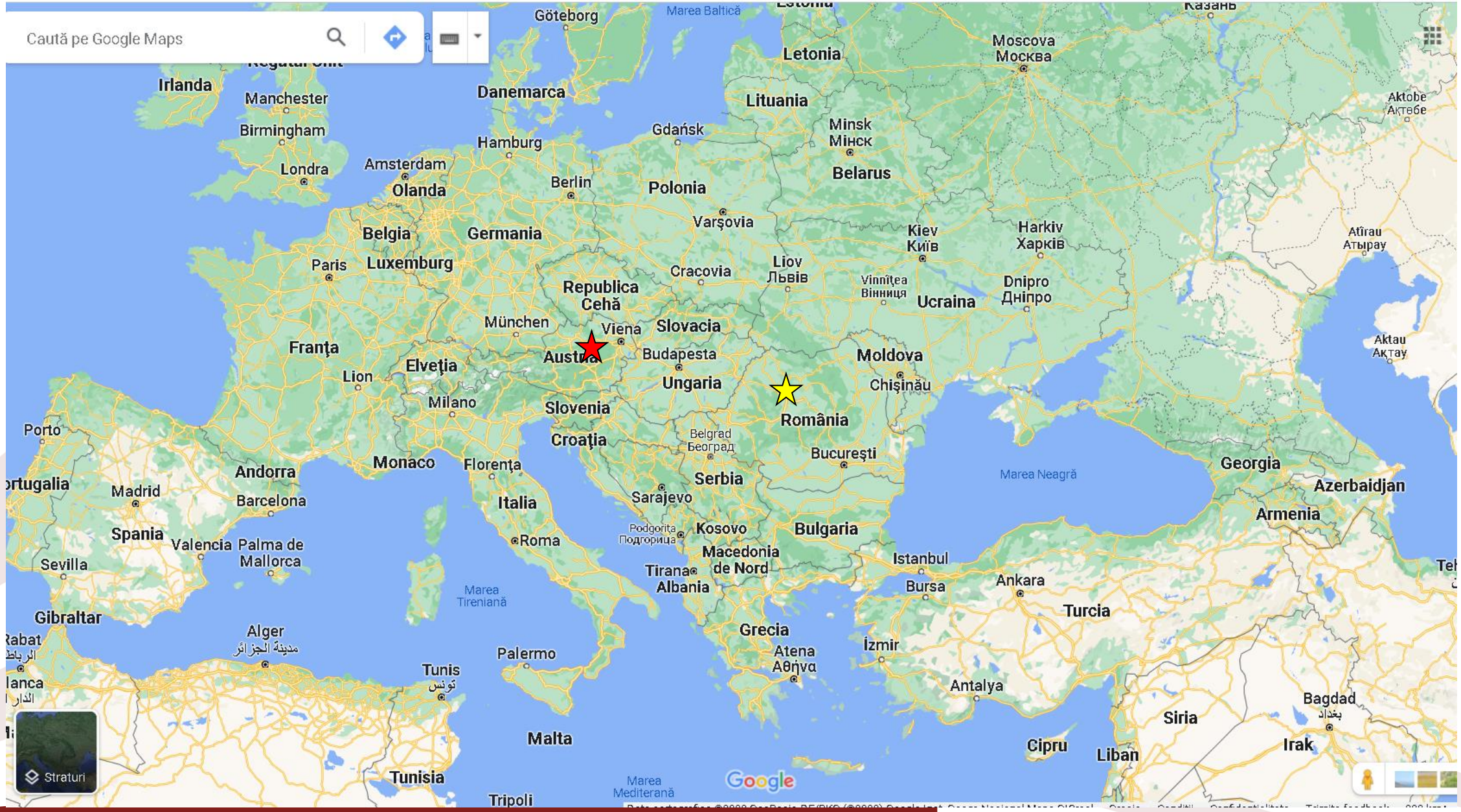


Micro/Nanostructured Systems for Biomolecular Sensing, Imaging and Therapeutic Applications

Sanda Boca-Farcau, *Molecular and Biomolecular*

Physics Department, INCDTIM, Romania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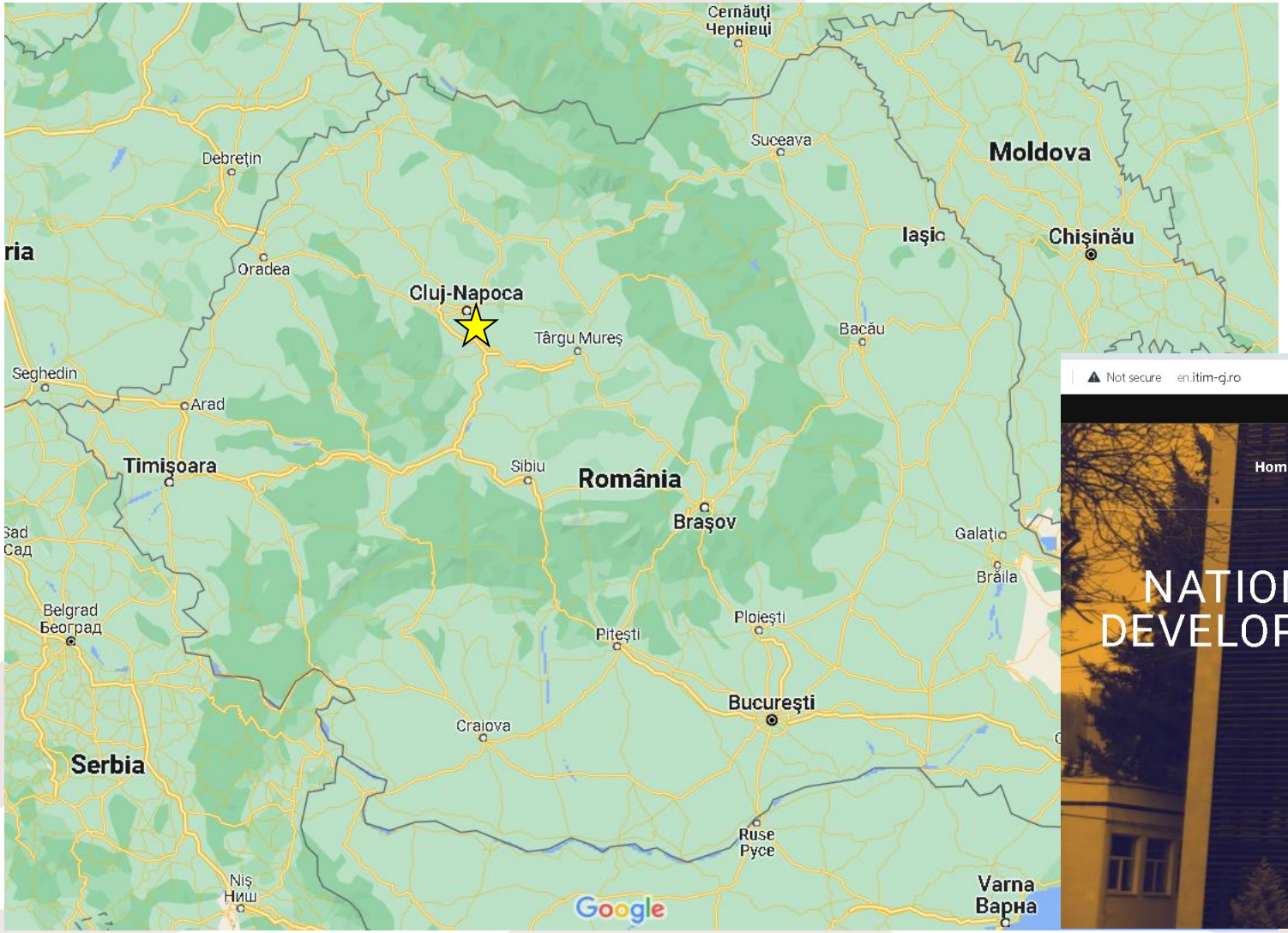
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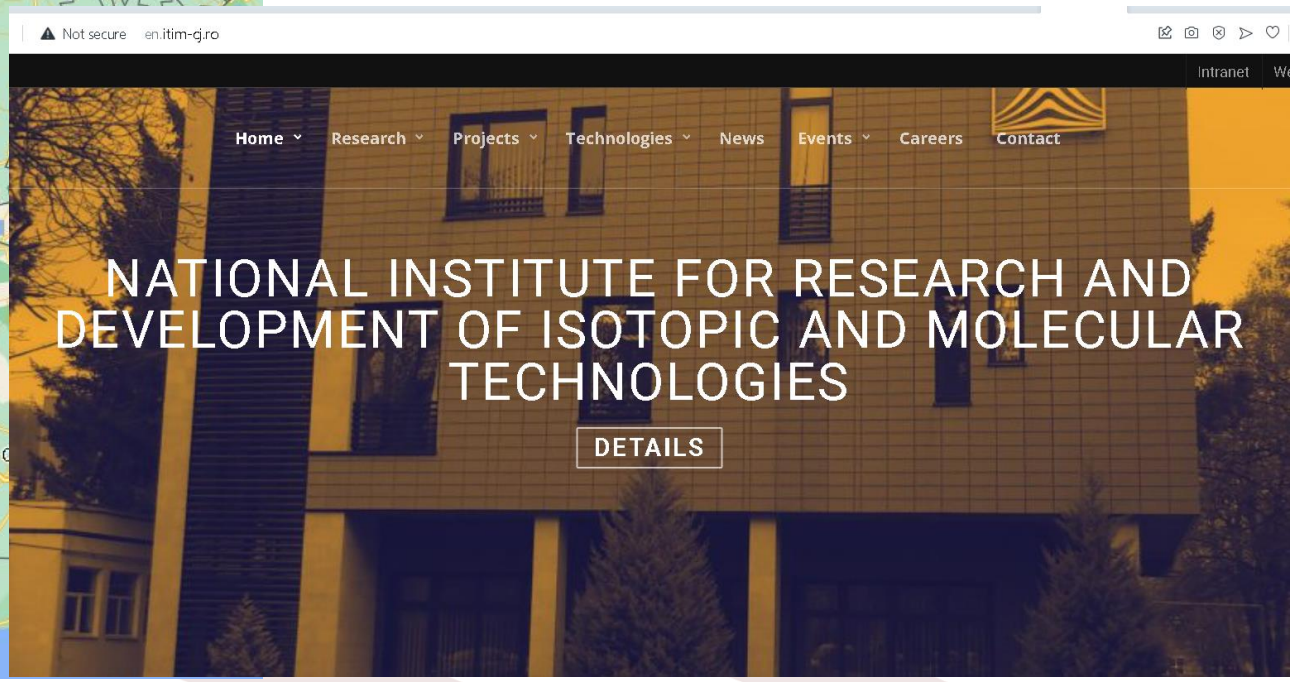
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NATIONAL INSTITUTE FOR RESEARCH AND DEVELOPMENT OF ISOTOPIC AND MOLECULAR TECHNOLOGIES
DETAILS

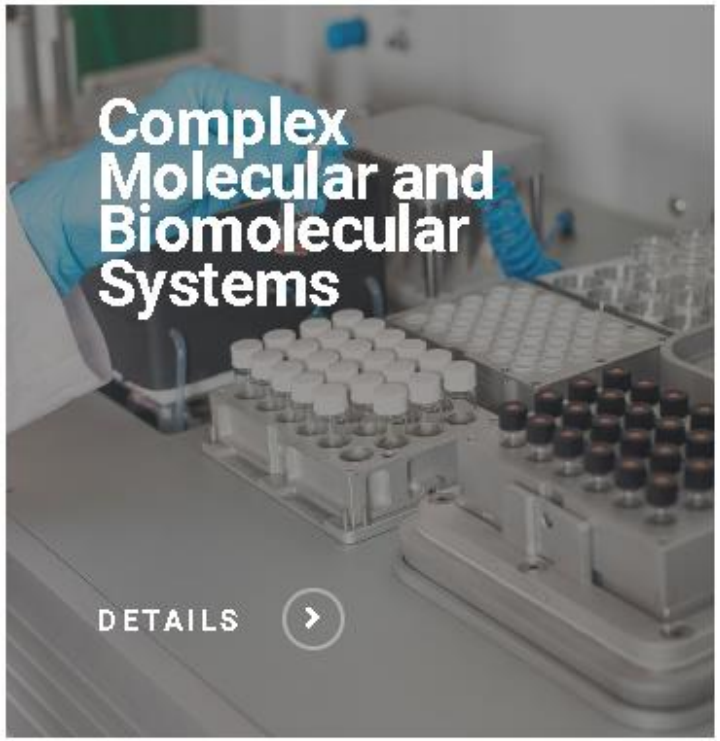


The *Molecular and Biomolecular Physics* Department is a multidisciplinary scientific research entity (fundamental and applicative) in the field of physics and molecular and biomolecular systems' technology. The department has some of the most modern and performant RDI equipment and highly trained research personnel. The mission of the department targets RDI activities aiming sustainable economical growth, development of novel molecular technologies with applications in medicine, bioeconomy, eco-technologies and emerging bionanotechnologies. The three research teams active within the department are the following:

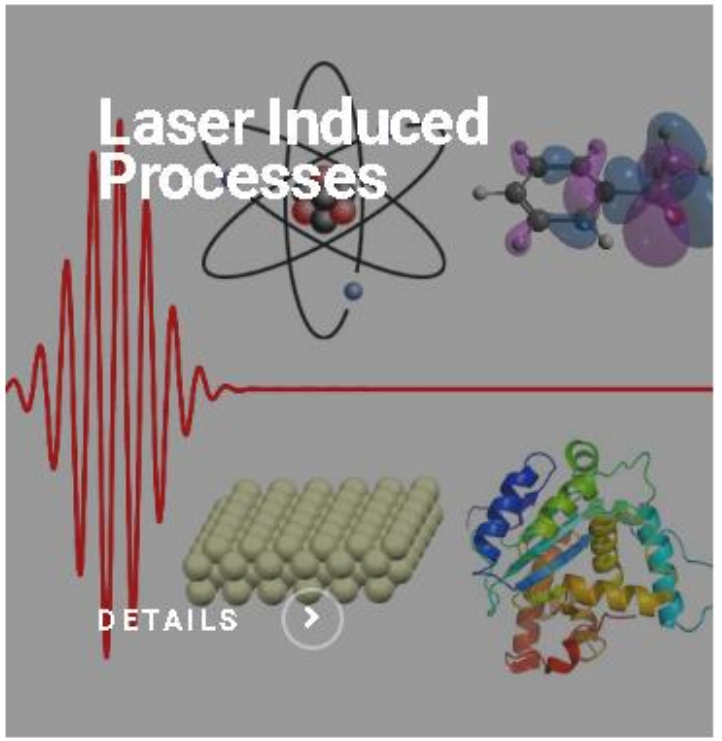
http://en.itim-cj.ro/research/departments/molecular-and-biomolecular-physics

Molecular and Biomolecular Physics

Head of Department: Dr. Ioan Turcu

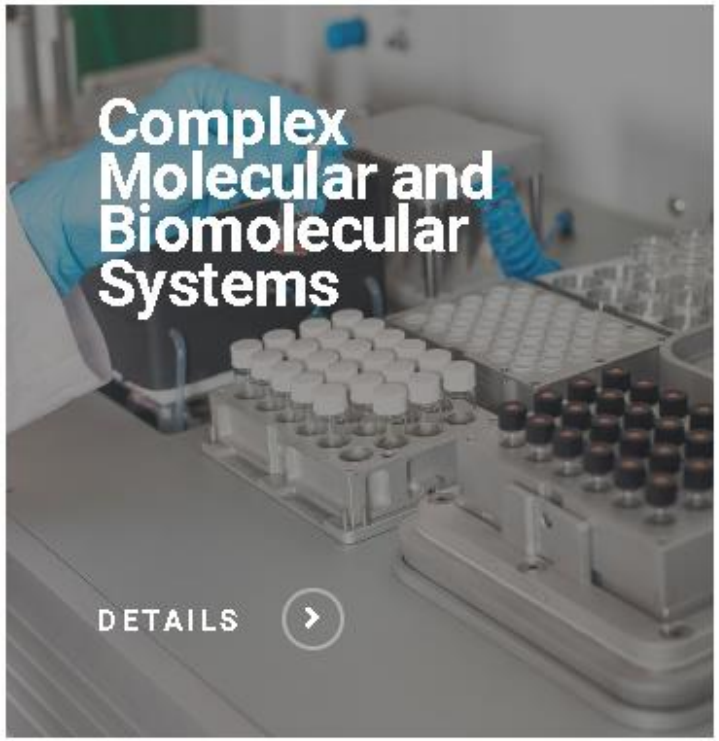






Molecular and Biomolecular Physics

Head of Department: Dr. Ioan Turcu



Complex Molecular and Biomolecular Systems – Team leader: Dr. Claudiu FILIP

Complex *Molecular and Biomolecular Systems* research team is developing its own RD&I topics and, through collaboration with other groups, provides support for the synthesis / characterization of systems / materials of interest in areas like: health, pharmaceutical and nutraceutical industries, advanced materials, biotechnology, structural biology, biomimetics.

Research topics

- Competitive binding of API's to plasmatic proteins
- Bioactive compounds (synthetic or natural) with improved solubility and bioavailability by solid form optimization and molecular encapsulation
- Stability studies of bioactive compounds to the action of the excipients and environment
- Structural biology: (i) protein structures by cryo- Electron Microscopy; (ii) structural and dynamical investigations by NMR spectroscopy on isotopically labeled proteins
- Biomimetics: antibacterial effect of natural *micropatterned* surfaces; identify real-life technological solutions to mimic the natural surfaces
- Cells – nanomaterials interaction: biocompatibility and cito-toxicity studies for various types of nanomaterials

Expertize

- Obtaining new solid forms and inclusion complexes of bioactive compounds (synthetic or natural)
- Surface *micro-patterning* methods: NIL – *Nanoimprint Lithography*
- Extraction and purification of protein complexes (soluble and membrane-bound proteins)
- Biocompatibility, cito-toxicity, imunochemistry și and ultrastructural analytical methods for biological samples
- NMR Spectroscopy: on liquids and solids
- X-Ray Diffraction: on single crystals and micro-crystalline powders
- NMR Crystallography
- Electron Microscopy: SEM, TEM, HR-TEM, SAED-TEM
- Elemental analysis: EDX, EBSD
- Atomic Force Microscopy: AFM
- Thermal analysis: DSC, ITC, phototermic techniques, active thermography
- Vibrational Spectroscopy: FT-IR, Raman, VCD
- Molecula modelling: *ab initio*, DFT – *density functional theory* molecular mechanics methods on restricted or extended (crystal lattice) systems
- Modelling of complex phenomena: heat propagation in multi-layer systems

Obtaining and characterization of new solid forms of pharmaceutical compounds

➢ *Laboratory of Crystallography and Polymorphism*



Crissy Small Scale Crystallization Equipment used in screening of solid forms



Eyela large-scale crystallization equipment used in the development of a crystallization process in order to transfer it to the industrial scale



Multivapor P-12 EasyVac
allows the evaporation of 12 solutions in parallel and isolated



The Retsch mill offers the opportunity to investigate rapid API co-crystallization tendency

Characterization of the solid forms

Stream of parallel crystallization

> 100 solid materials of one API

Crystals



Powders



Single-crystal X-Ray Difraction (SCXRD)

Identification of new solid forms

X-Ray powder diffraction (XRPD)

Mortared crystals

XRPD verification

mixture of forms?

No

Yes

Full characterization of solid forms

- **solid-state NMR**
- **molecular modelling**
- IR spectroscopy
- DSC, TGA thermal analysis
- solubility
- dissolution rate
- Accelerated stability

Solid-state NMR molecular modelling characterization



- completes the structural characterization of the new forms by X-ray diffraction (on powders and single crystals)
- 13C CP-MAS spectra provide information on: crystallinity and purity of the sample, the number of molecules in the asymmetric unit, the existence of static or dynamic disorder
- 15N CP-Mas spectra provide information on the change in the ionization state of N atoms
- magnetic shielding calculations, together with measured NMR chemical shifts, confirm the structural models determined by X-ray diffraction

Molecular and Biomolecular Physics

Head of Department: Dr. Ioan Turcu



Molecular and Biomolecular Technologies – Team leader: Dr. Ioan TURCU

The *Molecular and Biomolecular Technologies* team is involved in advanced research that explores and develops novel micro/nanostructured systems targeting emerging technologies, theranostic biomedical applications, biomimetics, molecular and biomolecular sensors, molecular electronics etc.

Initiated / Developed themes

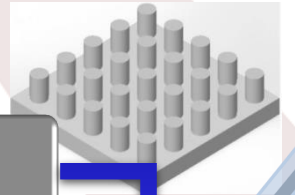
- Molecular recognition and self-association processes, intra and inter-molecular interactions
- Supramolecular structures with controlled architecture and functionality
- Bioinspired intelligent micro/nanostructures with applications in medicine, industry and counter-fitting
- Real-time identification and detection of microorganisms using ultrasensitive spectroscopy techniques
- *In silico* investigation of molecular systems layed onto metallic surfaces, quantum transport processes, and of biomolecular complexes
- Identification of novel antimicrobial and anticancer peptides
- Transport mechanisms through membrane models, protein channels, biological and solid-state nanotubes/nanopores
- Development of exozome-based innovative platforms for theranostic biomedical applications

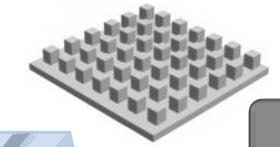
Expertise

- Fabrication of ***molecular structures with controlled architecture and functionality***, using of molecular beam epitaxy (MBE) in ultra-high vacuum, and of ***micro-/nano-structured surfaces***, using nano-imprint lithography (NIL), for applications in molecular sensory and molecular electronics
- ***Nanoscale topographical*** characterization of surfaces using ***microscopic scanning techniques*** (STM and AFM) in ultra-high vacuum
- ***Microorganisms detection*** by means of Raman and surface-enhanced Raman spectroscopies (SERS), and their ***differentiation*** through multiple chemometric analyses (PCA, LDA, PCA-LDA on vibrational spectra)
- Rational design, generation and characterization of ***short antimicrobial/anticancer peptides***
- ***Atomic to molecular scale*** (coarse-grained) molecular modelling and simulation of complex biophysical systems (proteins/short peptides, DNA/RNA, bacterial and mammalian membrane models) by means of molecular dynamics and quantum chemistry
- Development of "tight-binding" and ab-initio models for various molecular systems
- *In silico* computation of ***free energy profiles***/PMFs for transmembrane molecular transport, (self)association, membrane affinity, by means of equilibrium (Umbrella Sampling), non-equilibrium (FR method), flat-based histrogram ((MW)2-XDOS method), molecular docking (affinities)
- Characterization of ***biomolecules*** (with therapeutic/pharmaceutical potential, biomimetical, proteins involved in molecular signalling associated to cancer, oxidative stress/neuro-degenerative diseases) by means of ***computational simulations*** (molecular dynamics, molecular docking); ***biochemical and biophysical methods***: SEC-MALS, spectroscopic techniques (UV/Vis, fluorescence, Raman), immunodetection (Western Blot), electrophoresis and gel densitometry; ***biochemical and microbiological methods***: antibacterial activity (MIC/MBS and diffusometric method), testing for cellular viability (IC50), enzymatic activity (TTC), metabolic activity (MTT), membrane integrity (LDH), antioxidant activity (SOD, CAT, GPx, GSH), inflammatory markers
- ***Bacterial*** cellular ***growth***, ***Proteins' expression*** in E. coli (cloning in expression vectors, PCR, point mutation genesis, DNA segment assembly cloning); ***Protein purification***

Fabrication and characterization of micro/nanostructured surfaces

Micro/nanostructured surfaces



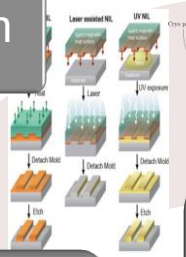


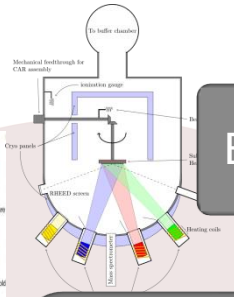
Nano/micro fabrication

Characterization methods

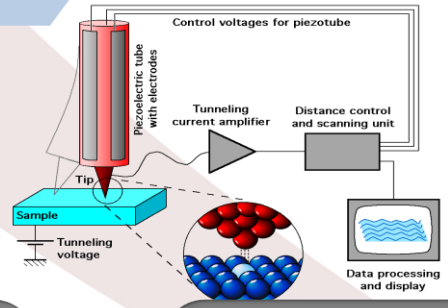


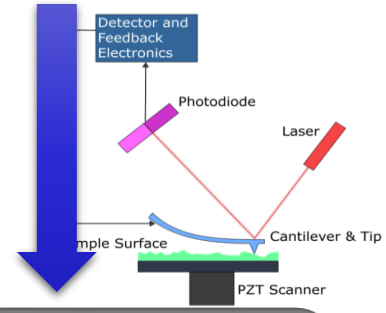
Top down





Bottom-up





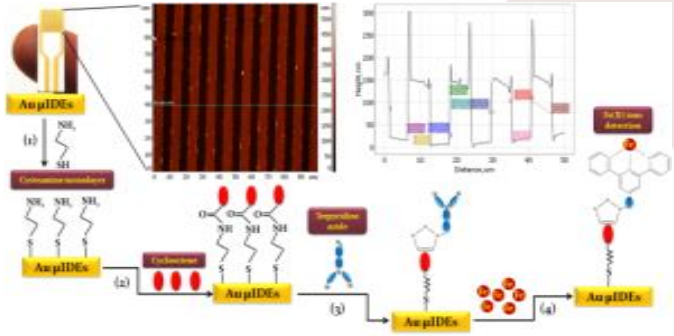
Nanoimprint Lithography

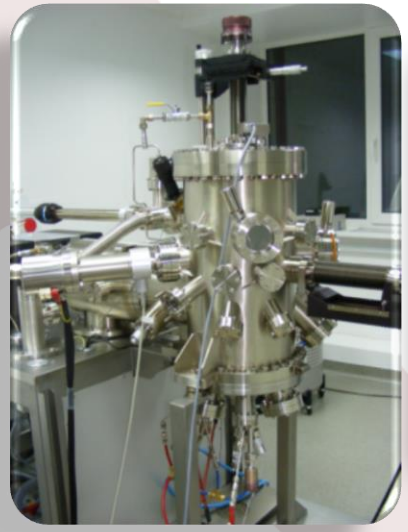
Physical vapor deposition
- Molecular Beam Epitaxy
- Pulsed Laser Deposition
- Magnetron Sputtering

- Scanning Tunneling Microscopy
- Atomic Force Microscopy
- Scanning Electron Microscopy

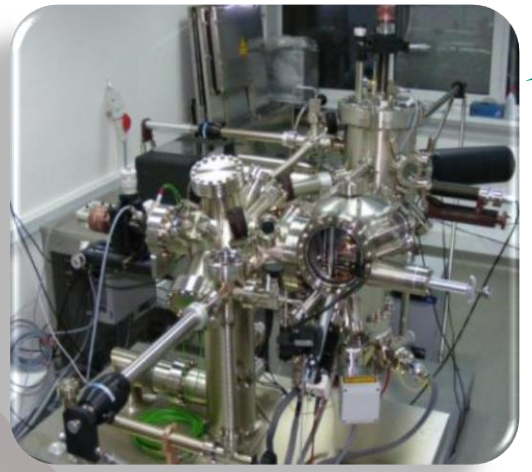
Fabrication under ultra-high purity conditions

Nanopatterned surfaces
Nanobiosensors



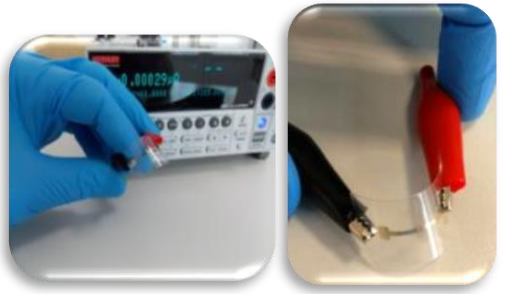


Molecular epitaxy

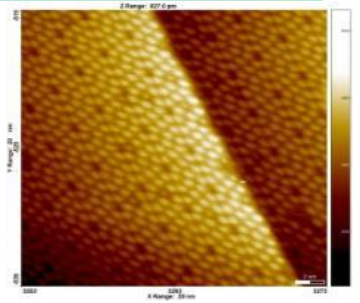


STM and AFM scanning microscope in ultra-high vacuum and low temperatures

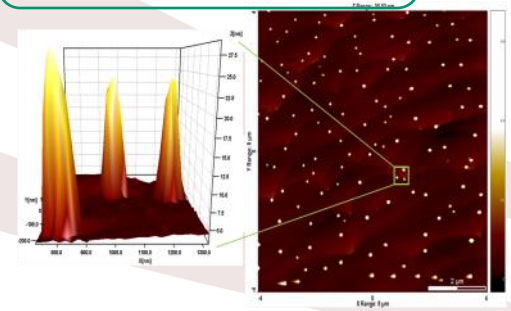
Molecular electronics



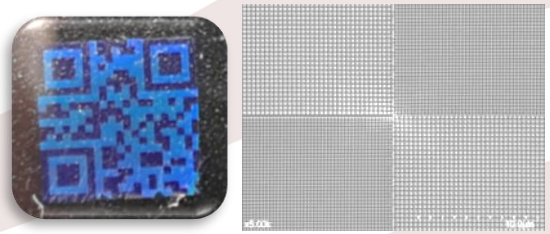
Ultra-flat metal surfaces



Self-assembled atomic monolayers



3D optical elements



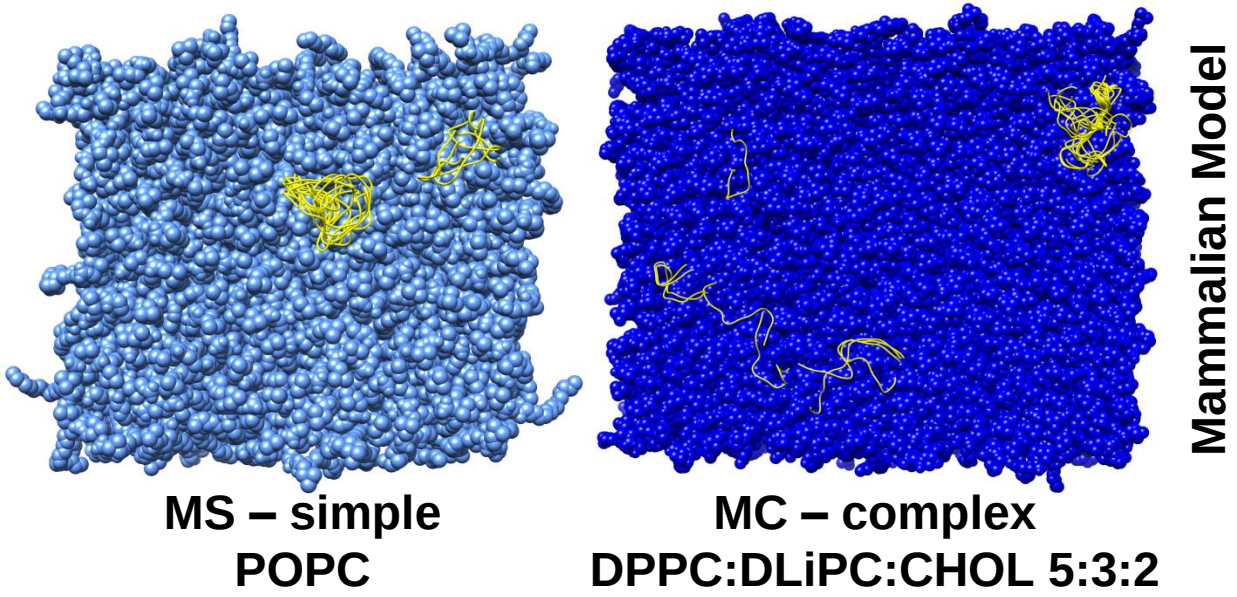




Integrated equipment for nanoimprinting technology

Rational design of antimicrobial peptides

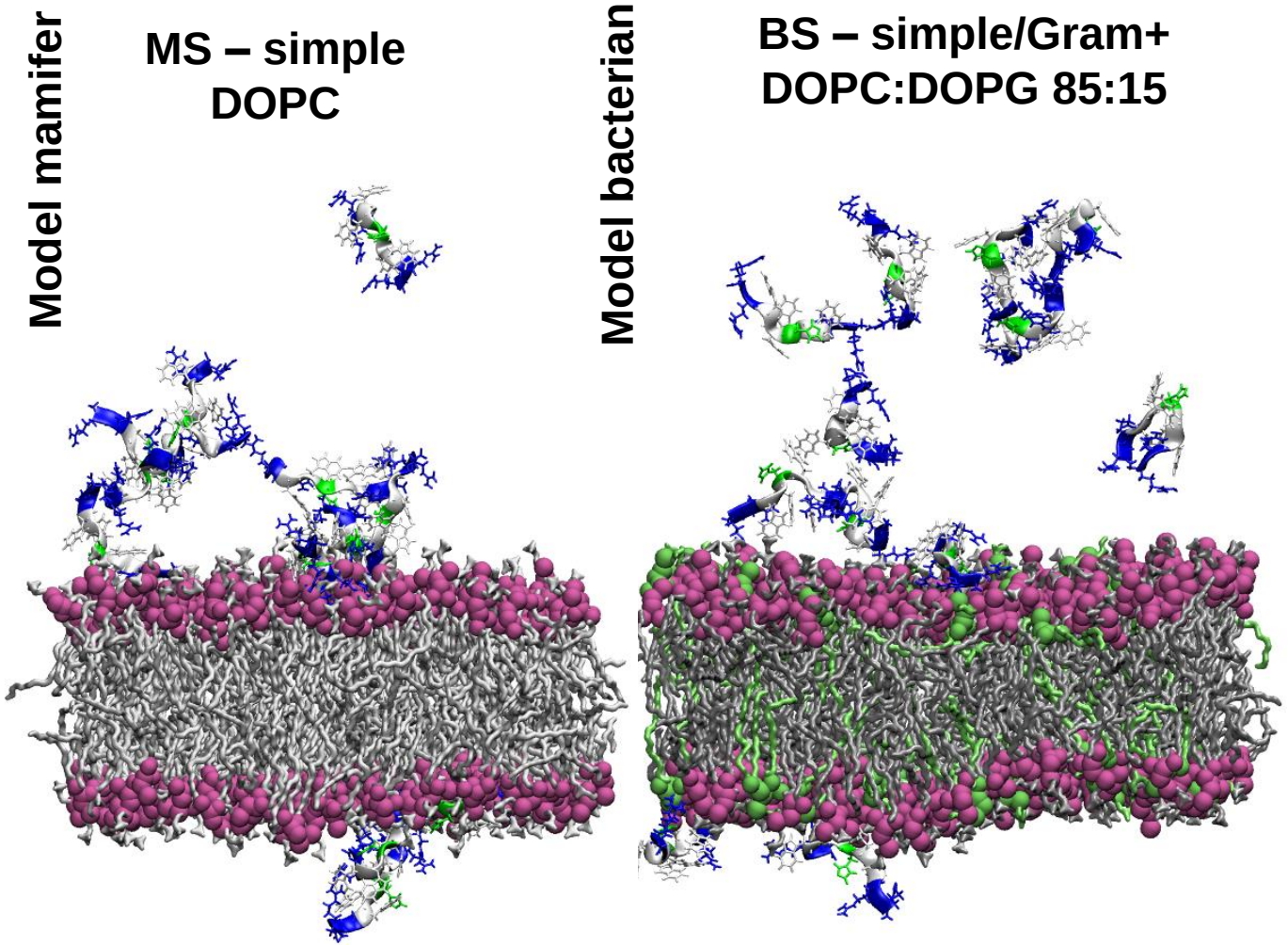
1. Molecular Docking



- Using the size, charge, and hydrophobicity of amino acids to extract peptide candidates
- Mammalian and bacterial model cell membranes
- Molecular **Docking**

Rational design of antimicrobial peptides

2. Molecular dynamics simulations

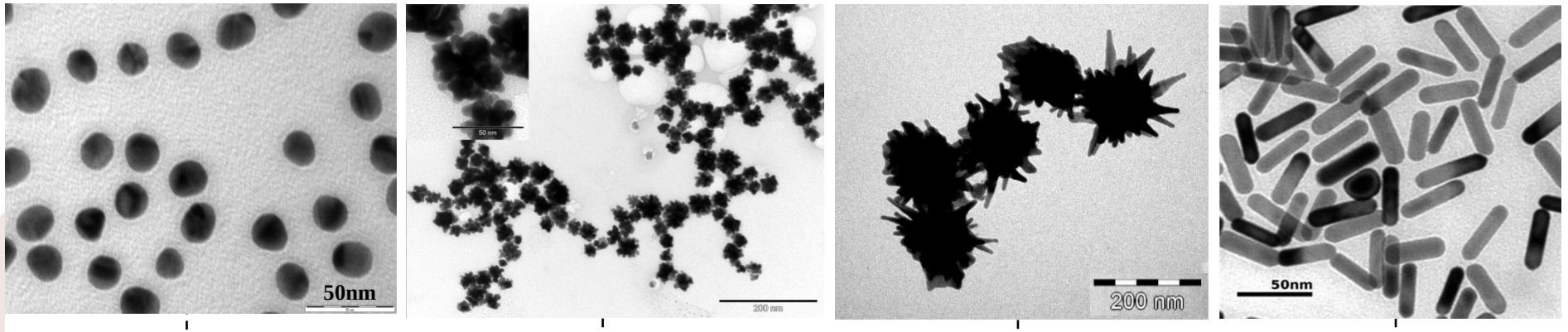


- Specificity (bacterial and mammalian cell membranes)
- Dynamics of peptides at the membrane surface
- Molecular mechanism of peptides action mode

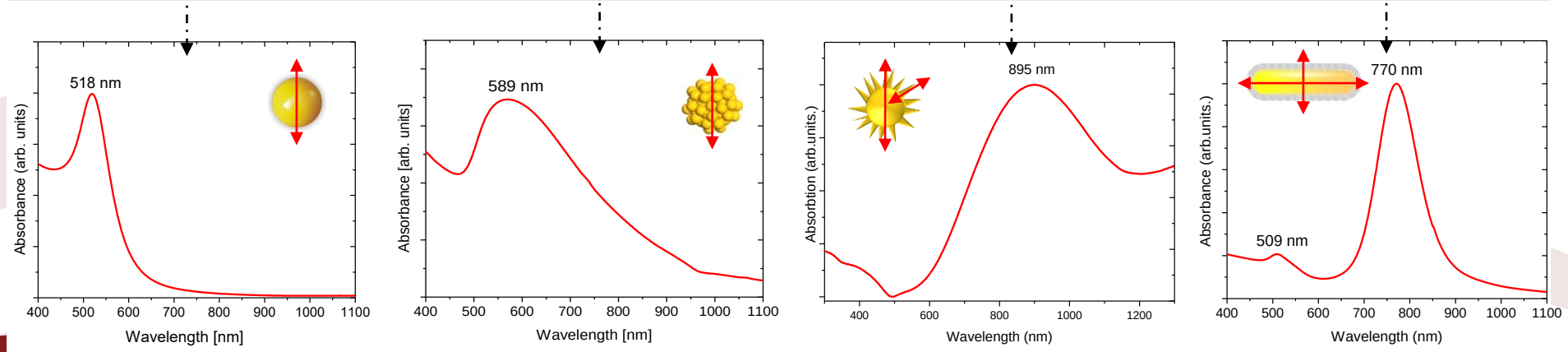
[1] Mihaela Bacalum, Lorant Janosi, Ioan Turcu, Mihai Radu, *BBA – General Subjects,* **1861**, 1844-1854 (2017).
[2] L. Janosi, AA. Gorfe, *Interaction Between Proteins and Biological Membranes* , 293-314, (2022).

Nanoparticle chemical synthesis

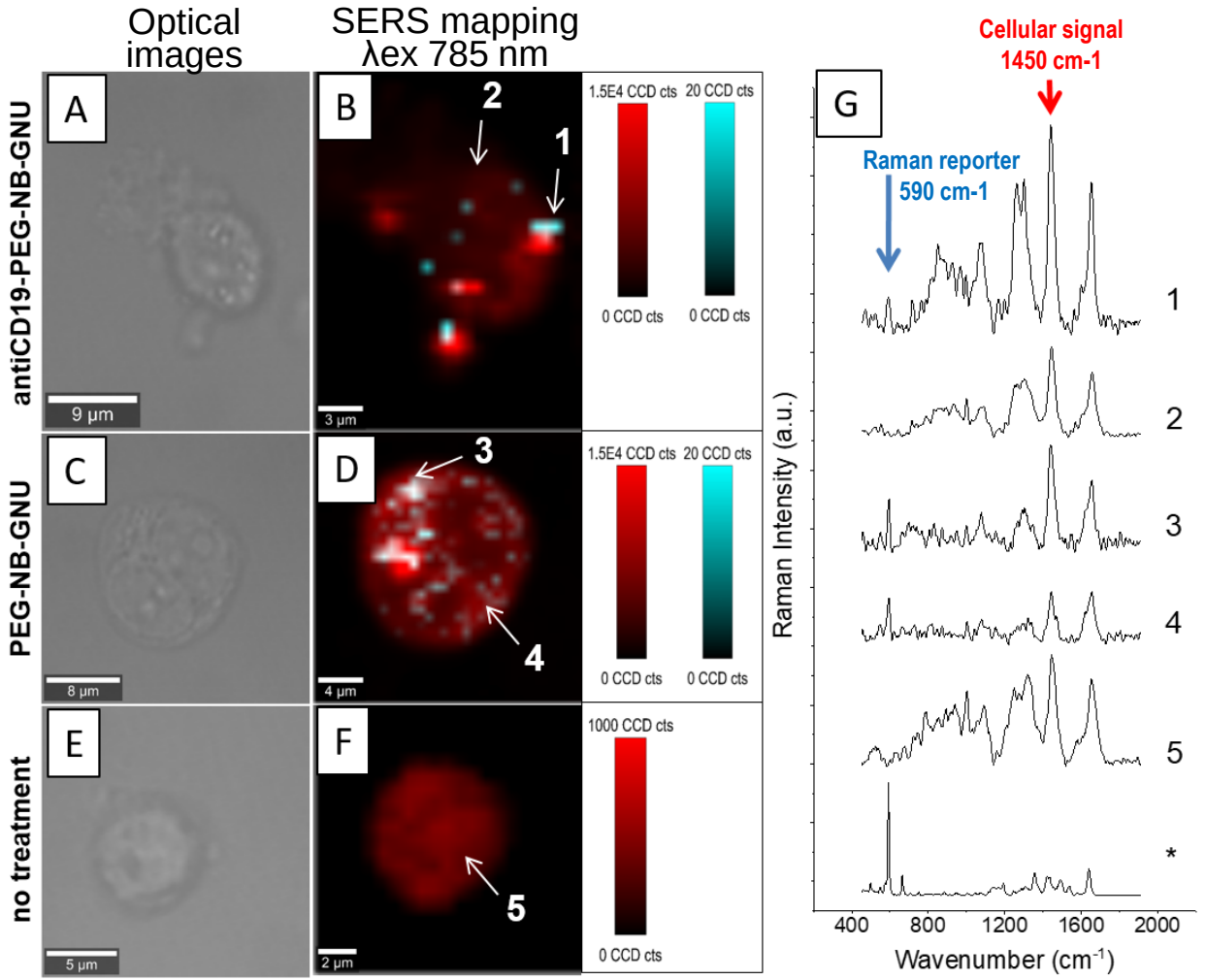
TEM Imaging



Optical absorption spectroscopy



Intracellular SERS imaging using Raman tagged gold nanoparticles

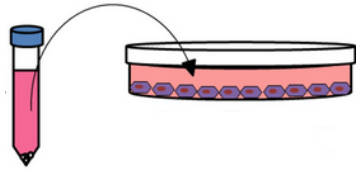


Position (cm-1)	**Band assignment**
590	NB C-C-N, C-N-C, phenoxazine ring stretching
661	NB in plane CCC, NCC
1357	NB ring stretching
1639	NB C-C ring stretching
1450	Amide I protein CH deformation vibration

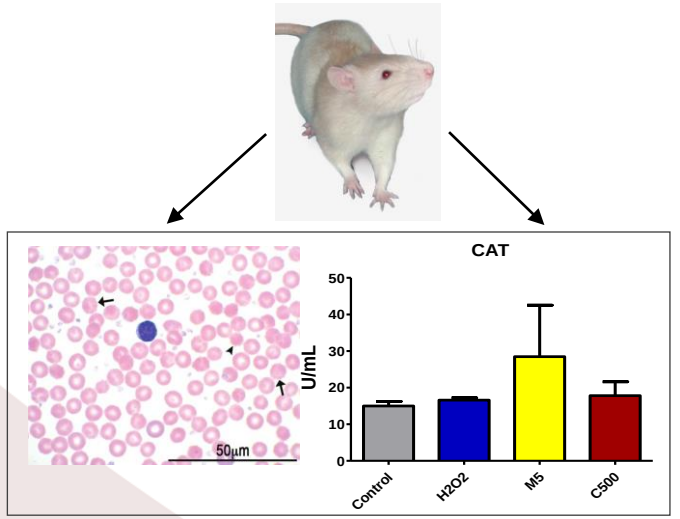
Tatar A, Jurj A, Tomuleasa C, Florea A, Berindan-Neagoe I, Cialla-May D, Popp J, Astilean S, Boca S, *CD19-targeted, Raman tagged Gold Nanourchins as theranostic agents against Acute Lymphoblastic Leukemia*, Coll. Surf. B: Biointerfaces, 2019, https://doi.org/10.1016/j.colsurfb.2019.110478

In vitro and in vivo biological tests

- Cell cultures *in vitro* – determination of oxidative stress from culture medium/cell lysates



- *In vivo* studies – experimental model Rattus norvegicus/Wistar breed
  - toxicity studies in different tissues
  - morphological evaluation of peripheral blood
  - monitoring of the estrous period by cytological examination
  - assessment of oxidative stress by various methods (biochemical/ELISA)

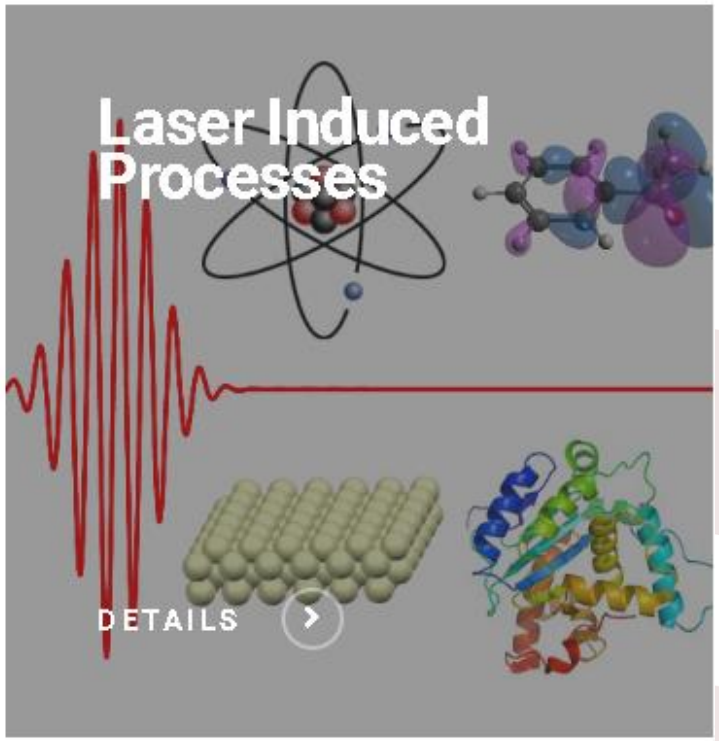


AD Farcas, AC Mot, C Zagrean-Tuza, V Toma, C Cimpoiu, A Hosu, M Parvu, I Roman, R Silaghi-Dumitrescu, *Chemo-mapping and biochemical-modulatory and antioxidant/prooxidant effect of Galium verum extract during acute restraint and dark stress in female rats*, PLoS ONE, 2013 13(7): e0200022

AD Stoica, B Sevastre, M Suciu, AE Pârvu, M Pârvu, VA Toma, I Roman, C Dobre, *Chemoprotective Effect of Plantago sempervirens Crantz Extract on Ovarian Structure and Folliculogenesis*, Appl. Sci. 2023, 13(5), 3134

Molecular and Biomolecular Physics

Head of Department: Dr. Ioan Turcu



Laser Induced Processes – Team leader: Dr. Cosmin FARCĂU

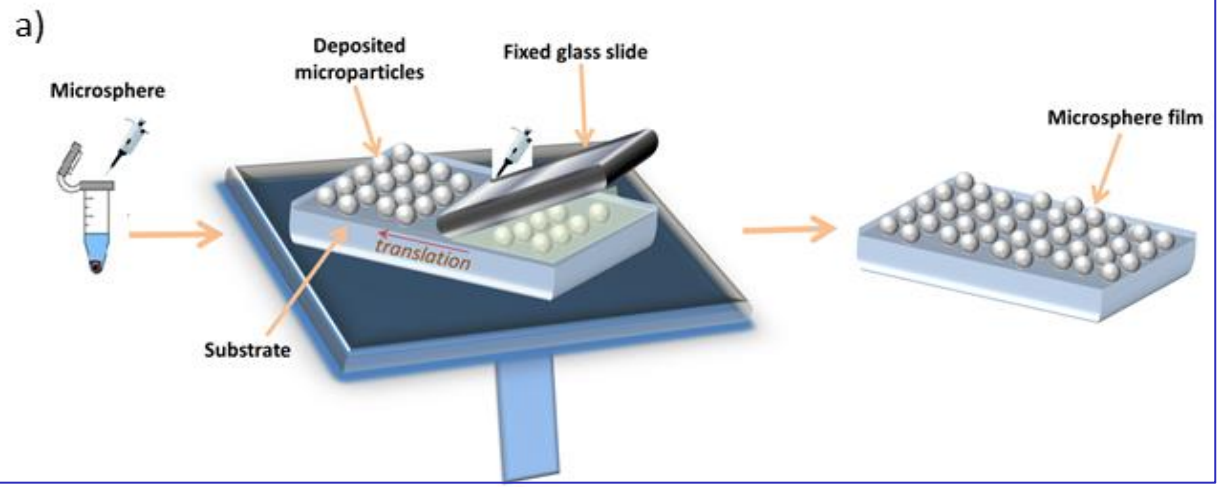
The *Laser Induced Phenomena* research group develops theoretical and experimental research related to physico-chemical processes induced by coherent electromagnetic radiation in interaction with atomic, molecular and biological systems.

Research topics:

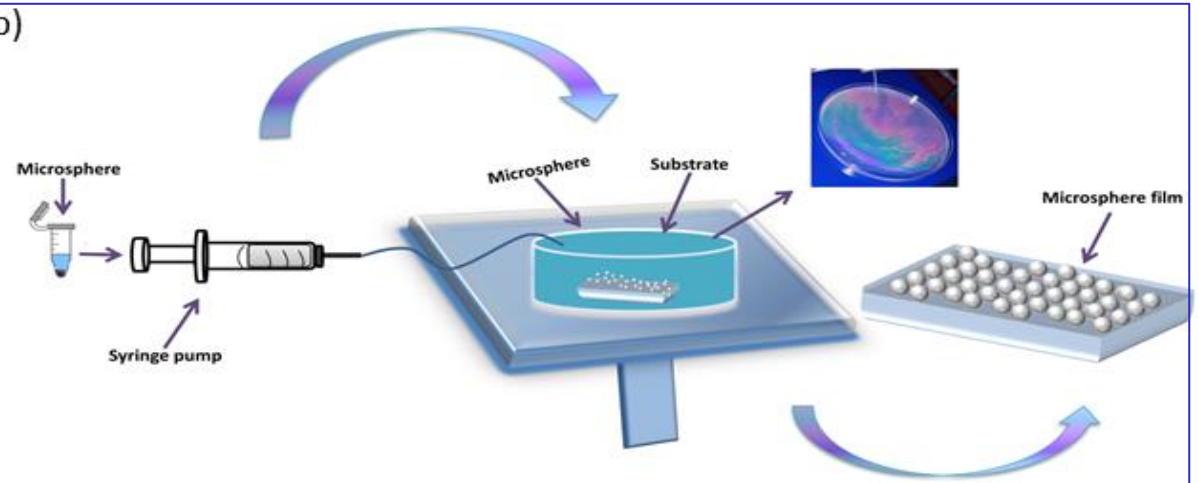
- Temporal / spectral characterization of ultrashort laser pulses using deep learning algorithms. *Projects:* ELI-RO
- Propagation of femtosecond pulses and generation of attosecond pulses in laser-fabricated integrated photonic circuits. *Projects:* X-Pic
- Ultrashort laser pulses' interaction with atoms: modeling high-order harmonic generation in macroscopic conditions, attosecond pulse formation
- Analysis of excited state dynamics induced by coherent electromagnetic radiation in molecular and supramolecular systems; *Projects:* PN-III-P4-ID-PCE-2020-0770
- Fabrication of nanostructured films with controlled optical/plasmonic properties via colloidal self-assembly and colloidal lithography; *Projects:* PN-III-P4-ID-PCE-2020 1607
- Direct laser-writing lithography, from nano to millimetric scale structures
- Development of molecular optical sensors exploiting the plasmonic enhancement of analyte-laser light interactions (SERS, SEF). *Projects:* RO-NO-2019-0517, PN-III-P2-2.1-PED-2019-5473
- Photoinduced ultrafast phenomena in hybrid metal-semiconductor nanomaterials investigated by time-resolved spectroscopy. *Projects:* PN-III-P1-1.1-TE-2019-1141
- Characterizations through optical coherence tomography techniques and development of contrast agents
- Determination of thermal parameters of porous solids through photopyroelectric calorimetry: methodology development and optimization of experimental conditions

Fabrication of plasmonic nanostructures based on microsphere arrays – Colloidal self-assembly

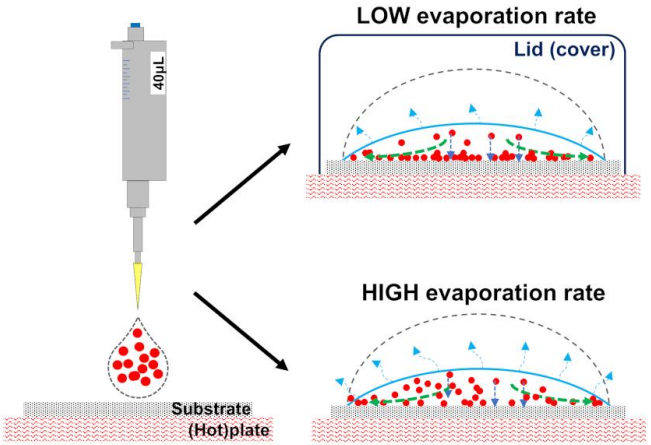
- Convective self-assembly



- Interface self-assembly



- Drop-coating self-assembly

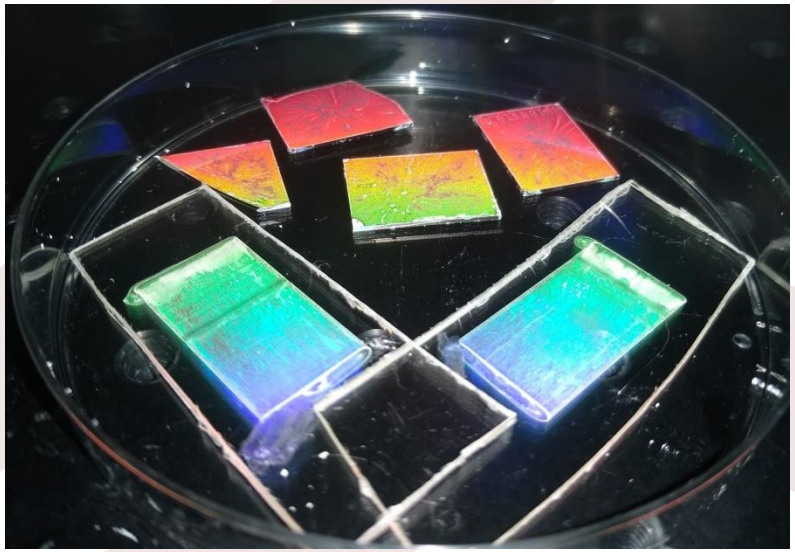


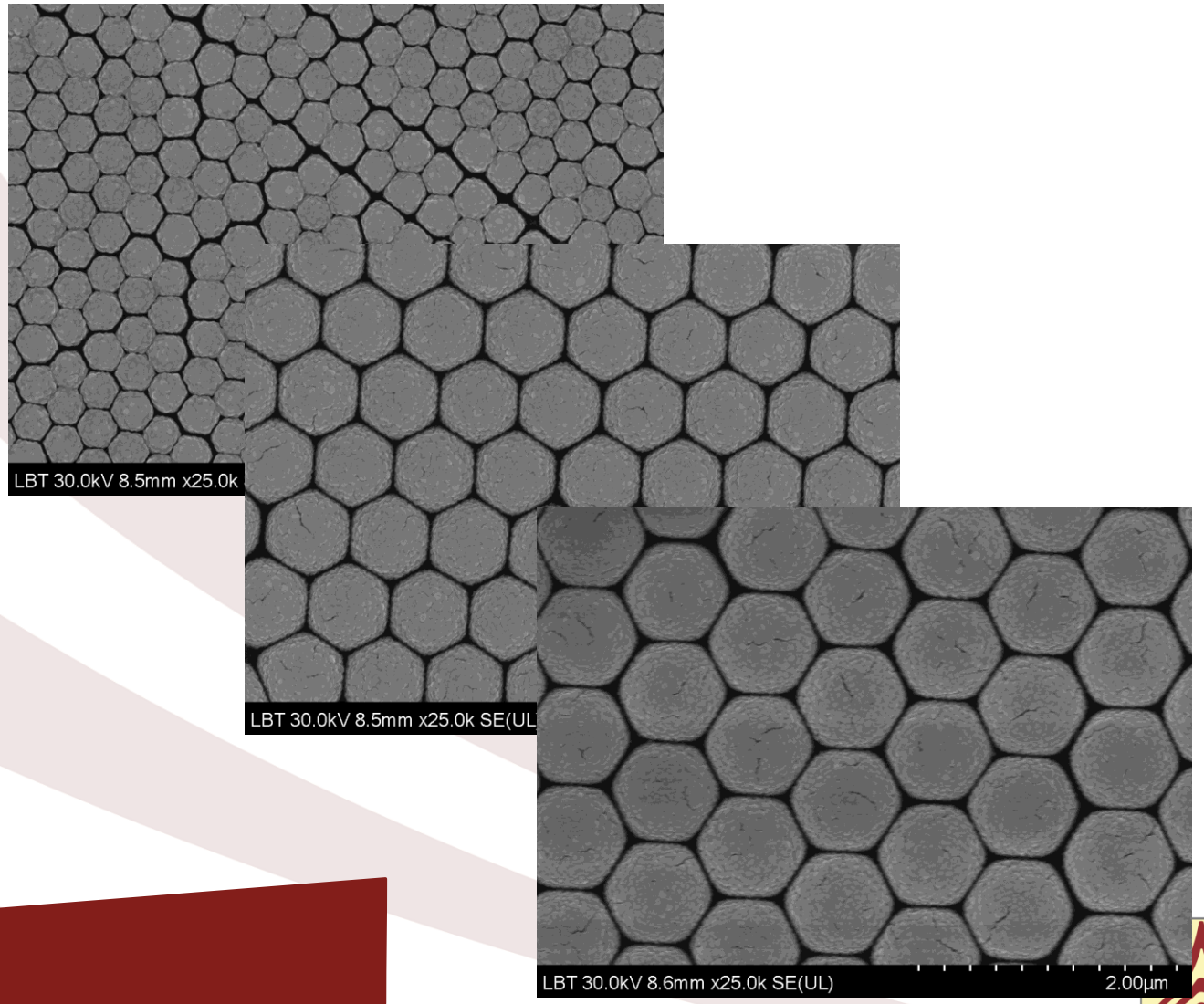
- **NSM159**

Nanofabrication

- Metal-coated microsphere arrays

colloidal self-assembly
metal deposition by physical methods

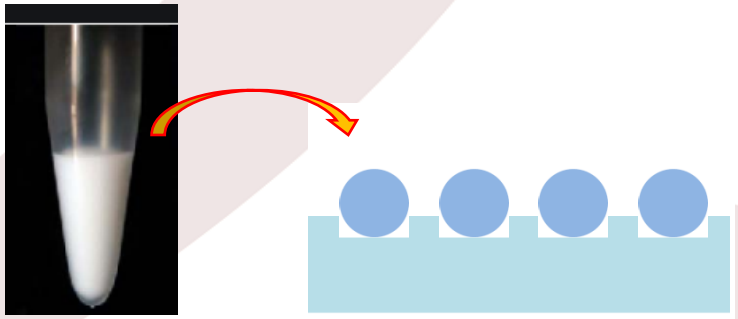




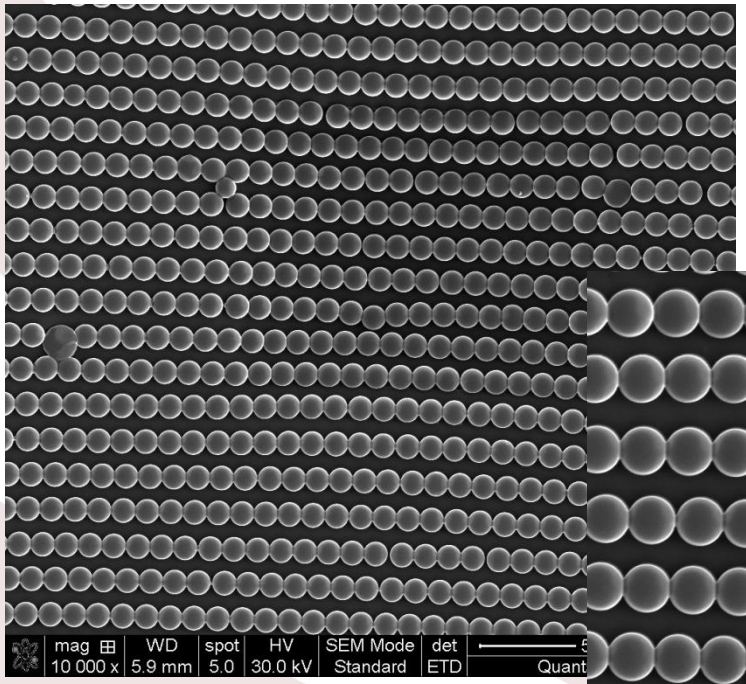
Nanofabrication

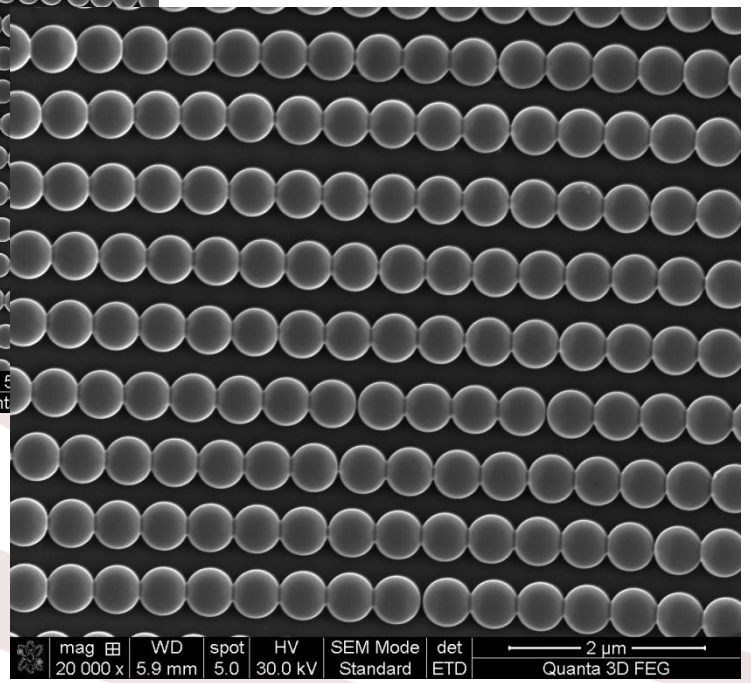
- Linear arrays of metal-coated microspheres

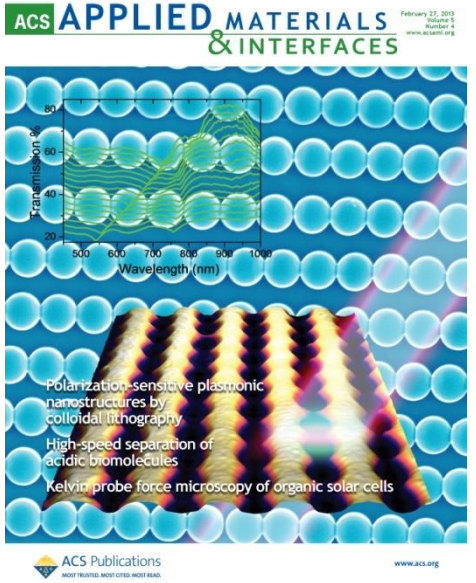
self-assembly on patterned substrates



- polystyrene colloids in water;
- diameter 500 nm;
- 2% vol.;







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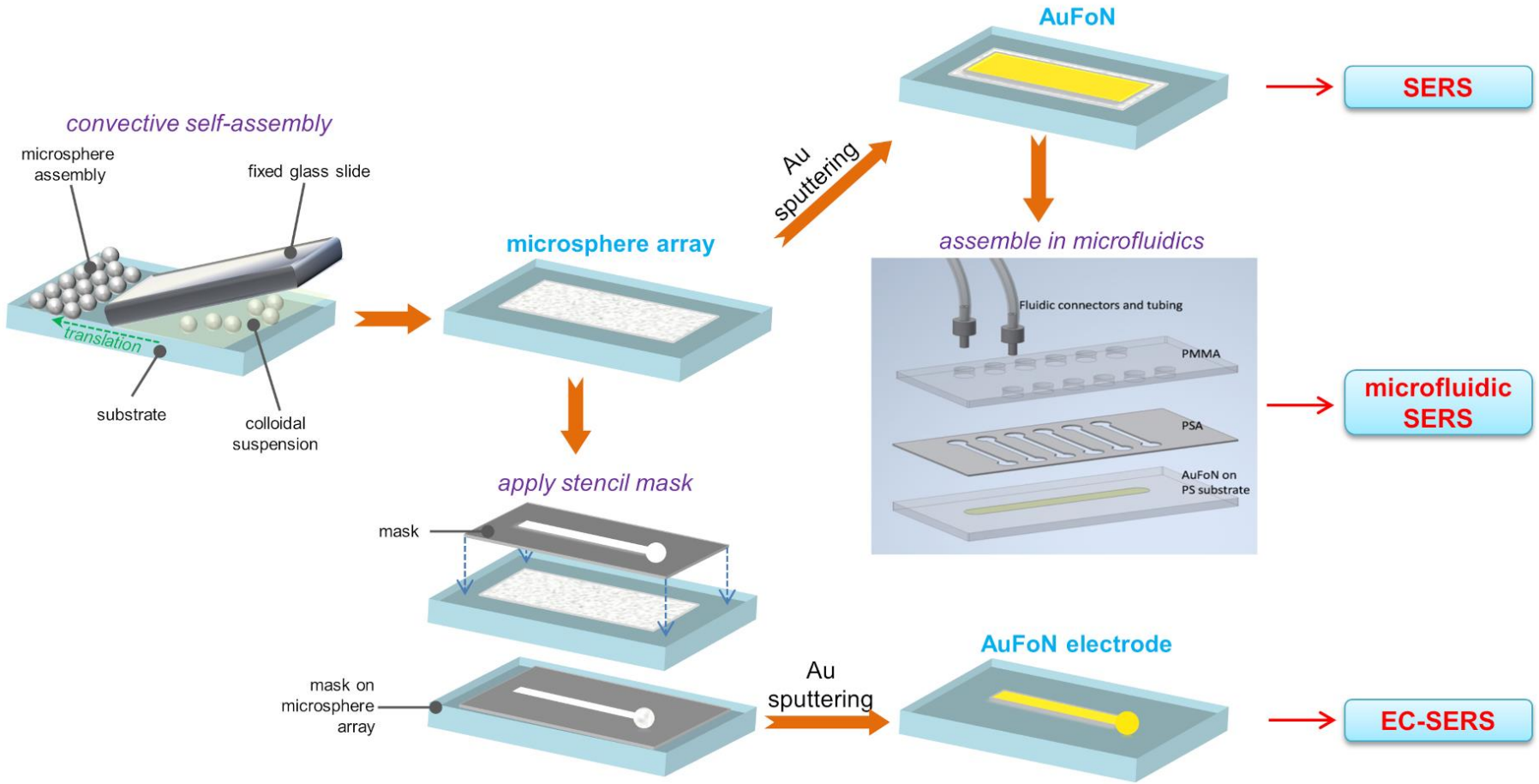
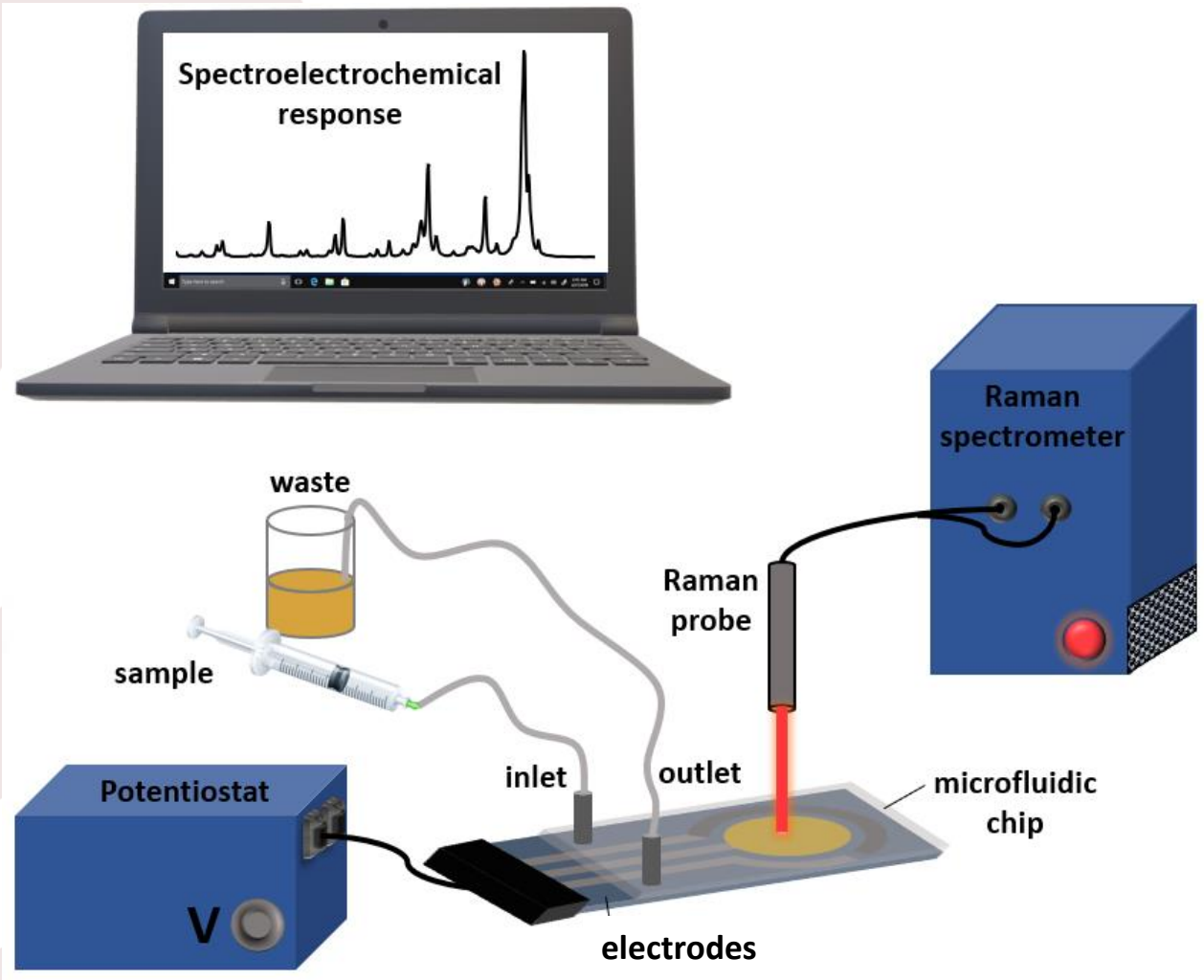
Plasmon-enhanced spectroscopy-based optical sensing-SERS applications

- Metal-coated microsphere arrays in SERS applications



Microfluidic-electrochemical-SERS



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Microfluidic-electrochemical-SERS

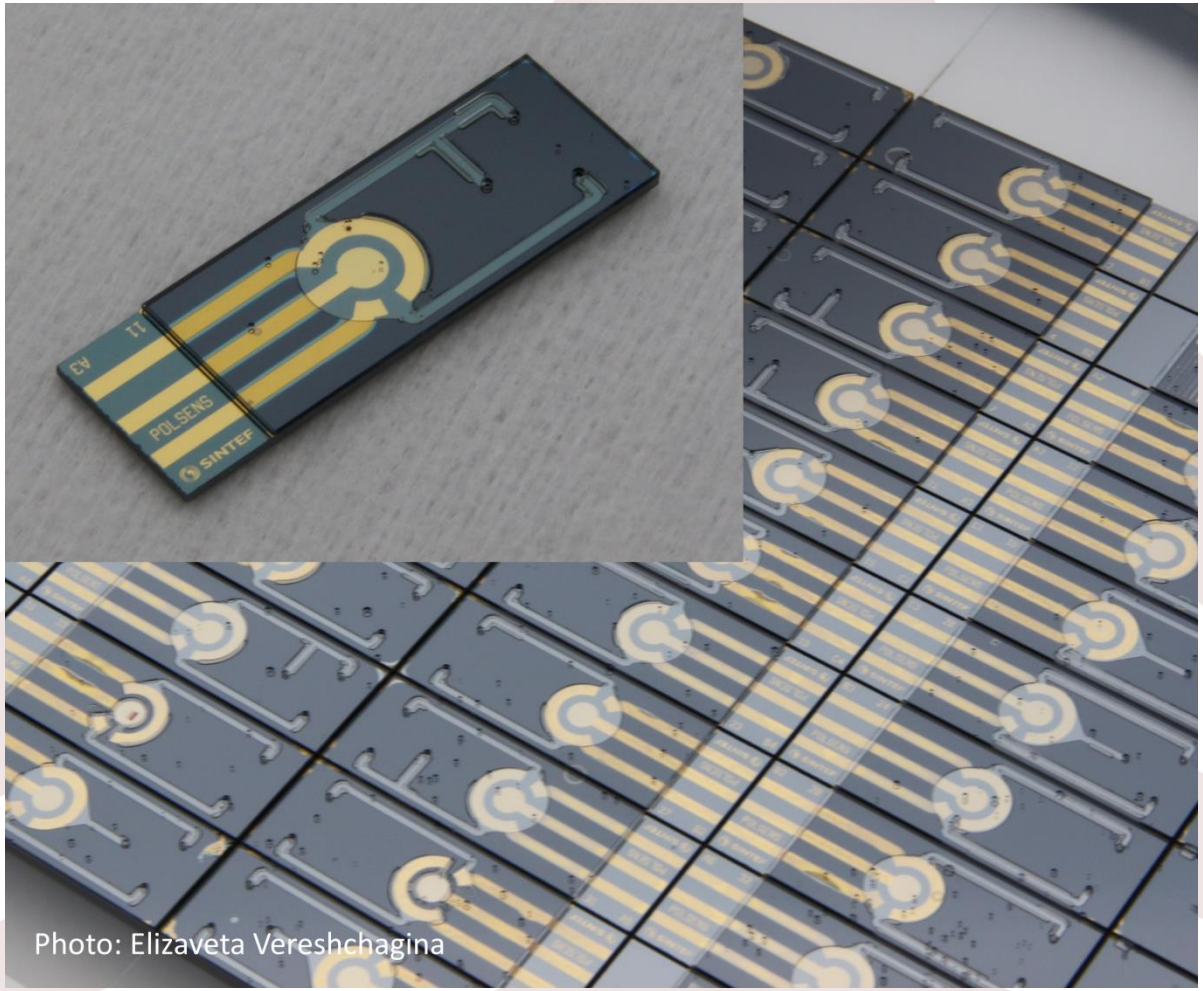
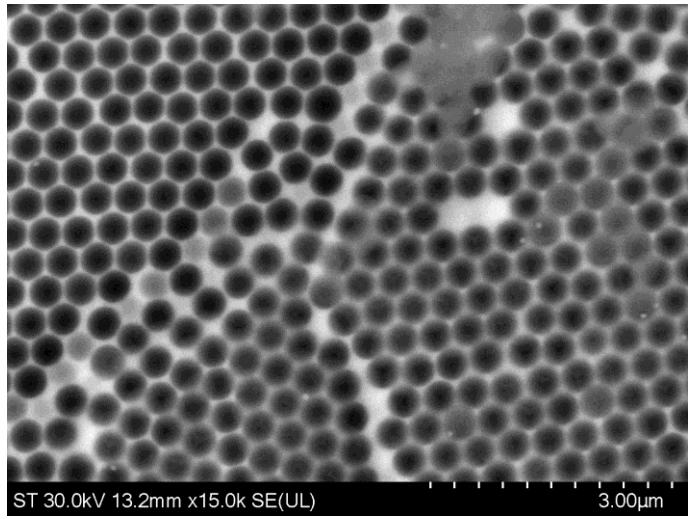
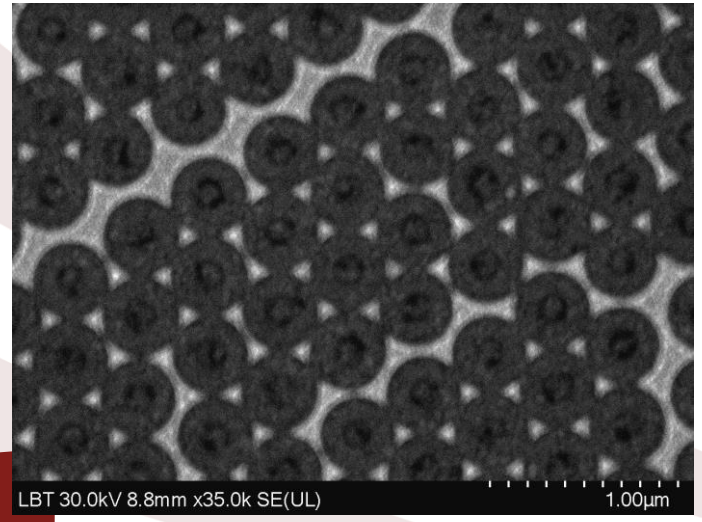


Photo: Elizaveta Vereshchagina





Acknowledgement

- InsBIOration - Bio-inspired interfaces for the development of next generation degradable multi-phase materials, 2022-2025 M-ERA.NET Start Date: 28.06.2022 End Date: 30.01.2025.
- x-Pic - eXtreme ultraviolet to soft-X-ray Photonic Integrated Circuits, H2020-EU.1.2.1., Start Date: 01.04.2021, End Date: 31.03.2025.
- Polsens - Nanostructured microfluidic analytical platform for dual SERS-electrochemical detection of emerging environmental pollutants, NO Grant – Collaborative Research Projects, Start Date: 01.09.2020, End Date: 31.08.2023.
- CONSOL-ITIM, Contract No. 37PFE/30.12.2021
- National Plan for Research, Development, and Innovation 2022–2027, project PN 23 24 01 02
- PN-III-P4-ID-PCE-2020-1607

Thank you for your attention!