СумДУ

Erasmus+

Jean Monnet Programme

BRC
BIOMEDICAL RESEARCH CENTRE

EUBiomt

Матеріали в медицині: метали, кераміка, полімери. Європейське законодавство щодо застосування біоматеріалів

«Modern European trends in biomedical higher education: Bionanomaterials.» № 620717-EPP-1-2020-1-UA-EPPJMO-MODULE

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BIOMATERIALS

- “a systemically and pharmacologically inert substance designed for implantation within or incorporation with living systems”
- “a nonviable material used in a medical device, intended to interact with biological systems”
- “materials of synthetic as well as of natural origin in contact with tissue, blood, and biological fluids, and intended for use for prosthetic, diagnostic, therapeutic, and storage applications without adversely affecting the living organism and its components”
- “any substance (other than drugs) or combination of substances, synthetic or natural in origin, which can be used for any period of time, as a whole or as a part of a system which treats, augments, or replaces any tissue, organ, or function of the body”

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Some history

- There is evidence that sutures may have been used as long as 32,000 years ago (NATNEWS, 1983)
- 3000 B.C.: earliest report of a surgical suture (An ancient Egypt)
- Galen of Pergamon (circa 130–200 a.d.) described ligatures of gold wire.
- 900 A.D.: estimated year (from carbon dating) of the first dental implant found in Europe, which was found to have properly integrated bone
- 1829: H.S. Levert studies canine responses to implanted metals
- 1886: German doctor H. Hansmann is the first surgeon to use metal plates for internal fixation
- Glass contact lens made by Adolph Fick based on da Vinci's idea (1887)
- 1931: Boston surgeon Smith Peterson develops a metal cup for partial hip implants

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Some more history

- 1937 – PMMA was introduce in surgery
- 1939 – 1945: WWII spurs the development of many new materials and orthopaedic surgical techniques
- Dialysis machine made from cellulose membranes by Kolff (1943)
- First intraocular lens made from polymethyl methacrylate used by Kolff (1949)
- 1960- Polyethylene and stainless steel being used for hip implants
- In 1957, Dr. Willem Kolff and a team of scientists tested the artificial heart in animals
- In 1952 the first vessel prosthesis was successfully implanted in a human
- Coronary stents were developed in the mid-1980s
- 1980s – till now revolution in biomaterials

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Biomaterial requirements

- Technical functionality and mechanical properties tuned to the specific application
- Sufficient stability against physiological media
- Residue-free metabolization for biodegradable biomaterials
- High biocompatibility
- Non-allergenic
- Non-inflammatory
- Non-carcinogenic
- Simple processing
- Sterilizable without changes in form and composition
- Sufficiently long shelf-life

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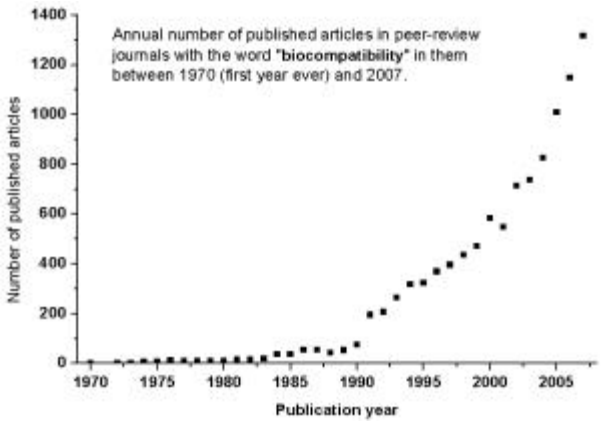
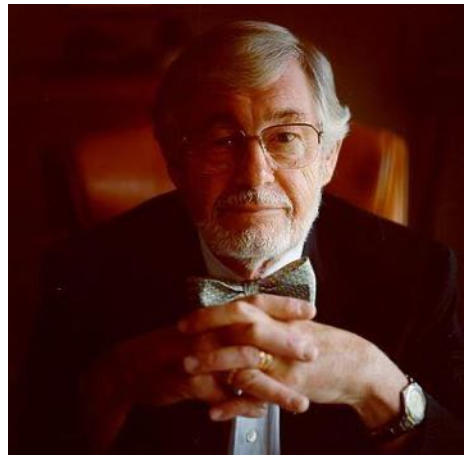
Biocompatibility

"Refers to the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimising the clinically relevant performance of that therapy"

First time refered

Homsy, Charles (1970). "Bio-Compatibility in selection of materials for implantation". *Journal of Biomedical Materials Research*. **4** (3): 341–356. doi:10.1002/jbm.820040306





Per-Ingvar Brånemark

Discovering of OSSEOINTEGRATION

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Biomaterial classification

Uses of Biomaterials

Problem Area	Examples
Replacement of diseased or damaged part	Artificial hip joint, kidney dialysis machine
Assist in healing	Sutures, bone plates, and screws
Improve function	Cardiac pacemaker, intraocular lens
Correct functional abnormality	Cardiac pacemaker
Correct cosmetic problem	Augmentation mammoplasty
Aid to diagnosis	Probes and catheters
Aid to treatment	Catheters, drains

Parida P. et al.

http://iaesjournal.com/online/index.php/IJAAS

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Biomaterial classification

Biomaterials in Organs

Organ	Examples
Heart	Cardiac pacemaker, artificial heart valve, total artificial heart, blood vessels
Lung	Oxygenator machine
Eye	Contact lens, intraocular lens
Ear	Artificial stapes, cochlea implant
Bone	Bone plate, intramedullary rod
Kidney	Catheters, stent, Kidney dialysis machine
Bladder	Catheter and stent

Parida P. et al.

http://iaesjournal.com/online/index.php/IJAAS

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Biomaterial classification

Biomaterials in Body Systems

System	Examples
Skeletal	Bone plate, total joint replacements
Muscular	Sutures, muscle stimulator
Nervous	Hydrocephalus drain, cardiac pacemaker, nerve stimulator
Endocrine	Microencapsulated pancreatic islet cells
Reproductive	Augmentation mammoplasty, other cosmetic replacements
...	

Parida P. et al.

http://iaesjournal.com/online/index.php/IJAAS

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What materials used for….

- Metals
- Ceramic
- Polymers
- Composites
- Nanomaterials

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Metals

Properties

- High strength
- Inert nature
- Relatively easy to produce
- Biocompatibility
- Easy to modify

What metals used?

- Titanium
- Tantalum
- Stainless steel
- Vanadium
- Zirconium
- Iron
- Zink
- Magnesium

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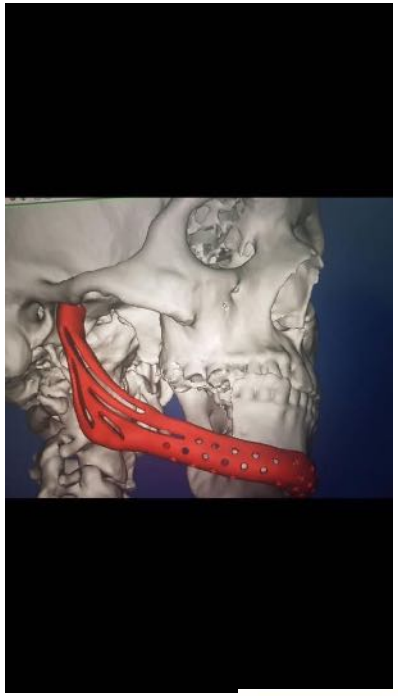
Examples

Conventional

Personalized



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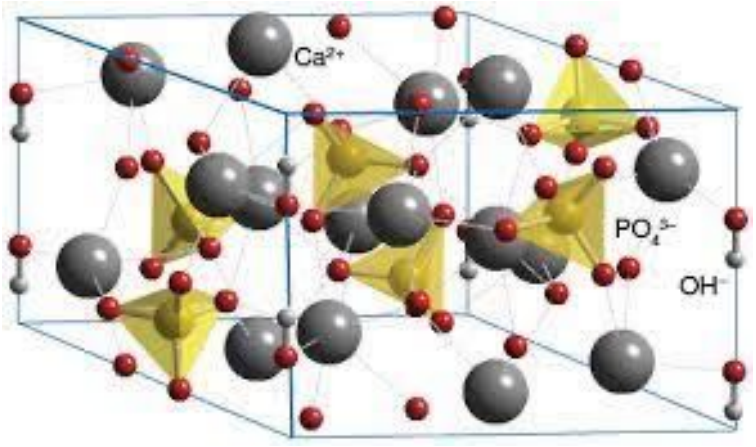
Ceramic

- A **ceramic** is an inorganic non-metallic solid made up of either metal or non-metal compounds that have been shaped and then hardened by heating to high temperatures.



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Ceramic types

Type	Example
Non-absorbable (inert)	Alumina, zirconia, silicone nitrides, and carbons
Bioactive or surface reactive (semi-inert)	Glass ceramics and dense hydroxyapatites
Biodegradable or resorbable (non-inert)	Calcium phosphates and calcium aluminates

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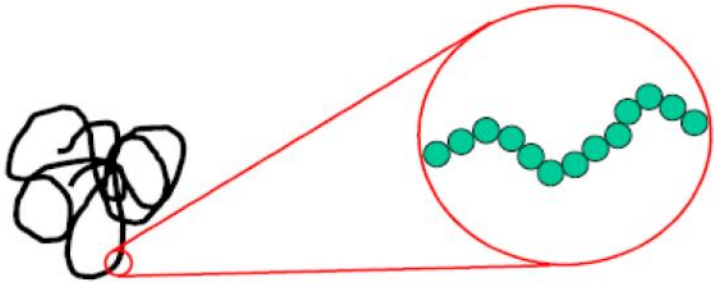
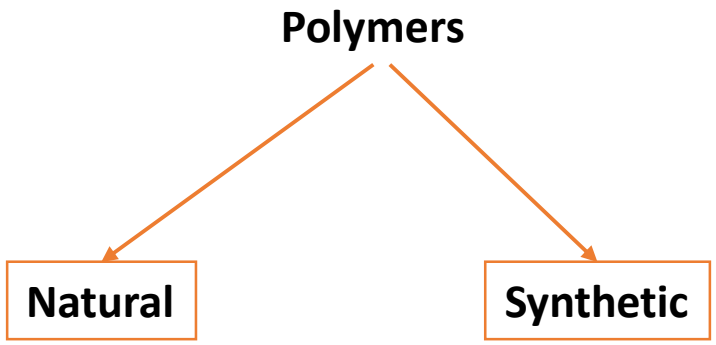
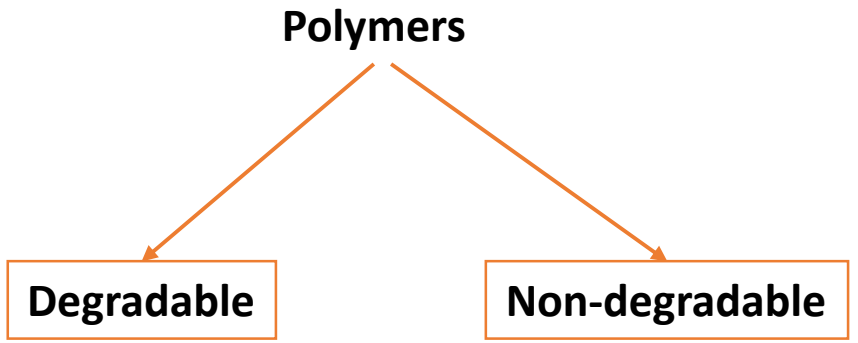
Polymers

- Macromolecule consisting of repetition units







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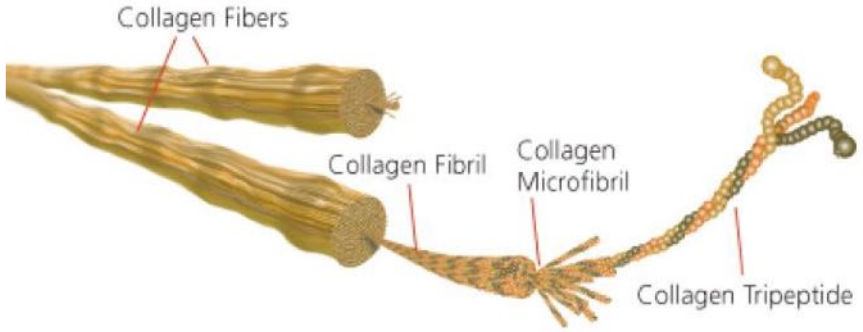
Examples of natural polymers

- **Polyesters** (Polylactic acid)
- **Proteins** (silk, soy protein)
- **Polysaccharides** (gelatin, chitosan, cellulose)
- **Polyphenols** (lignin, tannin)
- **Lipids** (Waxes)
- **Specialty polymers** (Natural rubber, PDA)



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Application

- Cardiovascular and general surgery: Implants (bladder, skin, heart)
- Dental Applications (Implants, Fillers,…)
- Surgery
- Sensors, biochips, implants, microoptic devices
- Contact lenses
- Drug transporter
- Tissue engineering
- …

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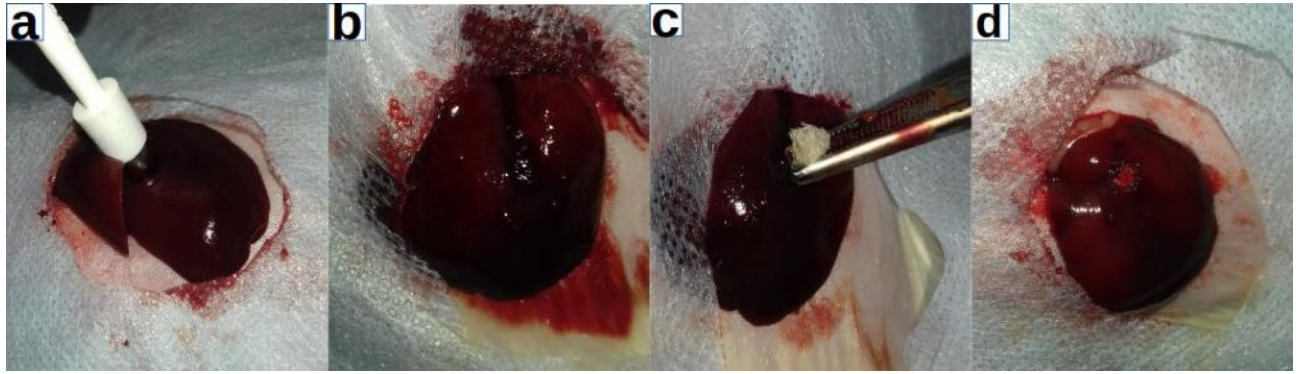
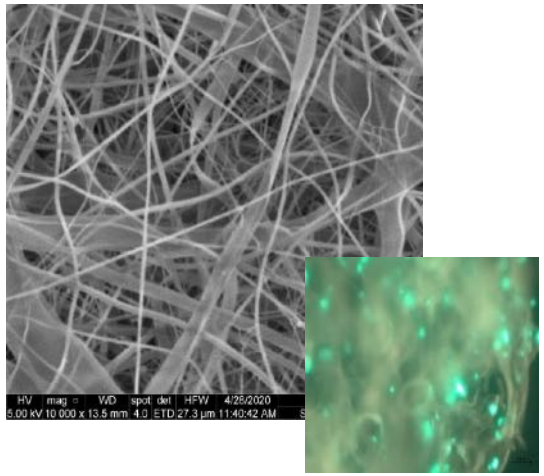
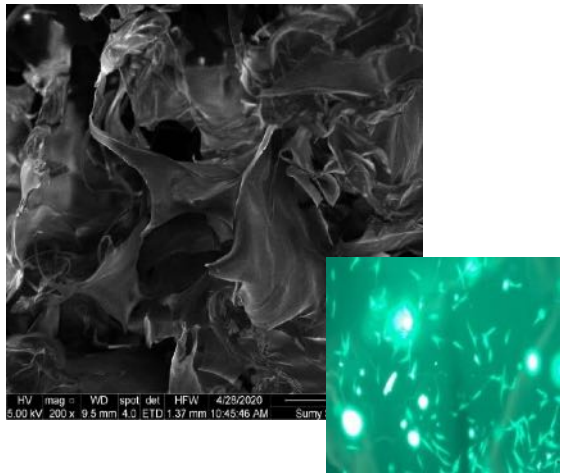
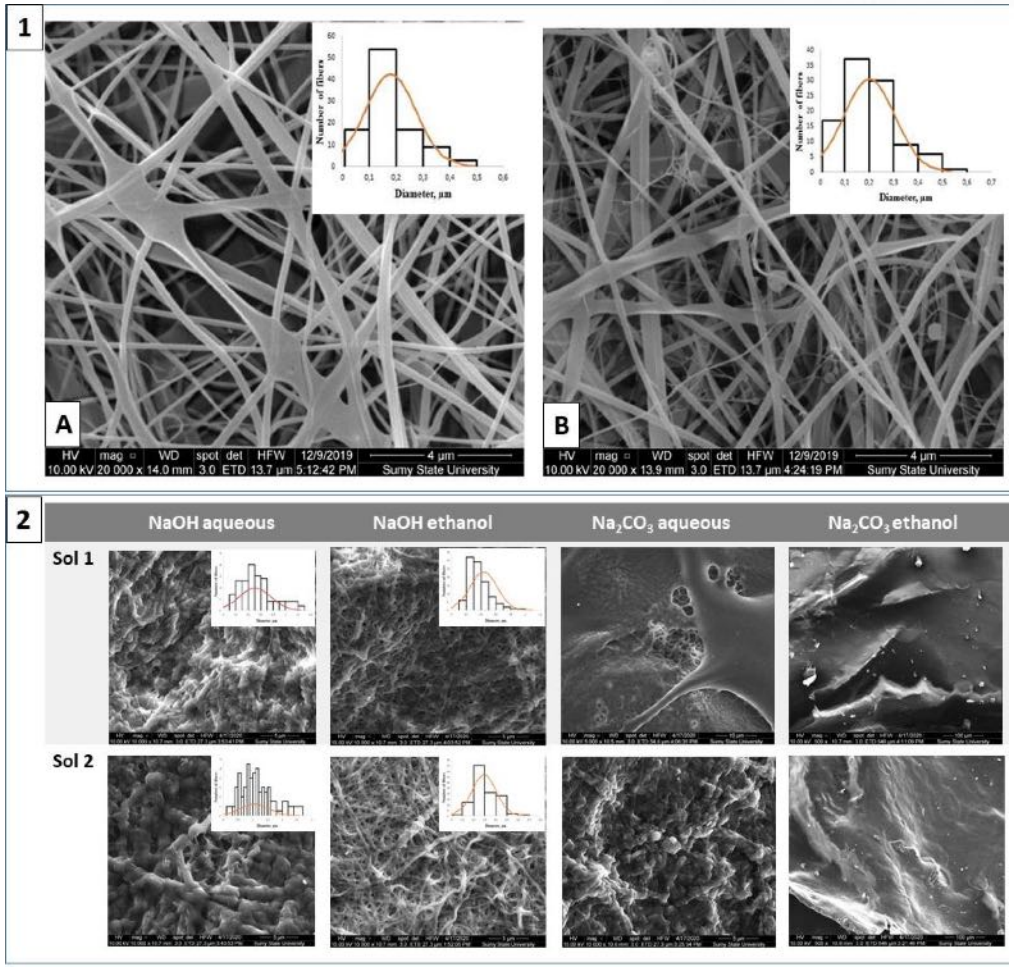
Our results



Procedure of punch biopsy liver trauma (a), liver bleeding (b), hemostatic application (c) and stopped bleeding (d).







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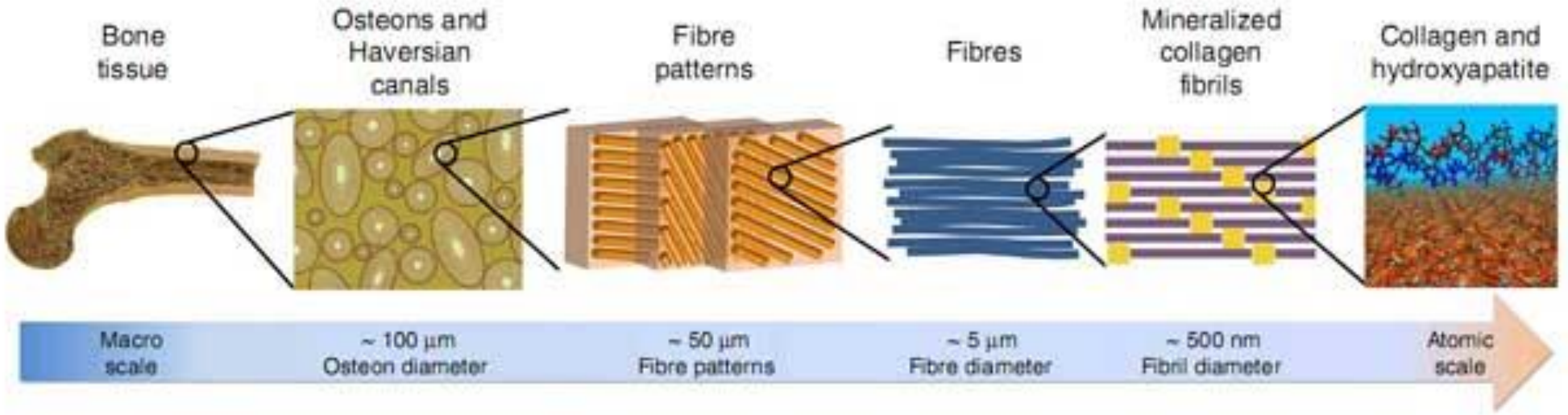
Composites

- Materials, contain more then one phase or materials



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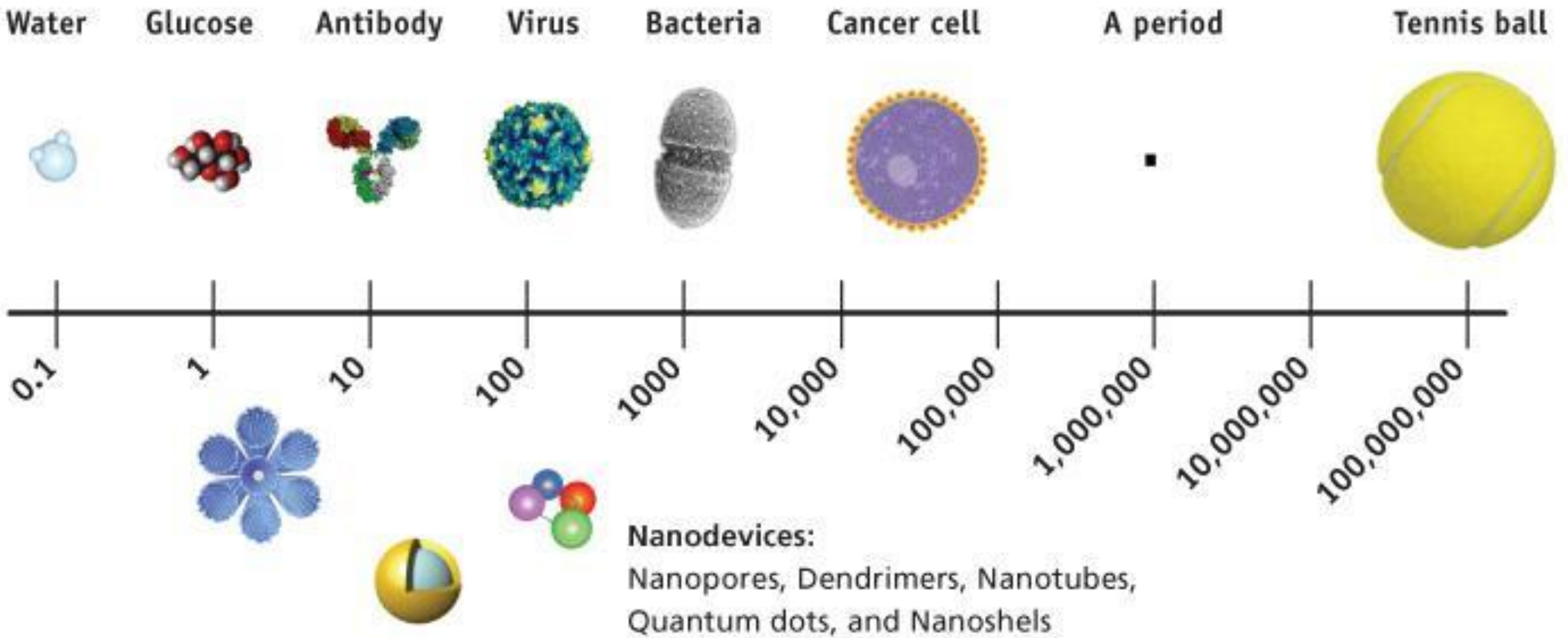
Nanomaterials



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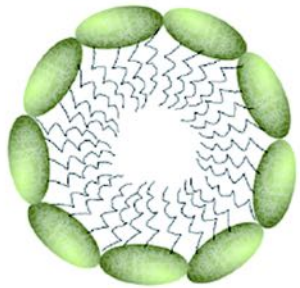
Examples of Nanomaterials

Organic nanoparticles

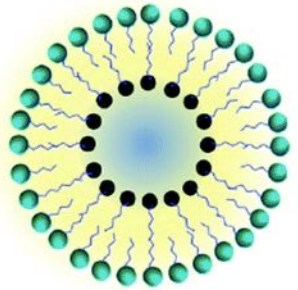
Polymeric nanosphere

Polymeric nanocapsule

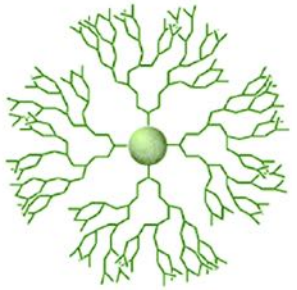
Polymeric micelle



Liposome



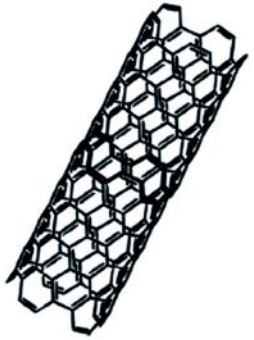
Dendrimer



Inorganic nanoparticles

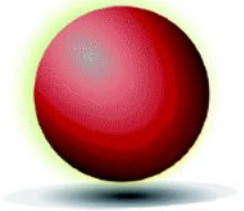
Mesoporous silica nanoparticle

Carbon nanotube

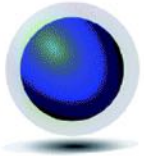


Iron oxide nanoparticle

Gold nanoparticle



Quantum dot



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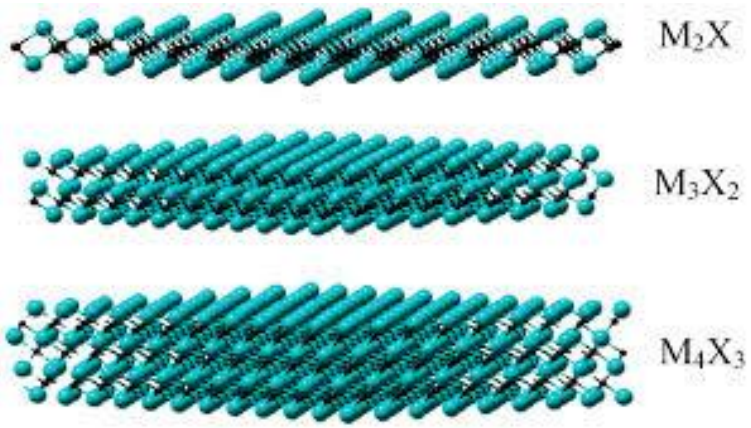
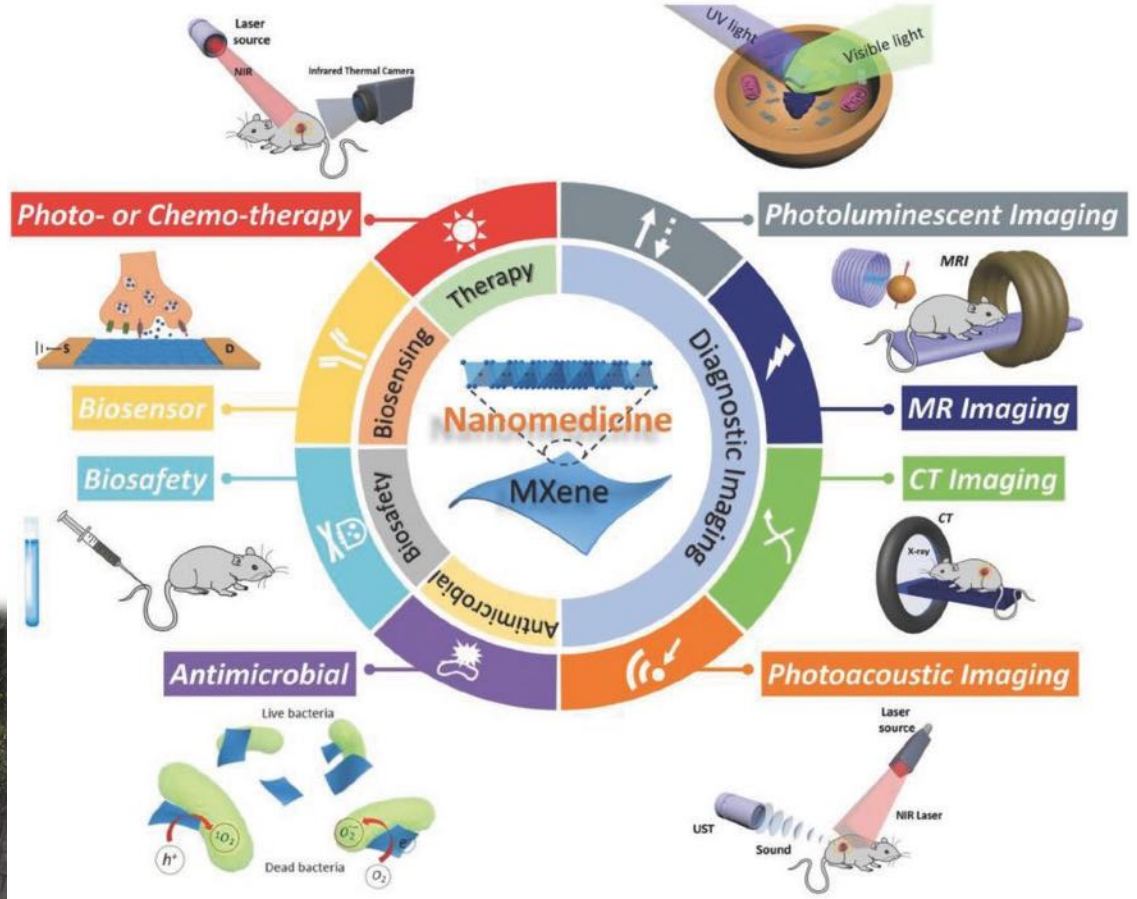
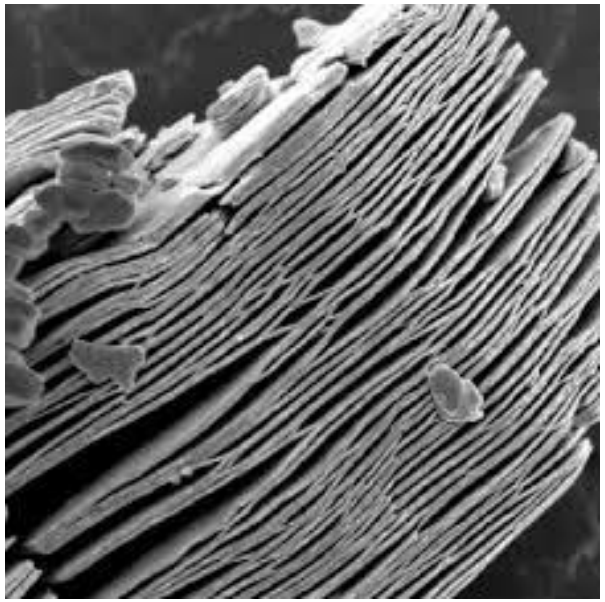
2D nanolaminates (MXene, as example)







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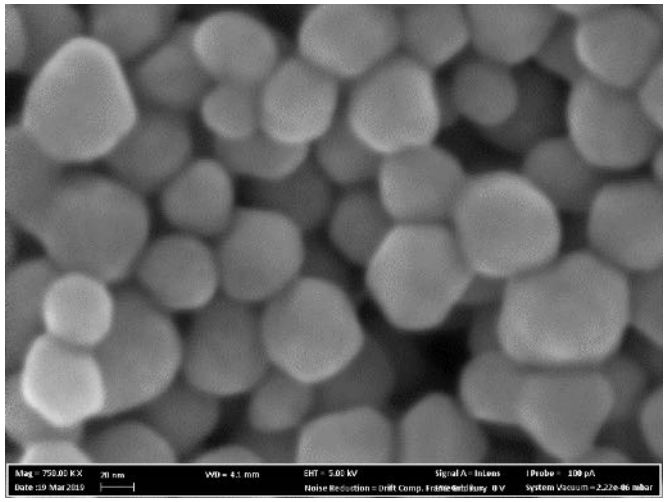
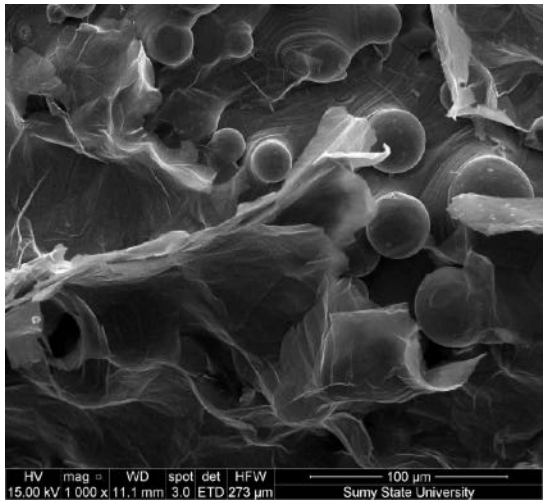
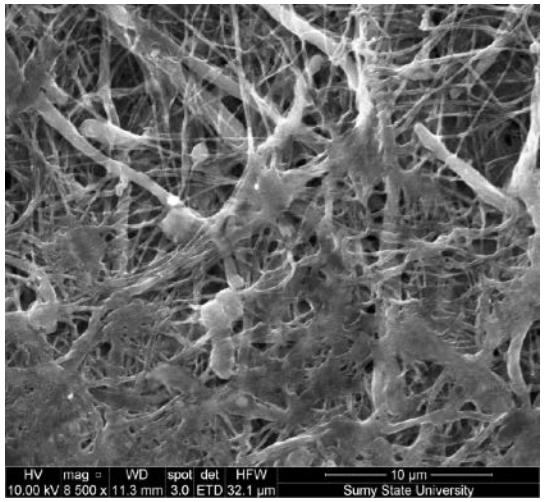
Our example

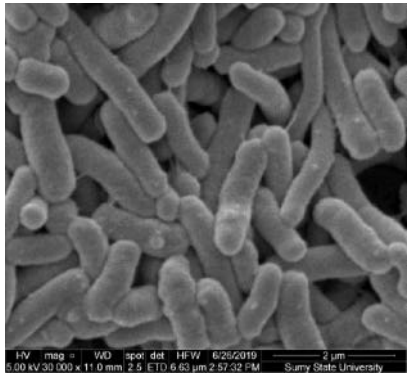


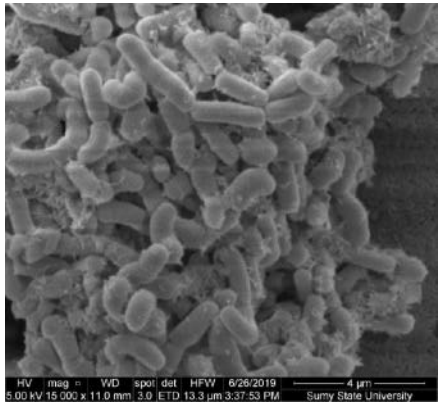


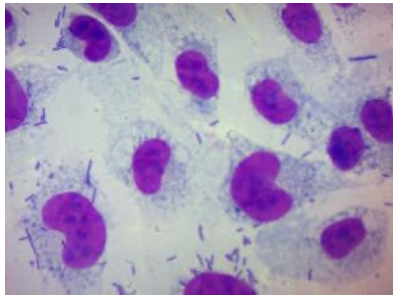


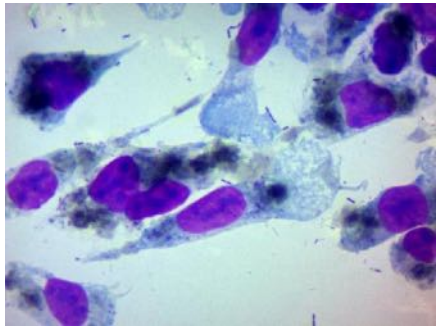
Silver Nanoparticles, made in SumDU

MXene-coated 3D metal and PCL scaffold









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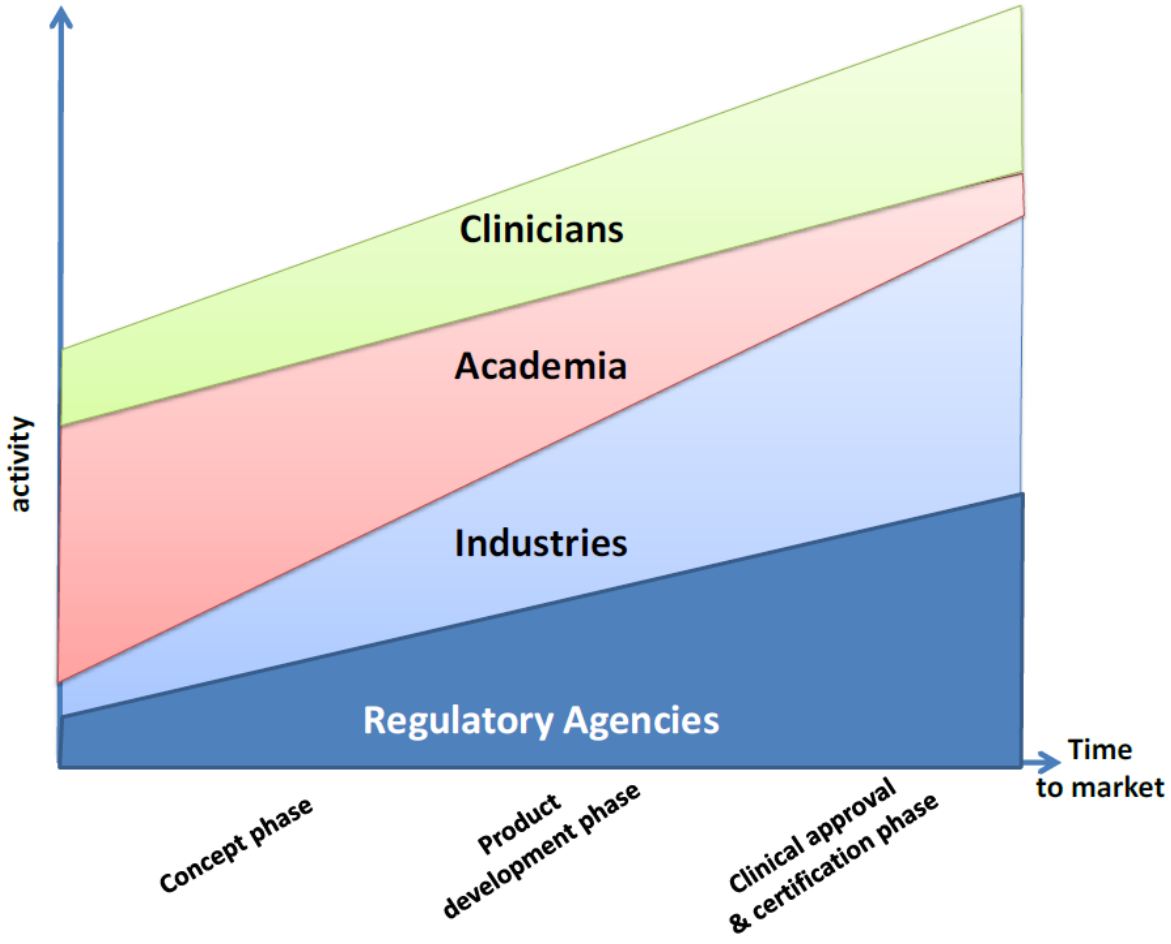
Biomaterials: European Regulatory and Legal Aspects

Technology Readiness Levels as applicable to Healthcare

Level		
1	Basic Principles Observed and Reported	Potential scientific application to defined problems is articulated.
2	Technology Concept and/or Application Formulated	Hypothesis(es) generated. Research plans and/or protocols developed, peer reviewed, and approved.
3	Analytical and Experimental Critical Function and/or Characteristic Proof of Concept	Basic research, data collection, and analysis. First hypotheses tested
4	Validation in Laboratory/Field Environment	Non GxP laboratory research to refine hypothesis
5	Component and/or Breadboard Validation in a Relevant (Operating) Environment	Intense period of nonclinical and pre-clinical GxP research studies involving
6	Prototype Demonstration in a Realistic (Operating) Environment or Context	Phase I Clinical Trials
7	System Prototype Demonstration in an Operational Environment or Context	Phase II Clinical Trials
8	Actual System Completed and Qualified through Test and Demonstration	Phase III Clinical Trials
9	Actual System Operationally Proven through Successful Mission Operations	Post Marketing Studies

Involvement of the various stakeholders in in biomaterials research



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ISO 10993 standard

- ISO 10993-1:2018 Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process
- ISO 10993-2:2006 Biological evaluation of medical devices Part 2: Animal welfare requirements
- ISO 10993-3:2014 Biological evaluation of medical devices Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity
- ISO 10993-4:2017 Biological evaluation of medical devices Part 4: Selection of tests for interactions with blood
- ISO 10993-5:2009 Biological evaluation of medical devices Part 5: Tests for in vitro cytotoxicity.
- ISO 10993-6:2016 Biological evaluation of medical devices Part 6: Tests for local effects after implantation
- ISO 10993-7:2008 Biological evaluation of medical devices Part 7: Ethylene oxide sterilization residuals
- ISO 10993-8:2001 Biological evaluation of medical devices Part 8: Selection of reference materials (withdrawn)
- ISO 10993-9:2010 Biological evaluation of medical devices Part 9: Framework for identification and quantification of potential degradation products
- ISO 10993-10:2013 Biological evaluation of medical devices Part 10: Tests for irritation and skin sensitization

ISO 10993 standard

- ISO 10993-23:2021 Biological evaluation of medical devices Part 23: Tests for irritation
- ISO 10993-11:2018 Biological evaluation of medical devices Part 11: Tests for systemic toxicity
- ISO 10993-12:2012 Biological evaluation of medical devices Part 12: Sample preparation and reference materials (available in English only)
- ISO 10993-13:2010 Biological evaluation of medical devices Part 13: Identification and quantification of degradation products from polymeric medical devices
- ISO 10993-14:2009 Biological evaluation of medical devices Part 14: Identification and quantification of degradation products from ceramics
- ISO 10993-15:2009 Biological evaluation of medical devices Part 15: Identification and quantification of degradation products from metals and alloys
- ISO 10993-16:2018 Biological evaluation of medical devices Part 16: Toxicokinetic study design for degradation products and leachables
- ISO 10993-17:2009 Biological evaluation of medical devices Part 17: Establishment of allowable limits for leachable substances
- ISO 10993-18:2020 Biological evaluation of medical devices Part 18: Chemical characterization of medical device materials within a risk management process
- ISO/TS 10993-19:2006 Biological evaluation of medical devices Part 19: Physico-chemical, morphological and topographical characterization of materials
- ISO/TS 10993-20:2006 Biological evaluation of medical devices Part 20: Principles and methods for immunotoxicology testing of medical devices
- ISO/TR 10993-22:2017 Biological evaluation of medical devices Part 22: Guidance on nanomaterials

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to be continued...

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СумДУ

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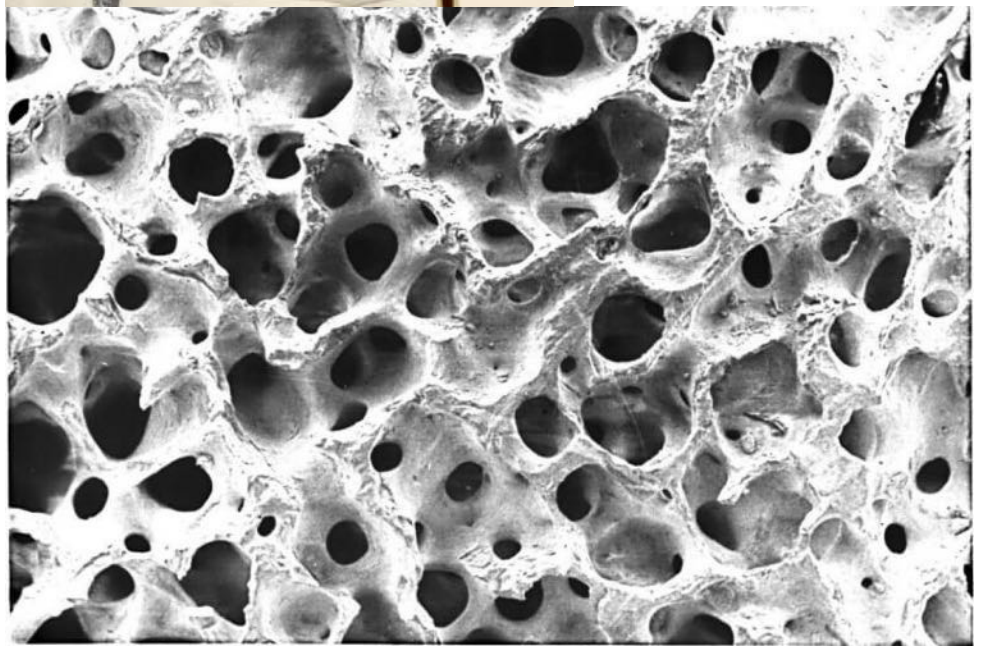
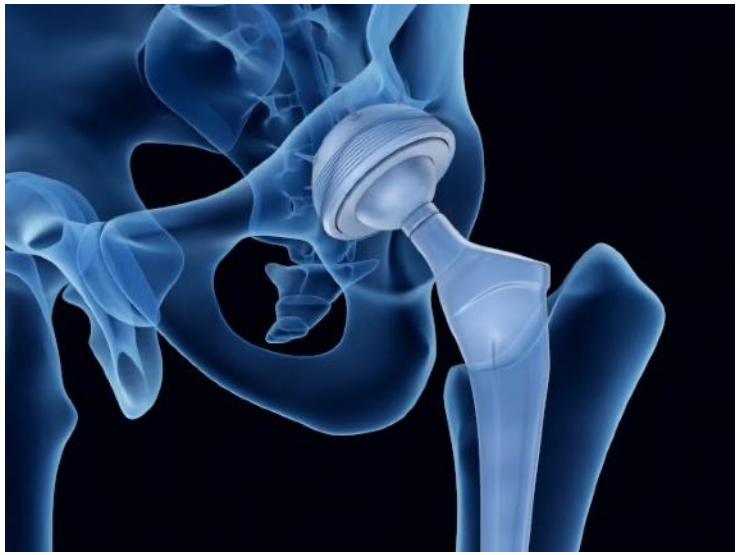


BIOCERAMICS – OBTAINING AND APPLICATION



«Modern European trends in biomedical higher education: Bionanomaterials.»
№ 620717-EPP-1-2020-1-UA-EPPJMO-MODULE

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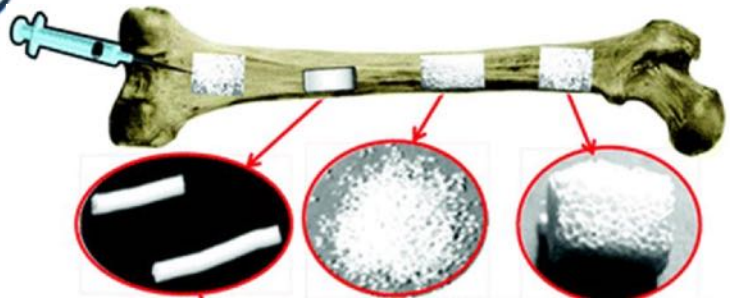
Ceramics is one of the most important classes of biomaterials



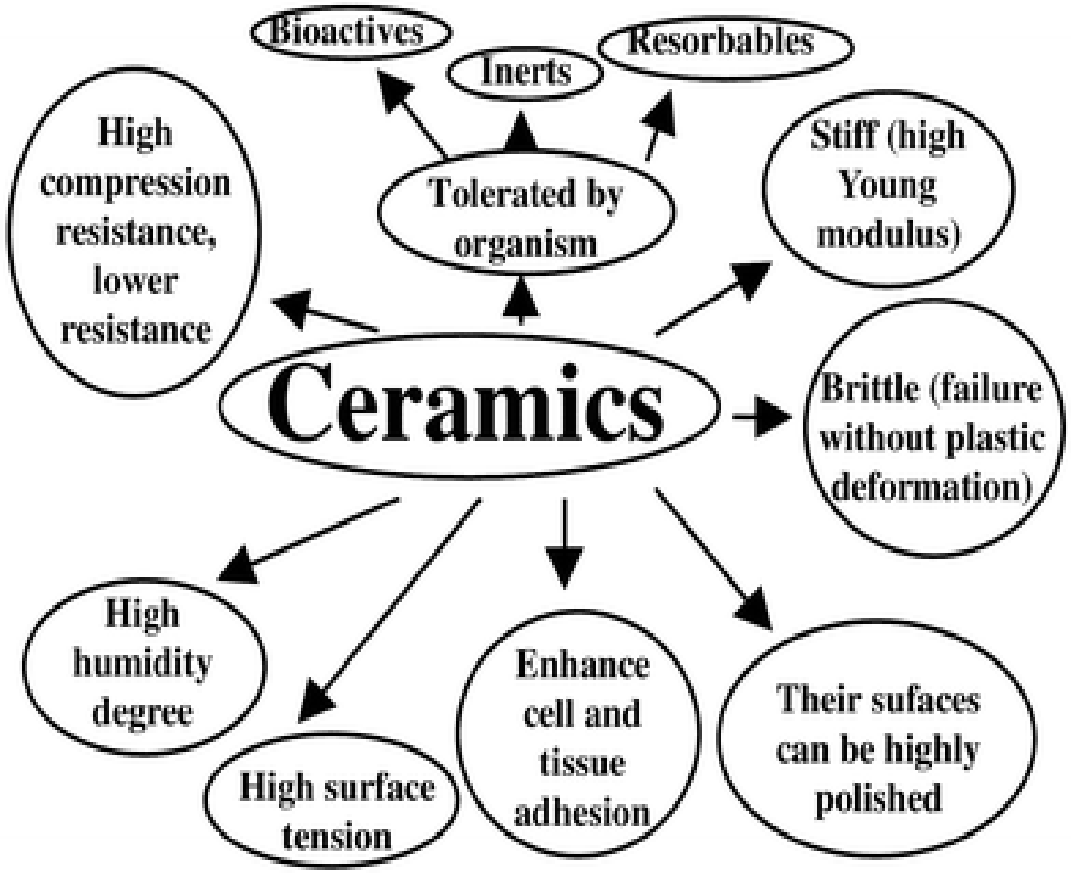
- **Biomaterials** must be distinguished from **biological materials** because the former are ***the materials that are accepted by living tissues and, therefore, they might be used for tissue replacements***, while the latter are the materials being produced by various biological systems.
  Further, **bioceramics (or biomedical ceramics) might be defined as biomaterials of the ceramic origin**. In general, bioceramics can have structural functions as ***joint or tissue replacements***, be used as ***coatings*** to improve the biocompatibility of metal implants, as well as function as ***resorbable lattices***, providing temporary structures and frameworks those are dissolved and/or replaced as the body rebuilds the damaged tissues [1]

- **Bioceramics** are a large class of specially designed crystalline, semicrystalline, or amorphous materials used for the repair and reconstruction of diseased or damaged parts of the body (Hench, 1991).

Bioceramics

inert	bioactive	biodegradable
Al_2O_3	HA, HCA	$CaSO_4$
ZrO_2	Biglasses	Coral – $CaCO_3$: *aragonite*
Carbons	Glass-ceramics: *A-W, Ceravital*	Ca-phosphates:
Sintered HA		α-TCP
$CaAl_2O_4$	*Particle size, crystallinity, porosity*	β-TCP
Si_3N_4		OCP
SiC		DCPA
		DCPD
		TetCP
		HA: 10 μm
		also with: ZnO, Al_2O_3, Fe_2O_3,-

HA: hydroxyapatite
HCA: hydroxycarbonate apatite
A-W: apatite - wollastonite
TCP: tricalcium phosphate
OCP. octacalcium phosphate
DCPA: dicalcium phosphate anhydrous
DCPD: dicalcium phosphate dihydrate
TetCP: Tetracalcium phosphate monoxide



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Classification of bio ceramics

Bioceramics for bone replacement graft (BG)

Silicate bioceramics

Natural based
(e.g. marine sponges)

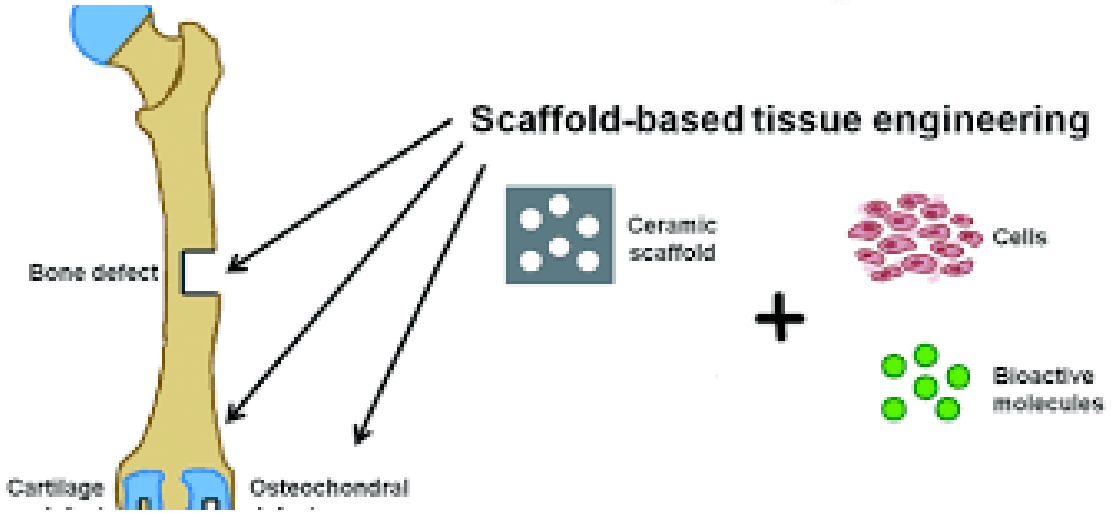
Glass based
(e.g. Bioglass 45S5, S53P4)

Non-silicate bioceramics

Oxide based
(e.g. TiO_2, ZrO_2)

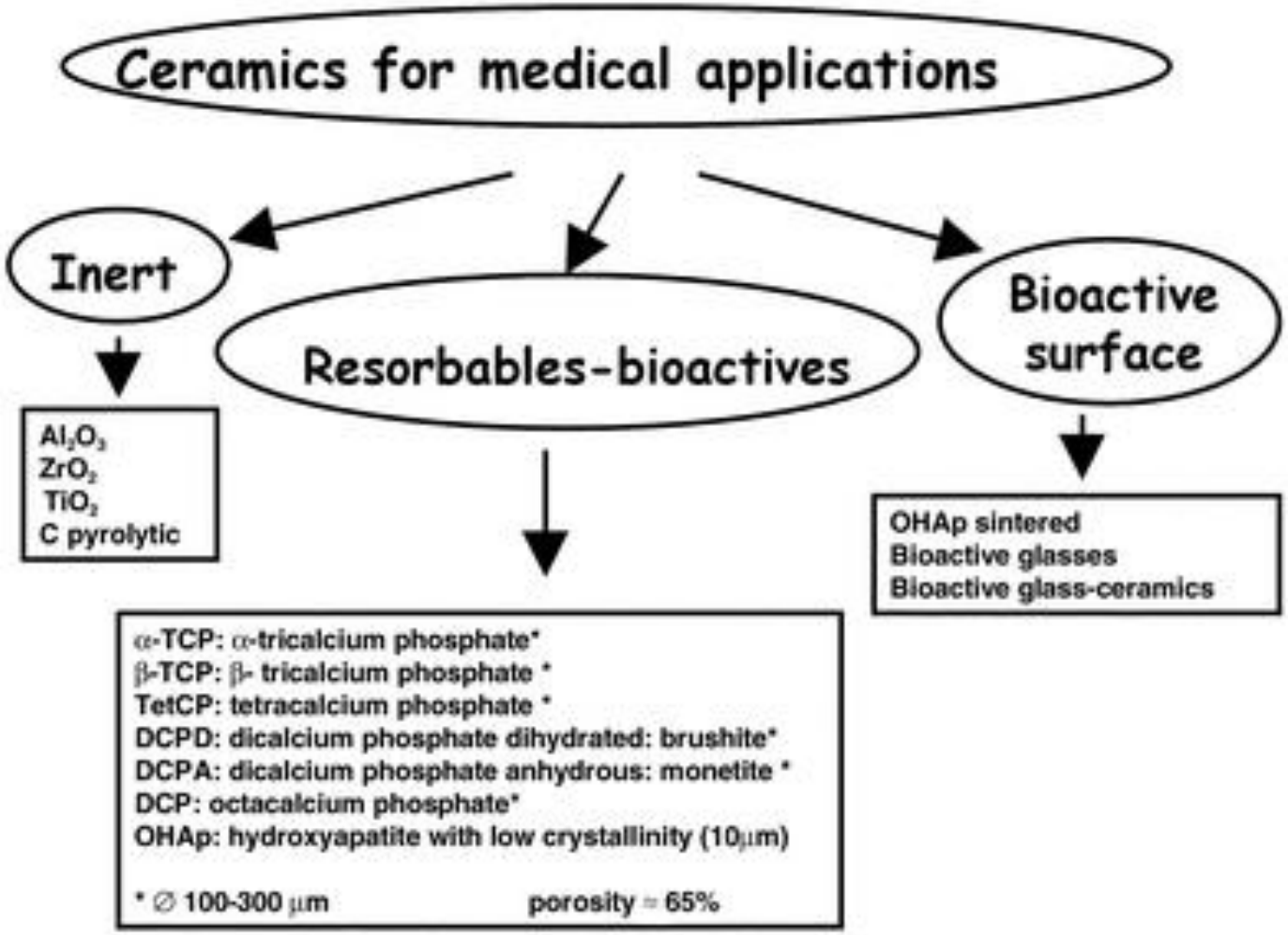
Non-oxide based
(e.g. CaPx, HA, α or βTCP)

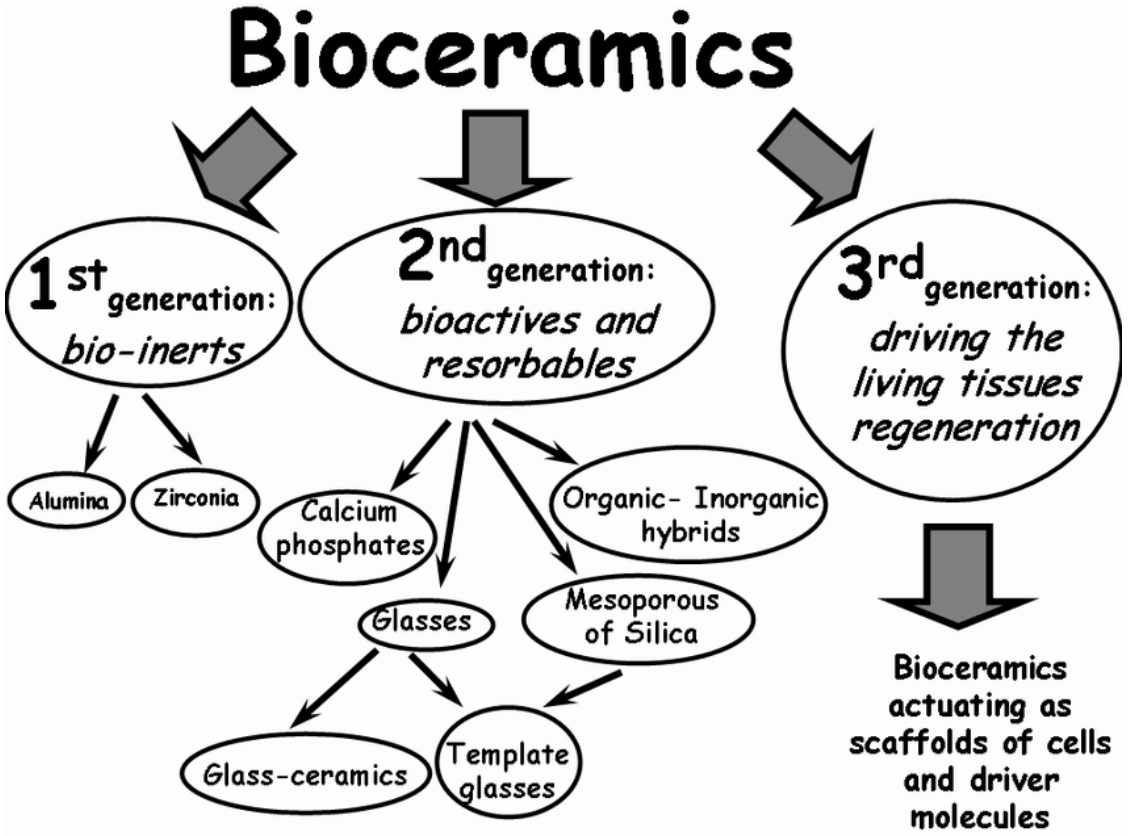
Natrual based
(e.g. corals, bovine human, equine bone)



- Calcium phosphate (CaP) bioceramics are widely used in the field of bone regeneration, both in orthopedics and in dentistry, due to their good biocompatibility, osseointegration and osteoconduction [1]

Classification of ceramics





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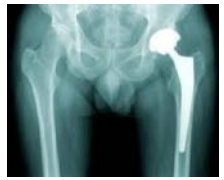
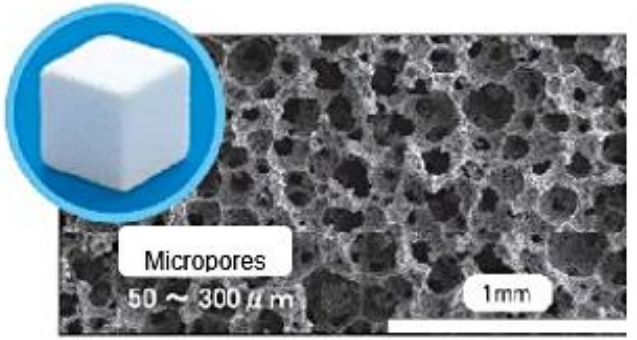
BIOMATERIALS

BIOCERAMICS BIOMETALS ORGANIC BIOMATERIALS



BIOCERAMICS

CHEMICALLY BONDED SINTERED CERAMICS GLASSES GLASS-CERAMICS



Porous artificial bones made of bioceramics

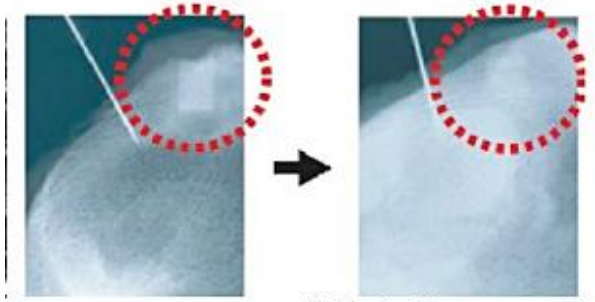
Figure 1: Example of products using bioceramics

CHEMICALLY BONDED BIOCERAMICS (CBBCs)

BODY TEMPERATURE CBBCs HIGH TEMPERATURE CBBCs

BODY TEMPERATURE CBBCs

ACID-BASE REACTION WATER UP-TAKE POLYMERISATION REACTION

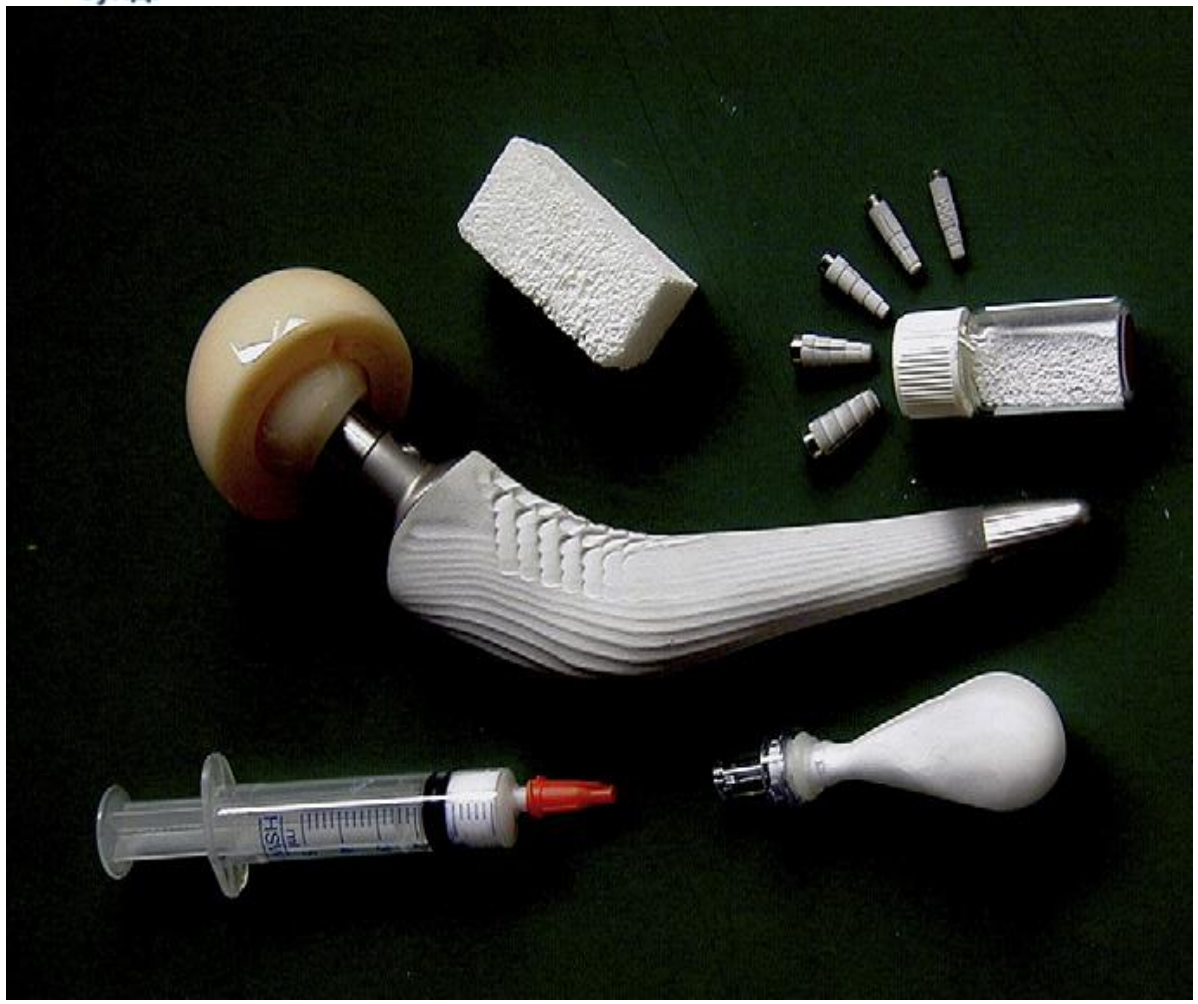


Subject before bone surgery operation

Subject with progress after the surgery operation

Figure 2: Pictures of bioceramics assimilating with operated-on bone

History of bioceramics



Several examples of commercial calcium orthophosphate-based bioceramics

- A strong interest in use of ceramics for biomedical applications appeared in the late 1960's. Used initially as alternatives to metals in order to ***increase a biocompatibility of implants***, bioceramics have become a diverse class of biomaterials, presently including ***three basic types: relatively bioinert ceramics, bioactive (or surface reactive) and bioresorbable ones***. Furthermore, any type of bioceramics could be porous to provide tissue ingrowth. During the past 30–40 years, there have been a number of major advances in this field. Namely, after the initial work on development of bioceramics that was tolerated in the physiological environment, emphasis was shifted towards the use of bioceramics that interacted with bones by forming a direct chemical bond.
  By the structural and compositional control, it became possible to choose whether the bioceramics of calcium orthophosphates was ***biologically stable*** once incorporated within the skeletal structure or whether it was ***resorbed over time***. Potential future applications of calcium orthophosphate bioceramics will include ***drug-delivery systems***, as well as they will become effective ***carriers of growth factors***, bioactive peptides and/or various types of cells for tissue engineering purposes.
  [2]

Types of ceramic materials

First generation:

Inerts

- Alumina
- Zirconia

Second generation:

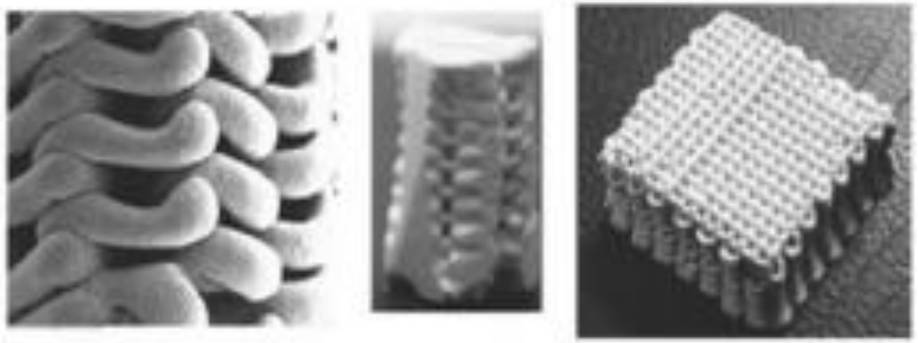
Bioactives and bioresorbables

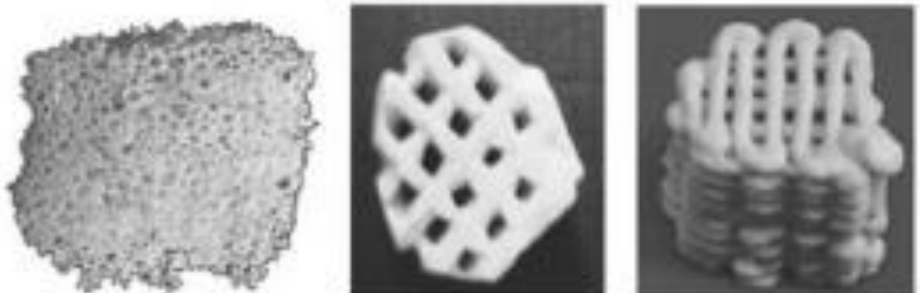
- Calcium phosphates
- Glasses
- Glass-ceramics

Third generation:

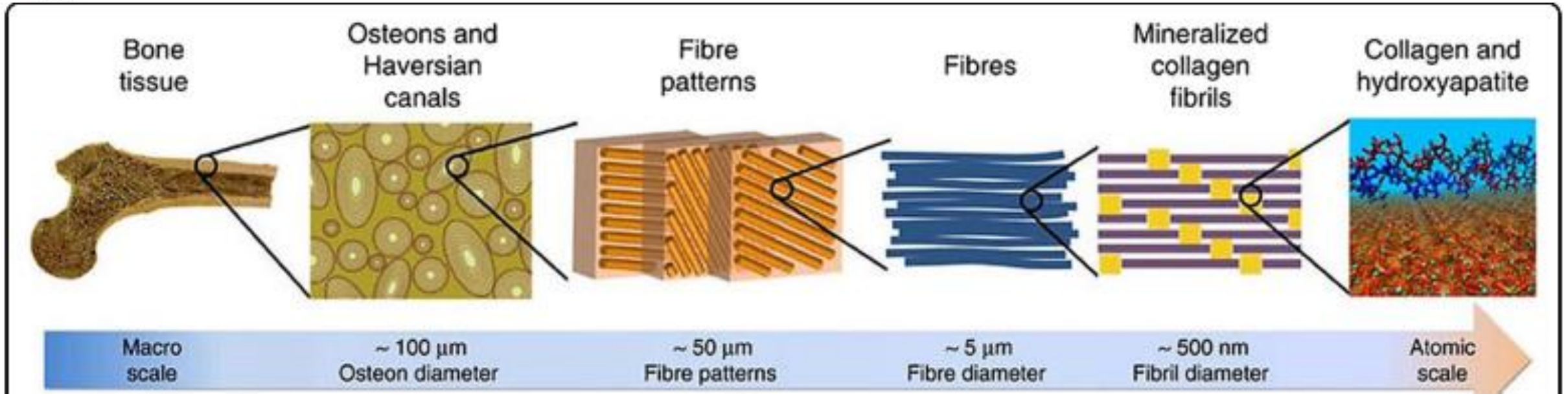
Tissue self-regeneration inducers

- Second generation porous bioceramics
- Novel advanced bioceramics
  - Mesoporous silica
  - Organic-inorganic hybrids
  - Templated glasses





Hierarchical structure of bone ranging from mesoscale skeleton collagen and HA [3]



The existence of calcium phosphates in bones was first discovered in 1769, and in the 1800s, calcium phosphates that exist in bones were subdivided into different categories. Since the 1900s, synthetic calcium phosphates have been actively studied for clinical use. Thereafter, bone regenerative applications such as bone cements, scaffolds, implants, and coating techniques using calcium phosphates have emerged, and some have been commercialized. Similar to these, the characteristics of calcium phosphates have been studied for bone regenerative applications [3].

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Typical compositional values of the inorganic phase of adult human calcified tissues [3]

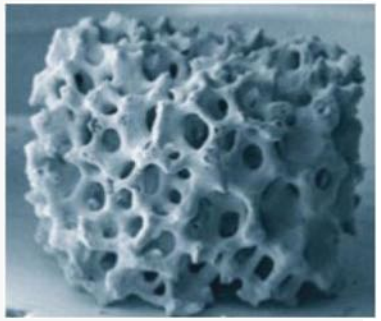
Composition	Enamel	Dentin	Bone	Hydroxyapatite
Calcium [wt.%]	36.5	35.1	34.8	39.6
Phosphorus [wt.%]	17.7	16.9	15.2	18.5
Ca/P (molar ratio)	1.63	1.61	1.71	1.67
Sodium [wt.%]	0.5	0.6	0.9	–
Magnesium [wt.%]	0.44	1.26	0.72	–
Potassium [wt.%]	0.08	0.05	0.03	–
Carbonate [wt.%]	3.5	5.6	7.4	–
Fluoride [wt.%]	0.01	0.06	0.03	–
Chloride [wt.%]	0.30	0.01	0.13	–
Pyrophosphate [wt.%]	0.022	0.10	0.07	–
Total inorganic [wt.%]	97	70	65	100
Total organic [wt.%]	1.5	20	25	–
Water [wt.%]	1.5	10	10	–
Ignition products (800 °C)	β-TCP + HAP	β-TCP + HAP	HAP + CaO	HAP

- The properties of calcium phosphates affect bioactivity, such as adhesion, proliferation, and new bone formation in osteoblasts. To exhibit these bioactive features, degradation and ion release in calcium phosphates are important
- First, calcium ions affect cells and living systems in several ways. Calcium is one of the ions that form the bone matrix, and it exists mostly in the form of calcium phosphates in bone tissues. These calcium ions cause bone formation and maturation through calcification. In addition, calcium ions affect bone regeneration and stimulate the osteoblastic bone synthesis.
- Over 80% of phosphorous ions are present in bone in the form of calcium phosphates along with calcium ions. Phosphorous mainly exists in the form of phosphate (PO_4^{3-}), which has great influence on tissue formation and growth
- Cell adhesion is strongly influenced by the ability to adsorb extracellular matrix proteins. It is influenced by the surface characteristics of calcium phosphates, such as surface roughness, crystallinity, solubility, phase content, porosity, and surface energy

Bioactive and bioresorbable ceramics

Biocompatible nanoceramics or nanostructured bioceramics used for hard tissue substitution in tissue engineering

Mineral	Name of compound	Abbreviation	Formula	Ca/P ratio
Bioinert oxide ceramics				
Alumina	Aluminum oxide		Al_2O_3	
Zirconia	Zirconia oxide		ZrO_2	
Bioactive ceramics				
Glasses				
Bioglass	Silicium oxide		SiO_2 CaO Na_2O P_2O_5	
A/W glass ceramic	Oxyapatite and wollastonite		MgO CaO SiO_2 P_2O_5 CaF_2	
Calcium phosphates				
Whitelockite	Tricalcium phosphate	TCP	$Ca_3(PO_4)_2$	1.5
Hydroxyapatite	Pentacalcium-hydroxy-triphosphate	HA	$Ca_{10}(PO_4)_6(OH)_2$	1.67
Fluorapatite	Pentacalcium-fluoride-triphosphate	FA	$Ca_{10}(PO_4)_6F_2$	1.67
Hilgenstockite	Tetracalcium phosphate	TTCP	$CaO.Ca_3(PO_4)_2$	2.0



Existing calcium orthophosphates and their major properties [1,2]

Ca/P molar ratio	Compound	Formula	Solubility at 25 °C, -log(K_s)	Solubility at 25 °C, g/L	pH stability range in aqueous solutions at 25 °C
0.5	Monocalcium phosphate monohydrate (MCPM)	$Ca(H_2PO_4)_2 \cdot H_2O$	1.14	~18	0.0–2.0
0.5	Monocalcium phosphate anhydrous (MCPA)	$Ca(H_2PO_4)_2$	1.14	~17	[c]
1.0	Dicalcium phosphate dihydrate (DCPD), mineral brushite	$CaHPO_4 \cdot 2H_2O$	6.59	~0.088	2.0–6.0
1.0	Dicalcium phosphate anhydrous (DCPA), mineral monetite	$CaHPO_4$	6.90	~0.048	[c]
1.33	Octacalcium phosphate (OCP)	$Ca_8(HPO_4)_2(PO_4)_4 \cdot 5H_2O$	96.6	~0.0081	5.5–7.0
1.5	α-Tricalcium phosphate (α-TCP)	$\alpha\text{-}Ca_3(PO_4)_2$	25.5	~0.0025	[a]
1.5	β-Tricalcium phosphate (β-TCP)	$\beta\text{-}Ca_3(PO_4)_2$	28.9	~0.0005	[a]
1.2–2.2	Amorphous calcium phosphate (ACP)	$Ca_xH_y(PO_4)_z \cdot nH_2O$, $n = 3–4.5$; 15–20% H_2O	[b]	[b]	~5–12[d]
1.5–1.67	Calcium-deficient hydroxyapatite (CDHA)[e]	$Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x}$[f] $(0 < x < 1)$	~85.1	~0.0094	6.5–9.5
1.67	Hydroxyapatite (HA or OHAp)	$Ca_{10}(PO_4)_6(OH)_2$	116.8	~0.0003	9.5–12
1.67	Fluorapatite (FA or FAp)	$Ca_{10}(PO_4)_6F_2$	120.0	~0.0002	7–12
2.0	Tetracalcium phosphate (TTCP or TetCP), mineral hilgenstockite	$Ca_4(PO_4)_2O$	38–44	~0.0007	[a]

[a] These compounds cannot be precipitated from aqueous solutions.

[b] Cannot be measured precisely. However, the following values were found: 25.7 ± 0.1 (pH = 7.40), 29.9 ± 0.1 (pH = 6.00), 32.7 ± 0.1 (pH = 5.28). The comparative extent of dissolution in acidic buffer is: ACP >> α-TCP >> β-TCP > CDHA >> HA > FA.

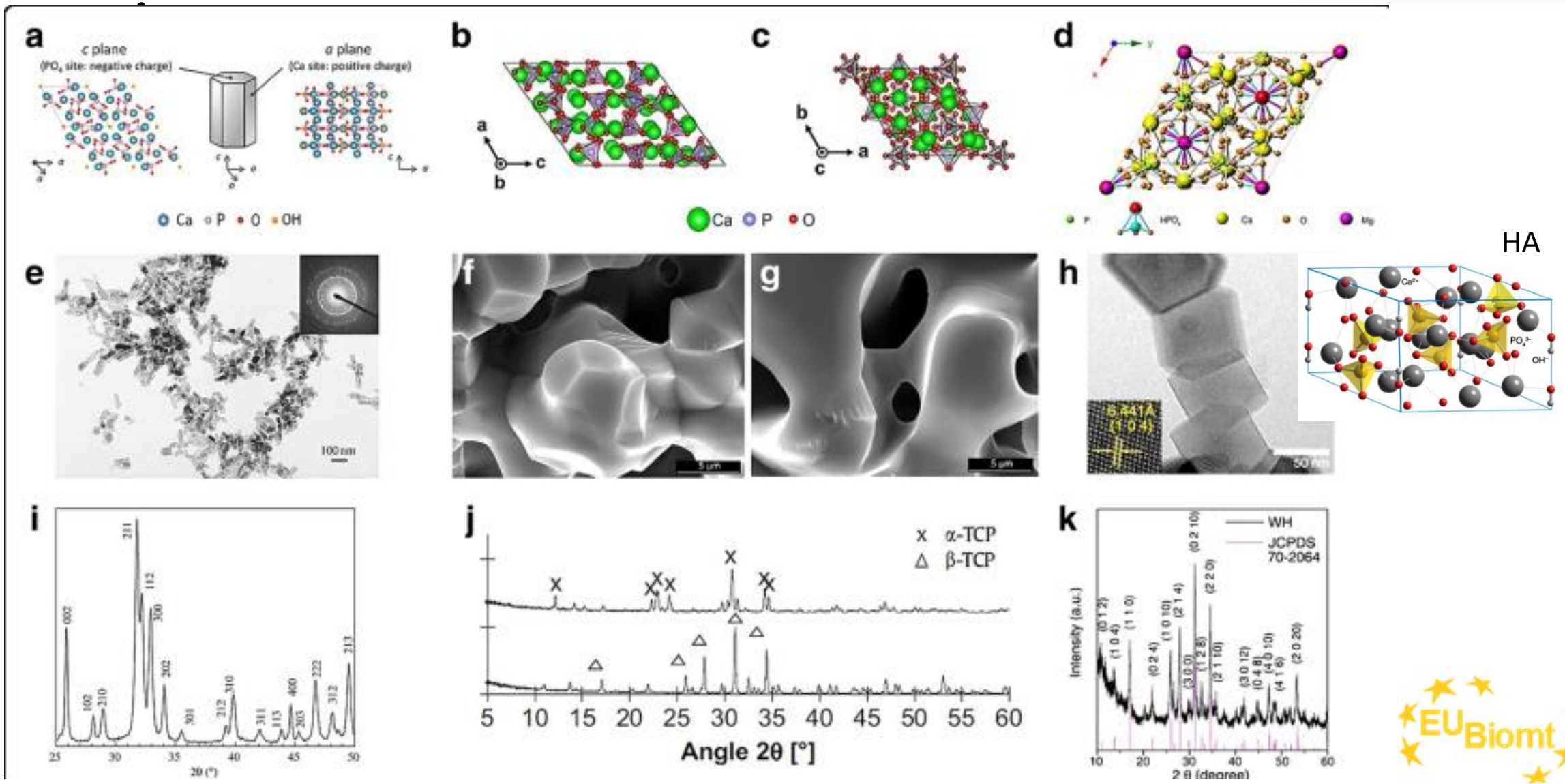
[c] Stable at temperatures above 100 °C.

[d] Always metastable.

[e] Occasionally, CDHA is named as precipitated HA.

[f] In the case $x = 1$ (the boundary condition with Ca/P = 1.5), the chemical formula of CDHA looks as follows: $Ca_9(HPO_4)(PO_4)_5(OH)$.

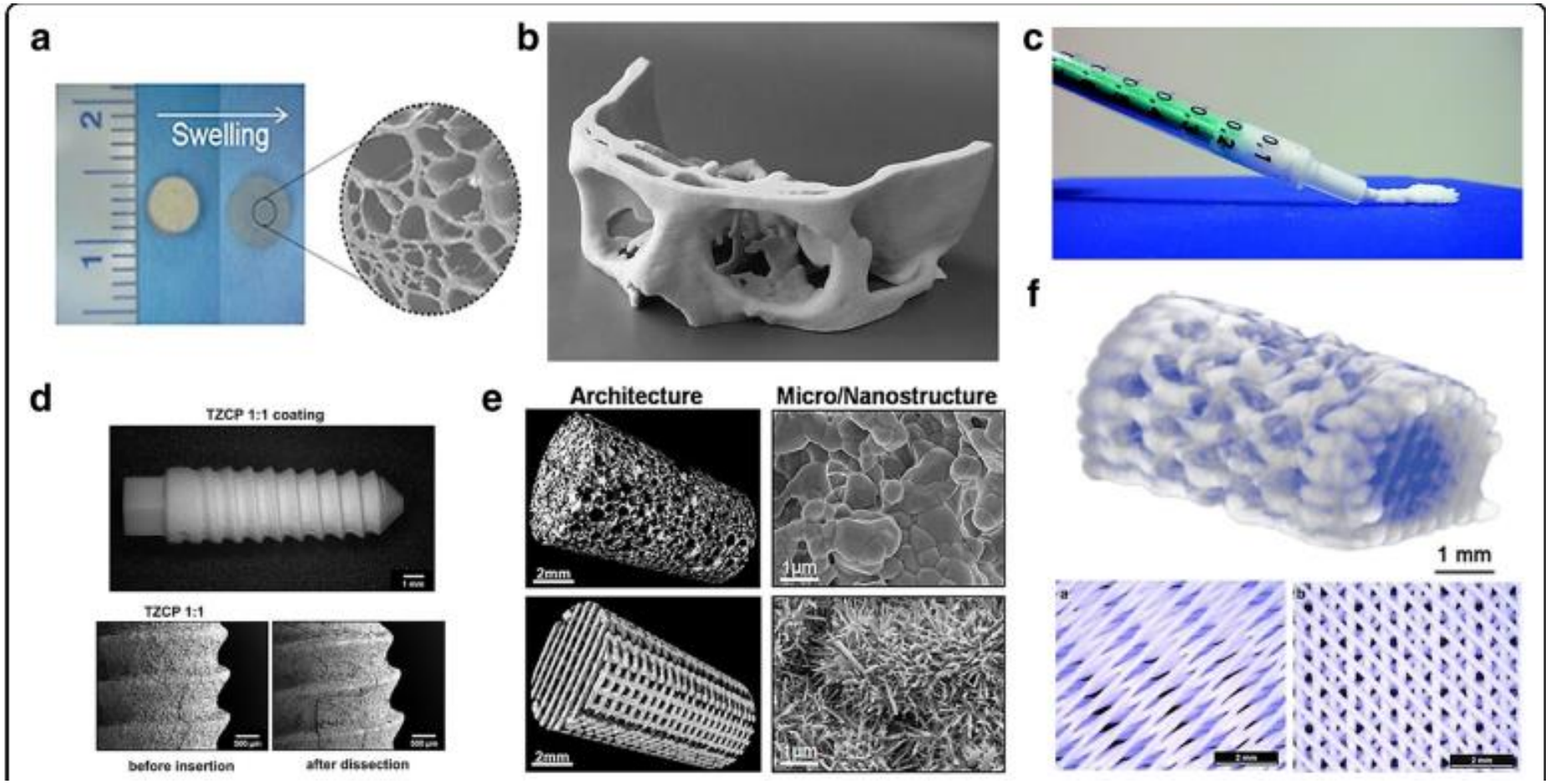
Illustration of the crystal structure of (a) HA , (b) α-TCP, (c) β-TCP, and (d) WH. Copyright 2013 American Chemical Society. TEM and SEM images of (e) HA, (f) α-TCP, (g) β-TCP, and (h) WH. XRD data of (i) HA, (j) α-TCP and β-TCP, and (k) WH [3]



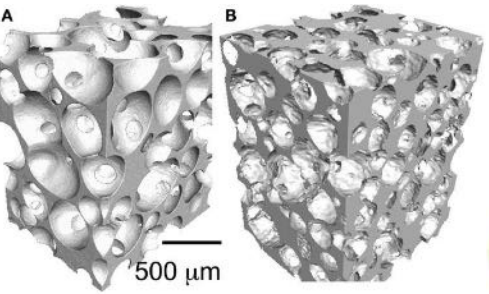
Examples of the commercial calcium orthophosphate-based bioceramics and biomaterials

Calcium orthophosphate	Trade name and producer
CDHA	Cementek (Teknimed, France) Osteogen (Impladent, NY, USA)
HA	Apaceram (Pentax Corp., Japan) Calcitite (Zimmer, IN, USA) Bonefil (Mitsubishi Materials Corp., Japan) Bonetite (Mitsubishi Materials Corp., Japan) Boneceram (Sumitomo Osaka Cement Co., Japan) Ostegraf (Ceramed, CO, USA) Cerapatite (Ceraver, France) Synatite (SBM, France) Ostim (Heraeus Kulzer, Germany) Bioroc (Depuy-Bioland, France)
HA/polyethylene	HAPEX (Gyrus, TN, USA)
HA/$CaSO_4$	Hapset (LifeCore, MIN, USA)
Coralline HA	Interpore, ProOsteon (Interpore, CA, USA)
Algae-derived HA	Algipore (Dentsply Friadent, Germany)
Bovine bone apatite (unsintered)	Tutoplast (IOP, CA, USA) Lubboc (Ost-Developpement, France) Laddec (Ost-Developpement, France) Oxbone (Bioland biomateriaux, France) BioOss (Geitslich, Switzerland)
Bovine bone apatite (sintered)	Endobon (Merck, Germany) PepGen P-15 (Dentsply Friadent, Germany) BonAP Cerabone (aap Implantate, Germany) Osteograf (Ceramed, CO, USA)
β-TCP	Bioresorb (Sybron Implant Solutions, Germany) Biosorb (SBM S.A., France) Calciresorb (Ceraver, France) ChronOS (Synthes, PA, USA) Ceros (Thommen Medical, Switzerland) Cerasorb (Curasan, Germany) Conduit (DePuy Spine, USA) JAX (Smith and Nephew Orthopaedics, USA) Graftys BCP (Graftys, France) Osferion (Olympus Terumo Biomaterials, Japan)
BCP (HA + β-TCP)	MBCP (Biomatlante, France) Triosite (Zimmer, IN, USA) Ceraform (Teknimed, France) Biosel (Depuy Bioland, France) TCH (Kasios, France) Calciresorb (Ceraver, France) Osteosynt (Einco, Brazil) 4Bone (MIS, Israel) Kainos (Signus, Germany) SBS (Expanscience, France) Eurocer (FH Orthopedics, France) OptiMX (Exactech, USA) BCP (Medtronic, MN, USA) Hatric (Arthrex, Naples, FL, USA) Tribone (Stryker, Europe)
BCP (HA + α-TCP)	Skelite (Millennium Biologix, ON, Canada)
BCP/collagen	Allograft (Zimmer, IN, USA)
BCP/fibrin	TricOS (Baxter BioScience, France)
BCP/silicon	FlexHA (Xomed, FL, USA)
Carbonateapatite	Healos (Orquest, CA, USA)

Calcium phosphate based applications

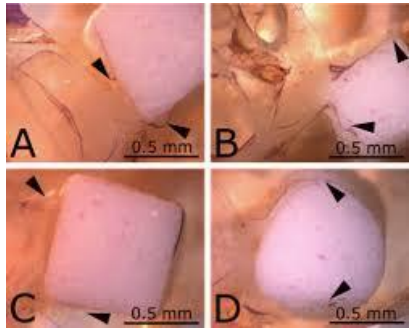


(a) WH incorporated hydrogel scaffold [4]. (b) Cranial segment made of tetracalcium phosphate and β-TCP [5]. (c) The injectable paste included calcium phosphate nanoparticles [6]. (d) Mixed zirconia calcium phosphate deposited on dental implant [7]. (e) 3D printed calcium-deficient HAP scaffolds [8]. (f) 3D printed calcium phosphate cement [3-8]



Bioactive glass - Alchetron

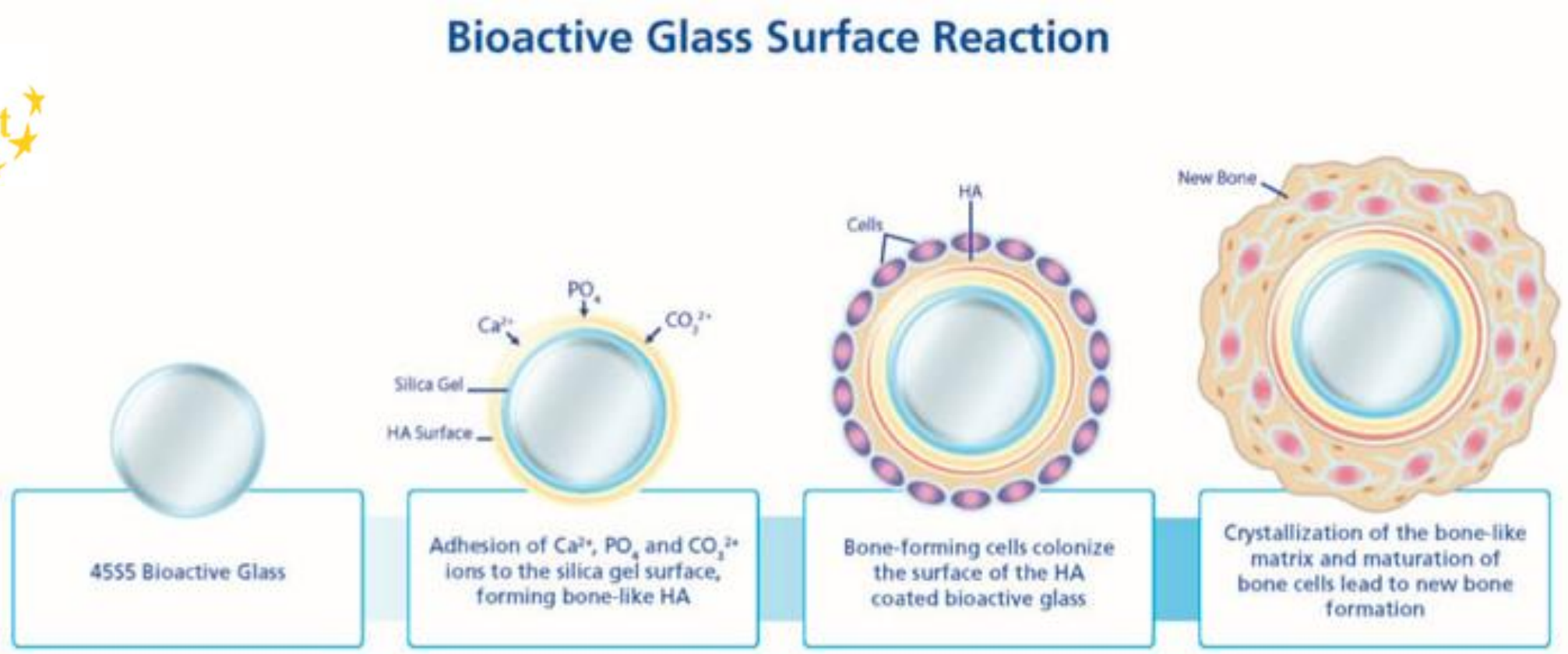
Cerabone



Bioverit

- **Bioactive Glass-ceramics**
  - **Commercialized glass-ceramics**
    - **Cerabone ®** Developed by Kokubo *et al.*
    - **Bioverit ®** Developed by Höland *et al.*
    - **Biosilicate ®** Developed by Zanotto *et al.*
    - **Ceravital ®** Developed by Brömer *et al.*
  - **Further investigations are required**
    - **Miscellaneous glass-ceramics**
      - **Apatite-mullite glass-ceramic** Developed by R.G. Hill *et al.*
      - **Canasite-apatite glass-ceramic** Developed by C.C. Wolcott *et al.*
      - **Rhenanite glass-ceramic** Developed by E. Apel *et al.*
      - **Calcium pyrophosphate glass-ceramic** Developed by T. Kasuga *et al.*
      - **Chlorapatite glass-ceramic** Developed by R.G. Hill *et al.*
      - **K-fluorrichterite glass-ceramic** Developed by M. Mirsaneh *et al.*
      - **Alkali-free glass-ceramic** Developed by J.M.F. Ferreira *et al.*
    - **Coatings**
      - On ceramic implants
      - On metallic implants
    - **3D porous scaffolds**
    - **Gel-derived & mesoporous**
    - **Composites**
      - GC-reinforced polymer
      - Metal-reinforced glass-ceramic
    - **Hyperthermia treatment**

Bioactive Ceramics. Bioactive materials are those that chemically bond with bone or tissue of the hosts [1]. The most important applications of bioactive bioceramics has been metal coatings to provide bone-implant interfacing, this lowers the risk of rejection and transmission of diseases [2].



- Glass is made of Silica, Calcium oxide, and Sodium oxide (SiO_2-Na_2O-CaO), and bioglasses used for implantation are based on glass with at least 65 weight percent Silica. Bioglasses have high mechanical strength and are bioinert, but are also brittle and have poor tensile properties. They are normally used in bone plating, dental implants, spinal fusions, and more. In 1971 the first bioglass, 45S5 bioglass, was created. It was unusually weak with a composition of 45% Silica, 24.5% Calcium oxide, and 24.5% Sodium oxide. The high bioactivity of 45S5 is attributed to the later addition of 6% Phosphorus pentoxide (P_2O_5) by weight [1]

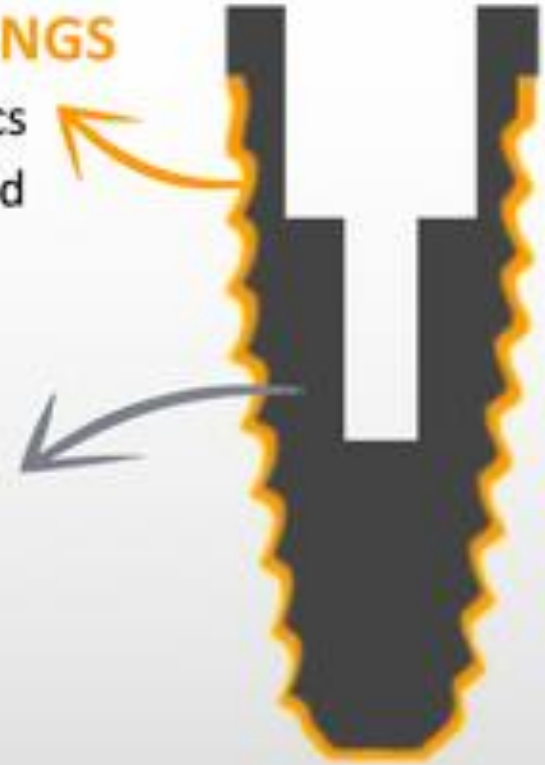
Ceramic coatings

BIOACTIVE COATINGS

- Silica-based ceramics
- Bioactive glasses and glass-ceramics

SUBSTRATES

- Ti-based
- Stainless Steel
- Mg-based

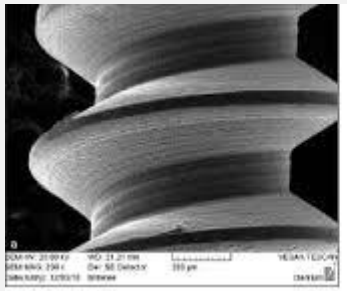


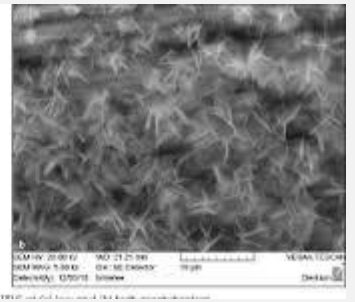
INVESTIGATED AREAS

- Deposition methods
- Coating adhesion to substrates
- Immersion in SBF
- *In vitro* experiments
- *In vivo* experiments

Ceramic coatings The requirement for a sufficient mechanical stability necessitates the use of a metallic body for such devices to improve the contacts at the interface. The major way is to coat metals with calcium orthophosphate bioceramics that generally exhibit bone bonding ability between the metal and bone

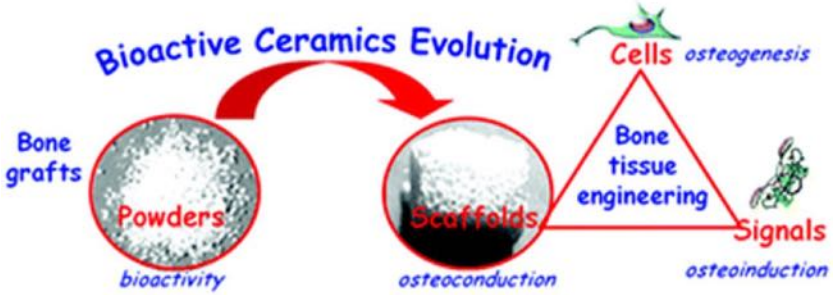
Technique	Thickness	Advantages	Disadvantages
Thermal spraying	30–200 μm	High deposition rates; low cost	Line of sight technique; high temperatures induce decomposition; rapid cooling produces amorphous coatings
Sputter coating	0.5–3 μm	Uniform coating thickness on flat substrates; dense coating	Line of sight technique; expensive; time consuming; produces amorphous coatings
Pulsed laser deposition	0.05–5 μm	Coating by crystalline and amorphous phases; dense and porous coating	Line of sight technique
Dynamic mixing method	0.05–1.3 μm	High adhesive strength	Line of sight technique; expensive; produces amorphous coatings
Dip coating	0.05–0.5 mm	Inexpensive; coatings applied quickly; can coat complex substrates	Requires high sintering temperatures; thermal expansion mismatch
Sol–gel technique	<1 μm	Can coat complex shapes; low processing temperatures; relatively cheap as coatings are very thin	Some processes require controlled atmosphere processing; expensive raw materials
Electrophoretic deposition	0.1–2.0 mm	Uniform coating thickness; rapid deposition rates; can coat complex substrates	Difficult to produce crack-free coatings; requires high sintering temperatures
Biomimetic coating	<30 μm	Low processing temperatures; can form bonelike apatite; can coat complex shapes; can incorporate bone growth stimulating factors	Time consuming; requires replenishment and a pH constancy of simulated body fluid
Hot isostatic pressing	0.2–2.0 μm	Produces dense coatings	Cannot coat complex substrates; high temperature required; thermal expansion mismatch; elastic property differences; expensive; removal/interaction of encapsulation material
Electrochemical deposition	0.05–0.5 mm	Uniform coating thickness; rapid deposition rates; can coat complex substrates; moderate temperature, low cost	The coating/substrate bonding is not strong enough





A number of factors influence the properties of calcium orthophosphate coatings including

- coating thickness (this will influence coating adhesion and fixation – the agreed optimum now seems to be within 50–100 mm),
- crystallinity (this affects the dissolution and biological behavior), phase purity,
- chemical purity,
- porosity,
- Adhesion



HA coating as a system of fixation of hip implants was found to work well in the short to medium term (8 years, 10–15.5 years, 15 years, 17 years and 19 years). Similar data for HA-coated dental implants are also available. The longer-term clinical results are awaited with a great interest

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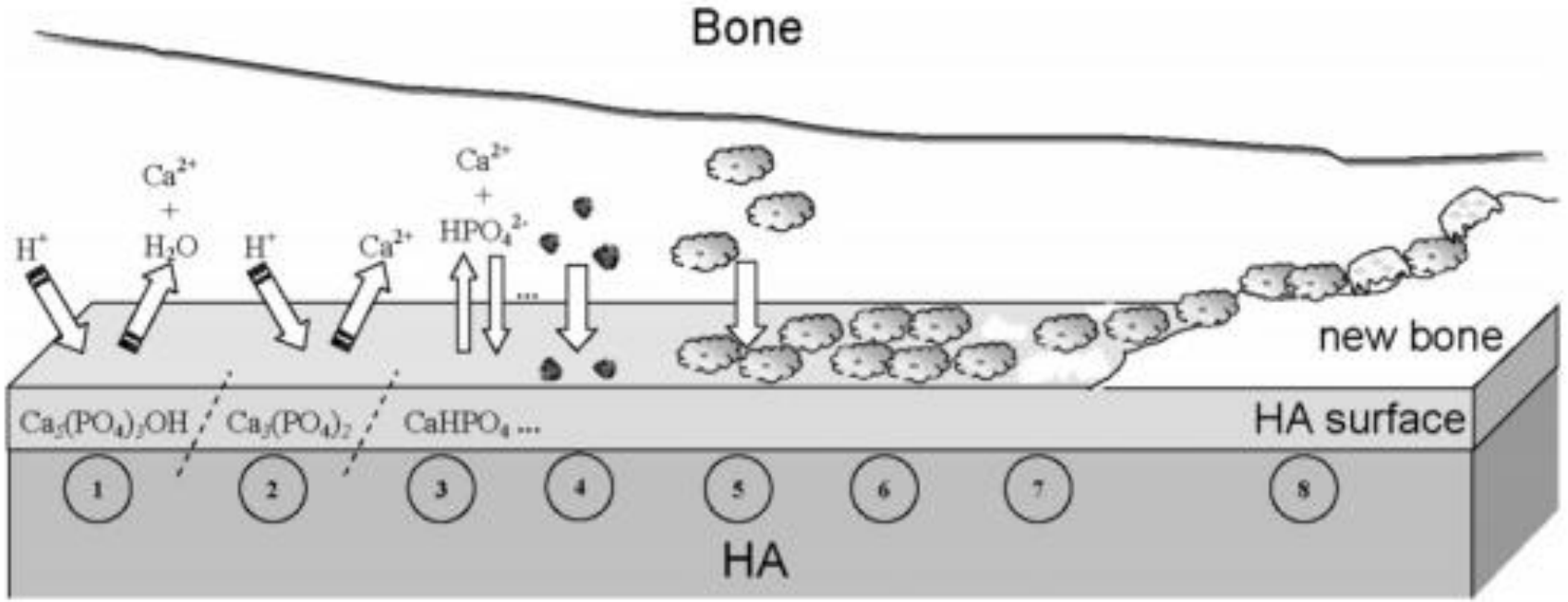
A schematic diagram representing the phenomena that occur on HA surface after implantation



(1) beginning of the implant procedure, where a solubilization of the HA surface starts;

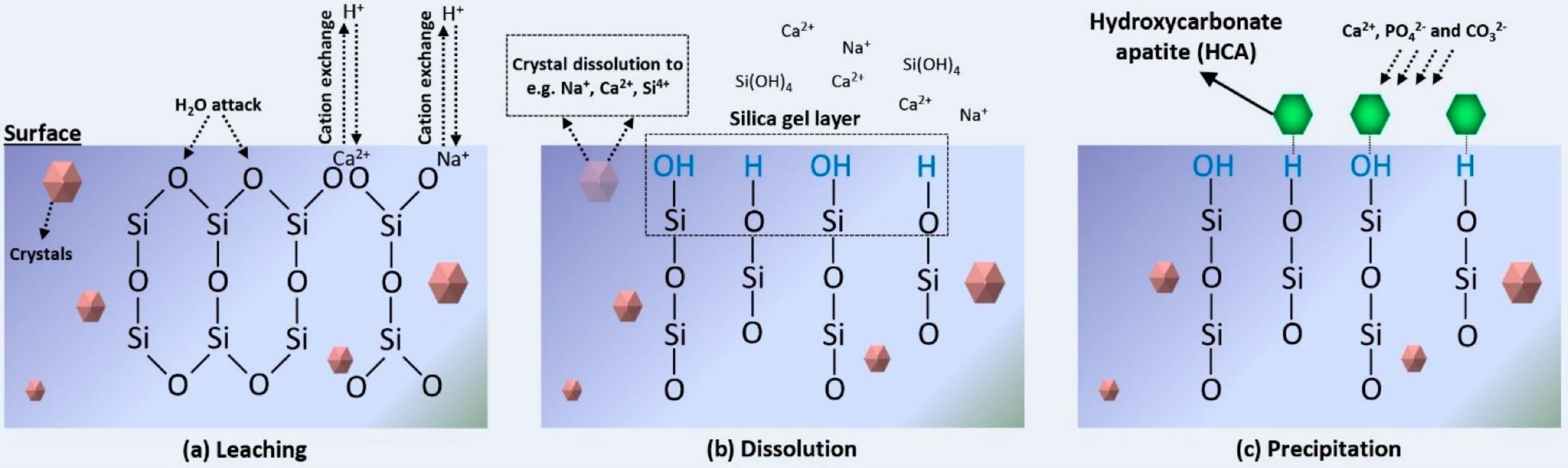
(2) continuation of the solubilization of the HA surface; (3) the equilibrium between the physiological solutions and the modified surface of HA has been achieved (changes in the surface composition of HA does not mean that a new phase of DCPA or DCPD forms on the surface); (4) adsorption of proteins and/or other bioorganic compounds; (5) cell adhesion; (6) cell proliferation; (7) beginning of a new bone formation; (8) new bone has been formed. Reprinted from Ref. [1].

Properties required from calcium phosphates for medical applications [11]

Property	Definition/Function
Bioactivity	The inherent ability of a material to participate in specific biological reactions or have an effect on living tissues
Biocompatibility	The ability of a material to perform with an appropriate host response in a specific application
Bioactive fixation	Reactive surfaces form chemical bonding with bone, thus minimizing the fibrous capsule formation
Biostability	The ability of a material to maintain its properties *in vivo*
Crystallinity	Higher level of crystallinity prevents fast resorption (dissolution) of the bioceramic in body fluids
Interfacial stability and good adhesion	Prevent mechanical failures under load-bearing conditions
Osseointegration	Direct anchorage of an implant by the formation of bony tissue around it without growth of fibrous tissue at the bone/implant interface
Osteoconduction	Ability to provide a scaffold for the formation of new bone
Osteoinduction	The process by which osteogenesis is induced. This term means that primitive, undifferentiated and pluripotent cells are somehow stimulated to develop into the bone-forming cell lineage
Resorption	Gradual degradation over time to replace the biomaterial with the natural host tissue
Therapeutic capabilities	Templates for the in situ delivery of drugs and growth factors at required times
Wettability	The property that indicates a material's ability to attract/repel water molecules

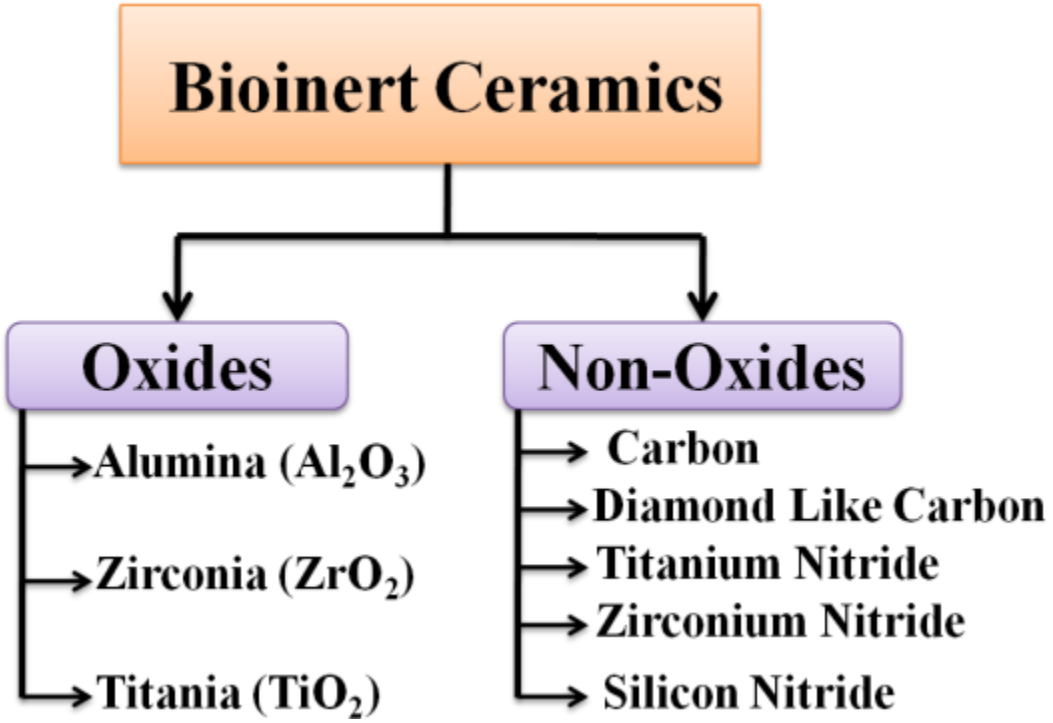
In-vitro behaviour of glass-ceramic in SBF

Piece of glass-ceramic in a simulated body fluid which contains Ca^{2+}, H^+, K^+, Mg^{2+}, Na^+, Cl^-, HCO_3^-, HPO_4^{2-}, OH^- and SO_4^{2-}



(a) Leaching (b) Dissolution (c) Precipitation

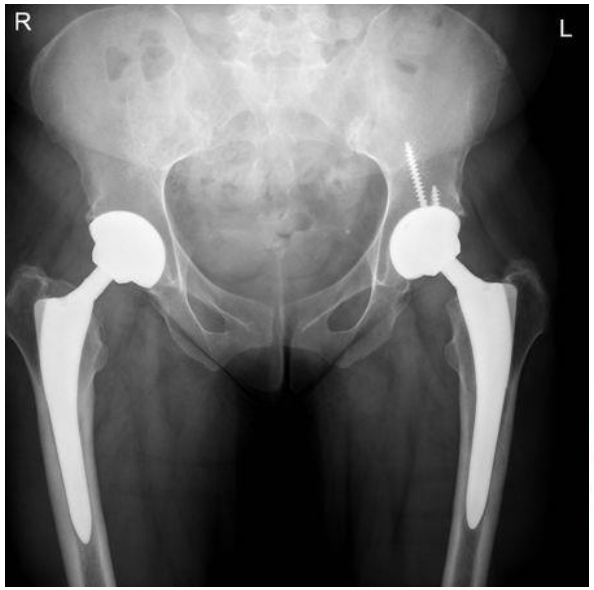
Classification of bioinert ceramics



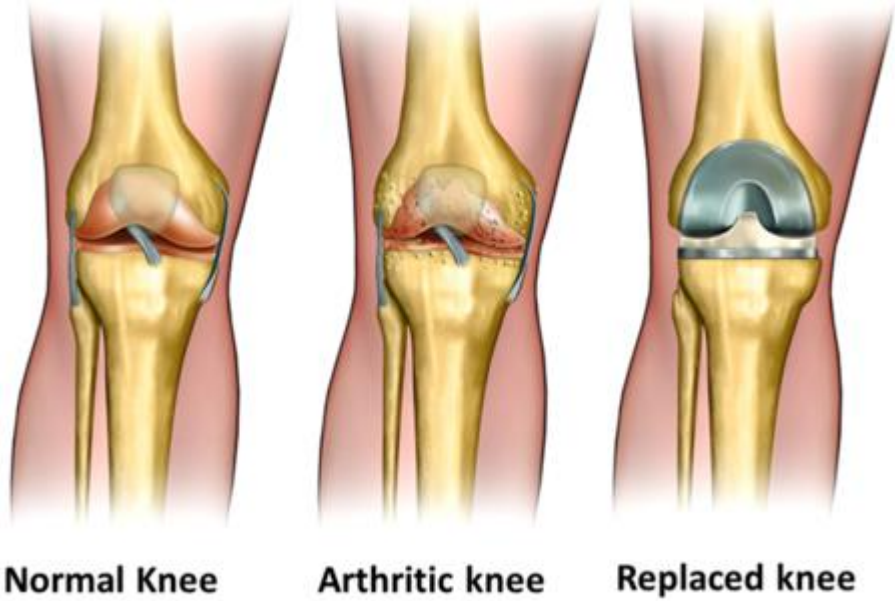
Bioinert ceramics are one type of the bioceramics and which classified based on their biological response in human body. Bioinert ceramics are usually defined as biologically inert nature or bioinert ceramics when implanted into biological system do not instigate an appropriate response or interact with the adjacent biological tissue Bioinert ceramics are corresponds to first generation of biomaterials and widely used as hip, knee replacements and dental implant, crown etc due to astonishing characteristics such as high mechanical properties like tensile, compressive, hardness, low wear, toughness and good anticorrosion in biological fluid. There are mainly three type of metal based bioinert ceramics such as alumina, zirconia and titania have been used in musculoskeletal applications [10].

Bioinert ceramics

Total Hip Replacement (Source)

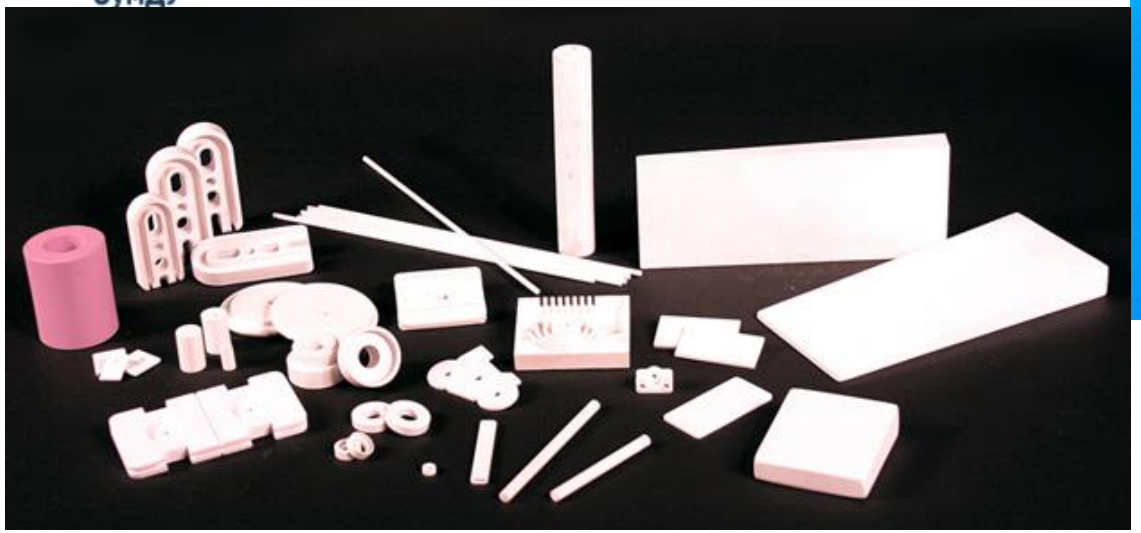


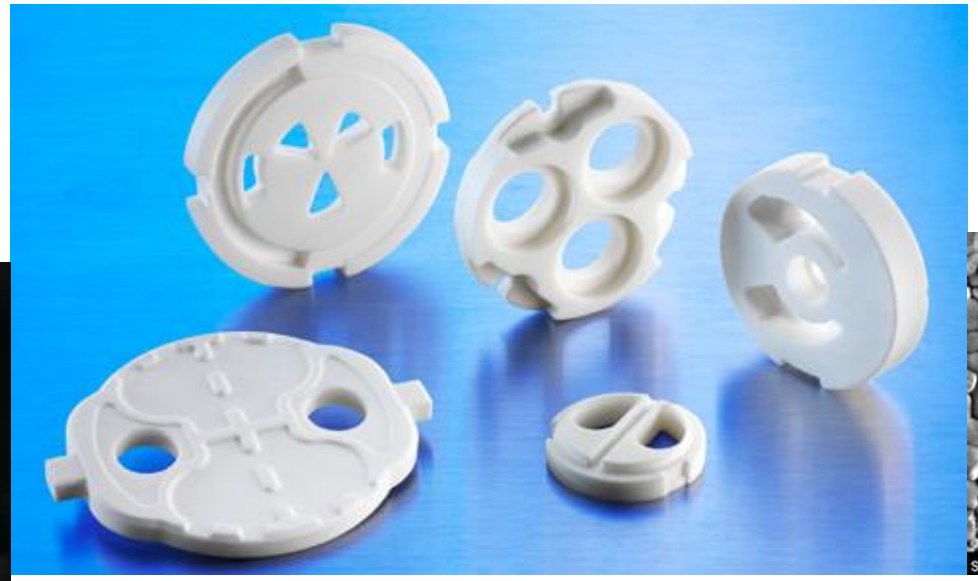
Total Knee Replacement (Source)

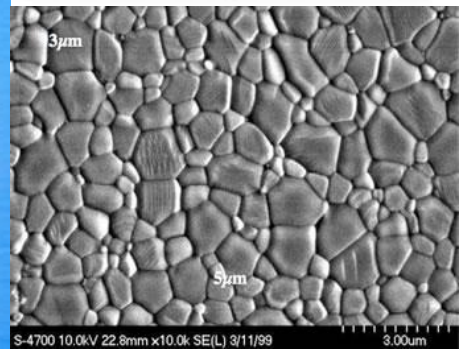


- ***Ceramics that retain structure after implantation and do not induce an immunologic response in the host***.[*10*]
- **Alumina (Al_2O_3)** Highly inert, especially under physiological conditions, and has a corrosive resistances. It also has excellent wear resistance and hardness. Has dental applications, function as vertebrae spacers and extensors.[9] The body normally reacts to alumina by forming non-adherent fibers around the implant.
- **Zirconia (ZrO_2)** Zirconia is inert under physiological conditions like Alumina. Partially stabilized Zirconia (PSZ) has a higher flexural strength, toughness, reliability, and a lower Young's modulus. Zirconia is good for long-term clinical use. It is widely used in total hip replacement (THR), and as a replacement for knees, tendons, ligaments, and teeth. Examples of Zirconia based bioceramics include Yttrium Stabilized Tetragonal Polycrystalline Zirconia (Y-TZP), and Zirconia/Alumina composites.[9]

Al_2O_3 Ceramics





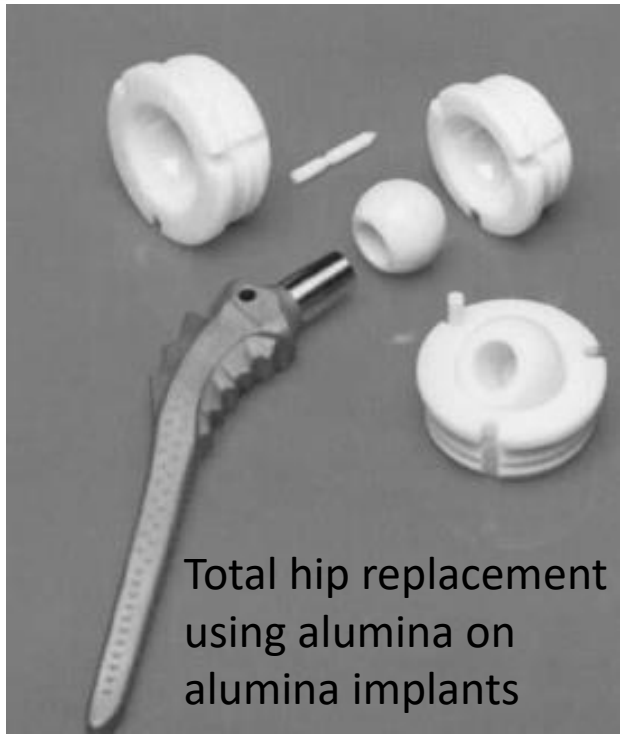


There are Properties of Alumina/Aluminum Oxide:

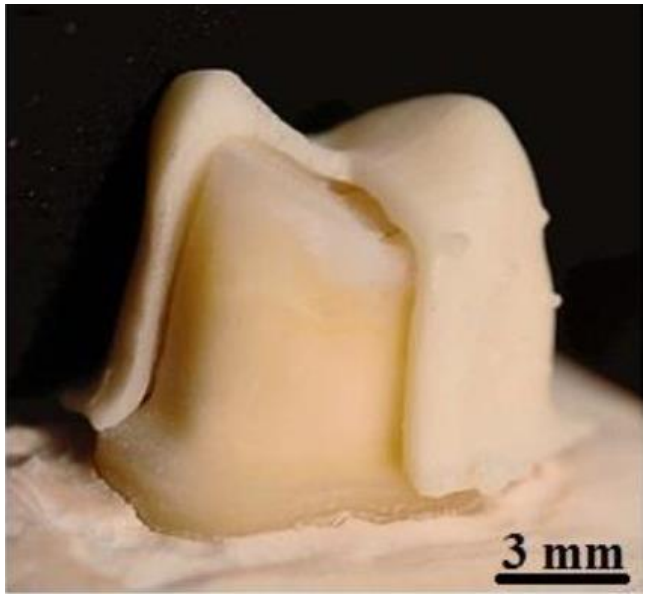
Good gliding properties	Low density
Bioinert and food compatible	Very good electrical insulation
Moderate to extremely high mechanical strength	
Very high compressive strength	High hardness
Moderate thermal conductivity	High corrosion and wear resistance

- The Alumina (Aluminum oxide, Al_2O_3) is one of the most clinical usage biomaterials with 45 years of clinical record in orthopeadic surgeries. The alumina can still employ successfully as pure form or with combination of other components in high performance composite form in bone tissue engineering. The key reason for the selecting alumina as bone substitute and dental implants due to its strong hardness, resistance of abrasion, low wear, corrosion resistance, excellent mechanical strength, good hydrodynamic stability and biologically compatible nature. Alumina used to develop as nanocomposites with combination of bioactive ceramics, polymers and carbon based materials for biomedical applications [10]

Application of Al_2O_3 Ceramics


Total hip replacement using alumina on alumina implants

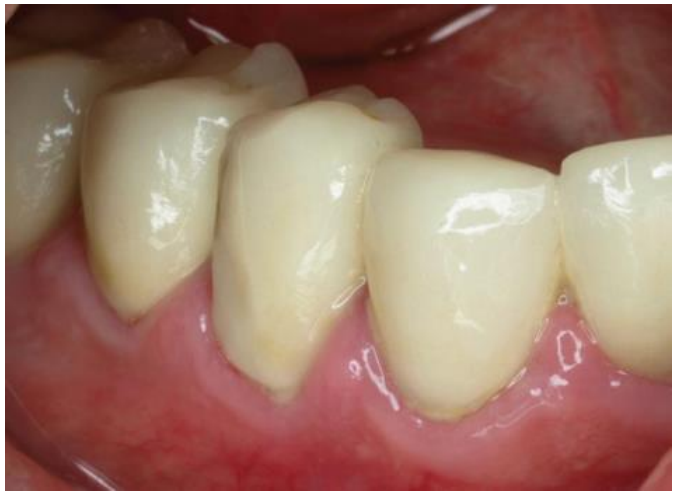
Since 1989, the USA using ceramic femoral heads coupled to polyethylene in total hip replacements and non USA countries clinical surgeons were demonstrated the advantages of modern alumina-on-alumina for younger and highly active patients. In 2003 February, the FDA was successfully approved the BIOLOXR forte alumina inlays (CeramTec GmbH, Plochingen, Germany) to use in USA for orthopeadic applications.
Ceram Tec AG products in the period of 2000-2013, in which 2.78 and 3.2 million of alumina matrix composite ceramic ball heads and pure alumina were used worldwide.



Ultraviolet-Stereolithography produced Alumina crown for dentistry

- For the last few decades, high strength alumina materials are using in all parts of mouth to develop the coping and frameworks for crowns and fixed dental implants also used to increase the mechanical strength of dental porcelains. They reported that alumina toughened zirconia substrates showed significant higher digital histology index when compared with titanium at time of 56 days. Hence, they concluded that this type of prosthetic implants can be favorable materials for dental applications.

ZrO_2 Ceramics



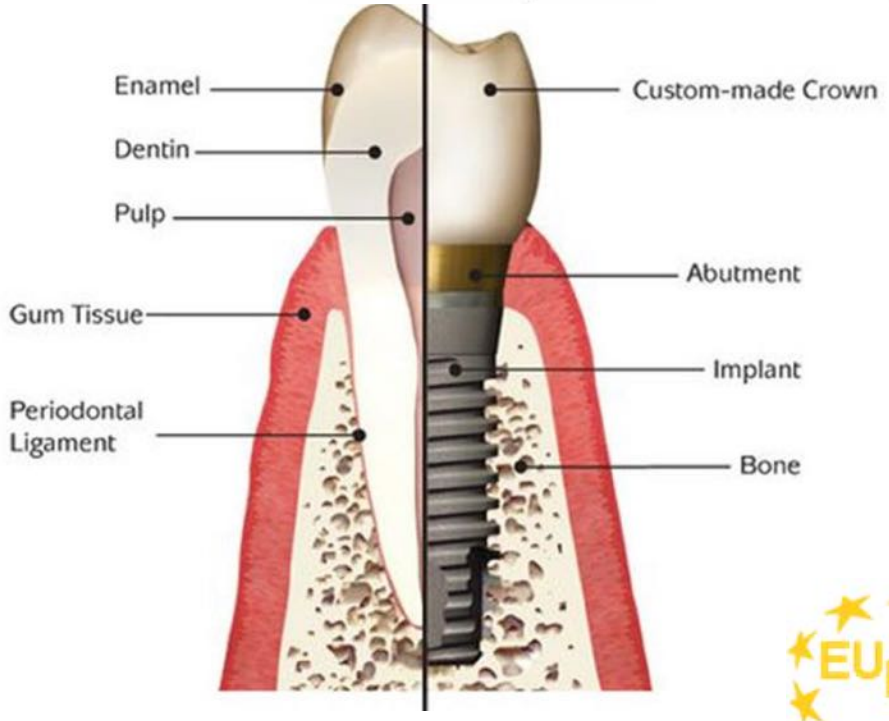
Zirconia full-coverage crown in dental applications

Hip prosthesis by titanium alloy with zirconia ball head and (B) zirconia femoral head

- In mid of 1980s, the zirconia ceramic was developed as a biomaterials to overcome the mechanical property limits of alumina ceramics. Zirconia was successfully employed as an alternative material to alumina with improvement of fracture toughness and used as femoral head in total hip replacements along with knee replacements. Zirconia is highly biological compatible and has excellent anticorrosion behavior in presence of human physiological conditions. As mentioned earlier that zirconia has superior mechanical properties such as fracture toughness and bending strength when compared to alumina, which made zirconia, could be highly suitable implant materials to use in large load bearing areas.

Bioinert ceramics

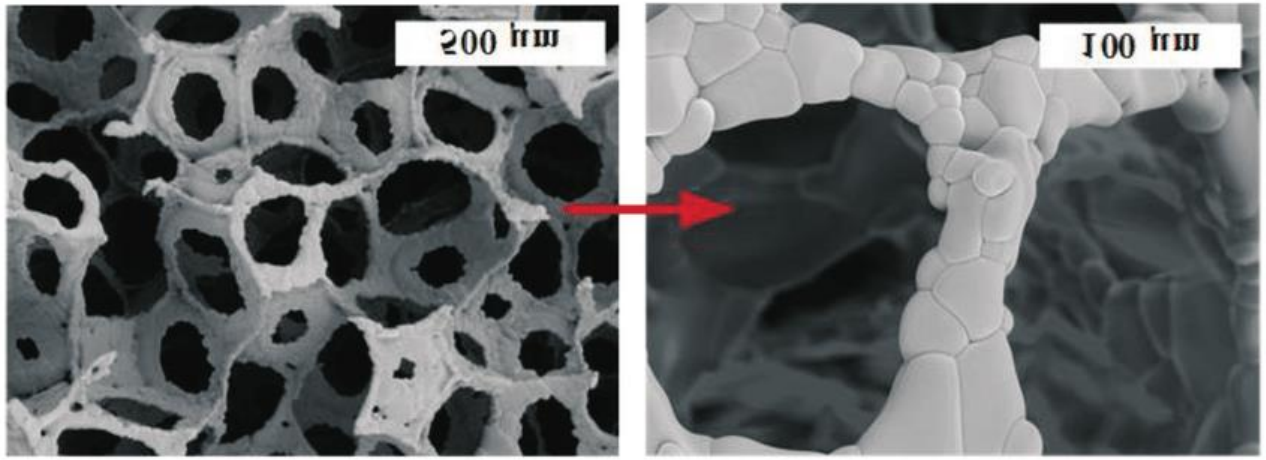
- **Issues of Y-TZP (Yttrium Stabilized Tetragonal Polycrystalline Zirconia)**
- Biomedical grade Y-TZP had the best mechanical properties of the bioinert ceramics investigated, and quickly became a standard for hip and knee replacements. In 2001, patients with Y-TZP implants reported that the implant was failing, revealing a downside to Y-TZP. It was found that due to its meta-stability, it is prone to low temperature degradation in the presence of water, which triggers a progressive aging that eventually results in surface roughening and micro-cracking. The micro-cracks eventually cause more surface defects and lead to delayed failure of the implant [11].
- For dental applications, Y-TZP was also proven to lack stability in an oral environment in long term in vivo studies. In-vitro studies performed also suggested that aging might be an issue with Y-TZP used in an oral environment [11].



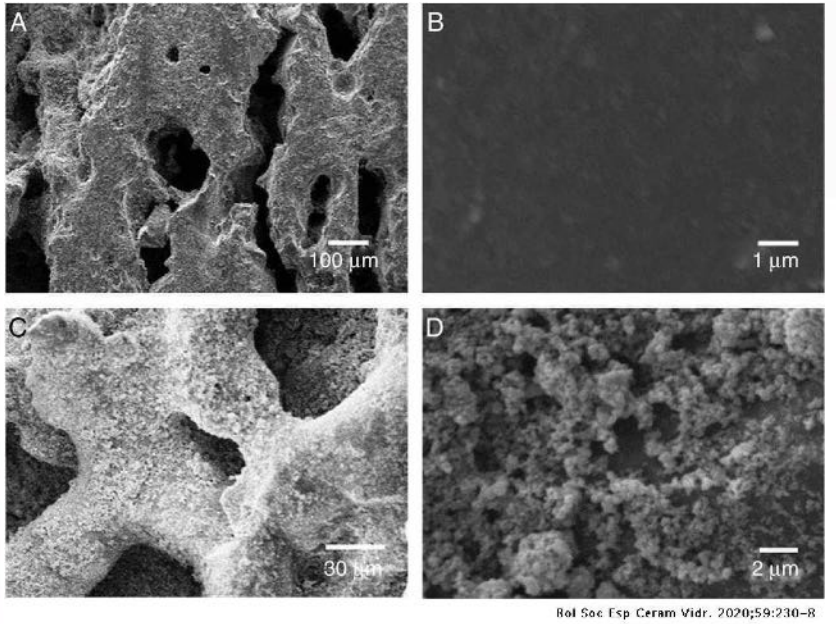
Pyrolytic Carbon

Pyrolytic Carbon are brittle and do not perform well in load bearing applications, but do not suffer from fatigue. It is commonly used in heart valves due to high strength, wear resistance, durability, and thromboresistance, or resistance to blood clotting. It can also be used for spinal inserts [11].

TiO_2 Ceramics



SEM image of TiO2 ceramics



SEM image of ceramics supported by TiO_2 nanoparticles

- Titania has been used potentially in medical applications due to their excellent low toxicity, biological compatibility, corrosion resistance behaviour, chemical resistivity and superior mechanical properties. In recent years, many researchers reported on the nanostructured TiO_2 for wide range of applications such as dental, orthopeadic, drug delivery and cell imaging. For the last few years, pure Ti and its alloys highly recommended to use in orthopedics such as fracture fixation devices, spinal fusion and artificial joints. However, Ti and its alloys have weak in bacterial restriction behaviour, osteointegration and osteoinduction property which cause failure of implants and leads to effect on their long term life span in patients. Recent reports proved that the development of nanotechnology to alter the surface property of Ti and its alloys by different techniques to create the nanoarchitectures of TiO_2

Conclusions

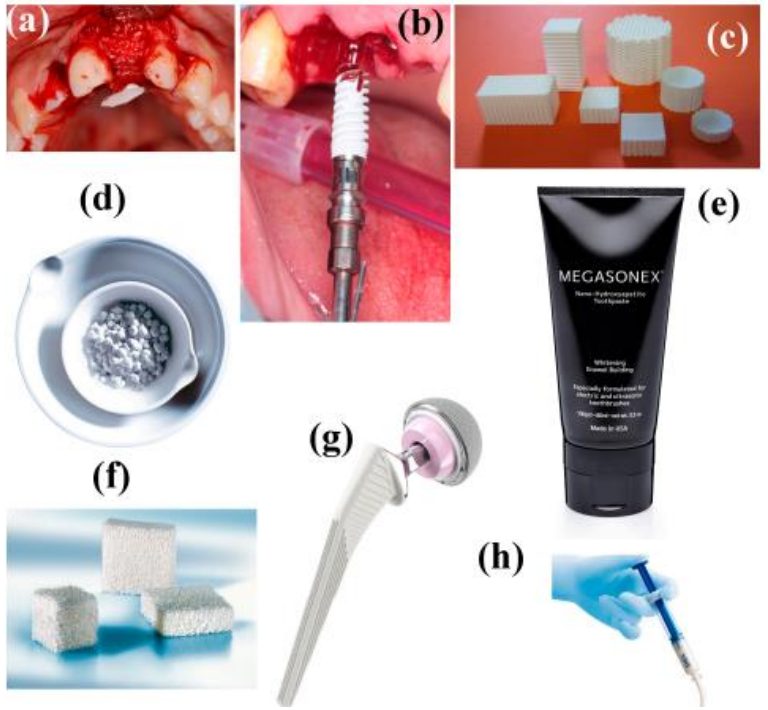
1) **WHAT ARE BIO CERAMICS?**
Bio ceramics are ceramic materials primarily used for the repair, reconstruction and replacement of diseased or damaged parts of musculo-skeletal system

2) **CHARACTERISTICS OF BIO CERAMICS** Ultra-hard, Biocompatible, Chemically inert, Physically stable, High strength, Excellent surface finish, Porous. And resistant to high temperature, Wear, corrosion and bending.

3) **MATERIALS USED AS BIO CERAMICS**
Materials that can be classified as bio ceramics include: Alumina, Zirconia, Calcium phosphates, Silica based glasses or glass ceramics, and Pyrolytic carbons

4) **TYPES OF BIOMATERIALS**
When these synthetic materials are placed within the human body, the tissues react towards the implant in a variety of ways.

5) **THE MECHANISM OF TISSUE INTERACTION** at a nanoscale level is dependant on the **RESPONSE TO THE IMPLANT SURFACE**. As such three terms for description of a biomaterial, representing the tissues responses, have been defined.These are: **BIOINERT BIOACTIVE AND BIODEGRADABLE**



Various applications and forms of commercially available CaP-related products. (a) Bone augmentation after extraction of the tooth. (b) Coated dental implant. (c) 3D Scaffold bone substitute material (3D-printed CaP cement). (d) Calcibon self-setting cement granules consisted of α-TCP, $CaHPO_4$, $CaCO_3$ and HA; (e) Megasonex® Nano-Hydroxyapatite toothpaste.

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«Modern European trends in biomedical higher education: Bionanomaterials.» № 620717-EPP-1-2020-1-UA-EPPJMO-MODULE

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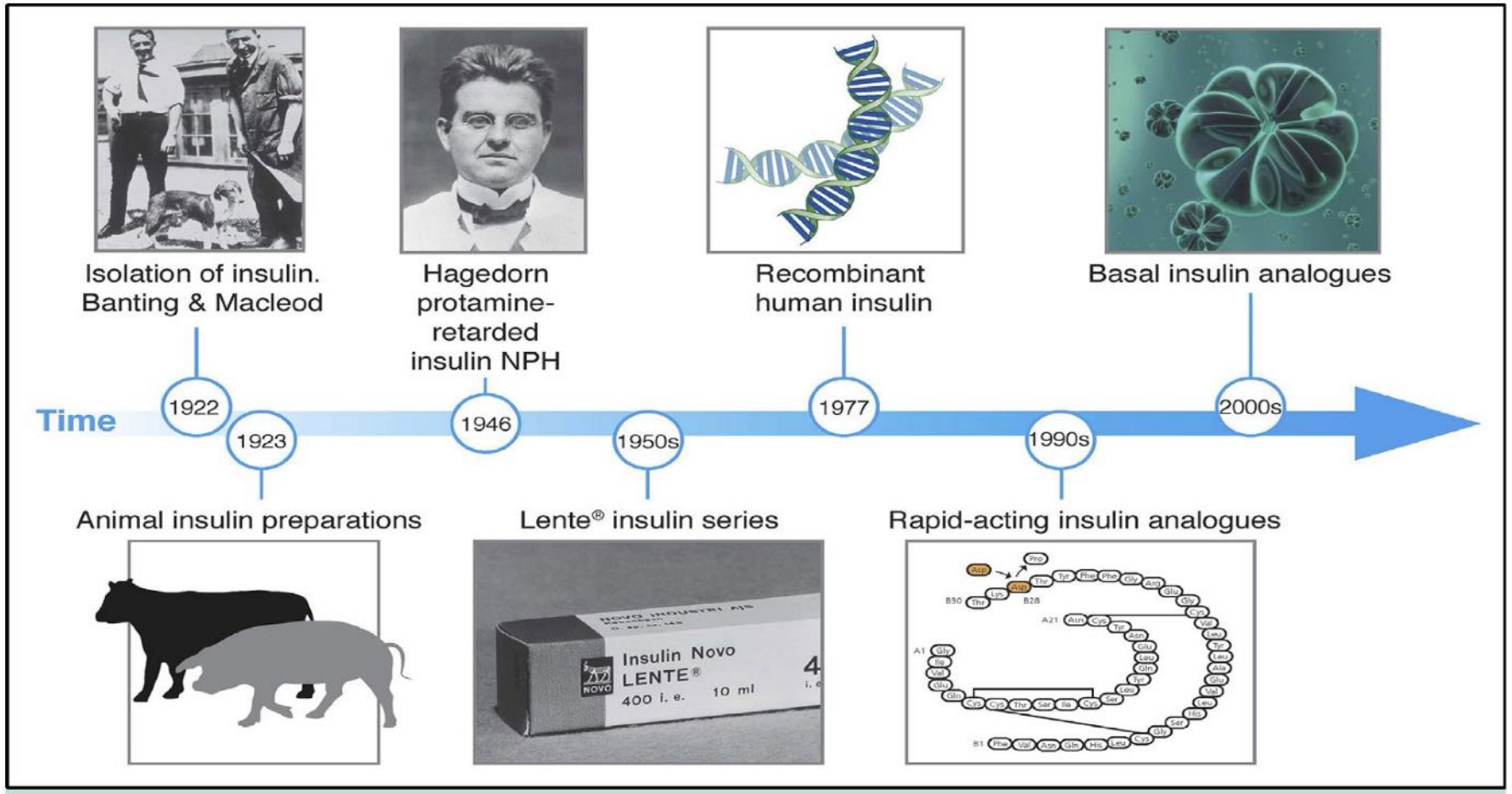

Figure 1 Milestones in the evolution of insulin therapy. NPH = neutral protamine Hagedorn.

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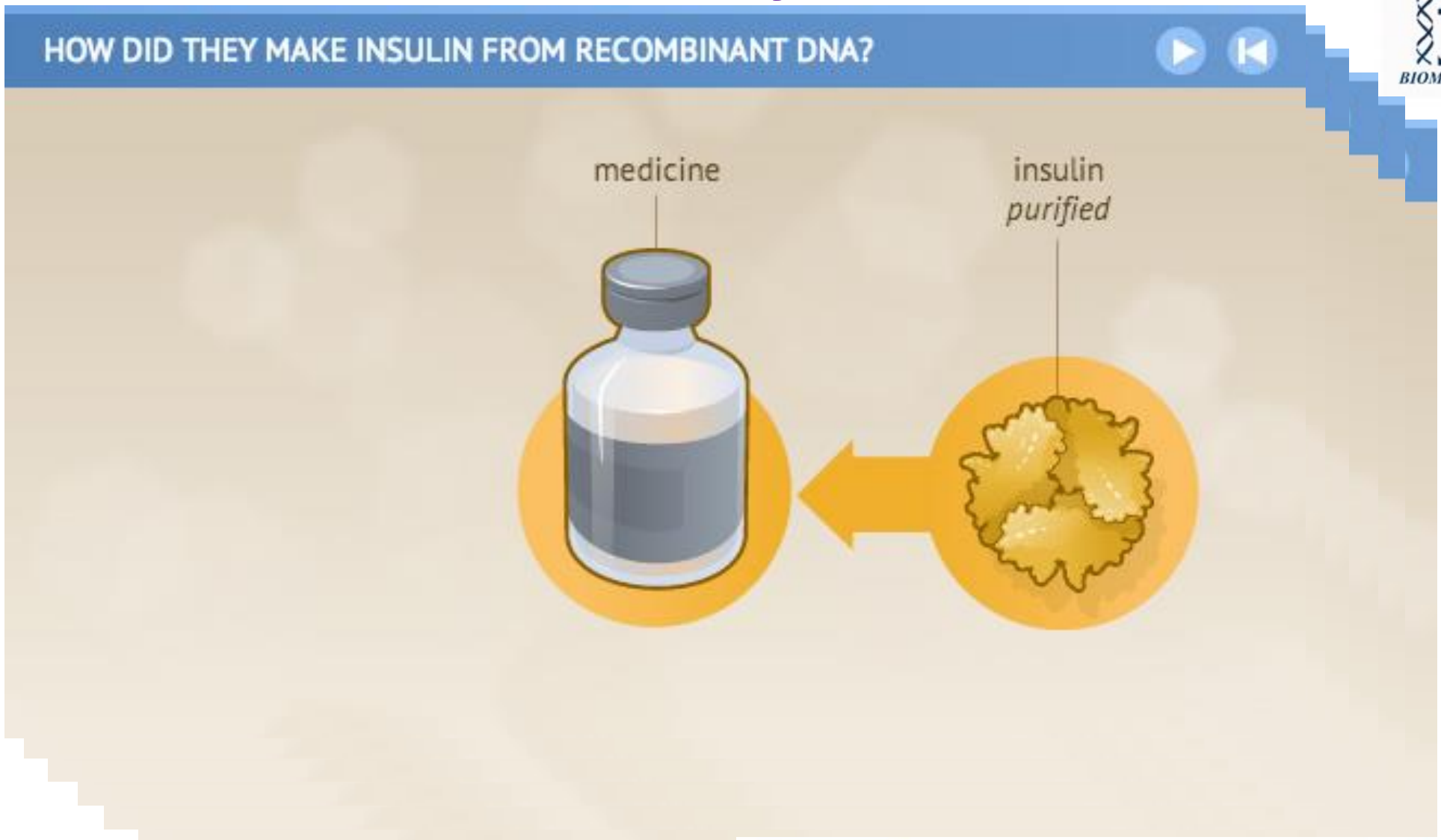
How do they do it?



https://www.nlm.nih.gov/exhibition/fromdnatobeer/exhibition-interactive/recombinant-DNA/r
alternative.html#:~:text=Recombinant%20DNA%20is%20a%20technology,insulin%20gene%20ir

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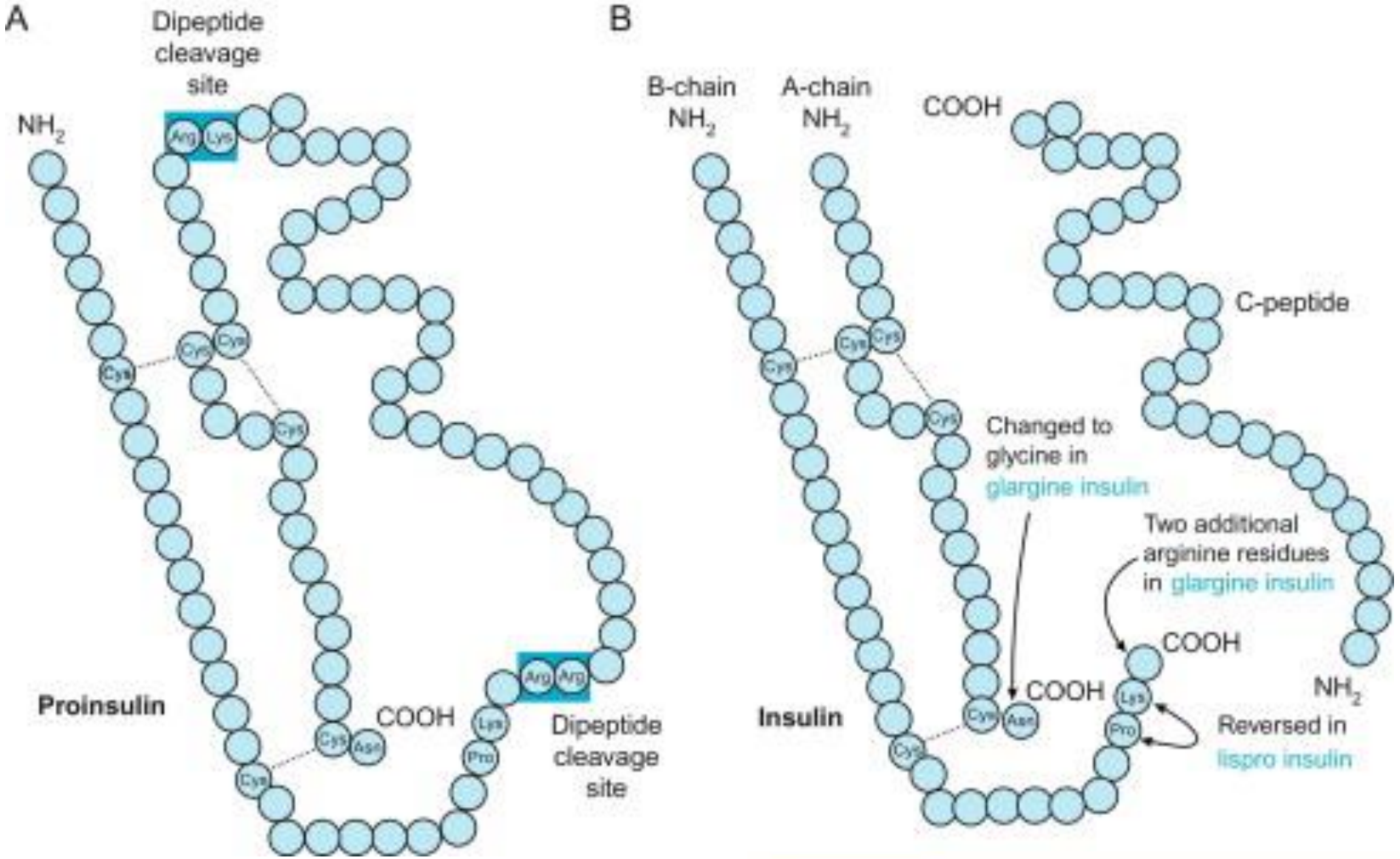

https://www.sciencedirect.com/topics/chemistry/insulin-derivative

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THE FIRST GENERATION OF THERAPEUTIC PROTEINS				
Humulin	Insulin	Eli Lilly	Diabetes	Diabetes
Hematrope	Recombinant somatropin	Eli Lilly	Hormones	Growth failure
Genotropin	Somatropin	Pfizer	Hormones	Growth failure
Saizen	Somatropin	Serono	Hormones	Growth failure
Nutropin/Protropin	Somatropin/Somatrem	Genetech	Hormones	Growth failure
Intron A	Interferon alpha 2b	Schering-Plough	Anti-infective	Viral infections
Avonex	Interferon beta-1a	Biogen Idec	Multiple sclerosis	Chronic inflammatory demyelinating polyneurophathy
Betaseron/Betaferon	Interferon beta-1b	Schering AG	Multiple sclerosis	Multiple sclerosis
Procrit/Eprex	Epoetin alpha	J&J	Blood modifier	Anemia
Epogen	Epoetin alpha	Amgen	Blood modifier	Anemia
NeoRecormon	Epoetin beta	Roche	Blood modifier	Anemia
Kogenate	Factor VIII	Bayer	Blood modifier	Hemophilia
NovoSeven	Factor VIIa	Novo Nordisk	Blood modifier	Hemophilia
Benefix	Factor IX	Wyeth	Blood modifier	Hemophilia
Fabrazyme	Agalsidase beta	Genzyme	Enzymes	Fabry disease
Replagal	Agalsidase alfa	TKT Europe	Enzymes	Fabry disease
Pulmozyme	Domase alpha	Genetech	Enzymes	Cystic fibrosis
Activase/Acitlyse	Alteplase	Genetech	Blood factor	Myocardial infarction

Medical Biotechnology

Phuc V. Pham, in Omics Technologies and Bio-Engineering, 2018

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THE SECOND GENERATION OF THERAPEUTIC PROTEINS

Humalog/Liprolog	Insulin Lispro	Eli Lilly	Diabetes	Diabetes
Lantus	Glargine insulin	Sanofi-Aventis	Diabetes	Diabetes
Levemir	Detemir insulin	Novo Nordisk	Diabetes	Diabetes
Pegasys	Pegylated interferon alpha -2a	Roche	Interferon	Hepatitis C
Peg-Intron	Pegylated interferon alpha -2a	Schering Plough	Interferon	Hepatitis C
Aranesp	Darbepoetin alpha	Amgen	Blood modifier	Anemia
Neulasta	PEG-Filgrastim	Amgen	Blood modifier	Neutropenia
Refacto	Factor VIII	Wyeth	Blood modifier	Hemophilia
Amevive	Alefacept	Biogen Idec	Inflammation/Bone	Plaque psoriasis
Enbrel	Etanercept	Amgen	Anti-arthritic	Arthritis
Ontak	rIL-2-diptheria toxin	Ligand Pharmaceuticals	Cancer	Cancer

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081211	Fragment Template is pTe102	restrictases
pTe131 pET27b-FGF2-His6	FGF2-cds-2C/2B	NdeI-XhoI
pTe132 pET28b FGF2-His6	FGF2-cds-2A/2B	NcoI-XhoI
pTe133 pET28b-His6-Thrombin-FGF2	FGF2-cds-2C/2D	NdeI-XhoI
pTe134 pColdTF-FGF2	FGF2-cds-2C/2D	NdeI-XhoI
pTe135 pET32a-Trx-His6-Fgf2	FGF2-cds-2A/2D	NcoI-XhoI

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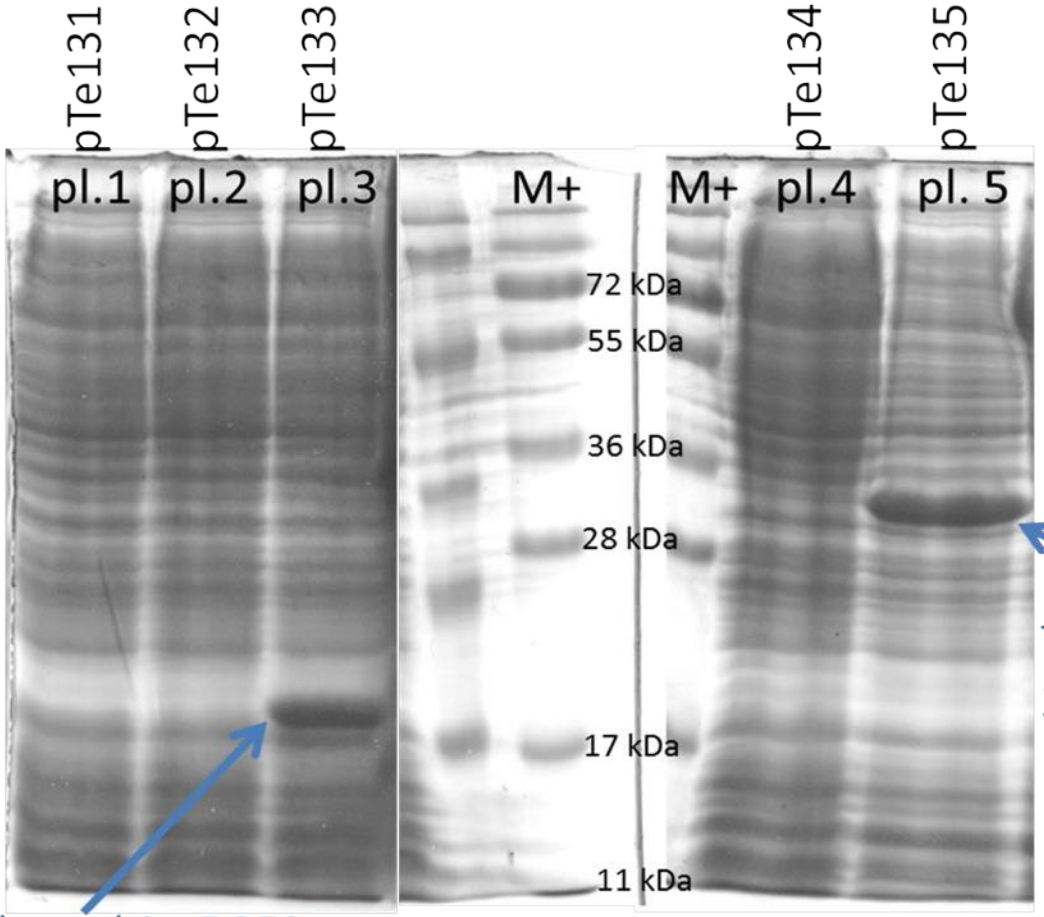
Induction 19Dec2011 in BL21(DE3), soluble fractions



His6-Thrombin-FGF2
19,4 kDa

Trx-His6-EK-FGF2
34,4 kDa

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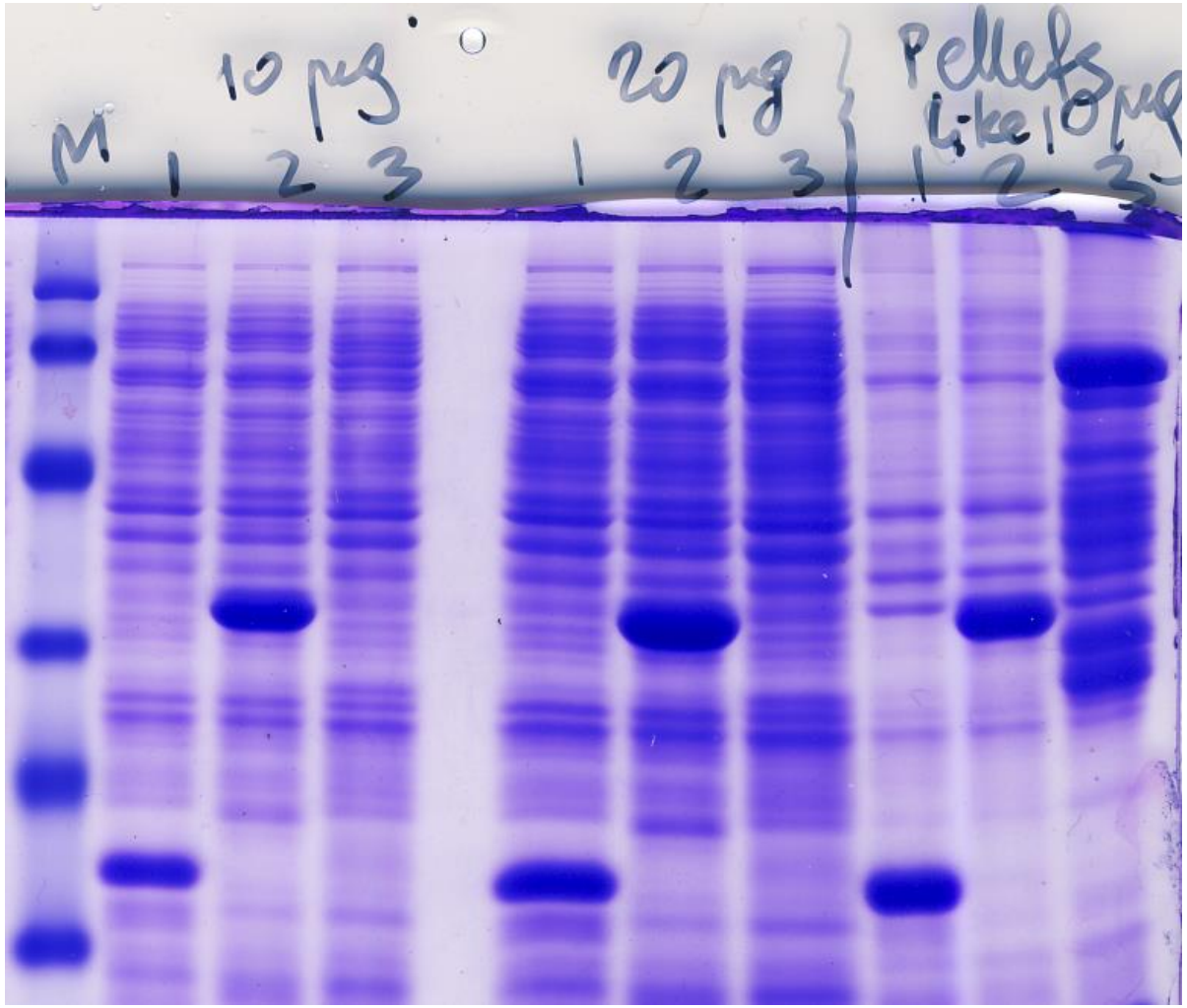
EnBase fermentation 15Feb2012



←34,4 kDa

←19,4 kDa

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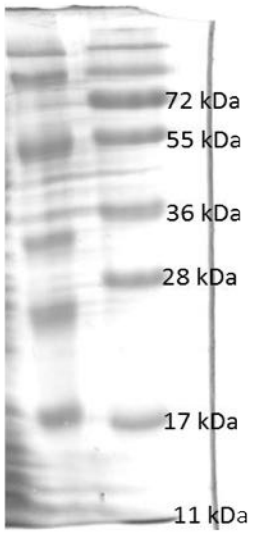
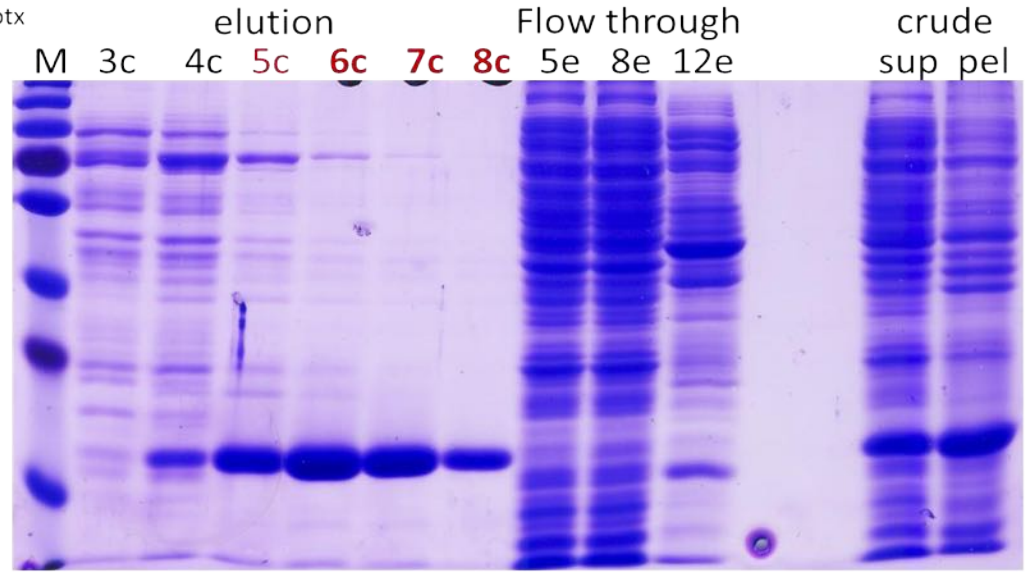
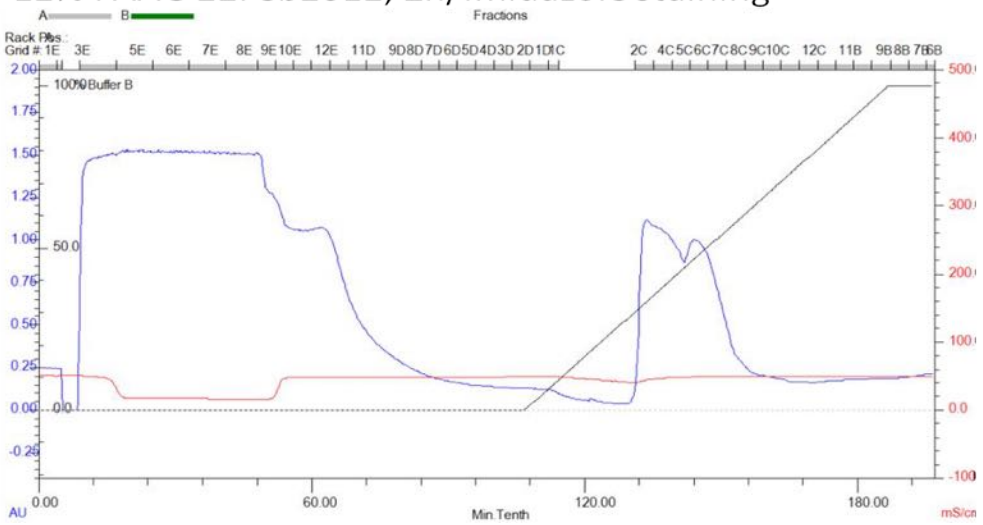
FGF2-133 purification 210212.pptx





FGF2-133
19,4 kDa

12% PAAG 22Feb2012, Zn/Imidazole staining



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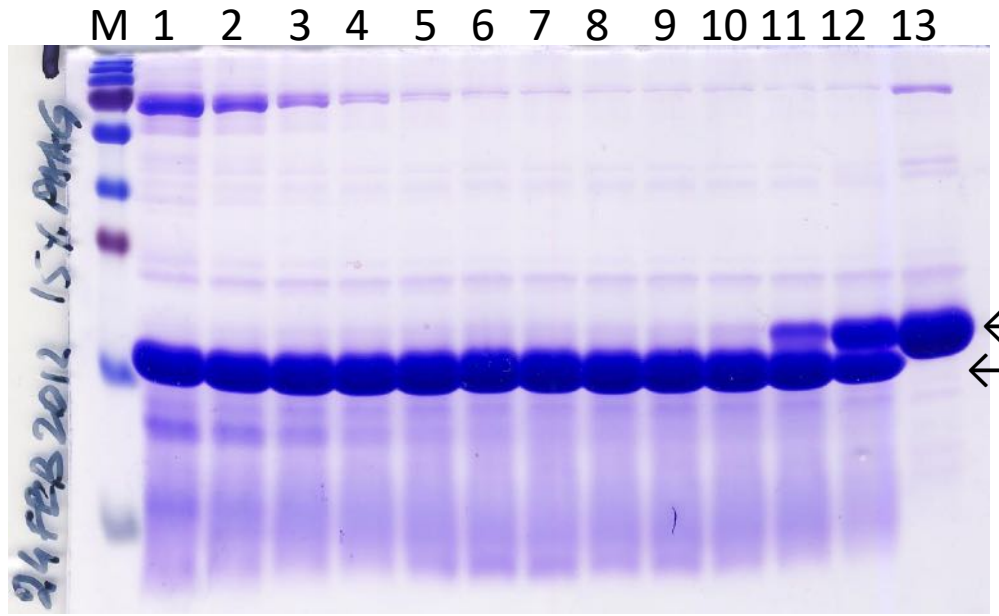
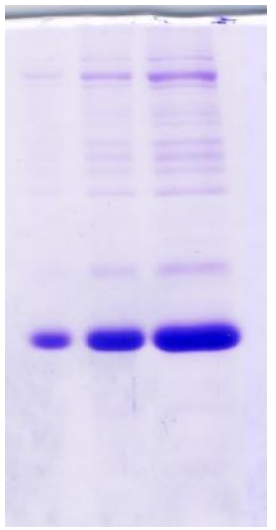
Thrombin cleavage FGF2-133



DP – pellet after dyalysis



0,1ul 0,4ul 1ul loaded

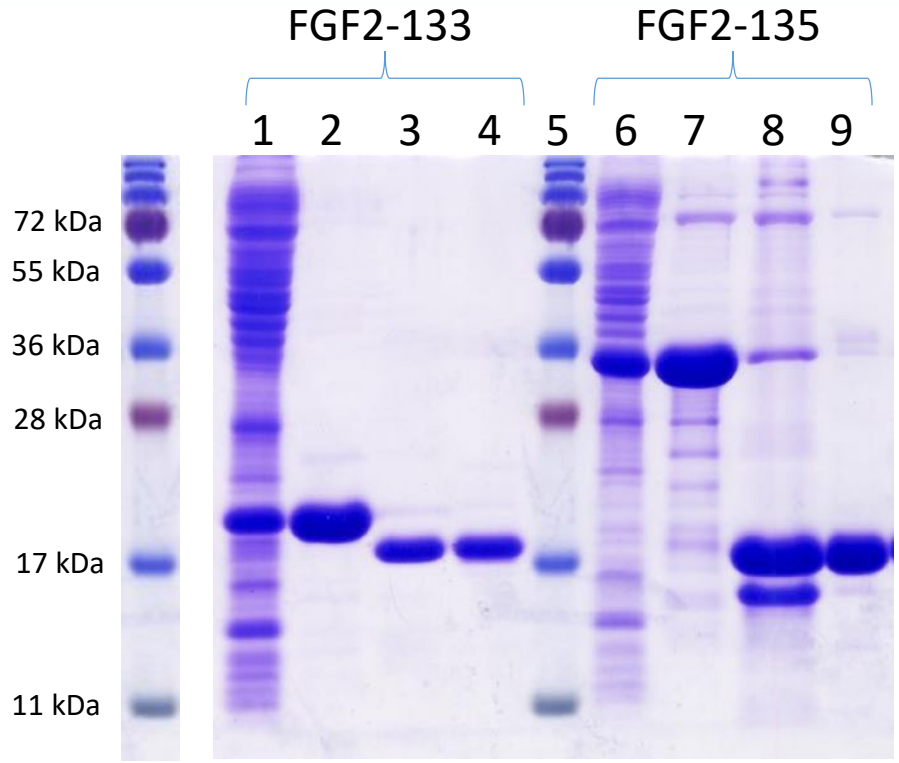
7,5 ul of the soluble dyalyzed protein loaded per lane – from 16 ml of over 2 mg/ml FGF2-133

Info is in the file

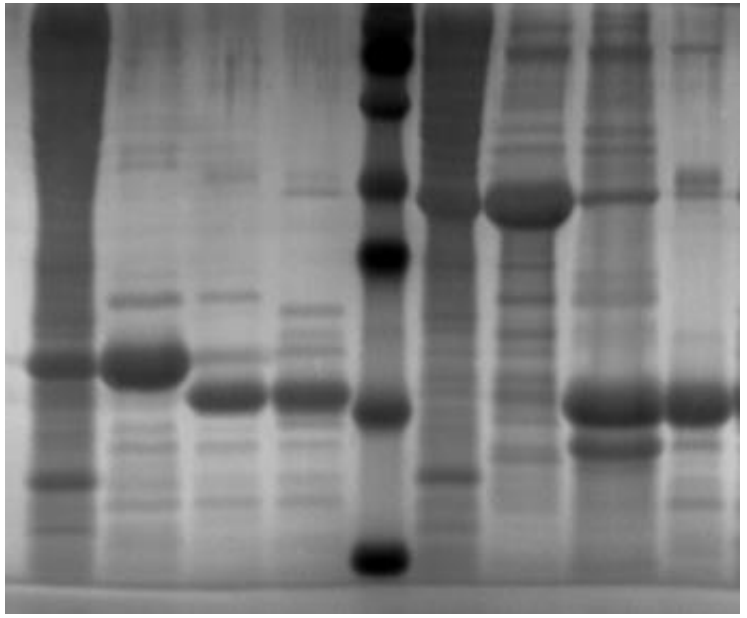
FGF2-133 thrombin cleavage 23Feb2012

We assumed that not more than 18 mg of protein got precipitated, while Over 32 mg of FGF2-133 remained in soluble form. Then, the purity of the Precipitated protein is much worse (5-7 folds more dirt) than the soluble protein.

	1	2	3	4	5	6	7	8	9	10	11	12	13				
	prot 1	prot 2	prot 3	prot 4	prot 5	prot 6	prot 7	prot 8	prot 9	prot 10	prot 11	prot 12					
	100 ul FGF	50 ul FGF	50 ul FGF	50 ul FGF	50 ul FGF	50 ul FGF	50 ul FGF	50 ul FGF	50 ul FGF	50 ul FGF	50 ul FGF	50 ul FGF					
	+ 1 u / 1 ul	+ 50 ul pr1	+ 50 ul pr2	+ 50 ul pr3	+ 50 ul pr4	+ 50 ul pr5	+ 50 ul pr6	+ 50 ul pr7	+ 50 ul pr8	+ 50 ul pr9	+ 50 ul pr10	+ 50 ul pr11	------				
excess, x	10	5	2,5	1,25	0,63	0,31	0,16	0,08	0,04	0,02	0,01	0,005	0				
	1 u/100 ul	0,5	0,25	0,125	0,0625	0,031	0,016	0,008	0,004	0,002	0,001	0,0005			1 u per about 200 ug protein...		
Thrombin: 0,005-0,01 units cleaved 100 ul of protein with about 2 or more mg/ml...																	
	which means that for 1 ml of protein we should take 0,05-0,1 units of Thrombin.																
		which means that for our 15 ml protein - around 30 or more mg total - we should use 1,5 units of Thrombin.															
			we could use 1 unit, or 0, 75 units per this amount,														
				and, on the other hand, we can increase this amount safely to at least 3 units per 15 ml													



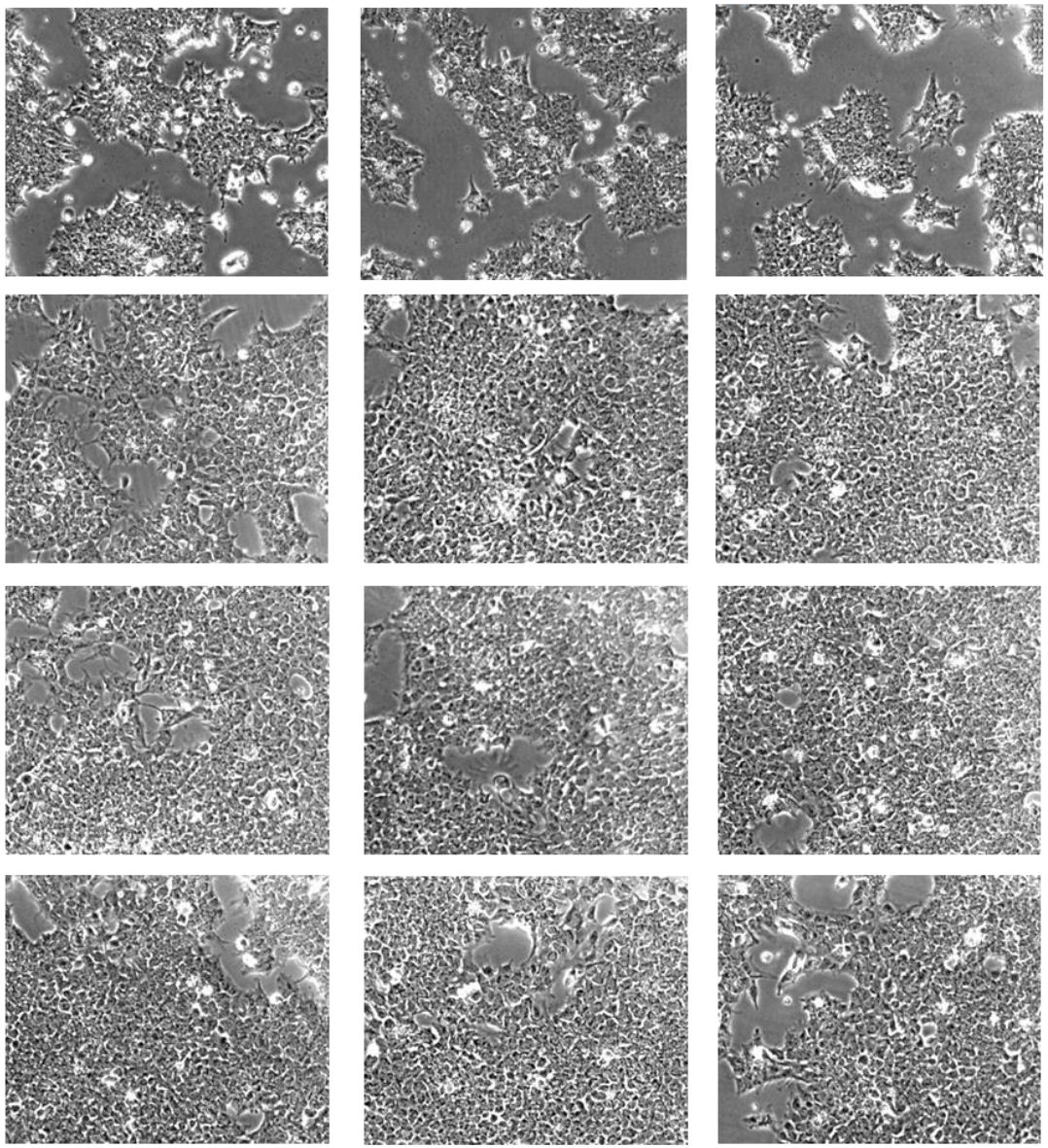
Coomassie staining



Zn-Imidazole staining (more sensitive)

1 – FGF2-133 fusion crude soluble, 19,4 kDa (fused to His-tag)
2 – FGF2-133 fusion Ni-NTA purified, 19,4 kDa
3 – FGF2-133 digested with thrombin, 17,6 kDa
4 – FGF2-133 Heparin purification, 17,6 kDa - final
5 – Mol weight marker
6 – FGF2-135 fusion crude soluble, 34,4 kDa (fused to His-Thioredoxin tag)
7 – FGF2-135 fusion Ni-NTA purified, 34,4 kDa
8 – FGF2-135 digested with Enterokinase, 17,3 kDa
9 – FGF2-135 Heparin purification, 17,3 kDa - final

L12cp36-6 on Matrigel



No FGF2

FGF2-133 cleaved

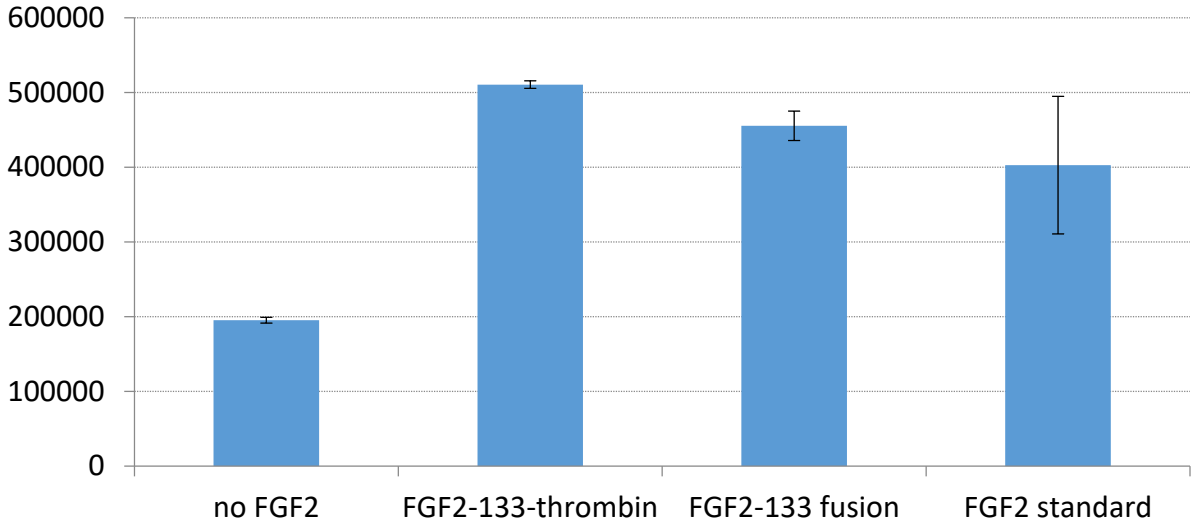
FGF2-133 fused

FGF2 standard

Cells plated at density of 20 000/cm2, grown for 3 days
3 representative pictures shown for each treatment

Cell counts

L12cp36/6 on Matrigel in 24x wells



Cells plated at density of 20 000/cm2, grown for 3 days

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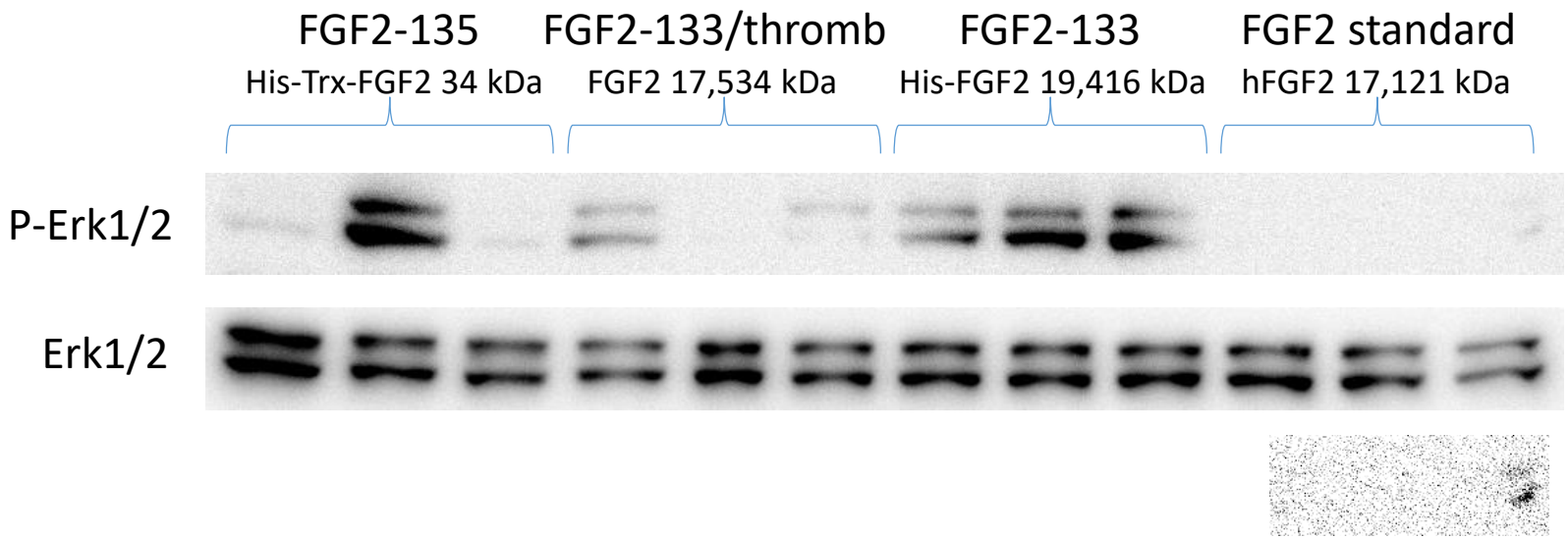

L12cp36/6 were plated at 20 000 cells/cm2 in 24x plate in cHES medium without FGF2.
Cells were allowed to grow for 3 days.
The recombinant FGF2 variants were added each day (3 times), meaning that the controls had FGF2 added 24 hrs before.

For FGF2-135, the cells were used which were not exposed to any FGF2 for all 3 days.

For western, cells were treated with fresh portions of FGF2 variants for 10 min – lyzed in Fermentas´ lysis buffer.

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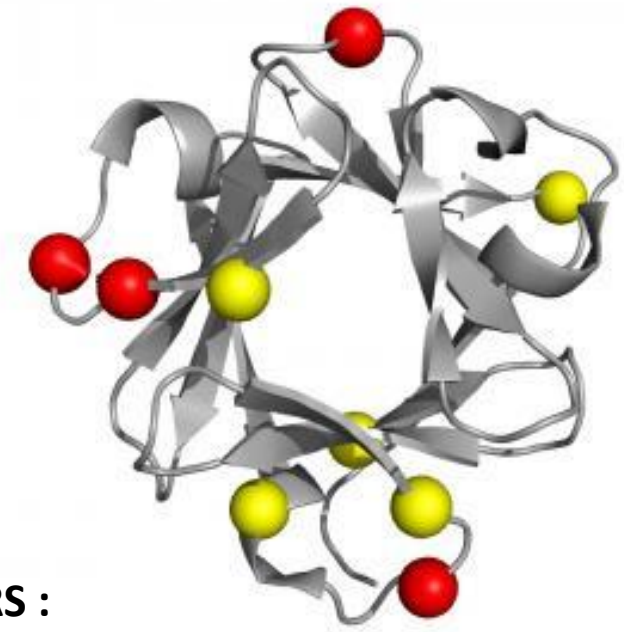
FGF2-STAB

- retains full biological activity even after twenty days at 37°C
- half-life of biological activity of a wild type FGF2 is 9 hours at 37°C

- FGF2 for cultivation media
- FGF2 for cosmetics
- FGF2 for veterinary medicine
- FGF2 for wound healing



TECHNOLOGY / IP OWNERS :
Masaryk University Enantis s.r.o.

https://biospot.eu/technology/hyperstable-fibroblast-growth-factor-2-fgf2-stab/

СумДУ

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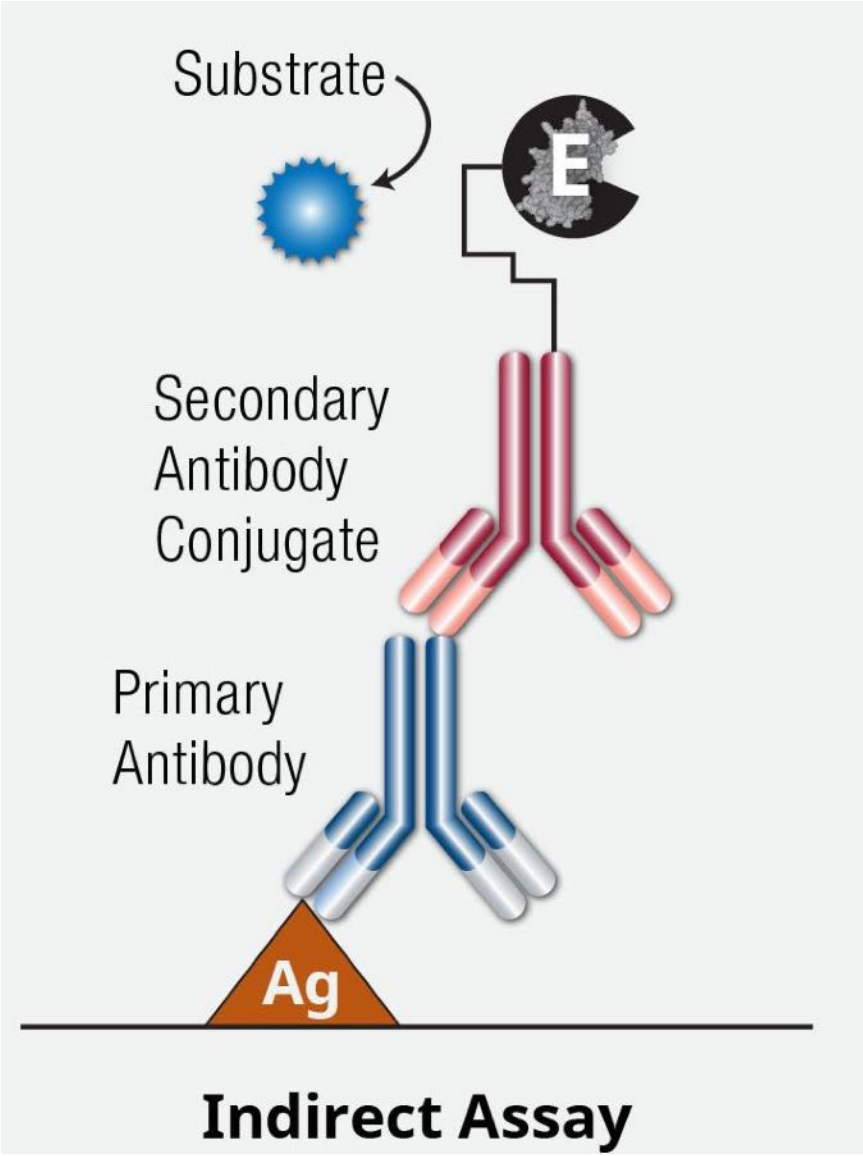
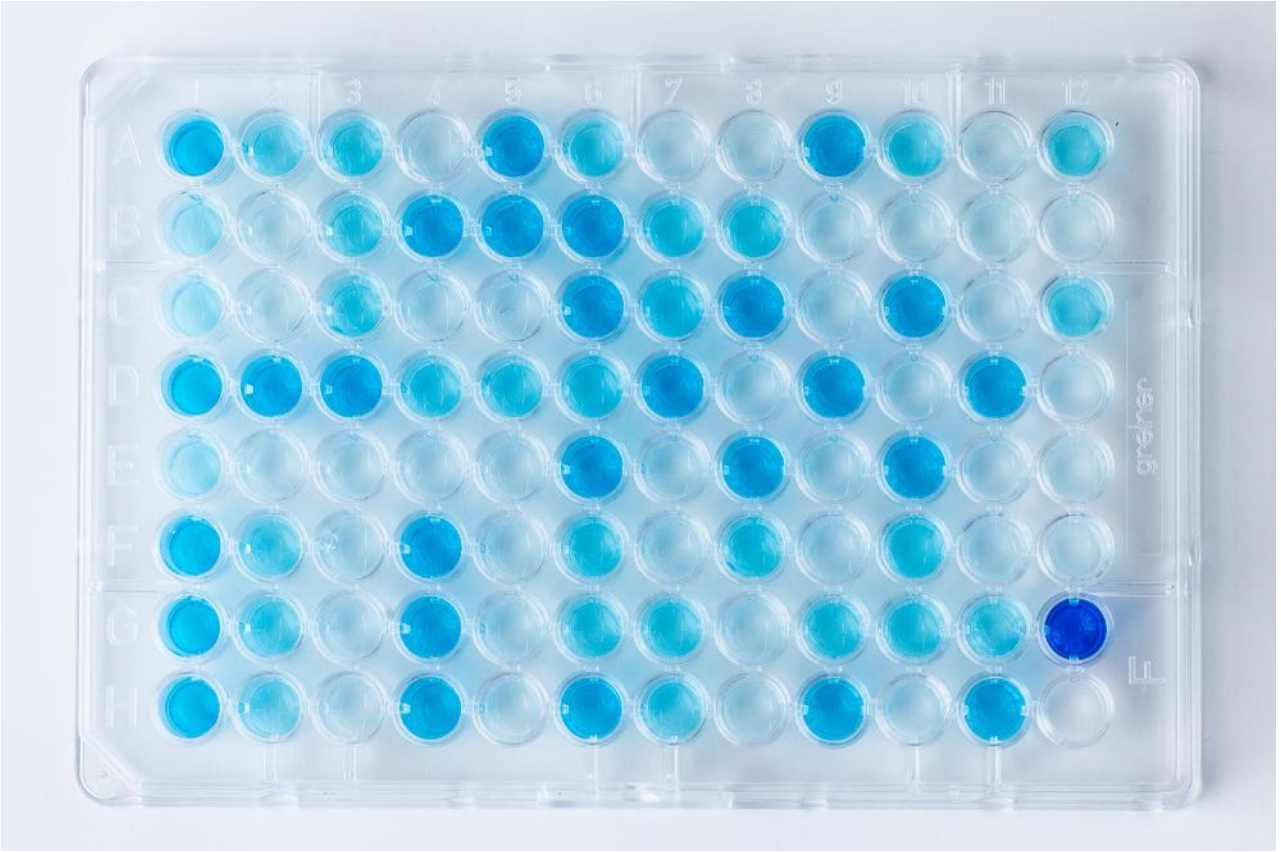
Recombinant antigens





https://media.cellsignal.com/www/images/resources/applications/elisa/elisa-indirect-assay.jpg

https://www.integra-biosciences.com/sites/default/files/styles/large/public/images/elisa-viaflo-96-384-8993.jpg?itok=5rolbtIn

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vitrotest.ua/-produkciiya-.html

Vitrotest®
ELISA kits & components

Про нас | Продукція | Новини | Корисне | Контакти | UA | RU | EN

ОСНОВНІ ХАРАКТЕРИСТИКИ ПРОДУКЦІЇ ТОВ «ВІТРОТЕСТ БІОРЕАГЕНТ»

- Час проведення аналізу 2-2,5 години;
- Лунки стрипів відокремлюються в усіх наборах;
- Зміна кольору розчинів на різних етапах постановки;
- Можливість постановки вручну та на автоматизованому роботі;
- Усі реагенти мають чітке маркування та кольорову індикацію;
- Діагностичні характеристики підтверджені на комерційних панелях сироваток;

Продукція

Головна / Продукція /

Інфекційні захворювання | **Алергія** | **Компоненти in bulk**

Інфекційні захворювання

Імуноферментні тест-системи для діагностики вірусних та бактеріальних інфекцій, протозойних гельмінтних інвазій.

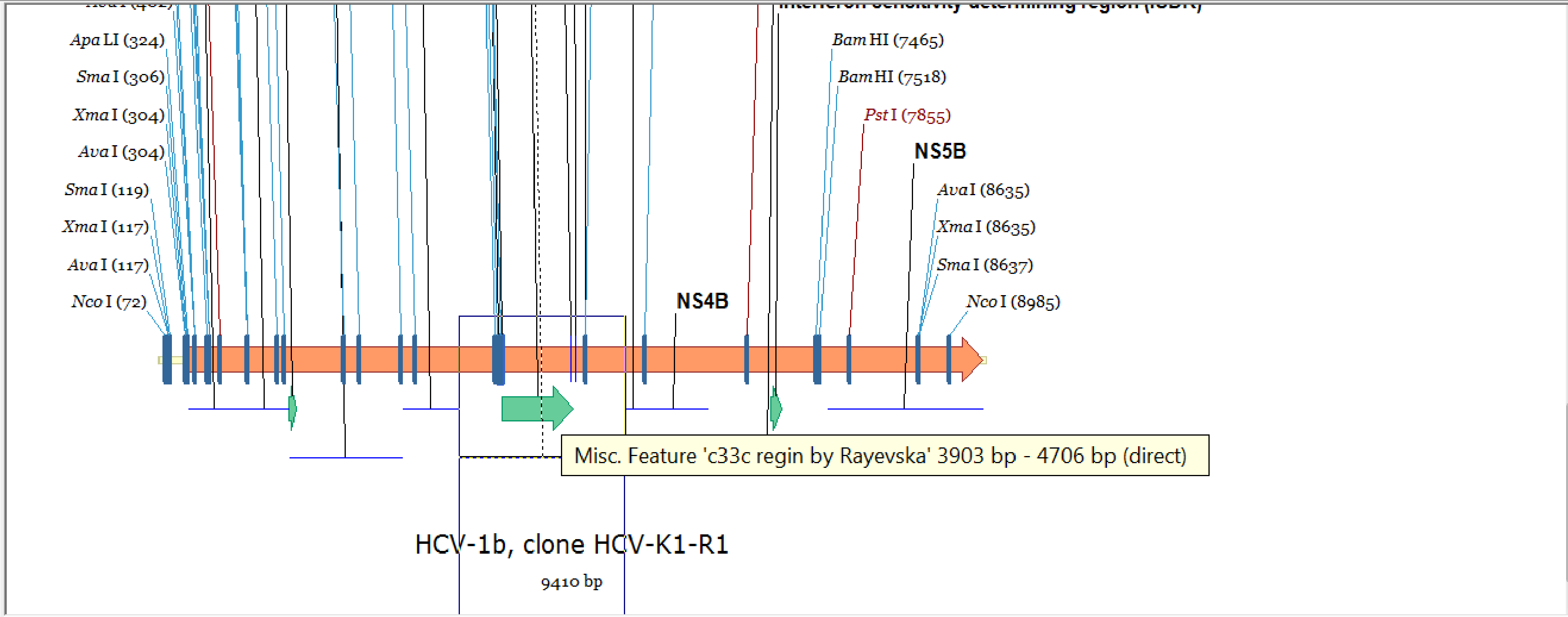
- Вірусний гепатит В
- Вірусний гепатит С
- Вірусний гепатит А
- Токсоплазмоз
- Краснуха
- Цитомегаловірусна інфекція
- Простий герпес
- Інфекційний мононуклеоз
- Мікоплазменна пневмонія
- Урогенітальний мікоплазмоз
- Уреаплазмоз
- Урогенітальний трихомоніаз
- Урогенітальний хламідіоз
- Сифіліс
- Хелікобактеріоз
- Лямбліоз (гіардіоз)
- Аскаридоз
- Опісторхоз
- Токсокароз
- Ехінококоз
- Трихінельоз
- Хвороба Лайма (бореліоз)
- Вірус Варіцелла-Зостер
- Кір
- Дифтерія
- COVID-19

Vector NTI - [HCV-1b, clone HCV-K1-R1]

File Edit View Analyses Cloning Gel List Align Assemble Tools Window Help

Active Pane:

- HCV-1b, clone HCV-K1-R1
  - General Description
  - Standard Fields
  - References
  - Comments
  - Annotations
  - Feature Map
  - Imported Features Not Shown on Map
  - Restriction/Methylation Map

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      CTGACCCGGG TGTGTCCGGA TGCTCTGGAC CGCCATCGCC AGCTCGGGCA GCAGAAGAGG CTGTACCTTT AGTTCTAGTA GTGGACCCCC CCTCTGTGGC

3301  CGGCGTGTGG GGACATCATT ATGGGTCTAC CTGTCTCCGC CCGAAGGGGG AGGGAGATAC TCCTAGGACC AGCCGACAGT CTTGAGGGGC AGGGGTGGCG
      GCCGCACACC CCTGTAGTAA TACCCAGATG GACAGAGGCG GGCTTCCCCC TCCCTCTATG AGGATCCTGG TCGGCTGTCA GAACTCCCCG TCCCCACCGC

3401  ACTCCTCGCG CCCATCACGG CCTACTCCCA ACAGACGCGG GGCCTGTTTG GCTGCATTAT CACCAGCCTC ACGGGCCGGG ACAAGAACCA AGTCGAGGGG
      TGAGGAGCGC GGGTAGTGCC GGATGAGGGT TGTCTGCGCC CCGGACAAAC CGACGTAATA GTGGTCGGAG TGCCCGGCCC TGTTCTTGGT TCAGCTCCCC

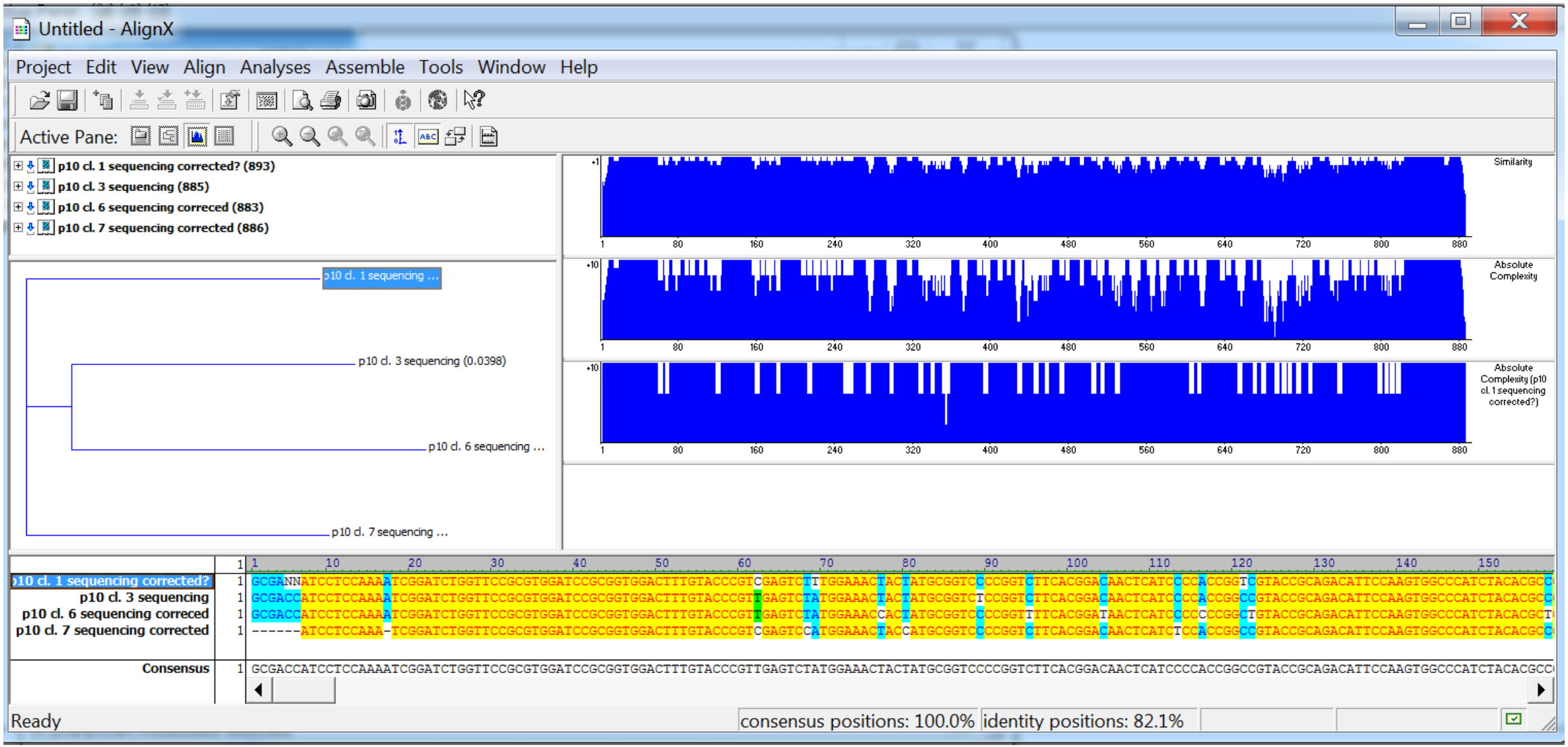
3501  GAAGTTCAAG TGGTTTCCAC CGCGACGCAG TCTTTCCTAG CGACCTGCGT CAACGGCGTG TGCTGGACTG TCTACCACGG CGCCGGCTCA AAGACCCTAG
      CTTCAAGTTC ACCAAAGGTG GCGCTGCGTC AGAAAGGATC GCTGGACGCA GTTGCCGCAC ACGACCTGAC AGATGGTGCC GCGGCCGAGT TTCTGGGATC

3601  CCGGCCCAAA GGGTCCAATC ACCCAAATGT ACACCAATGT AGACCAGGAC CTCGTCGGAT GGCCGGCGCC CCCCGGAGCG CGGTCCTTGA CACCATGCAC
      GGCCGGGTTT CCCAGGTTAG TGGGTTTACA TGTGGTTACA TCTGGTCCTG GAGCAGCCTA CCGGCCGCGG GGGGCCTCGC GCCAGGAACT GTGGTACGTG

3701  CTGCGGCGGC TCGGACCTTT ACTTGGTCAC GAGACACGCT GATGTCATTC CGGTGCGCCG GCGGGGTGAC AGCAGGGGGA GCTTACTATC CCCCAGGCCC
      GACGCCGCCG AGCCTGGAAA TGAACCAGTG CTCTGTGCGA CTACAGTAAG GCCACGCGGC CGCCCCACTG TCGTCCCCCT CGAATGATAG GGGGTCCGGG

                                                                                                  AvaI
                                                                                                  SmaI
```

Ready   3408 bp - 5300 bp (1893 bp)   5301 bp (3')

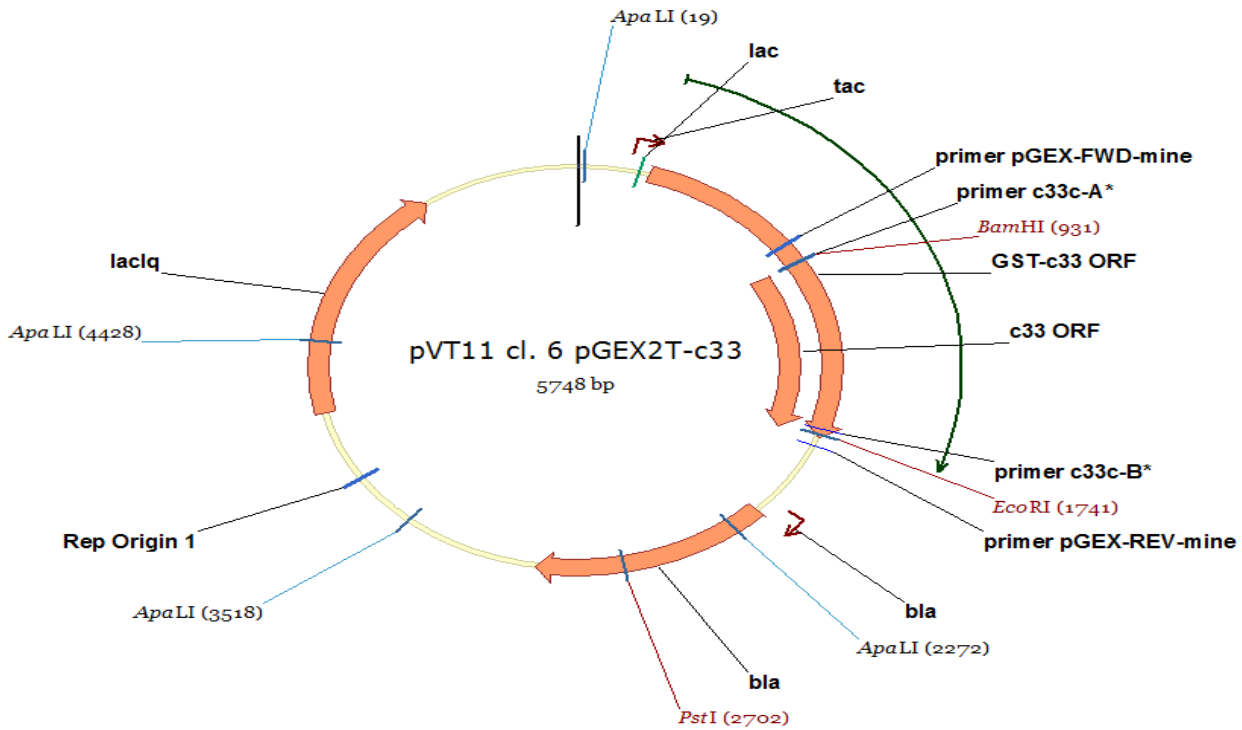

Untitled - AlignX
Project Edit View Align Analyses Assemble Tools Window Help
Active Pane:
p10 cl. 1 sequencing corrected? (893)
p10 cl. 3 sequencing (885)
p10 cl. 6 sequencing correced (883)
p10 cl. 7 sequencing corrected (886)
p10 cl. 1 sequencing ...
p10 cl. 3 sequencing (0.0398)
p10 cl. 6 sequencing ...
p10 cl. 7 sequencing ...
Similarity
Absolute Complexity
Absolute Complexity (p10 cl. 1 sequencing corrected?)
p10 cl. 1 sequencing corrected?
p10 cl. 3 sequencing
p10 cl. 6 sequencing correced
p10 cl. 7 sequencing corrected
Consensus
Ready
consensus positions: 100.0%
identity positions: 82.1%

Vector NTI - [pVT11 cl. 6 pGEX2T-c33]

File Edit View Analyses Cloning Gel List Align Assemble Tools Window Help

Active Pane:

- pVT11 cl. 6 pGEX2T-c33
- General Description
- Standard Fields
- Comments
- Annotations
- Component Fragments
- Feature Map
- Imported Features Not Shown on Map
- Restriction/Methylation Map
- Open Reading Frames



ApaLI

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        TGCAATAGCT GACGTGCCAC GTGGTTACGA AGACCGCAGT CCGTCGGTAG CCTTCGACAC CATACCGACA CGTCCAGCAT TTAGTGACGT ATTAAGCACA

   101  CGCTCAAGGC GCACTCCCGT TCTGGATAAT GTTTTTTGCG CCGACATCAT AACGGTTCTG GCAAATATTC TGAAATGAGC TGTTGACAAT TAATCATCGG
        GCGAGTTCCG CGTGAGGGCA AGACCTATTA CAAAAAACGC GGCTGTAGTA TTGCCAAGAC CGTTTATAAG ACTTTACTCG ACAACTGTTA ATTAGTAGCC
  +3
```

Ready 1 bp

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Antiserum

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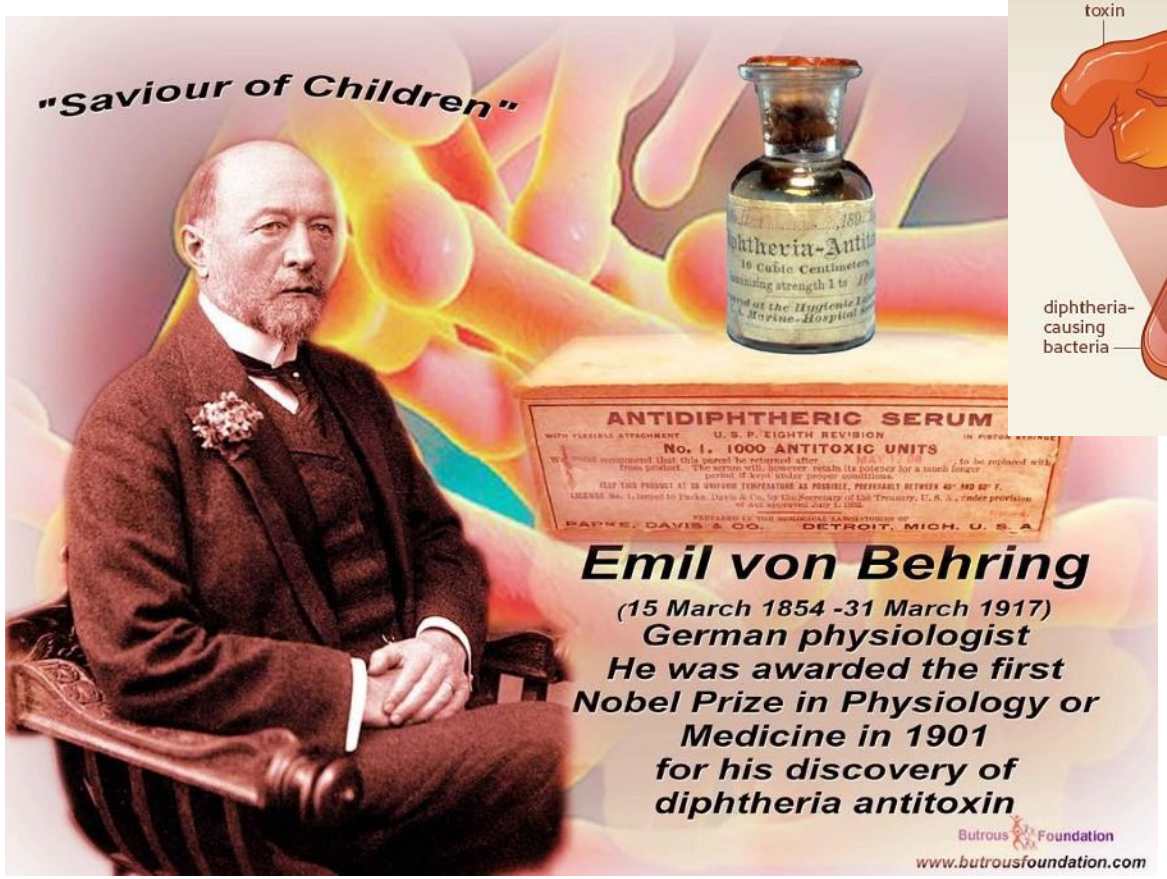

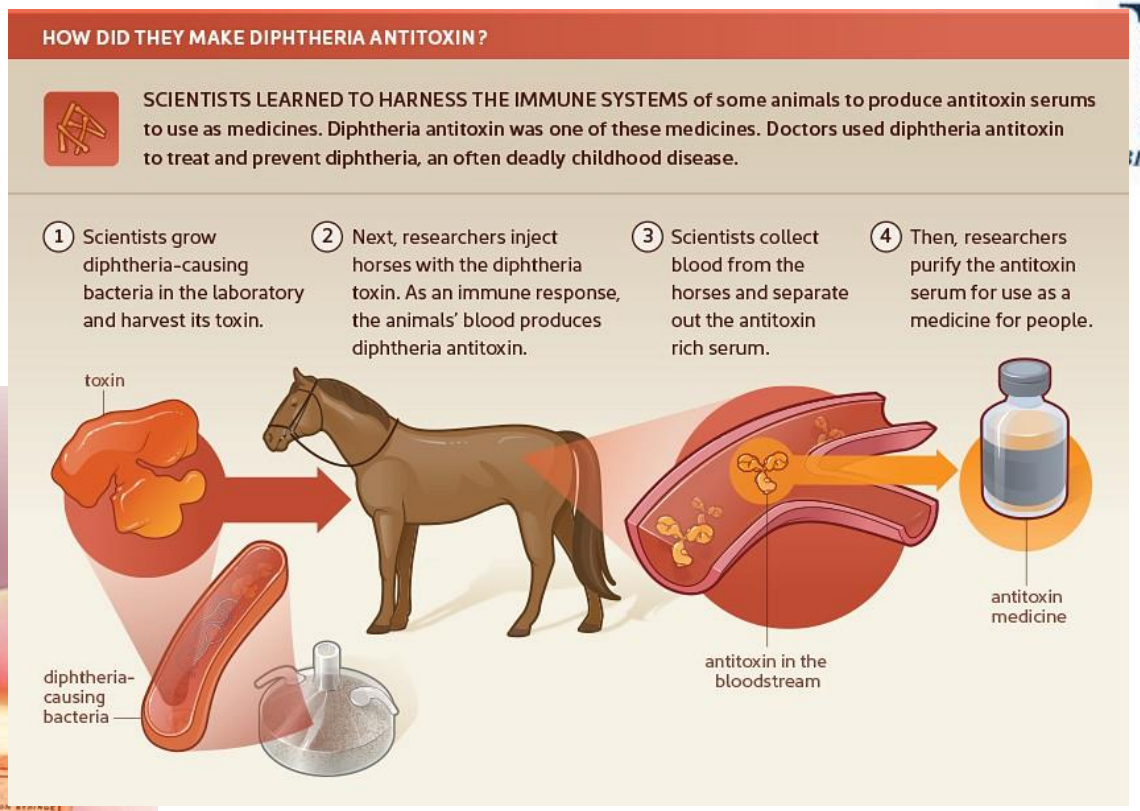

https://denispombriant.medium.com/lets-make-an-antiserum-for-corona-virus-bb1a96dc5808

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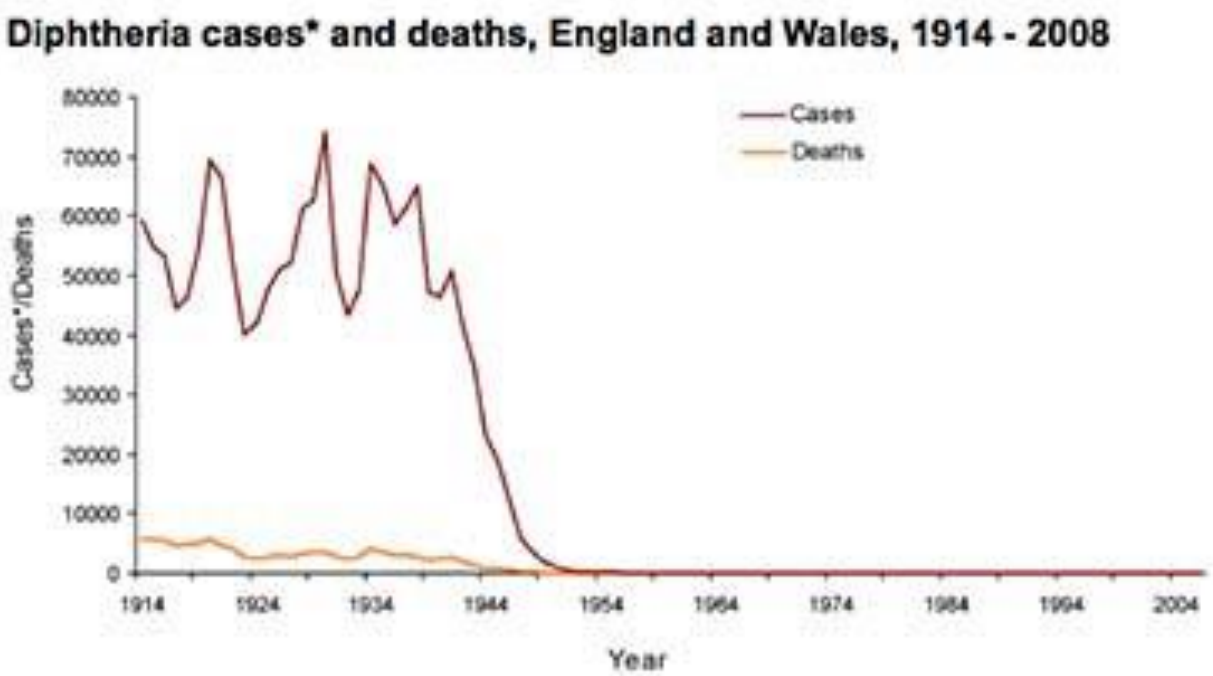

https://denispombriant.medium.com/lets-make-an-antiserum-for-corona-virus-bb1a96dc5808

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Research Highlight | Published: 12 January 2021

AUTOIMMUNITY

mRNA vaccine shows promise in autoimmunity

Alexandra Flemming

Nature Reviews Immunology **21**, 72(2021) | Cite this article

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Recombinant antibodies

COVID-19 treatment:

1.2 grams of both

- **casirivimab**
- **imdevimab**

https://www.nytimes.com/2020/11/21/health/regeneron-covid-antibodies-trump.html

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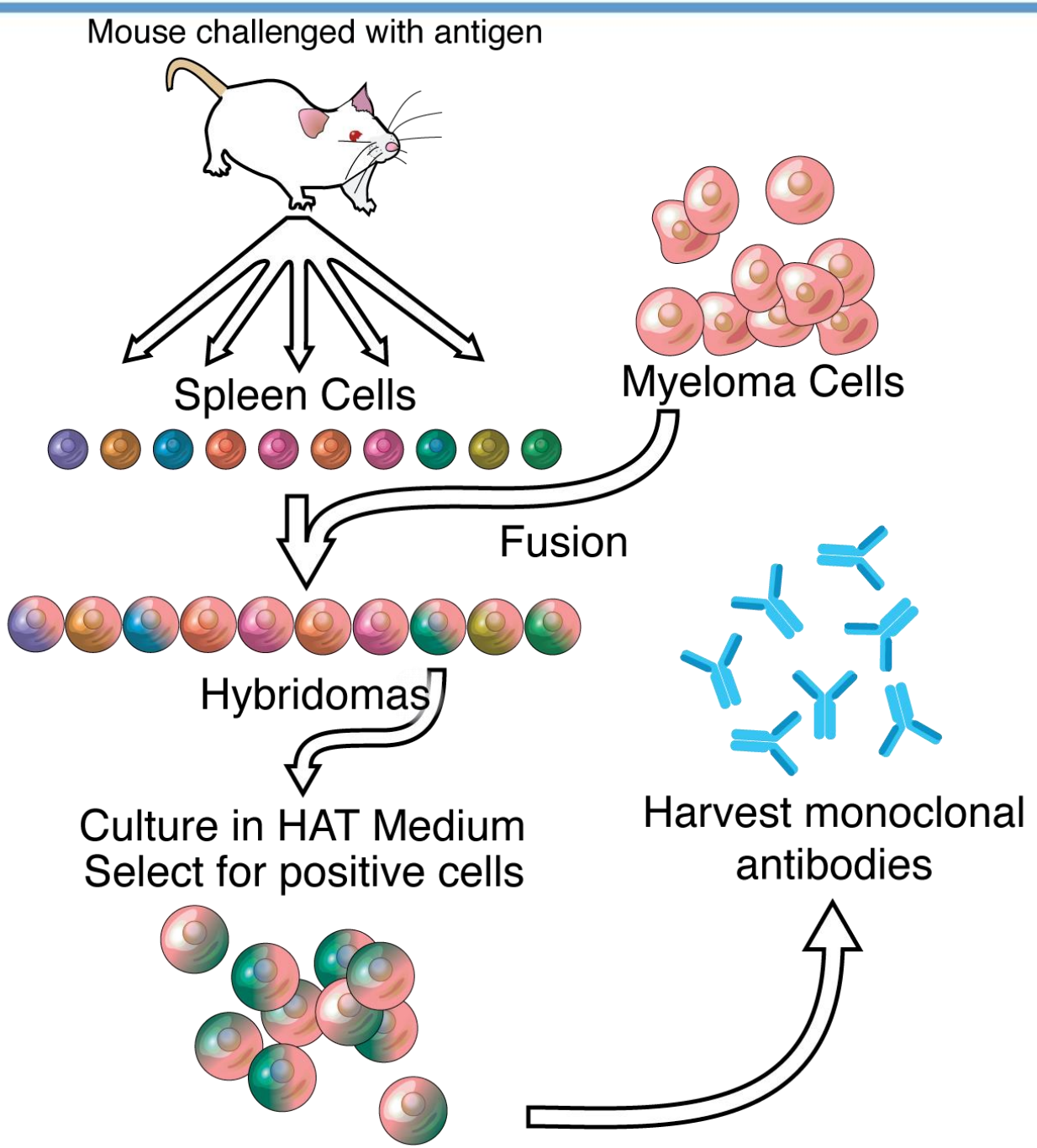


https://upload.wikimedia.org/wikipedia/commons/9/9a/Monoclonals.png

The Nobel Prize in Physiology or Medicine 1984

Photo from the Nobel Foundation archive.

Niels K. Jerne

Prize share: 1/3

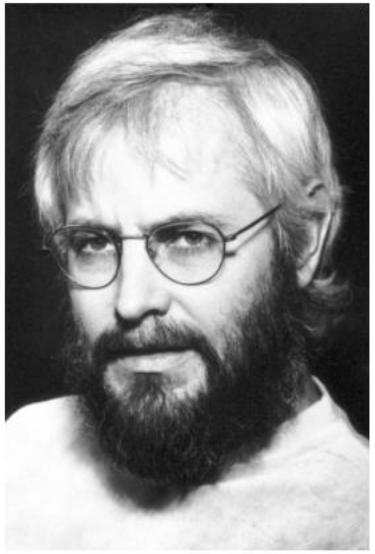


Photo from the Nobel Foundation archive.

Georges J.F. Köhler

Prize share: 1/3

Photo from the Nobel Foundation archive.

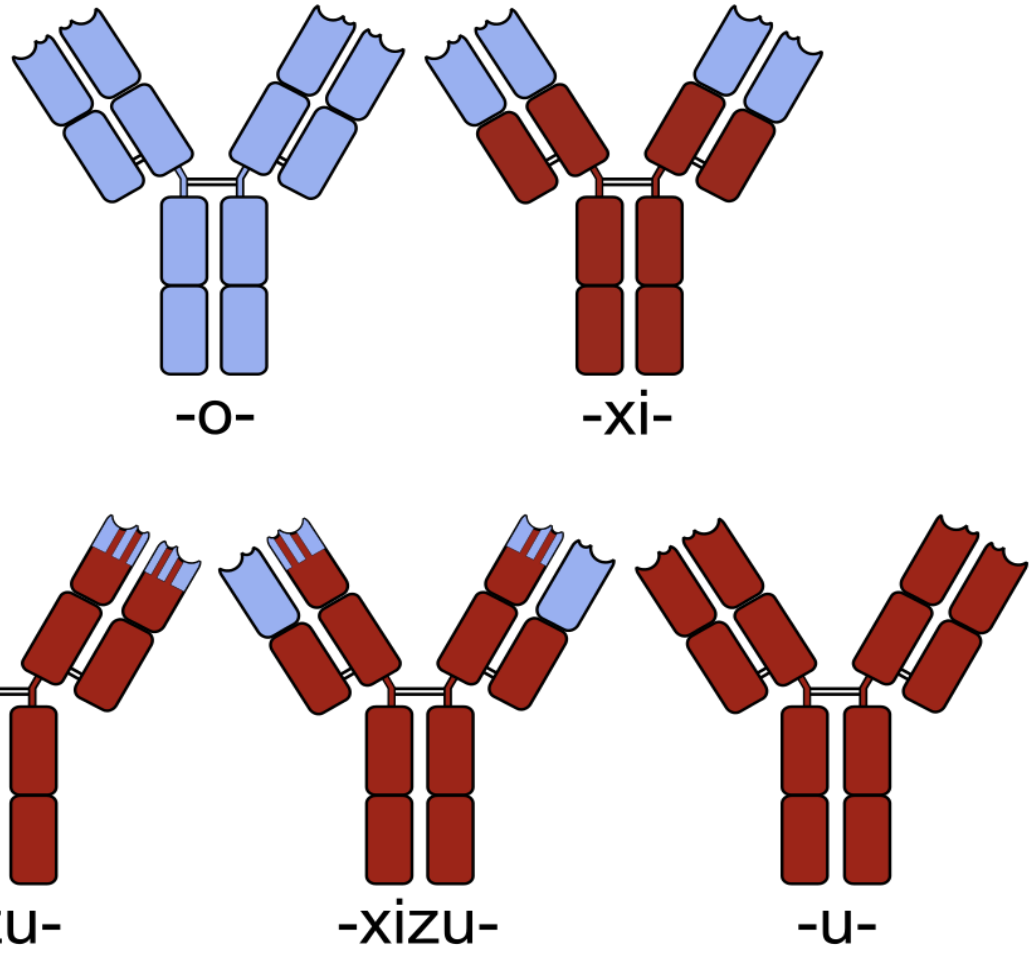
César Milstein

Prize share: 1/3

The Nobel Prize in Physiology or Medicine 1984 was awarded jointly to Niels K. Jerne, Georges J.F. Köhler and César Milstein "for theories concerning the specificity in development and control of the immune system and the discovery of the principle for production of monoclonal antibodies."

https://www.nobelprize.org/prizes/medicine/1984/summary/

Recombinant antibodies



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US FDA-approved monoclonal antibody on the market

mAb	Brand name	Company	Target	Format	Technology	Indication[&]	US[#] Approval
Muromonab-CD3	Orthoclone OKT3	Centocor Ortho Biotech Products LP.	CD3	Murine IgG2a	Hybridoma/Janssen Biotech, Inc	Kidney transplant rejection	1986*
Abciximab	Reopro	Centocor Inc./Eli Lilly/Janssen Biotech Inc.	GPIIb/IIIa	Chimeric IgG1 Fab	Hybridoma	Prevention of blood clots in angioplasty	1994
Rituximab	MabThera, Rituxan	Biogen Inc./Roche, F. Hoffmann-La Roche Ltd./Genentech Inc.	CD20	Chimeric IgG1	Hybridoma	Non-Hodgkin lymphoma	1997
Palivizumab	Synagis	MedImmune/AbbVie Inc.	RSV	Humanized IgG1	Hybridoma	Prevention of respiratory syncytial virus infection	1998
Infliximab	Remicade	Janssen Biotech Inc.	TNFα	Chimeric IgG1	Hybridoma	Crohn's disease	1998
Trastuzumab	Herceptin	Roche, F. Hoffmann-La Roche, Ltd./Genentech Inc.	HER2	Humanized IgG1	Hybridoma	Breast cancer	1998
Alemtuzumab	Campath, Lemtrada	Berlex Inc./Genzyme Corp./Millennium Pharmaceuticals Inc.	CD52	Humanized IgG1	Hybridoma	Chronic myeloid leukemia	2001
Adalimumab	Humira	AbbVie Inc.	TNFα	Human IgG1	Phage display	Rheumatoid arthritis	2002
Ibritumomab tiuxetan	Zevalin	Biogen Inc./Schering AG/Spectrum Pharmaceuticals Inc.	CD20	Murine IgG1	Hybridoma	Non-Hodgkin lymphoma	2002
Omalizumab	Xolair	Roche, F. Hoffmann-La Roche, Ltd./Genentech	IgE	Humanized IgG1	Hybridoma	Asthma	2003

https://jbiomedsci.biomedcentral.com/articles/10.1186/s12929-019-0592-z

US FDA-approved monoclonal antibody on the market

						carcinoma	
Emapalumab	Gamifant	NovImmmune	IFNγ	Human IgG1	Phage display	Primary hemophagocytic lymphohistiocytosis	2018
Fremanezumab	Ajovy	Teva Pharmaceutical Industries, Ltd.	CGRP	Humanized IgG2	Hybridoma	Migraine prevention	2018
Ibalizumab	Trogarzo	Taimed Biologics Inc./Theratechnologies Inc.	CD4	Humanized IgG4	Hybridoma	HIV infection	2018
Moxetumomab pasudodox	Lumoxiti	MedImmune/AstraZeneca	CD22	Murine IgG1 dsFv	Phage display	Hairy cell leukemia	2018
Ravulizumab	Ultomiris	Alexion Pharmaceuticals Inc.	C5	humanized IgG2/4	Hybridoma	Paroxysmal nocturnal hemoglobinuria	2018
Caplacizumab	Cablivi	Ablynx	von Willebrand factor	Humanized Nanobody	Hybridoma	Acquired thrombotic thrombocytopenic purpura	2019
Romosozumab	Evenity	Amgen/UCB	Sclerostin	Humanized IgG2	Hybridoma	Osteoporosis in postmenopausal women at increased risk of fracture	2019
Risankizumab	Skyrizi	Boehringer Ingelheim Pharmaceuticals/ AbbVie Inc.	IL-23 p19	Humanized IgG1	Hybridoma	Plaque psoriasis	2019
Polatuzumab vedotin	Polivy	Roche, F. Hoffmann-La Roche, Ltd.	CD79β	Humanized IgG1 ADC	Hybridoma	Diffuse large B-cell lymphoma	2019
Brolucizumab	Beovu	Novartis Pharmaceuticals Corp.	VEGF-A	Humanized scFv	Hybridoma[$]	Macular degeneration	2019
Crizanlizumab	Adakveo	Novartis Pharmaceuticals Corp.	P-selectin	Humanized IgG2	Hybridoma	Sickle cell disease	2019

https://jbiomedsci.biomedcentral.com/articles/10.1186/s12929-019-0592-z

Fibrin sealant

With the support of the Erasmus+ Programme of the European Union

KIITOS

DĚKUJI

ДЯКУЮ

СПАСИБО

THANK YOU

DANKE SCHÖN

MUITO OBRIGADO

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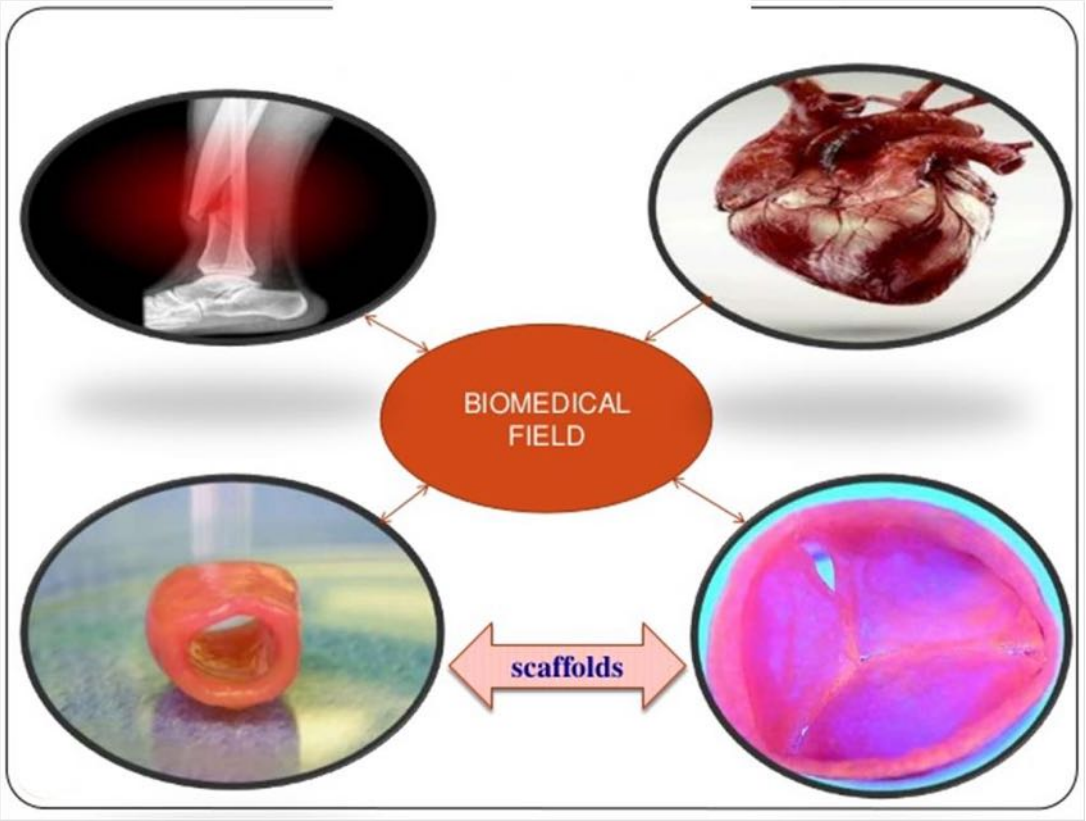
With the support of the Erasmus+ Programme of the European Union

With the support of the Erasmus+ Programme of the European Union

Polymeric biomaterials – production and application



«Modern European trends in biomedical higher education: Bionanomaterials.» № 620717-EPP-1-2020-1-UA-EPPJMO-MODULE

With the support of the Erasmus+ Programme of the European Union

INTRODUCTION

BIOMATERIALS

- Non-living materials mainly used for medical purposes.
- Designed to interact with biological systems.

BIODEGRADABLE MATERIAL

- Its mechanical properties does not change during its life time.
- It gets degrades gradually without leaving trace.

TISSUE ENGINEERING

Maintenance, replacement or regeneration of damaged biological tissues.

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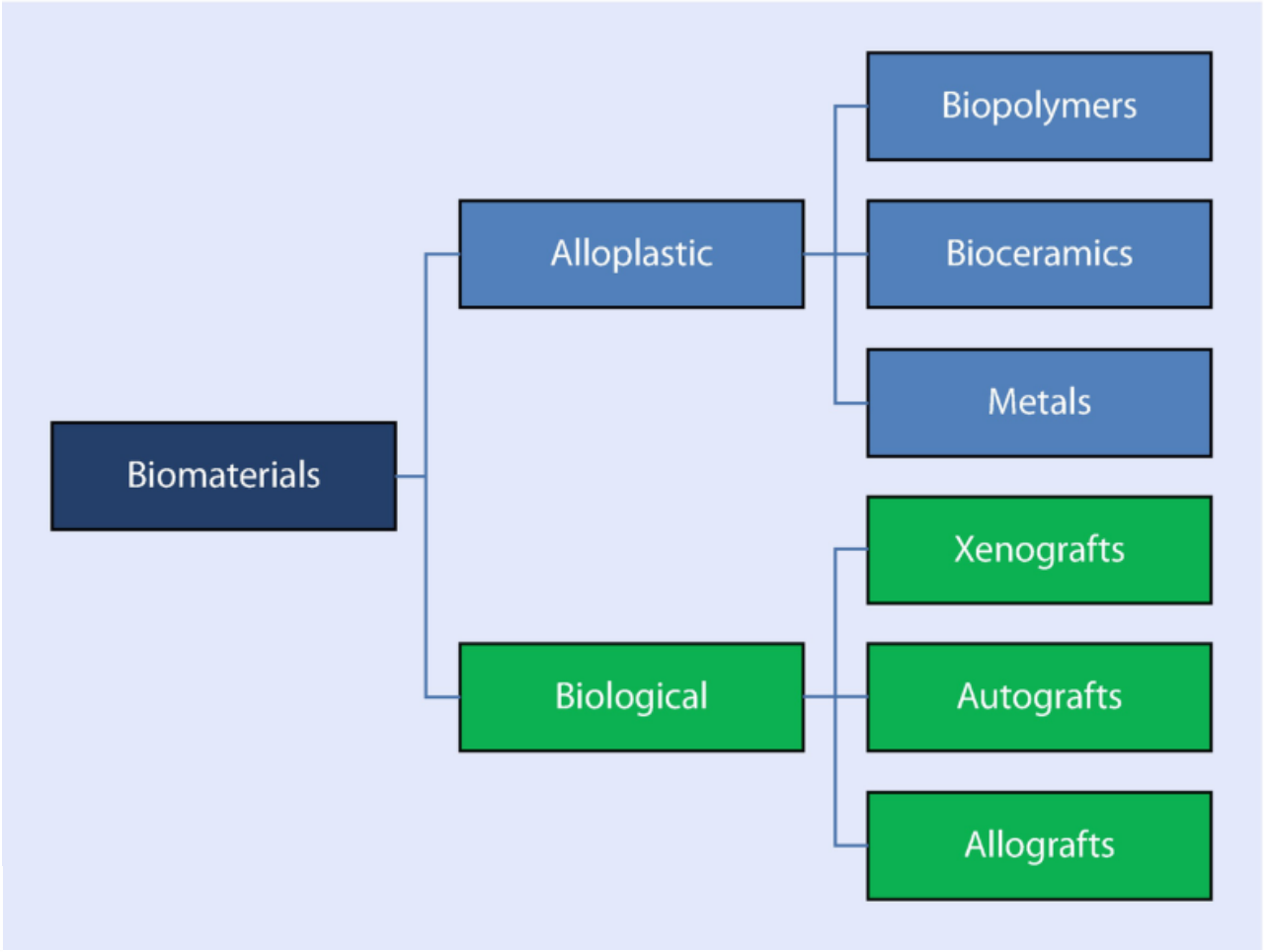
Polymeric biomaterials - application in regenerative medicine and tissue engineering



Based on the chemical composition

The artificial material substituted for tissue grafts is called **alloplastic**.

Xenograft - a tissue graft or organ transplant from a donor of
* a different species from the recipient

doi.org/10.1007/978-3-319-74854-2_6

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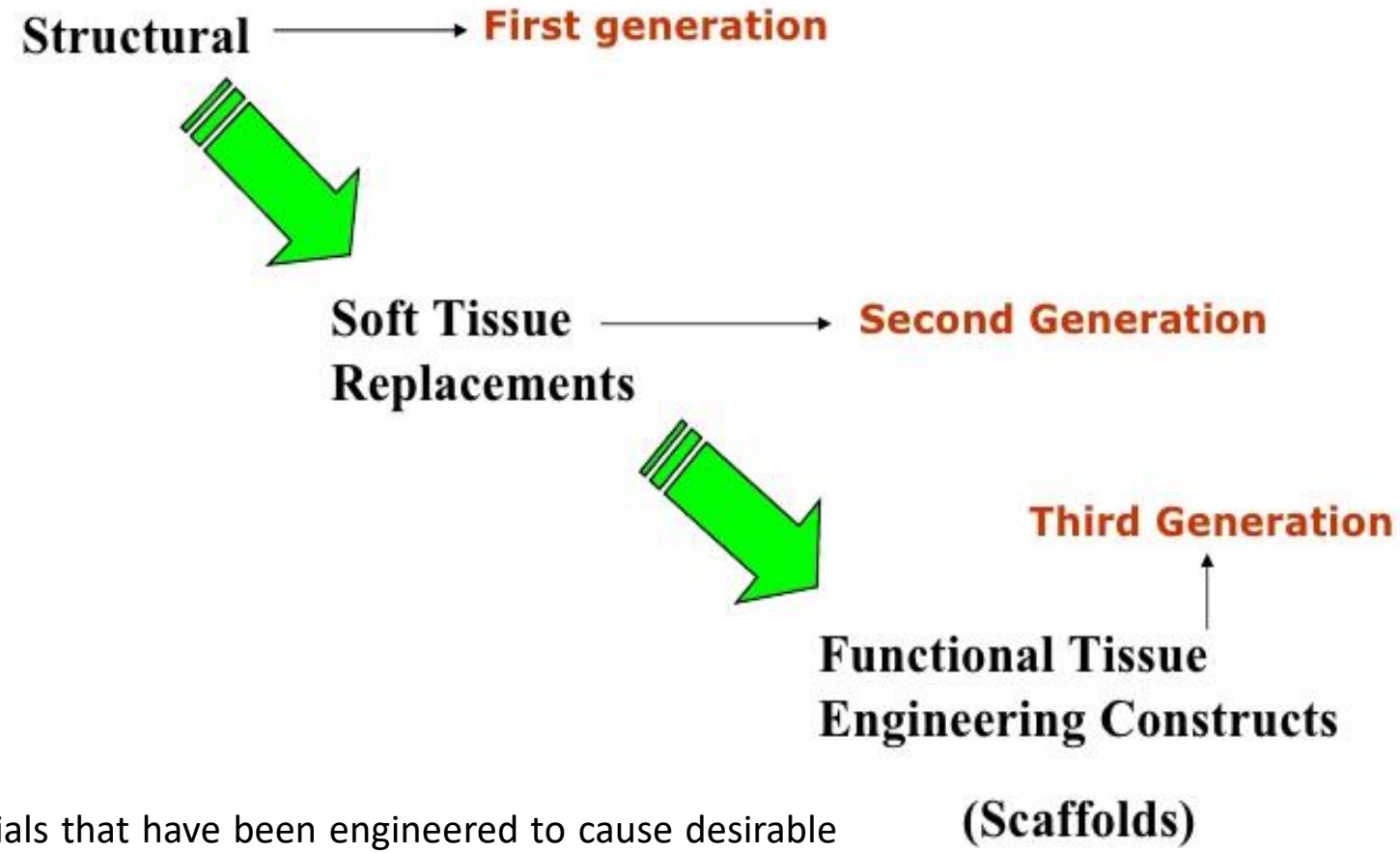
Evolution of Biomaterials



***Scaffolds** are materials that have been engineered to cause desirable cellular interactions to contribute to the formation of new functional tissues for medical purposes. Cells are often 'seeded' into thes structures capable of supporting three-dimensional tissue formation.

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Properties Of Biomedical Polymers

- Flexibility;
- Resistance to biochemical attack;
- Good biocompatibility;
- Light weight;
- Available in a wide variety of compositions with adequate physical and mechanical properties and
- Can be easily manufactured into products with the desired shape.

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Selection Parameters For Biomedical Polymers

The design and selection of biomaterials depend on different properties –

Host Response

- Biocompatibility
- Biofunctionality
- Functional Tissue Structure and Pathobiology
- Toxicology
- Appropriate Design and Manufacturability
- Mechanical Properties of Biomedical polymers

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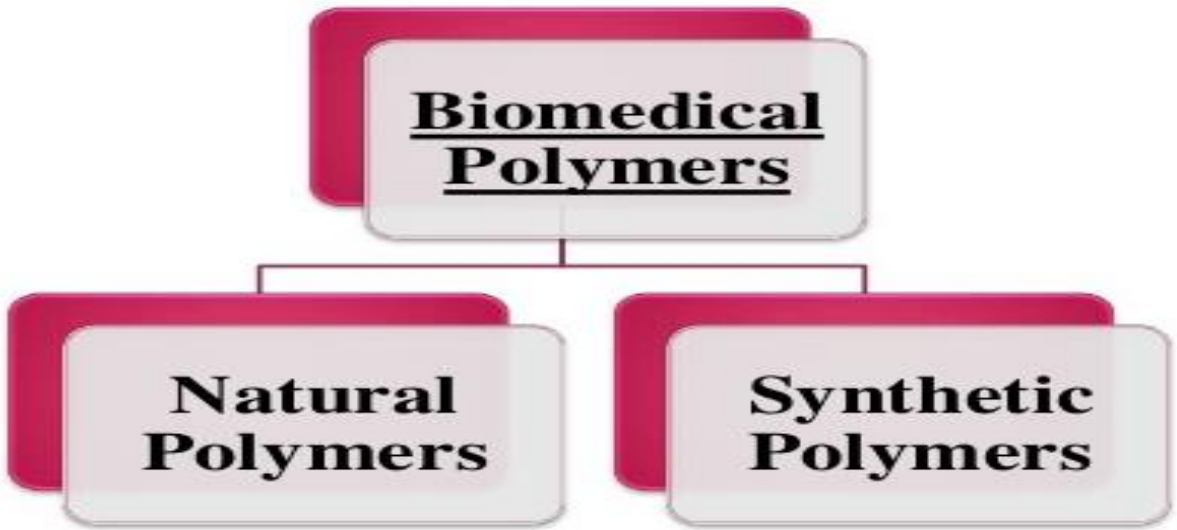
Classification



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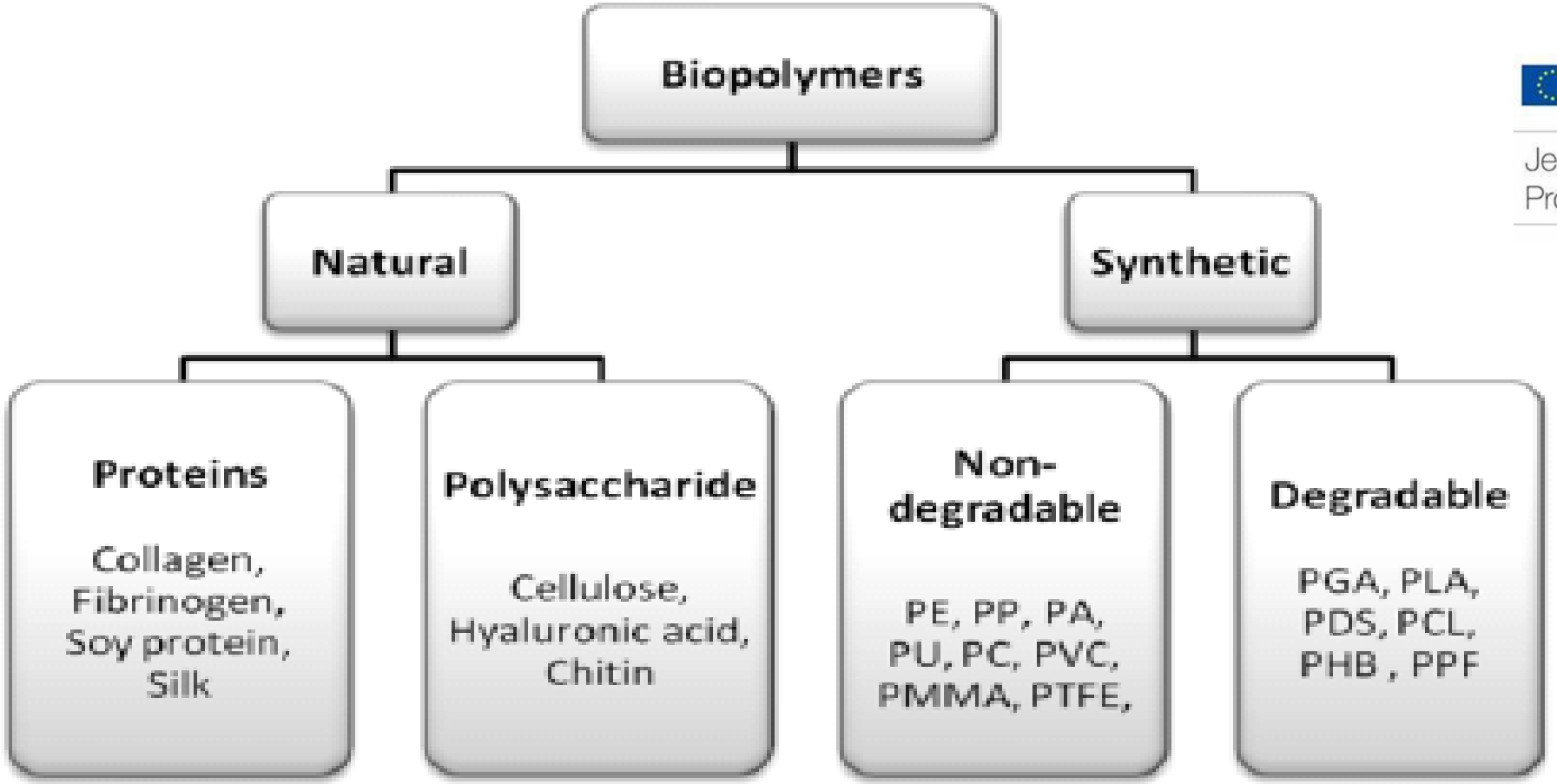

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Natural polymers

Natural polymers, or polymers, derived from living creatures, are of great interest in the biomaterials field.

Properties of natural polymers:

- Biodegradable;
- Non-toxic/ non-inflammatory;
- Mechanically similar to the tissue to be replaced;
- Highly porous;
- Encouraging of cell attachments and growth;
- Easy and cheap to manufacture
- Capable of attachment with other molecules (to potentially increase scaffold interaction with normal tissue).

Example of natural polymers

. Collagen

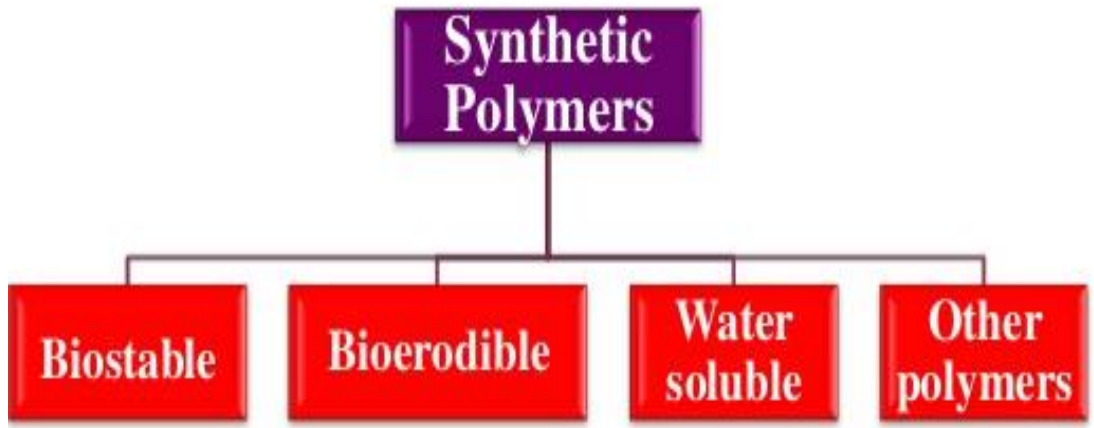
. Cellulose

. Alginates

. Dextrans and

. Chitosan

Classification of synthetic polymers



Applications:

Medical disposable supplies, Prosthetic materials, Dental materials, implants, dressings, polymeric drug delivery, tissue engineering products

16

Synthetic Polymers

- Advantages of Synthetic Polymers
  - ➢Ease of manufacturability
  - ➢process ability
  - ➢reasonable cost
- The Required Properties
  - ▪ Biocompatibility
  - ▪ Sterilizability
  - ▪ Physical Property
  - ▪ Manufacturability

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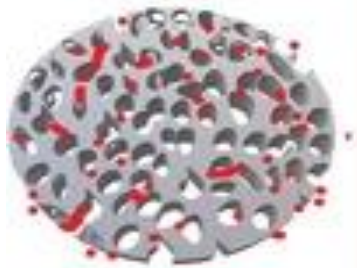
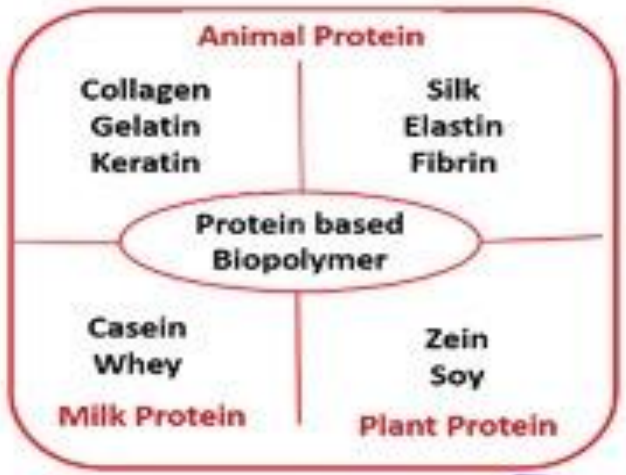
Protein based biopolymers and their formulation

Electrospun Fibers



Interconnected porous scaffolds



3D printing scaffolds

Therapeutic molecule loaded Polymer particles

Hydrogel

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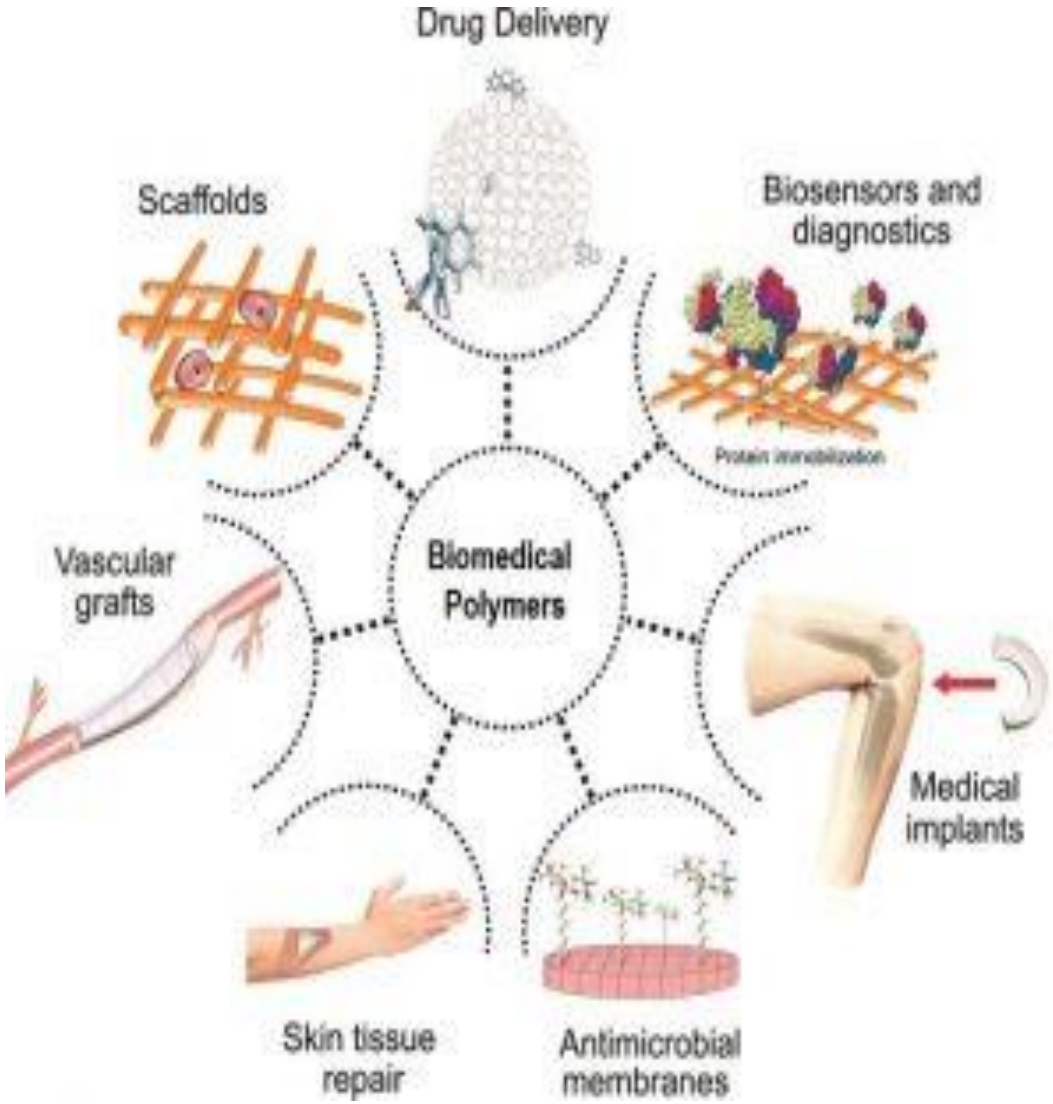

Application

- Cardiovascular Applications
- Bones, Joints, And Teeth
- Contact Lenses And Intraocular Lenses
- Artificial Kidney And Hemodialysis Materials
- Oxygen-Transport Membranes
- Surgical Sutures
- Tissue Ingrowth Polymers
- Controlled Release Of Drugs

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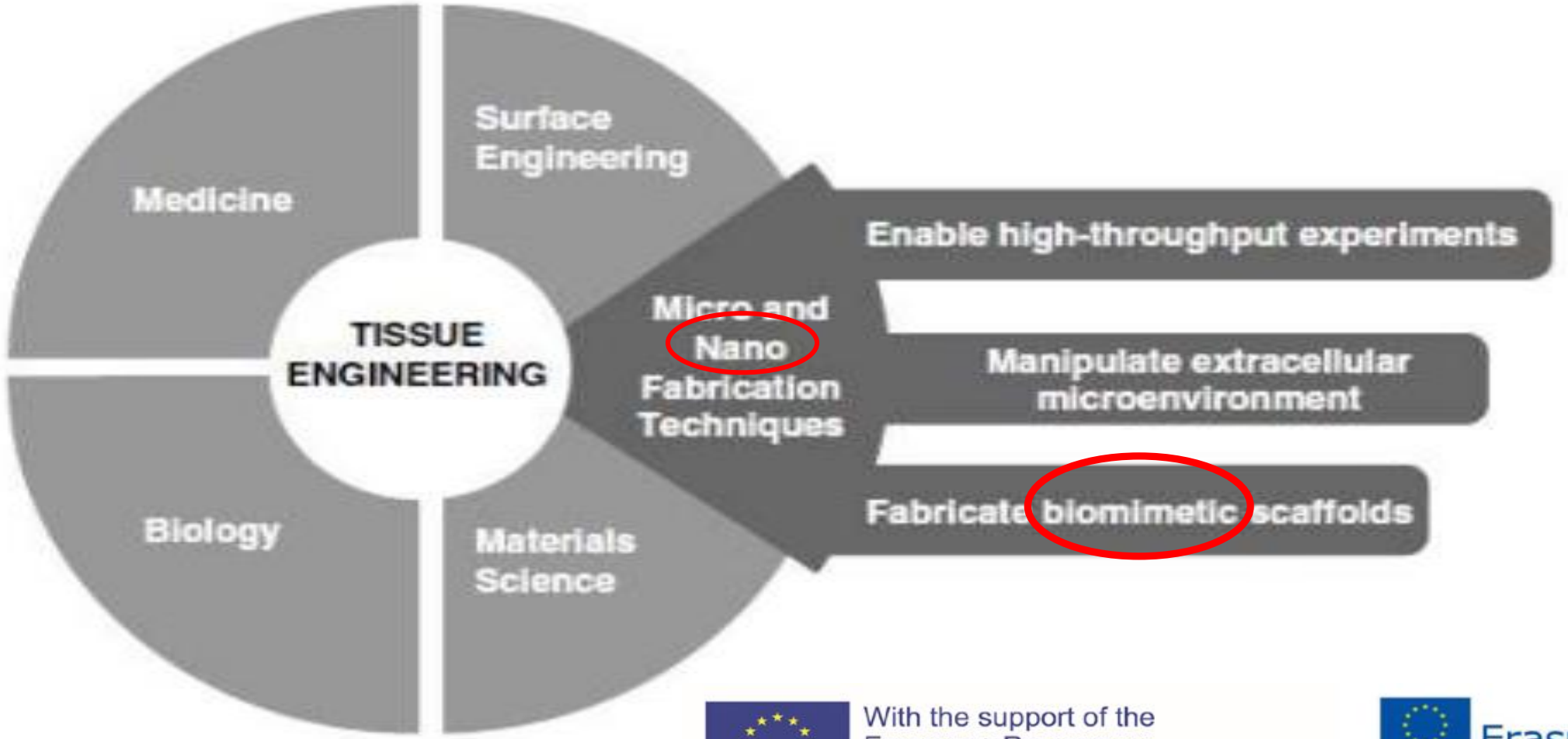

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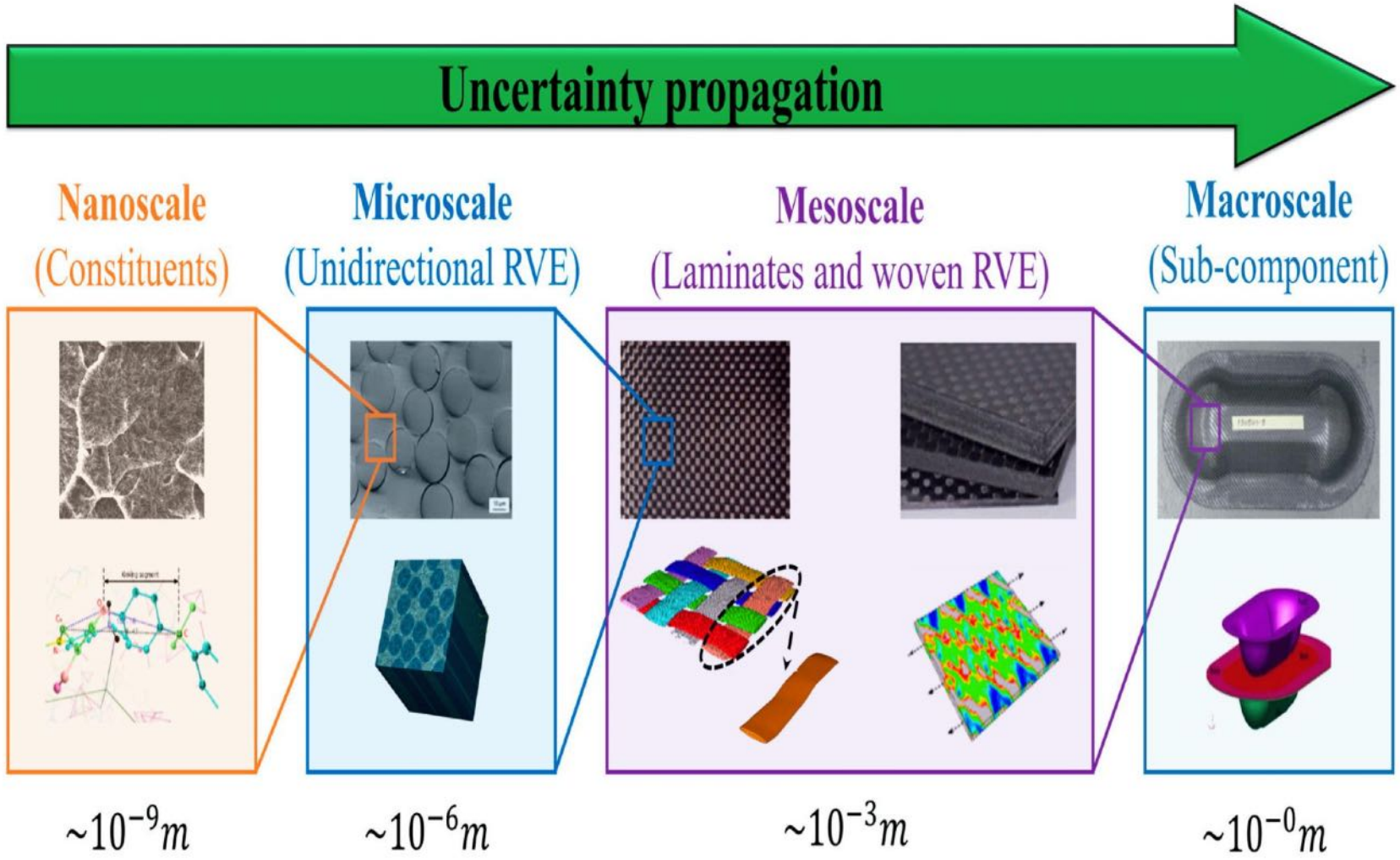

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What are scaffolds?

Scaffolds: Serve as temporary or permanent artifical Extracellular Matrices (ECM) to accommodate cells and support 3D tissue regenerations .

What is ECM?

blend of macromolecules (proteins and carbohydrates) **around cells—as space fillers.**

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Biomemtic Scaffolds

- **Biomimetics** is defined as the application of methods and systems, found in nature, to technology and engineering.
- Mimicking the naturally occurring extracellular matrix (ECM) and how this is a promising approach to effectively tailor cell response and to successfully engineer replacement tissues.

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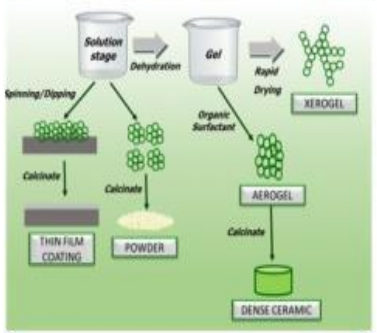
BIOMATERIALS

SYNTHESIS

Sol – gel



Composites

Natural Synthetic

CHARACTERIZATION

Techniques

- XRD
- FTIR
- UV/Vis
- NMR
- Raman
- AFM
- SEM – EDS
- TEM – EDX
- ICP
- μCT
- BET
- CONFOCAL

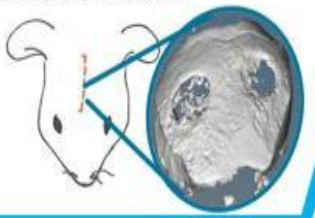
TESTING

In Vitro Testing

- Simulated conditions
- Human cell response
- Antibacterial

In Vivo Testing

- Mouse model



APPLICATIONS

Dentistry and Orthopedic

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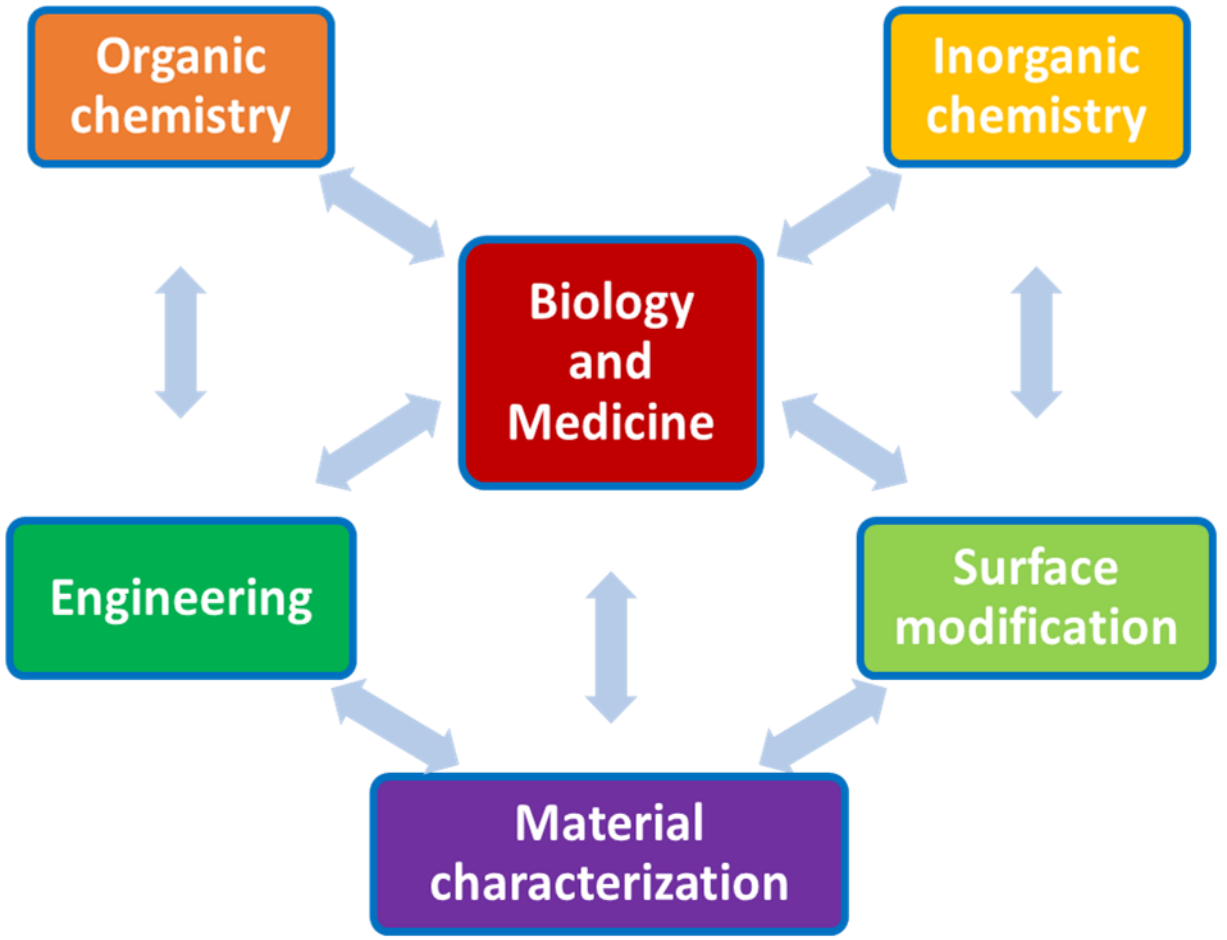
Multidisciplinary approach



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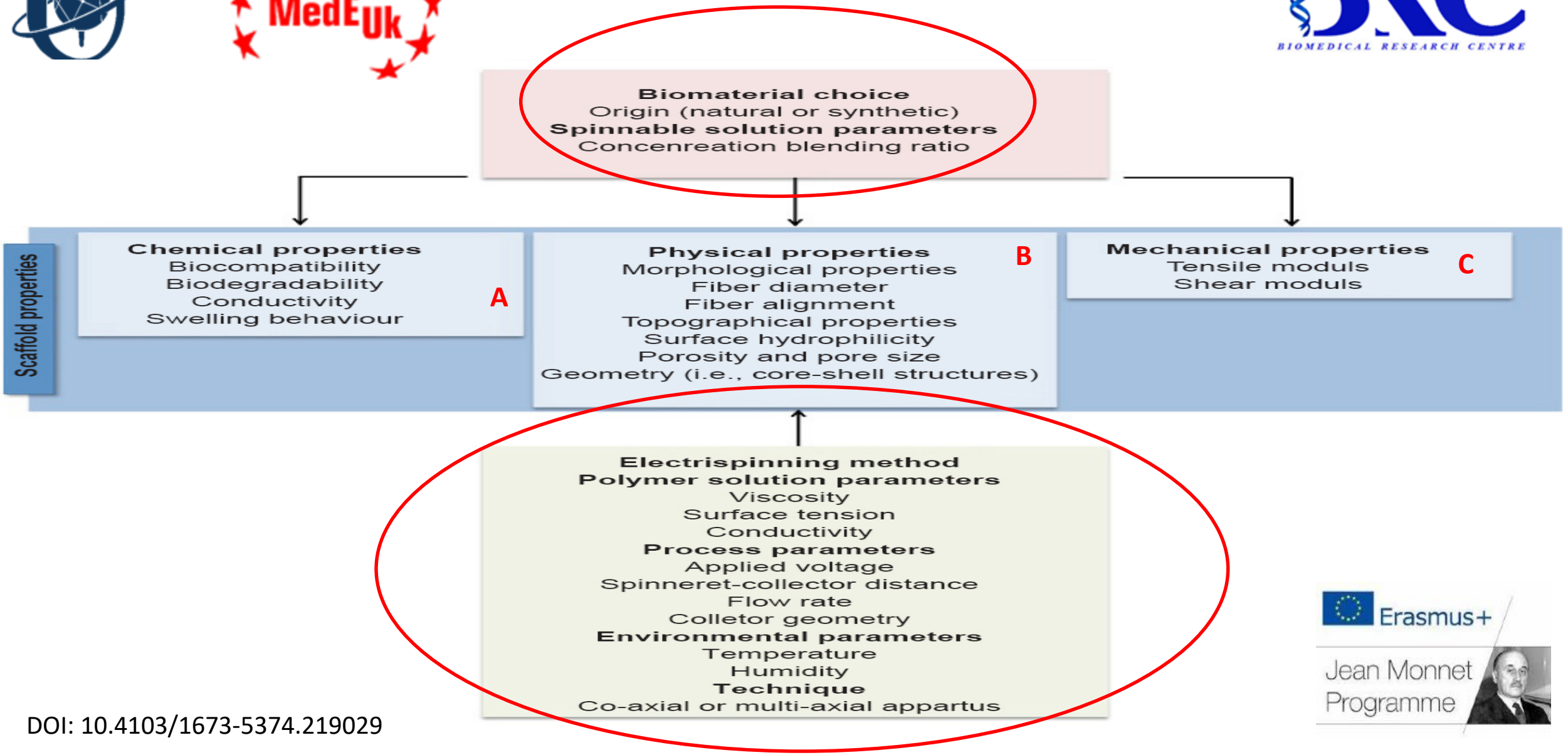
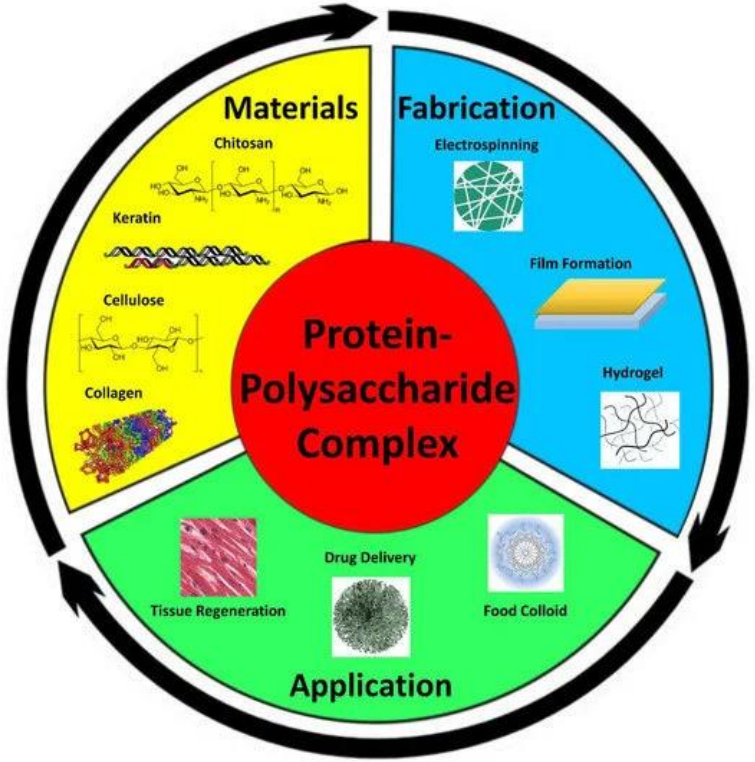
Electrospinning

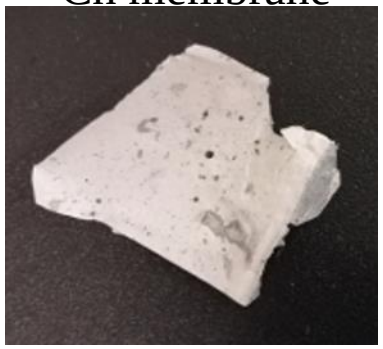


DOI: 10.4103/1673-5374.219029

Material / Method



Ch membrane



electrospinning

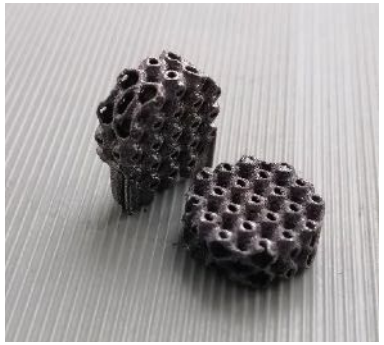
Ch sponge

chemical crosslinking process

Ti6Al4V alloy

ZrNb alloy

anodization in electrolytic bath



selective laser melting machine

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State of the art

Natural polymers

Bio-compatibility

Bio-degradability

Non-immunogenic properties

Natural abundant polysaccharides

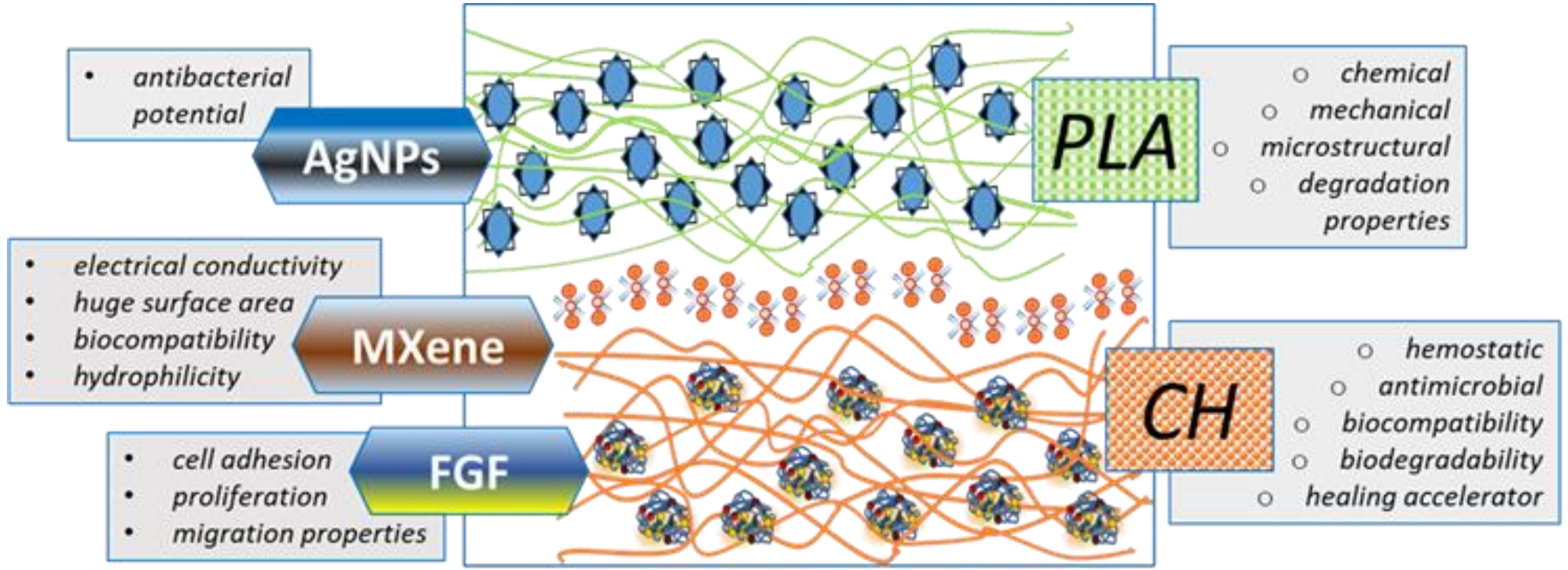
structural similar with biological macromolecules

easily recognized by the bioenvironment

easily metabolized to residues that are nontoxic and naturally eliminated

- ***TISSUE ENGINEERING SCAFFOLDS***
- ***DRUG DELIVERY VEHICLES***
- ***PERMEABLE MEMBRANES***

Project concept focused on the properties of their compounds



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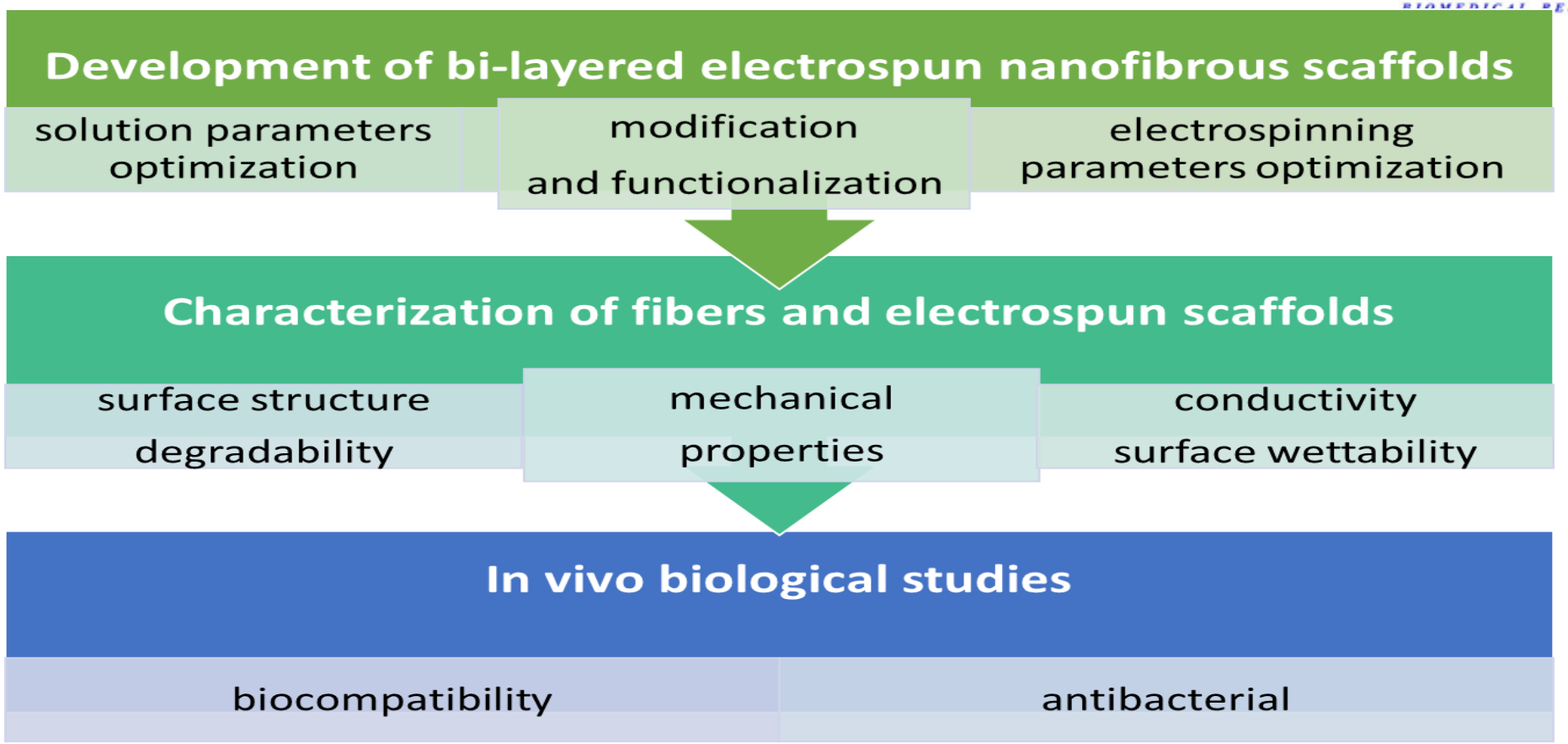
Scientific objectives



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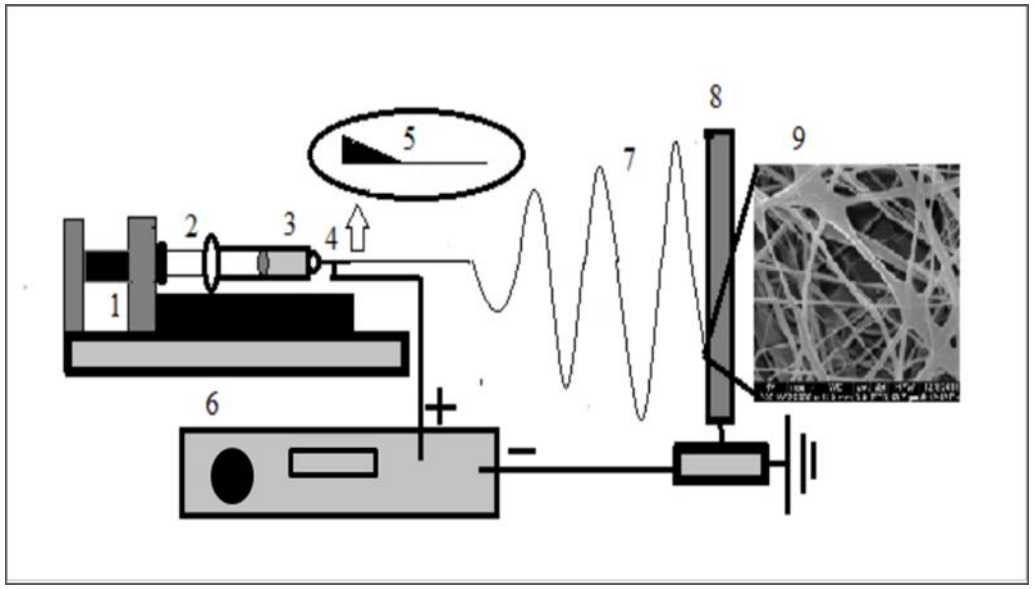
Electrospinning setup

Electrospinning system
(Linari Engineering, Italy)



Scheme of electrospinning setup for chitosan membrane production: 1 – pump; 2 – syringe; 3 – solution; 4 – needle; 5 – Taylor cone; 6 – power supply; 7 – jet; 8 – collector; 9 – nanofibers

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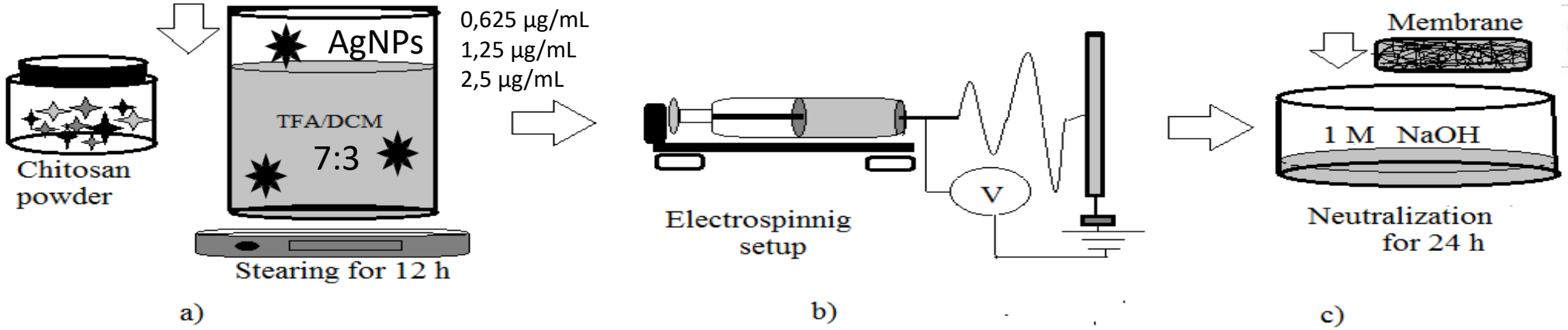
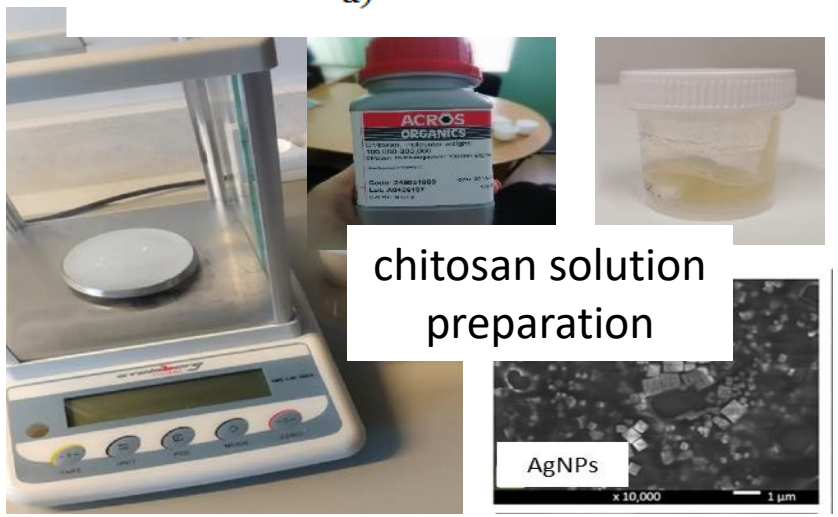
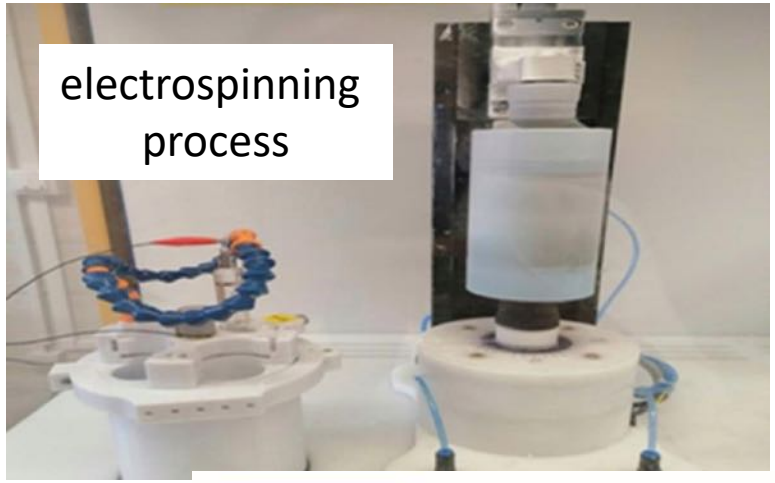
Fabrication of Ch-AgNPs nanofibers MATERIALS/METHODS







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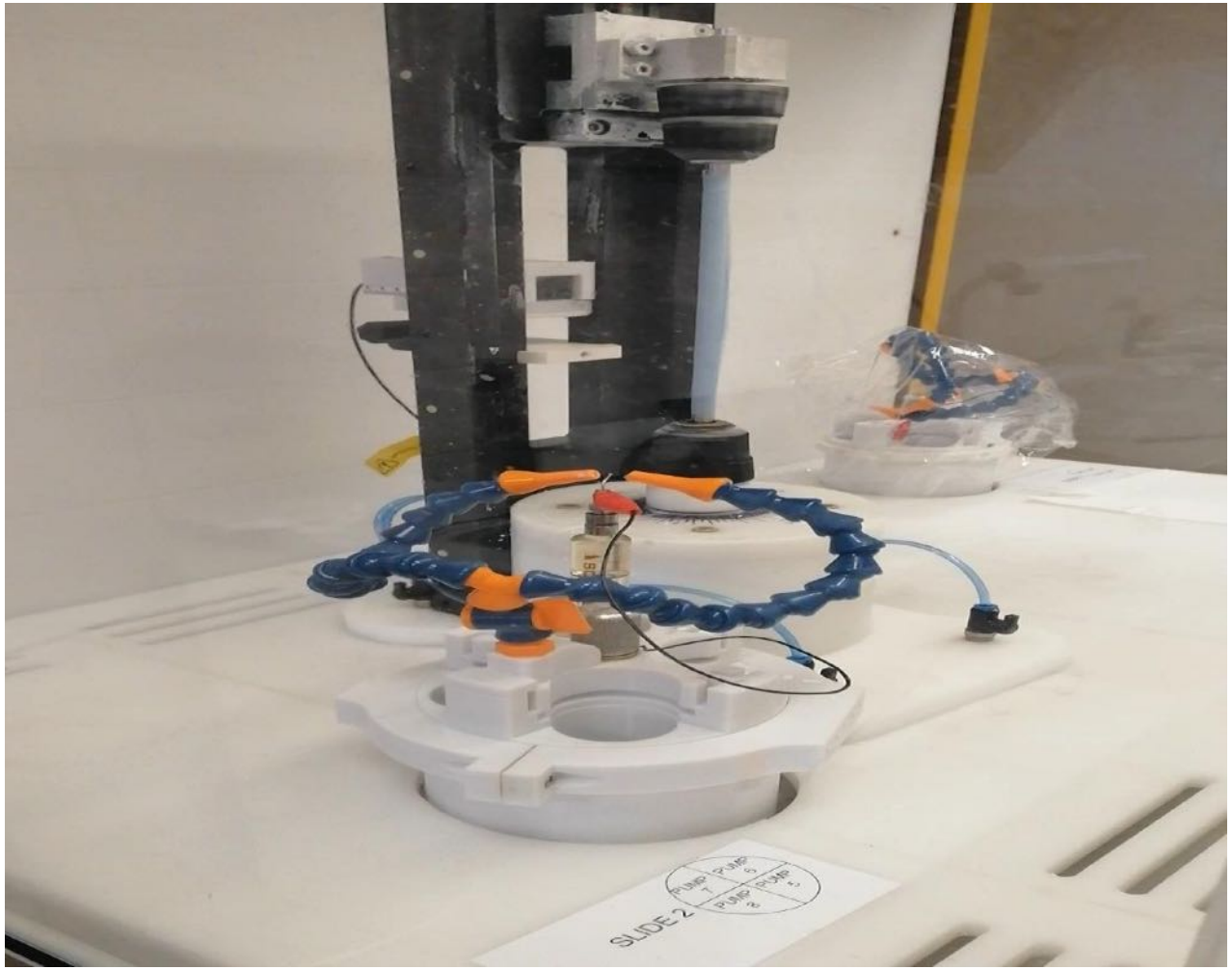
Fabrication of Ch-AgNPs nanofibers



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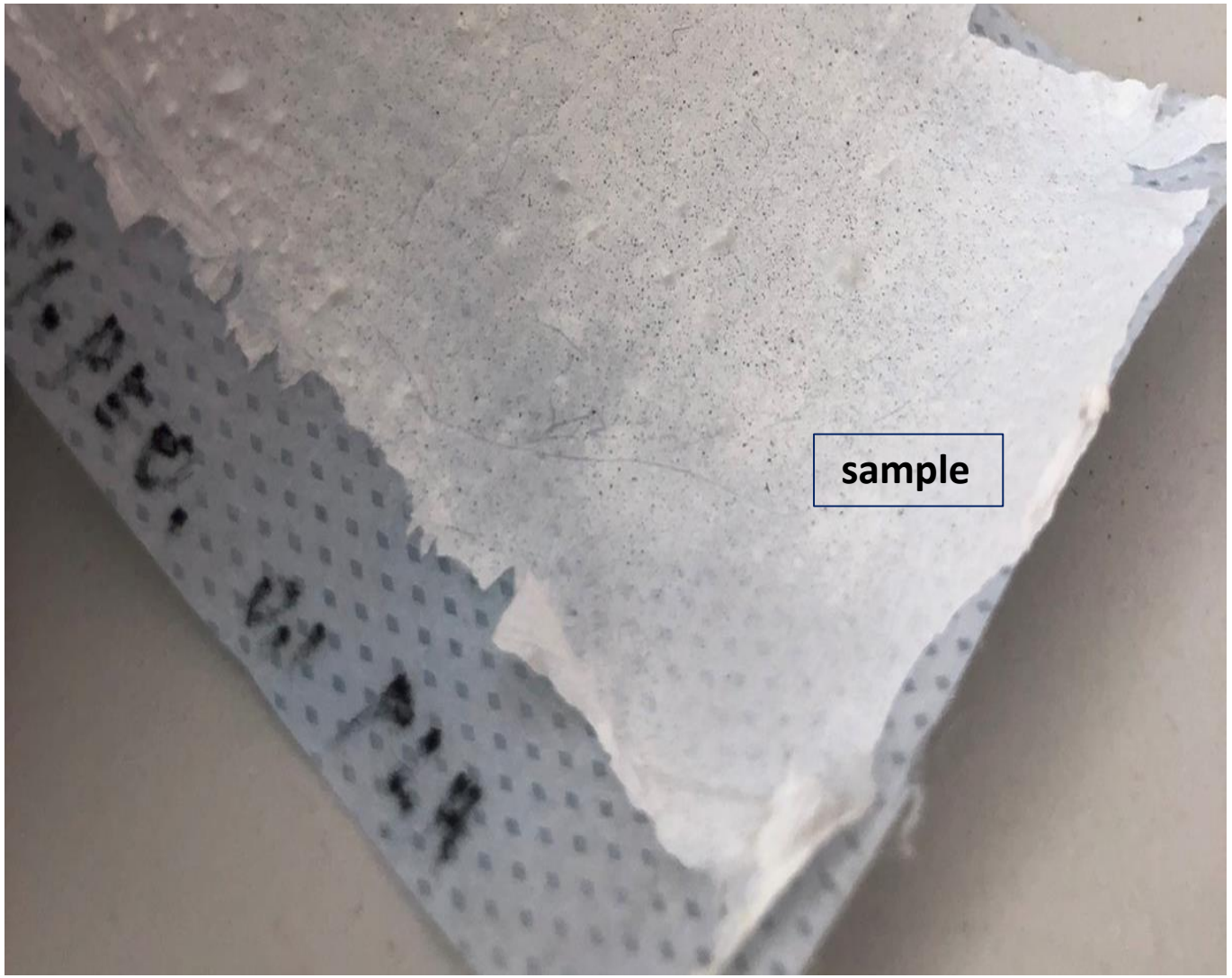
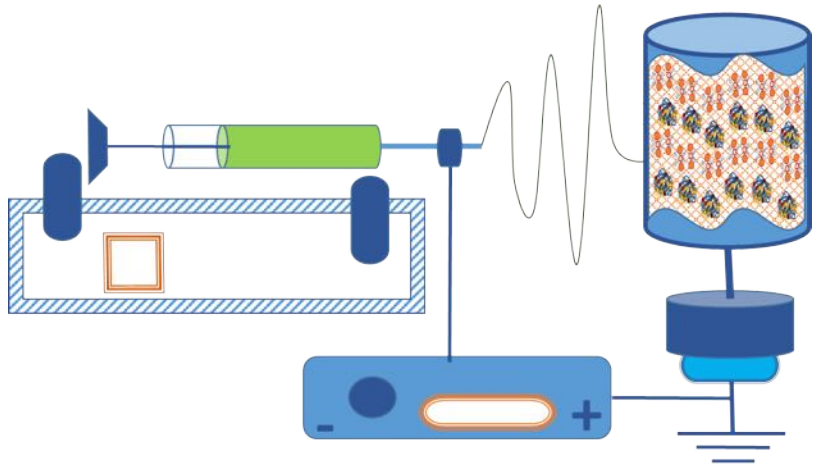
Electrospinning setup



How does it work?



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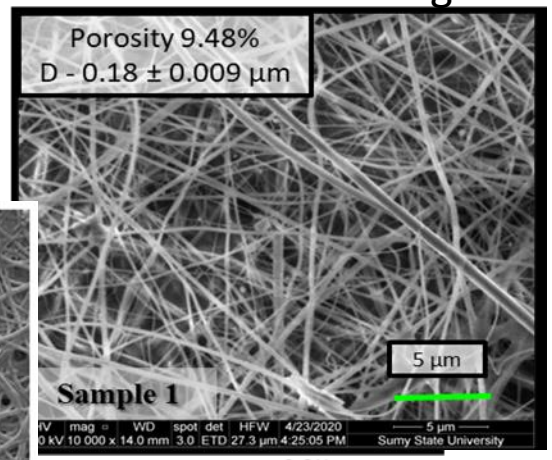
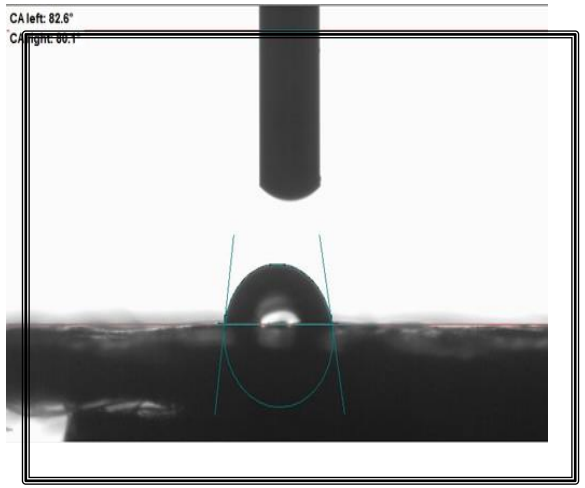
Characterization of nanofibrous electrospun scaffolds: testing of structural, chemical and surface properties

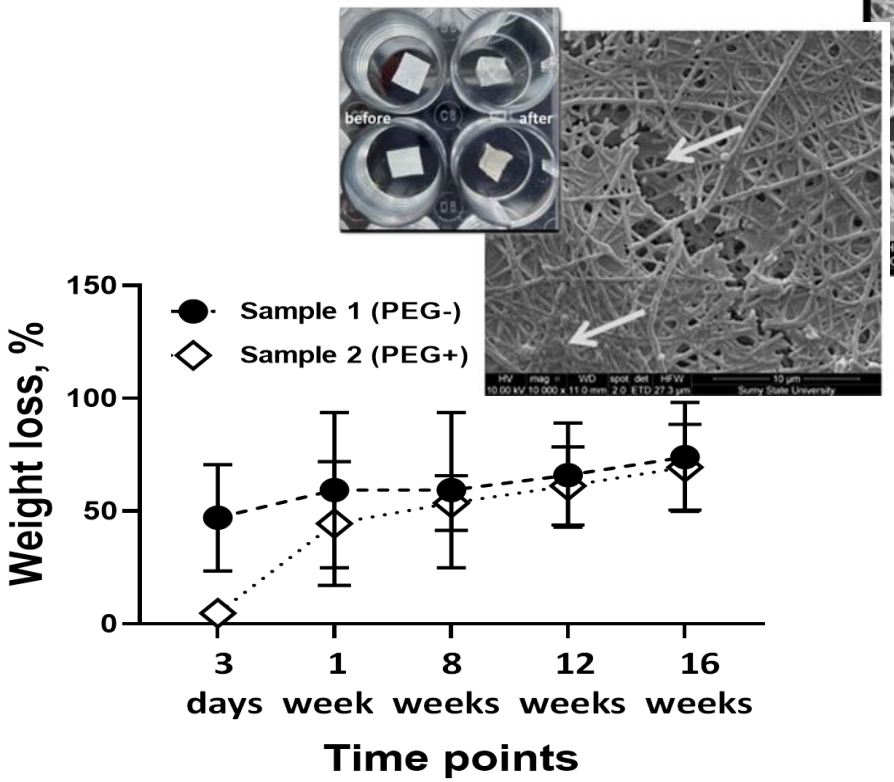
SEM image

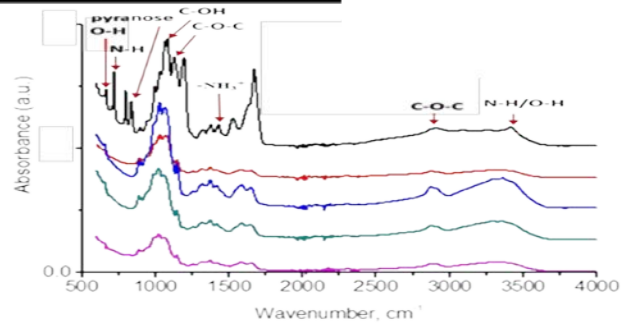


Surface CA



Degradation kinetics





FTIR spectra

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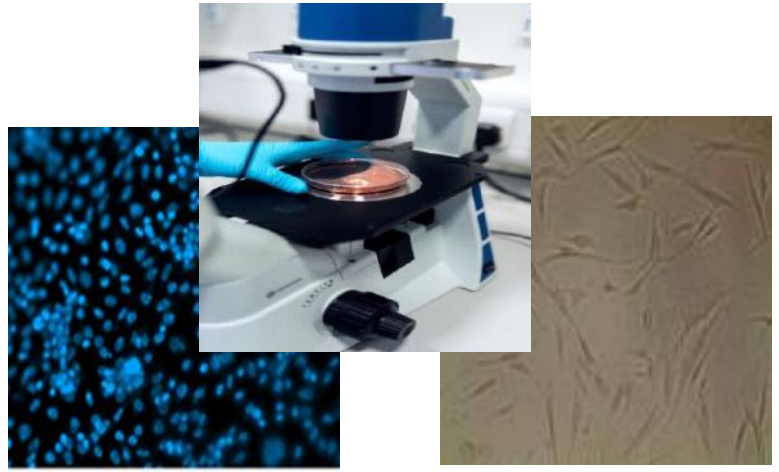
In vitro testing

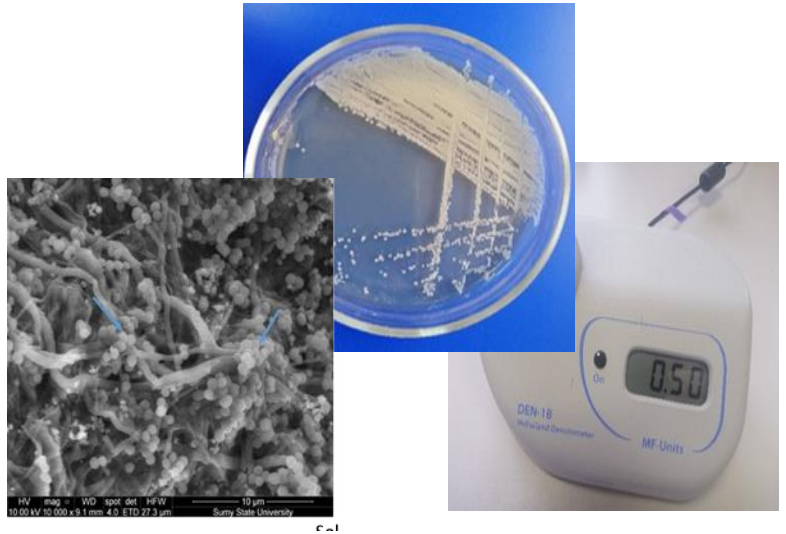
To assess the cell toxicity

- normal human dermal fibroblasts culture
- resazurin reduction assay / CCK-based assay
- fluorescent microscopy

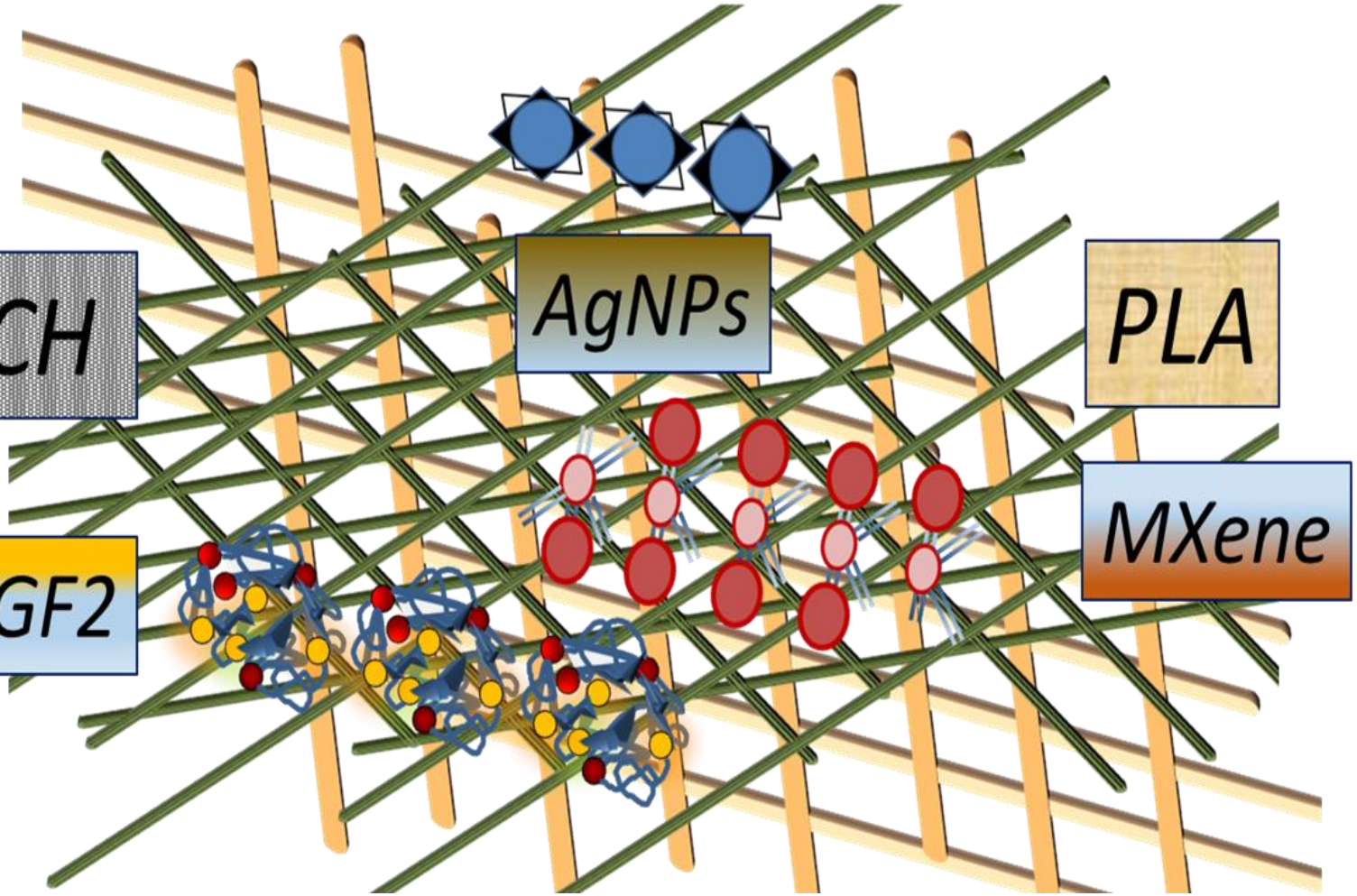


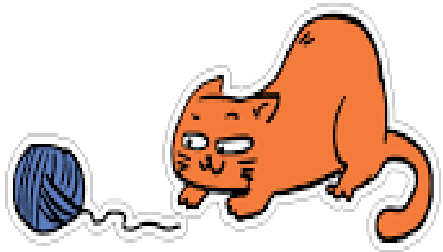
To assess antibacterial properties

- Staphylococcus aureus and Escherichia coli bacteria
- time-dependent bacterial growth assay
- alamar blue biofilm susceptibility testing
- SEM



Conclusions





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Антибактеріальні наночастинки розробка та дослідження

«Modern European trends in biomedical higher education: Bionanomaterials.»
№ 620717-EPP-1-2020-1-UA-EPPJMO-MODULE

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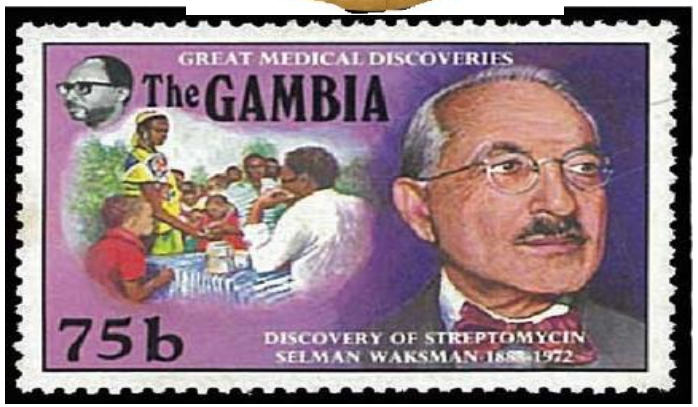
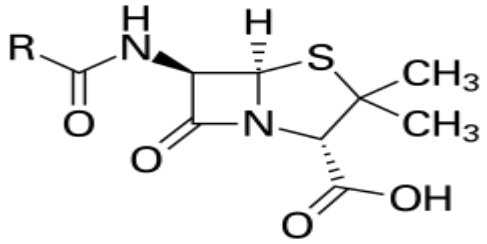
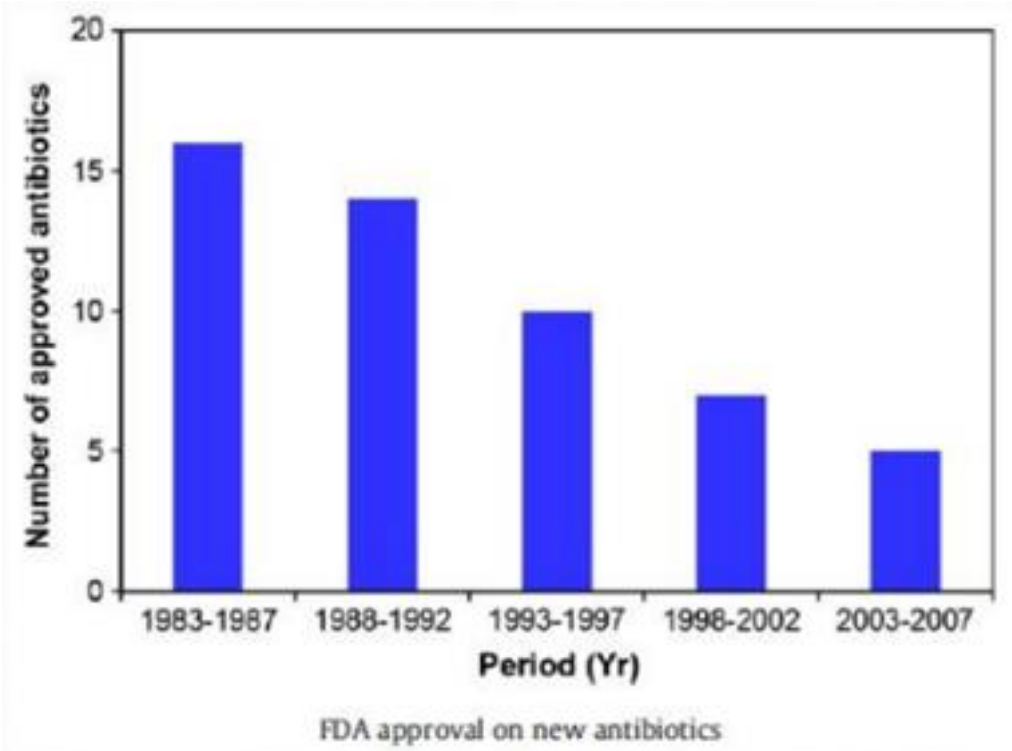
Future of Antibiotics ?







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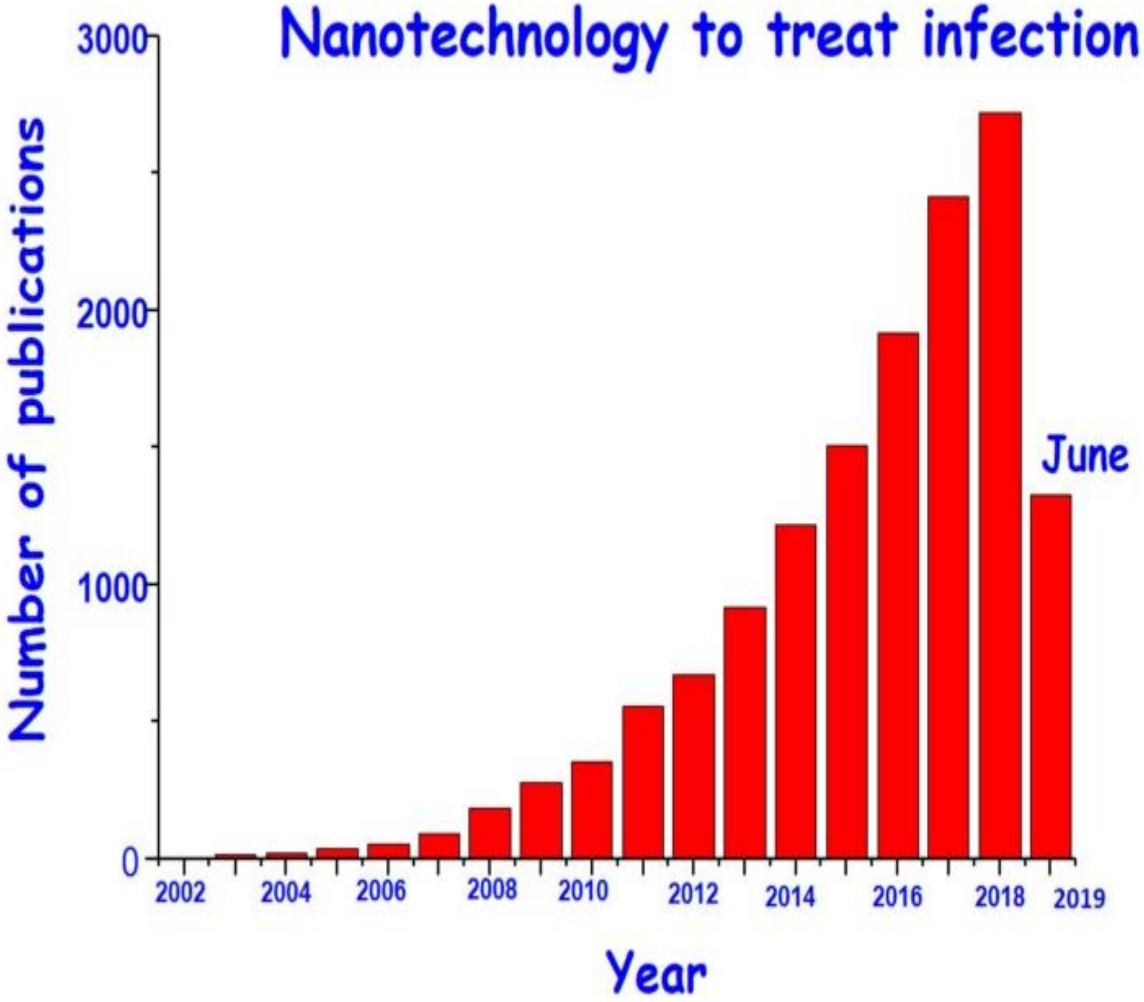

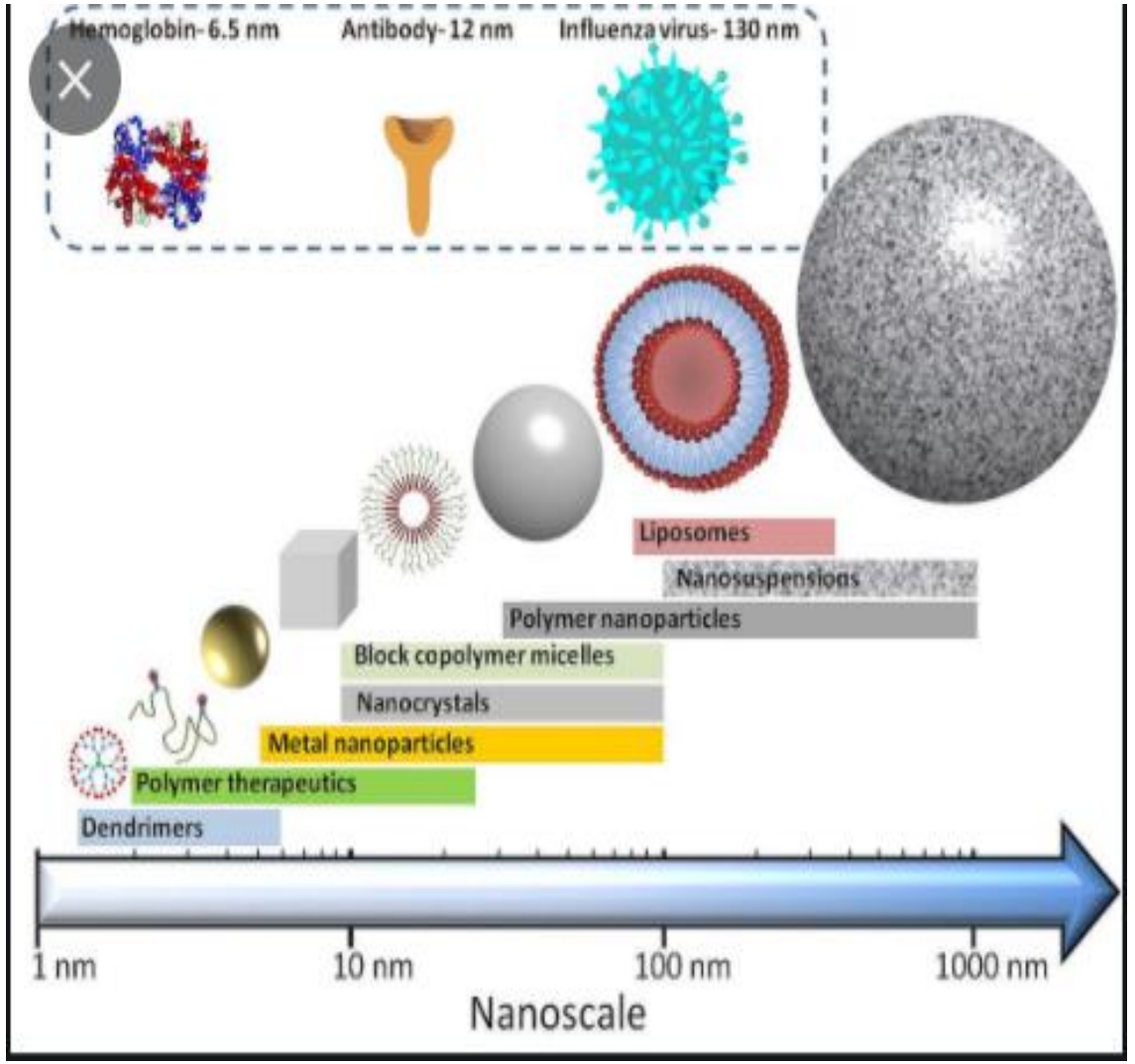

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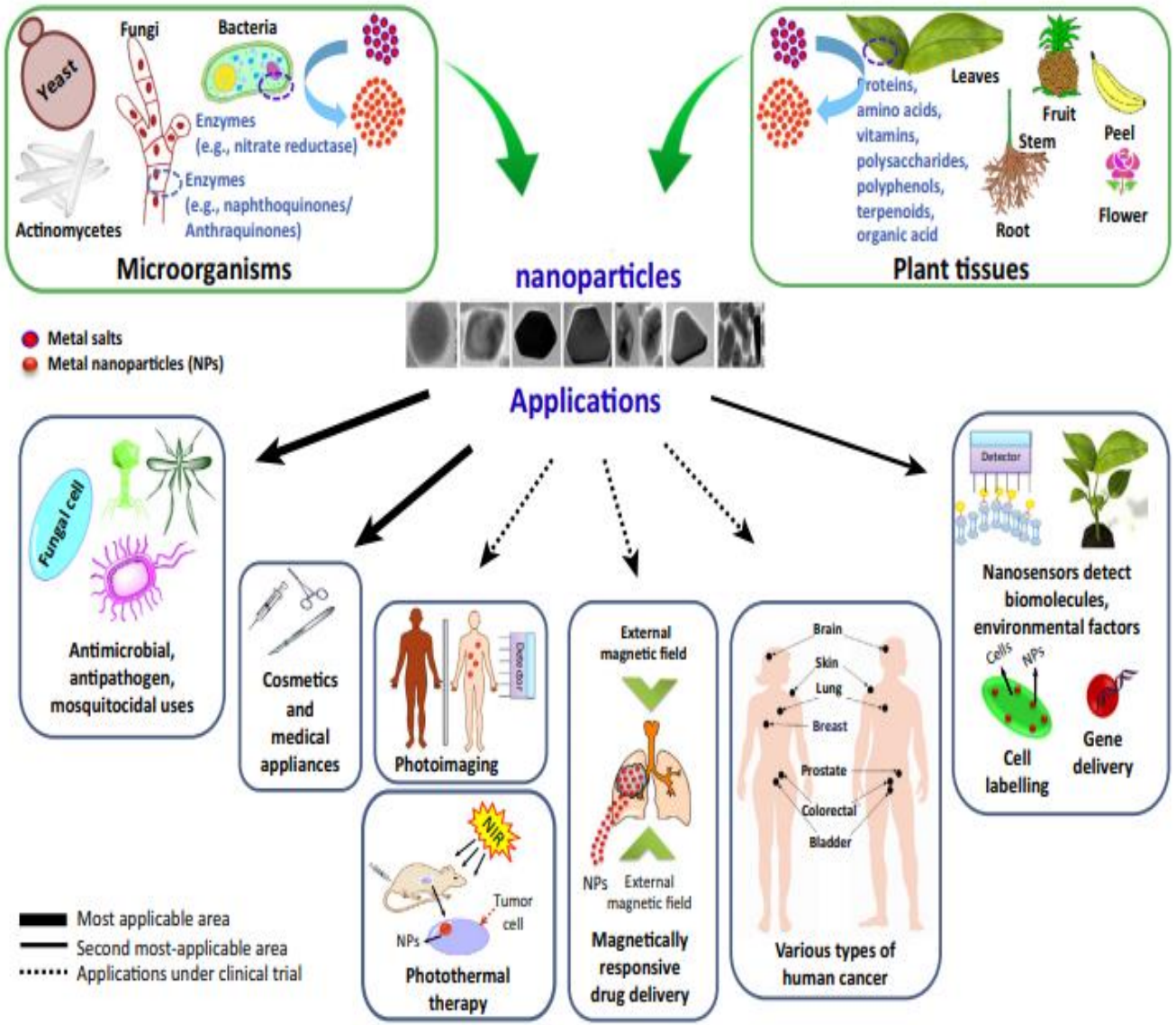

Needs for using Nanoparticles in Antimicrobial Field

- Multidrug Resistance
- Side effects of antibiotics if directly used
- For drug delivery
- For long term storage

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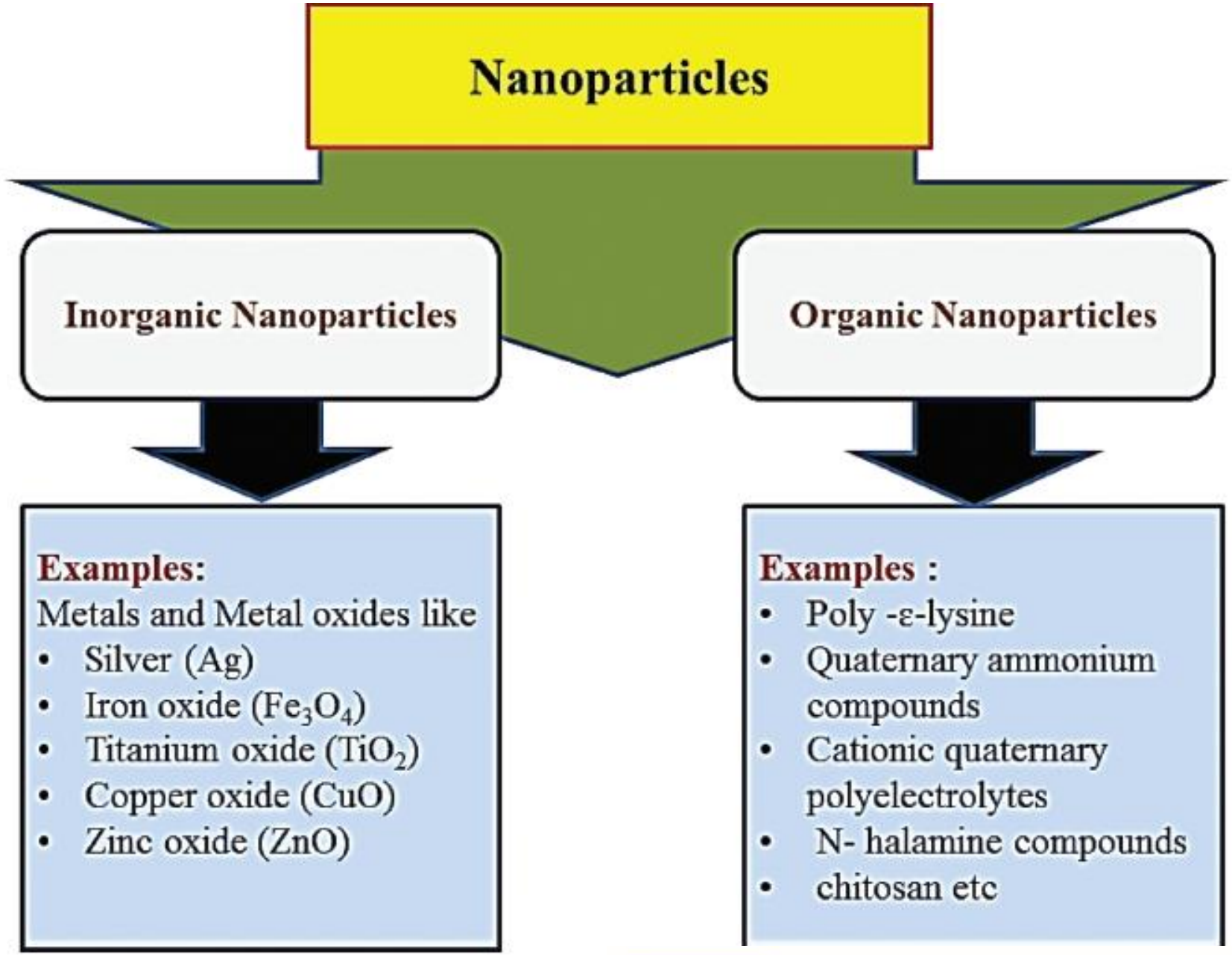

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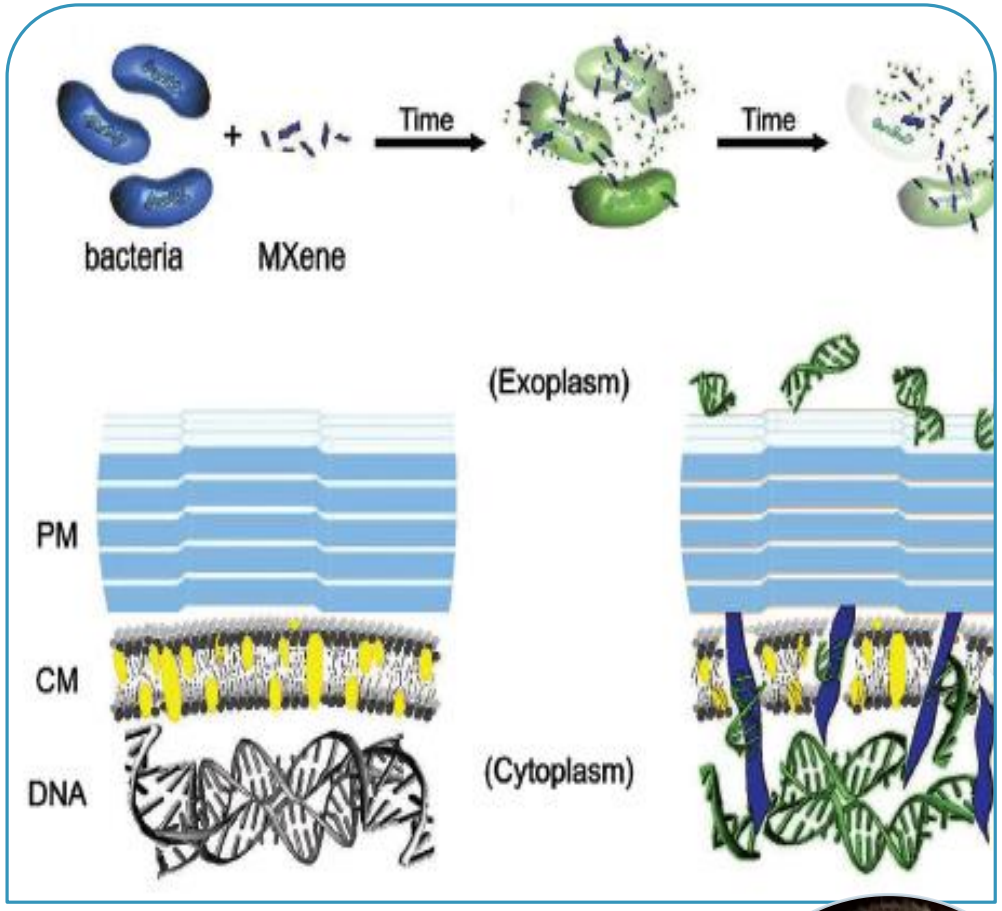
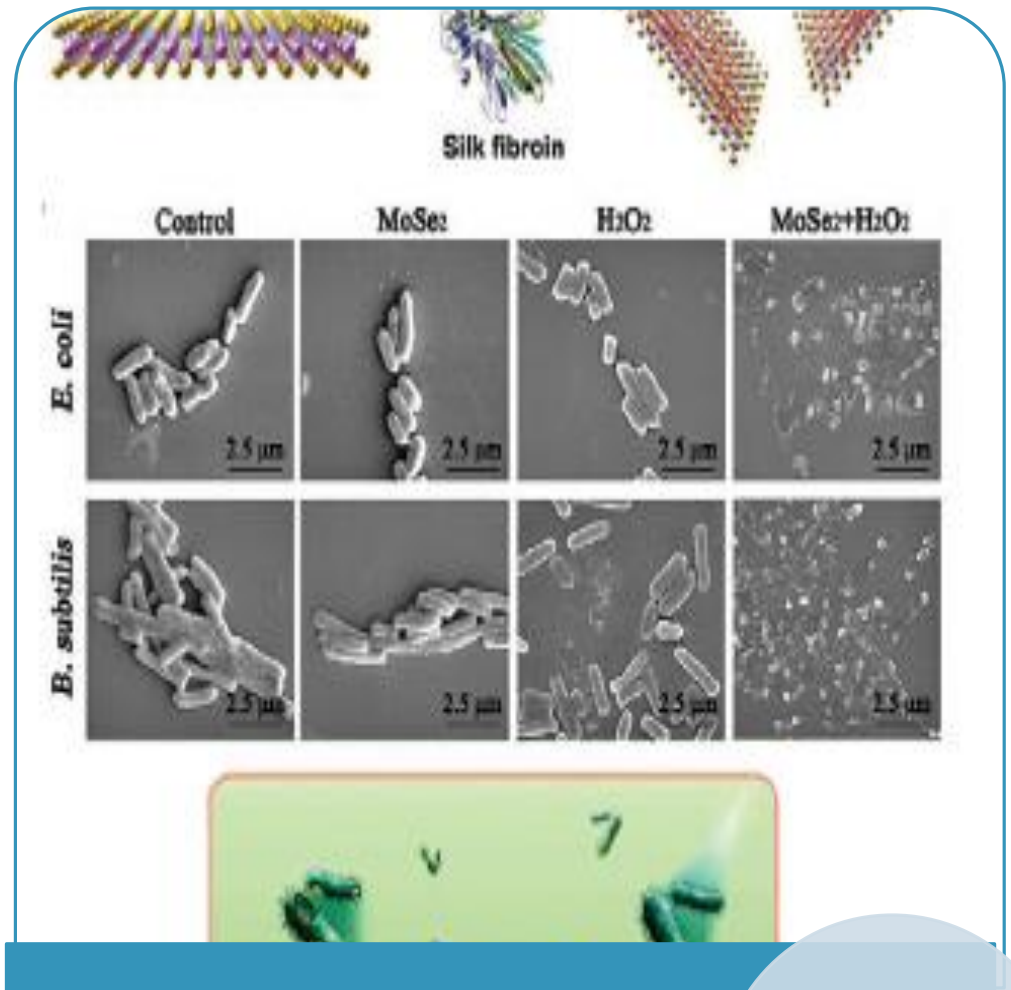


MXenes



Transition Metal Dichalcogenides

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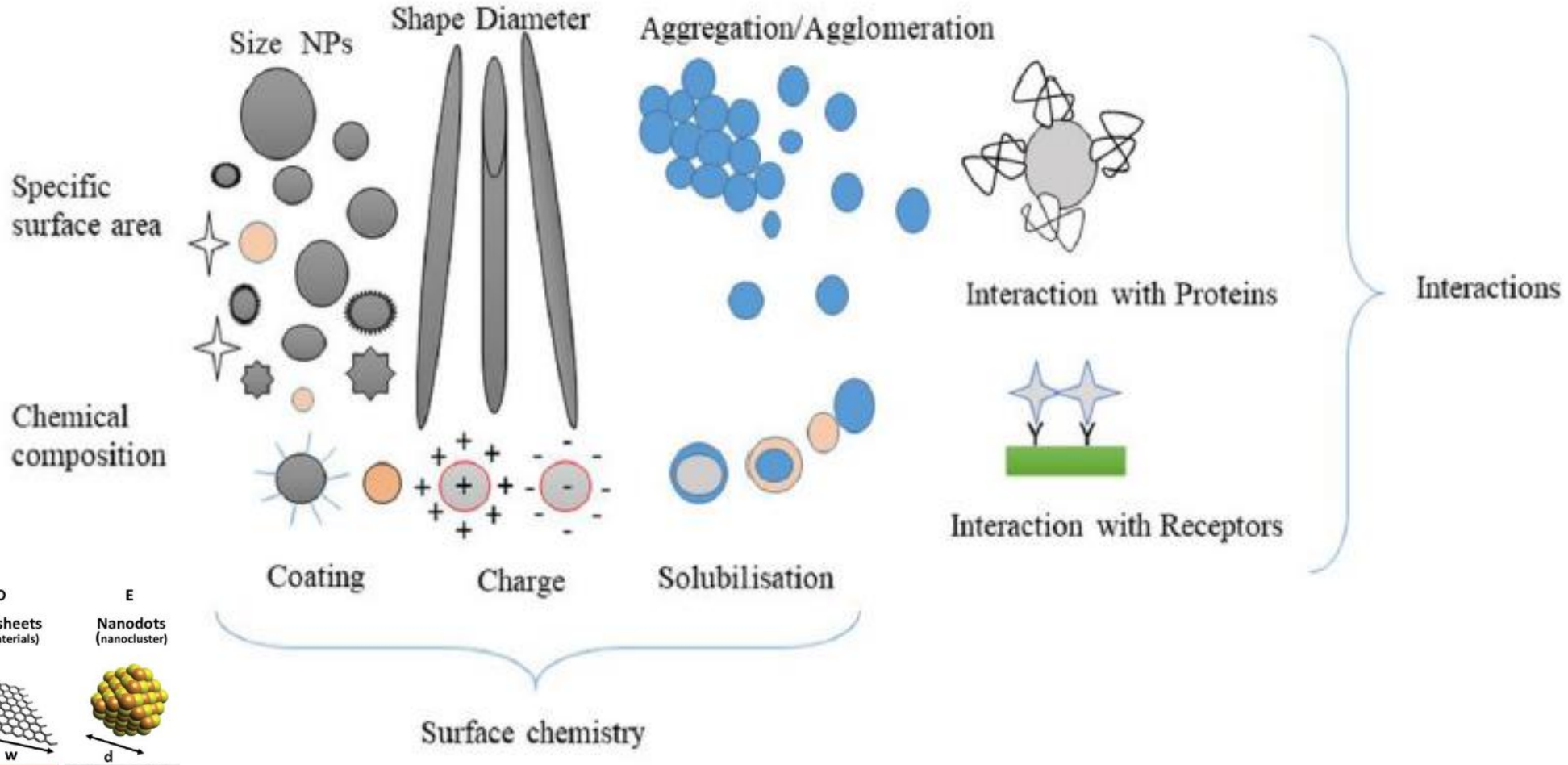
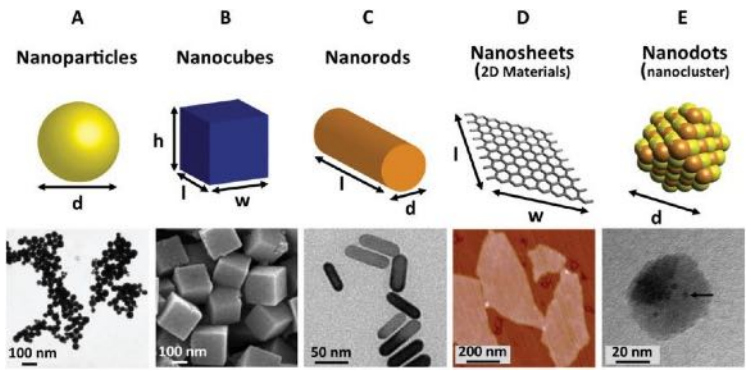
Physicochemical properties of the NPs involved in biological activity





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Antimicrobial NPs :

➢ Advantage:

- Targeted drug delivery via specific accumulation
- Lowered side effects of chemical antimicrobials
- Extended therapeutic lifetime due to slow elimination
- Controlled drug release
- Broad therapeutic index
- Low cost

➢ Disadvantage:

- High systemic exposure to locally administrated drugs
- Nanotoxicity (lung, kidney, liver, brain, germ cell, metabolic, etc.)
- Lack of characterization techniques.

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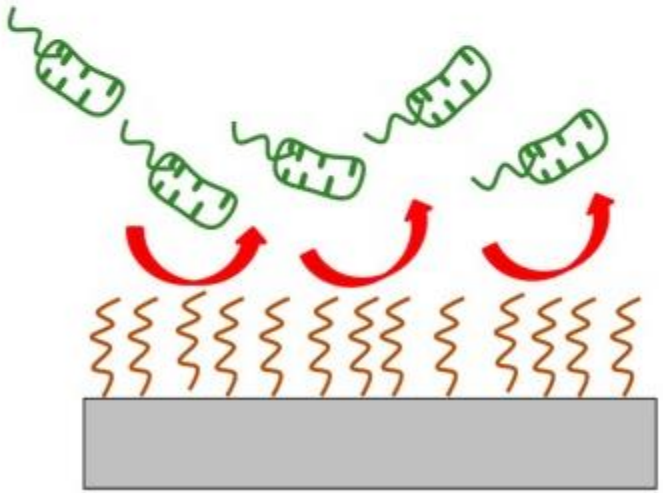
The challenge

Preventing infection

Inhibiting bacterial adhesion and biofilm formation

Non-fouling surfaces

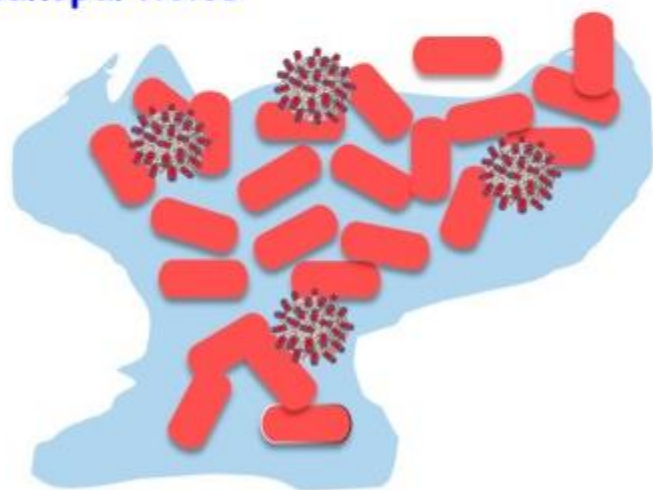


Combating infection

Destroying the biofilm and killing bacteria

Antimicrobial Nanoparticles

Nanocarriers



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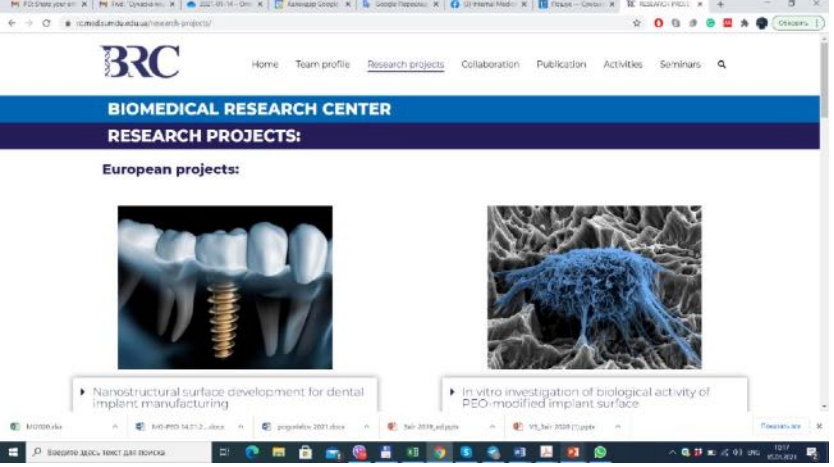
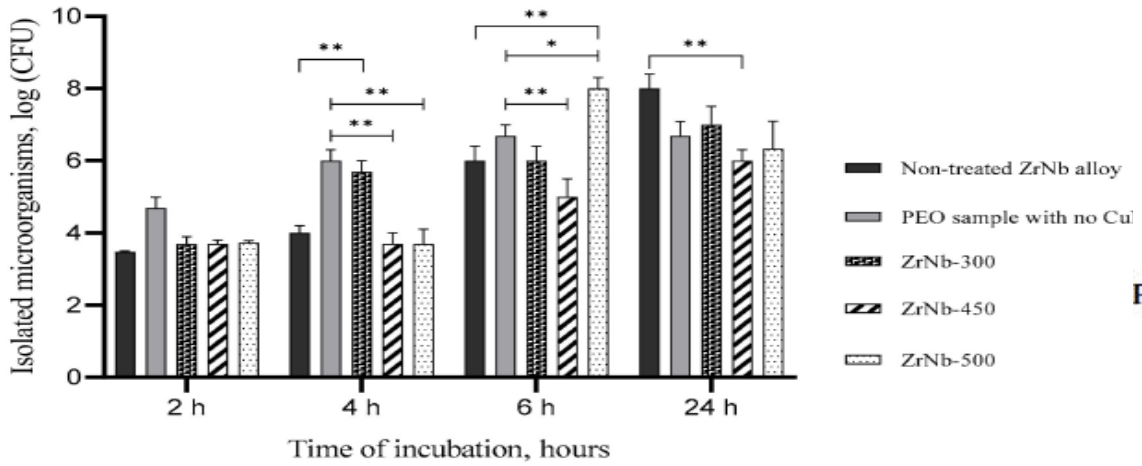
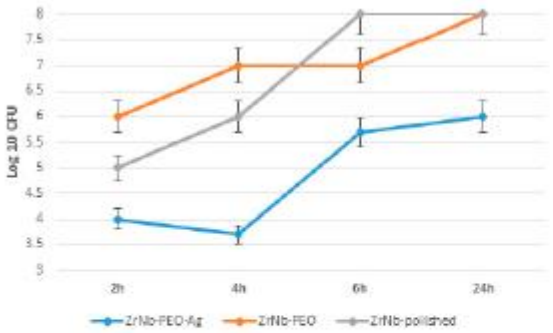
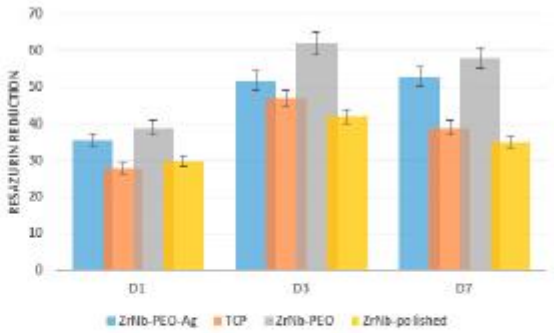
Preventing the Bacterial Adhesion









(a) (b)

Figure 6. Bacterial adhesion over 24 h (**a**) and osteoblast adhesion and 7-day proliferation (**b**) on the

materials MDPI

Article

Formation of a Bacteriostatic Surface on ZrNb Alloy via Anodization in a Solution Containing Cu Nanoparticles

Viktoriia Korniienko [1], Oleksandr Oleshko [1], Yevheniia Husak [1], Volodymyr Deineka [1], Viktoriia Holubnycha [1], Oleg Mishchenko [2], Alicja Kazek-Kęsik [3], Agata Jakóbik-Kolon [3], Roman Pshenychnyi [1], Katarzyna Leśniak-Ziółkowska [3], Oksana Kalinkevich [4], Aleksei Kalinkevich [4], Marcin Pisarek [5], Wojciech Simka [2,3,*] and Maksym Pogorielov [1,2,*]

materials MDPI

Article

Ag Nanoparticle-Decorated Oxide Coatings Formed via Plasma Electrolytic Oxidation on ZrNb Alloy

Oleksandr Oleshko [1], Volodymyr Deineka V [1], Yevgeniia Husak [1], Viktoriia Korniienko [1], Oleg Mishchenko [2], Viktoriia Holubnycha [1], Marcin Pisarek [3], Joanna Michalska [4], Alicja Kazek-Kęsik [4], Agata Jakóbik-Kolon [4], Wojciech Simka [2,4,*] and Maksym Pogorielov [1,2,*]

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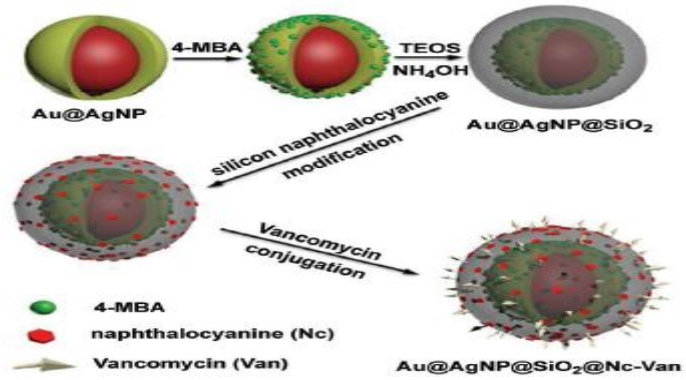
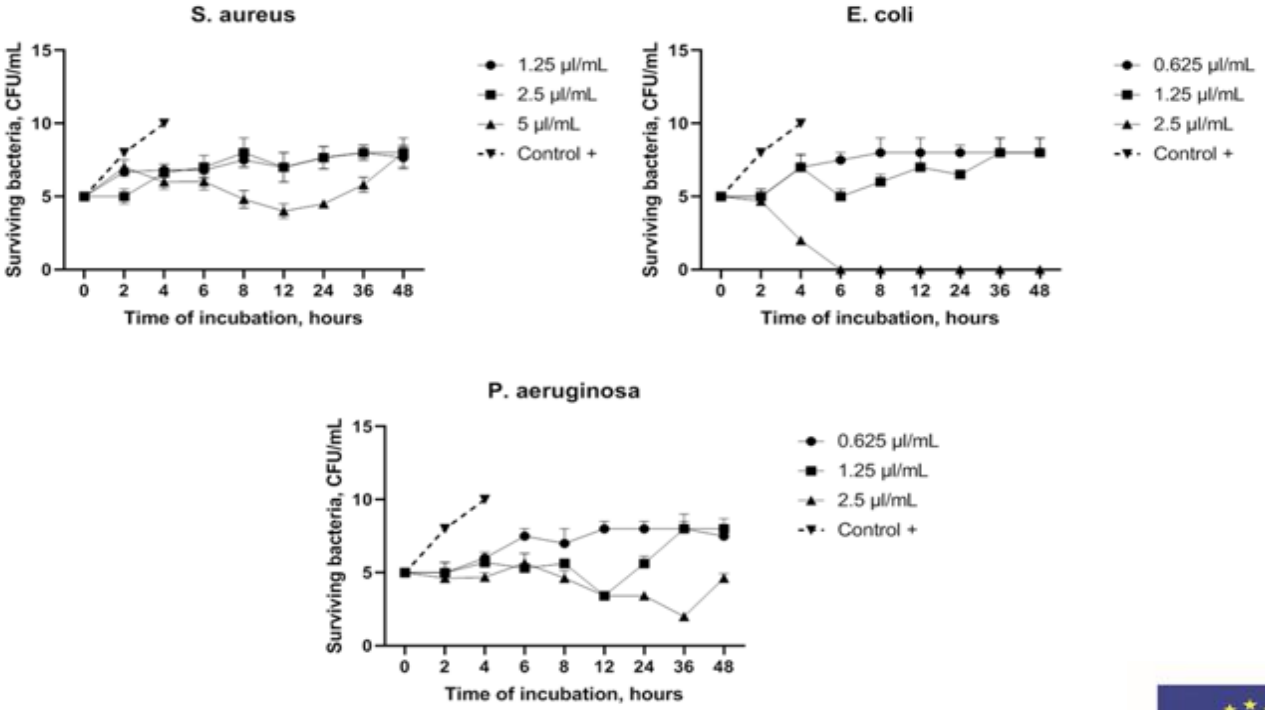
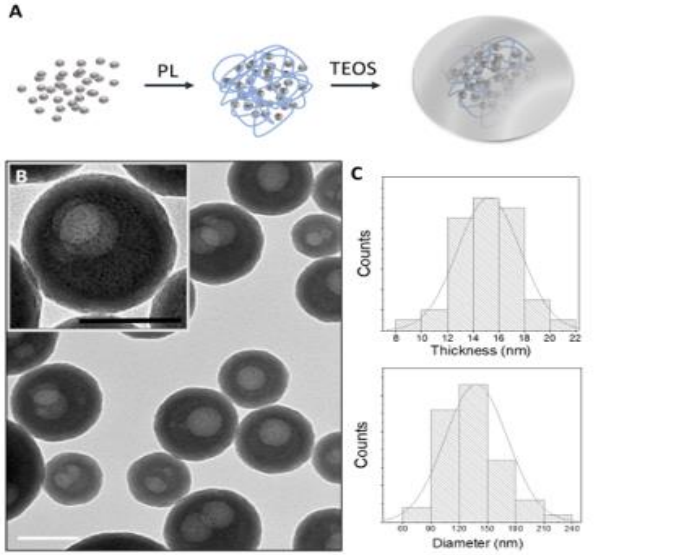
Nanomaterials with Unique Features as Potential Weapons to Fight Infections

1. Nanoparticles with Inherent Antibacterial Properties
2. Nanomaterials as Nanocarriers: Mesoporous Silica Nanoparticles







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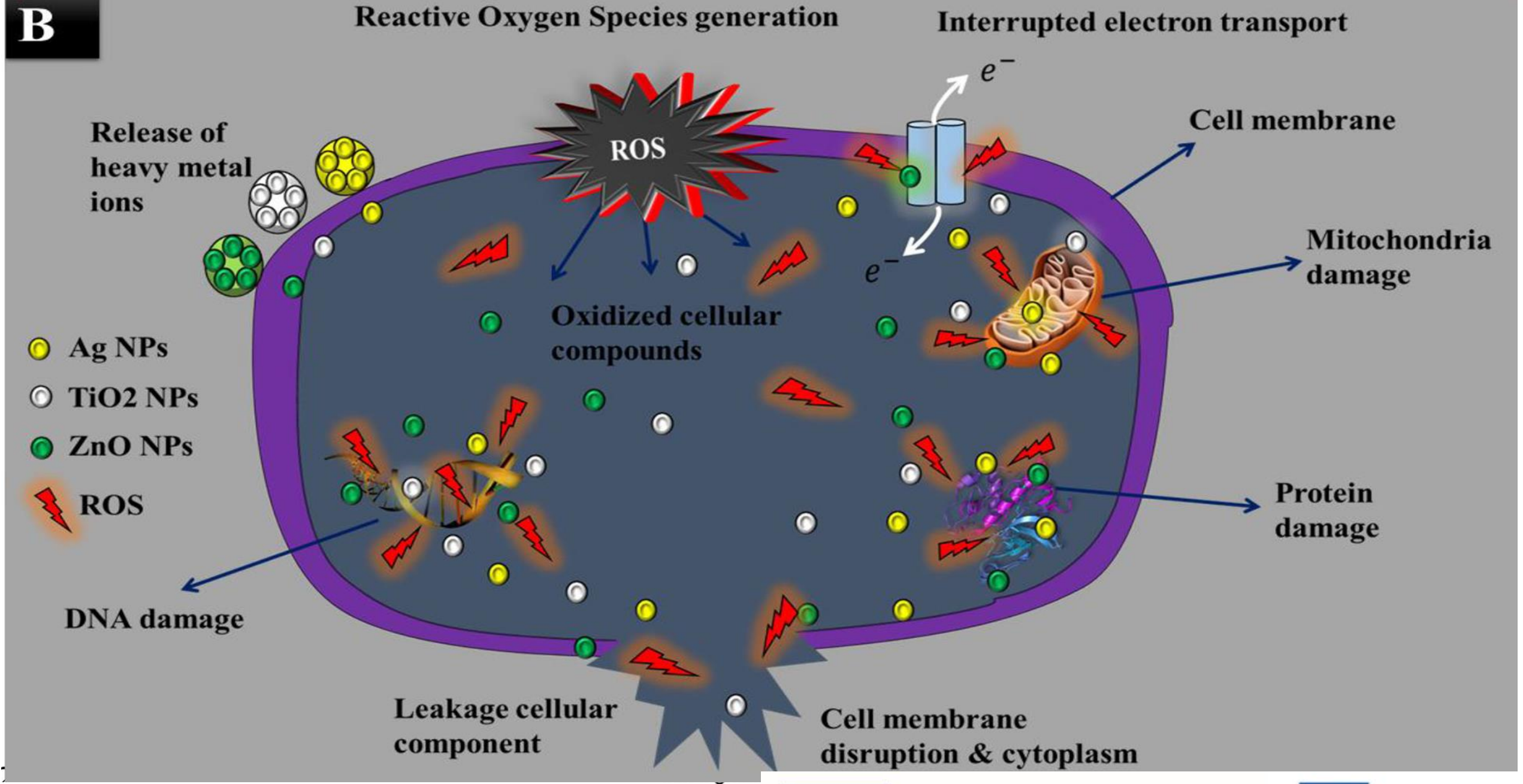

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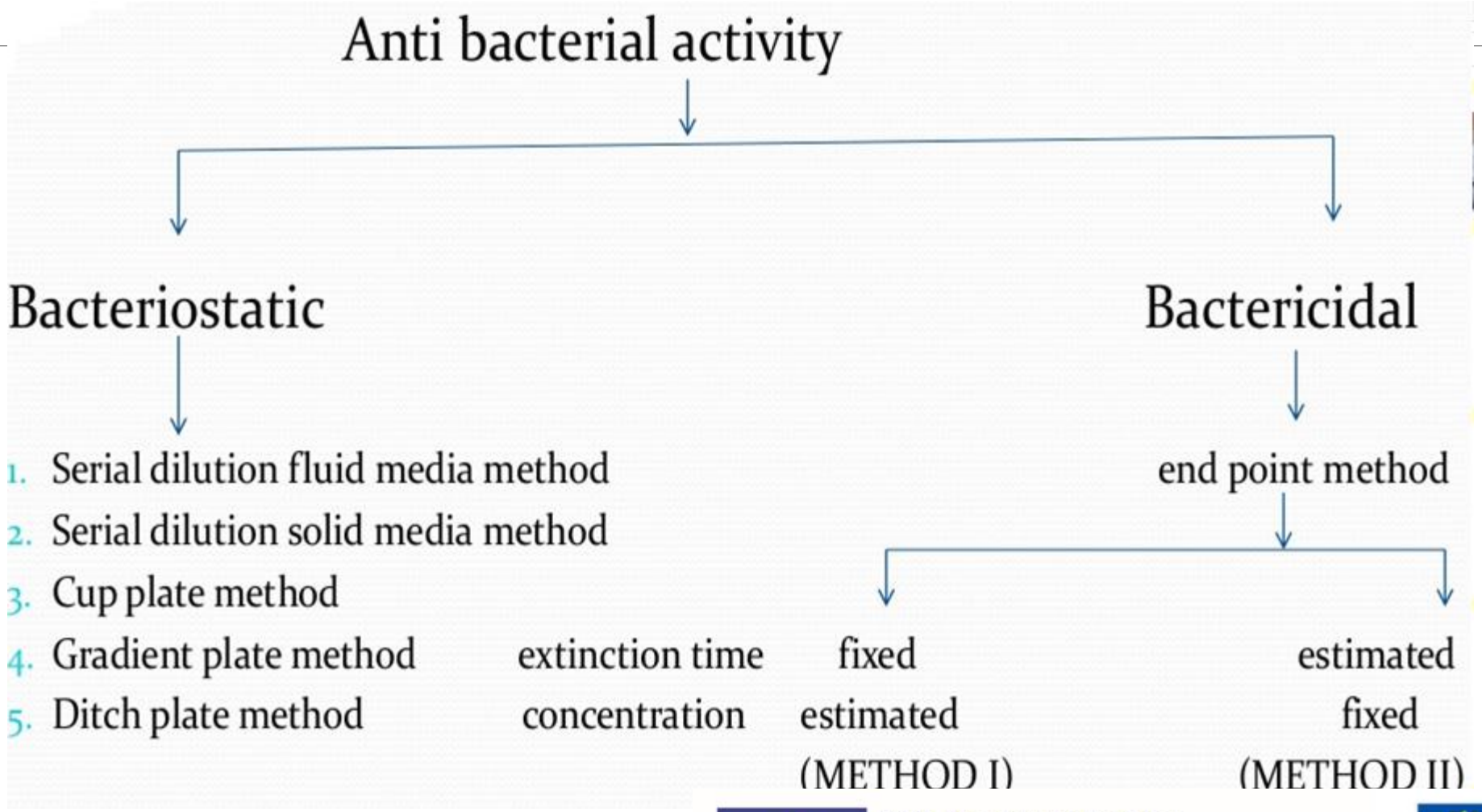
In vitro antibacterial activity screening



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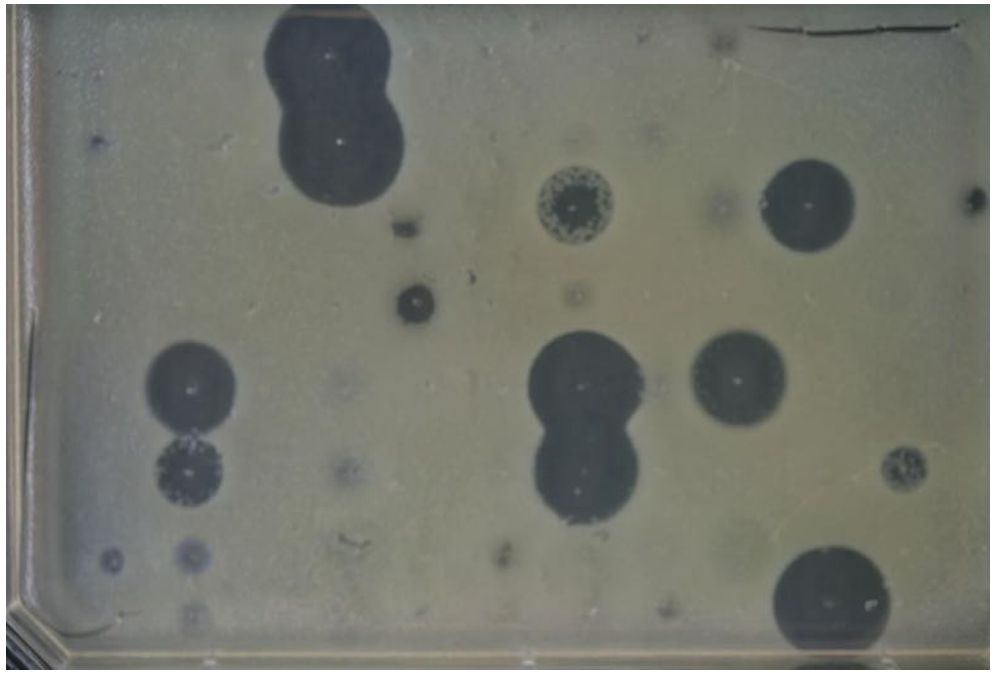
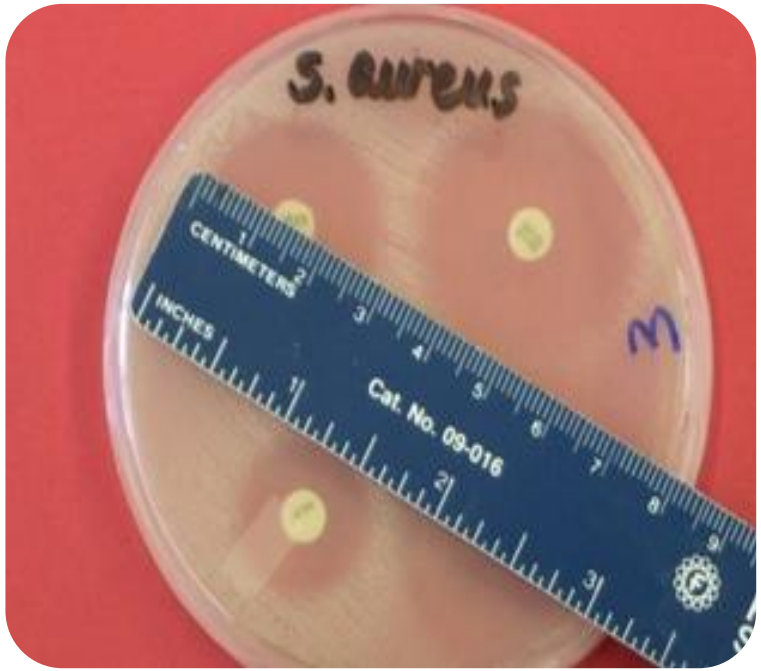
Qualitative methods

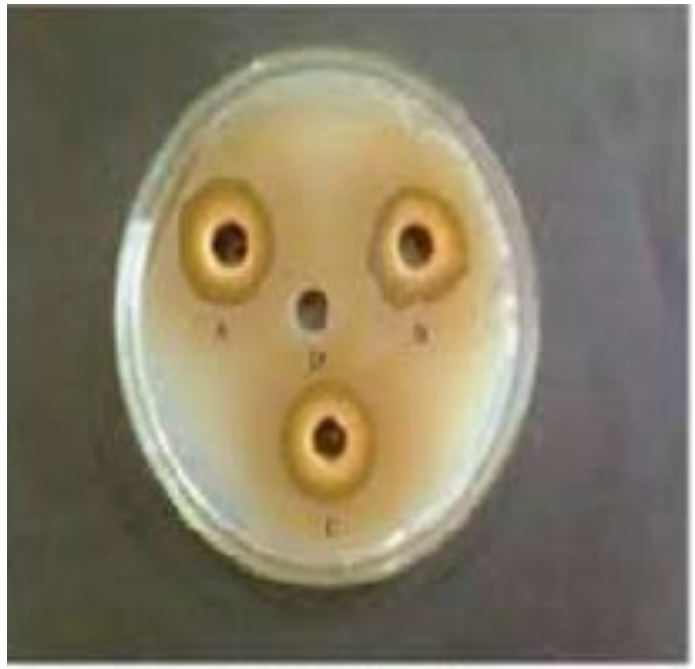
LAWN ASSAY



DISC DIFFUSION METHOD



CUP DIFFUSION METHOD



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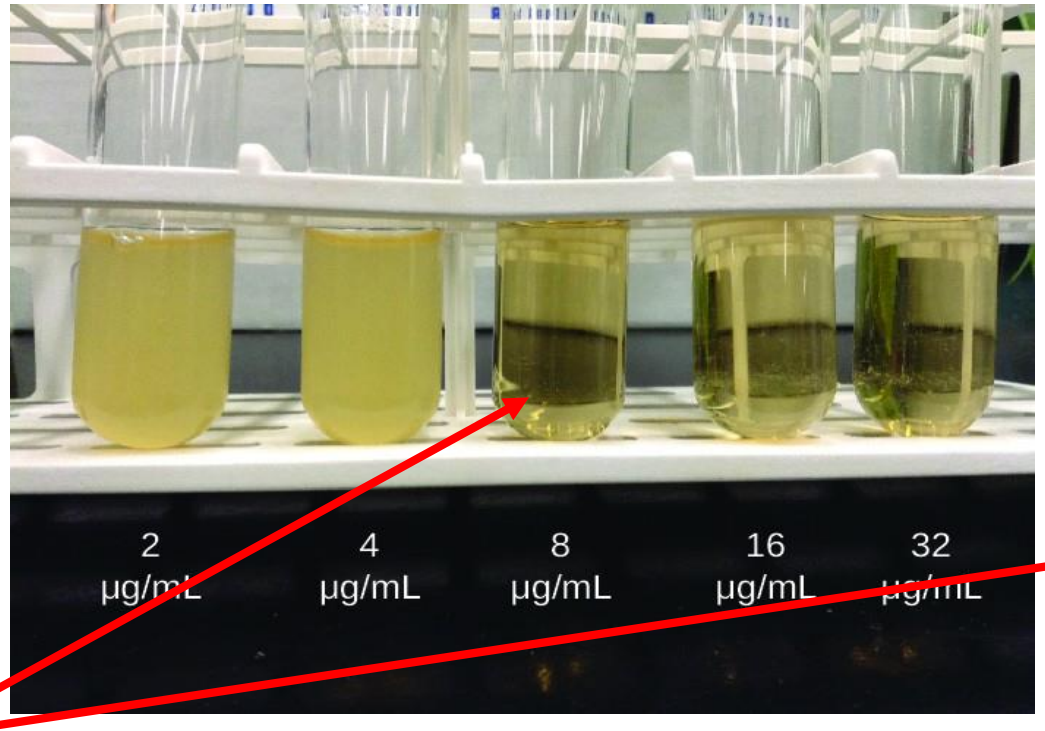
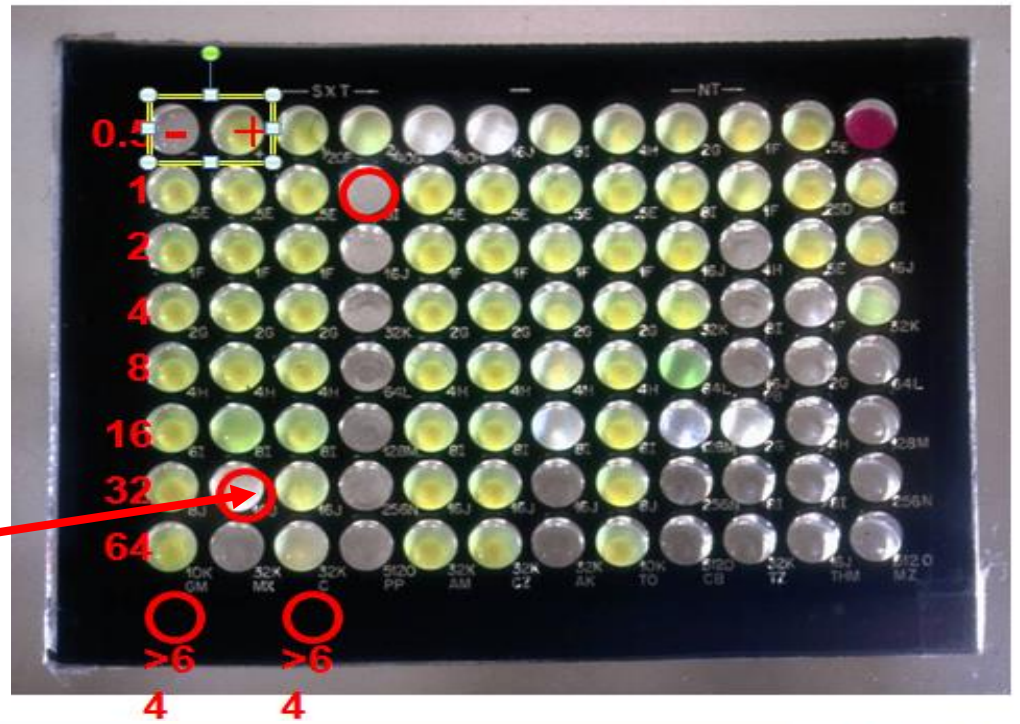
Quantitative methods

MACRO DILUTION (TUBE)



MICRODILUTION

96 well microtiter plate



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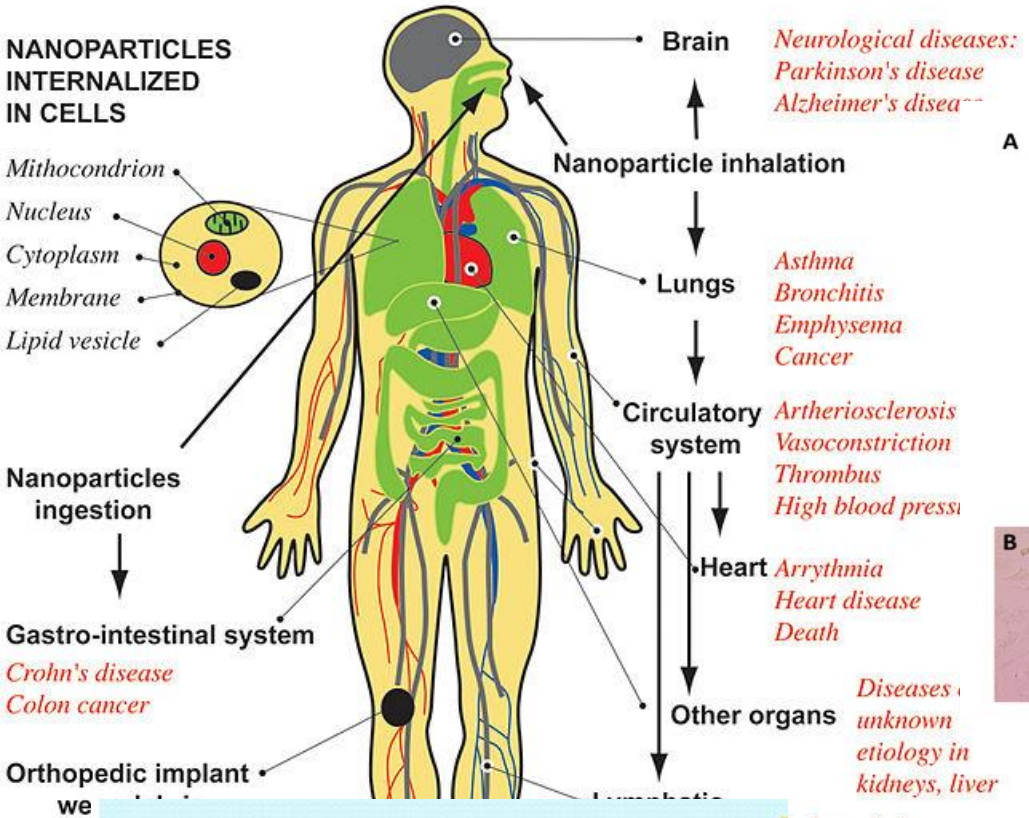
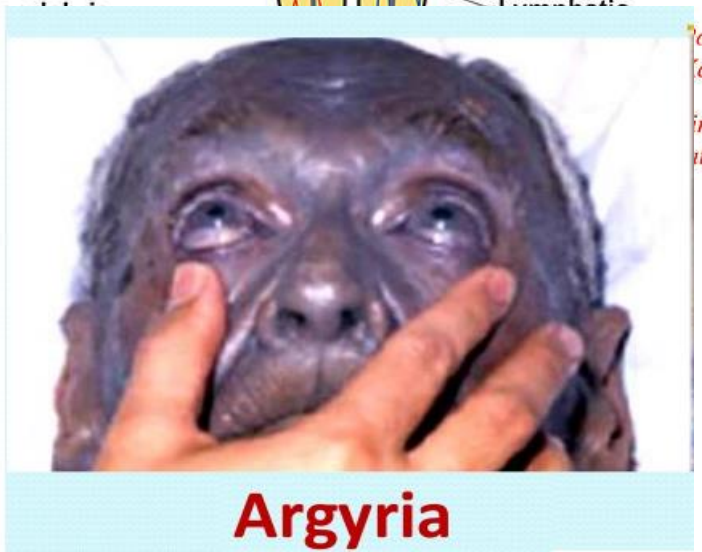
DISEASES ASSOCIATED TO NANOPARTICLE EXPOSURE

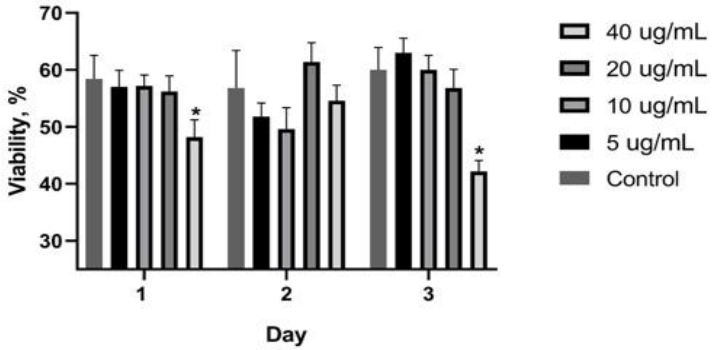
C. Buzea, I. Pacheco, & K. Robbie, Nanomaterials and nanoparticles: Sources and toxicity, Biointerphases 2 (2007) MR17-MR71

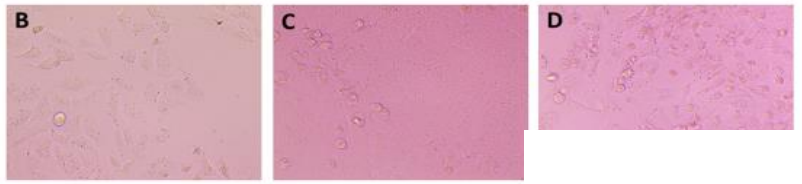




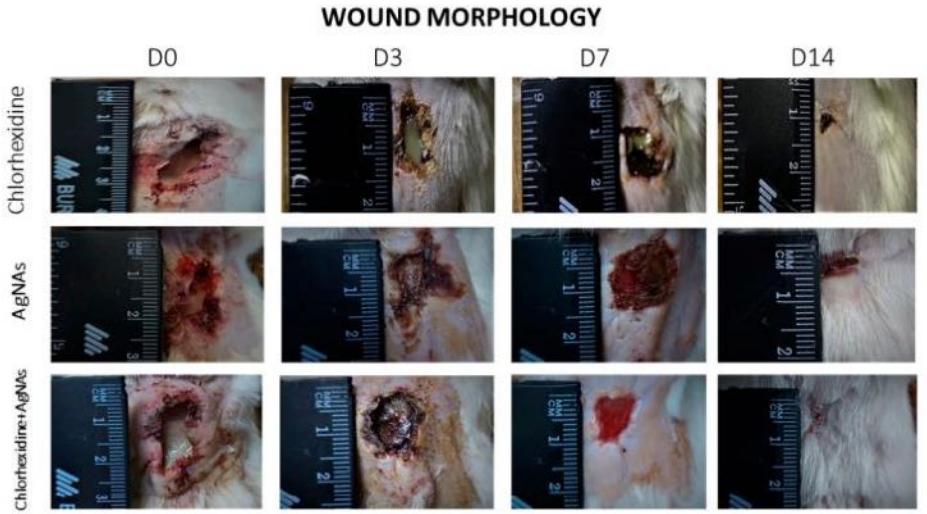
Assessment of NPs toxicity

Cell cultures (in vitro)





On animals' model (in vivo)



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Silver NPs

Medical and dental applications

1) Bone cement
2) Implantable devices
3) Additive in polymerizable dental materials
4) Toothpastes
5) Surgical gowns
6) Face masks
7) Wound dressing and burn treatments
8) Coating plastic catheters
9) Coating of endotracheal tube
10) Disinfecting medical devices

Disinfectants

Nasal spray

Toothpaste

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Other applications

1) Food storage packaging

2) Textile coatings, socks and athletic clothing

3) Packaging

4) Cosmetics

5) Water treatment

6) Washing machines

7) Detergents, soaps and shampoos

8) Air and water filters

Socks

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Thank you very much for your attention!!!

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https://www.youtube.com/watch?v=r1beoT9e38I

https://www.youtube.com/watch?v=aYxpA0GL8Ss&list=TLPQMTkwNDIwMjE_MulXMpTR8Q&index=4

https://www.youtube.com/watch?v=NYDOZzpH99E

EUBiomt

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«Modern European trends in biomedical higher education: Bionanomaterials.» № 620717-EPP-1-2020-1-UA-EPPJMO-MODULE

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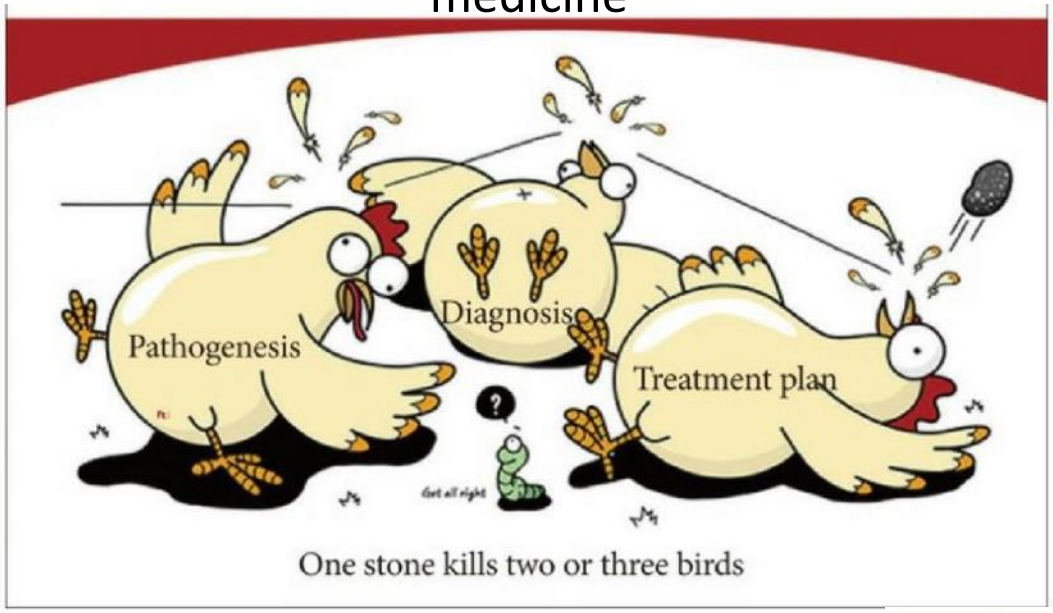
Theranostics:

combination of diagnosis and therapeutics,
focuses on patient-centered care.
Provides a transition from conventional medicine to personalized medicine



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https://www.thno.org/v08p4925.htm

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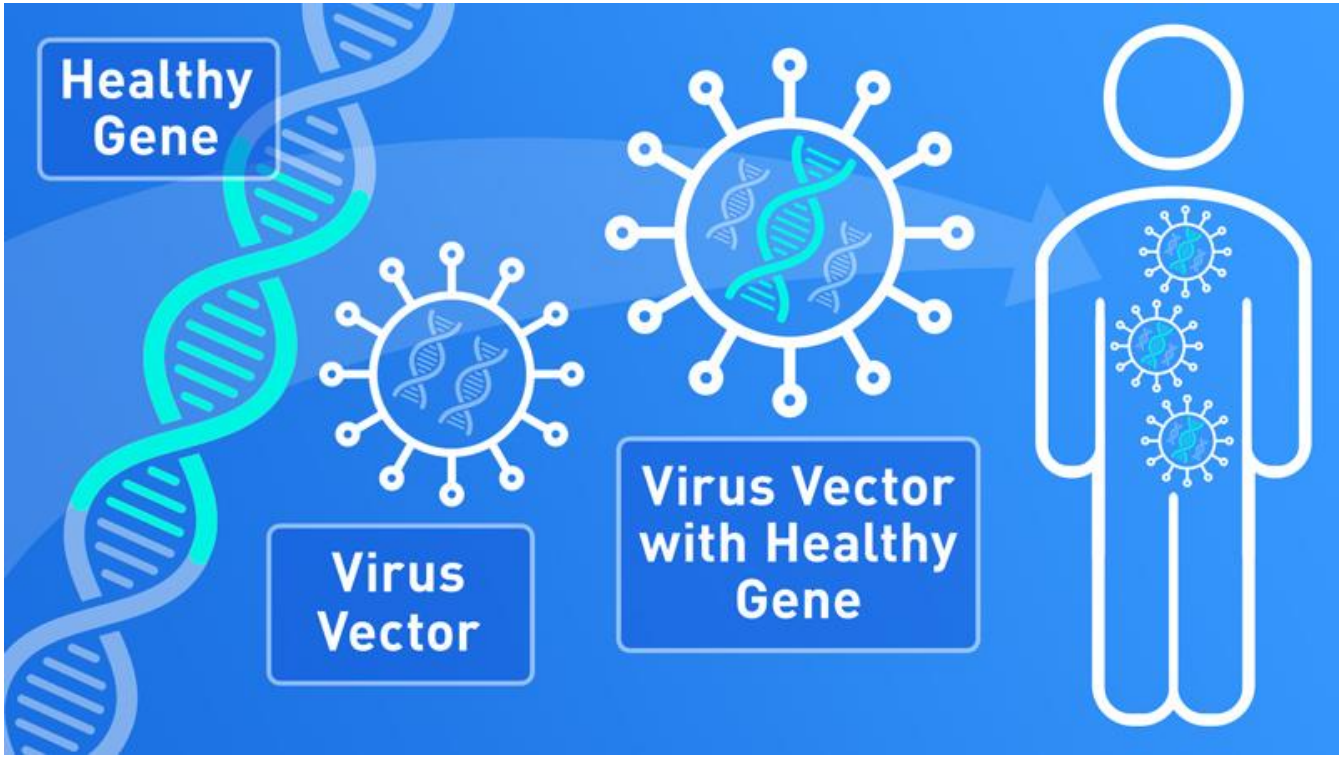
Gene therapy



https://www.fda.gov/media/109812/download

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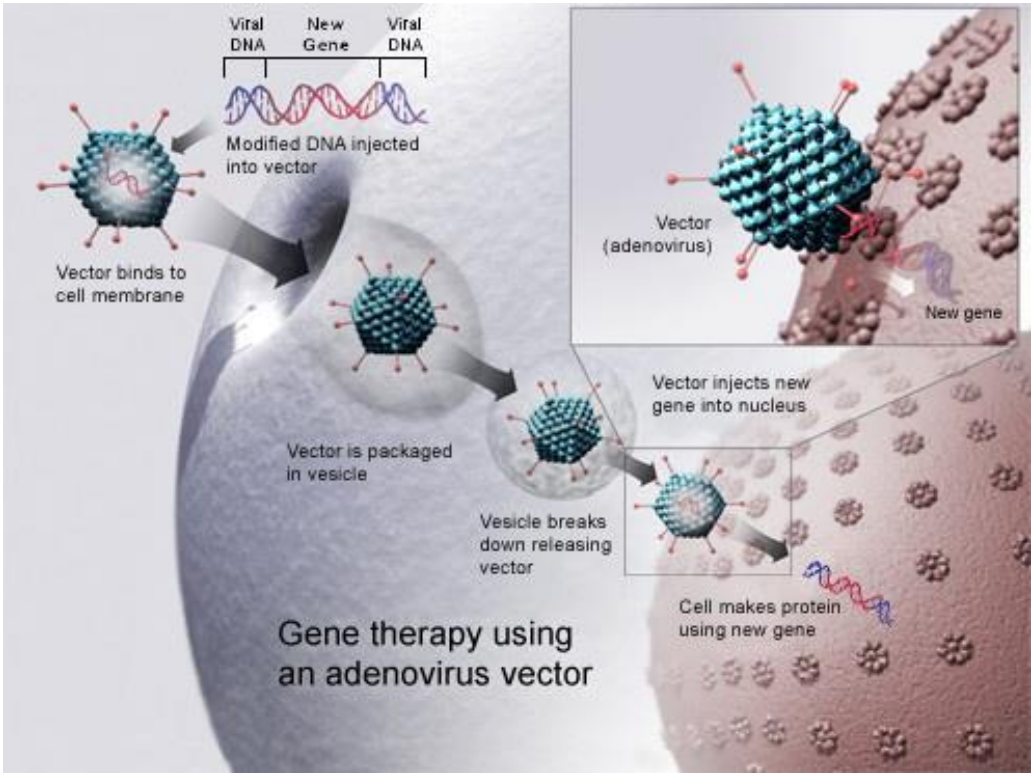
The concept of gene therapy is to fix a genetic problem at its source



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

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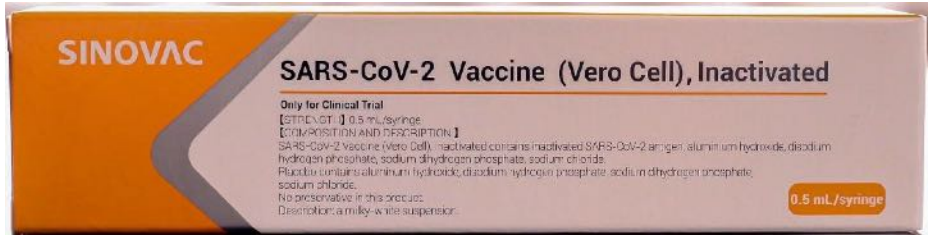

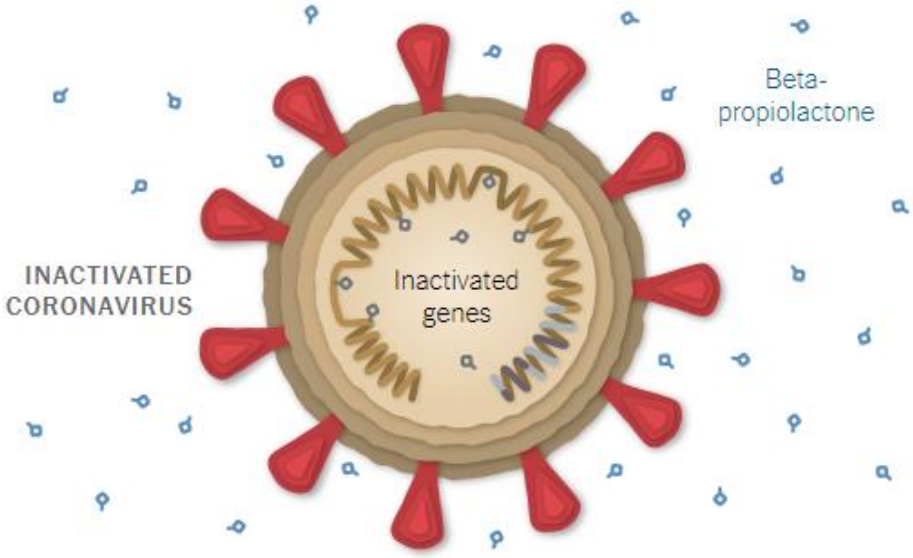

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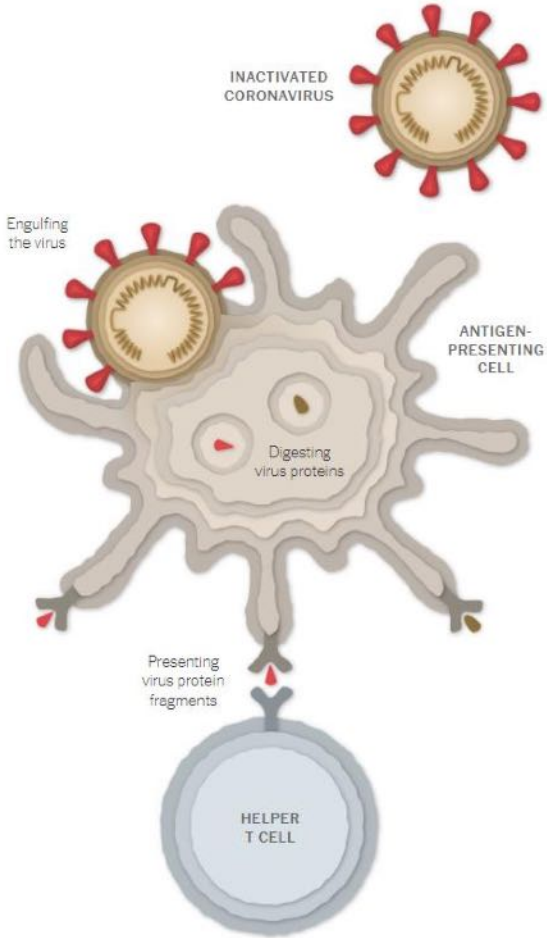

https://www.nytimes.com/interactive/2020/health/sinovac-covid-19-vaccine.html

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Curr Med Chem. 2011;18(17):2630-7. doi: 10.2174/092986711795933740.

Aluminum vaccine adjuvants: are they safe?

L Tomljenovic [1], C A Shaw

Affiliations + expand

PMID: 21568886 DOI: 10.2174/092986711795933740

Abstract

Aluminum is an experimentally demonstrated neurotoxin and the most commonly used vaccine adjuvant. Despite almost 90 years of widespread use of aluminum adjuvants, medical science's understanding about their mechanisms of action is still remarkably poor. There is also a concerning scarcity of data on toxicology and pharmacokinetics of these compounds. In spite of this, the notion that aluminum in vaccines is safe appears to be widely accepted. Experimental research, however, clearly shows that aluminum adjuvants have a potential to induce serious immunological disorders in humans. In particular, aluminum in adjuvant form carries a risk for autoimmunity, long-term brain inflammation and associated neurological complications and may thus have profound and widespread adverse health consequences. In our opinion, the possibility that vaccine benefits may have been overrated and the risk of potential adverse effects underestimated, has not been rigorously evaluated in the medical and scientific community. We hope that the present paper will provide a framework for a much needed and long overdue assessment of this highly contentious medical issue

https://pubmed.ncbi.nlm.nih.gov/21568886/

https://upload.wikimedia.org/wikipedia/commons/thumb/a/a2/Oxid_hlinit%C3%BD.PNG/440px-Oxid_hlinit%C3%BD.PNG

Ark Therapeutics Oy

https://nordicpropertynews.com/uploads/article_images/3259/2109_0_top_thumb.jpg

doi:10.1016/j.ymthe.2005.07.357

REVIEW

Gene Therapy for Malignant Glioma: Current Clinical Status

Kalevi J. Pulkkanen[1,2] and Seppo Yla-Herttuala[1,3,4,*]

[1]Department of Molecular Medicine, A. I. Virtanen Institute, University of Kuopio, P.O. Box 1627, FIN-70211 Kuopio, Finland
[2]Department of Oncology, [3]Department of Medicine, and [4]Gene Therapy Unit, Kuopio University Hospital, Kuopio, Finland

*To whom correspondence and reprint requests should be addressed. Fax: +358 17 163030. E-mail: Seppo.YlaHerttuala@uku.fi.

Available online 10 August 2005

Glioblastoma is an aggressive brain tumor with a dismal prognosis. Gene therapy may offer a new option for the treatment of these patients. Several gene therapy approaches have shown anti-tumor efficiency in experimental studies, and the first clinical trials for the treatment of malignant glioma were conducted in the 1990s. HSV-tk gene therapy has been the pioneering and most commonly used approach, but oncolytic conditionally replicating adenoviruses and herpes simplex virus mutant vectors, p53, interleukins, interferons, and antisense oligonucleotides have also been used. During the past few years, adenoviruses have become the most popular gene transfer vectors, and some recent randomized, controlled trials have shown significant anti-tumor efficacy in clinical use. However, efficient gene delivery into the brain still presents a major problem, and there is a lack of definitive phase III trials, which would avoid potential problems associated with a small number of patients, inadvertent patient selection, and overinterpretation of results based on a few long-time survivors. For clinical efficacy, median survival is one of the most rigorous endpoints. It is used here to evaluate the usefulness of various treatment approaches and current clinical status of gene therapy for malignant glioma.

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https://antiworldnews.files.wordpress.com/2012/04/thefuture.jpg

With the support of the Erasmus+ Programme of the European Union

Published: 12 January 2018

mRNA vaccines — a new era in vaccinology

Norbert Pardi, Michael J. Hogan, Frederick W. Porter & Drew Weissman

Nature Reviews Drug Discovery **17**, 261–279(2018) | Cite this article

1.64m Accesses | **524** Citations | **4714** Altmetric | Metrics

Key Points

- Recent improvements in mRNA vaccines act to increase protein translation, modulate innate and adaptive immunogenicity and improve delivery.
- mRNA vaccines have elicited potent immunity against infectious disease targets in animal models of influenza virus, Zika virus, rabies virus and others, especially in recent years, using lipid-encapsulated or naked forms of sequence-optimized mRNA.
- Diverse approaches to mRNA cancer vaccines, including dendritic cell vaccines and various types of directly injectable mRNA, have been employed in numerous cancer clinical trials, with some promising results showing antigen-specific T cell responses and prolonged disease-free survival in some cases.
- Therapeutic considerations and challenges include scaling up good manufacturing practice (GMP) production, establishing regulations, further documenting safety and increasing efficacy.
- Important future directions of research will be to compare and elucidate the immune pathways activated by various mRNA vaccine platforms, to improve current approaches based on these mechanisms and to initiate new clinical trials against additional disease targets.

https://cdn.aarp.net/content/dam/aarp/health/drugs_supplements/2020/12/1140-mnra-covid-vaccine.imgcache.rev.web.900.513.jpg

https://www.nature.com/articles/nrd.2017.243

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Katalin Karikó, a senior vice president at BioNTech overseeing its mRNA work, in her home office in Rydal, Penn.
JESSICA KOURKOUNIS FOR THE BOSTON GLOBE

https://www.statnews.com/2020/11/10/the-story-of-mrna-how-a-once-dismissed-idea-became-a-leading-technology-in-the-covid-vaccine-race/
https://european-biotechnology.com/up-to-date/latest-news/news/biontech-and-fosun-pharma-kick-off-chinese-covid-19-trials.html

J Biol Chem. 2004 Mar 26;279(13):12542-50. doi: 10.1074/jbc.M310175200. Epub 2004 Jan 16.

mRNA is an endogenous ligand for Toll-like receptor 3

Katalin Karikó [1], Houping Ni, John Capodici, Marc Lamphier, Drew Weissman

Affiliations + expand

PMID: 14729660 DOI: 10.1074/jbc.M310175200

Free article

Abstract

Toll-like receptors (TLRs) are the basic signaling receptors of the innate immune system. They are activated by molecules associated with pathogens or injured host cells and tissue. TLR3 has been shown to respond to double stranded (ds) RNA, a replication intermediary for many viruses. Here we present evidence that heterologous RNA released from or associated with necrotic cells or generated by in vitro transcription also stimulates TLR3 and induces immune activation. To assess RNA-mediated TLR3 activation, human embryonic kidney 293 cells stably expressing TLR3 and containing a nuclear factor-kappaB-dependent luciferase reporter were generated. Exposing these cells to in vitro transcribed RNA resulted in a TLR3-dependent induction of luciferase activity and interleukin-8 secretion. Treatment with in vitro transcribed mRNA activated nuclear factor-kappaB via TLR3 through a process that was dose-dependent and involved tyrosine phosphorylation. Furthermore, in vitro

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Hum Gene Ther. 2019 Feb;30(2):168-178. doi: 10.1089/hum.2018.145. Epub 2018 Oct 2.

Purification of mRNA Encoding Chimeric Antigen Receptor Is Critical for Generation of a Robust T-Cell Response

Jessica B Foster [1 2], Namrata Choudhari [3 4], Jessica Perazzelli [1], Julie Storm [1], Ted J Hofmann [1], Payal Jain [3 4], Phillip B Storm [2 3 4 5], Norbert Pardi [6], Drew Weissman [6], Angela J Waanders [1 2 4], Stephan A Grupp [1 2], Katalin Karikó [7], Adam C Resnick [2 3 4 8], David M Barrett [1 2]

Affiliations + expand

PMID: 30024272 PMCID: PMC6383579 DOI: 10.1089/hum.2018.145

Free PMC article

https://pubmed.ncbi.nlm.nih.gov/30024272/

Abstract

T cells made with messenger RNA (mRNA) encoding chimeric antigen receptor (CAR) offer a safe alternative to those transduced with viral CARs by mitigating the side effects of constitutively active T cells. Previous studies have shown that mRNA CAR T cells are transiently effective but lack persistence and potency across tumor types. It was hypothesized that the efficacy of mRNA CARs could be

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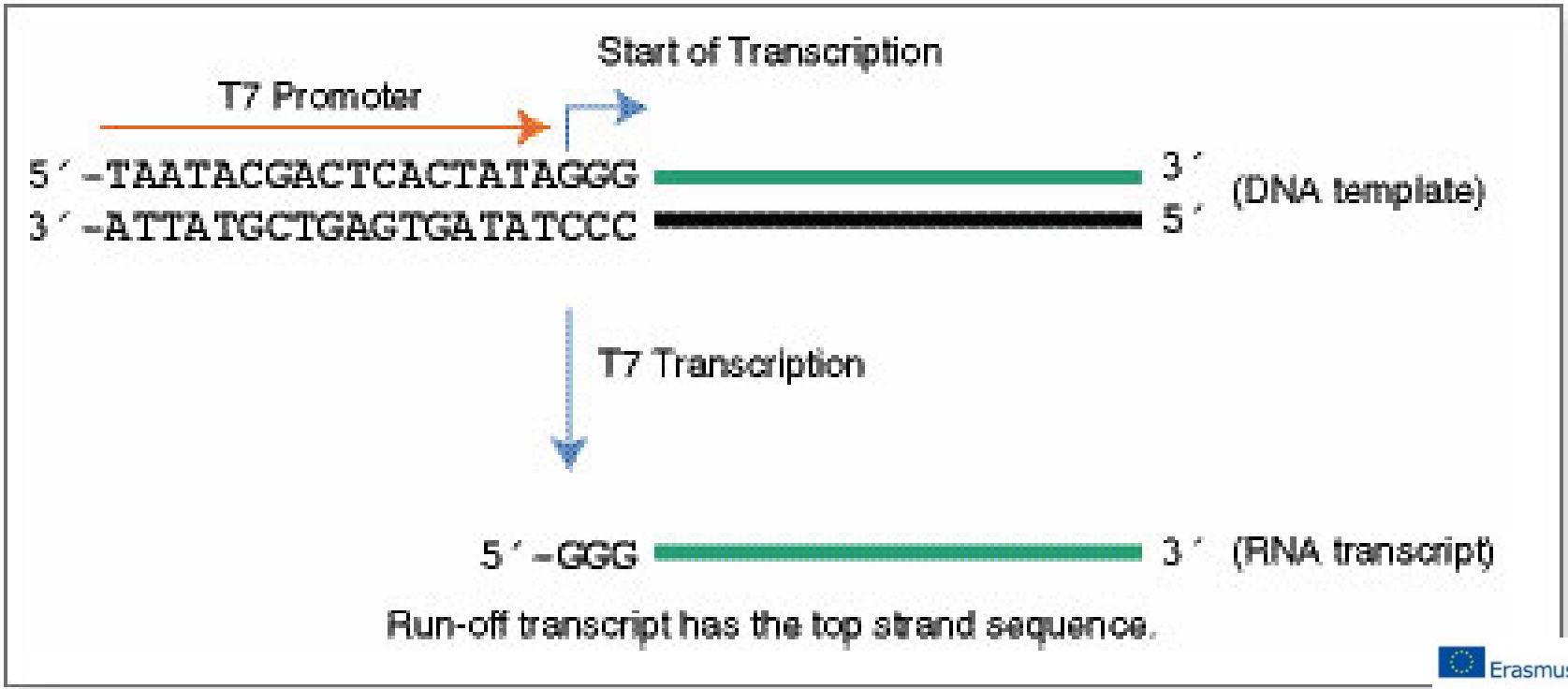
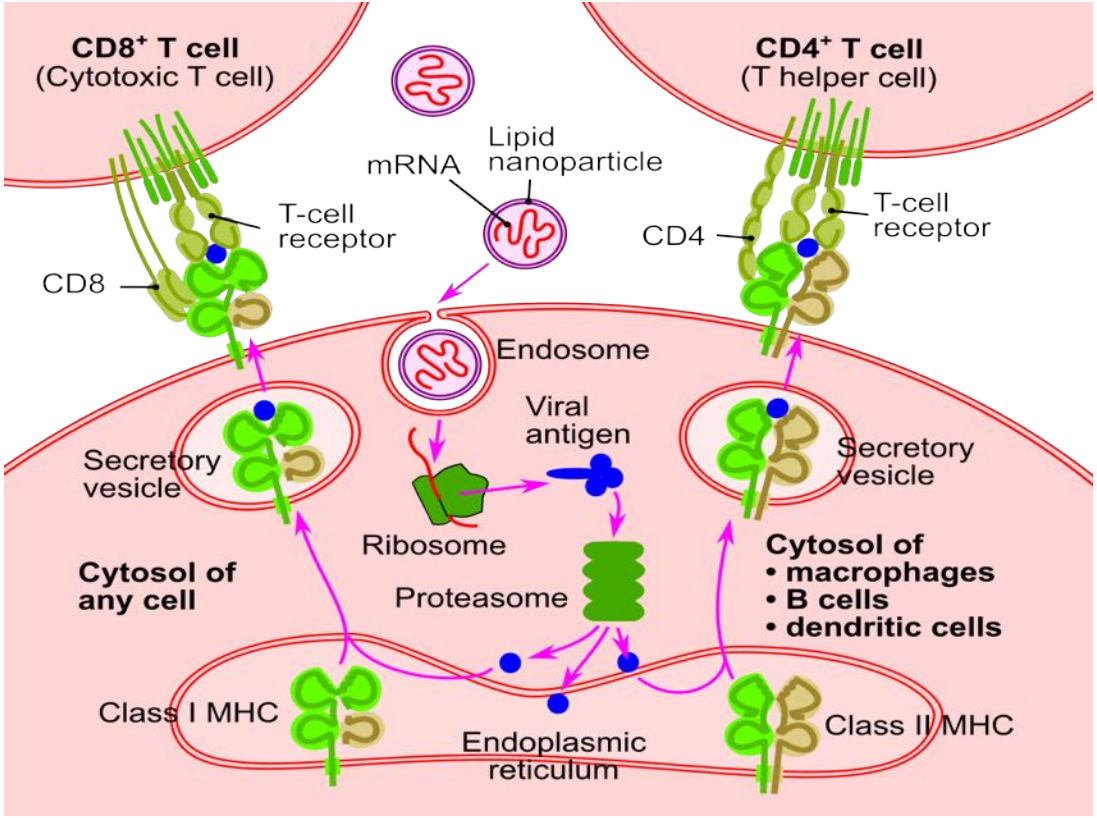


https://www.neb.com/products/e2040-hiscribe-t7-high-yield-rna-synthesis-kit#Product%20Information



https://en.wikipedia.org/wiki/RNA_vaccine#cite_note-21

With the support of the Erasmus+ Programme of the European Union

Research Highlight | Published: 12 January 2021

AUTOIMMUNITY

mRNA vaccine shows promise in autoimmunity

Alexandra Flemming

Nature Reviews Immunology **21**, 72(2021) | Cite this article

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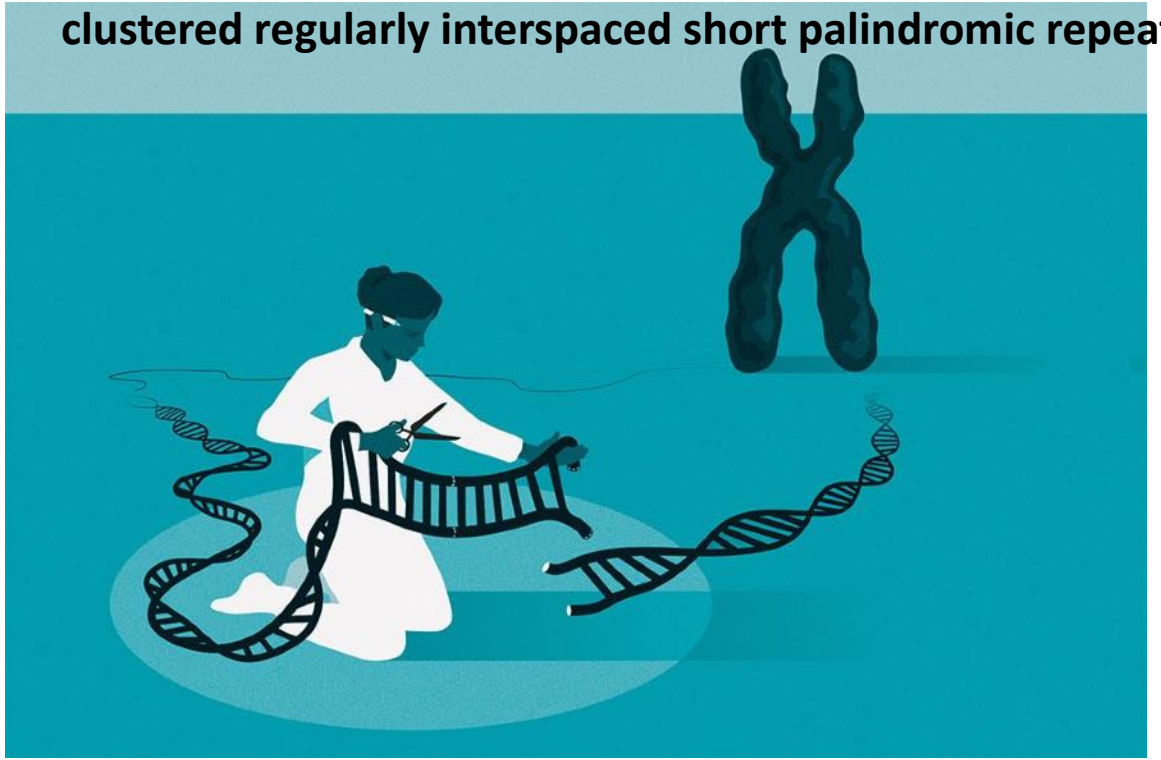
Gene editing: CRISPR/Cas9

clustered regularly interspaced short palindromic repeats



https://www.nobelprize.org/uploads/2020/10/che-carrier.jpg

With the support of the Erasmus+ Programme of the European Union

A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity.

Jinek M, Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentier E.

Science. 2012 Aug 17;337(6096):816-21. doi: 10.1126/science.1225829. Epub 2012 Jun 28.

PMID: 22745249 Free PMC article.

https://pubmed.ncbi.nlm.nih.gov/22745249/

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https://img2.chinadaily.com.cn/images/202010/08/5f7e7bd4a31024adbd985bf9.jpeg

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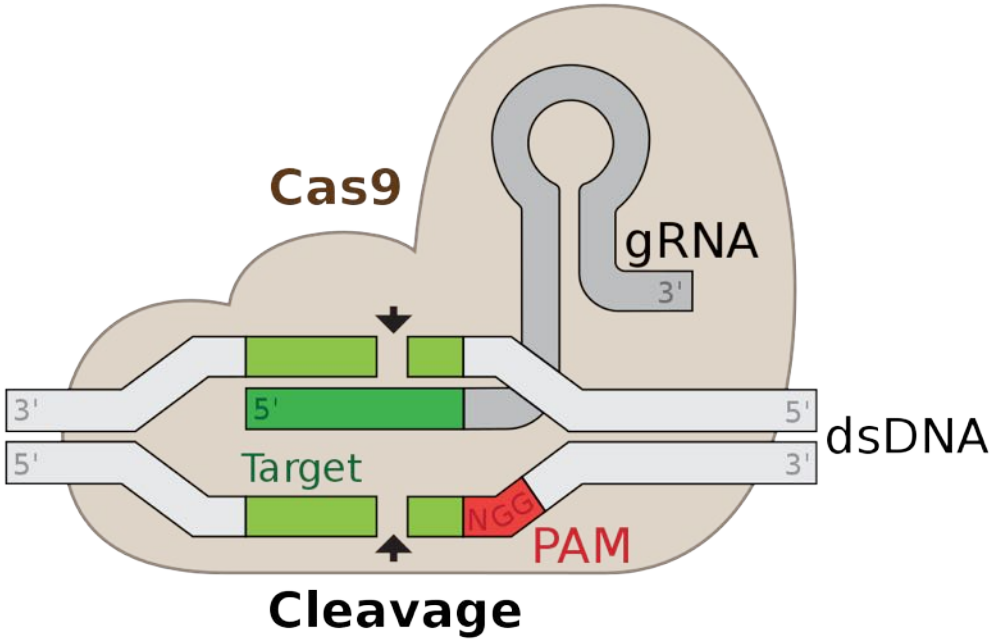
Gene editing: CRISPR/Cas9



https://upload.wikimedia.org/wikipedia/commons/thumb/5/57/GRNA-Cas9.svg/1024px-GRNA-Cas9.svg.png

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He Jiankui affair 2018

CRISPR/Cas9 mediatged knockout of CD195 gene

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

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Nanosystems

THERAPY


Chemotherapeutic drugs

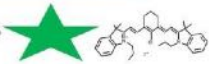

Nucleic acids


Peptides/proteins

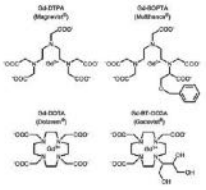

Antibodies

IMAGING


Florescent probes



Contrast agents



Quantum dots

Cancer Theranostics

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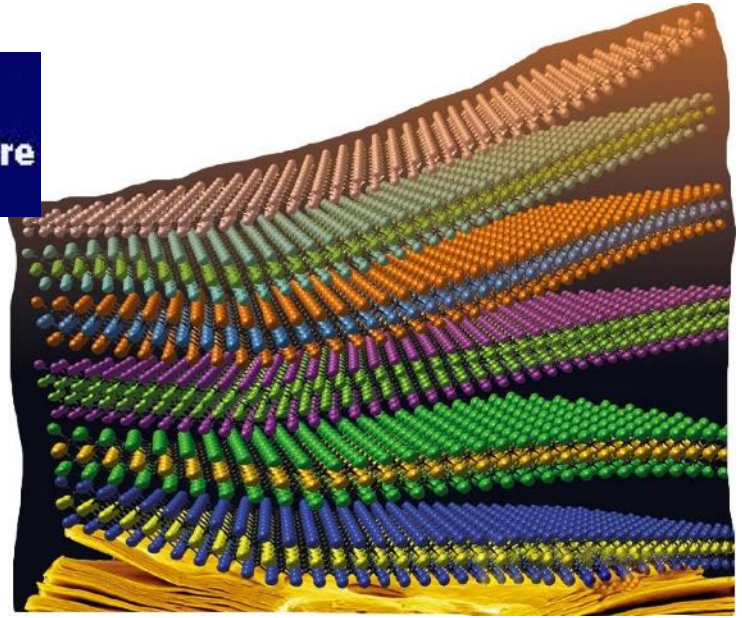
Photothermal effects of $Ti_3C_2T_x$ MXenes in cell cultures



MXene picture courtesy of **B. Anasori & Y. Gogotsi** (Ed.), 2D Metal Carbides and Nitrides (MXenes), Springer 2019

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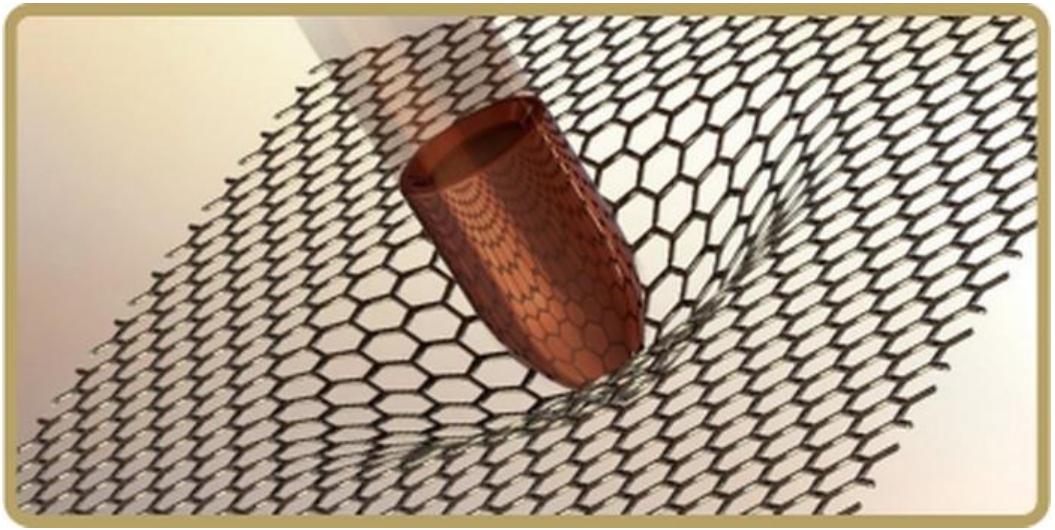
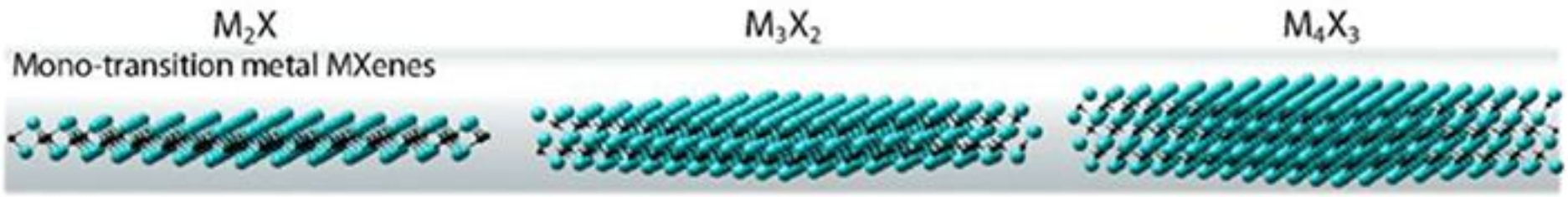
MXenes ≠ graphene





https://nanografi.com/blog/military-applications-of-graphene/
https://www.mdpi.com/2079-4991/10/4/702

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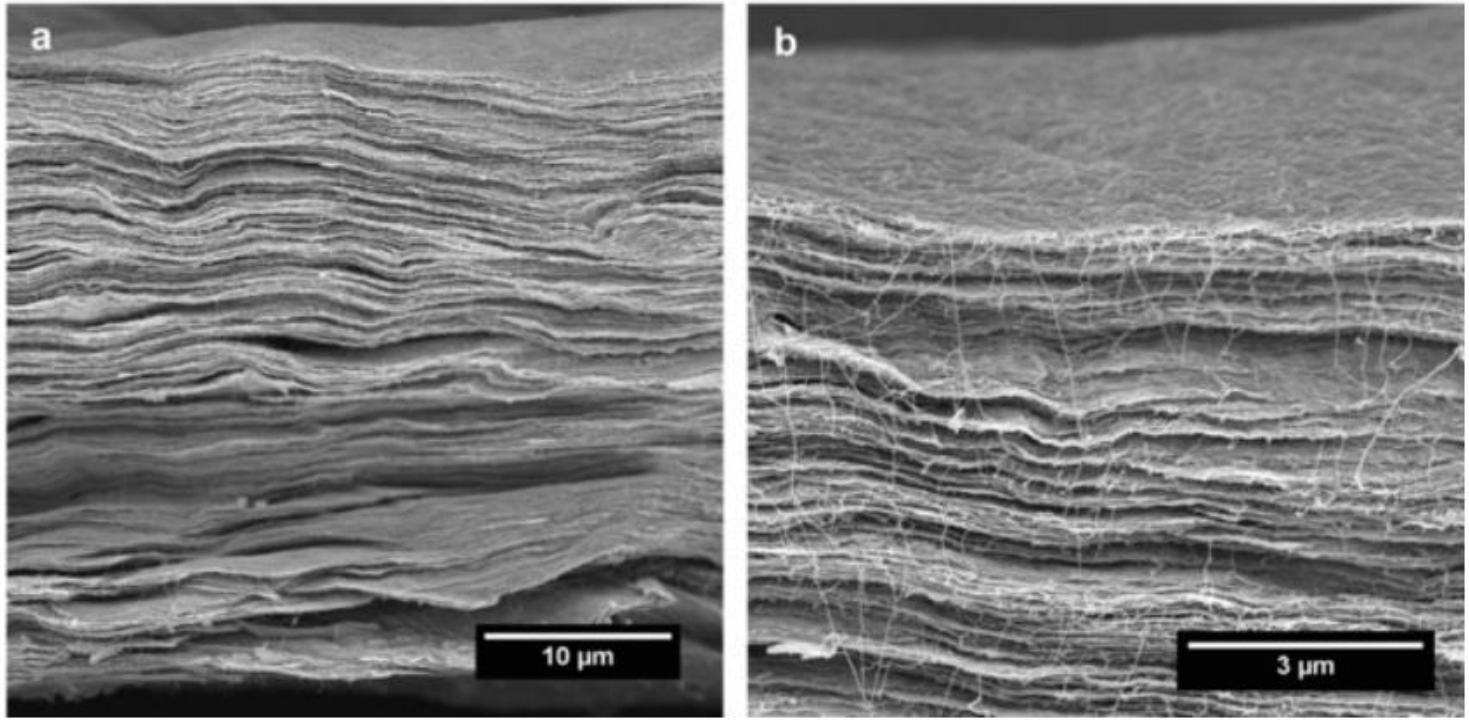

Thickness-independent capacitance of vertically aligned liquid-crystalline MXenes
May 2018 Nature 557(7705) DOI: 10.1038/s41586-018-0109-z

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Treatment parameters from the literature:

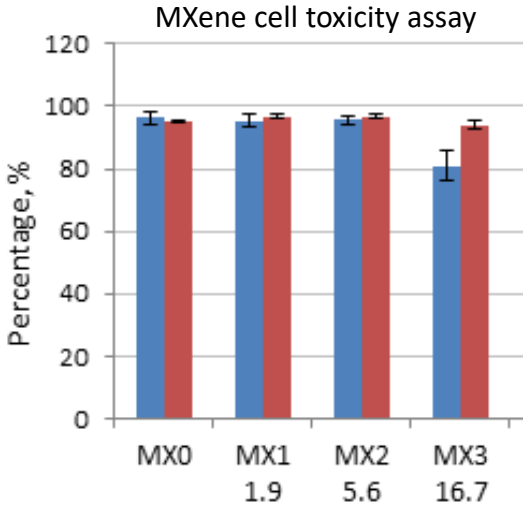
1.5 W/см2 10 min

https://dx.doi.org/10.1021/acsami.0c14752

1.0 W/см2 300 sec (5 min)

10.1021/acsami.8b08314

Background info: for depilation the following parameters in the laser machine are used:
755 nm laser – 7 msec, 8-15 J/cm2, 1 impuls
1064 nm laser – 7 msec, 25-45 J/cm2, 1 impuls



Conc. of MXenes, final:	
MX0	0
MXA	0.4 ug/ml
MXB	0.8 ug/ml
MXC	1.6 ug/ml
MXD	3.2 ug/ml

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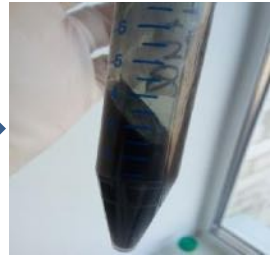
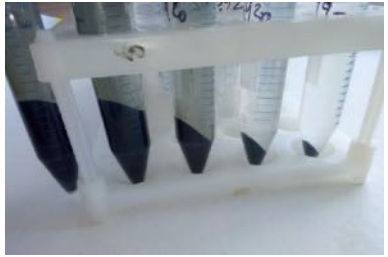
Delamination: segregation of multilayered MXenes into single layer flakes





Increased layer spacing is clearly observable

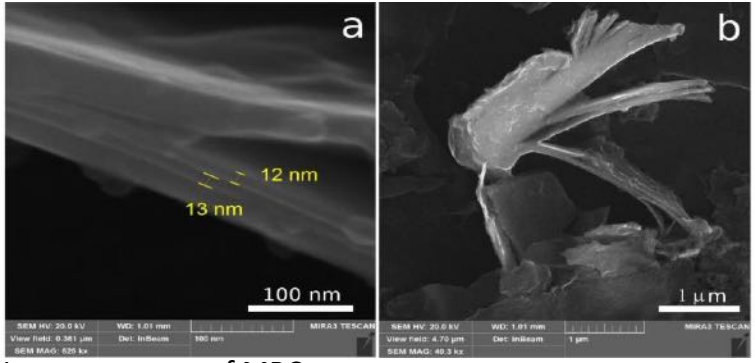
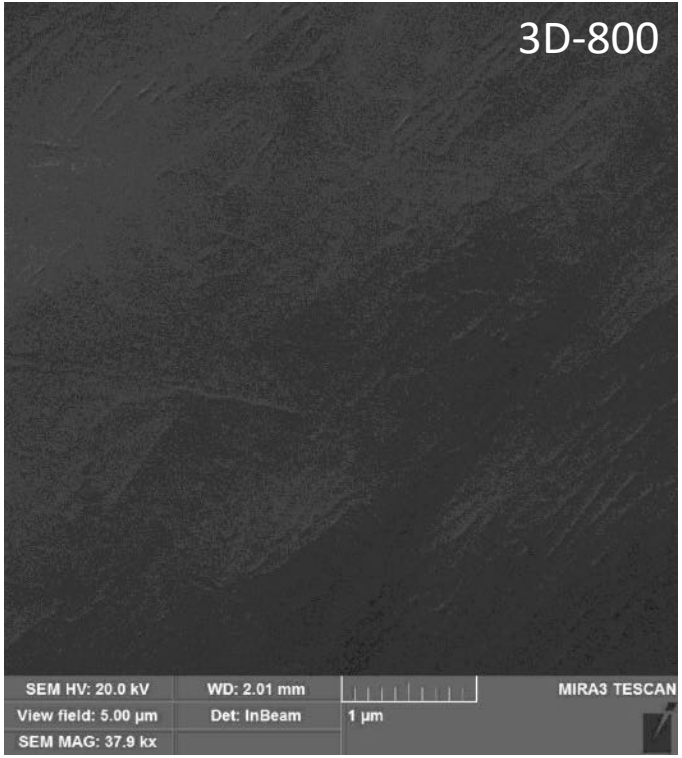


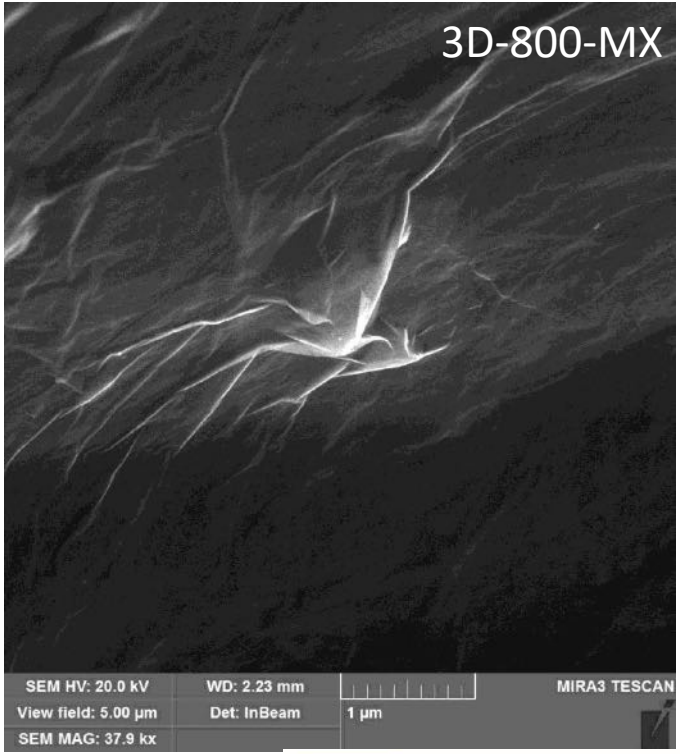
Image courtesy of MRC

Electrospun nanofiber mats

3D porous Ti scaffolds

Like a gold leaf in gilding?





Courtesy for images: MRC

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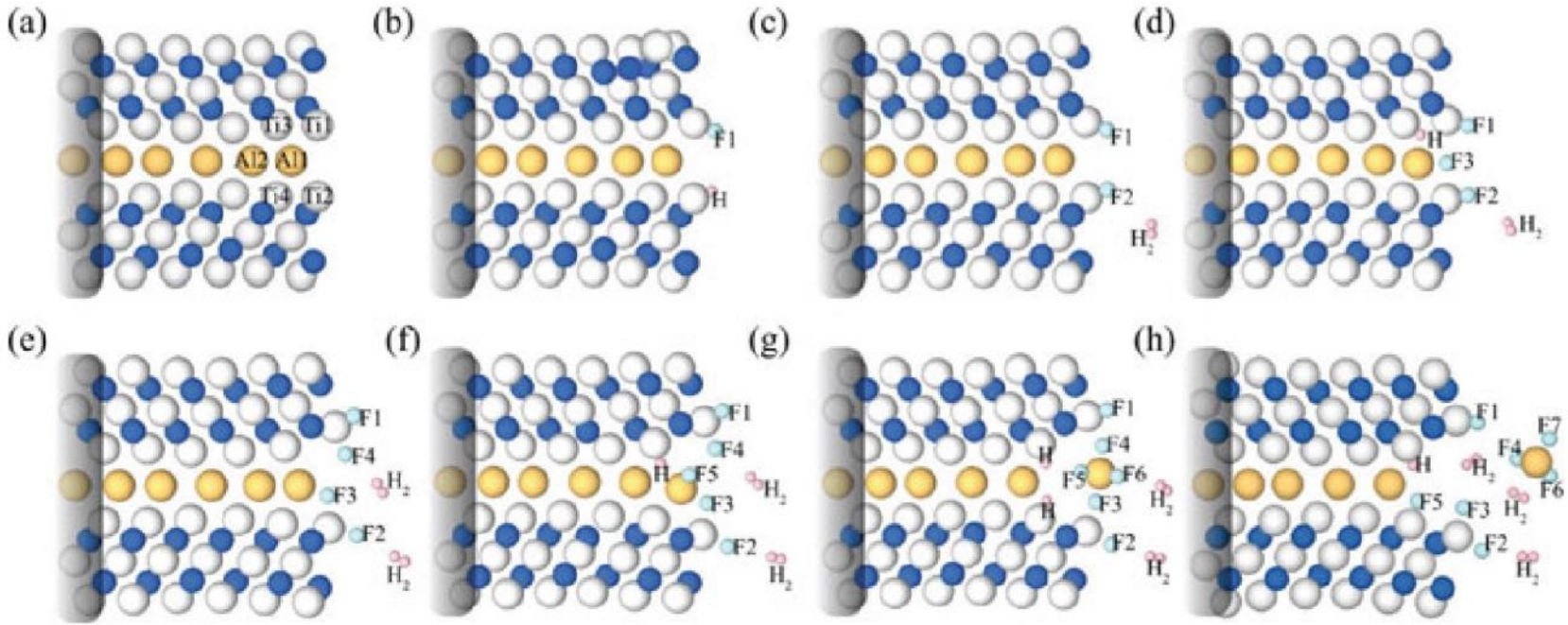
Possibilities for covalent functionalization of MXenes



2D Metal Carbides and Nitrides (MXenes). Edited by **B. Anasori & Y. Gogotsi,** Springer 2019.

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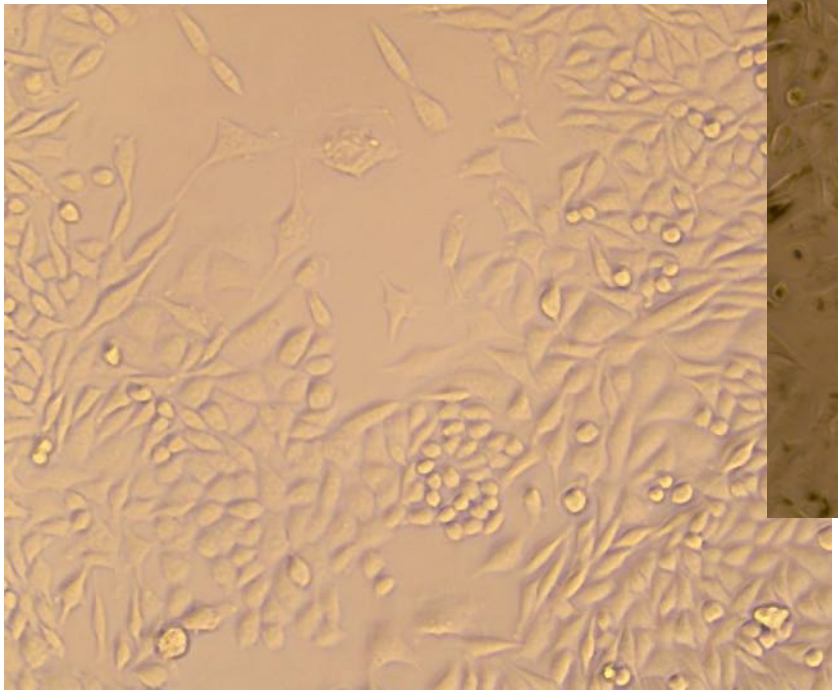

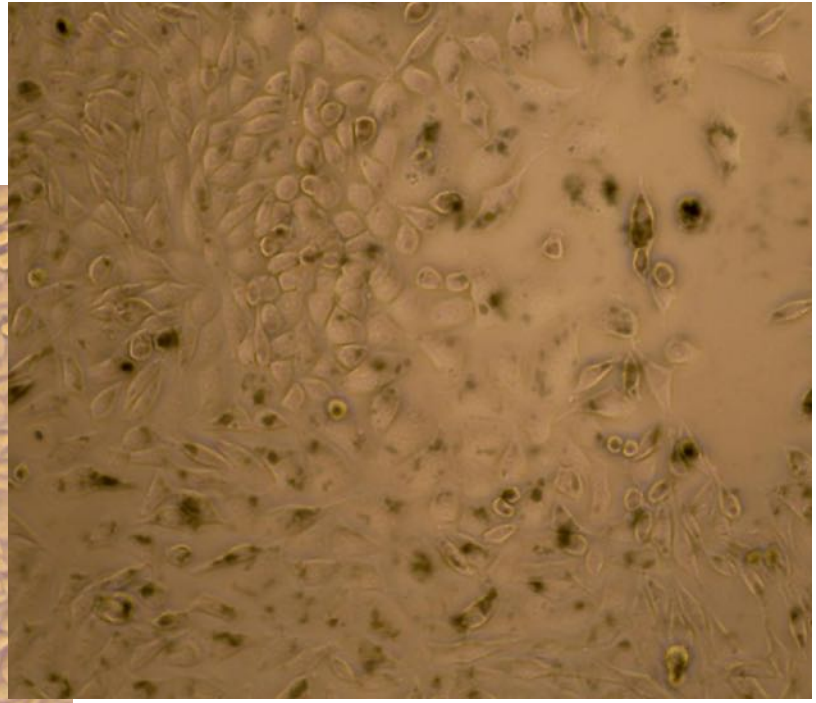

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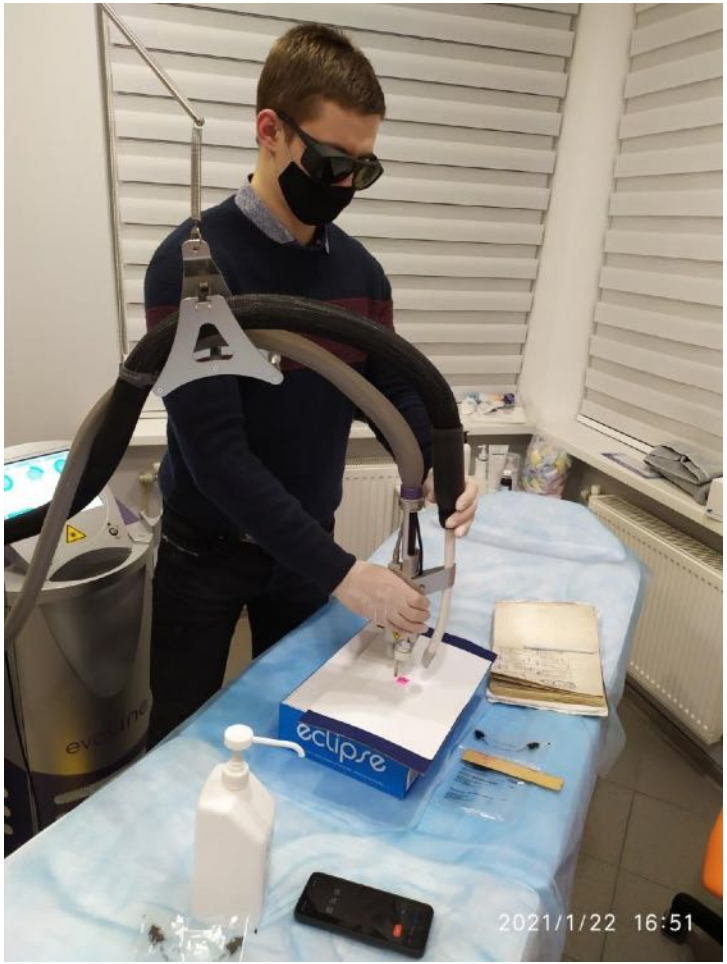

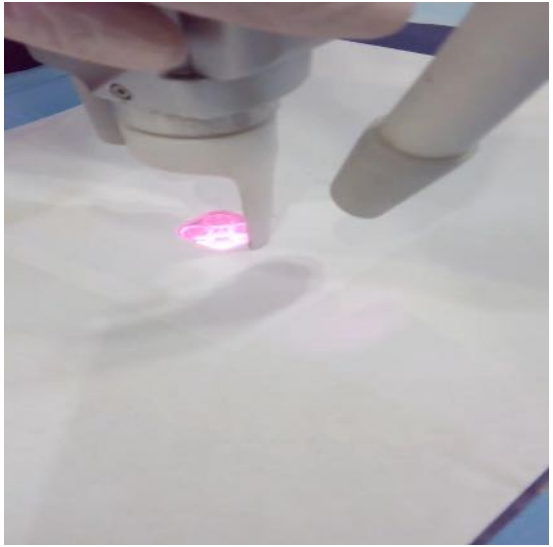

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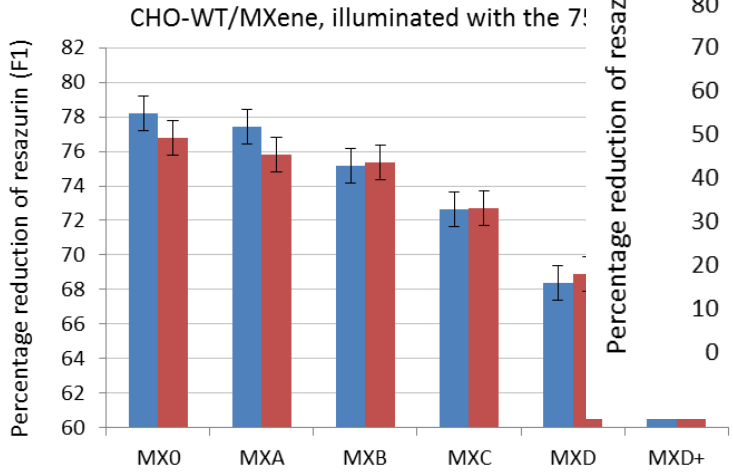

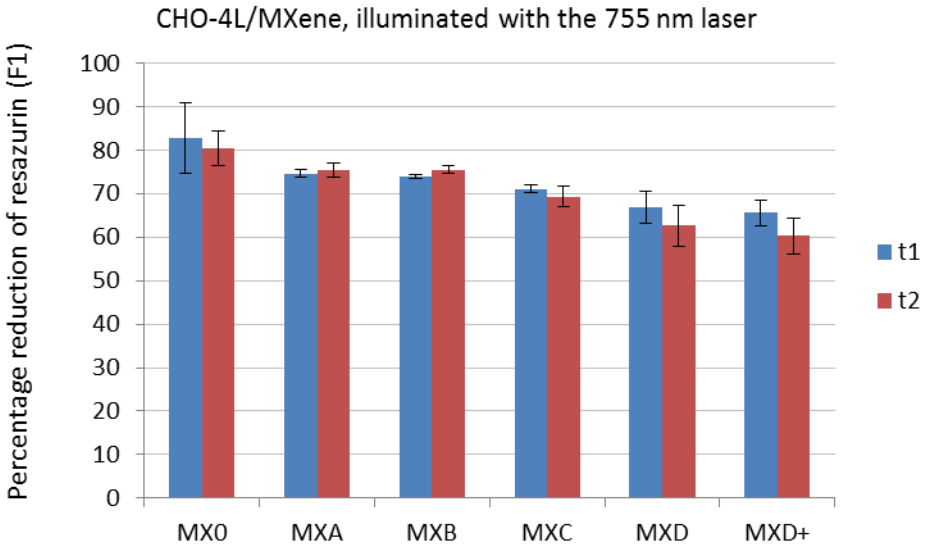

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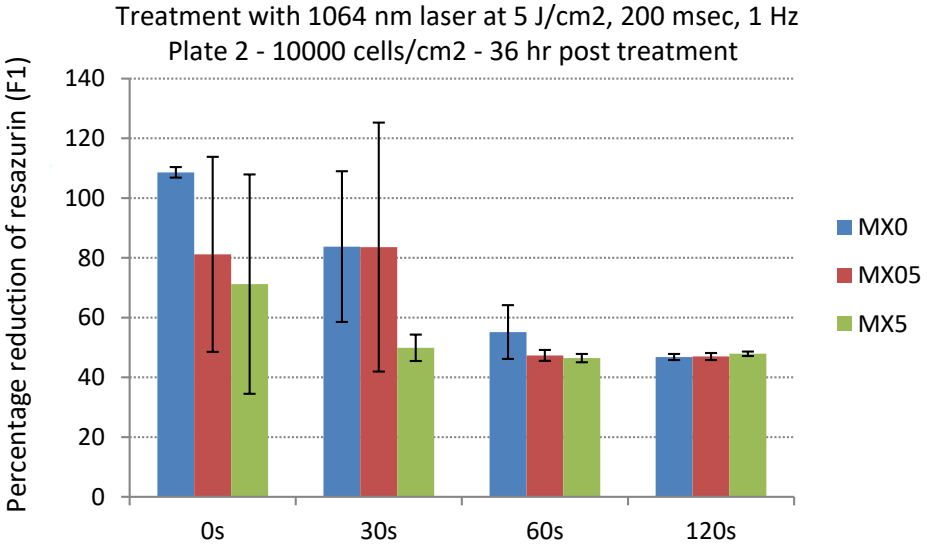

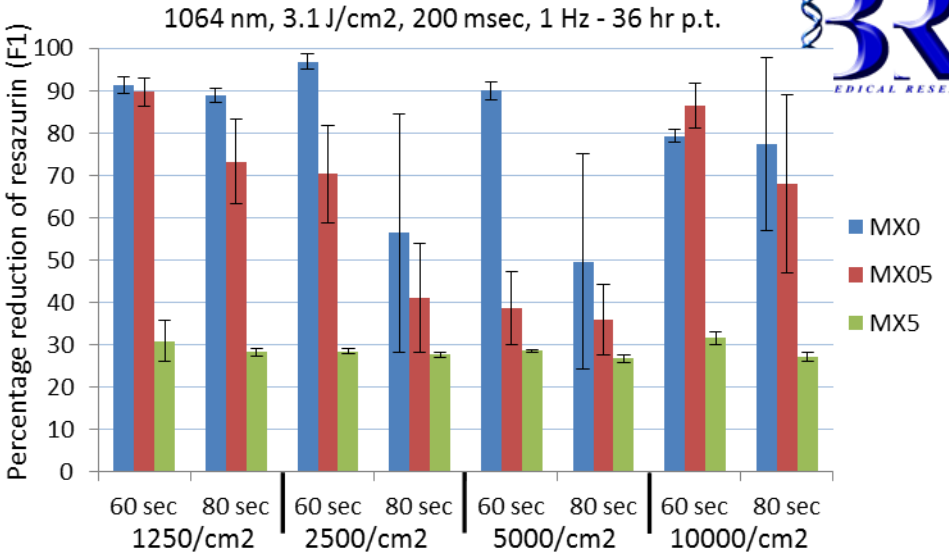

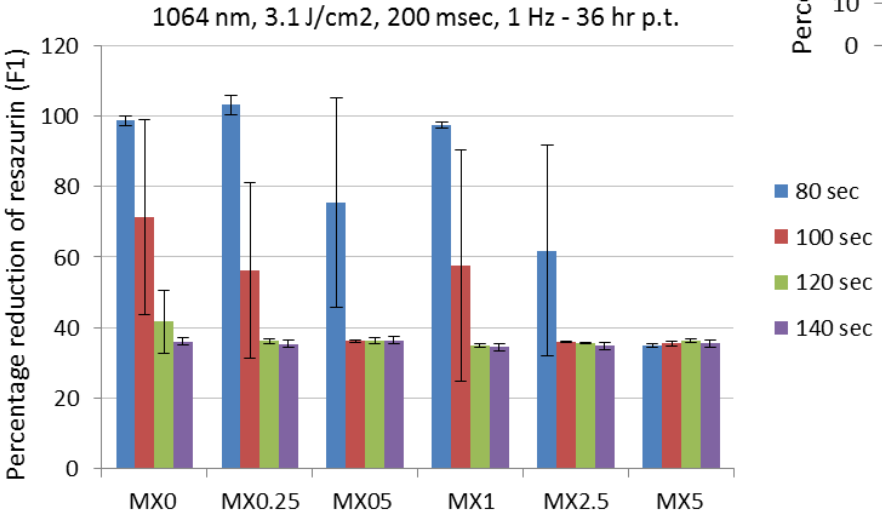

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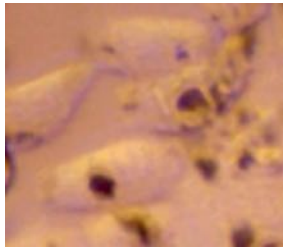
● Selective affinity of MXenes to tumor cells: covalent modification of MXenes and immobilization of antibodies



MXenes in cells: histochemistry, immunocytochemistry, SEM, TEM etc,

●

● Refining parameters for PTT (in vitro, in vivo)

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EUBiomt

MRC »» Materials Research Centre

Drexel

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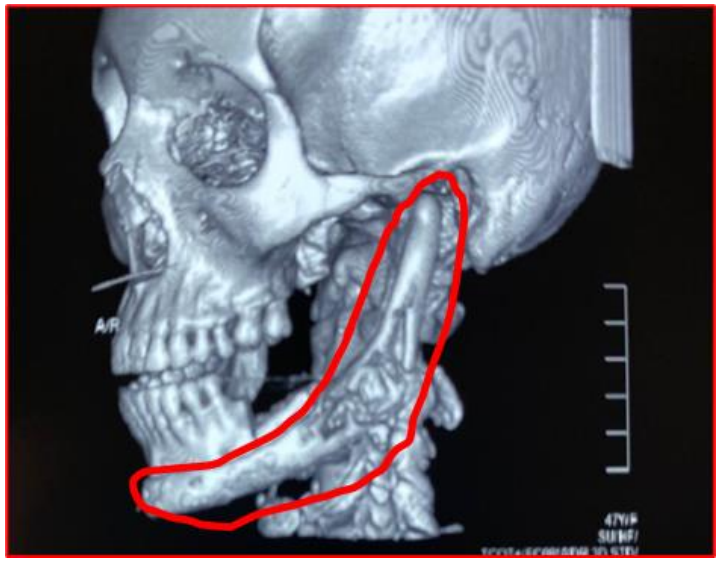
Методи вивчення якості імплантів

«Modern European trends in biomedical higher education: Bionanomaterials.» № 620717-EPP-1-2020-1-UA-EPPJMO-MODULE

With the support of the Erasmus+ Programme of the European Union

Functional surfaces of bone implants is stratergy of new generation of the biomaterials



Surface modification

HYDROPHILICITY

PROTEIN ADSORPTION

CELL PROLIFERATION

TISSUE FORMATION

ANTIBACTERIAL PROPERTIES

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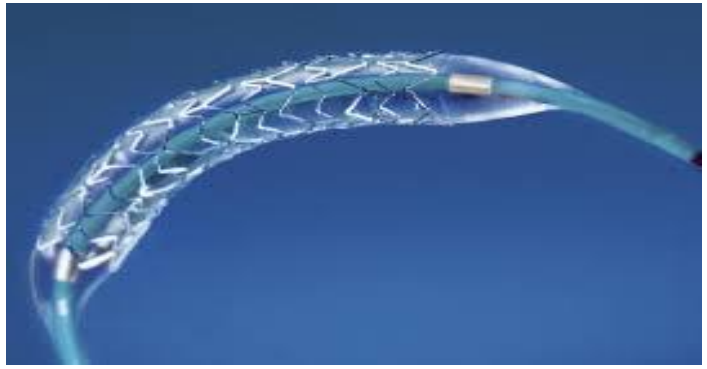
Mg and its alloys as degradable materials

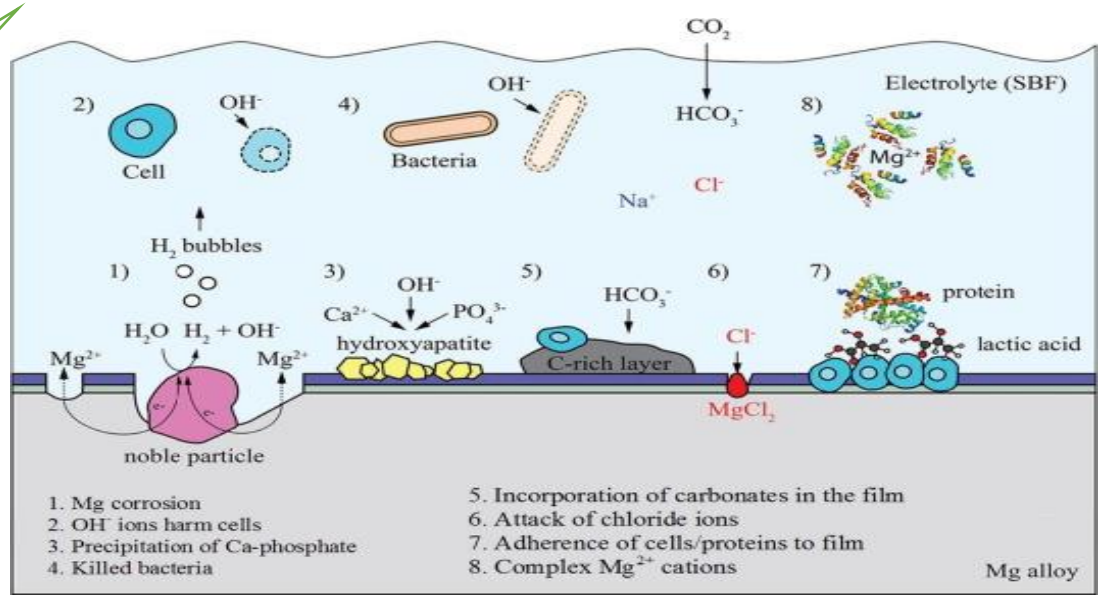


Application

(a) cardiovascular stents
(b) screw
(c) microclip for laryngeal microsurgery (pure magnesium)
(a) biodegradable orthopedic implants
(b) wound-closing devices

Advantages

- ProperYoungs modulus
- Natural degradability
- Good biocompability
- Good osteopromotive property



https://doi.org/10.1016/j.matdes.2019.108259

https://doi.org/10.1016/j.matdes.2019.108259

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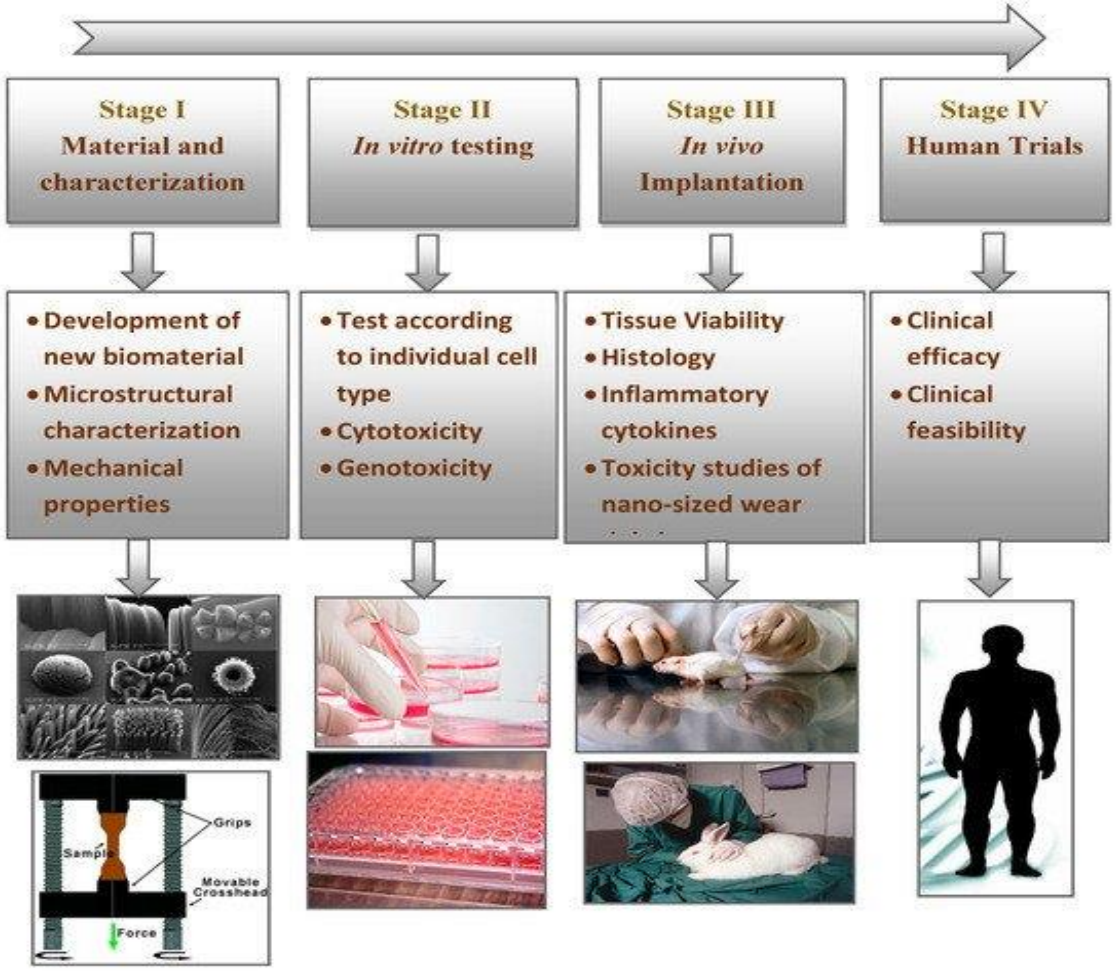
Properties of biomaterials for medical applications.
Steps involved in the translation of newly developed biomaterials.

Biocompatability
- Promoting biological tissue for implant integration
- Promoting cell adhesion
- Providing pathways for vascularization
- Noncarcinogenesis, Nopyrogenicty, Nontoxicity, and nonallergic response

Sterilizability
- Ability to undergo sterilization
- Auto clave, and dryheating
- Ethylenoxide gas and radiation

Functionability
- Modulus of elasticity for the stiffness fo the material
- Ultimate tensile strength to withstand a load
- Dimensional accuracy on economically fabrication process

Manufacturability
- Ease of molding
- Undergo extrusion process
- Machinability
- Ability for fiber forming



Materials **2020**, *13*(1), 92; https://doi.org/10.3390/ma13010092

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Erasmus+ Jean Monnet Modules

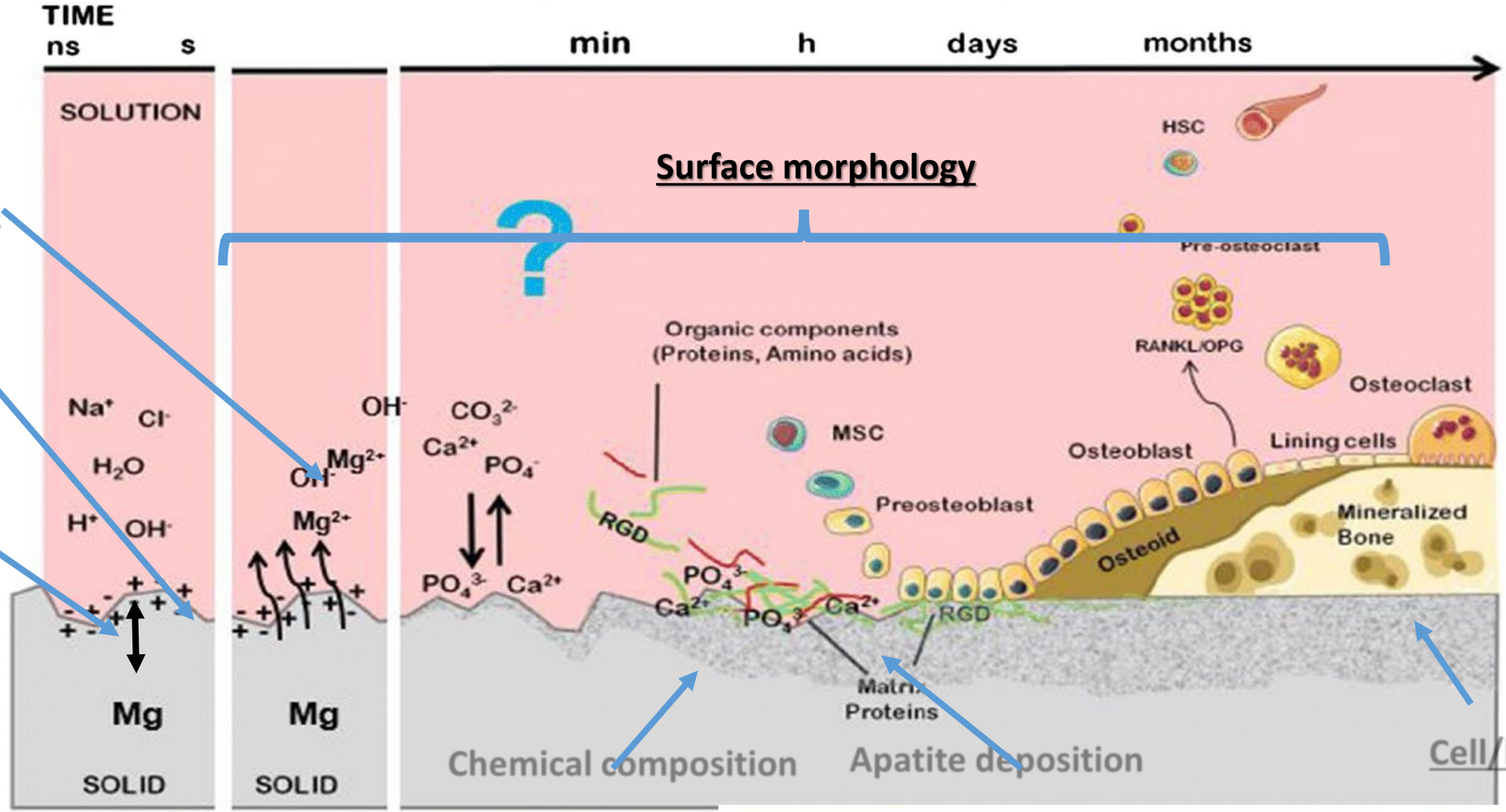
What can be measured when analyzing oxide coating surface?

Corrosion characteristics

Hydrophilicity

Roughness

Surface morphology



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MATERIALS AND METHODS

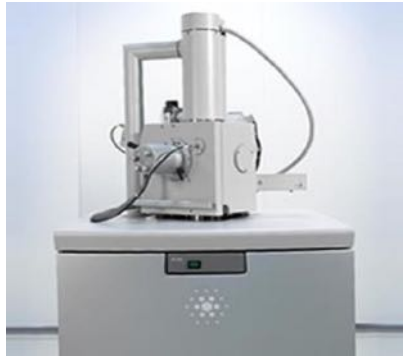
Sample code	Composition of the bath electrolyte
Bath electrolyte 1 (sapmle S1)	10g/L $Na_2S_iO_3$ + 5g/L NH_4F + 10g/L NaOH
Bath electrolyte 2 (sapmle S2)	10g/L Na_2HPO_4 + 5g/L NaOH

- ***Plasma Electrolytic Oxidation (PEO)***
- ***Scanning Electron Microscopy (SEM)***
- ***SBF Immersion Test***
- ***Contact Angle Measurement (CA)***
- ***Roughness Measurement***
- ***Bacterial adhesion assay***

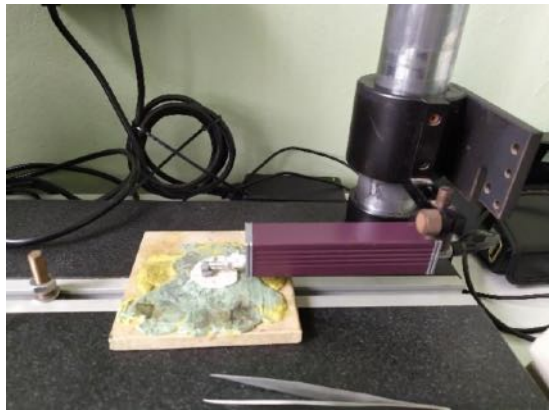
Samples

CA

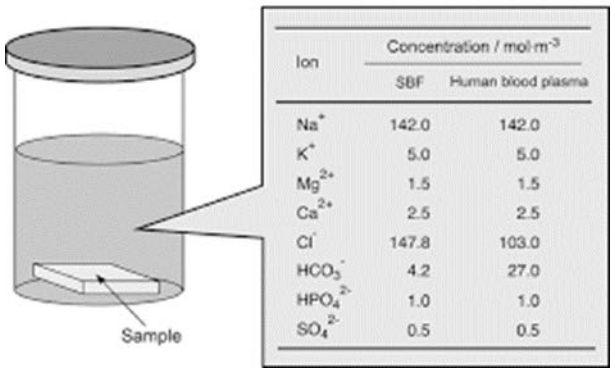
SEM



Roughness measurement



SBF immersion test

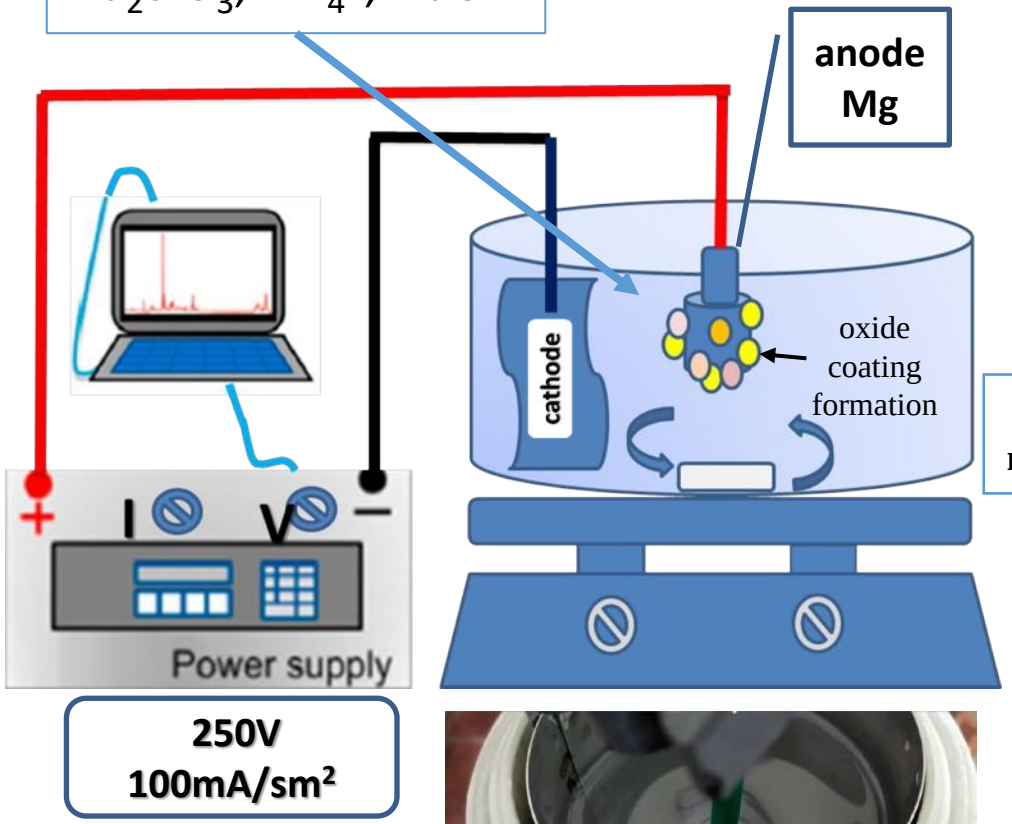


Ion	Concentration / mol·m^{-3}	
	SBF	Human blood plasma
Na^+	142.0	142.0
K^+	5.0	5.0
Mg^{2+}	1.5	1.5
Ca^{2+}	2.5	2.5
Cl^-	147.8	103.0
HCO_3^-	4.2	27.0
HPO_4^{2-}	1.0	1.0
SO_4^{2-}	0.5	0.5

Plasma Electrolytic Oxidation (PEO)

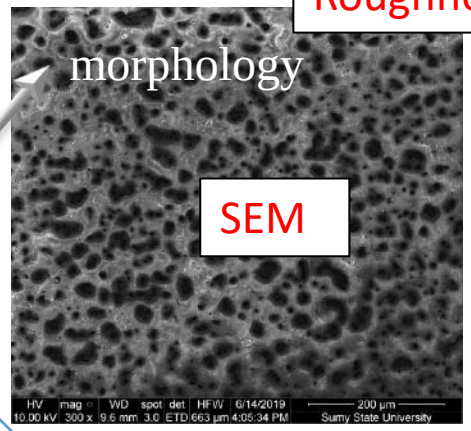
The **aim** of this study was to compare the effect of the silicate and phosphate-based electrolytes on the morphology structure and bacterial adhesional properties of coatings obtained by PEO on a pure Mg surface.

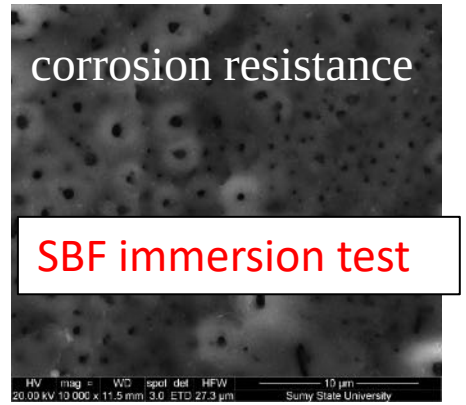
Na_2SiO_3, NH_4F, NaOH



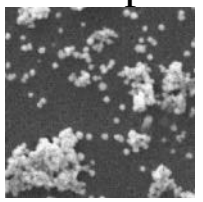
surface modification

Roughness



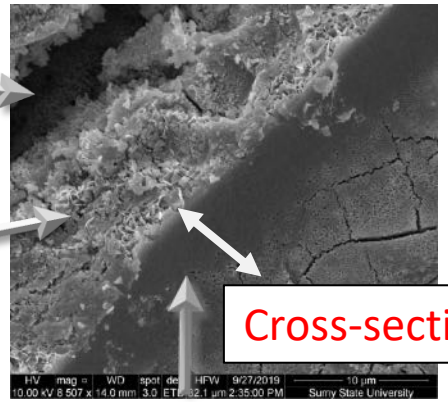


NPs incorporation



EDX

roughness



chemical composition

coating thickness

hydrophilicity

Contact angle

Sumy State University

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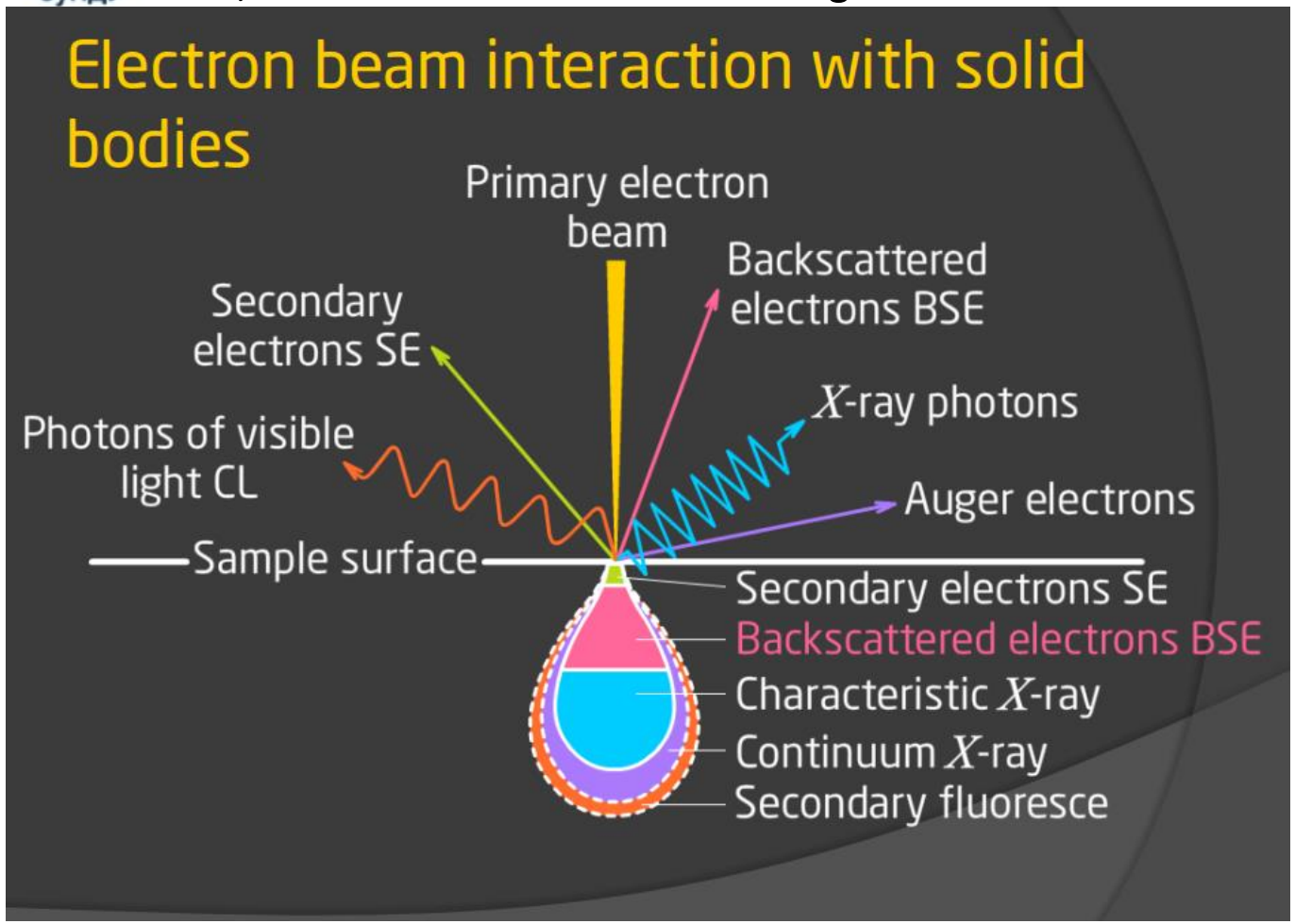
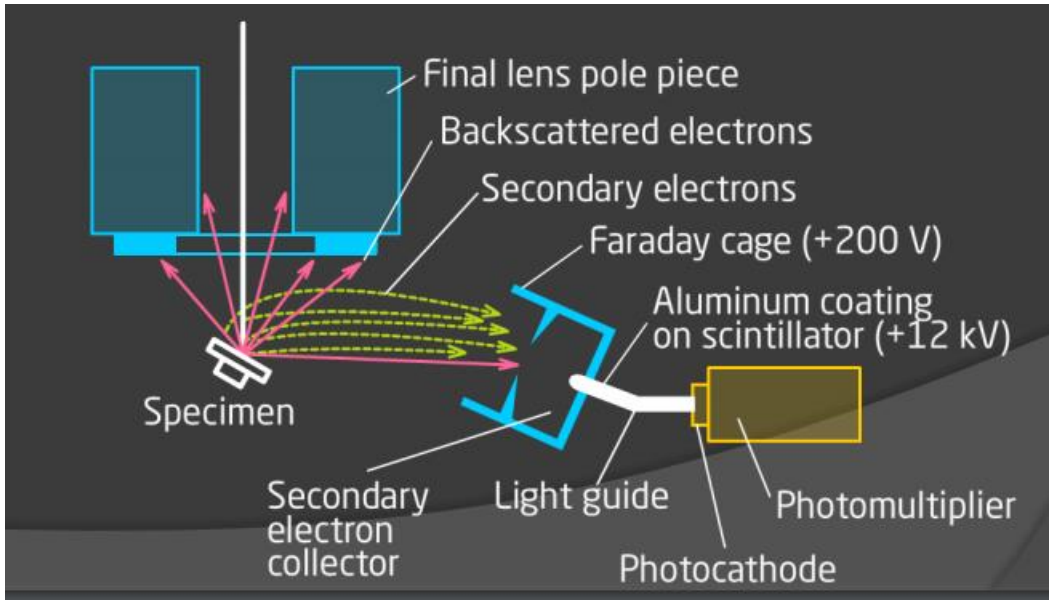
The beam is hitting the sample. It knocks off some secondary electrons from the sample. And we have a detector sideways.
So, it collects it and measures the signal.





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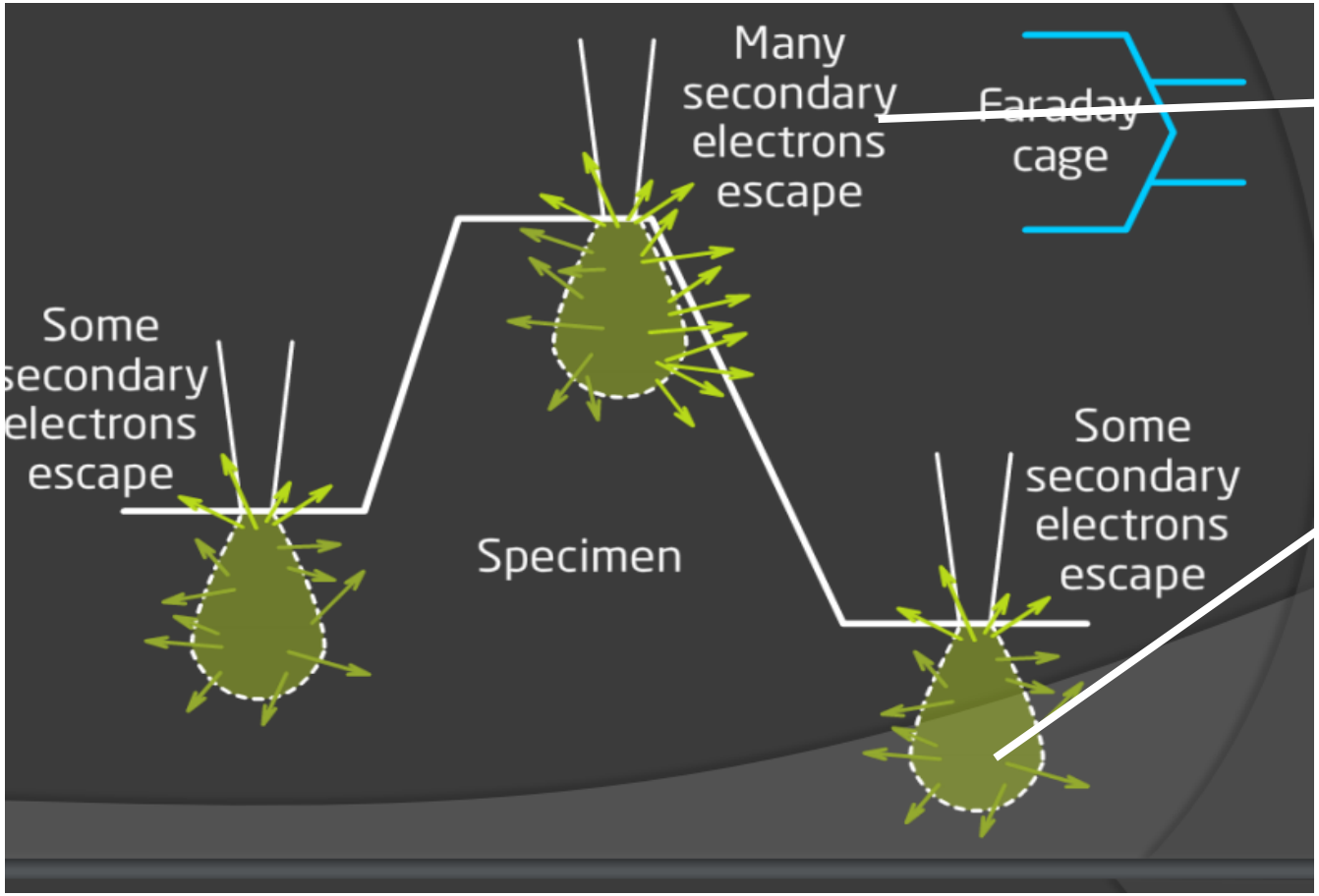
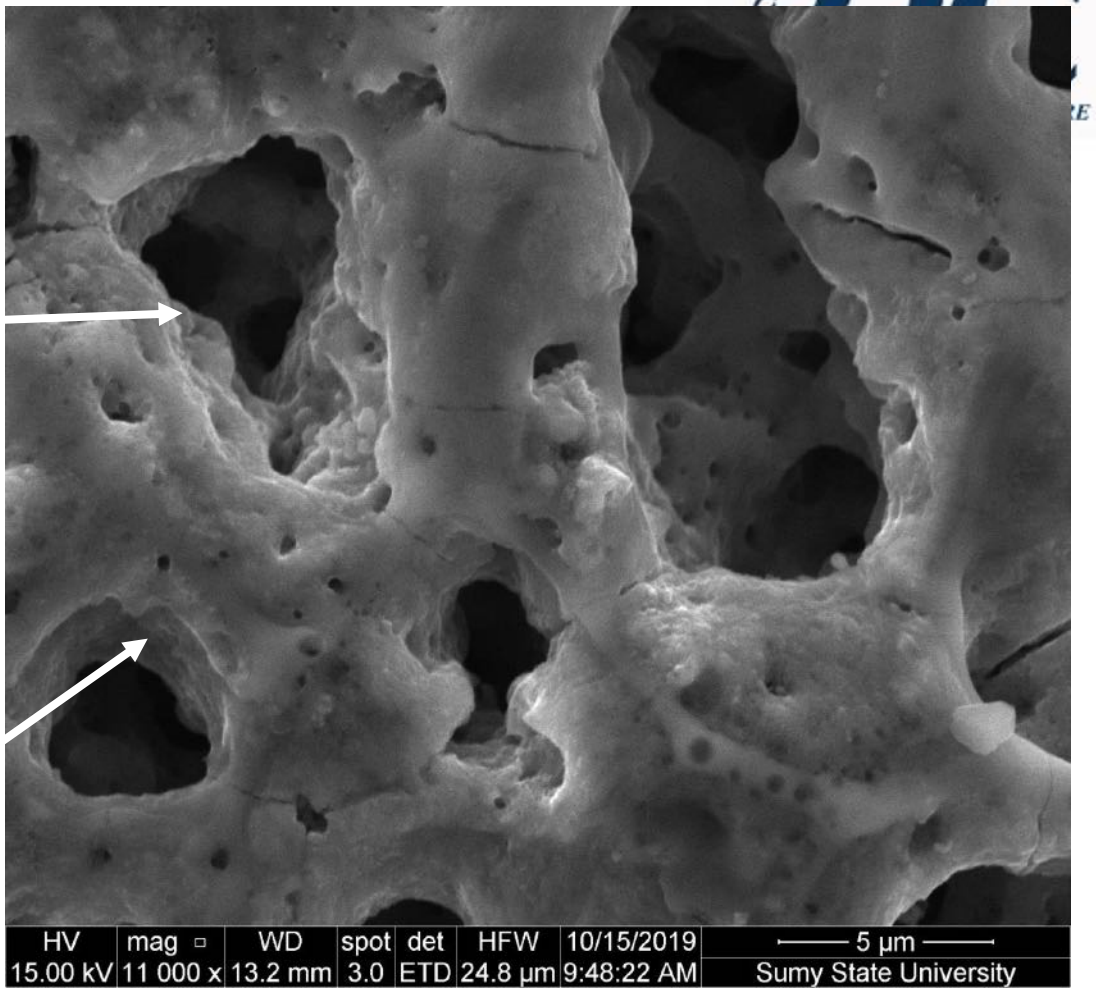
The lighter area on the sample is closer to the detector from which the electrons can go to the detector easier.





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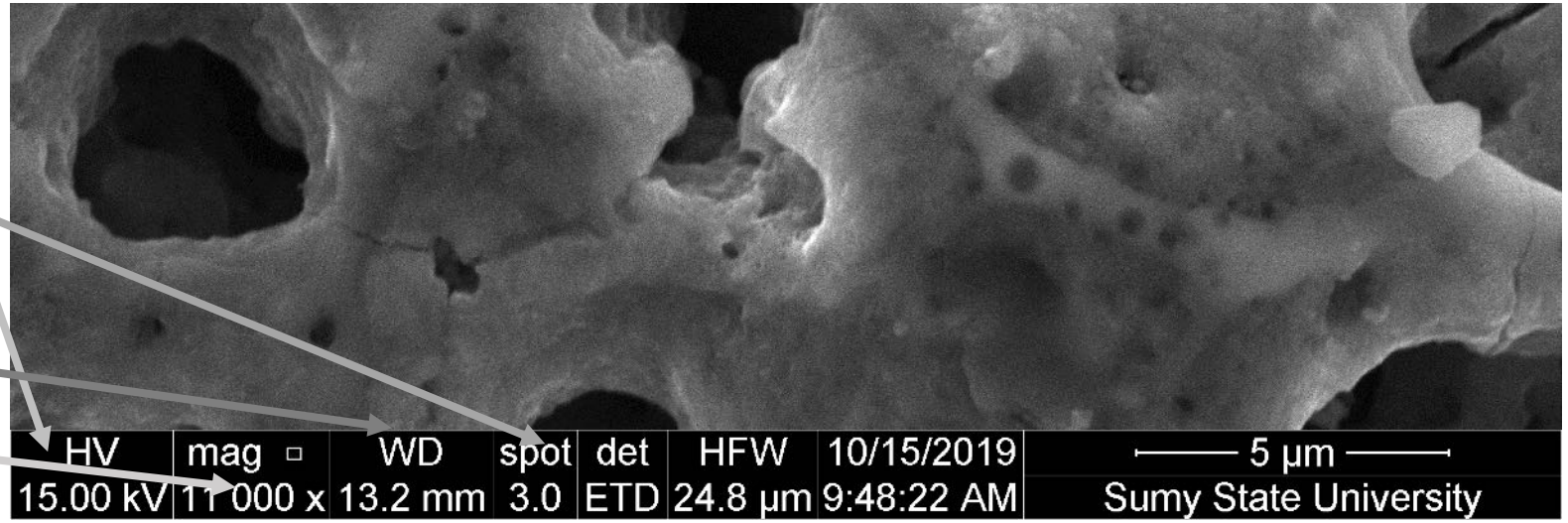
Basic parameters

To obtain a good quality image you must predict and think about all the parameters at the same time.

- Accelerating voltage
- Beam current
- Scanning speed
- Working distance
- Scanning area size
- Image resolution



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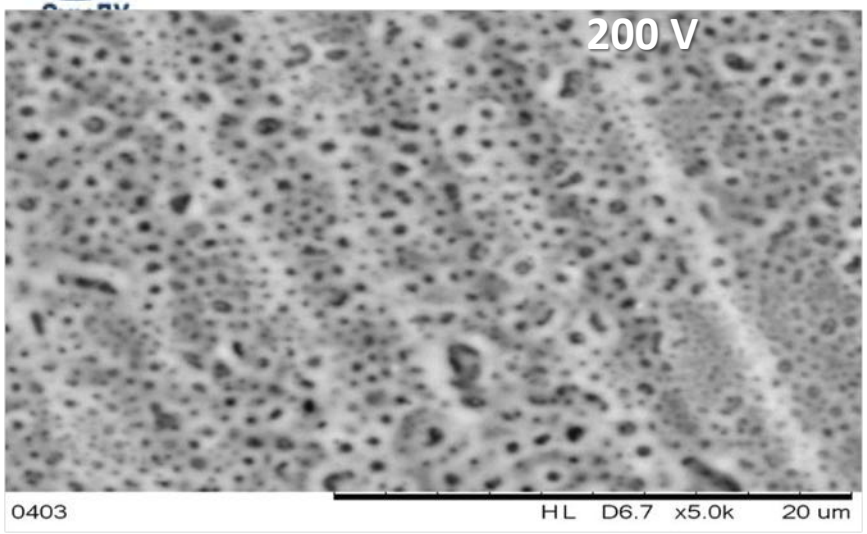
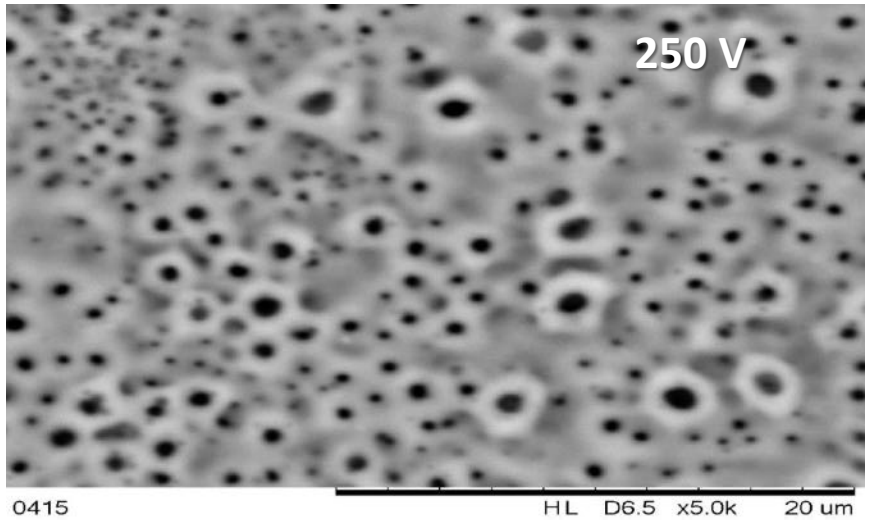
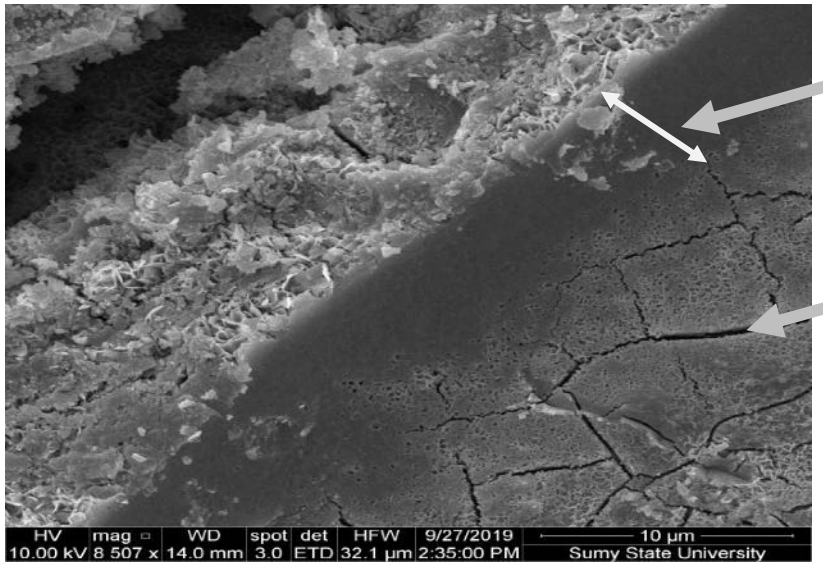
SEM

Surface morphology





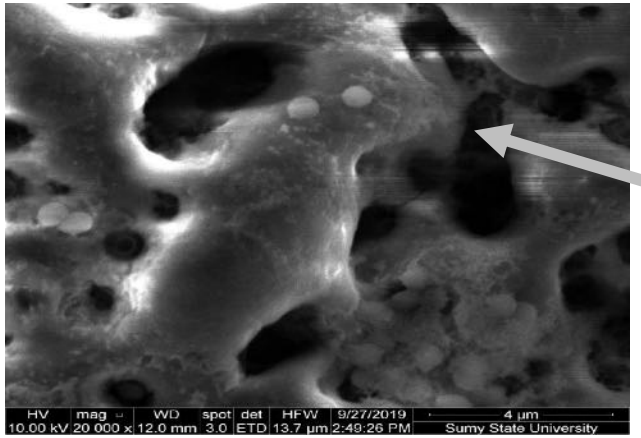
Cross section



Coating thickness

Corrosion features

Adhesion properties



200V	250V
Pore number, N/µm^2	
0,675	0,225
Pore size, µm	
0,43±0,16	1,073±0,27

Bacterial cell adhesion

S. aureus

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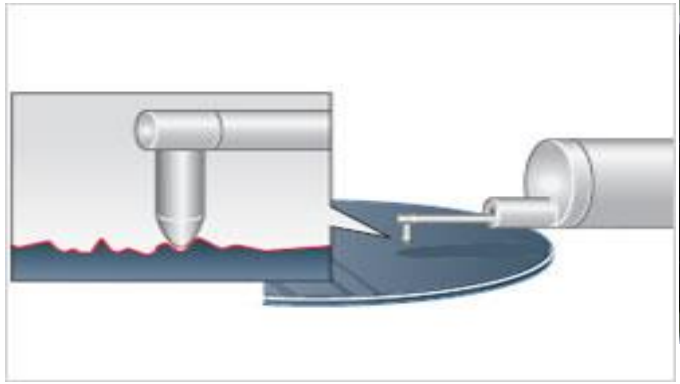
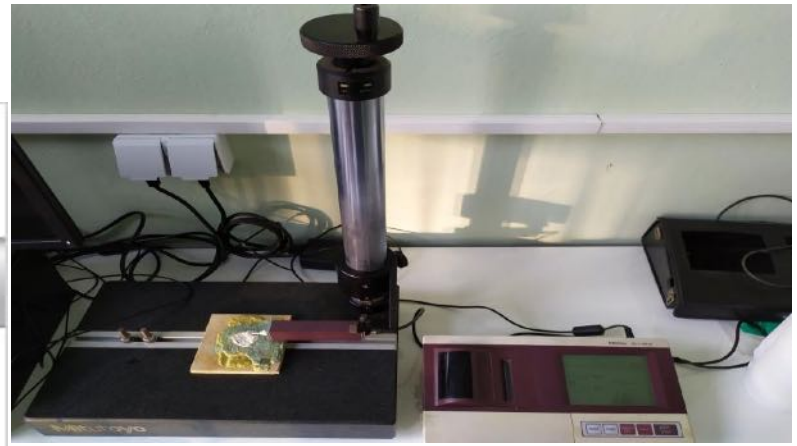
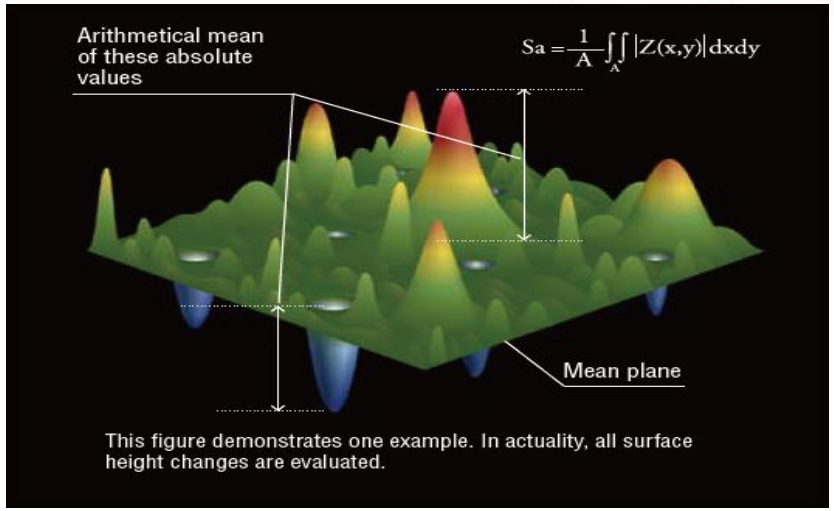
Surface roughness can be measured by contact type 2D and non-contact type 3D

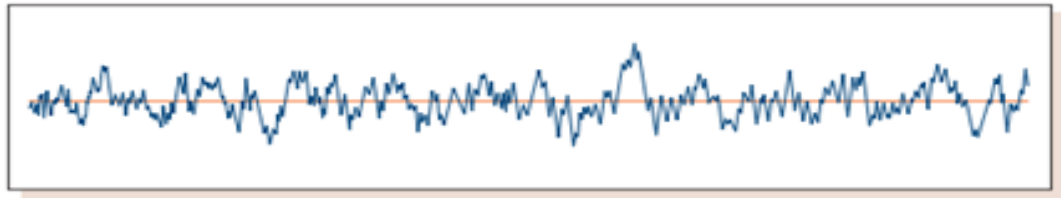






Roughness is a measurement of the small-scale variations in the height of a physical surface. It consists of surface irregularities which result from the various machining process. These irregularities combine to form surface texture.

Ra expresses, as an absolute value, the difference in height of each point compared to the arithmetical mean of the surface.



The roughness profile with its mean line (high-pass filtering of the primary profile with a cut-off wavelength of λc)

Rz is defined as the sum of the largest peak height value and the largest pit depth value within the defined area.

Rz

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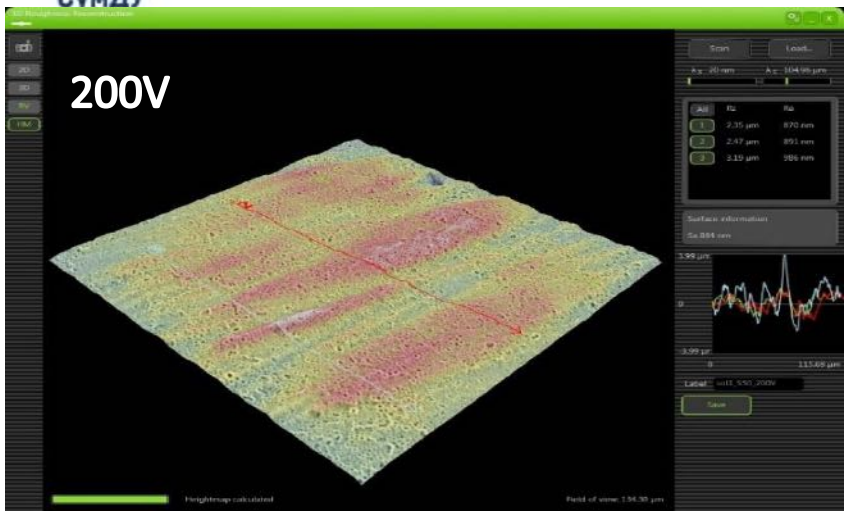
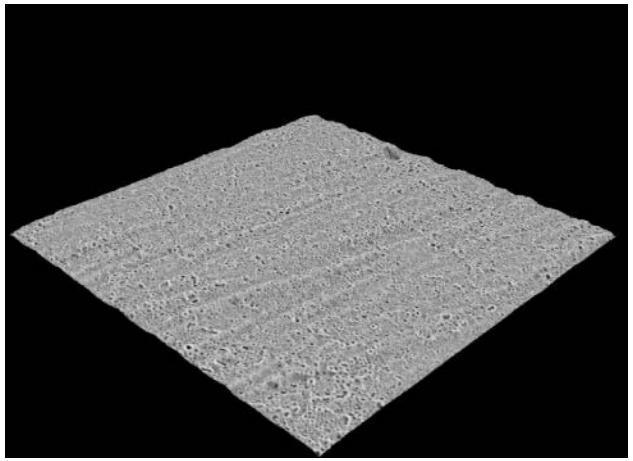
Roughness measurements

3D

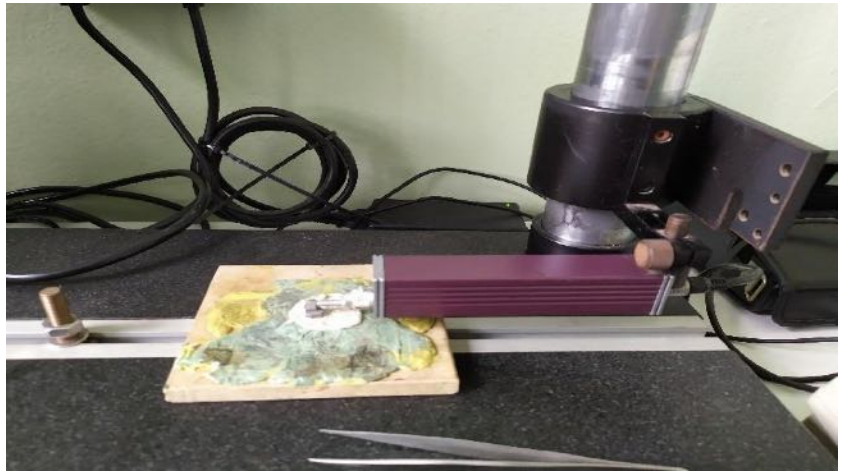
2D

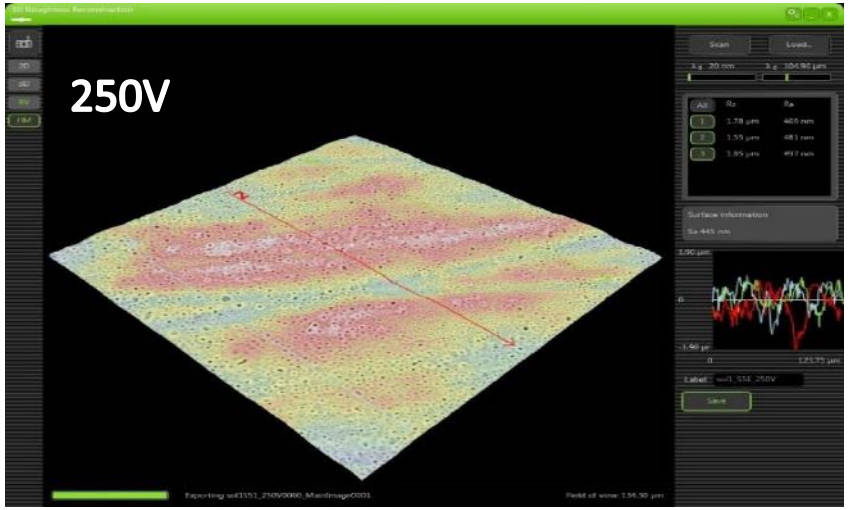


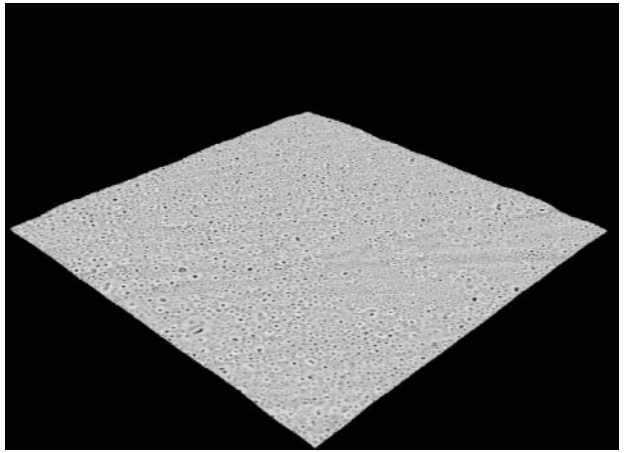


Rz = **3.01** (µm)

Ra = **430.0** (nm)







Rz = **2.83** (µm)

Ra = **393.3** (nm)

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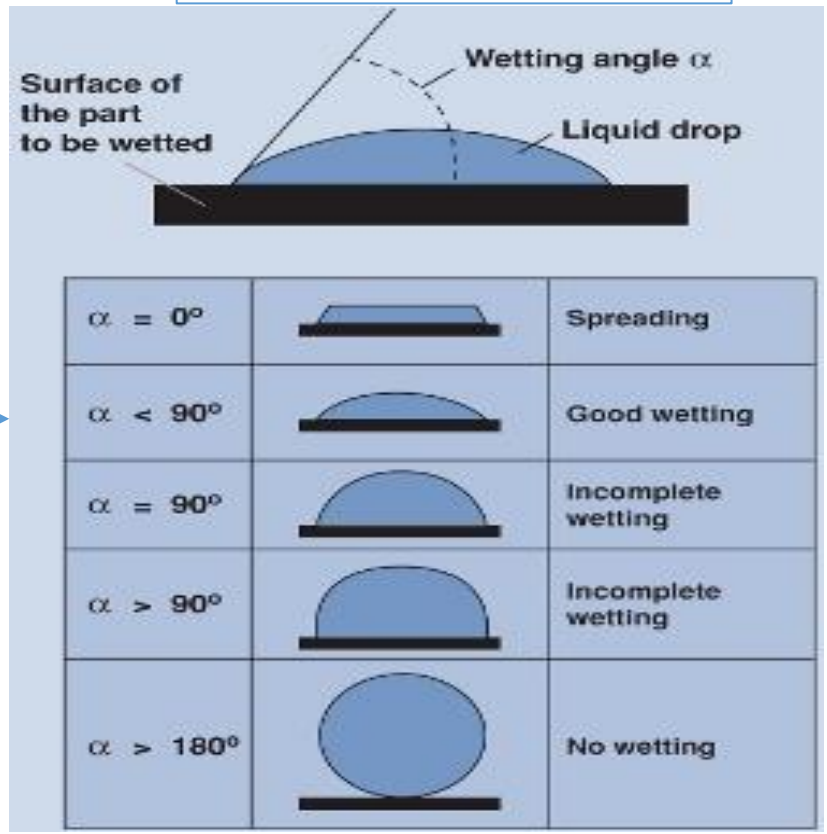
Other methods of surface analyses

CA

-200V – 26.22°

-250V – 22.7°



EDX (elemental composition)

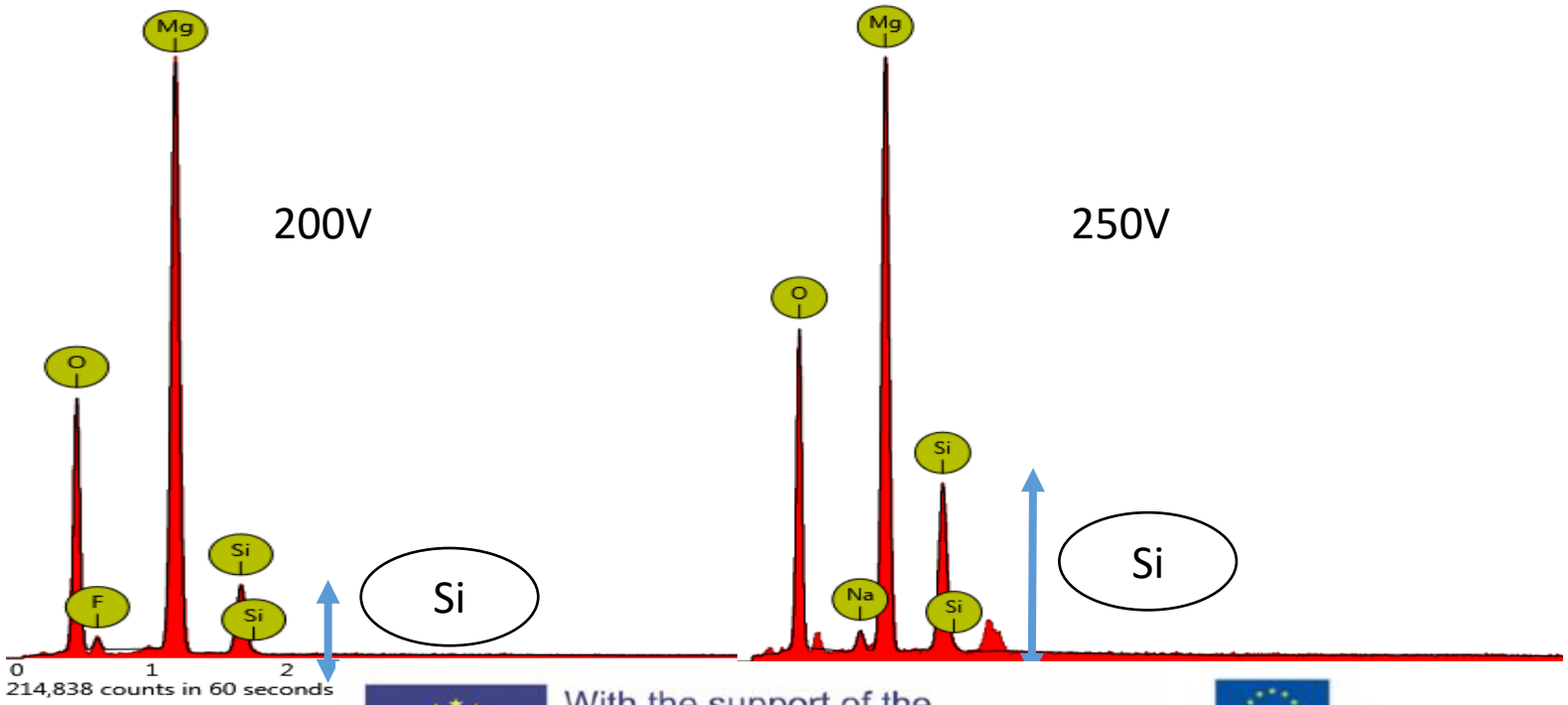
The main crystalline phase - MgO

The value of F - 3.41±0.36%

The Si weight percentage of samples:

200 V - 8.3±0.08%

250 V - 15.16±0.09%



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General characterization method

❖ Microscopy

1- Scanning Electronic Microscopy (SEM)

2- Transmission Electron Microscopy (TEM)

3- Scanning Tunneling Microscopy (STM)

❖ Spectroscopy

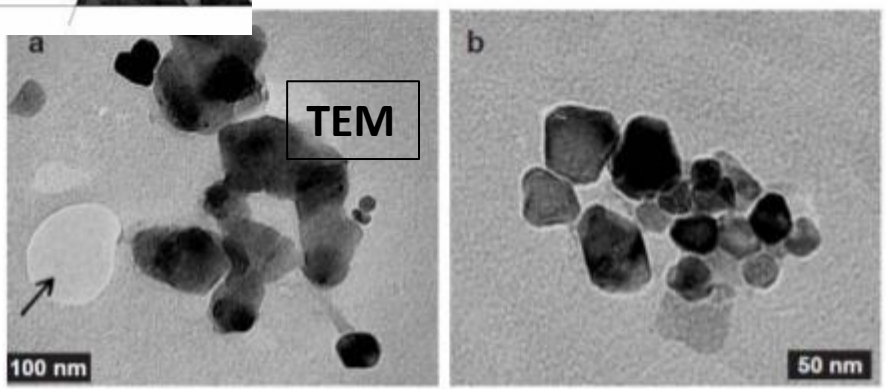
1- X-ray Diffraction (XRD)

2- Small Angle X-ray Scattering (SAXS)

3- X-ray Photoelectron Spectroscopy (XPS)

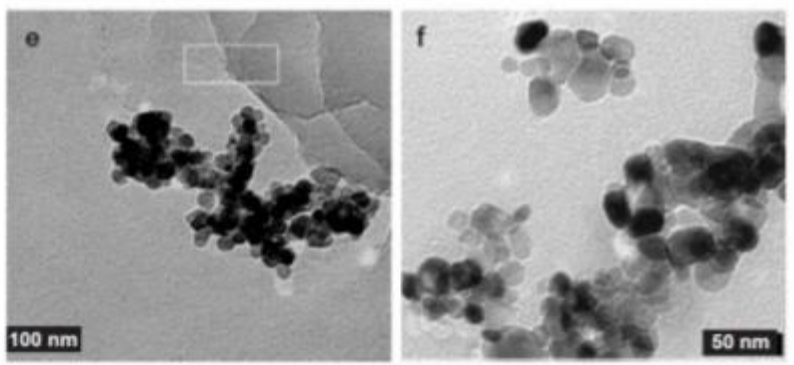
4- UV-vis spectroscopy

5- FT-IR spectroscopy



Large Ceria Nanoparticles ←

Small Ceria Nanoparticles →



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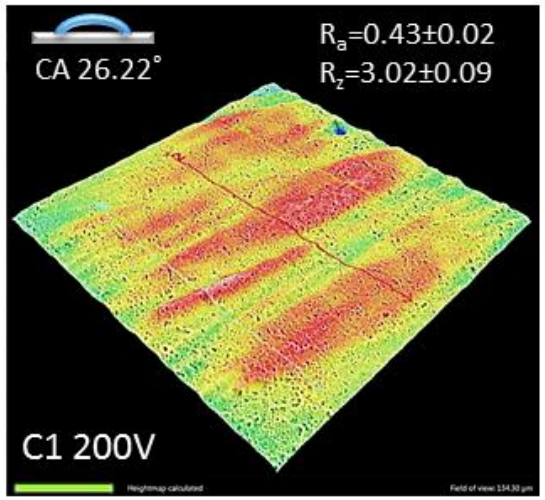

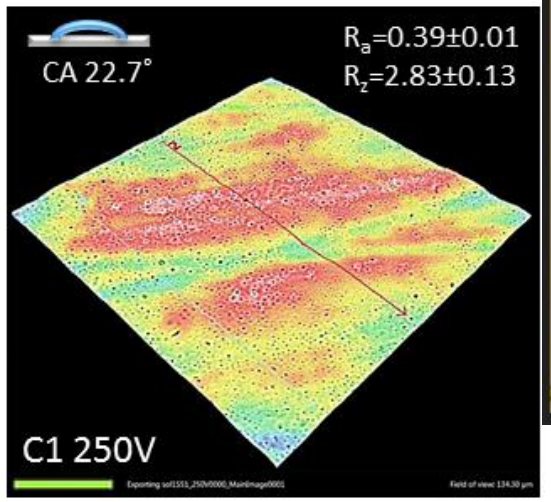

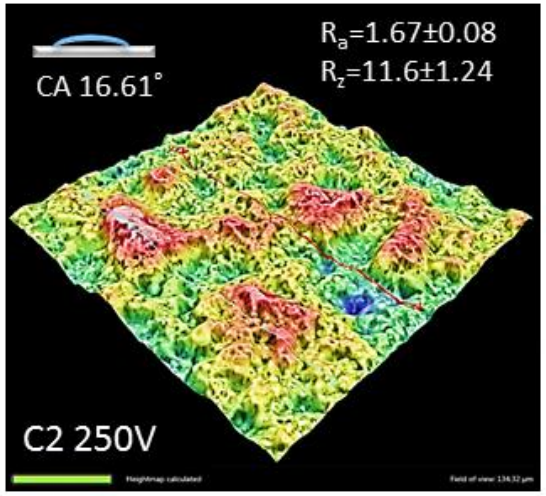

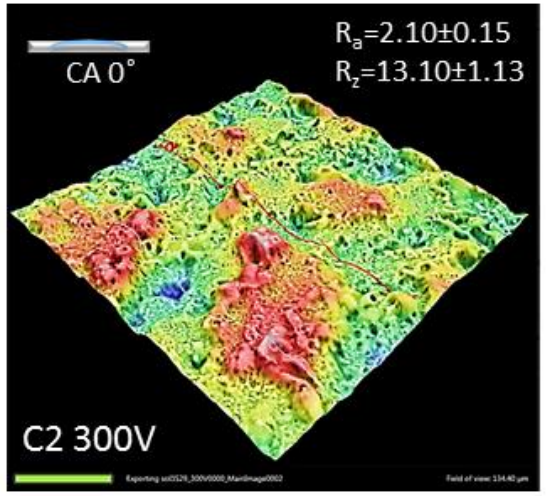

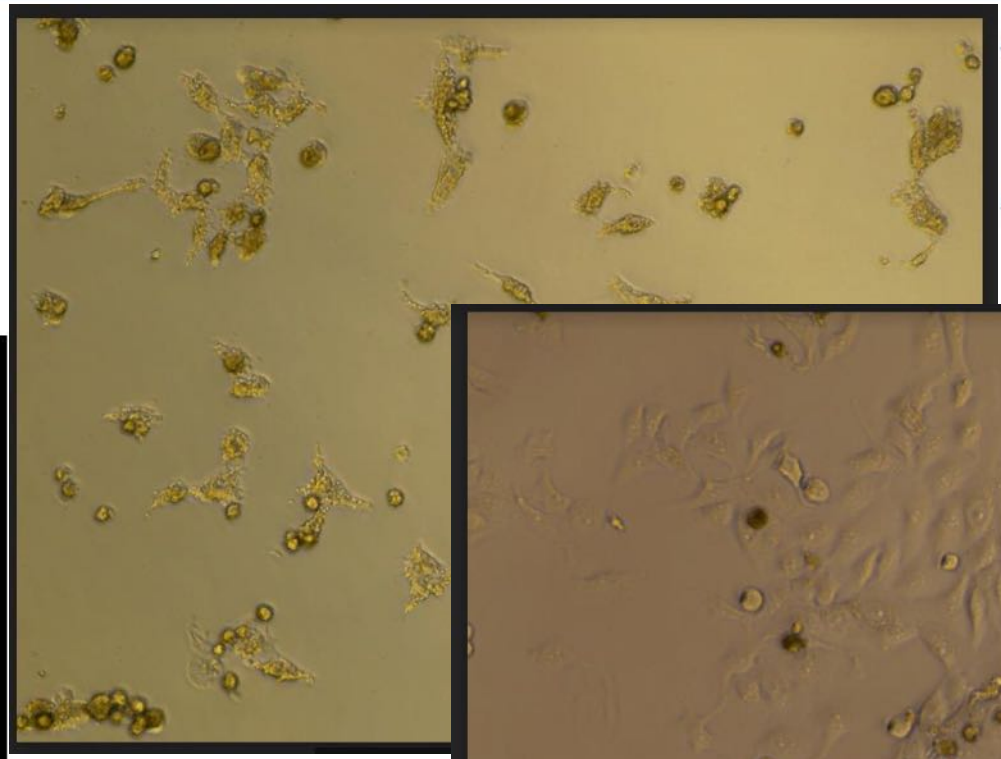

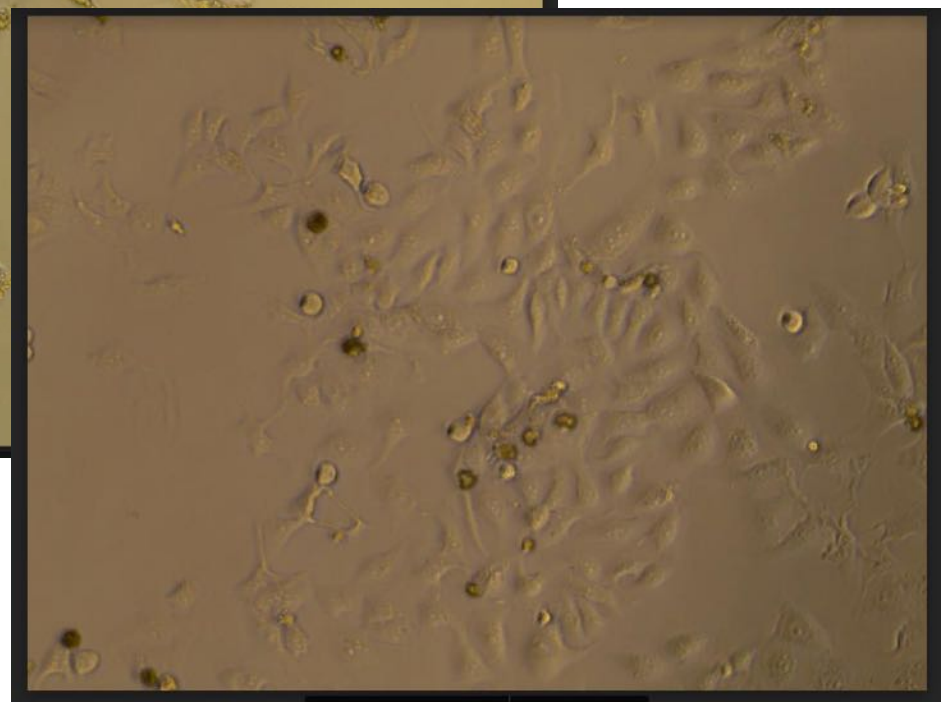

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- Thank you for attention!

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