



September 21th 2022

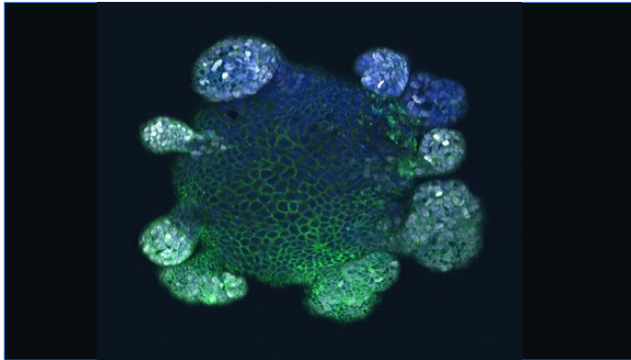
Biomaterials for MX

MSE – 471

Prof. Maartje M.C. Bastings

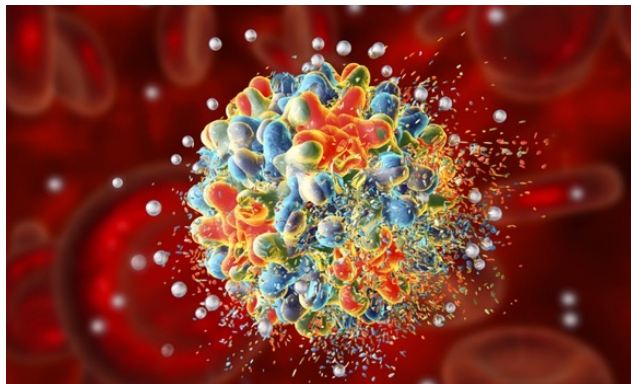
Course 1: Introduction





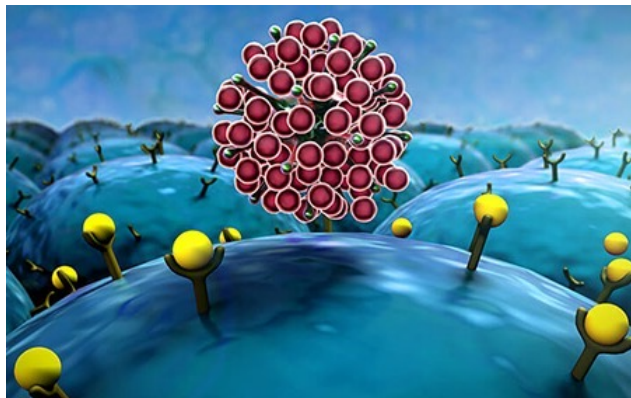
How can Biomaterials help in **vaccine** development?

What are the **risks** after implantation?



Can we **design drug release** by material choice?

When do cells **adhere** to a material surface?



What happens to **degradation** products?

How is **translation** to the **clinic** regulated?

Organization Lectures & Labs

Lectures:

Wednesdays	9.15-10.00 10.15-11.00
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Lectures focus on:

- Introduction
- Background
- Biomaterial types
- State of the art research
- Challenges
- Translation to industry

ASKING QUESTIONS

Labs: Thursdays

8.15-10.00

Laboratory project focus on:

- Lab skills
- Project oriented thinking
- Team work
- Experimental planning
- Labjournal
- Living matter!
- Theory translation
- Prep for practical projects (thesis)**

Presence of labs is registered and is mandatory!

ALL MATERIAL WILL BE AVAILABLE ON MOODLE

- 1) Course notes and relevant background papers
- 2) Experimental protocols and lab notebook template

(FEEL FREE TO PRINT AND BIND AT THE REPRO)

Course Content & Time Table

BLOCK 1: Introduction and materials overview

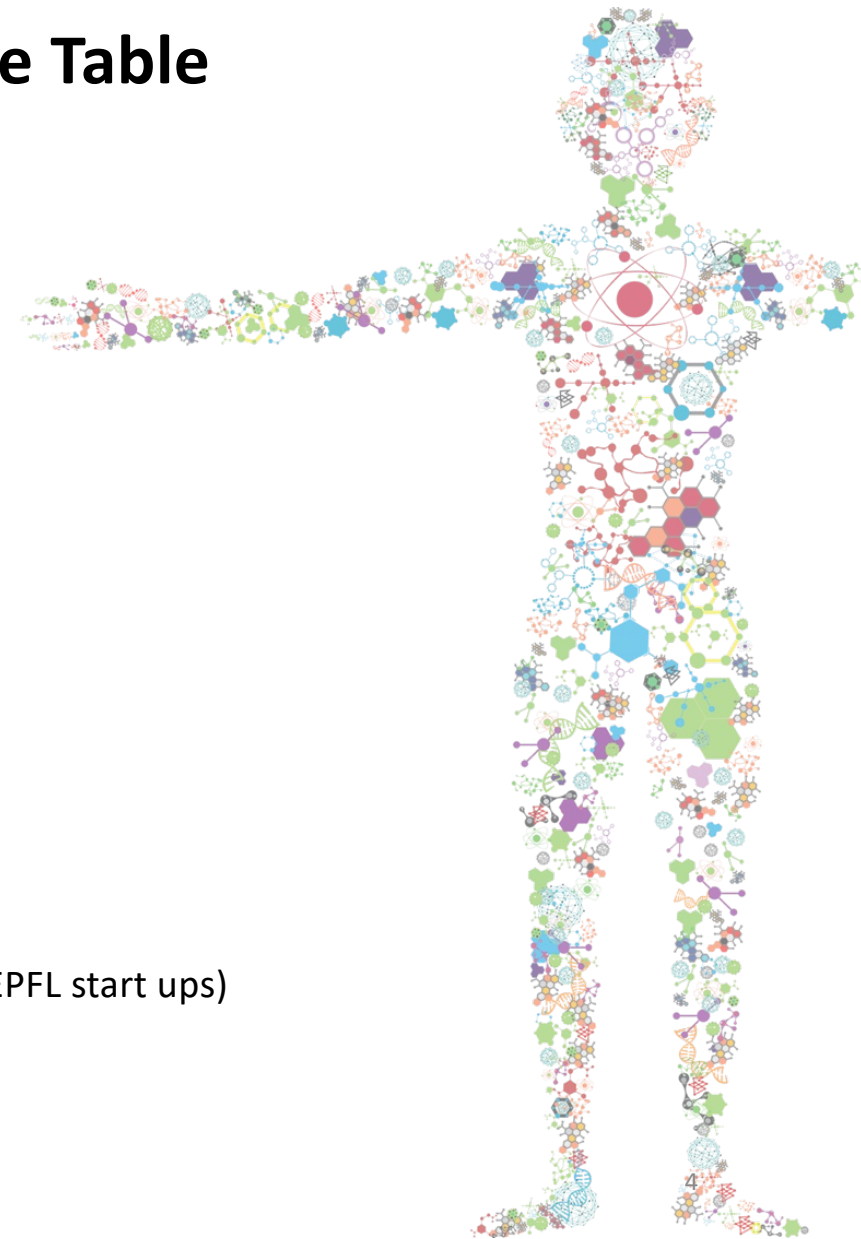
11-9	Lecture 1.	Intro to biomaterials and biology
18-9	Lecture 2.	Naturally derived biomaterials
25-9	Lecture 3.	Polymers and nanoparticles
2-10	Lecture 4.	Surfaces

BLOCK 2: Interactions and specific applications

9-10	Lecture 5.	Materials for drug delivery and targeting
16-10	Lecture 6.	Materials for cell adhesion
---	Break	
30-10	Lecture 7.	Materials for immune engineering
6-11	Lecture 8.	Materials for tissue engineering

BLOCK 3: Measurements, regulation and translation

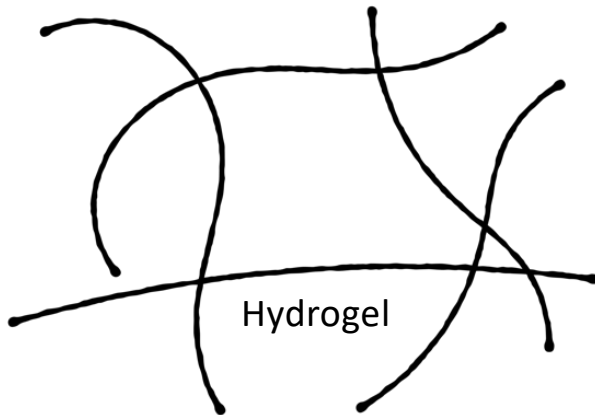
13-11	Lecture 9.	Characterization and performance
20-11	Lecture 10.	Sensors and diagnostic devices
27-11	Lecture 11.	Translation to industry, patents, spin-offs (EPFL start ups)
4-12	Lecture 12.	Regulatory aspects and trials (EPFL TTO)
11-12	Lecture 13.	Revision and conclusion
18-12	Open discussion and hand in of lab papers	



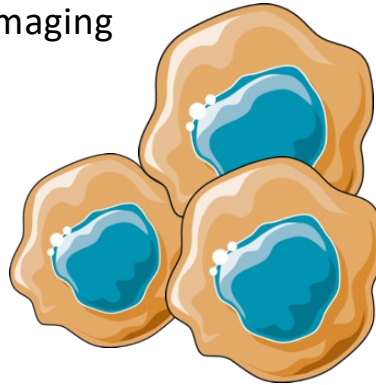
Labs : hands on research project in biomaterials

3 modules: from **chemistry**, via **characterization** and **image analysis**, to **biology**

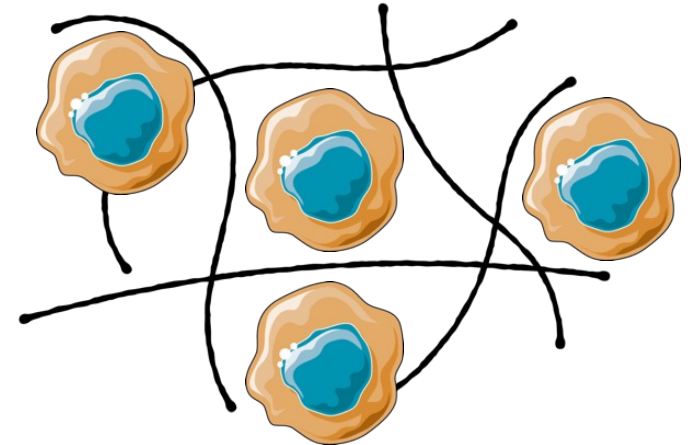
Soft biomaterials



Cell culture
& Imaging



Tissue engineering



PLANNING

1 week intro, 2x 5 weeks, last 2 weeks for assay writing.

GROUPS

Limit chaos and overcrowding at DLL, split in groups and rotate

NB: the preparation is mandatory and will allow for a smooth sailing of the lab work

INDIVIDUAL

lab reports (will be graded!) final hand in last class of semester (18th December @ noon)

Experimental Planning

12-9 TP 1. Intro to labwork + SAFETY (MED2 2423)

BLOCK 1: Biomaterials mechanics and composition

19-9 TP 2. Preparation of materials and calculations

26-9 TP 3. Gelation experiments Ca vs Gelatin (split groups)

3-10 TP 4. Gelation experiments Ca vs Gelatin (split groups)

10-10 TP 5. Rheology and data analysis

BLOCK 2: Cell culture and surface interactions

17-10 TP 6. Cell splitting / microscopy (split groups)

--- break ---

31-10 TP 7. Cell splitting / microscopy (split groups)

7-11 TP 8. Cytotoxicity / sterilization (split groups)

14-11 TP 9. Cytotoxicity / sterilization (split groups)

21-11 TP 10. Live – Dead / Imaging (split groups)

28-11 TP 11. Live – Dead / Imaging (split groups)

BLOCK 3: "Tissue Engineering"

5-12 TP 12. Gel – Cell function / Essay prep (split groups)

12-12 TP 13. Gel – Cell function / Essay prep (split groups)

18-12 Open discussion and hand in of lab essay papers

Don't wait till the end to write the essay!

Plan a bit of time every week and

ASK TA's for HELP

Exams and Grading

LAB-PAPER:

Based on your experimental design choices and data, you will write a short publication style report (max 5 pages, TOTAL), highlighting your hypothesis, results, discussion and conclusions.

30% of grade

Individual papers, submitted on last day of class, WEDNESDAY DECEMBER 18 AT NOON (PDF)

LATE SUBMISSION = -0.5 on the grade of your lab paper.

WRITTEN EXAM:

In the exam period, on the material covered during the lectures.

70% of grade

House rules:

1. As a courtesy to all your colleagues and myself, please, don't be late...
2. ...if you are late, wait till the break.
3. I will give 1-5 sample questions at the end of each lecture, these are optional, but *could* reappear in your exam (will be in style of exam)
4. Lab hours are mandatory and very limited time, be in time and be prepared
5. **Thursday 8.15-10**
6. Per block, work on your data interpretation and discuss with the TAs
7. There are recordings from 2020 of the full course, but be aware the materials change
8. Don't wait until the last week of the semester to write your report...
9. Reports are **INDIVIDUAL**, no plagiarism! Failed experiments do not mean a bad report

Course Outline

BLOCK 1: Material Classes

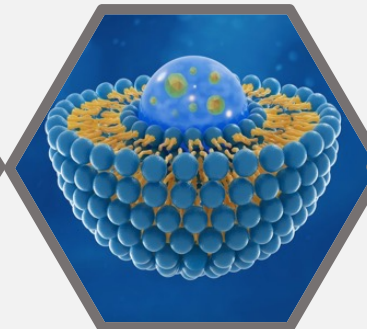
Intro



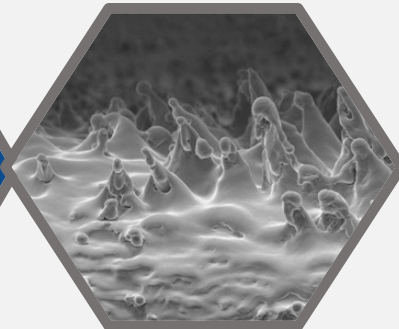
Natural



Polymers & Particles

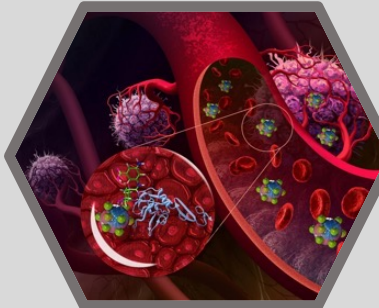


Surfaces

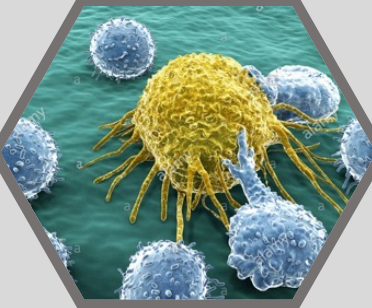


BLOCK 2: Applications

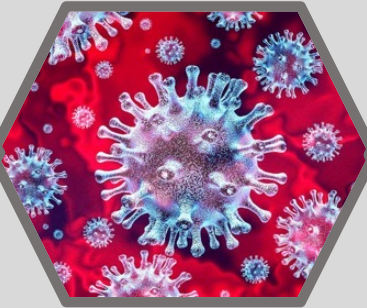
Drug delivery



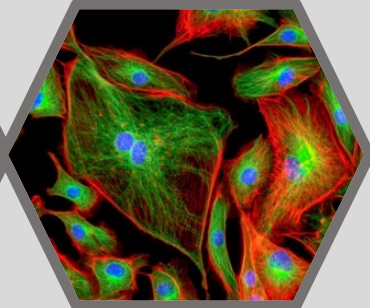
Cell adhesion



Immune engineering

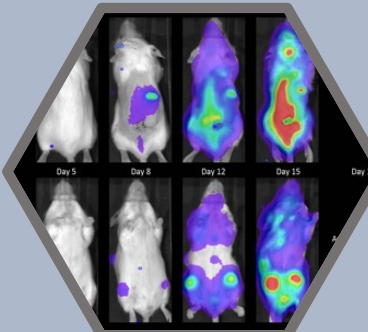


Tissue engineering

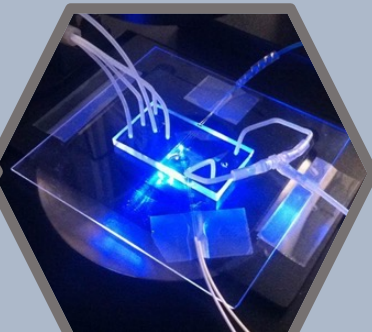


BLOCK 3: Quantification and performance

Characterization



Sensors



Translation



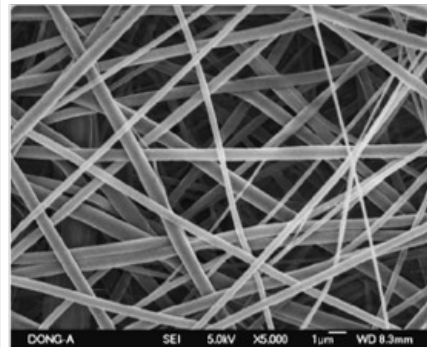
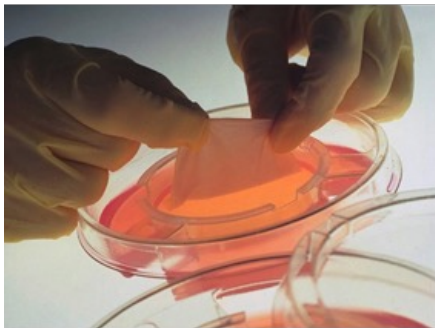
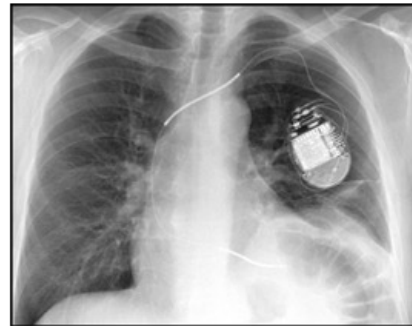
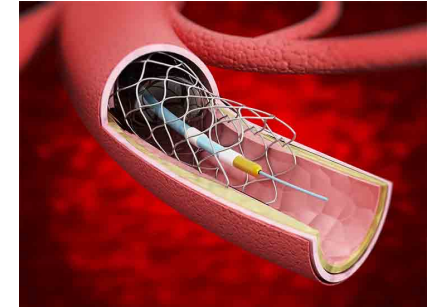
Regulation



When are materials BIOMaterials?

- A: When they are made from natural products
- B: When they are used by humans
- C: When they are biocompatible
- D: When they are used in contact with living matter

Everyday examples



Definition of Biomaterials

‘Any nonviable material (synthetic or natural) that comes in contact with a biological environment (cell, tissue, organ), and is intended for use in biomedical applications (prosthetic, diagnostic, therapeutic or storage) without adversely affecting the living organism and its components’

Biomaterials are defined by their **application**, NOT by the chemical composition or physical property

TIME

Biomaterial use is **time** dependent!

Biocompatibility is the ability of a material
to *perform with an appropriate host response*
in a *specific application during a certain time*

Physical / mechanical properties

- Strength
- (visco)-elasticity
- Pore size

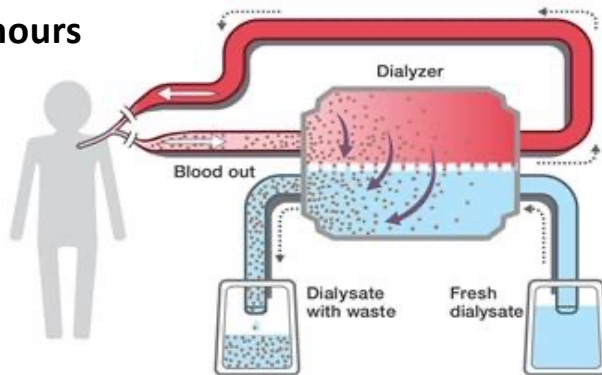
Chemical properties

- Degradability
- Toxicity
- Water content

Biological properties

- Cell adhesion
- Release of active components

hours



days



years



Processing

Biomaterials are defined by their application,
NOT by the chemical composition or physical property

Titanium



Screws



Hammer



Ring



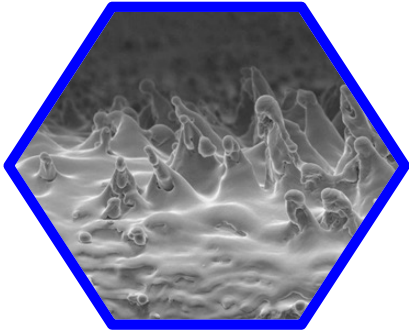
Watch



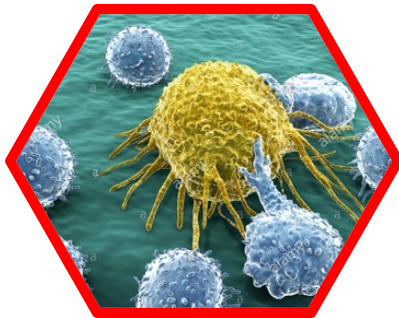
Dental Implant

Outside versus Inside

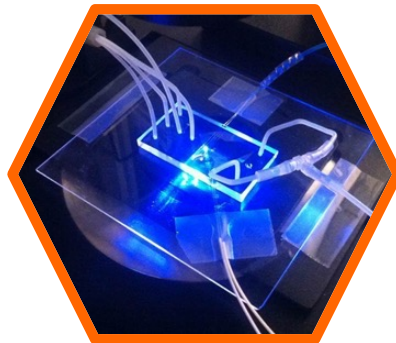
Surfaces



Cell adhesion



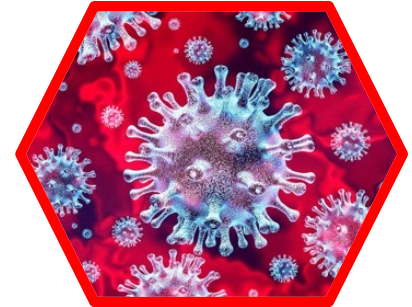
Sensors



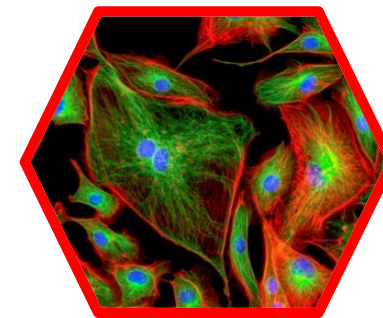
Regulation



Immune engineering



Tissue engineering



bulk versus surface
tolerance or rejection
toxicity
degradation

Why should we care?

Table 1. Estimates of number of medical devices used worldwide each year

Intraocular lenses	~14 million
Contact lenses	125 million
Vascular grafts	~400 000
Hip and knee prostheses	2 million
Catheters	>1 billion
Heart valves	300 000
Stents (cardiovascular)	>1 million
Breast implants	~600 000
Dental implants	3 million
Pacemakers	600 000
Renal dialyzers	~1.2 million
Left ventricular assist devices	>20 000

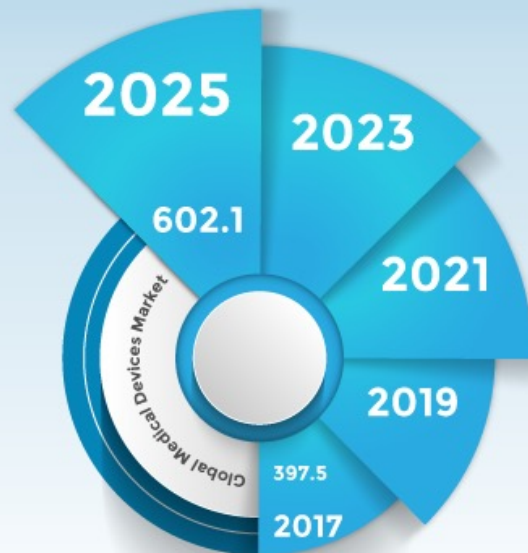
Increase in driven by :

- superior properties of biomaterials
- increasing funds for research purposes
- increasing wound healing therapy & plastic surgery
- increasing aging/geriatric population,
- rise in prevalence of cardiovascular diseases
- increasing awareness of regenerative medicine
- increasing orthopedic disorders
- growing demand for implantable devices

Why should we care?

MEDICAL DEVICES MARKET

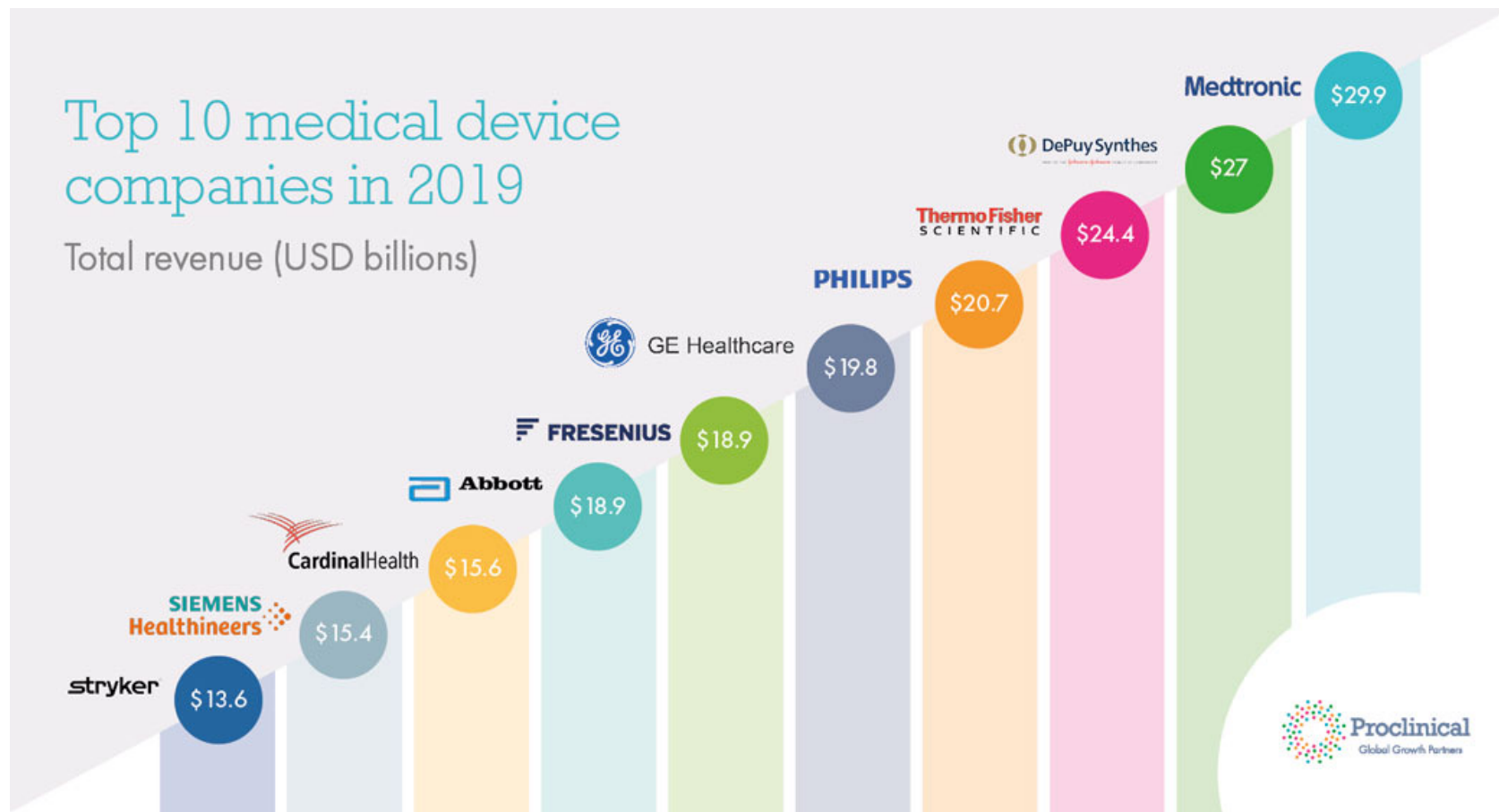
Global Medical Devices Market
(US\$ Bn), 2017 to 2025



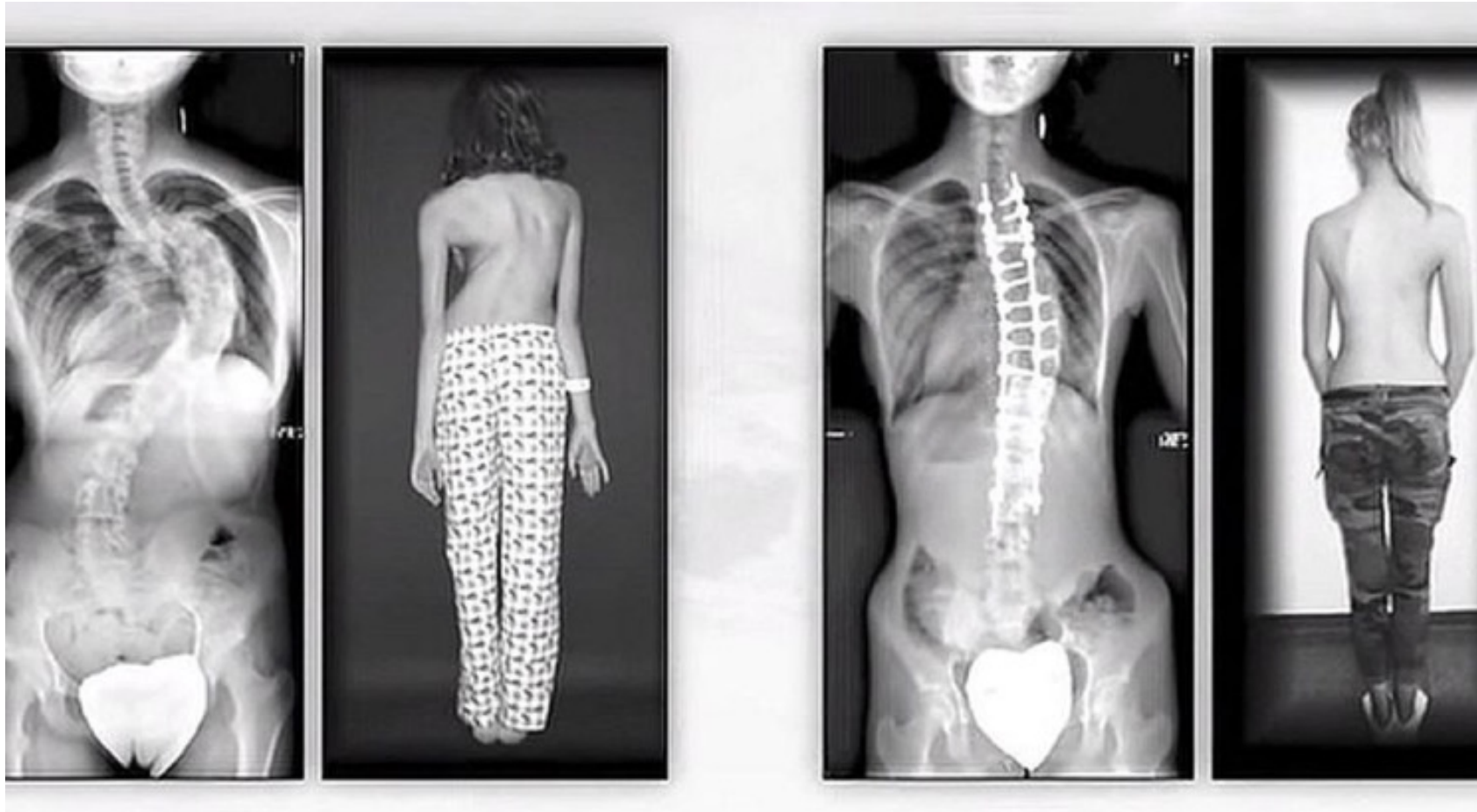
North America Medical Devices
Market, 2017



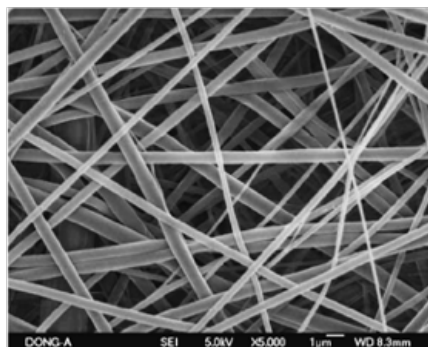
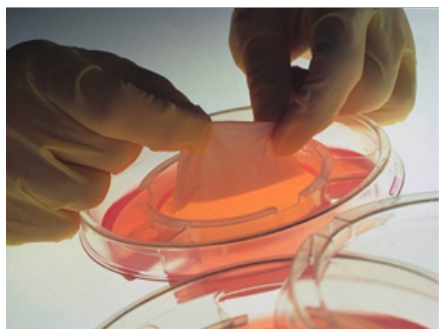
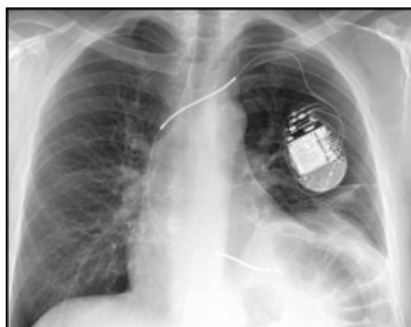
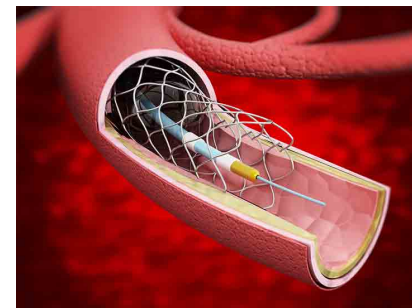
Why should we care?



Why should we care?



Quality of Life!

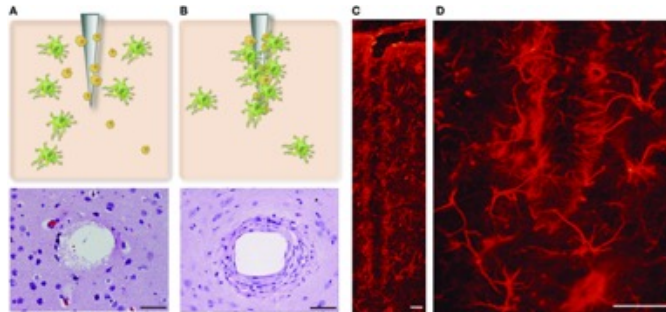


Causes of failure

The presence of a biomaterial in contact with the tissues will induce 2 responses in parallel.

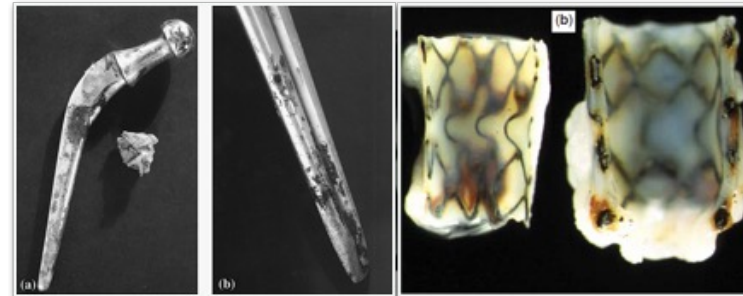
Host response

- Proteins adsorption
- Immune system reactions
- Specific to the body area/tissue
- Encapsulation/tissue adaptation



Materials response

- Corrosion, leaching or swelling
- Fatigue, creep
- Wear, debris release
- Inert/biodegradable/bioactive



➔ Improvement of the medical device performance is based on the acquisition of knowledge and understanding about materials-tissue interactions in a specific application.

Challenges and current problems

- IOLs (25% re-operation rate)
- Hip Prostheses (still a 10-15 years life time)
- Dental Implants (infection)
- Vascular Grafts (no endothelialization)
- Heart Valves (calcification or thrombosis)
- Percutaneous Devices (no “seal” to the skin)
- Stimulatory electrodes (encapsulation)
- Breast Implants (capsular contracture)
- Catheters (90,000 deaths/yr)
- Cell Culture Surfaces (cell phenotype drifts)



BREAK

A short history



Let's start back 4000 years ago

A short history

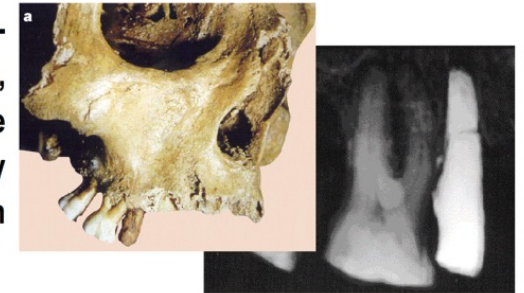


An artificial big toe found on the foot of an Egyptian mummy in 2000 in a tomb near the ancient city of Thebes. Archaeologists speculated the 50- to 60-year-old woman the prosthesis came from might have lost her toe due to complications from diabetes. The wood and leather prosthesis dates from 1069 to 664 B.C. (Cairo museum).



“Nacre” dental implants fused with the jaw bone found in a 1931 Honduran excavation (600 AD). A Mayan woman had implanted in her jaw bone three tooth-shaped shells. Compact bone formation around 2 of them.

Wrought iron implant from a Gallo-Roman necropolis at Chantambre, from the 1st or 2nd century AD. The implant and the socket fit perfectly together and the osseointegration appears viable.



Bobbio, Bull Hist Dent 2013;

Crubzy E et al., Nature 1998

Just imagine for a moment coming up with the concept of using natural materials to replace missing body parts... in those days!

Many others...

SUTURES

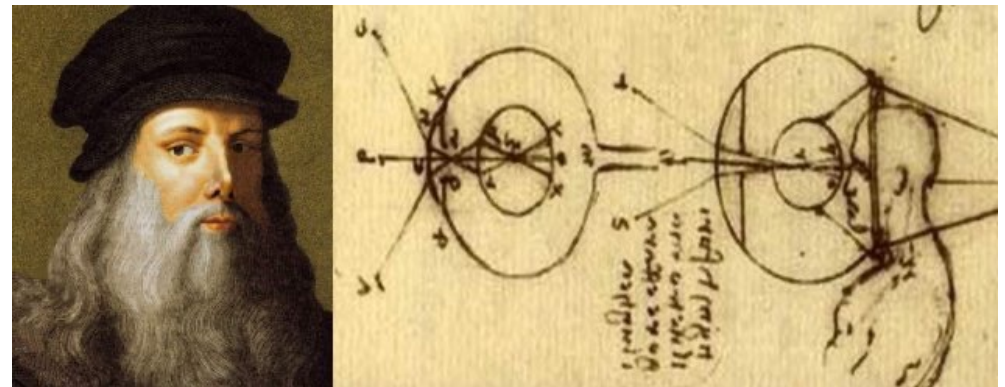
- Catgut sutures (absorbable sutures) in 1600 BC.
- Linen sutures used by early Egyptians (150 AC).
- Metallic sutures mentioned in early Greek literature:
 - 200 AC gold wires,
 - 1800 lead wires,
 - 1850 silver wires.
 - 1887 first sterile sutures (!!!)



<https://www.jnj.com/our-heritage/history-of-sutures-ethicon>

CONTACT LENSES

- Designed by Leonardo da Vinci (1508).
- Rene Descartes (1632) proposed the corneal contact lens.
- Glass contact lens experimented in 1860.
- ~ 1940 development of plastic (PMMA) contact lenses.



<https://enlightenmentmatters.wordpress.com/tag/leonardo-davinci/>

Before the modern era...

No knowledge of sterilization, toxicology, immunological reaction, and biodegradation.

Materials in medicine ... a short history

19th century medicine

from fully empirical to
driven by science

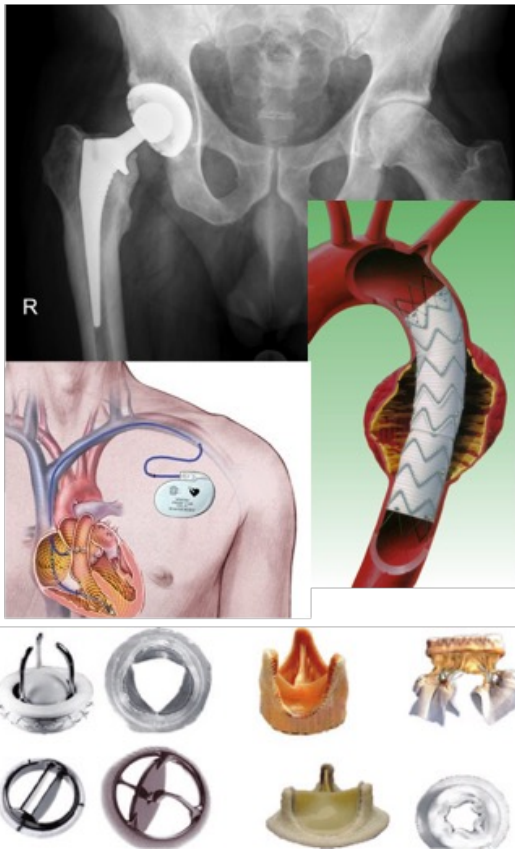


Era	Off-the shelf materials	Designed materials for implants and devices	Surgeons, medical doctors were hero's, pioneers No regulatory obligations, medical doctors allowed to test «for the benefit of the patient» in case of extreme situation.			
Examples	PMMA, Nylon, SS, Chrome-based alloys	Silicone, Teflon, Polyurethane				
Applications	Intra-ocular lenses, hip and knee prostheses, stents, vascular grafts, pacemakers, heart valves, breast implants					
Key function	Reduced toxicity	Inertness				
Specialists	Surgeons (brave ones!)	Surgeons, Mechanical Engineers				
	1950	1960	1970	1980	1990	2000

Materials in medicine ... a short history

20th century medicine

technology driven,
pushed by WWI/II



Biocompatible materials for Tissue Engineering 1.0

Hydroxyapatite, Poly(lactic-glycol acid), Titanium

Scaffolds for tissue engineering, bioactive implants, drug delivery systems, model materials

Bioactivity

Surgeons, Mechanical Engineers, Materials Engineers, Chemists, Cell Biologists

- 1960s, engineers take the lead;
- we can talk about biomaterials and medical devices engineering,
- new industrial sector
- Regulatory obligations created.



The end of World War I and II brought new materials, restricted during the war, to the public:

- Nylon
- Teflon
- Silicones
- Polyurethane
- Methacrylate
- Titanium
- Stainless Steel

1980

1990

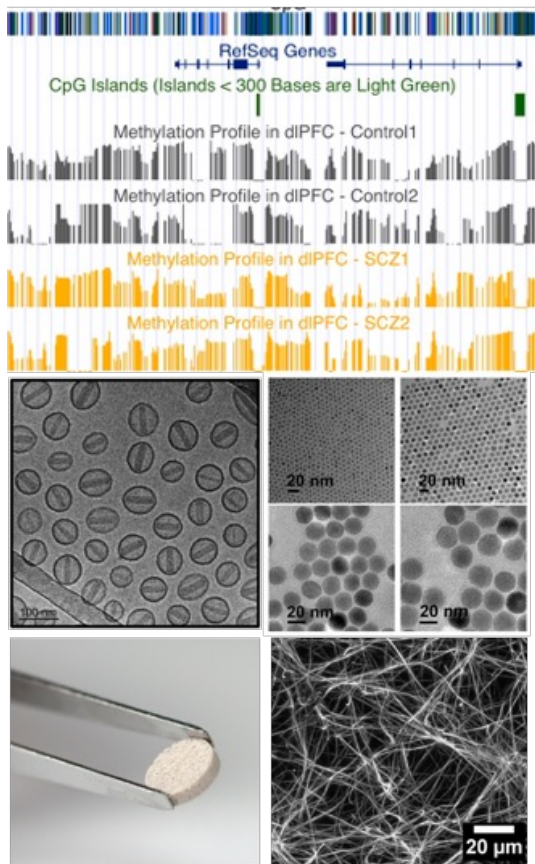
2000

2010

Materials in medicine ... a short history

21th century medicine

nanotechnology,
data driven, AI



Bimolecular
materials for Tissue
Engineering 2.0

Smart
supramolecular
gels, nanoparticles

Smart drugs, gene
delivery systems,
multifunctional cell-
responsive ECMs

Bioresponsiveness

BioEngineers,
Chemists,
Biologists,
Physicists

2000

2010

- Truly multidisciplinary
- Data and computer scientist
- Smaller length scales
- Interactions within cells
- Smart functions
- Regulatory obligations strict

Era	Off-the shelf materials	Designed materials for implants and devices	<i>Biocompatible</i> materials for Tissue Engineering 1.0	<i>Bimolecular</i> materials for Tissue Engineering 2.0
Examples	PMMA, Nylon, SS, Chrome-based alloys	Silicone, Teflon, Polyurethane	Hydroxyapatite, Poly(lactic-glycol acid), Titanium	Smart supramolecular gels, nanoparticles
Applications	Intra-ocular lenses, hip and knee prostheses, stents, vascular grafts, pacemakers, heart valves, breast implants		Scaffolds for tissue engineering, bioactive implants, drug delivery systems, model materials	Smart drugs, gene delivery systems, multifunctional cell-responsive ECMs
Key function	Reduced toxicity	Inertness	Bioactivity	Bioresponsiveness
Specialists	Surgeons (brave ones!)	Surgeons, Mechanical and Electrical Engineers	Surgeons, Mechanical Engineers, Materials Engineers, Chemists, Cell Biologists	BioEngineers, Chemists, Biologists, Physicists
1950 1960 1970 1980 1990 2000 2010				

Materials in medicine ... a short history

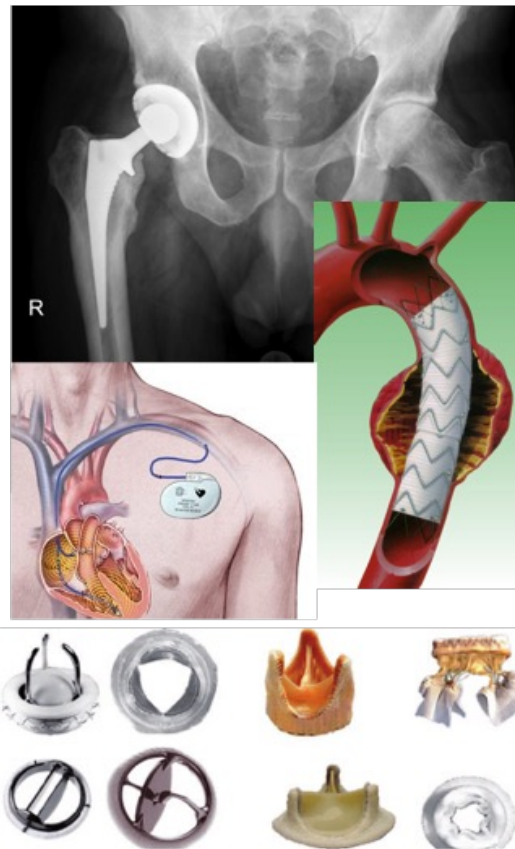
19th century medicine

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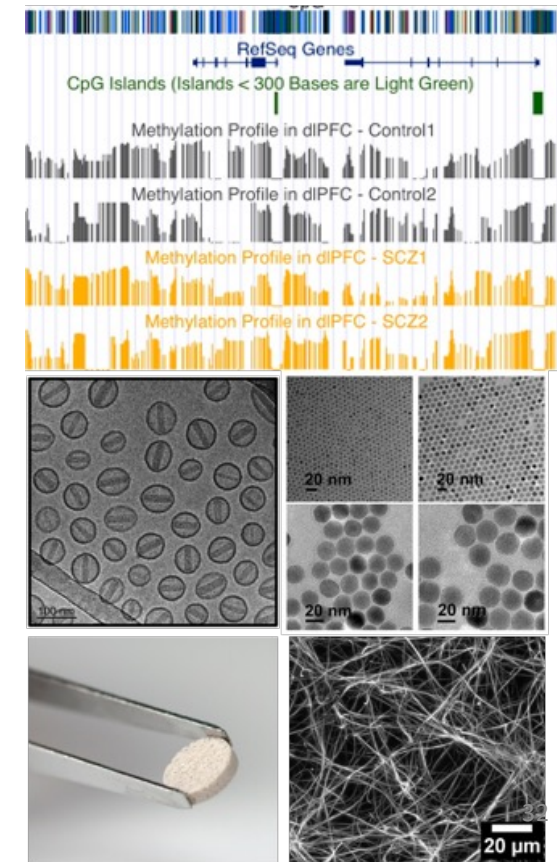
20th century medicine

technology driven,
pushed by WWI/II



21th century medicine

nanotechnology,
data driven, AI



Materials in medicine ... a short history

**SIZE OF MATERIAL AND
BIOLOGICAL TARGET**

organ / tissue

(intra) cell
nm-um
technology,
data driven, AI

full b
cm-

THERE IS AN INHERENT NEED TO UNDERSTAND AND CONTROL

ACCURACY, EFFICIENCY, SPECIFICITY, TOXICITY

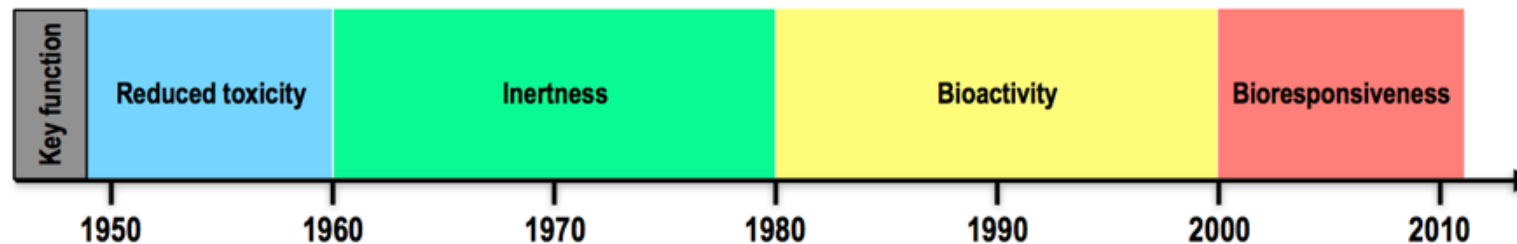
OF MATERIALS USED AS THERAPEUTIC / DIAGNOSTIC

implants

tools

**COMPLEXITY OF
BIOLOGICAL FUNCTION**

Lots of design parameters



Bulk properties

- mechanical (e.g. modulus)
- chemical (e.g. stability)
- optical (e.g. clarity)
- Toxicity
- Processing aspects
- Sterilisation

Surface properties

- adsorption
- adhesion
- optical (e.g. clarity)
- Degradation
- Immunogenicity
- Processing
- Functionalization

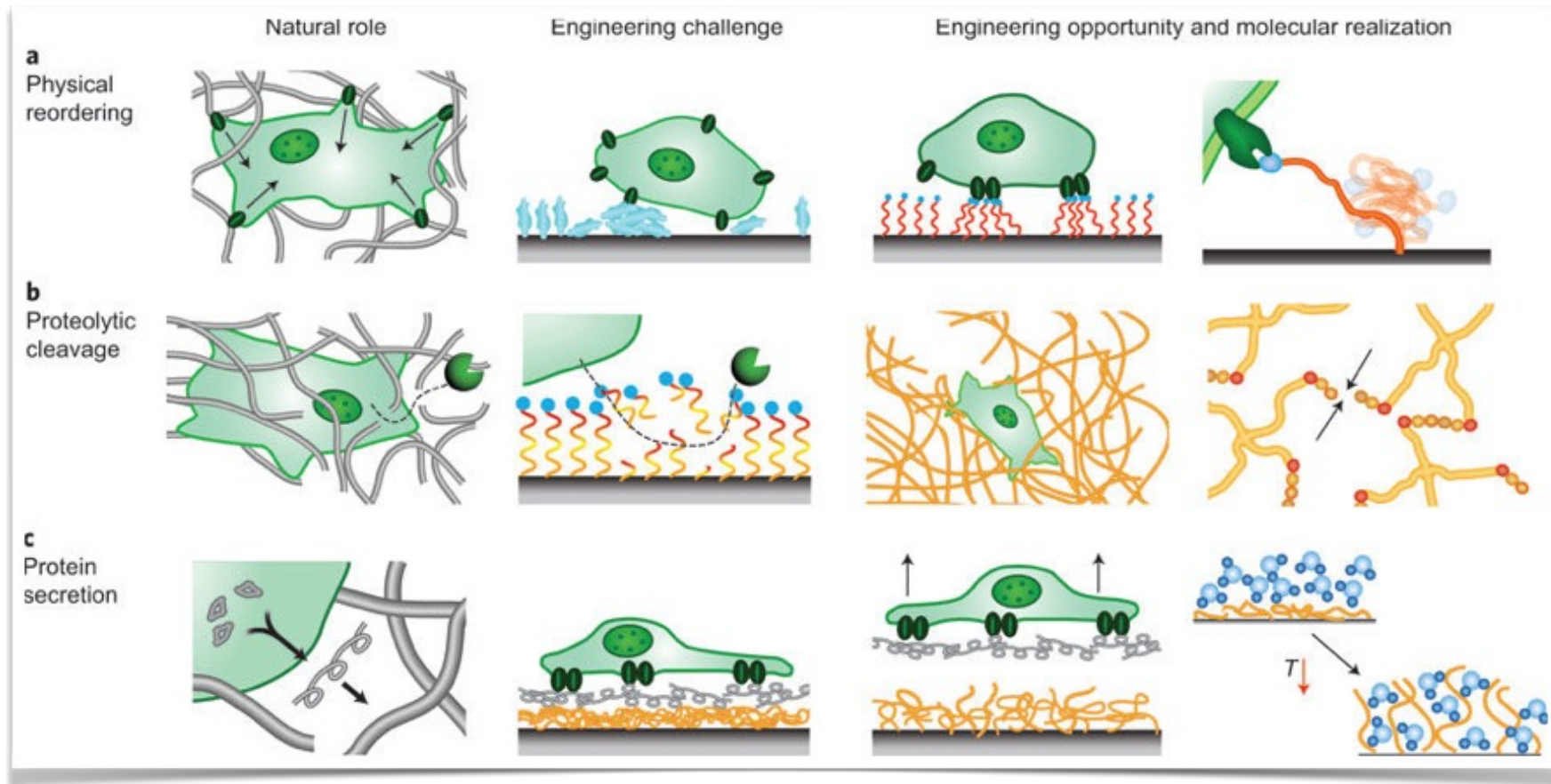
Biomolecular properties

- Designing materials based on molecular principles of cell-matrix interaction

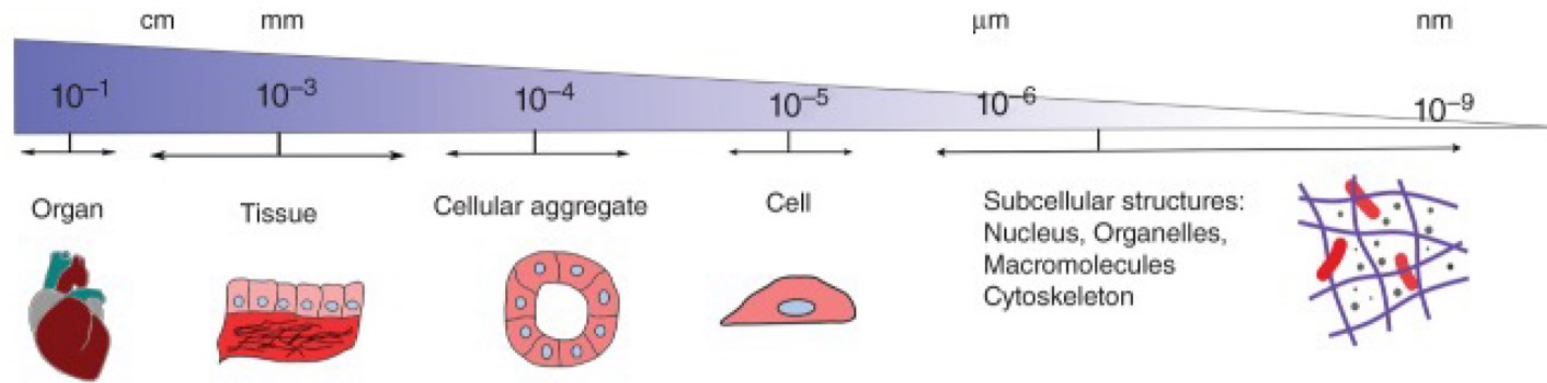
Multidisciplinary!

Modern biomaterials

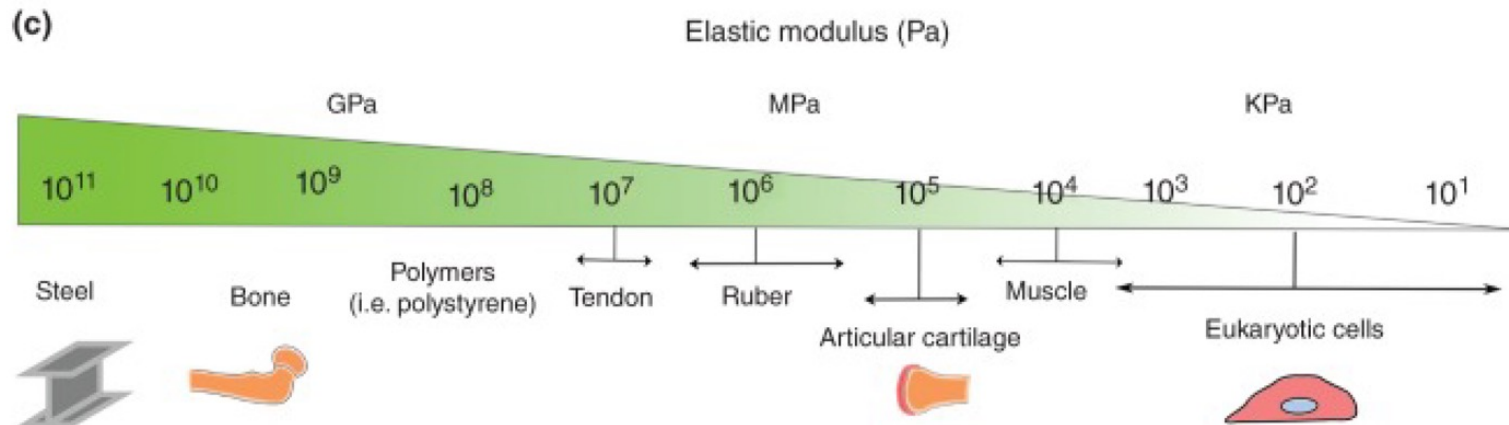
Synthetic (or naturally derived) materials that contain the necessary signals to recapitulate developmental processes in tissue- and organ-specific differentiation and morphogenesis



Length scales



Strength scales



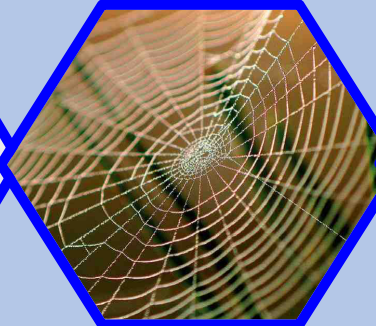
Various Classes of Biomaterials

BLOCK 1: Material Classes

Intro



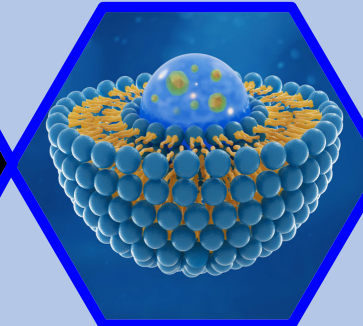
Natural



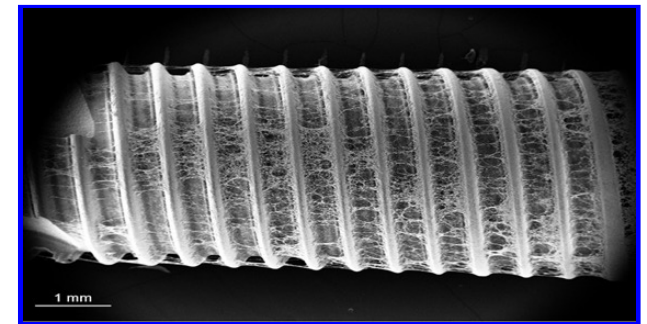
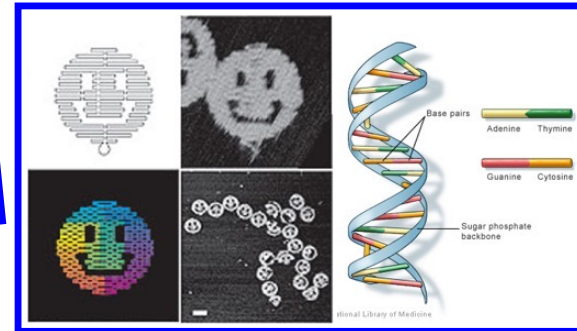
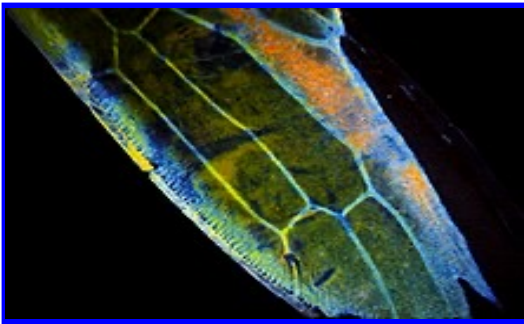
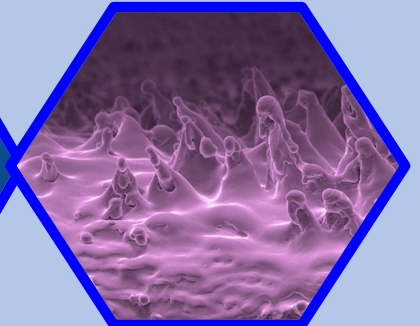
Synthetic



Polymers & Particles

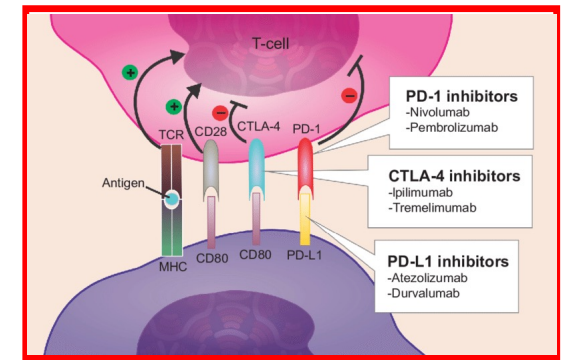
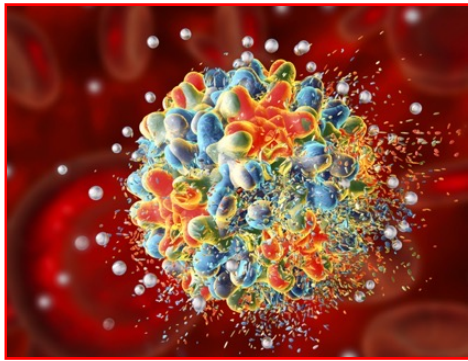


Surfaces



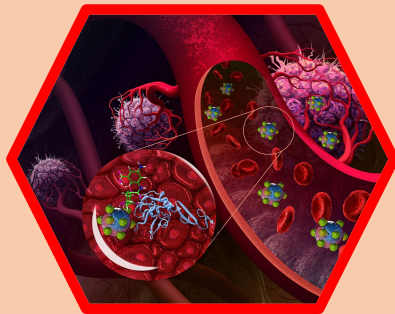
New targets

Current state of the art research examples

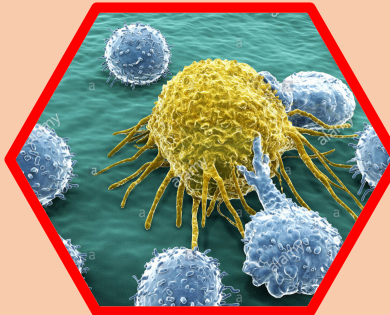


BLOCK 2: Applications

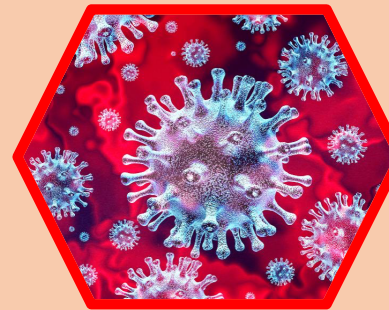
Drug delivery



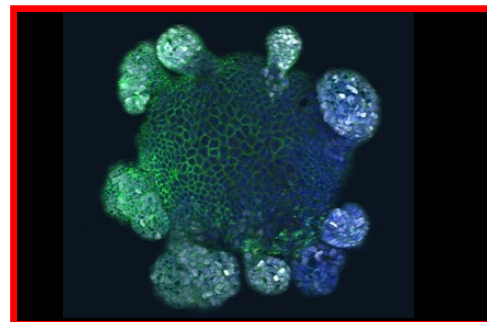
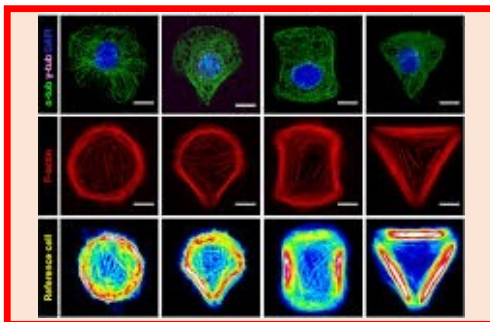
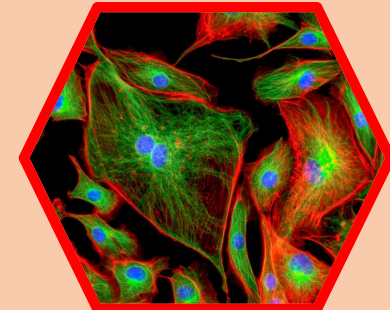
Cell adhesion



Immune engineering

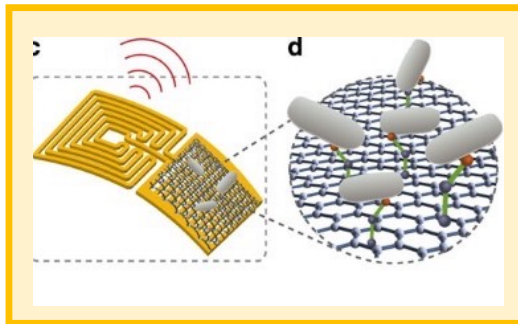
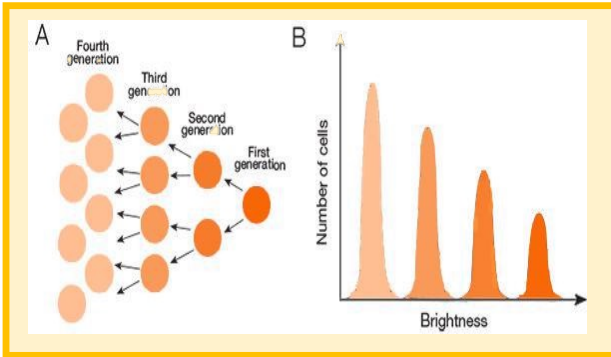


Tissue engineering



Applications and Regulations

How biomaterials are used and how useful they are...



Characterization

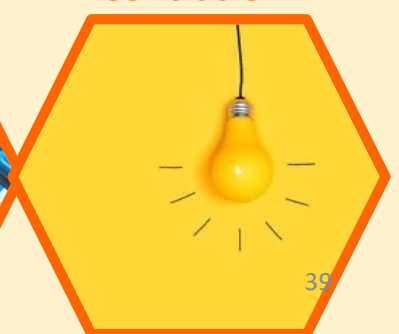
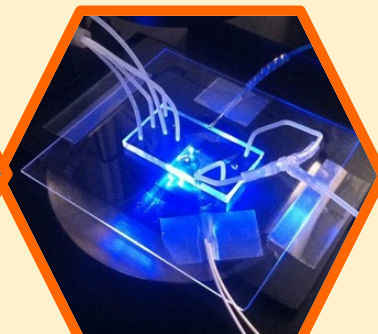
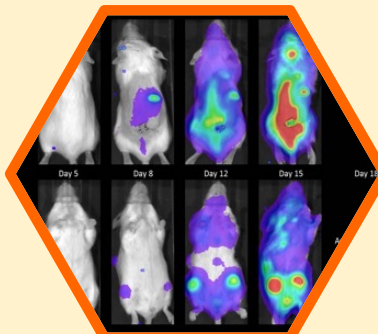
Sensors

Translation

Regulation

Conclusion

BLOCK 3:
Quantification



Conclusion

- Research in biomaterials is **extremely multidisciplinary**, any material can be a biomaterial, depending on its processing and function
- Natural and manmade materials offer us an enormously **rich 'toolbox'** that we can begin to use for developing sophisticated, multifunctional (smart) biomaterials and novel technologies.
- But: we need to understand both, the **engineering concepts** as well as the **fundamental biological processes** that control cell behavior, in order to harness it.



Which we will get a taste of in the lab!