

Ph D in Chemistry

Priority Research Projects for Cycle XXIX (2014 – 2016)

1) Title: sintesi e valutazione in vitro di inibitori di prolilpeptidasi

Proposer: Prof. Fabio Benedetti (e-mail: benedett@units.it), Department of Chemical and Pharmaceutical Sciences.

Research Programme: Proteasi specifiche per dipeptidi Xaa-Pro sono coinvolte in diverse patologie: HIV-PR é essenziale per la replicazione del virus HIV, mentre POP e FAP sono bersagli emergenti, coinvolti, rispettivamente, in disturbi della psiche e in tumoiri della pelle. Il progetto si propone di:

1. mettere a punto metodologie innovative per la sintesi di isosteri di dipeptidi Xaa-Pro.
2. sintetizzare composti peptidomimetici, basati su isosteri di dipeptidi Xaa-Pro, progettati sulla base della struttura delle diverse proteasi bersaglio.
3. valutare l'attività inibitoria dei peptidomimetici verso le proteasi bersaglio

2) Title: Synthesis and Self-assembly of BN-doped Polyaromatic Hydrocarbons.

Proposer: Dott. Davide Bonifazi (e-mail: dbonifazi@units.it), Department of Chemical and Pharmaceutical Sciences.

Research Programme:

Project description: The objective of this work is thus to prepare and explore the reactivity of hexasubstituted borazine derivatives as new scaffolds for engineering novel extended p-conjugated organic materials. Being sure that the outcome of this research work will feature novel hybrid organic materials with unconventional photophysical properties concerning emission and absorption of light, the main objective remains focused on the development of new synthetic methodologies to prepare differentially-substituted borazine derivatives peripherally bearing electron active moieties. At first, we will prepare multiad derivatives exploring alternative substitution reactions at the borazine cores, which could be then ultimately fused in a graphene-like fashion. In the second part of this project, we will be focused on the development of alternative synthetic routes to engineer asymmetrically substituted borazine monomers as building blocks for the synthesis of linear oligoborazinyll derivatives.

Reference: "S. Kervyn, N. Kalashnyk, M. Riello, B. Moreton, J. Tasseroul, J. Wouters, T. S. Jones, A. De Vita,* G. Costantini* and D. Bonifazi* *Angew. Chem. Int. Ed.*, 2013, 52, 7410-7412; S. Kervyn, O. Fenwick, F. Di Stasio, Y. Sig Shin, J. Wouters, G. Accorsi,* S. Osella, D. Beljonne,* F. Cacialli,* D. Bonifazi* *Chem. Eur. J.*, 2013, 19, 7771-7779.

3) Title: Innovative synthesis of fine chemicals

Proposer: Prof. Lucia Pasquato (e-mail: lpasquato@units.it), Department of Chemical and Pharmaceutical Sciences.

Research Programme:

This research project develops in the field of synthesis and mechanistic studies of organic reactions to which the group has a long standing tradition.

The research project is focused on to find novel approaches for the synthesis of fine chemical compounds and intermediates of interest in the pharmaceutical industry. Moreover, object of research is also the study of the mechanism of specific reactions aimed to: better understand the parameters that influence the reaction, to characterize reaction intermediates and in general to a more deep understanding of the selected reaction.

Particular attention will be devoted to the analysis of the scientific literature and of the patented publications. Research studies will be carried out using modern spectroscopic instrumentations, chromatographic techniques and other methods of characterization of organic compounds, eventually in collaboration with other research groups and industrial partners, as for X-ray analysis, computer modeling, etc.

References:

L. Pasquato, G. Modena, L. Cotarca, P. Delogu, S. Mantovani

"Conversion of Bis(trichloromethyl)carbonate to Phosgene and Reactivity of Triphosgene, Diphosgene and Phosgene with Methanol"

J. Org. Chem., **2000**, 65, 8224.

F. Formaggio, A. Barazza, A. Bertocco, C. Toniolo, Q. B. Broxterman, B. Kaptein, E. Brasola, P. Pengo, L. Pasquato, P. Scrimin

"Role of Secondary Structure in the Asymmetric Acylation Reaction Catalyzed by Peptides Based on Chiral C α -Tetrasubstituted α -Amino Acids"

J. Org. Chem. **2004**, 69, 3849-3856.

E. Zambon, R. Giovanetti, L. Cotarca, L. Pasquato

"Mechanistic Investigation of 2-aza-spiro[4,5]decan-3-one formation from 1-(aminomethyl)-cyclohexylacetic acid (gabapentin)"

Tetrahedron, **2008**, 6739-6743.

4) Titolo: Hierarchical Materials for Energy and Environmental Applications

Proponente: Prof. P. Fornasiero

Co-Proponente: Prof. M. Prato

The main goal of the research project is the development of hierarchical materials by modular approaches involving the use of advanced and functionalized carbonaceous scaffolds and metal core-oxide shell based catalyst and photocatalysts. The obtained systems will be further functionalized by the adsorption of molecular catalysts and tested towards various important reactions, including solar fuel production, adsorption and photocatalytic reduction of CO₂ or abatement of green-house gasses.

The control of dimension and morphology of the crystals of the (photo)active materials will represent the key to obtain new properties in order to reach process efficiencies high enough to make these technologies competitive for the sustainable production of energy. The design and the realization of catalytic materials with architecture controlled on the nanometric scale will be achieved controlling important parameters such as the electronic and morphological properties.

Nanocomposite materials will be synthesized with the aim to improve their catalytic performances. Mono and bimetallic nanoparticles will be the starting building blocks for the preparation of metal core – oxide shell systems. The chemical composition of the core and of the shell will be designed depending on the desired application, comprising mainly noble metal for the metal core and CeO₂- and TiO₂-based materials for the shell. These materials will be included in the preparation of nanocomposite coupling the core-shell moieties with carbon nanostructures (nanotubes, graphene, nanohorns etc.). Particular attention will be devoted to the hierarchical functionalization of the carbon nanostructures, with the aim to introduce moieties able to increase the local concentration of reactants close the (photo)active centers.

The structural and morphological characterization will be performed making use of various advanced instrumental techniques, also taking advantage of the numerous and fruitful collaborations with national and international research institutions.

Some representative catalytic processes will be investigated dedicating particular attention to fundamental aspects that control the performances and the optimization of the processes under consideration. Hydrogen-rich mixtures will be produced through the photocatalytic reforming of aqueous solutions containing renewable organic substrates, such as future generation ethanol, glycerol or carbohydrates C5 and C6 (obtained from the hydrolysis of lignocellulosic residues). The adsorption and photoreduction of CO₂ will be investigated in order to produce aqueous solution containing formic acid, formaldehyde and methanol or CH₄ and/or CO in gaseous phase. Furthermore, the abatement of pollutant compounds, such as methane or volatile organic compounds, will be investigated in order to significantly reduce the emissions of green-house gases.

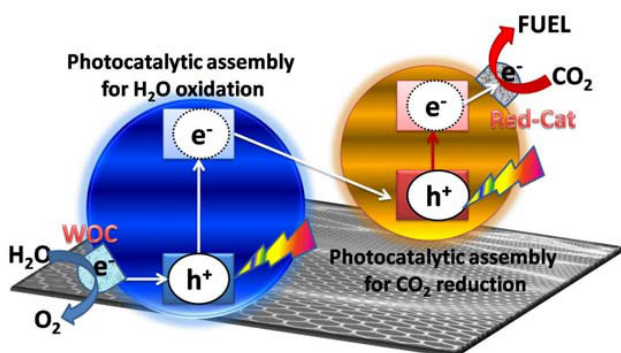
References:

- Cargnello, M.; Grzelczak, M.; Rodríguez-González, B.; Syrgiannis, Z.; Bakhmutsky, K.; La Parola, V.; Liz-Marzán, L.; Gorte, R. J.; Prato, M.; Fornasiero, P., *J. Am. Chem. Soc.*, 2012, 134, 11760.
- Cargnello, M.; Delgado Jaén, J.J.; Hernández Garrido, J.C.; Bakhmutsky, K.; Montini, T.; Calvino Gámez, J.J.; Gorte, R.J.; Fornasiero, P., *Science* 2012, 337, 713.

5) Titolo: Functionalization of Carbon Nanostructures for Catalytic Applications

Proponente: Prof. M. Prato

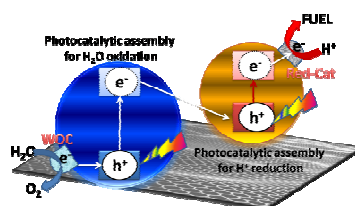
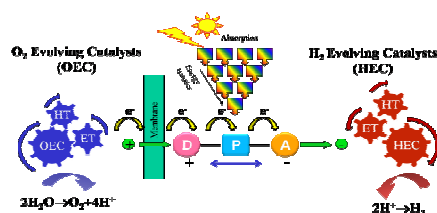
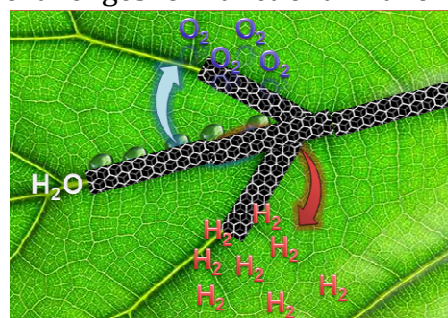
Carbon Nanostructures include nanotubes and graphene, which are ideal substrates for integration with catalysts for energy conversion processes. The project will address the functionalization of these nanostructures with innovative synthetic approaches to provide the best interface in the combination with selected catalysts for solar fuel production and photocatalytic CO₂ reduction. The modification of the nano-scaffold surface will be achieved by covalent and/or supramolecular anchoring of peripheral groups and extended metal-oxide coatings. The final aim is the shaping the outer surface to functional applications, including dark or illuminated catalysis, electrochromic/emitting properties for responsive devices. In general the scientific objectives are aimed at exploring alternative design approaches that would possibly reduce any undesirable inter-molecular or inter-cluster unfavorable interactions (for example energy transfer processes, chemical degradation of the molecular guest) between the different functional counterparts determining parasite mechanisms, which ultimately lessen the performances of the multifunctional material under working conditions. MWCNTs covered with layers of mesoporous oxides will be prepared, embedding catalytically active metal particles in intimate contact with the CNTs framework. The functionalized metal particles will be preformed ex situ; the porous oxide shell of well-controlled thickness will be formed by an in situ process on the MWCNT, using a metal alkoxide as the precursor. The ex situ preformed metallic particles will be added to this process. As a first demonstration of the benefits of such catalyst design, the water-gas shift reaction (WGSR) and the preferential oxidation of CO (PROX) in a reducing H₂ atmosphere will be studied. Both reactions are highly relevant to produce high purity H₂, which is as much as possible free of CO that would inhibit the fuel cell electrocatalysts. For the WGSR, it is expected that the direct contact between the metal particles and the CNTs would allow preventing catalyst deactivation during reaction carried out under reducing conditions where the metal is electronically deactivated by the reduced support, as is the case in the WGSR using conventional Pd/CeO₂. As a second energy-related application, the electro-oxidation of alcohols will be explored, as encountered in direct alcohol fuel cells, using the modified CNTs as anode material. While the majority of the work has till now been directed to methanol oxidation, we will focus on oxidation of ethanol, which will be the abundant low cost renewable fuel of the future. Here it will be probed whether a porous oxide matrix (TiO₂, CeO₂, RuO₂, SnO₂..) surrounding the CNT anode has beneficial effects on the activity of the Pd particles (current density, lifetime). It is expected that intimate interaction between metal oxide and metal nanoparticle will promote full oxidation to CO₂ and will prevent particle aggregation, ultimately leading to strongly reduced use of the scarce noble metals.



6) Titolo: Carbon-based Nano-Hybrid Architectures for Artificial Photosynthesis

Proponente: Prof. M. Prato

The artificial “off-leaf” transposition of photosynthesis, is one major goal of energy research, aiming at the continuous production of hydrogen as solar fuel, through the photo-catalytic splitting of H₂O. Success in this task primarily depends on the interplay of light-activated multi-electron oxidation and reduction routines and on the invention of stable and robust water splitting catalytic systems performing with fast rates, high quantum yield, and long-term activity. The research project will address the key challenges of functional nano-materials in the frame of solar energy conversion and storage finalized to water splitting and hydrogen production. In this scenario, the design of photosynthetic nano-structures, mimicking the natural process, is pivotal for regenerative atmosphere, green-house gas remediation, and carbon-neutral renewable fuels. For this purpose selected catalyst/sensitizer units will be assembled on carbon-based nanoscaffolds as carbon nanotubes (CNTs) and functionalized graphene. The project will address (i) the homogeneous screening of new catalyst packages for both oxidative and reductive half-reactions under photo-assisted conditions; (ii) innovative synthetic methods for carbon nanostructure processing, purification and solubilization. (iii) the surface anchorage of both catalysts and sensitizers on carbon nanostructures; (iii) material engineering for system compartmentalization.



The main goals will include the optimization of the interface between nanocarbon scaffolds and inorganic/catalytic moieties, the evaluation of synergistic effects based on interfacial charge and energy transfer processes, and the development of novel hybrid architectures with controlled morphologies and pore structures. The project will contribute to the current understanding of functional nanomaterials, hybrids and their controlled molecular assembly.

References

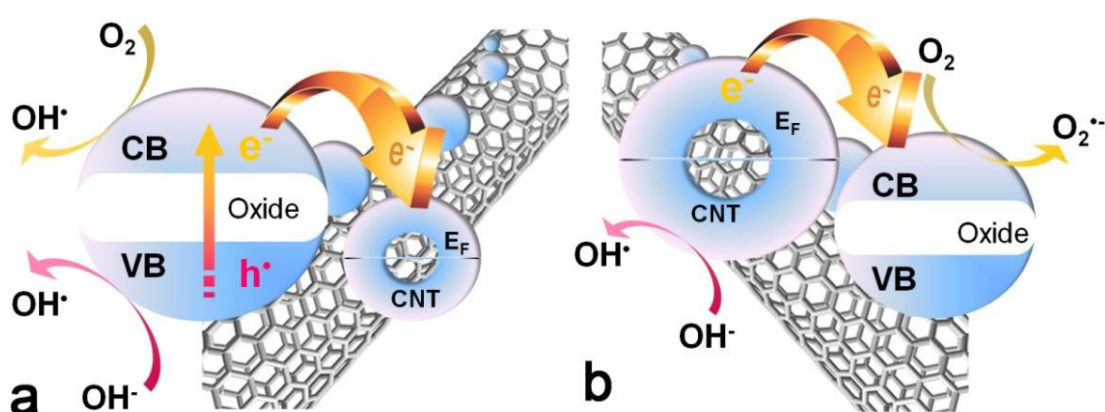
1. a) M. Prato, M. Bonchio, et al. Efficient Water Oxidation at Carbon Nanotube/Polyoxometalate Electrocatalytic Interfaces. *Nature Chem* 2010, 2, 826–831; b) F. Paolucci, M. Prato, M. Bonchio et al. Knitting the Catalytic Pattern of Artificial Photosynthesis to a Hybrid Graphene Nanotexture. *ACS Nano* 2013, 7, 811–817.
2. a) M. Quintana, E. Vazquez, M. Prato, Organic Functionalization of Graphene in Dispersions. *Acc. Chem. Res.* 2013, 46, 138–148; b). G. Van Tendeloo, C. Bittencourt, M. Prato, et al. Selective Organic Functionalization of Graphene Bulk or Graphene Edges. *Chem. Comm.* 2011, 47, 9330-9332.
3. a) C. Ehli, C. Oelsner, D. M. Guldi, A. Mateo-Alonso, M. Prato, C. Schmidt, C. Backes, F. Hauke, A. Hirsch, Manipulating single-wall carbon nanotubes by chemical doping and charge transfer with perylene dyes *Nature Chem.* 2009, 243-249, b) A. Sartorel, M. Carraro, F. M. Toma, M. Prato, M. Bonchio, Shaping the beating heart of artificial photosynthesis: oxygenic metaloxide nano-clusters *Energy Environ. Sci.* 2012, 5, 5592-5603

7) Titolo: Functionalization of Carbon Nanostructures for Energy Applications

Proponente: Prof. M. Prato

The preparation of innovative devices in our labs often requires the setting-up of innovative interfaces, where carbon nanomaterials, such as nanotubes and graphene, play a fundamental role. However, the integration of these carbon structures is made difficult by their intractability. This project aims at understanding and controlling the reactivity of these carbon forms, with the objective of integrating them with catalysts for water splitting devices.

The project involves the development of innovative functionalisation protocols to improve the dispersion and processability of high purity nanocarbons; the preparation of the nanocarbon surface to create nanocarbon assemblies and to enhance the decoration with inorganic coatings from either molecular precursors or thin amorphous, polycrystalline or single-crystalline film deposition for nano-hybrid fabrication. In nanocarbon-inorganic hybrids, the nanocarbon is coated by the inorganic material in the form of a thin amorphous, polycrystalline or single-crystalline film. In contrast to nanocomposites, in which the volume fraction of the nanocarbon is normally less than a few percent, hybrids are formed by both components with similar volume fractions. Typically, the inorganic compound is deposited from molecular precursors directly onto the surface of the nanocarbon, although the attachment of presynthesised building blocks via anchor molecules is also possible. Furthermore, the aim is to provide the hybrid nanocarbon surface with a tailored array of functional groups like terminal hydroxyl, carboxyl or amine groups and/or orthogonal synthons for further upgrade to hierarchical complexity, and to shape functional organic-inorganic hierarchical interfaces to enhance interfacial processes with specific target including (i) photoinduced electron transfer and charge separation life-time, (ii) evolution to metal-centered catalytic transients for water oxidation and/or hydrogen generation (iii) promote multi-electronic events at low overpotential facilitating coupled proton transfer (iv) implement self-healing remediation of the functional surface or active nano-layer of the hybrid architecture.



8) Title: Design, synthesis and biological evaluation of GSK-3 β inhibitors

Proposer: Prof. Giampiero Spalluto, (e-mail: spalluto@units.it), Department of Chemical and Pharmaceutical Sciences.

Abstract: Glycogen synthase kinase 3 β (GSK-3 β) is a key regulator of numerous signaling pathways. Furthermore, the involvement of GSK-3 β in signaling mechanisms that activate nuclear factor κ B (NF- κ B), as well as the resulting effects on NF- κ B-mediated gene expression, indicate that GSK-3 β acts as a regulator of neuroinflammation.

The goal of this project is to synthesize new GSK-3 β inhibitors which could be investigated as potential agents able to counteract the neuroinflammation mediated by microglia activation. In particular, starting from the observation that some GSK-3 β inhibitors possess the adenine nucleus, this project will focus on the synthesis of bicyclic derivatives which could be considered bioisosters of adenine nucleus: 2,5,7-trisubstituted[1,2,4]triazolo[1,5-a]triazine and 2,5,8-trisubstituted[1,2,4]triazolo[1,5-c]pyrimidine systems.

The great advantage of these heterocyclic systems is represented by the synthetic approach. In fact, the scaffolds could be easily prepared by a 3-4 steps synthesis in a very good overall yield. Using this approach, a library of new potential GSK-3 β inhibitors and, therefore, an accurate SAR profile, could be obtained. In addition, by computational studies, an optimization of the pattern of substitutions on these heterocyclic derivatives will be investigated.

References:

Wang MJ, Huang HY, Chen WF, Chang HF, Kuo JS (2010) Glycogen synthase kinase-3 β inactivation inhibits tumor necrosis factor- α production in microglia by modulating nuclear factor κ B and MLK3/JNK signaling cascades. *J Neuroinflammation* 7:99.

Eldar-Finkelman H, Martinez A (2011) GSK-3inhibitors: preclinical and clinical focus on CNS. *Front Mol Neurosci* 4:1.

9) Title: Design of core-shell catalysts for catalytic methane combustion

Proposer: Prof. Paolo Fornasiero (e-mail: pfornasiero@units.it), Department of Chemical and Pharmaceutical Sciences.

Abstract: The development of effective methane combustion catalysts would have a significant impact on a number of energy-based technologies. For example, it is possible to operate a diesel engine on methane if diesel fuel is added to the fuel mix in small quantities in order to ignite the methane. Unfortunately, some unconverted methane will appear in the exhaust and there is presently no reliable catalyst for converting that methane. Therefore, a reliable catalyst that could convert the methane at low temperatures would enable this and other technologies. Recently, it was reported that a Pd@ceria/alumina catalyst with a unique structure could provide activity that was at least 30 times higher for methane oxidation than the best previously reported catalyst.[1] Remarkably, the activity of this catalyst was also shown to increase after calcination to 850°C in air, while most other catalyst were severely deactivated by these conditions. [2] This new catalyst was prepared by synthesizing a palladium core particle with a porous cerium oxide shell to maximize the interaction between these components. To maintain these core-shell entities as isolated, single units, the solution-phase core-shell particles were then adsorbed onto functionalize supports.[3] The properties of these new catalysts have not been optimized and are largely unexplored. While these catalysts exhibit superb thermal stability, it is uncertain how these materials will be affected by steam and various impurities (e.g. SO₂) to which they will be exposed in real applications. These information will be essential to design further improvement in the catalytic performances by modifying the oxide shell or changing the metal core. In addition, it will be performed a careful understanding on how the changes in the size of the Pd core affect catalytic activity. In fact, the strong metal-support interactions, that are operative in these catalysts, play a critical role in enhancing their reactivity [4].

Reference:

1. Cargnello, M.; Delgado Jaén, J.J.; Hernández Garrido, J.C.; Bakhmutsky, K.; Montini, T.; Calvino Gámez, J.J.; Gorte, R.J.; Fornasiero, P., "Exceptional Activity for Methane Combustion over Modular Pd@CeO₂ Subunits on Functionalized Al₂O₃.", *Science* 2012, 337, 713.
2. Chen, C.; Cao, J.; Cargnello, M.; Fornasiero, P.; Gorte, R.J."High Temperature Calcination Improves the Catalytic Properties of Alumina-supported Exceptional Thermal Stability of Pd@CeO₂ prepared by Self-Assembly.", *J. Catal.* 2013, 306, 109-115.
3. Adijanto, L.; Bennett, D.A.; Chen, C.; Yu, A.S.; Cargnello, M.; Fornasiero, P.; Gorte, R.J.; Vohs, J.M. " Exceptional Thermal Stability of Pd@CeO₂ Core–Shell Catalyst Nanostructures Grafted onto an Oxide Surface.", *Nano Letters* 2013, 13, 2252-2257.
4. Cargnello, M.; Doan-Nguyen, V.; Gordon, T.R.; Diaz, R.E.; Stach, E.A.; Gorte, R.J.; Fornasiero, P.; Murray, C.B."Control of Metal Nanocrystal Size Reveals Metal-Support Interface Role for Ceria Catalysts.", *Science* 2013, 341, 771-773.

10) Title: Sviluppo e caratterizzazione di nuovi metodi per il rilevamento delle palitossine

Proposer: Dott. Silvio Sosa (e-mail: silvio.sosa@econ.univ.trieste.it), Department of Life Sciences.

Research Programme:

Le palitossine sono dei composti non proteici ad elevata tossicità prodotti da microalghe del genere *Ostreopsis* che, negli ultimi anni, sono stati rilevati anche negli organismi eduli marini dell'area mediterranea. Pur non essendo regolamentate, l'Autorità Europea per la Sicurezza Alimentare (EFSA) ha proposto il valore di 30 µg/kg quale limite massimo di palitossine nei molluschi eduli, sottolineando la necessità di sviluppare nuovi metodi, rapidi, sensibili e specifici, per il rilevamento e la quantificazione della palitossina e dei suoi analoghi. La ricerca, pertanto, sarà rivolta allo sviluppo ed alla caratterizzazione di nuovi metodi per il rilevamento delle palitossine (inclusa l'ovatossina-a, il principale analogo presente nel mare Mediterraneo), come ad esempio saggi colorimetrici di tipo recettoriale, basati sul bersaglio molecolare della palitossina, la Na⁺/K⁺-ATPasi, e /o sull'impiego di anticorpi anti-palitossina.

11) Title: Studio del problema dei fanghi prodotti in impianti di depurazione: diminuzione delle quantità generate mediante processi biologici e loro valorizzazione energetica

Proposer: Ing. Angelo Cortesi (e-mail: angelo.cortesi@di3.units.it), Department of Engineering and Architecture.

Research Programme:

La ricerca interviene in un settore di forte interesse ambientale, quale il trattamento di reflui civili e industriali, con lo scopo di ridurre la produzione di fanghi durante il normale funzionamento degli impianti depurativi. Vuole inoltre considerare possibili trattamenti post-depurazione atti a ridurre la quantità di fanghi di supero che, attualmente e fino a quando le normative lo consentiranno, vengono semplicemente dispersi nell'ambiente quali concimi o ammendanti per terreni agricoli o avviati alla deposizione in discarica.

Il progetto prevede una serie di obiettivi indicati di seguito:

- Studio dei possibili trattamenti applicabili in impianto depurativo atti alla riduzione di fanghi;
- Allestimento in laboratorio di un processo OSA (Oxic Settling Anaerobic) che modifica il processo convenzionale a fanghi attivi;
- Valutazione dei parametri ottimali per il funzionamento del reattore;
- Passaggio ad una scala superiore (impianto pilota) del processo OSA da allestire presso un impianto depurativo industriale;
- Studio dei possibili trattamenti post-depurazione per lo smaltimento dei fanghi in alternativa all'utilizzo agricolo;
- Allestimento di un impianto di digestione anaerobica da laboratorio e sperimentazione per analizzare la possibile valorizzazione dei fanghi con produzione di biogas;
- Valutazione di possibili processi co-digestivi dei fanghi con altre biomasse utilizzate (reflui zootecnici, insilato di mais, FORSU etc.) tesa alla ottimizzazione della carica dei fanghi in digestori esistenti.