Stimuli-responsive liquid crystal hydrogel implants by electrospinning technique

F. Pierini

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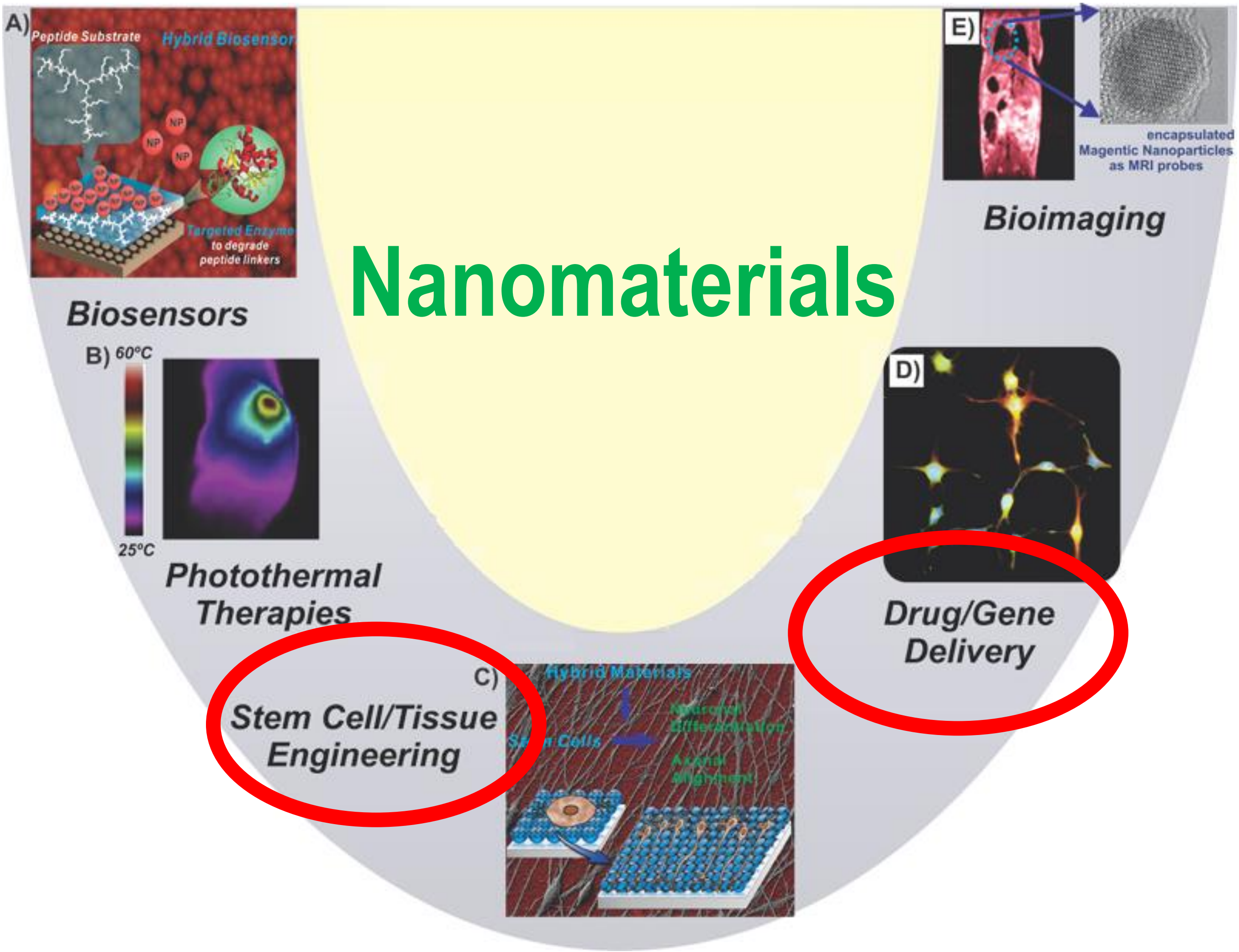
Institute of Fundamental Technological Research, Polish Academy of Sciences

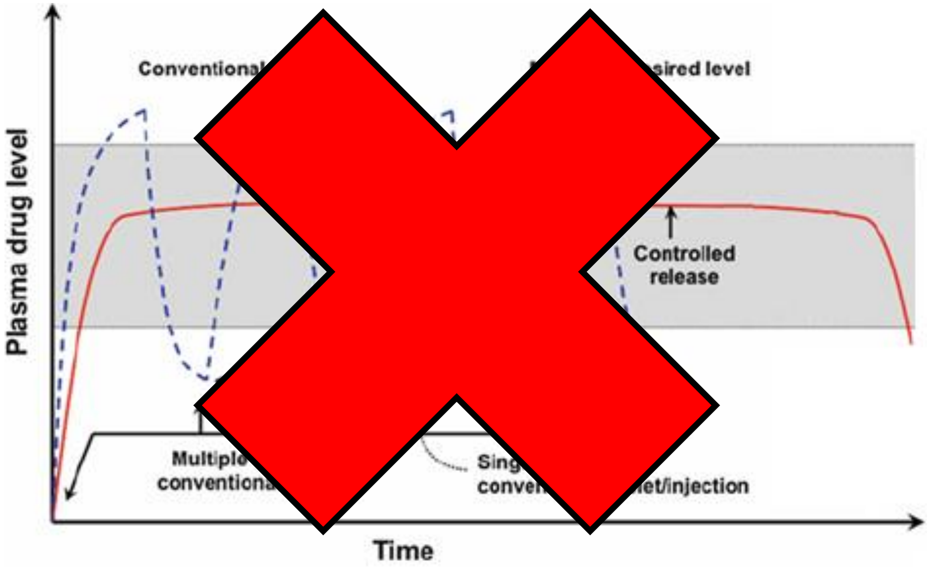
Biomedical applications of nanomaterials



Drug Delivery System Challanges

Targeted drug delivery: systems allow selective targeting of the drug to a specific tissue, organ or specific cells inside the body to achieve a targeted drug action.

Controlled release drug delivery: systems capable to mantain the adequate end desired release of drug over an extended period of time.



A drug-delivery system release the drug into the target and match the desired kinetics of the release.

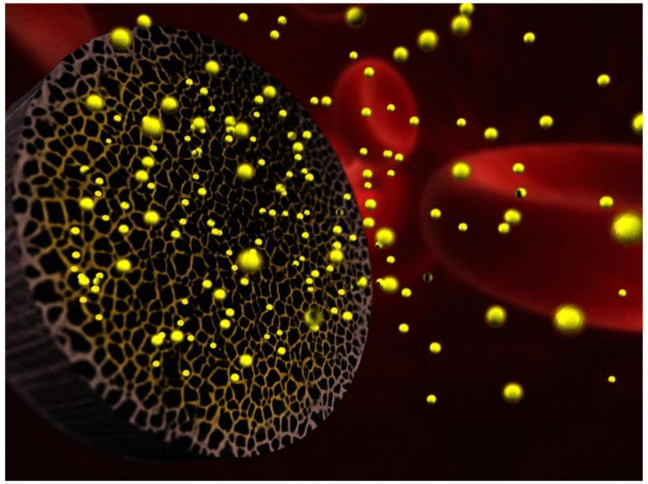
"Smart" Drug Delivery Systems

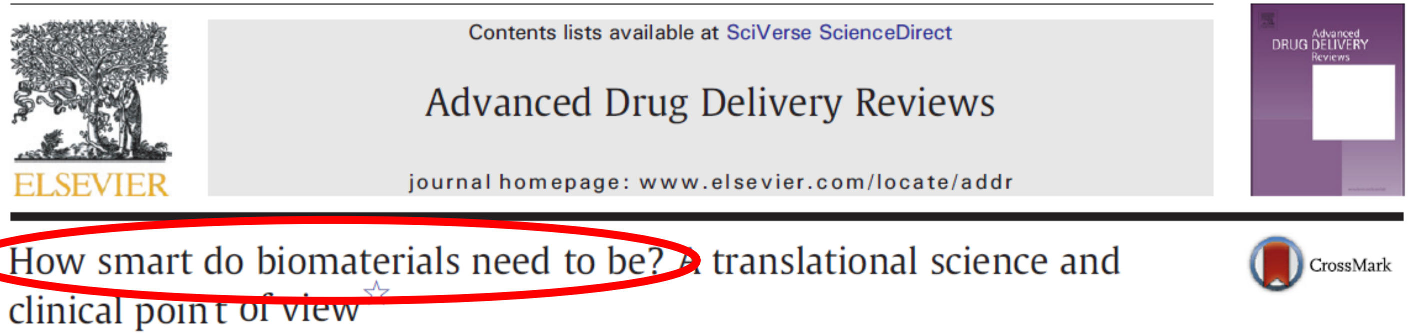
The future of drug delivery systems will involve smart systems.

These will address the issue of keeping the drug at the desired therapeutic level in the body thus avoiding frequent administration.

The ultimate goal is to administer drugs at the right time, at the right dose anywhere in the body with specificity and efficiency.

Systems use detection of external stimuli to prompt the release of drugs.




Contents lists available at SciVerse ScienceDirect

Advanced Drug Delivery Reviews

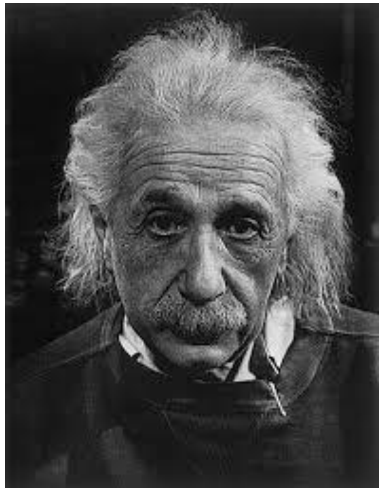
journal homepage: www.elsevier.com/locate/addr

How smart do biomaterials need to be? A translational science and clinical point of view

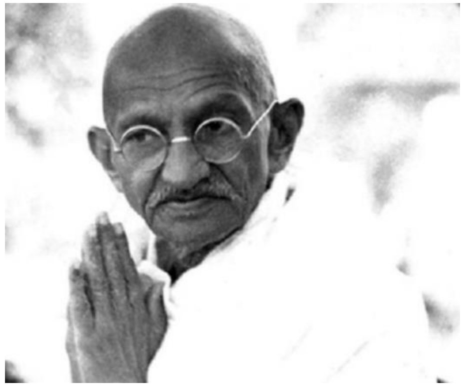
Smart/intelligent materials

Smart

'Intelligent' or 'Smart' materials may be defined as 'Those materials which sense any environmental change and respond to it in an optimal manner' (Roger et al.).



Intelligent



Wise materials?

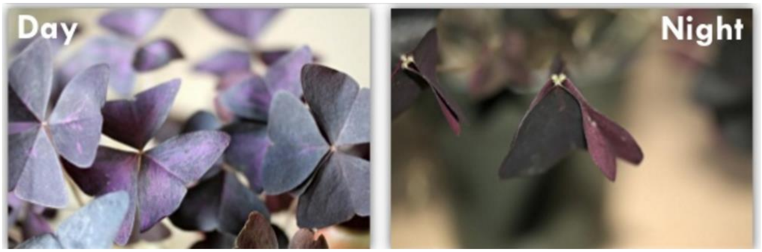
IPPT PAN

Smart Materials

A smart material can be described as a material that has a useful response to external stimuli.

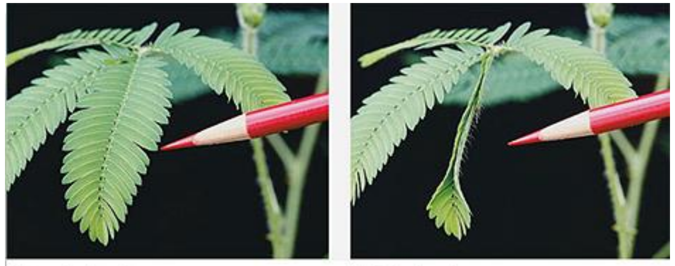
The change in the material can also be reversible, as a change in stimulus can bring the material back to its previous state.

Nature is Smart



Clover – Shamrock flower (Koniczyna)

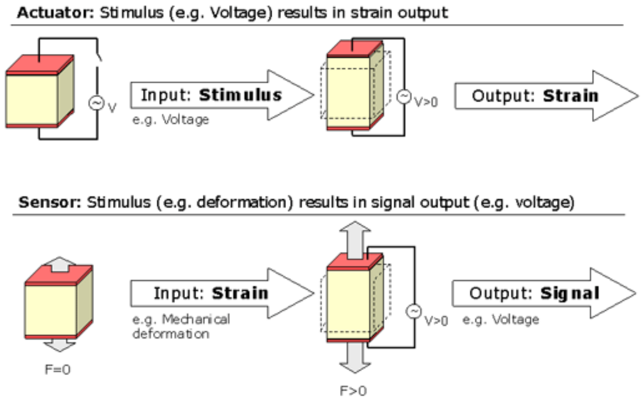
Tulips



(a) Unstimulated (b) Stimulated

Mimosa pudica (Mimoza wstydliwa)

Anthropogenic smart materials



Piezoelectric materials

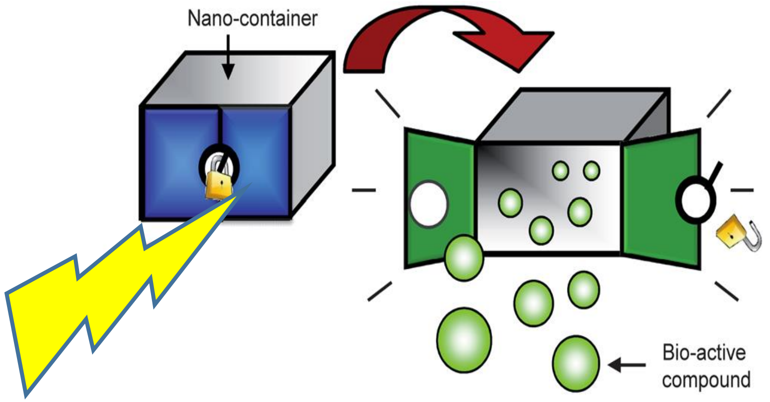
Photochromic lenses

Smart nanomaterials in medicine

The achievement of nanomaterials able to release therapeutic agents and change their physical properties in a controlled fashion and is a major challenge in the field of nanomedicine.

The full realization of their potential anticipates a bright future in life-science.

Drug delivery



[S.Sortino, *J. Mater. Chem.*, 2012, 22, 301]

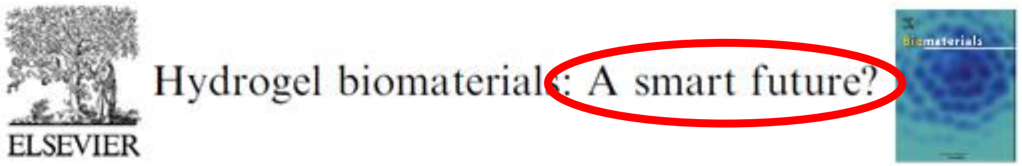
Stimulus can include:

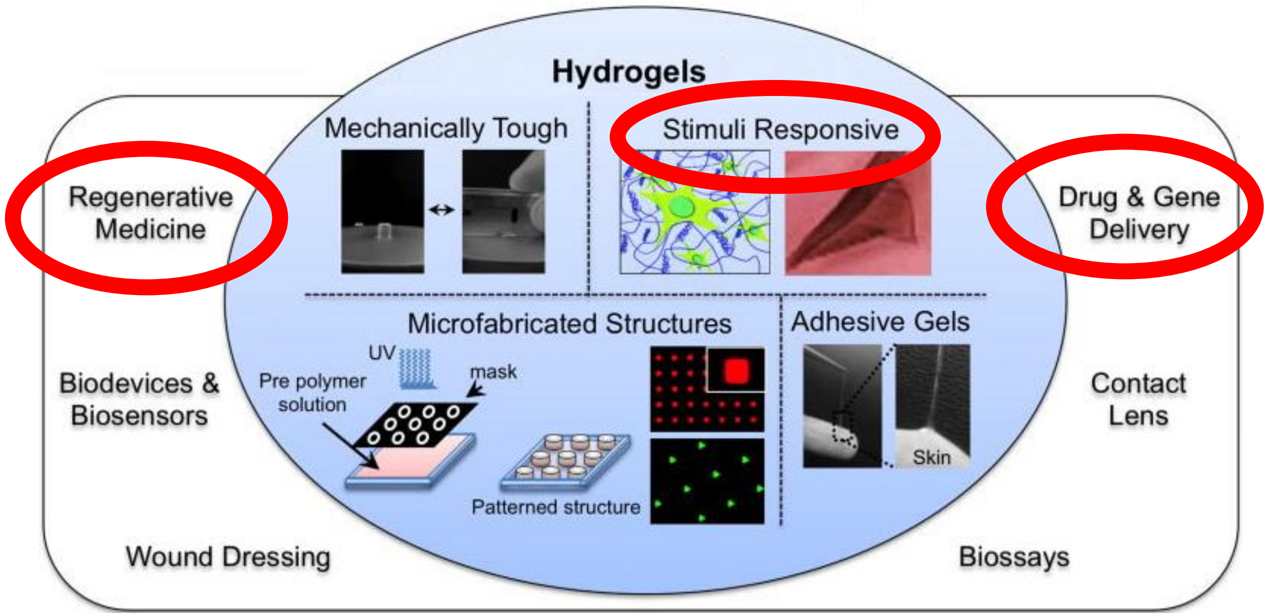
- Light
- Magnetic field
- pH
- Temperature
- Electrical field
- Mechanical stimuli

Tissue engineering

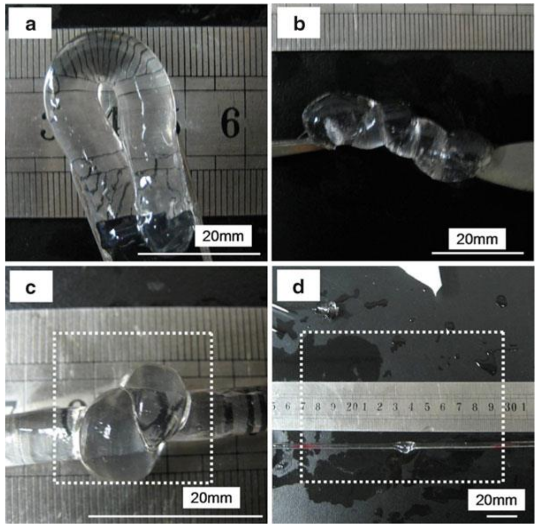
Hydrogels

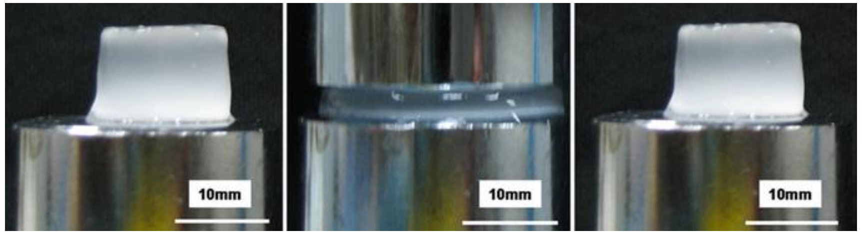
- Three dimensional networks of hydrophilic polymers that are insoluble but can swell in water.
- Solid-like and liquid-like properties in one material.
- Biocompatibility.
- Controlled drug release.

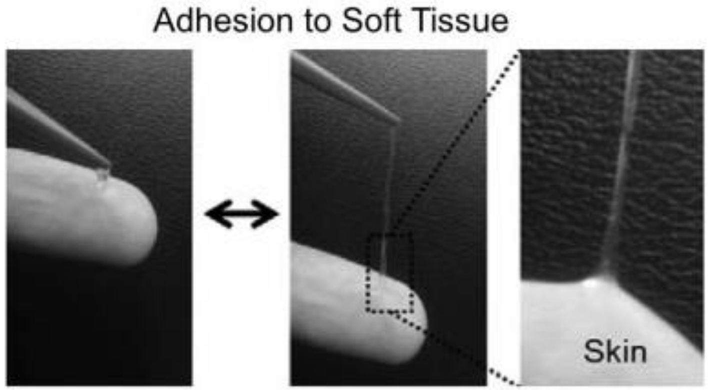


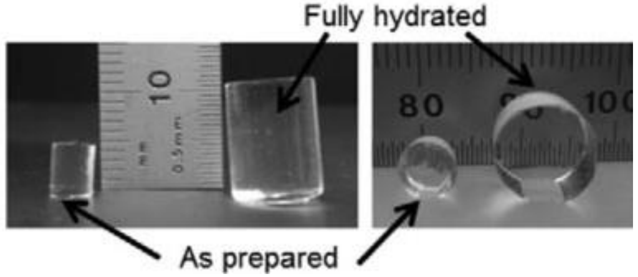


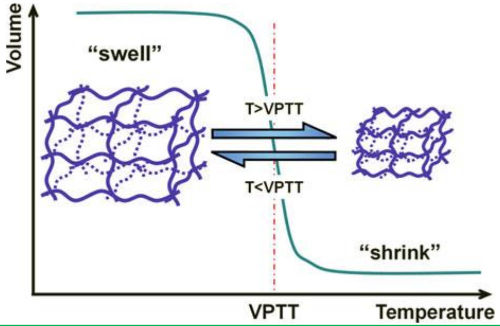
Hydrogel mechanical properties











Mechanical properties are influenced by:

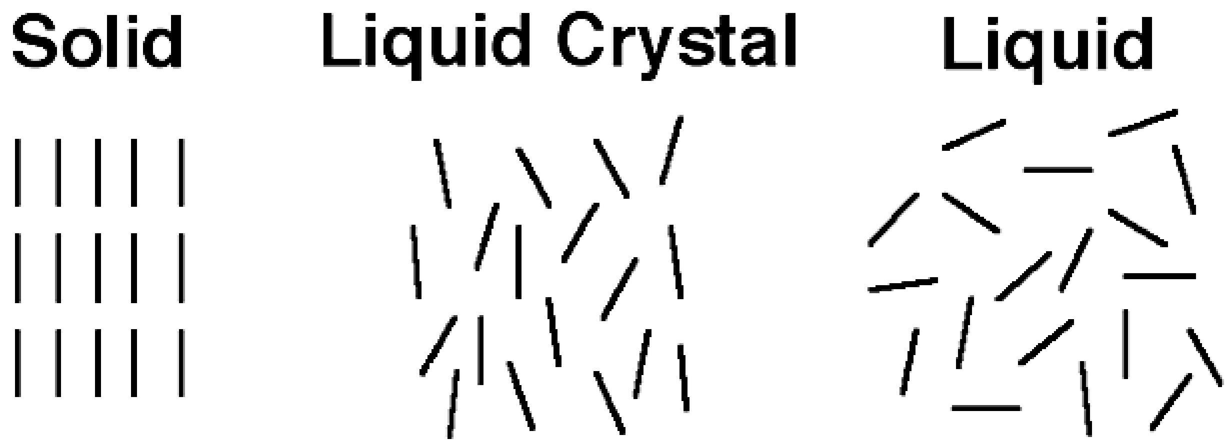
- Type and composition of monomers.
- Cross-linking.
- Environmental factors (e.g. temperature, pH and ionic strength).

[L.Y. Chu et al., *Smart Hydrogel Functional Materials*]

Liquid crystals

Freidrich Reinitzer discovers liquid crystals (1888).

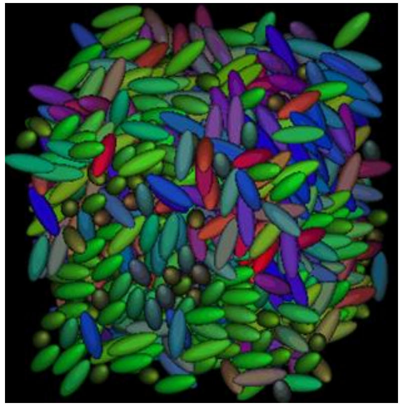
Crystals: 3D long range order Molecules with both orientation and positional orders.
Glasses: just short range order, positions of molecules statistically distributed.



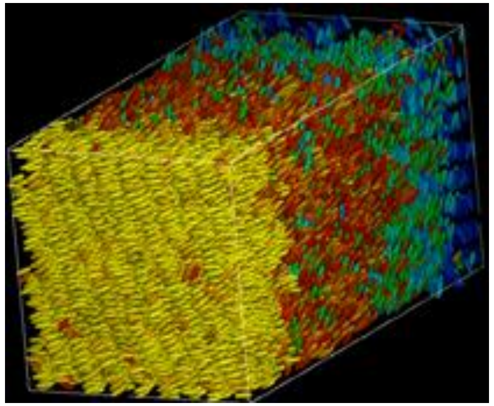
Molecules with no long orientation and positional orders.

A stable phase of matter characterized by anisotropic properties without the existence of a 3-dimensional crystal lattice.
It differs from liquid that there are still some orientational order possessed by the molecules.

Liquid crystals



Isotropic materials:
have uniform properties in all directions
(liquids and gases).



Anisotropic materials:
directionally dependent properties
(liquid crystals).

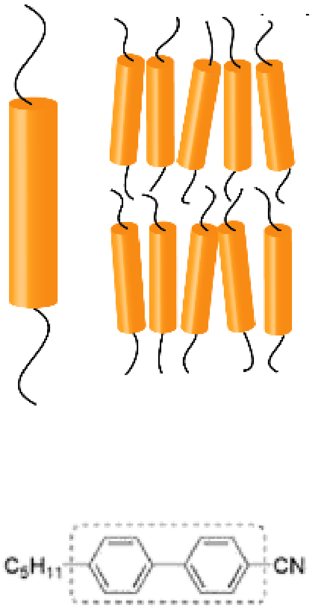
Molecule requirments

The molecule must be elongated in shape-length should be significantly greater than its width.

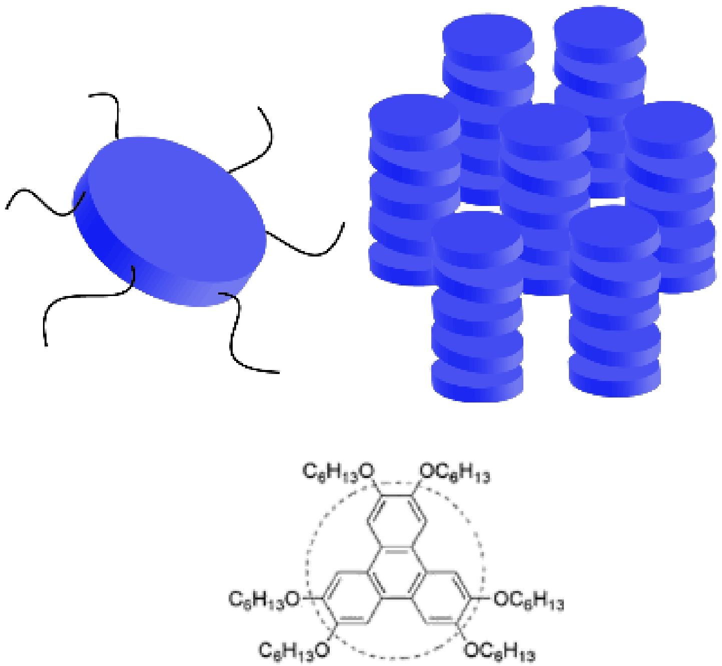
Molecule must have some rigidity in its central region.

The ends of the molecule are somewhat flexible.

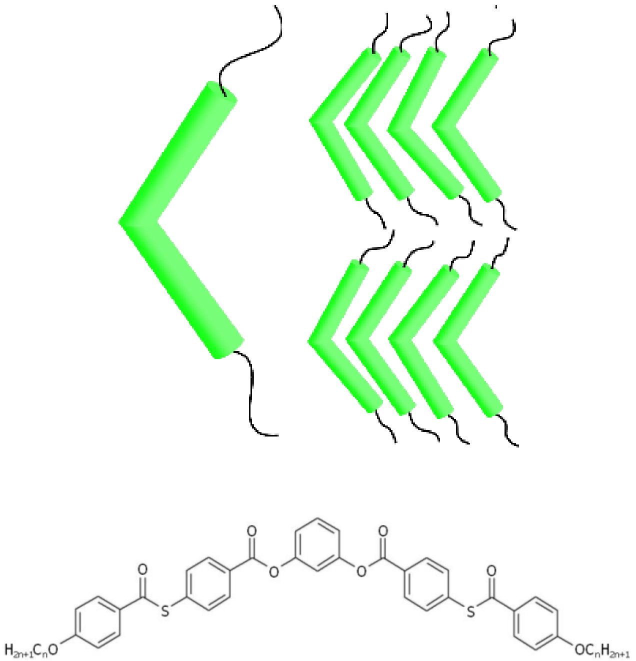
Morphological classification



Calamitic



Discotic



Banana shape

Mechanism classification

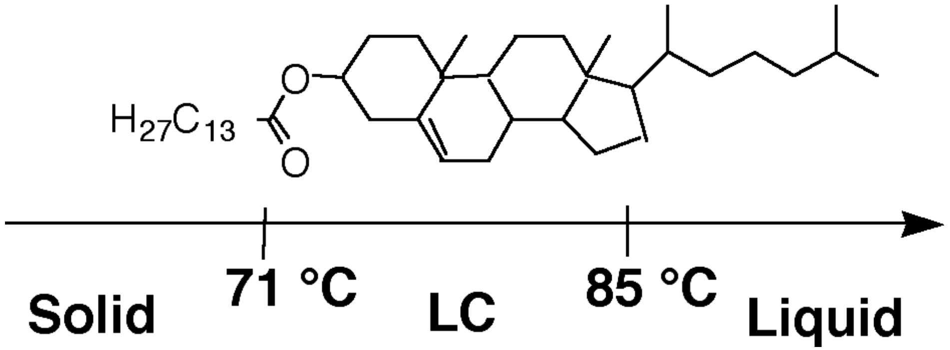
Thermotropic Liquid Crystals

LC phase transitions resulted from temperature changes.

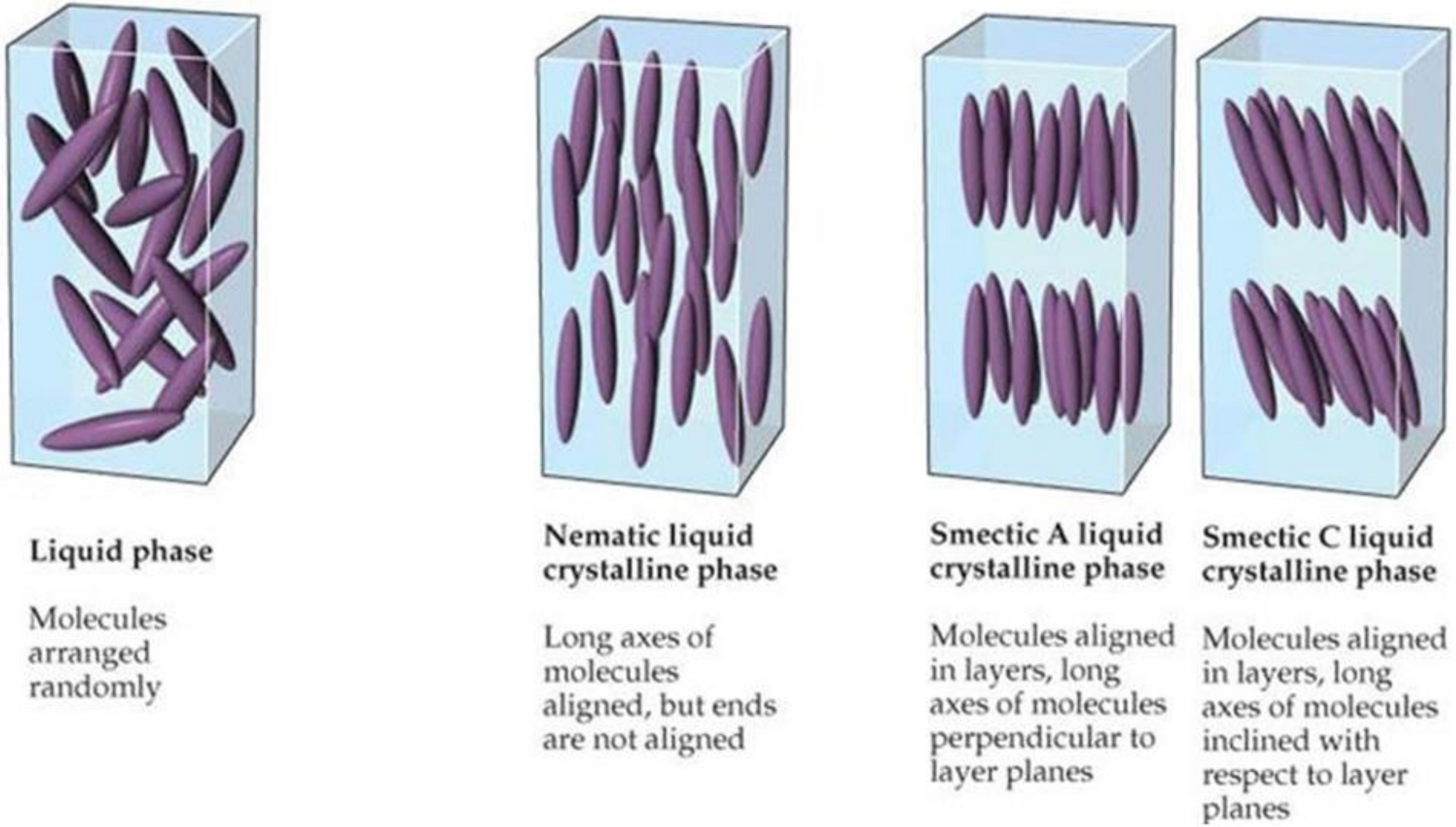
Lytropic Liquid Crystals

LC phase is formed when a molecule is dissolved in a suitable solvent (with specific concentration at a particular temperature).

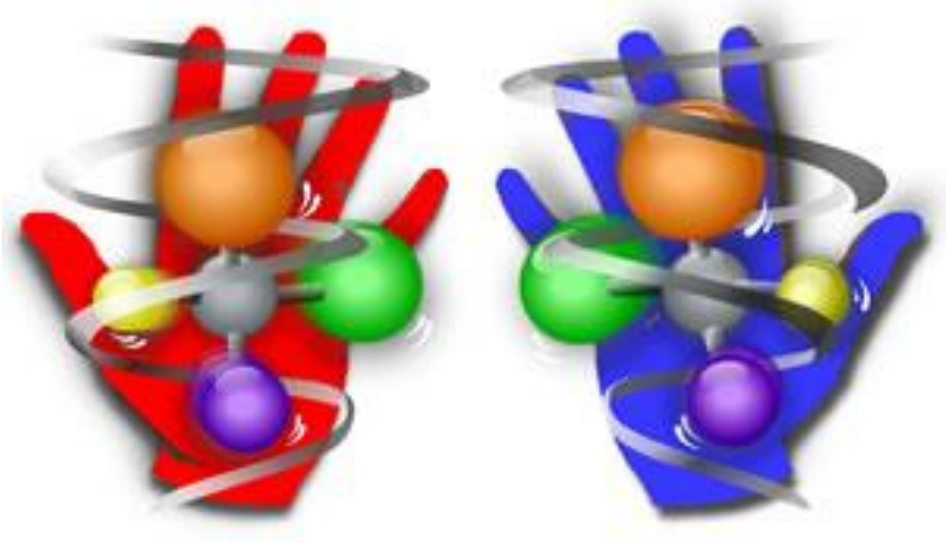
Cholesteryl Myristate



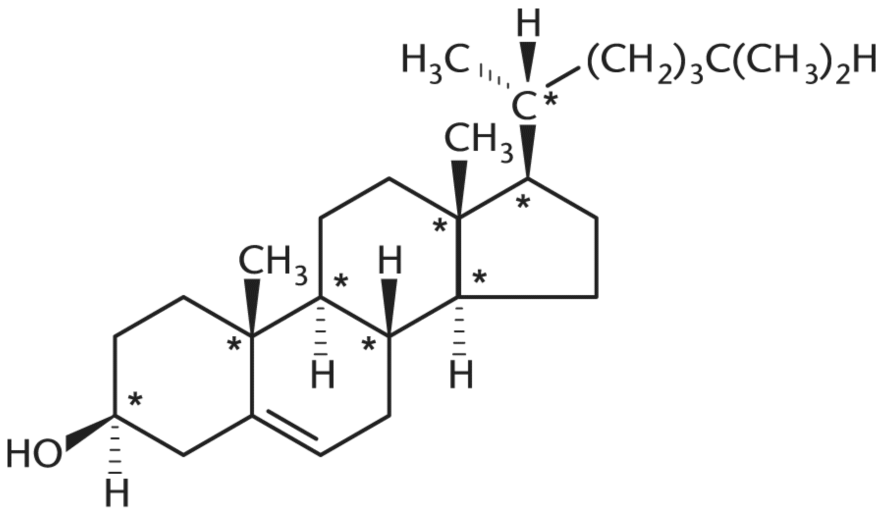
Liquid crystal phases (mesophases)



Chiral Nematic Phase (Cholesteric Liquid Crystal)



A chiral molecule is a type of molecule that has a non-superposable mirror image.

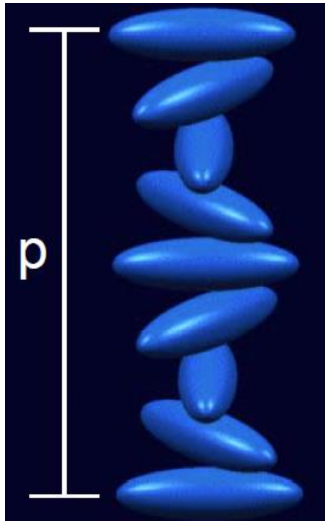


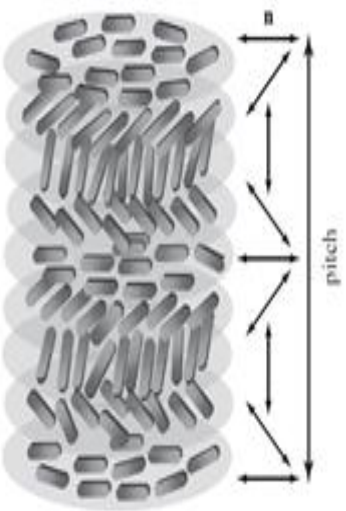
The feature that is most often the cause of chirality in molecules is the presence of an asymmetric sp^3 carbon atom.

Chiral Nematic Phase (Cholesteric Liquid Crystal)

Molecules with intermolecular forces that favor alignment between molecules at a slight angle to one another.

The director is not fixed in space as in a nematic phase, it rotates throughout the sample.





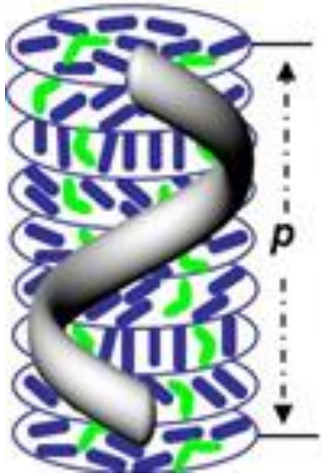
Spatial diposition

Calamitic

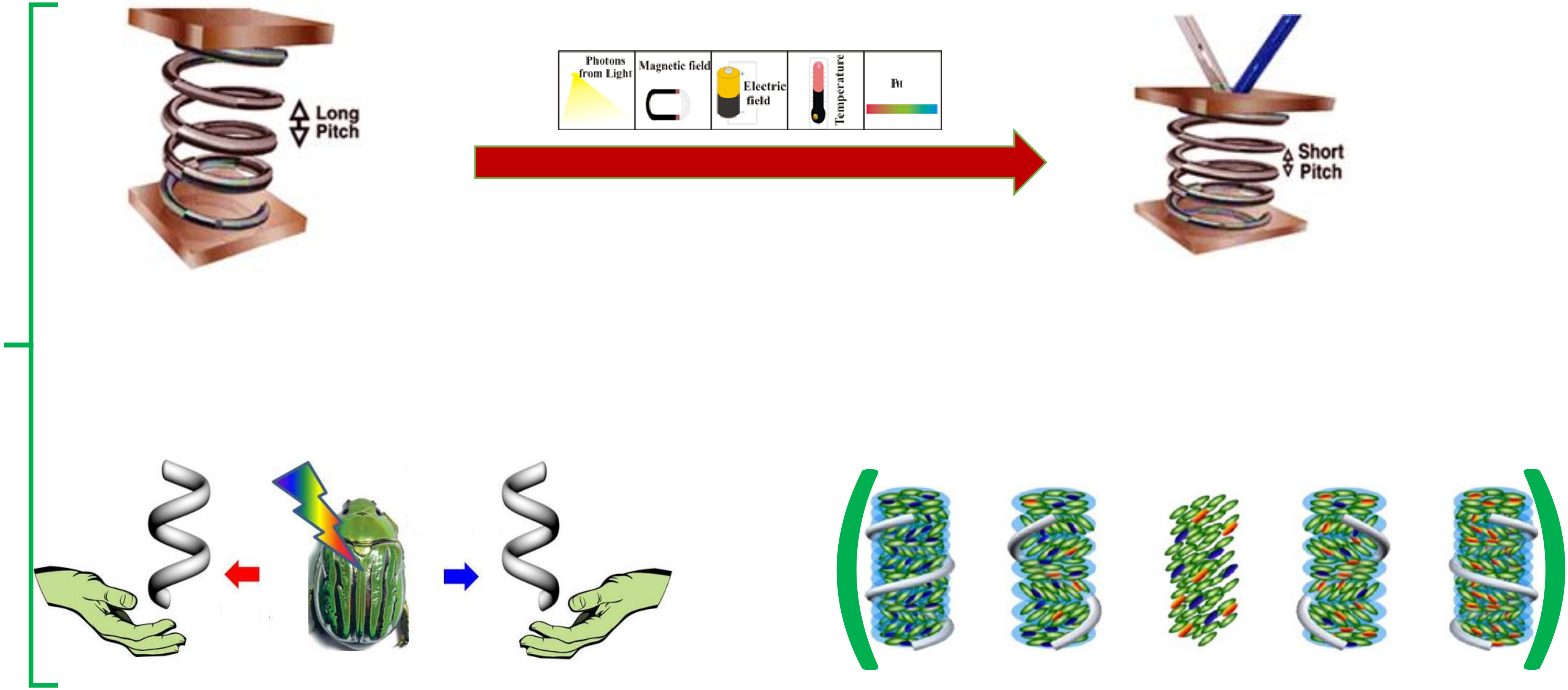
Discotic

[Lagerwall et al., *Curr. Appl. Phys.*, 2012, 12, 1387]

Liquid crystals as stimuli-responsive materials



Helical structure



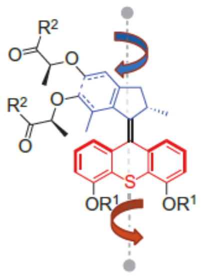
[H.K. Bisoyi et al., *Angew. Chem. Int. Ed.*, 2016, 55, 2994]

The seed of the project

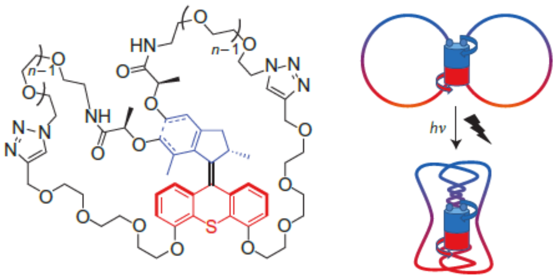
nature nanotechnology LETTERS
PUBLISHED ONLINE: 19 JANUARY 2015 | DOI: 10.1038/NNANO.2014.315

Macroscopic contraction of a gel induced by the integrated motion of light-driven molecular motors

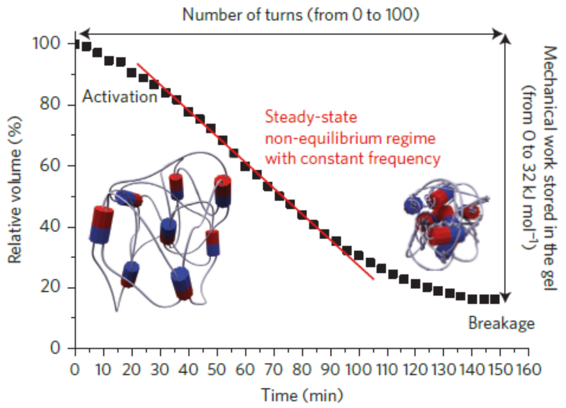
Q.Li, G.Fuks, E. Moulin, M.Maaloum, M.Rawiso, I. Kulic, J.T.Foy and N.Giuseppone



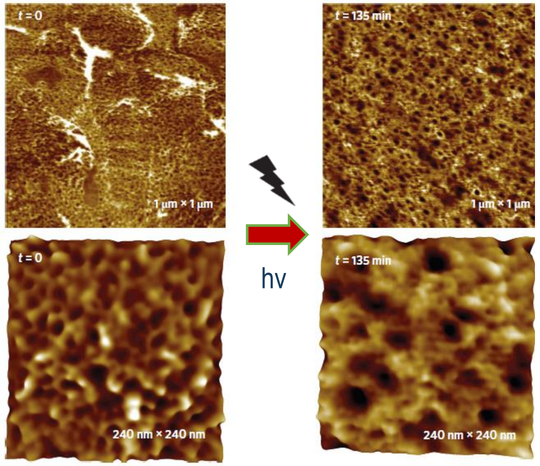
Molecular motor



Molecular motor gel



Nanoscale



Tunability

Morphology
(shape, dimension, porosity)

Mechanical properties
(stiffness)

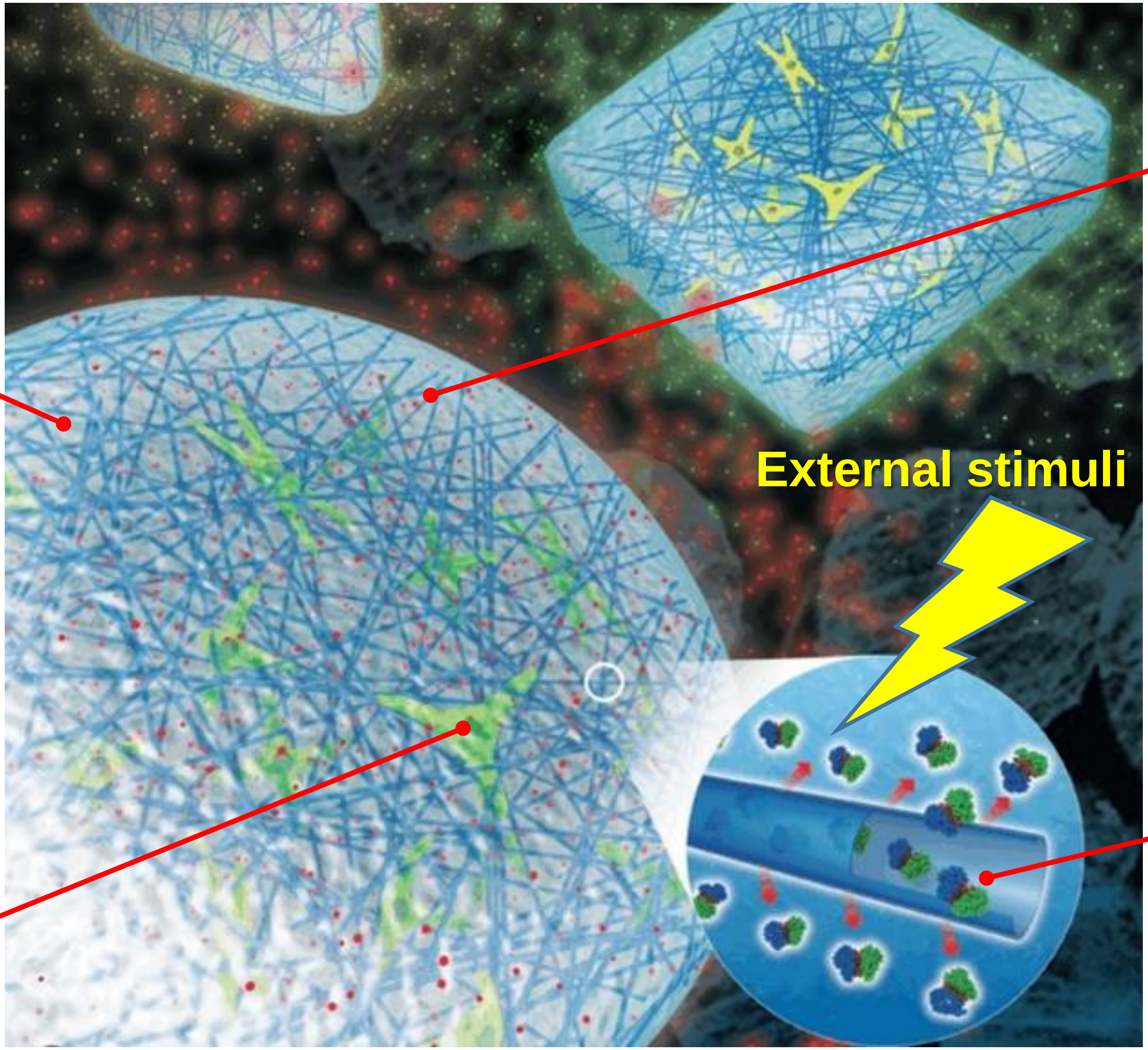
Surface properties
(surface area)

Macroscale

The final material

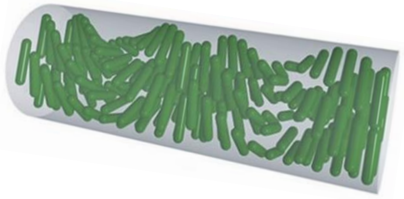
Soft polymer (hydrogel)

Biocompatible



Nanostructurated (electrospinning)

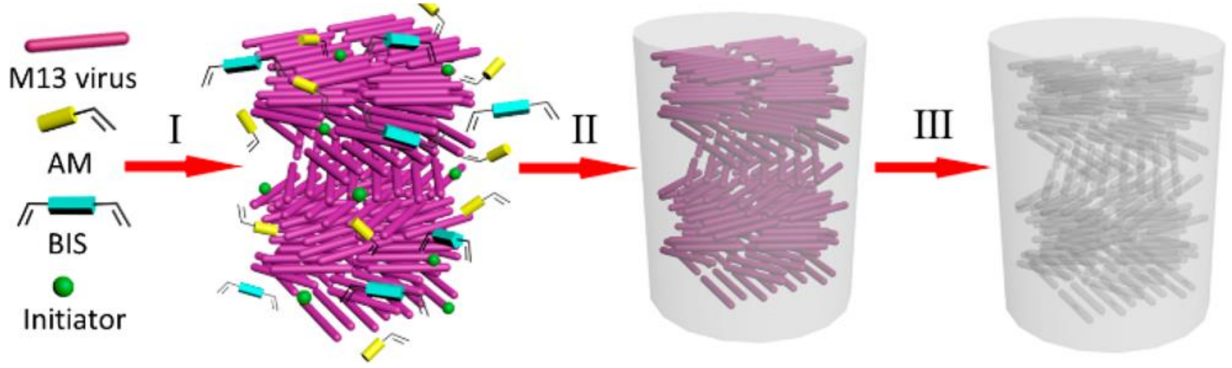
Smart drug delivery system (liquid crystals)

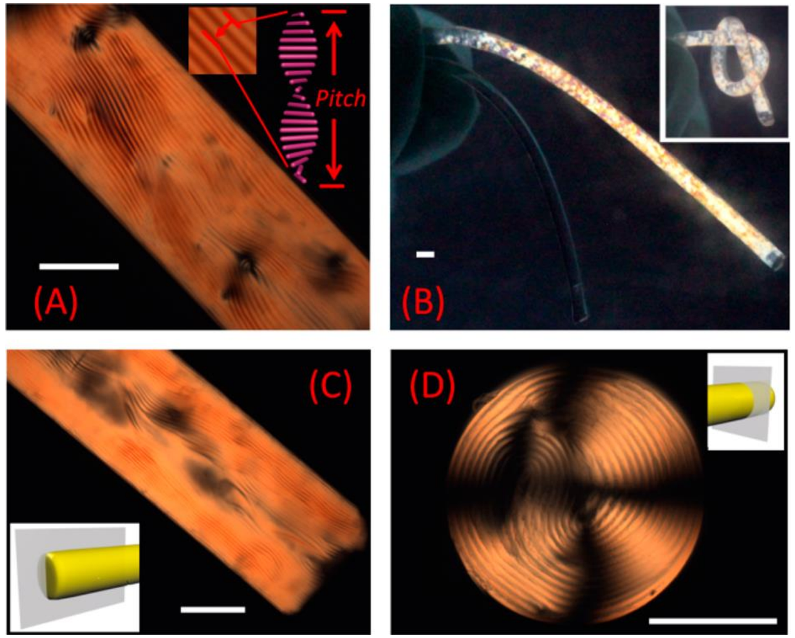


Macrohydrogel with chiral nematic phase

ACS Macro Letters
Letter
pubs.acs.org/macroletters

Pure Anisotropic Hydrogel with an Inherent Chiral Internal Structure Based on the Chiral Nematic Liquid Crystal Phase of Rodlike Viruses



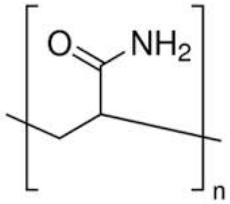


Project plan

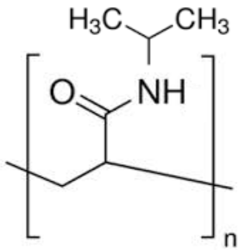
1. Development of the coaxial electrospinning technique.
2. Optimization of the shell removing process.
3. Structural and mechanical characterization of the developed hydrogels.
4. Analysis of the drug release properties.
5. Study of the nanostructure hydrogels external stimuli-response.
6. Evaluation of the hydrogel biocompatibility.

Hydrogels

Polyacrylamide



Poly(N-isopropylacrylamide)

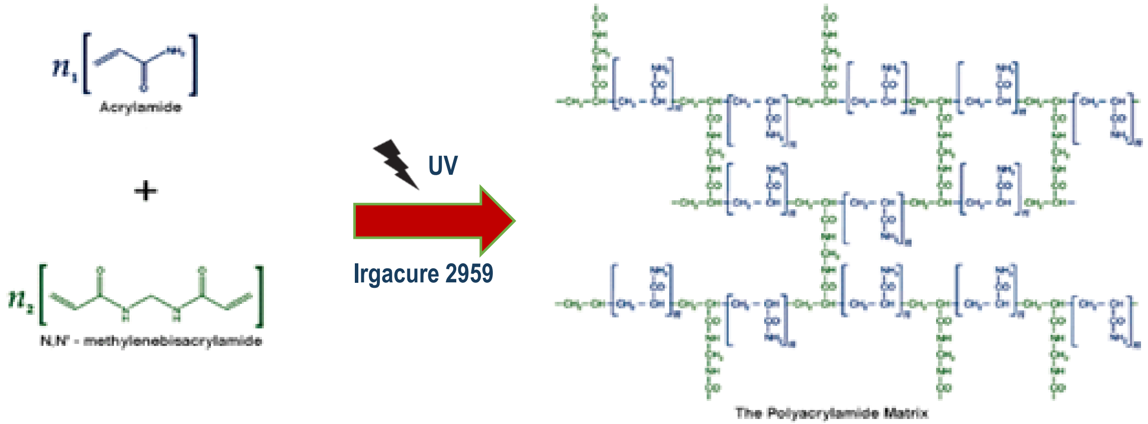


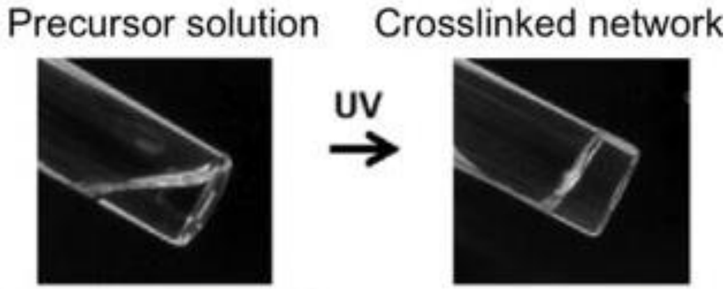
Matrerials:
Acrylamide (Aam)
N,N'-methylene bisacrylamide (BIS-Aam)
Fluorescein-o-acrylate (FITC-acr)
Irgacure 2959

Samples:
- EA1 mass ratio of AAm/BIS-AAm (w/w): 37.5:1
- EA2 mass ratio of AAm/BIS-AAm (w/w): 20:1
- EA3 mass ratio of AAm/BIS-AAm (w/w): 4:1

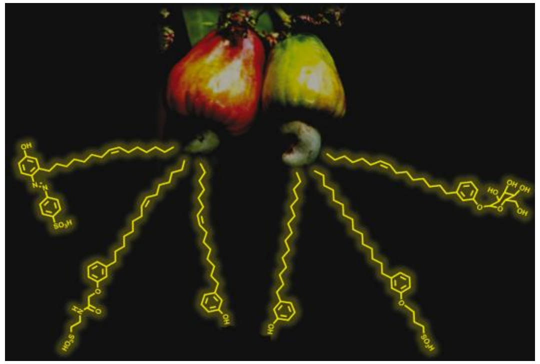
Matrerials:
N,N-isopropylacrylamide (NIPAAm),
N,N'-methylene bisacrylamide (BIS-Aam)
Fluorescein-o-acrylate (FITC-acr)
Irgacure 2959

Samples:
- EN1 mass ratio of NIPAAm/BIS-AAm (w/w): 37.5:1
- EN2 mass ratio of NIPAAm/BIS-AAm (w/w): 20:1
- EN3 mass ratio of NIPAAm/BIS-AAm (w/w): 4:1





Cholesteric Liquid Crystal



Cashew

Nanercz zachodni [edytuj]

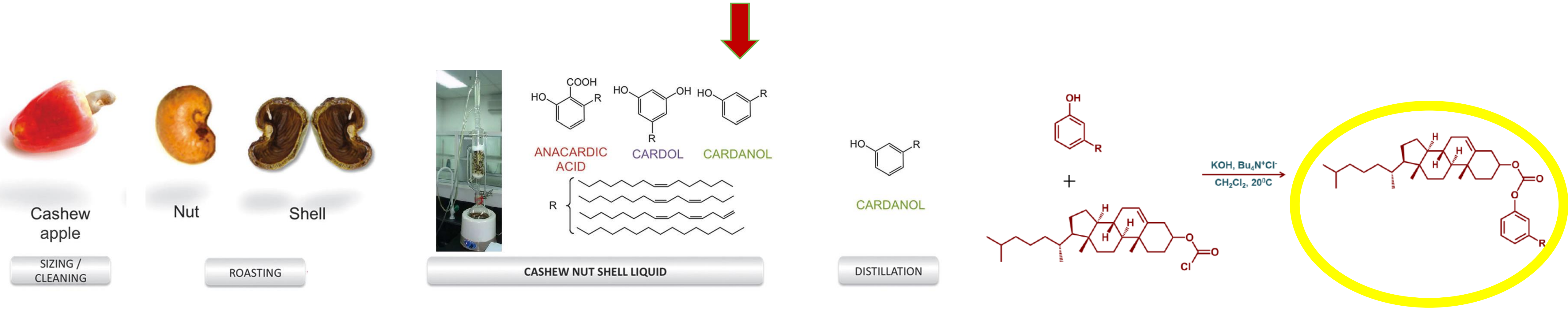
Nanercz zachodni (*Anacardium occidentale* L.), zwany też nerkowcem zachodnim, orzechem nanerczowym albo orzechem cashew — gatunek drzewa z rodziny nanerczowatych, bliski krewniak mango. Pochodzi z obszarów tropikalnych Ameryki Południowej[2]. Jest uprawiany w większości krajów obszaru tropikalnego.

ChemPubSoc Europe — ChemistrySELECT Full Papers

Organic & Supramolecular Chemistry

Tweaking the Organization of Liquid Crystallinity and Molecular Gelation in Cholesterol Tagged Cardanol by Self-Assembly

Neethu K. Sadanandhan, Sarojam Sivakala, and Sudha J. Devaki*[a]

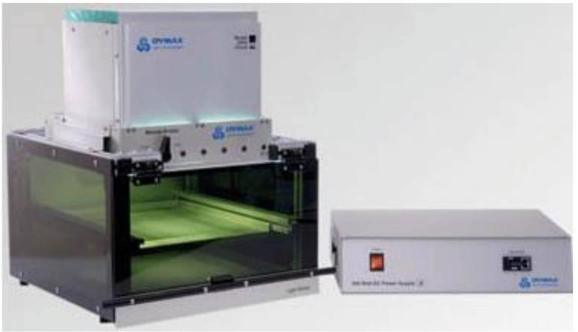


Coaxial electrospinning

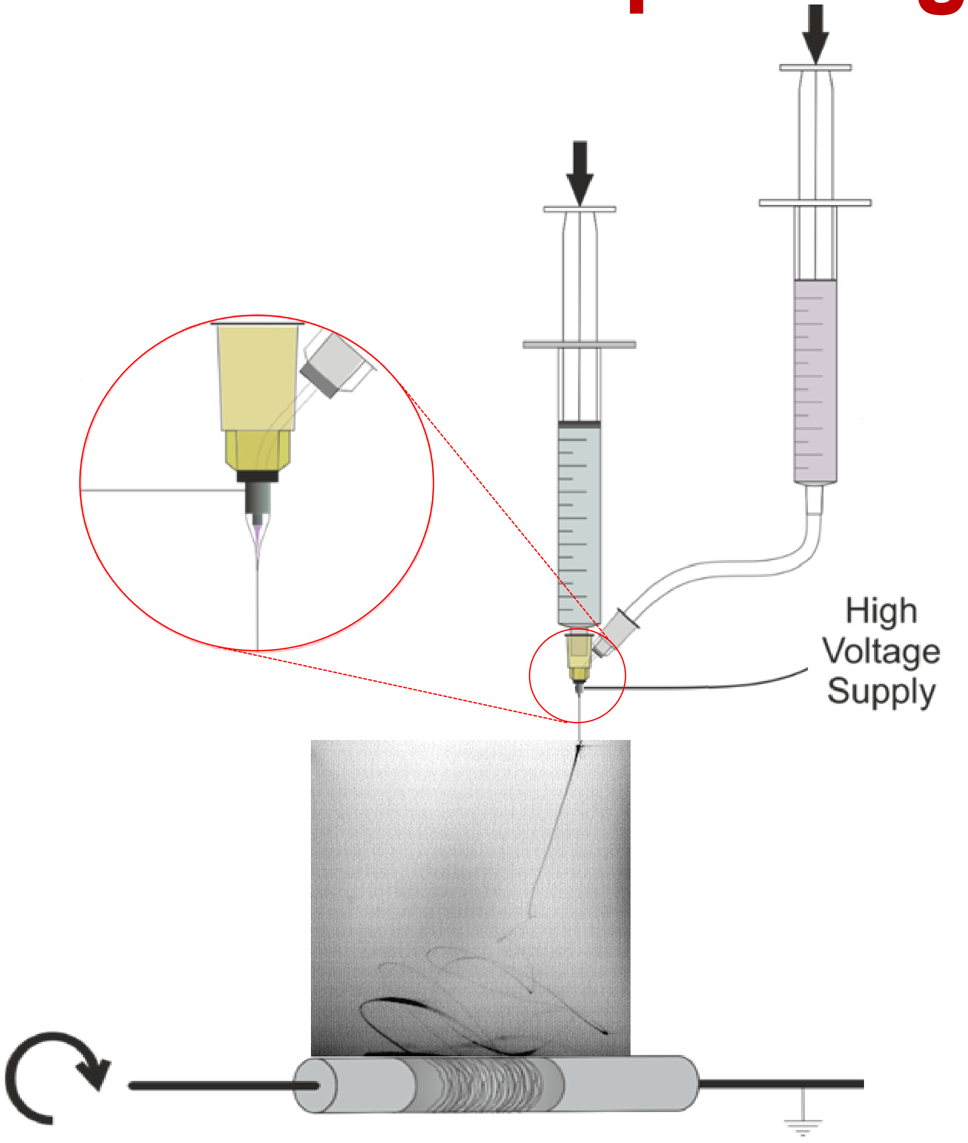
Electrospinning

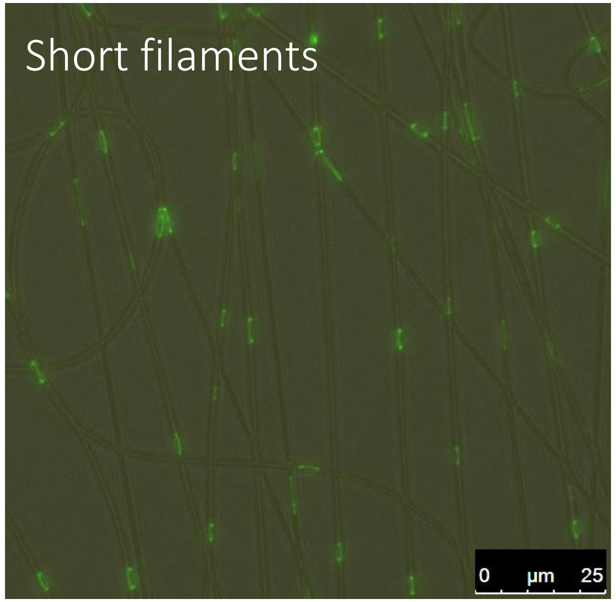
Core:
Hydrogel
Shell:
Poly(L-lactide-co-caprolactone) (PLCL) (70% L-lactyde and 30% caprolactone unit)

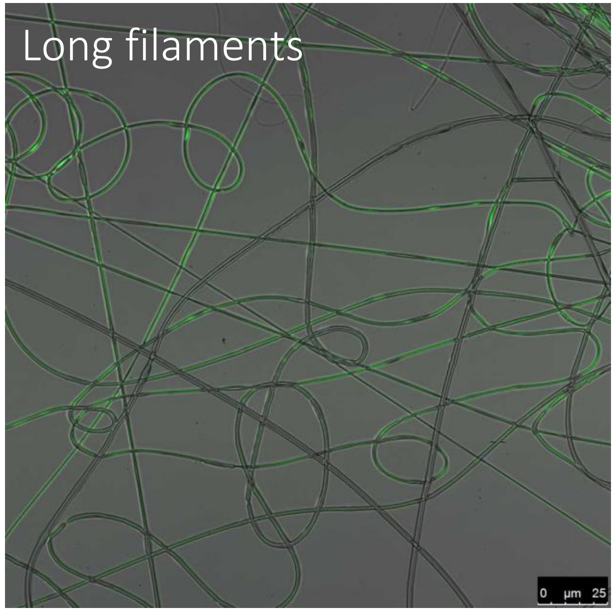
Post-electrospinning UV irradiation



Controlled temperature (< 10 ºC)



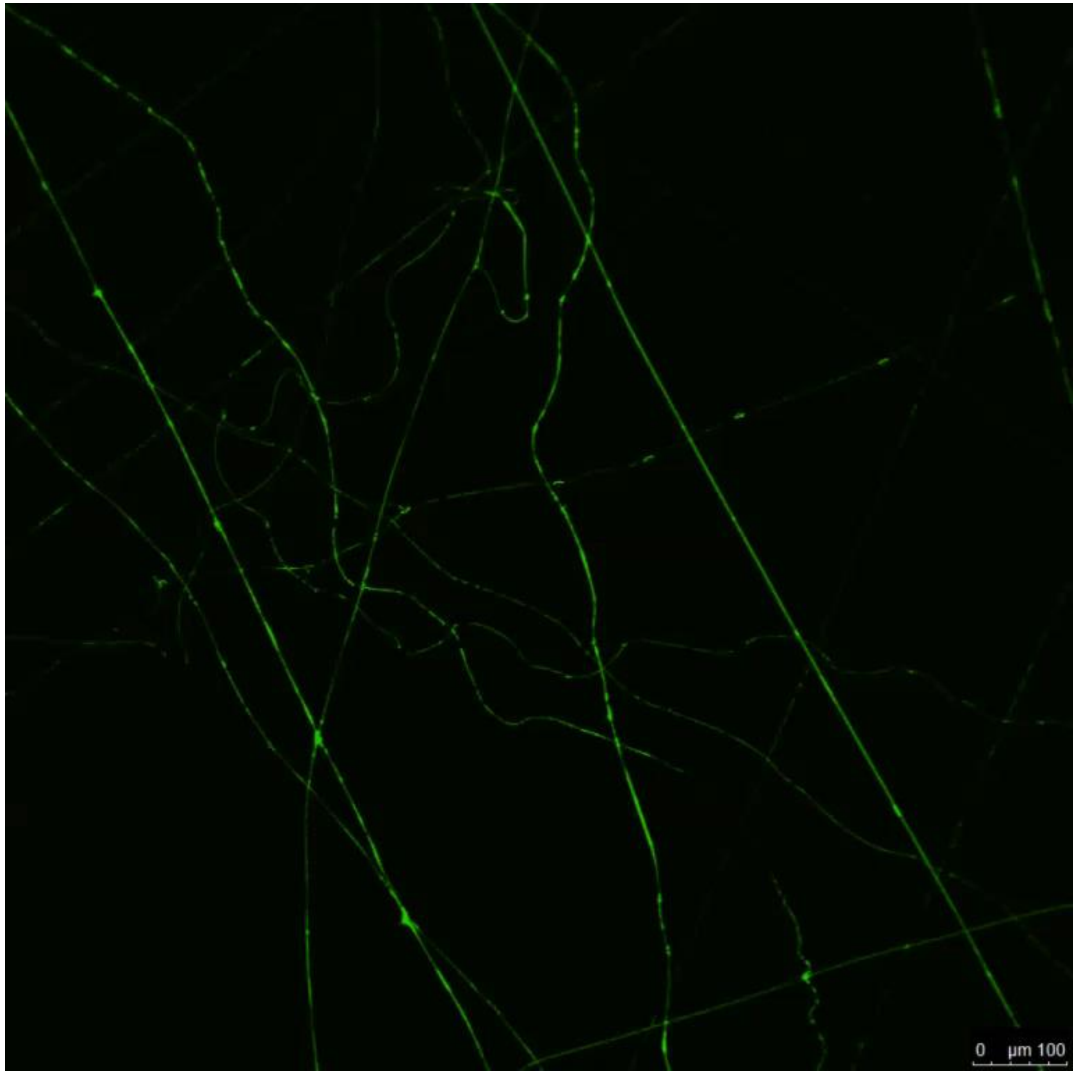




Coaxial electrospinning

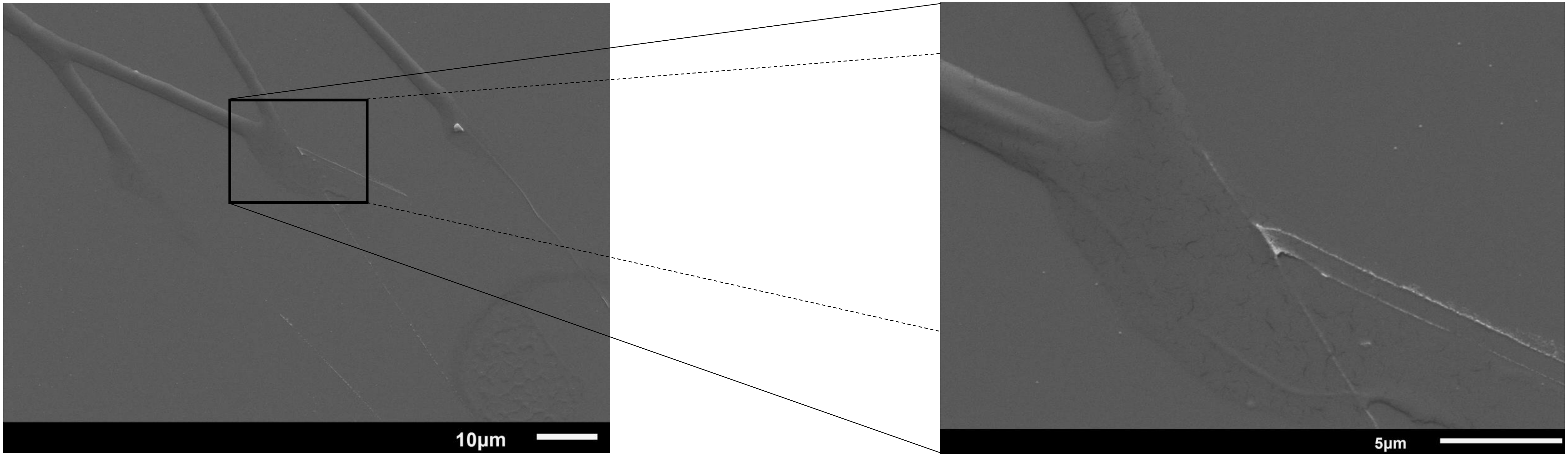
- Liquid Crystal (solubility, pitch length and toxicity).
- Covalent bonding of liquid crystal into the polymer matrix.
- Nanofibers (dimension).
- Hydrogels (stiffness).

Shell removing process



Sheel dissolution and filaments extraction in N,N-dimethylformamide (DMF)

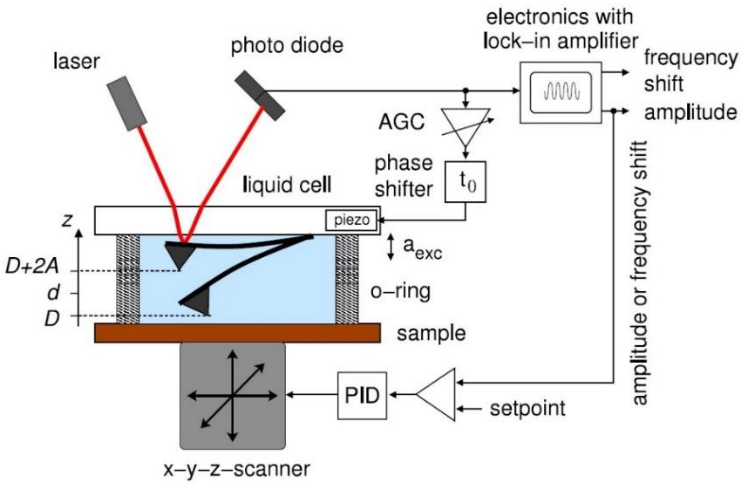
Shell removing process

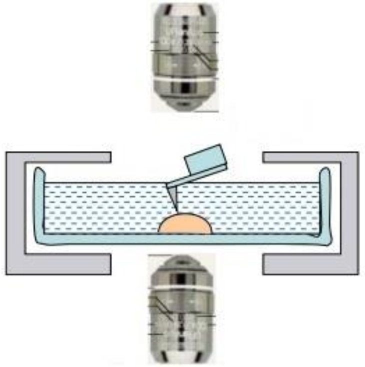


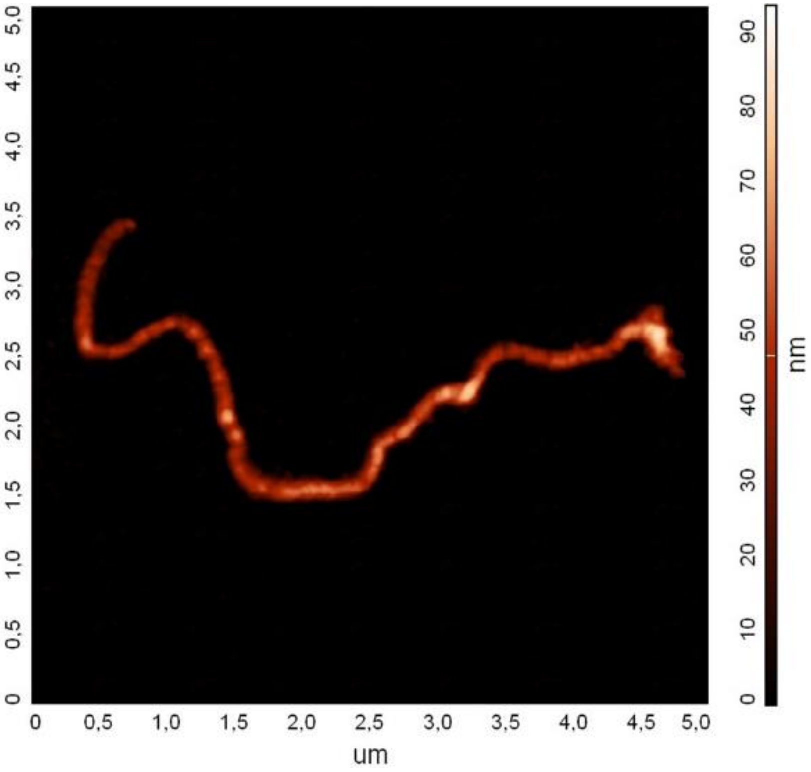
- Organic solvent (concentration)
- Method

Structural and mechanical characterization

AFM in liquid

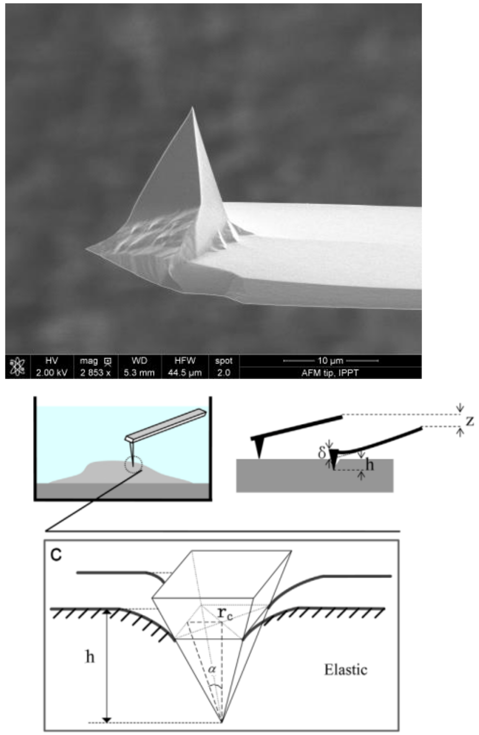


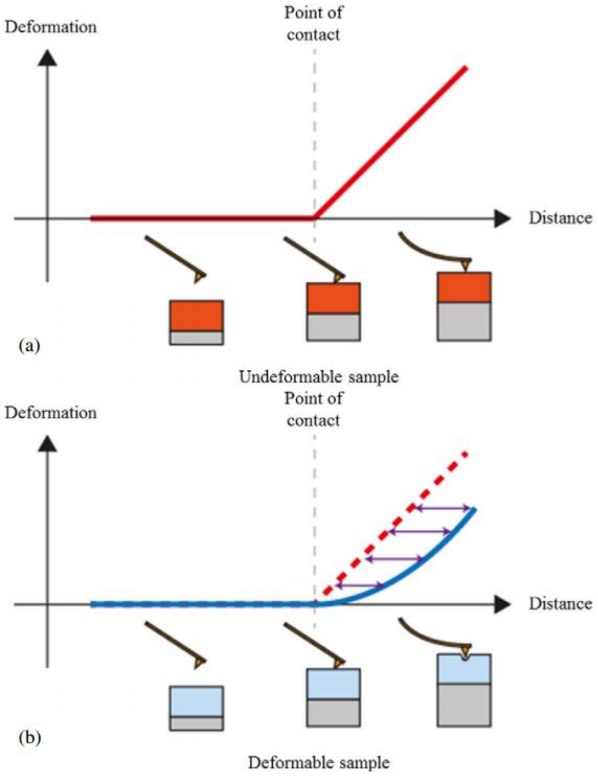




Structural and mechanical characterization

AFM nanoindentation in liquid





Hertz Model

$$E = F \cdot \frac{3}{4} \cdot \frac{1-\nu^2}{\sqrt{r} \cdot \delta^{\frac{3}{2}}}$$

where F is the applied force, E is elastic modulus of the sample, v is the Poisson`s ratio of the sample, δ is the indentation depth and r is the equivalent radius for a spherical indenter.

XRD analysis

Analysis of the drug release properties

- Nerve growth factor (NGF)

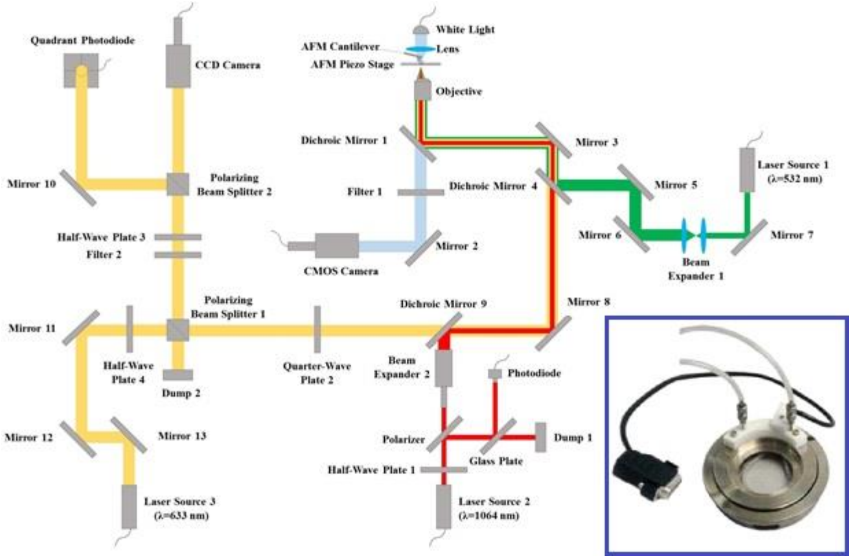
- Insulin-like growth factors (IFG)

Drug selection (applications, dimension, solubility, conentration, stability and detectability)

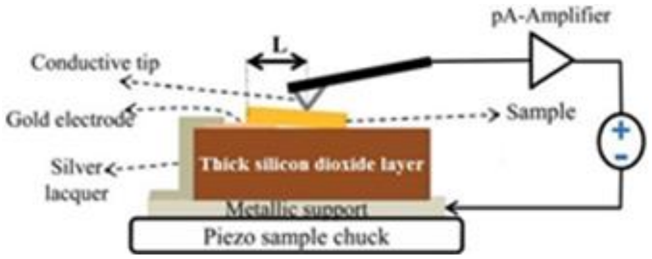
Hydrogel external stimuli-response

Given stimuli

- Light (532 nm, 633 nm and 1064 nm wavelengths).
- Temperature (37 ± 20 °C).
- pH (7,4 ± 2).



- Electrical Field (0 - 50 V).



Detected changes

- Morphology
- Mechanical properties
- Drug release

Hydrogel biocompatibility

Cells

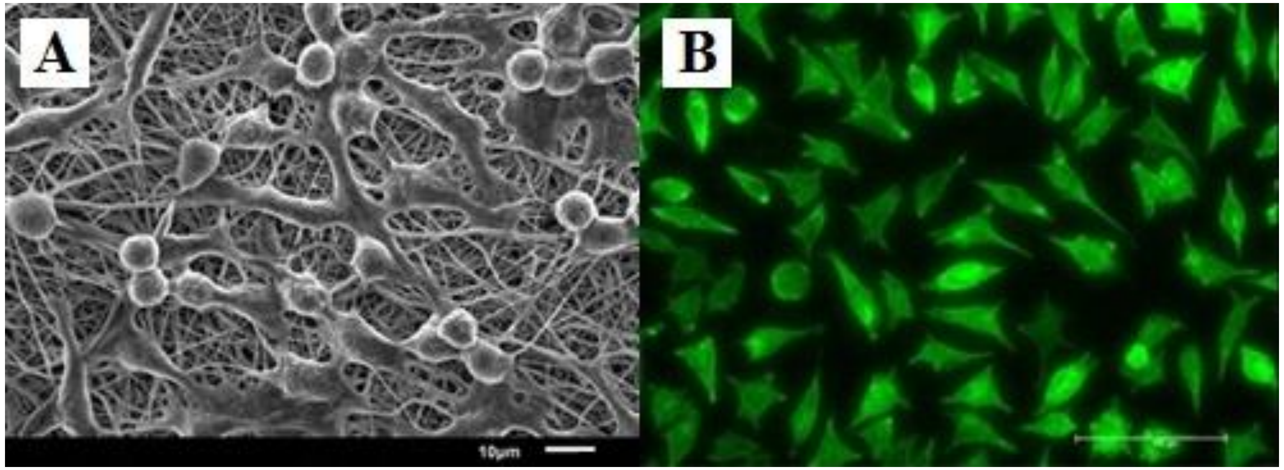
- Glial cells
- Neural cells

Neural tissue regeneration.

- Chondrocytes cells (cartilage regeneration).

⚠ **Cells selection**

Techniques



SEM and confocal microscopy