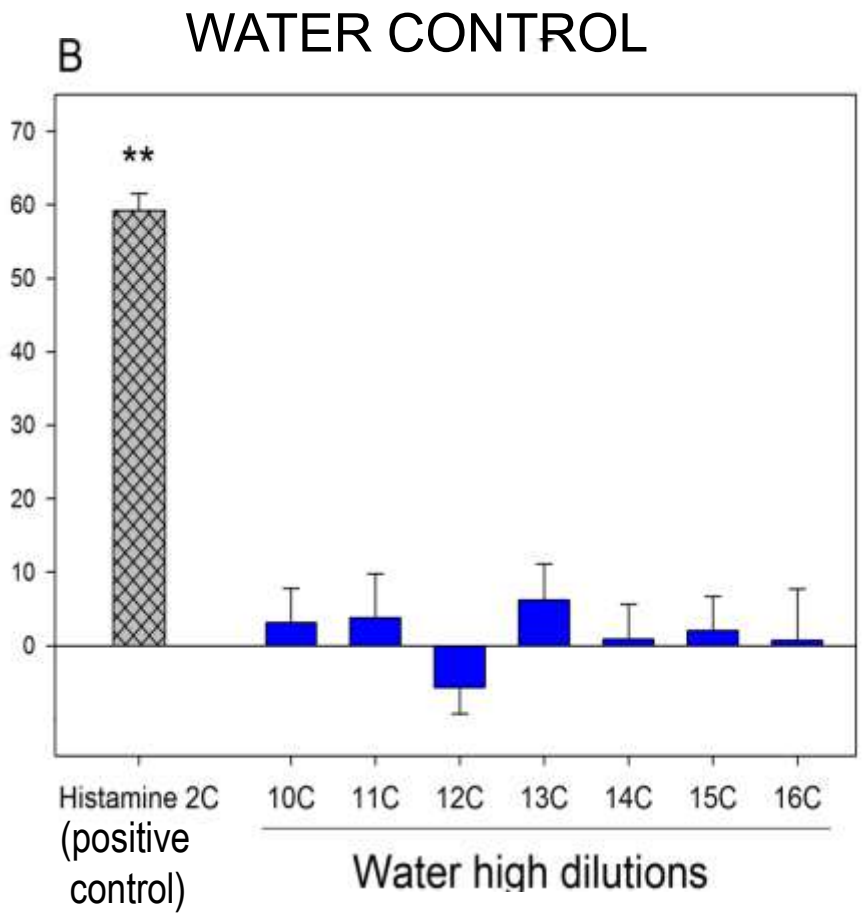
The inversion of biological effects dependent on the dose of the drug ("hormesis")
has been confirmed in a number of well-designed model systems, but is NOT a general rule for homeopathy.

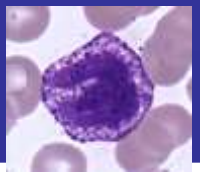
In fact, high homeopathic dilutions (extremely low doses, or «no doses») often act in the same direction of low dilutions (ponderal doses)

EFFECTS OF HISTAMINE AND ON HUMAN BASOPHILS

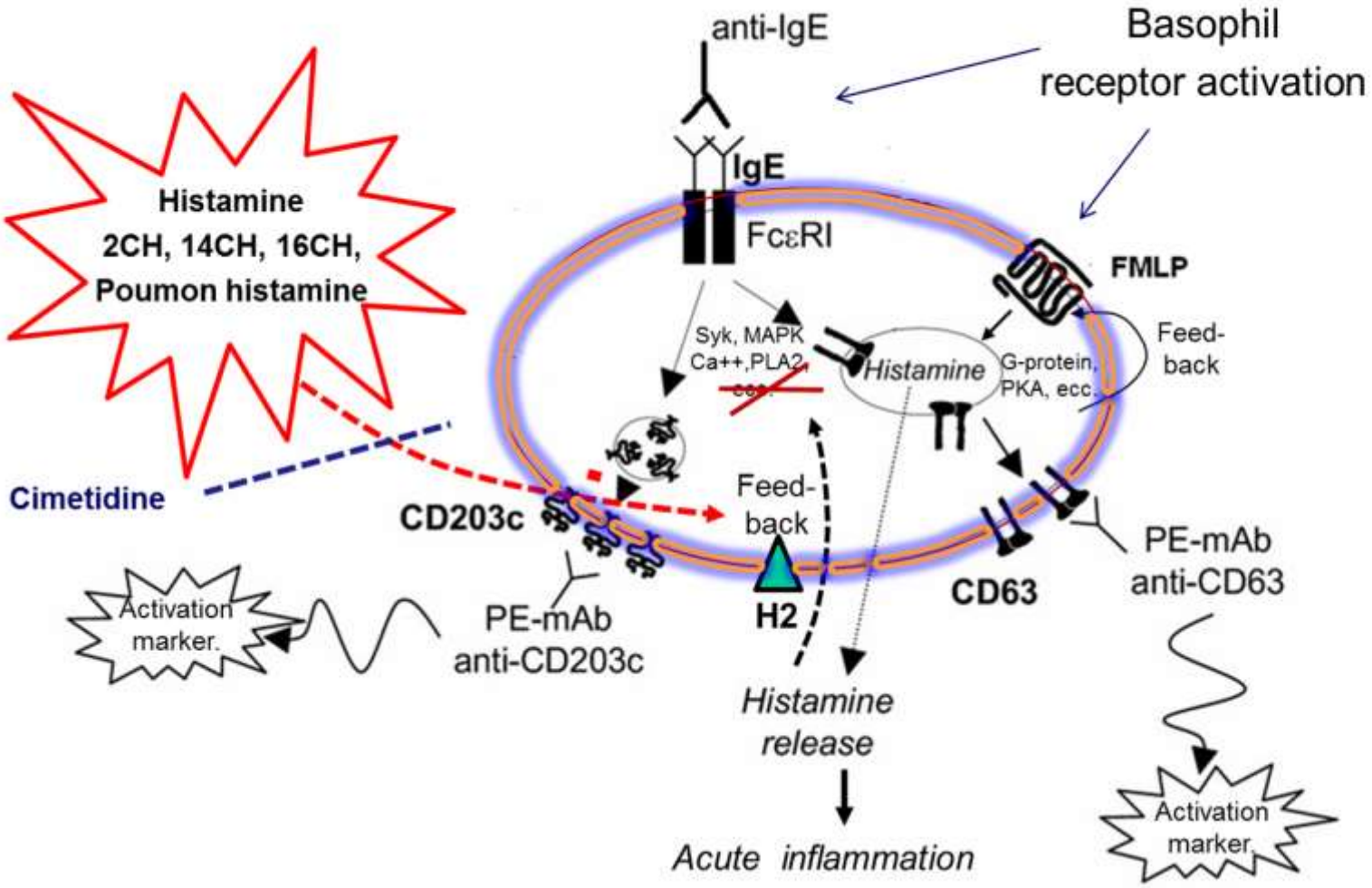
Chirumbolo , Bellavite et al., Inflammation Research 2009







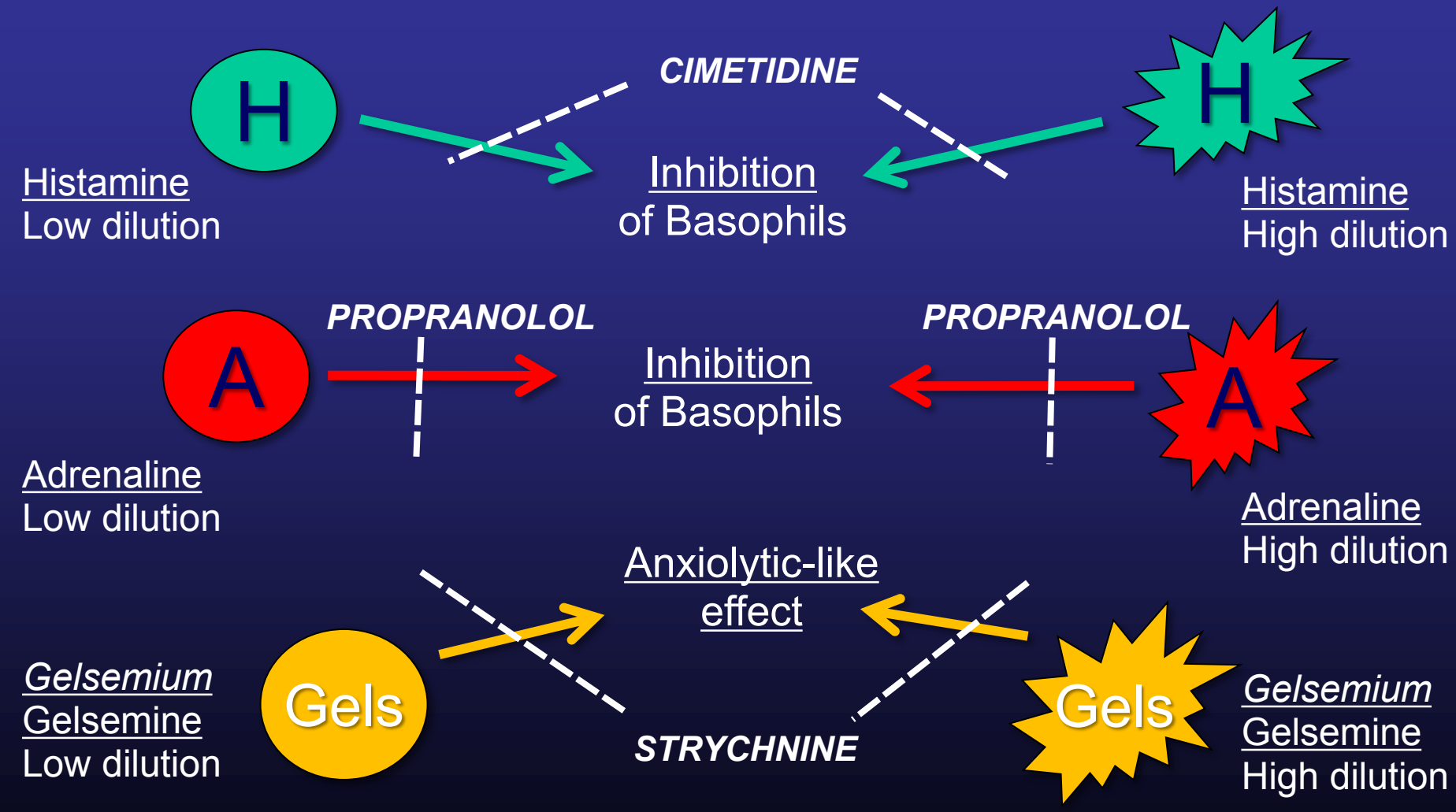
MODEL OF THE HISTAMINE ACTION ON BASOPHILS AND MAST CELLS (Belon, Mannaioni et al.)



Action of homeodrugs at receptor level

LOW DILUTIONS (e.g. 2CH-5CH)

HIGH DILUTIONS (e.g. 9CH-30CH)



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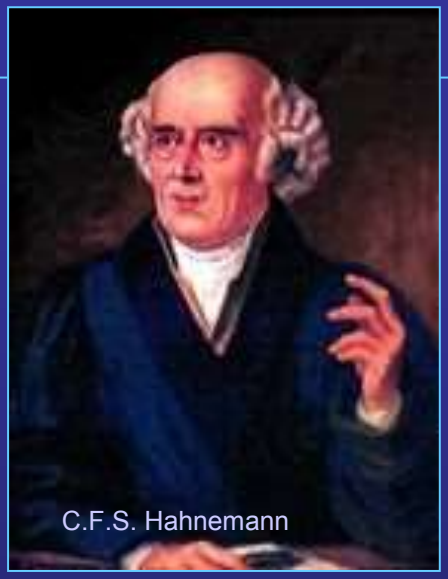
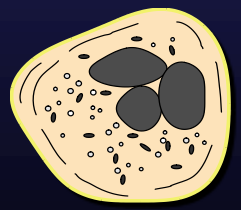


"A medicine whose selection has been accurately homoeopathic must be all the more salutary the more its dose is reduced to the degree of minuteness appropriate for a gentle remedial effect..."

C.F.S. Hahnemann, 1810
Organon, par. 277



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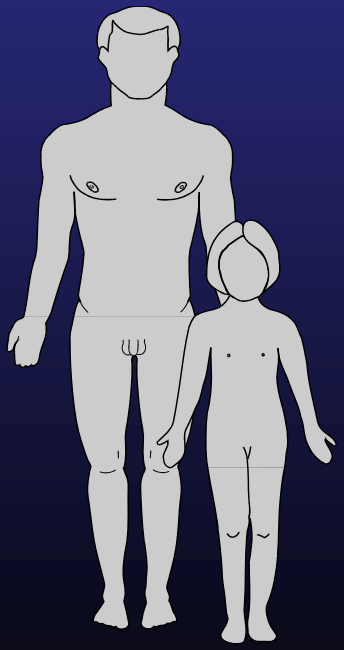
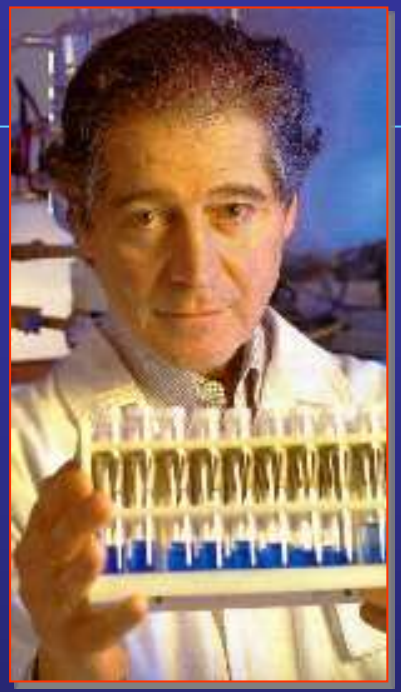
SCIENTIFIC RESEARCH





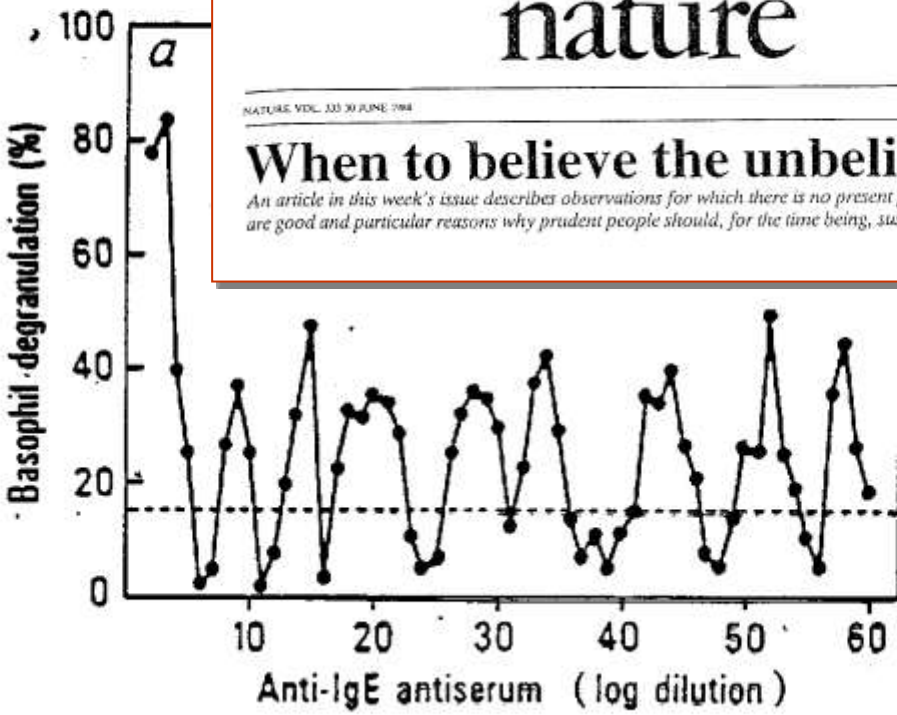
Jacques Benveniste
(1935 – 2004)

The famous and controversial paper of «Water memory»

Davenas, E., Benveniste, J., et al. *Nature* 333: 816-818, 1988.

Human basophil degranulation triggered by very dilute antiserum against IgE

E. Davenas, F. Beauvais, J. Ar
P. Fortner‡, P. Belon, J. Sainte-



nature

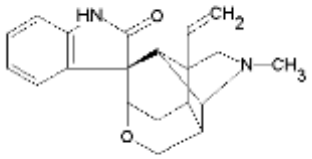
When to believe the unbelievable

An article in this week's issue describes observations for which there is no present physical basis. There are good and particular reasons why prudent people should, for the time being, suspend judgement.

EXAMPLES OF HIGH DILUTION EFFECTS "*IN VITRO*"

System	Agent	Dilution	Effect	Ref.
Human basophils	Apis, Histamine	12C-16C $10^{-24} \rightarrow 10^{-32}$	Inhibition of activation markers	Poitevin 1988, Belon 1999-2009 (and Verona Group)
Human basophils	Adrenaline	12C-16C $10^{-24} \rightarrow 10^{-32}$	Inhibition of activation markers	Mannaioni et al. 2010
Cicken embrio	Bursin	15 C (10^{-27}g)	Immunomodulatory and endocrine activity	Bastide, Youbicier-Simo 1993-97
Human neutrophils	Phosphorus	12 D to 30 D	Inhibition of superoxide production	Chirumbolo and Bellavite 1993
Wheat germination	Arsenic Silver nitrate	26 D (10^{-45})	Protect from toxicity Enhances growth	Betti 1997/2015 Pongratz 1998
Rat neurons	Glutamate	$10^{-18} \rightarrow 10^{-30}$	Protection from glutamate toxicity	Jonas et al., 2001
Neurocytes	Cycloheximide	10^{-27}	Increases viability	Marotta 2002
Bacteria	Arsenicum	30C	Protects from toxicity	Das et al 2011, De et al 2012
Neurocytes	Gelsemium s.	2-30 C	Prevalent gene down-regulation	Marzotto 2014, Olioso 2014
Colon cancer cells	Ruta grav.	MT-30C	Decrease viability, apo-ptotic gene expression	Arora and Tandon 2015
Macrophages	Arnica montana	2-15C	Modulates inflammatory genes	Olioso 2016, Marzotto 2016
Epitelial cells	Apis mellifera	3-30C	Modulates hundreds of genes	Bigagli 2016

Gelsemium sempervirens as a model of laboratory investigation of homeopathy
(Verona lab 2008-2018)



Gelsemine

Possible analogy with (SOME) human symptoms

Repertorial Materia Medica: Result of search by index in all repertories: [root:WALK] AND [root:AMEL]

- ✓**MIND - ANXIETY - walking - air, in open – amel. 7**
- ✓**MIND - ANXIETY - walking – amel. 8**
- ✓ **MIND - WALKING - air; in the open – amel. 20**
- ✓**GENERALS - WALKING - air; in open – amel. 135**
- ✓**GENERALS - WALKING - rapidly – amel. 19**
- ✓**GENERALS - WALKING - slowly – amel. 15**

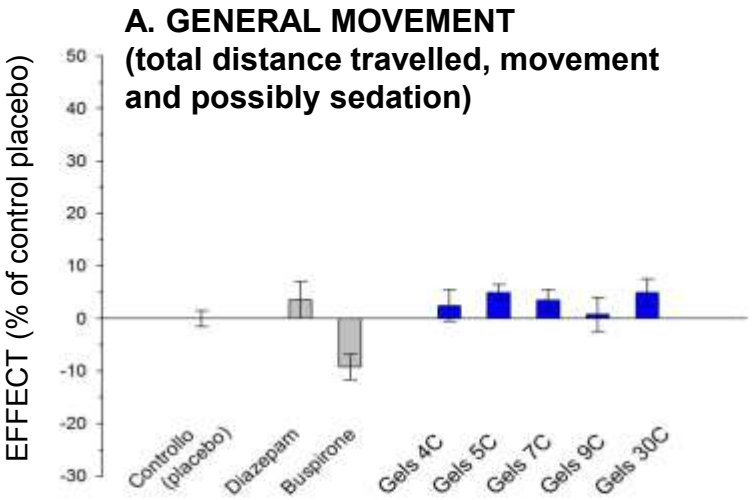
Materia Medica (Boenninghausen, Murphy):

- ✓**MIND: FEELING AS IN DANGER OF FALLING**
- ✓**MIND: DREAD/DESIRE OF BEING ALONE**
- ✓**MIND: IMPATIENT AND IRRITABLE**
- ✓**MIND: NERVOUS DREAD OF APPEARING IN PUBLIC**

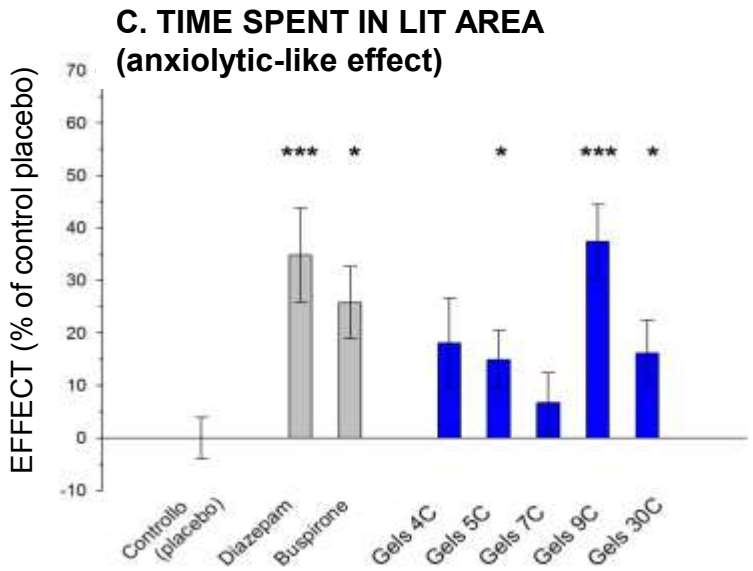
Anxiolytic-like effect on mice behaviour (Verona lab 2008-2012)

Open field

Light Dark



NO TOXIC EFFECTS



YES ANXIOLYTIC-LIKE EFFECTS

Main references (2012-2018):

https://www.ncbi.nlm.nih.gov/pubmed/29428604
https://www.ncbi.nlm.nih.gov/pubmed/22548123

Experimental neuropharmacology of Gelsemium sempervirens (review 2018)

Free online: https://www.ncbi.nlm.nih.gov/pubmed/29428604

Reported effects *Gelsemium* and its alkaloids in laboratory models.

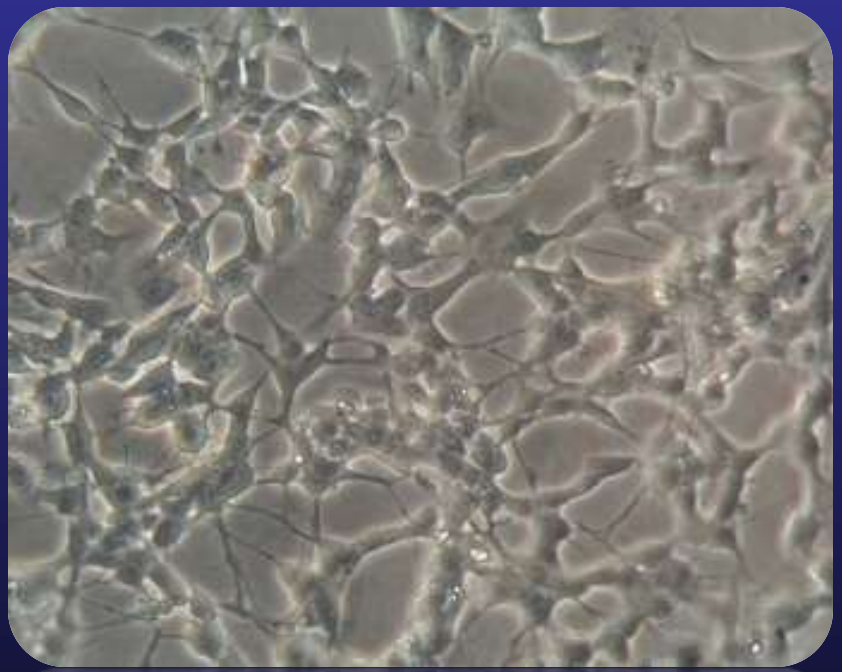
Issue	Model	Dose/dilution	Evidence
Toxicity	Goats	Ingestion of whole plant	Neurological signs characterized by marked progressive weakness and convulsions culminating in death [55]
Toxicity	Mice	Crude extract, high dose (*Gelsemium elegans*)	Convulsions, respiratory failure [5]
Toxicity	Mice and neurons	Homeopathic 5c, 9c, 15c, 30c dilutions	No evidence of toxicity *in vivo* and *in vitro* [11–13,15]
Epilepsy	Mice experimental seizures	Low dilution of mother tincture	Counteracts seizures induced by lithium and pilocarpine [31]
Anxiety	Mice behavior	Homeopathic 5c, 9c, 15c dilutions	Decreases anxiety after stress [30]
Anxiety	Mice behavior	Homeopathic 7c, 9c, 30c dilutions	Decreases anxiety parameters, no locomotion unspecific effects [11–13]
Anxiety	Rat behavior	Gelsemine (alkaloid of *Gelsemium* plants) 10^{-6} to 10^{-10} M	Decreases anxiety parameters [24]
Pain	Mice allodynia and thermal hyperalgesia	Koumine (0.28–7.0 mg/kg) and Gelsemine (2 and 4 mg/kg)	Decreases neuropathic pain and sleep disturbances [26,49]
Anxiety	Mice behavior	Gelsemine, koumine, and gelsevirine 0.4 –10 mg kg (biphasic effects)	Anxiolytic effects [47]
Dementia	Scopolamine-induced dementia in mice	Homeopathic mother tincture of *Gelsemium* (1 mg/kg)	Protects against scopolamine-induced cognitive discrepancies [2]
Action mechanism	Rat nervous tissue	Homeopathic *Gelsemium* and gelsemine 5c and 9c	Increases the anti-stress allopregnanolone hormone, through glycine receptors [32]
Action mechanism	Rat neuropathic pain	Koumine (alkaloid of *Gelsemium* plants) 0.28 –7.0 mg/kg	Increases allopregnanolone and the key synthethase enzyme 3alpha-hydroxysteroid [26,56] oxido-reductase (3alpha-HSOR)
Action mechanism	Intracerebral administration of strychnine	Gelsemine, koumine, and gelsevirine 0.4 –10 mg kg	Anxiolytic effects antagonized by strychnine, suggesting involvement of glycine receptor in the brain [47]
Action mechanism	Neurocyte SH-SY5Y cell line	*Gelsemium* 2c	Decrease of the prokineticin receptor 2 gene expression, whose ligand is a neuropeptide involved in nociception, anxiety and depression-like behavior [14]
Action mechanism	Neurocyte SH-SY5Y cell line	*Gelsemium* 2c (corresponding to a gelsemine concentration of about 10^{-10} M) and higher dilutions until 9c and 30c with lower effect	Decreases the expression of 49 genes involved in cell excitability [15]
Action mechanism	Transfected HEK293 cells and cultured spinal neurons	Gelsemine 10^{-6}–10^{-5} M	Directly modulates the function of glycine receptors (biphasic effects) [28]
Action mechanism	Immunohisto-chemical study	Gelsemine (4 mg/kg)	Decreases c-Fos expression in mice brain [49]
Action mechanism	Scopolamine-induced dementia in mice	Homeopathic mother tincture of *Gelsemium* (1 mg/kg)	Decreases beta-secretase and oxidative stress in brain [2]

Gelsemium s. in a neuronal model

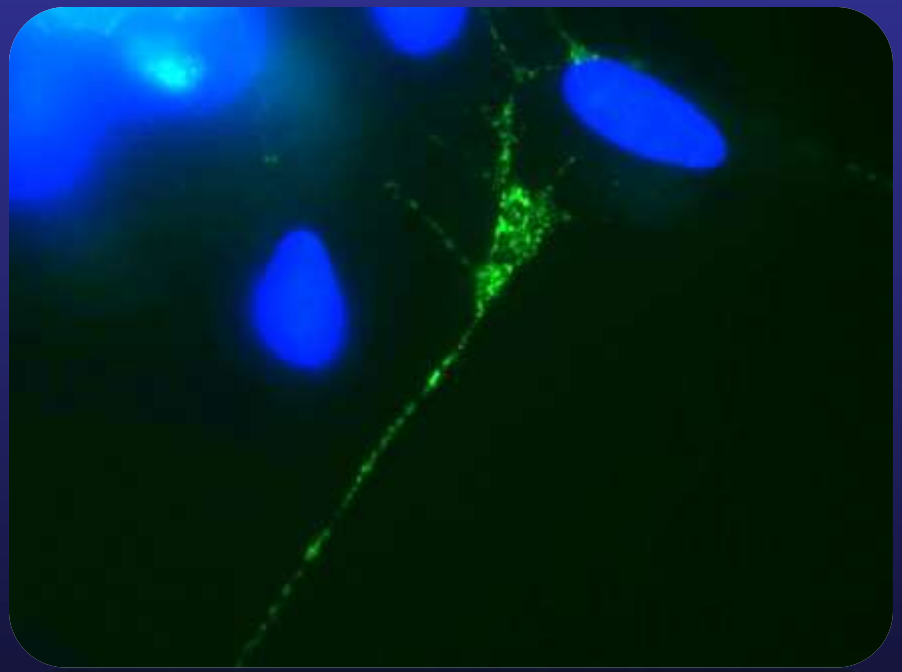
Verona research group 2010-2014, Review in 2018

https://www.ncbi.nlm.nih.gov/pubmed/24642002

SH-SY5Y neurocytes-human neuroblastoma cells



Inverted microscope image

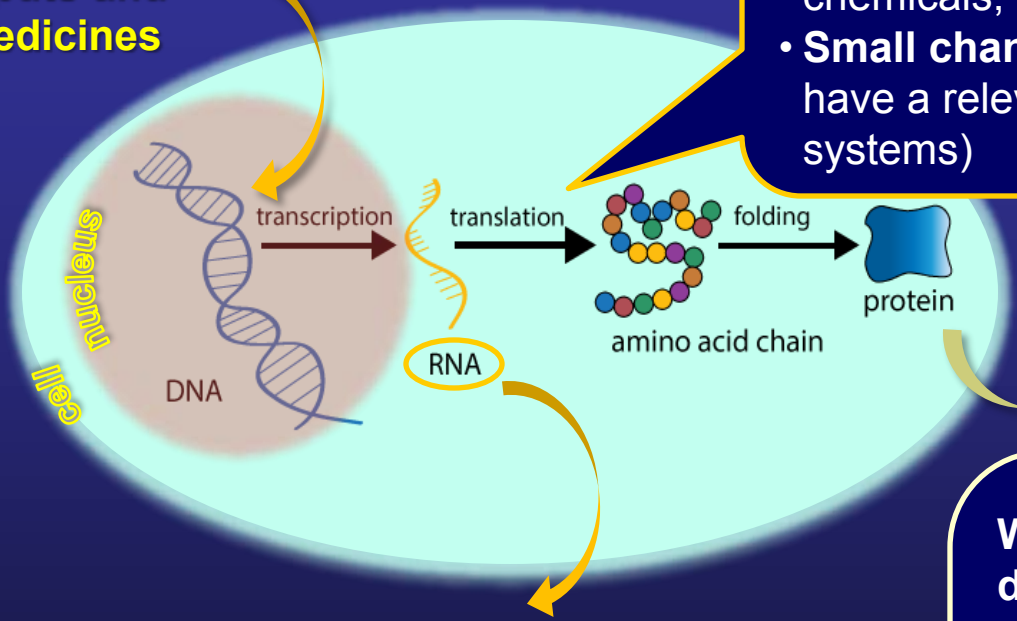


Confocal immunofluorescent image

Differential gene expression analysis

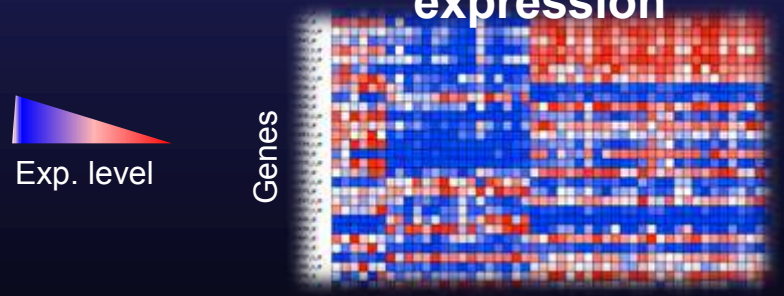
Environmental inputs and medicines

- **Gene expression** has been proven to be very **sensitive** also to small perturbations (low doses of chemicals, EMF, hypoxia)
- **Small changes** in the **gene regulatory networks** have a relevant impact in the cell (Dynamic critical systems)



Phenotype
Metabolic activity

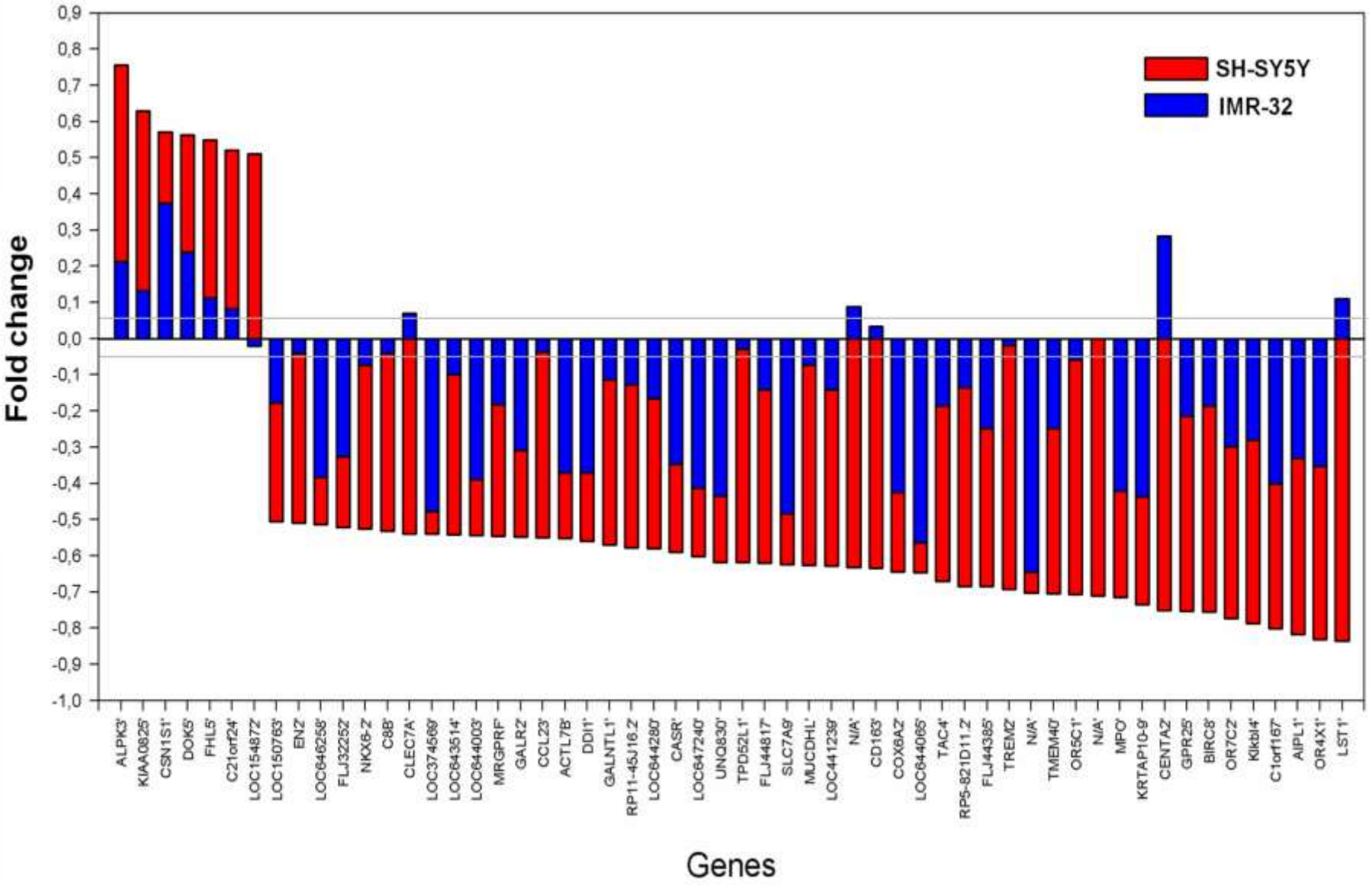
Differential gene expression



Which genes are being differentially expressed in the presence of *HD* ?

- ✓Quantification of the RNA expression levels of all the genes (microarray, RNA-seq)
- ✓Compare to control
- ✓High sensitivity but many replicates

Up (left) and down (right) regulated genes in two neuronal cell lines exposed to Gels. 2C



List of down regulated genes in SH neuronal cell line exposed to Gels. 2C

Exposure to the Gelsemium s. 2CH promoted the significant down-expression of 49 genes

while 7 genes were overexpressed

Many of these genes belong to:

- neuropeptide/receptor systems
- calcium signalling
- G-protein coupled transduction systems
- inflammatory pathways

DOWN

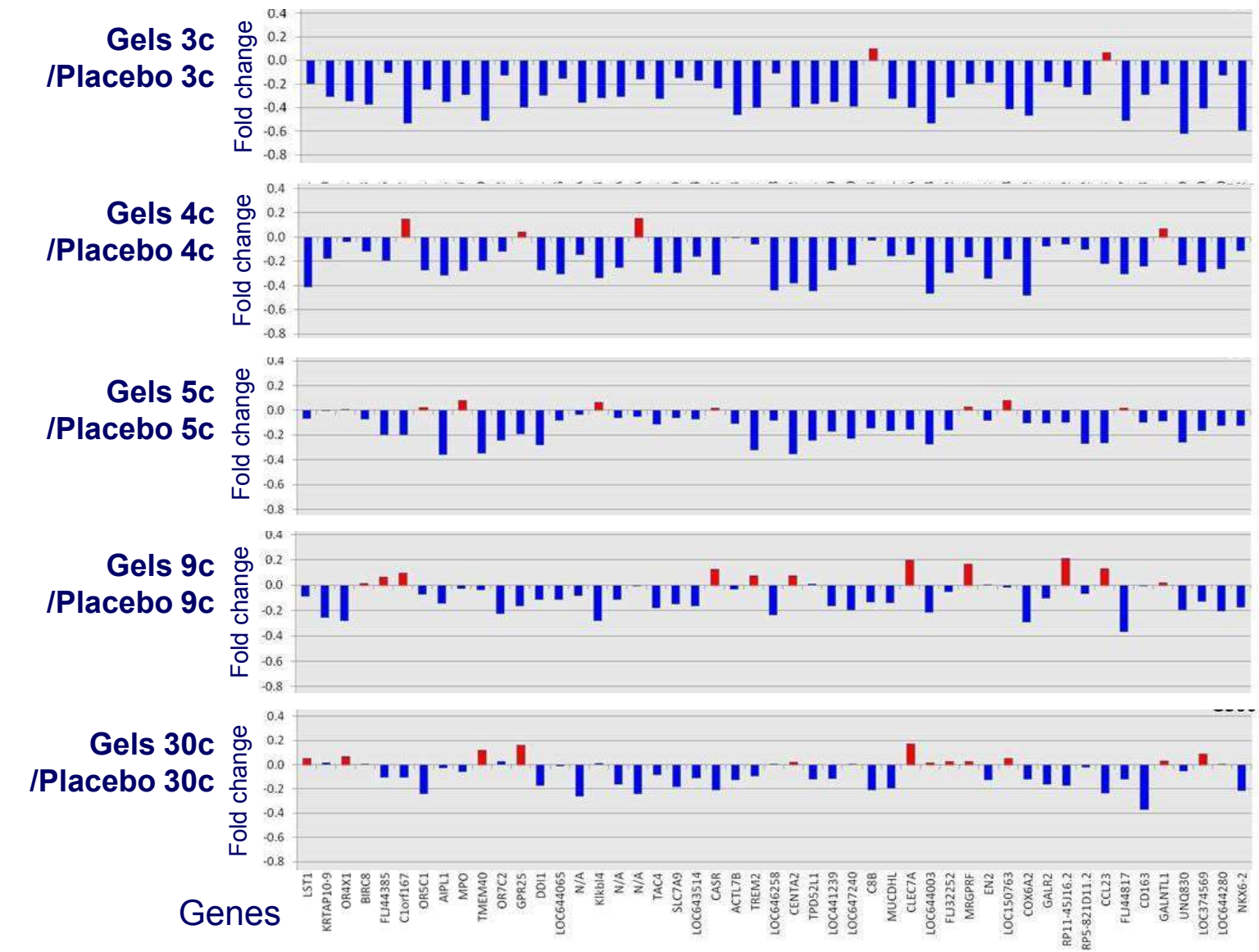
UP

Gene ID	Transcript ID	Symbol	Log2 fold change	p^1	Description
7940	AF000424	LST1	-0.84 ± 0.14	0.04	leukocyte specific transcript 1
390113	NM_001004726	OR4X1	-0.83 ± 0.06	0.01	olfactory receptor, family 4, subfamily X, member 1
23746	AJ830742	AIPL1	-0.82 ± 0.16	0.04	aryl hydrocarbon receptor interacting protein-like 1
284498	AL833920	C1orf167	-0.80 ± 0.17	0.05	chromosome 1 open reading frame 167
221191	AK058068	Klkbl4	-0.79 ± 0.12	0.04	plasma kallikrein-like protein 4
26658	NM_012377	OR7C2	-0.77 ± 0.07	0.01	olfactory receptor, family 7, subfamily C, member 2
112401	BC039318	BIRC8	-0.76 ± 0.11	0.00	baculoviral IAP repeat-containing 8
2848	NM_005298	GPR25	-0.75 ± 0.15	0.02	G protein-coupled receptor 25
55803	NM_018404	ADAP2	-0.75 ± 0.11	0.02	ArfGAP with dual PH domains 2
386676	NM_198690	KRTAP10-9	-0.73 ± 0.12	0.04	keratin associated protein 10-9
4353	X04876	MPO	-0.72 ± 0.15	0.04	Myeloperoxidase
N/A	AY358413	N/A	-0.71 ± 0.18	0.02	Homo sapiens clone DNA59853 trypsin inhibitor
392391	NM_001001923	OR5C1	-0.71 ± 0.05	0.04	olfactory receptor, family 5, subfamily C, member 1
N/A	AK094115	N/A	-0.70 ± 0.11	0.04	Homo sapiens cDNA FLJ36796 fis, clone ADRGL2006817
55287	BC020658	TMEM40	-0.70 ± 0.15	0.02	transmembrane protein 40
54209	NM_018965	TREM2	-0.69 ± 0.10	0.02	triggering receptor expressed on myeloid cells 2
150365	AK097834	RP5-821D11.2	-0.68 ± 0.17	0.02	similar to mouse meiosis defective 1 gene
400934	NM_207478	FLJ44385	-0.68 ± 0.09	0.04	FLJ44385 protein
255061	NM_170685	TAC4	-0.67 ± 0.14	0.01	tachykinin 4 (hemokinin)
644065	XM_931993	LOC644065	-0.65 ± 0.23	0.04	hypothetical protein LOC644065
1339	NM_005205	COX6A2	-0.64 ± 0.17	0.01	cytochrome c oxidase subunit VIa polypeptide 2
N/A	AK128093	N/A	-0.63 ± 0.09	0.04	Homo sapiens cDNA FLJ46214 fis, clone TESTI4012623.
53841	AY358368	CDHR5	-0.63 ± 0.11	0.04	mucin-like protocadherin
9332	NM_004244	CD163	-0.63 ± 0.18	0.03	CD163 molecule
441239	XM_499305	LOC441239	-0.63 ± 0.22	0.05	hypothetical gene supported by BC063653
7164	NM_001003397	TPD52L1	-0.62 ± 0.09	0.02	tumor protein D52-like 1
11136	NM_014270	SLC7A9	-0.62 ± 0.09	0.04	solute carrier family 7 member 9
389084	NM_206895	UNQ830	-0.62 ± 0.11	0.04	ASCL830
400224	XM_375090	FLJ44817	-0.62 ± 0.20	0.04	similar to pleckstrin homology domain protein (5V327)
647240	XM_934559	LOC647240	-0.60 ± 0.06	0.00	hypothetical protein LOC647240
846	BC104999	CASR	-0.59 ± 0.06	0.00	calcium-sensing receptor
116123	NM_138784	RP11-45J16.2	-0.58 ± 0.09	0.04	flavin-containing monooxygenase pseudogene
644280	XM_497769	LOC644280	-0.58 ± 0.06	0.05	hypothetical protein LOC644280
57452	AB032956	GALNTL1	-0.57 ± 0.17	0.05	alpha-D-galactosamine N-acetylgalactosaminyltransferase
414301	NM_001001711	DDI1	-0.56 ± 0.11	0.04	DDI1, DNA-damage inducible 1, homolog 1 (*S. cerevisiae*)
116535	BC016964	MRGPRF	-0.55 ± 0.17	0.01	MAS-related GPR, member F
8811	NM_003857	GALR2	-0.55 ± 0.07	0.04	galanin receptor 2
10880	NM_006686	ACTL7B	-0.55 ± 0.12	0.04	actin-like 7B
6368	NM_145898	CCL23	-0.55 ± 0.11	0.05	chemokine (C-C motif) ligand 23
64581	BC071746	CLEC7A	-0.54 ± 0.08	0.04	C-type lectin domain family 7, member A
644003	XM_927256	LOC644003	-0.54 ± 0.11	0.04	similar to Mucin-2 precursor (Intestinal mucin 2)
643514	XM_931594	LOC643514	-0.54 ± 0.10	0.03	hypothetical protein LOC643514
374569	XM_935431	LOC374569	-0.54 ± 0.07	0.04	Similar to Lysophospholipase
84504	BC101635	NKX6-2	-0.53 ± 0.13	0.03	NK6 transcription factor related, locus 2 (Drosophila)
732	NM_000066	C8B	-0.53 ± 0.06	0.05	complement component 8, beta polypeptide
146336	NM_182510	FLJ32252	-0.52 ± 0.03	0.01	hypothetical protein FLJ32252
150763	BC042847	LOC150763	-0.51 ± 0.10	0.04	hypothetical protein LOC150763
2020	NM_001427	EN2	-0.51 ± 0.08	0.04	engrailed homolog 2
646258	XM_929203	LOC646258	-0.51 ± 0.11	0.04	hypothetical protein LOC646258
154872	NM_001024603	LOC154872	0.51 ± 0.10	0.03	hypothetical LOC154872
400866	NM_001001789	C21orf24	0.52 ± 0.12	0.05	chromosome 21 open reading frame 24
9457	NM_020482	FHL5	0.55 ± 0.19	0.04	four and a half LIM domains 5
55816	NM_018431	DOK5	0.56 ± 0.04	0.03	docking protein 5
1446	NM_001890	CSN1S1	0.57 ± 0.09	0.04	casein alpha s1
285600	AK130941	KIAA0825	0.63 ± 0.06	0.01	KIAA0825 protein
57538	NM_020778	ALPK3	0.76 ± 0.10	0.01	alpha-kinase 3

https://www.ncbi.nlm.nih.gov/pubmed/24642002

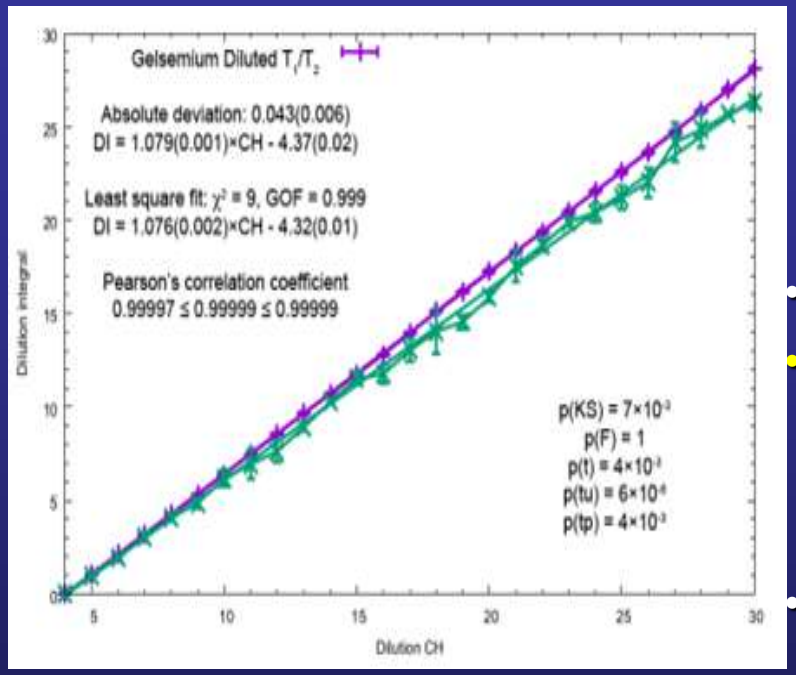
Effects of *Gelsemium s.* increasing dilutions/dynamizations on the 49 neurocyte genes

https://www.ncbi.nlm.nih.gov/pubmed/24642002



	N. Genes UP/DOWN	P (Fisher)
Gels 3c /Placebo 3c	2↑ 47↓	<0.001
Gels 4c /Placebo 4c	3↑ 42↓	<0.001
Gels 5c /Placebo 5c	3↑ 38↓	<0.001
Gels 9c /Placebo 9c	9↑ 30↓	<0.01
Gels 30c /Placebo 30c	7↑ 27↓	<0.01

Nuclear Magnetic Resonance characterization of *Gelsemium sempervirens*



(DYN-HOM research project)

Van Wassenhoven M et al.
Homeopathy. 2017 Nov;106(4):223-239

- **RESULTS:**
- The discrimination between experimental slopes and slopes associated with random noise data was very good at a five-sigma level of confidence (i.e. probability 3×10^{-7}).
- All potentized samples show very good discrimination (at least nine-sigma level) against aqua pura, lactose or simple dilution.

- **CONCLUSION:**
- There is clear evidence that homeopathic solutions cannot be considered as pure water as commonly assumed.

https://www.ncbi.nlm.nih.gov/pubmed/29157472

Gelsemium s. key-notes

- The effect of highly diluted compounds used in humans with anxiety-related symptoms has been statistically proven also in laboratory animals
- Human neurons are sensitive to *Gelsemium s.* with down-expression of dozens of genes involved in various receptors and signaling pathways
- The effect is higher with low dilutions (2-3CH, about 10^{-8} moles/L) but it occurs even at ultra low doses and high dilutions (9CH and 30CH, beyond “Avogadro”)
- There is NMR evidence that homeopathic *Gelsemium s.* cannot be considered as pure water.

Ref. https://www.ncbi.nlm.nih.gov/pubmed/29428604

How *Arnica m.* works in wound healing – role of macrophages

Inflammation and trauma

Pain management

Postoperative setting

Antinflammatory antimicrobial activity and **wound healing promotion …but the mechanisms of action are largely unknown**

Important role of **macrophages MΦ**

chemokines, matrix metalloproteinases (MMPs), and other inflammatory mediators

function of immune regulation and tissue remodelling

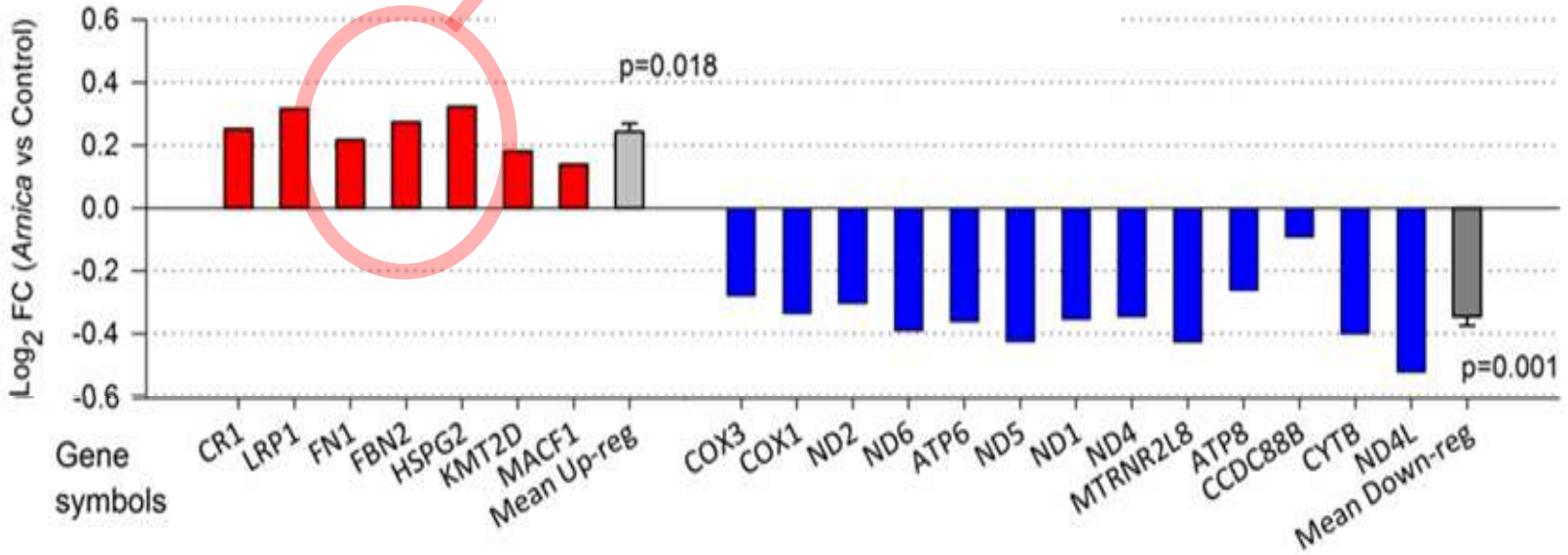
Clinical Review in https://www.ncbi.nlm.nih.gov/pubmed/25171757

Effect of *Arnica m.* 2c on gene expression by IL-4-polarized human macrophages (RNA-seq study)

Arnica m. 2c = 10^{-8} Mol/L of sesquiterpenes

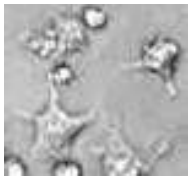
EXTRACELLULAR MATRIX GENES:

fibronectin (p < 0.001)
fibrillin (p < 0.05)
heparan sulfate proteoglycan (p < 0.05)



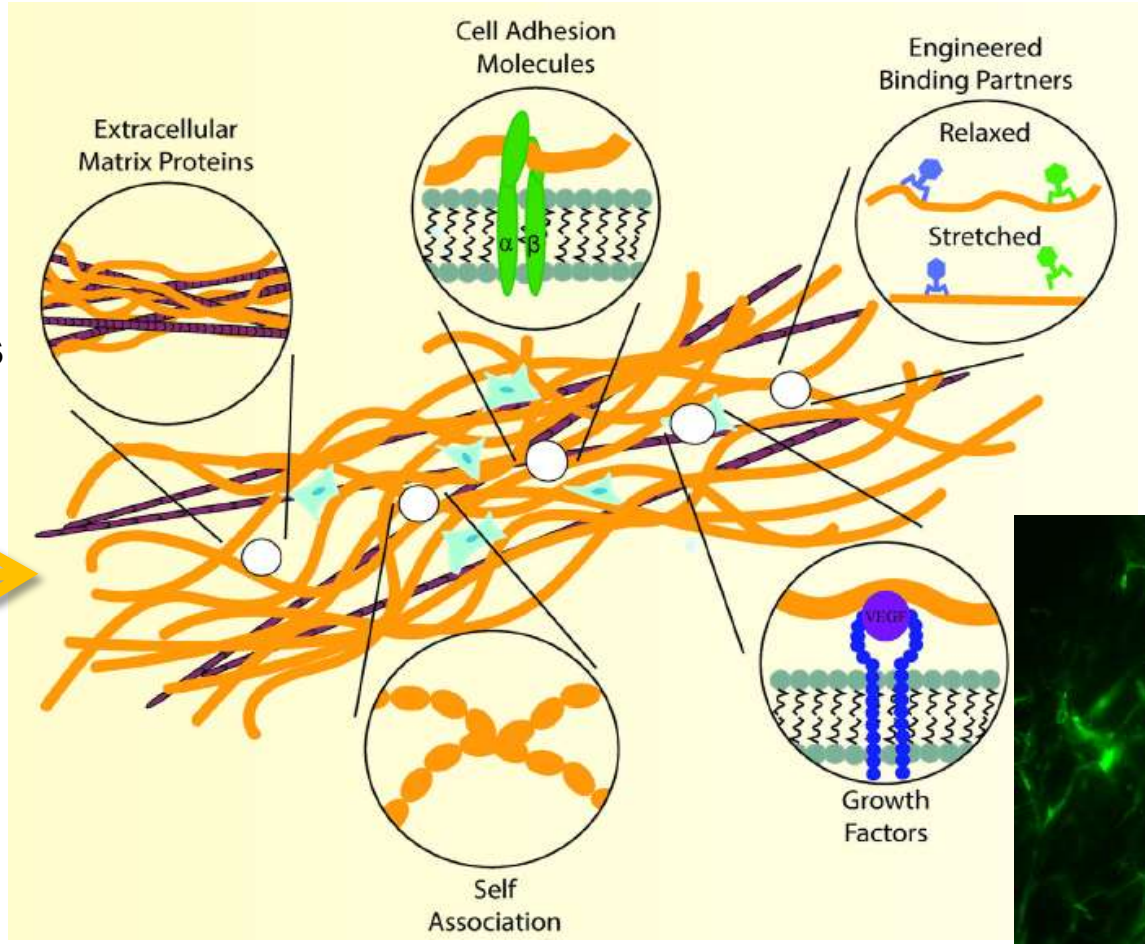
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0166340

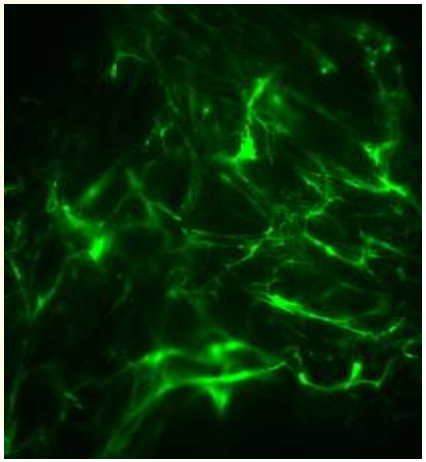
Fibronectin is the major protein that organizes the connective tissue during the first phase of wound healing and inflammation



IL-4 Macro phages

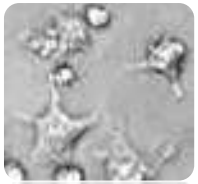
Fibro nectin

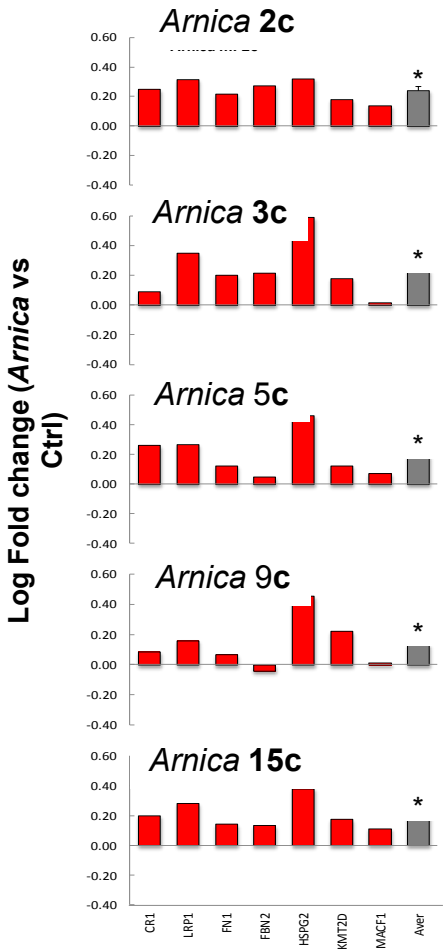




Immunofluorescence image of cells in culture

Effect of *Arnica m.* on macrophages pre-treated with different agents





pool of 5 exp

http://www.highdilution.org/index.php/ijhdr/article/view/861

A.R. Khuda-Bukhsh

REVIEW ARTICLE

The contribution of homeogenomic and homeogenetic studies in the support of the practice of Homoeopathy

Peter H. Kay[1*], Anisur R. Khuda-Bukhsh[2]

ABSTRACT

Almost two decades ago, it was postulated that homoeopathic remedies could deliver their benefits by interacting with the genetic blueprint. Over the years, the results of many homeogenomic gene expression studies have confirmed this postulate. The results of homeogenomic studies have begun to recognize which of the estimated 25,000 human genes are targeted by different homoeopathic remedies and how the expression profiles of these targeted genes are rearranged.

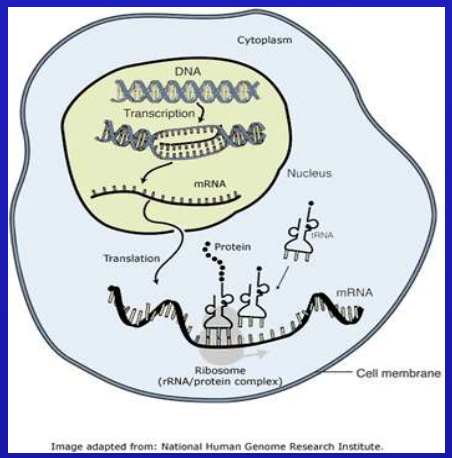
How to cite this article: Kay PH, Khuda-Bukhsh AR. The contribution of homeogenomic and homeogenetic studies in the support of the practice of Homoeopathy. Indian J Res Homoeopathy 2016;10:101-7.

Gene expression studies of homeopathic drugs

Test compound	Potencies	Cell type	Effect	REF.
Conium m., Sabal s., Thuja o.* (complex), *Carcinosinum	30C, 200C, 1000C	Rat primary prostate cancer cells	no change expression of specific genes (cytokines, apoptosis)	Thangapazham et al., 2006
Canova complex	7x-24x	Mϕ from treated rats	↓↑ Gene expression (whole genome analysis)	De Oliveira et a., 2008
Carcinosinum	MT, 30C, 200C	DLA cells	↑ specific gene expression (p53 pro-apoptotic)	Sunila et a., 2009
Nux v., Calendula o.	10C, 12C	Human gastric epithelial cells KATO-III infected with H. pylori	↓ expression of HB-EGF-like gene	Hofbauer et al., 2010
Arsenicum album	30C	*S. cerevisiae, E. coli*	↓↑ expression of specific genes (apoptotic gene, stress response proteins)	Das et al., 2011, De et al., 2012
Carcinos., Hydrastis, Ruta, Thuja	200C	DLA cells	↑ Apoptosis, ↓↑ Gene expression (whole genome analysis)	Preethi et al., 2012
Rhus tox.	30X	Primary cultured mouse chondrocytes	↑ specific gene expression (COX-2), ↑ inflammatory response (PGE2 release), ↓ specific gene expression (collagen II; de-differentiation role)	Huh et al., 2013
Arsenicum album	45X	Arsenic-intoxicated wheat seeds	↑ increase germination ↓↑ Gene expression (whole genome analysis)	Marotti et al., 2014
Condurango	30C	H460-non-small-cell lung cancer (NSCLC) cells	↓↑ expression of specific genes (apoptotic markers), ↑ Apoptosis, oxidative stress, mitochondrial depolarization	Sikdar et al., 2014
Gelsemium s.	2C,3C, 5C, 9C, 30C	Human neurocytes SHSY5Y	↓49 genes ↑7 genes (whole genome analysis), ↓ gene expression (PROK2R)	Marzotto et al., 2014; Olioso et al., 2014
Apis mellifica	3C, 5C, 7C	human prostate cancer cells HEK93	↑↓ expression of different groups of genes (whole genome analysis)	Bigagli et al. 2014
Sulphur	6C, 30C, 200C	H460-(NSCLC) cells	↓↑ expression of specific genes (apoptotic markers), ↑ Apoptosis,	Saha et al., 2015
Arnica m.	2C,3C, 5C, 9C, 15C	Human macrophages THP-1	↑↓Gene expression (whole genome analysis) ↑chemokine genes, ↓inflammatory genes	Marzotto et al., 2016; Olioso et al., 2016
Copper (III) suphate	10^{-6} , 10^{-17}M	HEK93 cells	↑↓ expression of different groups of genes (whole genome analysis)	Bigagli et al., 2010
Na butyrate	200C	HEK93 cells	↓↑ expression of specific genes (IL2, TNFa)	Olsen et a., 2017
Taxans (paclitaxel and docetaxel)	6X, 5C, 15C	Breast cancer cells MCF-7	↓↑ expression cancer-related genes, retain anti-cancer action	Şeker et al., 2018

LOOKING FORWARD: HOMEOGENOMICS AND HOMEOGENETICS

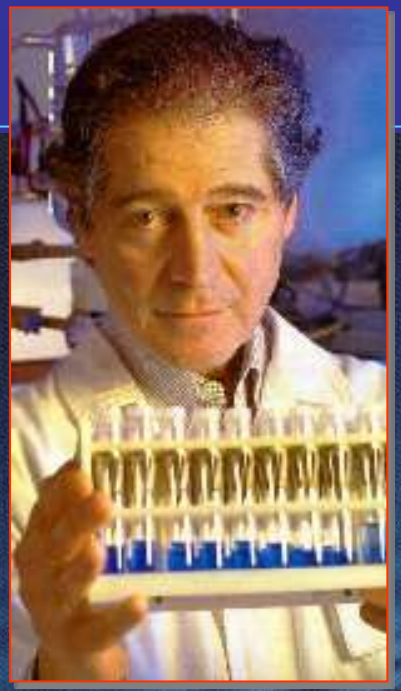
Gene «expression» → Basic mechanisms



- Cell and tissue targets
- Effects of homeodrugs on whole cell transcriptome

Pharmacogenetics → Better prescription?

- Individual genetic sensitivity to specific homeodrugs
- Group classifications («constitutions», «miasms»?)



May water have a «memory»?

"No one really understands water.
It's embarrassing to admit it, but the stuff that covers two-thirds of our planet is still a mystery."

Ball P. "Water-an enduring mystery". Nature2008 Mar 20; 452(7185):291-2.

Philip Ball

What some Nobel laureates had to say on homeopathy

Brian David Josephson
Physicist
(Nobel Laureate in Physics - 1973)

"Simple-minded analysis may suggest that water, being a fluid, cannot have a structure of the kind that such a picture would demand.
But cases such as that of liquid crystals, which while flowing like an ordinary fluid can maintain an ordered structure over macroscopic distances, show the limitations of such ways of thinking.
There have not, to the best of my knowledge, been any refutations of homeopathy that remain valid after this particular point is taken into account."

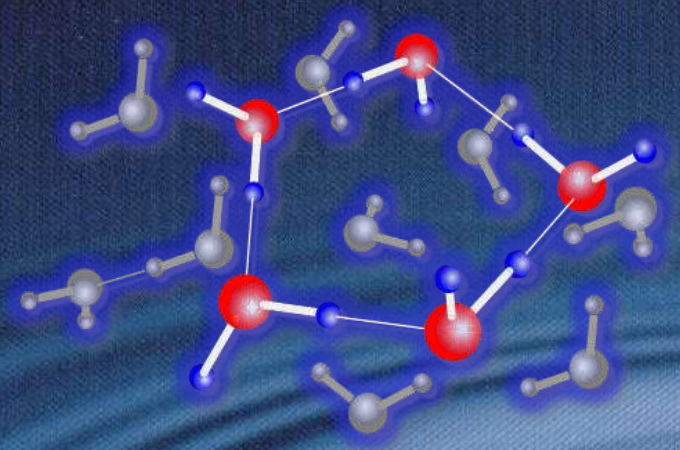
http://www.tcm.phy.cam.ac.uk/~bdj10/water.memory/ns/homeopathy.html

PHYSICO-CHEMICAL METHODS FOR INVESTIGATION OF HIGH-DILUTIONS

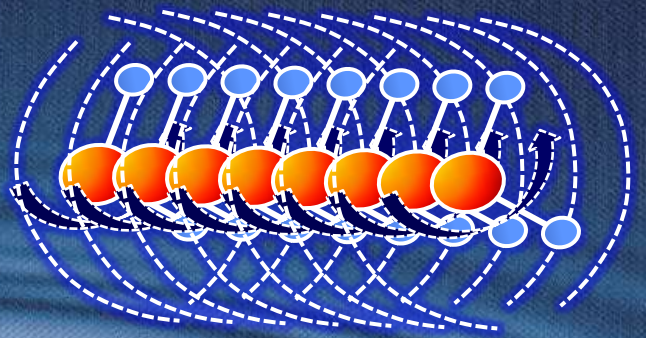
- Spectroscopy (UV and Infrared)
- Differential calorimetry
- Conductimetry, pHmetry
- Dynamic light scattering/Zeta potential
- Field emission scanning electron microscopy
- Thermoluminescence
- Nuclear magnetic resonance
- Aquaporin permeability
- Spectroscopy of solvatochromic dyes
- Delayed luminescence
- Fluorescence microscopy
- Electrical properties of the polymer film of poly(vinylidene fluoride-co-hexafluoropropylene

Recent Review (2018): Klein et al. https://www.ncbi.nlm.nih.gov/pubmed/29377709

WATER IS NOT “FRESH WATER”



Hydrogen-bonded chratrates (clusters)



Coherence domains (CD) Superradiance

Nanoparticles, nanobubbles, aggregates

http://www.ncbi.nlm.nih.gov/pubmed/24439452
http://www.ncbi.nlm.nih.gov/pubmed/24439453

LMHI CONGRESS 2018
5-8 SEPTEMBER CAPE TOWN
Contributing to Sustainable Healthcare

Evidence for homeopathic principles in the basic sciences

1. Introduction
2. Similia
3. Microdose and «potency»
4. Key points

Note: Tables and figures of this presentation are available at:
http://www.paolobellavite.it/news.html

Basic Sciences: Essential points

a) Homeopathic drugs have reproducible effects in laboratory models (receptors, gene expression, biochemical changes, growth)
b) The inversion of effects according to the given dose is observed in particular experimental conditions
c) In general, low dilutions/higher doses (e.g 2CH) show higher activity than higher dilutions/lower doses (e.g. 9CH, 30CH), as expected from conventional scientific wisdom
d) In studies of increasing dilutions, often the trend shows irregular peaks interspersed with inactive doses (an increase of activity with increasing dilutions was never observed)
e) Very often the pharmacological activity of diluted/dynamized substances is maintained even at dilutions beyond Avogadro constant.
f) The high-dilution effect is better observed in cells that were pre-sensitized
g) Gene expression is a particularly sensitive cell response to homeopathic high dilutions
h) Water is not pure "fresh water"

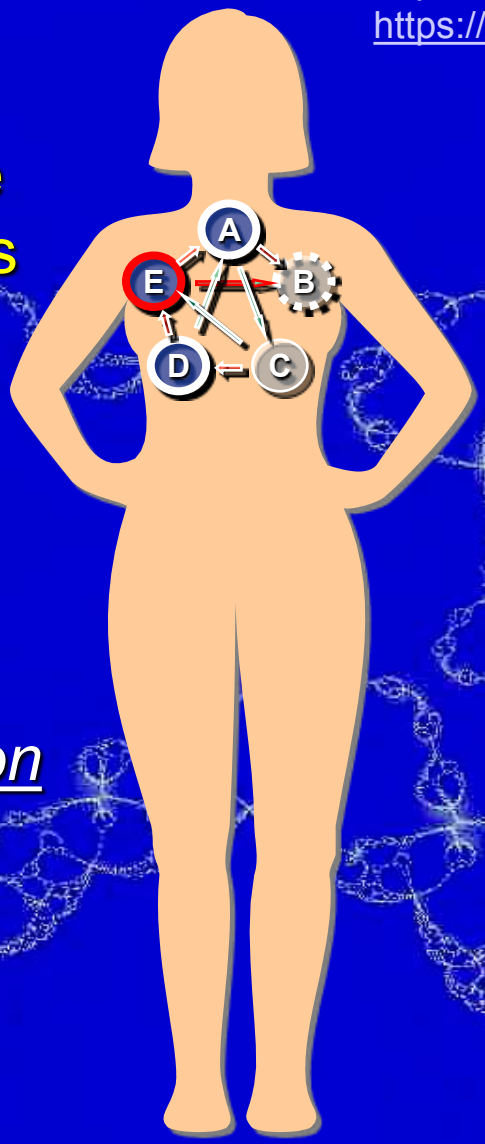
Ref. https://www.ncbi.nlm.nih.gov/pubmed/29428604
https://www.ncbi.nlm.nih.gov/pubmed/29526239

THE RATIONAL VIEW OF HOMEO-THERAPEUTICS - 1

https://www.ncbi.nlm.nih.gov/pubmed/14587687
https://www.ncbi.nlm.nih.gov/pubmed/24280484

1. Most diseases have multifactorial causes
2. Diseases are dynamic processes
3. They involve the whole individual

→→ Disease is a "*systemic information disorder*" (excess, defect, loss of connections)

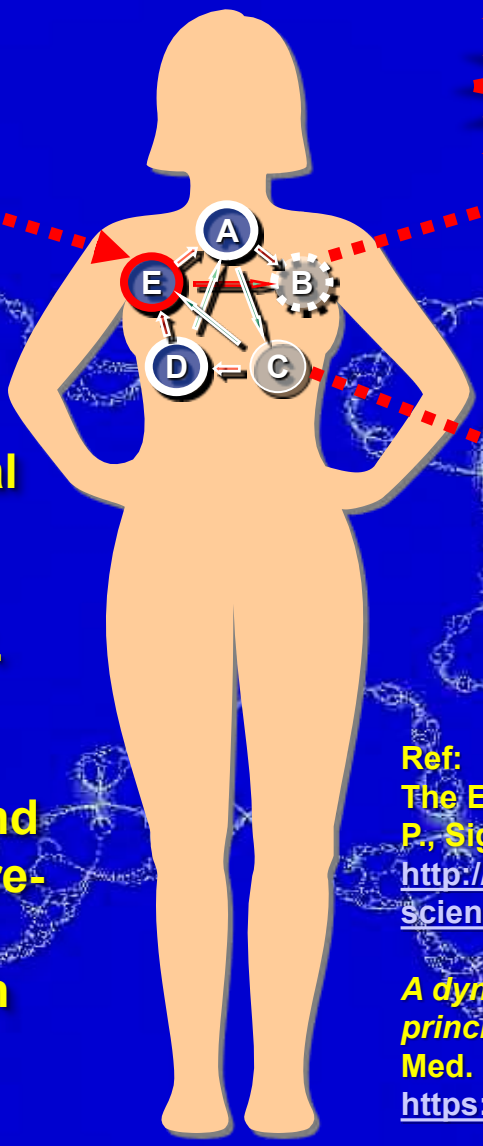


These complex features claim for a new attitude of medicine, both in "diagnostics" and in "therapeutics".

Homeopathy may provide a «heuristic» model to understand and to treat these complexities.

THE RATIONAL VIEW OF HOMEO-THERAPEUTICS - 2

PATHOGENIC FACTORS (disease) or DRUGS (proving)



BIOCHEMICAL CHANGES

Basic Research

SIGNS AND SYMPTOMS

Classical Homeopathy

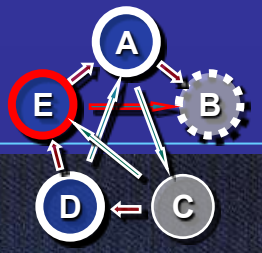
The pharmacodynamic action of remedies ("homeo-therapeutics") acts by providing subtle informational inputs to specific regulation centres (receptors, DNA) involved in the "vital energy".

These small inputs are perceived as perturbations and trigger a reaction capable of re-establish a behavior more proximal to the optimal health and "vital harmony".

Ref:
The Emerging Science of Homeopathy. Bellavite P., Signorini, A. North Atlantic, Berkeley, 2002
http://www.paolobellavite.it/the-emerging-science.html

***A dynamic network model of the similia principle*. Bellavite P et al. Complement Ther Med. 2013: 21(6):750-61**
https://www.ncbi.nlm.nih.gov/pubmed/24280484

WORKING HYPOTHESIS



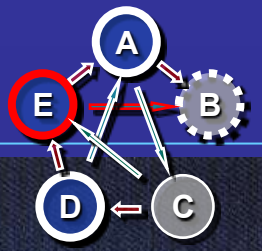
Point 1/5

1. The "similia" (or similarity) principle holds that the medicine capable of regulating a diseased organism (individualized homeopathic therapy) is the same medicine which is capable of inducing a similar pattern of symptoms in a healthy organism.

Homeopathic pharmacopoeia is based on careful experimentation of hundreds of substances on healthy people to detect their specific and global perturbing power.

Main references:
ECAM Journal: https://www.ncbi.nlm.nih.gov/pubmed/17549232
Homeopathy: https://www.ncbi.nlm.nih.gov/pubmed/24439453, https://www.ncbi.nlm.nih.gov/pubmed/25869978
Complement. Ther. Med.: https://www.ncbi.nlm.nih.gov/pubmed/24280484

WORKING HYPOTHESIS



Point 2/5

2. The therapeutic similarity of drug action may be fundamentally based on the widespread phenomenon of inversion of biological effects dependent on the dose of the substance (Arndt-Schulz rule, “hormesis”) and/or on the physiological state of the receiver organism (sensitized or stressed living systems may have opposite reactions to the same drug as compared with normal systems).

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ECAM Journal: https://www.ncbi.nlm.nih.gov/pubmed/17549232
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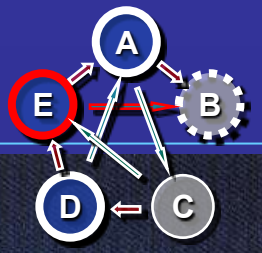
WORKING HYPOTHESIS



Point 3/5

3. Very low doses or high dilutions of homeopathic drugs work by inducing small changes of cell regulatory systems (receptors, enzymes, gene expression) when they are put in a far from equilibrium behavior in the space of energy, due to stress and/or pathology.

In a far-from-equilibrium state, subtle but specific information brought by homeopathic drugs may play a critical role to change the dynamic evolution of the system

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Homeopathy: https://www.ncbi.nlm.nih.gov/pubmed/24439453, https://www.ncbi.nlm.nih.gov/pubmed/25869978
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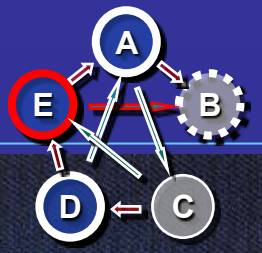


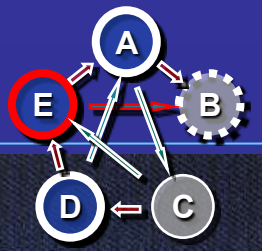
Point 4/5

4. The medicine that has been chosen according to the similia principle may be perceived by specific and sensitive ("primed") regulatory systems - that have a crucial role in the dynamic of the diseaseas - as "disturbing" signal, which may trigger a homeodynamic compensatory reaction, that shifts the targeted system (cell, tissue, or whole organism) toward a new dynamical state (attractor), proximal to the healthy state.

The energy of the transition is provided by the body, not by the medicine.

Main references:
ECAM Journal: https://www.ncbi.nlm.nih.gov/pubmed/17549232
Homeopathy: https://www.ncbi.nlm.nih.gov/pubmed/24439453, https://www.ncbi.nlm.nih.gov/pubmed/25869978
Complement. Ther. Med.: https://www.ncbi.nlm.nih.gov/pubmed/24280484

WORKING HYPOTHESIS



Point 5/5

5. The pharmacological information of homeopathic medicines may have either:

- ✓ chemical nature in low potencies (ultra-low-dose, with presence of a few molecules of active principle) or
- ✓ chemical-physical nature in highly diluted/dynamized remedies (nanoparticles, water clusters, coherent domains)

Main references:
ECAM Journal: https://www.ncbi.nlm.nih.gov/pubmed/17549232
Homeopathy: https://www.ncbi.nlm.nih.gov/pubmed/24439453, https://www.ncbi.nlm.nih.gov/pubmed/25869978
Complement. Ther. Med.: https://www.ncbi.nlm.nih.gov/pubmed/24280484

The research ways: Evidence and Plausibility

CLINICAL RESEARCH

«EVIDENCE»

Homeopathy acceptation and progress

«PLAUSIBILITY»

BASIC RESEARCH

What some Nobel laureates had to say on homeopathy

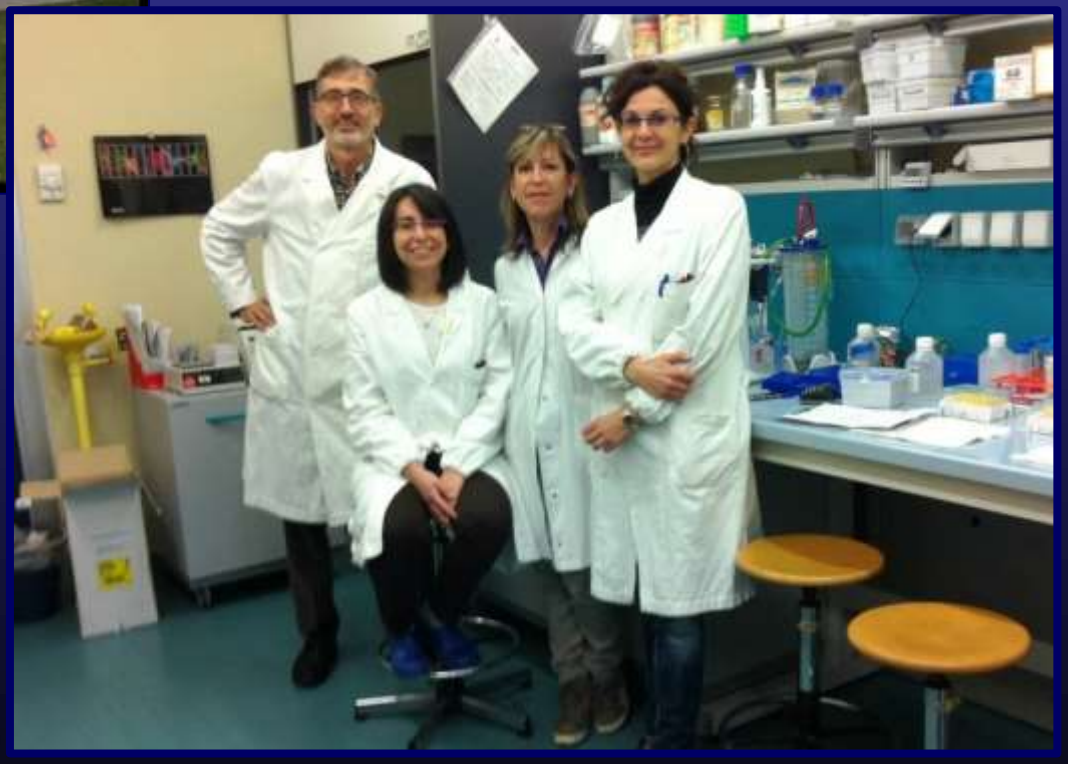
Luc Antoine Montagnier
Virologist
(Nobel Laureate in Physiology and Medicine 2008)

"These are real phenomena that deserve further study"

https://en.wikipedia.org/wiki/Luc_Montagnier

Thanks for your attention!

Paolo Bellavite
Clara Bonafini
Marta Marzotto
Debora Olioso



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