APPLICATION OF SILK ON COSMETICS

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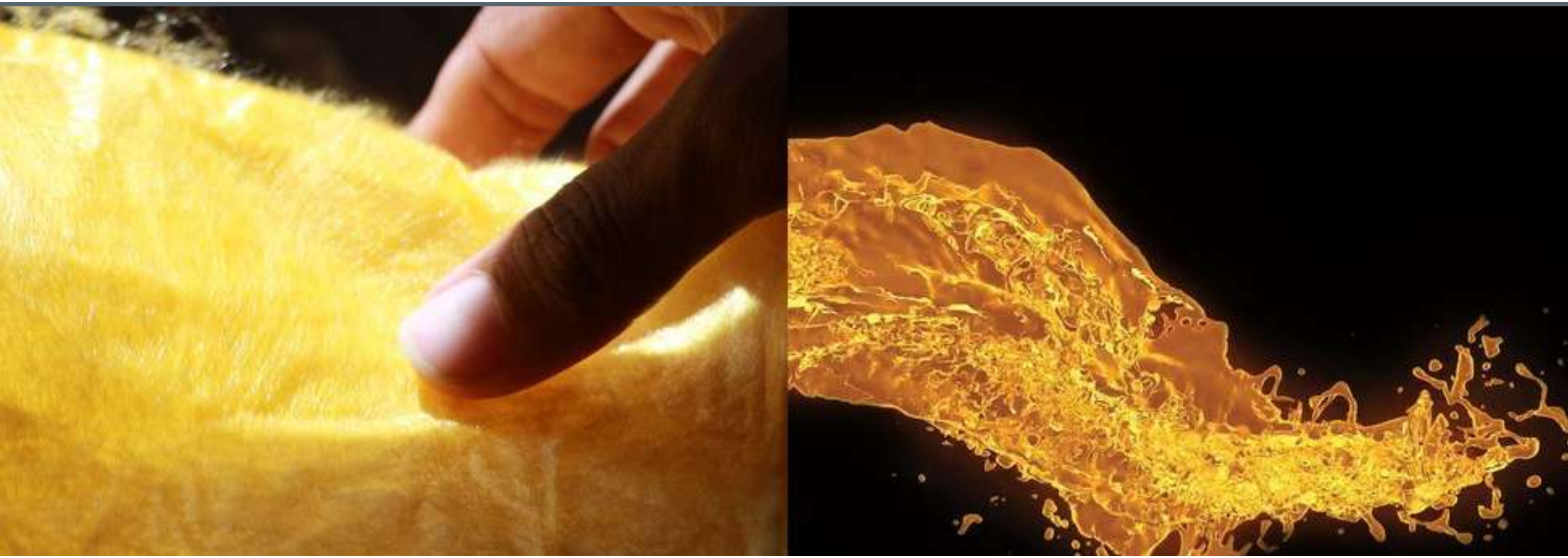

FIBROIN

70,051 patents! and 5,105 patents related to cosmetic products

A process for the preparation of aqueous, low-electrolyte solutions of silk fibroin

ELECTROKINETIC PHENOMENA

XIII. A Comparison of the Isoelectric Points of Dissolved and Crystalline Amino Acids*

By HAROLD A. ABRAMSON and LAURENCE S. MOYER†

(From The Biological Laboratory, Cold Spring Harbor, Long Island, The Medical Service and Laboratories of the Mount Sinai Hospital, New York, and the Department of Botany, University of Minnesota, Minneapolis)

(Accepted for publication, March 12, 1938)

DE549460C
Germany

Find Prior Art Similar

Other languages: German

Inventor: Dr Heinrich Fink, Dr Ernst Rossner

Current Assignee : BASF SE

Worldwide applications

0 • *BE BE* NL 1929 • ~~DE~~ 1930 • ~~DE US FR GB~~ 1931 • ~~FR GB~~

Application DEI40238D events

1929-12-23 • Application filed by IG Farbenindustrie AG

1929-12-23 • Priority to DEI40238D

1930-06-11 • Priority to DE575867T

PATENTS OF FIBROIN FOR COSMETIC

Personal care products.

Classifications

A61K8/987 Cosmetics or similar toilet preparations characterised by the composition containing materials, or derivatives thereof of undetermined constitution of animal origin of species other than mammals or birds

It is known that respectively the chemically pulped silk substance. represents the fibroin, a valuable construction and nutrient for the skin and the hair. The digested silk substance can consist Rohseidensubstanz, ie from fibroin and sericin, as well as from entbasteter silk, be made ie from fibroin. The usual AufschluB by means of soda-BEZW.

CH237512A
Switzerland

Find Prior Art Similar

Other languages: German

Inventor: Doswald Albert

Worldwide applications

1944 · CH

Application events

1944-01-28 • Application filed by Doswald Albert

1944-01-28 • Priority to CH237512T

1945-04-30 • Publication of CH237512A

SERICIN

CLIV. THE PREPARATION AND PHYSICO-CHEMICAL PROPERTIES OF SERICIN.

By KEIZO KODAMA.

From the Sir William Ramsay Laboratories of Physical and Inorganic Chemistry, University College, London.

(*Received October 20th, 1926.*)

ELECTROKINETIC PHENOMENA

XIII. A Comparison of the Isoelectric Points of Dissolved and Crystalline Amino Acids*

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(*From The Biological Laboratory, Cold Spring Harbor, Long Island, The Medical Service and Laboratories of the Mount Sinai Hospital, New York, and the Department of Botany, University of Minnesota, Minneapolis*)

(Accepted for publication, March 12, 1938)

A method of weighting of silk.

AT73180B

Austria

Find Prior Art Similar

Other languages: German

Worldwide applications

1915 AT

Application events

1914-10-31	Priority to DE73180X
1915-10-22	Application filed by Schmid Fa Geb
1917-03-10	Application granted
1917-03-10	Publication of AT73180B

Info: Similar documents, Priority and Related Applications

External links: Espacenet, Global Dossier, Discuss

SERICIN PATENT

- 1995-1998 has a big rise in sericin patent applications.
- Total of 5,707 patents regarding sericin have been filed.
- Recently, China has the highest number of patent filing on sericin.

Top 1000 results by filing date

Relative count of top 5 values

Assignees	Inventors	CPCs

Allergan, Inc. A61F2/00 A61F2 A61F2/02 D10B2509/00	3.6%
浙江大学 A61K8/00 A61K8/73 A61Q19/00 A61K8/64	3.6%
苏州大学	3.1%
浙江理工大学	2.5%
セーレン株式会社	2.2%
华中科技大学同济医学院附属协和医院 A61L2430/32 C08J3/24 C12N5/0693 C12N5/0602	2.2%
Trustees Of Tufts College A61K47/30 C08L A61K47/42 A61L	1.9%
Kimberly-Clark Worldwide, Inc. A61L15/42 A61L15/22 A61L15/00 A61L15	1.6%
河南民兴生物科技股份有限公司 C02F3/00 C02F1/001 C02F2303/00 C02F2303/16	1.6%
国立大学法人岩手大学	1.4%
カシロ産業株式会社	1.4%
Seiren Co., Ltd. A61K8/64 A61K8/30 A61K8/18 A61K8/00	1.4%
Gumma Prefecture	1.1%
株式会社ベスト工房	1.1%
住友商事株式会社 D06M16 D06M16/00 D06M16/003 D06M13	1.1%
独立行政法人農業生物資源研究所 A01K2267/00 A01K A01K2217 A01K67	1.1%
浙江省农业科学院	1.1%
群馬県	1.1%
天津工业大学	1.1%

Collapse

PATENTS OF SERICIN FOR COSMETIC

Procedure for the manufacture of capillary cosmetic products (Ma binding)

Abstract

Process for manufacturing capillary cosmetic products in shampoo or similar lotion characterized in that sericin is incorporated into vehicles and ingredients commonly used in cosmetics. (Machine-translation by Google Translate, not legally binding)

ES250726A1
Spain

Find Prior Art Similar

Other languages: Spanish

Current Assignee : ROMAIN DUMAS LOUIS

Worldwide applications

1959 · ES

Application ES0250726A events

1959-07-01 • Application filed by ROMAIN DUMAS LOUIS

1959-07-01 • Priority to ES0250726A

1959-12-16 • Publication of ES250726A1

SILK PROTEINS IN COSMETIC

- Fibroin needs to decompose an amino group into an oligopeptide (MW 1,000-2,000 Da)
- Sericin needs also to decompose and final concentration of SS solution should not exceed 5%

WHY SILK PROTEINS IN COSMETIC

- Silk proteins are similar to human keratin structure and have good affinity for dialysis keratin protein
- They are rich in nutrients (~97% pure protein)
  - Leucine, serine, threonine and glycine are the nutrient elements of skin.
  - When the nutrient elements of silk enter the cortex, they are organically bound to human cortical cells and absorbed by epidermal cells, especially for the elasticity of damaged epidermal cells.
  - Long-term use of cosmetics with silk proteins can promote skin metabolism, prevent premature aging of the skin, and increase the vitality of skin. The silk proteins contain more than ten amino acids similar to the amino acids contained in skin.

WHY SILK PROTEINS IN COSMETIC

- They have good film-forming properties and beneficial for maintaining the normal function of skin surface film. On the outermost side of human skin epidermis, there is a film of several mm thick, usually called sebum film, which can prevent the external factors from irritating, prevent the evaporation of water, and protect the skin
- Silk proteins have good hygroscopicity, can maintain a certain water content of the skin, and have the function of natural humidity-regulating factor.
  - Hygroscopic properties: Since silk fibroin is a random coil structure, the peptide chain is loose and disordered, and the hydrophilic group is on the surface of molecular space structure. These hydrophilic groups can transfer water in human body to the stratum corneum of epidermis. It also keeps the moisture content in skin, make skin elastic, smooth and soft, and effectively prevent dryness, wrinkles and aging of skin.

SILK PROTEINS PROPERTIES FOR COSMETIC APPLICATION

- Natural moisturizing and nourishing skin property

The experiment showed that the moisture absorption rate of silk protein solution at 2.5% was equivalent to the moisture absorption rate of 48% glycerol at a temperature of 27°C, a relative humidity of 86% and a moisture absorption time of 12 hours.

Products: Moisturizers, facial cleansers, shower gels, shampoos and conditioners

- Skin melanin inhibition

Tyrosine, tryptophan and phenylalanine in silk proteins can effectively absorb ultraviolet rays.

Silk proteins at 25% showed the inhibition rate for producing melanin was about 70%, which is unmatched by other cosmetic additives.

SILK PROTEINS PROPERTIES FOR COSMETIC APPLICATION

- Promote skin tissue regeneration, prevent cracking and chemical damage

Silk protein is very effective in promoting skin wound healing. Sericin can promote collagen production.

Products: Moisturizers, facial serum, anti-aging products

- Inhibition of skin cancer
- Antioxidant function of silk proteins

Silk protein and ascorbic acid were added under heat treatment conditions at 100° C for 120 minutes, and the amount of oxidation was confirmed under the same conditions. Although ascorbic acid lost its antioxidant ability due to heat, silk fibroin exhibited thermal stability. Moreover, silk protein is better than vitamin C with antioxidant function.

FIBROIN AS RAW MATERIAL

- Powder form
- Cosmetic, food, pharmaceutical, medical and analytical grade

- China sells all grades of fibroin powder ranging from 10-200 USD/kg
- Sigma (USA) is the only supplier for fibroin solution (50 mg/mL) in analytical grade (25 USD/mL)
- Cosmetic, food and Pharmaceutical grade

SERICIN AS RAW MATERIAL

- Powder and liquid form
- Cosmetic, food, pharmaceutical, medical and analytical grade

- China sells all grades of sericin powder ranging from 10-87 USD/kg
- India sells cosmetic and medical grade sericin powder ranging from 10,000-100,000 USD/kg
- Sigma (USA) is the only supplier for analytical grade sericin

  (100,000 USD/kg)
- Thailand and Japan are only 2 suppliers for sericin liquid form (cosme grade). The price ranges from 110-140 USD/liter
- Cosmetic, food and Pharmaceutical grade

FIBROIN AS FINISHED PRODUCTS

All cosmetics!

- Cream
- Lotion
- Soap
- Mask
- Hair care

SERICIN AS FINISHED PRODUCTS

All cosmetics
ame as fibroin

BENEFITS OF SERICIN FOR COSMETIC INGREDIENT

- High water solubility
- Various activities due to extraction methods and MW
- Great activity
- Negligible allergic reactions
- Affordable price

CONCERNS ON SILK PROTEIN SUPPLIES

- For powder:
  - Purity: Cocoon, extraction method
  - Solubility data: Amorphous → crystalline
  - MW
- For solution:
  - Purity
  - Concentration
  - Gel formation?

SILK PROTEINS FOR FUTURE USES

- Medical
  - Wound dressing
  - Cream for dermatological treatment
  - Drug delivery
- Food supplement

FUTURE FOR SILK PROTEIN AS RAW MATERIAL

Expression of sericin in *E. coli* expression system

Cloning	- Three genes with encode different repeated unit	→ Choose the major form of sericin at mRNA level
	- Big gene (2583 bp for sericin1) with alternative splicing	→ Many protein isoforms
	- High GC rich and long sequence repeat - Lot of serine (appro.44%)	→ Difficult to clone and sequence → Does not have enough tRNA for repeated unit
		Choose synthetic gene with specific repeated unit as reported in previous paper
	- Codon bias	→ Overcome this problem by optimized codon
Expression & purification	- Low level of expression	→ Optimize condition: media, bacterial strain, temperature
	- Insoluble protein	→ Difficult to purify
	- High contaminated proteins	→ Add HIS taq but it still has a lot of contamination → Requires many steps of purification resulting in low yield of final protein.

Thank you for your attention

Thank you

for your attention

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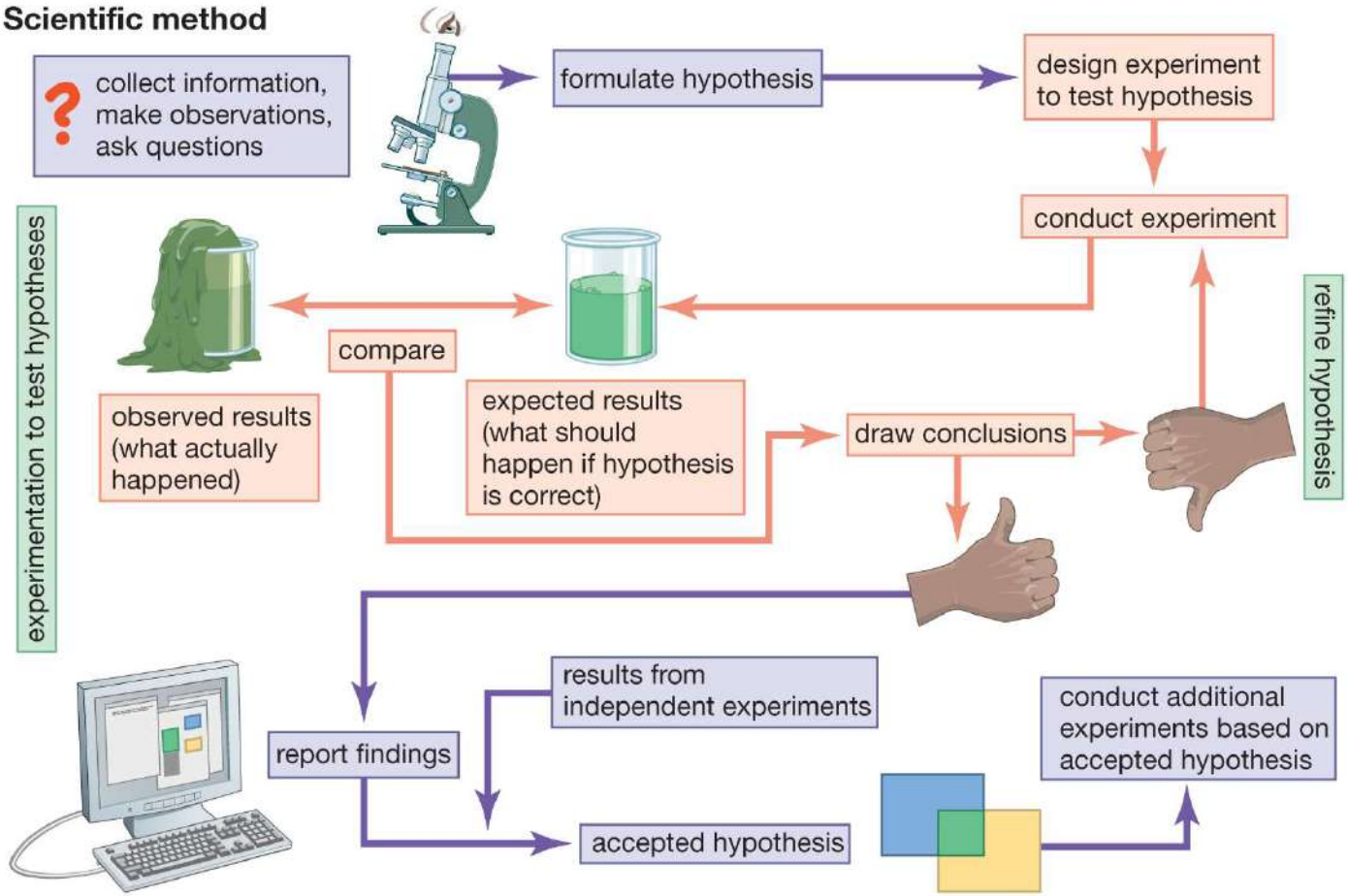
Design of experiment

An introduction with applications in biomaterials

Alessio Bucciarelli, PhD
MST Group, FBK
Bucciarelli@FBK.eu

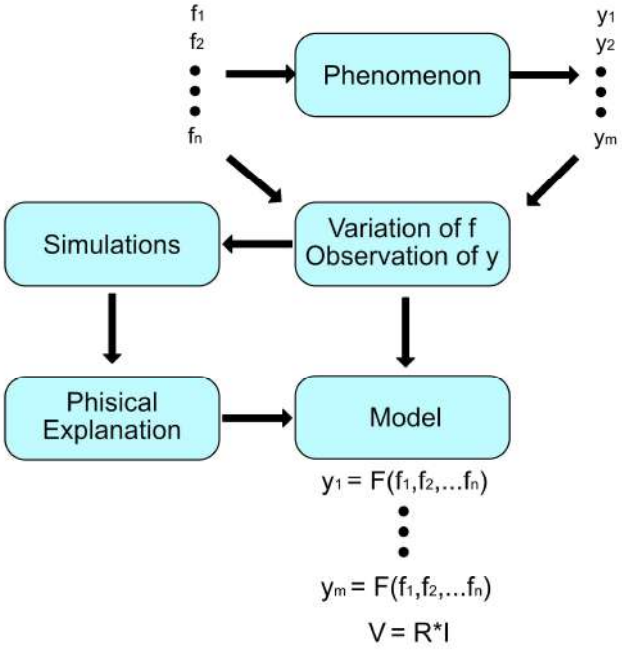
What is an experiment?

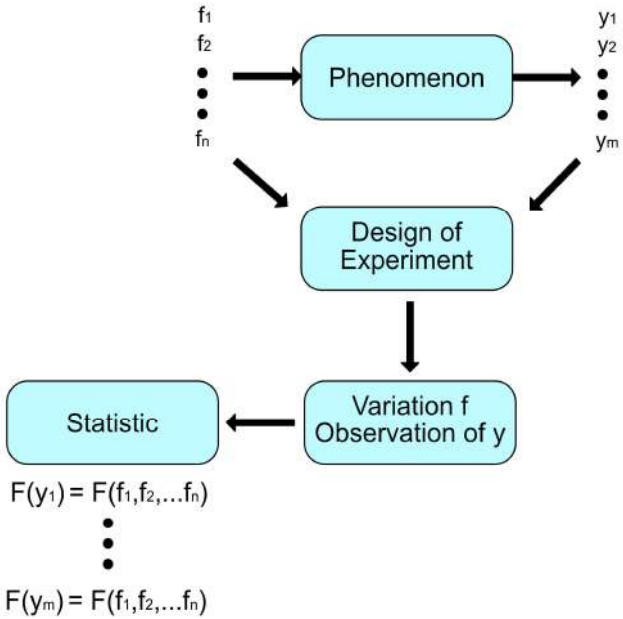


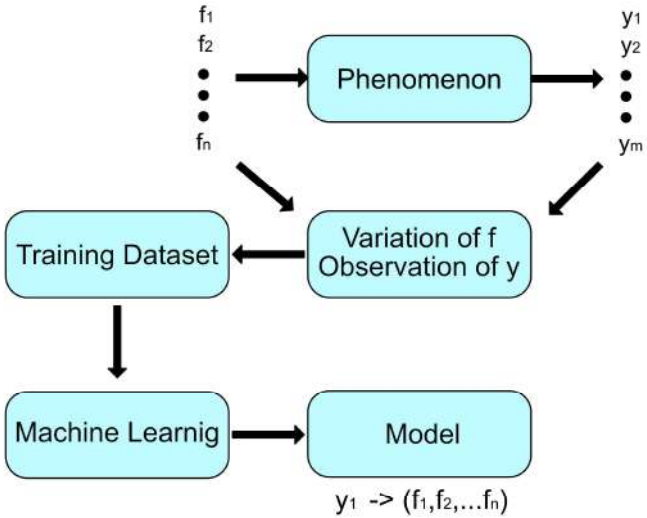
This method works on all the scientific field in which the observation is the base of our initial hypothesis.

The experiment is an analytical observation of the phenomenon that we want to study in which we set some inputs and we get some outputs

The approach







Find the physical mechanism:

MECHANISTIC MODEL

Experimentally determinined model:

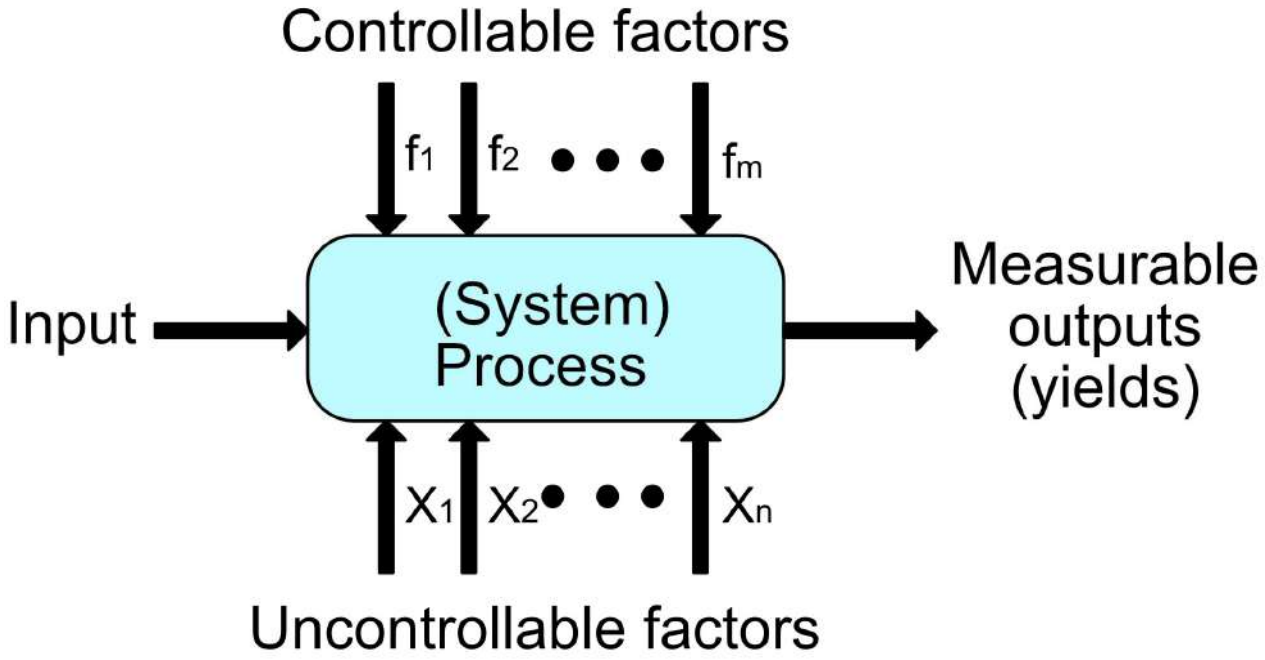
EMPIRICAL MODEL

Experimentally determinined model:

MACHINE LEARNING MODEL

A general model of the process

A well-designed experiment is important because the results and conclusions that can be drawn from the experiment depend to a large extent on the manner in which the data was collected.



Montgomery DC. Design and Analysis of Experiments Eighth Edition.; 2012. doi:10.1198/tech.2006.s372

Best Guess

It often works reasonably well, too, because the experimenters often have a great deal of technical or theoretical knowledge of the system they are studying, as well as considerable practical experience.

Disadvantages:

1) suppose the initial best-guess does not produce the desired results. Now the experimenter has to take another guess at the correct combination of factor levels.

2) Suppose the initial best-guess produces an acceptable result. Now the experimenter is tempted to stop testing, although there is no guarantee that the best solution has been found.

Montgomery DC. Design and Analysis of Experiments Eighth Edition.; 2012. doi:10.1198/tech.2006.s372

OFAT (One factor at time)

Consists of selecting a starting point, or baseline set of levels, for each factor, and then successively varying each factor over its range with the other factors held constant at the baseline level. After all tests are performed, a series of graphs are usually constructed showing how the response variable is affected by varying each factor with all other factors held constant.

Disadvantages:

1) fails to consider any possible interaction between the factors. An interaction is the failure of one factor to produce the same effect on the response at different levels of another factor.

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Design of experiment (Factorial)

This is an experimental strategy in which factors are varied together, instead of one at a time. This allows us to get an insight about how they do interact. No data point is lost, if the model is not enough (presence of curvature, in the central control point of an initially supposed linear model) it is expandable thus efficient!

DATA ANAYSIS

High Flexibility
Is free

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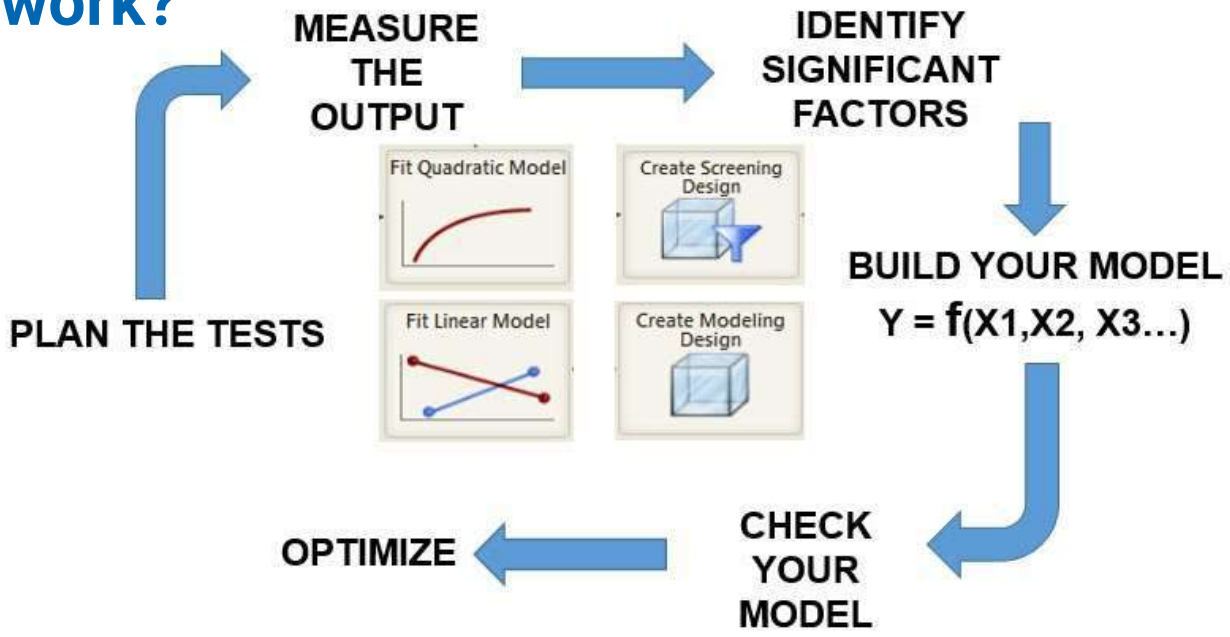
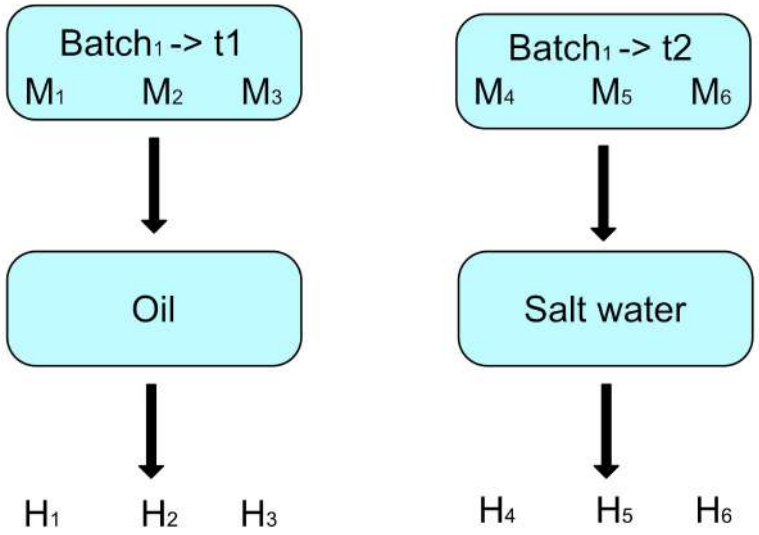
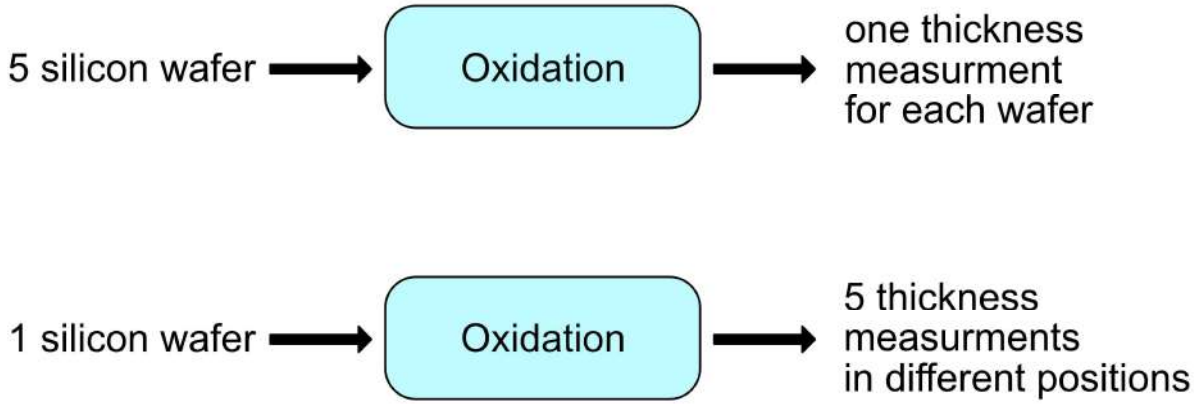
How does it work?



Randomization



Replication



Taste

Maximize the number of people that likes it.

Brand

Expensive versus Cheap

Time

4 minutes versus 6 minutes

Power

75% versus 100%

Full factorial 2^3 design

Factor	Name	Units	Low Level (–)	High Level (+)
A	Brand	Cost	Cheap	Costly
B	Time	Minutes	4	6
C	Power	Percent	75	100

	Main effects			Interaction effects				Taste
N	A	B	C	AB	AC	BC	ABC	Y1
1	-	-	-	+	+	+	-	74
2	+	-	-	-	-	+	+	75
3	-	+	-	-	+	-	+	71
4	+	+	-	+	-	-	-	80
5	-	-	+	+	-	-	+	81
6	+	-	+	-	+	-	-	77
7	-	+	+	-	-	+	-	42
8	+	+	+	+	+	+	+	32
Effect	-1	-20.5	-17	0.5	-6	-21.5	-3.5	66.5

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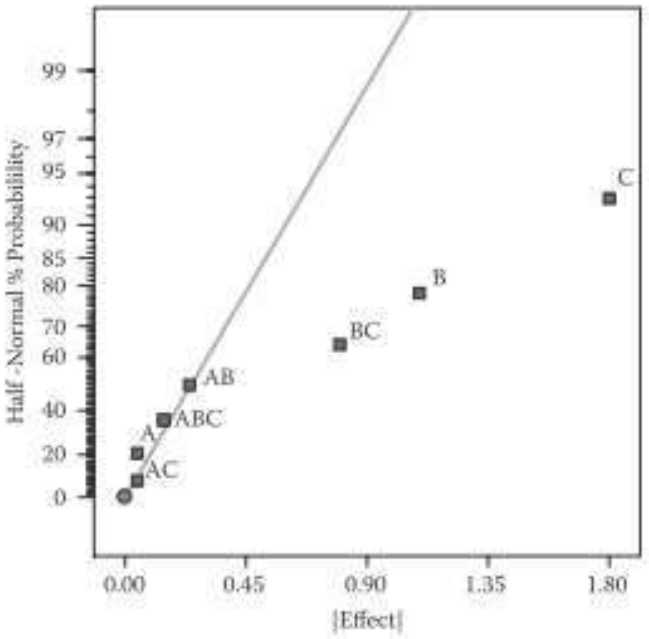
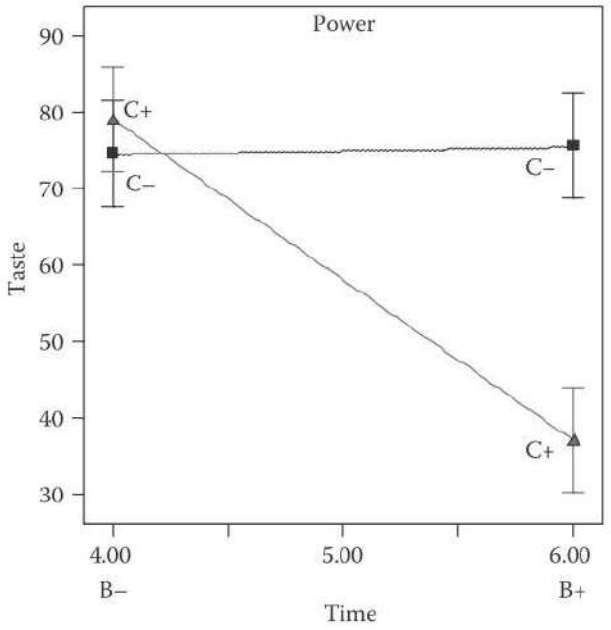
Full factorial 2^3 design

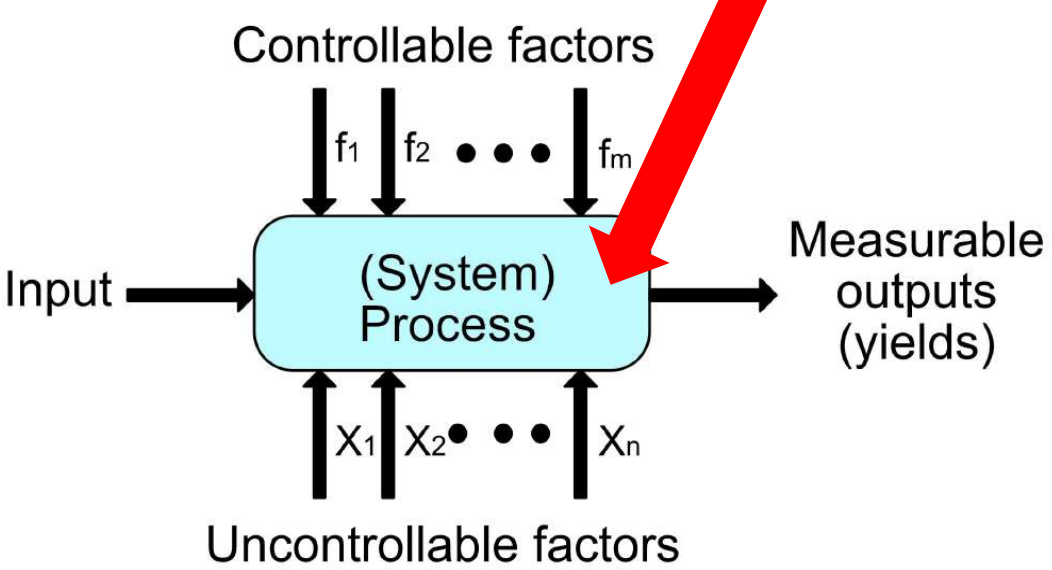
$$\hat{Y} = 66.5 - 10.25\,B - 8.50\,C - 10.75\,BC$$

Point	Factor	|Effect|	Cumulative Probability (%)
1	A	0.05	7.14
2	AC	0.05	21.43
3	ABC	0.15	35.71
4	AB	0.25	50
5	BC	0.80	64.29
6	B	1.10	78.57
7	C	1.80	92.86

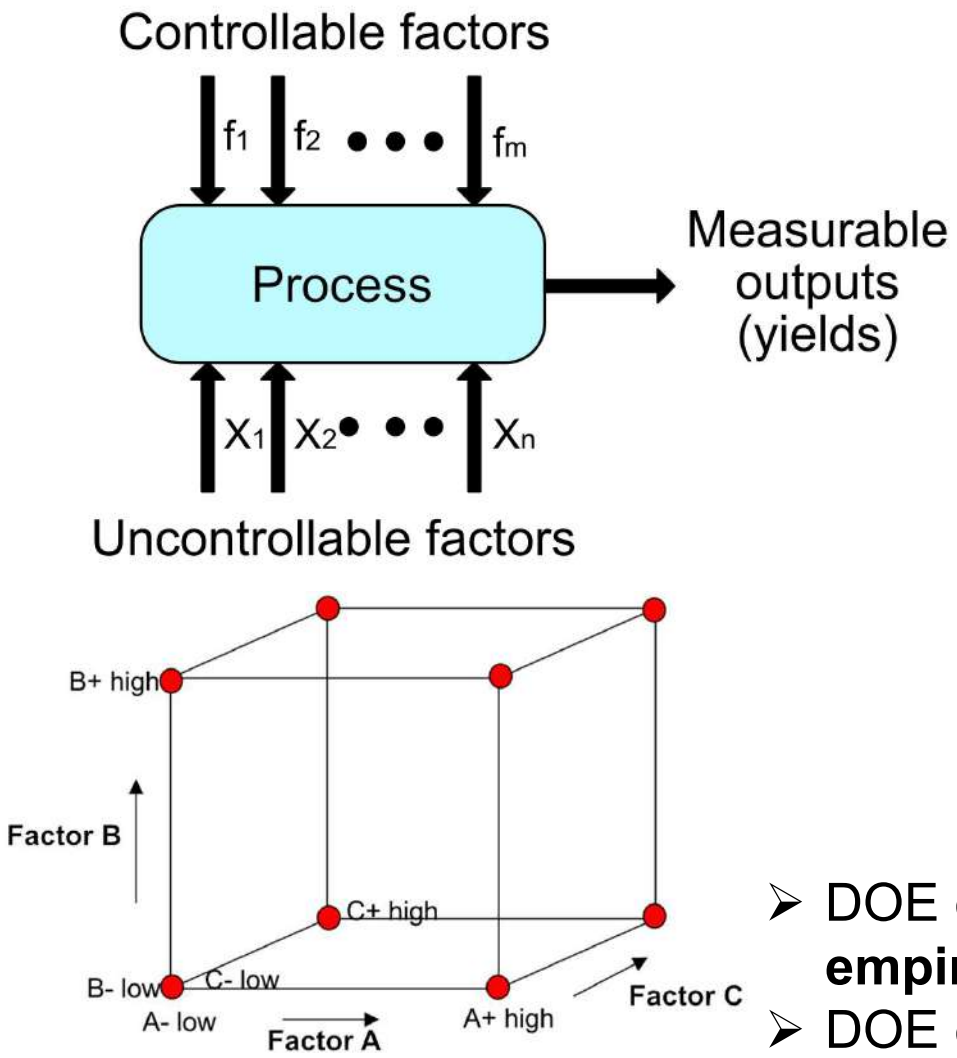




HOW IS POPCORN RELATED TO SCIENCE?



Full factorial 2^3 design



	Main effects		
N	A	B	C
1	-	-	-
2	+	-	-
3	-	+	-
4	+	+	-
5	-	-	+
6	+	-	+
7	-	+	+
8	+	+	+

$$F(\hat{Y}) = \beta_0 + \beta_1 A + \beta_2 B + \beta_3 C + \beta_4 AB + \beta_5 AC + \beta_5 BC + \beta_7 ABC$$

- DOE can be used as method to create an **empirical model of material properties**.
- DOE can be used to **optimize a process** by choosing factors that, in changing the level, resulted to have a dramatical change in the material properties.

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Common Applications

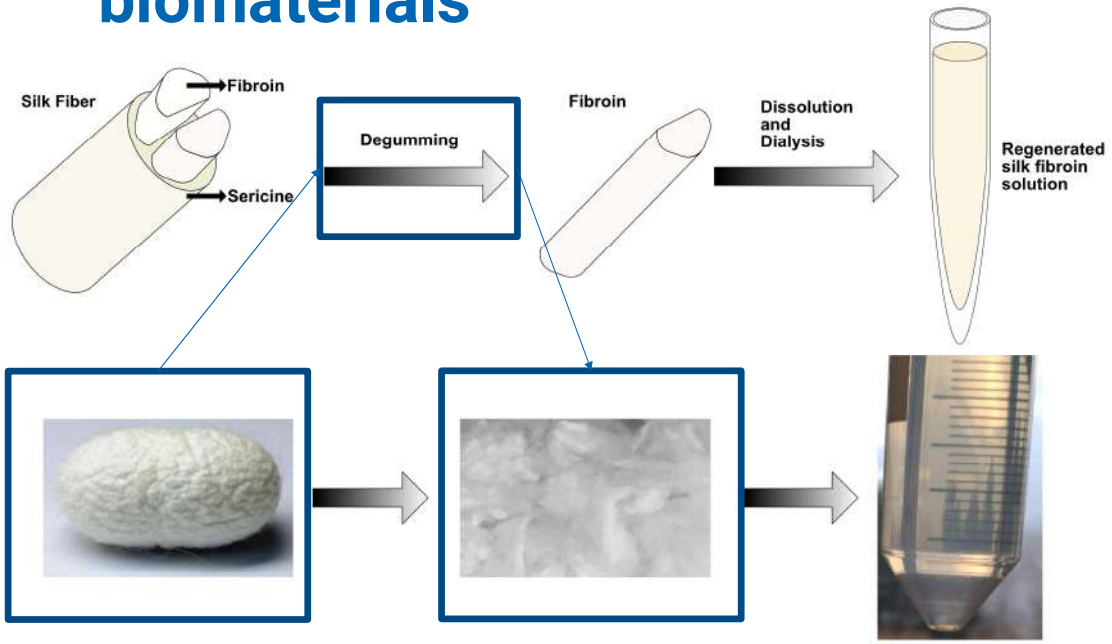
INDUSTRY -> Process development

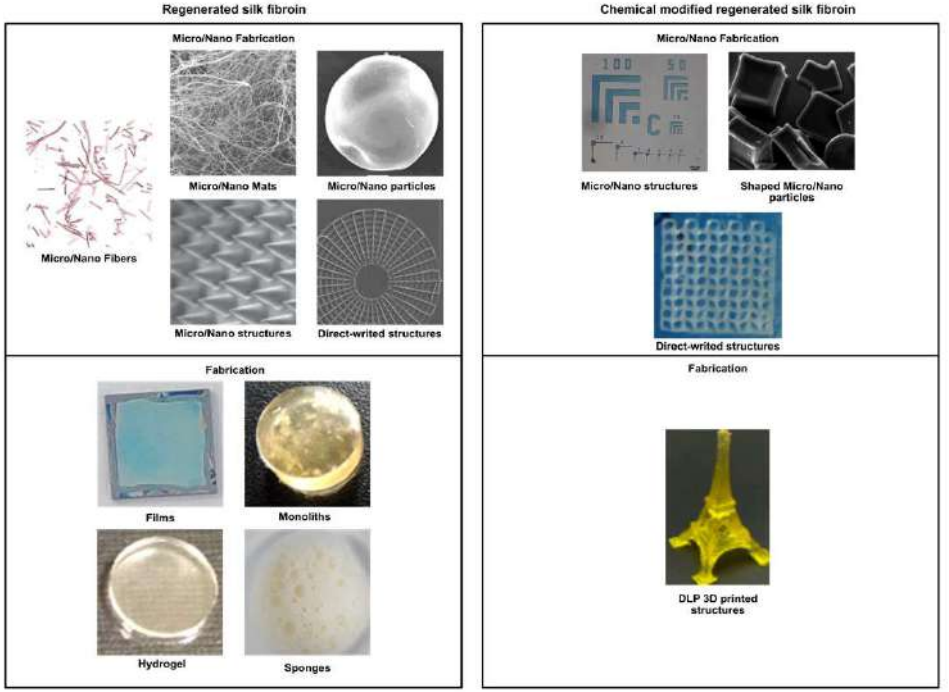
- Improved process yields
- Reduced variability and get a closer conformance to nominal or target requirements
- Reduced development time
- Reduced overall costs

Engineering Design -> Development or improving product

- Evaluation of different **designs**
- Evaluation of different **materials**
- Selection of design parameters so that the product will work well under a wide variety of field conditions, so that the product is **robust**
- Determination of **key product design parameters** that impact product performance

The use in biomaterials





Raw materials → **Transformed Materials** → **Final Product** → **Commercial Product**

Process Development → **Material Testing** → **Scale up**

Laboratory Scale → **Is the process reliable?** → **Industrial Scale**

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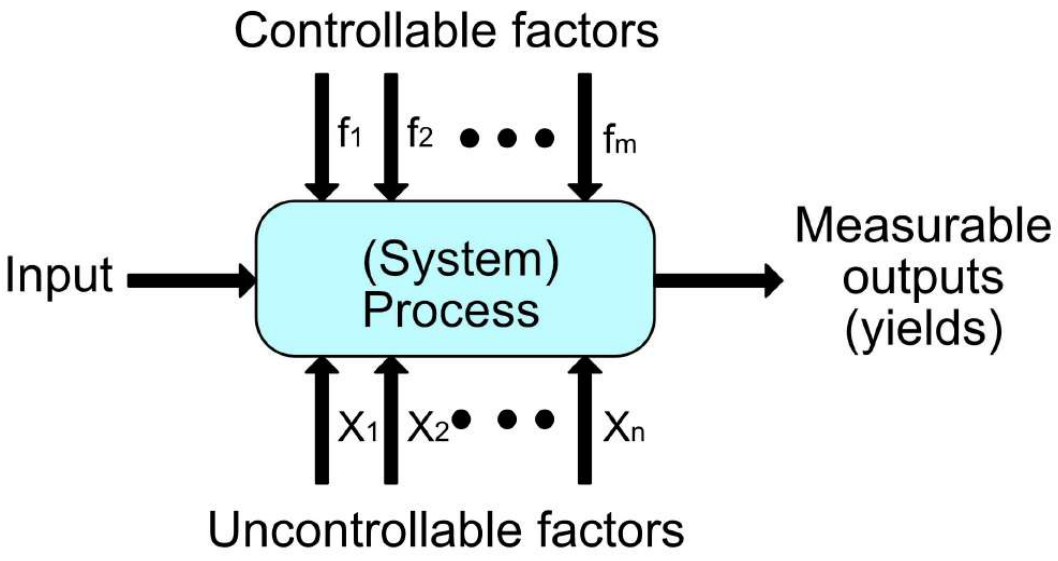
Process Control: degumming of silk



System: Function, model, process used to convert the input in the output.

The degumming process.

Input: provided material or energy into the process.

Silk cocoons.

Response: outcome of a process or performance of a system.

Physical, Chemical properties of the outcoming degummed silk.

Controllable factors: Factor that can be controlled by the experimenter.

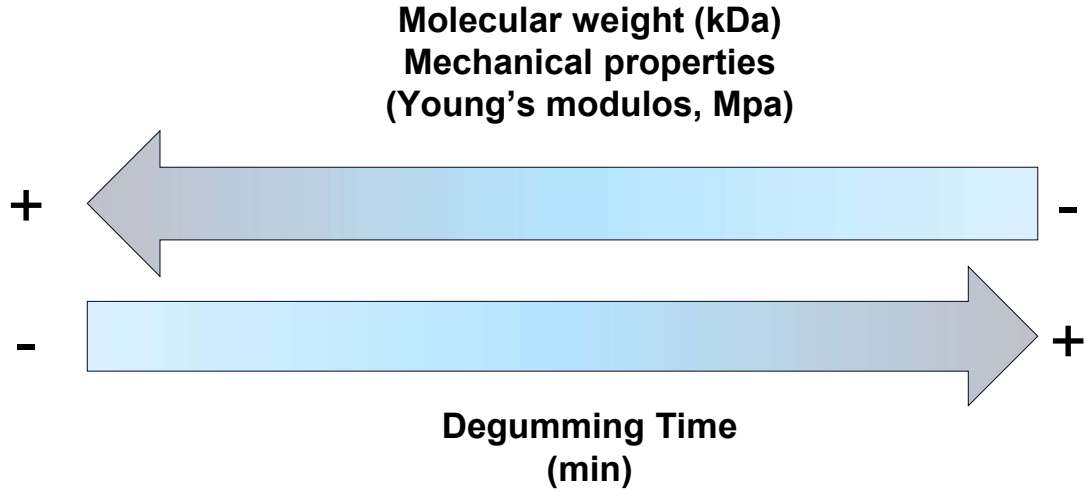
Process time and temperature, the number of bath, the concentration of salt.

Uncontrollable factors: noise factor that cannot be controlled.

Environmental temperature, the humidity of the air, the purity of the used water…

What is known in literature

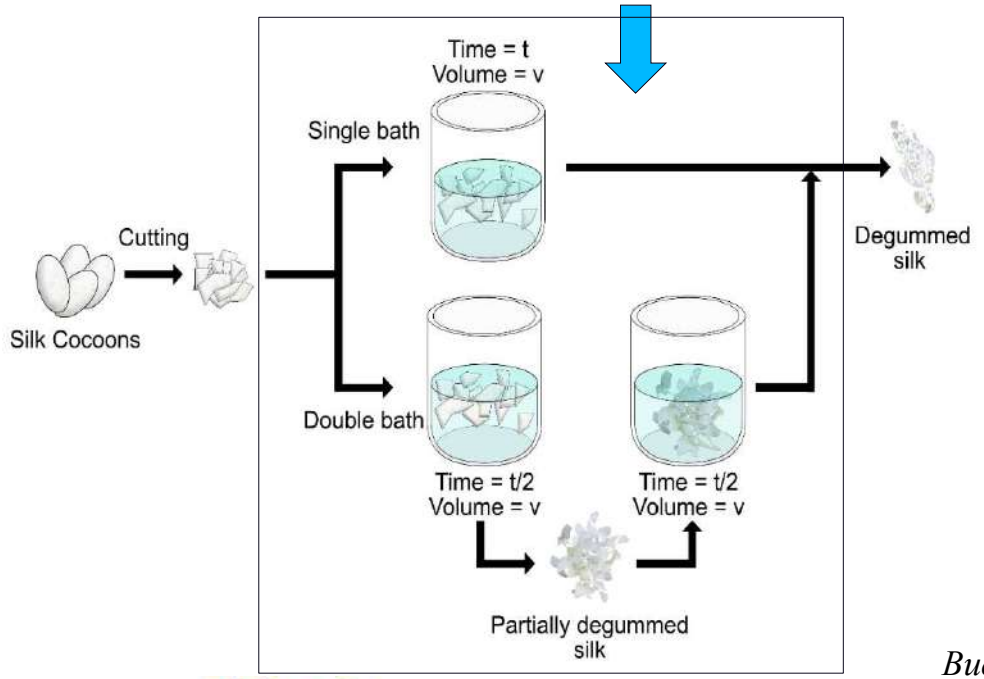
1. The increase of the degumming time decrease the molecular weight of the protein and consequently decrease also the tensile strength.
2. Understand the advantages and also the limits of the «traditional» Na_2CO_3 degumming, comparing the outcome with the the golden referencedefined in the Rockwood protocol (t=30min,T=100°C, [Na_2CO_3]=2.14 g/L, V=400mL/g).
3. Fully understand the relations between the process and the fibroin properties, both intensive and extensive.
4. Find optimal an optimal degumming in which more then one properties is maximised or minimized according to specific requirment.



Experimental Design

$$F(Y) = c_0 + c_1 * A + c_2 * B + c_3 * C + c_4 * D + c_5 * A * B + c_6 * A * C + c_7 * A * D + c_8 * B * C + c_9 * B * D + c_{10} * C * D + c_{11} * A * B * C + c_{12} * A * B * D + c_{13} * A * C * D + c_{14} * B * C * D + c_{15} * A * B * C * D$$

Factor	Variable	Type	+1 Level	-1 Level
A	N. Baths	Discrete	1	2
B	t (min)	Continuous	20	90
C	T (°C)	Continuous	70	98
D	[Salt] (g/mL)	Continuous	0.1	1.1
Cofounded Factor				
E (cof. A)	Vt(mL/g)	Continuous	133.3	266.6



Control:

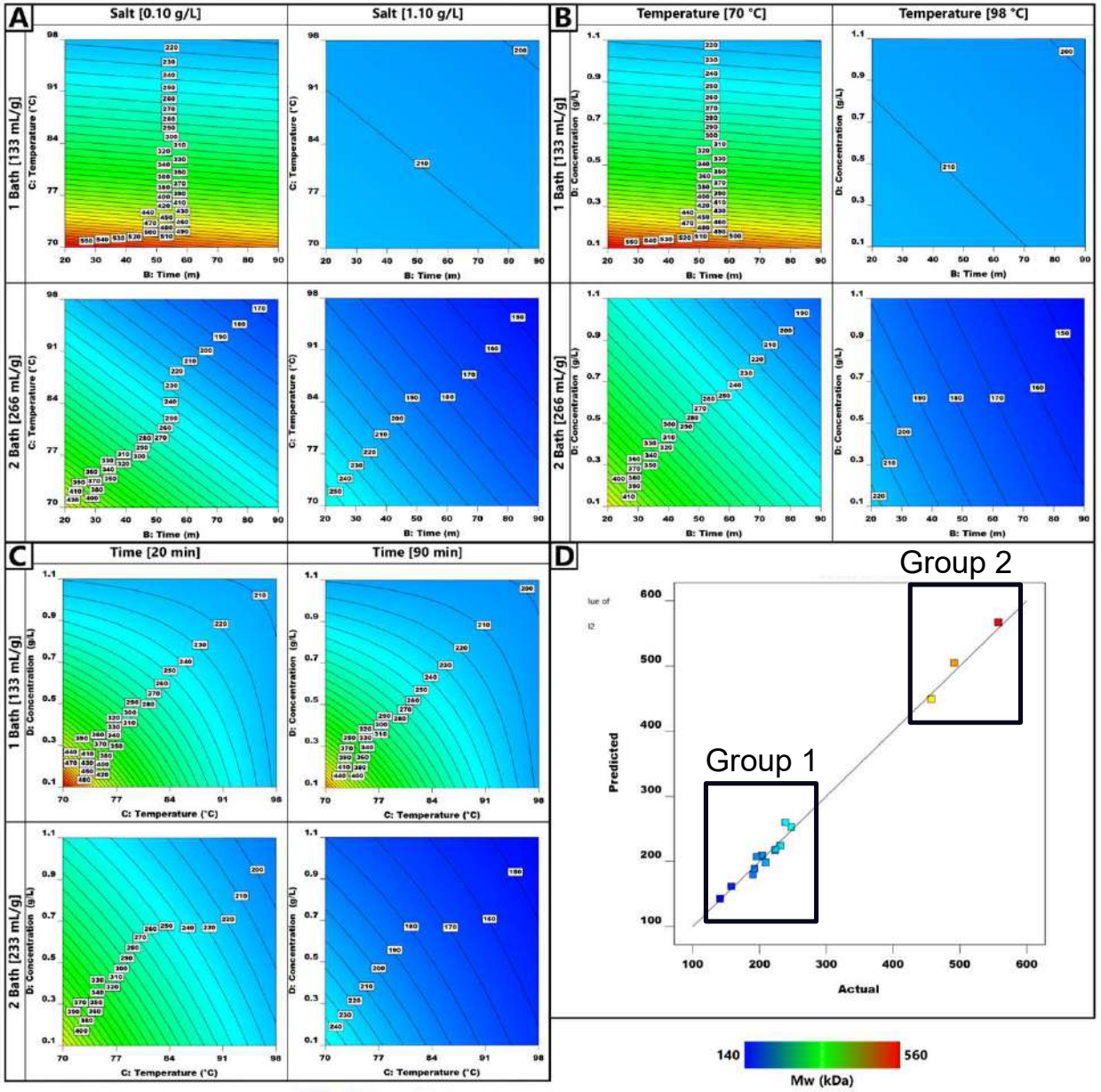
- Degummed fiber by Rockwood protocol
- Fibers from the cocoon

Studied properties:

- Weight Loss (%)
- Elastic Modulus (GPa)
- Stress at break (MPa)
- Strain at break (%)
- Fibers diameter (μm)
- Secondary structures
- Molecular weight

Bucciarelli A, Greco G., Corridori I., Nicola M. P., Antonella A, *A design of experiment rational optimization of the degumming process and its impact on the silk fibroin properties*, in revision ACS Biomaterial Science and Engineering.

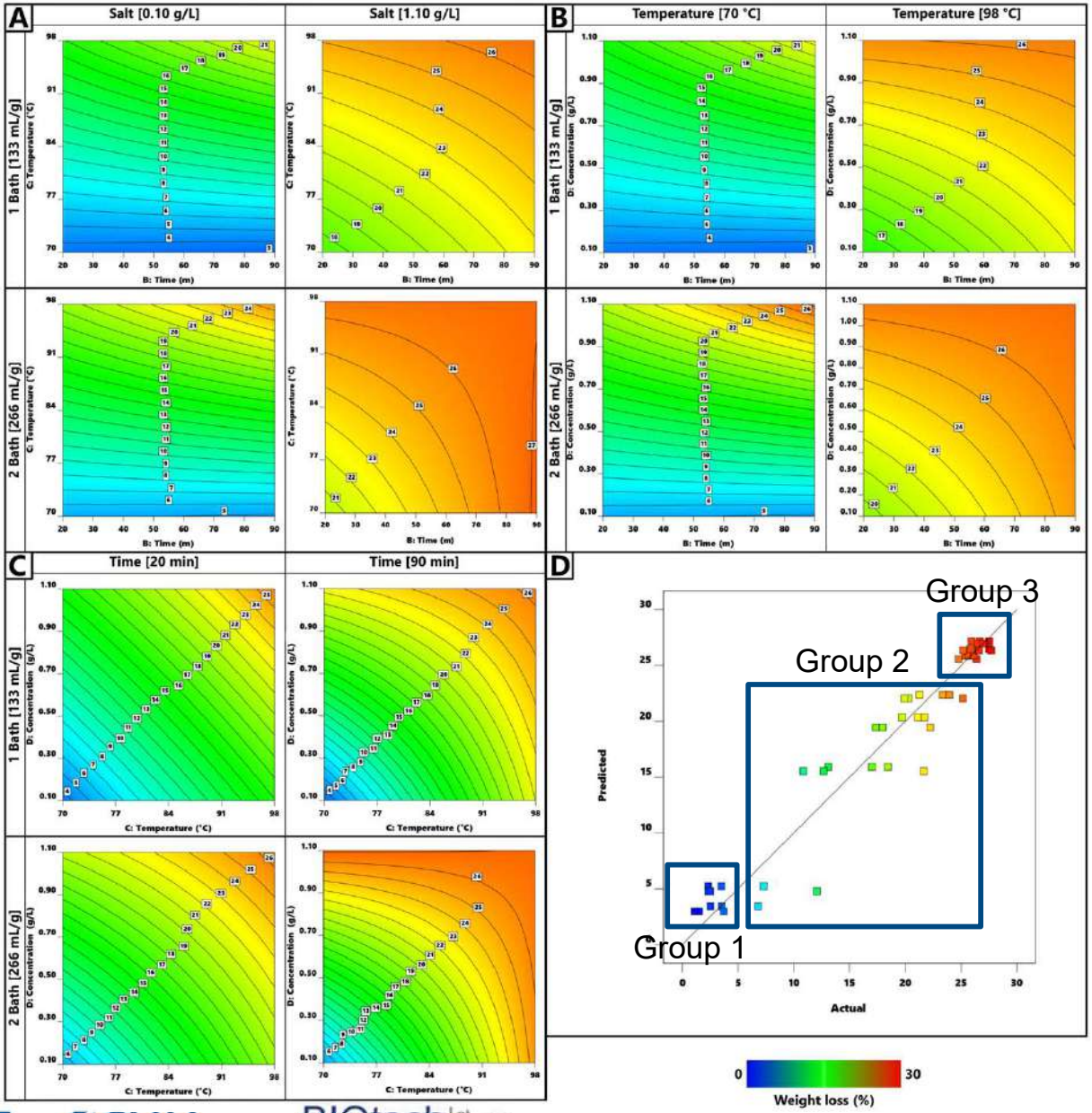
Molecular weight Mw



Molecular weight:

- The weight avaraged molecular weight has been modeld.
- The data can be divided in 2 groups.
- The first group include Mw between 100 and 300 kDa in which the degumming.
- The second group is between 450 and 600 kDa
- The higher molecular weight is obtained with the milder conditions, low salt concentration, low time, and low temperature.

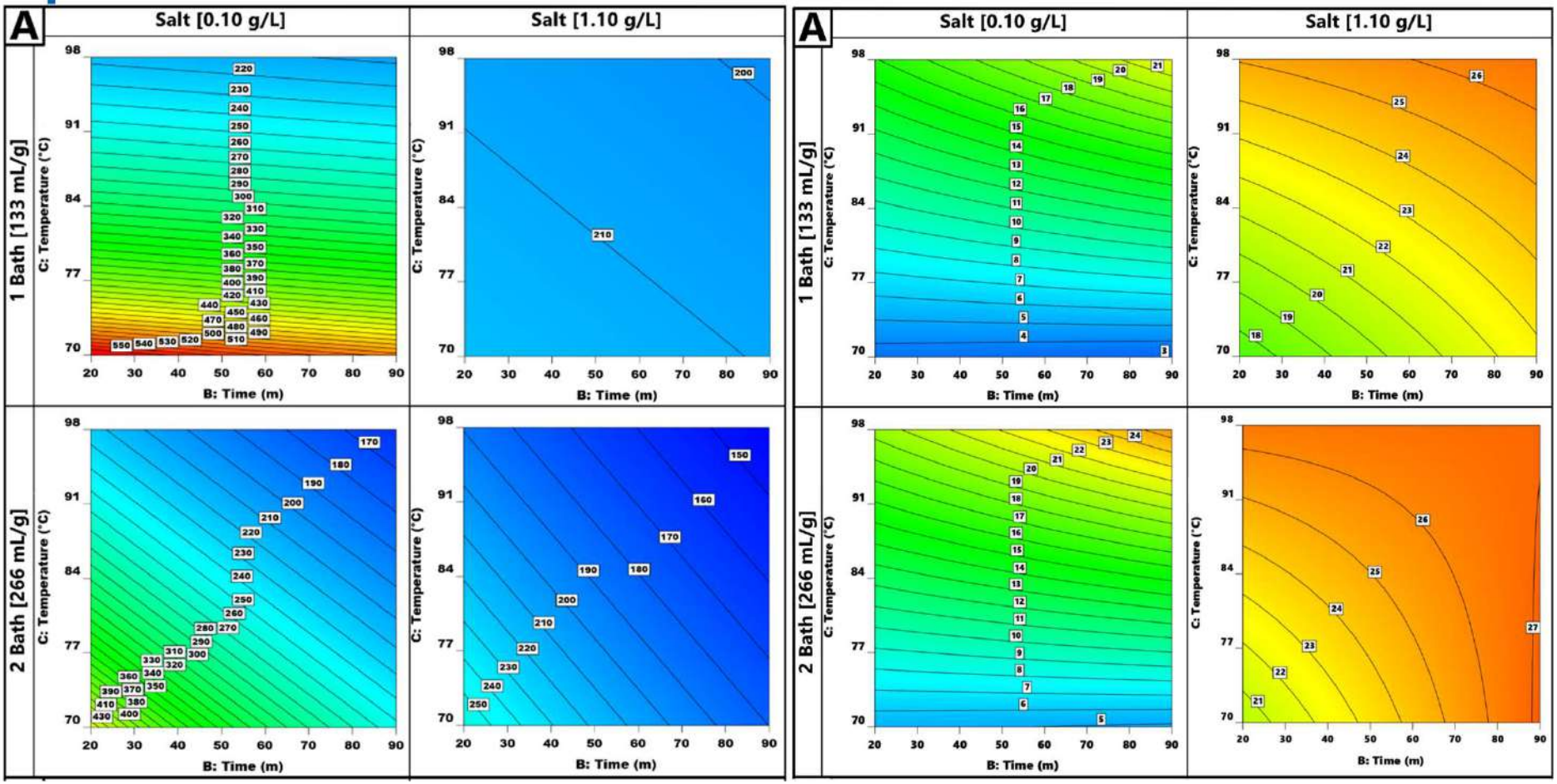
Weight Loss



Weigh Loss:

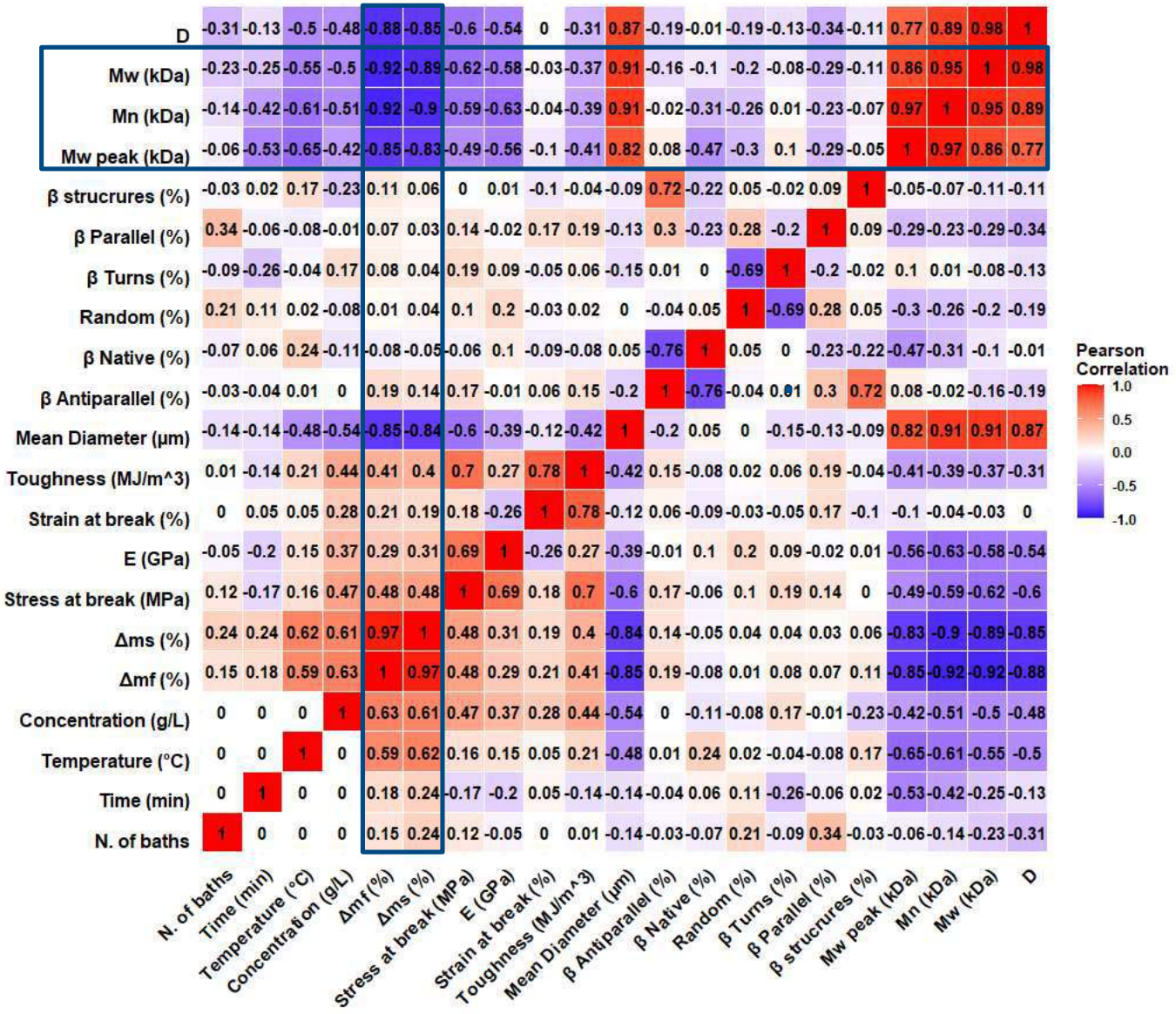
- Data can be divided in 3 groups.
- Group1: Not degummed silk (between 0 and 5%) in which the data is not scattered.
- Group2: Partially degummed silk group (between 4 and 25%) in which the data is scattered.
- Group3: Totally degummed group (>25%) the data is not scatered again.
- A perfect uniformity on the amount of sericine leaved in the treatment can be obtained only with a full degumming!

Optimization



- The increasing of Mw and degumming ratio are in opposed trend.
- The problem is then non-trivial: we can optimize it by use the models equations and a numerical method, the desirability approach.

Pearson’s index of correlation



A numerical method to optimize the outcome

$$\Delta m_{f(1bath)}(\%) = -23.56037 - 0.298006B + 0.373219C + 6.16206D + 0.00401586BC + 0.565710\,BD + 0.05CD - 0.00659559BCD$$

$$\Delta m_{f(2baths)}(\%) = -27.83598 - 0.298006B + 0.455753\,C + 23.99304D + 0.00401586BC + 0.565710BD - 0.1565CD - 0.00659559BCD$$

$$^{1}/_{M_{w(1baths)}}(kDa) = -0.006211 + 3.044E(-6)B + 0.000110C + 0.009177D - 0.000091CD$$

$$^{1}/_{M_{w(2baths)}}(kDa) = -0.004122 + 0.000024B + 0.000082C + 0.03570D - 0.000028CD$$

$d_{\Delta m_f}$

d_{M_w}

$$d_i = \begin{cases} 1 & if\ Y_i \geq U_i \\ \dfrac{Y_i - L_i}{U_i - L_i} & if\ L_i \geq Y_i \geq U_i \\ 0 & if\ Y_i \leq L_i \end{cases}$$

Mimimize

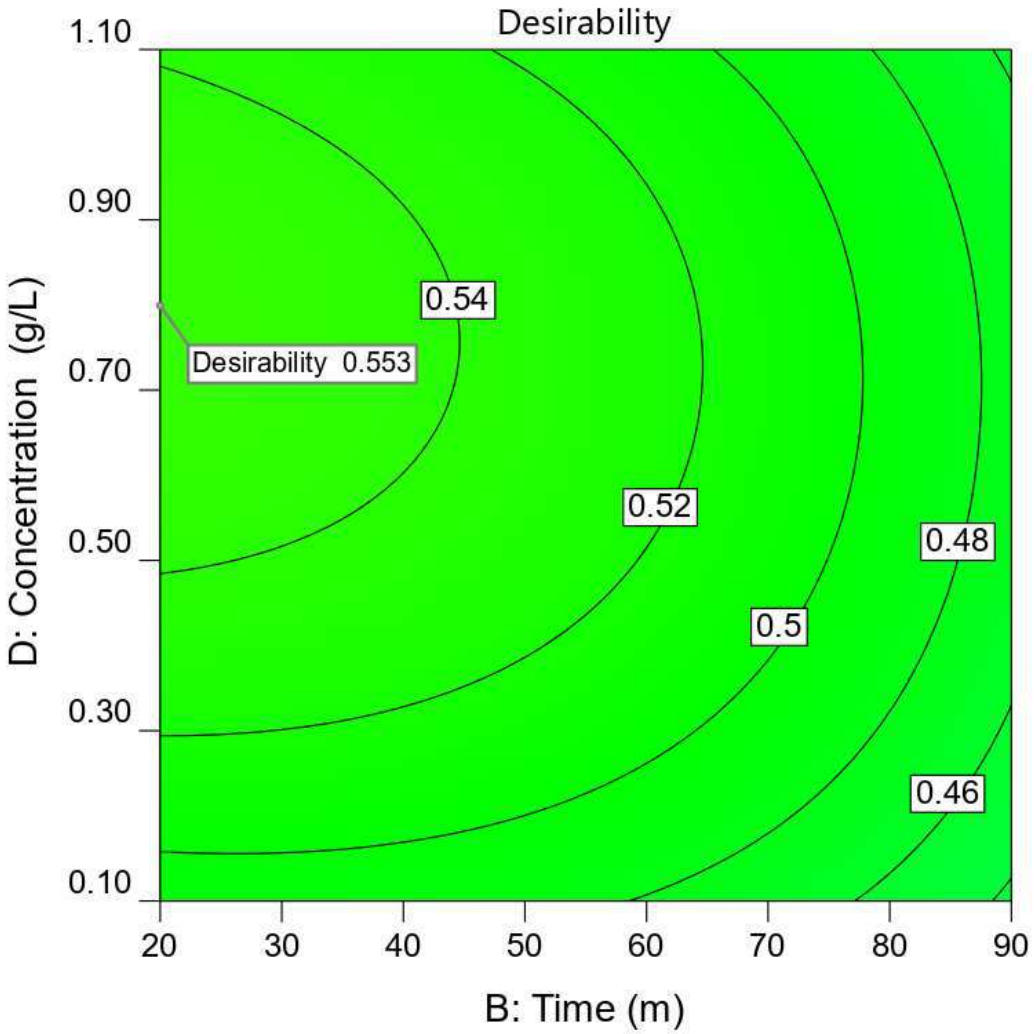
$$d_i = \begin{cases} 0 & if\ Y_i \geq U_i \\ \dfrac{Y_i - L_i}{U_i - L_i} & if\ L_i \geq Y_i \geq U_i \\ 1 & if\ Y_i \leq L_i \end{cases}$$

Maximise

$$d_{tot} = (d_1 d_2 d_3 \dots d_k)^{\frac{1}{k}}$$

$$d_{tot} = (d_{\Delta m_f} d_{M_w})^{\frac{1}{2}}$$

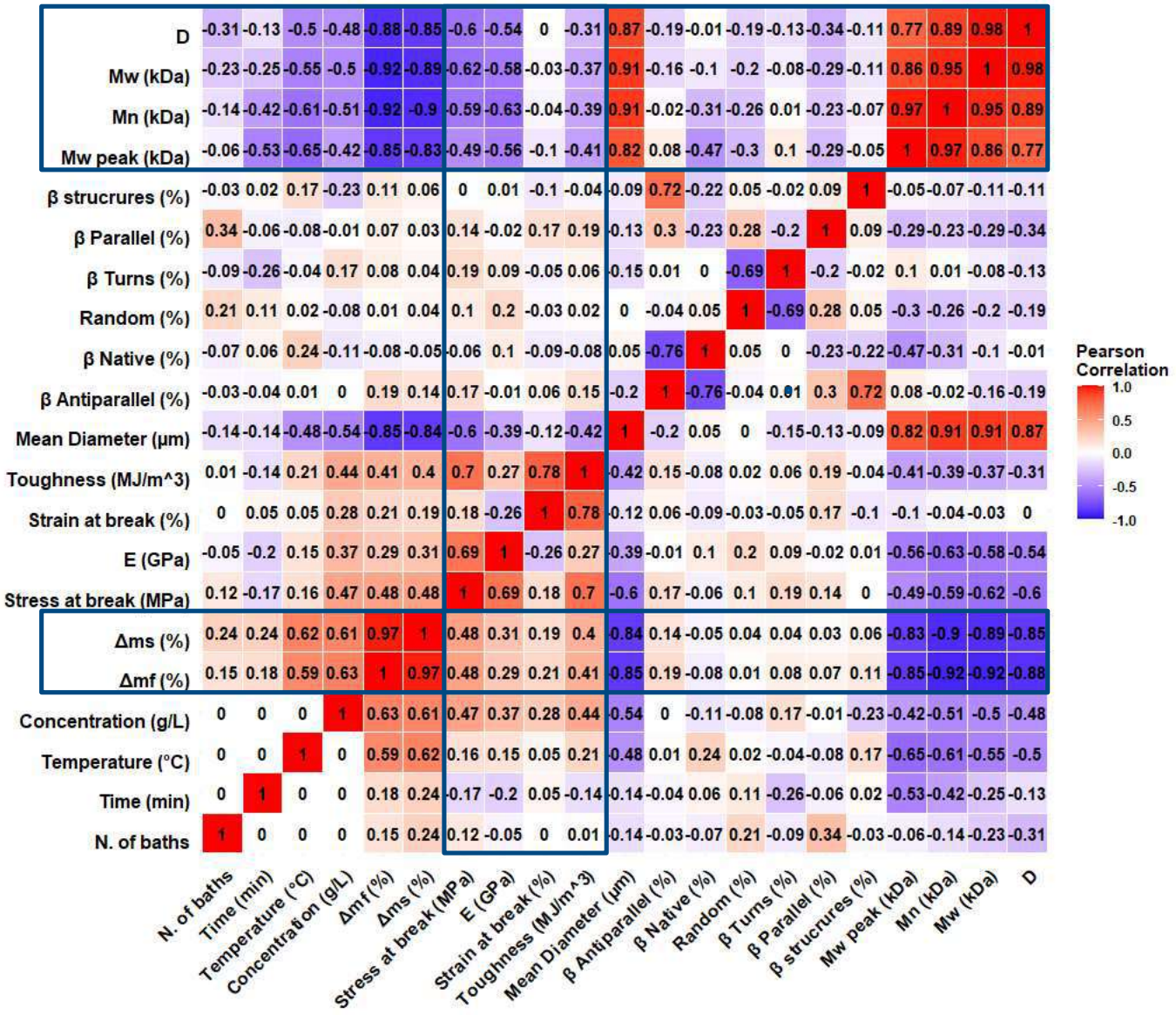
Desirability Approach



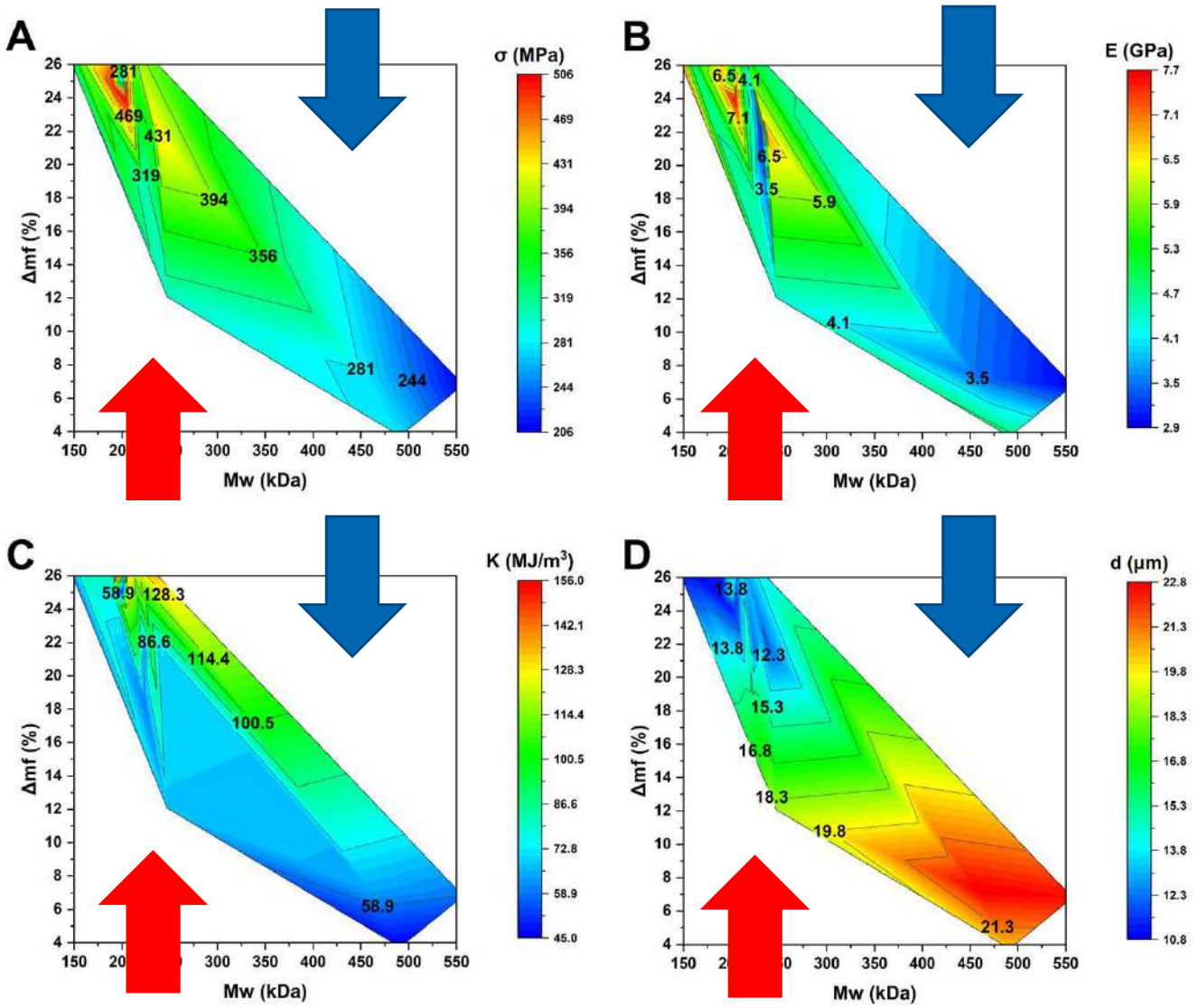
Numerical Solution:

- The solution is not one of the point that we tested.
- The desirability is in the [0,1] range
- In this case becouse the two trends are in opposite direction the solution is close to the middle of the range.

Mw and mechanical performances



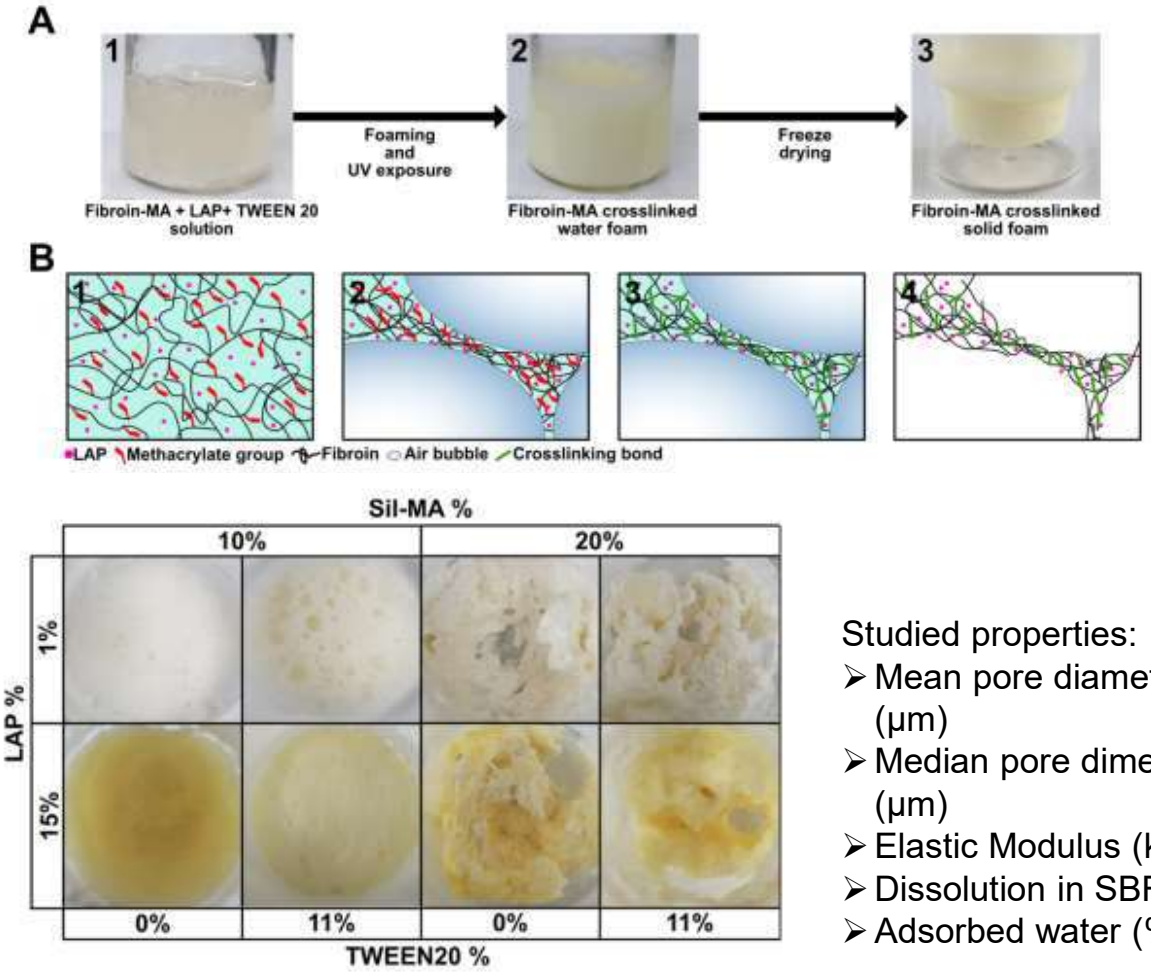
Mw and mechanical performances



Numerical Solution:

- The white portion (blue arrow) indicates the area with a high Mw and high degumming ratio that is out of our processing range.
- The white portion indicated (red arrow) indicates the area with a low Mw and low degumming ratio also this is out of the range of our degumming process. Interesingly this tell us also that the sericine is a good protective layer.

Composition Control: A methacrilated sponge



Studied properties:

- Mean pore diameter (µm)
- Median pore dimeter (µm)
- Elastic Modulus (kPa)
- Dissolution in SBF (%)
- Adsorbed water (%)

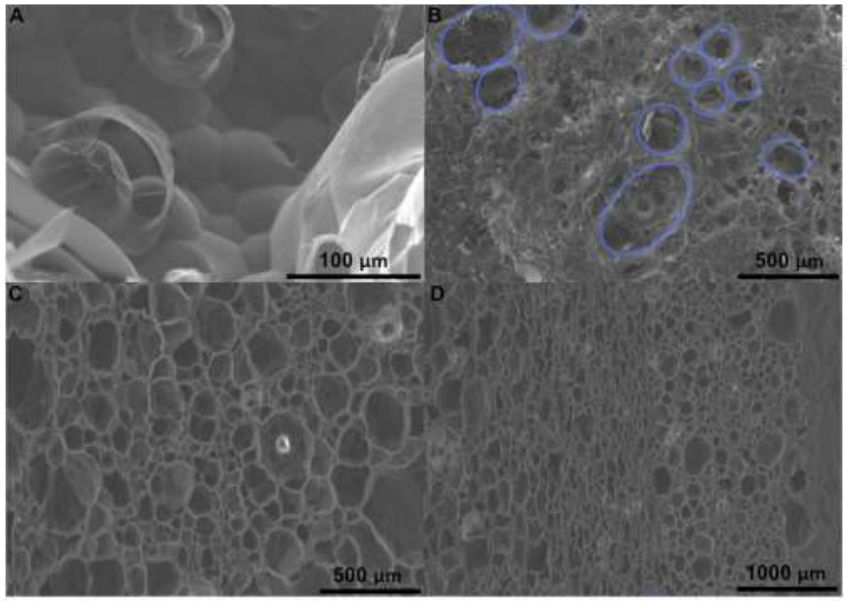
$$\hat{Y} = \beta_0 + \beta_1 * A + \beta_2 * B + \beta_3 * C + \beta_4 * A * B + \beta_5 * A * C + \beta_6 * B * C + \beta_7 * B * C + \beta_8 * A * B * C$$

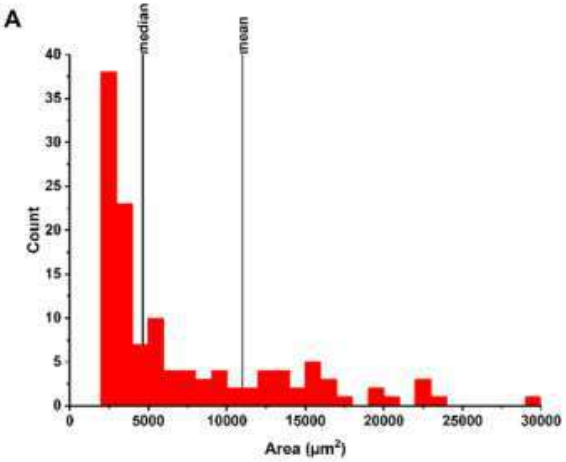
Factors	Levels	
	-1	+1
Fibroin - MA concentration [%]	10	20
Tween 20 volume [µL]	0	50
LAP mass [mg]	5	75

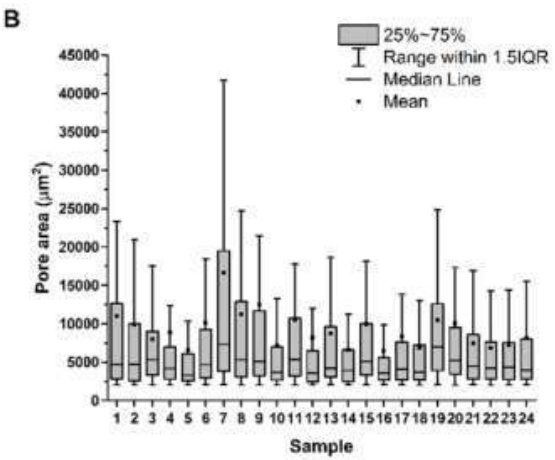
Constants	
Amount of fibroin per sponge [mg]	500
Exoposure Time [m]	20
Exposure distance [cm]	5
Velocity of the emulsifer [rpm]	35000
Foaming time [min]	5
Freeze drying time [h]	12

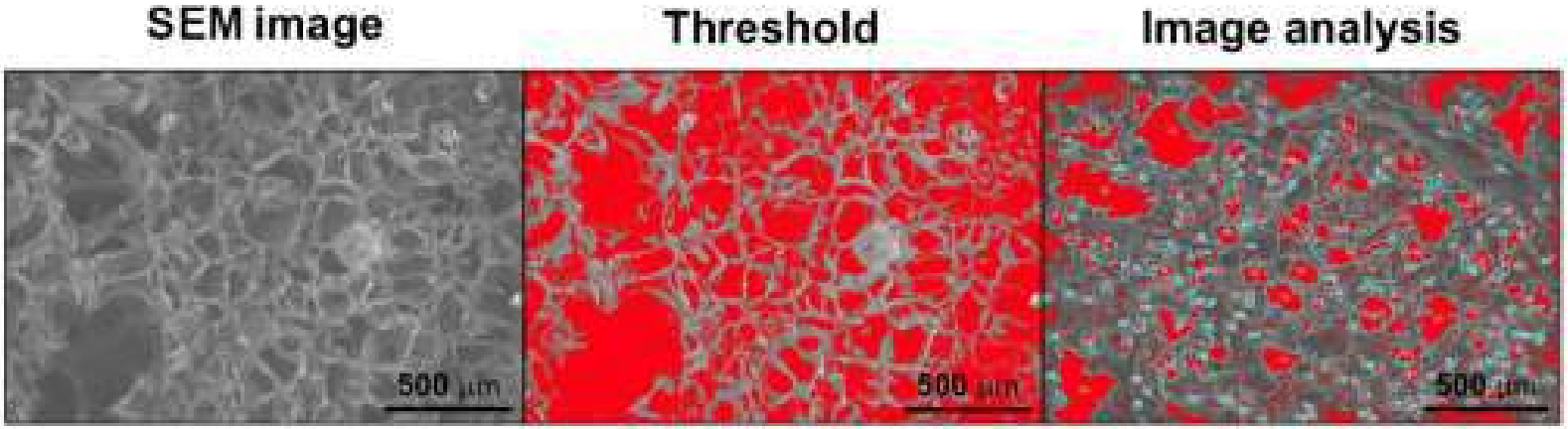
Bucciarelli, A.; Muthukumar, T.; Kim, J. S.; Kim, W. K.; Quaranta, A.; Maniglio, D.; Khang, G.; Motta, A. *Preparation and Statistical Characterization of Tunable Porous Sponge Scaffolds Using UV Cross-Linking of Methacrylate-Modified Silk Fibroin*. ACS Biomater. Sci. Eng. 2019. https://doi.org/10.1021/acsbiomaterials.9b00814.

A case study: A methacrilated sponge

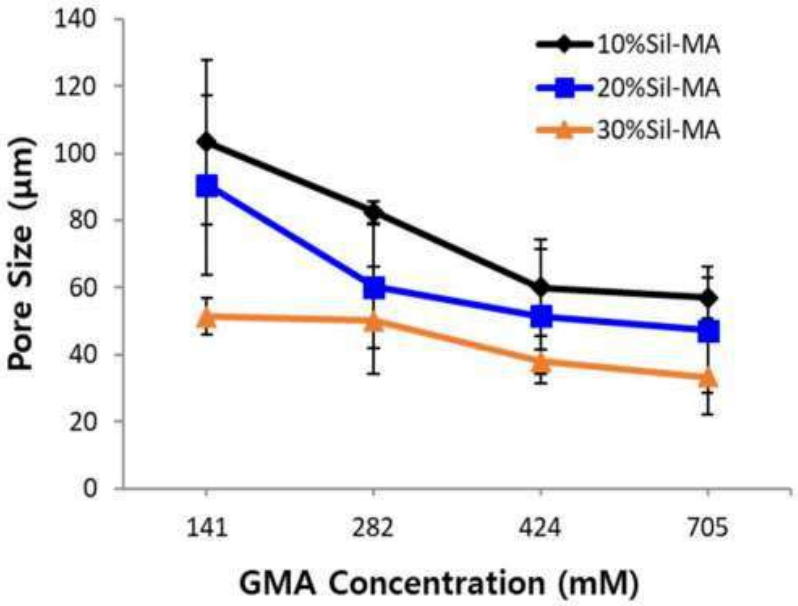


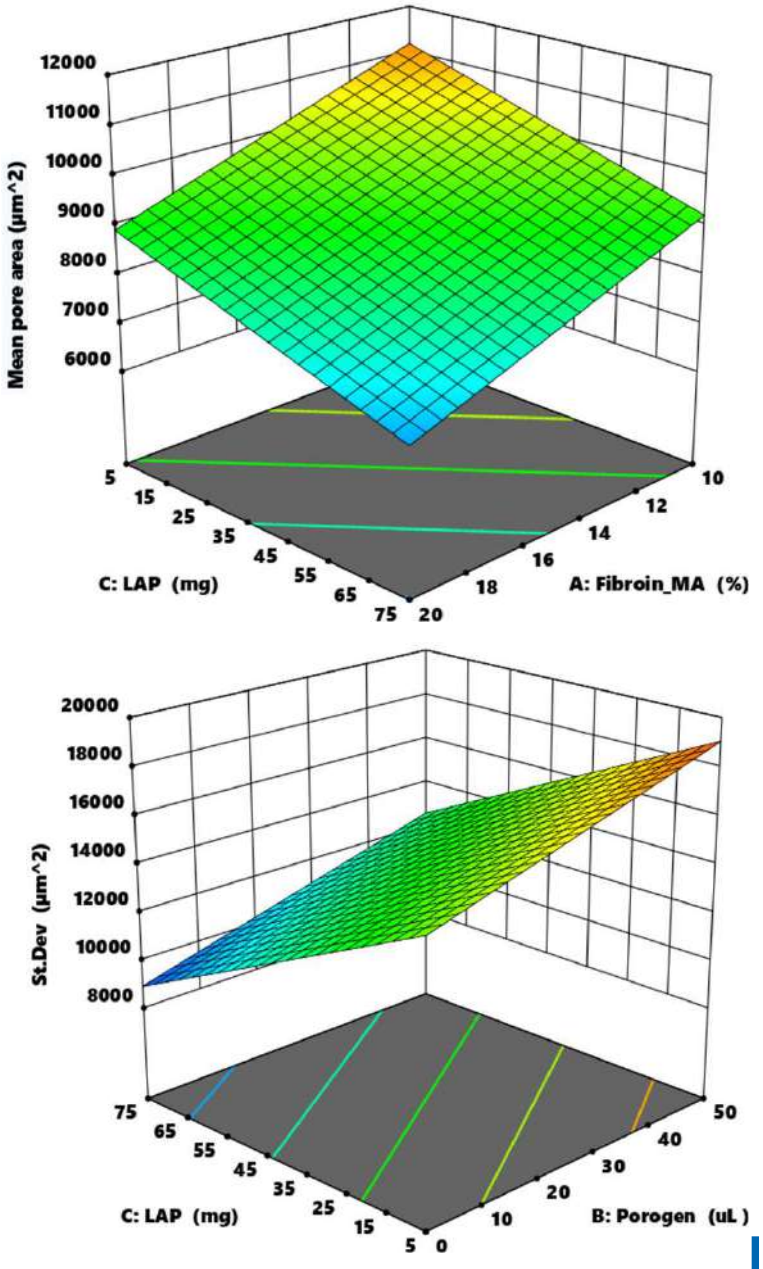






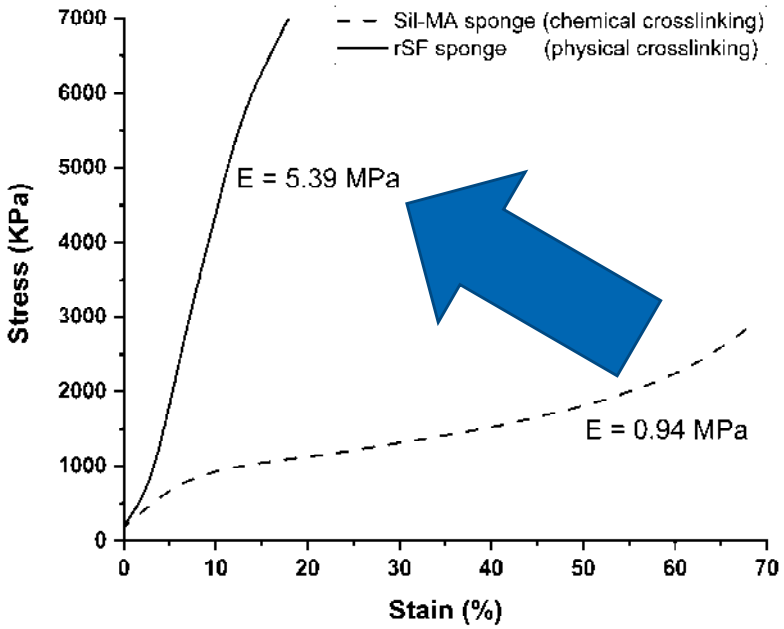
Tunability

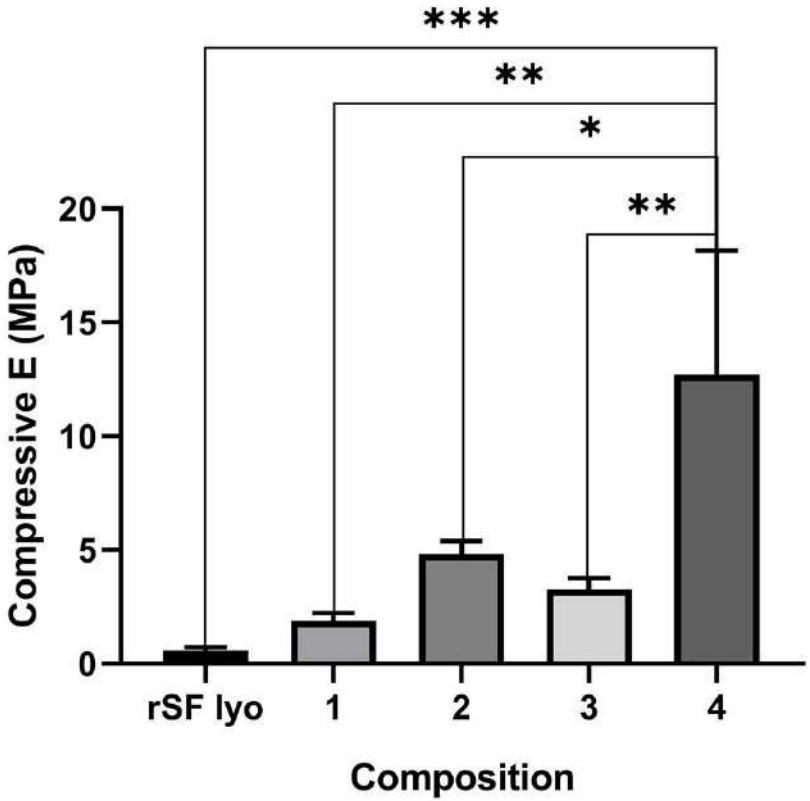


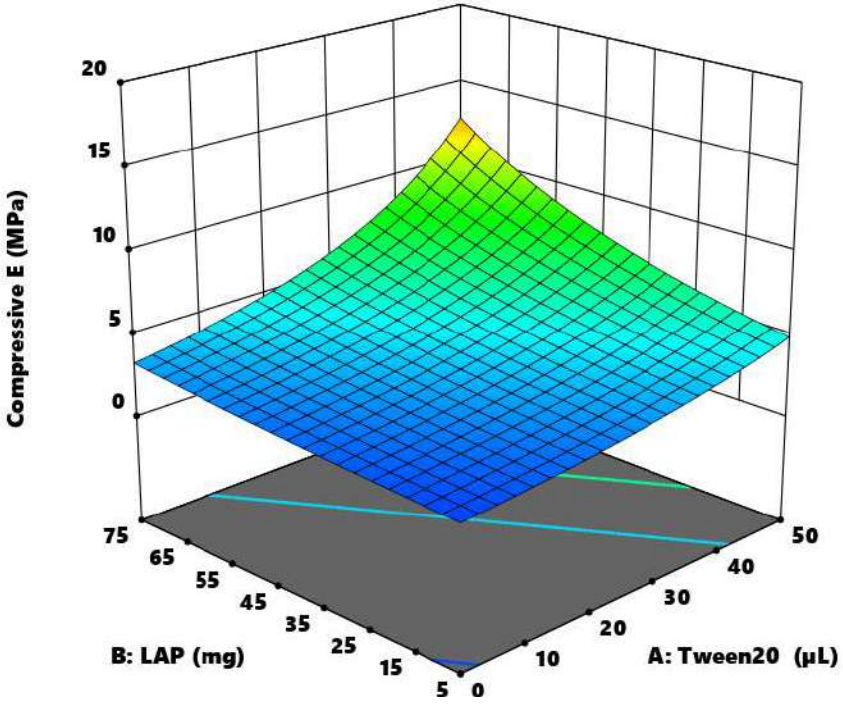


Tunability means control, is not sufficient to prove that there is a change of one variable against the other

Methacrylated fibroin scaffold





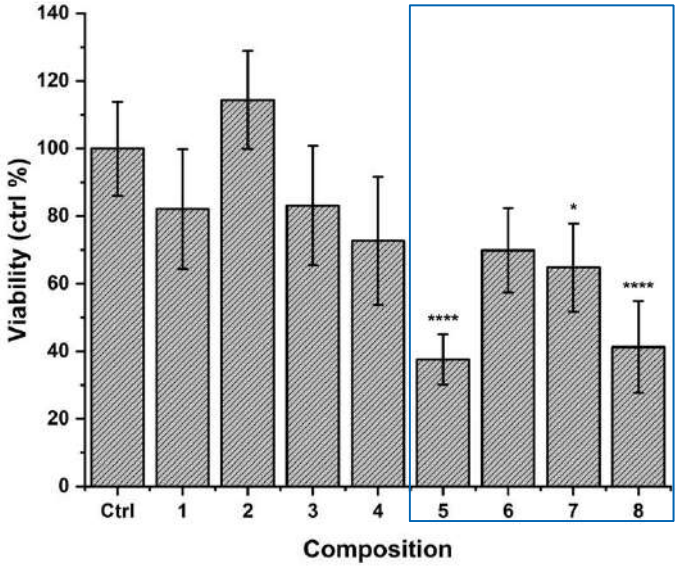


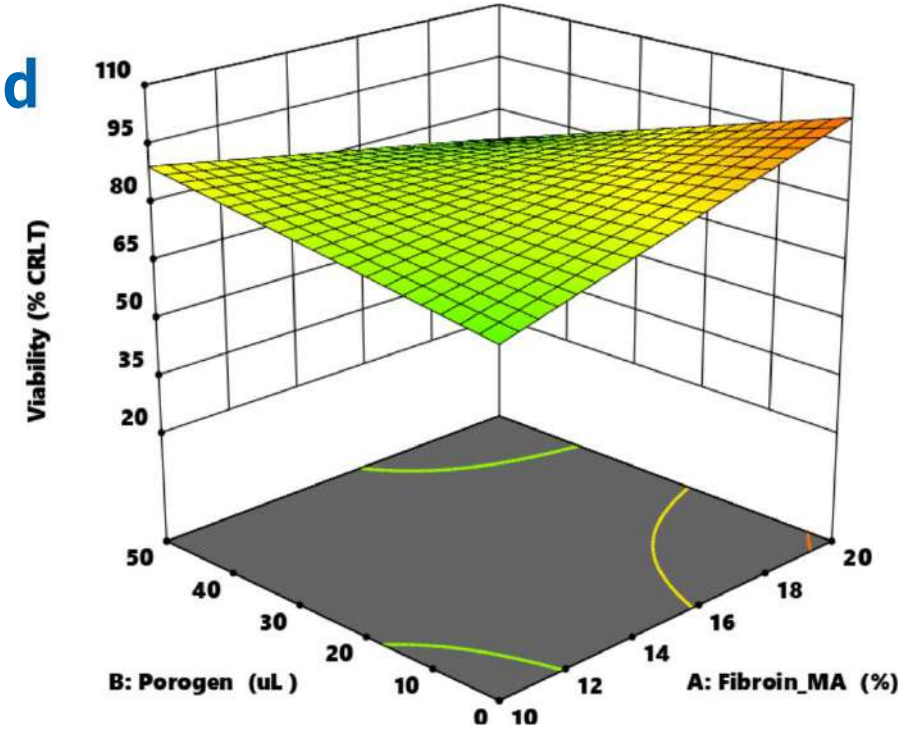
$$1/\sqrt{E} = 0.511 - 0.133 * A - 0.083 * B$$

$$1/\sqrt{E_{(CI\ 95\%\ Low)}} = 0.475 - 0.169 * A - 0.119 * B$$

$$1/\sqrt{E_{(CI\ 95\%\ High)}} = 0.547 - 0.097 * A - 0.047 * B$$

Methacrylated fibroin scaffold

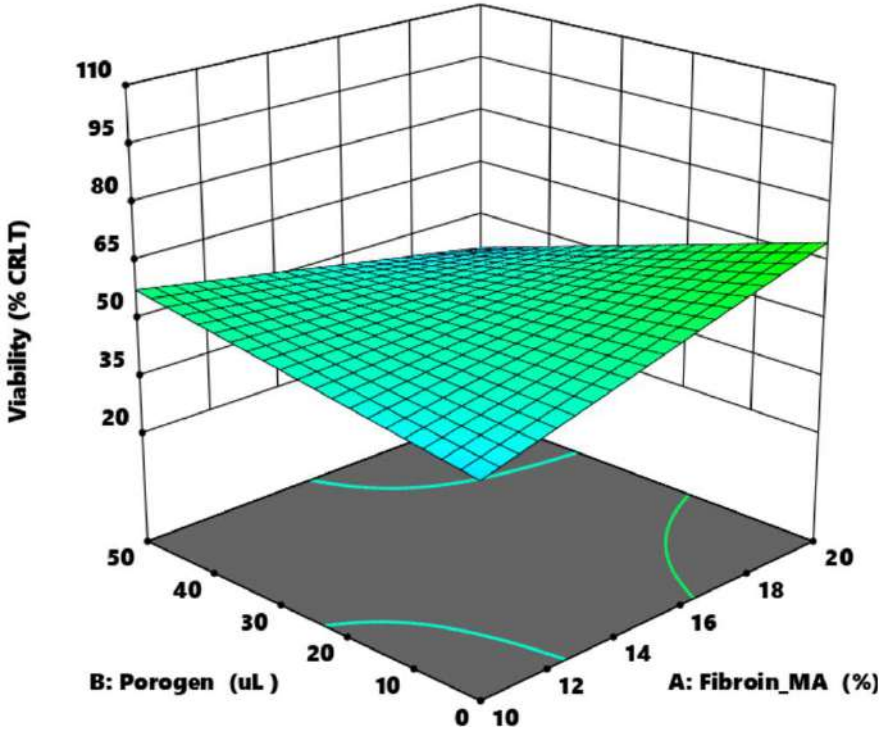




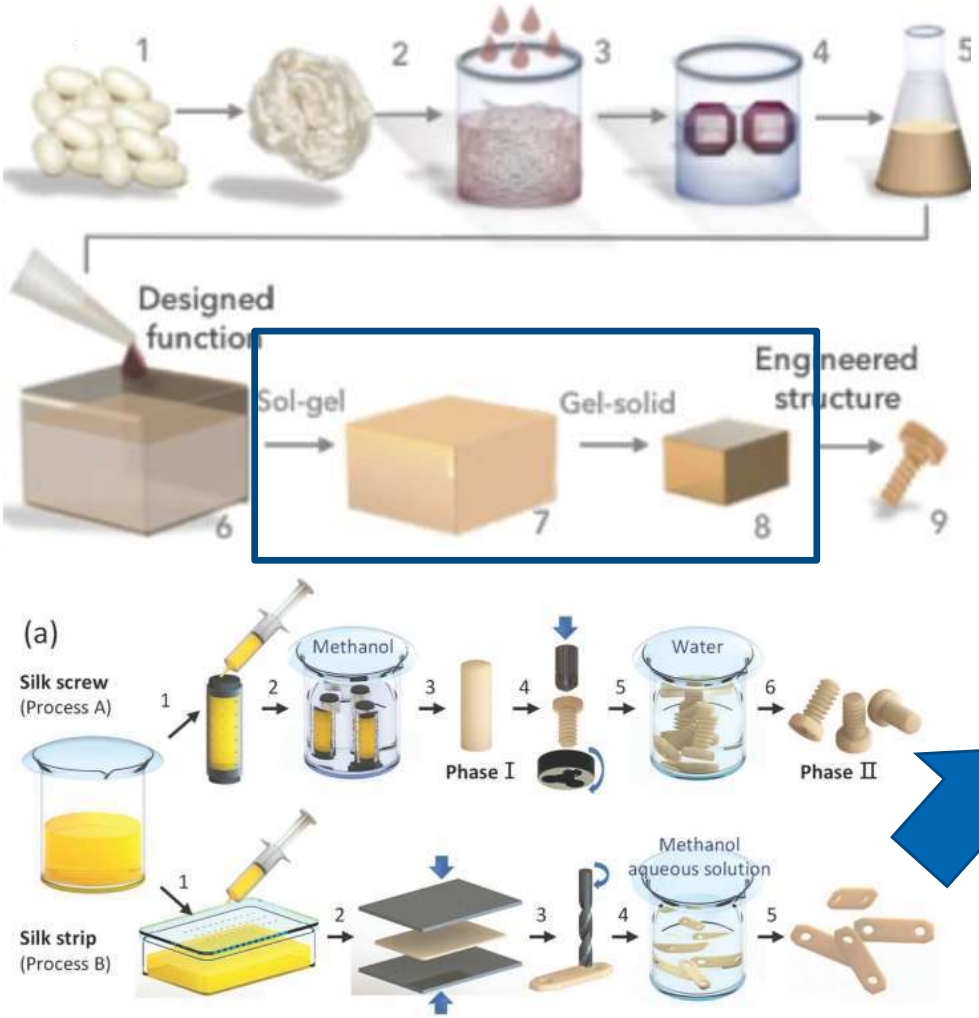
$$V_{\%} = 69.00 + 2.29 * A - 3.86 * B - 15.81 * C - 10.93 * A * B$$

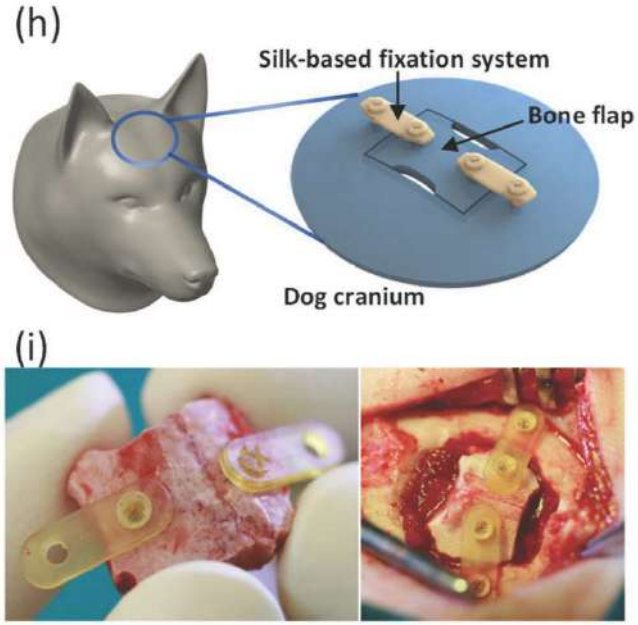
$$V_{\%(CI\ 95\%\ Low)} = 61.39 - 5.31 * A - 11.47 * B - 23.42 * C - 18.54 * A * B$$

$$V_{\%(CI\ 95\%\ High)} = 76.60 + 9.90 * A + 3.75 * B - 8.21 * C - 3.33 * A * B$$

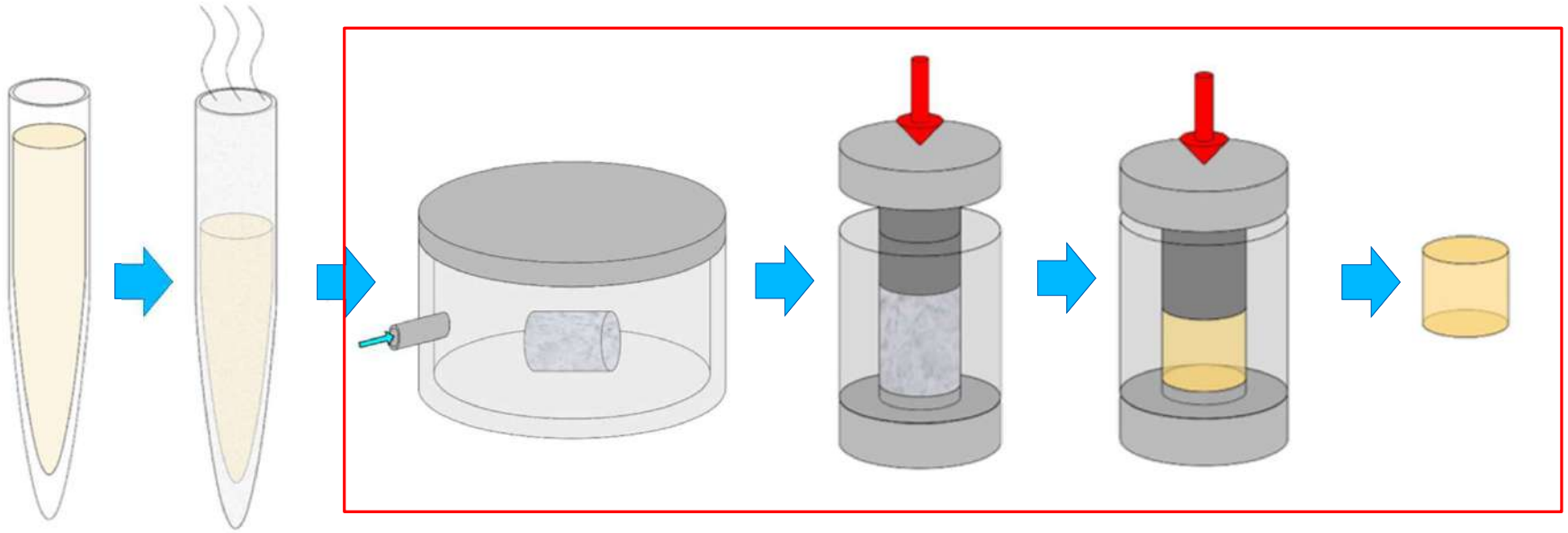


In search of new solutions: solid fibroin

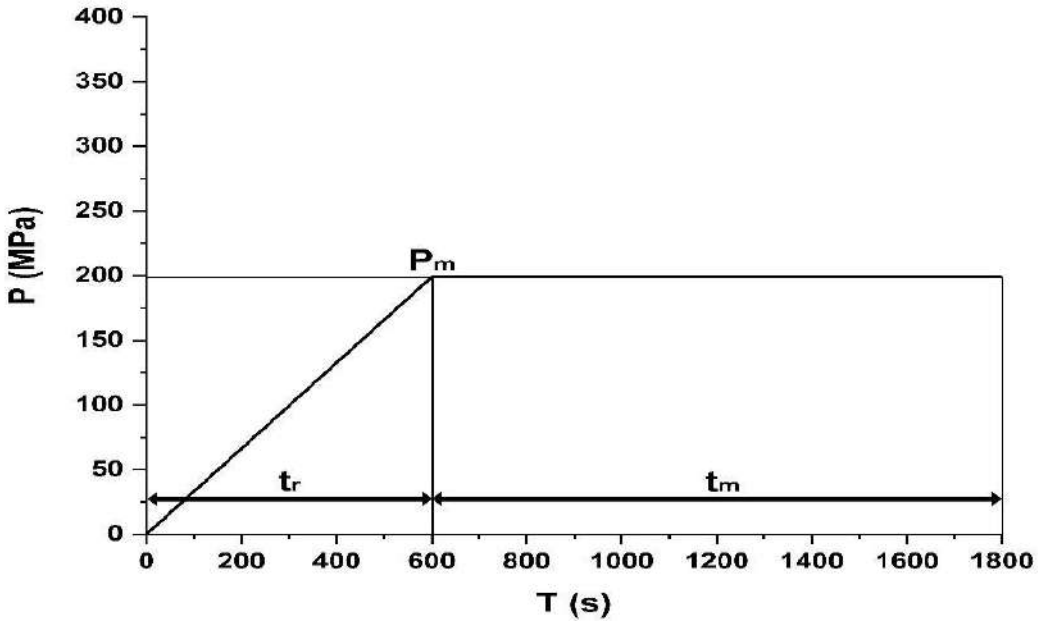


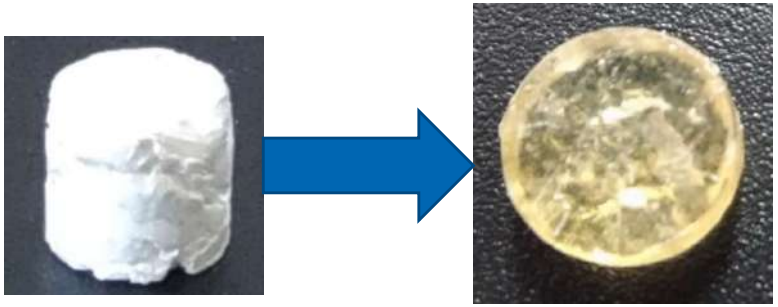


A sintering process



Sintering process



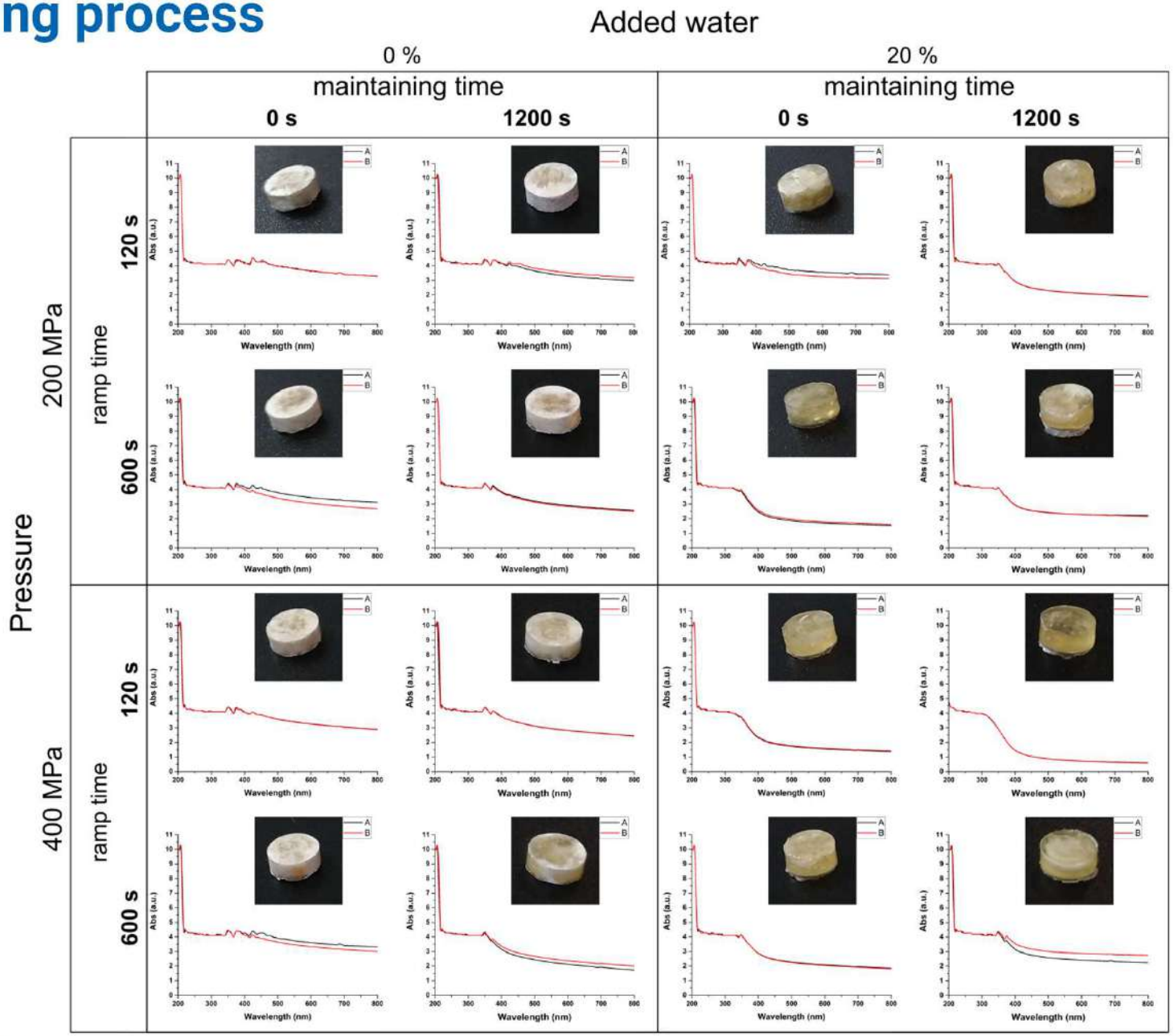


Variable	+1 level	−1 level
t_{ramp} [s]	600	120
P_{max} [MPa]	400	200
t_{maint} [s]	1200	0
$m_{\%W}$ [% w/w]	20	0

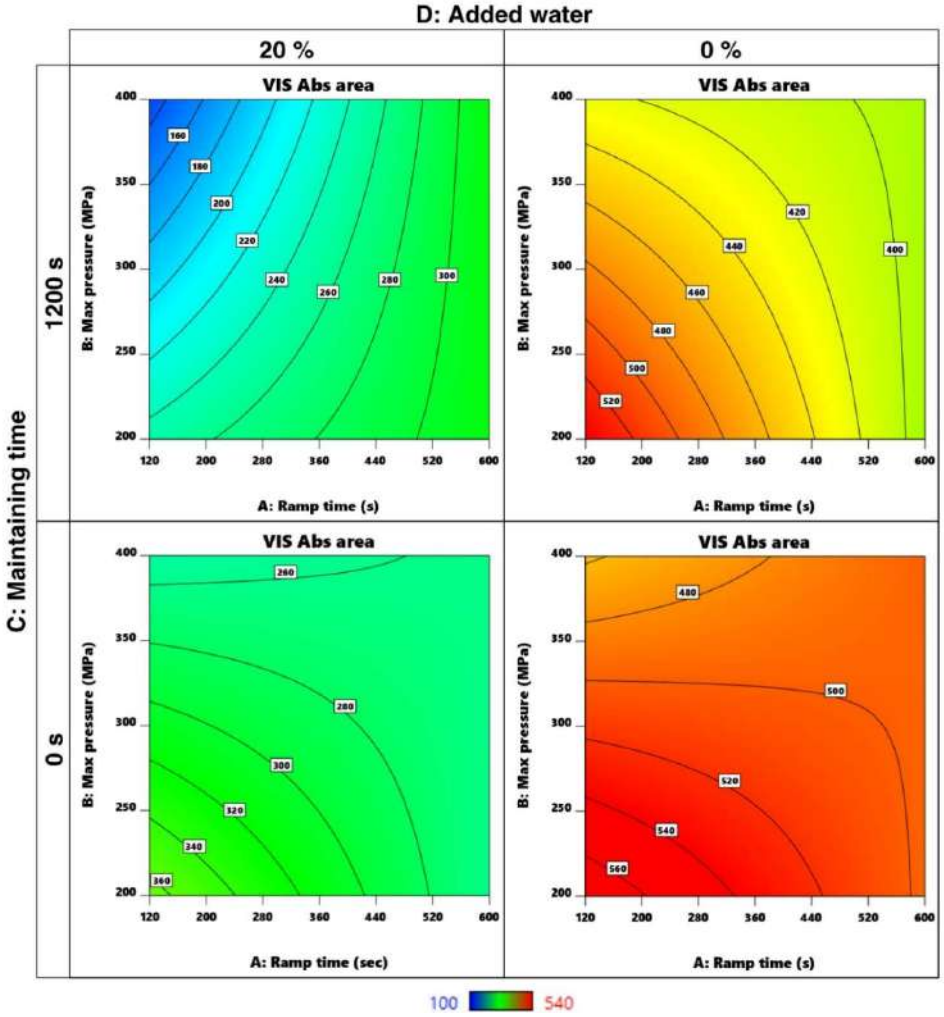
$$Y = c_1{*}t_{ramp} + c_2{*}P_{max} + c_3{*}t_{maint} + c_4{*}m_{\%W} + c_5{*}t_{ramp}{*}P_{max} + c_6{*}t_{ramp}{*}t_{maint} + c_7{*}t_{ramp}{*}m_{\%W} + c_8{*}P_{max}{*}t_{maint} + c_9{*}P_{max}{*}m_{\%W} + c_{10}{*}t_{maint}{*}m_{\%W} + c_{11}{*}t_{ramp}{*}P_{max}{*}t_{maint} + c_{12}{*}t_{ramp}{*}P_{max}{*}m_{\%W} + c_{13}{*}t_{ramp}{*}t_{maint}{*}m_{\%W} + c_{14}{*}P_{max}{*}t_{maint}{*}m_{\%W} + c_{15}{*}t_{ramp}{*}P_{max}{*}t_{maint}{*}m_{\%W}$$

Yields	
Transparency	**Stiffness**
400÷800 nm optical path normalized	Compressive Young Modulus

Sintering process



| Sintering process



$$A_{Abs} = 370.47 - 3.53 * A - 28.63 * B - 25.53 * C - 101.74 * D + 29.59 * A * B + 12.24 * A * C + 23.58 * A * D + 8.99 * C * D + 30.62 * A * C * D$$

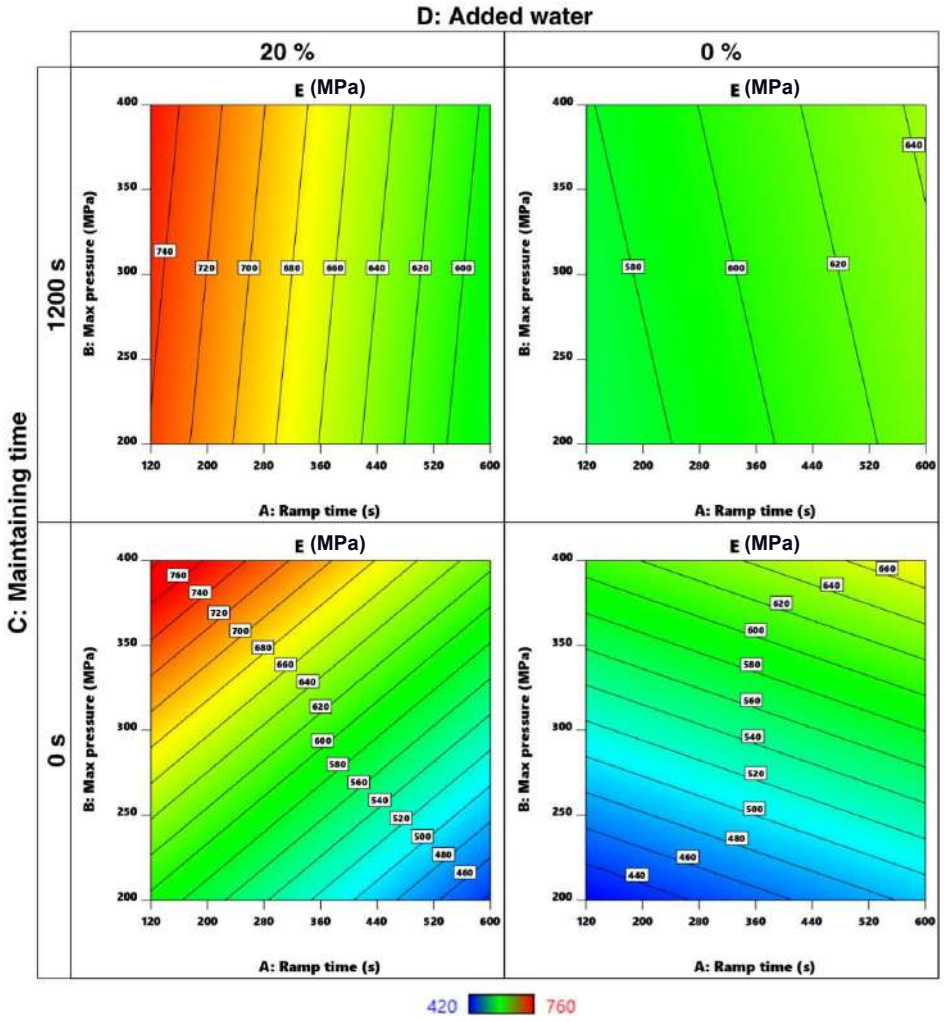
$$A_{Abs(95\%\ CI\ Low)} = 340.35 - 33.65 * A - 58.76 * B - 55.65 * C - 131.87 * D - 0.53 * A * B - 17.70 * A * C - 6.54 * A * D - 21.14 * C * D + 0.49 * A * C * D$$

$$A_{Abs(95\%\ CI\ High)} = 400.60 - 26.60 * A - 1.49 * B - 4.59 * C - 71.62 * D + 59.72 * A * B + 42.55 * A * C + 53.70 * A * D + 39.11 * C * D + 60.74 * A * C * D$$

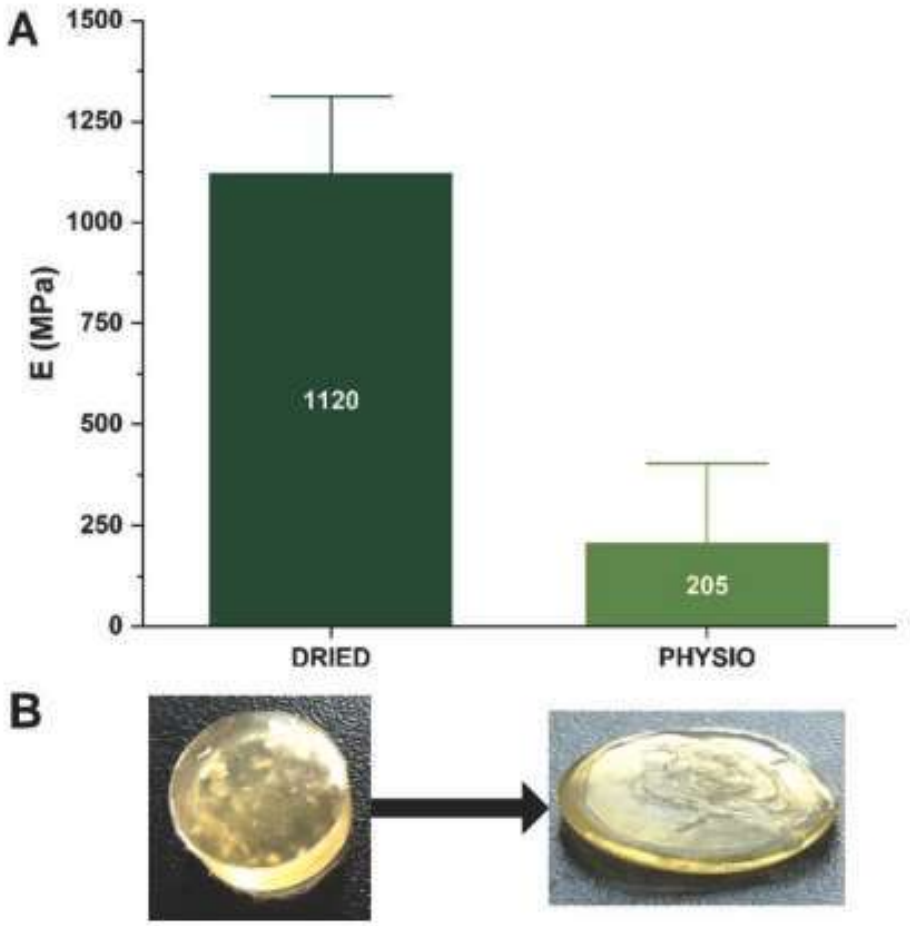
$$E_{comp} = 607.13 - 23.12 * A + 51.12 * B + 28.13 * C + 31.38 * D - 56.13 * A * D - 43.62 * B * C$$

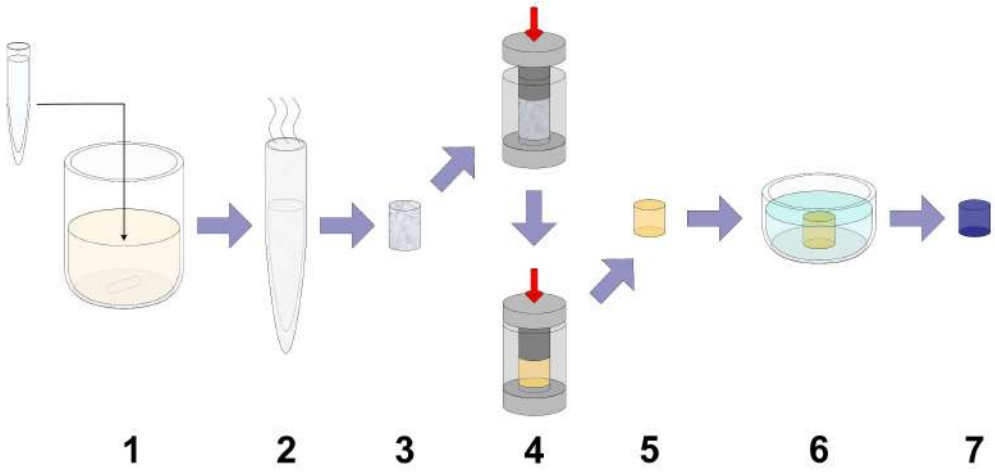
$$E_{comp(95\%\ CI\ Low)} = 564.03 - 66.22 * A + 8.03 * B - 14.97 * C - 11.72 * D - 99.22 * A * D - 86.72 * B * C$$

$$E_{comp(95\%\ CI\ High)} = 650.22 - 19.97 * A + 94.22 * B + 71.22 * C + 74.47 * D - 13.03 * A * D - 0.53 * B * C$$



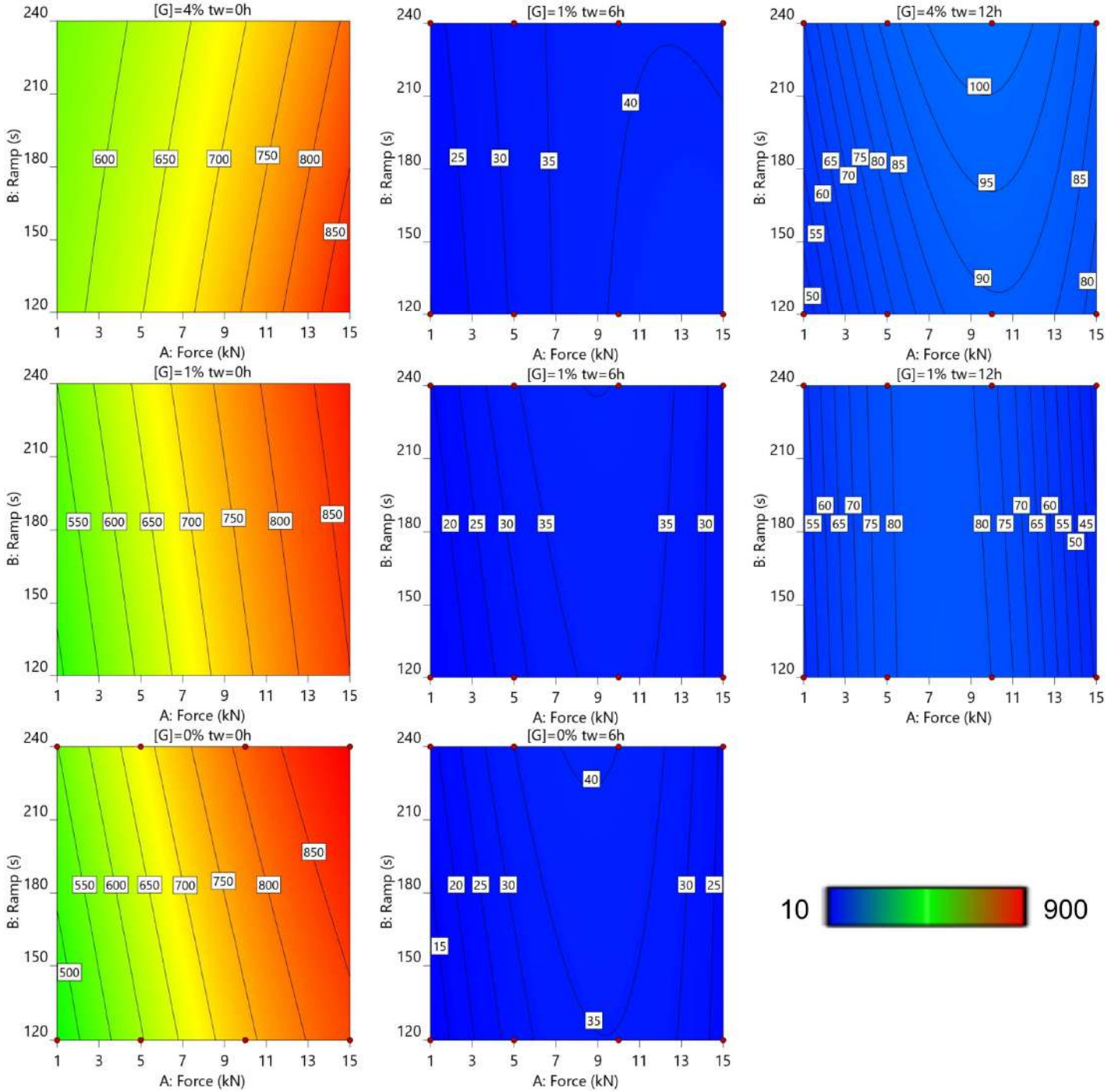
Sintering process





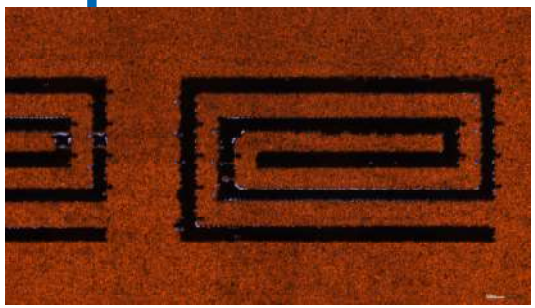
Factor name	Factor Code	Measurement unit	Levels
Force	A) F	kN	1, 5, 10, 15
Ramp time	A) t_r	s	120, 240
Time socked in water	A) t_w	h	0, 6, 12
Temperature	A) T	°C	80, 120
Genipin concentration	A) [G]	% w/w	0, 1, 4

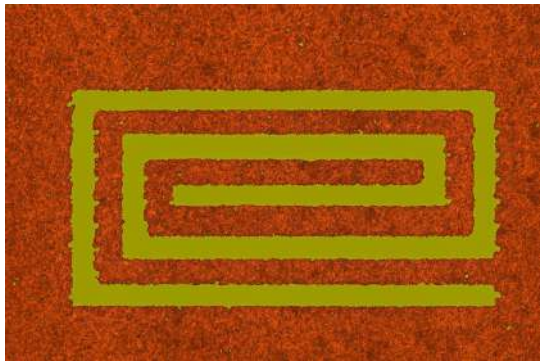
A Response Surface Method

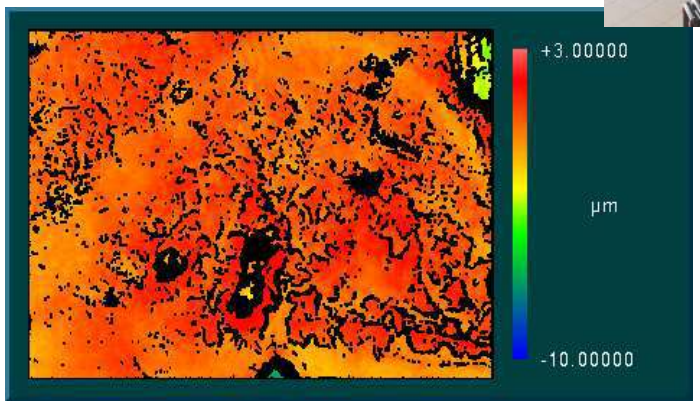


Bucciarelli et al., Enhancement of the mechanical properties of bulk silk throught genipin crosslinking, Manuscript in preparation

An industrial problem: Inkjet deposition



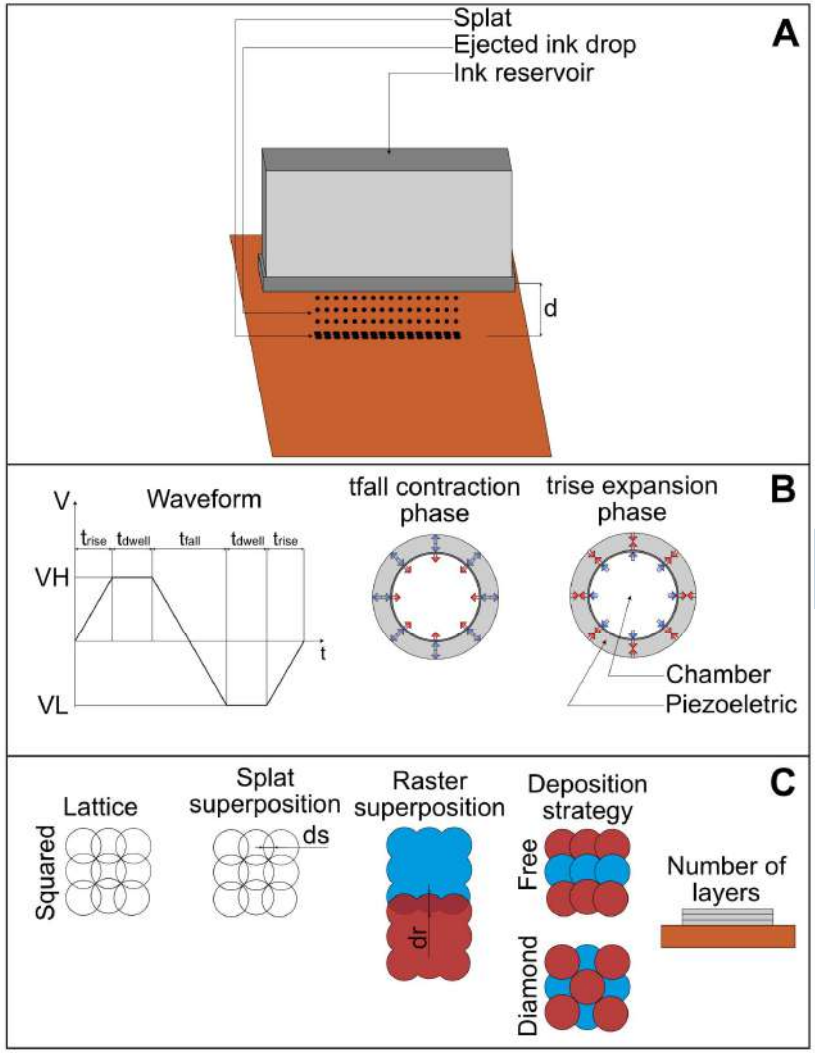




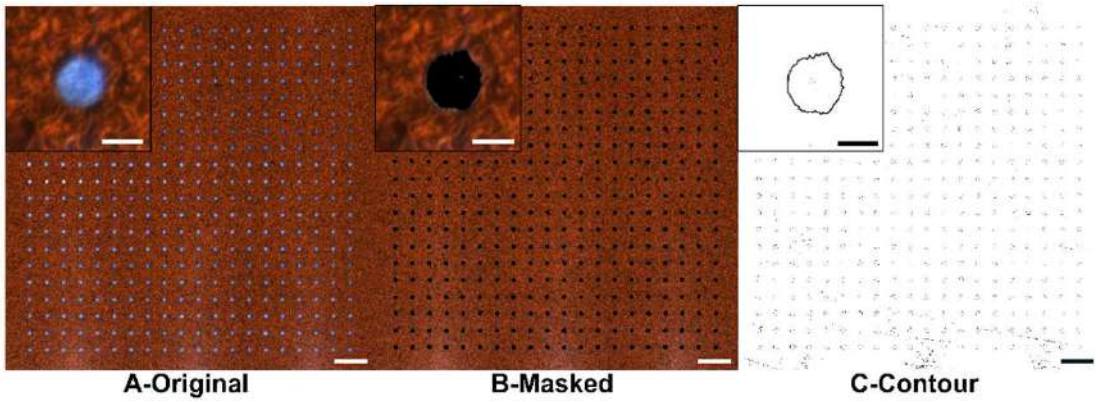
DOE to study the correlation between the deposition method and the properties of the outcoming antennas.

1.Bucciarelli et al., Multivariable optimization of inkjet printing process of Ag nanoparticle ink on Kapton, IEEE proceedings FLEPS, 2020.
2.Bucciarelli et al., Precise dot inkjet printing thought multifactorial statistical optimization of the piezoelectric actuator waveform, IOP flexible and printed electronics, 2020.
3.Bucciarelli et al., Design of experiment rational optimization of an InkJet deposition of silver on Kapton, Manuscript in preparation.

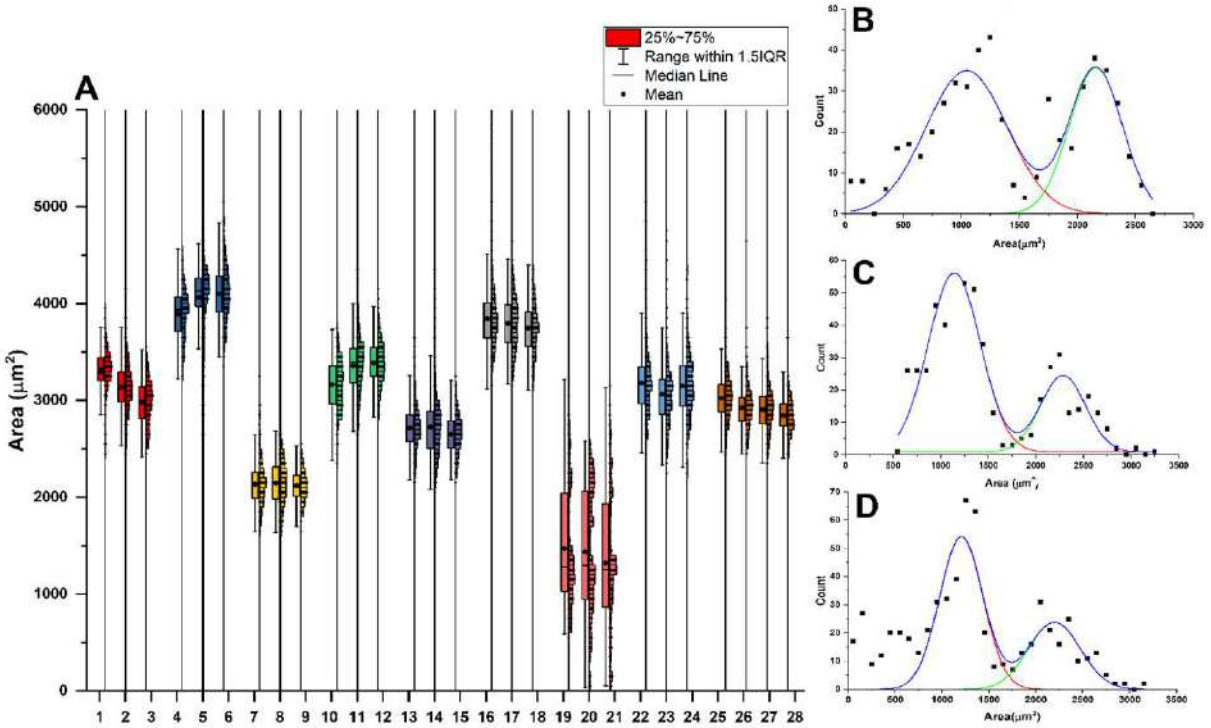
An industrial problem: InkJet printing

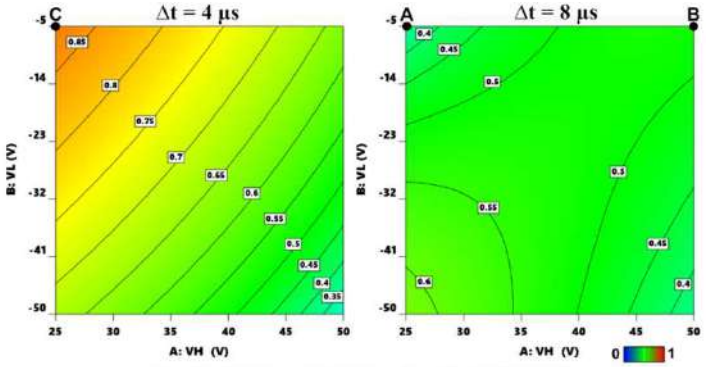


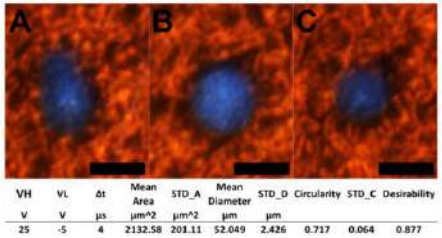
Waveform	Factor A	Factor B	Factor C	Replicas Number
N	VH	VL	Δt	
	V	V	µs	
1	25	-50	4	3
2	50	-50	4	3
3	25	-5	4	3
4	50	-5	4	3
5	25	-50	8	3
6	50	-50	8	3
7	25	-5	8	3
8	50	-5	8	3
9	37.5	-27.5	6	4



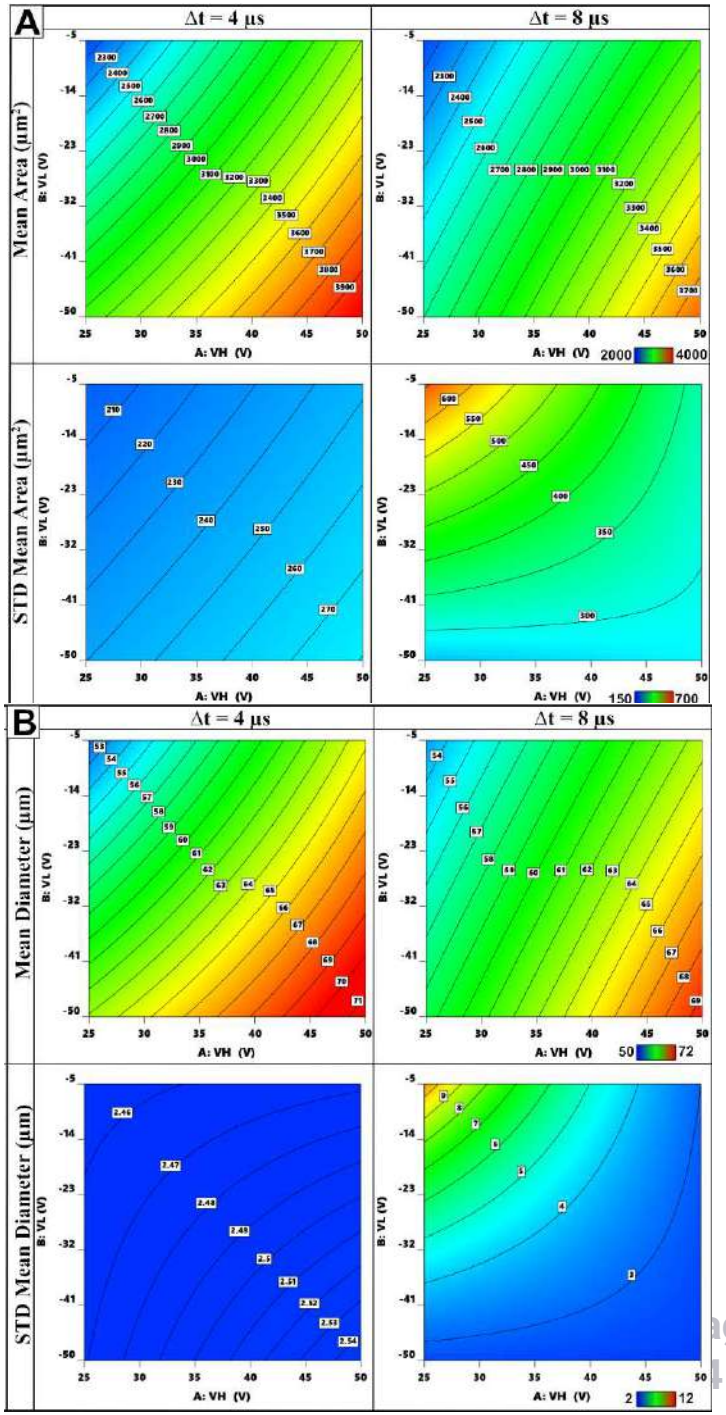
An industrial problem: InkJet printing





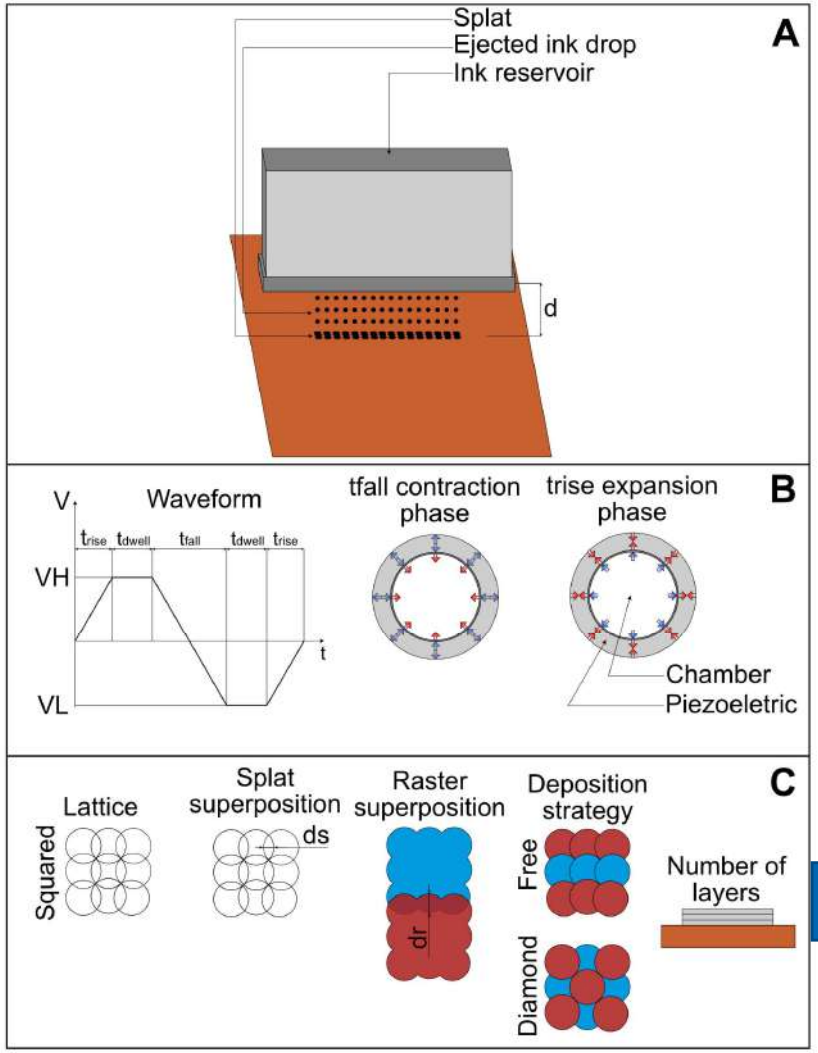


VH	VL	Δt	Mean Area	STD_A	Mean Diameter	STD_D	Circularity	STD_C	Desirability
V	V	μs	μm^2	μm^2	μm	μm			
25	-5	4	2132.58	201.11	52.049	2.426	0.717	0.064	0.877



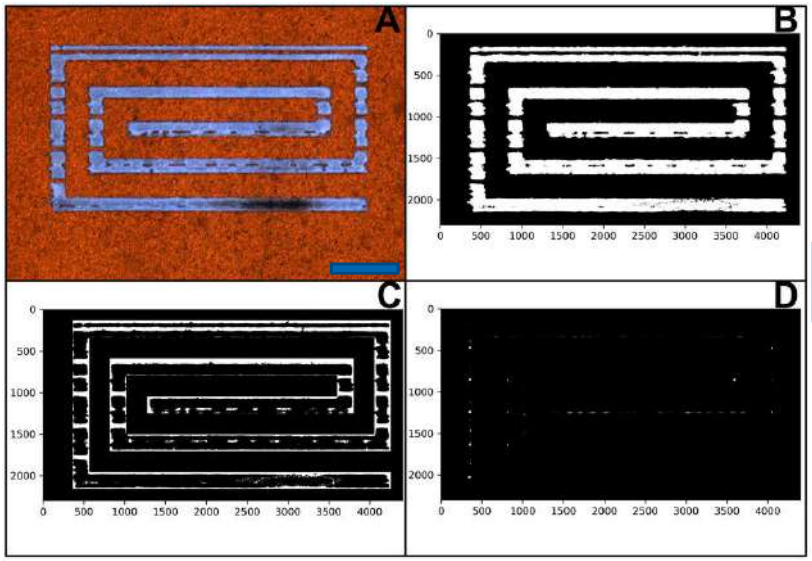
CMM
CENTER FOR MATERIALS AND MICROSYSTEMS
FONDAZIONE BRUNO KESSLER

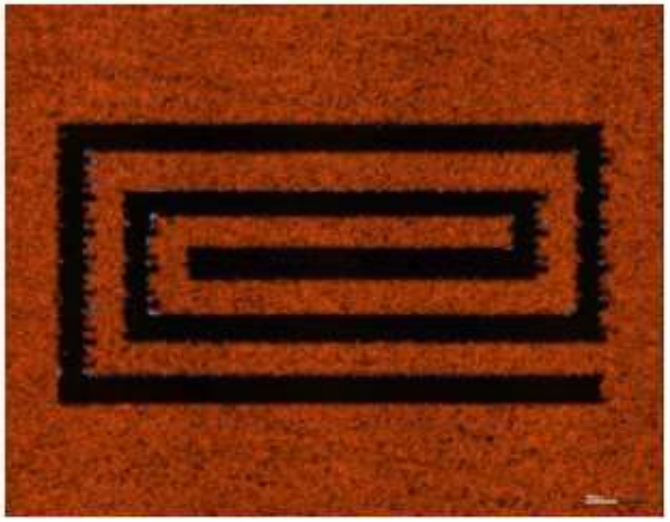
An industrial problem: InkJet printing

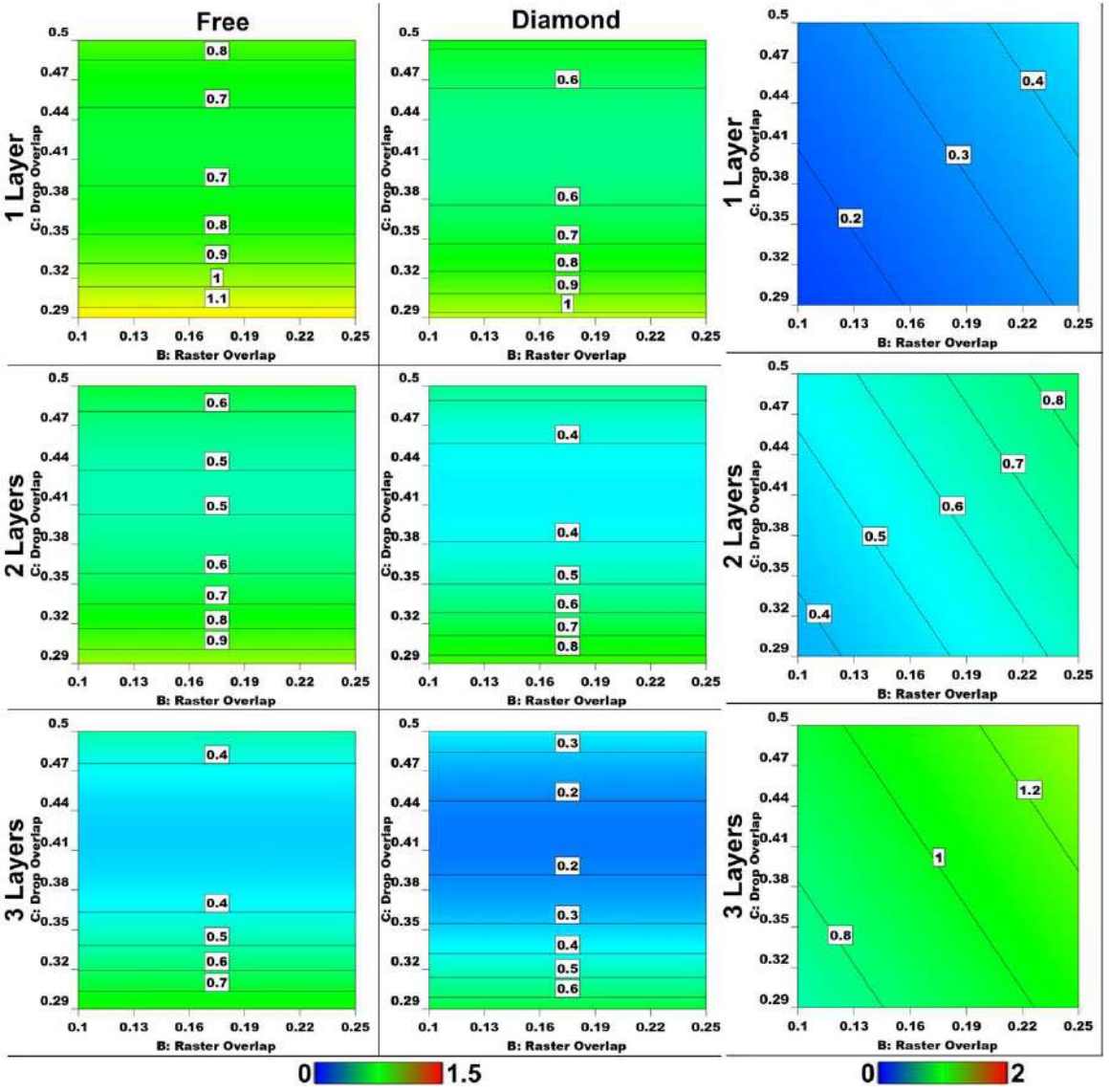


	Ensamble	Lattice		Raster Overlap respect to the nozzle distance	Drop Overlap respect to the diameter	Priming NPFab	Priming Widht um	N Layers Nlayer	Samples N DOE SAMPLES
1	1	Squared	Free	0.00	0.00	0	0	1	1,2
2	2	Squared	Free	0.00	0.33	0	0	1	3,4
3	3	Squared	Free	0.00	0.50	0	0	1	5,6
4	4	Squared	Free	0.25	0.00	0	0	1	7,8
5	5	Squared	Free	0.25	0.33	0	0	1	9,10
6	6	Squared	Free	0.25	0.50	0	0	1	11,12
7	7	Squared	Diamond	0.00	0.00	1	0	1	13,14
8	8	Squared	Diamond	0.00	0.33	1	0	1	15,16
9	9	Squared	Diamond	0.00	0.50	1	0	1	17,18
10	10	Squared	Diamond	0.25	0.00	1	0	1	19,20
11	11	Squared	Diamond	0.25	0.33	1	0	1	21,22
12	12	Squared	Diamond	0.25	0.50	1	0	1	23,24
13	13	Centered Squared	Free	0.00	0.00	0	0	1	25,26
14	14	Centered Squared	Free	0.00	0.33	0	0	1	27,28
15	15	Centered Squared	Free	0.00	0.50	0	0	1	29,30
16	16	Centered Squared	Free	0.25	0.00	0	0	1	31,32
17	17	Centered Squared	Free	0.25	0.33	0	0	1	33,34
18	18	Centered Squared	Free	0.25	0.50	0	0	1	35,36
19	1	Squared	Free	0.00	0.00	0	0	3	37,38
20	2	Squared	Free	0.00	0.33	0	0	3	39,40
21	3	Squared	Free	0.00	0.50	0	0	3	41,42
22	4	Squared	Free	0.25	0.00	0	0	3	43,44
23	5	Squared	Free	0.25	0.33	0	0	3	45,46
24	6	Squared	Free	0.25	0.50	0	0	3	47,48
25	7	Squared	Diamond	0.00	0.00	1	0	3	49,50
26	8	Squared	Diamond	0.00	0.33	1	0	3	51,52
27	9	Squared	Diamond	0.00	0.50	1	0	3	53,54
28	10	Squared	Diamond	0.25	0.00	1	0	3	55,56
29	11	Squared	Diamond	0.25	0.33	1	0	3	57,58
30	12	Squared	Diamond	0.25	0.50	1	0	3	59,60
31	13	Centered Squared	Free	0.00	0.00	0	0	3	61,62
32	14	Centered Squared	Free	0.00	0.33	0	0	3	63,64
33	15	Centered Squared	Free	0.00	0.50	0	0	3	65,66
34	16	Centered Squared	Free	0.25	0.00	0	0	3	67,68
35	17	Centered Squared	Free	0.25	0.33	0	0	3	69,70
36	18	Centered Squared	Free	0.25	0.50	0	0	3	71,72

From a qualitative to a quantitative approach







CMM
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FONDAZIONE BRUNO KESSLER

Swot analysis

strengths

Modelling, Reduce the time to get to wanted results, No data is wasted.

weaknesses

Lack of physical significance, It require times to get into it.

opportunities

Is rarely applied in processing and at the lab scale.

threats

In industry is a quite known methods.

Acknowledgements

BIOtech at UNIVERSITY OF TRENTO - Italy
Biomedical Technologies

REMIX – Regenerative Medicine Innovation Crossing

POLIGRAFICO E ZECCA DELLO STATO ITALIANO

FONDAZIONE BRUNO KESSLER
CMM CENTER FOR MATERIALS AND MICROSYSTEMS

Curcumin and Its Anti-angiogenesis Effects: How to put it to use?

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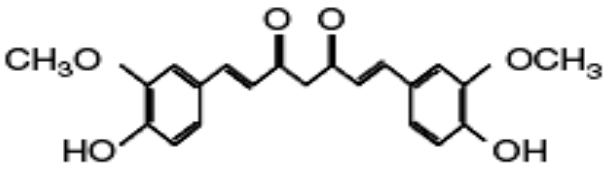
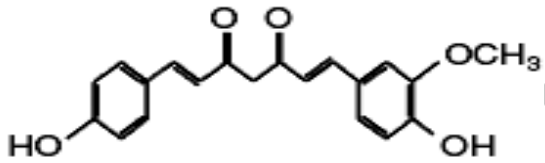
Hindawi
Evidence-Based Complementary and Alternative Medicine, 2019, Article ID 1390795, 9

Curcuminoids

Bis-(feruloyl)methane or 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione ($C_{21}H_{20}O_6$) MW 368.39

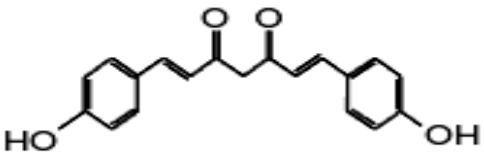


Curcumin I
(77%)



Curcumin II

Demethoxycurcumin
(17%)



Curcumin III

Bis-Demethoxycurcumin
(3%; less active)

- **Insoluble in water and ether**
- **Soluble in alcohols, glacial acetic acid, chloroform, ketone, alkali and fats**
- **Anti-oxidation, anti-inflammatory, anti-viral, anti-parasitic and chemopreventive agent against cancer**
- **Sensitive to UV lights and basic pH (pH<7) environments**
- **Curcumin (in DMSO) in 0.1 M phosphate buffer (pH 7.2) degraded upto 90% in 30 minutes**
- **Low absorption & low bioavailability & rapid clearing**
- **Toxic to liver at high dose**

The products available as foods, herbal supplements, and cosmetics in Thailand

Indication for use: Stomachache, Flatulence

150 baht
(4 Euros)
Per 100 capsules of 500 mg

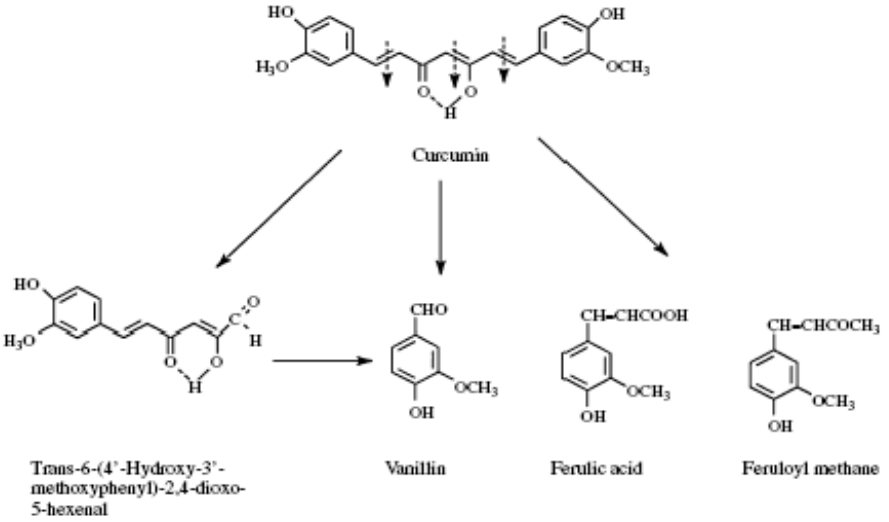
Drink

cosmetics

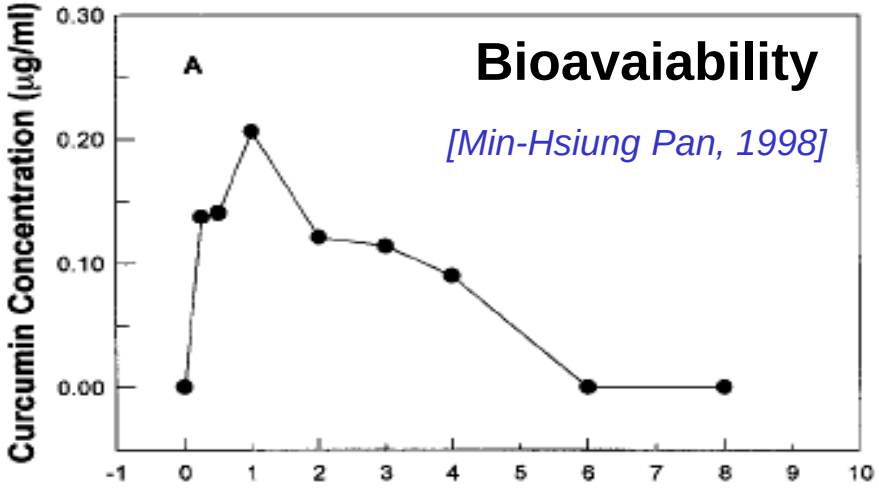
Degradation of curcumin in 0.1 M phosphate buffer (pH 7.2)

[Wang et.al, 1996]

fetal calf serum (FCS), human blood and antioxidants such as ascorbic acid, N-acetylcysteine or glutathione can protect curcumin degradation in cell culture medium



Concentration in plasma (BALB/c nude mice, 6-7 weeks, 18-20g.) after feeding at 1 g/kg body weight was highest at 1 hr after feeding (at 22 micrograms/ml plasma)



The therapeutic potential of curcumin: A review of clinical trials

(European Journal of Medicinal Chemistry 163 (2019) 527-545)

❖ Anti-inflammatory activity

-Significant reduction of inflammation markers (IL-1b, IL-6,
sCD40L, sVCAM-1) and ESR
-Decreased COX-2 secretion
-Reduced TNF-a, TGF-b,
IL-6, substance P, hs-CRP, CGRP and MCP-1 levels

❖Skin disorders

Radiation dermatitis, Pruritis, Psoriasis, Vitiligo

❖Eye disorders

-Various ophthalmic disorders
-Uveitis, Chorioretinopathy

❖Central nervous system disorders

-Alzheimer disease
-Dejerine-Sottas disease
-Anxiety and depression

❖Respiratory system disorders

-Recurrent respiratory tract infections

❖ Urogenital system disorders

Renal transplantation, Diabetic nephropathy, Lupus nephritis, Chronic kidney disease, Chronic bacterial prostatitis, type II, Chronic prostatitis/Chronic pelvic pain syndrome, type III

❖Cardiovascular system disorders

-Decrease serum lipid peroxides
-Reduce TC and LDL-C levels; increase HDL-C Levels

❖Gastrointestinal system disorders

-Hepatoprotective effects
-Pancreatitis, Gallbladder, Biliary dyskinesia
-Irritable bowel syndrome
-Inflammatory bowel disease, Peptic ulcer
-Helicobacter pylori infection

❖Metabolic disorders.

-Type II diabetes
-Obesity
-b-thalassemia

❖Toxin neutralizing effects

-Chronic arsenic exposure
-Alcohol intoxication

❖ Cancer Therapy

-Skin lesions, Myeloma
-Orbital pseudotumors
-Head and neck squamous cell carcinoma
-Breast, Lung, Prostate, Pancreatic, Colorectal Cancers

Curcumin Related Clinical Trial Publications: 9,600+ to-date

	REF
Curcumin and inflammatory bowel diseases: From *in vitro* studies to clinical trials	Molecular Immunology 130 (2021) 20–30
The effects of nano-curcumin supplementation on Th1/Th17 balance in migraine patients: A randomized controlled clinical trial	Complementary Therapies in Clinical Practice 41 (2020) 101256
Effects of curcumin supplementation on blood glucose, insulin resistance and androgens in patients with polycystic ovary syndrome	Phytomedicine 80 (2021) 153395
Significant immunomodulatory properties of curcumin in patients with osteoarthritis; a successful clinical trial in Iran	International Immunopharmacology, (2020), Vol 85, 106607
Efficacy and safety of curcumin in combination with paclitaxel in patients with advanced, metastatic breast cancer	Complementary Therapies in Medicine Vol 51, (2020), 102447
Efficacy of curcumin for management of oral submucous fibrosis: a systematic review of randomized clinical trials	Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology(2019) Vol127, 4, p300-308

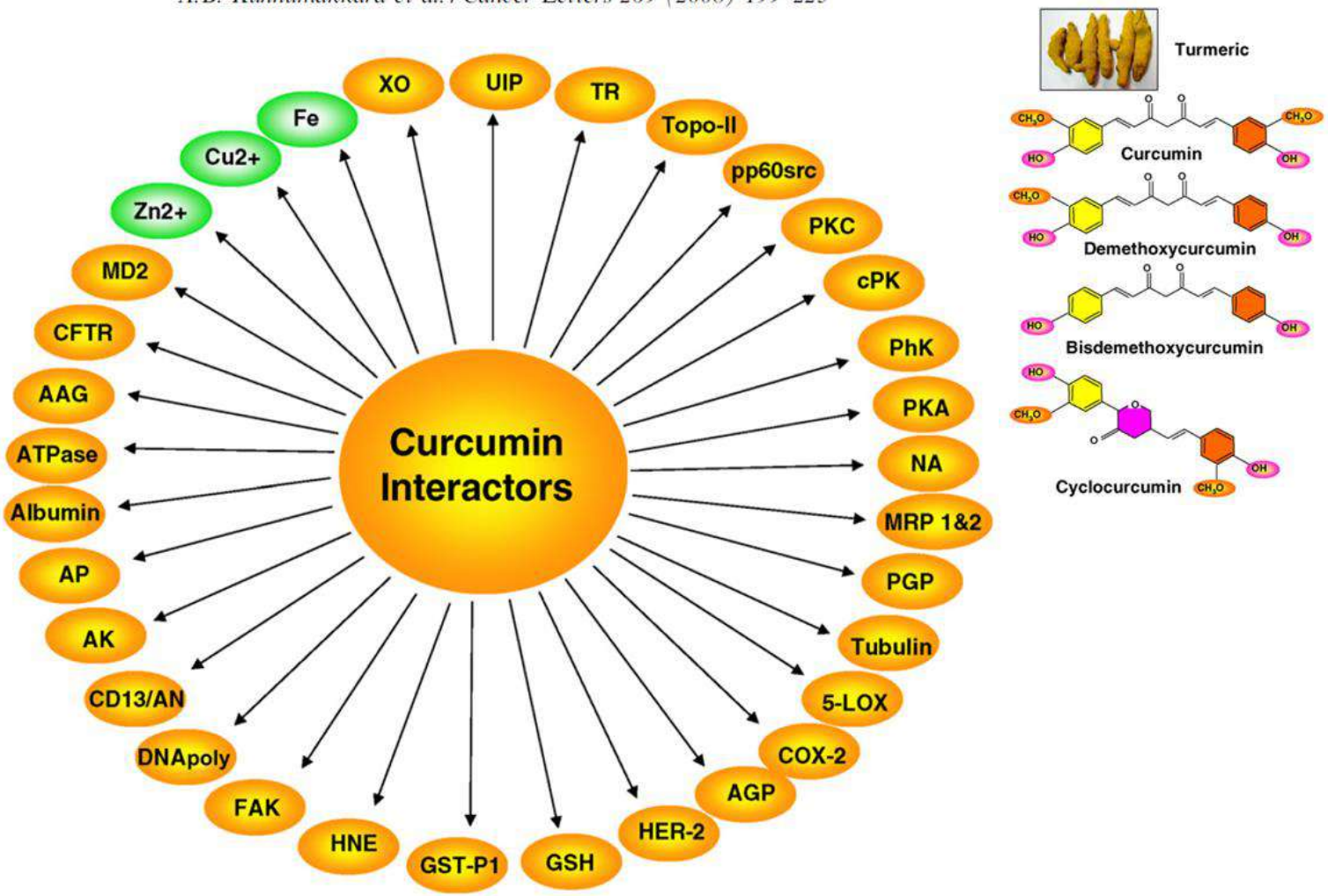


Fig. 3. Curcumin has been shown to bind to numerous molecules. AGP, human alpha1-acid glycoprotein; AK, autophosphorylation-activated protein kinase, AP, amyloid protein; CD13/AN, CD13/aminopeptidase N; CFTR, cystic fibrosis transmembrane conductance regulator; COX-2, cyclooxygenase; cPK, protamine kinase; DNA poly, DNA polymerase; FAK, focal adhesion kinase; GSH, glutathione; HER-2, human epidermal growth factor receptor; HNE, 4 hydroxy-2-nonenal; NA, nucleic acid; LOX, lipoxygenase; PGP, P-glycoprotein; PkA, protein kinase A, PkC, protein kinase C, PhK, phosphorylase kinase; pp60src, pp60c-src tyrosine kinase; TR, thioredoxin reductase; Topo-II, topoisomerase II; UIP, ubiquitin isopeptidase; XO, xanthine oxidase.

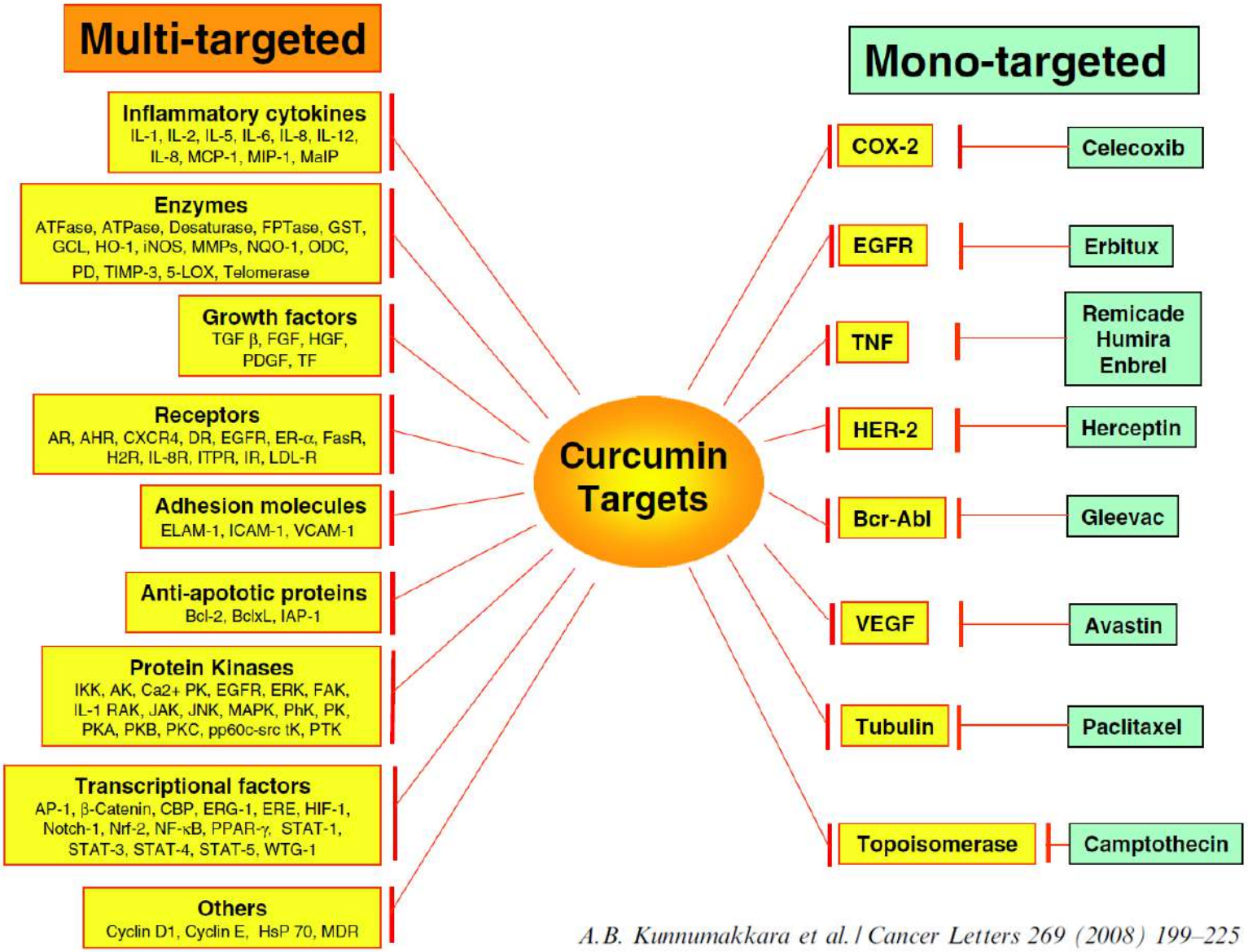
Table II. Molecular Targets of Curcumin in Human Participants

Disease	Biomarkers	Reference
Colorectal cancer	GST ↓	(13)
	PGE_2 ↓	(14)
	M_1G ↓	(15)
	TNF-α↓, Bcl-2 ↓,p53 ↑, Bax ↑	(18)
Pancreatic cancer	MDA ↓, GSH ↑	(19)
	IL-6↓, IL-8↓, IL-10↓, NF–κB↓, COX-2↓, pSTAT3↓	(12)
Prostate cancer	PSA↓	(22)
Multiple myeloma	Paraproteins ↓, NTT ↓	(23)
	NF–κB ↓, COX-2 ↓, pSTAT3 ↓	(24)
Cancer lesions	Vitamin C↑, vitamin E↑, MDA↓, 8-OHdG↓	(30)
Head and neck cancer	IKKβ ↓, IL-8 ↓	(31)
Inflammatory bowel disease	CRP ↓, ESR ↓, CDAI ↓	(32)
	p38 MAPK ↓, IL-1β↓, MMP-3↓, IL-10↑	(35)
Osteoarthritis	CRP↓	(40)
	IL-1β↓, IL-6↓, sCD40L↓, sVCAM1↓, ESR↓	(41)
H. pylori infection	sPGII↓, sPG I↓	(47)
Psoriasis	PhK↓, TRR↓, CD8 + T cells↓	(51)
Acute coronary syndrome	TC↓, LDL↓, HDL↑, TG↑	(56)
Atherosclerosis	Lipid peroxides↓, TC↓, HDL↑	(57)
Type 2 diabetes	MDA↓, ET-1↓, IL-6↓, TNF-α↓	(59)
	HOMA-β↑, adiponectin↑, C-peptide↓, HOMA-IR↓	(61)
Diabetic nephropathy	TGF- β↓, IL- 8↓	(62)
Renal transplantation	Creatinine↓, HO-1↑	(65)
β-Thalassemia	MDA↓, SOD↓, GSH-Px↓, NTBI↓, GSH↑	(67)
Hepatoprotection	AST↓, ALT↓, Bilirubin↓, ESR ↓	(71)
Arsenic exposure	Catalase↑, GSH↑, SOD↑, GPX ↑, ROS↓	(72)

↓, Downregulation;↑, upregulation

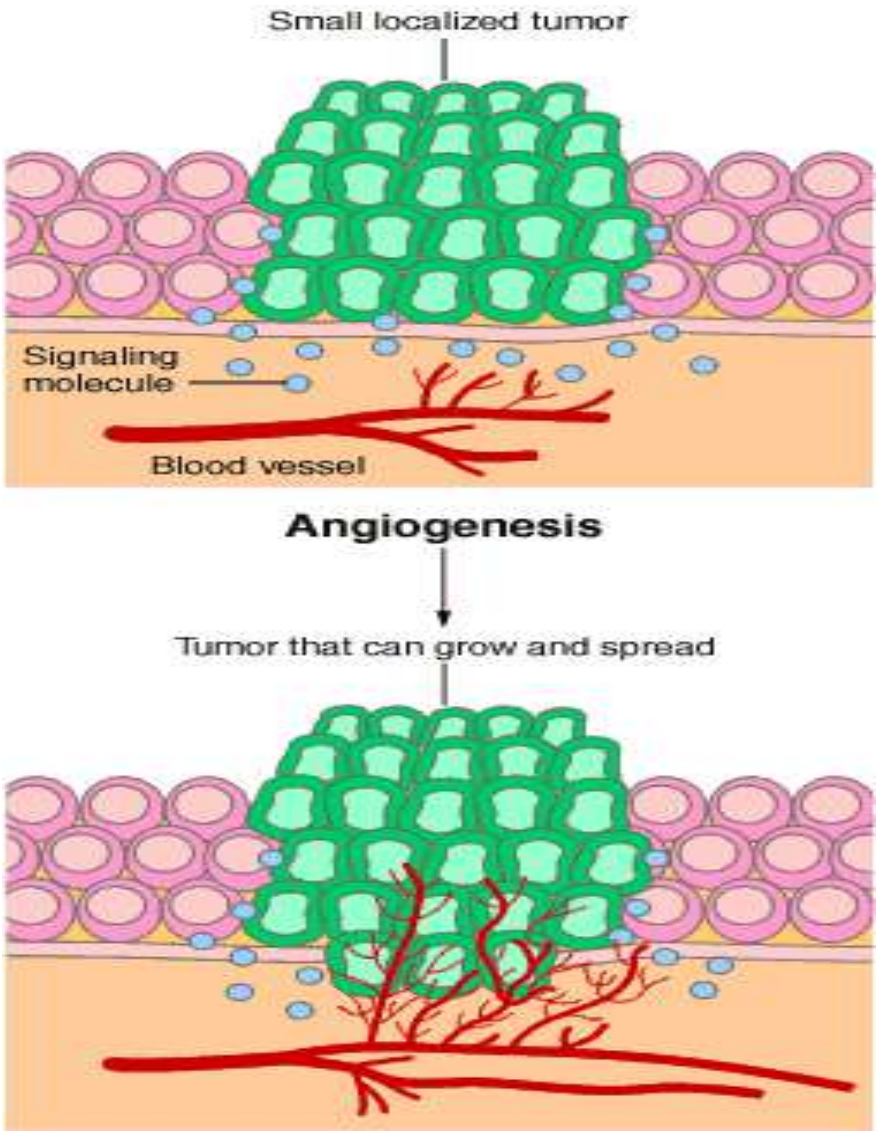
8-OHdG 8-hydroxydeoxyguanosine, *ALT* alanine transaminase, *AST* aspartate transaminase, *Bax* Bcl-2–associated X protein, *Bcl-2* B cell lymphoma-2, *CD* cluster of differentiation, *CDAI* Crohn disease activity index, *COX-2* cyclooxygenase 2, *CRP* C-reactive protein, *ET-1* endothelin-1, *ESR* erythrocyte sedimentation rate, *GSH* glutathione, *GST* glutathione S-transferase, *GPX* glutathione peroxidase, *HDL* high-density lipoprotein, *HO-1* hemoxygenase-1, *H. pylori Helicobacter pylori*, *HOMA* homeostasis model assessment, *IL* interleukin, *IR* insulin resistance, *LDL* low-density lipoprotein, *MAPK* mitogen-activated protein kinase, *MDA* malondialdehyde, *M_1G* pyrimido[1,2-*a*]purin-10(*3H*)-one, *MMP-3* matrix metalloproteinase-3, *NF–κB* nuclear factor kappa-light-chain-enhancer of activated B cells, *NTBI* non-transferrin bound iron, *NTT* N-telopeptide of type 1 collagen, *PGE_2* prostaglandin E_2, *PhK* phosphorylase kinase, *PSA* prostate-specific antigen, *pSTAT3* phosphorylated form of signal transducer and activator of transcription 3, *ROS* reactive oxygen species, *sCD40L* soluble cluster of differentiation 40 ligand, *SOD* superoxide dismutase, *sPG I* serum pepsinogen I, *sPG II* serum pepsinogen II, *sVCAM* soluble vascular cell adhesion molecule, *TC* total cholesterol, *TG* triglyceride, *TNF-α* tumor necrosis factor-α, *TRR* transferrin receptor

AAPS J. 2013 Jan; 15(1): 195–218.



A.B. Kunnumakkara et al. / Cancer Letters 269 (2008) 199–225

Angiogenesis



Stimulator	Mechanism
FGF	Promotes proliferation & differentiation of endothelial cells, smooth muscle cells, and fibroblasts
VEGF	Affects permeability
VEGFR and NRP-1	Integrate survival signals
Ang1 and Ang2	Stabilize vessels
PDGF (BB-homodimer) and PDGFR	recruit smooth muscle cells
TGF-β, endoglin and TGF-β receptors	↑extracellular matrix production
MCP-1	
Histamine	
Integrins $\alpha_V\beta_3$, $\alpha_V\beta_5$ (?[6]) and $\alpha_5\beta_1$	Bind matrix macromolecules and proteinases
VE-cadherin and CD31	endothelial junctional molecules
ephrin	Determine formation of arteries or veins
plasminogen activators	remodels extracellular matrix, releases and activates growth factors
plasminogen activator inhibitor-1	stabilizes nearby vessels
eNOS and COX-2	
AC133	regulates angioblast differentiation
Id1/Id3	Regulates endothelial transdifferentiation

Angiogenesis: various signaling pathways, related factors, and receptors are involved.

3 stages of angiogenesis:

1: Tip cells, or endothelial cells inside the capillary react to the angiogenesis factor VEGF-A

2: Proliferative response, the tip cells responded to VEGF-A through guided Migration and proliferation by the activation of VEGF-A on VEGFR-2

3: Maturation of newly formed vessels (endothelial proliferation inhibition, new capillaries migration, and stabilization of new vascular tubes

Angiogenesis inhibitors:

1) Direct angiogenesis inhibitors: inhibitors that are sensitive for endothelial cells than tumor cells

2) Indirect inhibitors, have no direct effects on endothelial cells, but may regulate angiogenesis via downregulating an angiogenesis stimulator

Curcumin affects the whole process of angiogenesis through downregulating transcription factors such as NF-κB and pro-angiogenesis factors such as VEGF, bFGF, and MMPs, all of which are closely and directly linked with tumorigenesis

Hindawi
Evidence-Based Complementary and Alternative Medicine, 2019, Article ID 1390795, 9

Dual actions of Curcumin in different microenvironments

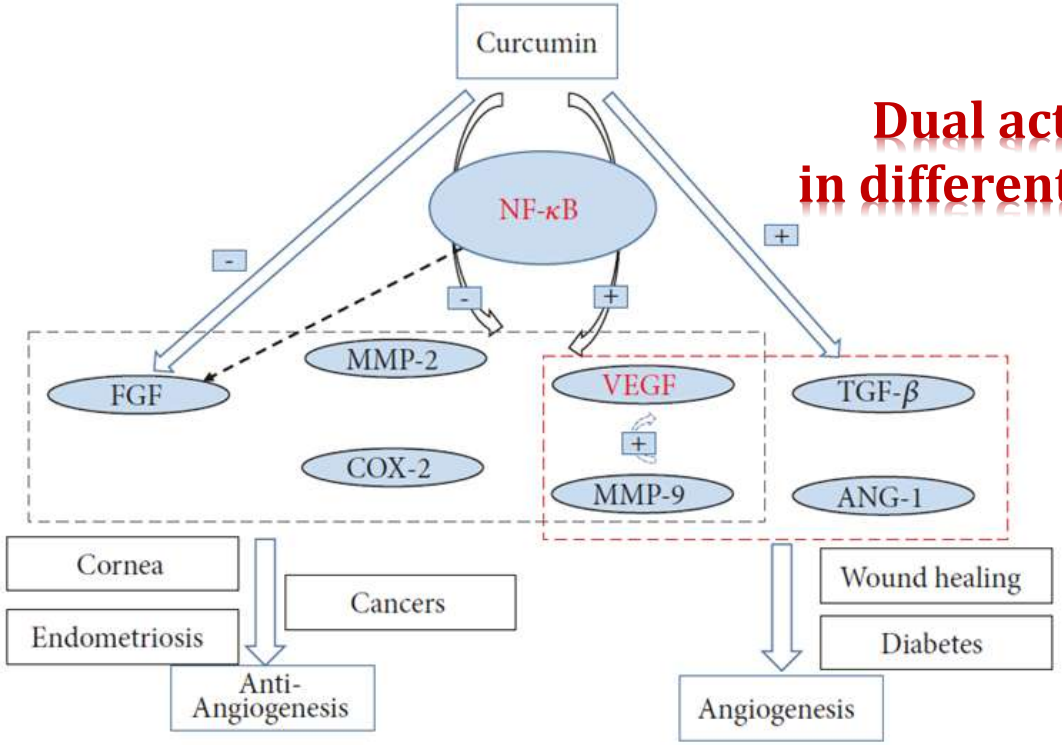


FIGURE 4: Possible mechanism on dual effect of curcumin on angiogenesis.

Studies have confirmed that curcumin shows different effects in different microenvironment

-In a microenvironment that lack of exogenous stimuli and exposed to growth factors such as FGF, curcumin may present an an-tiangiogenesis effect

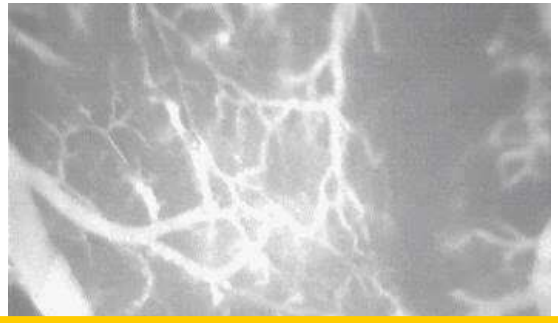
-If the process was mediated through VEGF and PI3K-Akt pathway in different microenvironment proangiogenesis effects

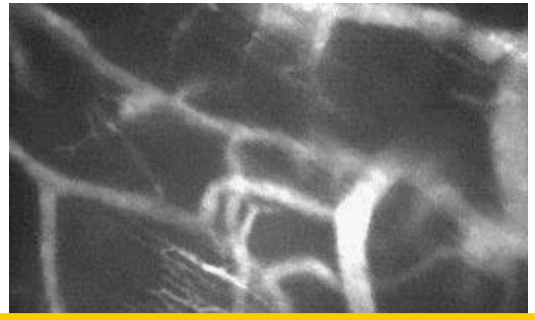
-Dosage of curcumin may determine if the curcumin will stimulate pro-angiogenesis (low dose, 20 mg/Kg/day) or anti-angiogenesis activity (high dose, 100-300 mg/Kg/day)

control

Treatment with curcumin (3,000 mg/kgBW)

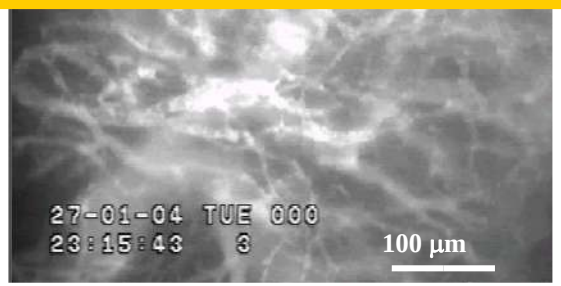
7 days

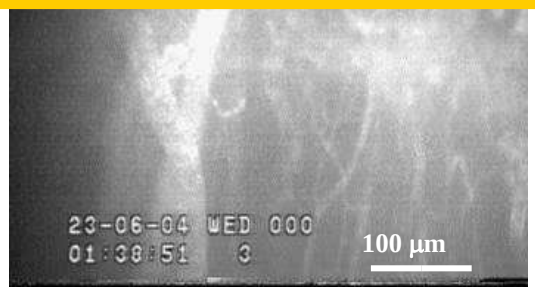




= Need delivery system for anti-tumor curcuminoids for
- **Lower dosage**
- **Enhance drug effectiveness**
- **Sustained-release effect**

14 days





25-77% reduction of cancer in mice when fed orally at high dose (toxic)

- *Yoysungnoen P, et.al, Clinical Hemorheology and Microcirculation vol.33, 2005 :127-136*
- *Yoysungnoen P, et.al., Clinical Hemorheology and Microcirculation vol.34, 1,2, 2006 :109-116.*

Results: Seven of twenty-four subjects (30%) experienced only minimal toxicity that did not appear to be dose-related. No curcumin was detected in the serum of subjects administered 500, 1,000, 2,000, 4,000, 6,000 or 8,000 mg. Low levels of curcumin were detected in two subjects administered 10,000 or 12,000 mg.

Conclusion: The tolerance of curcumin in high single oral doses appears to be excellent. Given that achieving systemic bioavailability of curcumin or its metabolites may not be essential for colorectal cancer chemoprevention, these findings warrant further investigation for its utility as a long-term chemopreventive agent.

Table 1: All adverse events by dose levels

Dose level[a]	Type
1000 mg	Diarrhea
4000 mg	Headache
8000 mg	Rash
	Yellow Stool
10000 mg	Yellow Stool
	Headache
12000 mg	Diarrhea

[a] Total of 3 subjects at each dose level
[b] National Cancer Institute, Common Toxicity Criteria v.2.0 [10]

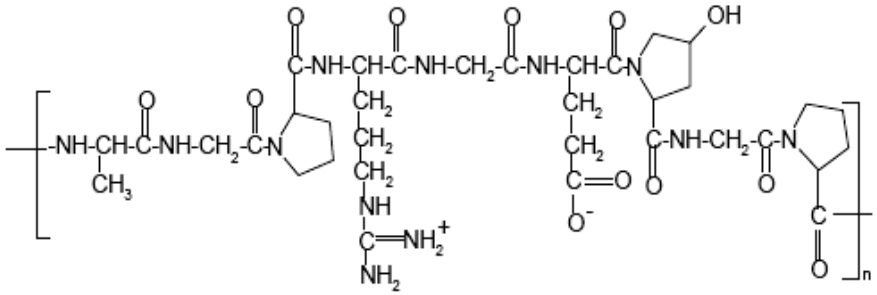
How much curcumin a person can take?

-Very low bioavailability
-Low toxicity level
-No reports of significant long term adverse effects

Table 2: Serum curcumin levels in ng/ml for two subjects

Dose	Baseline	One hour	Two hour	Four hour
10000 mg	approx. 6.0	30.4	39.5	50.5
12000 mg	approx. trace	29.7	57.6	51.2

BMC Complementary and Alternative Medicine 2006, **6**:10



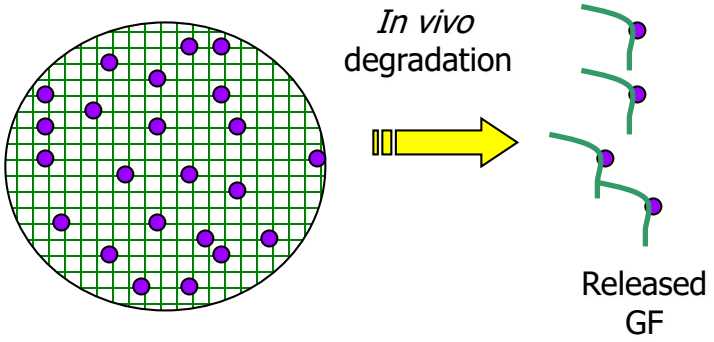
Structure of gelatin

-[Ala-Gly-Pro-Arg-Gly-Glu-4Hyp-Gly-Pro]-$_n$

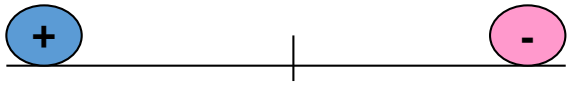
Gelatin

A water soluble protein from denatured collagen, rich in glycine, proline and hydroxyproline

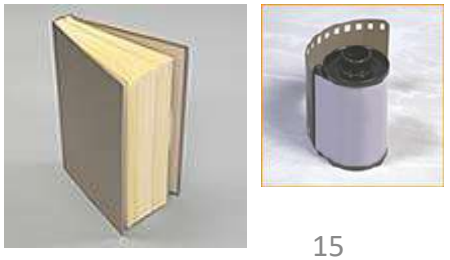
Crosslinked gelatin for controlled release of ionic active agents



Electrostatic interaction between
cationic GF and anionic polymer network



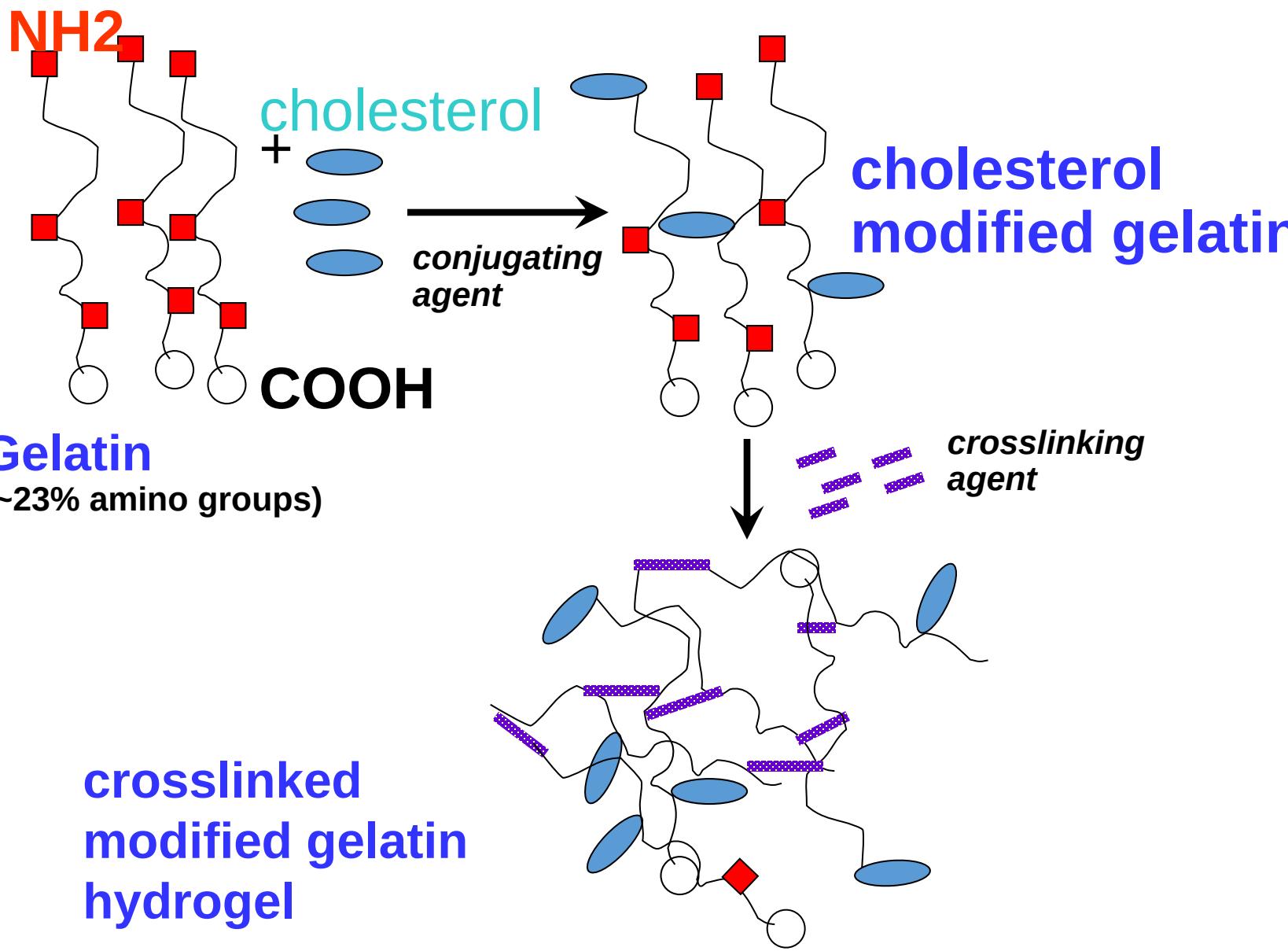
applications



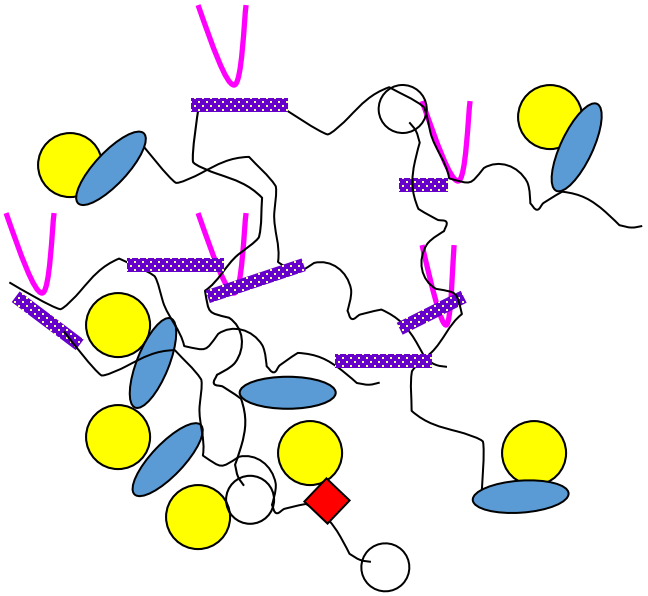
Availability of amino group [NH_3^+] in gelatin (Type A, pI 9, Nitta gelatin , Japan)
23% including N-terminal (TNBS methods compared to amino acids)

Amino acid s	(% by mole)
Glycine	33.00
Alanine	11.17
Valine	25.90
Leucine	24.00
Isoleucine	0.95
Serine	3.47
Threonine	1.79
Aspartic acid	4.58
Glutamic acid	7.21
Cysteine	0.00
Methionine	0.36
Lysine	2.66
Hydroxylysine	0.64
Arginine	4.90
Histidine	0.40
Phenylalanine	1.36
Tryosine	0.26
Tryptophan	0.00
Proline	13.19
Hydroxyproline	9.07

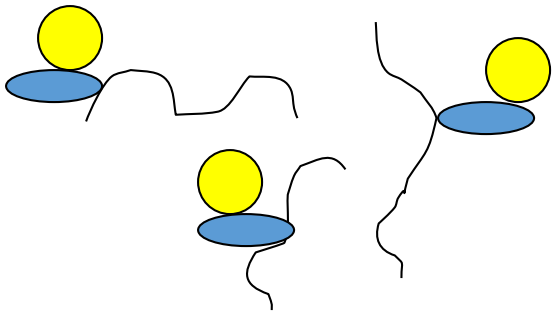
Concept


NH2
cholesterol
+
conjugating agent
COOH
cholesterol modified gelatin
Gelatin
(~23% amino groups)
crosslinking agent
crosslinked modified gelatin hydrogel

crosslinked modified gelatin hydrogel



Enzyme digestion
In vivo



Drug releases

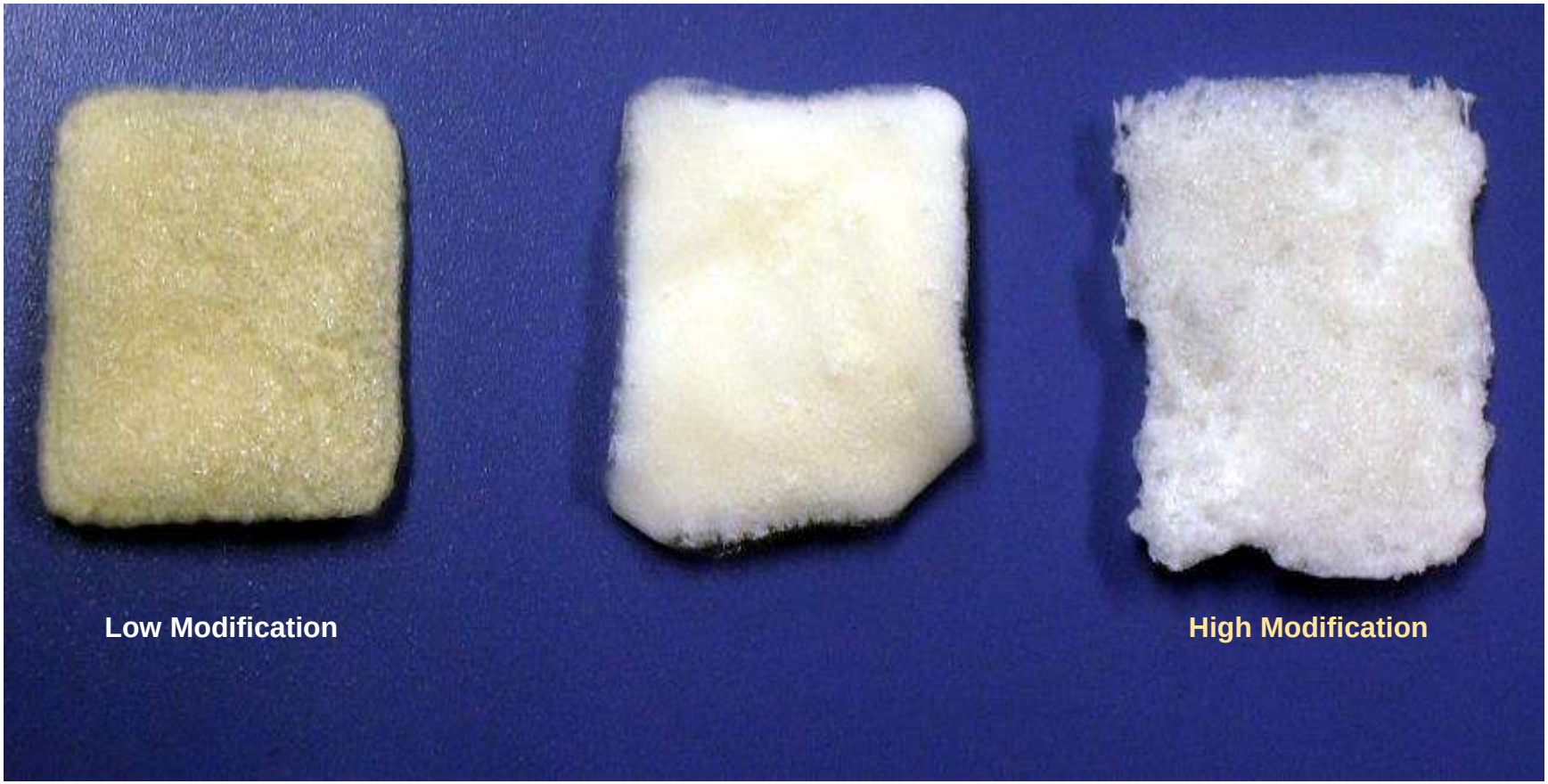
Characterization of Modified Gelatin

code	Modified gelatin			Crosslinked modified gelatin hydrogel sheets			
	Cholesterol:-NH_2 goups (mole:mole)	-NH_2 groups reduction (%)	Water contact angle (degrees)	Degrees of crosslink (%)	Water swelling (times)	Degradating temperature (Td) (^oC)	Half-live (days)[$]
G	0	-	69.88 ± 0.86	78.70 ± 0.01	1.91 ± 0.43	293	n/a
CG25	25	13.06#	76.48 ± 0.63	71.39 ± 0.02	3.21 ± 0.02	290	14.68 ± 0.33
CG50	50	20.68#	88.98 ± 0.58 #	71.10 ± 0.00#	4.55 ± 1.19	287	12.32 ± 0.06
CG66	66	23.47#	86.38 ± 1.63	68.98 ± 0.01	4.74 ± 0.63	286	11.34 ± 0.23
CG75	75	28.95#	90.27 ± 0.47 #	55.54 ± 0.01	4.86 ± 0.42	285	8.63 ± 0.02
CG100	100	33.94#	93.35 ± 1.66#	43.37 ± 0.03	5.76 ± 0.77	282	4.77 ± 0.01
CG125	125	40.73#	102.08 ± 1.17 #	38.86 ± 0.01 #	6.78 ± 0.97	280	2.43 ± 0.17

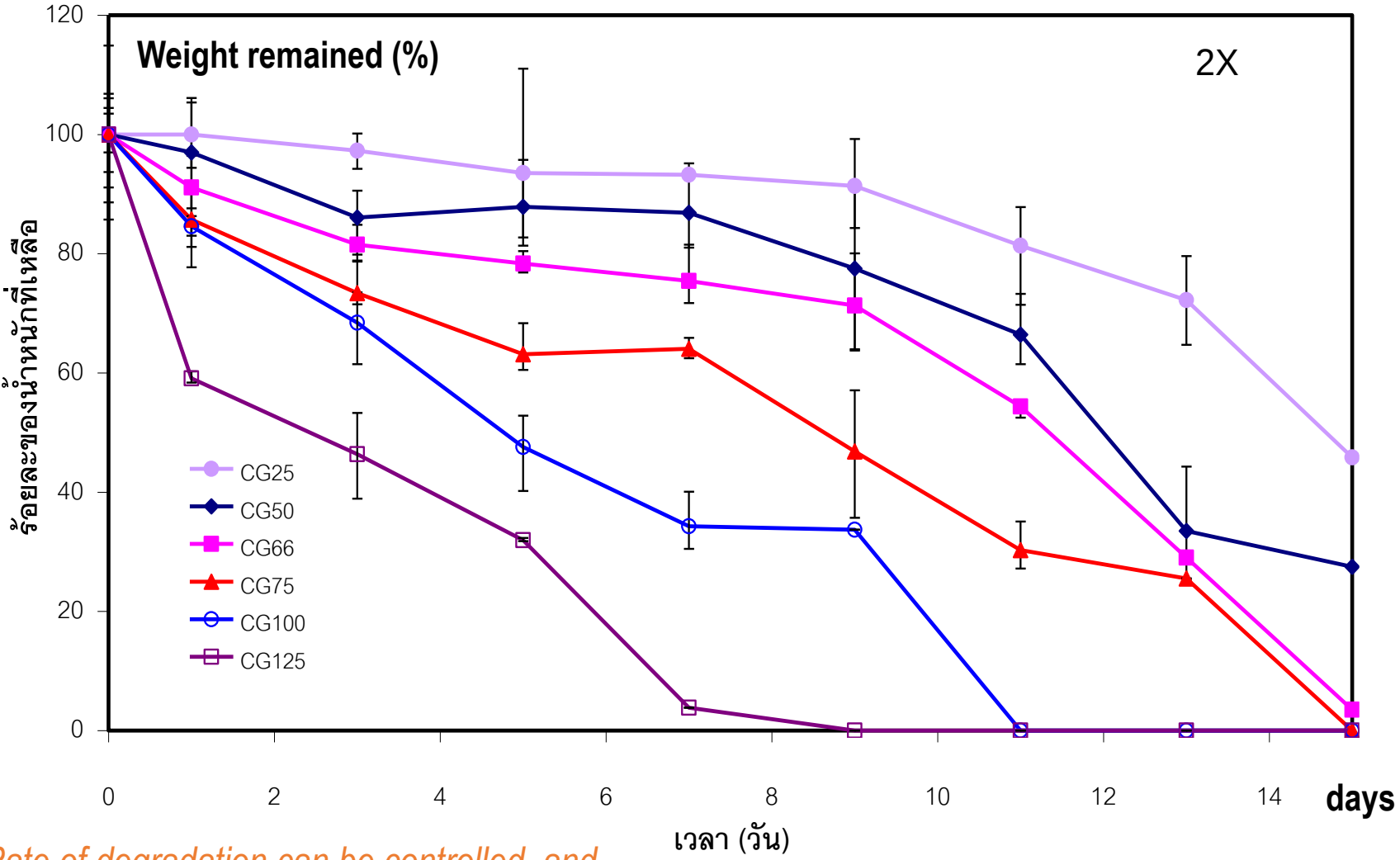
- **Gelatin was more hydrophobic and more degradable !**
- **Degrees of modification are controllable**
- **Rate of biodegradability is controllable**

Rate of biodegradability = Rate of drug released

Hydrophobic Gelatin Sponges



In vitro degradation of modified gelatin sheets

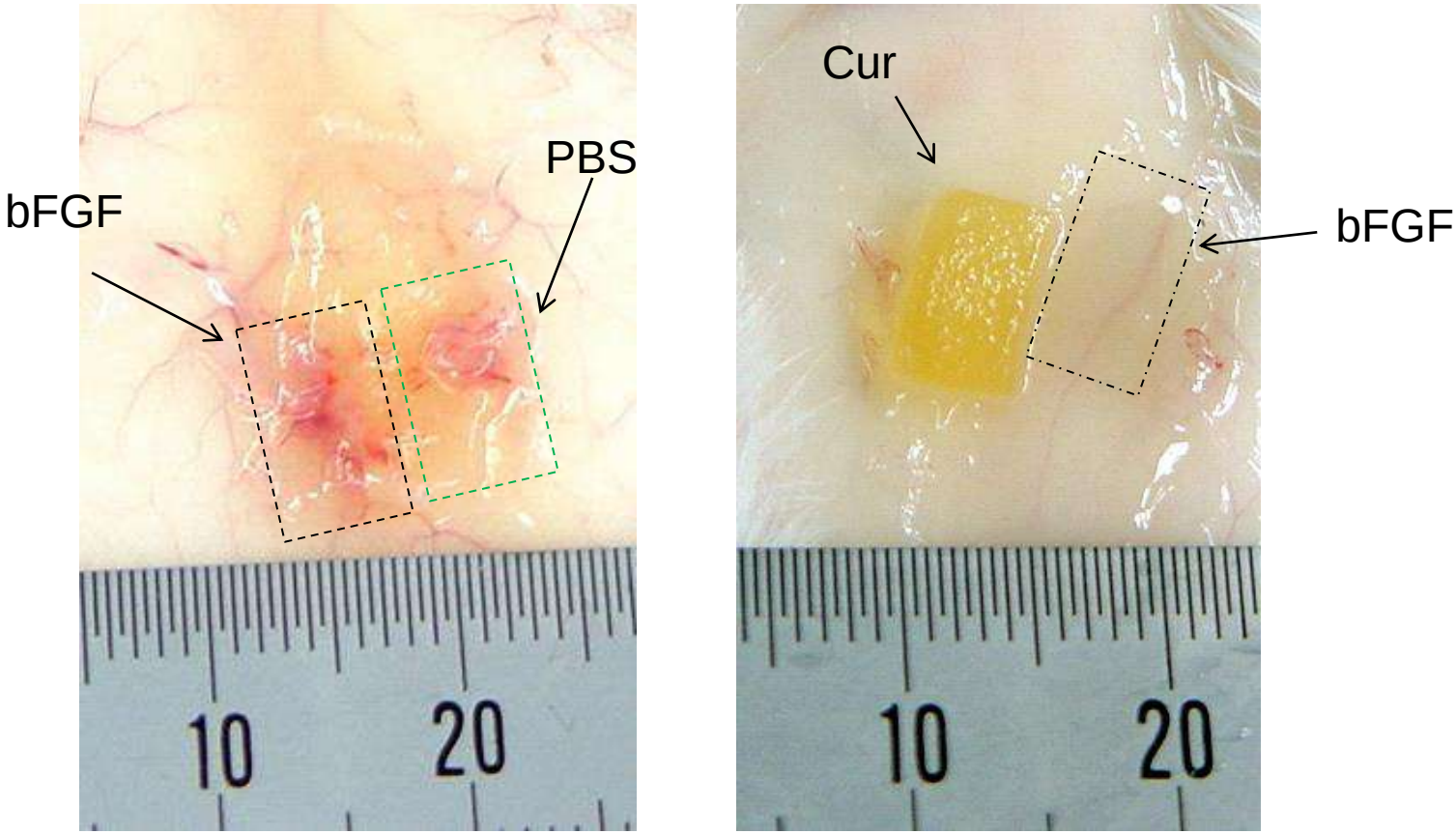


Rate of degradation can be controlled, and depends on the degrees of modification.

In collagenase solution (1 unit) at 37 ℃, pH 7.5

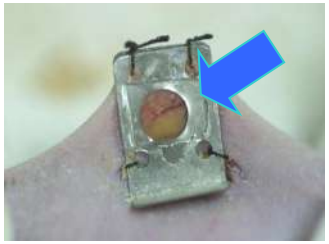
bFGF hydrogel + PBS hydrogel

bFGF hydrogel + curcumin (60 μg) hydrogel



Angiogenesis in wild type mice after 3 days of implantation of bFGF-adsorbed hydrogels

Effects of Curcumin Released from the Modified Gelatin Sheets on HepG2 Solid Tumors in Nude Mice

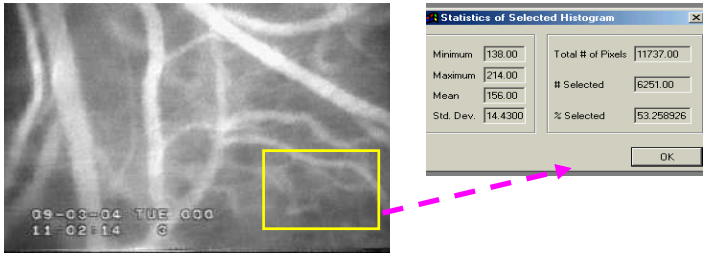


HepG2 inoculation.
Applied a modified gelatin hydrogel sheet loaded with curcumin (10 mg/g sheet) 1 week after inoculation.

BALB/cA mice (male), 22-25 g, 6-8 weeks (n=6)

Control : No HepG2 inoculations
HepG2 : HepG2 inoculated + implanted with a "Blank" hydrogel sheet implanted
HepG2-cur : HepG2 inoculated + implanted with a hydrogel sheet loaded with 10 mg/g curcumin

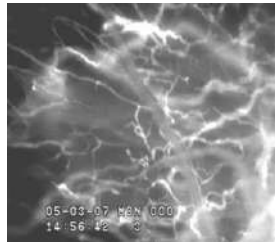
CD was determined within the selected window using "Histogram" of Global Lab II software.



Neocapillary density (%) =
$\frac{\Sigma \text{ number of pixels within the capillaries}}{\text{Total number of pixels within the selected area}} \times 100$

Neocapillaries density (CD)



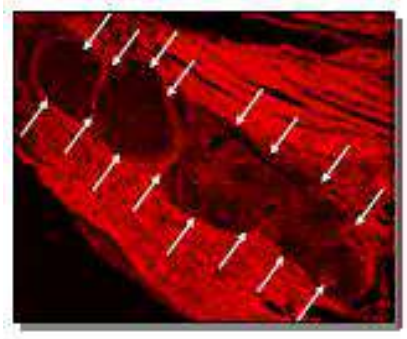


a). Control 14 days b). HepG2 14 days c). HepG2-cur 14 days

	Control	HepG2	HepG2-cur
%CD	32.18±3.37	68.69±0.9*	20.73±1.9**

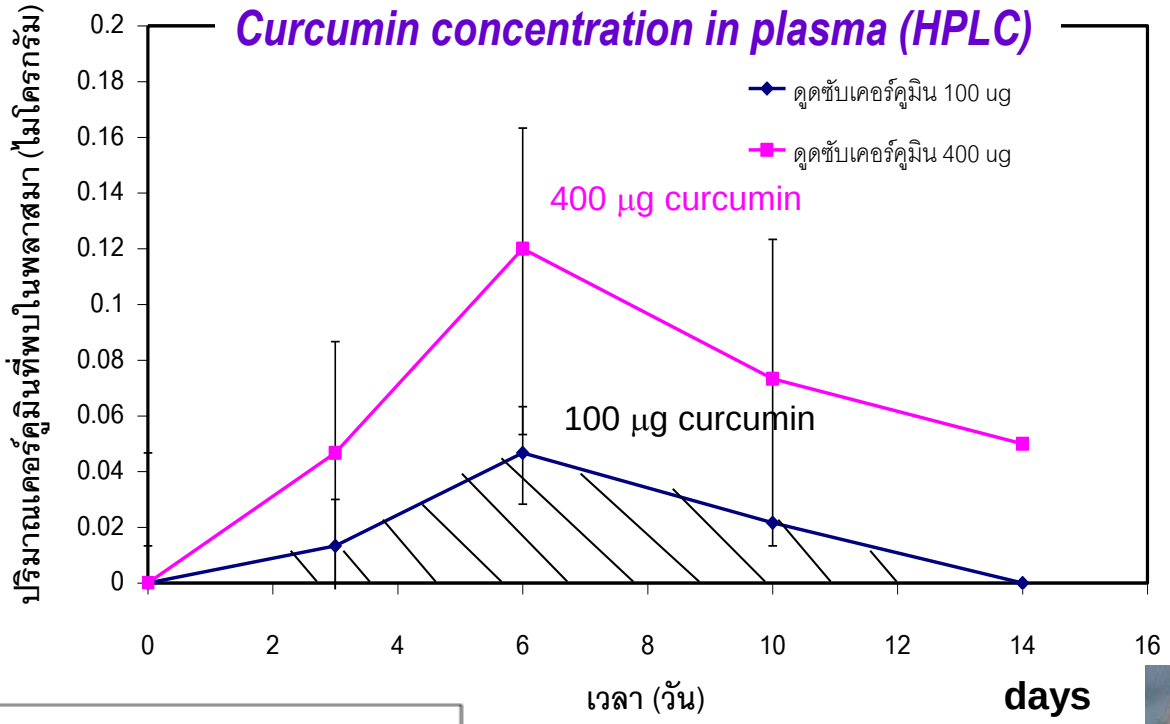
** P < 0.001 compared to control, ** P < 0.001 compared to HepG2*

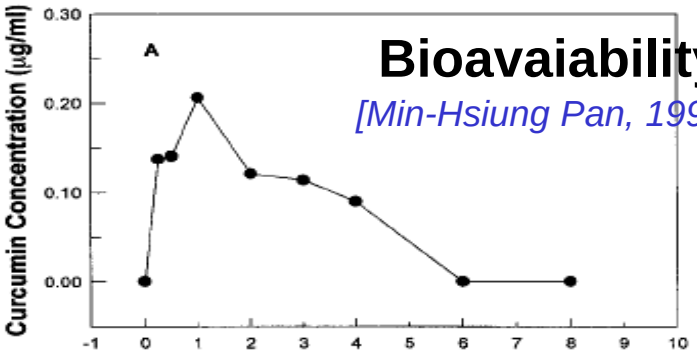
Tumor sizes (H&E staining)


HepG2 14 days


HepG2-cur 14 days

Sustained releases of curcumin from 1 curcumin patch in mice





Bioavaiability

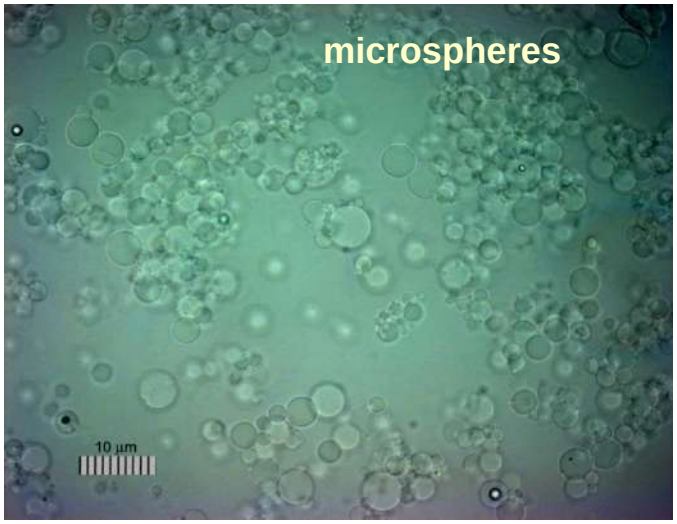
[Min-Hsiung Pan, 1998]

Oral dose
300X higher

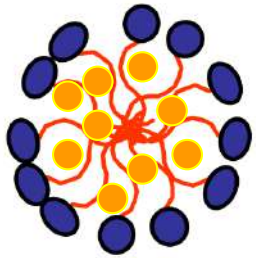
BALBc mice, male, 6-8 weeks, 22-25 grams (n=3)

Other forms of carriers

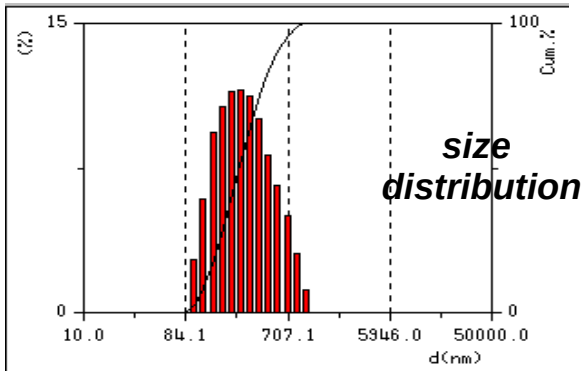
Microspheres



Lower degree of modification



Micelles
(high degree of modification)



size distribution

Sample	% Cholesterol introduced (per mole of NH2 group in gelatin)	Average size of micelles (nm)/p.d. before freeze drying	Average size of micelles (nm)/p.d. after freeze drying	% Drug loading (per mg of micelles)	Drug loading Efficiency (%)
1	100	359/0.4	260/0.0	8.88	22.2
2	66.7	682/0.4	260/0.0	7.39	18.5
3	50	1080/0.5	248/0.0	9.99	24.5

NH2

cholesterol

+

conjugating agent

COOH

Gelatin

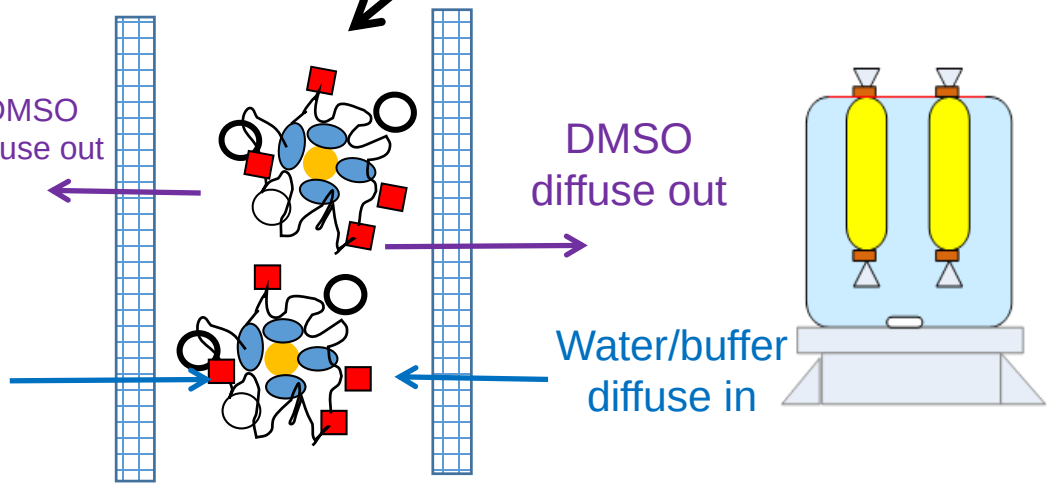
(~23% amino groups)

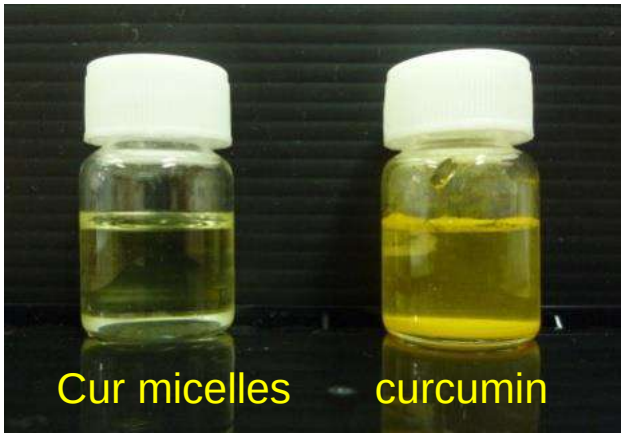
cholesterol modified gelatin

in DMSO

Making protein micelles of curcumin

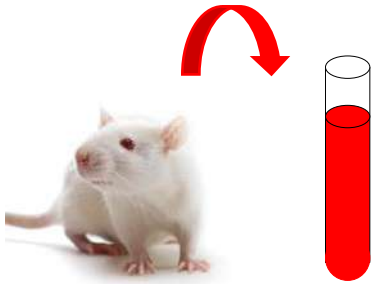
add curcumin



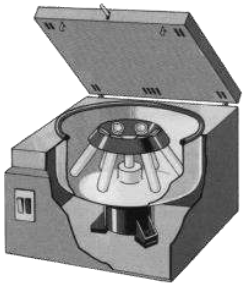


Micelle formation in dialysis process

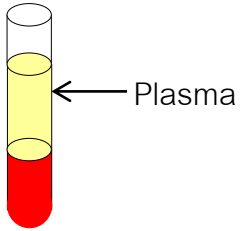
The effect of micelles on curcumin in blood plasma



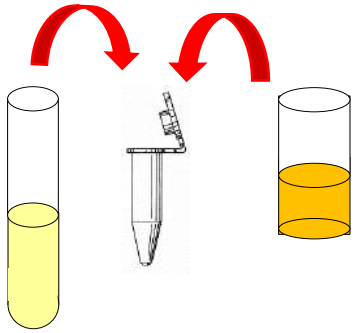
Wistar rats (female)



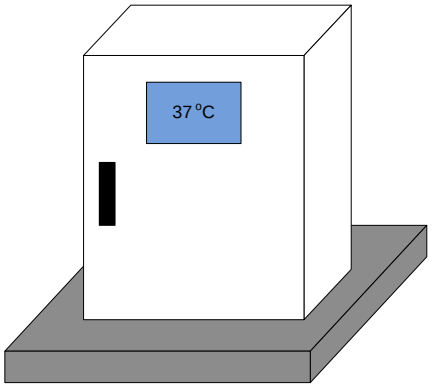
Centrifuge at 4300 g, 4 °C, 10 min



Collect plasma



Incubate with curcumin or curcumin micells (0.00625 g/ul plasma



37 °C in the dark

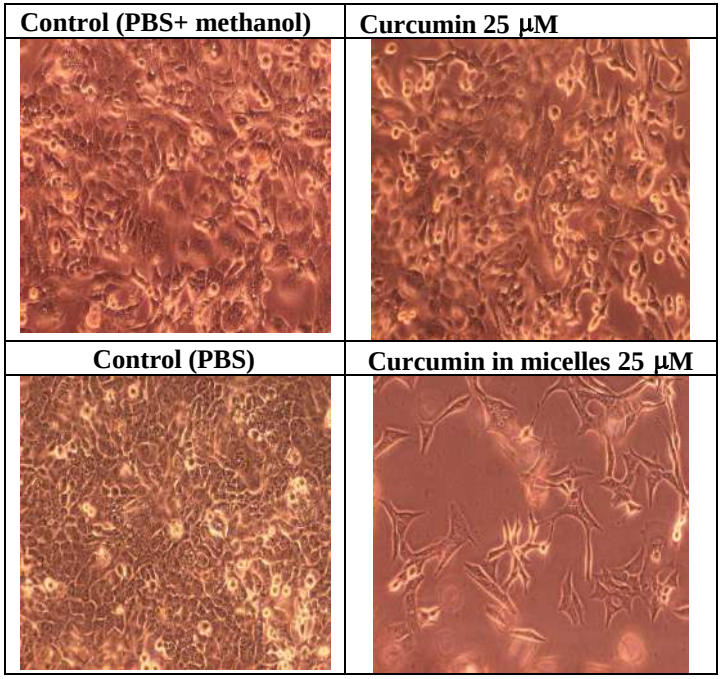
Extract curcumin in plasma using enzymes or non enzymatic methods

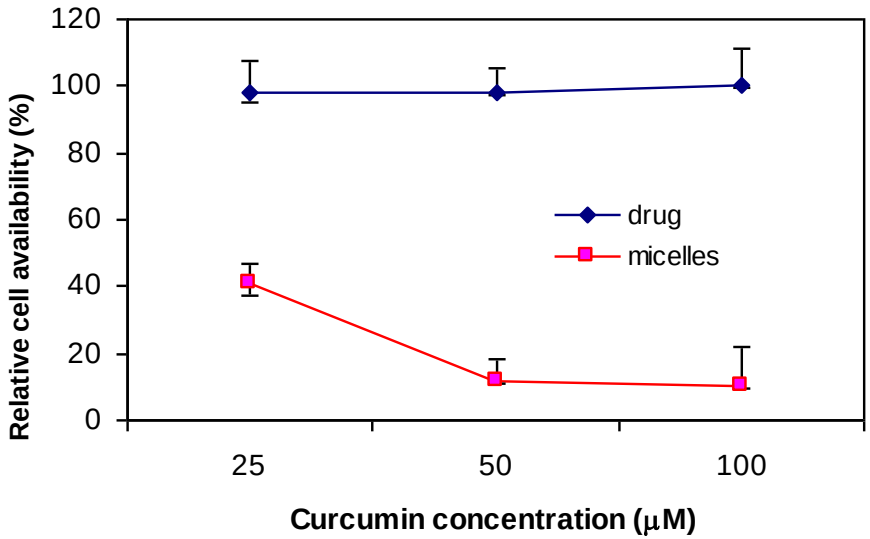
Gelatin-cholesterol micelles protect metabolism or complexation with proteins in blood plasma.

Time of incubation (min.)	Curcumin micelles		Curcumin solution	
	Free Curcumin found (μg/ml)	%	Free Curcumin found (μg/ml)	%
0	3.07	100.00	3.11	100.00
30	2.13	68.57	1.28	41.73

Amounts of curcumin detected (HPLC) in plasma after incubating micelles or curcumin solution in plasma *in vitro*.

Gelatin-cholesterol micelles increases curcumin solubilization in physiological fluids

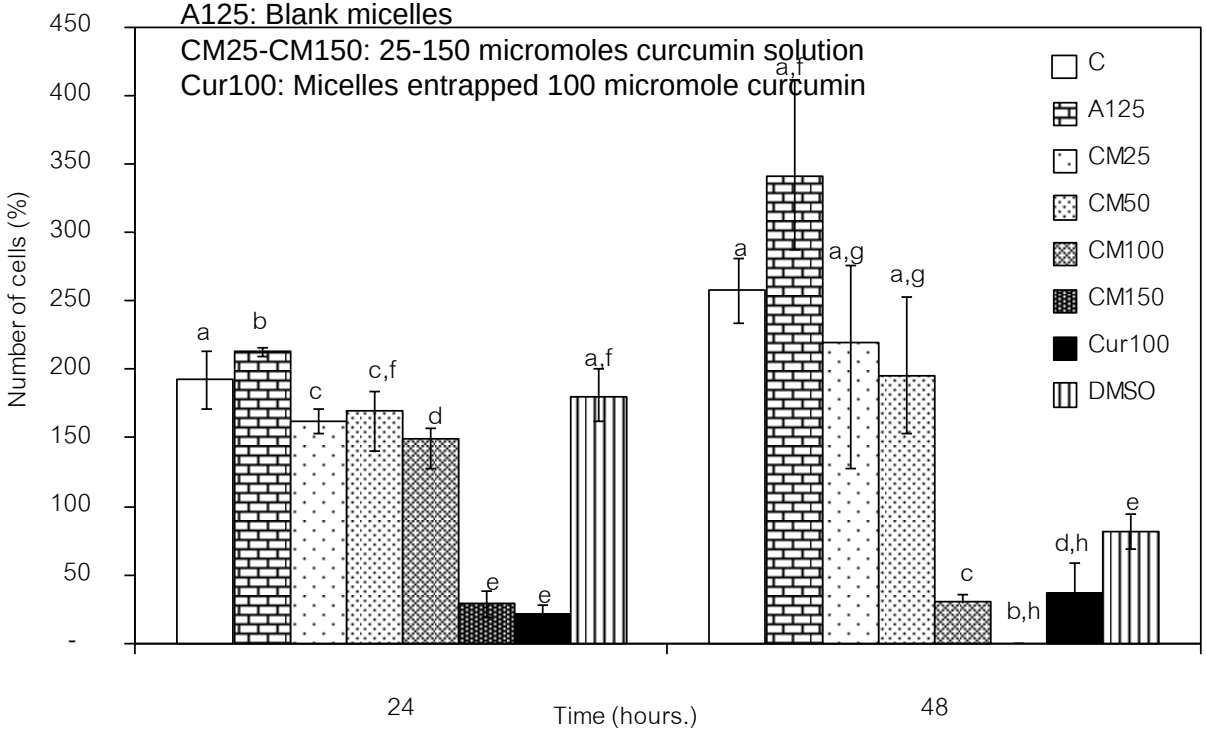




Effect of micelles additions on cultured Lewis lung carcinoma cells

Gelatin-cholesterol micelles increases curcumin solubilization in physiological fluids

C: control
A125: Blank micelles
CM25-CM150: 25-150 micromoles curcumin solution
Cur100: Micelles entrapped 100 micromole curcumin



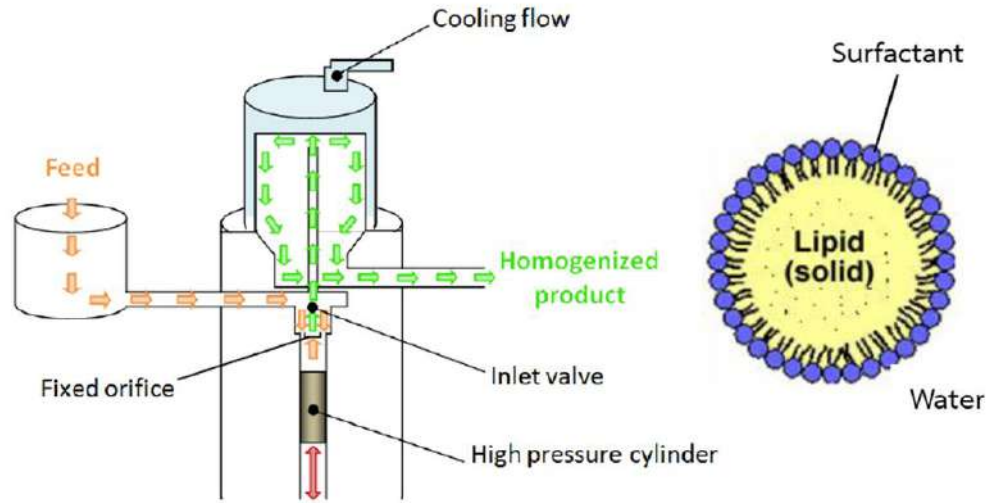
sample	PDT (hours.)
G125	27.86
CM25	25.05
CM50	30.69
CM100	33.13
CM150	-116.87
Cur100	-24.40
DMSO	-28.73

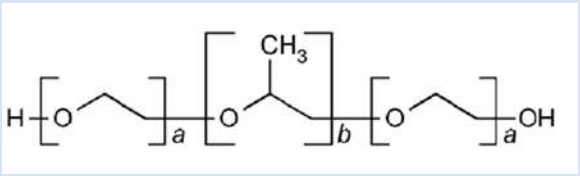
PDT: Population doubling time

Effect of micelles additions on cultured HEPG2 (Human hepatoma cancer cells)

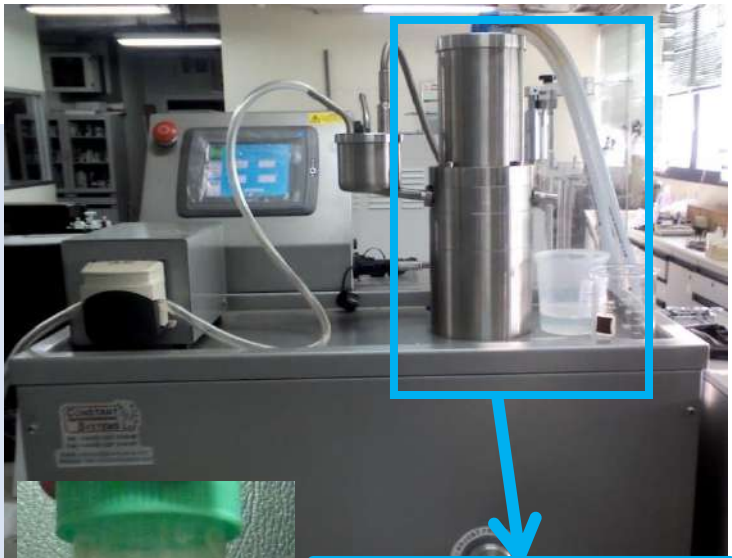
Solid Lipid Nanoparticles

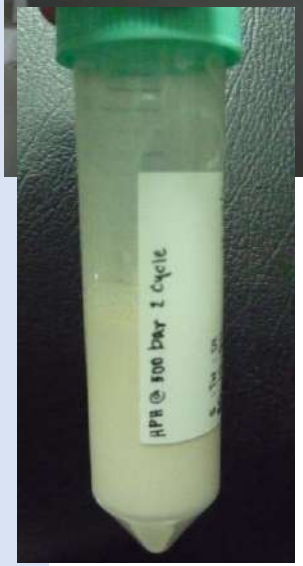
High pressure homogenizer





Poloxamer 188™
a=80, b=27
MW 7680-9510
HLB 29



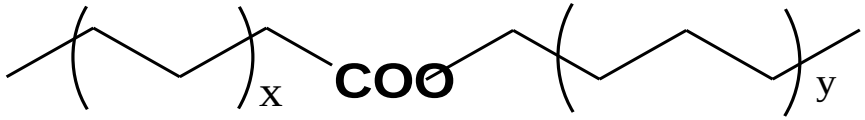


Shellac-Wax

white shellac

Shellac wax (5-10%)

- Very hard wax
- Properties comparable to Candelilla or Carneuba Wax
- Produce high-gloss surfaces



80-82% waxy ester, 10-14% free wax acids, 1% free wax alcohols, 2-6% hydrocarbon [Roeper, Germany]

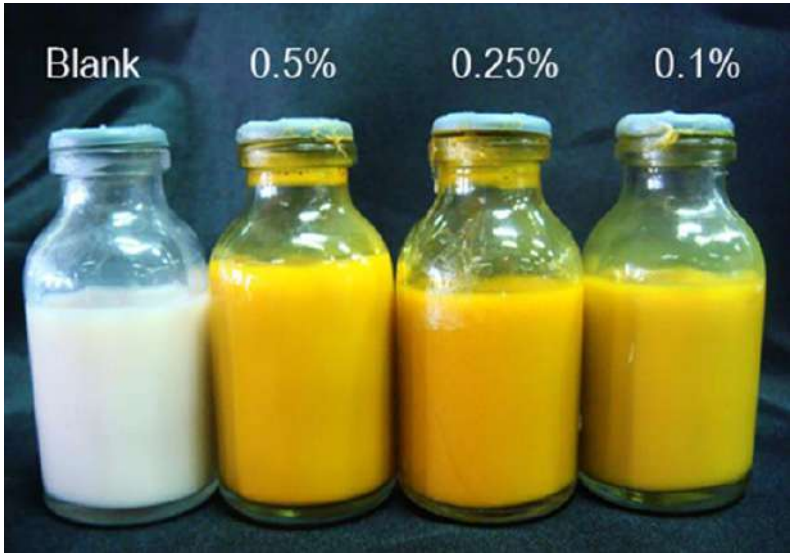
Now commercially available at:

Roeper GmbH, Germany (http://www.roeper.de/en/produktdetail.html?nummer=150)

SHELLAC.IN Group (http://www.shellac.in/shellacwax.html)

Raj Kumar Shellac Industries (http://www.shellac-india.com/)

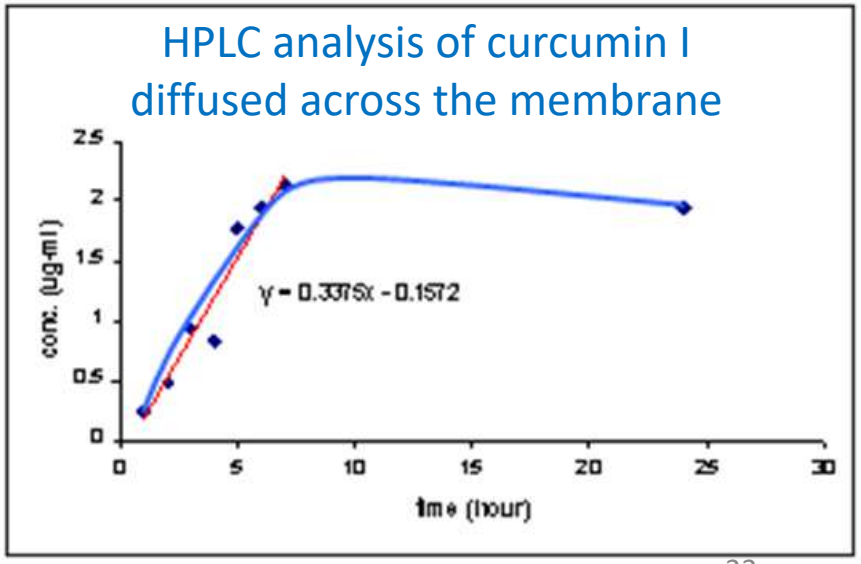
Curcumin SLN



Shellac wax:Poloxamer:Water
10:10:80
Zeta potential -27

Polyethersulfone membrane (MILLIPORE)

Cut off: 500,000 Da



โศรดา กนกพานนท์[1], อุรชา รักษ์ตานนท์ชัย[2], พันธ์สิริ ศิริรัชตพงษ์[1], และ พิชญ์นรี ลลิตาภรณ์[1]*

[1]ภาควิชาวิศวกรรมเคมี คณะวิศวกรรมศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

[2]ศูนย์นาโนเทคโนโลยีแห่งชาติ อุทยานวิทยาศาสตร์ประเทศไทย 2551

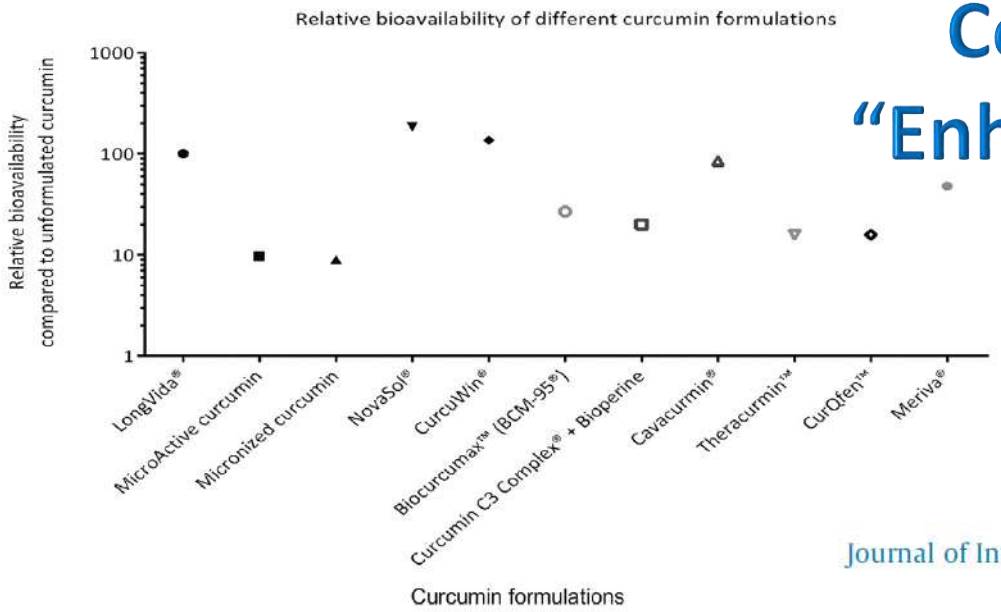
Conclusions: 1) Increase curcumin bioavailability (dose), sustained release, and stability, 2) Right microenvironment, chemicals (FGF, MMP-2, COX-2), to put it to good uses in cancer therapy

Table 3
Pharmaceutical strategies for improving the oral bioavailability of curcumin by increasing the gastrointestinal stability.

Gastrore-sistant polymers	Preparation	Cmax (Preparation vs. control)	AUC (Preparation vs. control)	Observation
Silica	Liposome	446.66 vs 71.35 ng/L (50 mg/kg)	673.79 vs 203.64 ng.h/L (50 mg/kg)	CUR-SLs had significantly higher gastrointestinal track stability compared with cur liposome.
Chitosan	Polymeric micelles	5.365 ± 1.246 vs. 0.61 ± 0.109 μg/mL (15 mg/kg)	77.261 ± 12.485 vs. 5.107 ± 1.629 μg.h/mL (15 mg/kg)	LHR can improve the stability of cur micelles.
	Nanoemulsion	/	/	Chitosan coating can improve the gastrointestinal stability of cur.
	Polymeric micelles	/	/	Cur loaded micelles had improved gastrointestinal track stability.
	Solid lipid nanoparticles (SLNs)	0.73 ± 0.31 vs. 0.29 ± 0.11 μg/L (50 mg/kg)	4.98 ± 2.28 vs. 0.56 ± 0.14 μg.h/L (50 mg/kg)	Cur SLNs have enhanced stability, controlled release characteristics in SIF, and higher oral bioavailability.
	Nanoparticle	/	/	Cur nanoparticle did not degrade more rapidly than free cur in mouse plasma.
Eudragit	Liposome	/	/	Cur is protected against harsh conditions of the gastro-intestinal tract.
	Liposome	/	/	Eudragit-nutriosomes had enhanced stability compared with Eudragit-hyaluronan liposomes under gastrointestinal fluids.
Pluronic F-127 (PF-127), Gelucire ® 44/14 (GL44)	Micelles	0.24 ± 0.04 vs 0.08 ± 0.03 μg/ml (10 mg/kg)	6.13 ± 0.22 vs 0.11 ± 0.04 h/μg/ml (10 mg/kg)	The cytotoxic activity (3-folds) and oral bioavailability (around 55-folds) were also improved.
mPEG-PCL	Micelles	197.88 ± 61.71 vs. 27 ± 1.37 ng/ml. (75 mg/kg)	1.02 ± 0.93 vs. 0.11 ± 0.029 μg/ml h (75 mg/kg)	Cur solubility, stability and antioxidant activity were enhanced.
Solutol®HS15	Solid dispersion	95.60 ± 53.8 vs. 15.65 ± 12.6 ng/ml (50 mg/kg)	72.84 ± 36.4 (50 mg/kg) vs. 15.31 ± 19.7 ng/ml.h (50 mg/kg)	Oral bioavailability was enhanced compared with native cur; 1.3% of cur was degraded in pH 1.2 buffer, while 2.4% of cur was degraded in pH 6.8 buffer, 4.2% of cur was degraded in pH 7.4 buffer.
Casein, soy soluble polysaccharide	Emulsion	29.97 ± 0.012 vs 3.99 ± 0.01 ng/mL (50 mg/kg)	452.695 ± 0.75 vs. 8.561 ± 0.872 h ng/mL (50 mg/kg)	The oral bioavailability of cur emulsion was 11-fold higher than cur suspension.
Hydroxypropylmethyl(HPMC)	Emulsion	/	/	The oral bioavailability was enhanced.
Bile salts	Liposome	/	/	Eudragit-nutriosomes had enhanced stability
Caseinate (NaCas), Pectin	Solid lipid nanoparticles (SLNs)	/	/	The physico-chemical stability of cur SLNs was enhanced.
TPGS /Brij78	Solid lipid nanoparticles (SLNs)	7.51 ± 0.44 vs. 2.12 ± 0.34 μg/mL (50 mg/kg)	136.27 ± 10.85 vs. 14.29 ± 1.58 μg.h/mL (50 mg/kg)	Nanosuspensions and CUR/TPGS nanosuspensions were 3.7 and 3.18-fold higher than cur suspension.
bovine serum albumin (BSA)	Nanoparticle	/	/	The oral bioavailability of cur was enhanced.
Zein	Nanoparticle	/	/	In vitro gastrointestinal stability of cur nanoparticles was enhanced;

Table 1
Composition, manufacturer and reported relative human bioavailability of different formulations.

Formulation	Manufacturer	Formulation details
Meriva®	Indena SpA., Italy	Phytosome technology (curcumin, soy lecithin, microcrystalline cellulose, and 18%–20% curcuminoids)
LongVida®	Verdure Sciences, USA	SLCP™ technology (solid lipid curcumin particle lipids, phosphatidylcholine, and 20% curcumin)
CurQfen™	Spiceuticals, India (Akay Group)	Fenugreek soluble fiber blend, and 40% curcumin
MicroActive curcumin	BioActives LLC, USA	25% curcuminoids, a proprietary mixture of polyglycerol esters of fatty acids, medium-chain triglycerides, hydroxypropyl methylcellulose, sodium alginate, and microcrystalline cellulose
Micronized curcumin	Raps GmbH & Co., KG, Germany	Micronized powder (58.3% triacetin, 16.7% panodan, and 25% curcumin powder)
NovaSol®	Frutarom, Israel	Liquid micelles (93% Tween 80, and 7% curcumin powder)
CurcuWin®	OmniActive Health Technologies, India	63%–75% polyvinyl pyrrolidine, 10%–40% cellulosic derivatives, 1%–3% natural antioxidants, and 20%–28% turmeric extract
Biocurcumax™ (BCM-95®)	Arjuna Natural Extracts Ltd. India (Dolcas Biotech)	Curcuminoid, essential oil of turmeric (45% ar-turmerone), and curcuminoids
Curcumin C3 Complex® + Bioperine	Sabinsa, USA	Bioperine, and curcuminoids
Cavacurmin®	Wacker Chemie AG, Germany	γ-Cyclodextrin, and ~15% (w/w) total curcuminoids
Theracurmin™	Theravalues Corp., Japan	Colloidal-nanoparticles (12% curcuminoids, 46% glycerin, 4% gum ghatti, 38% water, and 10% curcumin)



Commercialized "Enhanced Curcumin"

Journal of Integrative Medicine 16 (2018) 367–374

Pharmacokinetics parameters of different commercialized "enhance" curcumin

Table 4
Pharmacokinetic parameters of curcumin from the different curcumin-based formulations and reference (unformulated curcumin).

Formulation	Intervention	Dose	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng · h/mL)	$t_{1/2}$ (h)	RB curcumin	References
Meriva®	Formulation[a]	297 mg curcumin	50.3 ± 12.7	3.8 ± 0.6	538.0 ± 130.7[1]	NR	48	[22]
	Control[a]	1295 mg curcumin	9.0 ± 2.8	6.9 ± 2.2	122.5 ± 29.3[1]	NR		
LongVida®	Formulation[a]	650 mg curcuminoids	22.4 ± 1.9	2.4 ± 0.4	95.3 ± 4.6[1]	7.5 ± 2.4	100	[23]
	Control[a]	650 mg curcuminoids	< 1	ND	ND	ND		
CurQfen™	Formulation[b]	600 mg curcumin	0.4 ± 0.2 (μg/g)	1	8100 ± 287[2] (μg · h/g)	NR	15.8	[24]
	Control[b]	1000 mg curcumin	0.02 ± 0.01 (μg/g)	0.5	510 ± 123[2] (μg · h/g)	NR		
MicroActive curcumin	Formulation[c]	500 mg curcumin	NR	4[d]	887.5 ± 549.9[3]	NR	9.7	[25]
	Control[c]	500 mg curcumin	NR	NR	91.8 ± 50.0[3]	NR		
Micronized curcumin	Formulation[b]	410 mg curcumin	15.3 ± 8.9	8.8 ± 6.4	214.6 ± 106.4[3]	NR	9	[26]
	Control[b]	410 mg curcumin	2.6 ± 4.9	7.5 ± 8.2	24.1 ± 42.6[3]	NR		
NovaSol®	Formulation[b]	410 mg curcumin	1189.1 ± 518.7	1.1 ± 0.4	4474.7 ± 1675.2[3]	NR	185	[26]
	Control[b]	410 mg curcumin	2.6 ± 4.9	7.5 ± 8.2	24.1 ± 42.6[3]	NR		
CurcuWin®	Formulation[a]	376 mg curcuminoids	27.3 ± 6.4	1.4 ± 0.5	307.6 ± 44.6[3]	NR	136.3	[27]
	Control[a]	1800 mg total curcuminoids	2.3 ± 0.3	7.4 ± 1.0	10.8 ± 1.7[3]	NR		
Biocurcumax™ (BCM-95®)	Formulation[c]	2000 mg curcuminoids	456.9[d] (μg/g)	3.44[d]	3201.3[d4] (μg · h/g)	4.96[d]	27	[28]
	Control[c]	2000 mg curcuminoids	149.8[d] (μg/g)	2[d]	461.9[d4] (μg · h/g)	2.63[d]		
Curcumin C3 Complex® + Bioperine	Formulation[a]	2000 mg curcumin with bioperine	180 ± 30	0.69 ± 0.07	80 ± 10[5]	0.11 ± 0.02	20	[29]
	Control[a]	2000 mg curcumin	6 ± 5	1[d]	4[d5]	NR		
Cavacurmin®	Formulation[a]	376 mg curcuminoids	73.2 ± 17.5	1[d]	327.7 ± 58.1[3]	NR	85	[30]
	Control[a]	1800 mg total curcuminoids	ND	12[d]	3.9 ± 0.5[3]	NR		
Theracurmin™	Formulation[b]	30 mg curcumin	29.5 ± 12.9	1[d]	113 ± 61[2]	NR	15.9	[31]
	Control[b]	30 mg curcumin	1.8 ± 2.0	6[d]	4.1 ± 7.0[2]	NR		

Control: unformulated curcumin.
NR: not reported; ND: not detected; AUC: area under the drug concentration–time curve; C_{max}: maximum drug concentration; RB: relative bioavailability; T_{max}: time at maximum drug concentration.
[a] Mean ± standard error of mean.

We needs to be serioused on using curcumin for therapeutic applications

Thank you

Institute for Frontier Medical Sciences, Kyoto University

Prof. Yasuhiko Tabata

Prof. Suthiluk Patumraj
Center of Excellence for Microcirculation
Pattayapat buidling, Faculty of Medicine,
Chulalongkorn University

NANOTEC
a member of NSTDA

National Nanotechnology Center

National Science and Technology Development Agency, Thailand

Thailand Research Fund

Graduate Students:
Ms. Juthamas Rujisomnapa
Ms. Nuengruthai Jaichawa
Ms. Marisa Wareechuensook

	18/01/21 Monday	19/01/21 Tuesday	20/01/21 Wednesday	21/01/21 Thursday	22/01/21 Friday
Chairperson for the day	**Antonella Motta**	**Gilson Khang**	**Juthamas Ratanavaraporn**		
9.00-10.00 CET	Grazia Pellegrini Modena Regenerative Medicine Institute	Pornanong Aramwit CHU	Siriporn Damrongsakkul CHU		
	Regenerative Medicine approved in Europe: hurdles in translations	*Application of silk on cosmetics*	*Phospholipid induced silk fibroin gel and its possible applications*		
10.00-11.00 CET	Gilson Khang JBNU	Alexandre Barros UMINHO	Anabela Carvalho Patentree - proposed by UMINHO		
	The Issues of Biocompatibility for TERM Products	*Spin-offs and Start-ups: possible models and approaches-Part 1*	*Spin-offs and Start-ups: possible models and approaches-Part 2*		

REMIX Seminar Series on TERM
Jan. 18th 2021 (Mon) 10:00~11:00 pm

The Issue of Biocompatibility for TERM Products

Professor Gilson Khang PhD
Dept of PolymerNano Sci Tech, Chonbuk Natl Univ

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Korea's Representative
Globally Prestigious University

CHONBUK NATIONAL UNIVERSITY

Where, Jeonju ?

2020 Global Top 100 CBNU
당신과 함께 이룬 전북대의 미래입니다.

Where, Jeonbuk National University ?

2020 Global Top 100 CBNU
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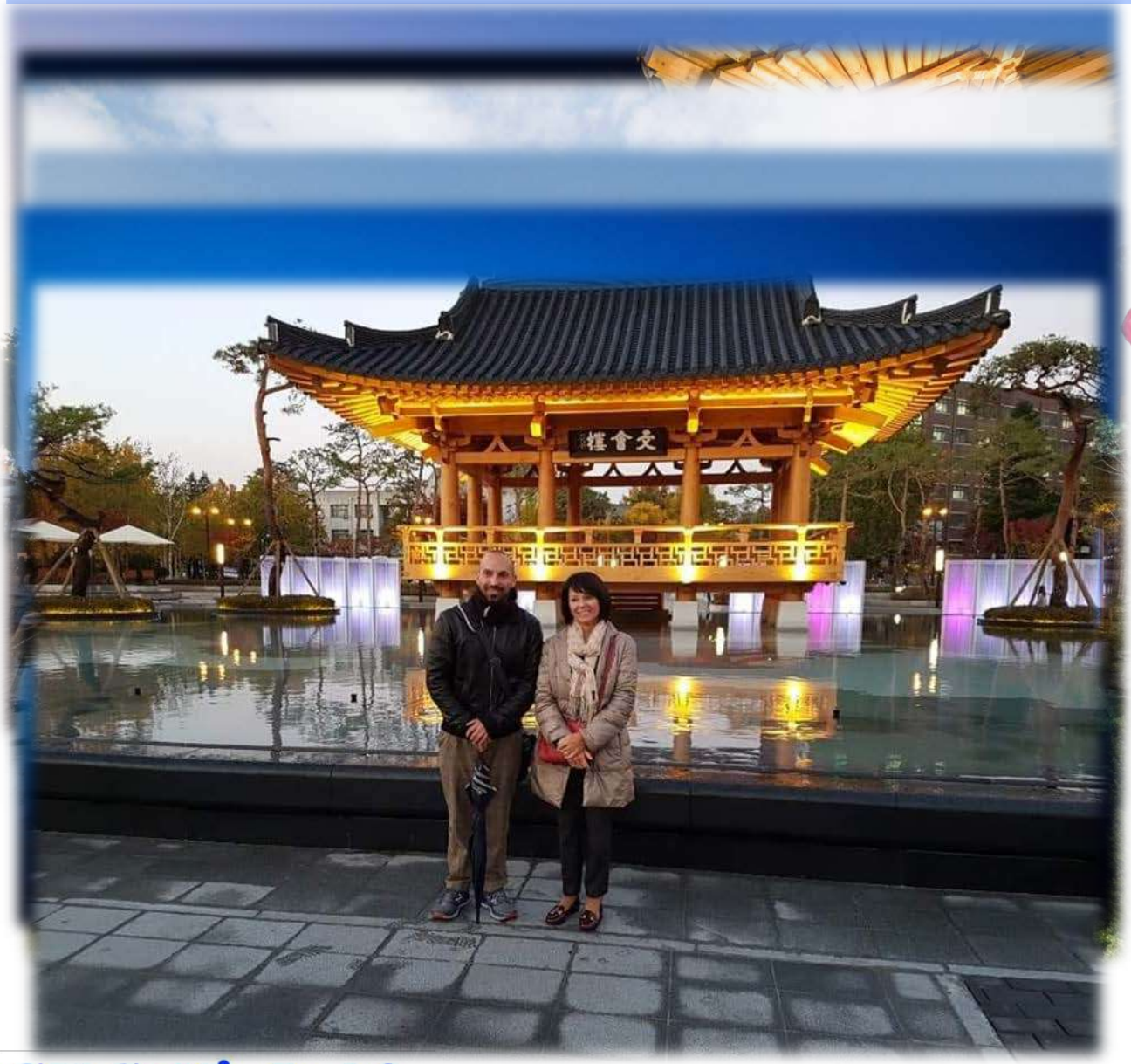

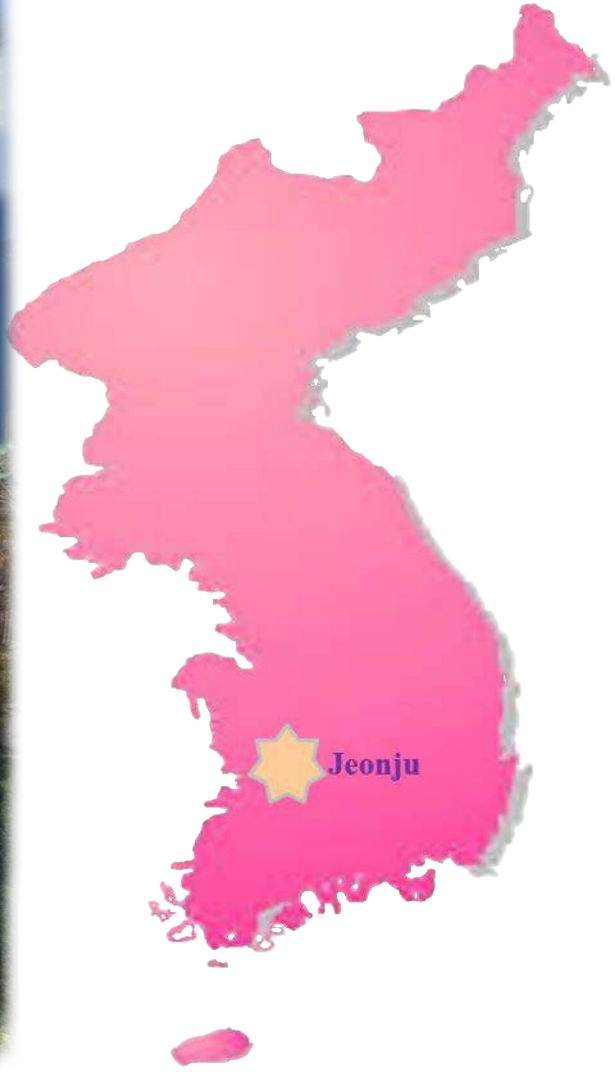

Chonbuk National University ?

2020 Global Top 100 CBNU
당신과 함께 이룬 전북대의 미래입니다.

Started with 2,700 students of 5 colleges with 16 departments by integrating Jeonju Myeongnyun School and Gunsan Hakgwan into Iri Provincial Agricultural College **in 1946**, Chonbuk Nnational University has grown up to a **leading region-based university** currently having 4 professional schools, 22 faculties with 36 departments in 14 colleges, and graduate school and special graduate schools.

CBNU hosted the **70th** Anniversary Celebration
On September 18th 2018

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당신과 함께 이룬 전북대의 미래입니다.

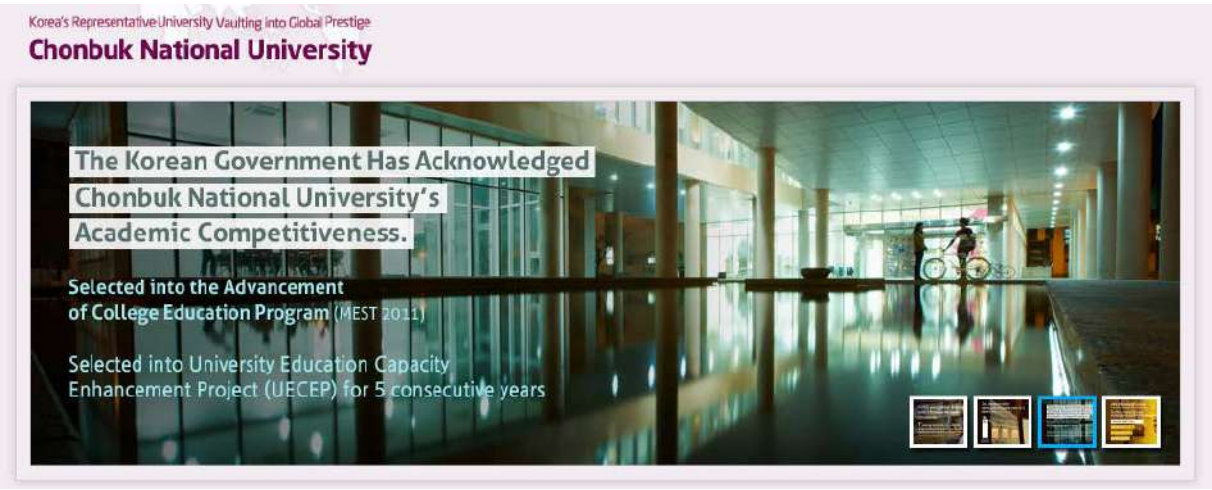
Jeonju campus provides **approximately 30,000 students** and **2,500 faculty and staff members** with educational, research and support facilities. CBNU maintains cooperative programs with international educational institutions, and **more than 2,500 international students** are enrolled in its degree programs, in addition **to around 500 international researchers**.

Fullfill your global dreams with Chonbuk Natl. Univ

GILSON's Lab®

Chonbuk National University ?

2020 Global Top 100 CBNU
당신과 함께 이룬 전북대의 미래입니다.



The Korean Government has acknowledged Chonbuk Natl. Univ.'s Academic Competitiveness

QS(Quacquarelli Symonds), England: Ranked in 74th/507 Univ in Asia, 2014

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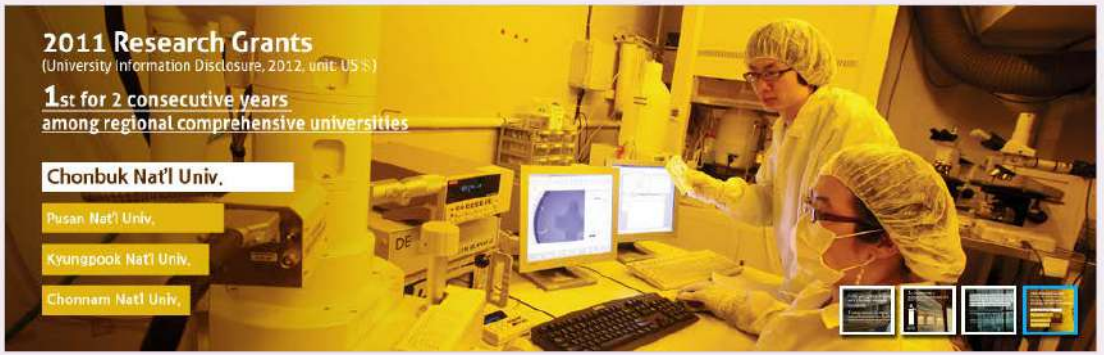
Chonbuk National University ?

2020 Global Top 100 CBNU
당신과 함께 이룬 전북대의 미래입니다.



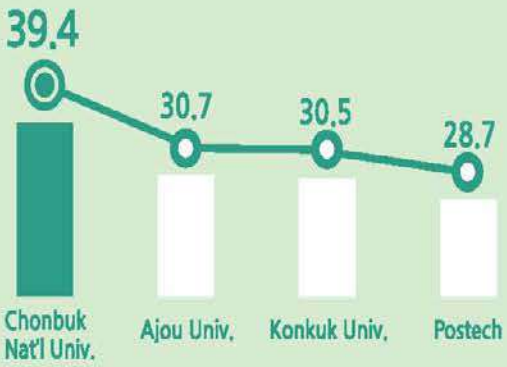
World Class

2011 Research Grants
(University Information Disclosure, 2012, unit US $)

1st for 2 consecutive years among regional comprehensive univ.

1st, Increase in publication of world-class (SCI) papers
(MEST, 2009, unit %)

1st, Increase rate in publication of world-class (SCI) papers (MEST, 2009, unit: %)



2011 Research Grants
(University Information Disclosure, 2012, unit: US $)

1st for 2 consecutive years among regional comprehensive universities

Chonbuk Nat'l Univ.	124million
Pusan Nat'l Univ.	116million
Kyungpook Nat'l Univ.	110million
Chonnam Nat'l Univ.	108million

2011 Research grants per faculty member
(University Information Disclosure, 2012, unit: US $)

1st for 2 consecutive years among regional comprehensive universities

Chonbuk Nat'l Univ.	116,000
Mokpo Nat'l Univ.	103,000
Pusan Nat'l Univ.	89,000
Kyungpook Nat'l Univ.	89,000

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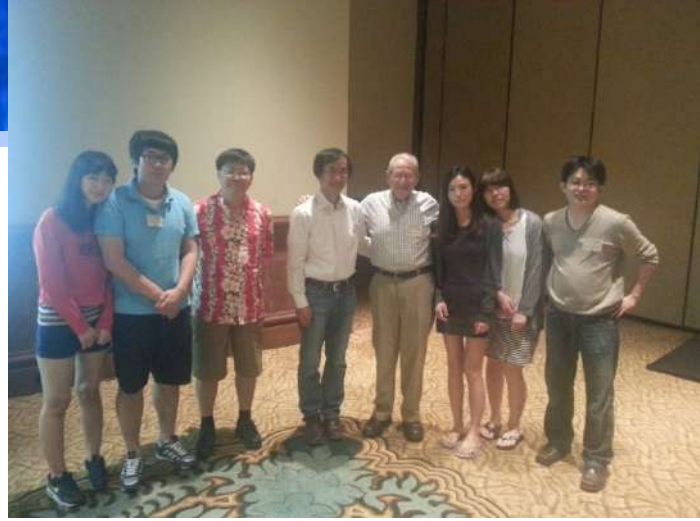


In Memory of Professor Sung Wan Kim

He was an Academic Giant, Pioneer, Supervisor and a dear Friend. There are many happy memories I'll forever cherish. He has contributed so much to Univ of Utah's research and education, and has been a wonderful role model, both as a scholar and as a person.

He has always been proud of all colleagues.

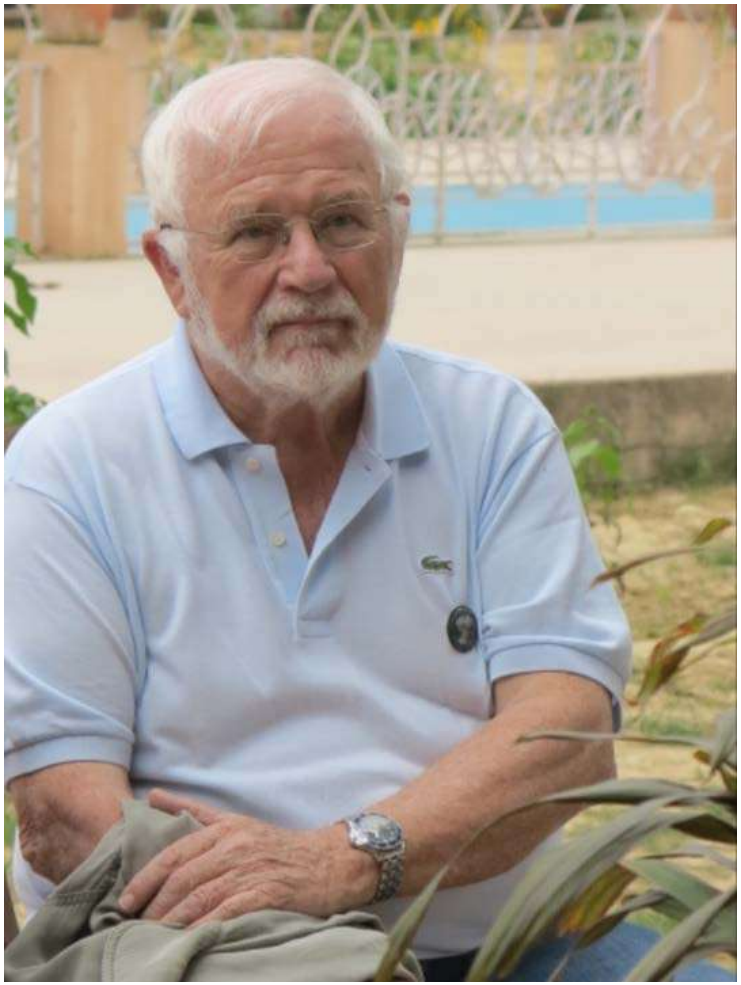
GILSON's Lab®

1. **Biocompatibility**
2. **SO_3^- for PU**
3. **Artificial Heart with Kolff: Jarvik7**
4. **Drug Delivery System**
5. **Gene Therapy**
6. **PEO-PLGA-PEO: Regel**
7. **Tissue Engineering and so on**

1. **Allan S Hoffman**
2. **Joe Robinson**
3. **Jim Anderson**
4. **Jan Feijen**
5. **Bob Langer**

Professor Robert Nerem
GIT

Professor Paul Vanhoutte
국립홍콩대, NUHK



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투표 스코어보드 내 수정 제안

배지를 받으셨습니다!

세계 여행가 배지 획득!

축하합니다! 국가 25개의 정보를 수정하셨습니다.

생활이 그대를 속일지라도 절대로 슬퍼하거나 노하지마라

소개 수정

- World Traveler
- Termis Global President Elect
- 전북대학교 교수
- World Traveler에서 million miler(으)로 근무했음
- 한국화학연구원에서 책임연구원으로 근무했음
- University of Iowa에서 Stem Cell and Regenerative Biology 전공
- 인하대학교에서 고분자공학 전공
- 여의도고등학교 졸업
- 전라북도 완주 거주

상세 정보 수정

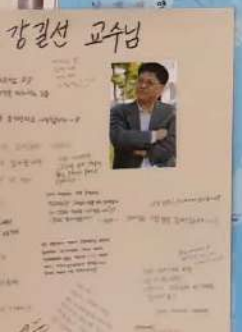
010-9111-7579

김찬삼의 세계여행기

-과학자장점: 세계여행

-세계적으로 친구를 사귐

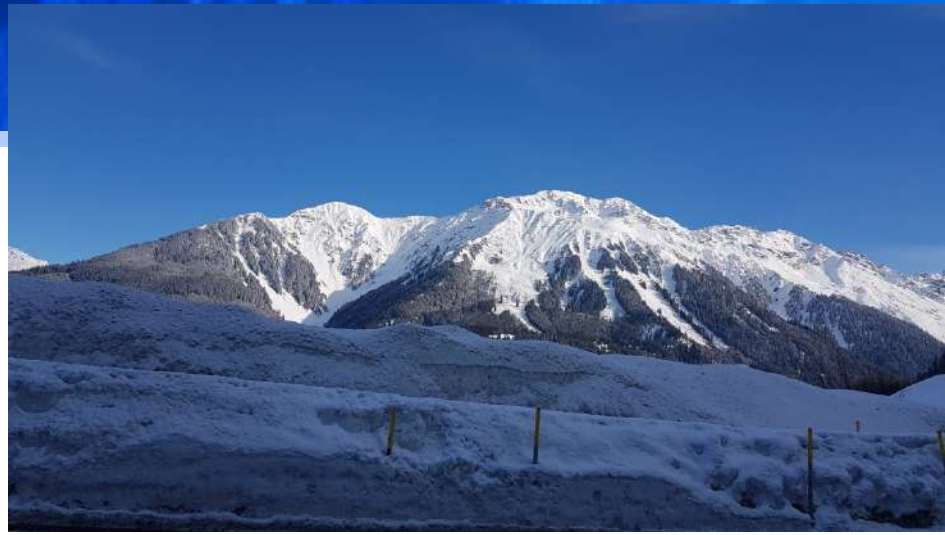
-세계 음식을 맛볼 수 있음



세계지도

Iceland, Raykavik

Vaduz, Liechtenstien



Zernez, Swiss

Toblino, Italy

Bondo, Italy

Univ Bologna, Italy, 1088년 개교
Alma Mater Studiorum
모든 학문이 퍼져나간 곳

Univ Padova, Italy, 1222년 개교
Universa Universis Patavina Libertas
세계 모든 이를 위한 파도바의 자유

Coimbra Univ, Portugal, 1290년 개교

갈릴레오 갈릴레이

남카롭고 야무진 이미지의 갈릴레이(1578~1630년경의 작품)

Universidad de Salamanca, Spain,

1218년 개교, 1254년 세계 최초로 Universidad라는 단어를 쓰기 시작함

Quod natura non dat, Salmantica non praestat (what nature does not give, Salamanca does not lend: 자연이 주지 않은 것은 살라망카 대학교도 만들지 않는다.)

Cuba, Habana

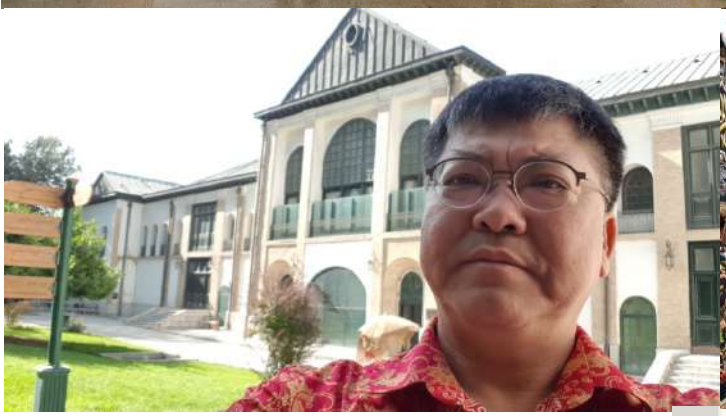

La Muñequita Azul
MERCERIA

Cuba의 화폐체계
MN: 내국인용, CUC: 외국인용, 1CUC=1euro
25배정도 차이1CUC = 25MN

현대선박엔진: 힘쎈엔진


Clinical Excellency by Tissue Engineering
The First International Iranian
Tissue Engineering and
Regenerative Medicine Congress
1st ITERM


LALEH INTERNATIONAL HOTEL



Regenerative Medicine Innovation Crossing

REMIX

EU HORIZON2020-MSCD-RISE 2017~2025 (8yrs)

GILSON's Lab®

Students Exchange btn Uminho, UTrento & CBNU

Sept 07 2016 MUST, Ulanbator


SOUVENIR SHOP

2016 Summer School for BRM at Riva del Garda, July 2016 (2)

GILSON's Lab®

REMIX Kick-Off Meeting, Nov 20th, 2017

Secondment of REMIX on Feb 2018 (1)


BioTech


Bolzano


Trento


Bondo


BioTech


Sudtirol

Secondment of REMIX on Feb 2018 (2)

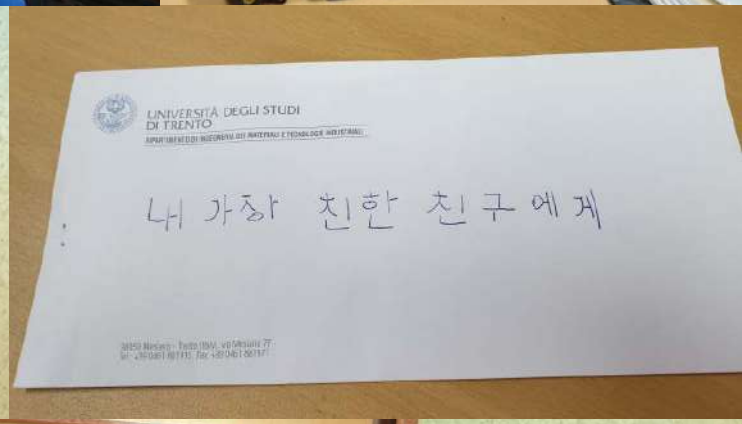
Toblino

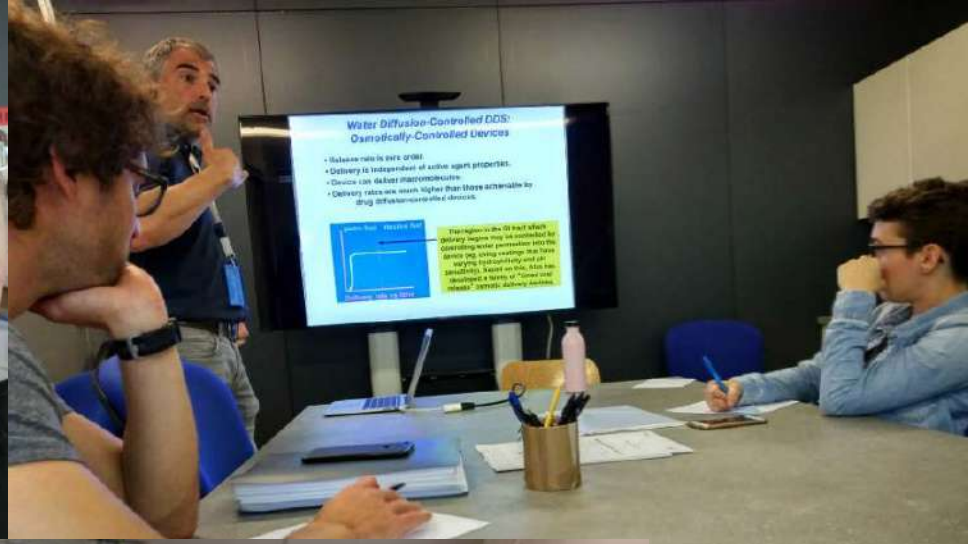
Levico TERME

AUSBME, Jeju Island, 2018

Secondment of Cristiano, Alex & Devid (1)

Secondment of Cristiano, Alex & Devid(2)



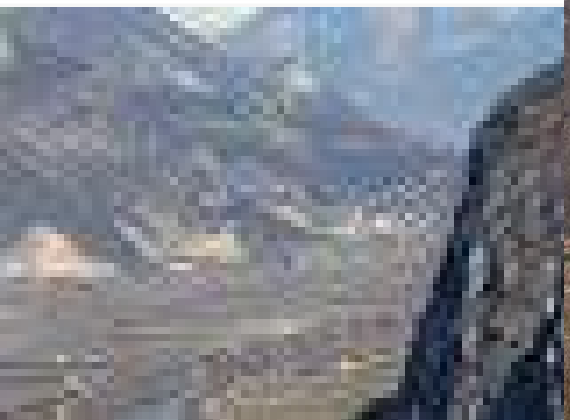


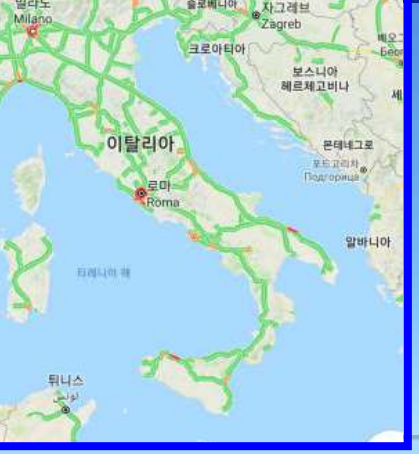
Secondment of my students at UTrento

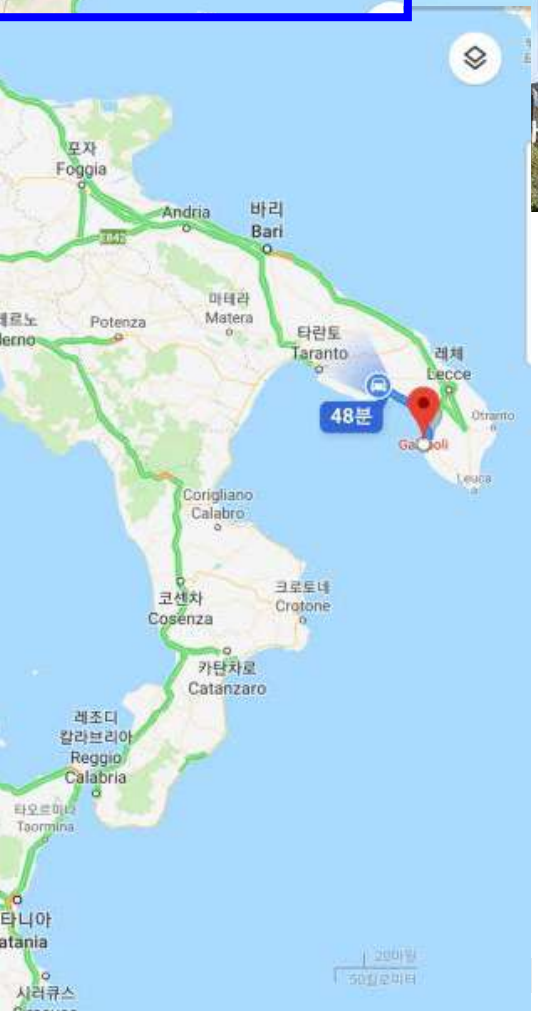
Riva Del Garda

GILSON's Lab®

Castel Beseno







Salina
Saline
Salt
(Saltzbrugh)
Salaria
Salary

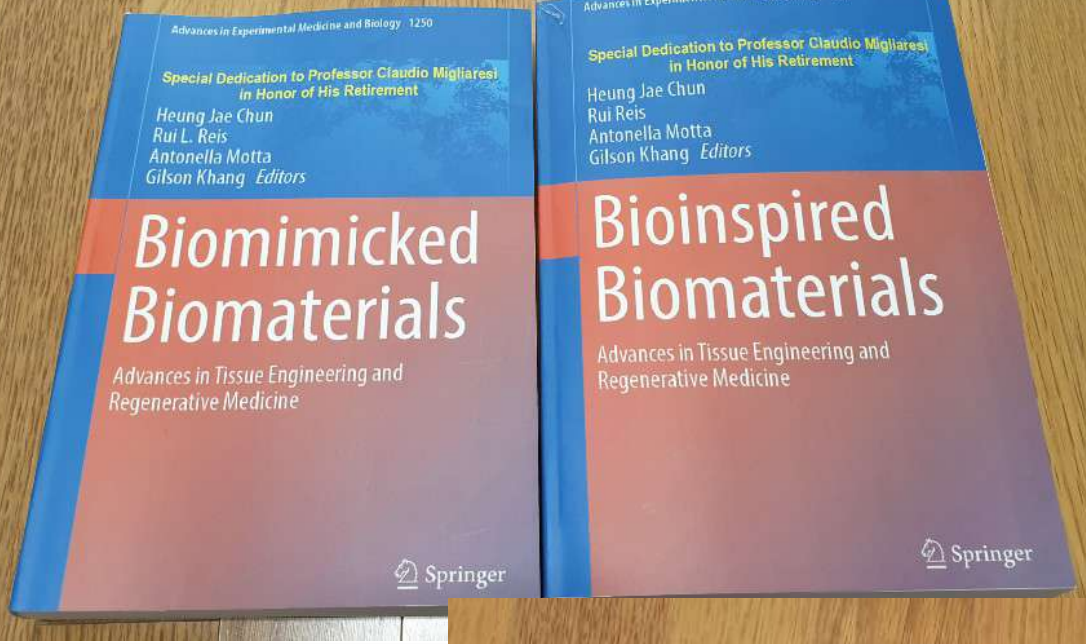
Wine Museum at Manduria

Verona: Romeo and Juliet's home

Silk Conference2019, Trento

Congratulation of the Retirement & Emeritus Professor for *Prof Claudio!!!*

GILSON's Lab®


Advances in Experimental Medicine and Biology 1250
Special Dedication to Professor Claudio Migliaresi in Honor of His Retirement
Heung Jae Chun
Rui L. Reis
Antonella Motta
Gilson Khang Editors
Biomimicked Biomaterials
Advances in Tissue Engineering and Regenerative Medicine
Springer
Advances in Experimental Medicine and Biology 1249
Special Dedication to Professor Claudio Migliaresi in Honor of His Retirement
Heung Jae Chun
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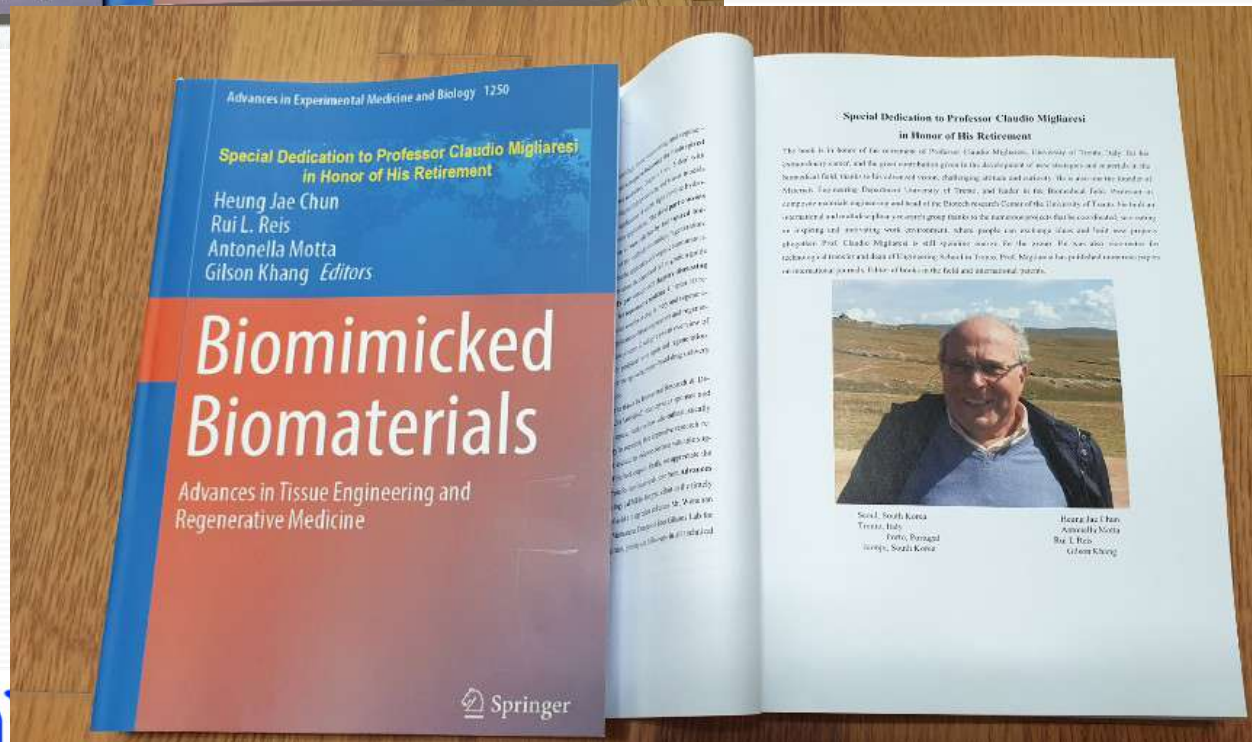
Springer


Advances in Experimental Medicine and Biology 1250
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Heung Jae Chun
Rui L. Reis
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Biomimicked Biomaterials
Advances in Tissue Engineering and Regenerative Medicine
Springer
Special Dedication to Professor Claudio Migliaresi in Honor of His Retirement


Biomimicked
Biomaterials
Bioinspired
Biomaterials

Secondment of Silvia & Sofia

Summer School in MUST, Mongolia, Sept 2019

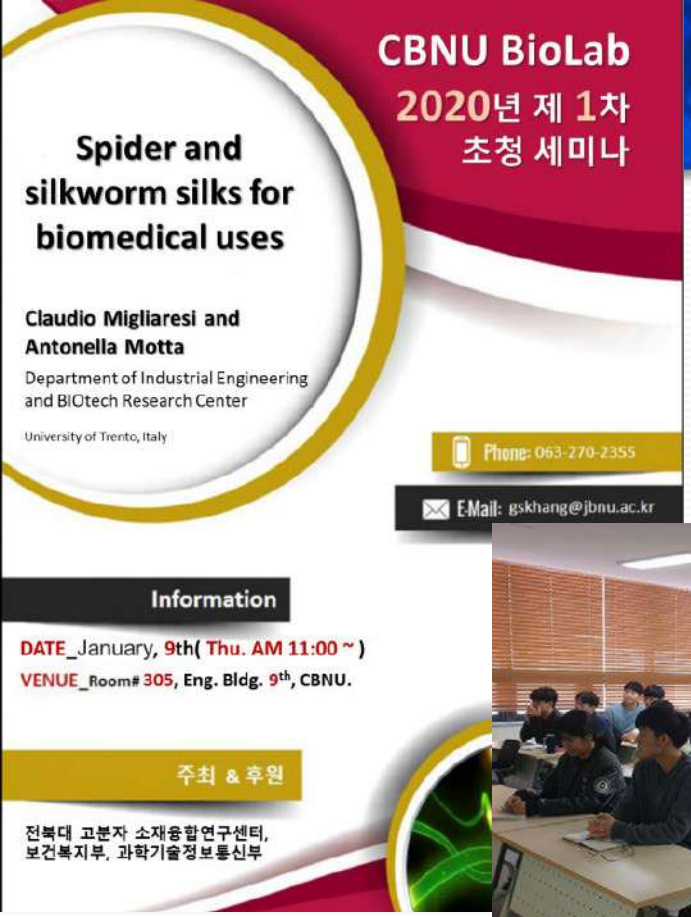
Claudio Visit Jan 2020

Medipost Jan 2020

Kyunghee Univ Jan 2020

Catholic Univ Jan 2020

SAMSUNG Biologics Jan 2020



CBNU Jan 2020

Doowon Meditech
Jan 2020

CGBio Jan 2020

Sewon CellonTech Jan 2020

GILSON's Lab®

National NanoFAB Center, KAIST Jan 2020

Busan Jan 2020

Winter School of Tissue Engineering and Regenerative Medicine, Thailand, Jan 15~19, 2020

Last Trip to Society

Regenerative Medicine Innovation Crossing REMIX

SUMMER SCHOOL

On Tissue Engineering And Regenerative Medicine

Current Perspectives and Challenges in Tissue Engineering and Regenerative Medicine

Advances Toward Future Tissue Engineering Research and Industry

Information

27-30 Jun 2021

JEONBUK NATIONAL UNIVERSITY

Jeonju, KOREA

Supported by

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E-Mail: gskhang@jbnu.ac.kr


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Umbria
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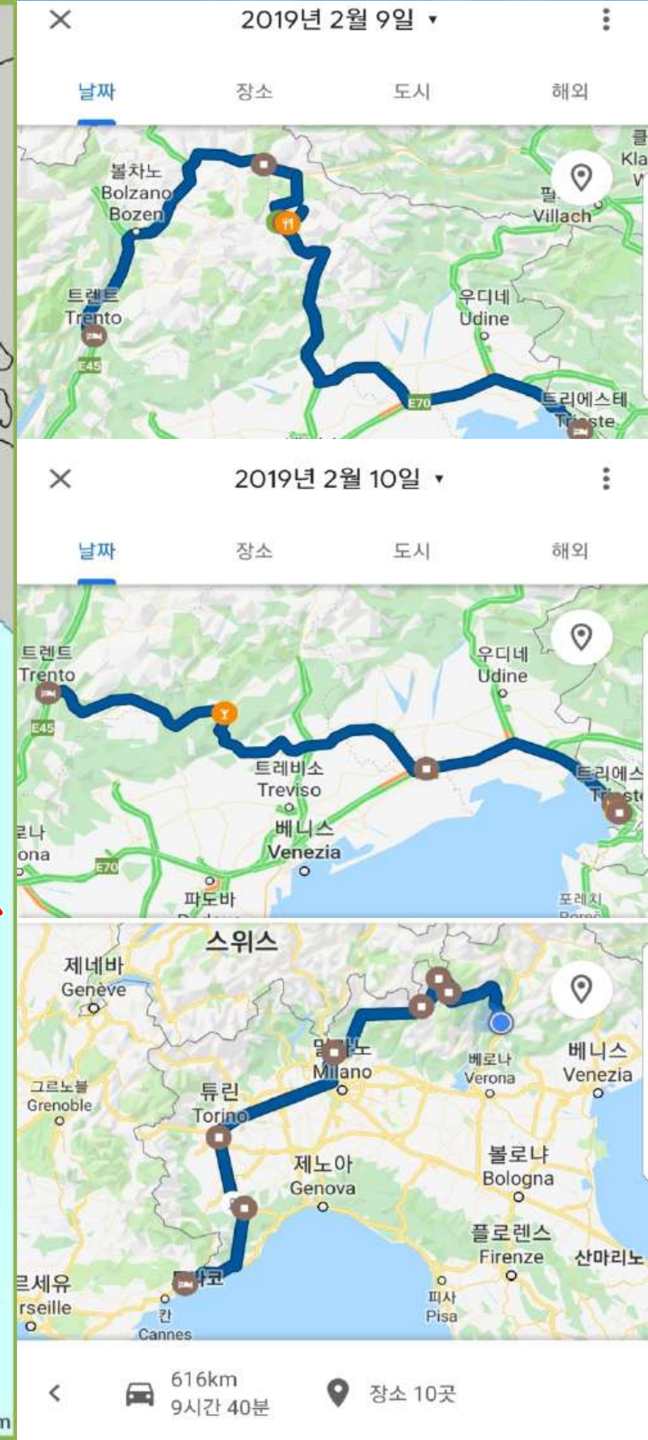
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볼차노 Bolzano Bozen
트렌토 Trento
우디네 Udine
Villach
트리에스테 Trieste
2019년 2월 10일
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트렌토 Trento
우디네 Udine
트레비소 Treviso
베니스 Venezia
트리에스테 Trieste
스위스
제네바 Geneve
밀라노 Milano
튜린 Torino
베로나 Verona
베니스 Venezia
제노아 Genova
볼로냐 Bologna
플로렌스 Firenze
피사 Pisa
칸 Cannes
616km
9시간 40분
장소 10곳

My Culture-Travelog Book

Culture-Travelog For Portugal: Fado and A World Voyage

~300 pages

포르투갈은 2006년에 처음 방문하게 되었다. 그때 당시 직장동료였던 연배 높은 친구가 자기가 초청을 받았는데 갈 수 없으니 네가 나대신 대타로 갔다 오라고 해서 처음 갔었다. 원래 이 인간은 그랬다. 자기가 좋은 것은 자기가 홀딱 해 처먹고 자기가 하기 싫거나 자기가 해서 손해나는 것은 죄다 남 시켰다. 죽을 때 까지 그랬다. 상사라고 하기보다는 나는 언제나 일회용, disposable 용품이었다. 다들 떠났는데 나만 바보 같이 끝까지 속아서 남아 있었다. 그런데 어떠한 인생의 전기에는 이렇게 대타의 경우가 종종 횡재을 치는 경우가 많았다. 주연이 감기에 걸려서 대타로 나갔더니 주연이 되고 호응이 의외로 좋았던 경우가 허다하다.

이때 처음 도착했던 학회개최지가 파로Faro였는데 이 도시의 옆에는 알가브Algarve, 라고스Lagos와 사그레스Sagres가 있었다. 그 포르투갈의 대항해를 시작한 10대 주앙 왕과 엔히크 왕자가 세웠던 그 시대의 대항해 전문학원이 있었고, 1400여년부터 포르투갈의 대내외 문제점들을 타개해 나가고, 사나이들로서의 기개를 보여주기 위한 대항해를 시작했던, 그 유라시아Eurasia 대륙의 제일 끝자락인 사그레스가 아니던가! 사실 2006년도에 처음 방문했을 때는 이런 것도 모르고 그냥 갔었다. 학회 중간 하루 오후를 잡아서 사그레스로 가고 사진도 찍고 하였었다. 솔직히 그때는 사그레스와 라구스가 가지고 있는 역사적 의미에 대하여 아무것도 몰랐다. 정신없이 그냥 잡다운 것이다. 이들 도시가 가진 세계인류문명사적인 의미를 알게 되는 데만도 거의 10년이 흐른 후였다. 이렇듯 여행을 다닌다고 해도 공부를 하지 않으면 그 의미를 알게 되는 것도 쉽지 않다.

그림 1-6.

2019년 3월에 포르투갈 타이파스 연구단지 소재 미뉴대학 3B's 연구소에서 만난 포르투갈 대통령 마르셀루 헤벨루 지 소자. 리스본대학 법학과 교수이기도 하다. 포르투갈은 대통령은 우파, 수상은 좌파이다.

가운데 사람은 두잉고 브라간자기마랑이스시 시장), 오른쪽은 리카르도 코스타기마랑이스시 시의회 재정담당 의원. 이 두 분들하고는 자주 만남고 그리고 페이스 북 친구이기도 하다.

2013년도, 서울에서 실바 전대통령과 전북대학교 서거석 총장과 산학공동연구 계약서를 인식.

인생이 다할 때 까지 인간은 공부를 해야 된다. 무엇인가를 계속 공부를 하고 업그레이드 시켜야한다. 이럼풋이 알게 된 전기는 한두 달 이상 중장기로 체류하면서 렌트카로 직접 이 도시 저 도시를 고속도로가 아닌 지방도로로 방문하여보니 좀 알게 된 것이다. 이렇게 알게 된 결과를 정리하는 것도 의미가 있으리라 하여 정리를 시작하였다.

문제는 어떻게 정리하고 어떻게 대항해 시대의 유물과 사상들을 맞춰 나가는가하는 것이었다. 고민을 하다가 방문한 대표적 도시별로 정리하는 것도 나쁘지 않을 것 같았다. 결국 많은 고민 끝에 기마랑이스를 출발점으로 건국한 순서대로 도시별로 정리하고 마무리도 인근 도시인 포루토·브라가·타이파스로 끝내기로 하였다. 포르투갈의 왕조 역사 등도 상세히 아는 것도 좋지만, 이 왕조의 연대기를 우리나라의 무슨 이조시대의 비주알고주알 모두를 알도록 그렇게 어렵게 할 필요가 있을까 싶어 일단은 쉽게 가기로 하였다.

기마랑이스(3장;아폰수1세) → 오비두스(3장;아폰수2세) → 코임브라(4장;디니스대왕) → 사그레스(5장;엔히크왕자) → 라구스(5장) → 마데이라(아조레스, 6장) → 리스본(시네스, 7장;바스코 다 가마, 8장;페르비스) → 빌라 헤알(사브로사, 9장;마젤란) → 살라망카(9장) → 카보 다 로카(10장;카몽이스) → 신트라(10장) → 나자레(10장) → 포루토(11장) → 브라가(11장) → 타이파스(11장) → 파티마(12장) → 아베이루(12장) → 토마르(12장)

그림 1-7. 포르투갈을 여행한 대표적인 도시

Awe Park, Taipas: 우리나라의 대덕연구단지와 같은 곳에 Rui 교수의 3B's연구소가 있음(2008)

루이 교수 연구소의 가족들과 함께(2018)

그림 11-3. 세계 최초의 카페인 마제스티 카페. 우측은 건국대의 이정일 교수인데 전세계를 돌아 다니면서 모든 사진에 박구 배다를 다 넣는다. 한국 사람들 천지이다. 커피 값과 에그 타르트 값이 비싸다.

(6) 볼량 마켓

볼량 마켓Mercado temporario Bolhao도 주위에 있는데 나는 포르토에 가면 여기 볼량 마켓에서 식사 한 끼는 꼭 한다. 값도 싸고 양도 많다. 흥성 장날이나 유성 장날과 같은 운치를 느낄 수 있다. 요즈음은 상권이 많이 죽은듯하여 옛날 전통시장의 맛은 덜하다. 우리 집사람도 좋아한다. 특히 주방에서 쓰는 가정주부들의 집기 등이 좋은 것이 많다.

그림 11-4.

볼량마켓 주방 용품점에서 물건을 고르는 우리 집사람. 흥정이 좋고 싸다고한다. 물론 입이 사왔다.

볼량마켓 내의 맛집 식당. 우리나라의 매일시장과도 유사하게 맛집이 많고 값도 싸고 양도 많다.

볼량마켓 내의 2층에서 이탈리아 트렌토대학의 갈라우디오교수와 안토넬라교수와 함께 쇼핑하다가 찍은 사진

1.8 공학자로서의 세계문명여행

그 결과로 여느 여행가이드북의 형태는 지양하였다. 지금부터 정확히 700여 년 전의 포르투갈이 대항해로 글로벌화를 시작했던 것처럼 우리나라의 상황을 살펴보고자 그리고 우리나라의 상황을 타개해 나가고 미래를 조망하는데 일조가 되었으면 하는 마음으로 구성하였다.

다행인 것이 2015년 이후 포르투갈에 대한 우리나라 사람들의 관심이 부쩍 늘어났다. 이는 비긴어게인2 등의 몇몇 TV프로그램에서 촬영한 덕분이다. 하루에도 3~5팀의 여행객들이 포르투와 리스본을 찾는다고 하고 설문조사에서 가보고 싶은 나라 상위에 랭크되기도 한다.

덧붙일 말은 본 저자는 요즈음 유행하는 인문학자가 아니라 공학자이다. 따라서 "공학자의 눈으로 보는 포르투갈 여행기" 또는 "포르투갈 문명기행기"라고 하는 것도 적당할 듯싶다. 다음과 같은 도시 순서로 포르투갈과 인접국인 스페인의 주요 인물들을 연관시켜 대항해 이야기를 엮어가려 한다.

2장; 포르투갈은 똑똑하고 진취적이며 위대한 나라이다.

3장; 기마랑이스·오비두스: 포루투갈이 생겨나고 레콩키스타가 본격적으로 시작되다

4장; 코임브라·에보라: 2번째 수도

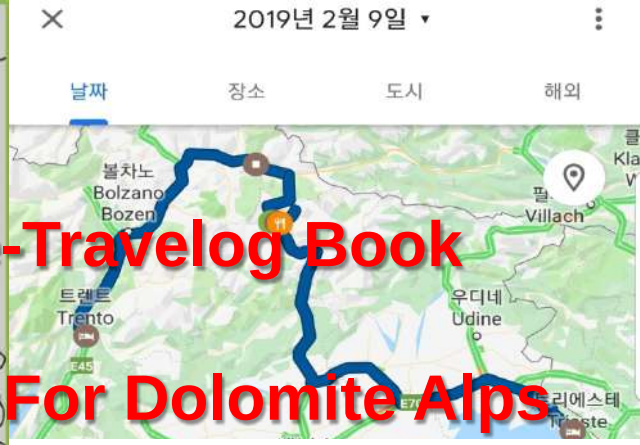
5장; 사그레스·과로·라구스: 엔히크 왕자의 세계 대항해의 출발지

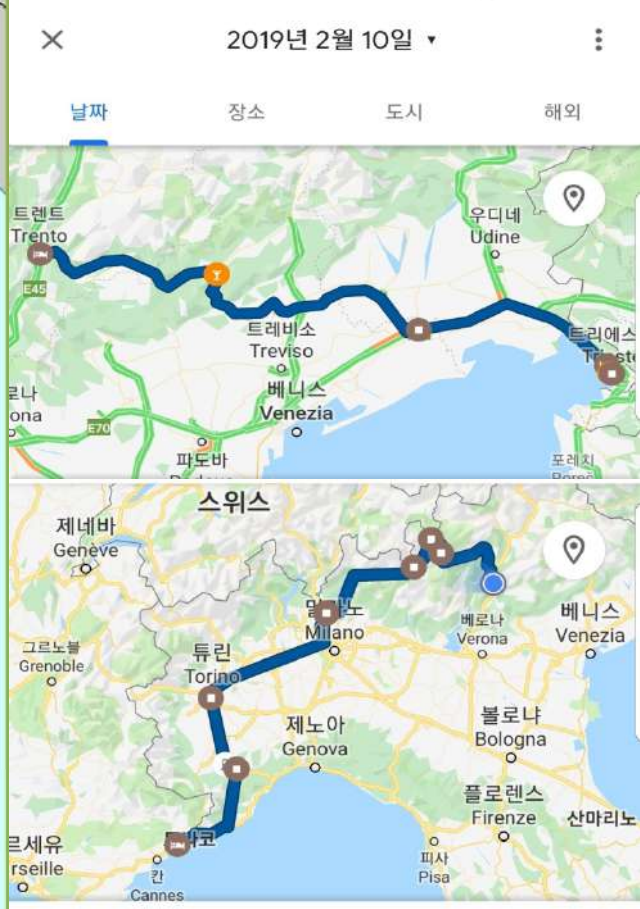
그림 1-8. 본 책에서 다루어질 도시들. 숫자는 각 장에 해당한다. 비록 15년여에 걸쳐 방문했다. 이웃 스페인도 렌트카로 그리고 웬만하면 고속도로가 아닌 지방도로로 비교적 살살이 방문하였다. 몇몇 도시에서는 1~2개월의 장기 체류도 하여 어느 정도 정도 들었다.

- 부자 망하면 삼년은 간다고, 포르투갈이 그렇다. 2차 대전 중에 이들이 중립국을 표방하자 세계대전 후 미국의 경제 영역에서 자연히 멀어져 간다. 정부공무원의 무능으로 주력 산업군의 결정이 안 되니까, 현금원이 자연히 소멸되어 2010년 우리나라의 IMF와 같은 경제 사태가 발생한다. 이 이후에 많은 기간산업이 중국자본가로 넘어 간 상태에서 경기는 조금씩 좋아 지고 있다.
- 마데이라는 내가 가본 섬 중에서 산토리니 섬, 제주도와 함께 최고로 멋진 섬이다.

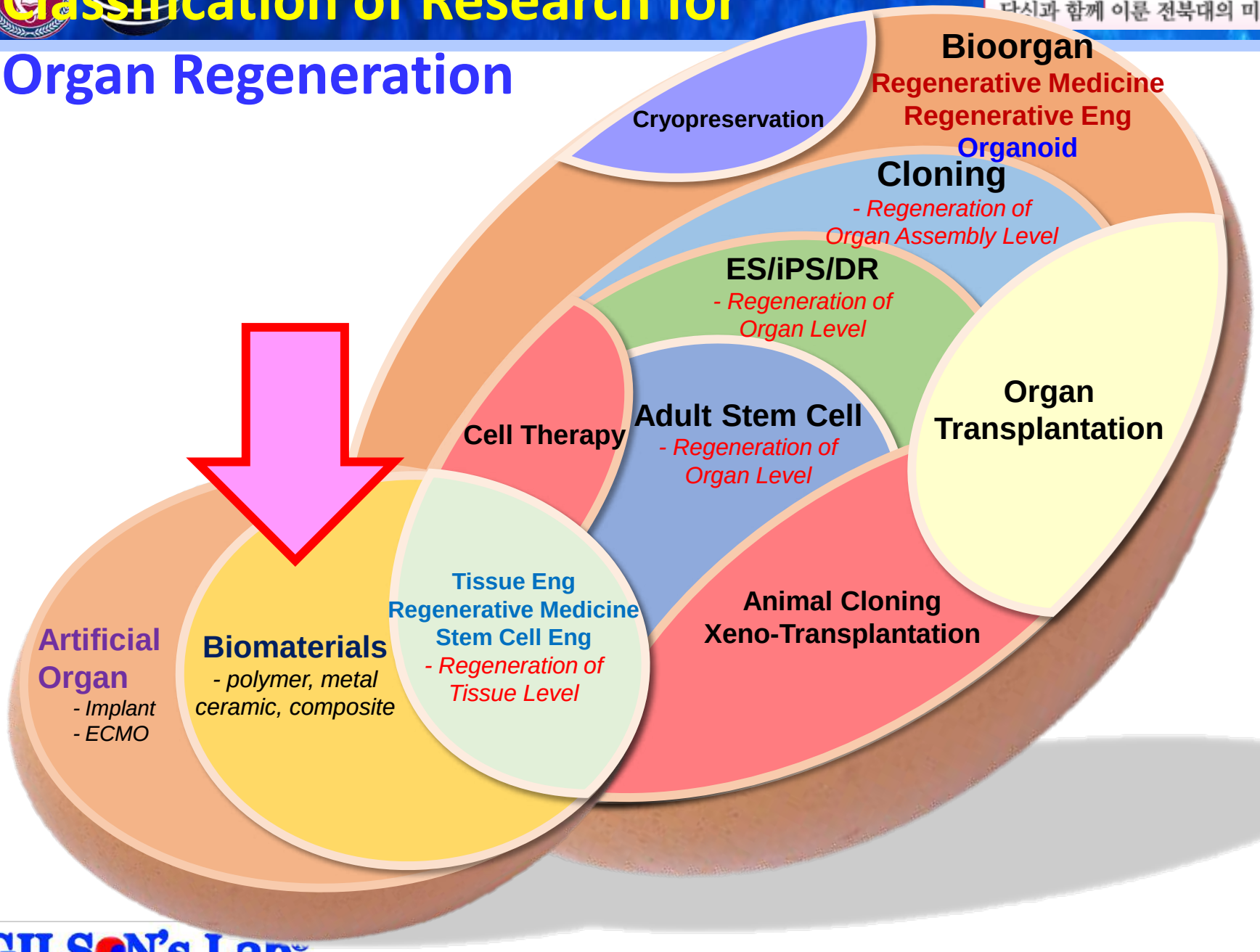
My 2nd Culture-Travelog Book

Culture-Travelog For Dolomite Alps





Classification of Research for Organ Regeneration



A. 1987~1995: Biocompatibility of Biomedical Polymers

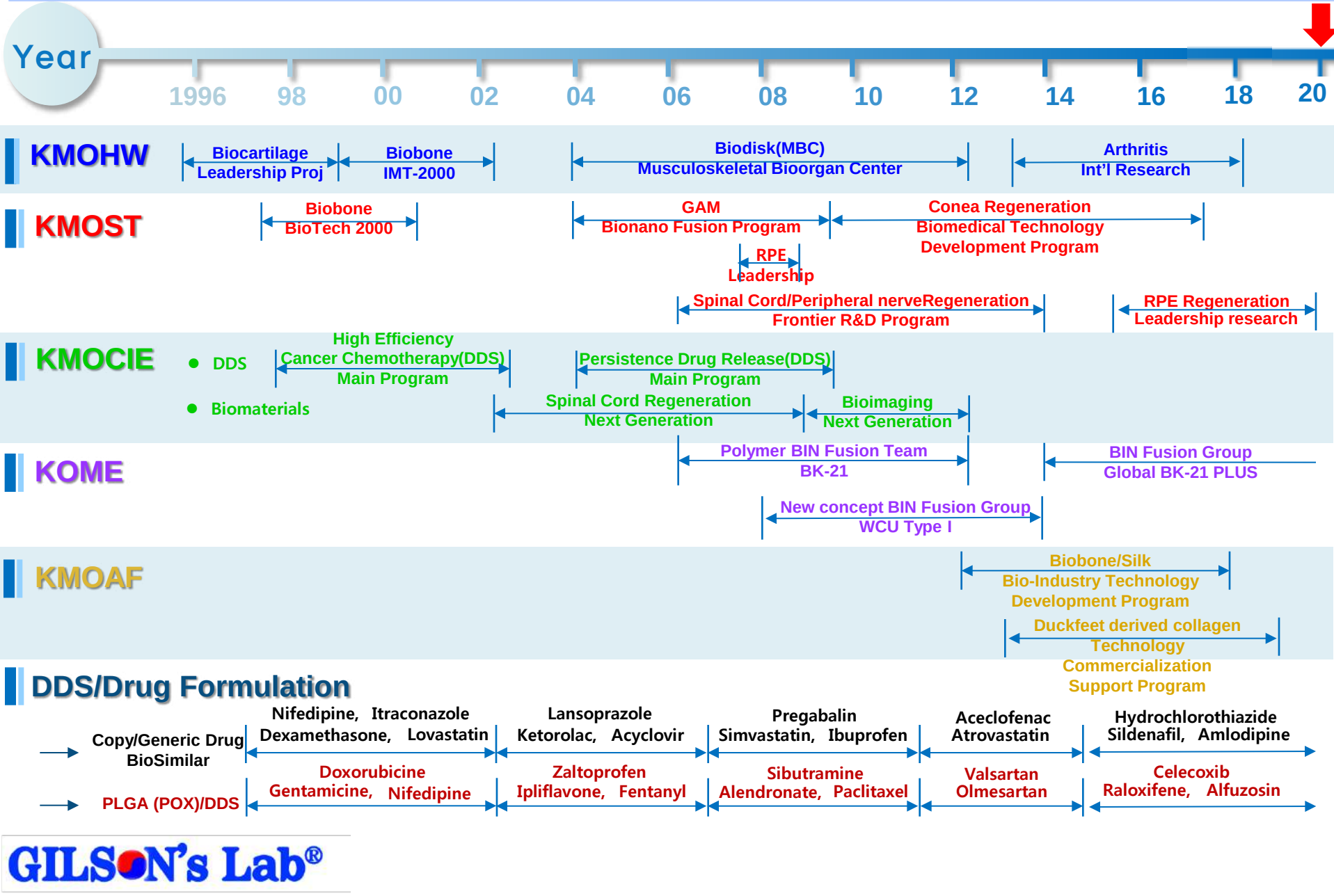
- PVC Blood Bag, PHEMA-PVP Soft Contact Lenz
- PET Vascular Graft
- Surface Modification by Corona/Plasma Discharge
- Gradient Surface & Graft Copolymerization

B. 1995~: Tissue Engineering & DDS

- Generic/Copy Formulations
- PLGA Microspheres & Osmotic Pump
- TE: Cartilage, bone, CNS/PNS, RPE, Disc, Cornea
- Inflammation Reaction of PLGA; Biocompatibility
- Stem Cell: BMSC, iPS, DR
- New Source of Biomaterials: Duck Feet Collagen, GG

Chronological Order of Gilson's Lab

2020 Global Top 100 CBNU
당신과 함께 이룬 전북대의 미래입니다.



GILSON's Lab®

Walk Like an Amputated Egyptian

Science Steps In To Discover Wonders Of Toe-tankhamun

Science Daily — An artificial big toe attached to the foot of an ancient Egyptian mummy could prove to be the world's earliest functional prosthetic body part, say scientists.

Research at The University of Manchester is hoping to prove that the wood and leather artefact in the Cairo Museum not only looked the part but also helped its owner walk 'like an Egyptian'.

If true, the toe will predate what is currently considered to be the earliest known practical prosthesis - an artificial leg from 300BC - by several hundred years.

Jacky Finch, who is carrying out the study at tre for Biomedical g volunteers whose right order to test an exact e.

clock method, in

© University of Manchester

A wooden toe—the world's oldest known prosthesis—is still lashed to the patient's mummified foot by a textile lace (above). Skin regrew where the big toe was amputated (right), proving the surgery was a success.

Discover, April, 2001, pp 12

Bioaritificial Organ By Biomaterials

All Biomaterials;

- Polymeric biomaterials
- Bioceramic
- Biometal
- Biocomposites

Contact lens;

- Hard lens: PMMA, silcone-acrylate, F-sa
- Soft lens: cros-PHEMA, cros-P(HEMA-NVP)
- Silicone/fluoro hydrogel
- High water contents, extended wearable, oxygen permeable
- Disposable lens: TPX poly(2-methyl-1-pentene)

Dental implant;

- Ti metal

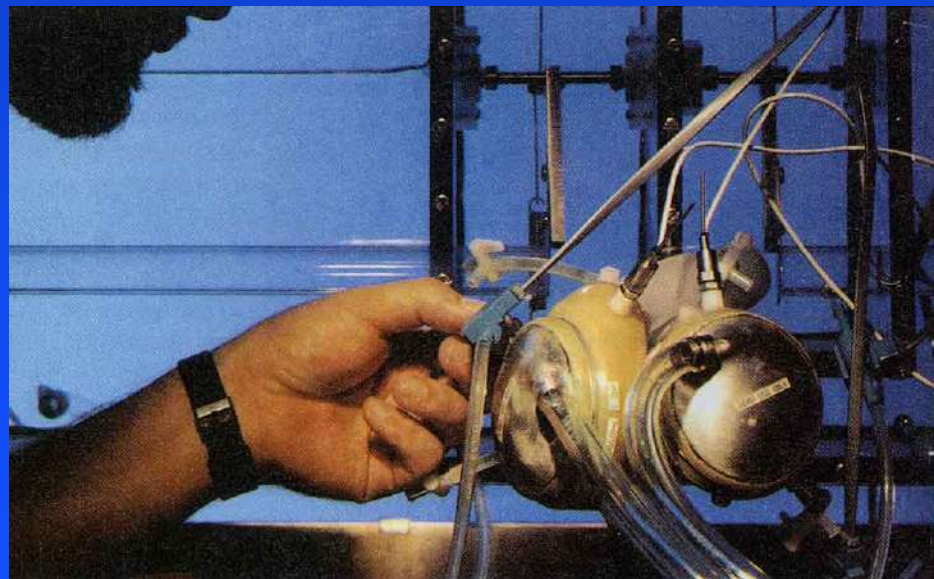
External fixation device;

- Stainless steel, Ti biometal

인공폐
Artificial Lung:
Polysulfone, Crupro

인공심장
Artificial Heart;
PMMA, stainless steel

인공심장
Artificial Heart
Javick 7:
Polyurethane
Polyester,
Ti,
Pyrolitic carbon



Artificial leaflet

탄소복합재료의족
Artificial leg:
Carbon composite

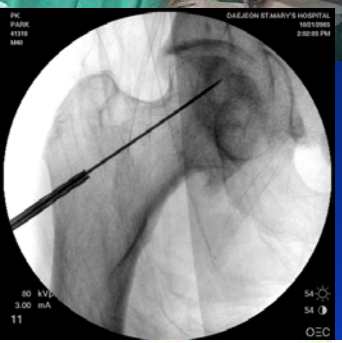

TDK
ISA


REUTERS

척추골절고정용 나사못
Nail:
Titanium

인공 고관절, 슬관절
Total Hip/Knee Athroplasty: THA/TKA

- Co-Cr-Mo alloy, Ti
- UHMWPE
- Oxidized alumina



Engineering: The simpler, The better!!!

Original Article | Clinics in Orthopedic Surgery 2013;5:110-117 • http://dx.doi.org/10.4055/cios.2013.5.2.110

Fifteen-year Results of Precoated Femoral Stem in Primary Hybrid Total Hip Arthroplasty

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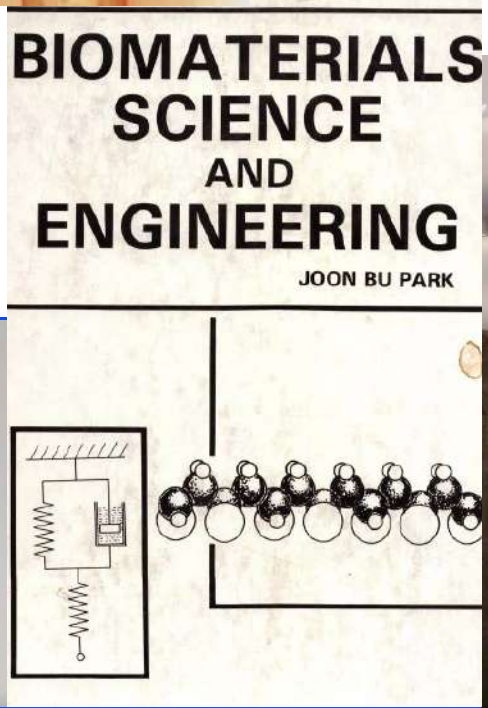
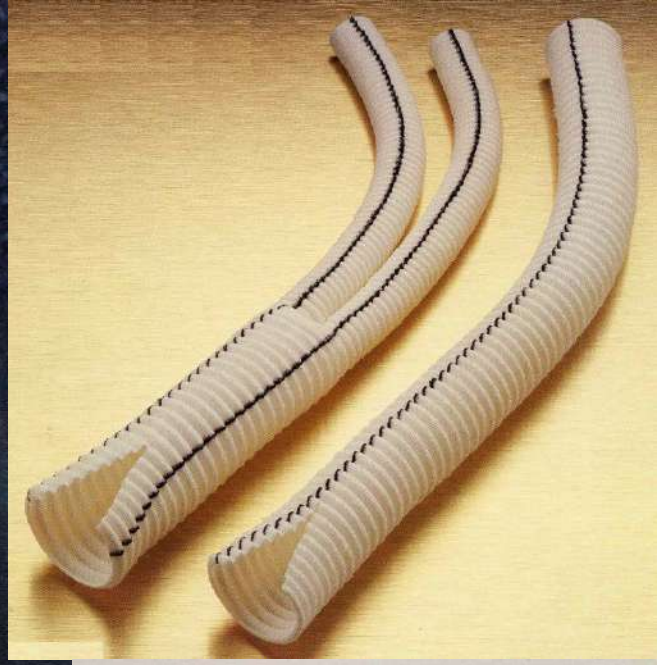
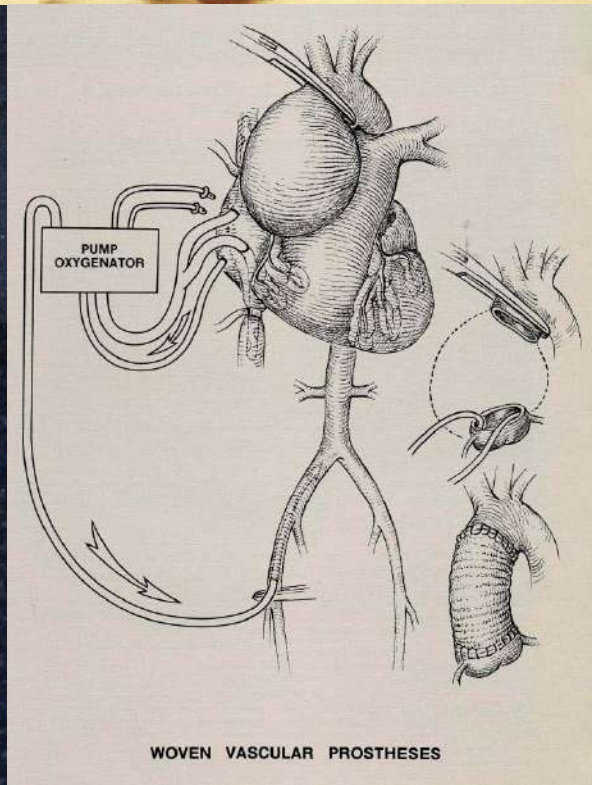


인공 혈관
Artificial Vascular Graft:
Polyester with crimping



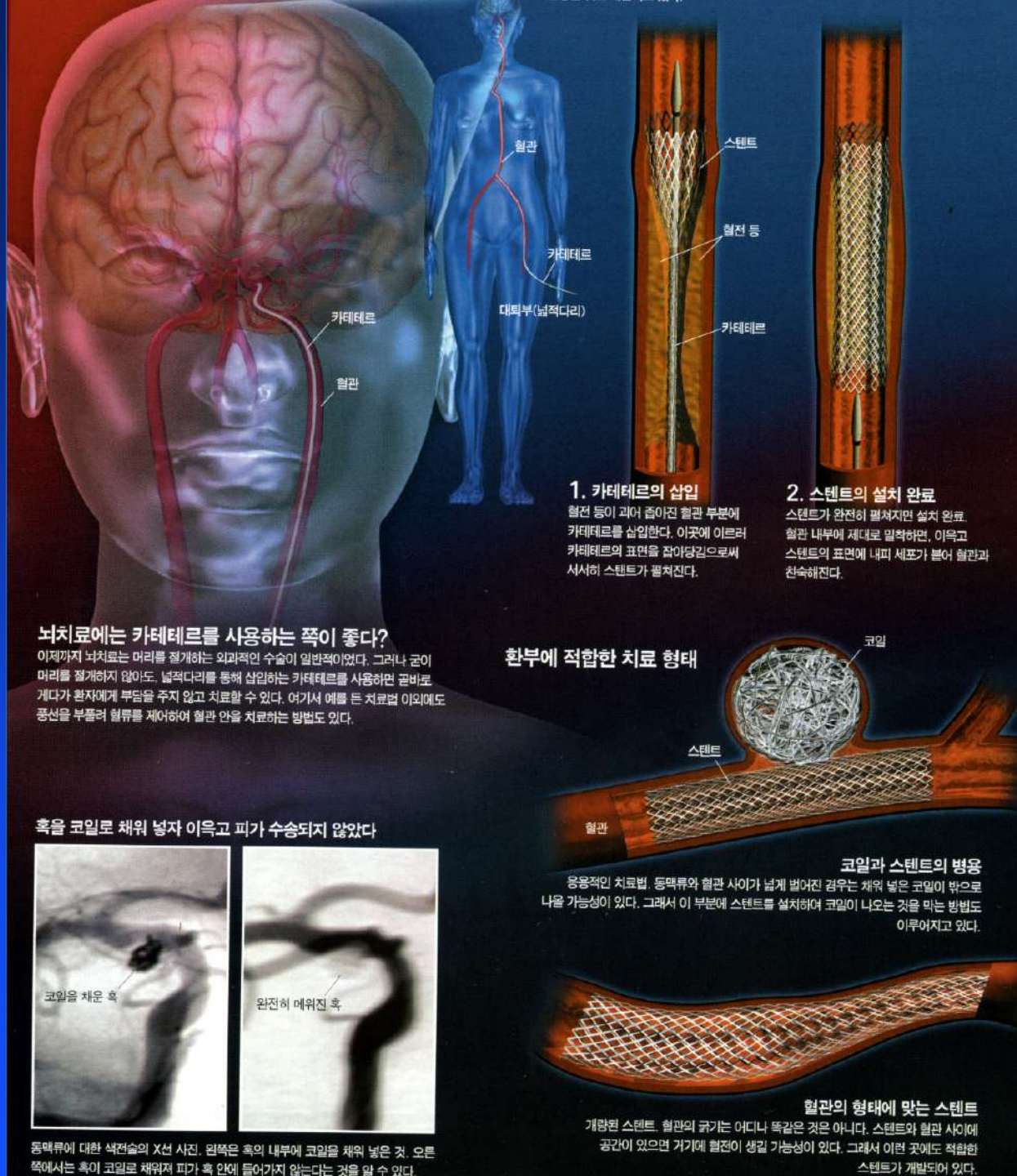


WOVEN VASCULAR PROSTHESES

인공 투석기
Artificial Kidney:

Polysulfone, Cupro,
PVC, PP, rubber, polyacetal
PMMA, epoxy resin

뇌혈관 치료용 카테타
Catheter: Nitinol, PP, PE, Guide wire



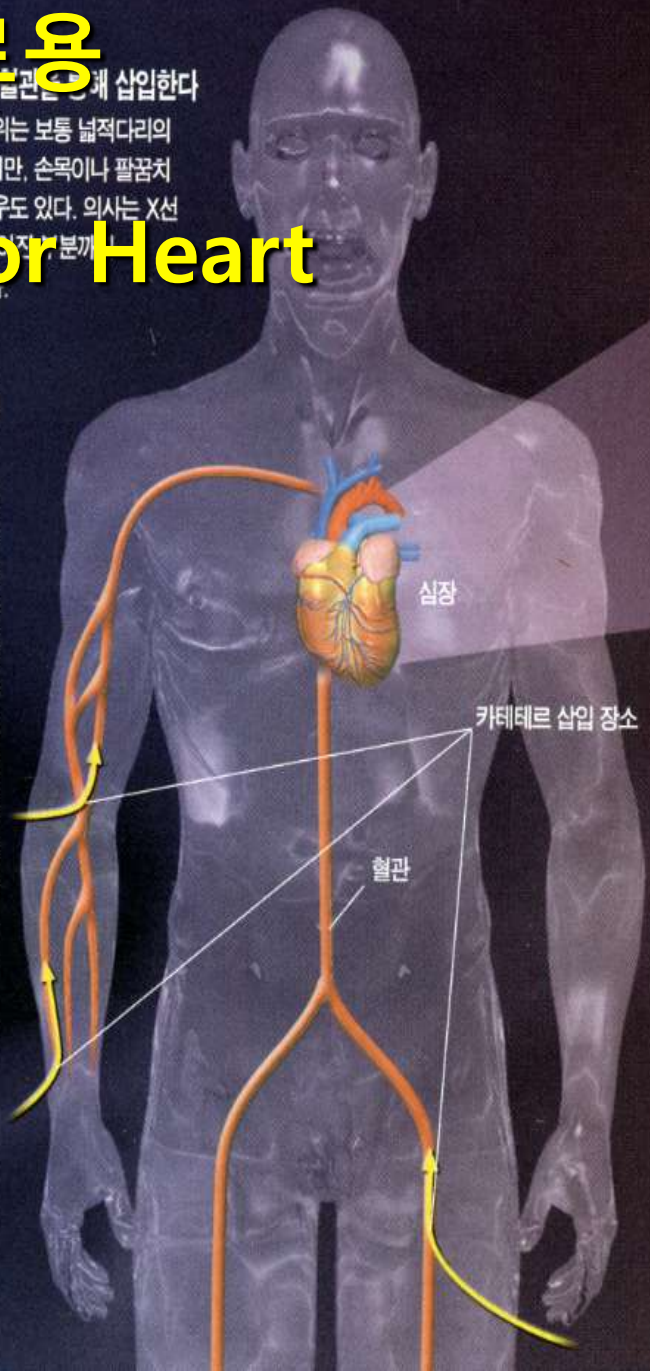
심장병 치료용 카테타
Catheter for Heart

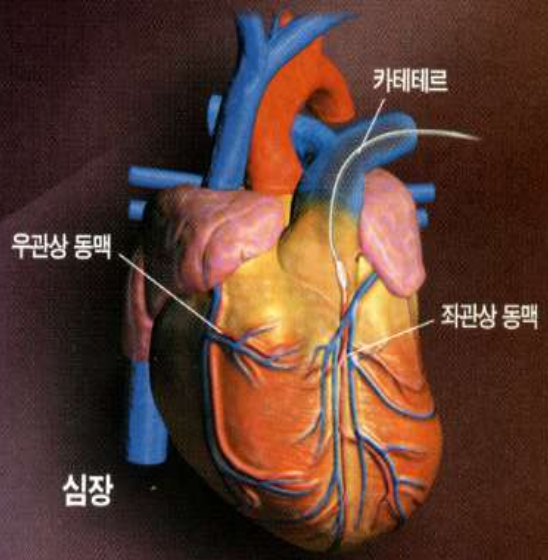
삽입한다

를 삽입하는 몸의 부위는 보통 넓적다리의
로 카테테르를 삽입하지만, 손목이나 팔꿈치
부분의 혈관으로 삽입하는 경우도 있다. 의사는 X선
분까
카테테르를 삽입하여 치료한다.

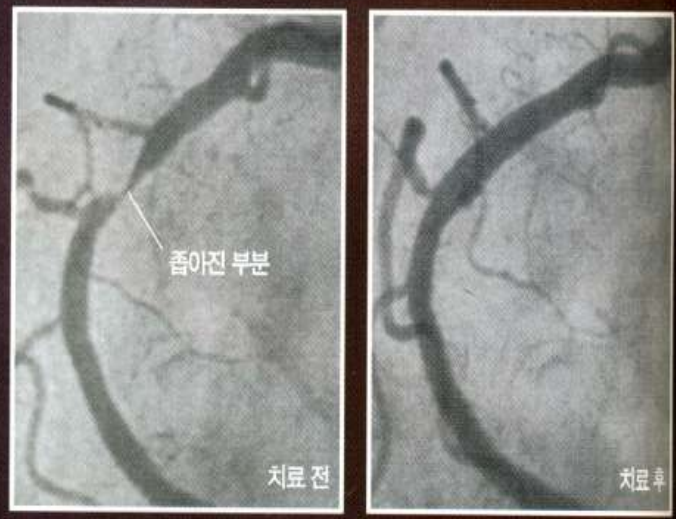
카테테르 치료는 환자의 부담을 줄인다

종래의 외과적 심장 수술은 반나절 이상의 시간이 소요되고 몇 주 동안 입원이 불가피하였다. 환자의 부담이 커 성공하여도 결국 세상을 떠나는 사람이 있을 정도이다. 그에 대하여 카테테르 수술은 간단하면 30분이면 끝나 다음날에는 퇴원 가능한 경우도 있다. 중증인 심장병이라면 외과 수술은 불가피하지만, 가벼운 병이라면 카테테르 치료를 선택할 수 있다.



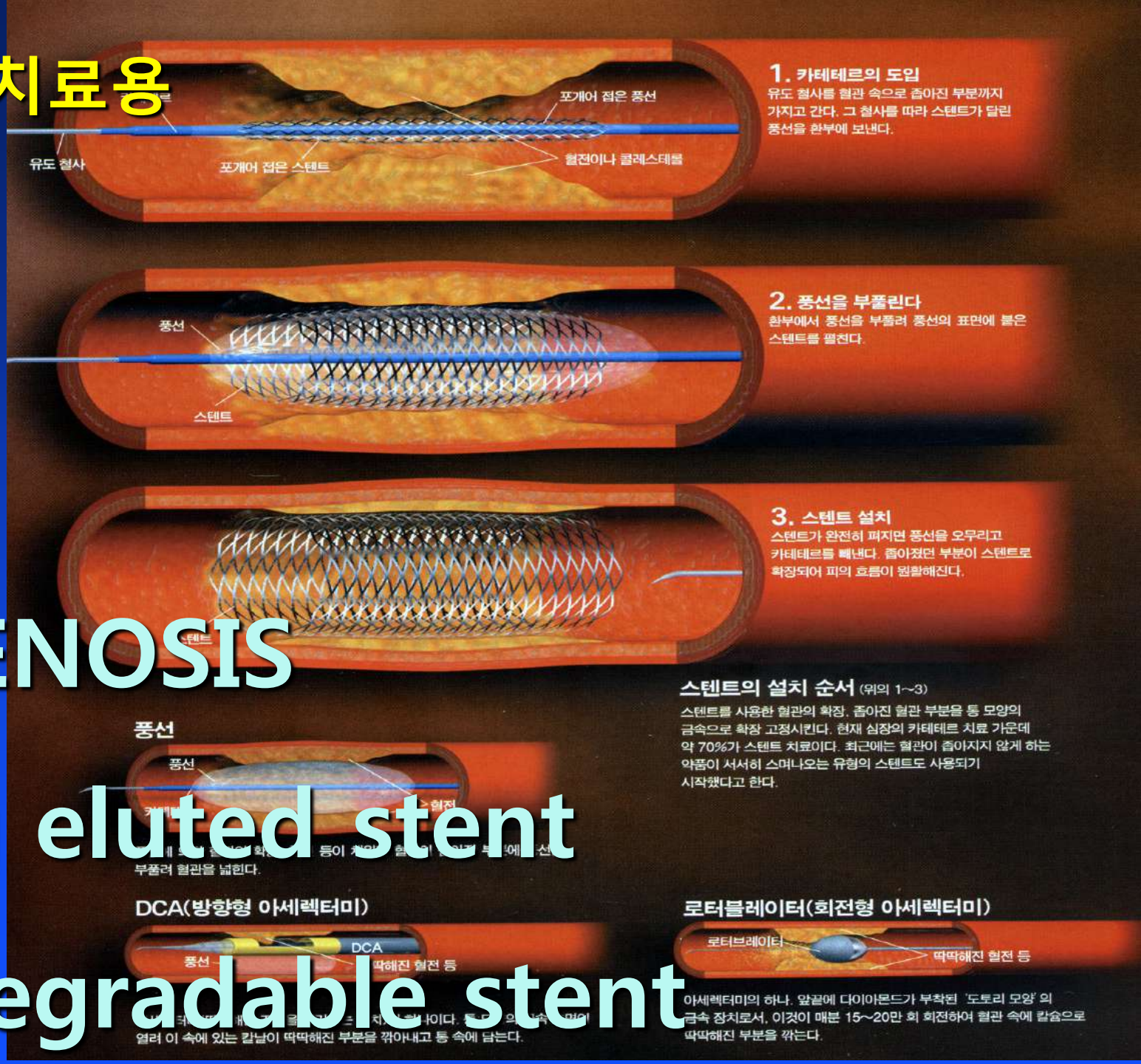


스텐트에 의한 카테테르 치료 전과 치료 후



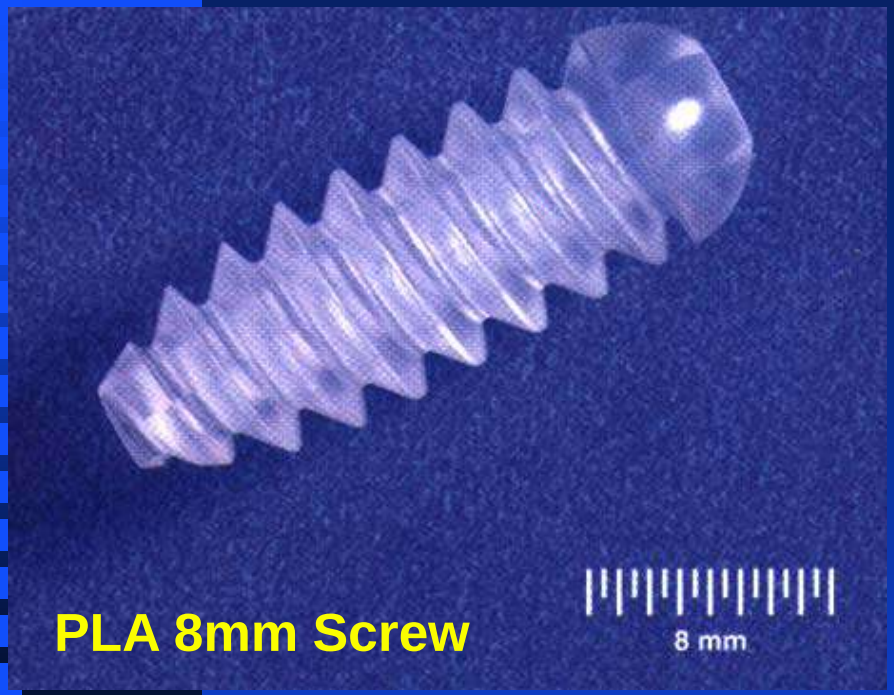
카테테르 치료 전후의 X선 사진. 관상 동맥의 좁아진 부분이 스텐트의 설치에 의하여 제대로 확장되어 있다는 것을 알 수 있다.

심장병 치료용 카테타



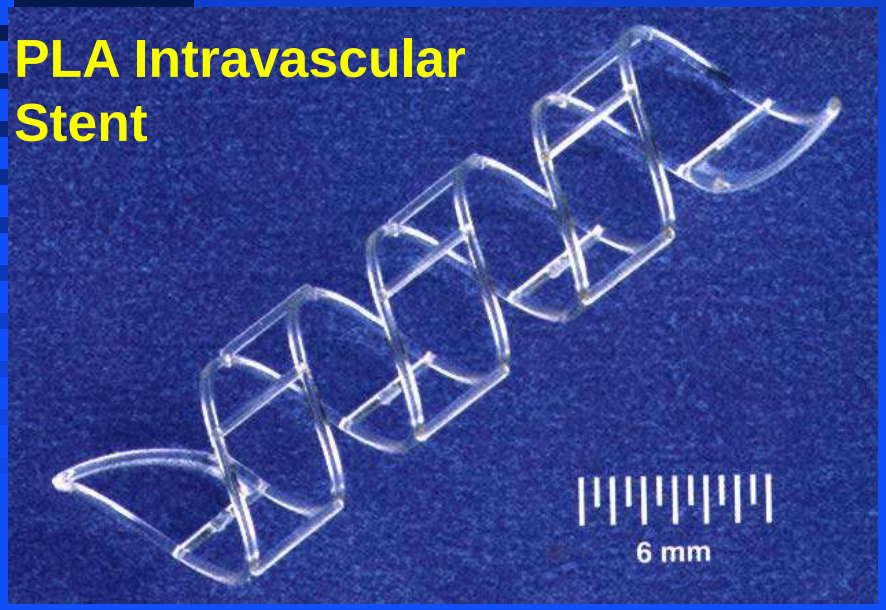
RESTENOSIS

- Drug eluted stent
- Biodegradable stent



PLA 8mm Screw

Maxillofacial Screw,
Suture Anchor

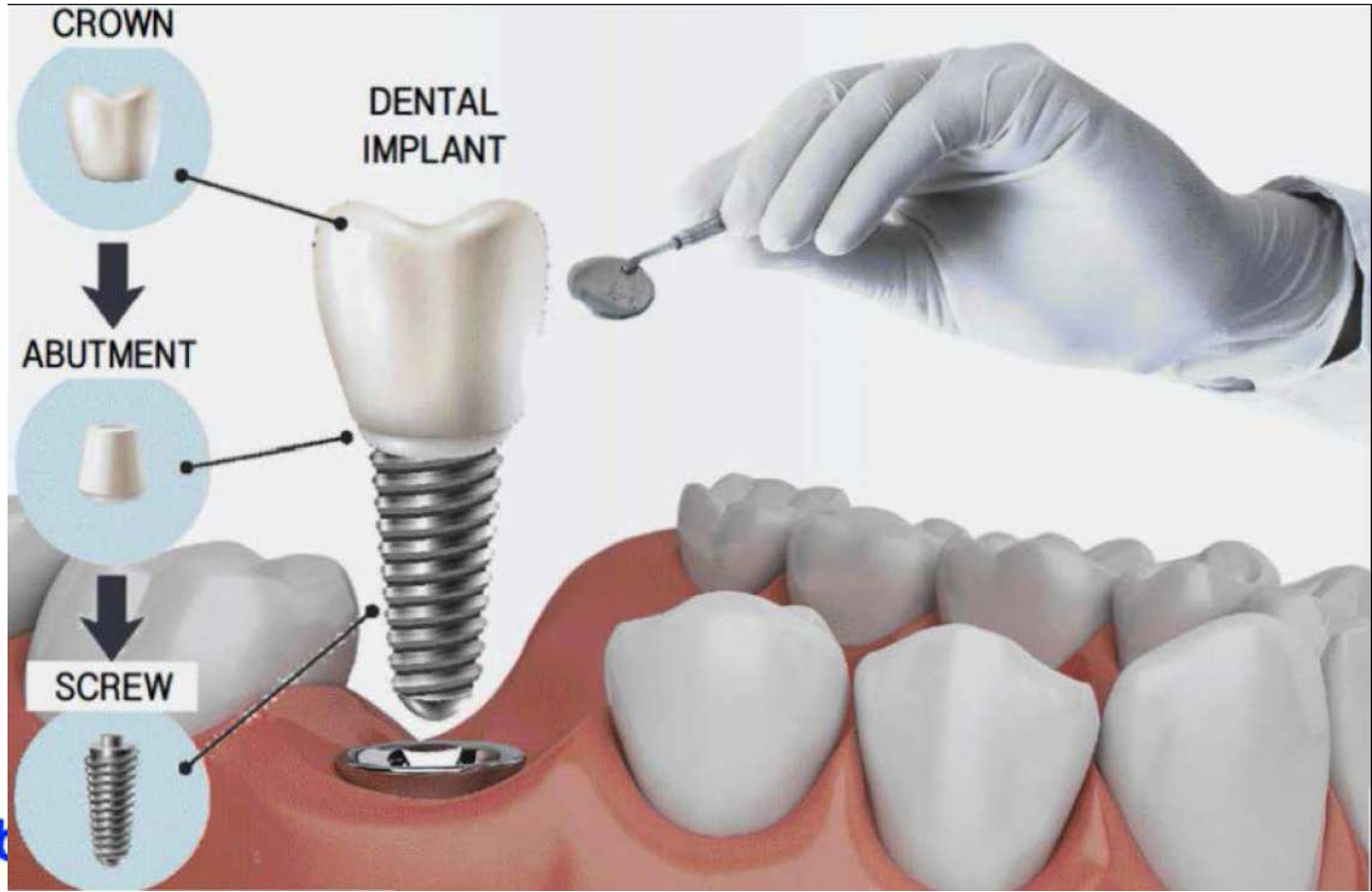


PLA Intravascular
Stent

“ACRU/ACRS”
Cartilage
Repair Unit

Dental Implants:

PMMA bone cement, epoxy resin
Titanium, alginate, (광경화)



<조선일보 2012.05.05 토>

어둠에 갇혀있던 삶, 전자 망막으로 빛을 만나다

인공망막
Artiicial
Retina

英 실명[illegible] 인공 [illegible]
현재는 흑백으로 형체 구별
6m 앞[illegible]

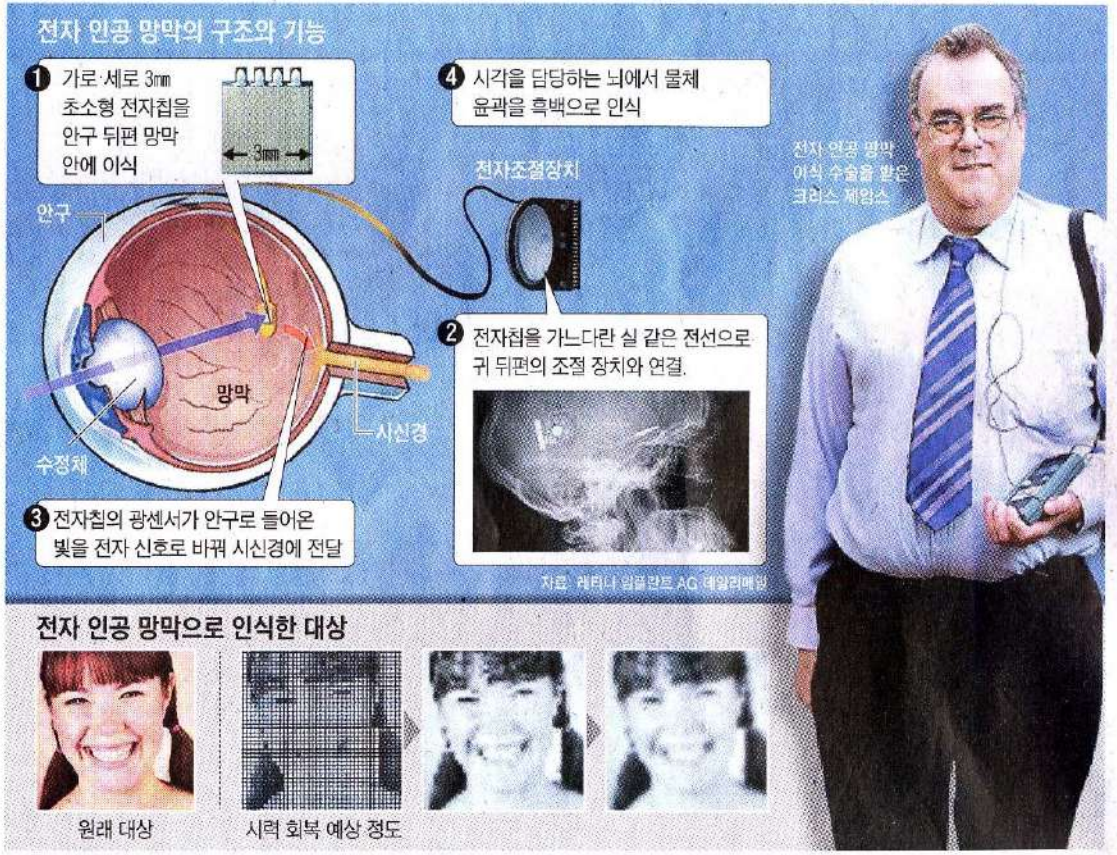
"10년 전 시력을 잃은 후 늘 빛을 볼 수 있는 날만 꿈꿔 왔다. 스위치를 켜는 순간 나한테 마법 같은 일이 벌어졌다. 전구(電球)에 불이 번쩍 들어오는 느낌이었다."

실명(失明) 환자들에게 시력 회복의 서광이 비쳤다. 영국에서 인공 전자 망막을 시각 장애인에게 이식해 시력을 일부 회복시키는 데 성공했다고 BBC가 3일 보도했다. '600만 불 사나이'가 현실에서도 가능해진 것이다.

런던 옥스퍼드대 안과 병원과 킹스 칼리지 안과 병원 의료팀은 지난달 망막색소변성증으로 시력을 잃은 영국인 2명에게 안구 뒤쪽 망막에 초소형 전자칩(인공 전자 망막)을 이식하는 데 성공했다고 밝혔다. 환자들은 수술 후 3주가 지난 현재 빛을 감지하고 사물의 형체를 흑백으로 구별할 수 있을 정도로 시력을 찾았다. 망막색소변성증은 빛을 감지해 이를 전기신호로 바꾸어 시신경에 전달하는 망막의 광수용체(光受容體) 세포 기능이 망가져 종국에는 시력을 잃는 질환이다. 이런 경우 시신경의 기능은 살아 있기 때문에 망[illegible]서 빛의 자극을 전기 신호로 바꾸어 준다면 시력을 되찾을 수 있는데, 그 역할을 인공 전자 망막이 한 것이다.

수술 환자 중 한 명인 크리스 제임스는 "지난 10년을 어둠 속에서 살았다. 하지만 인공 망막이 작동하는 순간 누군가 내 눈앞에서 플래시를 켜고 사진을 찍는 것처럼 빛이 번쩍 들어오는 것을 느꼈다"고 말했다. 연구팀은 앞으로 환자들의 시력이 점차 더 향상되어 시계(時計)를 볼 수 있고, 6m 거리에 있는 연인의 미소를 볼 수 있을 것이라고 말했다. 의료진은 지금까지 이런 방식으로 빛을 감지할 수 있을 정도의 실험 결과들은 있었지만, 이번 임상 시험은 예상 밖의 놀라운 결과라고 평했다.

인공 전자 망막은 독일 '레티나(retina·망막) 임플란트 AG'가 개발한 반도체 칩이다. 가로·세로 3㎜인 이 칩에는 망막 광수용체 세포 기능을 하는 1500개 전자 화소(픽셀)가 장착돼 있다. 여기서 감지된 빛을 전기 신호로 전환해 시신경으로 보내준다. 의료진은 이 칩을 10시간의 수술을 통해 안구로 들어온 빛이 모이는 망막 부위 안에 심었다. 칩은 실같이 미세한 전기선으로 귀 뒤쪽 피부 밑에 심어진 자기(磁氣) 조절 장치와 연결됐다. 조절 장치는 다시 외부 배터리 장치와 연결된다. 환자들은 이 배터리 장치를 통해 인공 망막이 빛을 감지하는 강도를 조절할 수 있다.



레티나 임플란트 AG 측은 "이번 임상 시험 성공으로 망막색소변성증을 앓는 영국인 2만명과 시력 감퇴를 겪는 많은 환자에게 희망의 빛을 줄 수 있을 것"이라고 말했다. 망막색소변성증은 증상 정도의 차이에 따라 4000~5000명에 한 명꼴로 유전적 요인이 작용해 발생한다. 올해 독일과 중국에서 추가로 10명의 환자에게 인공 망막이 이식될 예정이다. 연구팀은 "배터리를 머리 뒤쪽 두피 안에 심어 인공 망막이 무선(無線)으로 작동되도록 개발할 계획"이라며 "인공 망막이 널리 사용되기까지에는 추가 실험과 연구가 더 필요하다"고 밝혔다.

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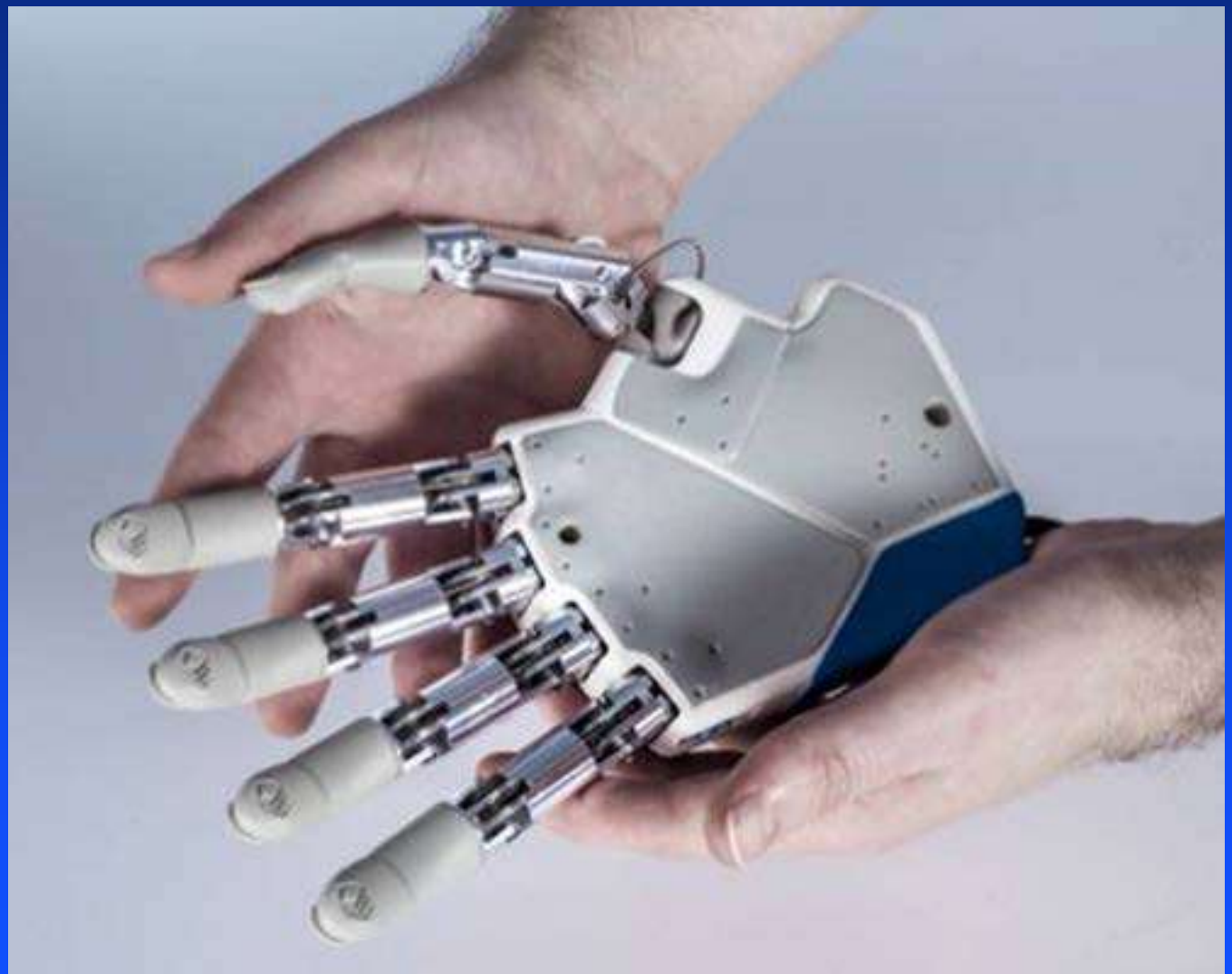
doctor@chosun.com
이송원 기자 lssw@chosun.com

인공와우(전자식)

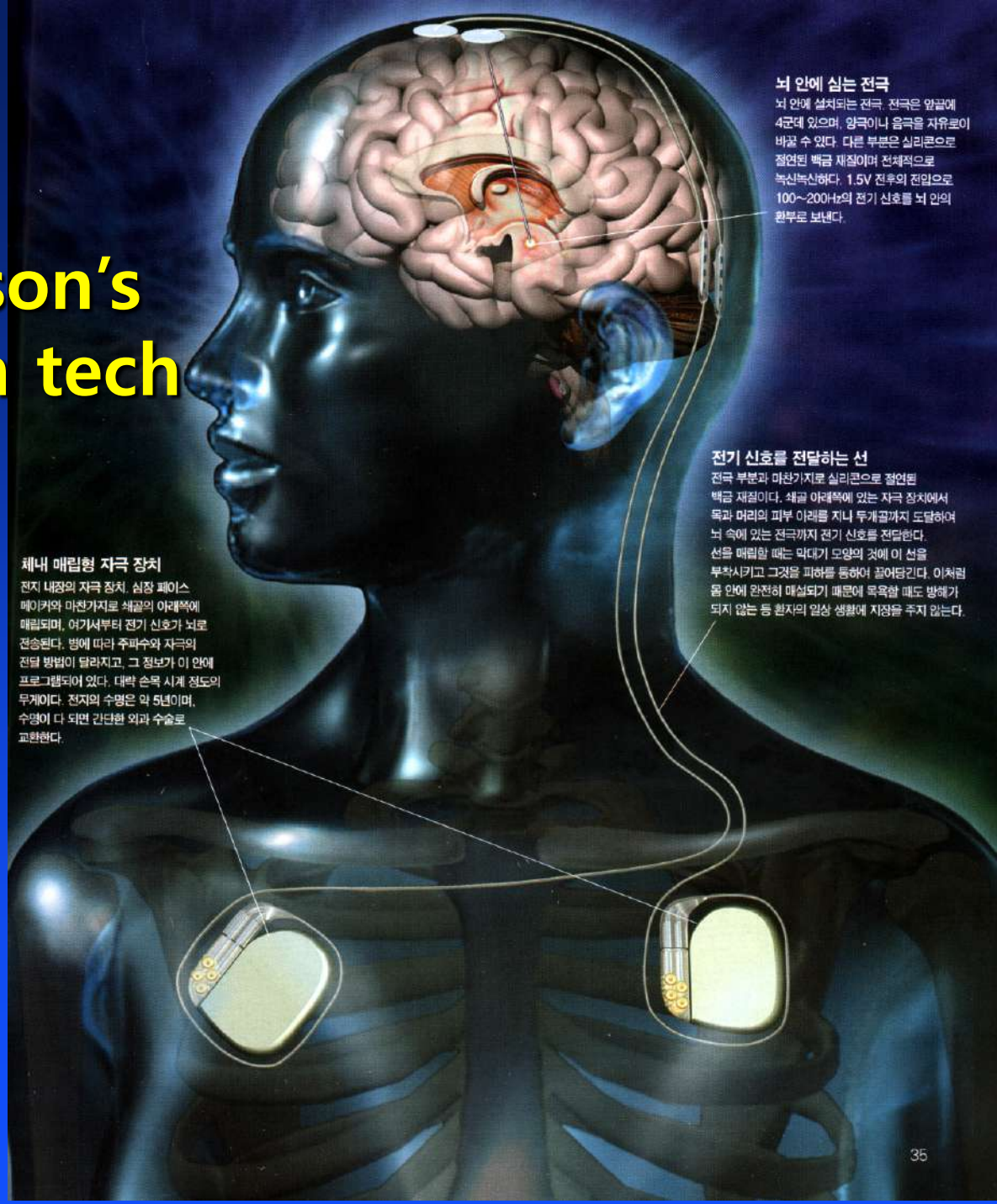
Artificial Hearing

BT/IT/NT Fusion tech

의수
Computerized artificial hands
BT/IT/NT Fusion tech

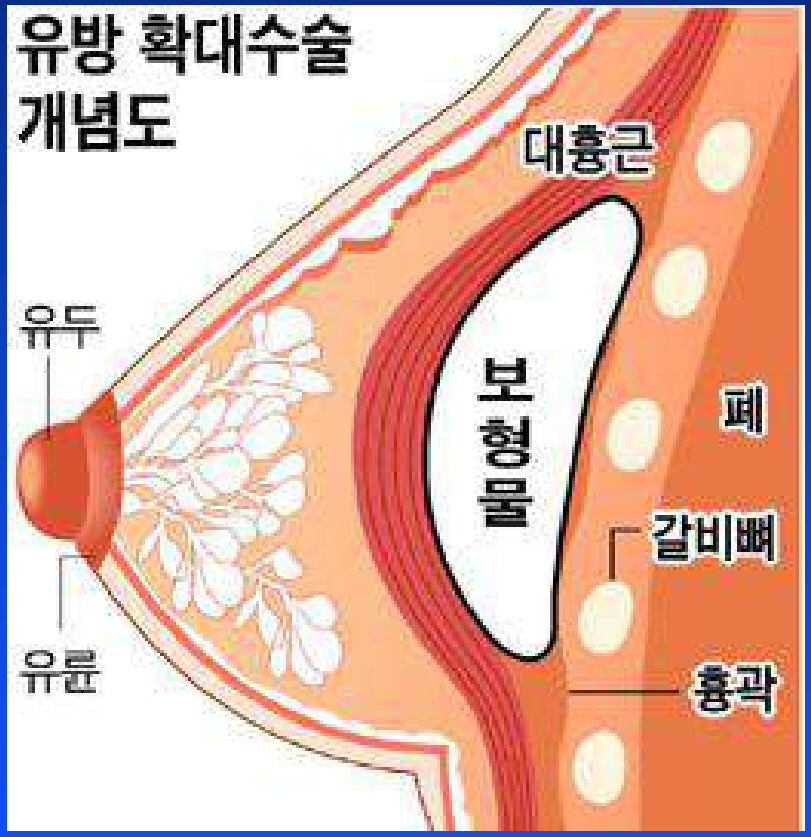


파킨슨씨병 치료용 전극
Patch for Pakinson's
BT/IT/NT Fusion tech

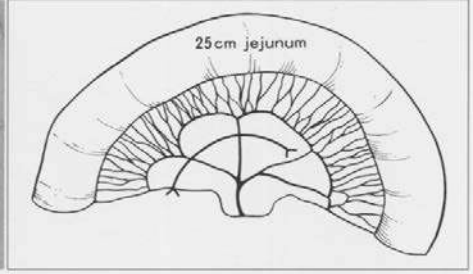


하리수
인공가슴
여성홀몬 패취:DDS

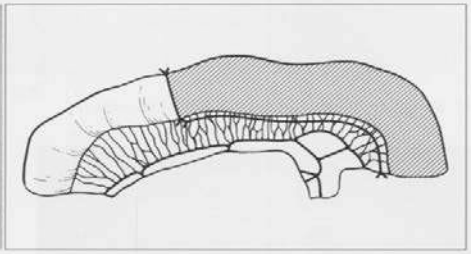
인공 가슴



바이오질
(성소수자:0.174%)



（a） 25 cm の空腸片を採取。アーケードに至る口側の腸間膜を切離する。



（b） 腸間膜切開に加え肛門側の腸管を犠牲腸管とすることにより，長い血管茎が得られる。

Fig. 7·24 （a, b） A 35 year old male transsexual underwent MTF gender reassignment surgery.

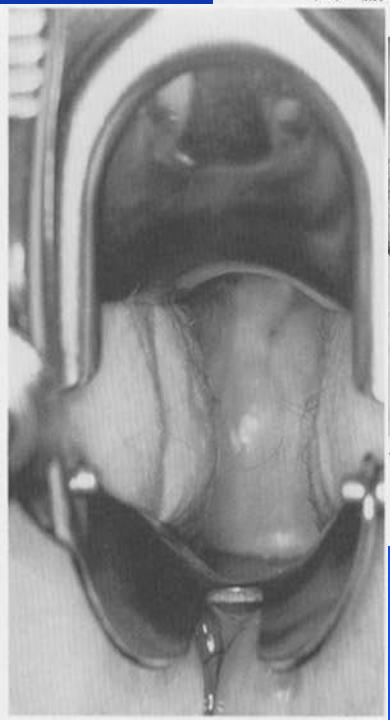


Fig. 7·25 The depth of neovagina was measured to be about 9-10 cm.

（c） 鼠径部で下腹壁動脈および大伏在静脈に空腸動静脈を吻合する。再建腟入口部より 20 cm 以上の血管茎が得られている。

（d） 空腸片は血流再開後，シリンジで作成した mold とともにポケット腟内に挿入する。

図 4·6 手 技

바이오성기

a b c
d e

（a） 術　前
（b） 陰茎全切断術直後の移植部の状態。陰茎海綿体の断端が縫合され，尿道にバルーンが留置されている。
（c） デルトイド皮弁のデザイン。
（d） 術後6カ月の再建陰茎。
（e） 術後6カ月の採取部。

図 6･3　陰茎癌症例における陰茎全切断後の一期的陰茎再建

Problem Statement:
What is the exact definition
of Biocompatibility with several examples

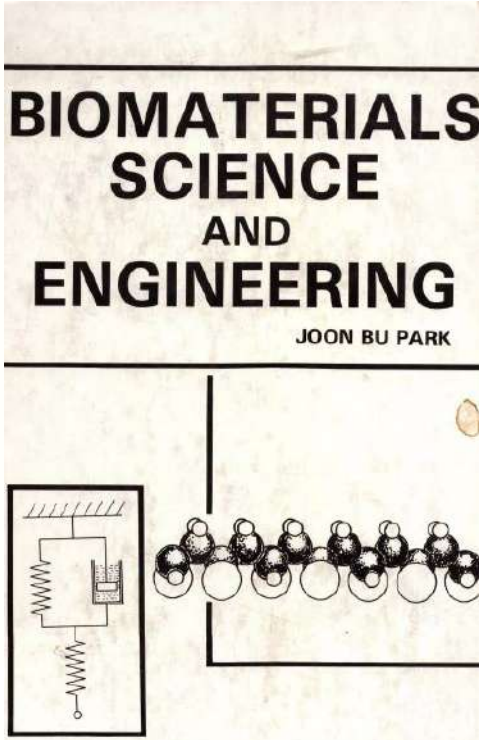
FOR COMMERCIALIZATION of
TISSUE ENGINEERED PRODUCTS

1.1. DEFINITION OF BIOMATERIALS

The word *biomaterials* can be defined in two ways: as commonplace biological materials such as tissues and woods or as any materials that replace the function of the living tissues or organs. In legal terms (Clemson Advisory Board for Biomaterials "Definition of the word 'biomaterials,'" The 6th Annual International Biomaterial Symposium, April 20–24, 1974) "a biomaterial is a systemically, pharmacologically inert substance designed for implantation within or incorporation with a living system." This definition clearly emphasizes biomaterials as implant materials although the conventional usage of the prefix *bio* is somewhat violated; for example, biochemistry and biophysics refer to the study of biological materials rather than man-made materials. In order to avoid confusion, *biomaterials* will refer to implants replacing and restoring living tissues and their functions. From this definition, (implantable) *biomaterials* includes anything that is intermittently or continuously exposed to body fluids although they may actually be located outside of the body proper. Included in this category are most dental materials although traditionally they have been treated as separate entities. Devices such as external artificial limbs, hearing aids, and external facial "prostheses" are not implants.

Because the ultimate goal of using biomaterials is to restore function of natural living tissues and organs in the body, it is essential to understand relationships among properties, functions, and structures of biological materials. Thus, three aspects of study on the subject of biomaterials can be envisioned: biological materials, implant materials, and interaction between the two in the body. This is a very difficult task to master unless one possesses a fundamental knowledge of the whole system under study.

1984



생체재료의 정의

생체재료의 정의에 대한 필요성이 부각되면서 미국의 국립보건원은 1984년에 생체재료를 '인체조직 및 장기의 기능을 치료, 개선 및 대체하는 목적으로, 단기간 및 장기간의 모든 기간 동안, 의약을 제외한 시스템의 전체 또는 일부로 사용되는 모든 천연물질과 합성물질 및 이 물질들의 조합'으로 정의하였다. 또한 1989년 영국에서 개최된 유럽 생체재료학회에서는 생체재료를 '일정기간 인체에 접촉 또는 삽입되어 인체 조직 또는 기관을 일부 또는 전부 대체하거나 복구하여 그 기능을 회복시킬 수 있는 합성, 천연 및 복합재료'로 정의하였고, 이때 의약품은 제외하였다. 한국의 식품의약품안전처는 유럽 생체재료학회의 생체재료 정의를 인용하여 의료기기의 생물학적 안전에 관한 공통기준규격(고시 제 2014-115호, 2014. 4. 24, 개정)에서 생체재료를 '신체의 조직, 기관 또는 기능을 평가, 치치, 수복 또는 대체하기 위해 생물학적 시스템과 상호접촉(interface)하여 사용하는 물질'로 정의하고 있다.

생체재료는 좁은 의미에서 생체의 손상된 조직 및 장기의 일부를 대체 또는 복구하여 기능을 보완 및 복원시킬 수 있는 물질로 정의할 수 있으며, 넓은 의미로는 인체의 질병을 진단 및 치료하기 위한 재료로서 인체에 접촉 또는 이식될 때 생체적합하고 독성이 없는 물질로 정의될 수 있다.

김영하등, 생체재료학 2판, 생체재료학회 간

BIOMATERIALS SCIENCE

An Introduction to Materials in Medicine 2nd Edition

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2004

Biocompatibility

The understanding and measurement of biocompatibility is unique to biomaterials science. Unfortunately, we do not have precise definitions or accurate measurements of biocompatibility. More often than not, biocompatibility is defined in terms of performance or success at a specific task. Thus, for a patient who is doing well with an implanted Dacron fabric vascular prosthesis, few would argue that this prosthesis is not "biocompatible." However, the prosthesis probably did not recellularize (though it was designed to do so) and also is embolic, though the emboli in this case usually have little clinical consequence. This operational definition of biocompatible ("the patient is alive so it must be biocompatible") offers us little insight in designing new or improved vascular prostheses. It is probable that biocompatibility may have to be specifically defined for applications in soft tissue, hard tissue, and the cardiovascular system (blood compatibility). In fact, biocompatibility may have to be uniquely defined for each application.

표 2. 인공장기와 이에 사용되는 의료용 고분자소재

인공장기 부위별 명 칭	고 분 자 소 재
콘택트렌즈	PMMA, PHEMA
안내렌즈	PMMA
인공귀	실리콘
인공치, 의치, 충전재료	PMMA, 메타아크릴산유도체의 고분자
인공식도	PE, 천연고무
인공심장	PU, 실리콘
인공심장판막	실리콘, 테프론
인공폐(체외순환)	실리콘, PP 다공질막
인공유방	실리콘
인공간장(체외순환)	활성탄, 고분자비드
인공신장(체외순환)	셀룰로오스, 초산셀룰로오스, EVA, PMMA, 폴리설폰, PAN, PE, 체외 션트 테프론, 실리콘
인공혈관	폴리에스터, 테프론, 연신테프론
인공고관절	UHMWPE
뼈시멘트	상온중합형 PMMA
인공손가락관절	실리콘, PP
인공손톱	아크릴계통의 고분자
인공무릎	UHMWPE
인공인대	폴리에스터, PP, 연신테프론
인공뼈	PMMA, 탄소강화불포화폴리에스터 복합재료
인공힘줄	실리콘
뼈고정용 나사못과 보철판	PLA
흡수성 봉합사	PGA
생체접착제	폴리시아노아크릴레이트, 피브린
약물전달시스템	PLA, PLGA, 폴리시아노아크릴레이트

표 3. 의료용 고분자재료가 갖추어야 할 세부조건

Ⅰ. 생화학적 특성
- A. 생체적합성
  - ① 독성 및 발암성이 없어야 된다.
  - ② 각 기관의 장애를 일으키지 말아야 한다.
- B. 혈액적합성
  - ① 혈구파괴가 없어야 된다.
  - ② 혈장단백질의 변화가 없어야 된다.
  - ③ 혈전형성이 없어야 된다.
- C. 세포조직적합성

Ⅱ. 화학적 특성
- A. 용 출 성
  - ① 재료로부터 이행성분이 없어야 된다.
- B. 안 정 성
  - ① 재료의 열화가 일어나지 말아야 된다.
  - ② 재료의 변질이 없어야 된다.
  - ③ 생체성분과의 부반응이 없어야 된다.
  - ④ 생체성분과의 부착흡착이 없어야 된다.

Ⅲ. 물리적 기계적 특성
- A. 투 명 성
  - ① 투명성이 좋아야 된다.
- B. 유 연 성
  - ① 유연성이 좋아야 된다.
- C. 내 구 성
  - ① 크리프 특성이 좋아야 된다.
  - ② 재질파괴가 일어나지 말아야 된다.

Ⅳ. 멸균특성
- A. 내 열 성
  - ① 고온에 견뎌야 된다.
- B. 경 시 성
  - ① 멸균 후에 재료의 변형이나 변화가 없어야 된다.
  - ② 멸균시에 부반응물이 생성되면 안된다.

Ⅴ. 성형 가공 특성
- A. 성 형 성
  - ① 각종 성형성이 좋아야 된다.
    - 압출, 사출, 중공, 칼렌다 성형 등
- B. 가 공 성
  - ① 2차 가공이 좋아야 된다.
    - 접착, 고주파 가공, 초음파 가공

Ⅵ. 생 산 면
- A. 생 산 비
  - ① 재료가 싸야 된다.
  - ② 성형 및 가공단가가 저렴해야 된다.
- B. 품질관리
  - ① GMP 상당의 체제가 이루어져야 한다.

Requirements of Biomaterials

BIOCOMPATIBILITY

I. Biochemical Property: Nontoxic, Noncarcinogenic, Blood compatibility, Tissue/Cell compatibility, etc

II. Chemical Property: Non-leachable, Safety, etc

III. Physical/Mechanical Property: Transparent, Flexibility, Durability, Anti-creep. etc

IV. Sterilizability: Heat-resist, Anti-aging, etc

V. Processablity: Injection, Calendaring, Extrusion, etc

VI. GMP: Cheap, etc

BIOMATERIALS SCIENCE

An Introduction to Materials in Medicine 2nd Edition

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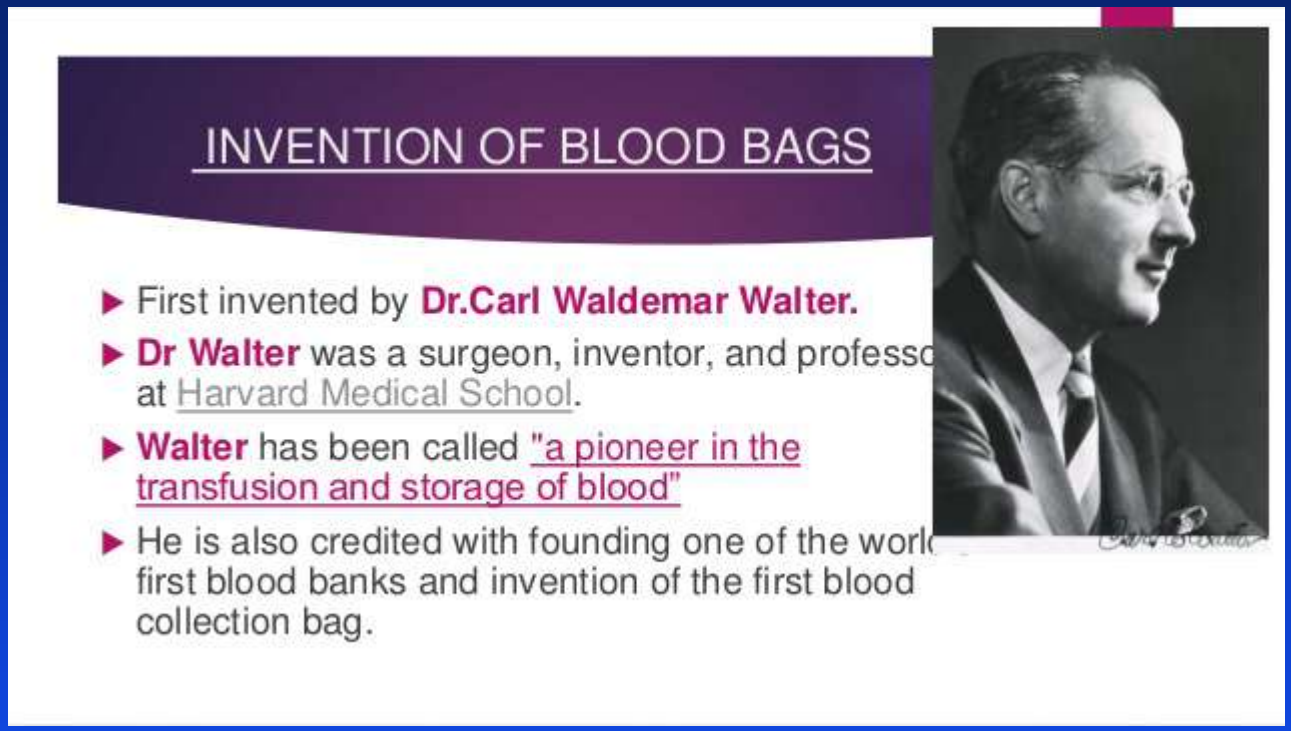
2004

Biocompatibility

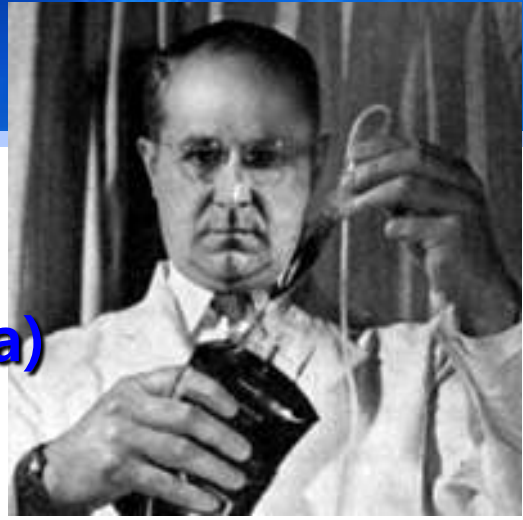
The understanding and measurement of biocompatibility is unique to biomaterials science. Unfortunately, we do not have precise definitions or accurate measurements of biocompatibility. More often than not, biocompatibility is defined in terms of performance or success at a specific task. Thus, for a patient who is doing well with an implanted Dacron fabric vascular prosthesis, few would argue that this prosthesis is not "biocompatible." However, the prosthesis probably did not recellularize (though it was designed to do so) and also is embolic, though the emboli in this case usually have little clinical consequence. This operational definition of biocompatible ("the patient is alive so it must be biocompatible") offers us little insight in designing new or improved vascular prostheses. It is probable that biocompatibility may have to be specifically defined for applications in soft tissue, hard tissue, and the cardiovascular system (blood compatibility). In fact, biocompatibility may have to be uniquely defined for each application.

1. PVC Blood Bag



Blood transfusion:
"Real Organ Transplantation"
as red blood cell, white blood cell, platelets and so on

- Pyrex glass bottle: coagulation
- Blocking with air



Blood Bag: Plasticized PVC (panacea)

Plasticizer: DOP: Endocrine Disruptor

(환경호르몬)

Trying to change non-DEHP bag

:Polyolefin bag

Baxter, Travenol, Fresenious, Terumo

FIGURE 102.—Blood donations secured at 15th Medical General Laboratory, Naples. Note froth at top of bottle on left, and completely filled bottle on right. Glucose solution will be added to the bottle on left, to fill up space now occupied by froth, partly for preservative effect of solution on red blood cells, and partly to prevent sloshing of blood during transportation.

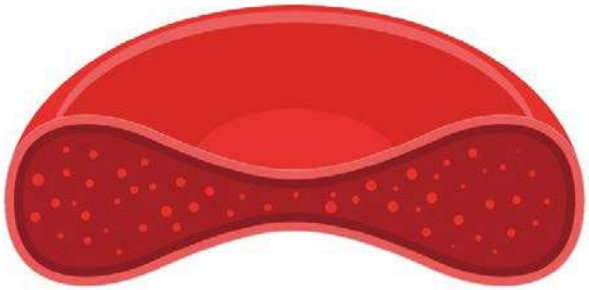
FIGURE 180.—Plastic equipment, standardized as replacement for glass bottles during Korean War. In center is collecting bottle formerly used.

FIGURE 185.—Refrigerated container, developed at Fort Totten after Korean War and still in use (1962). Note ice in plastic container in cover.

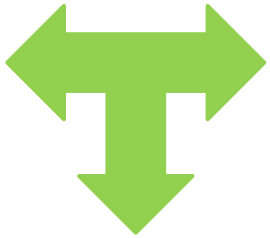
Self life of whole blood

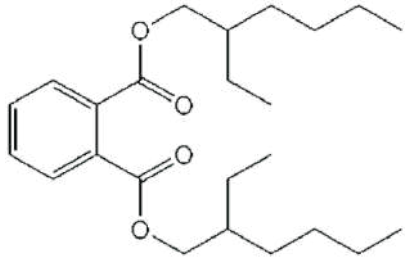
- Plasticized PVC bag: 1 week
- PO bag: 4 days

- Calendering of Processing of PVC
  - DEHP: 55 phr, ESO: 5 phr, stabilizer: 2~5 phr
  - 35 ~ 40 % DEHP (small molecules)
  - Migration of DEHP to blood
  - So many of metabolites ➡ Toxic !!
  - HCl, Phthalic acid, DBP etc

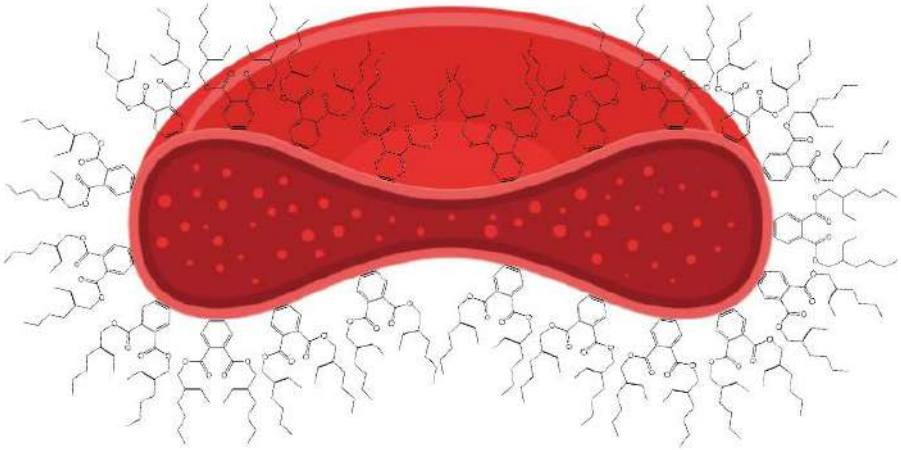


Red Blood Cell





DEHP



- In terms of preservation, DEHP (DOP) plasticized-PVC might be more biocompatibie with polyolefin bag

Solution Bag:

1. Bottle
2. PVC Bag: ~1980
3. PO Bag: ~2000 ~ present
4. Non-DEHP PVC Bag (6 kind of plasticizers

PO Bag


MEDIPHARMAPLAN
CATEGORY OF PRODUCTS by MPP
READYMADE NON-PVC(PP) IV BAGS SPECIFICATIONS
CLOSURE & CAPS(PORT CAPS)
OVERWRAPPING BAG/POUCH
HOT PRINTING TRANSFER FOIL/FILM
ENGINEERING & PLANT


롯데
설레임
밀크쉐이크
MILK SHAKE

Ringer bag; Contaminations (I)

Ringer bag; Contaminations (II)

In terms of Cost: Biocompatibility

IV Set & Nutrition Access Line:

1. PO set: ~1 USD/ea
2. Non-DEHP PVC set: ~1 USD/Dz

Cryo Bag for the preservation of UBCMSC

- In -198°C for more 15 years
- Polyolefin bag

Salary, Labor Costs

1. Korea: 1,800USD/month
2. China: ~800 USD/month
3. Vietnam: ~400 USD/month
4. Philliphines: ~200~300 USD/month
5. North Korea: 40 USD/month

↓

Cheap Labors

↓

Sanitation Problems

2. Silicone for Artificial Breast

Korean Actor
As Transgender:
Risu Ha


이희진


윤은혜


이지혜


조여정

Main Actress, Miss Cho, of “Parasite” which wins best picture at OSCAR2020

인공 엉덩이
Artificial Hip

인공 가슴
Artificial Breast:
Crosslinked silicone

!!BIOCOMPATIBILITY!!

1985~1990: Droplet of oligomeric silicone (Dow Corning Co) were found in knee cartilage in some woman

All implants were retrieved with 200,000 ~ 700 USD of compensation

Cohesive Gel:
Crosslinked Silicone gel

Dow Corning Co:
Chapter 11

2017. Jan 17, SBS 뉴스

실리콘 보형물 파열 후 실리콘이 유선을 타고 유출되어 아기가 모유를 먹었음

			(mg/kg)	(㎍/kgbw/day)
1	Al	알루미늄	0.032	0.017
2	Pb	납	< 0.001	0.001
3	Cr	크롬	0.017	0.009
4	Co	코발트	< 0.001	0.001
5	Ni	니켈	0.009	0.005
6	Cu	구리	0.001	0.001
7	Ba	바륨	0.005	0.003
8	Hg	수은	< 0.001	0.001
9	Fe	철	0.165	0.090
10	Mn	망간	0.002	0.001
11	Zn	아연	0.038	0.021
12	Ca	칼슘	0.354	0.193

After the textured surface treatment of silicone surface in order to improve to adhere with host tissue

Allergan, BIOCELL, Natrelle, 110,000 ea/10 yrs

BIA-ALCL (Anaplastic Large Cell Lymphoma):
Seroma, irritation, Swelling, etc

프랑스, 공업용 유방 보형물 공포

전 세계 65개국 30만 명 시술
1명 숨지고 8명 암·림프종 투병
정부서 무료 제거 수술 나서

프랑스 니스의 한 병원에서 성형외과 의사가 26일(현지시간) 폴리 앵플랑 프로테즈(PIP)의 유방 보형물을 들고 있다. [니스 로이터=뉴시스]

"일어나서 잠들 때까지 불안해요. 몸에 시한폭탄을 달고 사는 기분입니다."

'공업용 유방 보형물'로 가슴 수술을 받은 프랑스 노르망디 출신 47세 여성의 걱정이다. 월급 150만원을 쪼개 모은 돈으로 40대 들어 간신히 수술을 받았건만 기쁨은 잠깐이었다. 우울증까지 도졌다. 수술 전의 극심한 몸매 콤플렉스가 수술 후엔 부작용 걱정으로 바뀐 것이다.

공업용 보형물 파문은 일파만파로 번지고 있다. 프랑스 폴리 앵플랑 프로테즈(PIP)는 보형물 제작단가를 낮추기 위해 의료용에 비해 가격이 3분의 1에 지나지 않는 공업용 실리콘젤을 사용했다. 이 사실이 알려지면서 해당 제품으로 수술받은 전 세계 여성 30만 명이 공포에 떨고 있다. 26일(현지시간) 네덜란드 보건부가 "PIP 보형물이 'M-임플란트'란 상표로 네덜란드 여성 1000여 명에게 판매됐다"고 밝혀 피해 여성은 더 늘어날 전망이다. PIP는 세계 3위의 유방 보형물 업체였다. 연간 10만 개를 생산해 이 중 84%를 유럽·라틴아메리카 등 세계 65개국에 팔았다. 이 보형물은 한때 자연스러운 모양으로 인기를 끌었다.

하지만 지금은 부작용의 폭풍이 거세다. 1000여 명이 파열을 겪었고 지난 11월엔 마르세유에 살던 여성 1명이 그 후유증으로 목숨을 잃었다. 이외에도 프랑스에서만 8명이 유방암·림프종·백혈병을 앓고 있다. 프랑스 보건당국은 "보형물과 암 사이의 연관성은 아직까지 알려지지 않았다"고 밝혔다. 하지만 조만간 PIP 임직원 4~6명에 대해 사기 및 기만 혐의로 형사고발할 것이라고 발표하는 등 과장을 줄이는 데 부심하고 있다. 1996년부터 수십 건의 소송을 당한 PIP는 지난해 3월 안전성과 기능 이상 문제로 리콜 파문을 겪은 이후 파산했다. 책임을 떠안을 주체가 없어지다시피 한 것이다.

결국 프랑스 정부가 나섰다. 자비에 베르트랑 프랑스 보건부 장관은 지난 23일 "문제 보형물을 이식한 여성 전원에게 제거 수술을 권고하고 비용 전액을 건강보험에서 부담하기로 했다"고 발표했다.

아르헨티나·브라질 등 남미에서도 무료 재수술을 요구하는 집단소송이 시작됐다. 특히 베네수엘라의 경우 부모가 딸의 15세 생일 기념 선물로 수술을 해주는 등 유방 수술이 보편화돼 있어 문제가 더욱 커질 것으로 보인다. 아랍에미리트 보건당국도 위험성을 경고했다. 이스라엘도 피해 여성을 위한 핫라인을 개설하는 등 관련 조치에 나섰다.

한편 한국 식품의약품안전청은 "프랑스 PIP의 보형물은 수입허가를 내준 적이 없다"고 밝혔다. 국내 유통 중인 실리콘젤 인공유방은 모두 미국 앨리건·멘토 제품이다.

민경원·정종훈 기자 storymin@joongang.co.kr

Industrial silicone for AB

3. Soft Contact Lenz

Otto Wichterle: Extended Soft Contact Lenz

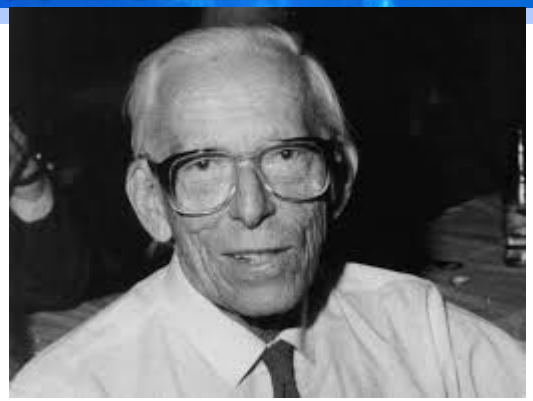
Crosslinked PHEMA: 38% wc

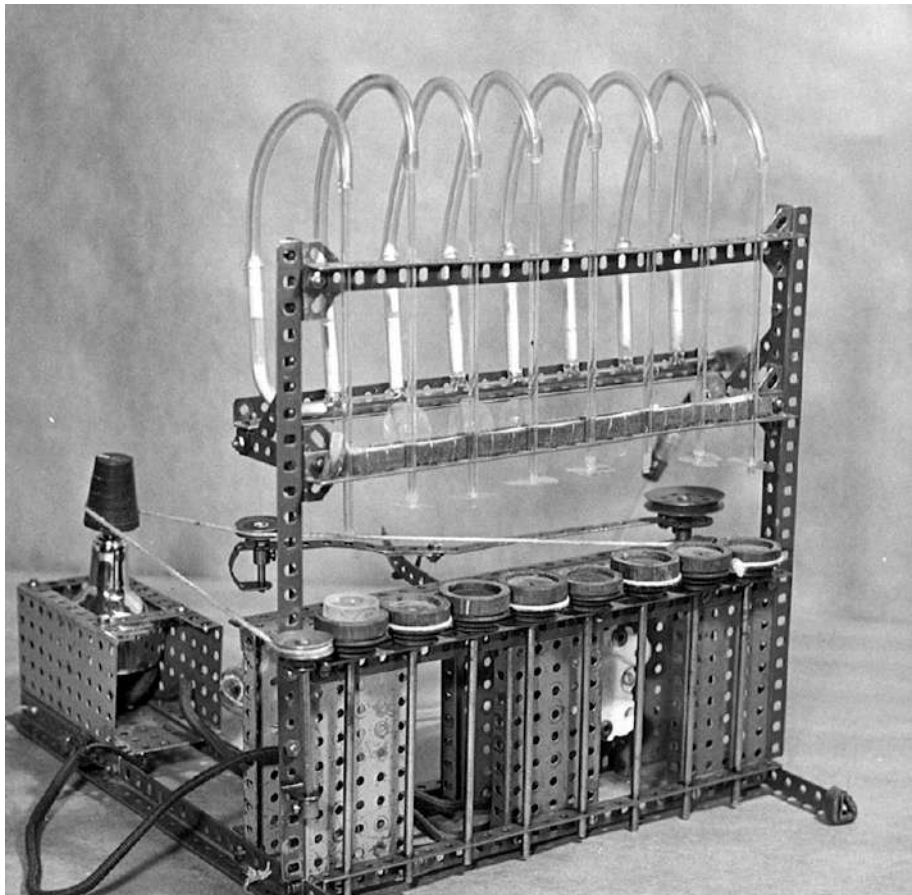
XL MMA/NVP copolymers: 78 wc

O_2 permeable

Bausch-Lomb

Spin Casting/Lathe Cut





Otto Wichterle, 1963-1968

Czech patents

- 1963 *Method of making colour and similar effects in the bulk mass of hydrogel products especially in contact lenses*
- 1965 *Method of manufacture of coloured contact lenses and eye prostheses*
- 1968 *Method of making colour effects on hydrogel contact lenses and eye prostheses*

Contact Lenz with 27 layers (2017.07.16)

백내장 수술 하러 온 할머니 눈에서 발견된 '렌즈 27겹'

김나영 기자

2017.07.16 17:53

Rupal Morjaria

[인사이트] 김나영 기자 = 백내장 수술을 하러 온 할머니의 눈에서 겹겹이 쌓인 콘택트렌즈 더미가 발견돼 충격을 주고 있다.

지난 15일(현지 시간) 영국 일간 메트로는 말라붙은 '렌즈 27겹'을 눈에 끼고 살아온 67세 할머니의 사연을 전했다.

영국 버밍엄주 솔리헐(Solihull)에 거주하는 익명의 할머니는 앞이 잘 보이지 않고, 눈에 이물감이 계속 느껴져 근처 안과를 찾았다.

당시 병원에 온 할머니는 "노안이나 백내장 때문에 눈이 불편한 것 같다"며 수술을 하고싶다는 의사를 전했다.

이에 백내장 수술을 하기 위해 눈 검사를 실시하던 의사 루팔 모르자리아(Rupal Morjaria)는 할머니의 눈에서 발견된 정체 모를 이물질에 경악을 금치 못했다.

Rupal Morjaria

조사 결과 할머니의 눈에서 발견된 '푸른 빛깔' 덩어리는 말라붙어 겹겹이 쌓인 콘택트렌즈였다.

덩어리를 분리하자 총 '17장'의 렌즈가 나왔으며 이외에도 할머니의 눈에서는 계속해서 10장의 렌즈가 더 발견됐다.

루팔은 "총 27겹의 렌즈 더미를 눈에 끼고 있었다는 사실이 정말 놀랍다"며 "피로감과 이물감이 엄청났을 텐데 어떻게 이걸 모르고 살 수 있었는지 의문이다"라고 신기해했다.

렌즈를 제거하고 한 2주 뒤쯤 할머니는 "눈이 한결 편안해지고 모든 것이 또렷하게 보이기 시작했다"며 만족감을 드러냈다고 알려졌다.

한편 할머니는 약 35년간 꾸준히 1개월 용 렌즈를 착용해 왔으며 최근 들어 노안 때문에 눈이 불편한 것이라고만 생각해 병원을 찾지 않았다고 한다.

김나영 기자 nayoung@insight.co.kr

인사이트 뉴스 2017.07.16

인사이트 뉴스 2017.07.16

4. Filler

Side effects of filler(I)

Side effects of filler(II) 필러 부작용 (II)

Side effects of filler(III) 필러 부작용 (III)

5. Total Hip Arthroplasty

Sir John Charnley:
인공 고관절
Total Hip Arthroplasty

Sir John Charnley

- The "Father of Modern Total Hip Replacement"
- Contributions:
  - "Low-friction arthroplasty," where a metal head articulates against a plastic socket
  - Introduced PMMA bone cement for fixation
  - Introduced high-density polyethylene as a bearing surface
  - Many advances in biomaterials, surface replacement, biomechanics, operating techniques and operating instruments
- Knighted in 1977 by Queen Elizabeth

SIR JOHN CHARNLEY
(1911-1982)

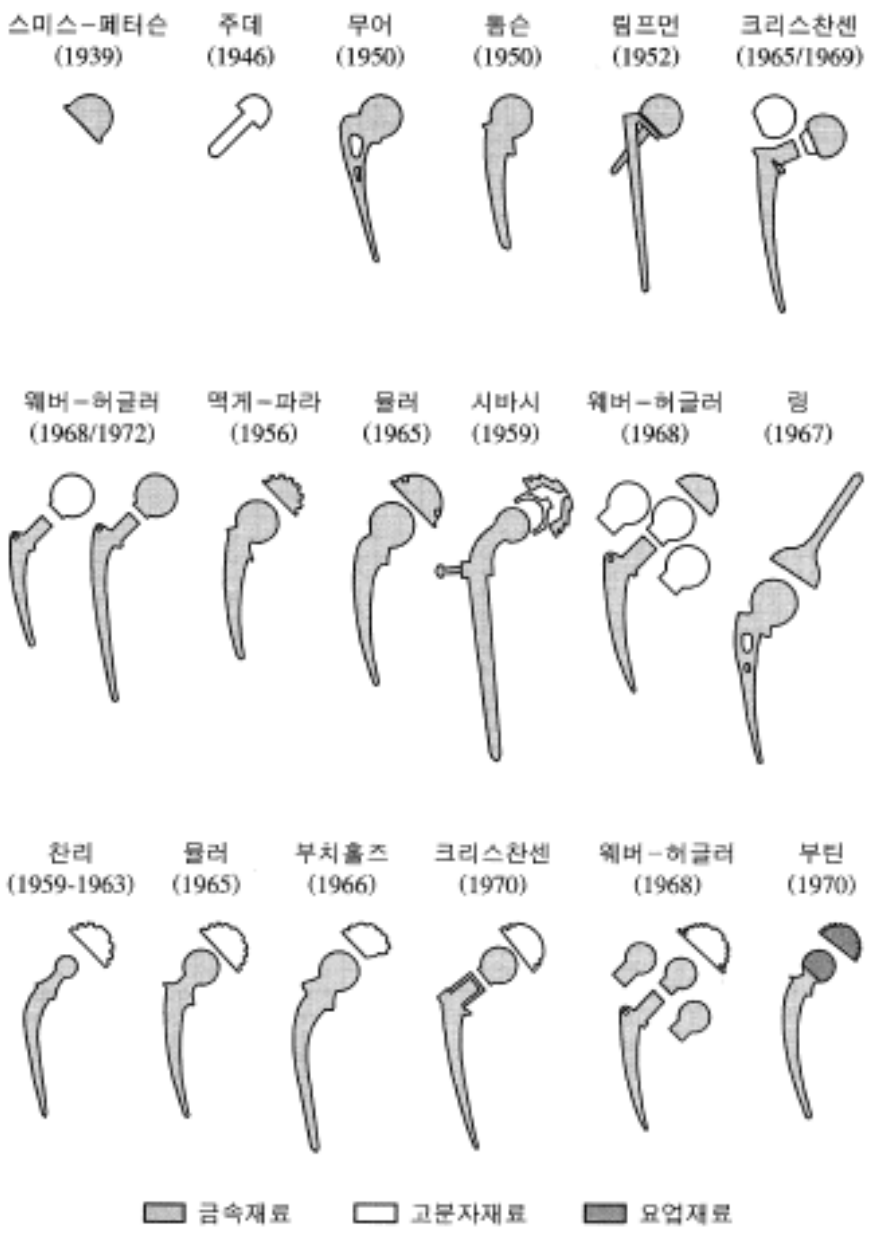
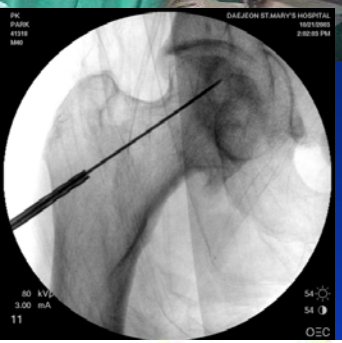


그림 14. UHMWPE의 관골구와 Co-Cr-Mo 합금의 대퇴골두 스템으로 이루어진 인공고관절의 발전역사(이들의 체내에 고정시 PMMA 베시멘트가 사용된다)



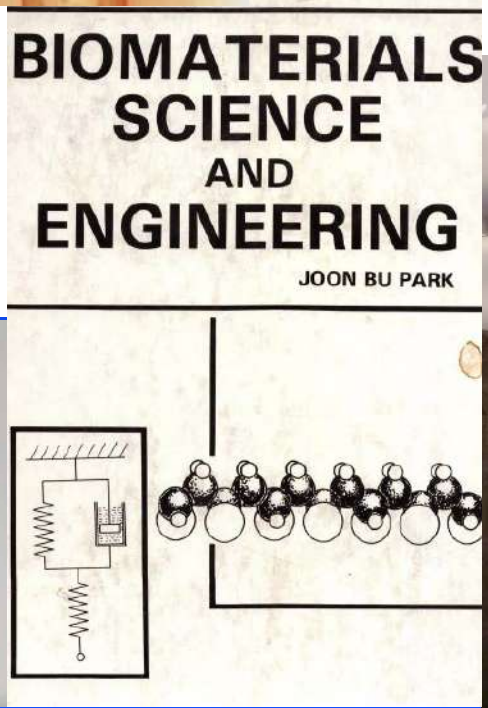
Engineering: The simpler, The better!!!

Original Article | Clinics in Orthopedic Surgery 2013;5:110-117 • http://dx.doi.org/10.4055/cios.2013.5.2.110

Fifteen-year Results of Precoated Femoral Stem in Primary Hybrid Total Hip Arthroplasty

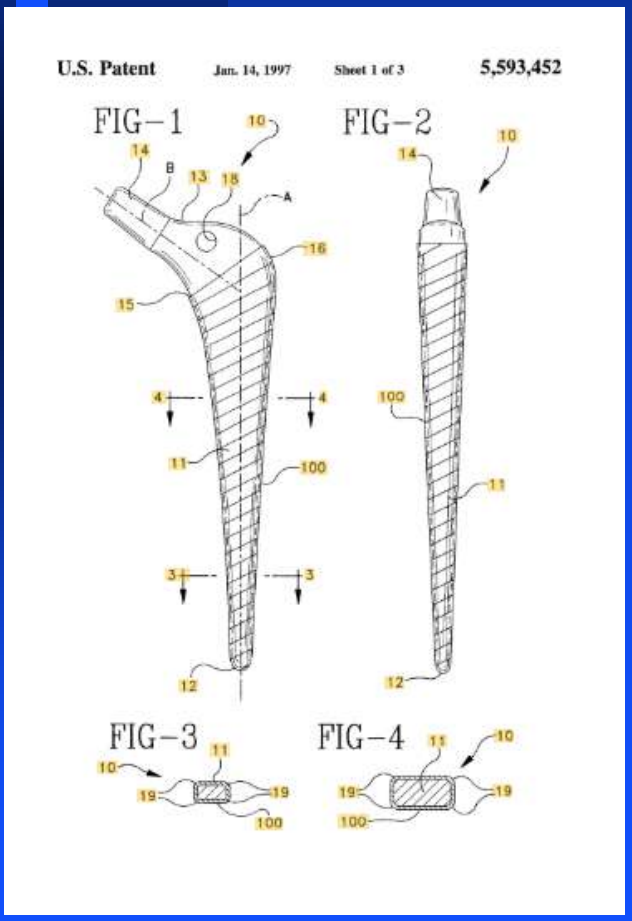
Dong Hun Suh, MD, Ho Hyun Yun, MD*, Sung Kwang Chun, MD†, Won Yong Shon, MD†

Department of Orthopaedic Surgery, Korea University Ansan Hospital, Ansan,
†Department of Orthopaedic Surgery, Seoul Veterans Hospital, Seoul,

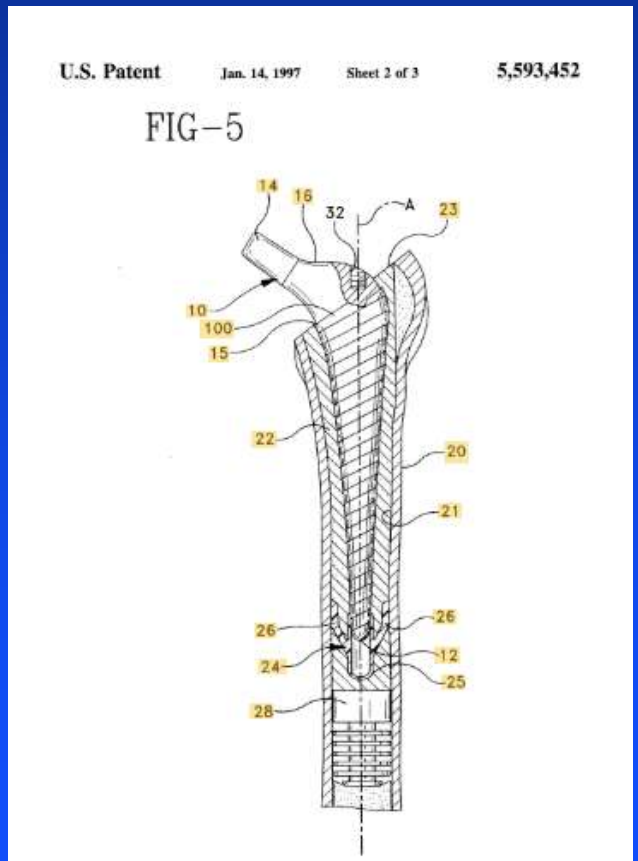


Biocompatibility in terms of Loosening of THA

- Physical property of PMMA bone cement
- Pore formation on PMMA bone cement
- Shrinkage of PMMA during polymerization
- Lack of good cement distribution around implant
- Interface between PMMA and metal surface



Bone Cement Precoated Implants



U.S. Patent Dec. 28, 1982 4,365,359

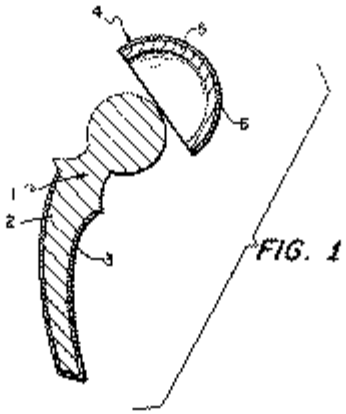


FIG. 1

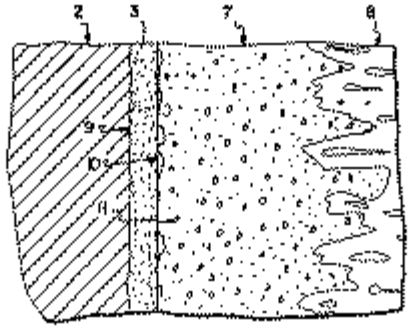
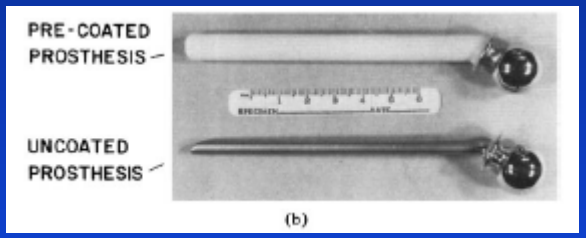
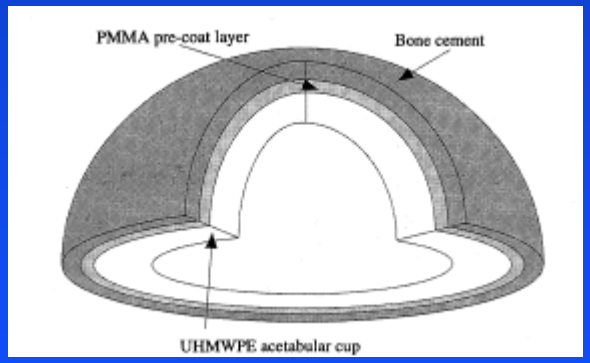


FIG. 2



(b)

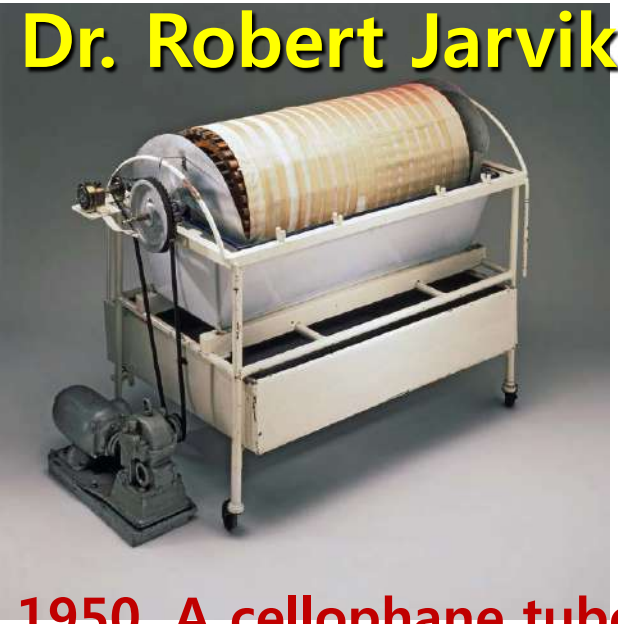


6. Artificial Kidney and Vascular Graft

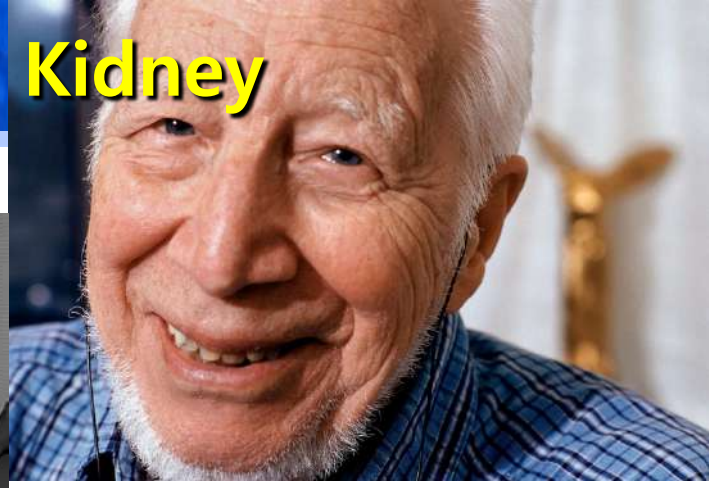
Willem J Kolff MD, PhD: Artificial Kidney

Farther of Artificial Organ

Dr. Robert Jarvik



1950, A cellophane tube
in salt bath
at Cleveland Clinic

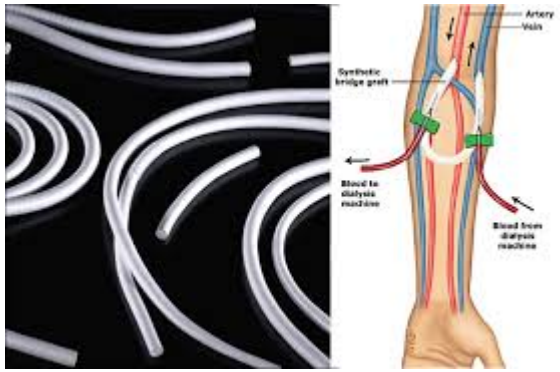


William DeVries
MD PhD

Jarvik-5; cow (1981)
Jarvik-7: human trial (1982)
Barney Clark at Univ Utah

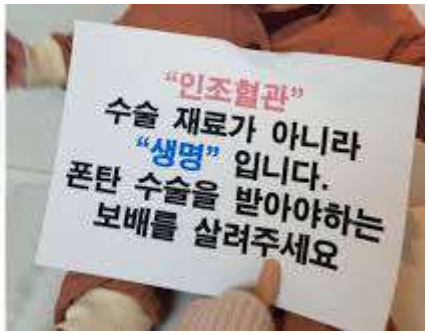
Michael E. DeBakey MD

Artificial Vascular Graft: 인공 혈관: Artificial Heart
한국동란: 낙하산: Vynion: 튜브형태



Polyester

Gore Tex



Requirements of Biomaterials

BIOCOMPATIBILITY

I. Biochemical Property: Nontoxic, Noncarcinogenic, Blood compatibility, Tissue/Cell compatibility, etc

II. Chemical Property: Non-leachable, Safety, etc

III. Physical/Mechanical Property: Transparent, Flexibility, Durability, Anti-creep. etc

IV. Sterilizability: Heat-resist, Anti-aging, etc

V. Processablity: Injection, Calendaring, Extrusion, etc

VI. GMP: Cheap, etc

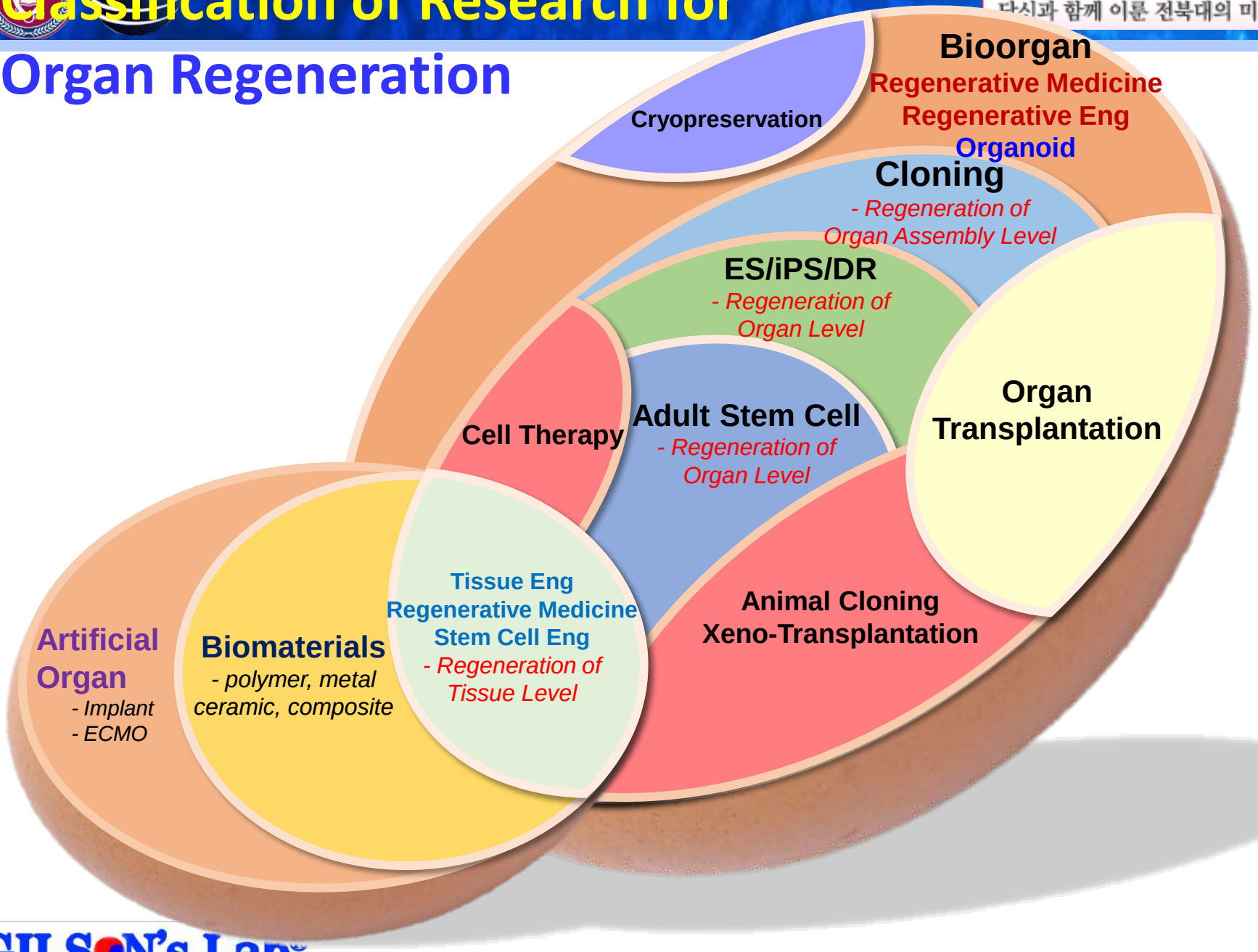
Surface Treatment

- It is recognized that the behavior of the adhesion and proliferation of different types cells and tissue on polymeric materials depend on the surface characteristics such as wettability (hydrophilicity /hydrophobicity or surface free energy), chemistry, charge, roughness, and rigidity.
- A large number of research groups have studied the interactions of different types of cultured cells with various polymers with different wettabilities to correlate the relationship between surface wettability and blood-, cell-, or tissue-compatibility.
- One problem derived from the study using different kinds of polymers is that the surfaces are heterogeneous both chemically and physically (different surface chemistry, roughness, rigidity, crystallinity, etc.), which may result in considerable variation.

표면개질:Surface Modification

1. **Physical coating:** Solv, LB, additives, parylene
2. **Covalent coating;** graft, γ-ray, EB, plasma
3. **Vapor deposition:** Ion beam, CVD, flame
4. **Chemical grafting rxn:** ozonization
5. **Silanization**
6. **Biomolecule immobilization**
7. **Physical treatment:** EB etching, EB implat'n, plasma etching, corona deposit'n, ion exchange, UV
8. **Chemical Treatment:** Oxidation, Fucntioal group rxn, additional rxn

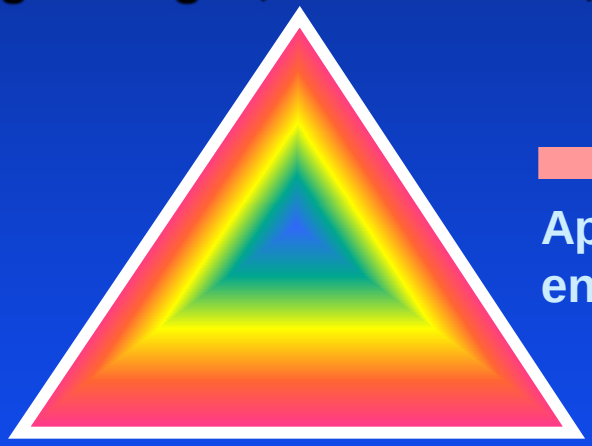
Classification of Research for Organ Regeneration



Tissue Engineering **is an interdisciplinary field that applies the principles of the engineering and the life sciences toward the development of biological substitutes that restore, maintain, or improve tissue functions.**

2D ➡ 3D culture

Scaffolds
(eg. Collagen, bone mineral, synthetics)



Time

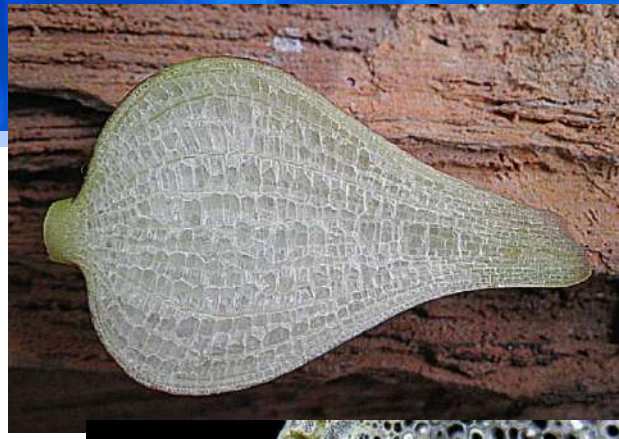
Appropriate environment

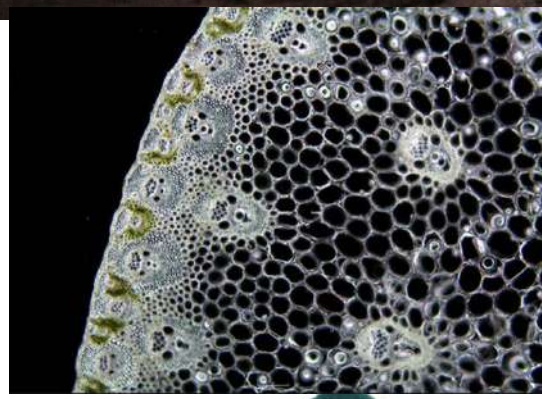
Regeneration of tissues/organ

Cells
(eg. Osteoblasts, fibroblasts, chondrocytes, and so on)

Signaling molecules
(eg. Growth factors, morphogens, adhesins)

➡**Tissue engineering generally combines 3 key elements: scaffolds (matrics), signaling molecules (growth factors), and cells. By combining these elements, tissue regeneration can often be accomplished.**



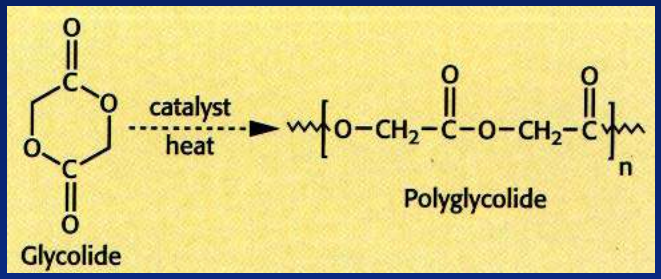


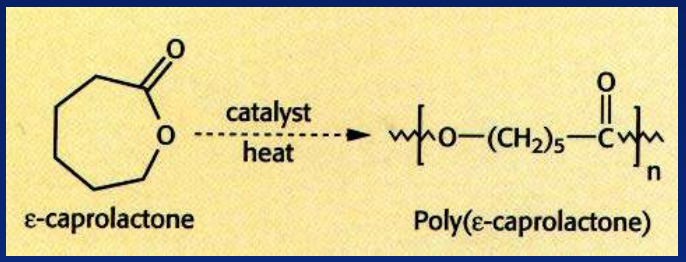
Joseph Vacanti, MGH

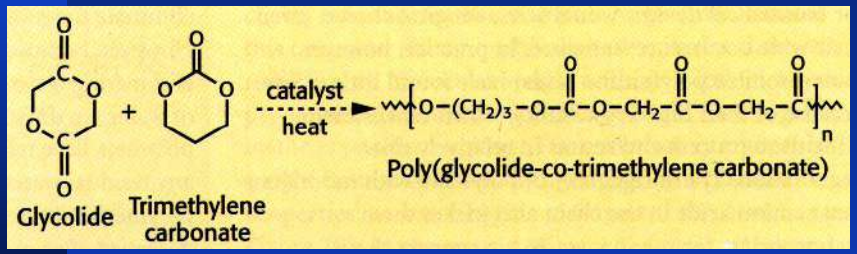
Robert Langer, MIT

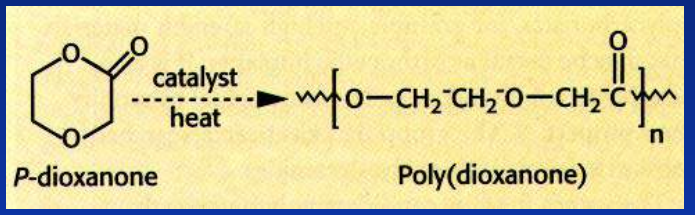
BiodegradablePolymers for Tissue Engineering

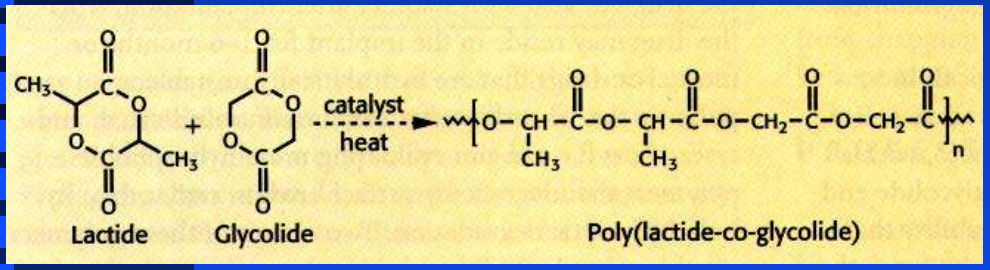
- Poly(α-hydroxyesters): PGA, PLA, PLGA
- Poly(ε-caprolactone)
- Poly(ortho esters)
- Polyanhydrides
- Poly(3-hydroxybutyrate): PHB, PHV, PHBV
- Polyphosphagenes
- Poly(propylene fumarate)
- Sodium alginates
- Collagen, etc.

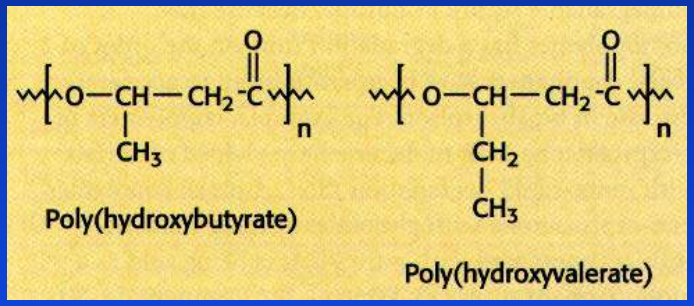

catalyst
heat
Glycolide
Polyglycolide

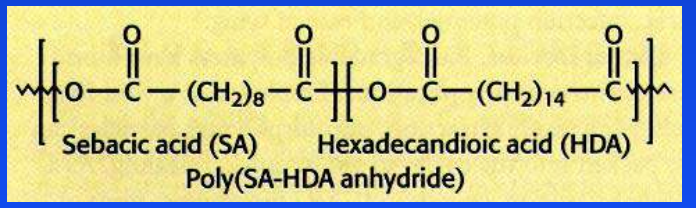

catalyst
heat
ε-caprolactone
Poly(ε-caprolactone)

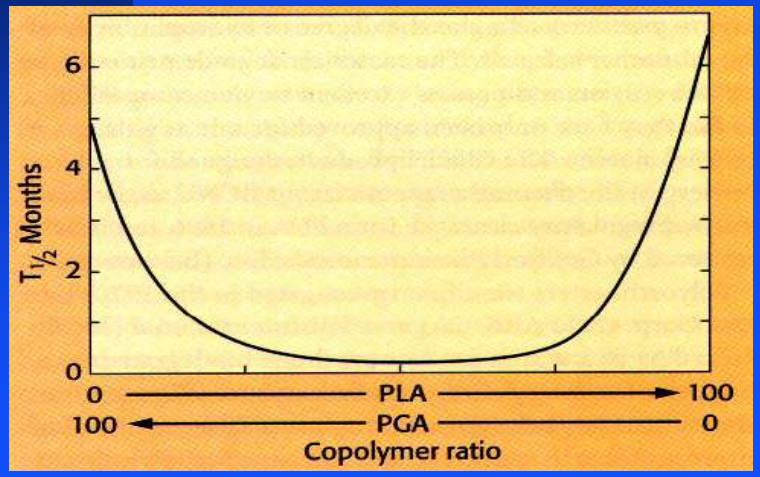

catalyst
heat
Glycolide
Trimethylene carbonate
Poly(glycolide-co-trimethylene carbonate)

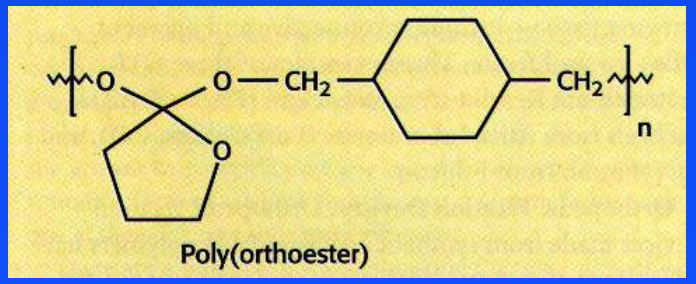

catalyst
heat
P-dioxanone
Poly(dioxanone)


catalyst
heat
Lactide
Glycolide
Poly(lactide-co-glycolide)

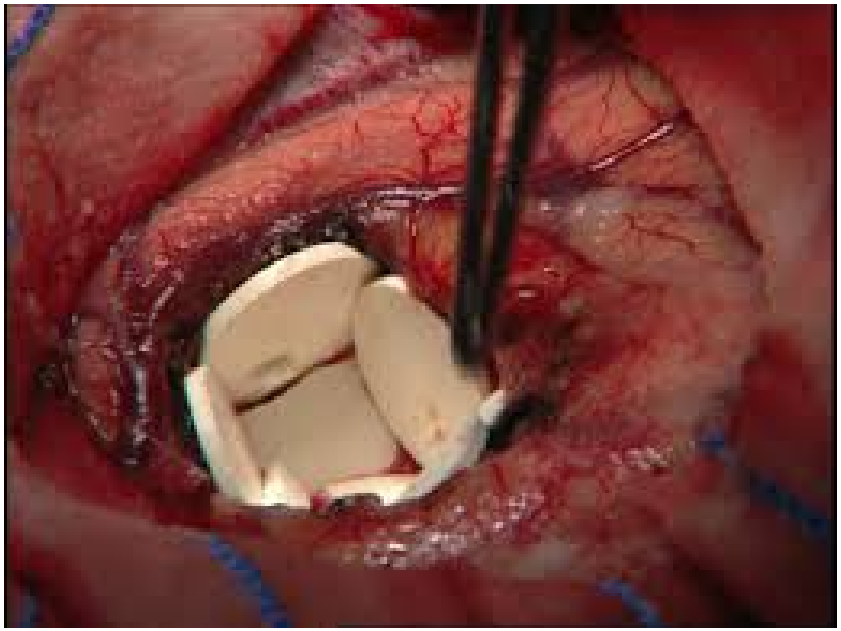

Poly(hydroxybutyrate)
Poly(hydroxyvalerate)

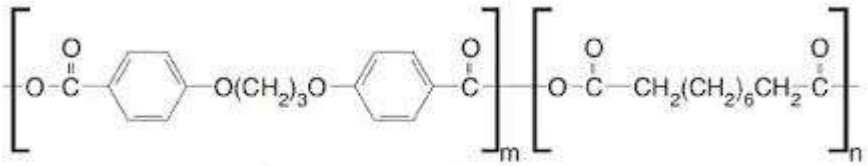

Sebacic acid (SA)
Hexadecandioic acid (HDA)
Poly(SA-HDA anhydride)

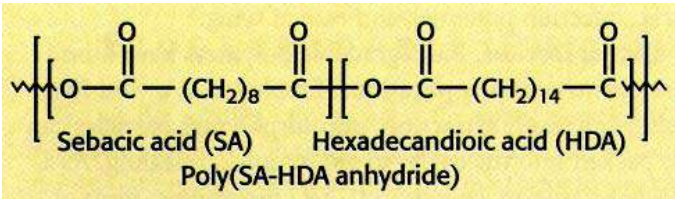

T½ Months
6
4
2
0
0
PLA
100
100
PGA
0
Copolymer ratio


Poly(orthoester)

Gliadel Wafer







Tissue Engineering

Robert Langer* and Joseph P. Vacanti

The loss or failure of an organ or tissue is one of the most frequent, devastating, and costly problems in human health care. A new field, tissue engineering, applies the principles of biology and engineering to the development of functional substitutes for damaged tissue. This article discusses the foundations and challenges of this interdisciplinary field and its attempts to provide solutions to tissue creation and repair.

Every year, millions of Americans suffer tissue loss or end-stage organ failure (Table 1). The total national health care cost for these patients exceeds $400 billion per year (*1*, *2*). Approximately 8 million surgical procedures are performed annually in the United States to treat these disorders and 40 to 90 million hospital days are required (*2*). Physicians treat organ or tissue loss by transplanting organs from one individual into another, performing surgical recon-

tial limitations include failure of the infused cells to maintain their function in the recipient, and immunological rejection.

2) Tissue-inducing substances. The success of this approach depends on the purification and large-scale production of appropriate signal molecules, such as growth factors, and, in many cases, the development of methods to deliver these molecules to their targets.

3) Cells placed on or within matrices,

their continuous productio
and cathecholamines they
lieve chronic intractable p

Nerve regeneration has
Peripheral nerves are capab
after transection injury. T
can sometimes be clinically
to-end approximation of
fine sutures. When nerve
gaps that are too wide for
gous nerve grafts are used
thetic nerve guides (condu
these cases by protecting
nerve from infiltrating sca
recting new axons toward
eral laboratories have show
els that synthetic guides co
polymers (laminin, collag
sulfate) or synthetic polym

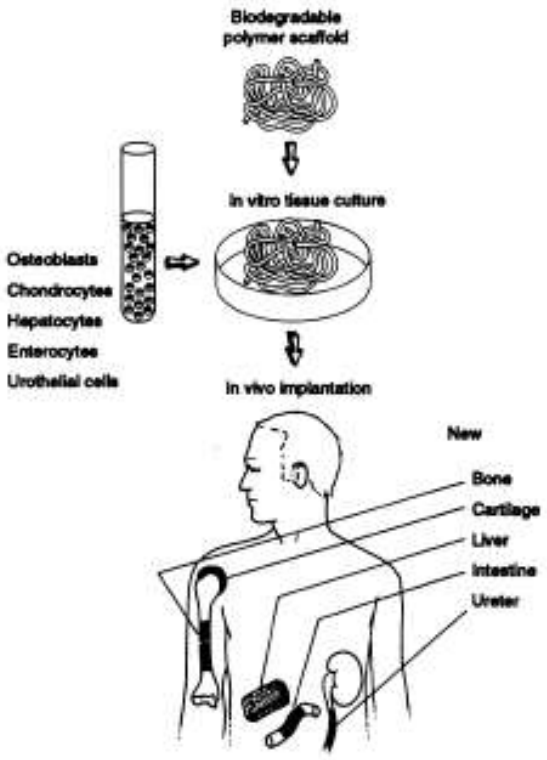


Fig. 2. In one approach to open-system implants, three-dimensional highly porous scaffolds composed of synthetic polymers serve as cell transplant devices. These devices may facilitate formation of structural and functional tissue units by the transplanted cells. This approach is based on the following observations: (i) Every tissue undergoes remodeling. (ii) Isolated cells tend to reform the appropriate tissue structure under appropriate experimental conditions. For example, when capillary endothelial cells are placed on the proper substrate in vitro, they form tubular structures. (iii) Although isolated cells have the capacity to form the appropriate tissue structure, they do so only to a limited degree when placed as a suspension into tissue. Such cells begin without any intrinsic organization and have no template to guide restructuring. (iv) Tissue cannot be implanted in large volumes—cells will not survive if they are located more than a few hundred micrometers from the nearest capillary. Thus, the open-system implants are designed so that the polymer scaffold guides cell organization and growth and allows diffusion of nutrients to the transplanted cells (*32*). Ideally, the cell-polymer matrix is prevascularized or would become vascularized as the cell mass expands after implantation. Vascularization could be a natural host response to the implant or could be artificially induced by slow release of angiogenic factors. The polymer could be degradable or nondegradable. Materials that disappear from the body after they perform their function obviate concerns about long-term biocompatibility.

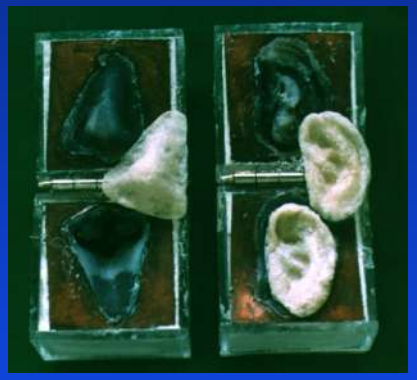
4. **Langer R, Vacanti JP.** Tissue engineering. *Science* 1993; 260: 920–6.

Fig. 1b Photograph of infamous mouse with the human ear, depicting new tissue-engineered cartilage generated in the shape of a human ear.

1. Carving by Gypsum

2. Fabrication of Silicon Mold

3. Scaffolds by PGA nonwoven



4. Molding for ear and nose

5. Isolation of chondrocyte from rabbit ear

6. Seeding of chondrocyte on PGA scaffold

7. Implant of tissue engineered nose and ear on the back of nude mice

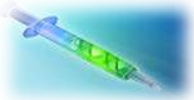
1996

Approved Regenerative Medicine Products

Canada	Europe	Japan	Japan	Europe	USA	USA
Allogeneic BM Derived MSC	First Stem Cell Therapy In EU	Allogeneic BM Derived MSC	Self musculi skeleti Derived Cell sheet	autologous CD34+	autologous CD19 CAR-T	CD19-gene-modified autologous T cells
Acute GvHD	Severe Limbal Stem Cell Deficiency	Aucte GVHD	Massive heart failure	severe combined immunodeficiency	B cell acute lymphoblastic leukemia	corpulency B cell lymphoma
Osiris	Chiesi	TEMCELL® HS (JCR)	HeartSheet (Terumo)	Strimvelis (GSK)	Kymriah™ (Novartis)	Yescarta™ (Kite Pharma)





Tissue-based Product


initial approved in Europe

First CAR-T cell medicine

2011.7 2012.1 2012.5 2014.7 2015.2 2015.09 2016.06 2017.7 2017.8 2017.10

2011 2012 2013 2014 2015 2016 Korea's first Gene medicine 2018

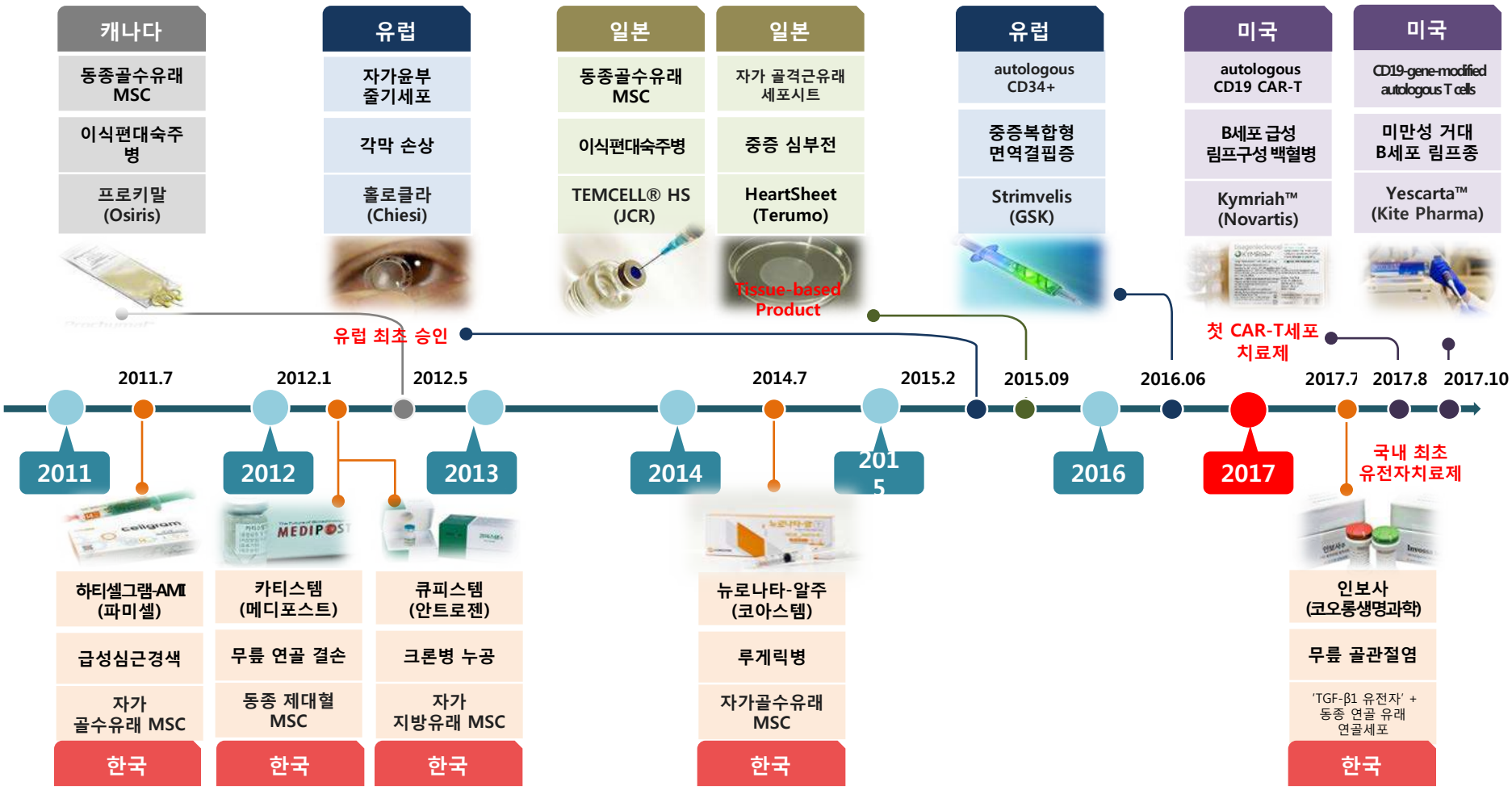




Pharmicell	Medipost	Anterogen	Corestem	Invossa
AMI	Cartilage Injury	Anal Fistula Crohn's Disease	Lou Gehrig's Disease	Cartilage Injury
Autologous BM Derived MSC	Allogeneic Umbilical Cord Boold Derived MSC	Autologous Adipose MSC	Aurologous BM Derived MSC	'TGF-β1 gene' + homogenous Cartilage Derived Chondrocyte
Korea	Korea	Korea	Kore	Korea

※ Reference : MFDS, EMA, MHLW Homepage & GSRAC processing

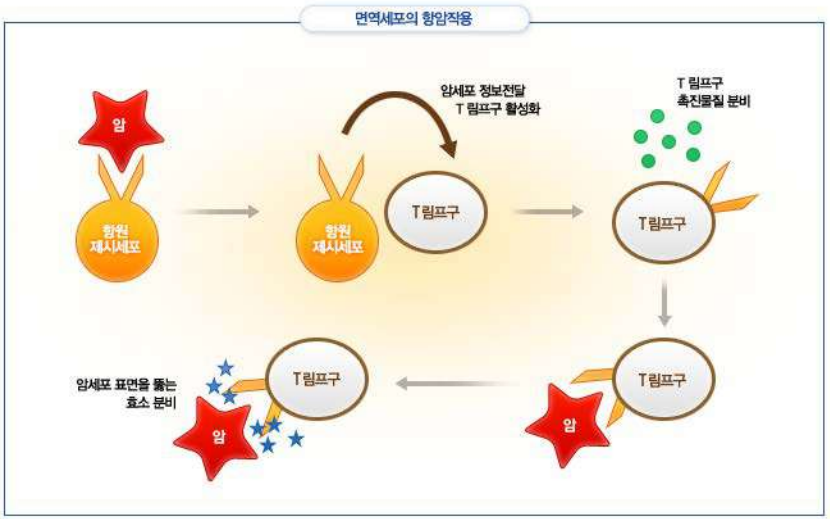
Approved Regenerative Medicine Products

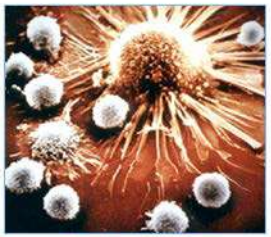


※ 출처 : MFDS, EMA, MHLW 홈페이지 & GSRAC 가공

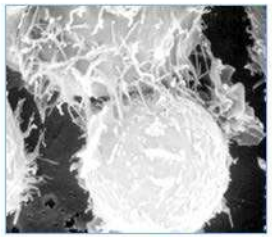
7. Autologous Activated Lymphocyte for Hepatic Cancer

- **Immuncell-LC, Green Cross Cell, 2007. August** (Originally developed by Innocell, Co.)
- CIK: cytokine-induced killer cell
- CTL, activated Tc cell

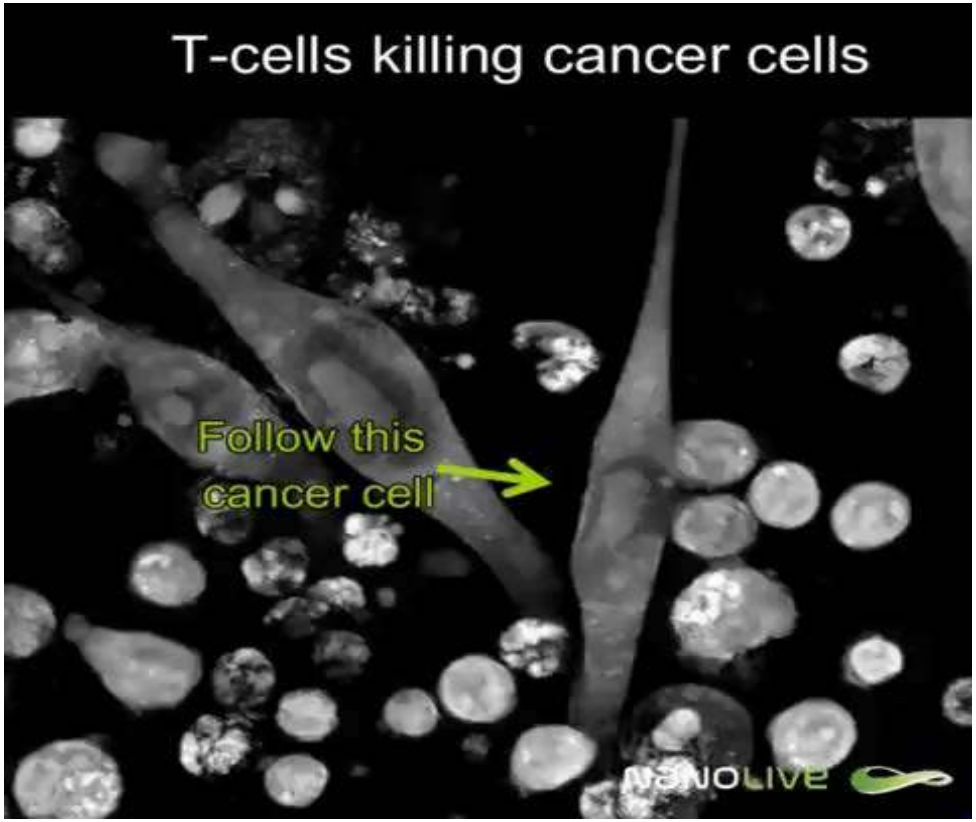




암세포로 몰려드는 면역세포



암세포에 구멍을 뚫는 효소를 방출하여 암세포 사멸시킴



Bringing CAR-T (chimeric antigen receptor) Cell Therapy to Patients

Joseph Jimenez,
Former Chief Executive Officer of Novartis, 2010 -2018

"I look at [CAR-T cell therapy] and think about the potential breakthrough that it could be. You could be looking at a transformation of the treatment of cancer."

Aug 2012 : Novarties entris collaboration with the University of Pensylvenia

April 2013 : Initial from first two patresults ients treated at the Children's Hospital of Pennsylvenia(CHOP) published in the *New England Journal of Medicine*

July 2014 : US Food & Drug Administration (FDA) designates CTL019 as Breakthrough Therapy in (r/r) adult and pediatric acute lymphoblastic leukemia(ALL)

Oct 2014 : Results from single-center trial led by CHOP published in *the New England Journal of Medicine*

Feb 2015 : FDA accepts Novartis Investigational New Drug (IND)Application for CTL019

June 2016 : European Medicines Agency PRIonty Medicines(PRIE) designation for CTL019 in r/r pediatric ALL

April 2017 : FDA grants CTL019 Breakthrough Therapy designation in r/r diffuse large b-cell lymphoma(DLBCL)

March 2017 : Novartis BLA for CTL019 in r/r ALL accepted by the FDA for Priority Review

Feb 2017 : Novartis submits Biologics Licensing Application (BLA) to FDA for CTL019 for pediatric/young adult r/r ALL

Dec 2016 : Novartis presents results from ELIANA, the first global trial of CTL019 in pediatric/young adult r/r ALL patients

June 2017 : Novartis presents interim results for CTL019 from JULIET study

June 2017 : Novartis presents 60month follow-up for CTL019 ELIANA study

July 2017 : US FDA Advisory Committee votes unanimous in favor of CTL09 approval

July 2017 : approves KYMRYAH (tisagenlecleucel formerly CTL019) for treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse

CAR-T Type	Cancer indication	Phase 1	Phase 2/ pivotal	Phase 3	Submitted	Approved
CD19 CAR-T	Pediatric & young adult r/r ALL[1]				EU	US
CD19 CAR-T	r/r DLBCL[2]				US/EU	
CD19 CAR-T	DLBCL in 1st relapse[2]			Starting 2018		
CD19 CAR-T	r/r FL[3]		Starting 2018			
CD19 CAR-T	r/r DLBCL[2] in combination with pembrolizumab	Starting 2018				
CD19 CAR-T	CLL[4]		Starting 2018			
CAR-T-BCMA	r/r Multiple Myeloma		Starting 2018			
CAR-T-EGFRvIII	Recurrent GBM[5]	Started				
CAR-T-Meso	Advanced ovarian cancer, Mesothelioma	Started				

8
years of clinical trial experience

235+*
patient years of experience

pALL FDA approval
5 weeks before PDUFA

manufactured CAR-T cells for
300+
In 11 countries

32
certified treatment centers

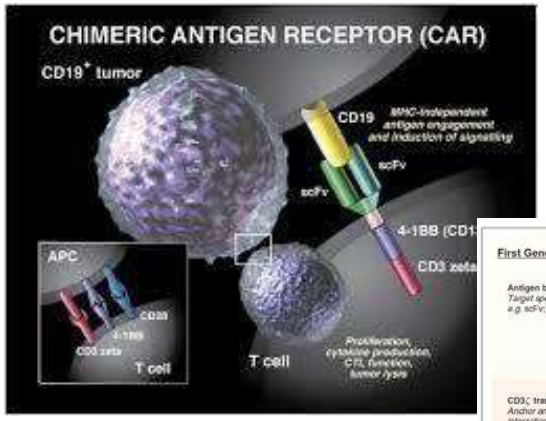
5
third-party collaborations to bring CTL019 to patients

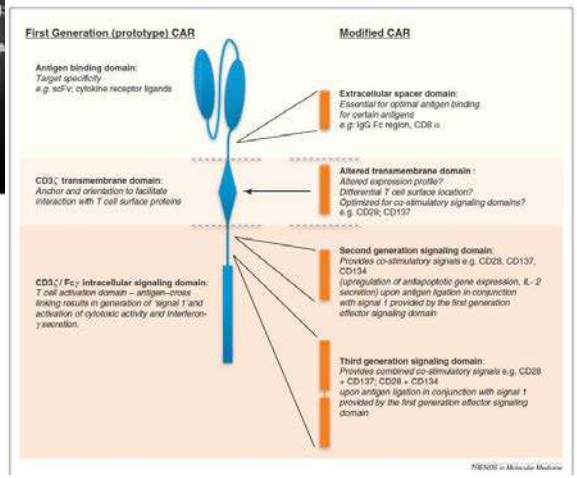
Penn Medicine
cryoport
Oxford BioMedica
Fraunhofer
ThermoFisher SCIENTIFIC

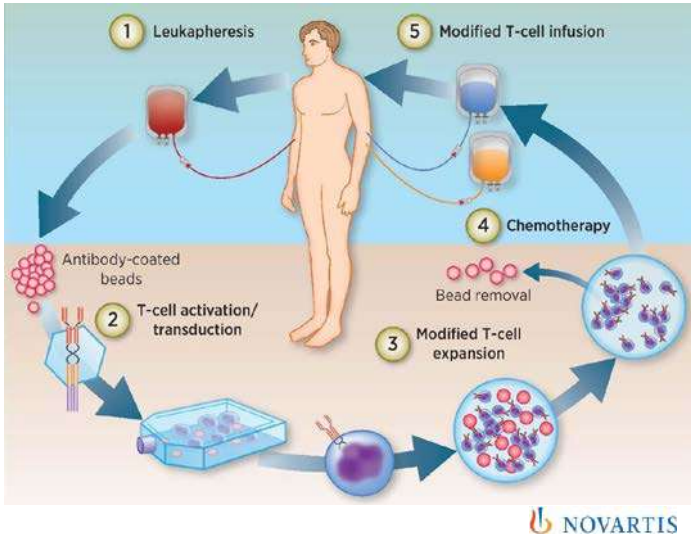
500+
employees supporting the product

CAR-T Cells to Treat Cancers

CAR-T cells: Chimeric antigen receptor-modified T cells





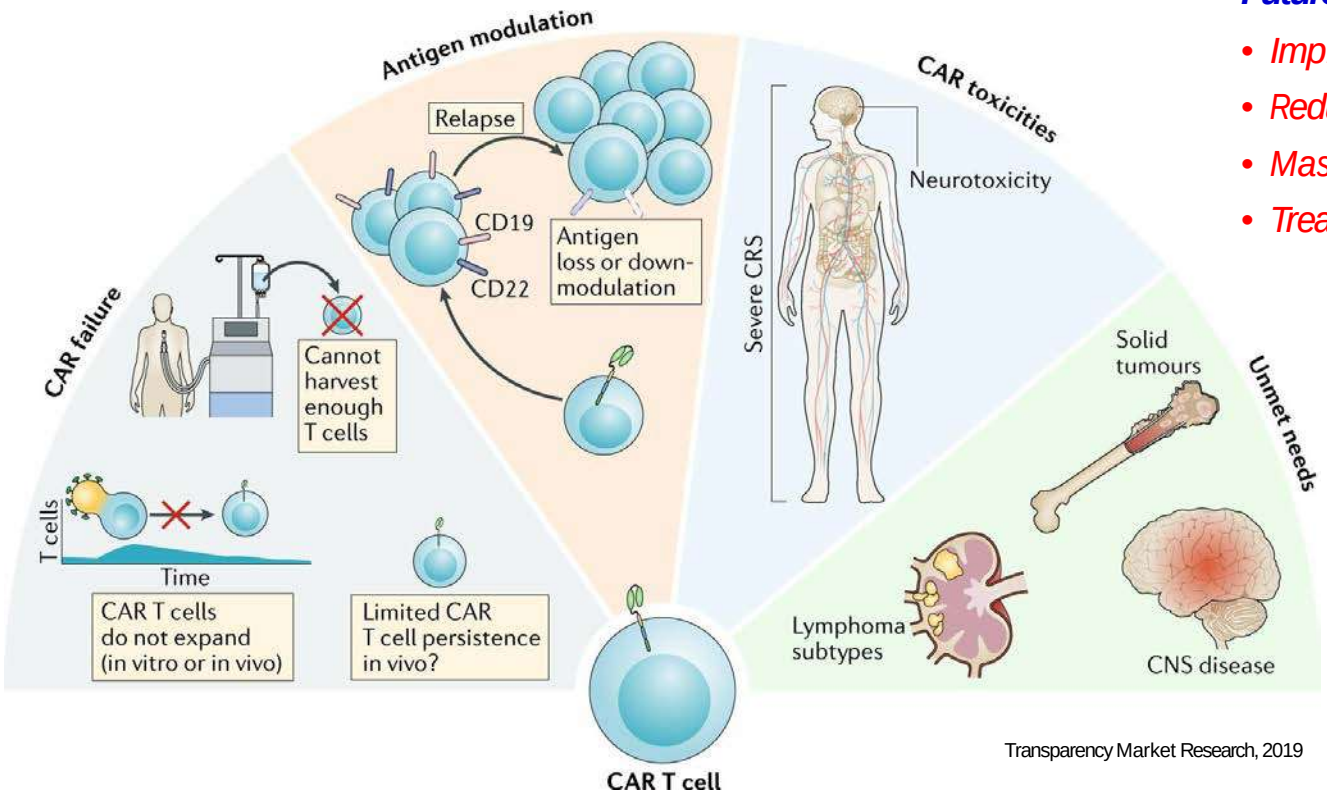


CAR-T innovation & Opening of the gene therapy era

Cade Hildreth, CEO of BioInformant (Jan. 2018)

Limitations in the Current CAR-T Therapy

Many technical hurdles are ahead



Transparency Market Research, 2019

Future goals

- *Improve activity & efficacy*
- *Reduce toxicity*
- *Mass production*
- *Treat solid tumors*

List of Gene Therapies(I)

	Trade name	Company	Characteristics	Cells	Indications	Year	Country
1	Gendicine	Shenzhen SiBiono GeneTech	Adenovirus expressing wt p53		Head and neck squamous cell carcinoma	2003. 10	China
2	RIGVIR	Rigvir Group	Oncolytic, live & non-pathogenic picornavirus (ECHO-7)		Melanoma	Latvia (2004. 04), Georgia, Armenia, Uzbekistan	
3	Oncorine (H101)	Shanghai Sunway Biotech	Oncolytic adenovirus w/o E1B55K and E3		Late stage refractory nasopharyngeal cancer (w/ chemotherapy)	2005. 11	China
4	Rexin-G (Orphan)	Epeius Biotech	Non-replicative MLV-based amphotrophic retrovirus expressing cryptic collagen binding motif and cytocial cyclin G1		All solid tumors	2007. 00	Philippines
5	Neovasculgen	Human Stem Cell Institute	pCMV-VEGF165		Peripheral arterial disease (Chronic limb ischemia)	2011. 12	Russia
	~~Glybera (Orphan)~~	~~Uniqure~~	~~AAV1 expressing human lipoprotein lipase (LPL)~~		~~LPL gene deficiency~~	~~2012. 10 (Withdrawn)~~	~~EU~~
6	Imlygic (T-VEC)	BioVex/Amgen	HSV1 expressing GM-CSF		Advanced melanoma	US(2015. 10), EU (2015. 12)	
7	Strimvelis (Orphan)	GSK	Autologous CD34+ cells expressing ADA gene	Yes	ADA-SCID	2016. 05	EU
8	Zalmoxis (Orphan)	Mol Med	Allogeneic Tcells expressing LNGFR& HSV-TK	Yes	Blood cancer (w/HSCT)	2016. 08	EU
	~~Invossa~~	~~Kolon Lifescience~~	~~Allogeneic chondrocytes w/ & w/o TGF-b1 expression~~	~~Yes~~	~~Osteoarthritis~~	~~2017. 07 (Cancelled)~~	~~KR~~

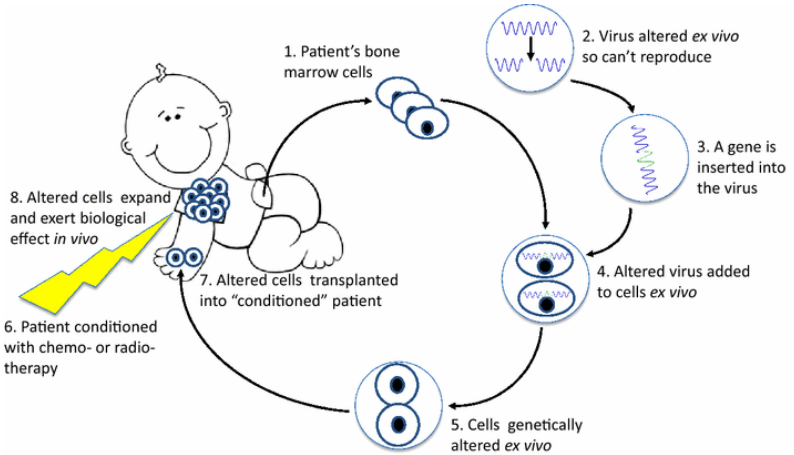
List of Gene Therapies(II)

	Tradename	Company	Characteristics	Cells	Target Disease	Year	Country
9	Kymriah	Novartis	Auto, CAR-T targeting CD19	Yes	ALL refractory or in second or later relapse	US(2017. 08), EU& Canada (2018. 09), Australia (2018. 12)	
					Refractory large B cell lymphoma (DLBCL)	US(2018. 05), EU& Canada (2018. 09), Australia (2018. 12)	
10	Yescarta	Kite Pharma/Gilard	Auto, CAR-T targeting CD19	Yes	Refractory large B cell lymphoma (DLBCL), Primary mediastinal large B cell lymphoma (PMBCL)	US(2017. 10), EU(2018. 08)	
11	Luxturna (Orphan)	Spark Therapeutics	AAV expressing hRPE65		Biallelic RPE65-deficient retinal dystrophy	US(2017. 12), EU(2018. 11)	
12	Collategene	AnGes	A plasmid expressing HGF		Severe limb ischemia	2019. 03	Japan
13	Zolgensma (Orphan)	AveXis	AAV expressing SMN1 (survival motor neuron 1) gene		Pediatric spinal muscular atrophy with SMN1 deficiency	2019. 05	US
14	Zynteglo (Orphan)	Bluebird Bio	Auto, $CD34^{+}$ HSCs with a lentiviral vector encoding $b^{A\text{-}T87Q}$-globin gene	Yes	Transfusion-dependent beta thalassemia (TDT)	2019. 05	EU

	Tradename	Company	Characteristics	Cells	Target Disease	Year	Country
1	Spinraza (Orphan, Drug)	Biogen	siRNA modulating alternative splicing of SMN2 gene to increase its expression		Pediatric spinal muscular atrophy with SMN1 deficiency	US(2016. 12), Canada, Japan, Brazil	
2	Onpattro (Orphan, Drug)	Alnylam Pharma	siRNA targeting TTR (transthyretin) gene		Polyneurophathy of hATTR mediated amyloidosis	2018. 08	US

Gene-modified Cells-Strimvelis to Treat ADA-SCID

Bone marrow cells gene-modified to express ADA (adenosine deaminase)



ADA-SCID is a very rare disorder caused by a faulty gene inherited from both parents. This faulty gene stops the production of an essential protein called adenosine deaminase (ADA), which is required for the production of lymphocytes (a type of white blood cell). Children born with ADA-SCID do not develop a healthy immune system so cannot fight off everyday infections, which results in severe and life-threatening illness. Without prompt treatment, the disorder often proves fatal within the child's first year of life. ADA-SCID is estimated to occur in approximately 15 patients per year in Europe.

Within the primary data package which formed the basis of marketing authorisation, a 100% survival rate at 3 years post-treatment with Strimvelis (primary endpoint) was observed for all 12 children in the pivotal study, with 92% having intervention-free survival (i.e. did not require enzyme replacement therapy for a period of >3 months post-treatment or hematopoietic stem cell transplantation). All 18 children treated with Strimvelis who contributed data to the marketing authorisation application are alive today with a median follow-up duration of approximately 7 years, with the first of these having received this gene therapy over 13 years ago. Intervention-free survival within the evaluable population (n=17) was 82%.

Biocompatibility of Poly(α-hydroxy acid) Family SCAFFOLDS

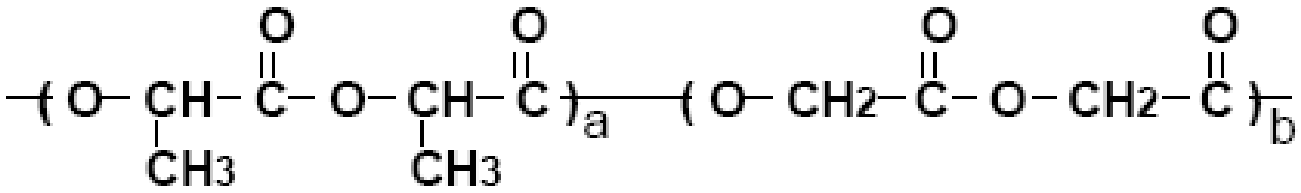
- First autologous chondrocytes/PGA nonwoven hybrid constructs had been submitted for the approval to US FDA on 1992 by ATS. No one doubted to approve this TEMPS.

- However, the approval of these tissue engineered products has been retarded up to now.

- This means we must solve this problem In terms of

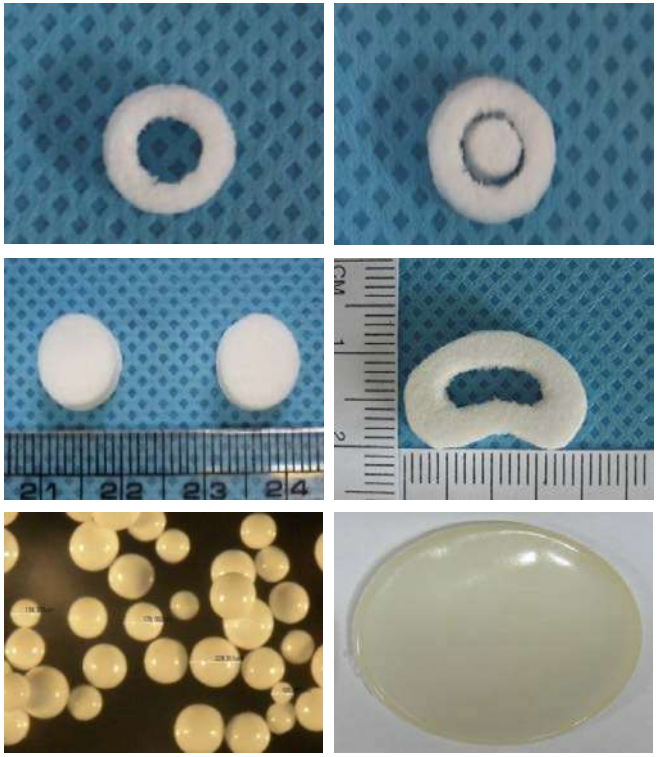
SAFETY and EFFICACY.

PLGA



LA GA

- a group of poly(α-hydroxy acid)
- approved for human clinical use by FDA.
- extensively used and tested for scaffold materials as a bioerodible material (sutures, bone plates, screws and drug delivery vehicles)
- good biocompatibility,
- good mechanical property
- lower toxicity
- controllable biodegradability.

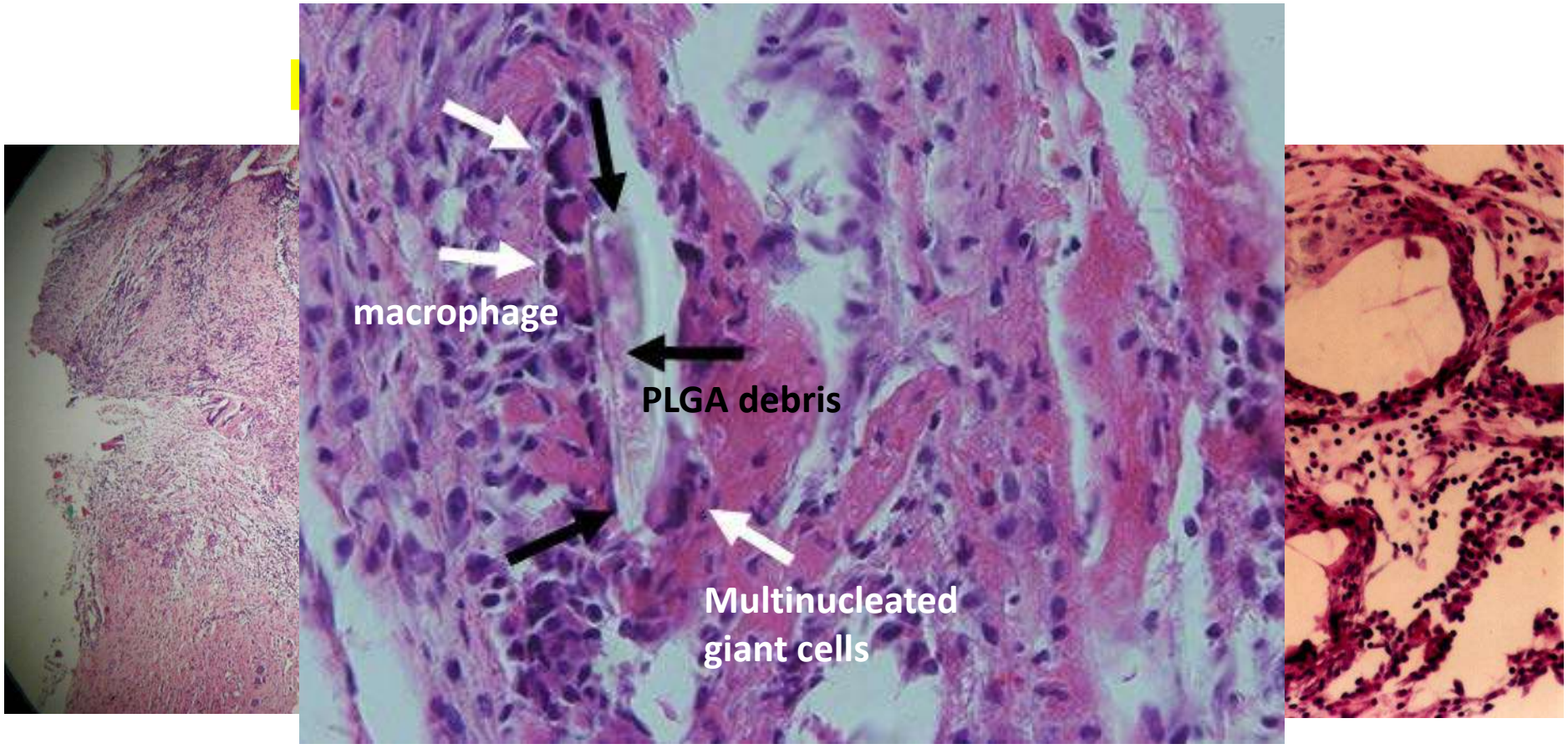


Immunologic reactions

- Sequential events of immunologic reactions in response to injury caused by implantation procedures and result in **acute inflammation** marked by a dense infiltration of inflammation-mediating cells at the materials-tissue interface.

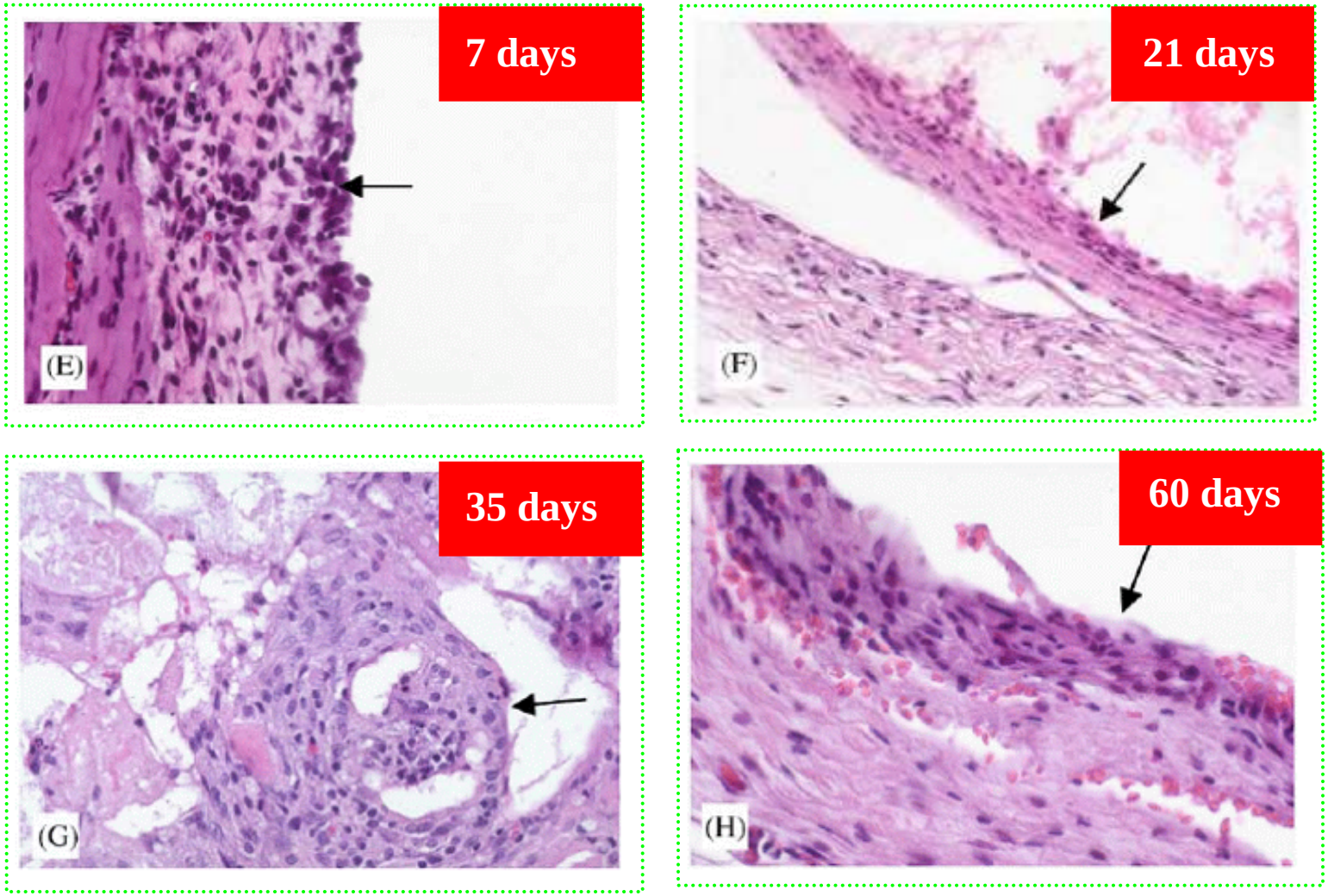
- Prolonged irritations provoked by implanted biomaterials advance acute inflammation into chronic adverse tissue response characterized by **the accumulation of dense fibrotic tissue encapsulating the implants.**

Problems of PLGA, PGA:
High Inflammation Reaction



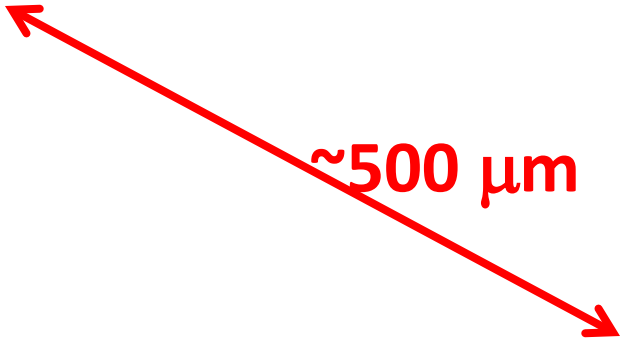
- Foreign body granuloma. Small PLGA debris broken off from the PLGA film and is surrounded by macrophages and multinucleated giant cells.
- These induced macrophages and multinucleated giant cells were remaining over 2 months.

Photomicrographs(400 x) of H&E after PLGA implantation



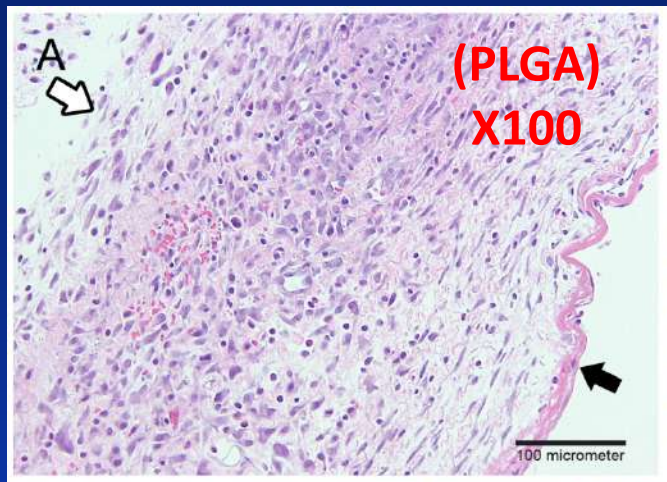
R. Langer *et al*, *Biomaterials* (2003).

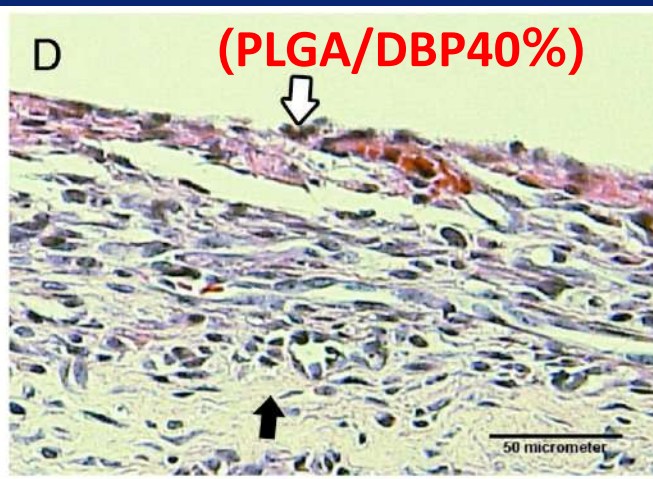
Formation of fibrotic wall

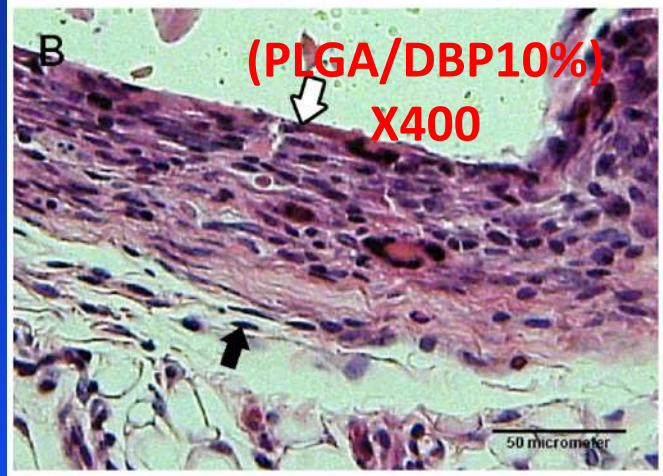


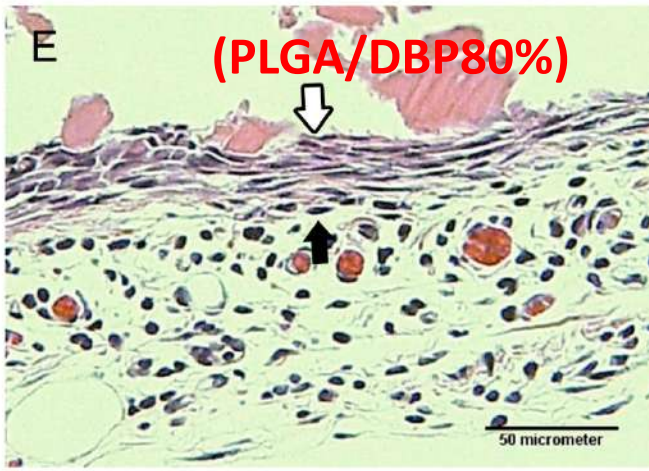
Formation of fibrotic wall (H&E, x400)

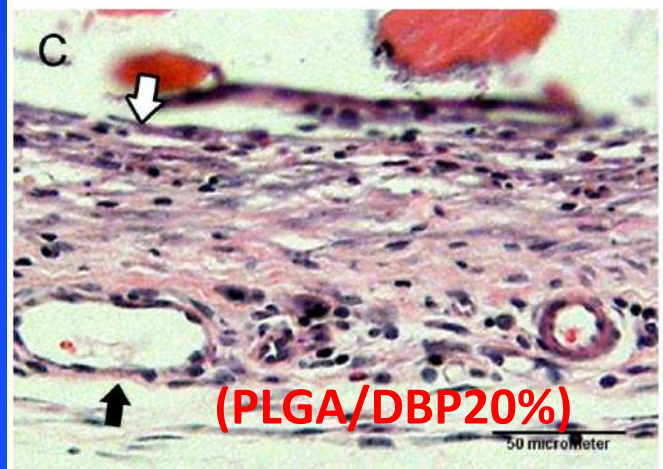
- The number of inflammatory cell and fibrous band thickness in vicinity to tissue implanted samples was decreased as DBP content in PLGA film was increased.







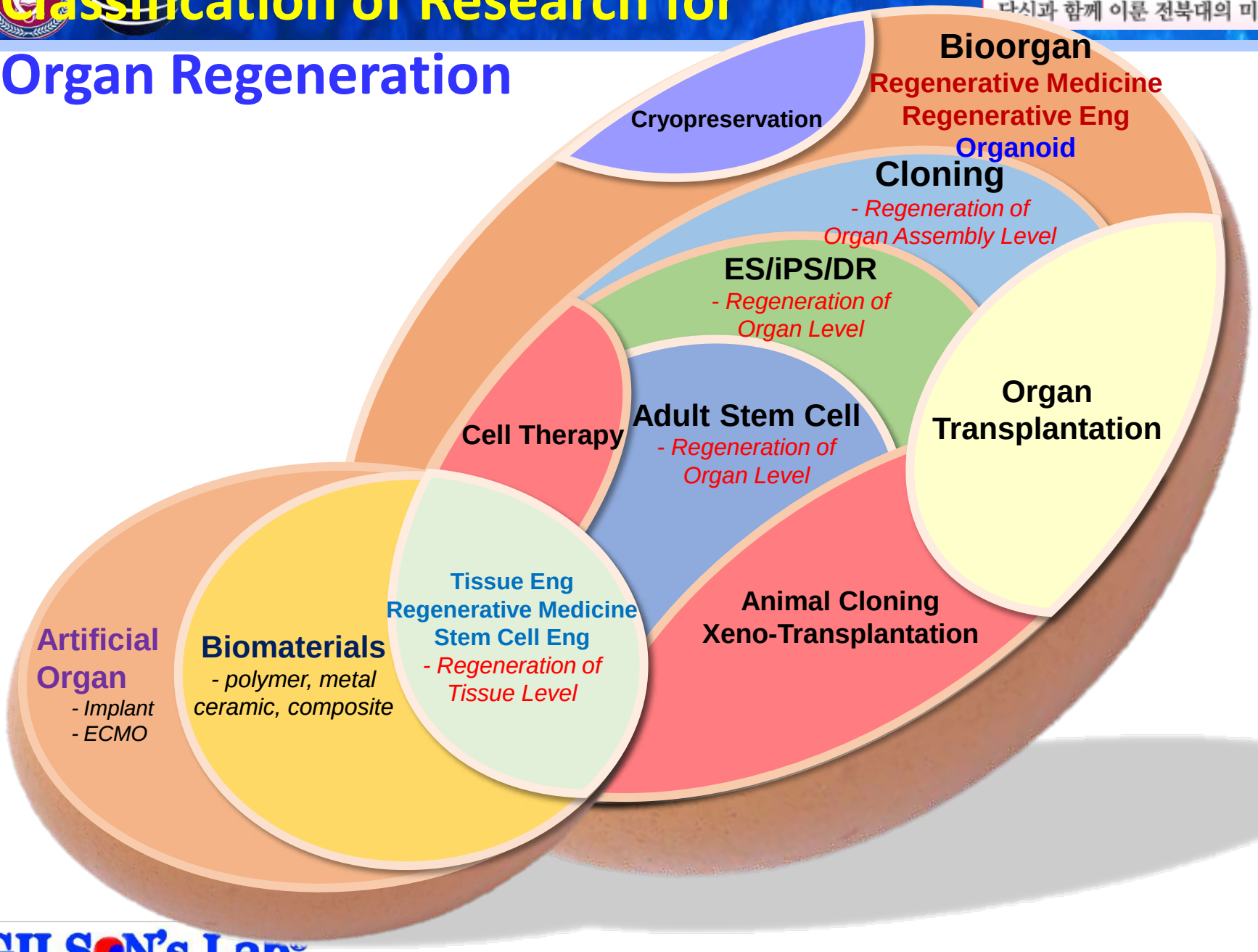




Conclusion

1. It must be solved the exact definition of biocompatibility of scaffold biomaterials for tissue engineering products.
2. Massive and systemic human clinical study for tissue engineered products must be carried out.

Classification of Research for Organ Regeneration



1990s

Tissue Engineering

Somatic Cell

Scaffolds

FDA Approval

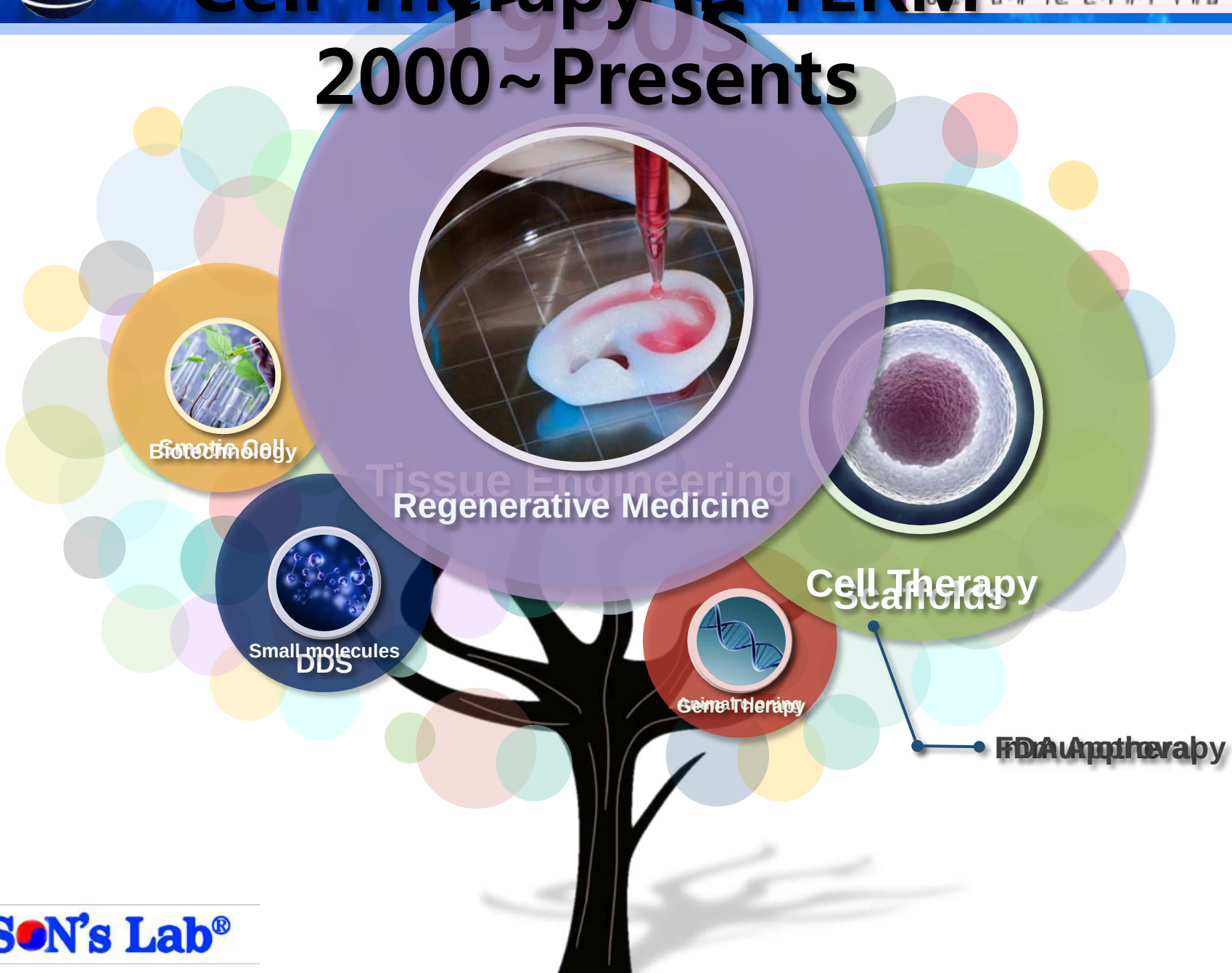
DDS

Animal cloning

Cell Therapy in TERM

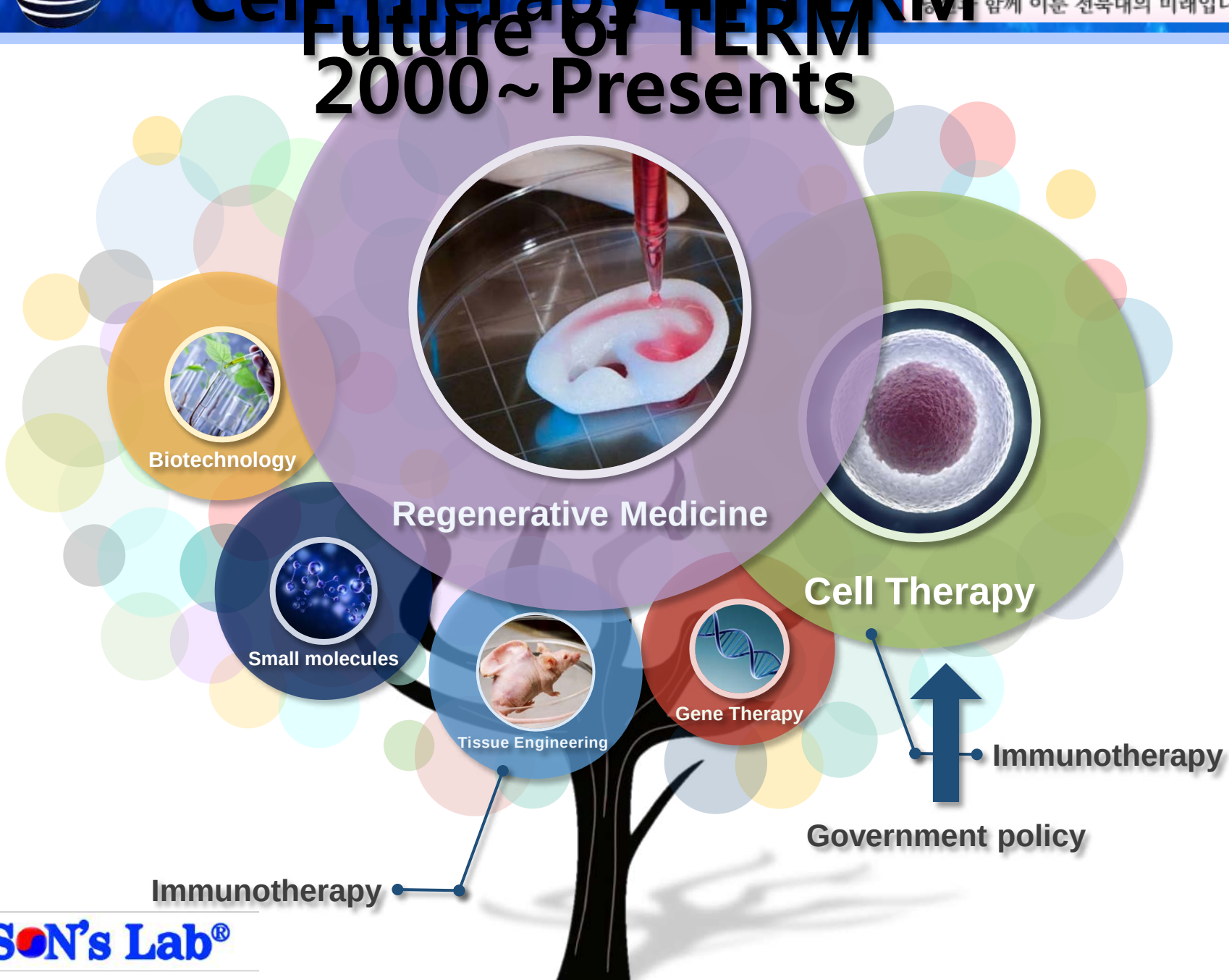
1990s

2000~Presents



Cell Therapy in TERM

Future of TERM
2000~Presents



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☆ NI Fusion team : Development of Nanotherapeutics

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· Stem Cell Engineering

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· The University of Hong Kong
· New Drug Development & Biosimilar Drugs

· Peter M Kang, MD
· Havard Medical School
· Translational Medicine in Cardiovascular Diseases

· Alan Kintak Lau, PhD
· The Hong Kong Polytechnic University
· Bionano Composite

· Shinwoong Kang, PhD
· Kent State University
· Bioliquid Crystal

Chonbuk National University

· Yoon-Bong Hahn, PhD
· Biosensor

· Joong Hee Lee, PhD
· Bionano Composite

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- Prof Chan Heum Park MD

Georgia Tech Ins/Emory Univ
- Prof Robert Nerem
- Prof Hanjoong Jo

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- Prof Hak Soo Choi
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