BIOGRAPHICAL SKETCH

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NAME: Andrea, Mattevi

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Full Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

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 main task for many proteins inside living cells is to catalyze chemical reactions. Proteins having such a catalytic function are called enzymes. The structural biology group headed by Dr. Andrea Mattevi in the Dept. of Biology and Biotechnology structural basis of enzyme catalysis and the dynamic properties of proteins. A common theme for the research projects in the laboratory (www.unipv.it/biocry) is the investigation of medically relevant enzymes with interesting chemical properties, such as complex multifunctional systems and proteins performing unusual catalytic functions. The core of the research activity is represented by X-ray crystallography and cryo-electron microscopy that is employed to study protein three-dimensional structures. This is complemented by other approaches such as site-directed mutagenesis, analysis of enzyme kinetics, and computational chemistry.

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

2022 - Advisory Editor, ACS Bio & Med Chem Au
2020 - Advisory Editor, Biochemistry
2018 - 2018 Chair , EMBO workshop on “Enzymes, biocatalysis and chemical biology: The new frontiers”
2018 - Chair of Life Science-1 panel , the European Research Council (ERC)
2018 - Associate Editor , Journal Biological Chemistry
2016 - 2017 Vice Chair and Chair (first non-US chair), 70th Gordon Research Conference on “Enzymes, Coenzymes and Metabolic Pathways”
2015 - Member of the Scientific Committee , Italian Association of Cancer Research
2014 - Advisory Editor , FEBS Journal

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 2013-2024 resulted in papers in leading journals such as Nature Struct Mol Biol, 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.

A recently started project 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. This work led to the first-time characterization of this essential pathway and its regulation.

- 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 described the full elucidation of the enzymatic steps in the biosynthesis of coenzyme Q*

Over the last decade, it 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 I/II clinical trials (in collaboration with Imago biosciences).

- 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. *Work describes multiple cryoEM structures of histone demethylase LSD2 complexes bound the nucleosome revealing a novel mechanism of nucleosome engagement*.
- Targeting the CoREST complex with dual histone deacetylase and demethylase inhibitors. Kalin, J.H., Wu, M., Gomez, A.V., Song, Y., Das, J., Hayward, D., Adejola, N., Wu, M., Panova, I., Chung, H.J., Kim, E., Roberts, H.J., Roberts, J.M., Prusevich, P., Jeliazkov, J.R., Roy Burman, S.S., Fairall, L., Milano, C., Eroglu, A., Proby, C.M., Dinkova-Kostova, A.T., Hancock, W.W., Gray, J.J., Bradner, J.E., Valente, S., Mai, A., Anders, N.M., Rudek, M.A., Hu, Y., Ryu, B., Schwabe, J.W.R., Mattevi, A., Alani, R.M., Cole, P.A. (2018) *Nature Commun*. 9, 53. *Pioneering work discovering the first dual deacetylase-demethylase epigenetic inhibitors.*
- Polymyxins and quinazolines are LSD1/KDM1A inhibitors with unusual structural features. Speranzini, V., Rotili, D., Ciossani, G., Pilotto, S., Marrocco, B., Forgione, M., Lucidi, A., Forneris, F., Mehdipour, P., Velankar, S., Mai, A., Mattevi, A. (2016) *Science Adv.* 2, e1601017. *Defines a new class of substrate-competing LSD1 demethylase inhibitors and the potential for inhibition by clinically-used natural products*.
- Interplay between nucleosomal DNA, histone tails and CoREST underlies LSD1-mediated H3 demethylation. Pilotto, S., Speranzini, V., Tortorici, M., Durand, D., Fish, A., Valente, S., Forneris, F., Mai, A., Sixma T.K., Vachette, P., Mattevi, A. (2015) *Proc. Natl. Acad. Sci. USA* 112, 2752-2757. *Work describes the mechanism of nucleosome recognition by the flavin-dependent histone demethylase LSD1 using an innovative covalent cross-linking methodology to obtain 3D structures*.

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.

- 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).*

The group became interested in enzyme evolution as highlighted by our work on flavin-dependent monoxygenases, a large family of membrane-bound enzymes that are heavily involved in detoxification and metabolism. 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.

- 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.*

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. The know-how gained from this work is crucial for our project.

- 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://www.ncbi.nlm.nih.gov/myncbi/mattevi.andrea.1/bibliography/public/
https://scholar.google.it/citations?user=Vgm8bHkAAAAJ&hl=it&oi=ao

D. Recent Research Support

MUR-PRIN
01/01/22-31/12/24
Mechanistic understanding of NADPH oxidases and their roles in ROS biology
Role: Coordinator

MUR-FISR
1/05/21-30/09/24
Methylome Dysregulation in Cancer: a Synergistic Multidisciplinary Approach for Fighting Disease
Role: Unit PI

H2020-EU
04/01/19-03/31/23
Modifications of Aromatics through Biocatalytic Oxidations
Role: Unit PI

Italian Association for Cancer Research
01/01/24-12/31/28
Exploring coenzyme Q biosynthesis as a drug target
Role: PI

MUR-PRIN
01/01/24-31/12/25
Targeting a professional ROS generator in cancer and inflammation
Role: Coordinator

King Abdullah University of Science and Technology ("KAUST")
Study of the Transcriptional And Epigenetic Roles of Lsd1/Kdm1a Splicing Variants During Neuronal Development
01/07/20-30/06/23
Role: Unit PI

Fondazione Cariplo
01/05/21-30/4/23
Cracking the problem of the enzymatic conversion of glycerol to make the most of an overwhelming waste product in biodiesel production
Role: Coordinator

European Recent Council (ERC) Advanced grant
15/09/23-12/31/28
When enzymes join forces
Role: Coordinator