PROJECT N°: 1A

Progetto di Dottorato, relatore P.Decleva, correlatore D. Toffoli

Il progetto di Dottorato e' centrato sullo studio delle dinamiche elettroniche e nucleari in esperimenti pump-probe molecolari, resi accessibili dalle piu' recenti sorgenti di radiazione, impulsi laser near infrared ultracorti, generazione di alte armoniche (HHG) e laser a elettroni liberi (FEL), per quest'ultimo specialmente il FEL FERMI a Trieste. In particolare si esplorera' l'uso della fotoionizzazione angolarmente risolta (PAD) come probe, sia dopo l'allineamento parziale prodotto dall'impulso di pump, sia la distribuzione angolare completa nel frame molecolare, esperimento piu' difficile e delicato [1,2], ma in fase di sviluppo presso diversi laboratori, e in particolare a Fermi. La disponibilita' delle nuove sorgenti ha permesso un salto qualitativo nella rivelazione dei fotoelettroni, fornendo informazioni molto piu;' ricche e dettagliate [3]. Tuttavia la sola rivelazione delle energie di ionizzazione e' un'informazione molto parziale e spesso non riesce a distinguere stati elettronici iniziali diversi [3,4], che possono essere discriminati dalle PAD. Un aspetto di interesse sara' lo studio della chiralita' risolta in tempo attraverso la fotoionizzazione chirale. Il progetto si basera' sui programmi per il calcolo della fotoionizzazione molecolare, sia a un fotone, ampiamente sviluppati nel nostro laboratorio, sia su nuovi sviluppi per il calcolo della ionizzazione multifotonica e in campo forte, e la generazione di HHG, e lo sviluppo di algoritmi close coupling ab initio sempre piu accurati. Il lavoro di tesi sara' centrato sullo sviluppo di codici per la trattazione del moto nucleare in piccola dimensionalita', e l'interfaccia con il programma MCTDH e i metodi di surface-hopping per affrontare sistemi di maggiori dimensioni
Verranno affrontati due tipi di esperimenti

1. La dinamica nucleare non adiabatica in molecole di medie dimensioni, in particolare di interesse biologico, studiate a FERMI, nel regime di femtosecondi (10-1000), con la dinamica nucleare surface-hopping classica (SHARC e Newton-X), interfacciata al calcolo dei parametri di fotoionizzazione, anche in collaborazione con l'istituto Rudjer Boscovich e l'Universita/CNR di PISA.
2. Dinamica elettronica negli attosecondi [5] iniziata da impulsi molto larghi capaci di di generare pacchetti coerenti di stati elettronici, fino all'onset del moto nucleare, nel regime 100as – 10 fs. In questo caso l'intero pacchetto elettronico nucleare e' coerente, e richiede l'uso di una trattazione quantistica, finora non disponibile. In collaborazione con Pisa si procedera' per stadi di complessita' crescente, includendo il moto nucleare dapprima attraverso i fattori di Franck-Condon (o Herzberg-Teller) a diversi livelli di approssimazione (FCclasses), e successivamente usando modelli di accoppiamento non-adiabatico lineare e quadratico attraverso l'interfacciamento col codice MCTDH
3. Calcoli accurati su piccoli sistemi con la trattazione quantistica completa, in base B-spline, del moto nucleare, includendo gli accoppiamenti non adiabatici, a partire da 1 grado di liberta' vibrazionale (biatomiche), e successivamente fino a 3 (triatomiche e sistemi modellizzati in bassa dimensionalita'

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PROJECT N°: 2A

IRREVERSIBLE DEUBIQUITINASE INHIBITORS AS ANTICANCER AGENTS

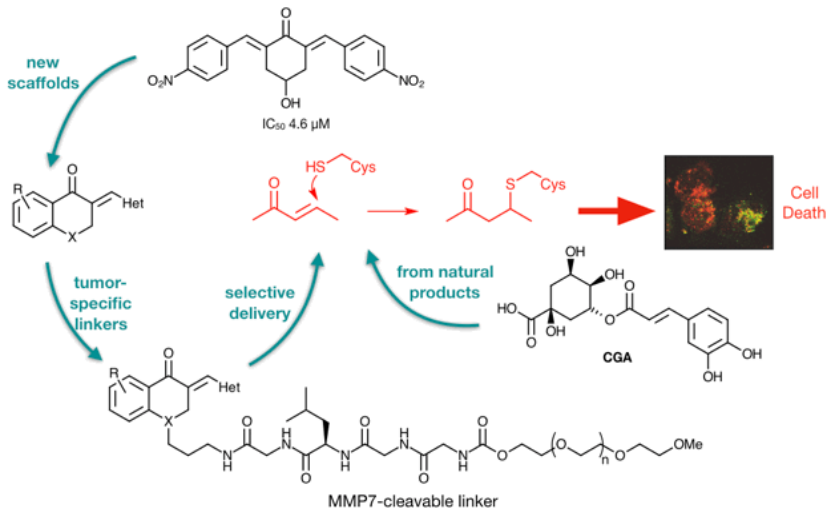
SUPERVISOR: PROF: FULVIA FELLUGA

The ubiquitin-proteasome system (UPS) is the main cellular system for the selective degradation of damaged, modified, or misfolded proteins. Cancer cells are highly dependent on the correct functioning of this system, and this has made the UPS an attractive target for the development of selective anticancer drugs [1,2]. Protein degradation by the UPS takes place in three steps:

1. **Ubiquitination,** allowing the target protein to be recognized by the proteasome.
2. **Deubiquitination** by specific enzymes (deubiquitinases, DUBs, isopeptidases). Six families of DUBs are known, five of which are cysteine-dependent.
3. **Proteolysis** by the proteasome specific activity.

Bis-arylidenecyclohexanones are powerful deubiquitinase inhibitors and exhibit anticancer activity at the uM level, both *in vitro* and *in vivo* [3-5]. The present project aims at the development of second-generation inhibitors with improved activity and selectivity. This will be addressed by three interconnected and complementary approaches, based on:

i. modifications of the scaffold, guided by molecular modelling and by X-ray crystallographic studies of the complexes between selected covalent inhibitors and deubiquitinases;
ii. the search for new deubiquitinase inhibitory activities among natural products and analogs;
iii. synthesis of conjugates selectively targeted at cancer cells and/or activated by cancer cells.



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PROJECT N°: 3A

Dottorato XXXIV ciclo

Supervisore: Cristina Forzato

Sviluppo di un sensore per la determinazione dei principali polifenoli presenti nell'olio d'oliva

Recentemente l'Unione Europea ha stabilito un elenco di indicazioni sulla salute consentite sui prodotti alimentari. Per l'olio d'oliva tale indicazione riguarda il livello di idrossitirosolo e suoi derivati, che deve essere di almeno 5mg per 20g di olio d'oliva. In questo caso il produttore potrà riportare sull'etichetta questa indicazione. Nel presente dottorato, verranno sviluppati dei sensori economici, di facile utilizzo e con una risposta rapida, specifici per alcuni polifenoli presenti nell'olio d'oliva, che permetteranno al produttore di verificare durante tutto il ciclo di lavorazione il contenuto di polifenoli senza dover ricorrere ad analisi lunghe e costose. Il lavoro consisterà in una attività preliminare allo sviluppo del sensore che riguarda l'identificazione degli elementi di riconoscimento che verranno poi applicati ad un sensore e che permetteranno di identificare i composti da dosare. Si utilizzerà la tecnica dell'imprinting molecolare che vedrà coinvolti diversi potenziali monomeri, tra cui anche amminoacidi e peptidi e che porteranno all'ottenimento di materiali polimerici. Tali materiali polimerici potranno anche contenere componenti altamente fluorescenti in grado di conferire loro la proprietà di emettere luce visibile, che potrà cambiare colore ed intensità in presenza dei polifenoli da dosare.

PROJECT N°: 4A

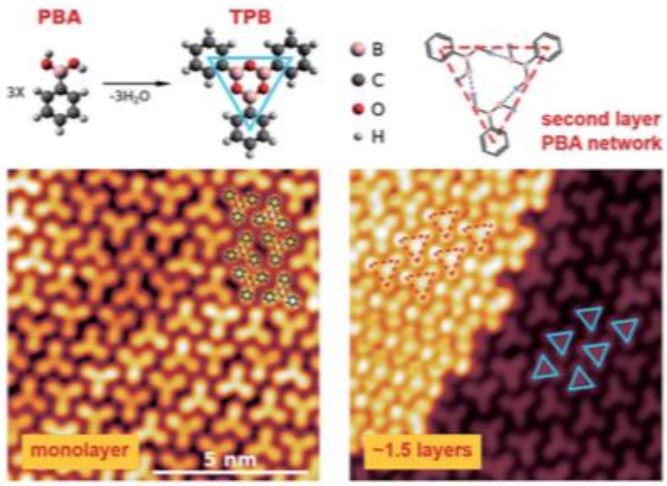
Title: Computational NEXAFS studies on the controlled formation of metal-supported 2D supramolecular structures

Supervisor: Giovanna Fronzoni (DSCF, email: fronzoni@units.it), Co-supervisor: Daniele Toffoli (DSCF, email: toffoli@units.it)

Progetto non cofinanziato

The focus of the project is the investigation of the adsorption and assembly of medium-sized organic molecules on metal surfaces and on Ni supported N-doped graphene. NEXAFS is a powerful tool to investigate the geometry of molecules adsorbed on surfaces [1]. Density Functional Theory (DFT) and its time-dependent generalization (TD-DFT) will be used to accurately simulate core spectroscopies such as XPS and NEXAFS (Near Edge X-ray Absorption Fine Structure) of gas phase molecules and their 2D polymerization products on the surfaces of interest. The computational protocol consists in *i)* an accurate modelling of the surface/adsorbate interface with periodic boundary conditions and plane-wave basis sets (by using solid-state programs such as QUANTUM ESPRESSO [2]) followed by *ii)* the generation of a suitable set of clusters (cut from the periodic structure) from which angularly resolved NEXAFS spectra are calculated with standard techniques of quantum chemistry and localized basis sets, implemented in the ADF suite [3].

Systems of current interest are the polymerization of boronic acids (such as tetrahydroxyl diborane and phenyl diboronic acid) on Au(111), Cu(111) and Ni(111) covered by *N*-doped graphene. These systems are studied in close collaboration with experimentalists working at the ALOISA beamline of the ELETTRA Synchrotron Lab of Trieste. The aim of the project is to obtain a deeper and detailed understanding of the surface/adsorbate interaction and an atomistic description of the initial stages of the association and polymerization process on the metallic surface. This aspect is crucial for the controlled formation of 2D templates that can be used in diverse fields of applied research relevant for catalysis and materials science [4,5].



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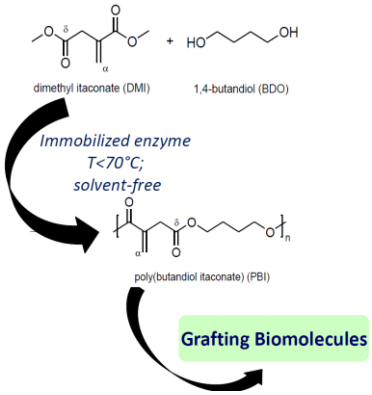
PROJECT N°: 5A

Advanced functional polymers for pharmaceutic and cosmetic applications by targeted enzymatic synthesis and derivatiozation.

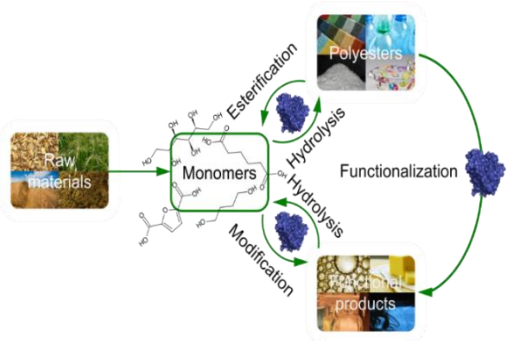
Tutor: Prof. Lucia Gardossi, Laboratory of Applied and Computational Biocatalysis

Aim: The project will aim at the synthesis of renewable and biodegradable polymers (polyesters and polyamides) with the ultimate aim of introducing chemical functionalities that can be exploited for the anchoring of bioactive molecules for advanced applications in the biomedical, cosmetic and packaging sectors. UN has estimated that the yearly environmental cost of plastic use amounts to US$75 billions. Most of this cost is due to extraction and processing of petrol based raw materials. Therefore, the recycling of plastics is not sufficient for mitigating the problem. Rather, the polymer sector is under the urge to develop more sustainable polymers, but also endowed with new and advanced functionalities. The project intends to close the cycle, by synthetizing advanced polymers that can be bio-degraded but that are also made from renewable raw-materials.



Background: In the last years, the group of Applied and Computational Biocatalysis has developed the first examples of fully-renewable and biodegradable polyesters starting from bio-based monomers. The application of enzymes in polyester synthesis not only overcomes the use of toxic metal catalysts: they are also able to control the polymer architecture maintaining functional groups on polyester sequence without causing cross reactivity. Indeed, by operating under very mild conditions (50-80°C), polycondensation can be carried out also starting from sensitive and functionalized monomers that would degrade under classical conditions (>150°C). Finally, enzymes were used to catalyze the selective modification of the surface of polymeric materials while maintaining their bulk properties, in collaboration with Boku-Vienna University, using different hydrolases. The work led to the publication of 17 papers (2014-2017) and a patent has been filed, which demonstrates the feasibility of enzymatic polycondensation in thin-film turbo reactors at pilot scale [Cerea et al., EP 2 620 462 A1.].

Expected progress beyond the state of the art: Bio-based plastics are made from renewable resources, they are not necessarily biodegradable. The project will aim at the synthesis of polyesters containing enzyme-susceptible breaking points that greatly enhance their biodegradation. Moreover, hydroxyl-, thiol- or carboxyl functional pendant groups along the macromolecular chains will be inserted to facilitate covalent anchorage of pro-drugs or biomolecules. Computational studies will guide "substrate engineering" approaches, for selecting monomer structures favorable to chain elongation and enzymatic attack to enhance biodegradability. The project will be carried out in collaboration with Vienna University and leading Italian companies in the field of bio-based plastics.



Impact: Global bio-based plastics production capacity is set to increase from around 4.2 million tonnes in 2016 to approximately 6.1 million tonnes in 2021.

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More at: https://www.units.it/data/curricula/5281.pdf

PROJECT N°: 6A

Structural characterization of the human Kir2.1 channel using X-ray Crystallography and Electron Microscopy (Supervision: Silvano Geremia, email: sgeremia@units.it)

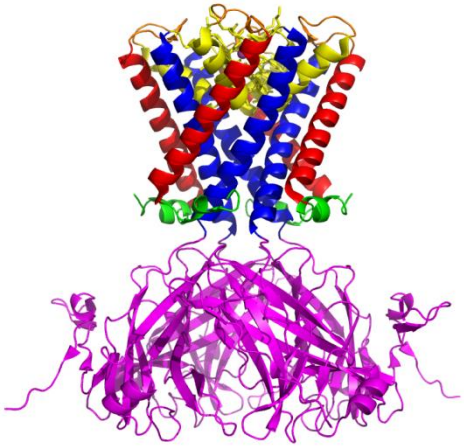

Figure: Structure of the bacterial channel KirBac3.1.

Inward rectification is the physiological process that allows the regulation of the potential of cell membranes using ion channels that conduct positive ions in the inward direction at negative potentials, but that are blocked at higher membrane potentials. The inwardly rectifying potassium (Kir) channels are a superfamily of K^+ channels that regulate membrane potential and potassium ion transport in many cell types. Kir channels are involved in crucial processes .in the human body, among which regulation of myocardial muscle, heart rate, vascular tone, secretion of insulin, renal transport, neuronal signaling and electrolyte transport across epithelia. Mutations in Kir channel genes cause dysfunctions and diseased such as Anderson's syndrome (Kir2.1), Bartter's syndrome (Kir1.1) and insulin secretory disorders (Kir6.2) [1].While homologous bacterial channels (Figure) have been fully characterized in both the closed [2] and open [3] conformations, structural information is not available for human Kir channels, despite their pharmacological importance. In addition, questions regarding the role of lipids in allosteric regulation of Kir channels are still unanswered.

In collaboration with Prof. Catherine Venien-Bryan, our laboratory is undertaking a structural study of Kir channels through the combined information derived from Cryo-Electron Microscopy and X-ray crystallography. The PhD student involved in this project will purify the human Kir2.1 protein from yeast membranes, characterize it through mass spectrometry, electrophoresis and spectroscopic techniques, and set up crystallization trials. The second step will be the structural determination through X-ray diffraction techniques at the Elettra synchrotron (beamline: XRD1). In parallel, the laboratory of Prof. Venien-Bryan in Paris (Pierre and Marie Curie University) will use the purified protein to obtain Cryo-Electron Microscopy (EM) data. The PhD student will have the opportunity to spend some months in Prof. Venien-Bryan's laboratory, where he/she will be trained in both EM data collection from frozen samples and image analysis. The comparison between the results obtained with the different structural techniques will offer new insights into the mechanism of action of this important channel and open the way to the development of drugs that have Kir2.1 as target.

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PROJECT N°: 7A

ORPHAN DRUGS: NEW INHIBITORS OF CERAMIDE GLUCOSILTRANSFERASI FOR THE TREATMENT OF GAUCHER DISEASE

Supervisor: Teresa GIANFERRARA

A disease is defined as rare when its incidence does not exceed an established prevalence threshold that for the European Union is 0.05% of the population. An approved drug for the treatment of a rare disease is called an orphan drug because it does not have a sufficient market to repay the costs of its development. The known rare diseases are 6-7,000 and for most of them an adequate therapy is not available. According to the Orphanet portal for rare diseases and orphan drugs in Italy rare patients are 1-2 million, of which 70% are pediatric (<14 years).[1]

Gaucher disease (GD) is a lysosomal storage disease (LSD) which results from the deficient activity of glucocerebrosidase, a degradative enzyme involved in the catabolism of cerebrosides in macrophage cells, which causes the lysosomal accumulation of harmful amounts of cerebrosides and leads macrophages to a permanent activation state, with production of a large amount of chemokines and interference with tissue metabolism and immune system. There are three types of GD: i) type I: non-neuropathic form; ii) type II: an infantile, acute neuropathic form that can lead to early death by 2 to 4 years of age; iii) type III: chronic form, with neurological symptoms comparable to type II but with a slower progression with a life expectancy of 30-50 years.[2]

Enzyme replacement therapy (ERT) is a therapeutic approach that controls the systemic manifestations of GD, except those of the nervous system, since the intravenously administered enzyme is unable to cross the blood–brain barrier (BBB). Currently, three recombinant enzymes have been approved for GD treatment: imiglucerase, velaglucerase alfa and taliglucerase alfa.

Substrate reduction therapy (SRT) is an alternative approach and two inhibitors of glucosylceramide synthase (GCS, which catalyzes the reverse reaction of glucocerebrosidase) have been approved: miglustat **1** and eliglustat **2** (Figure 1A), which are respectively an iminosugar and a glucosylceramide analog. Furthermore, it has been observed that overexpression of GCS increases multi-drug resistance (MDR) in many tumor cells,[3] therefore GCS inhibitors might also be useful in treating oncologic diseases. Although **2** is a small molecule able to cross the BBB, its concentration in the brain is limited since it is a substrate of the P-glycoprotein (MDR1), which has extrusion function and it is highly expressed in BBB.[4] Eliglustat can be administered only to patients who are not ultrafast metabolizers via CYP2D6, in whom the achievement of therapeutic plasma concentrations is critical. On the contrary, high plasma doses can lead to arrhythmias, so it is necessary to avoid **2** in patients treated with CYP2D6 and CYP3A4 inhibitors and/or with pre-existing cardiac diseases.[5] So far the only GCS inhibitors reported in literature are analogous of **1** and **2**. Recently it has been reported that two antitumor compounds structurally different from eliglustat (Figure 1B, **3** and **4**) act with multiple mechanism of action that seems to involve the inhibition of GCS.[6]

As discussed above, the search for GCS inhibitors with better pharmacokinetic and pharmacodynamic characteristics is a field that has not been yet thoroughly explored and represents an open challenge in the treatment of GD, especially of the neuropathic forms (type II and III), for which currently no established therapy is available. Based on these observations, the aim of the project is to identify new classes of small molecule inhibitors of GCS and to optimize the lead compound(s). To this end, the development of a library of low molecular weight molecules is a valuable strategy. In order to synthesize molecules with the maximum structural diversity, compounds **2**, **3** and **4** were selected. Basically, the idea is to combine significantly different synthons to develop a high-affinity GCS inhibitor with a lack of recognition by MDR1 to achieve a pharmacological response in the brain (Figure 1C). The library will be characterized in vitro using enzyme assays with the commercially available glucosylceramide synthase. Enzyme screening will allow a quick selection of the most promising compounds which will be studied in vitro on cells to develop and optimize the selected structures.

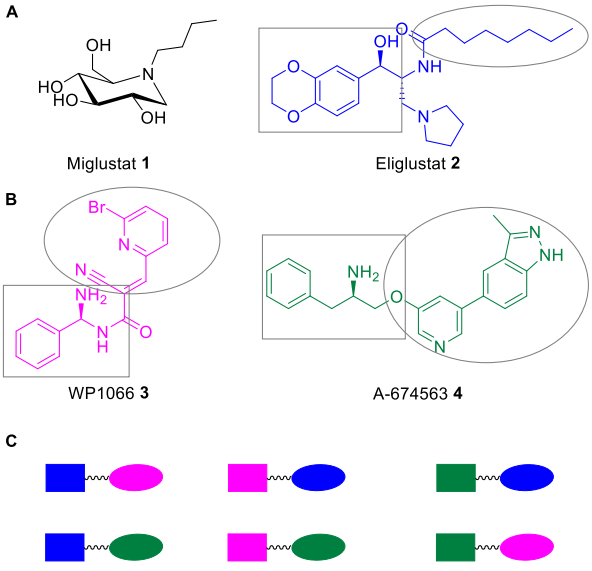

Figure 1: A) GSC inhibitors; **B)** antitumor compound with potential inhibitor mechanism of GSC; **C)** schematic representation of the library of compounds.

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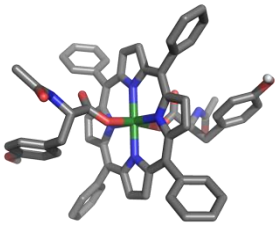
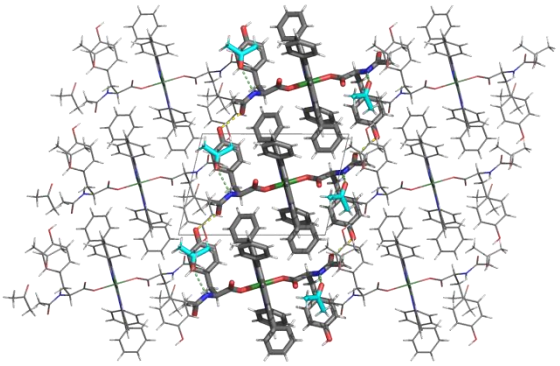
PROJECT N°: 8A

Field Inorganic Chemistry
Supervisor Prof. Elisabetta Iengo, email eiengo@units.it
Title Sn(IV)-porphyrins: novel interpretations of the versatility of well-documented functional metal scaffolds.

The properties of Sn(IV) porphyrin metal fragments, i.e. planarity, six-coordination and robust binding of oxyanions, plus visible absorption, luminescence and ease of reduction, concomitant to the possibility of fine-tuning of the opto-electronic characteristics by structural variation of the macrocycle, are constantly attracting the interest of different research fields. These range from supramolecular self-assembly to biomedical, sensing, photocatalysis and artificial photosynthesis. In particular, the efficient formation of Sn(IV)-di(carboxylate)-porphyrin derivatives from a carboxylic acid and a Sn(IV)-di(hydroxo)-porphyrin, with the elimination of water, makes the $Sn(OH)_2$-porphyrins ideal core building blocks for a wide variety of derivatives [1].
The present project focus on the development of our recent studies on the use of tin-porphyrins as metal scaffold for the modular preparation of supramolecular discrete 3D supramolecular architectures for molecular recognition, and antenna/electron-acceptor:: electron-/proton-donor conjugates for charge separation activated by photoinduced proton-coupled electron-transfer (PCET) [2]. As example, the single crystal X-ray molecular structure of a simple conjugate featuring two N-acetyl-L-tyrosinato residues axially coordinated to the metal center of a Sn(IV)-porphyrin, together with the intermolecular H-bonding interactions found in the crystal packing, is shown in the Figure (left and right, respectively). For this system unprecedented long-lived charge separation was achieved by photoinduced PCET, in the presence of pyrrolidine as a base. Quite unexpectedly, there are only two reported examples of derivatives consisting of chiral amino acid residues axially connected to a tin-porphyrin chromophore, via an amino acid carboxylate group, and their use as synthons in the supramolecular realm, while intriguing, is yet unexplored.





More in particular, the project will address: i) development of libraries Sn-porphyrin/amino acids constructs aimed at exploiting PCET to achieve relevant charge separation, and in parallel at better understanding the fundamental rules of this photochemical process; ii) 3D discrete container assemblies with variable size/shape cavities and built in physicochemical/photophysical properties. The combinatorial flexibility and the possibility to follow a modular approach offered by the metal-mediated strategy should facilitate the access to a wide variety of molecular modules. At the same time, a transfer of the inherent designed properties of the modules to the final architectures is expected and should allow successive fine-tuning/implementation steps.
Inorganic, organic and supramolecular synthetic methodologies will be employed for the preparation, isolation and/or purification of the molecular modules and their derived structures.
A collection of characterization techniques will be employed in solution (ESI-MS spectrometry, NMR, UV-vis and Emission spectroscopies) and in the solid state (IR spectroscopy and single crystal X-ray diffraction with the use of synchrotron light source).
The properties of the units and of the assemblies, with specific regards to the photo/electro/catalytic active response, thermodynamics and kinetics of the up-take and release of guests, will be monitored with the appropriate techniques (e.g. ultrafast spectroscopy, gas chromatography, etc), in collaboration with local, national and foreign research groups.
A six month stay in a foreign research group with complementary scientific expertise will be strongly recommended, in order to increase the project rate of success, expand and differentiate the PhD fellow skills, research methodologies, as well as working and social environment.

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PROJECT N°: 9A

Development of Pd complexes with hybrid N-X ligands as potential catalysts for polymerization reactions

Supervisor: **Prof. Barbara Milani**
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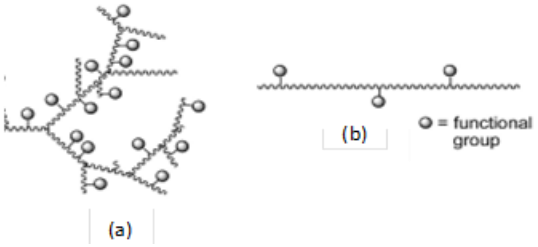
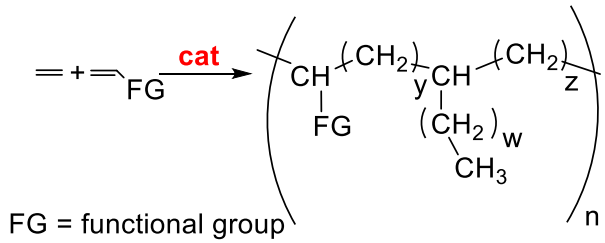
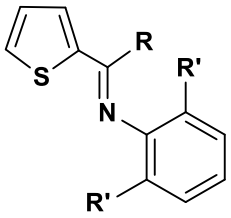
One of the major unsolved problems in the field of polymer chemistry is represented by the synthesis of **functionalized polyolefins**. Polylefins are the non-naturally-occurring materials of excellence. Nevertheless, they suffer of scarce surface properties such as adhesion, dyeability, printability and compatibility. The introduction of polar functional groups into the polyolefin skeleton will improve such properties, expanding the range of applications. Among the different typologies of functionalized polyolefins, two classes are highly desirable: (a) branched polyolefins having randomly distributed functional groups; (b) linear polyolefins having the polar monomer into the main polymer chain.



The direct, homogeneously catalyzed, copolymerization of ethylene with polar vinyl monomers is the most powerful tool to obtain these polymeric materials through a sustainable technology.[1] However, the catalytic systems reported so far show productivity values thus far below for any industrial exploitation of the reaction. Thus, there is a strong requirement for novel catalysts that lead to an enhancement of catalyst efficiency of two or three orders of magnitude and that, at the same time, incorporate around 20 % of the polar monomer.[1]



Since several years, the group of Prof. Milani has been active in the field of catalysis for polymerization, mainly studying Pd(II) complexes with bidentate nitrogen-donor ligands, N-N.[2] The **present research project** deals with the **development of homogeneous catalysts** for the target reaction based on **palladium(II) complexes** having **new hybrid N-X molecules** as ancillary ligands. The ligands of choice belong to the class of thiopheneimines characterized by different aryl rings on the iminic carbon atoms.



The research activity of the successful candidate encompasses the typical steps of a project in homogeneous catalysis. In particular, the PhD student will be involved in: ***i.*** the synthesis and characterization of a library of the thiopheneimines; ***ii.*** the synthesis and characterization of the relevant Pd(II) complexes; ***iii.*** the study of their catalytic behaviour in the target copolymerization reaction; ***iv.*** the characterization of the produced macromolecules, mainly by NMR spectroscopy. The research will be carried out in the frame of several national and international collaborations and some periods in other research groups can be foreseen.

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PROJECT N°: 10A

Catalysis for a sustainable development

Ph.D. supervisor: Dr. Tiziano Montini

The sustainable development of the modern society requires the replacement of fossil compounds as fuels and raw materials for the production of commodities. In this context, great interest is devoted in the conversion of cheap and abundant gaseous compounds into high added-value products with the extensive use of solar light as primary energy source. Among them, the reduction of CO_2 or atmospheric N_2 into fuels and fertilizers represent an exciting challenge. The aim of this Ph.D. project is the development of innovative heterogeneous catalysts to be applied in the conversion of CO_2 into fuels (CH_4, CO, CH_3OH or HCCOH) and the fixation of N_2 into ammonia. The design and synthesis of innovative catalysts will take advantage of the bottom-up chemical methodologies that allow to control size and shape of the desired products and to combine different components into final nanocomposite materials. The photoactive semiconductors (TiO_2, CeO_2, metal titanates etc.) will be synthesized by hydro/solvothermal methods in the presence of adequate directing agents in order to control size and shape of the nanocrystals. Adequate co-catalysts will be selected among metal nanoparticles (Pd, Pt, Au, Ru or their combination) or other oxides and calchogenides in order to promote electron mobility within the materials, favouring charge separation in photocatalytic reactions and electron transport in electrocatalytic applications. Post-synthetic treatments (H_2 reduction, adsorption of molecular dyes etc.) will allow the exploitation of visible light, improving the efficiencies of the investigated processes. The structure and morphology of the synthesized materials will be characterized by advanced microscopy and spectroscopic techniques, also within a network of collaborations with international research centres. The functional properties of the materials will be tested in photocatalytic and electrocatalytic reduction of CO_2 and N_2, opening the possibility of their application in photoelectrocatalytic devices.

Related publications:

- Manfredi, N.; Cecconi, B.; Calabrese, V.; Minotti, A.; Peri, F.; Ruffo, R.; Monai, M.; Romero-Ocaña, I.; Montini, T.; Fornasiero, P.; Abbotto, A. "Dye-sensitized photocatalytic hydrogen production: distinct activity in a glucose derivative of phenothiazine dye" *Chem. Commun.* **2016**, *52*, 6977.
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PROJECT N°: 11A

DEVELOPMENT OF SUSTAINABLE CATALYTIC PROCEDURES FOR THE SELECTIVE SYNTHESIS OF NOVEL ORGANOFLUORO COMPOUNDS

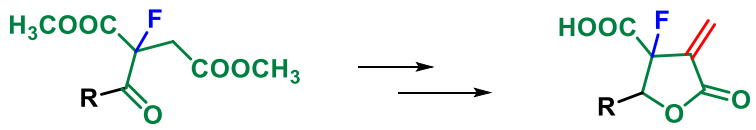
Supervisor P. Nitti (email pnitti@units.it) ; co-supervisor E. Farnetti (email farnetti@units.it)

According to the Twelve Principles of Green Chemistry, the design of sustainable protocols for organic synthesis is best accomplished by use of catalytic procedures, using either enzymatic or transition metal-based catalysts. As a consequence, in the last decade much effort has been employed in the development of highly active and selective catalysts which promote reactions of interest in the synthesis of target molecules.

Paraconic acids are a class of natural highly functionalized **γ-lactones** , bearing a **carboxylic group** at C-beta and a methyl or a **methylene group** at C-alpha. Their enantioselective synthesis therefore represents an intriguing challenge for the organic chemist.[1] Natural paraconic acids having a **methylene** at C-alpha are typically biologically active[2] as they can act as alkylating agents in Michael type addition reactions, whereas their activity is characteristically lost if either the exo double bond is chemically reduced or exo-endo isomerization of the double bond occurs. This isomerization could be avoided by transforming the beta carbon in a quaternary centre, for this purpose the introduction of a **fluorine atom** in this position appears very interesting. Organofluorine compounds are widely used in various areas of chemistry, including agrochemistry, materials science, and medicinal chemistry. It is well known that the presence of **fluorine atoms** or fluorine-containing motifs in organic molecules alters their physical and chemical properties, such as their electronic nature, conformation, lipophilicity, and stability, and it can also affect their metabolism. In a medicinal chemistry context, the improved binding affinities and biological activities of fluorinated compounds have prompted organic chemists to develop new synthetic strategies for the selective incorporation of fluorine into organic compounds.

The project is focussed on the synthesis of **fluorinated alpha-acylated succinic esters**, in enantiomerically enriched form. The chiral non-racemic keto diesters thus obtained, will then be used as building blocks for the synthesis of non-natural **paraconic acids** having different structural complexity and a **fluorine atom** in beta position.

For this purpose, in the crucial steps of the synthesis (*e.g.* fluorination of beta-ketoester, selective reduction of carbonyl group[3]) catalytic strategies including transition-metal catalyzed reactions and enzymatic resolution procedures will be developed.



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PROJECT N°: 12A

CHEMISTRY OF MOLECULARLY PRECISE GOLD CLUSTERS

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

Ligand-protected metal clusters of molecular precision are attracting great attention because of their properties that impact the fields of catalysis, light harvesting and chemical sensors to name a few. These materials differ from metal nanoparticles in the sense that they are truly monodisperse systems of well-defined stoichiometry rather than polidisperse species. Their preparation relies on modifications of the method developed by Brust and Schiffrin for the synthesis of thiolate protected gold nanoparticles, associated to the thermodynamic selection of the most stable clusters. Overall, this has enabled, for instance, the X-ray total structure determination of gold clusters covered by thiolate ligands, unveiling a rich variety of structural motifs responsible for the grafting of the ligands on the gold core.

Despite the advances achieved in the past years on the controlled synthesis of ligand-protected metal clusters, the chemistry underlying the transformation of one stable cluster into another of a different size remains much less explored. Another little explored aspect in the chemistry of these systems is the development of functional clusters by introduction in their monolayer of specific functional groups or recognition units.

In these contexts we are primarily interested in developing new procedures enabling the preparation of gold clusters not easily accessible by conventional routes, with some focus to the analysis of the mechanistic details of these transformations. A variety of techniques will be used to characterize the final materials and to investigate their structure, their optical and electronic properties.

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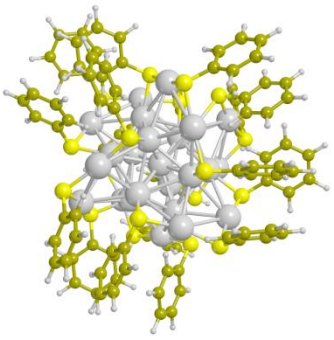
PROJECT N°: 13A

Chiral metal nanoclusters: origin, rationalization and design of optical properties by quantum chemistry

Supervisor: Mauro Stener stener@units.it

In the field of Monolayer Protected Clusters (MPC) the presence of chiral structures has been proven to be rather diffuse. However, the separation of the enantiomers from the racemic mixture is challenging, so only very recently it became possible to measure their CD spectra.[1] The present project consists in the investigation of the optical properties (photoabsorption and circular dichroism) of MPC by means of a recent, very efficient, new TDDFT algorithm, developed in the research group and implemented in ADF program.[2] The TDDFT equations are recast to a non-homogeneous linear system, whose size is much smaller than conventional formulations, allowing to calculate a wide portion of the absorption spectrum for large systems. The method has been already applied to very different systems in nature and size (up to $[Au_{309}]^{-}$)[3,4]. The new algorithm has the merit to calculate the spectrum at whichever photon energy and will be employed for a deep analysis of the results, in terms of Transition Contribution Maps,[5] plasmon scaling factor analysis[6], induced density analysis, and with a fragment projection analysis[7]. Circular Dichroism of very large systems is also affordable.[8]



The theoretical project will be in strict collaboration with the experimental group of Prof. T. Bürgi (Genève University), which will separate and characterize a series of silver/gold nanoalloyed chiral MPC. The theoretical machinery will be employed to understand the origin of CD in MPC, in particular if CD is generated by the metal core, by a chiral arrangement of the ligand shells or by the chiral ligands themselves, since these are still open questions in the field. More challenging topics, for example the role of the dynamics of the flexible ligands on CD as well as the phenomenon of Circularly Polarized Luminescence (CPL) will be also addressed in the project. The figure reports as an example the silver chiral cluster $[Ag_{25}(SC_6H_5)_{18}]^{-}$.

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PROJECT N°: 14A

DESIGN, SYNTHESIS, ANTIMYCOBACTERIAL ACTIVITY AND INIBITION ASSAY OF NEW ANTITUBERCULAR DERIVATIVES

SUPERVISORE: Prof. DANIELE ZAMPIERI

Tuberculosis (TB) is a debilitating disease that predominantly affects people in developing countries and it's in top-10 death causes in worldwide and one of the most serious infectious illnesses caused by single-pathogen, with 1.4 million death cases and 10 million new TB cases (2016) and the epidemic is larger than previously estimated (WHO TB report 2017) [(1)]. Moreover, people living with HIV accounted for 1.2 million (11%) of all new TB cases making treatment ever more difficult. The responsible pathogen is *Mycobacterium tuberculosis* (MT) which mainly affects the lungs, but also other tissues as well as kidneys, eyes, backbone, lever, lymph nodes and meningitis. Standard therapy consists of a lengthy regimen of antibiotic cocktail (isoniazid-rifampicin-ethambutol), which though often curative, suffers from poor patient compliance and diminished effectiveness due to the emergence of drug resistance. Progress in antimycobacterial drug development is slow and, recently, only two new drugs have been FDA approved (bedaquiline and delamanid) and, to date, are in advanced phases of clinical development. So, there is a dramatically need of new molecules gifted with low toxicity in humans and potent antimycobacterial activity, in particular towards multi-drug resistant strains (MDR).
The aim of his project is to synthesize new antimycobacterial derivatives gifted with a well-defined mechanism of action. In this respect, several selective MT targets are known and, among them, DprE1(decaprenylphosphoryl-beta-D-ribose 2'-oxidase)[(2)], alanine-racemase[(3)] and Men-B (menaquinone-B)[(4)]. For several years, our research group has been dealing with antimycobacterial and antifungal drugs targeting cytocrome P450 14α-demethylase (CYP-51) and, recently, also new molecules targeting Men-B.
Among various enzymes, DprE1 is one of the most promising MT target being implicated in biosynthesis of MT cell-wall. The latter is well known to be highly lipophilic and resistant towards exogenous substances and the research is focused to develop new DprE1 inhibithors, both gifted with covalent or non-covalent binding with DprE1 active site. The most interesting compound is BTZ043[(2)], a nitro benzothiazinone derivative which reached phases of clinical development due to its high activity against MT (20 fold more active than standard drug, isoniazid). The mechanism of action od BTZ043 is a "suicide-inhibition-like" due to a covalent binding with the active site in order to block the epimerization of decaprenyl-phosphoribose (DPR) a decaprenyl-phosphoarabinose (DPA), an essential process for the cell-wall assembly of MT.
The project aims to synthesize new compounds, i.e. new hybrid molecules, gifted with increased antimycobacterial activity and with good druggability both versus standard MT $H_{37}Rv$ strain and MDR strains and, on the other hand gifted with low human toxicity. Enzyme inhibition assay will also be performing in order to evaluate the ability of the new compounds to interact with the enzyme active site. Computational studies, performed with molecular modeling technics, will attend the synthesis of new compounds.

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