BIOGRAPHICAL SKETCH

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NAME: des Georges, Amédée

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

POSITION TITLE: Associate 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
Universite Pierre and Marie Curie, Paris	BS	09/2003	Biochemistry
Universite Pierre and Marie Curie, Paris	MS	07/2004	Biochemistry
University of Cambridge, Laboratory of Molecular Biology, Cambridge, Cambridgeshire	PHD	11/2008	Molecular Biology
Howard Hughes Medical Institute - Columbia University, New York, New York	Postdoctoral Fellow	08/2015	Structural biology

A. Personal Statement

I am an Associate Professor in the NYU College of Dentistry Department of Molecular Pathobiology and a member of the NYU Pain Research Center. The overarching goal of my research program is to understand the allosteric regulation of membrane proteins by small molecules and protein effectors. Those mechanisms are much less understood in membrane proteins compared to their soluble counterparts due to the challenges specific to the membrane environment. There is therefore a need to fill a gap in our understanding of the specificities of allosteric mechanisms in membrane proteins, an area of research with important biomedical applications. To this end, I am utilizing structural and computational techniques to study these inherently dynamic processes, such as cryo-electron microscopy, machine learning image analysis methods and molecular dynamics simulation, with the aim to better understand important regulatory processes and uncover new targets for pharmacological drug development.

During my PhD at the Laboratory of Molecular Biology in Cambridge, UK, I developed a strong background in biochemistry and cryo-electron microscopy while studying the regulation of microtubule dynamics. During my postdoctoral tenure under Dr. Joachim Frank, I pioneered structural studies of translation initiation—a significant protein translation regulatory checkpoint—via cryo-electron microscopy. With the advent of the cryo-EM resolution revolution, I was inspired to apply its enhanced capabilities to membrane proteins. Consequently, I spearheaded a collaboration with the labs of Wayne Hendrickson and Andrew Marks, culminating in the successful structure elucidation of the ryanodine receptor using cryo-EM in 2014. This breakthrough, being among the first membrane protein structures deciphered by single-particle cryo-EM, marked a significant stride for structural biology by showcasing cryo-EM's potential and underscored its biomedical significance, considering RyR's pivotal role in calcium signaling and cardiac function. This achievement paved the way for subsequent in-depth studies on the functionality and regulation of this vital calcium channel.

In 2015, I started my independent research group at the CUNY Advanced Science Research Center, a brand-new interdisciplinary research center located approximately 150 m away from the New York Structural Biology Center. There, I pursued my interest in deciphering the large repertoire of regulatory mechanisms controlling membrane proteins function using cryo-electron microscopy (cryo-EM) as major investigative tool. To foster closer ties with the physiology and diseases associated with membrane proteins function and dysfunction, I moved to the Department of Molecular Pathobiology at NYU College of Dentistry in November 2023. There, I strive to use and develop methods to open new possibilities in our quest to understand allosteric mechanisms at the molecular level: new methods to sort images of heterogeneous samples, to model dynamic processes, and to extract proteins from their membranes. I apply these principles and methods to understanding the

function of two types of membrane proteins: ion channels and G protein-coupled receptors. I am also interested in the molecular mechanisms at play during pathogen-host interaction and the dynamic events leading to virus and toxin entry into hosts, for which the methods my group develop are very relevant.

I am deeply committed to fostering diversity in the sciences by encouraging and mentoring students from underrepresented minorities. As part of this commitment, I currently mentor two Ph.D. students and three undergraduates from these communities. Furthermore, I actively participate in various summer initiatives, providing research opportunities for both high school and college students. Over the past three years, I have mentored three undergraduate and one high school student through these initiatives. Additionally, in July 2018, I was involved in the Summer Bridges to College and Career Success program (The G.O.O.D. Project) at A. Philip Randolph Campus High School.

As the cryo-EM technique is becoming increasingly used, my laboratory regularly hosts visiting scientists seeking to learn the techniques and to collect data on our high-end instruments, including international students from Sapienza University (Rome, IT), NIH NCI, Duke University and University of Maryland. I also teach cryo-EM courses at City University of New York as well as at the New York Structural Biology Center.

I am an ad-hoc reviewer of grant proposals for the NIH Biochemistry and Biophysics of Membranes and Macromolecular Structure and Function C Study sections, the Chan Zuckerberg Initiative, Human Frontier Science Program, and for the French agency Agence Nationale de La Recherche Scientifique. I am also reviewer for several journals including Nature, Nature Communications, Nature Structural and Molecular Biology, eLife, EMBO Journal, Journal of Structural Biology, IUCrJ, Proteins, TiBS, MBio, Science Advances, Nucleic Acid Research, and Communications Biology.

Ongoing and recently completed projects that I would like to highlight include:

Ongoing support:

5 R35 GM 133598-03
Des Georges (PI)
8/1/2019-6/30/2029
Understanding membrane proteins' allosteric modulation with cryo-EM

CT0060521- Institut de Recherches Servier research contract (foreign sponsor)
Des Georges (PI)
11/1/2017-10/31/2024
Develop methods to image small proteins by cryo-EM

CT0079525- Institut de Recherches Servier service contract (foreign sponsor)
Des Georges (PI)
10/2019-3/9/2025
Cryo-electron microscopy structural experiments of protein complexes

Past support:
1 R56 AI 152397-01A1
Weber (PI)
8/6/2021-7/30/2022
Structure-based targeting of the C. difficile toxin (CDT) from hypervirulent bacterial strains

19IPLOI34760706- American Heart Association Innovative Project Award
Des Georges (PI)
07/01/2019–06/30/2022
Deciphering GPCR signaling by allosteric and biased ligands using cryo-EM

G-2018-11286, City University of New York
des Georges (PI)

04/01/20-03/31/21
Junior Faculty Research Award in Science and Engineering

Citations:

1. Fedry J, Silva J, Vanevic M, Fronik S, Mechulam Y, Schmitt E, des Georges A, Faller WJ, Förster F. Visualization of translation reorganization upon persistent ribosome collision stress in mammalian cells. *Molecular Cell.* 2024. Feb 2:S1097-2765(24)00051-0. (Online ahead of print) PMID: 38340715

2. Marcink TC[$], Zipursky G, Cheng W, Stearns K, Stenglein S, Golub K, Cohen F, Bovier F, Pfalmer D, Greninger AL, Porotto M[$], des Georges A[$], Moscona A[$]. Subnanometer structure of an enveloped virus fusion complex on viral surface reveals new entry mechanisms. Science Advances. 2023 Feb 10;9(6):eade2727. PMCID: PMC9917000 (*[$]: co-corresponding authors*)

3. Dashti A, Mashayekhi G, Shekhar M, Ben Hail D, Salah S, Schwander P, des Georges A[$], Singharoy A[$], Frank J[$], Ourmazd A[$]. Retrieving functional pathways of biomolecules from single-particle snapshots. Nat Commun. 2020 Sep 18;11(1):4734. PMCID: PMC7501871. (*[$]: co-corresponding authors*)

4. Nguyen AH, Thomsen ARB, Cahill TJ 3rd, Huang R, Huang LY, Marcink T, Clarke OB, Heissel S, Masoudi A, Ben-Hail D, Samaan F, Dandey VP, Tan YZ, Hong C, Mahoney JP, Triest S, Little J 4th, Chen X, Sunahara R, Steyaert J, Molina H, Yu Z, des Georges A[$], Lefkowitz RJ[$]. Structure of an endosomal signaling GPCR-G protein-β-arrestin megacomplex. Nat Struct Mol Biol. 2019 Dec;26(12):1123-1131. PMCID: PMC7108872. (*[$]: co-corresponding authors*)

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2023 - present	Associate Professor, NYU College of Dentistry, Department of Molecular Pathobiology
2023	Associate Professor, CUNY Advanced Science Research Center, Structural Biology Initiative, NY, NY
2015 - 2023	Assistant Professor, CUNY Advanced Science Research Center, Structural Biology Initiative, NY, NY
2015 - 2023	Assistant Professor, The City College of New York, Department of Chemistry and Biochemistry, New York, NY
2009 - 2015	Postdoctoral fellow, HHMI - Columbia University, Biochemistry and Molecular Biophysics, New York, NY

Honors and Awards

2020 Junior Faculty Research Award in Science and Engineering, City University of New York.

C. Contribution to Science

1. **Structure and dynamics of transmembrane receptors**. Cryo-EM is ideally suited to solve a number of challenging structures of membrane proteins. This motivated me to initiate a collaboration with the laboratories of Andy Marks and Wayne Hendrickson with the objective of using cryo-EM to obtain the structure of the ryanodine receptor, a structure they had failed to solve by X-ray crystallography despite 9 years of effort. Together, we obtained a 5Å resolution structure of this important pharmacological target for heart and muscular diseases (d). Further improvements in data acquisition and processing applied to different states of the channel allowed us to further improve the resolution to 3.2Å and to elucidate its mechanism of activation by calcium, ATP and caffeine (c). To gain further insight into the allosteric control of this 2MDa, we obtained the free-energy landscape of the channel in multiple ligand states using geometric machine learning methods developed by the group of Abbas Ourmazd. This gave us complex molecular movies of the channel as it transitions between ligand states (a). We apply these methods to other membrane receptors of important pharmacological relevance, such as G protein-coupled receptors

and their complexes (b), with the aim of better understanding their allosteric modulation and help design drugs with greater specificity and efficacy.

a. Dashti A, Mashayekhi G, Shekhar M, Ben Hail D, Salah S, Schwander P, des Georges A[$], Singharoy A[$], Frank J[$], Ourmazd A[$]. Retrieving functional pathways of biomolecules from single-particle snapshots. Nat Commun. 2020;11(1):4734. PMCID: PMC7501871. (*[$]: co-corresponding authors*)

b. Nguyen AH, Thomsen ARB, Cahill TJ 3rd, Huang R, Huang LY, Marcink T, Clarke OB, Heissel S, Masoudi A, Ben-Hail D, Samaan F, Dandey VP, Tan YZ, Hong C, Mahoney JP, Triest S, Little J 4th, Chen X, Sunahara R, Steyaert J, Molina H, Yu Z, des Georges A[$], Lefkowitz RJ[$]. Structure of an endosomal signaling GPCR-G protein-β-arrestin megacomplex. Nat Struct Mol Biol. 2019 Dec;26(12):1123-1131. PMCID: PMC7108872. (*[$]: co-corresponding authors*)

c. des Georges A*, Clarke OB*, Zalk R*, Yuan Q, Condon KJ, Grassucci RA, Hendrickson WA, Marks AR, Frank J. Structural Basis for Gating and Activation of RyR1. Cell. 2016 Sep 22;167(1):145-157.e17. PMCID: PMC5142848. (**: co-first authors*)

d. Zalk R*, Clarke OB*, des Georges A*, Grassucci RA, Reiken S, Mancia F, Hendrickson WA, Frank J, Marks AR. Structure of a mammalian ryanodine receptor. Nature. 2015 Jan 1;517(7532):44-9. PMCID: PMC4300236. (**: co-first authors*)

2. **Structural study of pathogen-host interactions**. We are making strides towards a better understanding of pathogen-host interactions using state-of-the-art single-particle and tomographic cryo-EM. The entry of pathogens or pathogen toxins into their hosts are dynamic processes that cryo-EM is ideally suited to tackle. We have recently obtained the structure of the Clostridium difficile binary toxin by single-particle cryo-EM in collaboration with David Weber at University of Maryland (d), a critical first step towards understanding the pathogenicity of this hypervirulent bacterial strain. We are also actively collaborating with the laboratories of Anne Moscona and Matteo Porotto at Columbia University to decipher every step of entry of the respiratory paramyxovirus into their host using a combination of molecular and structural biology tools including cryo-electron tomography and sub-tomogram averaging (a,c). Knowledge gained and tools developed will be applicable to deciphering the mechanism of host entry of other viruses of this family, including COVID-19 (b).

   a. Marcink TC[$], Zipursky G, Cheng W, Stearns K, Stenglein S, Golub K, Cohen F, Bovier F, Pfalmer D, Greninger AL, Porotto M[$], des Georges A[$], Moscona A[$]. Subnanometer structure of an enveloped virus fusion complex on viral surface reveals new entry mechanisms. Science Advances. 2023 Feb 10;9(6):eade2727. (*[$]: co-corresponding authors*)

   b. Marcink, T.C., Kicmal, T., Armbruster, E., Zhang, Z., Zipursky, G., Golub, K.L., Idris, M., Khao, J., Drew-Bear, J., McGill, G. and Gallagher, T., Porotto M[$], des Georges A[$], Moscona A[$]. Intermediates in SARS-CoV-2 spike–mediated cell entry. *Science Advances*. 2022 Aug 19; 8(33), p.eabo3153. PMCID: PMC9390989. (*[$]: co-corresponding authors*)

   c. Marcink TC, Wang T, des Georges A[$], Porotto M[$], Moscona A[$]. Human parainfluenza virus fusion complex glycoproteins imaged in action on authentic viral surfaces. PLoS Pathog. 2020 Sep;16(9):e1008883. PMCID: PMC7529294. (*[$]: co-corresponding authors*)

   d. Xu X[#], Godoy-Ruiz R, Adipietro KA, Peralta C, Ben-Hail D, Varney KM, Cook ME, Roth BM, Wilder PT, Cleveland T, Grishaev A, Neu HM, Michel SLJ, Yu W, Beckett D, Rustandi RR, Lancaster C, Loughney JW, Kristopeit A, Christanti S, Olson JW, MacKerell AD, des Georges A[$], Pozharski E[$], Weber DJ[$]. Structure of the cell-binding component of the *Clostridium difficile* binary toxin reveals a di-heptamer macromolecular assembly. Proc Natl Acad Sci U S A. 2020 Jan 14;117(2):1049-1058. PMCID: PMC6969506. (*[#]: CUNY PhD student*; *[$]: co-corresponding authors*)

3. **High-resolution structure determination of biomolecular complexes by single-particle cryo-EM**. When I joined the laboratory of Joachim Frank in 2008, the highest-resolution structure of an asymmetrical molecule by single-particle cryo-EM was 6.7Å. The highest resolution structure of a eukaryotic ribosome was 10Å. I optimized the data collection strategy and data processing methods implemented in the SPIDER data processing software package and obtained a map of the *Trypanosoma brucei* ribosome at 4.9Å resolution. At the time of publication, this was the highest-resolution structure of an asymmetrical macromolecule obtained by cryo-EM (c,d). This included implementing an unbiased resolution estimation,

which was very uncommon before the implementation of "gold-standard" resolution estimation procedures (c). The quality of the map obtained allowed my coworker Yaser Hashem to model de-novo several peculiar features of this ribosome, which could serve as basis for the development of more specific anti-parasitic drugs. We continue to push technical developments, particularly towards imaging macromolecular complexes as close to their native state as possible. This led us to develop novel polymers to solubilize transmembrane proteins with their native lipids in collaboration with Dr. Youzhong Guo (a) and to image macromolecules directly in their cellular environment with Dr. Juliette Fedry (b).

a. Trinh, T.K.H., Cabezas, A.J., Joshi, S., Catalano, C., Siddique, A.B., Qiu, W., Deshmukh, S., des Georges, A. and Guo, Y., pH-tunable membrane-active polymers, NCMNP2a-x, and their potential membrane protein applications. Chemical Science, 2023;14(26),7310-7326. PMCID: PMC10321531
b. Fedry J, Silva J, Vanevic M, Fronik S, Mechulam Y, Schmitt E, des Georges A, Faller WJ, Förster F. Visualization of translation reorganization upon persistent ribosome collision stress in mammalian cells. *Molecular Cell.* 2024. Feb 2:S1097-2765(24)00051-0. (Online ahead of print) PMID: 38340715
c. des Georges A, Hashem Y, Buss SN, Jossinet F, Zhang Q, Liao H, Fu J, Jobe A, Grassucci RA, Langlois R, Bajaj C, Westhof E, Madison-Antenucci S, Frank J. Computational Methods for Three-Dimensional Microscopy Reconstruction. Herman GT, Frank J, editors. New York, NY: Springer New York, 2014;97-132.
d. Hashem Y*, des Georges A*, Fu J, Buss SN, Jossinet F, Jobe A, Zhang Q, Liao HY, Grassucci RA, Bajaj C, Westhof E, Madison-Antenucci S, Frank J. High-resolution cryo-electron microscopy structure of the Trypanosoma brucei ribosome. Nature. 2013;494(7437):385-9. PMCID: PMC3659406. (**: co-first authors*)

4. **Structures of translation complexes at important regulatory checkpoints**. The advent of more powerful algorithms for classifying electron microscopy images allowed me to study more heterogeneous and challenging samples involved in translation regulation. Together with my coworker Yaser Hashem, I obtained the first structure of a eukaryotic translation initiation complex, the 43S pre-initiation complex. It was the first time that key eukaryotic initiation factors were observed bound to the ribosome in a cryo-EM structure. I obtained the structure of this complex from the only 5% of particles having all factors bound in the dataset. This study represented the first report of in-silico purification of a heterogenous complex using the Bayesian image classification implemented in RELION (d). With a direct electron detector, I later improved the resolution of that structure to 6Å and from that map, my coworker Yaser Hashem built a polyalanine model of the multisubunit initiation factor eIF3 (a). Using the same strategies, we also obtained structures of the HCV IRES mRNA bound to the 40S ribosome showing how it displaces the initiation factor eIF3 (c) and the first sub-nanometer structure of a eukaryotic translation termination complex (b).

   a. Fedry J, Silva J, Vanevic M, Fronik S, Mechulam Y, Schmitt E, des Georges A, Faller WJ, Förster F. Visualization of translation reorganization upon persistent ribosome collision stress in mammalian cells. *Molecular Cell.* 2024. Feb 2:S1097-2765(24)00051-0. (Online ahead of print) PMID: 38340715
   b. des Georges A, Dhote V, Kuhn L, Hellen CU, Pestova TV, Frank J, Hashem Y. Structure of mammalian eIF3 in the context of the 43S preinitiation complex. Nature. 2015 Sep 24;525(7570):491-5. PMCID: PMC4719162.
   c. des Georges A, Hashem Y, Unbehaun A, Grassucci RA, Taylor D, Hellen CU, Pestova TV, Frank J. Structure of the mammalian ribosomal pre-termination complex associated with eRF1.eRF3.GDPNP. Nucleic Acids Res. 2014 Mar;42(5):3409-18. PMCID: PMC3950680.
   d. Hashem Y*, des Georges A*, Dhote V, Langlois R, Liao HY, Grassucci RA, Hellen CU, Pestova TV, Frank J. Structure of the mammalian ribosomal 43S preinitiation complex bound to the scanning factor DHX29. Cell. 2013 May 23;153(5):1108-19. PMCID: PMC3730827. (**: co-first authors*)

Complete List of Published Work in My Bibliography:

https://www.ncbi.nlm.nih.gov/myncbi/amedee.des georges.1/bibliography/public/