Hormesis-based anti-ageing products

a case study of a new cosmetic

Aarhus University - library

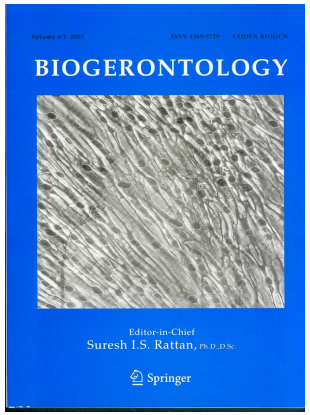
Aarhus University – science park

Biogerontology, class of 2009

Molecular Biology Dept - 2010

Suresh Rattan **PhD, DSc**

Editor-in-Chief, Biogerontology
Department of Molecular Biology
Aarhus University, Denmark



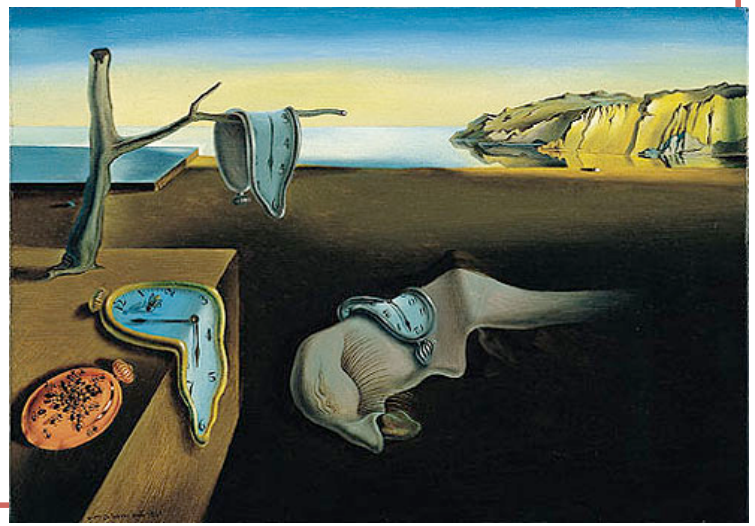
Recapitulating the rationale for the application of hormesis in ageing research and interventions….

Biogerontology tells that….

1. There are no gerontogenes whose sole function is to cause ageing.

2. Everything that happens during ageing is not bad.

3. Ageing is not a disease.



Survival is a constant challenge….

Oxygen metabolites
ROS, other free radicals

Nutritional metabolites
glyoxal, methylglyoxal, carbonyls acids, aldehydes

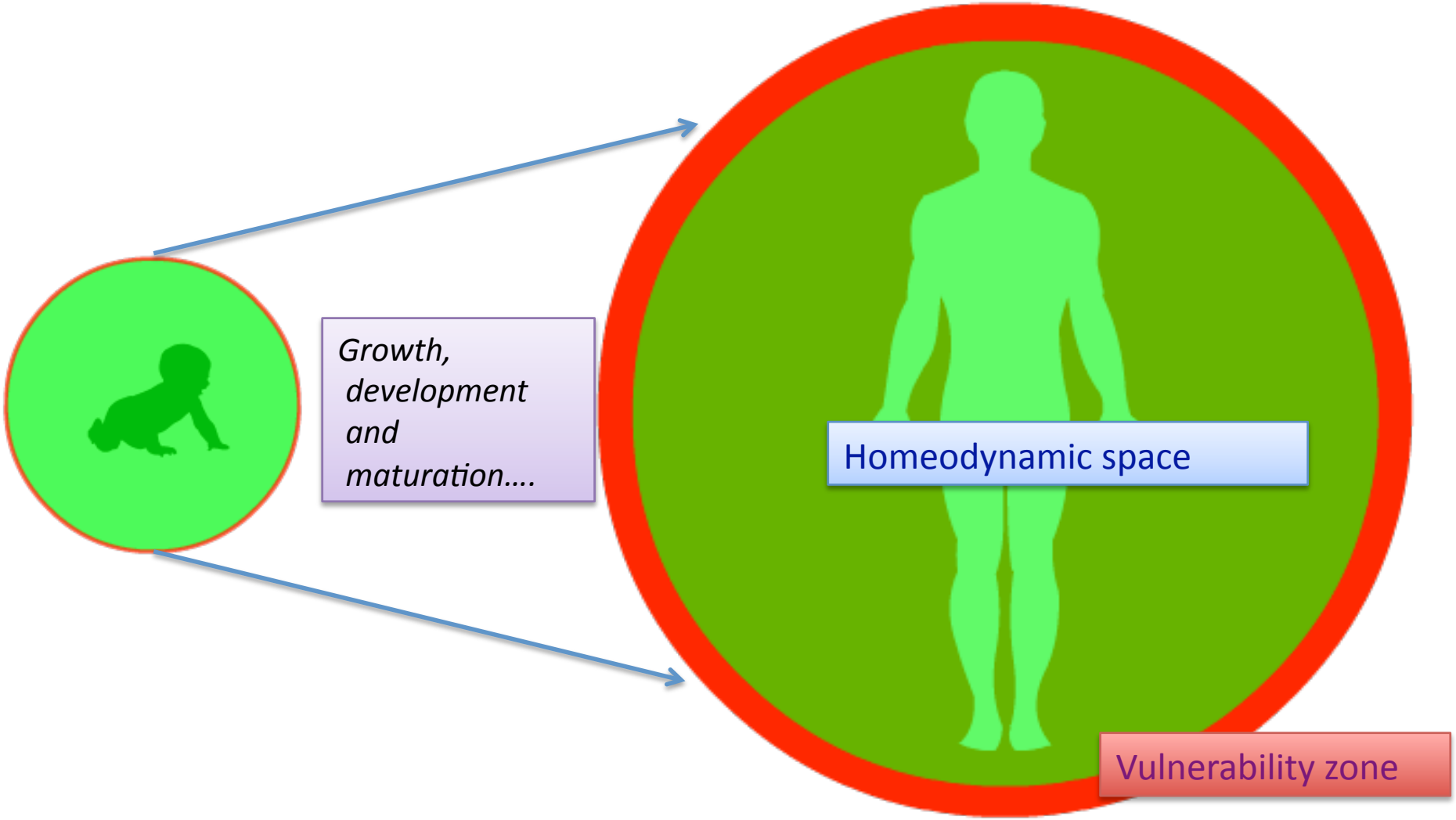
Biochemical infidelity
errors, modifications, misfolding

Sources of damage

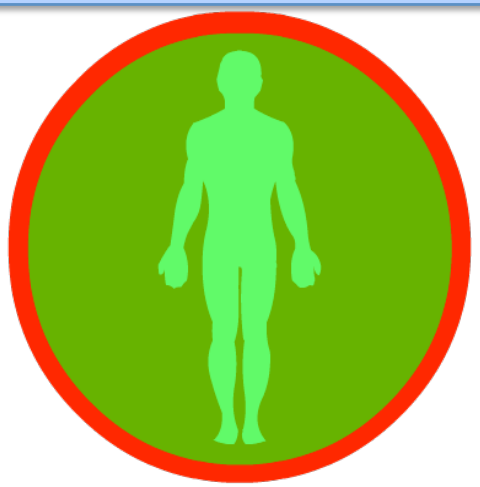
Maintenance and repair systems MARS

- Genomic stability
- Epigenomic stability
- Protein stability
- Macromolecular turnover
- Free radical counteraction

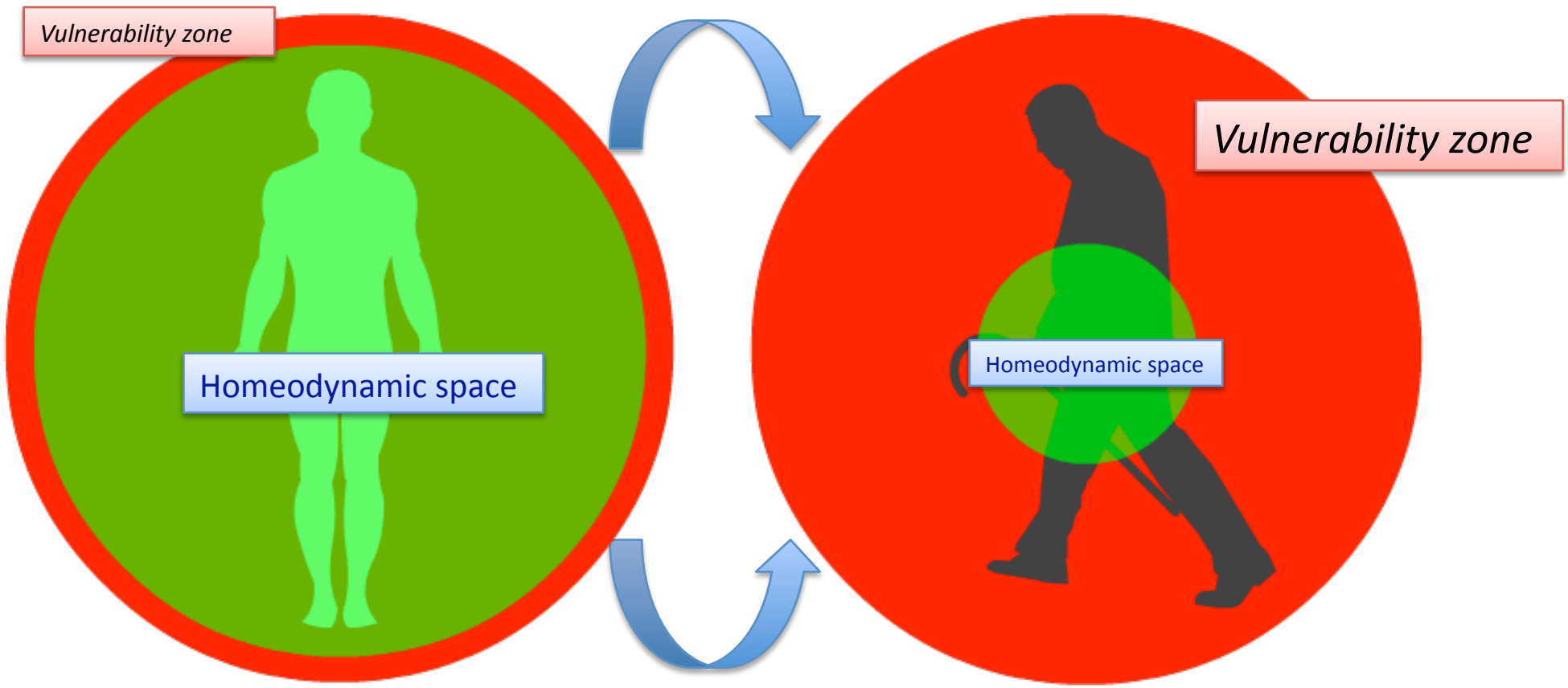
Our life depends on HOMEODYNAMIC SPACE



Characteristics of the homeodynamic space



1. Stress response and buffering capacity
2. Damage prevention, repair and removal
3. Cell and tissue functionality
4. Physiological networks, and continuous remodelling and adaptation



Ageing is the shrinkage of the homeodynamic space

A major shift in our approach towards ageing interventions is happening…

Instead of adopting an "enemy-oriented" approach against ageing,

the focus is now on "friend-oriented" approach in strengthening the homeodynamic processes of survival and longevity…

Hormesis

in ageing is based on the view that

deliberate challenging of the homeodynamic machinery

will transiently

stimulate compensatory, adaptive, and reparative processes.

Conditions that bring about hormesis are called: HORMETINS

- Physical hormetins

  exercise, heat, radiation...

- Psychological hormetins

mental activity, meditation…

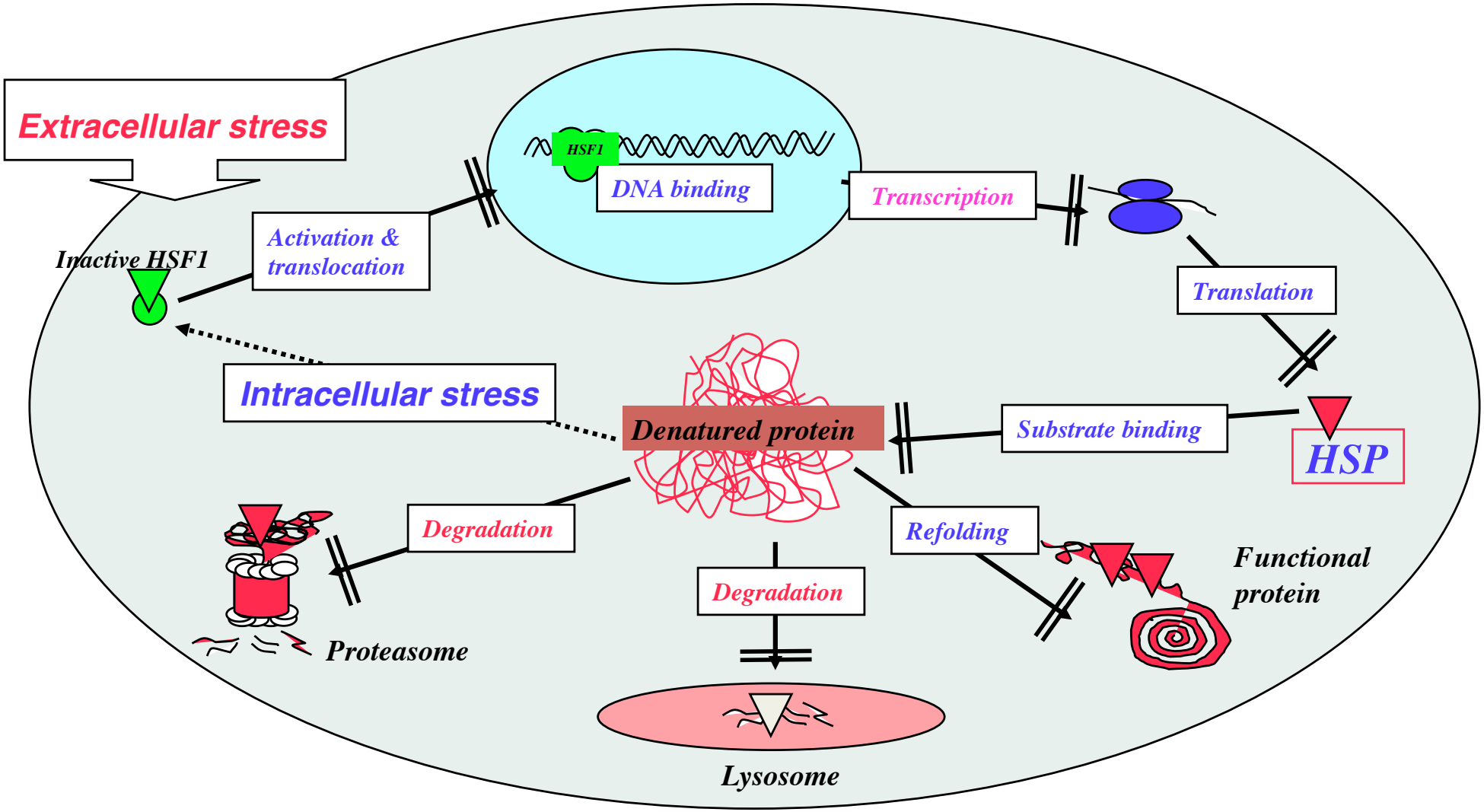
- Nutritional hormetins

  spices, polyphenols, micronutrients..

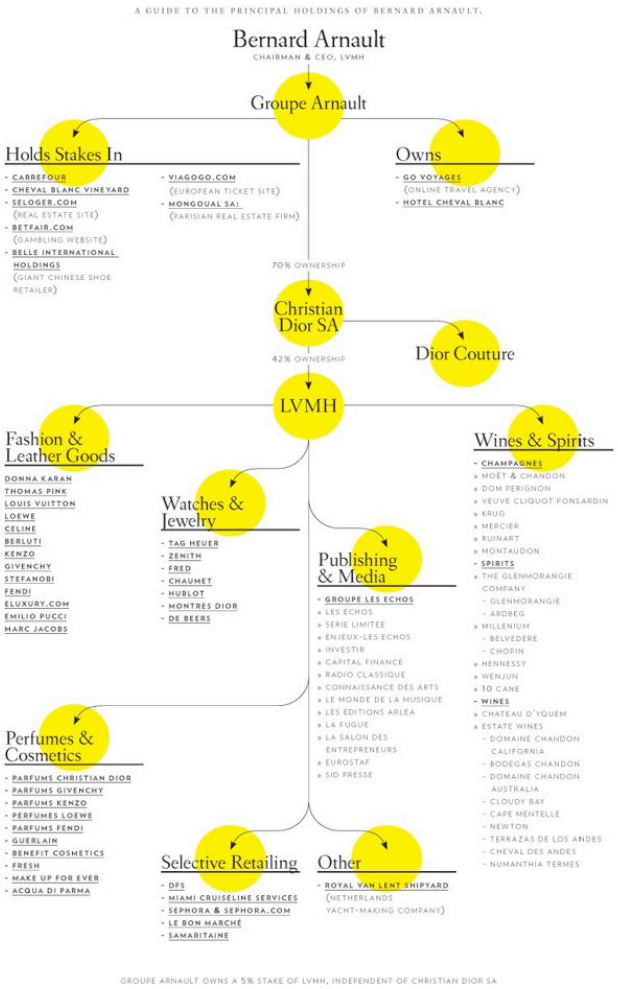
Biomarker of homeodynamics – STRESS RESPONSE

Response	*Stressors*	*Effectors*
Heat shock response	Heat, heavy metals, antibiotics, protein denaturation	Heat shock proteins, proteasome and other proteases
Unfolded protein response	Unfolded and misfolded proteins in endoplasmic reticulum	Chaperones, co-chaperones
Autophagic response	Food starvation, hypoxia, damaged organelles	Lysosomes
DNA-repair response	Radiation, oxidants, free radicals	DNA-repair enzymes
Antioxidant response	Free radicals, reactive oxygen species, pro-oxidants	Nrf-2, heme-oxygenase, FOXO
Sirtuin response	Energy depletion	Sirtuins
NF-κβ inflammatory response	Pathogens, allergens, damaged macromolecules	cytokines, nitric oxide synthase

Heat shock response in human cells



This is where LVMH-Givenchy come in…..



LOUIS VUITTON

LVMH
MOËT HENNESSY . LOUIS VUITTON

HERMÈS
PARIS

LVMH
MOËT HENNESSY . LOUIS VUITTON

GIVENCHY

Christian Dior
PARIS

LVMH labs screening for natural compounds for skin care –

starting in 2007

root extracts of

Panax notoginseng SAN CHI – *three-seven;*

BIOalternatives

Rapport de l'étude n° FX071118
Devis n° FX071118C

Effets de 32 composés sur l'expression du gène de la HSPA1A par des kératinocytes humains post-confluents en culture

Evaluation par RT-PCR quantitative

PROMOTEUR DE L'ÉTUDE

LVMH RECHERCHE

M. Marc DUMAS
Rue d'Enfer
45804 ST JEAN DE BRAYES
FRANCE
Tel : +33 (0)2 38 60 32 00

Fax : +33 (0) 2 38 60 3176

E-mail: mdumas@diormail.com

The first report of testing 32 compositions from Sanchi for the expression of HSP70 (HSPA1A) mRNA in human keratinocytes
(in 2008)

Scientific exploratory meeting with Dr. Carine Nizard of LVMH, in Paris University (2009)

Nom du gène	Abréviation	Gene Bank	cDNA bp
Liver glyceraldehyde 3-phosphate dehydrogenase	G3PDH	NM_002046	269
Homo sapiens heat shock 70kDa protein 1A	HSPA1A	NM_005345	213

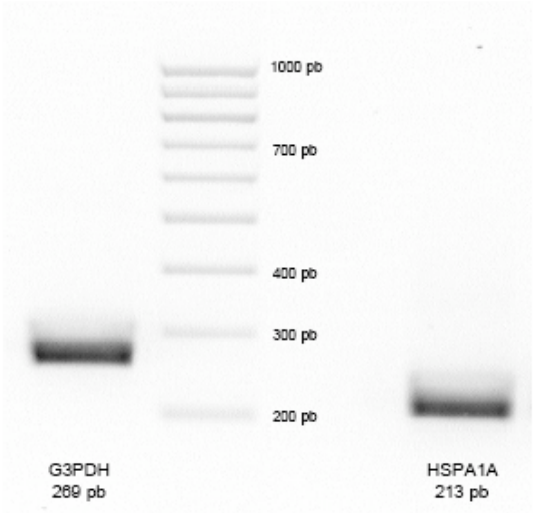
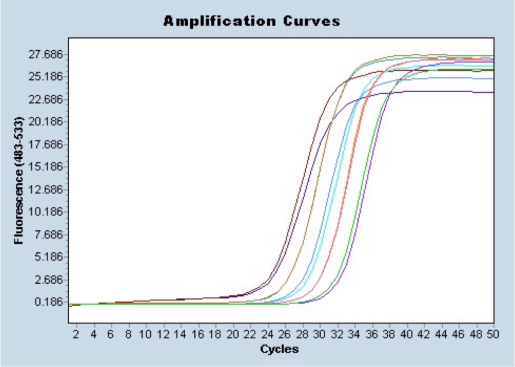


Figure 3 : Vérification par migration sur gel d'agarose de la taille (pb) des marqueurs d'intérêt

Homo sapiens heat shock 70kDa protein 1A (HSPA1A)



a : Courbe d'amplification du marqueur de référence HSPA1A

Some examples of data from the HSPA1A mRNA expression studies

stratiCell

CR/09/LVMH01: Influence de 2 éléments d'essai sur la quantité des protéines Hsp70, Hsp32 et Nrf2, suite à leur application sur des fibroblastes de derme.

StratiCELL
RAPPORT ANALYTIQUE n° CR/09/LVMH01
DONNEUR D'ORDRE: LVMH

Version finale CR/09/LVMH01 Date : 30 / 11 /2009

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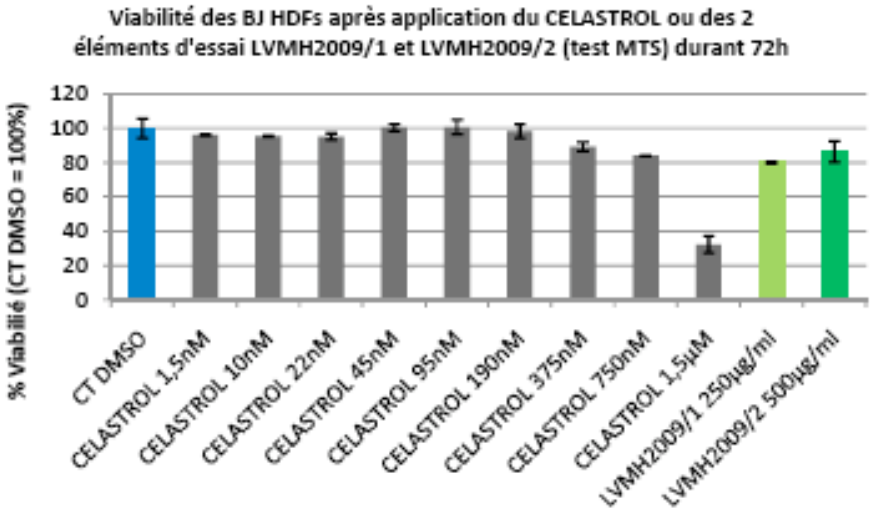
Phone : +32 (0)81 72 85 80
Fax : +32 (0)81 72 85 89

Science Park Crealys
Rue Jean Sonet 10 • 5032 Gembloux
BELGIUM

Email : info@straticell.com
Web : www.straticell.com

The final report of testing two compositions from Sanchi for the protein levels of HSP70 HSP32 and Nrf2 in human skin fibroblasts
(in November 2009)



Survival data for LVMH test compound

ure 2 : Viabilité des fibroblastes de derme après application du CELASTROL à différentes concentrations, ou des éléments d'essai MH2009/1 (250µg/ml) et LVMH2009/2 (500µg/ml), durant 72h (MTS).

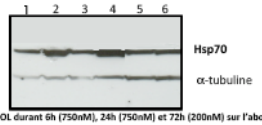


Figure 3A: Effet de l'application du CELASTROL durant 6h (750nM), 24h (750nM) et 72h (200nM) sur l'abondance de Hsp70 présente dans les BJ HDFs (WB). L'abondance de l'α-tubuline a été utilisée comme contrôle de charge. Piste 1 : CT 6h, piste 2 : CELASTROL 750nM 6h, piste 3 : CT 24h, piste 4 : CELASTROL 750nM 24h, piste 5 : CT 72h, piste 6 : CELASTROL 200nM 72h.

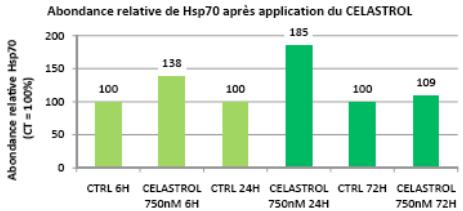


Figure 3B: Quantification par analyse d'image de l'abondance relative de Hsp70. Les données obtenues ont été rapportées à l'abondance protéique de l'α-tubuline. Les contrôles respectifs ont été arbitrairement fixés à 100%.

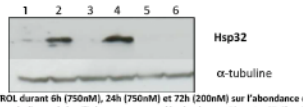


Figure 4A: Effet de l'application du CELASTROL durant 6h (750nM), 24h (750nM) et 72h (200nM) sur l'abondance de Hsp32 présente dans les BJ HDFs (WB). L'abondance de l'α-tubuline a été utilisée comme contrôle de charge. Piste 1 : CT 6h, piste 2 : CELASTROL 750nM 6h, piste 3 : CT 24h, piste 4 : CELASTROL 750nM 24h, piste 5 : CT 72h, piste 6 : CELASTROL 200nM 72h.

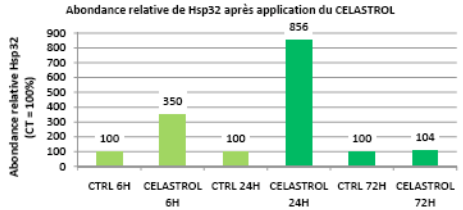


Figure 4B : Quantification par analyse d'image de l'abondance relative de Hsp32. Les données obtenues ont été rapportées à l'abondance protéique de l'α-tubuline. Les contrôles respectifs ont été arbitrairement fixés à 100%.

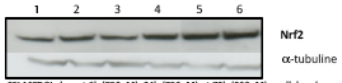


Figure 5A : Effet de l'application du CELASTROL durant 6h (750nM), 24h (750nM) et 72h (200nM) sur l'abondance de Nrf2 présente dans les BJ HDFs (WB). L'abondance de l'α-tubuline a été utilisée comme contrôle de charge. Piste 1 : CT 6h, piste 2 : CELASTROL 750nM 6h, piste 3 : CT 24h, piste 4 : CELASTROL 750nM 24h, piste 5 : CT 72h, piste 6 : CELASTROL 200nM 72h.

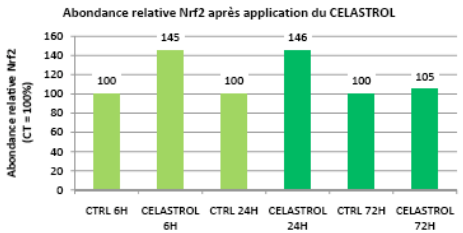


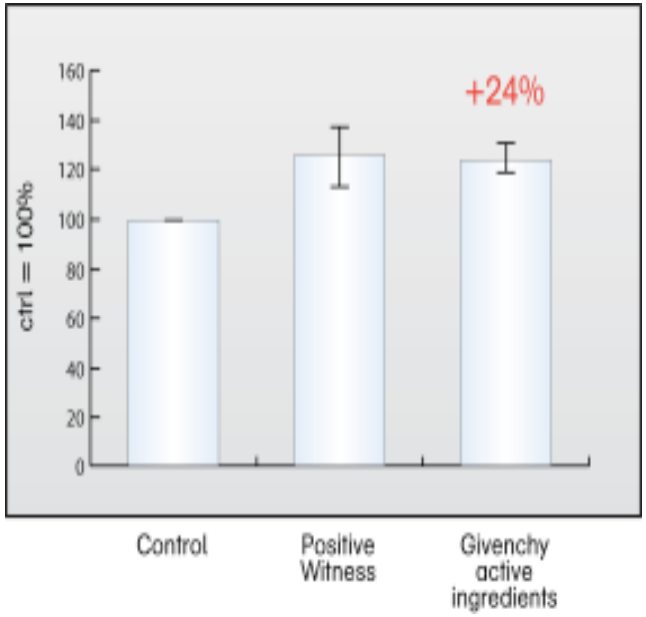
Figure 5B : Quantification par analyse d'image de l'abondance relative de Nrf2. Les données obtenues ont été rapportées à l'abondance protéique de l'α-tubuline. Les contrôles respectifs ont été arbitrairement fixés à 100%.

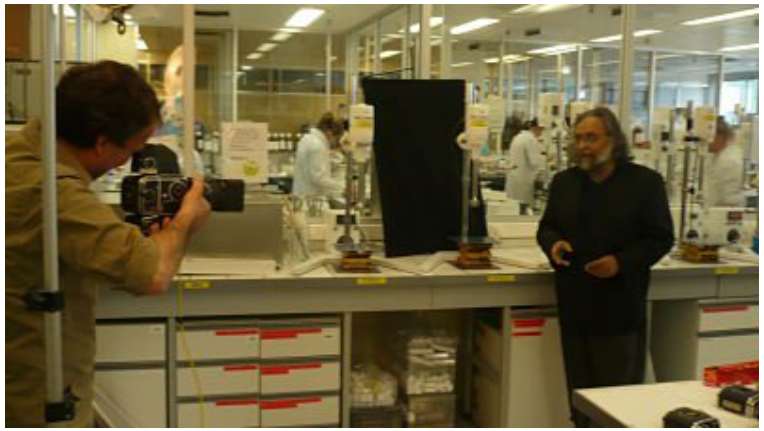
Induction of HSp70, Hsp32, and Nrf2 by a known stress-inducer, celastrol

		Hsp70			Hsp32			Nrf2		
	Concentration	6h	24h	72h	6h	24h	72h	6h	24h	72h
CELASTROL	750nM	+ 48%	+ 66%	+ 42%	+ 450%	+ 1167%	- 29%	- 67%	- 11%	-10%
LVMH2009/1	50µg/ml	+ 30%	+ 10%	- 4%	/	+ 16%	- 47%	- 95%	+ 23%	-8%
	100µg/ml	+ 20%	+ 15%	- 2%	+ 156%	+ 29%	- 29%	- 51%	- 4%	-9%
	250µg/ml	+ 10%	+ 16%	- 3%	+ 130%	+ 131%	- 6%	- 10%	+ 18%	-11%
LVMH2009/2	80µg/ml	- 5%	- 13%	- 64%	+ 240%	- 100%	- 64%	- 100%	- 50%	-26%
	250µg/ml	- 4%	- 17%	- 47%	+ 116%	- 67%	- 73%	- 96%	- 84%	-5%
	500µg/ml	- 5%	- 5%	- 41%	- 1%	- 34%	- 58%	- 98%	- 3%	-5%

En conclusion, en accord avec le donneur d'ordre, il a été décidé pour la suite de l'étude de mesurer, sur 3 cultures indépendantes, l'abondance relative de Hsp70, Hsp32 et Nrf2 après 6h et 24h d'incubation en présence des éléments d'essai LVMH2009/1 et LVMH2009/2.

Induction of stress protein Hsp70 by LVMH test compound





Communicating hormesis to world media

IN VIVO TESTS RESULTS

1. FIRMNESS IS MAINTAINED

2 tests conducted:

- Measured Test: Effect on the skin's capacity for fatigue (evaluation with the help of a cutometer*, comparison before/after) / Panel: 32 persons / Immediate
- Clinical Test: evaluation by a dermatologist / Panel: 43 persons / 1 month

Conclusion: skin's capacity for fatigue is unchanged so firmness is maintained

2. SKIN IS PROTECTED AGAINST AGGRESSIONS

Measured Test: Evaluation of the protective effect.
Panel: 10 persons / 48 hours
Instrumental test, measured 48 hours after aggressive washing

Conclusion: The skin is protected by 31% against aggressions

3. WRINKLE FORMATION IS SLOWED DOWN

Measured Test: Orientation and appearance of wrinkles.
Panel: 18 persons / 1 month
Test realized on one side of the face with our product (treated zone) and placebo on the other side of the face (non treated zone)

Conclusion: on the treated zone, wrinkle formation is slowed down. On the non-treated zone, the wrinkle formation appears and starts to deepen.

** A cutometer is a device which measures the stretch capacity and residual deformation of the skin using the vacuum principle, sucks up a defined area of skin surface.*

The first hormesis-based skin care hormetin product VAXIN FOR YOUTH is launched in Paris in June 2010.

STRESS RESPONSES for discovering hormetins

Table 1: Major pathways of stress response in human cells

Stress response	Stressors	Effectors
Heat shock response (HSR)	Heat, heavy metals, antibiotics, protein denaturation	Heat shock proteins, proteasome, and other proteins
Unfolded protein response (UPR)	Unfolded and misfolded proteins in endoplasmic reticulum	Chaperones and co-chaperones
Autophagic response	Food limitation, hypoxia, damaged organelles	Lysosomes
DNA-repair response	Radiation, oxidants, free radicals	DNA-repair enzymes
Antioxidant response	Free radicals, reactive oxygen species, pro-oxidants	Nrf-2, heme oxygenase, FOXO
Sirtuin response	Energy depletion	Sirtuins
NFκB inflammatory response	Pathogens, allergens, damaged macromolecules	Cytokines, nitric oxide synthase

A successful translation of scientific ideas into products….