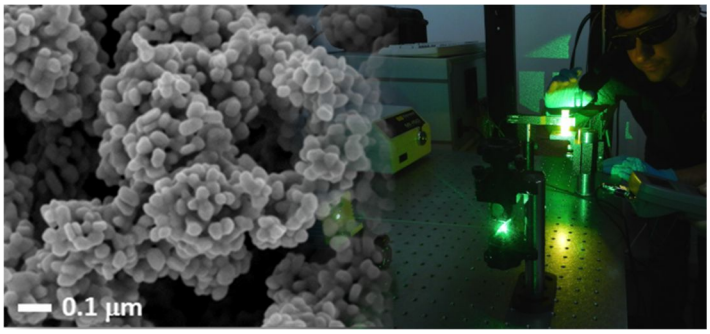
Exploring the *nano-bio interface* with SERS spectroscopy in view of clinical applications of metal nanostructures.

prof. Alois BONIFACIO (supervisor), prof. Valter SERGO



A better understanding of the interaction between metal nanostructures, such as metal nanoparticles, and biological fluids (e.g. serum, saliva) is a necessary step toward the application of nanotechnology to biological systems, and in particular to humans. Gold and silver nanoparticles and other nanostructured surfaces are promising for a variety of applications, from photo-thermal therapy to drug delivery, from drug monitoring to diagnostics, as antibacterial agents or as sensors. Many of these application require the direct contact between these nanomaterials and a biofluid, so that a better insight on how there nano-objects interact with these complex biological samples is crucial.

While most studies on the "nano-bio interface" concerned the role of proteins, especially in the formation of an adsorbed layer ("protein corona") on gold and silver nanoparticles, the interaction of small-molecules, such as metabolites, with metal nanostructures ("non-protein corona") still needs to be studied.

The reason of this delay has been the lack of experimental techniques able to investigate small molecules adsorbed on these metal surfaces in the context of chemically complex samples, such as biofluids. Surface-Enhanced Raman Spectroscopy (SERS) is an analytical technique capable of detecting the vibrational spectra of species adsorbed on nanostructured metal surfaces, and thus to identify adsorbed metabolites.

Candidates will use SERS to study the interaction of different biofluids, starting from model solutions or proteins and metabolites, with gold and silver nanoparticles and nanostructured surfaces. Besides SERS, other techniques will be used to characterize the nanostructures and the nano-bio interface, also in collaboration with other centers, such as electron microscopy (TEM, SEM), Dynamic Light Scattering (DLS), and FT-IR among others. While studying the nano-bio interface, candidates will be also encouraged to explore and develop possible bioanalytical or clinical applications relying on their findings.

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Biophysical assays for metastatic breast cancer diagnosis

Refs: Pietro Parisse, Loredana Casalis-NanoInnovation Lab, Elettra

Metastatic breast cancer is still the leading cause of death among women worldwide. Genetic analyses of large cohorts of patients are quickly increasing our knowledge of the alterations at the foundation of this malignancy, underscoring the tremendous intensification of genetic mutation frequency in metastatic cancer and providing useful insights for patient management. In order to translate this knowledge into a personalized clinical practice, genetic data must be supported by other molecular and phenotypic data. Non-invasive detection of circulating cancer-related cells and biomolecules in patients' blood would be the quintessential method to habilitate personalized therapeutic strategies. In particular, the nano-sized extracellular vesicles (EVs) have received increased attention as the main players in cell-cell communication since they have been shown to have a fundamental role in cancer progression and metastatic spreading. However, EVs-enriched genetic and proteomic analysis carries important challenges related to the complex heterogeneity of EVs, which covers size and biogenesis dispersion of the EVs subpopulations, and is hampered by the lack of standardized sorting protocols. In this work based on our preliminary results, we propose to optimize EVs isolation, purification, and classification based on physical and molecular biomarkers, in order to collect separated EVs subclasses from metastatic breast cancer patients' plasma. Biophysical assays, based on the quantitative evaluation (via Atomic Force Microscopy) of the biomechanical changes induced by these EVs on breast cancer cell lines of different aggressiveness, will be integrated with analysis of EVs-enriched miRNA and cancer-related proteins content in order to have functional output combined with mechanistic molecular details. The proposed translational platform will provide a detailed biophysical, molecular and functional portrait of cancer-derived EVs allowing to use this information to possibly guide the choice of specific therapeutic regimens.

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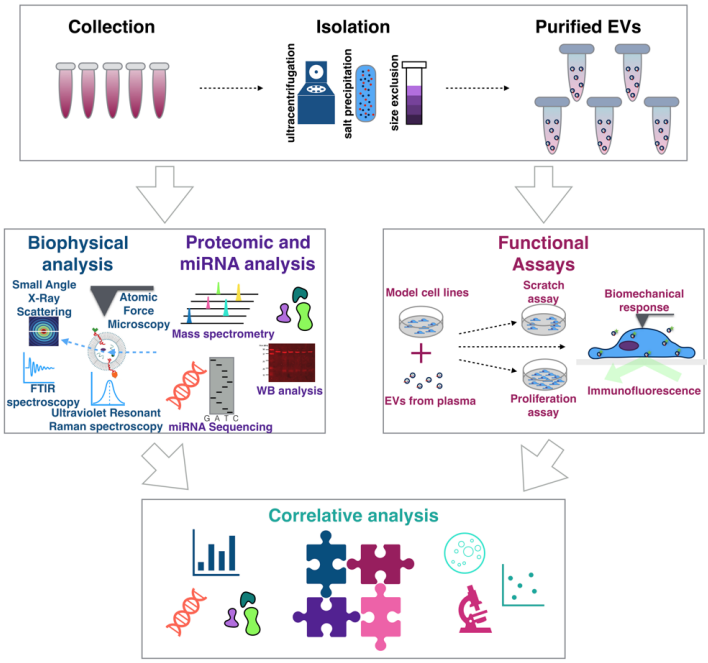
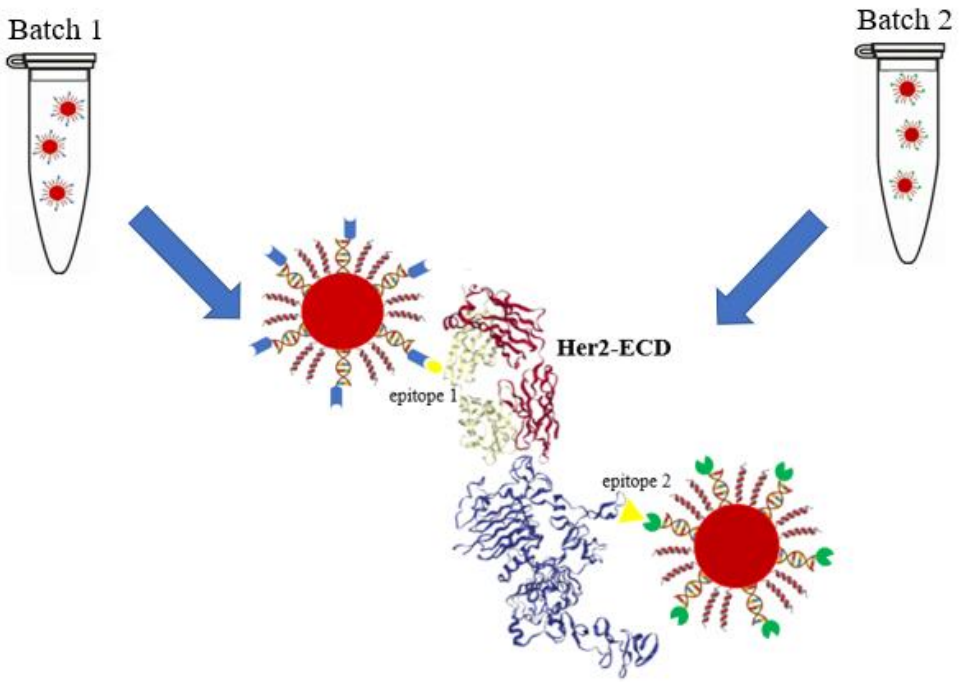


Development of nanoparticles-based biosensors for serological assays

Refs: Loredana Casalis, Pietro Parisse-NanoInnovation Lab Elettra

In the last years, nanodiagnostics has increasingly focused on nanoparticle-based assays for the detection of minute amounts of targeted analytes of clinical interests. Among them, gold nanoparticles (AuNPs) as well as metal core- Au shell NP systems are increasingly becoming an ideal candidate for developing simple, cost-effective, sensitive biosensors. In our group, we exploited the potential of self-assembled, mixed DNA/alkanethiol functional AuNPs as a novel colorimetric nanosensing platform. Short DNA fragments are used to link to the particles DNA-labeled binders for the recognition of specific antigens, through DNA hybridization, while ethylene glycol terminated alkanethiols protect the particles from unspecific binding. Charge redistribution at the NP surface at each functionalization step (i.e. SAM formation; immobilization of binders; antigen recognition) affects the optical properties of particles, an effect known as localized surface plasmon resonance (LSPR), which adsorb UV-Vis light at different wavelengths. To enhance assay sensitivity, through this project we will develop antigen induced particles aggregation strategies, in the context of the detection of cancer molecules circulating in the blood, as the extracellular domain of Her2 in Her2 positive tumors. Similar sensors will be also useful in the context of the development of serological assay to detect antibodies circulating in the blood, for instance against SARS-COV-2 spike proteins.

https://www.nature.com/articles/srep44358
https://pubs.acs.org/doi/abs/10.1021/acsami.5b01191



Nanodiamonds in Theranostics

Supervisor: Tatiana Da Ros
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Nanodiamonds (NDs) could be considered the oldest carbon-based nanomaterials as they were discovered many years ago but their popularity is quid recent, with the development of nanotechnology. They have an sp^3 diamond core and their surface is generally present a mixture of sp^2 and sp^3 hybridized atoms. The possible surface groups of pristine materials are characterized as ketone, aldehyde, carboxylic acid, ester, anhydride, cyclic ketone, lactone, amine, epoxide, etc., so various surface functionalizations could be performed in order to introduce new biological and electronic properties.[1] According to the primary particle size, NDs can be classified in three main groups: nanocrystalline diamond particulate (10-100 nm), ultrananocrystalline diamond particulate (0-10 nm), diamondoids (~1 to ~2 nm).[2] Among these, ultrananocrystalline diamonds are the most promising nanomaterials for microelectronics, biotechnology and medical applications, in particular when mean size is 4-5 nm.

Nanodiamonds are chemically and physically stable nanomaterials, but their surface can be chemically modified for various purposes. They present some properties of bulk diamond (high Young's modulus and mechanical strength, high thermal conductivity), but also better characteristics: good dispersibility, high adsorption ability, solid lubricating ability and biocompatibility.[3] Thanks to the large variety of surface groups, different functionalizations could be performed and many different surface groups can be attached on NDs using wet chemistry methods[4] and a variety of molecules with valuable properties (biological, fluorescence etc.) can be introduced for example by amidation on ND–COOH.

NDs may be used for a broad range of applications such as mechanical applications, electrochemical applications and medical purposes[5] and in this respect various derivatization methodologies will be optimized and dedicate to the preparation of derivatives with theranostic applications.

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Development of bioinspired artificial nanocatalysts for energy conversions

Supervisor: Prof Paolo Fornasiero

Sustainability and energy are two of the keywords of today's research focus. Implementation of new sustainable schemes for the synthesis of industrial-relevant chemicals, or for the establishment of alternative energy schemes that do not rely on fossil fuels are among the most modern scientific challenges. Nanotechnology offers a powerful tool for the faster development of such schemes.

The successful PhD candidate for this project will have the opportunity to work on the fascinating world of nanomaterials, with the aim to design and synthesize nanomaterials with suitable functionality to perform catalytic tasks in relation to energy conversions and biomass valorization. Some of the materials of interest will be built upon the concept of *interfacing* different components, as this strategy has proven to be ingenious approach for boosting catalytic performance of nanocatalysts thanks to synergistic effects. In particular, the multi-component nanomaterials will arise from the opportune hybridization of two or three different phases including: 1) metal nanoparticles/single atoms, 2) metal oxides/dichalcogenides/nitrides, 3) (functionalized or doped) carbon nanostructures. However, the correct combination has to be mastered at atomic level, therefore requiring deep knowledge in synthesis and reactivity, which will be the central part of the candidate's gradual growth as a scientist.

The catalytic processes which will be under the lens include photo- and electro-activated reactions connected with green energy conversions, such as the reduction of CO_2, O_2 or N_2, the formation of H_2, the oxidation of H_2O. For each of this reaction, the design of the catalytic ensemble will be rationally constructed around the specific reaction restrictions and hurdles. The purpose is that the different phases will cooperatively carry out individual functions that will result in an overall increase of the activity, selectivity and stability of the hybrid nanocatalyst. Our group has vast experience in this field of research, proven by the various reported examples in high-impact journals, where the synergy between the carbon nanoscaffold (able to improve electron mobility and transfer), the metal oxide (capable of tuning binding states of the reaction intermediates) and the metal nanoparticles (that act as the active site) trigger the conversion with significantly high efficiency, establishing in several cases new state-of-the-art.[1,2,3]

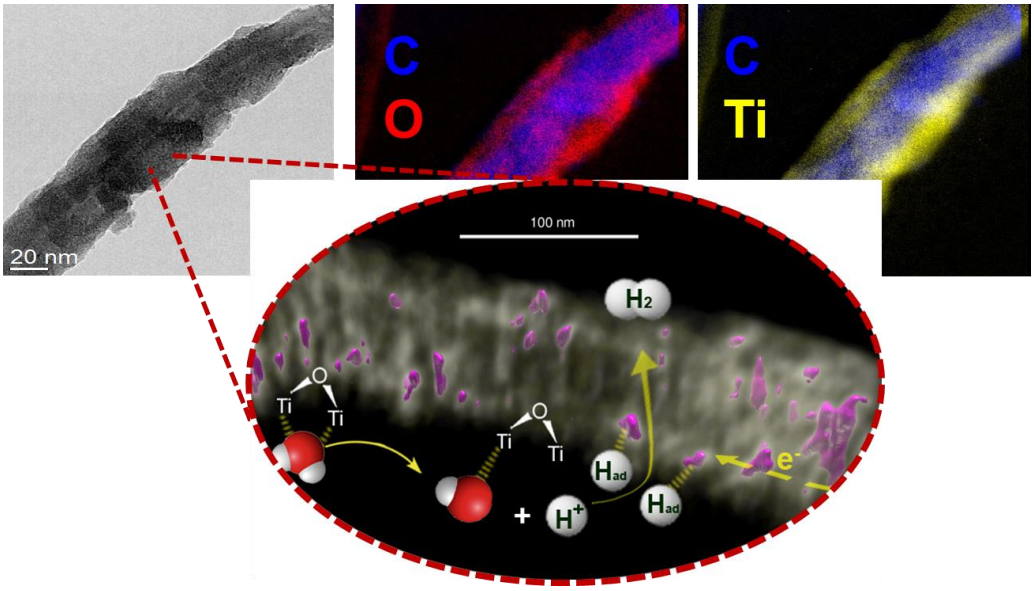

Figure 1. TEM, EDX , tomography and mechanism of formation of H_2 by a catalyst consisting of carbon nanotubes, Pd nanoparticles and TiO_2 mutually integrated

In addition, development of nanostructured catalysts for the photocatalytic conversion of biomasses will be also investigated. We have recently proven that atom efficiency through use of the concept of single atom catalysts (SACs) in combination with nanocarbon or metal derivatives can be exceptionally exploited for the transformation of organic substrates.[4,5] These themes are emerging as the new frontier of research in science for sustainability, and the assortment of synthetic and characterization methodologies reveals an important element of creativity and ingenuity, which will shape the candidate's attitude towards modern science, increasing her/his chances for future career upgrades.

The successful candidate will therefore develop a very valuable interdisciplinary portfolio of skills, ranging from classic organic synthesis to advanced inorganic preparative methods, enriched with acquisition of competence in modern characterization techniques of nanomaterials, such as TEM, AFM, Raman, XAS, XPS, NMR, electrochemical analysis, XRD and others. The project is in close connection with ongoing European projects (project DECADE and project SUN2CHEM), and will bring the possibility to interact with high-profile European Research groups in several EU countries.

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NANOSTRUCTURED BIOMATERIALS for TISSUE REGENERATION & INNOVATIVE THERAPY

Supervisor: Prof. S. Marchesan www.marchesalab.com

Molecular self-assembly is defined as the spontaneous and reversible process resulting from the self-organization of simple building blocks into complex structures with a higher level of supramolecular order, and with well-defined properties. This phenomenon is widely diffuse in nature and it has been a source of inspiration for nanotechnologists to allow the construction of reversible structures. Self-assembled systems are formed through the natural organisation of a high number of simple components linked together *via* weak non-covalent interactions that can be easily disrupted and reformed, to allow for dynamic processes to occur, such as self-healing, growth, and differentiation. Amongst the various building blocks for nanostructured biomaterials, self-assembling short peptides have attracted great interest and have been identified as an emerging research field with high potential for the future of chemistry,[1] and in the natural sciences in general.[2]

Upon design, short peptides can self-organise into fibrils that form a three-dimensional network resulting in a hydrogel; they can can be fine-tuned to display also bioactive sequences, for instance to direct cell fate towards cell adhesion (see **Fig. 1**),[3] which in principle can be used to regenerate human tissue that has been damaged, by delivering (stem) cells within a matrix that favours cell growth and profileration. These nanostructured hydrogel biomaterials can also be designed to display additional properties, such as antimicrobial activity[4] or catalysis to mimic enzymes.[5] Although the basis have been laid for the development of these biomaterials, much remains to do in order to provide complex nanostructured biomaterials designed *ad hoc* for specific solutions, for instance to regenerate specific tissue such as the nerve tissue and the brain,[6] and/or that release drugs[7-8] and other bioactive compounds upon application of a stimulus. Research in this hot area will involve the preparation and characterization of small peptides for their assembly into nanostructured biomaterials that will thus be designed to specifically interact with cells for the regeneration of tissue and the development of innovative therapies. The research is highly multidisciplinary, with the nanostructures being characterised with different *in silico* and experimental techniques that encompass the areas of chemistry, biology, and physics, and that will include synchrotron techniques.

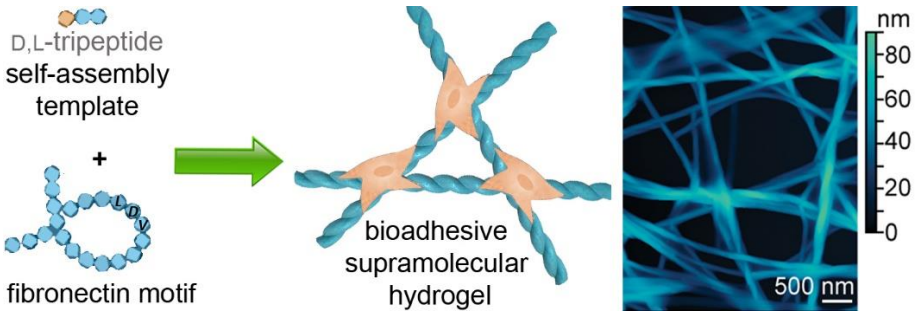

Fig. 1. Two short peptides assemble into a nanostructured and bioactive hydrogel that directs cells towards adhesion. The noafibrils can be seen by atomic force microscopy (right).[3]

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CONTROL OF SELF-ASSEMBLY OF FUNCTIONAL GOLD NANOPARTICLES

Supervision: Lucia Pasquato and Paolo Pengo, Department of Chemical and Pharmaceutical Sciences, University of Trieste, e-mail: lpasquato@units.it, ppengo@units.it

Directed self-assembly of nanometer-sized materials into ordered arrays are the most widely studied targets of current research. The bottom-up approach for the fabrication of functional materials is very attractive since it utilizes small and rather simple building blocks that will self-assemble into larger, more complex nanostructures. For these approaches, (bio)chemists are inspired by Mother Nature, who uses a large variety of covalent and non-covalent interaction mechanisms. In this context we are interested in developing new protocols to self-assemble anisotropic hybrid organic-inorganic nanoparticles with a control over the assembly process to give rise to well defined architectures. Particularly interesting will be to trigger the assembly/disassembly process upon application of external chemical stimuli. The project foresees the design and synthesis of anisotropic gold nanoparticles, their modification with selected functional groups and/or functional building blocks and the study of their self-assembling process driven by different conditions. A variety of techniques will be used to characterize the final material and to investigate their optical and electronic properties.

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EXPLORING THE MULTIDIMENSIONAL COMPLEXITY OF SELF-ASSEMBLED MONOLAYER PROTECTED METAL NANOPARTICLES BY ADVANCED COMPUTATIONAL TECHNIQUES

Supervisor: Paola Posocco (University of Trieste)

The chemistry of surface-stabilizing species plays a critical role in determining the properties, interactions and reactions of myriad nanomaterials, including the archetypal self-assembled monolayer-stabilized gold nanoparticles (SAM-AuNPs). While experimental efforts have led to significant developments in synthesis and functionality, harnessing the technological potential of these nanomaterials demands that we extend to nanoscale chemical entities the predictive structure–function correlations currently taken for granted in the molecular world.

The distinct surface-bound environment imposes very specific conditions on molecular reactivity and interactions. The parameter space that defines the interfacial environment at the surface of colloidal nanomaterials is far more complex than that typically encountered for bulk solution systems. Molecular and nanoscale parameters influence numerous other structural and physicochemical features. In turn, each of these will affect interactions and reactions at the nanoparticle–molecule–solvent interface. This complexity presents a huge unmet challenge.

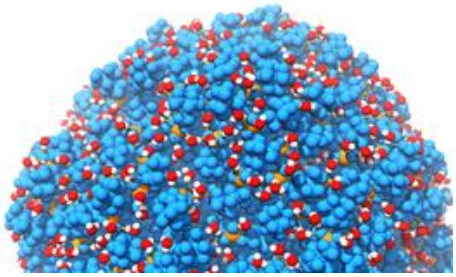
Developing *ad hoc* computational models and combining them with advanced computational techniques will allow us to reveal not only unprecedented details on molecular structures in isolation, but also to consider the emergent consequences of confining several molecules on a nanoparticle surface and the collective interactions between many nanoparticles at the same time.

This will pave the way to a new era of chemistry incorporating nanoscale building blocks that is just as predictable as present-day chemical technology based on molecules. Furthermore, SAM-AuNPs provide a general platform for studying surface chemistry, which is critical to many applications, from (bio)sensors and heterogeneous catalysts to hierarchically, molecularly-controlled, and reconfigurable 3D assemblies.

In this context, the PhD activity will focus on the development of new computational models of a variety of SAM-AuNPs. The main goal is to understand the key molecular factors, forces and properties that control self-assembly, structure, reaction and recognition properties of SAM-AuNPs. Via the integration of many technique (e.g. quantum mechanics, atomistic and coarse-grained dynamics) and the use of classical and advanced molecular simulation approaches (e.g., molecular dynamics, enhanced sampling techniques such as metadynamics, thermodynamics integration, etc.), the selected PhD candidate will investigate structure and behavior of SAM-AuNPs on a wide spatio-temporal scale.

We are seeking people with:

- experience in molecular modelling and common packages (e.g. LAMMPS, GROMACS, AMBER)
- programming skills (preferably Python or C++) and knowledge of parallel computing environment
- strong motivation and enthusiasm for research
- good attitude to work in team
- good written and spoken English



Self-assembled monolayer on a spherical nanoparticle and selected bonded water molecules.

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Do not hesitate to write for any further information!

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Carbon Dots for Biocompatible Organocatalysis

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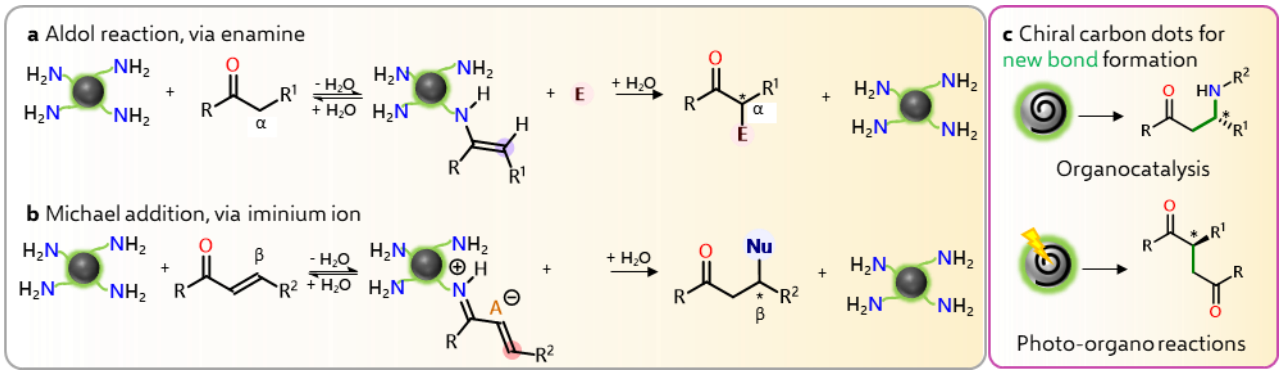
This project aims at engineering carbon dots for their use as safe and inexpensive organocatalyst, capable of operating in a biological environment.

Carbon dots are carbon-based quasi-spherical nanoparticles with a size below 10 nanometres. In contrast with other carbon-based nanomaterials, they show good water solubility; moreover, they have low toxicity. These features make them suitable for both technological and biological applications. For these reasons, our group is particularly interested in the chemistry of carbon dots, from the investigation and engineering of their properties, up to their application.[1]

A frontier development in the chemistry of carbon dots is their use as a catalyst to perform organic transformations. To this regard, carbon dots may become game-changer in green organocatalysis and *in-vivo* drug synthesis [2] With this idea in mind, so far we have demonstrated their ability as photo- and organo-catalyst able to perform organic transformations under mild conditions, and in water.[3]



Carbon dots as organocatalyst: General scheme for carbon dots-catalyzed (**a**) aldol and (**b**) Michael reaction; (**c**) synthetic targets accessible unlocking enantioselective catalysis by carbon dots.

In the coming years, we aim at expanding the capabilities of carbon dots as organocatalyst, by developing enantioselective transformations, and merging photocatalysis with organocatalysis. This project involves the design, synthesis, and use as organocatalyst of novel (chiral) carbon dots.

The PhD student will become fluent in organocatalysis and develop synthetic skills. The designed materials will be characterized using state-of-the-art spectroscopy and microscopy techniques. Extensive use of nuclear magnetic resonance (NMR) will be employed to monitor the catalytic activity of carbon dots. For the optimal development of collaborative projects, it is likely for PhD students to perform a research stay abroad.

Our group is a lively cluster committed to interdisciplinarity and the student will also be exposed to several aspects of carbon nanotechnology, that represent the core expertise of the group. Typically, the PhD work starts from an ongoing project. Then, the individual interests and attitudes of the student come into play and shape the development of his path into research.

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Machine-Learning-Guided Discovery of Carbon Dots for New Applications

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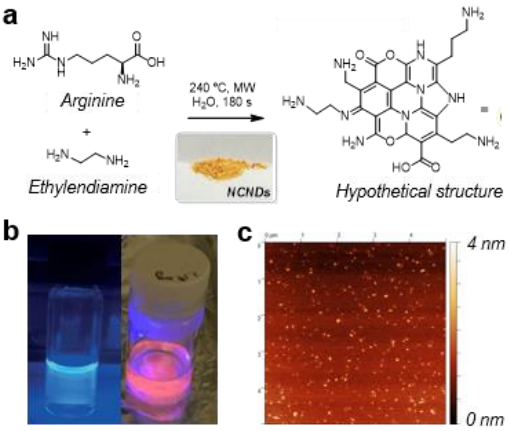
This project aims at the use of machine-learning strategies for the discovery of carbon dots with improved properties. Applications are envisioned for photonic or bioimaging purposes.



Carbon dots: (**a**) typical synthetic strategy; (**b**) blue and red-emitting carbon nanodots; (**c**) AFM image of the studied material.

Carbon dots are carbon-based quasi-spherical nanoparticles with a size below 10 nanometres. In contrast with other carbon-based nanomaterials, they show good water solubility and are fluorescent; moreover, they have low toxicity. These features make them suitable for both technological and biological applications.

Our group is particularly interested in the chemistry of carbon dots, from the investigation and engineering of their properties, up to their applications.[1] The synthesis of this material is typically performed with a simple and inexpensive microwave reaction.[2] In this process, different organic precursors are chosen (e.g. amino acids, small aromatic and aliphatic molecules) to tailor the properties of the target material. However, optimization of the synthetic conditions is obtained using a "one-variable at a time" approach, which is inefficient and may not afford the optimal material. To overcome this limitation, machine-learning techniques will be employed, to identify the optimal synthetic conditions.[3] This approach will be used first to optimize an existing material and then to discover new carbon nanodots with desirable properties, such as near-infrared emissive nanoparticles suitable for bioimaging applications. The same strategy can be extended to target application in photo- and electro-catalysis, and drug delivery.

The PhD student will develop synthetic, analytical, and coding skills. The latter will be developed in collaboration with Prof. Medvet (Department of Engineering and Architecture, expert in machine learning). The obtained materials will be analyzed with state-of-the-art spectroscopic methods, including nuclear magnetic resonance (NMR), optical spectroscopies, atomic force and transition electron microscopies (AFM, TEM) and infrared spectroscopy (IR). Our group has also a strong track record of fruitful collaborations, that involve also the use of X-ray facilities at the synchrotron (Trieste) or MRI facilities at CIC biomaGUNE (San Sebastian, Spain). For the optimal development of collaborative projects, the PhD students will have a chance to perform part of their research abroad.

Currently, seven members of the group are involved in this frontier research line, thus creating a lively and stimulating environment for the professional development of new members. Our group is committed to interdisciplinarity and the student will be exposed also to other fields related to carbon nanomaterials, that represent the group core expertise.

Typically, the PhD work starts from an ongoing project. Then, the individual interests and attitudes of the student come into play and shape the development of his/her path into research.

References:

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[3] "How to explore chemical space using algorithms and automation" P. S. Gromski, A. Henson, J. Granda, L. Cronin, *Nat. Rev. Chem.* **2019**, 3, 119.