BIOGRAPHICAL SKETCH

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NAME: Megan Young

eRA COMMONS USER NAME (credential, e.g., agency login): may023

POSITION TITLE: Graduate Student Researcher

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)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
UC San Diego	BS	09/2016	03/2020	Biochemistry/Chemistry
UC San Diego	PhD	09/2020	05/2025 (Expected)	Biomedical Science

A. Personal Statement

My interest in research and biomedical science comes from an interest in developing pharmaceuticals to provide novel therapeutics. Everyone has a family member or friend affected by a disease, and without the aid of modern medicine my family would be very different. This caused me to want to make a contribution to fighting rare and harmful diseases. In high school, I participated in a drug development study in collaboration with California State University at Fullerton to reduce methane emissions from domestic cows. This sparked my interest in research and development of pharmaceuticals. I pursued this avenue of study during my undergraduate career, in which I conducted research in the Chemical Biology lab of Dr. Michael Burkart at UC San Diego. During my three years in his lab, I studied proteins in the fatty acid synthase cycle of *E. coli* and their interactions with the acyl-carrier protein that shuttles substrates between them. This led to several publications that I had the pleasure of co-authoring. I conducted my own research projects under funding by several undergraduate research scholarships, and developed skills in protein purification and an interest in protein structural biology. Becoming immersed in the research culture of UC San Diego allowed me to seek out other labs that could combine my two interests: protein structure and development of pharmaceuticals. In the winter of 2020 I discovered Dr. Geoffrey Chang's lab in Skagg's School of Pharmacology, and knew right away that his research interests coincided with mine. Upon acceptance into UC San Diego's Biomedical Science PhD program, I began working with Dr. Chang to develop a research project that we both felt strongly about. I was immediately drawn to his involvement in studying the mechanisms behind transport of substrates through membrane proteins. The project soon manifested into the study of membrane transporters implicated in the export of toxins and often with multidrug resistance properties. This work will allow me to learn and develop skills in molecular biology and pharmacology, in structural determination and applications for drug development. Dr. Chang is heavily involved in the pharmacology department at UC San Diego and in collaborations with other researchers, providing me the opportunities and technical training necessary to pursue this research.

1. Bartholow, T.G., Sztain, T., Patel A., Lee, D.J., Young, M.A. Abagyan, R., Burkart, M.D. Elucidation of transient protein-protein interactions within carrier protein-dependent biosynthesis. *Commun Biol* **4,** 340 (2021). https://doi.org/10.1038/s42003-021-01838-3
2. Sztain, T., Bartholow, T.G., Lee, D.J., Casalino, L., Mitchell, A., Young, M.A., Wang, J., McCammon, A.J., Burkart, M.D. Decoding allosteric regulation by the acyl carrier protein. *PNAS*. **118,**16 (2021).
3. Bartholow, T.G., Sztain, T., Young, M.A., Davis, T.D., Abagyan, R., Burkart, M.D. Protein-protein interaction based substrate control in the E.coli octanoic acid transferase, LipB. *RSC Chemical Biology*. (2021).

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2020 – Present	Graduate Student Research Assistant, UC San Diego
2019 – 2020	Chemistry Research Assistant, Turning Point Therapeutics
2018	Chemistry Supplemental Instruction Leader, UC San Diego
2017 – 2020	Undergraduate Research Assistant, UC San Diego

Honors

2020	Graduate Summa Cum Laude from UC San Diego
2020	Joseph E. Mayer Award for Outstanding Undergraduate Research in Chemistry
2019-2020	UC San Diego Physical Sciences Dean's Undergraduate Award for Excellence
2019	Undergraduate Summer Research Scholarship, UC San Diego
2018	William A. Lee Undergraduate Research Scholarship, UC San Diego
2017	Frontiers in Innovations Scholars Fellowship, UC San Diego

C. Contributions to Science

Pharmaceuticals (High School): In a collaboration between Dana Hills High School Biotechnology class and California State University at Fullerton, I was involved in a research project studying the bacteria in cow rumen. The goal of the project was to discover the mechanism by which the bacteria in the gut of a cow produce methane, and then to inhibit this mechanism and reduce this greenhouse gas emission. I was involved in expression of the DNA of the gut bacteria, sequencing the protein-encoding DNA via PCR, and verifying the results of PCR via gel electrophoresis. This allowed for the study of methods and techniques of biochemistry research.

Protein Structural Biology (Undergraduate): In the longstanding research of the fatty acid cycle and how proteins drive chemical reactions, this research marks an important achievement in determining most of the individual structures of the fatty acid synthases and transferases with ACP as a partner protein. Tuberculosis, though an immunizable disease, remains a threatening infection in many developing countries. Understanding the process that this bacteria develops fatty acids is an important step in developing therapeutics. By investigating enzymes of the *E.coli* fatty acid synthase (FAS) pathway, our lab utilized crosslinking to study the structures of protein-protein interactions. My work consisted of expressing both LipB and AcpP in *E.coli* and purifying via iterative nickel column chromatography and FPLC. These two proteins could then be concentrated and combined using a chemoenzymatic technique developed in the Burkart laboratory to attach a crosslinking probe to ACP. My assistance in protein expression in *E.coli* and protein purification were a large contribution to the physical methods of the paper.

1. Bartholow, T.G., Sztain, T., Young, M.A., Davis, T.D., Abagyan, R., Burkart, M.D. Protein-protein interaction based substrate control in the E.coli octanoic acid transferase, LipB. *RSC Chemical Biology.* (2021).

Protein Structural Elucidation and Druggability (Graduate): The current direction of my graduate level research project is to investigate the protein transporters implicated in multidrug resistance pathways. The structure and function of many of these transporters are currently unknown, and even when known there is no information about the mechanism of small molecule transport across the membrane. I am proposing to clone and purify these proteins in order to study their structure in apo form and in complex with known endogenous ligands. This will be done using x-ray crystallography and cryo-EM methods, as has been demonstrated in the Chang lab previously with a similar target P-glycoprotein. I will also be utilizing the Chang lab's approach to determine nanobody (Nb) binders to specific proteins. This utilizes a cell surface expression system of a library of Nbs, and exposure of this library to a protein of interest. Combined with FACS, this allows the sorting of cells

expressing Nb bound specifically to protein and subsequent study of their interaction. Determining the structure and mechanism of action of these membrane transporters will provide valuable information about cell signal regulation and inform the design and development of pharmaceuticals.

D. Scholastic Performance

Undergraduate Biochemistry/Chemistry UC San Diego:

Year	Course Title	Grade
2016	General Chemistry I	A
2016	Diversity	A
2016	Calculus/Science & Engineering	A
2016	Great Performances on Film	A+
2016	First Year Experience	P
2017	Biology I: The Cell	A
2017	General Chemistry II	A+
2017	Justice	A
2017	Calculus & Analytical Geometry/Science and Engineering	A
2017	General Chemistry III	A
2017	General Chemistry Lab – Chemistry Majors	A-
2017	Imagination	A-
2017	Intro/Differential Equations	A
2017	Organic Chemistry I	A+
2017	Intro Asian-American Literature	P
2017	Linear Algebra	A
2017	Physics - Mechanics	A-
2018	Organic Chemistry II	A
2018	Organic Chemistry Laboratory I	A-
2018	Physics – Electricity and Magnetism	A
2018	Organic Chemistry III	A
2018	Film & History in Latin America	A
2018	Physics – Fluids, Waves, Thermodynamics, Optics	A+
2018	Physics Lab – Electricity and Magnetism	B+
2018	Analytical Chemistry Lab	A
2018	Biochemistry Structure & Function	A+
2018	New American Fiction: WWII - Present	A+
2019	Biochemistry Energetics & Metabolism	A+
2019	Pharmacology and Toxicology	A
2019	Physical Chemistry: Quantum Mechanics	A
2019	Biochemistry Biosynthesis of Macromolecules	A+
2019	Physical Chemistry: Thermodynamics	A+
2019	Organic Chemistry Lab II	A
2019	Protein Biochemistry Lab	A
2019	Inorganic Chemistry	A
2019	Research Project	P
2019	The American Renaissance Literature	P
2020	Physical Chemistry Laboratory	A-
2020	Recombinant DNA Laboratory	A
2020	Structural Biology of Viruses	A+

*All courses taken for a letter grade on the normal scale or for Pass/Fail (P/F)

Graduate Biomedical Sciences UC San Diego:

Year	Course Title	Grade
2020	Molecules to Organisms: Concepts	A
2020	Molecules to Organisms: Approaches	A

2020	Seminars in Biomedical Research	A+
2020/21	Biomedical Sciences Research Rotation	S
2020	Contemporary Topics in Pharmacology	S
2021	Introduction to Computational Biology/Biomedical Research	A
2021	Molecular Pharmacology Drug & Disease Therapy A	A
2021	Seminars in Pharmacology	A
2021	Ethics in Scientific Research	S
2021	Seminars in Molecular and Cell Biology	A
2021	Statistical Inference in Medicinal Science	A
2021	Careers in Biomedical Sciences	S
2021	Molecular Pharmacology Drug & Disease Therapy B	B+

*All courses taken for a letter grade on the normal scale or for Satisfactory/Unsatisfactory (S/U)

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NAME: **Chang, Geoffrey A**.

eRA COMMONS USER NAME (credential, e.g., agency login): **gchang1**

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
University of Pennsylvania, Philadelphia, PA	B.A./M.S.	1989-1993	Biophysics
University of Pennsylvania, Philadelphia, PA	Ph.D.	1994-1996	Biophysics
California Institute of Technology, Pasadena, CA	Postdoc	1996-1999	Chemistry

A. Personal Statement

My lab maintains a very active research program in three areas, including pharmacology (**medicine**), increasing crop production (**food**), and marine science (**environment**). The projects are inter-related with a common scientific theme understanding the mechanism of transporters located in the cell membrane using their high-resolution structures. The lab is a major component of a NIH funded membrane protein center called TransportPDB as part of the Protein Structural Initiative (PSI) and is now expanded/continued as CROPS (Center for Research On Plant TransporterS), which is part of the NSF Plant Genome Research Program (PGRP). The focus of our center is to solve the x-ray structures of human and plant transporters relevant to disease and food, respectively. We have several structure-function projects on P-glycoprotein, human MATE transporters, organic cation/anion transporters, the mitochondrial pyruvate carrier, the malarial chloroquine resistance transporter, several plant transporters, and transporters from sea urchin and tuna. We are involved in the area of neuroscience with collaborative studies focused on gamma secretase complex addressing β-amyloid formation and their different physiological species relevant to Alzheimer's disease and Downs syndrome (DS). Our lab pioneered one of the first systems for introducing and re-engineering oil transporters in algae for the secretion of biofuels in partnership with the US Air Force Research Laboratory. We have also pioneered a new and powerful method for synthetic affinity maturation of antibodies and other molecular scaffolds funded by the NIH Eureka mechanism. In this proposal, we leverage our core expertise and technology platform for discovering a panel of Synthetically-Evolved Nanobodies (SENs) selective for certain isoforms of Cβ controlled for Cα.

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

R01ES027921-01A1
Hamdoun (Co-PI)/Chang (Co-PI)
6/1/18-5/31/23
Identity, mechanisms and early life impacts of transporter interfering compounds

2020-67013-31188
Bogdonave (PI)/Chang (Co-I)
5/1/20-4/30/23
Susceptibility To Bacterial Leaf Streak Mediated By A Putative Sulfate Transporter In Rice: Mechanism And Intervention. Discover panels of Nbs and molecular structure determination for SulTR 3;6

1R03TR003639-01
Chang (Co-PI); Insel (Co-PI)
4/1/21-3/31/22
Nanobody inhibitors of proton-sensing G protein-coupled receptors. Obtain panels of Nbs selective for GPR68 and GPR65 receptors

1R01NS121604-01
Chang (Co-PI); Cleveland (Co-PI)
4/01/21-03/22/26
TDP-43 acetylation, phase separation, aggregation, and clearance by antibody-mediated degradation. Obtain panels of Nbs selective for TDP-43 and acetylated forms.

Citations:

1. Maity, K., et al., Cryo-EM structure of OSCA1.2 from Oryza sativa elucidates the mechanical basis of potential membrane hyperosmolality gating. Proc Natl Acad Sci U S A, 2019. 116(28): p. 14309-14318.
2. Doshi, R., et al., Functional characterization and discovery of modulators of SbMATE, the agronomically important aluminium tolerance transporter from Sorghum bicolor. Sci Rep, 2017. 7(1): p. 17996.
3. Doshi, R., et al., In vitro nanobody discovery for integral membrane protein targets. Sci Rep, 2014. 4: p. 6760.
4. Ward, A.B., et al., Structures of P-glycoprotein reveal its conformational flexibility and an epitope on the nucleotide-binding domain. Proc Natl Acad Sci U S A, 2013. 110(33): p. 13386-91.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2013-present	Professor, Skaggs School of Pharmacy and Pharmaceutical Sciences and Dept. of Pharmacology UCSD School of Medicine
2006-2012	Associate Professor, The Scripps Research Institute, La Jolla, CA
2002-2012	Skaggs Institute for Chemical Biology of The Scripps Research Institute, Member
1999-2005	Assistant Professor, The Scripps Research Institute, La Jolla, CA
1996-1999	Postdoctoral, California Institute of Technology, Pasadena, CA

Honors

2010	NIH EUREKA Award
2001	McDonald Armstrong Foundation Award
2001	Beckman Young Investigators Award
2001	Baxter Foundation Award
2000	Presidential Early Career Award for Scientists and Engineers
1997	Howard Hughes Post-Doctoral Associate
1996	Saul Winegrad, M.D. Award for Outstanding Doctoral Dissertation
1996	NIH Post-Doctoral Fellowship
1989-1996	University Scholar, University of Pennsylvania
1993	Phi Beta Kappa, University of Pennsylvania
1989-1993	Penn Medical Scholar/Associate, University of Pennsylvania
1989	All USA Academic Team, USA Today Newspaper

C. Contributions to Science

1. Structural biology of ion channels and water-soluble proteins.
My lab has recently determined structures of a rice channel by cryo-electron microscopy as well x-ray structures of sialidases involved in red meat consumption/microbiome, and also G-proteins regarding cancer biology. These projects are done as collaborations emphasizing biological relevance and impact.

A. Maity K, Heumann JM, McGrath AP, Kopcho NJ, Hsu PK, Lee CW, Mapes JH, Garza D, Krishnan S, Morgan GP, Hendargo KJ, Klose T, Rees SD, Medrano-Soto A, Saier MH, Jr., Pineros M, Komives EA, Schroeder JI, Chang G, Stowell MHB. Cryo-EM structure of OSCA1.2 from Oryza sativa elucidates the mechanical basis of potential membrane hyperosmolality gating. Proc Natl Acad Sci U S A. 2019;116(28):14309-18. doi: 10.1073/pnas.1900774116. PMID: 31227607; PMCID: PMC6628804
B. Zaramela LS, Martino C, Alisson-Silva F, Rees SD, Diaz SL, Chuzel L, Ganatra MB, Taron CH, Secrest P, Zuniga C, Huang J, Siegel D, Chang G, Varki A, Zengler K. Gut bacteria responding to dietary change encode sialidases that exhibit preference for red meat-associated carbohydrates. Nat Microbiol. 2019;4(12):2082-9. doi: 10.1038/s41564-019-0564-9. PMID: 31548686; PMCID: PMC6879853.
C. Kalogriopoulos NA, Rees SD, Ngo T, Kopcho NJ, Ilatovskiy AV, Sun N, Komives EA, Chang G, Ghosh P, Kufareva I. Structural basis for GPCR-independent activation of heterotrimeric Gi proteins. Proc Natl Acad Sci U S A. 2019;116(33):16394-403. doi: 10.1073/pnas.1906658116. PMID: 31363053; PMCID: PMC6697900.
D. Ribeiro CL, Conde D, Balmant KM, Dervinis C, Johnson MG, McGrath AP, Szewczyk P, Unda F, Finegan CA, Schmidt HW, Miles B, Drost DR, Novaes E, Gonzalez-Benecke CA, Peter GF, Burleigh JG, Martin TA, Mansfield SD, Chang G, Wickett NJ, Kirst M. The uncharacterized gene EVE contributes to vessel element dimensions in Populus. Proc Natl Acad Sci U S A. 2020. doi: 10.1073/pnas.1912434117. PMID: 32041869; PMCID: PMC7060721

2. Molecular structure determination of multi-drug resistance transporters including P-glycoprotein
My lab determined the x-ray structures of all four classes of multidrug resistance (MDR) transporters found in nature where the drug binding sites reside in the cell membrane. These efflux pumps cause resistance to drugs in the treatment of bacterial infections, cancers, and also HIV. These MDR transporters include those from the ATP-Binding Cassette (ABC), Major Facilitator Superfamily (MFS), Small Multidrug Resistance (SMR), and Multi-Antimicrobial Toxin Extrusion (MATE) families.

A. Kopcho N, Chang G, Komives EA. Dynamics of ABC Transporter P-glycoprotein in Three Conformational States. Sci Rep. 2019;9(1):15092. doi: 10.1038/s41598-019-50578-2. PMID: 31641149; PMCID: PMC6805939
B. Nicklisch SC, Rees SD, McGrath AP, Gokirmak T, Bonito LT, Vermeer LM, Cregger C, Loewen G, Sandin S, Chang G, Hamdoun A. Global marine pollutants inhibit P-glycoprotein: Environmental levels, inhibitory effects, and cocrystal structure. Sci Adv. 2016;2(4):e1600001. doi: 10.1126/sciadv.1600001. PMID: 27152359; PMCID: PMC4846432.
C. He X, Garza D, Nigam SK, Chang G. Multispecific Organic Cation Transporter 1 (OCT1) from Bos taurus Has High Affinity and Slow Binding Kinetics towards Prostaglandin E2. PLoS One. 2016;11(4):e0152969. doi: 10.1371/journal.pone.0152969. PMID: 27046168; PMCID: PMC4821612.
D. Szewczyk P, Tao H, McGrath AP, Villaluz M, Rees SD, Lee SC, Doshi R, Urbatsch IL, Zhang Q, Chang G. Snapshots of ligand entry, malleable binding and induced helical movement in P-glycoprotein. Acta Crystallogr D Biol Crystallogr. 2015;71(Pt 3):732-41. doi: 10.1107/S1399004715000978. PMID: 25760620; PMCID: PMC4356375.

3. Technology development
Membrane protein crystallization is still a technical challenge requiring innovation. Our laboratory has also been at the forefront developing new techniques to over-express, purify, and crystallize integral membrane proteins developing an *in vitro* membrane protein expression system and using structure validation techniques useful at moderate resolutions. Our lab also pioneered one of the first systems for introducing and re-engineering oil transporters in algae for the secretion of biofuels. We have also pioneered a new and powerful method for synthetic affinity maturation of antibodies and other molecular scaffolds.

A. Doshi R, McGrath AP, Pineros M, Szewczyk P, Garza DM, Kochian LV, Chang G. Functional characterization and discovery of modulators of SbMATE, the agronomically important aluminium tolerance transporter from Sorghum bicolor. Sci Rep. 2017;7(1):17996. doi: 10.1038/s41598-017-18146-8. PMID: 29269936; PMCID: PMC5740117.
B. Doshi R, Chen BR, Vibat CR, Huang N, Lee CW, Chang G. In vitro nanobody discovery for integral membrane protein targets. Sci Rep. 2014;4:6760. doi: 10.1038/srep06760. PMID: 25342225; PMCID: PMC4208029.
C. Doshi R, Nguyen T, Chang G. Transporter-mediated biofuel secretion. Proc Natl Acad Sci U S A. 2013;110(19):7642-7. doi: 10.1073/pnas.1301358110. PMID: 23613592; PMCID: PMC3651508.
D. Nguyen TA, Lieu SS, Chang G. An Escherichia coli-based cell-free system for large-scale production of functional mammalian membrane proteins suitable for X-ray crystallography. J Mol Microbiol Biotechnol. 2010;18(2):85-91. doi: 10.1159/000283512. PMID: 20160448; PMCID: PMC2919436.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/pubmed/?term=Chang+Geoffrey