# BIOGRAPHICAL SKETCH

**NAME**: Andrea, Mattevi

**POSITION TITLE:** Full Professor

**EDUCATION/TRAINING**

| INSTITUTION AND LOCATION | DEGREE (if applicable) | END DATE MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| The University of Pavia , Pavia | BS | 07/1988 | Biological Sciences |
| University of Groningen, Groningen | PhD | 10/1992 | Structural Biology |
| Laboratory of Molecular Biology, Cambridge | Postdoctoral Fellow | 10/1993 | EMBO Long term fellow |

**A. Personal Statement**

The general research theme of the structural - molecular biology group headed by Dr. Andrea Mattevi at the Dept. of Biology and Biotechnology of the University of Pavia is the structural, evolutionary, and chemical basis of enzyme catalysis and its mechanisms (http://www-9.unipv.it/biocry/). Their work is addressing the investigation of medically relevant enzymes with interesting mechanistic properties, such as complex multifunctional systems, proteins performing unusual catalytic functions, and, more recently, intact metabolons encompassing entire metabolic pathways. The research integrates biochemical, structural, and computational methods to investigate protein- and enzyme-based molecular mechanisms, with the goal of leveraging this knowledge for therapeutic development. The laboratory has been continuously funded by national and international grants (EU, ERC, NIH).

**B. Positions and Honors**

**Positions and Employment**

2002 - Full Professor, University of Pavia, Pavia
1994 - 2001 Assistant Professor, University of Pavia, Pavia

**Other Experience and Professional Memberships**

2018 - 2018 Chair , EMBO workshop on “Enzymes, biocatalysis and chemical biology: The new frontiers”
2018 - 2023 Chair of Life Science-1 panel , the European Research Council (ERC)
2018 - Associate Editor , Journal Biological Chemistry
2017 Chair (first non-US chair), 70th Gordon Research Conference on “Enzymes, Coenzymes and Metabolic Pathways”
2015 - 2023 Member of the Scientific Committee , Italian Association of Cancer Research
2014 - Advisory Editor , Journal of Biological Chemistry
2022 - Advisory Editor, ACS Bio & Med Chem Au
2024 - Editor Biochemistry

**Honors**

2005 - 2005 “Premio Borgia” , Academia dei Lincei, Rome
2001 - 2004 Young Investigator , EMBO
1992 – 1993 EMBO Long-term Fellowship, EMBO
2023 ERC Advanced Grant

**C. Contribution to Science**

Andrea Mattevi’s work from 2015-2026 resulted in papers in leading journals such as Nature Struct Mol Biol, Nature, Nature Catalysis, Nature Chemical Biology, Nature communications, Agewandte, Science Advances, JACS, PNAS, Chemical Reviews. His laboratory has focused on functional, structural and mechanistic work on oxygen-dependent enzymes, towards new insight into the oxidative modification of chromatin, redox signalling and ROS biology, and robust oxidative biocatalysts.

1) A recently started project, funded by an advanced-ERC grant, investigates how enzymes coordinate their function in the cell by forming metabolons. A first landmark result from this project led to the in vitro reconstruction of the mitochondrial metabolon responsible for the biosynthesis of coenzyme Q.

- In vitro construction of the COQ metabolon unveils the molecular determinants of coenzyme Q biosynthesis. Nicoll, C. R., Alvigini, L., Gottinger, A., Cecchini, D., Mannucci, B., Corana, F., Mascotti, M. L., **Mattevi*, A**. (2024). *Nature Catal.* 7, 148–160. *Work describes the full elucidation of the enzymatic steps in the biosynthesis of coenzyme Q*
- Complete Enzyme Clustering Enhances Coenzyme Q Biosynthesis via Substrate Channeling. Wang, D., Gottinger, A., Jeong, J., Nicoll, C. R., Liu, J., Kadavá, T., Cecchini, D., Malatesta, M., Heck, A. J. R., **Mattevi*, A**., & Shakhnovich, E. I. (2026). *Nature Commun,* in press. *An innovative computational-experimental approach to model the functioning of a metabolon*

2) Over the last decade, Mattevi' has worked collaboratively to identify the mechanism of nucleosome recognition by flavin-dependent enzyme complexes that oxidatively demethylate histone lysines. A crucial aspect of this work has been enabling medicinal exploitation (in academic and industry) of their basic science for the development of epigenetic drugs that target leukemia and are now in phase III clinical trials (in collaboration with Imago biosciences).

- Covalent adduct Grob fragmentation underlies LSD1 demethylase-specific inhibitor mechanism of action and resistance. Waterbury, A. L., Caroli, J., Zhang, O., Tuttle, P. R., Liu, C., Li, J., Park, J. S., Hoenig, S. M., Barone, M., Furui, A., **Mattevi*, A**., Liau, B. B. (2025). *Nature Commun*, *16*, 3156. *A novel mechanism of epigenetic drug action and drug resistance*
- UM171 glues asymmetric CRL3-HDAC1/2 assembly to degrade CoREST corepressors. Yeo, M. J. R., Zhang, O., Xie, X., Nam, E., Payne, N. C., Gosavi, P. M., Kwok, H. S., Iram, I., Lee, C., Li, J., Chen, N. J., Nguyen, K., Jiang, H., Wang, Z. A., Lee, K., Mao, H., Harry, S. A., Barakat, I. A., Takahashi, M., Waterbury, A. L., **Mattevi, A**. … Zheng, N. (2025). *Nature* 639, 232–240. *The discovery of a new molecular glue and the molecular mechanisms underlying cell transformation in glioblastoma.*
- The scaffolding function of LSD1 controls DNA methylation in mouse ESCs. Malla, S., Kumari, K., García-Prieto, C. A., Caroli, J., Nordin, A., Phan, T. T. T., Bhattarai, D. P., Martinez-Gamero, C., Dorafshan, E., Stransky, S., Álvarez-Errico, D., Saiki, P. A., Lai, W., Lyu, C., Lizana, L., Gilthorpe, J. D., Wang, H., Sidoli, S., Mateus, A., Lee, D. F., **Mattevi, A**., Roman A.G. Aguilo, F. (2024). *Nature Commun*. **15**, 7758. *Uncovers the essential functions of LSD1 in ESC differentiation.*
- Uncoupling histone modification crosstalk by engineering lysine demethylase LSD1. Lee, K., Barone, M., Waterbury, A. L., Jiang, H., Nam, E., DuBois-Coyne, S. E., Whedon, S. D., Wang, Z. A., Caroli, J., Neal, K., Ibeabuchi, B., Dhoondia, Z., Kuroda, M. I., Liau, B. B., Beck, S., **Mattevi*, A**., & Cole, P. A. (2024). *Nature Chem. Biol*. 21, 227-237. *Work describes the mechanism of cross-talks among epigenetic modifications using an innovative methodology.*
- A tail-based mechanism drives nucleosome demethylation by the LSD2/NPAC multimeric complex. Marabelli, C., Marrocco, B., Pilotto, S., Chittori, S., Picaud, S., Marchese, S., Ciossani, G., Forneris, F., Filippakopoulos, P., Schoehn, G., Rhodes, D., Subramaniam, S. **Mattevi*, A**. (2019). *Cell Reports* 27, 387-399.e7. *Multiple cryoEM structures of histone demethylase LSD2 bound to the nucleosome revealing a novel mechanism of nucleosome engagement*.

3) In the past years, the group has determined and published the first three-dimensional structure of a NADPH-dependent oxidase (NOX). This work has led to unprecedented insight into the family of these membrane-bound multi-subunit enzymes and their roles in redox signalling and innate immunity. We are currently expanding on this work to advance our understanding of NOXs' regulatory mechanisms and the design of much needed enzyme inhibitors as tools to modulate redox signalling and inflammation.

- Noce, B., Marchese, S., Massari, M., Lambona, C., Reis, J., Fiorentino, F., Raucci, A., Fioravanti, R., Castelôa, M., Mormino, A., Garofalo, S., Limatola, C., Basile, L., Gottinger, A., Binda, C., **Mattevi*, A**., Mai, A., & Valente, S. (2025). Design of Benzyl-triazolopyrimidine-Based NADPH Oxidase Inhibitors Leads to the Discovery of a Potent Dual Covalent NOX2/MAOB Inhibitor. *J. Med. Chem.* 68, 6292–6311. *The design of dual inhibitors that shut down the two most powerful enzymatic sources of ROS.*
- Ogboo, B.C., Patel, K.B., Massari, M., Marchese, S., Reis, J., Joyce, E.J., Lin, M.J., Rabb, J. D., Abidakun, O.A., Lin, Q., van der Vliet, A., **Mattevi, A**., & Heppner, D. E. (2025). Enhancing Selectivity and Potency of SNAr

Covalent Inhibitors of NADPH Oxidase Enzymes. *J. Med. Chem.* 68, 14072–14084. *The first isoform-selective NOX5 inhibitors*.

- Targeting ROS production through inhibition of NADPH oxidases. Reis, J., Gorgulla, C., Massari, M., Marchese, S., Valente, S., Noce, B., Basile, L., Törner, R., Cox, H., 3rd, Viennet, T., Yang, M.H., Ronan, M.M., Rees, M.G., Roth, J. A., Capasso, L., Nebbioso, A., Altucci, L., Mai, A., Arthanari, H., **Mattevi*, A**. (2023). *Nature Chem. Biol*. 19, 1540-1550. *The discovery of the first NADPH oxidase inhibitors.*
- An Elegant Four-Helical Fold in NOX and STEAP Enzymes Facilitates Electron Transport across Biomembranes-Similar Vehicle, Different Destination. Oosterheert, W., Reis, J., Gros, P., **Mattevi*, A**. (2020) *Acc. Chem. Res.* 53, 1969-1980. *An extensive structural analysis of the NOX family of enzymes.*
- A closer look into NADPH oxidase inhibitors: Validation and insight into their mechanism of action. Reis J, Massari M, Marchese S, Ceccon M, Aalbers FS, Corana F, Valente S, Mai A, Magnani F, **Mattevi*, A**. (2020) *Redox Biol.* 32, 101466. *Demonstrates that virtually all putative NOX inhibitors are simply ROS-scavengers.*
- Crystal structures and atomic model of NADPH oxidase. Magnani, F., Nenci, S., Millana Fananas, E., Ceccon, M., Romero, E., Fraaije, M.W., **Mattevi*, A**. (2017). *Proc. Natl. Acad. Sci. USA* 114, 6764-6769. *The first three-dimensional structure of a NADPH oxidase (NOX).*

4) The group became interested in enzyme evolution as highlighted by our projects on flavin-dependent monoxygenases, a large family of membrane-bound enzymes that are heavily involved in detoxification and metabolism, as well as on the enzyme catalyzing the synthesis of vitamin C and other natural products. Using ancestral sequence reconstruction, we determined the first structures of these enzymes, delivering step-change insight into their mechanism of function and the evolution of their diverging substrate scopes.

- Tjallinks, G., Angeleri, N., Nguyen, Q.T., Mannucci, B., Arentshorst, M., Visser, J., Ram, A.F. J., Fraaije, M.W., & Mattevi,* A. (2025). Structural and Mechanistic Characterization of the Flavin-Dependent Monooxygenase and Oxidase Involved in Sorbicillinoid Biosynthesis. ACS Chem. Biol. 20, 646–655. The discovery of the unlikely chemistry underlying the biosynthesis of sorbicillinoids.
- Boverio, A., Jamil, N., Mannucci, B., Mascotti, M.L., Fraaije, M.W., Mattevi*, A. (2024). Structure, mechanism, and evolution of the last step in vitamin C biosynthesis. Nature Commun. 15, 4158. Unveils the evolution of vitamin C biosynthesis in plants, fungi and animals.
- Ancestral sequence reconstruction unveils the structural basis of function in mammalian FMOs. Nicoll, C.R., Bailleul, G., Fiorentini, F., Mascotti, M.L., Fraaije, M.W., Mattevi*, A. (2020). Nature Struct. Mol. Biol. 27, 14-24. Ancestral sequence reconstruction reveals, for the first the time, the structure, function and evolution of a key family of enzymes in xenobiotic and drug detoxification.
- Characterization of Human FMO5: Unearthing Baeyer-Villiger Reactions in Humans. Fiorentini, F., Geier, M., Binda, C., Winkler, M., Faber, K., Hall, M., Mattevi*, A. (2016). ACS Chem. Biol. 11, 1039-1048. Work unveils the existence of a Baeyer-Villiger monooxygenase in humans.

5) The group has contributed substantially to projects towards methods for the engineering of hyperstable enzymes (up to 100 °C melting temperature) to be used as biocatalysts in chemical processes.

- Polycyclic Ketone Monooxygenase from the Thermophilic Fungus *Thermothelomyces thermophila*: A Structurally Distinct Biocatalyst for Bulky Substrates. Fürst, M.J., Savino, S., Dudek, H.M., Gómez Castellanos, J.R., Gutiérrez de Souza, C., Rovida, S., Fraaije, M.W., **Mattevi*, A**. (2017). *J. Am. Chem. Soc*. 139, 627-630. *Discovery and crystal structure of a monooxygenase working on a very bulky polycyclic compound of industrial interest*.
- Deciphering the enzymatic mechanism of sugar ring contraction in UDP-apiose biosynthesis. Savino, S., Borg, A.J.E., Dennig, A., Pfeiffer, A., De Giorgi, F., Weber, H., Dubey, K.D., Rovira, C., **Mattevi*, A**., Nidetzky, B. (2019). *Nature Catal.* 2, 1115-1123. *Work unveils the mechanistic enzymology of one the most complex sugar-modifying reactions*.
- Approaching boiling point stability of an alcohol dehydrogenase through computationally-guided enzyme engineering. Aalbers, F.S., Fürst, M.J., Rovida, S., Trajkovic, M., Gómez Castellanos, J.R., Bartsch, S., Vogel, A., **Mattevi, A**., Fraaije, M.W. (2020). *Elife* 9, e54639. *Work describes probably the world-record in protein stabilization, with enzymes resisting boiling-water temperatures.*

Complete List of Published Work in My Bibliography:
https://scholar.google.it/citations?user=Vgm8bHkAAAAJ&hl=it&oi=ao

**D. Recent Research Support**

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| Targeting a professional ROS generator in cancer and inflammation | Italian Ministry of Science | 01.04.2024 - 28.02.2026 |
| Exploring coenzyme Q biosynthesis as a drug target | AIRC | 01.01.2024 - 31.12.2029 |
| Chemical Genetic Approaches to Chromatin Complexes | NIH - USA | 01.05.2023 - 01.4.2025 |
| Molecule functionalization via biocatalytic halogenations | EU-H2020 | 01.01.2026 - 31.12.2029 |
| Enzyme Engineering for New Polymers | EU-H2020 | 01.3.2025 - 29.02.2028 |
| When Enzyme Joing forces (MetaQ) | ERC | 01.10.2023 - 30.09.2028 |