

# NANOTECNOLOGÍA APLICADA AL DESARROLLO DE PRODUCTOS PARA LA PIEL

**Olga López**

Bicosome S.L., IQAC-CSIC, C/Jordi Girona 18-26,  
08034 Barcelona Spain

bicosome®



## CONTENIDOS:

- Crecimiento del mercado de la nanotecnología a nivel global,.
- Empresas basadas en nanociencia y nanotecnología en España.
- ¿Por qué nanotecnología en el campo de la piel?
- Tecnología Bicosome.
- De la ciencia a la industria y de la industria al mercado.
- Líneas de negocio de Bicosome.



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# There's Plenty of Room at the Bottom

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*An invitation to enter a new field of physics.*

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*by Richard P. Feynman*

I imagine experimental physicists must often look with envy at men like Kamerlingh Onnes, who discovered a field like low temperature, which seems to be bottomless and in which one can go down and down. Such a man is then a leader and has some temporary monopoly in a scientific adventure. Perce

nothing; that's the most primitive, halting step in the direction I intend to discuss. It is a staggeringly small world that is below. In the year 2000, when they look back at this age, they will wonder why it was not until the year 1960 that anybody began seriously to move in this direction.

*Proc. Natl. Acad. Sci. USA*  
Vol. 78, No. 9, pp. 5275–5278, September 1981  
Chemistry

## **Molecular engineering: An approach to the development of general capabilities for molecular manipulation**

(molecular machinery/protein design/synthetic chemistry/computation/tissue characterization)

**K. ERIC DREXLER**

Space Systems Laboratory, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

*Communicated by Arthur Kantrowitz, June 4, 1981*

**ABSTRACT** Development of the ability to design protein molecules will open a path to the fabrication of devices to complex atomic specifications, thus sidestepping obstacles facing conven-

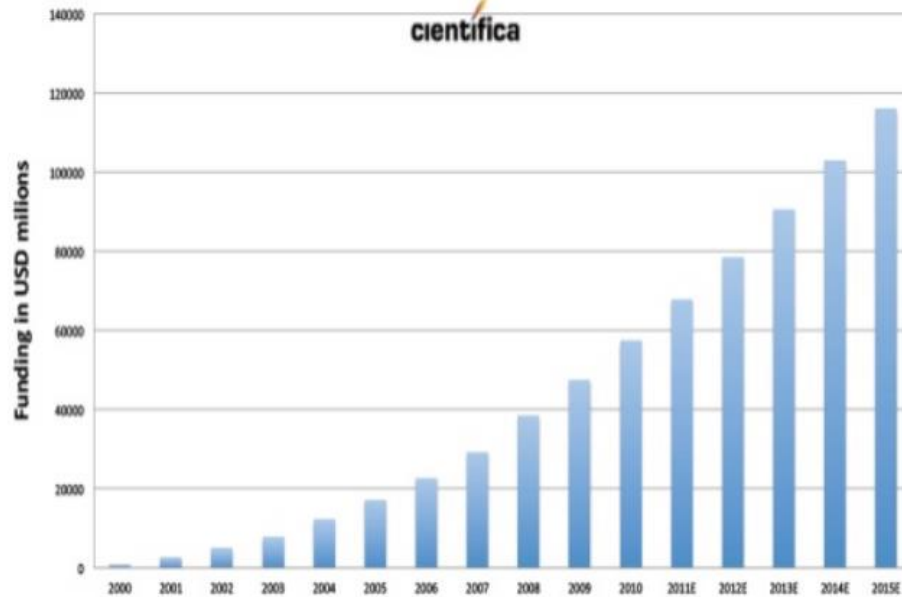
by mathematical proof. We commonly accept the feasibility of new devices without formal proof, where analogies to existing systems are close enough: consider the feasibility of making a



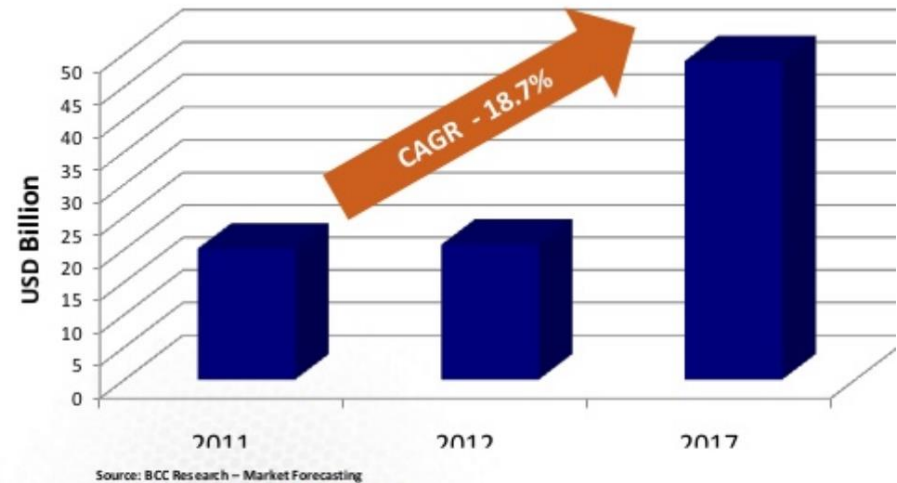
# NANOTECHNOLOGY MARKET

Total Global Nanotechnology Funding

cientifica

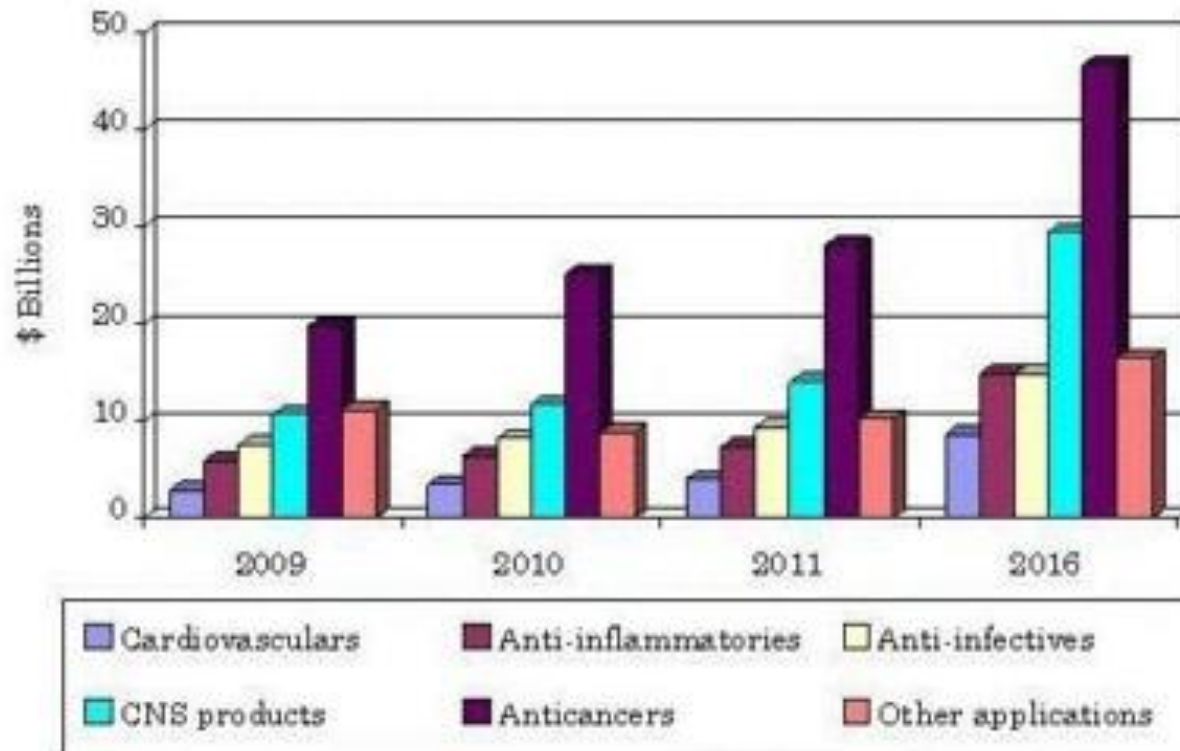


Nanotechnology - Global Market



# NANOMEDICAL MARKET

**SUMMARY FIGURE**  
**NANOMEDICAL GLOBAL SALES BY THERAPEUTIC AREA, 2009-2016**  
**(\$ BILLIONS)**



Source: BCC Research

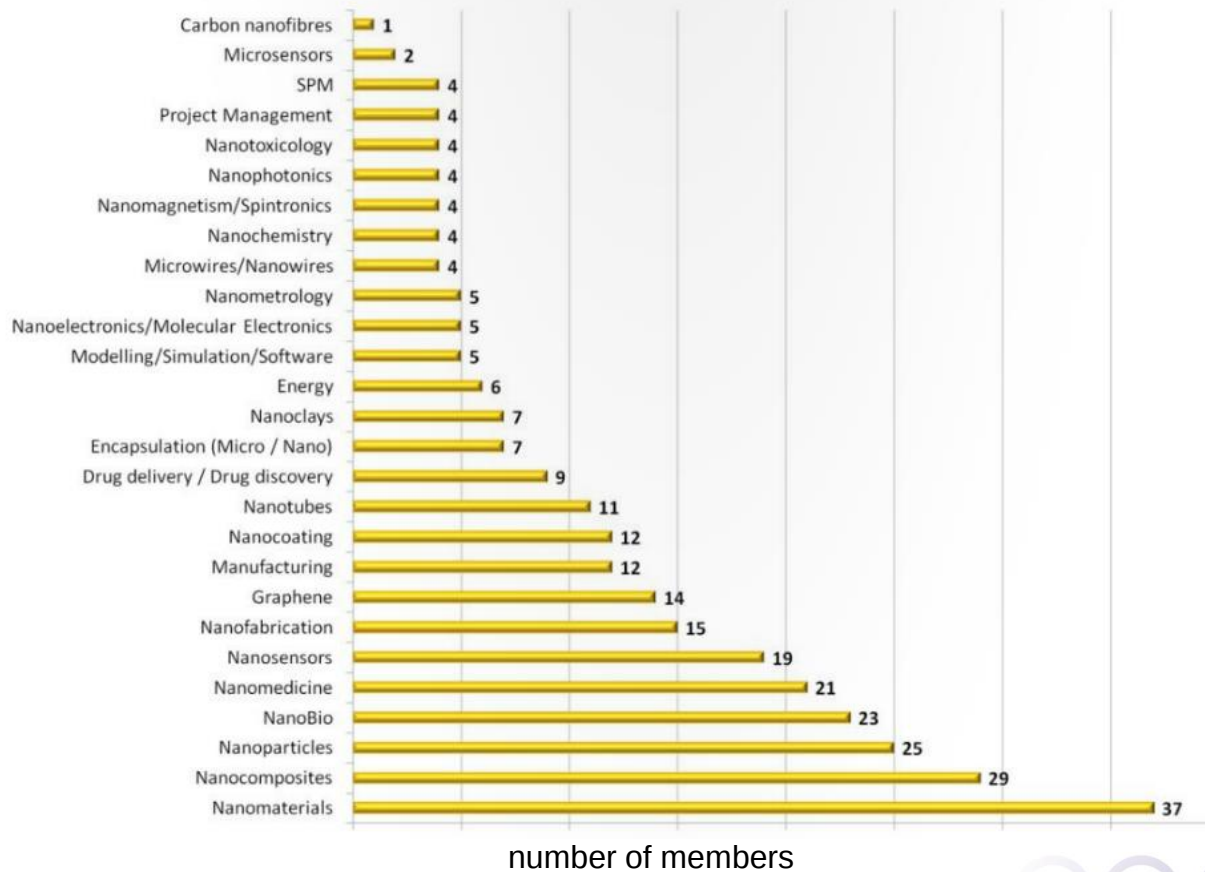


Red Española de Nanotecnología  
Spanish Nanotechnology Network

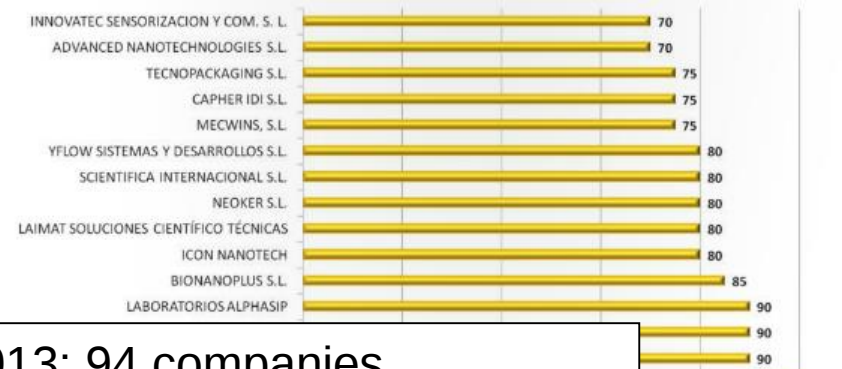
2007 → 234 Members, 1500 researchers

2013 → 342 Members, 2500 researchers

## Members per research topic



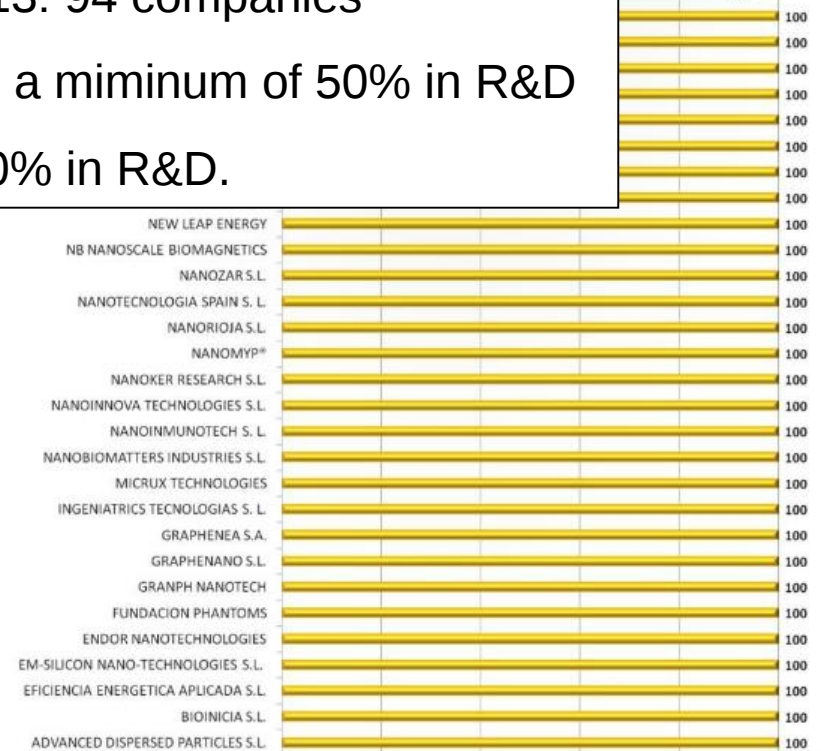
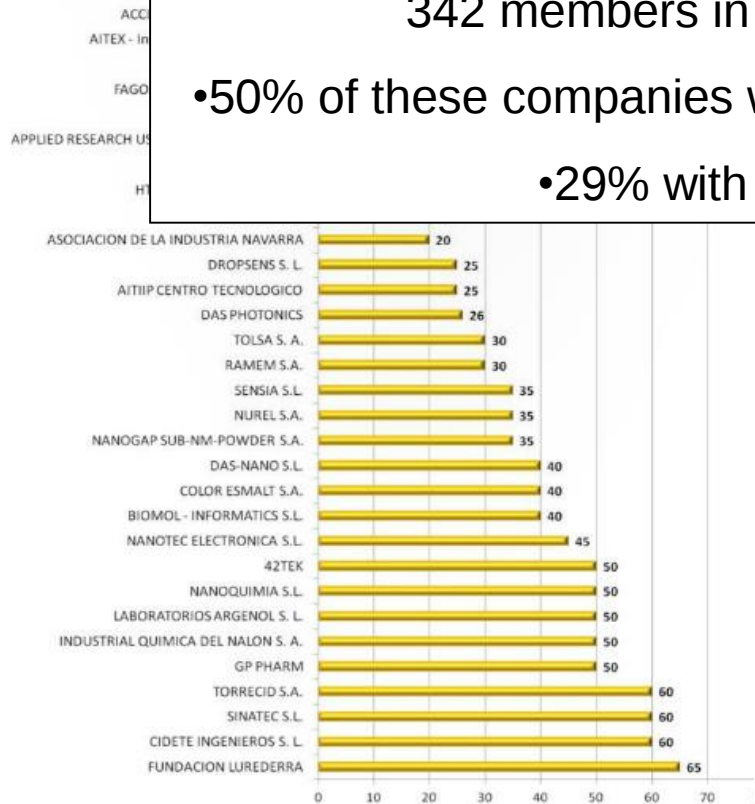
# % Activity in nanoscience and nanotechnology in R&D



342 members in 2013: 94 companies

•50% of these companies with a minimum of 50% in R&D

•29% with 100% in R&D.



## MAIN CHARACTERISTICS OF NANOTECHNOLOGY COMPANIES:

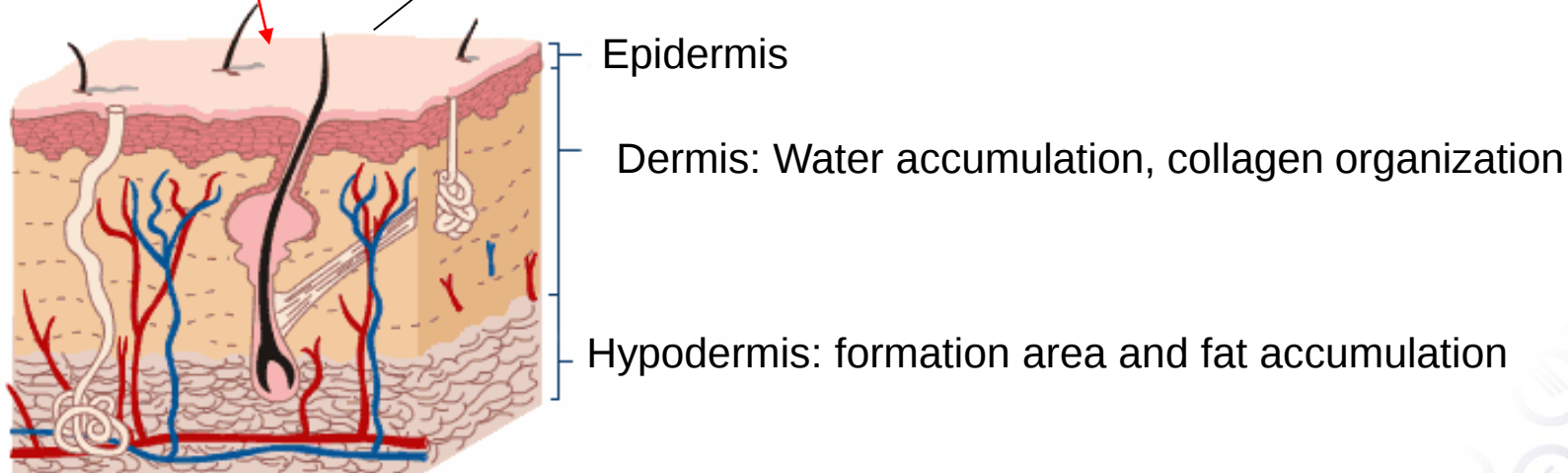
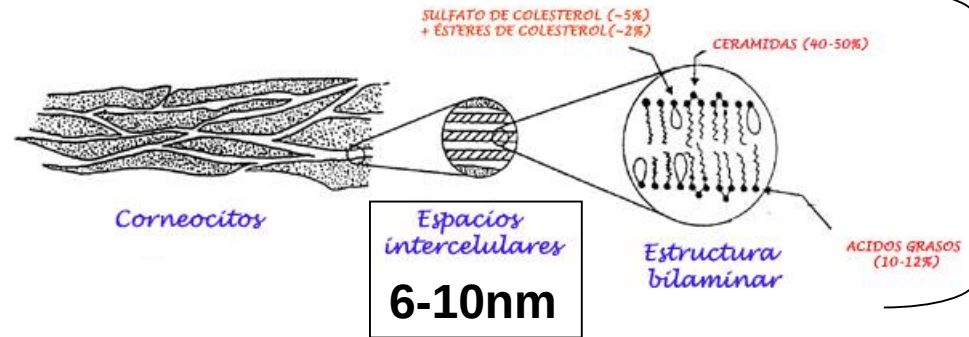
- High dedication in R&D activities
- Intellectual and technology proprietary (patents)
- Spin-off companies from public research institutions and Universities.
- Financiation from national and european projects.



# WHY NANOTECHNOLOGY IN THE SKIN ?



## Stratum corneum:



The specific composition and organization of the SC lipids are the responsible of the barrier function of the skin

## WHY NANOTECHNOLOGY IN THE SKIN ?

The intercellular spaces in the outermost layer of the skin are in the nano dimension.

### PROVIDES

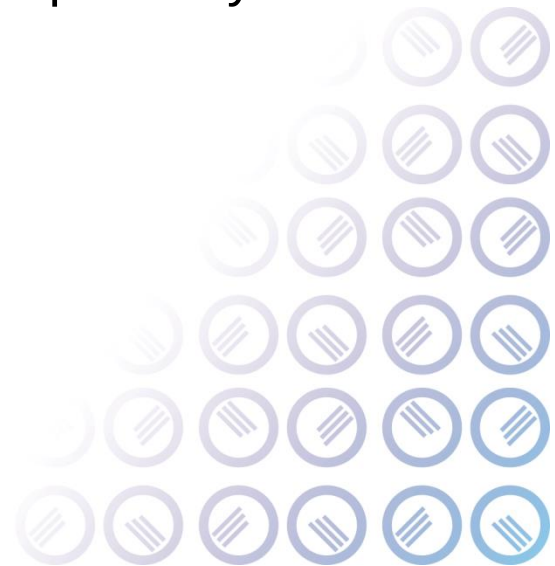
Methodologies of analysis and treatments able to cross the barrier.

### POTENTIALLY SOLVES

Improvement in treatments, more efficacy, more specificity.

### BUT: Potential risks

Development of new irritants, alergents, etc.

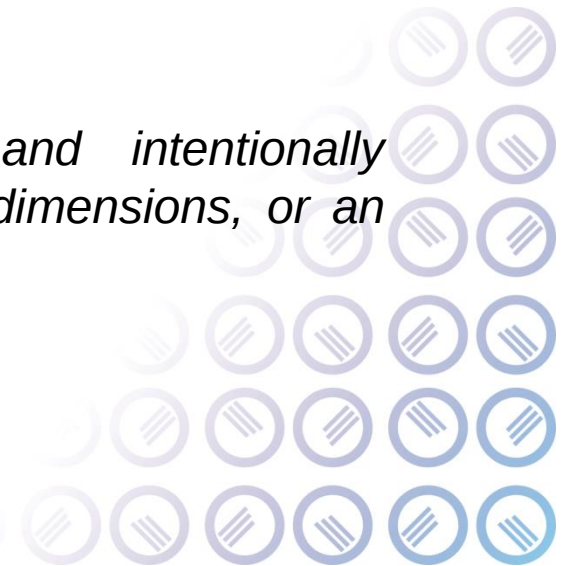


## NANOPARTICLES FOR SKIN PURPOSES

Hard insoluble nanoparticles: metal oxides, minerals, fullerenes .

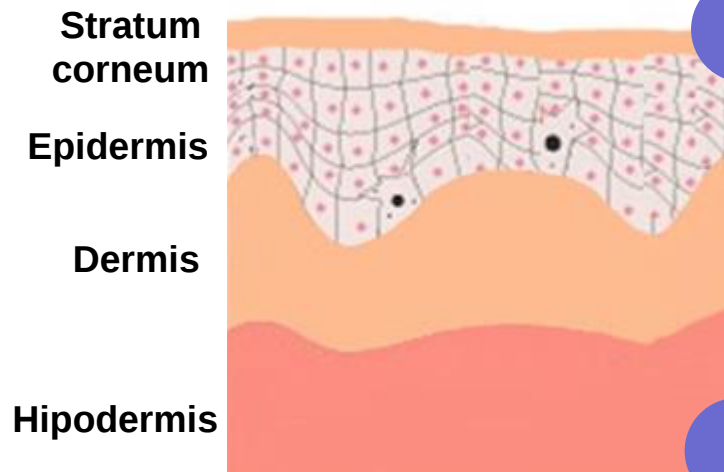
Soft dispersable nanoparticles: lipid nanostructures and amphiphilic-based assemblies

*Nanomaterial: “an insoluble or biopersistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm”*



# BICOSOME TECHNOLOGY: THE CHALLENGE OF SKIN TREATMENT

**Skin barrier function:** Protects the organism from external aggression but also difficult that actives with potential benefits go into the skin.



Representation of skin layers

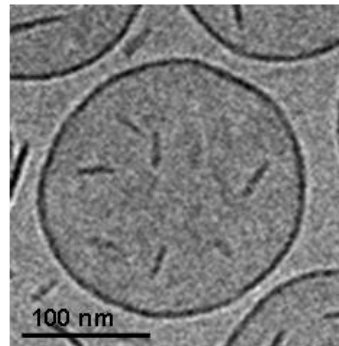
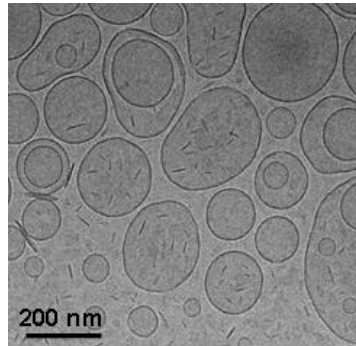
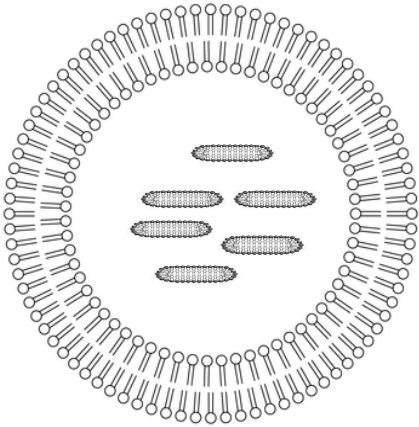
Products applied on the skin do not really penetrate the tissue, having effects only on the skin surface and disappearing after just a single wash

Other products penetrate aggressively the skin, promoting damages, and reaching the bloodstream

Effective treatment of the skin requires that actives **penetrate gently the skin and remain there** in target layers

# BICOSOME TECHNOLOGY

Bicosome is based on different lipid aggregates, smart structures enclosed in vesicles.



Smart structures: 6-20 nm

Vesicles: 150-250 nm

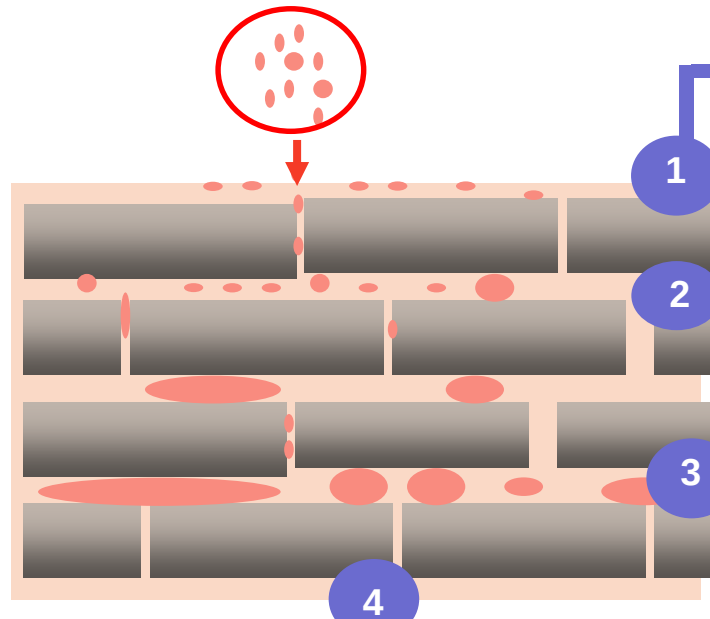
## Cryo-TEM micrograph of bicosome® structures

**Dynamic Light Scattering:** *Size of smart structures is appropriate for penetrate between the narrow intercellular spaces of the outermost layer of the skin, the stratum corneum.*

**X-Ray Scattering:** Bicosome is *structurally based on lipids bilayers* similar to those present in the skin.

**Microscopy:** *Great morphological versatility, these structures are able to adopt different sizes and shape depending on composition and environment.*

# BICOSOME: INTERACTION WITH SKIN



Smart structures of bicosome are small enough for passing through the narrow intercellular spaces of the stratum corneum, without damaging the tissue

Once inside, structures from bicosome suffer from a transformation, increasing in size.

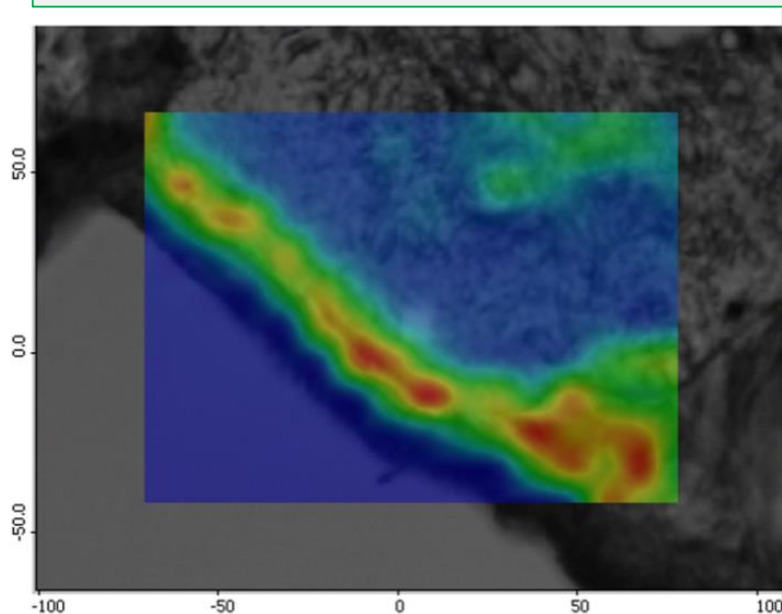
This increase in size allows these structures to be retained in between skin cells, and also allows for the slow delivery of the actives included in the bicosome.

Bicosome and actives remain there until the layer is lost by the normal desquamation process, resulting in higher efficacy and long lasting effects



# BICOSOME: SKIN PENETRATION

Synchrotron IR microspectroscopy of the skin treated with bicosome

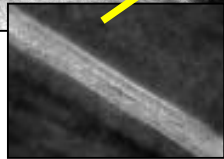
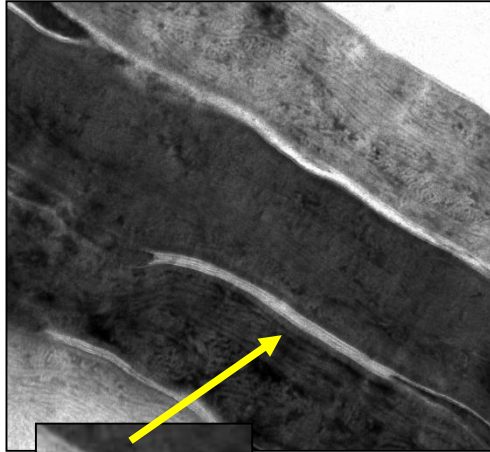


Red light zones correspond to the areas in which bicosome is retained

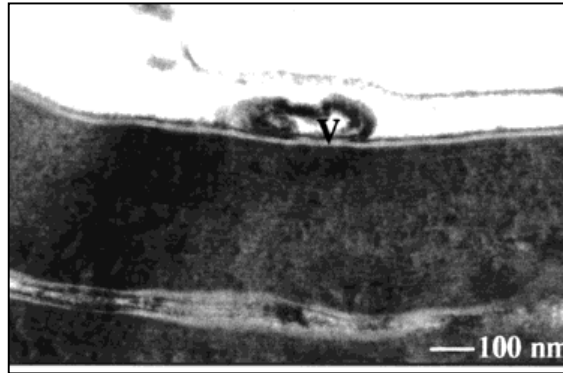
\* Intensity distribution map of  $\text{CD}_2$  stretching vibrations in skin treated with d-Bicosomes.

**BICOSOME PENETRATES AND REMAINS IN THE SKIN**

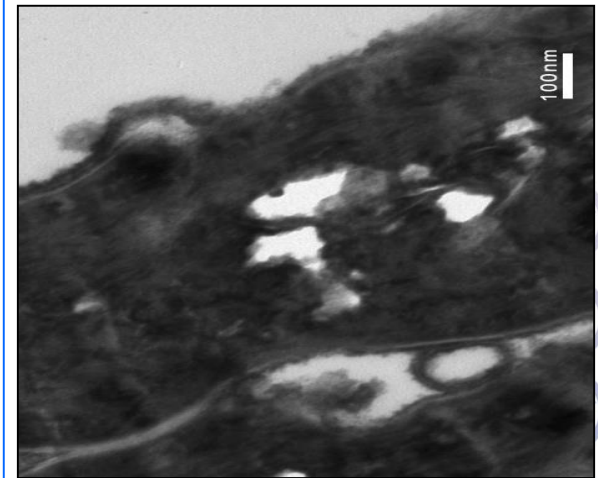
# BICOSOME: LIPID BARRIER REINFORCEMENT



*Native Skin  
Stratum Corneum*



*Skin Stratum  
Corneum treated with  
Liposomes*

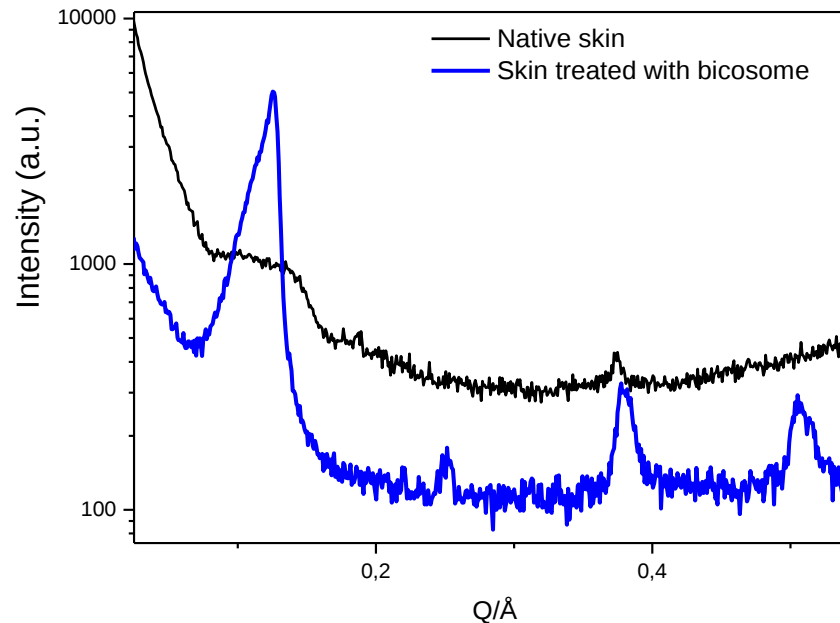


*Skin Stratum  
Corneum treated with  
Bicosomes*

**Bicosome reinforces the skin lipid structure** at two levels. New lamellar structures are formed inside the tissue and other are detected on the skin surface.

# BICOSOME: LIPID BARRIER REINFORCEMENT

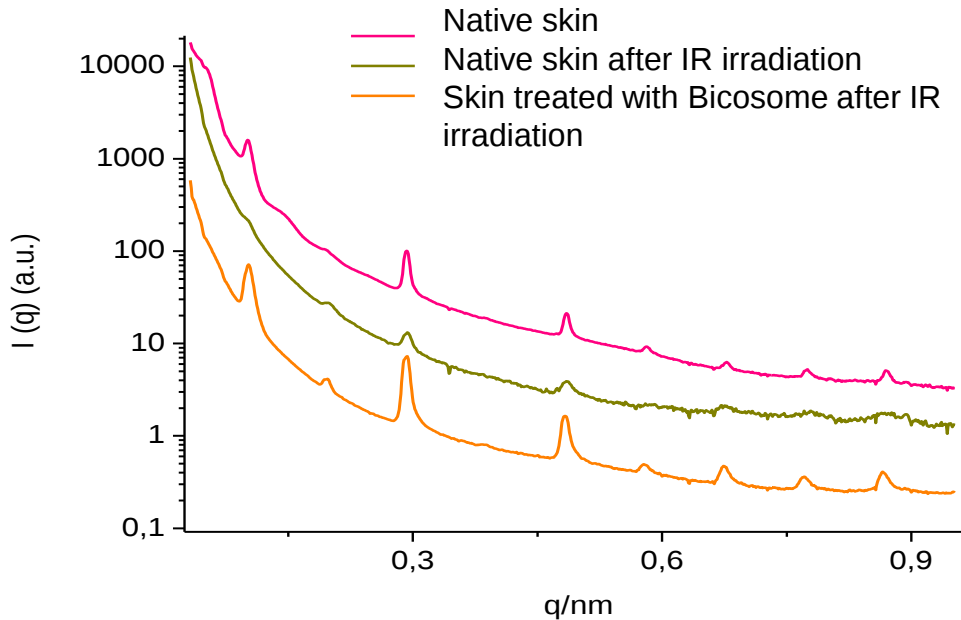
## Small Angle X-ray Scattering from stratum corneum lipids (SAXS)



**Bicosome** reinforces the skin lipid structure by **addition of new lipids** and by increasing the **order in the lipid organization**

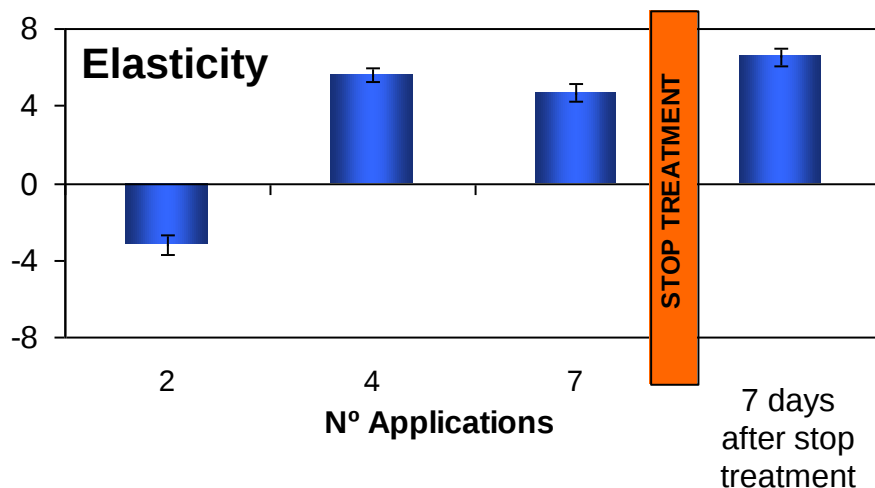
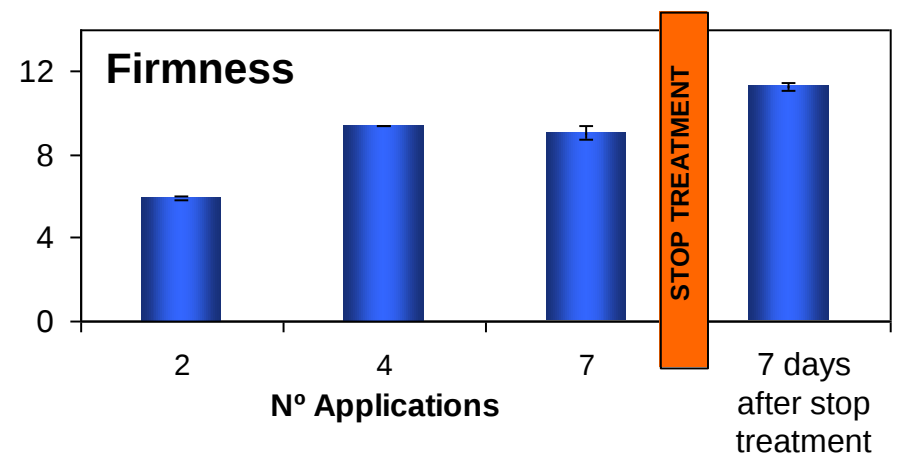
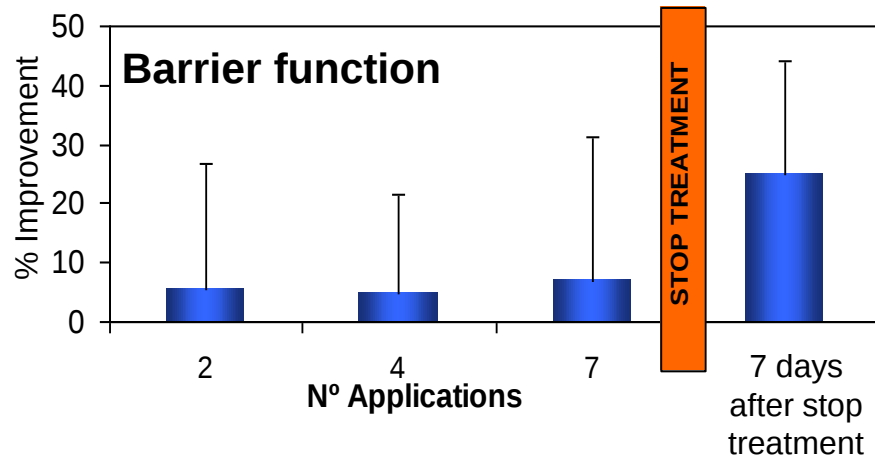
# BICOSOME: COLLAGEN PROTECTION

## Small Angle X-ray Scattering from skin collagen



**Bicosome exerts a protective effect on collagen fibers from degradation induced by IR radiation.**

# BICOSOME: LONG LASTING EFFECT IN VIVO

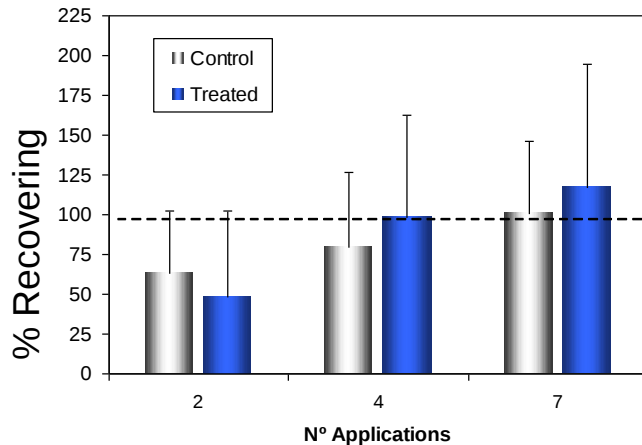


•Bicosome reinforces the skin barrier function (6%), firmness (9%) and elasticity (5%) after seven applications.

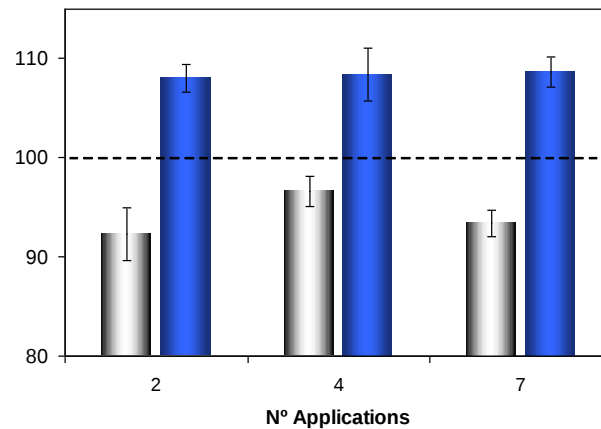
•These effects last for at least 7 days after stop treatment. Skin barrier function improves from 6 to 25% in this period.

# BICOSOME: REPAIRING EFFECT ON DAMAGED SKIN

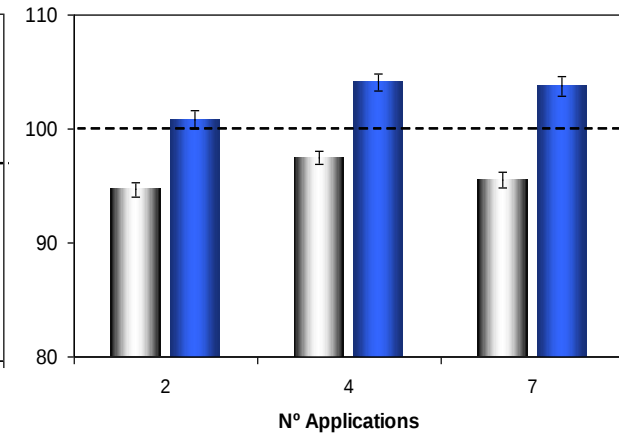
## Barrier function



## Firmness



## Elasticity



- Bicosome **recovers skin barrier function after 4 applications.**
- Firmnes and elasticity are recovered after 1 application.**

In vivo Erythema and Melanin studies were also performed. No alterations were detected during the days of experiment.

# BICOSOME: INCORPORATION OF DIFFERENT COMPOUNDS

Bicosomes have been tested for the incorporation of different molecules with both hydrophobic or hydrophilic characteristics.

Examples of actives incorporated in Bicosomes structures are:

- **skin lipids:** ceramides, cholesterol, cholesteryl sulfate
- **cosmetic actives:** caffeine, vitamins (E, A, or C), antioxidants
- **drugs:** antibiotic, antifungal and anti-inflammatory drugs
- **other:** iron, fluorescent probes, magnetic resonance markers, etc.

# BICOSOME CONTAINING BETACAROTENE

## Confocal Raman Microscopy: Distribution of betacarotene in skin

Skin treated with Bicosome

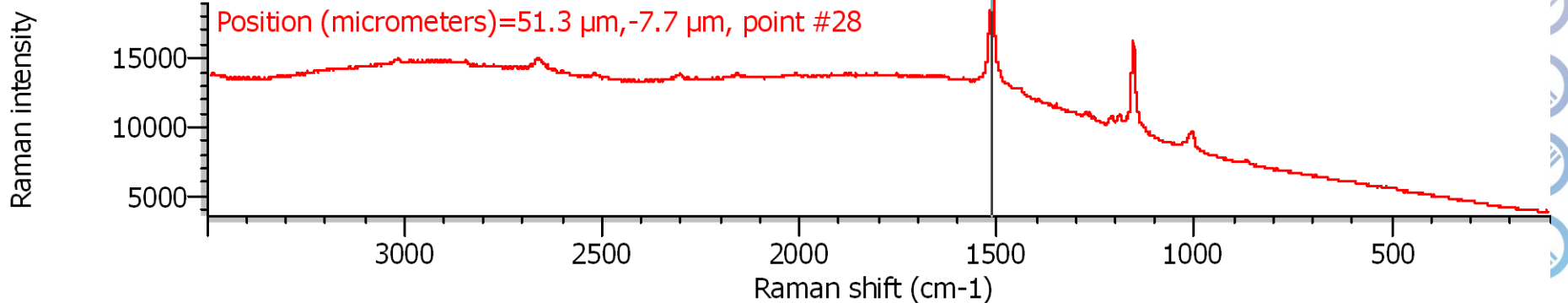
Penetration:  
40 $\mu$ m



Skin treated with Liposome

Penetration: 5  
 $\mu$ m

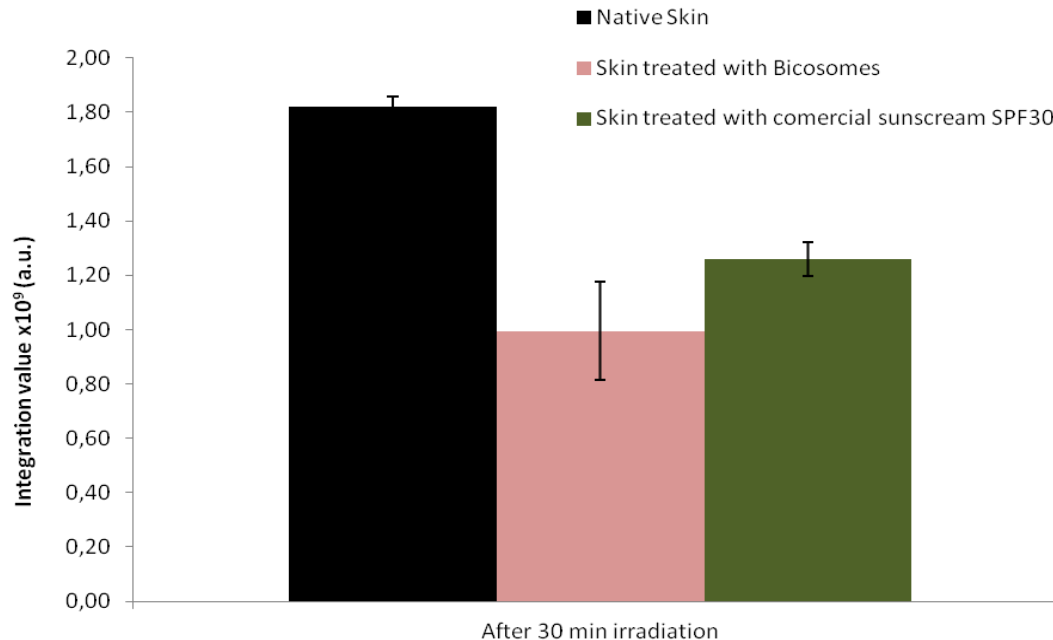
Raman spectra showing  
betacarotene peaks



# BICOSOME CONTAINING BETACAROTENE: FREE RADICAL SCAVENGER

Electron Paramagnetic Resonance technique (EPR) using the spin trap 5,5-dimethyl-1-pyrroline-N-oxide allows us to evaluate the formation of free radicals in skin after UV irradiation.

*Free radical species in skin after UV irradiation:*



•Treatment of the skin with Bicosome including betacarotene **inhibits the formation of free radical in the skin** by UV radiation with **higher efficacy** than a commercial sunscreen.

# BICOSOME CONTAINING NYSTATIN

**Nystatin in Bicosome**

| %             | mean  | CV   |
|---------------|-------|------|
| wash          | 29.50 | 3.16 |
| Mucosa tissue | 70.12 | 2.10 |
| f.r.          | --    | --   |
| recover       | 99.62 | 3.76 |

**Nystatin in commercial product**

| %             | mean  | CV   |
|---------------|-------|------|
| wash          | 89.60 | 2.71 |
| Mucosa tissue | 10.33 | 3.20 |
| f.r.          | --    | --   |
| recover       | 99.93 | 3.76 |

The amount of nystatin retained in mucosa was higher when the drug was included in bicosome than when was formulated in the commercial product.

**Bicosome increases the retention of drug in the tissue.**

***Lipid Biophysics Group and  
Interfaces (IQAC – CSIC)***

*20 years expertise on lipid  
systems and skin related studies*

TECNOLOGÍA  
PATENTADA



EMPRENDEDOR  
DISPUESTO A  
DEDICARSE FULL  
TIME AL PROYECTO

**bicosome®**

- 2010 Solicitud de patente por parte del CSIC.
- 2010-2014 Formación en negocios
- 2012 Fundación de la empresa, obtención de la licencia de la patente, obtención del préstamo INNCORPORA.
- 2013 Cierre de la primera ronda de inversión, obtención de préstamos ENISA y NEOTEC, concesión de un contrato TORRES QUEVEDO, primeras ventas.
- 2014 Completando el equipo, TORRES QUEVEDO, primeros co-desarrollos.

# BICOSOME BUSINESS MODEL

- Commercialization of proprietary pipeline

| PRODUCT                       | Feasibility                                                                       | Formulation                                                                       | Efficacy / Safety                                                                   | Production                                                                          | Market                                                                              |
|-------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Bicosome FS                   |  |  |  |  |  |
| Bicotene Antiox<br>UV Protect |  |  |  |                                                                                     |                                                                                     |
| Bicocel Anticelulitis         |  |  |                                                                                     |                                                                                     |                                                                                     |
| Bicowhite                     |  |                                                                                   |                                                                                     |                                                                                     |                                                                                     |

- Partnering for co-developments





[www.bicosome.com](http://www.bicosome.com)

[info@bicosome.com](mailto:info@bicosome.com)

T. (34) 93 400 61 63

c/ [Jordi Girona](#) 18

08034 Barcelona (Spain)

MANY THANKS