UNIVERSITÀ DEGLI STUDI
DELL'INSUBRIA

"Valorisation of industrial waste and natural molecules for the synthesis of biopolymers"

Coordinators: Prof.ssa Lorella Izzo, Prof. Massimo Mella

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Keywords: Renewable resources; upcycling; sustainable catalysis; biopolymers.

Purpose: The facility focuses on the selection - also through in silico studies - of molecules derived from natural sources and industrial waste, and on their valorisation through the production of polymeric materials, with the aim of:

i) replacing fossil-based feedstocks with renewable sources in the synthesis of polymers for industrial applications (e.g. elastomers, thermoplastics, and thermosets);

ii) replacing fossil-based feedstocks with renewable sources in the synthesis of polymers for industrial applications (e.g. elastomers, thermoplastics, and thermosets).

To achieve these goals, the facility develops synthesis methodologies for monomers and functional (bio)polymers from renewable sources, using sustainable catalysis techniques and following the principles of green chemistry. The development of these processes is supported by computational chemistry studies. The facility is able to perform microstructural and physicochemical characterization of the obtained polymers and to evaluate their potential biomedical applications in the case of multifunctional polymers.

Location: Department of Biotechnology and Life Sciences (via J. H. Dunant 3 – Varese) and Department of Science and High Technology (via Valleggio 9 – Como).

Organization: The facility is multidisciplinary in nature (organic and organometallic chemistry, catalysis, physical chemistry, computational chemistry, cellular and applied biology), providing a broad range of expertise for the valorisation of waste-derived or natural molecules through rational design-based structural modification, synthesis, and physicochemical/biological characterization of new (bio)polymers of industrial interest.

The facility is organized into three subunits:

a) In silico studies for the selection of potential monomers and analysis of their polymerization behaviour.
b) Synthesis and characterization of monomers and polymers from renewable sources.
c) Characterization of antineoplastic activity.

Connection with CRIETT Technological Platforms and University Scientific Facilities:

This facility operates in collaboration with:

- *Technological Platform* for Materials Analysis and Characterization.

- *Sustainability Platform* for the following objectives: design, synthesis, and characterization of polymers from renewable sources; sustainable catalysis; mechanistic studies.

- *Technologies for Energy, Health and Environment Platform* for the following objectives: drug design; super-resolution bioimaging; materials for health applications.

Subunit: “In silico studies for the selection of molecules as potential monomers and their polymerization behaviour”

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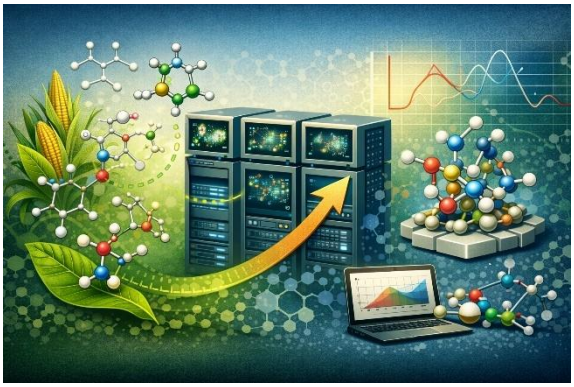
Keywords: thermodynamics; chemical kinetics; reaction mechanisms; general reactivity.



The subunit is equipped with computational clusters for the selection of molecules from natural sources or industrial waste as potential monomers for the design and synthesis of functional polymers with tailored properties (e.g. elastomers, thermoplastics, thermosets, and gels). It is also able to elucidate mechanistic aspects of polymerization, guiding both the selection of more efficient catalytic systems and the rational modification of monomer structures to improve their reactivity or to enable fine-tuning of the properties of the resulting macromolecules. Finally, it can perform studies on the release of biologically relevant molecules from micelles, surfaces, or polymeric membranes in solution at different pH values, using both computational and experimental approaches.

Subunit: "Synthesis and characterization of monomers and polymers from renewable sources"

Coordinators: Prof.ssa Lorella Izzo, Prof. Francesco Della Monica, Dott. Orlando Santoro, Prof. Enrico Caruso

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Keywords: sustainable catalysis, green chemistry, valorisation of natural products

The subunit focuses on the valorisation, through sustainable catalysis methodologies, of naturally derived molecules from various sources (e.g. biotechnological processes, plant extracts, agro-food waste products) with the aim of obtaining functional (bio)polymers of industrial interest. The subunit is equipped with chemical laboratories for the development of organic synthesis methodologies, organic/organometallic catalysis procedures, and polymerization reactions under inert atmosphere (e.g. controlled radical polymerizations, coordination–insertion processes, and ring-opening polymerizations), both in solution and in bulk. For the structural characterization of molecules, the subunit relies on NMR and GC-MS spectroscopy, FT-IR and UV-Vis spectroscopy, fluorimetry, and mass spectrometry. The subunit has access to a wide range of instruments for polymer microstructural characterization (NMR spectroscopy, FT-IR), molecular weight determination (SEC), thermal property analysis (DSC and TGA), mechanical tensile properties (e.g. stress–strain curves using a universal testing machine), and wettability measurements (e.g. Mail angle analysis). In addition, the subunit is equipped with a spin coater for the deposition of polymer coatings on various substrates (e.g. paper, textiles, etc.).

Subunit: "Characterization of antineoplastic activity"

Coordinators: Prof.ssa Marzia Gariboldi, Prof. Enrico Caruso

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Keywords: antineoplastic activity, antioxidant activity, cytotoxicity.

The facility is dedicated to the evaluation of the antineoplastic activity of bioactive metabolites and provides integrated support for the advanced stages of the discovery and development process, enabling functional validation of their potential as anticancer drugs. Activities include an initial assessment of the antiproliferative effects of selected metabolites using human tumor cell lines of different tissue origins, cultured both in monolayer and in three-dimensional (3D) models. It is also possible to investigate the molecular mechanisms underlying the observed effects for the most promising compounds, including analysis of cell death pathways, cell cycle interactions, tumor cell invasive capacity, and other processes associated with a more aggressive neoplastic phenotype. To this end, the facility is equipped with the main instruments for cell culture, including laminar flow hoods, CO_2 incubators, and inverted microscopes, as well as a FACScalibur flow cytometer (Becton Dickinson), a BIO-RAD plate reader, and a Nikon fluorescence microscope. The facility also includes hypoxia chambers for cell culture, allowing the accurate reproduction of the hypoxic microenvironment typical of solid tumors, which is responsible for phenotypic changes that increase tumor resistance to treatments.facility è dedicata alla valutazione dell'attività antineoplastica di metaboliti bioattivi e fornisce un supporto integrato alle fasi avanzate del processo di scoperta e sviluppo, consentendo la validazione funzionale del loro potenziale come farmaci antitumorali.

Publications

A) In silico studies for the selection of molecules as potential monomers and their polymerization behaviour

L Izzo, T. Tabanelli, F. Cavani, P. Blair Vàsquez, C. Lucarelli, M. Mella, The competition between dehydrogenation and dehydration reactions for primary and secondary alcohols over gallia: unravelling the effects of molecular and electronic structure via a two-pronged theoretical/experimental approach. *Catal. Sci. Technol.* **2020**, *10*, 3433–3449. https://doi.org/10.1039/C9CY02603G.

N. Schiaroli, F. Foschi, M. Mella, C. Lucarelli, C-Acylation of Guaiacol with Acetic Acid Over Solid Acid Catalysts Under Mild Reaction Conditions. *ChemCatChem* **2025**, *17*, e01112. https://doi.org/10.1002/cctc.202501112.

M. Monti, A. Tagliabue, S. Brenna, M. Mella, L. Izzo, On the role played by hydrogen bonding between water soluble polyacids and surfactants on their micellization as a function of pH. *Colloids Surf. A: Physicochem. Eng. Asp.* **2023**, *661*, 130923. https://doi.org/10.1016/j.colsurfa.2023.130923.

M. Mella, A. Tagliabue, G. Viscusi, G. Gorrasi, L. Izzo, How chemical structure and composition impact on the release of salt-like drugs from hydrophobic matrices: Variation of mechanism upon adding hydrophilic features to PMMA. *Colloids Surf. A: Physicochem. Eng. Asp.* **2022**, *646*, 128878. https://doi.org/10.1016/j.colsurfa.2022.128878.

M. Mella , M. V. La Rocca , Y. Miele, L. Izzo, On the origin and consequences of high DMAEMA reactivity ratio in ATRP copolymerization with MMA: An experimental and theoretical study. *J. Polym. Sci. A Polym. Chem.* **2018**, *56*, 1366–1382. https://doi.org/10.1002/pola.29017.

B) Synthesis and characterization of monomers and polymers from renewable sources

Vittore, P. Shamraienko, I. Hermes, Q. Li, B. Voit, L. Izzo, Biobased triblock thermoplastic elastomer with betulin- or carvacryl-methacrylate end-blocks by RAFT polymerization. Polym. Chem. 2025, 16, 3640-3649. https://doi.org/10.1039/D5PY00540J.

Vittore, O. Santoro, M. Candida, S. Vaghi, S. Pragliola, M. Mella, L. Izzo, A kinetic and mechanistic study of copper-based catalysts in the ARGET-ATRP of multifunctional natural molecules: The case of methacrylated eugenol. Polymer 2025, 324, 128228. https://doi.org/10.1016/j.polymer.2025.128228.

Maquilón, A. Brandolese, C. Alter, C. H. Hövelmann, F. Della Monica, A. W. Kleij, Renewable Beta-Elemene Based Cyclic Carbonates for the Preparation of Oligo(hydroxyurethane)s. ChemSusChem 2022, 15, e202201123. https://doi.org/10.1002/cssc.202201123.

Brandolese, F. Della Monica, M. À. Pericàs, A. W. Kleij, Catalytic Ring-Opening Copolymerization of Fatty Acid Epoxides: Access to Functional Biopolyesters. Macromolecules 2022, 55, 2566–2573. https://doi.org/10.1021/acs.macromol.2c00321.

O. Santoro, M. C. Malacarne, F. Sarcone, L. Scapinello, S. Pragliola, E. Caruso, V. T. Orlandi, L. Izzo, Inherently Antimicrobial P(MMA-ran-DMAEMA) Copolymers Sensitive to Photodynamic Therapy: A Double Bactericidal Effect for Active Wound Dressing. Int. J. Mol. Sci. 2023, 24, 4340. https://doi.org/10.3390/ijms24054340.

C) Characterization of antineoplastic activity

M. C. Malacarne, E. Caruso, M. B. Gariboldi, E. Marras, G. Della Bitta, O. Santoro, A. Simm, R. Li, C. T. J. Ferguson, Evaluation of Nanoparticles Covalently Bound with BODIPY for Their Photodynamic Therapy Applicability. *Int. J. Mol. Sci.* **2024**, *25*, 3187. https://doi.org/10.3390/ijms25063187.

V. De Leo, E. Marras, A. M. Maurelli, L. Catucci, F. Milano, M. B. Gariboldi, , Polydopamine-coated liposomes for methylene blue delivery in anticancer photodynamic therapy: effects in 2D and 3D cellular models. *International journal of molecular sciences* **2024**, *25*, 3392. https://doi.org/10.3390/ijms25063392.

N. Ferrario, E. Marras, V. Vivona, F. Randisi, A. N. Fallica, A. Marrazzo, G. Perletti, M. B. Gariboldi, Mechanisms of the antineoplastic effects of new fluoroquinolones in 2D and 3D human breast and bladder cancer cell lines. *Cancers* **2024**, *16*, 2227. https://doi.org/10.3390/cancers16122227.

M. Ballestri, E. Marras, E. Caruso, F. Bolognese, M. C. Malacarne, E. Martella, M. Tubertini, M. B. Gariboldi, G. Varchi, Free and poly-methyl-methacrylate-bounded BODIPYs: Photodynamic and antimigratory effects in 2D and 3D cancer models. *Cancers* **2022**, *15*, 92. https://doi.org/10.3390/cancers15010092.

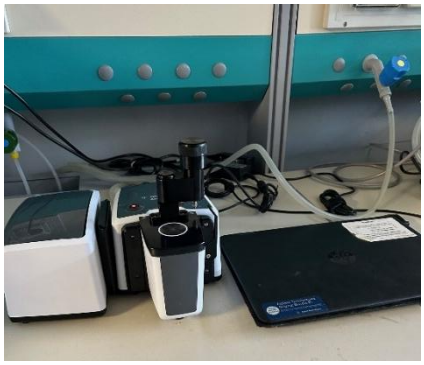
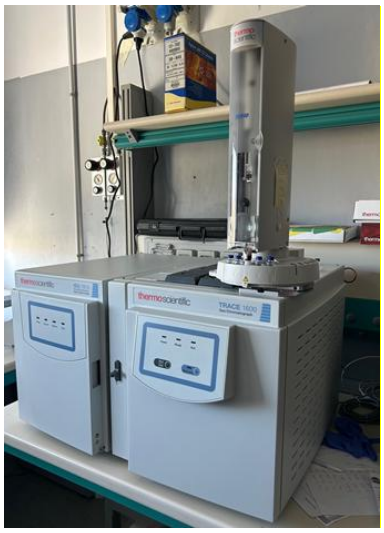
M. B. Gariboldi, E. Marras, I. Vaghi, A. Margheritis, M. C. Malacarne, E. Caruso, Phototoxicity of two positive-charged diaryl porphyrins in multicellular tumor spheroids. *Journal of photochemistry and photobiology. B, Biology* **2021**, *225*, 112353. https://doi.org/10.1016/j.jphotobiol.2021.112353.

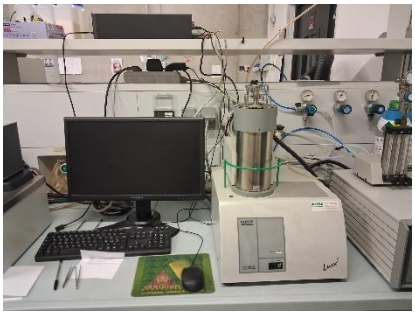
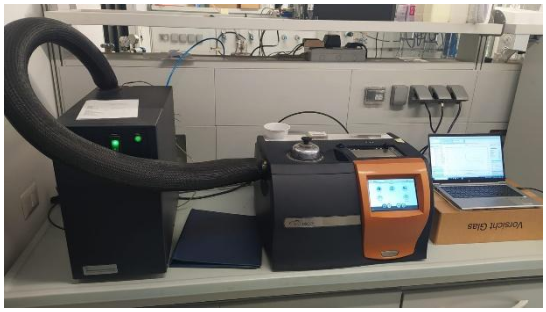
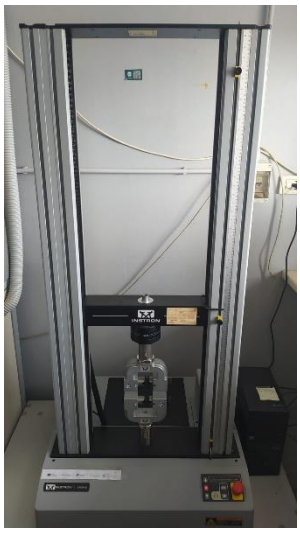
- **A) In silico studies for the selection of molecules as potential monomers and their polymerization behaviour**

	**Three servers with 20/48/64 processors** for electronic structure calculations (molecular structure, chemical reactivity, and excited-state studies) and statistical mechanics simulations (simulation of polymeric and polyelectrolyte systems, and solving kinetic systems).

- **B) Synthesis and characterization of monomers and polymers from renewable sources**

	**High-vacuum Schlenk lines** for handling moisture- and oxygen-sensitive compounds and for performing reactions under inert atmosphere (nitrogen).
	**Rotary evaporator** for solvent removal from solutions. Thanks to reduced pressure, evaporation occurs at low temperatures, preventing thermal degradation of the compounds.
	**Vacuum oven** for drying organic, inorganic, and polymeric samples obtained in the laboratory under vacuum and controlled temperature conditions according to a predefined program.

	**Fourier-transform infrared (FT-IR) spectrophotometer.** Part of the DBSV instrumentation, it is used for the identification of functional groups present in samples of organic, inorganic, and polymeric materials obtained in the laboratory. The instrument can analyze samples in solution and, thanks to the ATR (Attenuated Total Reflection) module, also solids and liquids.
	**Gas chromatograph coupled to a mass spectrometer (GC-MS).** Managed by DBSV, it is used for the separation, identification, and quantification of volatile substances with masses ranging between 1.2 and 1100 amu. Chromatographic analysis allows the separation of components in complex mixtures, while mass spectrometry enables the identification of each compound through fragmentation pattern analysis.
	**Liquid chromatography coupled to a mass spectrometer (LC-MS).** Managed by CRIETT, it is used for the separation, identification, and quantification of non-volatile and/or thermolabile compounds. Similarly to GC-MS, chromatographic separation enables the resolution of mixture components, while mass spectrometry ensures molecular identification.
	**Nuclear Magnetic Resonance (NMR) spectrometer.** Managed by CRIETT, it is used for structural elucidation of synthesized products. This technique allows the determination of atomic connectivity as well as the presence of impurities. The instrument operates in solution and enables the acquisition of both one- and two-dimensional spectra, analyzing signals from ^{1}H, ^{13}C, and heteronuclei such as ^{19}F and ^{31}P.

	**Thermogravimetric Analysis (TGA).** Managed by CRIETT, it is used to evaluate the thermal stability of substances. The instrument records sample weight changes as temperature increases, allowing the assessment of degradation processes, solvent loss, and/or the presence of inorganic residues. Measurements can be performed under either inert or air atmosphere.
	**Differential Scanning Calorimetry (DSC).** This instrument performs calorimetric analyses under nitrogen atmosphere and allows the measurement of thermal properties such as melting/crystallization temperatures and glass transition temperatures. It operates in a temperature range from -80 to +400 °C, according to predefined thermograms with controlled heating/cooling rates.
	**HPLC/SEC system.** Managed by CRIETT, HPLC is used for the separation, identification, and quantification of non-volatile and/or thermolabile compounds. In SEC mode, it is used for the analysis of polymer samples in THF to determine molecular weights and polydispersity indices relative to standards.
	**Instron 34TM-10 universal testing machine.** The instrument allows tensile and compression tests to be performed. It is equipped with two load cells (10 kN and 1 kN) and specimen holders for tensile testing, enabling the determination of properties such as Young's modulus, toughness, and elongation at break. The machine has a maximum travel distance of 1172 mm and a variable test speed ranging from 0.05 to 508 mm/min.
	**Spin coater.** It enables the preparation of thin and ultra-thin films for various applications, such as spectroscopic and morphological analyses (e.g., X-ray, IR, etc.). It also allows the coating of different substrates (e.g., paper, textiles, glass, etc.) with polymeric films.

<table>
<tr><th colspan="2">• D) Characterization of antineoplastic activity</th></tr>
<tr><td>  </td><td>Flow cytometer FACSCalibur, a DBSV instrument essential for assays aimed at characterizing the mechanisms of action underlying antitumor activity (cell death, ROS production, uptake, etc.).</td></tr>
<tr><td>  </td><td>iMark microplate reader (BIO-RAD), a DBSV instrument used to perform viability assays for evaluating the antiproliferative effects of identified natural active compounds, as well as ELISA tests and protein quantification for Western blot analysis.</td></tr>
<tr><td>https://www.uninsubria.it/ricerca/strutture-la-ricerca/centri-speciali/centro-di-ricerca-e-trasferimento-tecnologico-criett</td><td>The subunit can also use the confocal microscope managed by CRIETT for assessing the subcellular localization of fluorescent natural products.</td></tr>
<tr><td>  </td><td>The Billups-Rothenberg hypoxia chamber can be used to reproduce controlled hypoxic conditions by insufflating a gas mixture with an oxygen concentration of 0.1%.</td></tr>
<tr><td>  </td><td>Nikon Eclipse Ts2R fluorescence microscope. A DBSV instrument that allows the acquisition of images to be correlated with data obtained by flow cytometry.</td></tr>
<tr><td> 
</td><td>The laminar flow hood, managed at departmental level, is used in biological laboratories to protect the operator and the surrounding environment from biological agents (generally pathogenic microorganisms); it also prevents cross-contamination, ensuring sterile working conditions.</td></tr>
</table>

	The subunit can also use the **Tecan Infinite 200 PRO plate reader** for absorbance, fluorescence, and luminescence measurements. Thanks to its compatibility with multiwell plates, it allows simultaneous analysis of numerous samples, making it a key instrument for rapid and efficient biological profiling of the studied molecules.