

BIOGRAPHICAL SKETCH

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NAME: Mancia, Filippo

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

POSITION TITLE: 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)	Completion Date MM/YYYY	FIELD OF STUDY
Università di Pavia, Pavia, Italy	M.Sc.	03/1992	Chemistry
MRC Laboratory of Molecular Biology & University of Cambridge, Cambridge, England	Ph.D.	12/1996	Biology (adviser Dr. Philip R. Evans, FRS)
Columbia University Medical Center (CUIMC), New York, NY	Postdoctoral	12/2000	Struct Biol (adviser Dr. Wayne Hendrickson)

A. Personal Statement

I am a membrane protein biochemist and structural biologist with experience in x-ray crystallography and in single particle cryo-electron microscopy (cryo-EM), and in production and characterization of membrane proteins for both structural and functional studies. We use a structure-based integrated approach to investigate the molecular details of biological processes that occur at the cell membrane and we pioneered the development of structural genomics methods to achieve these goals. My labs main research interests, which often overlap are (a) to understand how the membrane bilayer and specific membrane enzymes and transporters, most often nutrients, interact to accommodate lipidic substrates and their constituents. To cite two examples, we have solved the structure of STRA6, the cell surface receptor for retinol-binding protein (RBP) bound vitamin A (in the form of retinol) allowing us to investigate the mechanism of transport of this essential nutrient across the membrane; we have integrated structural biology, functional assays, native mass spectrometry and molecular dynamics simulations to investigate how omega-3 fatty acids are transported specifically across the blood-brain barrier by MFSD2A. (b) To understand the molecular bases of drug resistance. Again, to cite two examples, we have determined the structure and probed the mechanism of aminoglycoside transferase (ArnT), the enzyme that mediates the resistance to polymyxins, last resort antibiotics. We have also determined the structure of the chloroquine resistance transporter from *Plasmodium falciparum* (PfCRT), combining cryo-EM, biochemistry, genetics and parasitology to start to unveil the molecular basis of resistance to the common antimalarials of the 4-aminoquinoline family (chloroquine and piperaquine).

In respect to my services to the scientific community, I have been a key member of the NIH Protein Structure Initiative-funded New York Consortium of Membrane Protein Structure (NYCOMPS), then the NIH-P41 funded Center on Membrane Protein Production and Analysis (COMPPA). I have also been the lead organizer of the two COMPPA Membrane Protein Production and Analysis Symposia (2018 and 2022), highlighting the recent developments in membrane protein molecular-level research, and each bringing together over 250 participants from all over the world in a 3-day format gathering. Furthermore, I have been a grant reviewer for many European entities, and also been a permanent member (2019-2023) and Chair of the Biochemistry and Biophysics of Membranes (BBM) NIH Study Section.

Ongoing projects that I would like to highlight include:

R35GM132120, NIH/NIGMS (PI Mancia, F.)

05/01/2019 – 04/30/2029

“Structural basis of integral membrane enzyme function”

The goal of this project is to determine the basic principles that govern how lipidic substrates are recognized and processed by membrane enzymes.

R01AI147628, NIH/NIAID (MPI; Mancía, F., Fidock, D. & Quick, M.) 07/01/2019 – 08/31/2024
“Leveraging PfCRT structure to discern function and predict emergence of drug-resistant Malaria”
 The goal of this proposal is to combine structural, biochemical and genetic experiments to understand the molecular basis for resistance to anti-malarial drugs mediated by the membrane transporter pfCRT.

R01CA275005 (MPI; Mancía, F. & Virshup, D.) 09/18/2023 – 08/31/2028
“Molecular Mechanisms of Wnt Transport”
 The goal of this proposal is to provide a molecular-level understanding of how transport of Wnts by their sole specific carrier Wntless (WLS) occurs.

R01EY027405, NIH/NEI (MPI; Mancía, F. & Khelashvili, G.) 04/01/2017 – 04/30/2028
“Structural basis of receptor-mediated cellular vitamin A uptake”
 Our objective is to investigate at the molecular level the relationship between the structure and the function of STRA6 as it may point at novel targets for therapeutic approaches in treatment of developmentally-related pathologies and diseases of the visual system.

Citations:

- a. Chen, Y., Clarke, O.B., Kim, J., Stowe, S., Kim, Y.K., Assur, Z., Cavalier, M., Godoy-Ruiz, R., von Alpen, D.C. Manzini, C. Blamer, W.S., Frank, J., Quadro, L., Weber, D.J., Shapiro, L., Hendrickson, W.A. and **Mancía, F.** (2016). Structure of the STRA6 receptor for retinol uptake. *Science*, doi: 10.1126/science.aad8266. PMID: PMC5114850.
- b. Cater, R.J., Chua, G.L., Erramilli S.K., Keener, J.E., Choy, B.C., Tokarz, P., Chin, C.F., Quek, D.Q.Y., Kloss, B., Pepe, J.G., Parisi G., Kossiakoff A.A., Khelashvili, G., Silver, D. and **Mancía, F.** (2021). Structural basis of omega-3 fatty acid transport across the blood-brain barrier. *Nature*, doi: 10.1038/s41586-021-03650-9. PMID: PMC8266758.
- c. Petrou, V.I., Herrera, C.M., Schultz, K.M., Clarke, O.B., Vendome, J., Tomasek, D., Banerjee, S., Rajashankar, K.R., Belcher Dufrisne, M., Kloss, B., Kloppmann, E., Rost, B., Klug, C.S., Trent, M.S., Shapiro, L. and **Mancía, F.** (2016). Structures of aminoarabinose transferase ArnT suggest a molecular basis for resistance to polymyxins. *Science*, doi: 10.1126/science.aad1172. PMID: PMC4963604.
- d. Kim, J., Tan, Y.Z., Wicht, K.J., Erramilli, S.K., Dhingra, S.K., Okombo, J., Vendome, J., Hagenah, L.M., Giacometti, S.I., Warren, A.L., Nosol, K., Roepe, P.D., Potter, C.S., Carragher, B., Kossiakoff, A.A., Quick, M., Fidock, D.A. and **Mancía, F.** (2019). Structure and drug resistance of the *Plasmodium falciparum* transporter PfCRT. *Nature*, doi: 10.1038/s41586-019-1795-x. PMID: PMC6911266.

B. Positions, Scientific Appointments and Honors

Positions and Employment

2022- Vice Chair, Dept of Physiology & Cellular Biophysics, CUIMC, New York
 2021- Professor, Dept of Physiology & Cellular Biophysics, CUIMC, New York
 2018- Co-Director, Graduate Program in Physiology, Columbia University, New York
 2017 – 2021 Associate Professor, Dept of Physiology & Cellular Biophysics, CUIMC, New York
 2009 – 2017 Assistant Professor, Dept of Physiology & Cellular Biophysics, CUIMC, New York
 2003 – 2009 Assoc Res Scientist, Dept of Biochem & Molecular Biophysics, CUIMC, New York
 2000 – 2003 Associate, Howard Hughes Medical Institute, CUIMC, New York

Honors / Other Experiences / Professional Memberships

2024- Foreign Member, Academy of Sciences of Lisbon, Portugal
 2024- Chair, Standing Independent Evaluation Committee, Human Technopole, Milano, Italy
 2023- Chair, CUIMC Scientific Research Advisory Committee (reports to the Dean)
 2023 Visiting Professor, Università del Piemonte Orientale, Novara, Italy
 2021 – 2023 Chair, Biochemistry and Biophysics of Membranes (BBM) Study Section, NIH
 2019 Visiting Professor in Biochemistry, Università La Sapienza, Rome, Italy
 2018 Structural Biology Lecturer, University of Warwick, Coventry, UK
 2019 – 2022 Permanent Member, Biochemistry and Biophysics of Membranes (BBM) Study Section, NIH
 2017 Visiting Professor, Università Politecnica delle Marche, Ancona, Italy
 2017 Clyde and Helen Wu Assistant Professor of Physiology and Cellular Biophysics, CUIMC
 2016 Visiting Professor in Biochemistry, Università La Sapienza, Rome, Italy
 2016 Schaefer Research Scholar
 1997 Human Science Frontier Program Organization (HSFPO) long-term fellowship

1996 European Molecular Biology Organization (EMBO) long-term fellowship
1995 Max Perutz student prize for the work as a graduate student.

C. Contributions to Science

1. Structural genomics of membrane proteins and CysZ-mediated sulfate uptake. I have developed methods for production of membrane proteins and complexes, for productions of reagents to aid in structural biology of membrane proteins, and for high-throughput screening of prokaryotic and eukaryotic membrane proteins to identify well-expressed, detergent-stable candidates for in-depth structural investigation. This work has been instrumental to the success of the New York Consortium of Membrane Protein Structure (NYCOMPS), which applied a structural genomics approach, combined with high-throughput technologies to identify membrane protein with increased likelihood of yielding structural information. I co-directed the protein production center of NYCOMPS, and I am now on the Executive and Operations Committees of its successor, the Center on Membrane Protein Production and Analysis (COMPPA). The development of methodology and technology in my lab and in collaboration with NYCOMPS and COMPPA has resulted in substantial contributions to the membrane protein field, leading to the solution of numerous problems, which could not have been otherwise approached. Our association with NYCOMPS has also led us to make use of a structural genomics approach to identify membrane proteins suitable for in-depth structural investigation. This has revealed many new and unexpected structures, yielding surprises and shedding light on the mechanistic details of several important biological processes. One such example from my lab is the transporter for sulfate CysZ, in which three structures of different orthologs have revealed an unprecedented fold comprising four TM helices of an inverted transmembrane topology dimer, arranged in a hexamer. We were able to study the function of these CysZ proteins combining multiple assays, shedding light on this novel transmembrane transport system for sulfate.

- a. Assur-Sanghai, Z., Liu, Q., Clarke, O.B., Belcher-Dufresne, M., Wiriyaerkmul, P., Giese, M.H., Leal Pinto, E., Kloss, B., Tabuso, S., Love, J., Punta, M., Banerjee, S., Rajashankar, K.R., Rost, B., Logothetis, D., Quick, M., Hendrickson, W.A. and **Mancia, F.** (2018). Structure-based analysis of CysZ-mediated cellular uptake of sulfate. *Elife*, doi: 10.7554/eLife.27829. PMCID: PMC5967866.
- b. Assur, Z., Hendrickson, W.A. and **Mancia, F.** (2012). Tools for Co-producing Multiple Proteins in Mammalian Cells. *Methods in Molecular Biology*, doi: 10.1007/978-1-61779-352-3_12. PMCID: PMC3773504.
- c. **Mancia, F.** and Love, J. (2010). High-throughput expression and purification of membrane proteins. *J. Struct. Biol.*, doi: 10.1016/j.jsb.2010.03.021. PMCID: PMC2933282.
- d. Love, J., **Mancia, F.**, Shapiro, L., Punta, M., Rost, B., Girvin, M., Wang, D.N., Zhou, M., Hunt, J.F., Szyperski, T., Gouaux, E., MacKinnon, R., McDermott, A., Honig, B., Inouye, M., Montelione, G. and Hendrickson, W.A. (2010). The New York Consortium on Membrane Protein Structure (NYCOMPS): a high-throughput platform for structural genomics of integral membrane proteins. *J Struct Funct Genom*, doi: 10.1007/s10969-010-9094-7. PMCID: PMC3099345.

2. Structure and function of integral membrane lipid-modifying enzymes. Cellular membranes are critical components of all free-living organisms. However, knowledge of their biosynthesis and modification has been hindered by the hydrophobicity engendered by their lipid constituents. To shed light on this question, we are studying the structure and function of distinct families of integral membrane lipid-modifying enzymes. These include (1) ArnT uses sugar-charged polyprenyl donors, and transfers the saccharide to lipid A on the cell surface of bacteria, altering antibiotic resistance properties. We have determined crystal structures of ArnT with and without a partial substrate, shedding light on the mechanism of this reaction. (2) We have determined the crystal structures of phosphatidylinositol-phosphate (PIP) synthase – an enzyme required for inositol-lipid synthesis – with a bound CDP-diacylglycerol substrate. This is a member of the CDP-alcohol phosphotransferase family (CDP-APs), which catalyze the defining step in glycerophospholipid biosynthesis across all kingdoms of life. (3) We have focused on enzyme that are involved in assembling the glycolipids of the mycobacterial cell envelope, crucial for growth and virulence and a major contributor to resistance against common antibiotics. We have determined the cryo-EM structures of arabinofuranosyltransferases D (AftD) and EmbB, representative enzymes that transfer a lipid carrier-linked sugar (arabinofuranose) to the nascent glyco-lipid mesh that constitutes the impermeable cell wall of mycobacteria. We have combined structural information, with biochemical assays and genetics to begin to understand how these enzymes function and are regulated. (4) We have employed an integrated structural biology approach to show how the last step in the assembly of intact lipopolysaccharide, an essential constituent of the outer membrane of Gram-negative bacteria, is catalyzed by the O-antigen ligase.

- a. Petrou, V.I., Herrera, C.M., Schultz, K.M., Clarke, O.B., Vendome, J., Tomasek, D., Banerjee, S., Rajashankar, K.R., Belcher Dufresne, M., Kloss, B., Kloppmann, E., Rost, B., Klug, C.S., Trent, M.S., Shapiro,

L. and **Mancia, F.** (2016). Structures of aminoarabinose transferase ArnT suggest a molecular basis for resistance to polymyxins. *Science*, doi: 10.1126/science.aad1172. PMID: PMC4963604.

- b. Clarke, O.B., Tomasek, D., Jorge, C.D., Belcher Dufrisne, M., Kim, M., Banerjee, S., Rajashankar, K.R., Shapiro, S., Hendrickson, W.A., Santos H. and **Mancia, F.** (2015) Structural basis for phosphatidylinositol-phosphate biosynthesis. *Nat. Commun.*, doi: 10.1038/ncomms9505. PMID: PMC4634129.
- c. Tan, Y.Z., Zhang, L., Rodrigues, J., Zheng, R.B., Giacometti, S.I., Rosário, A.L., Kloss, B., Dandey, V.P., Wei, H., Brunton, R., Raczkowski, A.M., Athayde, D., Catalão, M.J., Pimentel, M., Clarke, O.B., Lowary, T.L., Archer, M., Niederweis, M., Potter, C.S., Carragher, B. and **Mancia, F.** (2020). Cryo-EM structures and regulation of arabinofuranosyltransferase AftD from mycobacteria. *Mol Cell.*, doi: 10.1016/j.molcel.2020.04.014. PMID: PMC7263364.
- d. Ashraf, K.U., Nygaard, R., Vickery, O.N., Erramilli, S.K., Herrera, C.M., McConville, T.H., Petrou, V.I., Giacometti, S.I., Belcher Dufrisne, M., Nosol, K., Zinkle, A.P., Graham, C.L.B., Loukeris, M., Kloss, B., Skorupinska-Tudek, K., Swiezewska, E., Roper, D.I., Clarke, O.B., Uhlemann, A.C., Kossiakoff, A.A., Trent, M.S., Stansfeld, P.J. and **Mancia, F.** (2022). Structural basis of lipopolysaccharide maturation by the O-antigen ligase. *Nature*, doi: 10.1038/s41586-022-04555-x. PMID: PMC9884178.

3. Cellular uptake of Vitamin A. Vitamin A is an essential nutrient for all mammals. Many biological processes, including and foremost vision, are crucially dependent on its adequate supply for proper function. Alterations of vitamin A metabolism can result in a wide spectrum of ocular defects and lead to blindness. Retinol (vitamin A alcohol) is the predominant circulating vitamin A form in the fasting state. In times of need (i.e. in the absence of dietary vitamin A intake), in order to distribute vitamin A to the target peripheral tissues, retinol is released in the bloodstream from the liver, the main body storage site of the vitamin, bound to retinol-binding protein (RBP). Inside the cells, retinol binds specific intracellular carriers, namely cellular retinol-binding proteins, and it serves as a precursor for the active vitamin A forms: retinaldehyde, critical for vision, and retinoic acid, the ligand for specific nuclear receptors that regulate the transcription of hundreds of target genes. How retinol is released from the retinol-RBP complex and internalized by the cell has been subject of debate for decades. STRA6, the putative plasma membrane receptor for RBP, was identified in 2007. However, its mechanism of action has remained elusive, not least due to the absence of any structural information. We have determined the structure of STRA6 determined to 3.9 Å resolution by single-particle cryo-electron microscopy (improved to 3.1 Å resolution with protein reconstituted in nanodisc). The atomic model of STRA6 provides a template to guide our understanding at a molecular level on how this protein may function.

- a. Chen, Y., Clarke, O.B., Kim, J., Stowe, S., Kim, Y.K., Assur, Z., Cavalier, M., Godoy-Ruiz, R., von Alpen, D.C. Manzini, C. Blamer, W.S., Frank, J., Quadro, L., Weber, D.J., Shapiro, L., Hendrickson, W.A. and **Mancia, F.** (2016). Structure of the STRA6 receptor for retinol uptake. *Science*, doi: 10.1126/science.aad8266. PMID: PMC5114850.
- b. Varney, K.M., Wilder, P.T., Godoy-Ruiz, R., **Mancia, F.** and Weber, D.J. (2019). ¹H^N, ¹³C, and ¹⁵N resonance assignments of human calmodulin bound to a peptide derived from the STRA6 vitamin A transporter (CaMBP2). *Biomol NMR Assign.*, doi: 10.1007/s12104-019-09890-1. PMID: PMC7154012.
- c. Costabile, B.K., Kim, Y.K., Chen, Y., Clarke, O.B., Quadro, L. and **Mancia, F.** (2020). Sample preparation for structural and functional analyses of the STRA6 receptor for retinol-binding protein. *Methods Enzymol.*, doi: 10.1016/bs.mie.2020.03.005. PMID: PMC9394758.
- d. Young, B.D., Varney, K.M., Wilder, P.T., Costabile, B.K., Pozharski, E., Cook, M.E., Godoy-Ruiz, R., Clarke, O.B., **Mancia, F.** and Weber, D.J. (2021). Physiologically relevant free Ca²⁺ ion concentrations regulate STRA6-Calmodulin complex formation via the BP2 region of STRA6. *J Mol Bio.*, doi: 10.1016/j.jmb.2021.167272. PMID: PMC8568335.

4. Molecular mechanisms of drug resistance. Drug resistance in *Plasmodium falciparum* (Pf), the deadliest of the malaria parasites that threatens almost half the world's population, has been associated with mutations in specific genes. The protein responsible for parasite resistance to both previously and currently used first-line antimalarials, chloroquine (CQ) and piperazine (PPQ), is the 48-kDa *P. falciparum* chloroquine resistance transporter (PfCRT). PfCRT resides on the DV membrane and mediates drug resistance via active drug efflux. Using antigen-binding fragment technology and single-particle cryo-electron microscopy (cryo-EM), we have determined the structure of a CQ-resistant isoform of PfCRT to 3.2 Å resolution. Combining structural information, with biochemistry, genetics and parasitology, we have gained insights on the molecular mechanism of PfCRT-mediated drug resistance and identified markers for the development of resistance. We have also

explored the mechanistic structure of Arabinosyltransferase B (EmbB), an enzyme that belongs to a family of membrane-bound mycobacterial glycosyltransferases that build the lipidated polysaccharides of the mycobacterial cell envelope. EmbB is the known target of an anti-tuberculosis drug, ethambutol. We determined the structure of EmbB not only showing the overall fold of the enzyme and providing insight on the reaction mechanism, but also allowing us to map all the drug resistance-causing mutations, thus providing a valuable platform from which to understand and predict their effects

- a. Kim, J., Tan, Y.Z., Wicht, K.J., Erramilli, S.K., Dhingra, S.K., Okombo, J., Vendome, J., Hagenah, L.M., Giacometti, S.I., Warren, A.L., Nosol, K., Roepe, P.D., Potter, C.S., Carragher, B., Kossiakoff, A.A., Quick, M., Fidock, D.A. and **Mancia, F.** (2019). Structure and drug resistance of the *Plasmodium falciparum* transporter PfCRT. *Nature*, doi: 10.1038/s41586-019-1795-x. PMCID: PMC6911266.
- b. Tan, Y.Z., Rodrigues, J., Keener, J.E., Zheng, R.B., Brunton, R., Kloss, B., Giacometti, S.I., Rosário, A.L., Zhang, L., Niederweis, M., Clarke, O.B., Lowary, T.L., Marty, M.T., Archer, M., Potter, C.S., Carragher, B. and **Mancia, F.** (2020). Cryo-EM structure of arabinosyltransferase EmbB from *Mycobacterium smegmatis*. *Nat Commun.*, doi: 10.1038/s41467-020-17202-8. PMCID: PMC7341804.

5. Transfer and transport of lipids and their constituents. Wnts are evolutionarily conserved ligands that signal at short range to regulate morphogenesis, cell fate and stem cell renewal. The first and essential steps in Wnt secretion are their O-palmitoleation by the enzyme PORCN and subsequent loading onto the dedicated transporter WLS/Evi. O-palmitoleated Wnts associated with WLS then travel from the ER to the plasma membrane, where they are transferred to receptors, such as Frizzled, on the membranes of target cells, in turn triggering the activation of signaling pathways. We determined the 3.2Å resolution cryo-EM structure of palmitoleated human WNT8A in complex with WLS. We show, how the lipid is harbored, and that the WLS membrane domain has close structural homology to GPCRs. A large opening to the bilayer within WLS may delineate the route for how the PAM is shuttled from PORCN to WLS in an energetically favorable way. By comparing our structure to that of Wnt in complex with the binding domain of Frizzled, we noticed a large conformational change on a separate Wnt hairpin which may be the key to its one-way transfer to receiving cells.

The blood-brain barrier omega-3 fatty acid transporter Major Facilitator Superfamily Domain containing 2A (MFSD2A) is an atypical MFS protein because it transports large amphiphilic lysolipids as opposed to small, soluble substrates. We have determined the structure of MFSD2A in an inward-facing conformation complexed with a lysolipid substrate to 3Å resolution. Using an integrated approach of structural biology, cell-based functional assays, molecular dynamics simulations and native mass-spectrometry, we revealed details of how MFSD2A interacts with substrates and how Na⁺-dependent conformational changes allow for substrate release into the membrane. This work provides insight into the mechanism by which this atypical MFS transporter mediates uptake of omega-3 fatty acids into the brain.

Choline is an essential nutrient that humans need in vast quantities for cell membrane synthesis. The brain has a particularly high demand for choline, but how it enters the brain has remained elusive. Recently, we demonstrated both *in vivo* and *in vitro* that the MFS transporter FLVCR2 is a BBB choline transporter and is responsible for the majority of choline uptake into the brain. We determined structures of choline-bound FLVCR2 in the inward- and outward-facing states using cryo-EM to 2.49 and 2.77 Å resolution, respectively. Our work shows how the brain obtains choline and provides molecular-level insights into how FLVCR2 binds and mediates choline uptake.

- a. Nygaard, R., Yu, J., Kim, J., Ross, D., Parisi, G., Clarke, O.B., Virshup, D.M. and **Mancia, F.** (2021). Structural basis of WLS/Evi-mediated Wnt transport and secretion. *Cell*, doi:10.1016/j.cell.2020.11.038. PMCID: PMC7797000.
- b. Cater, R.J., Chua, G.L., Erramilli S.K., Keener, J.E., Choy, B.C., Tokarz, P., Chin, C.F., Quek, D.Q.Y., Kloss, B., Pepe, J.G., Parisi G., Wong, B.H., Clarke, O.B., Marty, M.T., Kossiakoff A.A., Khelashvili, G., Silver, D. and **Mancia, F.** (2021). Structural basis of omega-3 fatty acid transport across the blood-brain barrier. *Nature*, doi: 10.1038/s41586-021-03650-9. PMCID: PMC8266758.
- c. Cater, R.J., Mukherjee, D., Gil-Iturbe, E., Erramilli, S.K., Chen, T., Koo, K., Santander, N., Reckers, A., Kloss, B., Gawda, T., Choy, B.C., Zhang, Z., Katewa, A., Larphaveesarp, A., Huang, E.J., Mooney, S.W.J., Clarke, O.B., Yee, S.W., Giacomini, K.M., Kossiakof, A.A., Quick, M., Arnold, T. and **Mancia, F.** (2024). Structural and molecular basis of choline uptake into the brain by FLVCR2. *Nature*, doi: 10.1038/s41586-024-07326-y. Online ahead of print. PMID: 38693257.

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