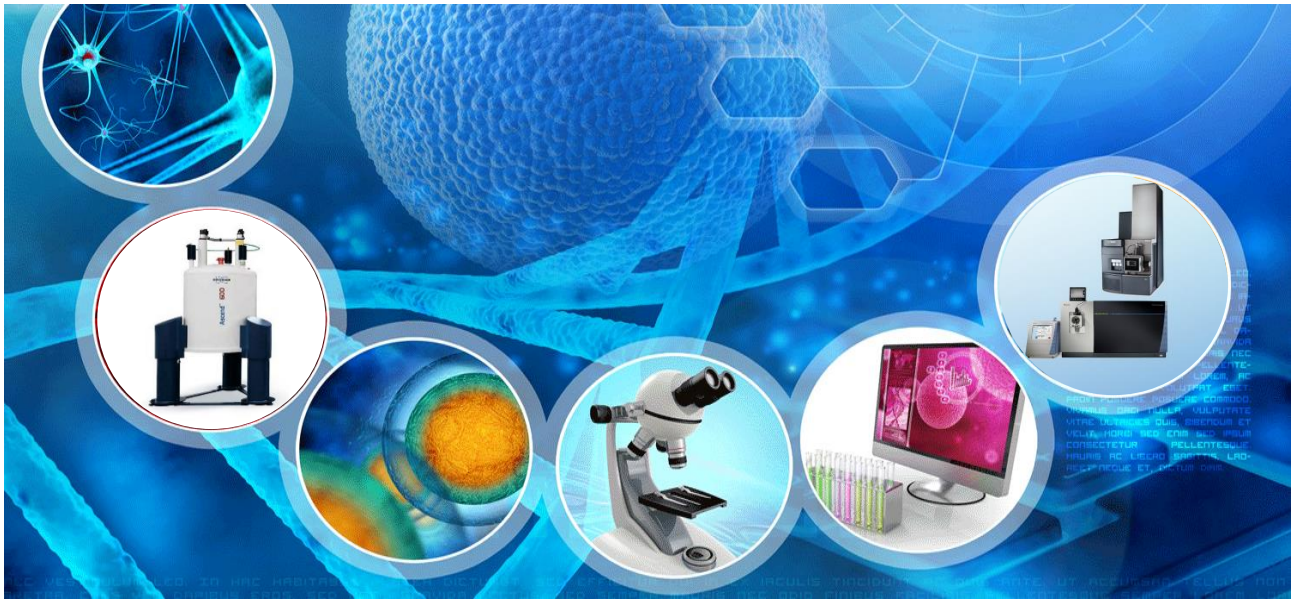
Department of Biotechnology and Biosciences

Research Facilities



UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

1998 | 2023

The Department of Biotechnology and Biosciences (BtBs) was established in 1999 and is committed to promoting both scientific and educational excellence. BtBs tackles biological complexity exploiting its multi-disciplinary and innovative experimental approaches. Four major areas are covered:

i) **Biomedicine**, to study the underlying mechanisms of diseases and improve diagnosis and treatment;

ii) **Biodiversity**, to analyze how the environment and ecosystems influence human and living organism well-being;

iii) **Industrial and microbial biotechnologies**, to generate new products and processes for human and environmental well-being;

iv) **Chemistry**, to identify therapeutic targets and develop hits and leads, either through synthesis or isolation from natural sources.

BtBs is nationally recognized as a breeding ground for young talents, producing over 250 master's graduates and more than 20 PhD students annually, with multidisciplinary mindset and the ability to apply a "problem-solving" scientific approach and critical data analysis.

BtBs offers **four educational programs:** two Bachelor's and two Master's degrees (3+2 years, respectively) in Biological Sciences or Biotechnology.

The Biology program trains individuals capable of interpreting ongoing ecological transition and approaching health and well-being with a multidisciplinary holistic perspective.

The Master's program in Industrial Biotechnology educates professionals in the fields of raw materials and energy production, as well food, nutraceutical, cosmetic, diagnostic, and pharmaceutical products, adhering to the principles of the Bioeconomy.

The double degree with the Université de Paris 7 allows the BtBs students to earn an international Master's diploma.

The **Doctoral Program in Convergent Technologies for Biomolecular Systems** housed in BtBs fosters responsible research and innovation approaches, promotes internationalization and collaborations with industries.

Facts and figures

Personnel

13 Full Professors

36 Associate Professors

40 Researchers

13 Technicians

250 Undergraduate/PhD students, post docts

Extramural funds (2019-2022)

144 funded project, success rate 42%

RESEARCH FACILITIES EQUIPMENT

Bruker Avance III 600MHz NMR spectrometer

EQUIPMENT DESCRIPTION

The spectrometer is equipped with three probes suitable for the analysis of liquid, solid, and heterogeneous samples.

The probe for liquid samples is a QCI (^{1}H, ^{13}C, ^{15}N, ^{31}P) cryo-probe, with a sensitivity about 40 times higher than a conventional probe, and therefore particularly suitable for the analysis of low-concentration samples such as for structural studies on biological macromolecules, or for rapid analysis of unstable samples, thus allowing the analysis of biological samples, such as unstable proteins or prone to change their folding or aggregation state over time.

The triple resonance (^{1}H, ^{13}C, ^{15}N) 4 mm rotor HR-MAS probe allows the analysis of the molecular composition of tissue fragments from biopsies, cell suspensions, gels, and, in general, heterogeneous samples.

A triple resonance double-broadband solid state $^{1}H/X/Y$ MAS (2.5 mm MAS rotor) probe allows the application of CP-MAS, HETCOR, and MQ-MAS techniques to detect structural information on a wide range of samples from materials science to polymers and biological systems.

APPLICATION

A wide range of pulse sequences is available that allow you to perform the most common one-dimensional and two-dimensional experiments, as well as advanced experiments including:

- three-dimensional experiments (all triple resonance experiments currently used to solve the three-dimensional structure of polymers and macromolecules of biological interest);
- experiments specifically designed to study molecular recognition processes such as receptor-ligand, protein-protein, protein-nucleic acid, and protein-polysaccharide interactions.

A wide range of samples containing molecules of chemical and biological interest:

- low and medium molecular weight molecules (drugs, metabolites, enzymatic modulators, synthetic intermediates);
- very high and very high molecular weight molecules (proteins, polysaccharides, nucleic acids), fragments of biological membranes and nanoparticles, fragments of cell organelles, cells, fragments of tissues.

EXAMPLES OF SERVICES

- acquisition and/or interpretation of 1D and 2D spectra;
- quantitative analysis (determination of the concentration/quantity of a compound of interest present in solution);
- assessment of the structural identity of organic compounds;
- identification of the structure of unknown organic compounds;

- ligand-receptor interaction studies;
- analysis of complex mixtures of organic compounds
- metabolomics analysis.

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Significant papers

1) Ciaramelli C, Palmioli A, Brioschi M, Viglio S, D'Amato M, Iadarola P, Tosi S, Zucconi L, Airoldi C. Antarctic Soil Metabolomics: A Pilot Study. Int J Mol Sci. 2023 Aug 2;24(15):12340. https://doi.org/ 10.3390/ijms241512340.

2) Ciaramelli C, Palmioli A, De Luigi A, Colombo L, Sala G, Salmona M, Airoldi C. NMR-based Lavado cocoa chemical characterization and comparison with fermented cocoa varieties: Insights on cocoa's anti-amyloidogenic activity. Food Chem. 2021 Mar 30;341(Pt 2):128249. https://doi.org/ 10.1016/j.foodchem.2020.128249.

3) Ciaramelli C, Fumagalli M, Viglio S, Bardoni AM, Piloni D, Meloni F, Iadarola P, Airoldi C. 1H NMR To Evaluate the Metabolome of Bronchoalveolar Lavage Fluid (BALf) in Bronchiolitis Obliterans Syndrome (BOS): Toward the Development of a New Approach for Biomarker Identification. J Proteome Res. 2017 Apr 7;16(4):1669-1682. doi: 10.1021/acs.jproteome.6b01038.

4) Guzzi C, Colombo L, De Luigi A, Salmona M, Nicotra F, Airoldi C. Flavonoids and Their Glycosides as Anti-Amyloidogenic Compounds: Aβ1–42 Interaction Studies to Gain New Insights into Their Potential for Alzheimer's Disease Prevention and Therapy. Chemistry – An Asian Journal 2017, 12 (1), 67–75. https://doi.org/10.1002/asia.201601291.

5) Palmioli A, Sperandeo P, Bertuzzi S, Polissi A, Airoldi C. On-Cell Saturation Transfer Difference NMR for the Identification of FimH Ligands and Inhibitors. Bioorganic Chemistry 2021, 112, 104876. https://doi.org/10.1016/j.bioorg.2021.104876.

Xevo G2-XS QTof Quadrupole Time-of-Flight Mass Spectrometer - Waters

EQUIPMENT DESCRIPTION

Waters' Xevo G2-XS quadrupole Time of flight Mass spectrometer is a high-resolution and high-performance mass spectrometer that allows a complete characterization of sample components. It can be used for targeted quantitative analysis with high sensitivity and selectivity thanks to mass accuracy, dynamic range, and speed provided by QuanTof technology and the enhanced quantitative capability of Tof-MRM data acquisition. In addition to accurate quantitative profiles, comprehensive qualitative information can be obtained through the application of the MSE approach, which delivers accurate mass precursor and fragment ion data for every detectable component, or FastDDA, for an automated targeted data acquisition method that provides rapid and intelligent accurate mass MS/MS capability for confirmation of known compounds or characterization of unknowns, for situations where only true MS/MS data will suffice.

The system is also equipped with a versatile chromatographic separation system to expand the sample types to be analyzed, namely the Acquity H-class Plus core system for liquid chromatography, configured for quaternary solvent delivery and connected to a UV detector, and the Agilent 7890A GC for gas chromatography, connected to the MS with the Water's Atmospheric Pressure GC (APGC) source.

A nano lock spray source, for infusion analysis, and an atmospheric pressure solids analysis probe (ASAP), for the direct sampling and introduction of solids and liquids, complete the instrument configuration.

APPLICATION

The Xevo® G2-XS QTof system, thanks to the interchangeable LC and GC configurations, offers maximum flexibility and robustness with no compromise in performance for the scientist who needs to identify, quantify, and confirm the broadest range of compounds in the most complex and challenging samples,

It can be applied to the quantitative and qualitative metabolomic and lipidomic analysis of biological or synthetic samples, and to top-down and bottom-up proteomics in biological samples.

EXAMPLE OF SERVICE

Metabolomics

- Quantification of targeted small molecules (i.e metabolites, drugs). For most assays, stable isotopically labeled analogs are used as internal standards for precise quantification. Detection limits range from high femtomoles to low picomoles.

- Untargeted metabolomics measurements, taking advantage of the high mass accuracy of the QTOF and the availability of metabolite databases, for identification of metabolites and their relative quantification.

Proteomics

- Intact protein characterization through exact mass measurement by direct infusion on the nano lock spray source.
- Protein identification and characterization after protein digestion of isolated proteins or protein mixtures.

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Significant papers

1) Ciaramelli C, Palmioli A, Brioschi M, Viglio S, D'Amato M, Iadarola P, Tosi S, Zucconi L, Airoldi C. Antarctic Soil Metabolomics: A Pilot Study. Int J Mol Sci. 2023 Aug 2;24(15):12340. doi: 10.3390/ijms241512340..

2) Cannavacciuolo C, Pagliari S, Giustra CM, Carabetta S, Guidi Nissim W, Russo M, Branduardi P, Labra M, Campone L. LC-MS and GC-MS Data Fusion Metabolomics Profiling Coupled with Multivariate Analysis for the Discrimination of Different Parts of Faustrime Fruit and Evaluation of Their Antioxidant Activity. Antioxidants (Basel). 2023 Feb 24;12(3):565. doi: 10.3390/antiox12030565.

3) Ciaramelli C, Palmioli A, Angotti I, Colombo L, De Luigi A, Sala G, Salmona M, Airoldi C. NMR-Driven Identification of Cinnamon Bud and Bark Components With Anti-Aβ Activity. Front Chem. 2022 Jun 8;10:896253. doi: 10.3389/fchem.2022.896253.

4) Pagliari S, Cannavacciuolo C, Celano R, Carabetta S, Russo M, Labra M, Campone L. Valorisation, Green Extraction Development, and Metabolomic Analysis of Wild Artichoke By-Product Using Pressurised Liquid Extraction UPLC-HRMS and Multivariate Data Analysis. Molecules. 2022 Oct 22;27(21):7157. doi: 10.3390/molecules27217157.

5) Pagliari S, Giustra CM, Magoni C, Celano R, Fusi P, Forcella M, Sacco G, Panzeri D, Campone L, Labra M. Optimization of ultrasound-assisted extraction of naturally occurring glucosinolates from by-products of Camelina sativa L. and their effect on human colorectal cancer cell line. Front Nutr. 2022 Jul 22;9:901944. doi: 10.3389/fnut.2022.901944.

Orbitrap Fusion Tribrid coupled to EASY-nLC 1000 UHPLC – Thermo Fisher

EQUIPMENT DESCRIPTION

The **Orbitrap Fusion** mass spectrometer enables the analysis of molecules and supramolecular complexes in the 50-6,000 m/z range, with high resolution (up to R=450,000), scan rate (MSn up to 20 Hz), mass accuracy (< 3 ppm), dynamic range (> 5,000) and sensitivity (100 fg total amount of the reserpine standard).

The instrument is characterized by a great flexibility of scan protocols based on multiple fragmentation modes, i.e. collision-induced dissociation (CID), higher-energy collisional dissociation (HCD), electron-transfer dissociation (ETD) and their combinations, that can be performed in two different collision cells (quadrupole or linear ion trap) and analyzed by two different analyzers (linear ion trap or Orbitrap).

The instrument is equipped with a regular and a nano electrospray ionization (ESI) sample source and can be coupled to a nano-flow UHPLC EASY-nLC 1000, enabling automated, high-performance LC/MS analyses of complex biological matrices.

APPLICATIONS

These features support bottom-up, top-down and middle-down proteomics studies and enable high-throughput and high-depth analysis of small molecules, peptides, proteins, post-translational modifications, protein-ligand interactions, and other polymers. Quantitative shotgun proteomics can be implemented by either stable-isotope or label-free approaches.

EXAMPLES OF SERVICE

- **Sample preparation**: buffer exchange/desalting, in-gel and in-solution enzymatic digestion, peptide enrichment, labelling for protein quantitation (iTRAQ and TMT)
- **Mass-spectrometry analysis**: ESI-MS by direct infusion or liquid chromatography, label-free or label-based shotgun proteomics, targeted quantitation and post-translational modification mapping
- **Data analysis and interpretation**: analysis of single spectrum, database search, mapping and quantitation
- Intact protein exact mass determination

- Phosphorylation characterization
- SDS-PAGE band identification
- Label-based or label-free protein quantitation.

For information:

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SIGNIFICANT PAPERS

1) Ponzini E, Ami D, Duse A, Santambrogio C, De Palma A, Di Silvestre D, Mauri P, Pezzoli F, Natalello A, Tavazzi S, Grandori R. Single-Tear Proteomics: A Feasible Approach to Precision Medicine. Int J Mol Sci. 2021 Oct 4;22(19):10750. doi: 10.3390/ijms221910750.

2) Santambrogio C, Natalello A, Brocca S, Ponzini E, Grandori R. Conformational Characterization and Classification of Intrinsically Disordered Proteins by Native Mass Spectrometry and Charge-State Distribution Analysis. Proteomics. 2019 Mar;19(6):e1800060. doi: 10.1002/pmic.201800060.

3) Li J, Santambrogio C, Brocca S, Rossetti G, Carloni P, Grandori R. Conformational effects in protein electrospray-ionization mass spectrometry. Mass Spectrom Rev. 2016 Jan-Feb;35(1):111-22. doi: 10.1002/mas.21465. Epub 2015 May 7. PMID: 25952139.

TSQ Quantum™ Access MAX - UltiMate 3000 UHPLC – Thermo Fisher Scientific

EQUIPMENT DESCRIPTION

The **TSQ Quantum Access MAX** instrument is a Triple Quadrupole analyzer equipped with a HESI ionization probe and a 90° high-efficiency square quadrupole collision cell. The instrument enables the analysis of molecules in the mass range of 10–3,000 m/z at a 5,000 µ/s scan rate and with 25 ms positive/negative switching. Scan functions include full scan MS in Q1 or Q3, selected ion monitoring (SRM) in Q1 or Q3, selected reaction monitoring (SRM), product ion scanning, precursor ion scanning, and neutral loss scanning. In SRM it is possible to define up to 3,000 timed segments and 2 ms dwell times. These features support targeted analysis of hundreds of compounds in a single run. In addition, the quantitation-enhanced data-dependent MS/MS (QED-MS/MS) provides simultaneous compound confirmation and quantification. Applications of small molecule quantitation cover environmental, food, pharma, and clinical research. The mass spectrometer is coupled with an UltiMate LPG-3400SD Gradient Pump that supports 4 eluents via a proportioning valve with a settable flow of 0.001 to 10.000 mL/min at pressures up to 620 bar. This LC system supports standard LC applications as well offers full compatibility with fast UHPLC separations. Data acquisition and analysis is performed by the software Xcalibur.

EXAMPLES OF SERVICE

- **Sample preparation**: extraction (solid phase, dispersive solid phase) and microextraction (single drop liquid phase, dispersive liquid-liquid, solid phase, dispersive solid phase), labelling for quantitation
- **Mass spectrometry analysis**: ESI-MS by flow infusion or liquid chromatography
- **Data analysis and interpretation**: analysis of a single spectrum or chromatogram

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LC Prep Autopurification system - Waters

EQUIPMENT DESCRIPTION

Waters' advanced LC Prep AutoPurification System offers robust, scalable solutions for every purification requirement. This is a flexible platform equipped with both an inclusiveness UV-based fraction collection for a few dozen samples and a mass-directed purification system for selective fraction collection in high throughput. Waters LC Prep AutoPurification System is a fully automated preparative system providing advanced functionality to satisfy all purification requirements without compromise. Its flexible configurations enable easy scale-up from analytical to preparative chromatography. This instrument offers versatile solutions that are capable of purifying micrograms to multigram quantities

Specific technical features

- 489 UV/Vis Detector (sensitive and versatile dual-wavelength absorbance detector 190-700 nm, with flexible sampling rates from 1 to 80 Hz)
- Acquity QDa Detector (m/z range 30-1250, single ion and full scan acquisition)
- FractionLynx Application Manager for full-cycle automation for purification.
- Proprietary Optimum Bed Density (OBD) Column design for high sample loading and unmatched column stability.
- System fluidic organizer with a binary gradient module for analytical and preparative separation with flow rate of 0.5-150 ml/min

APPLICATION

Preparative-scale chromatography plays a critical role in applications where compounds must be synthesized or identified, isolated, purified, characterized, screened, and tested for purity in different fields such as medicinal chemistry, synthetic chemistry, agrochemical industry, and natural products isolation.

EXAMPLES OF SERVICE

- Small molecule purification
- Peptide purification

For information:

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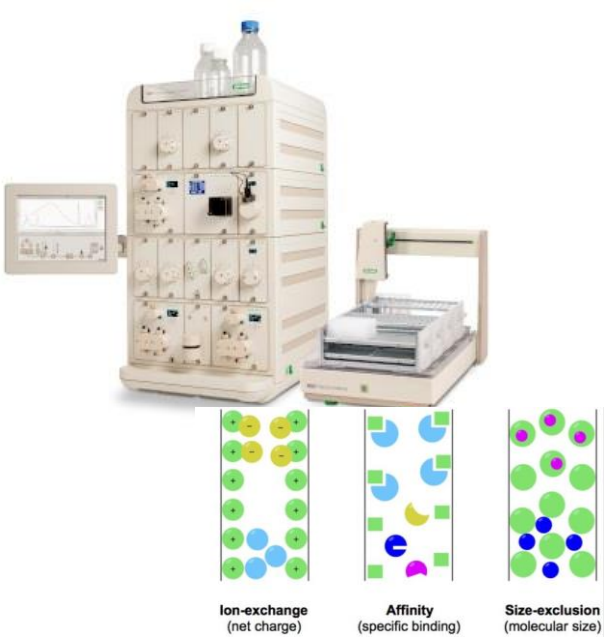
SIGNIFICANT PAPERS

1) Carol Ginsburg-Moraff, Jonathan Grob, Karl Chin, Grant Eastman, Sandra Wildhaber, Mark Bayliss, Heinrich M. Mues, Marco Palmieri, Jennifer Poirier, Marcel Reck, Alexandre Luneau, Stephane Rodde, John Reilly, Trixie Wagner, Cara E. Brocklehurst, René Wyler, David Dunstan, Alexander N. Marziale, Integrated and automated high-throughput purification of libraries on microscale, SLAS Technology, 2022; 27(6): 350-60, doi:10.1016/j.slast.2022.08.002.

2) Kagan M, Chlenov M, Melnikov S, McConnell O, Bach AC 2nd, Carter G, Failli A, Caggiano TJ, Shumsky JS, Lubda D. Normal-phase automated mass-directed HPLC purification of a pyrrolobenzodiazepine library with vasopressin agonist activity. J Comb Chem. 2009 Jul-Aug;11(4):704-19. doi: 10.1021/cc9000407.

3) Wang T, Barber M, Hardt I, Kassel DB. Mass-directed fractionation and isolation of pharmaceutical compounds by packed-column supercritical fluid chromatography/mass spectrometry. Rapid Commun Mass Spectrom. 2001;15(22):2067-75. doi: 10.1002/rcm.480.

NGC 10 Medium-Pressure Chromatography Systems- BIO-RAD



EQUIPMENT DESCRIPTION

The NGC Quest 10 Plus instrument is a complete system for the separation of biomolecules for their characterization and purification. It has automated 10 ml/min pumps that provide accurate gradients for high-resolution separations for any application. The multi-wavelength detector, with simultaneous four-wavelength monitoring, combined with conductivity measurements allows high-accuracy detection of proteins, peptides, and nucleic acids. Fractionated samples can be easily collected using the NGC Fraction Collector.

Specific technical features

- 10 ml/min pumps
- multi-wavelength (UV/Vis) detection
- conductivity detection
- automated sample injection
- automated fraction collector

APPLICATION

- Biomolecules purification (proteins, peptides, and nucleic acids)
- Purification of monoclonal antibodies
- Histidine-tagged recombinant protein purification and on-column refolding

EXAMPLES OF SERVICE

- Protein purification
- Studies on protein folding

For information:
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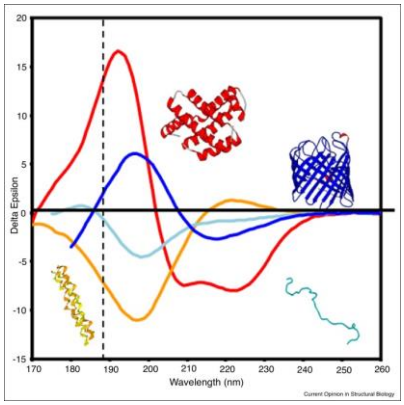
Significant papers

1) Sciandrone B, Ami D, D'Urzo A, Angeli E, Relini A, Vanoni M, Natalello A, Regonesi ME. HspB8 interacts with BAG3 in a "native-like" conformation forming a complex that displays chaperone-like activity. Protein Sci. 2023 Jul;32(7):e4687. doi: 10.1002/pro.4687.

2) Rinaldi C, Pizzul P, Casari E, Mangiagalli M, Tisi R, Longhese MP. The Ku complex promotes DNA end-bridging and this function is antagonized by Tel1/ATM kinase. Nucleic Acids Res. 2023 Feb 28;51(4):1783-1802. doi: 10.1093/nar/gkad062.

3) Visentin C, Pellistri F, Natalello A, Vertemara J, Bonanomi M, Gatta E, Penco A, Relini A, De Gioia L, Airoldi C, Regonesi ME, Tortora P. Epigallocatechin-3-gallate and related phenol compounds redirect the amyloidogenic aggregation pathway of ataxin-3 towards non-toxic aggregates and prevent toxicity in neural cells and Caenorhabditis elegans animal model. Hum Mol Genet. 2017 Sep 1;26(17):3271-3284. doi: 10.1093/hmg/ddx211.

Circular dichroism (CD) spectroscopy - Jasco J815



EQUIPMENT DESCRIPTION

Circular dichroism (CD) spectroscopy studies the intrinsic or induced chiral properties of biomolecules. At our Department is available the spectropolarimeter Jasco J815 (JASCO corporation, Japan) operating in the spectral range from 180 nm to 900 nm. Sample temperature can be controlled from -10°C to +110°C by a Peltier element.

CD spectroscopy provides information on protein secondary and tertiary structures and interactions, which is complementary to data obtained by other instrumental approaches available at our Department. For instance, the conformational properties and stability of peptides and proteins can be studied by means of CD, FTIR spectroscopy, and intrinsic and extrinsic fluorescence.
For the study of biomolecule interactions, CD spectroscopy is complementary to other analysis, such as surface plasmon resonance (SPR) spectroscopy, fluorescence and calorimetry.

APPLICATION

- Structural properties of biomolecules
- Protein secondary and tertiary structures Conformational stability of proteins
- Comparison with RLD (reference listed drug)
- Protein-ligand, protein-DNA, etc. interactions

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Significant papers

1) Wallace BA. The role of circular dichroism spectroscopy in the era of integrative structural biology. Curr Opin Struct Biol. 2019 Oct;58:191-196. doi: 10.1016/j.sbi.2019.04.001..

2) Tedeschi et al. Aggregation properties of a disordered protein are tunable by pH and depend on its net charge per residue. Biochim Biophys Acta Gen Subj. 2017 1861(11 Pt A):2543-2550. doi: 10.1016/j.bbagen.2017.09.002.

3) Natalello et al. Biophysical characterization of Met-G-CSF: effects of different site-specific mono-pegylations on protein stability and aggregation. PLoS One. 2012;7(8):e42511. doi: 10.1371/journal.pone.0042511.

Fourier transform infrared (FTIR) spectroscopy, Varian 670-IR

EQUIPMENT DESCRIPTION

Fourier transform infrared (FTIR) spectroscopy allows obtaining information on the biomolecule structural properties through the analysis of their absorption in the mid-IR range. Samples can be measured both in solution and in solid state (lyophiles and hydrated films) thanks to the possibility of collecting the FTIR spectra both in transmission and in attenuated total reflection (ATR) modes. Furthermore, FTIR micro-spectroscopy–obtained coupling an infrared microscope to the FTIR spectrometer – enables to analyse also the infrared response of intact cells, tissues, and biofluids that provides a biochemical fingerprint of the sample under investigation, giving information on the structure and content of its main biomolecules.

In our Department is available the high-performance FTIR spectrometer Varian 670-IR (Varian Australia Pty Ltd, Mulgrave VIC, Australia) provided with dynamic alignment and high-sensitivity detector (MCT). It is equipped with a sample-holder for transmission measurements and ATR accessory (diamond, one and nine reflections), both temperature-controlled. The spectrometer is coupled to the IR microscope Varian 610-IR.

FTIR spectroscopy makes it possible to obtain information complementary to those provided by other instrumental approaches available in our Department. For instance, the conformational properties and stability of peptides and proteins can be studied by means of FTIR spectroscopy, circular dichroism and intrinsic fluorescence.

APPLICATION

- Structural properties of biomolecules
- Protein secondary structure
- Protein aggregation and co-aggregation through the identification of specific IR- marker bands
- Conformational stability of proteins
- Comparison with RLD (reference listed drug)
- Material characterization
- Characterization of intact cells, tissues, and biofluids (for instance, in situ aggregation studies and identification of disease biomarkers) by FTIR spectroscopy coupled to machine learning approaches

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Significant papers

1) Ami et al. Contribution of Infrared Spectroscopy to the Understanding of Amyloid Protein Aggregation in Complex Systems. Front Mol Biosci. 2022 Apr 8;9:822852. doi: 10.3389/fmolb.2022.822852.

2) Ami et al. Tear-Based Vibrational Spectroscopy Applied to Amyotrophic Lateral Sclerosis. Anal Chem. 2021 Dec 28;93(51):16995-17002. doi: 10.1021/acs.analchem.1c02546.

3) Sala et al. Conformational Stability and Dynamics in Crystals Recapitulate Protein Behavior in Solution. Biophys J. 2020; 119(5):978-988. doi: 10.1016/j.bpj.2020.07.015.

4) Ami et al. ATR-FTIR Spectroscopy Supported by Multivariate Analysis for the Characterization of Adipose Tissue Aspirates from Patients Affected by Systemic Amyloidosis. Anal Chem. 2019; 91(4):2894-2900. doi: 10.1021/acs.analchem.8b05008.

5) Ami et al. In situ characterization of protein aggregates in human tissues affected by light chain amyloidosis: a FTIR microspectroscopy study. Sci Rep. 2016; 6:29096. doi: 10.1038/srep29096.

MicroCal PEAQ-ITC (ITC, Isothermal Titration Calorimetry)

EQUIPMENT DESCRIPTION

MicroCal PEAQ-ITC (Alfatest scientific instrumentation) is an instrument suitable for carrying out Isothermal Titration Calorimetry (ITC) experiments through direct measurements of the heat released or absorbed during a molecular interaction. This technique does not require any modification or treatment of the sample (such as, for example, immobilization or labelling), and allows to accurately determine bond affinity (K_D), reaction stoichiometry (n), enthalpy (ΔH), and entropy (ΔS). It is thus possible to obtain all the interaction parameters and the thermodynamic variables that regulate the process in a single experiment.

Specific technical features

- Amount of biomolecules required of about 10-100 µg (300 µl of sample volume),
- Affinity constants detectable in the range 10^{-2} a 10^{-12} M
- Amount of detectable heat: 0.04 µJ
- Short term noise level: 0.15 ncal / s
- Baseline stability: ⩽ 1 µCal / h
- Operating temperature range: 2 - 80 ° C, with stability +/- 0.00012 ° C at 25 ° C
- Automatic loading of the sample into the syringe, with bubble-free system compatible with high viscosity samples.
- Reaction cell made of Hastelloy, a chemically inert and corrosion resistant material (suitable for containing compounds with sulfhydryl groups or other reducing agents; acids, bases, biological buffers and different types of inorganic and organic solvents).

APPLICATION

- characterization of molecular interactions involving, for example, small molecules, proteins, antibodies, nucleic acids, lipids, metal ions and carbohydrates
- study of relationships between structure and activity (SAR)
- analysis of binding mechanisms (through enthalpy and entropy variations).
- analysis of enzymatic activity
- study of self-assembling processes and interaction of nanomaterials.

For information:

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Significant papers

1) Baranauskiene et al. Isothermal titration calorimetry for characterization of recombinant proteins. Curr Opin Biotechnol. 2019; 55:9-15. doi: 10.1016/j.copbio.2018.06.003.

2) Falconer et al. Applications of isothermal titration calorimetry in pure and applied research from 2016 to 2020. J Mol Recognit. 2021; 34(10):e2901. doi: 10.1002/jmr.2901.

3) Leavitt and Freire Direct measurement of protein binding energetics by isothermal titration calorimetry. Curr Opin Struct Biol. 2001; 11(5):560-6. doi: 10.1016/s0959-440x(00)00248-7.

Biacore X100 (SPR, surface plasmon resonance)

EQUIPMENT DESCRIPTION

Biacore X100 (Cytiva; https://www.cytivalifesciences.com/en/us/about-us/our-brands/biacore) is an instrument based on the phenomenon of Surface Plasmon Resonance (SPR) that allows the analysis of interactions between biomolecules in real-time and without the need for labelling. It is a system with high instrumental sensitivity, which requires the use of minimal quantities of sample volumes for the direct measurement of the kinetic and affinity parameters of the interaction.

Specific technical features

- The molecular weight of the interactors ranges from large molecules like proteins, DNA, RNA, antibodies, polysaccharides, lipids, cells, etc., to those with a molecular weight of ~100 Da.
- Operating temperature range: 4-40 ° C.
- Chips produced by Biacore technology: CM7, CM5, CM4, CM3 and C1 with carboxymethylated active groups; SA for biotinylated ligands; NTA for proteins with His Tag; HPA to create a lipid monolayer; L1 to create a lipid bilayer; AU to directly activate the ligands on gold foil. Capture kits are available for a wide variety of tags and molecules including GST fusion proteins; mouse IgG antibodies; human IgG antibodies.
- "Single Cycle Kinetics (SCK)" analytical approach, an alternative to the traditional multicyclic kinetic analysis technique, which allows reduction of analysis times, reduction of ligand consumption and simplified experimental design.
- Software implemented with a technique called CFCA (Calibration Free Concentration Analysis) for the accurate calculation of the active concentration of proteins in the absence of calibration, in addition to the traditional method of creating a sample standard curve.

APPLICATION

- Characterization of the molecular bond by determining the dissociation (kd) and association (ka) rate constants. Determination of the dissociation equilibrium constant for analytes and ligands of various nature and wide molecular mass range. Detection of k_d in the range of 10^{-5} - 0.1 s^{-1}, k_a in the range 10^{3}-10^{7} M^{-1} s^{-1}; K_D-Affinity range: 1pM-100µM.
- Characterization of binding specificity such as the search for biomarkers in small quantities in the serum.

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Significant papers

1) Sciandrone et al. HspB8 interacts with BAG3 in a "native-like" conformation forming a complex that displays chaperone-like

activity. Protein Sci. 2023 Jul;32(7):e4687. doi: 10.1002/pro.4687.

2) Franziska Pögel neé Steinicke et al. Performance qualification for reproducible Surface Plasmon Resonance analysis. Analytical Biochemistry, Volume 544, 2018, Pages 108-113, https://doi.org/10.1016/j.ab.2017.12.027.

3) Breveglieri G et al . Detection of the sickle hemoglobin allele using a surface plasmon resonance-based biosensor. Sens Actuators B Chem. 2019 Oct 1;296:126604. doi: 10.1016/j.snb.2019.05.081.

4)Wei Xie et al. A novel recombinant human Frizzled-7 protein exhibits anti-tumor activity against triple negative breast cancer via abating Wnt/β-catenin pathway. The International Journal of Biochemistry & Cell Biology, Volume 103, 2018, Pages 45-55, https://doi.org/10.1016/j.biocel.2018.08.004.

HPC infrastructure

EQUIPMENT DESCRIPTION

The HPC infrastructure consists of a multiprocessor and multi-GPU cluster that allows the performance of complex calculations at high speed in the context of molecular modeling and virtual high-throughput screening (HTS).

Specific technical features

- Nodes: 10
- Processors Intel Xeon-G 5210/node (600 CPUs in total)
- Accelerators: 4 x NVIDIA Tesla V100S 32GB
- RAM: 128G/node

APPLICATION

- Molecular Docking simulations for drug design (protein-small molecule, protein-peptide, protein-protein). The computing platform is equipped with classic, induced-fit and covalent docking software;
- Virtual HTS;
- Molecular Dynamics e enhanced sampling of biological macromolecules;
- Development of pharmacophore and QSAR models;
- Quantum chemistry and multi-scale calculations;
- 3D protein structure prediction.

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Significant papers

1) The ATP-bound conformation of the Mre11–Rad50 complex is essential for Tel1/ATM activation. Corinne Cassani, Jacopo Vertemara, Matteo Bassani, Antonio Marsella, Renata Tisi, Giuseppe Zampella, Maria Pia Longhese, Nucleic Acids Research, 2019, 47 (7)3550- 3567. DOI: 10.1093/nar/gkz038

2) Mechanism of Hydrogen Sulfide-Dependent Inhibition of FeFe Hydrogenase. Christina Felbek, Federica Arrigoni, David de Sancho, Aurore Jacq-Bailly, Robert B. Best, Vincent Fourmond, Luca Bertini, Christophe Léger, ACS Catalysys, 2021, 11, 24, 15162–15176. DOI: 10.1021/acscatal.1c04838

3) Synthesis, Molecular Modeling and Biological Evaluation of Metabolically Stable Analogues of the Endogenous Fatty Acid Amide Palmitoylethanolamide. Alessia D'Aloia, Federica Arrigoni, Renata Tisi, Alessandro Palmioli, Michela Ceriani, Valentina Artusa, Cristina Airoldi, Giuseppe Zampella, Barbara Costa, Laura Cipolla, International Journal of Molecular Sciences, 2020, 21, (23), 9074. DOI: 10.3390/ijms21239074

4) DNA binding modes influence Rap1 activity in the regulation of telomere length and MRX functions at DNA ends. Diego Bonetti, Carlo Rinaldi, Jacopo Vertemara, Marco Notaro, Paolo Pizzul, Renata Tisi, Giuseppe Zampella, Maria Pia Longhese. Nucleic acids research, 2020, 48 (5), 2424-2441. DOI: 10.1093/nar/gkz1203.

5) Epigallocatechin-3-gallate and related phenol compounds redirect the amyloidogenic aggregation pathway of ataxin-3 towards non-toxic aggregates and prevent toxicity in neural cells and Caenorhabditis elegans animal model. Cristina Visentin, Francesca Pellistri, Antonino Natalello, Jacopo Vertemara, Marcella Bonanomi, Elena Gatta, Amanda Penco, Annalisa Relini, Luca De Gioia, Cristina Airoldi, Maria E. Regonesi, Paolo Tortora. Human Molecular Genetics, 2017, 26 (17), 3271–3284. DOI:10.1093/hmg/ddx211

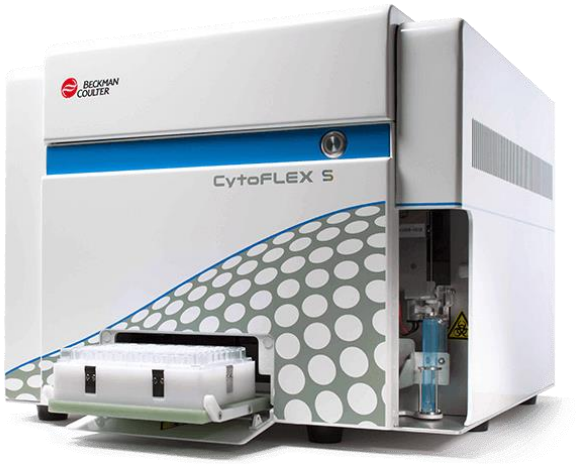
Cytoflex S - Beckman Coulter

EQUIPMENT DESCRIPTION

Cytoflex S is a benchtop flow cytometer, equipped with three lasers and nine fluorescent channels. Mainly used for qualitative and quantitative measurements of the physical and biological properties of mammalian and yeast cells.

Specific technical features

- Cytoflex S is equipped with three lasers and nine fluorescent channels.
  In details:
  88nm blue laser
  BP filters 525/40 - 690/50
  561nm yellow-green laser
  BP filters 585/42 -610/20 – 690/50 – 780/60
  638 nm red laser
  BP filters 660/20 – 712/25 – 780/60
- Cytexpert software, very user friendly, provides 7 decades of tunable dynamic range
- You can use sample volumes as low as 10µL and adjust flow rate from 10 to 240 µL/minute
- Optimal detection for particles as small as 300 nm
- In addition, the 561 nm laser is a much more efficient method for exciting red fluorescent proteins, which excite poorly with a 488 nm laser



APPLICATION

- Optimal Detection of Fluorescent Proteins
- DNA analyses
- Cell Viability
- Immunophenotyping

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BD FACSMelody™ Cell Sorter - BD

EQUIPMENT DESCRIPTION

BD FACSMelody is a cell sorter of the latest generation with fixed alignment and "cuvette based". BD FACSMelody is able to detect up to 11 parameters simultaneously: 9 fluorescences and 2 physical parameters. It has 3 spatially separate lasers; Blue 488 nm (20mW), Red 640 nm (40mW), Violet 405 nm (40mW). The Counting chamber is a gel-coupled quartz, to minimize background noise and to ensure maximal sensitivity. It can acquire up to 40,000 events / second on eleven parameters. It is equipped with a BD FACSMelody Reflection optical system and full digital electronics for signal processing and data acquisition.

A complete system of reagents, software and hardware work together to detect and sort low-density cell markers and rare cells. The system delivers reproducible results, enables sorting into tubes or a range of standard plates and is equipped with an optional custom class II biological safety cabinet, verified to meet personnel and product protection standards.

APPLICATION

BD FACSMelody assists in identifying and isolating cells in your sample.

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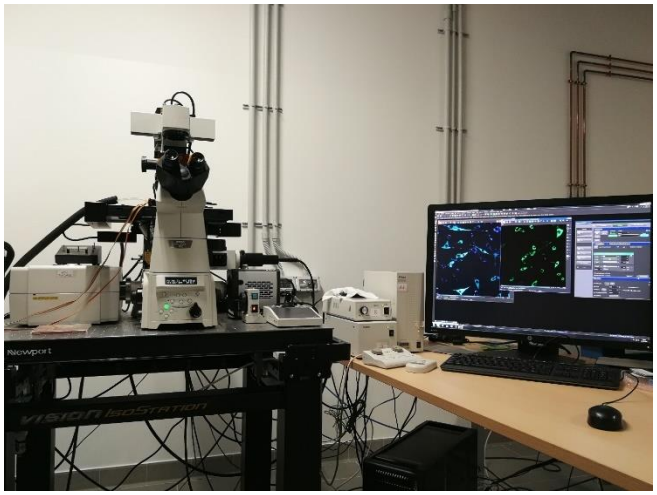
Confocal microscope A1R - Nikon

EQUIPMENT DESCRIPTION

The Nikon A1R confocal optical microscope is equipped with a hybrid scanner with the possibility of classical (galvanometric) and Resonant scanning to perform ultrahigh temporal resolution acquisitions ranging from 20 to 420 fps. The instrument is equipped with a 32-channels spectral detector (400-750 nm) for accurate spectral separation of overlapping fluorescences. A digital camera (Andor Zyla) and a microincubator (Okolab) allow measurements in epifluorescence and controlling temperature and CO2 respectively.



Specific technical features

- Inverted optical microscope with motorized stage in XY
- Double scanner with the possibility to select: 1) RESONANT scanner (super temporal resolution, scanning speed 420fps 512x32 pixels), 2) galvanometric scanner, 3) RESONANT+ GALVANO (simultaneous bleaching / stimulation measurements)
- 4 solid state lasers with AOTF system (405 nm;Ar , (457,488,514 nm); HeN (561 nm); HeN (633 nm)
- Hexagonal pinhole
- GaAsP detector (quantum efficiency 45%)
- Filter blocks: DAPI, FITCH, TRITCH, CY5, TEXAS RED
- High performance lenses (correction of chromatic aberrations): 10x, 20x, 40x, 60x, 100x
- Spectral analysis in emission: 32 channels
- Thermostat chamber for live imaging with T and CO2 control
- Phase contrast and interferential inserted in the optical path for use
- Focus stability during long-term time-lapse recordings (perfect focus)
- Motorized functions
- Flexible and easy-to-use acquisition and analysis software
- Image de-noise technique in post-processing

APPLICATION

The microscope allows imaging of isolated biological structures with a significant improvement in contrast, spatial and temporal resolution compared to classical optical microscopy techniques.

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Scanning Electron Microscope (SEM) FEG Gemini 500 - ZEISS

EQUIPMENT DESCRIPTION

Scanning electron microscope (SEM) complete with QUANTAX EDS 4000 microanalysis system (Bruker), equipped with "in-lens" detector (BSE/SE) for high-resolution images and a STEM detector for transmission observations of fine and biological samples. Thanks to its characteristics, this microscope is currently among the most advanced on the market for the collection of very high-resolution images.

Specific technical features

The Zeiss Gemini 500 SEM has a field emission source (FEG). The microscope can operate with accelerating voltages of 0.5-30 kV, beam currents of 3 pA-20 nA, and has a nominal resolution of 0.6 nm at 15 kV. In addition to the common "in-camera" detectors for secondary electrons (SE) and backscattered electrons (BSE), the instrument is equipped with "in-lens" detectors (BSE/SE) for high-resolution images and a STEM detector for in transmission of subtle and biological samples.

The FEG-SEM is also equipped with an integrated Bruker QUANTAX EDS/WDS (Energy Dispersive/Wave Dispersive) microanalysis system, particularly designed for the analysis of light elements, which notoriously place limits on microanalytical systems based on the fluorescence of X-ray. Finally, the FEG-SEM is equipped with a QUANTAX EBSD (Electron Backscattered Diffraction) system for the crystallographic analysis of the samples.

The EBSD system is equipped with Argus detectors for forward-scattered (FSE) and back-scattered electrons, for the acquisition of images in which the contrast is given by the different orientations of the grains.

The wide range of detectors with which the FEG-SEM is equipped makes it an extremely powerful instrument for the characterization at a submicroscopic scale of synthetic materials, and geological and biological samples.

APPLICATION

Ultrastructural analysis of geological and biological samples

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Transmission electron microscope (TEM) JEM 2100 Plus - JEOL

EQUIPMENT DESCRIPTION

The JEOL JEM 2100 Plus Transmission Electron Microscope (TEM) allows acquisitions with spatial resolution of 0.24 nm, very versatile and suitable for different types of investigations.

Specific technical features

The JEOL JEM 2100 Plus TEM has a LaB6 source and can work at acceleration voltages between 80 and 200 kV. The high-resolution polar pieces with which the instrument is equipped allow a spatial resolution of 0.24 nm; this, together with the wide tilt range (+/- 45° with a standard double tilt sample holder), makes it extremely versatile.

The instrument can also work in STEM mode (scanning) and is equipped with a detector for bright field observations (BF) and a ring detector for dark field observations with high diffraction angle (HAADF). The acquisition of the TEM images takes place through a Gatan camera with CMOS technology with a very sensitive 9 Mpixel sensor; this and the possibility of inserting a special "in-gap" opening under the sample which reduces the damage from radiation, make the instrument particularly suitable for working with sensitive samples.

The JEM 2100P is equipped with an Oxford EDS (Energy Dispersive System) nanoanalysis system with a 80 mm^2 sensor, particularly sensitive and efficient, even in compositional mapping, for which a drift correction system is provided. Finally, a special opening to be inserted upstream of the sample allows for the reduction of spurious peaks in the spectrum, improving the peak/background ratio.

APPLICATION

The variety of possible observation modes together with the great instrumental performance make the JEM 2100P a very versatile instrument suitable for the characterization of very different samples, such as synthetic materials, biological and geological samples and nanoparticles.

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THUNDER Imager 3D Tissue - Leica Microsystems

EQUIPMENT DESCRIPTION

Thunder Imager 3 D Tissue is able to analyze tissues quickly and precisely as well as to overlap and analyze tissue slices with precision that reaches the level of individual cells.

THUNDER mode helps to significantly increase image quality and improve contrast by implementing two technologies to eliminate background and light from unfocused planes

Specific technical features

- Fully automated tissue imaging system for multi-color image recording
- Acquisition in z-stack mode with motorized focusing device with very high precision. Decode 3D structures in real time
- System that allows you to remove the light coming from the out-of-focus planes without sacrificing the acquisition speed
- Device that allows the attenuation of the fluorescence that illuminates the sample in such a way as to guarantee maximum reproducibility even after prolonged use over time and for the reduction of the photobleaching phenomenon of the samples.
- Device with motorized wheel with 12 different field diaphragms (2 circular and 6 rectangular) that limit the portion of the field hit by the light, allowing to illuminate only the portion of the sample framed by the camera protecting the portions of fabric not illuminated by bleaching
- Filter wheel system for quick visualization and

acquisition of different fluorochromes (24 ms filter change speed between adjacent positions)
- Multi-Line LED source:
  1: 395/25
  2: 480/30
  3: 555/25
  4: 640/30
  5: 100% transmission
- HALO 3 Module software for Pathology and analysis of fluorescence images that allows simultaneous analysis of an unlimited number of fluorescent markers in any cell compartment

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Thunder Imager Live Cell - Leica Microsystem

EQUIPMENT DESCRIPTION

THUNDER Imager Live Cell is based on a fully motorized DMi8 microscope, Quantum Stage, and a multi-line, high-intensity fluorescence, LED light source.

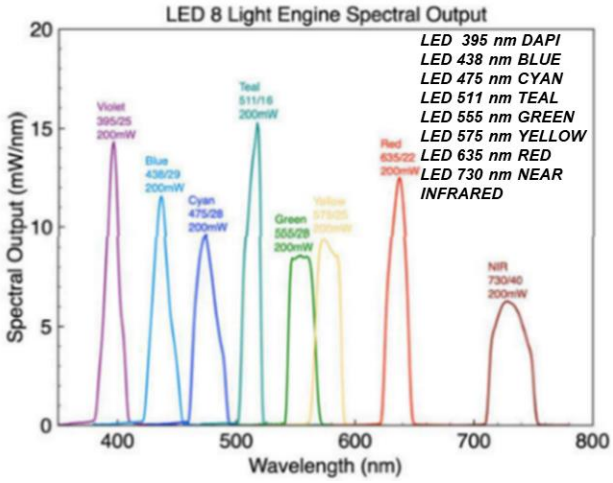
It is optimized for fast and precise multi-position, multi-channel imaging of 3D cell cultures.

THUNDER Imager features the innovative *Leica technology Computational Clearing*, which efficiently removes out-of-focus blur in real time.

The high sensitivity of the system ensures low phototoxicity and photobleaching.

Specific technical features

- Deconvolution technique
- Multi-Line LED source
- High sensitive sCMOS camera (DFC9000 GTC)
- External Filter wheel (high speed movements: 27 ms)
- Fluorescence filters cubes:
- Objectives
  - HC FL Plan 10x/0.25
  - HC PL FL L 20x/0.40 CORR PH1
  - HC PL FL L 40x/0.60 PH2 CORR
  - HC PL APO 63x/1.40 CORR
  - HC PL APO 100x/1.44 OIL CORR CS
  - HC PL APO 100x/1.40 Oil PH3
- Reproducible Z-positioning with a precision of up to 20nm
- Okolab incubator to ensure CO_2 and temperature control
- Software autofocus System - AFC (Adaptive Focus Control)
- LASX software, <u>for every Leica system</u>: with *Computational Clearing* method, combined with *deconvolution* technique



APPLICATION

- Fluorescence microscopy
- Live-cell Imaging
- 3D cell cultures
- Time-lapse
- FRET

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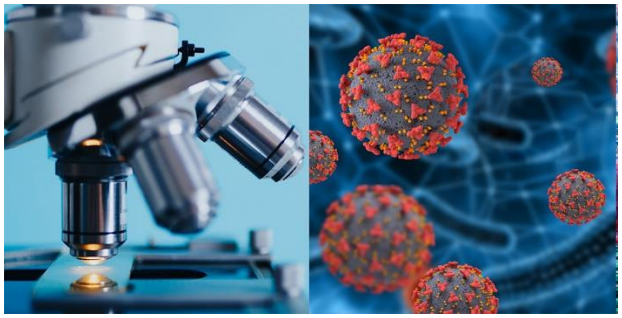
Operetta CLS – Perkin Elmer Inc



EQUIPMENT DESCRIPTION

The Operetta CLS instrument is a high-throughput microplate confocal microscope for High-Content Analysis (HCA). It is able to acquire, analyze, and manage fluorescence, brightfield, and digital phase contrast images.

The CLS Operetta instrument combines high autofocus capability, high-power LED excitation, and a large-format sCMOS camera to enable fast data acquisition.

Specific technical features

- Acquisitions on plates of 96 and 384 wells in kinetic and Time Lapse mode by returning several times to the same positions
- Plate housing chamber with CO_2 and temperature control included via software for performing Live Cell imaging experiments
- Brightfield reading mode, Digital Phase Contrast, Widefield fluorescence, and Confocal Spinning Disk
- air and immersion lenses
- 8 excitation/emission lines
- Unique software for instrument management, advanced image analysis, and statistical evaluations, suitable for morphological analysis of cell samples
- software with algorithms and advanced functions for machine learning, automatic recognition of objects / areas to be acquired

APPLICATION

- Fixed cell assays
- Live cell assays: Confocal optics and synchronized LED illumination provide stable excitation and minimize phototoxicity and bleaching issues
- Study of complex cellular models: The large-format sCMOS camera with immersion lenses in water provides sensitivity and high resolution, while advanced software helps you address imaging and analysis challenges presented by complex cell models
- Advanced assays FRET for investigating conformational changes and protein-protein interactions: the Operetta CLS system's sensitive imaging and dedicated analysis tools for ratiometric imaging, facilitate robust results
- Phenotypic fingerprinting

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Significant papers

1) D'Aloia A, Ceriani M, Tisi R, Stucchi S, Sacco E, Costa B. Cannabidiol Antiproliferative Effect in Triple-Negative Breast Cancer MDA-MB-231 Cells Is Modulated by Its Physical State and by IGF-1. Int J Mol Sci. 2022 Jun 27;23(13):7145. doi: 10.3390/ijms23137145.

2) Campioni G, Pasquale V, Busti S, Ducci G, Sacco E, Vanoni M. An Optimized Workflow for the Analysis of Metabolic Fluxes in Cancer Spheroids Using Seahorse Technology. Cells. 2022 Mar 2;11(5):866. doi: 10.3390/cells11050866.

3) D'Aloia A, Arrigoni E, Costa B, Berruti G, Martegani E, Sacco E, Ceriani M. RalGPS2 Interacts with Akt and PDK1 Promoting Tunneling Nanotubes Formation in Bladder Cancer and Kidney Cells Microenvironment. Cancers (Basel). 2021 Dec 16;13(24):6330. doi: 10.3390/cancers13246330.

4) Pasquale V, Ducci G, Campioni G, Ventrici A, Assalini C, Busti S, Vanoni M, Vago R, Sacco E. Profiling and Targeting of Energy and Redox Metabolism in Grade 2 Bladder Cancer Cells with Different Invasiveness Properties. Cells. 2020 Dec 11;9(12):2669. doi: 10.3390/cells9122669.

AGILENT SEAHORSE XFe96

EQUIPMENT DESCRIPTION

The Agilent Seahorse XFe96 analyzers measure the rate of oxygen consumption (OCR) and extracellular acidification rate (ECAR) of live cells in a 96-well plate format.
OCR and ECAR rates are key indicators of mitochondrial respiration and glycolysis, as well as the rate of ATP production. Together, these measurements provide a system-wide view of cellular metabolic function in cultured cells and ex vivo samples.

Specific technical features

- 96-well plate size meets many conditions in a single stroke, for flexible assay design, dose-response studies, and screening
- Report real-time metabolic rates in minutes, with no sample extraction or labeling
- Four-port injection system with automated mixing function for detecting live cell responses to substrates, inhibitors and other compounds in real time
- High-sensitivity analysis of a minimum of 5,000 cells per well using the 96-well plate
- Precisely controlled heating tray, maintains temperatures of 16–42°C (12–20°C above ambient conditions), for compatibility with a variety of sample types
- Quickly determines the dependence of cellular energy production on mitochondrial substrates
- Generates a metabolic phenotype within an hour for fast data processing

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Significant papers

1) Campioni G, Pasquale V, Busti S, Ducci G, Sacco E, Vanoni M. An Optimized Workflow for the Analysis of Metabolic Fluxes in Cancer Spheroids Using Seahorse Technology. Cells. 2022 Mar 2;11(5):866. doi: 10.3390/cells11050866.

2) Sforza A, Vigorelli V, Rurali E, Perrucci GL, Gambini E, Arici M, Metallo A, Rinaldi R, Fiorina P, Barbuti A, Raucci A, Sacco E, Rocchetti M, Pompilio G, Genovese S, Vinci MC. Liraglutide preserves CD34+ stem cells from dysfunction Induced by high glucose exposure. Cardiovasc Diabetol. 2022 Apr 9;21(1):51. doi: 10.1186/s12933-022-01486-9.

3) Raggi C, Taddei ML, Sacco E, Navari N, Correnti M, Piombanti B, Pastore M, Campani C, Pranzini E, Iorio J, Lori G, Lottini T, Peano C, Cibella J, Lewinska M, Andersen JB, di Tommaso L, Viganò L, Di Maira G, Madiai S, Ramazzotti M, Orlandi I, Arcangeli A, Chiarugi P, Marra F. Mitochondrial oxidative metabolism contributes to a cancer stem cell phenotype in cholangiocarcinoma. J Hepatol. 2021 Jun;74(6):1373-1385. doi: 10.1016/j.jhep.2020.12.031.

4) Pasquale V, Ducci G, Campioni G, Ventrici A, Assalini C, Busti S, Vanoni M, Vago R, Sacco E. Profiling and Targeting of Energy and Redox Metabolism in Grade 2 Bladder Cancer Cells with Different Invasiveness Properties. Cells. 2020 Dec 11;9(12):2669. doi: 10.3390/cells9122669.


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