BIOGRAPHICAL SKETCH

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NAME: **Marta Filizola**

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

POSITION TITLE: **Full Professor (with Tenure)**

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
University "Federico II", Naples, Italy	B.S.	10/1993	Chemistry
University "Federico II", Naples, Italy	M.S.	10/1993	Chemistry (Crystallography)
II University of Naples, Naples, Italy	Ph.D.	01/1999	Comput. Chemistry
Molecular Research Institute, Mt. View, CA	Post-Doc	06/2001	Comput. Biophysics

A. Personal Statement

I am a tenured Full Professor in the Department of Structural and Chemical Biology at the Icahn School of Medicine at Mount Sinai (formerly known as Mount Sinai School of Medicine) and co-Director of the PhD Program in *Biophysics and Systems Pharmacology* of the Graduate School of Biomedical Sciences at Mount Sinai. The overall goal of my research program is to obtain rigorous mechanistic insight into the structure, dynamics, and function of important classes of membrane proteins such as G protein-coupled receptors (GPCRs) and β3 integrins, which are prominent drug targets. Understanding the molecular mechanisms underlying the complex biological functions of these proteins has direct translational relevance because it informs the rational discovery of potentially improved therapeutic agents, as my recent, collaborative patent application on novel anti-thrombotic agents (with Dr. Barry Coller at Rockefeller University) demonstrates. I have contributed 90 peer-reviewed publications to the areas of computational chemistry/biophysics and drug discovery, I have served on several scientific review committees, and I have delivered >40 invited talks. My laboratory's research has consistently been funded by the National Institutes of Health since 2005. Not only do I have the leadership and expertise necessary to direct the computational research outlined in this application, but I have worked for several years on prototypic membrane proteins such as GPCRs and β3 integrins, analyzing the relationships between their structure, dynamics, and function. To this end, my lab has used several computational structural biology tools, ranging from molecular modeling, bioinformatics, cheminformatics, molecular dynamics simulations, a variety of enhanced sampling algorithms, and rational drug design approaches. We have pioneered the use of enhanced sampling algorithms in the study of ligand binding, activation, allostery, and oligomerization of GPCRs. Thus, my lab is very well suited to carry out the computational studies outlined in this application, and I to direct them in the role of Principal Investigator.

B. Positions and Honors

Positions and Employment

7/01-6/03 Instructor, Dept. of Physiology & Biophysics, Mt. Sinai School of Medicine, NYC.
1/04-6/05 Instructor, Dept. of Physiology & Biophysics, Weill Medical College of Cornell University, NYC
7/05-6/07 Assistant Research Professor, Dept. of Physiology & Biophysics, WMC of Cornell University, NYC
7/07-6/10 Adjunct Assistant Professor, Dept. of Physiology & Biophysics, WMC of Cornell University, NYC.

7/07-6/10 Assistant Professor (Tenure-Track), Dept. of Structural and Chemical Biology, Mt. Sinai School of Medicine, NYC

7/10-6/14 Associate Professor (with Tenure since Jan 2013), Dept. of Structural and Chemical Biology, Icahn School of Medicine at Mount Sinai, NYC

9/12-3/15 Co-Director of the Graduate Program in *Structural/Chemical Biology and Molecular Design (SMD)* of the Graduate School of Biological Sciences at Mount Sinai.

7/14-present Full Professor with Tenure, Dept. of Structural and Chemical Biology, Icahn School of Medicine at Mount Sinai, New York, NY.

3/15-present Co-Director of the Graduate Program in *Biophysics and Systems Pharmacology (BSP)* of the Graduate School of Biological Sciences at Mount Sinai.

Honors and Patents

Fellowship to perform studies abroad from University "Federico II" in Naples (Italy), 1994; Grant-in-aid within the "Human Capital Mobility" program of the European Union from Centre de Supercomputació de Catalunya in Barcelona (Spain), 1995-1997; Nominated - *European Doctor in Biotechnology* by European Association for Higher Education in Biotechnology, 1999; National Research Service Award T32 DA07135 from National Institute on Drug Abuse (NIDA), 2001; *The Doctor Harold and Golden Lamport Award* for Excellence in Basic Research from Mount Sinai School of Medicine in NYC, 2008; Independent Scientist Award (K02) from NIH-NIDA, 2009-present; Award from Teragrid/XSEDE computational resources (MCB080077), 2008-present; Director Discretionary Award UT-NTNL0149 from National Institute for Computational Sciences (NICS), 2011-2012; PCT patent application entitled: “Organic Compounds (Anti-platelet agents)”; International Application No. PCT/US11/44267, Filed on July 15, 2011; Patent application entitled: “Organic Compounds (Anti-platelet agents), Serial number: PCT/US2013/021749, Filed Jan. 16, 2013; Provisional patent application number: 61/768,205 “Kappa Opioid Receptor Selective Compounds, Compositions, and Uses Thereof”, Filed in the U.S. Patent and Trademark Office Feb. 22, 2013; Distinguished Speaker at Torrey Pines Institute for Molecular Studies, Port St. Lucie, FL, 2013; Member of the Faculty of 1000 for Pharmacology and Drug Discovery, 2013; Award of Tenure, Icahn School of Medicine at Mount Sinai, 2013.

Other Experience and Professional Memberships

Staff Scientist at Molecular Research Institute in Mountain View, CA, 2001; Honorary Editorial Board Member of *Open Access Bioinformatics*, Dove Press, 2008-present; Editorial Board Member, *Advances and Applications in Bioinformatics and Chemistry*, Dove Press, 2007-present; Grant Reviewer for: Cutting Edge Basic Research Award (CEBRA) from U.S. Army Research Office and NIH-NIDA, 2006; NIH-MNPS Study Sections 2/07, 6/07, 10/07, 2/08, 5/08, 2/15; NIH-NIDA ZRG1 MNPS-C(04)S 5/08; NIH-NIDA ZRG1 MDCN-C(02)M 6/ 08; NSF-MCB Biomolecular Systems 10/08, 9/09; NIH-ZRG1 BCMB-B (02) M 9/10; NIH-ZRG1 MDCN-P (91) S, 6/11; NIH-BPNS Study Section, 6/12; NIH-BST Study Section, 7/12; NIH-ZRG1 BCMB-D (40) P, 2/13; NIH- ZRG1 MDCN-R (40), 7/14; Guest Editor for *PLOS Computational Biology,* 2012, 2013; Edited a book entitled “G Protein-Coupled Receptor Modeling and Simulation” for Springer Science + Business Media, 2013; Member, NIH-BPNS Study Section, Center for Scientific Review, Appointed July 2013-June 2019; Scientific Advisory Board Member for the 2nd GPCR Targeted Screening Conference of the Global Technology Community (GTC) on May 7-8, 2015 in Berlin, Germany; Member of the GPCR Expert Target Panel for a knowledge management center for the NIH Program Illuminating the Druggable Genome, IDG Steering Committee Face-to-Face meeting, Apr 7-9, 2015 Albuquerque, NM; Edited a book entitled “G Protein-Coupled Receptors in Drug Discovery**”** in the *Methods in Molecular Biology* lab protocol series, Publisher: Springer, 2015.

C. Contributions to Science

1. Molecular Modeling and Enhanced Molecular Dynamics Simulations

Among the milestones that we were able to accomplish under the auspices of continued NIH funding over the past 10 years are the design, testing, and implementation of innovative computational strategies to build improved molecular models of GPCRs and to study, more efficiently, the conformational plasticity and dynamical nature of liganded or unliganded, single or interacting, receptors within their natural lipid environment. In particular, we pioneered the use of enhanced, molecular dynamics (MD)-based computational strategies in combination with either atomistic or coarse-grained (CG) system representations to improve dynamic molecular models of GPCR molecular recognition, activation, and oligomerization, with the ultimate goal of elucidating receptor allostery and functional selectivity for successful use in rational drug design. In particular, we were able:

(i) to obtain reliable models of ligand-bound conformations of GPCRs that do not require very long and computationally inefficient standard MD simulations, (ii) to establish a possible molecular basis for the functional selectivity of GPCRs through the prediction of ligand-specific conformations, and (iii) to advance current understanding of the role of oligomerization in receptor function through the generation of novel testable hypotheses of specific mutations that could eventually be used to modulate receptor function (see section 2, below). While the specific computational methods we explored are not new from an algorithmic standpoint, we developed some distinctive combinations of such methods, and showed in recent publications that they are indeed able to generate ligand-specific conformations of both isolated and interacting, inactive and active, GPCRs that are consistent with experimental data. Notably, the methodologies we developed represent fundamental tools that can be generalized to other transmembrane receptors, as well as broadly to other proteins.

a) Mobarec, J.C., Sanchez, R., and Filizola, M. "Modern Homology Modeling of G-Protein Coupled Receptors: Which Structural Template to Use?" *Journal of Medicinal Chemistry* (2009) 52 (16), 5207-5216. *(Cited 103 times)*
b) Provasi, D., Camacho-Artacho, M., Negri, A., Mobarec, J.C., Filizola, M. "Ligand-Induced Modulation of the Free-Energy Landscape of G Protein-Coupled Receptors Explored by Adaptive Biasing Techniques." *PLOS Computational Biology* (2011) 7(10):e1002193. *(Cited 34 times)*
c) Provasi, D. & Filizola, M. "Putative Active States of a Prototypic G-Protein Coupled Receptor from Biased Molecular Dynamics." *Biophysical Journal* (2010) 19(10):2347-2355. *(Cited 27 times)*
d) Schneider, S., Provasi, D. & Filizola, M. "The Dynamic Process of Drug-GPCR Binding at Either Orthosteric or Allosteric Sites Evaluated by Metadynamics" *Methods in Molecular Biology* (2015) in press.

2. <u>Mechanistic Insights into GPCR Dimerization/Oligomerization</u>

Compelling evidence that models of GPCR signaling must consider oligomeric assemblies rather than isolated monomers started to appear in the literature during my postdoctoral training. Many of the published studies described (i) effects resulting from activating one GPCR in the presence of another and (ii) modulation of the activity of one receptor using ligands targeting another one. Whether these effects resulted from downstream crosstalk or from differential signaling of a receptor complex has so far been difficult to ascertain for the largest subfamily A of GPCRs. My lab has been hard at work in the area of GPCR oligomerization, contributing to their recognition, nomenclature, storing, structural models, and estimates of relative stability. We are committed to providing a rigorous mechanistic insight into the spatio-temporal organization of GPCRs in living cells at a level of molecular detail that is unattainable using current experimental techniques alone, but is required for an ultimate understanding of the role of GPCR oligomerization in receptor function.

a) Pin, J.-P., Neubig, R., Bouvier, M., Devi, L., Filizola, M., Javitch, J.A., Lohse, M.J., Milligan, G., Palczewski, K., Parmentier, M., Spedding, M. "International Union of Basic and Clinical Pharmacology. LXVII. Recommendations for the Recognition and Nomenclature of G Protein-Coupled Receptor Heteromultimers." *Pharmacological Reviews* (2007) 59:1-9. *(Cited 209 times)*
b) Khelashvili, G., Dorff, K., Shan, J., Camacho-Artacho, M., Skrabanek, L., Vroling, B., Bouvier, M., Devi, L., George, S.R., Javitch, J.A., Lohse, M.J., Milligan, G., Neubig, R., Palczewski, K., Parmentier, M., Pin, J.-P., Vriend, G., Campagne, F., Filizola, M. "GPCR-OKB: A database for G protein-coupled receptor oligomers." *Bioinformatics* (2010) 26(14):1804-1805. *(Cited 51 times)*
c) Johnston, J.M., Wang, H., Provasi, D., Filizola, M. "Assessing the Relative Stability of Dimer Interfaces in G Protein-Coupled Receptors." *PLOS Computational Biology* (2012) 8(8): e1002649. *(Cited 28 times)*
d) Provasi, D., Boz, M.B., Johnston, J.M., Filizola, M. "Preferred Supramolecular Organization and Dimer Interfaces of Opioid Receptors from Simulated Self-Association" (2015) *PLOS Computational Biology* Mar 30;11(3):e1004148.

3. <u>Dynamic Models of Opioid Receptors</u>

Opioid receptors are important drug targets for pain management, drug abuse/addiction, and mood disorders. We have a long history of work on these GPCR subtypes, having contributed over the past 15 years to several structural and mechanistic insights into their pharmacology and signaling. Most recently, we have focused on their dynamics, seeking answers to questions like: How does an opioid drug bind to his receptor? How can sodium ions modulate opioid receptor activity? What are the likely interfaces of opioid receptor homodimers?

a) Provasi, D., Bortolato A., Filizola, M. “Exploring Molecular Mechanisms of Ligand Recognition by Opioid Receptors with Metadynamics.” *Biochemistry* (2009) 48 (42): 10020-10029. *(Cited 28 times)*
b) Filizola M. & Devi, L.A. “How opioid drugs bind to receptors” *Nature* (2012) 485, 314-7. *(Cited 27 times)*
c) Johnston, J.M., Aburi, M., Provasi, D., Bortolato, A., Urizar, E., Lambert, N.A., Javitch, J.A., Filizola, M. “Making Structural Sense of Dimerization Interfaces of Delta Opioid Receptor Homodimers”, *Biochemistry* (2011) 50(10):1682-1690 *(Cited 38 times).*
d) Shang, Y., LeRouzic, V., Schneider, S., Bisignano, P., Pasternak, G.W., Filizola, M. "Mechanistic Insights into the Allosteric Modulation of Opioid Receptors by Sodium Ions" *Biochemistry* (2014) 53(31):5140-9. *(Cited 6 times)*

4. *Structure-Guided Drug Discovery and Chemotype Optimization*

The recent high-resolution crystal structures of several GPCR or integrin types offer tremendous opportunities for computer-aided drug discovery/optimization approaches to discover novel and selective binders as some of our recent publications demonstrate. By combining our virtual screening, cheminformatics, and molecular dynamics simulations, with collaborative functional and structural studies, as well as chemical synthesis, we have recently contributed to the discovery of (i) a novel agonist of the kappa-opioid receptor (in collaboration with Jonathan A. Javitch at Columbia U. and Thomas Prisinzano at Kansas U.); (ii) novel positive allosteric modulators of the delta-opioid receptor (in collaboration with Neil Burford, Andy Alt, and Samuel Gerritz at BMS, Merixtell Canals and Arthur Christopoulos at Monash U., and John Traynor at U. of Michigan); (iii) a μOR-δOR heteromer-biased agonist with antinociceptive activity (in collaboration with Lakshmi Devi at Mount Sinai and Peter Hodder at Scripps), and (iv) novel antagonists of the αIIbβ3 receptor that limit conformational reorganization of the receptor, thus resulting in improved anti-platelets agents (in collaboration with Barry S. Coller at Rockefeller U. and Craig Thomas at the NIH). In particular, this latter discovery was protected by a patent application entitled: “Organic Compounds (Anti-platelet agents)” (Serial number: PCT/US2013/021749).

a) Negri, A., Rives, M.L., Caspers, M.J., Prisinzano, T.E., Javitch, J.A., and Filizola, M. “Discovery of a Novel Selective Kappa-Opioid Receptor Agonist Using Crystal Structure-Based Virtual Screening” *Journal of Chemical Information and Modeling* (2013) 53: 521-526*. (Cited 15 times)*
b) Burford, N., Livingston, K., Canals, M., Ryan, M., Budenholzer, L., Han, Y., Shang, Y., Herbst, J.J., O'Connell, J., Banks, M., Zhang, L., Filizola, M., Bassoni, D., Wehrman, T., Christopoulos, A., Traynor, J., Gerritz, S., Alt, A. "Discovery, Synthesis and Molecular Pharmacology of Selective Positive Allosteric Modulators of the δ-Opioid Receptor" (2015) *Journal of Medicinal Chemistry* Apr 22. [Epub ahead of print]
c) Zhu, J., Choi, W.-S., McCoy, J.G., Negri, A., Zhu, J., Naini, S., Li, J., Shen, M., Huang, W., Bougie, D., Rasmussen, M., Aster, R., Thomas, C.J., Filizola, M., Springer, T.A., and Coller, B.S. “Structure-Guided Design of a High Affinity Platelet Integrin αIIbβ3 Receptor Antagonist That Disrupts Mg^{2+} Binding to the MIDAS” *Science Translational Medicine* (2012) 4(125):1-13. *(Cited 21 times)*
d) Gomes, I., Fujita, W., Gupta, A., Saldanha, A.S., Negri, A., Pinello, C.E., Roberts, E., Filizola, M., Hodder, P., and Devi, L.A. “Identification of a μOR-δOR heteromer-biased agonist with antinociceptive activity” *Proc. Natl. Acad. Sci. USA* (2013) 110(29):12072-7. *(Cited 32 times)*

5. Contributions to Team-Science Projects

Through application and implementation of cutting-edge developments in theory and computer simulations, my lab contributes a level of molecular detail to biological and biomedical problems that is impossible or difficult to obtain experimentally. This information lays the foundation for novel experimental studies aimed at furthering our understanding of physiological functions, and at developing new therapeutic strategies.

a) González-Maeso, J., Ang, R., Yuen, T, Chan, P., Weisstaub, N.V., López-Giménez, J., Zhou, M., Okawa, Y., Callado, L.F., Milligan, G., Gingrich, J.A., Filizola, M., Meana, J.J., Sealfon, S.C. “Identification of a Novel Serotonin/Glutamate Receptor Complex Implicated in Psychosis” *Nature* (2008) 452(7183):93-97; *(Cited 409 times)*
b) Guo, W., Urizar, E., Kralikova,M., Mobarec, J.C., Shi, L., Filizola, M., Javitch, J.A. "Dopamine D2 Receptors Form Higher Order Oligomers at Physiological Expression Levels" *The EMBO Journal*, (2008) Sep 3;27(17):2293-304; *(Cited 212 times)*
c) Fribourg, M., Moreno, J.L., Holloway, T., Provasi, D., Baki, L., Mahajan, R., Park, G., Adney, S.K., Hatcher, C., Eltit, J.M., Ruta, J.D., Albizu, L., Li, Z., Umali, A., Shim, J., Fabiato, A., MacKerell, A.D. Jr., Brezina, V., Sealfon, S.C., Filizola, M., Gonzalez-Maeso, J., Logothetis, D.E. “Decoding the Signaling of

a GPCR Heteromeric Complex Reveals a Unifying Mechanism of Action of Antipsychotic Drugs" *Cell* (2011) 147 (5):1011-1023; *(Cited 95 times)*

d) Zhu, J., Zhu, J., Negri, A., Provasi, D., Filizola, M., Coller, B.S., Springer, T.A. "Closed headpiece of integrin αIIbβ3 and its complex with an αIIbβ3-specific antagonist that does not induce opening" *Blood* (2010) 116 (23):5050-5059. *(Cited 49 times)*

Complete List of Published Work in MyBibliography (from a total of 90 peer-reviewed publications): http://www.ncbi.nlm.nih.gov/sites/myncbi/marta.filizola.1/bibliography/40981871/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

R01 DA034049 (Filizola, PI) 07/01/12 - 06/30/17
NIH/NIDA
Dynamic Mechanisms of GPCRs Targeted by Drugs of Abuse
The overall goal of this project is to advance our current understanding of fundamental basic mechanisms of mu-opioid receptor function, and pave the way to novel therapeutic strategies against drug abuse and addiction.

K02 DA026434 (Filizola, PI) 04/01/09 - 03/31/19
NIH/NIDA
Structural Aspects of Oligomerization in the Function of GPCRs
This is an Independent Scientist Award (KO2) providing support for Dr. Filizola's continued career development as an independent investigator.

R01 HL019278 (Coller, PI; Filizola, PI of subcontract) 08/20/13 - 05/31/17
NIH/NHLBI
Integrin alphaIIbbeta3 Structure, Activation, and Ligand Binding
This project is focused on achieving a better understanding of ligand binding to alphaIIbbeta3 while searching for improved therapeutics based on rigorous criteria.

Therapeutics Discovery Institute (Coller, PI; Filizola PI of subcontract) 01/21/2015- 01/20/2017
Rockefeller University
A Novel, Non-activating Integrin αVβ3 Antagonist to Treat Renal, Hematologic, Neoplastic, Bone, and/or Fibrotic Diseases
The goal of this project is to develop pure antagonists of αVβ3 by combining computer-assisted rational drug design strategies with chemical synthesis and functional assays.

Overlap
None. Please note that the K02 is a career development award focused on investigating GPCR oligomerization. As such, the ongoing grants that focus on GPCRs are included within the K02 protected time.

Completed Support (within the past 3 years)
R01 HL019278; Integrin alphaIIbbeta3 Structure, Activation, and Ligand Binding; 08/01/08- 06/30/13; Filizola, PI of subcontract (Coller, PI).
R21 MH091360; Efficiency of Enhanced Sampling Methods in GPCR Research; 06/15/10-04/30/13; Filizola, PI
R01 MH084894; Structure and function of the 5HT2A/mGluR2 complex in schizophrenia; 07/20/09-02/28/12; Filizola, co-Investigator (Gonzalez-Maeso, PI).