BIOGRAPHICAL SKETCH

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NAME: Afrin, Shumaila

eRA COMMONS USER NAME (credential, e.g., agency login): S204987

POSITION TITLE: Postdoctoral researcher

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
Aligarh Muslim University, Aligarh	B.Sc.	2012	Biochemistry
Aligarh Muslim University, Aligarh	M.Sc.	2014	Biochemistry
Aligarh Muslim University, Aligarh	Ph.D.	2020	Biochemistry
UTSW Medical Center, Dallas, Texas	Postdoctoral Fellow	present	Structural studies of systemic amyloidosis

A. Personal Statement

I am a postdoctoral researcher at the Centers for Alzheimer's and Neurodegenerative Diseases, University of Texas Southwestern Medical Center, in the lab of Prof. Lorena Saelices. In the Saelices lab, our research focuses primarily on understanding the pathophysiology of transthyretin amyloidosis using structural tools like cryo-electron microscopy (cryo-EM). Additionally, we use this structural information to design diagnostic and therapeutic tools for ATTR amyloidosis. Transthyretin amyloidosis is a debilitating disease with current treatment ineffective at the late stage of the disease. My long-term goal is to understand the structural variabilities associated with ATTR amyloid fibrils and their correlation with disease progression and/or phenotype. To achieve this, I leverage my biophysical background and my expertise in cryo-EM and helical reconstruction of amyloid fibrils. Our recent work demonstrates structural polymorphism in cardiac ATTR amyloidosis at both patient and mutation levels (1). In the proposed work, we focus on the molecular mechanism of ATTR deposition in the brain using cryo-EM, mass spectrometry, and X-ray crystallography. Additionally, we will develop a structure-specific diagnostic tool for early detection of ATTR aggregates in the brain. This pilot study will serve as a basis for the development of cerebrospinal fluid-based detection tools, which are severely lacking in the field of neurodegenerative ATTR amyloidosis. I plan to collect cryo-EM data at the National Center for CryoEM Access and Training (NCCAT), New York Structural Biology Center, New York, USA, where I have been awarded scope time for my research.

1. Nguyen,Binh A.,, Afrin,Shumaila,, Singh,Virender,, Ahmed,Yasmin,, Pedretti,Rose,, Fernandez-Ramirez,Maria Del Carmen,, Benson,Merrill D.,, Sawaya,R. Michael,, Cao,Qin,, Boyer,David,, Pope,Alexander,, Wydorski,Pawel M.,, Chhapra,Farzeen,, Eisenberg,David S.,, Saelices,Lorena,. Structural polymorphism of amyloid fibrils in cardiac ATTR amyloidosis revealed by cryo-electron microscopy. [Preprint]. 2022 June 21. DOI: 10.1101/2022.06.21.496949 (*Accepted for publication, Nature Communications*)

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2021 - Postdoctoral researcher, UTSW Medical Center, Dallas, TX

2015 - 2020 Ph. D research fellow, Aligarh Muslim University, Aligarh

Honors

2017 - 2020 Senior Research Fellowship Award, Council of Scientific and Industrial Research (CSIR) Govt. of India

2015 - 2017 Junior Research Fellowship Award, Council of Scientific and Industrial Research (CSIR) Govt. of India

2012 - 2014 Prof. Abdul Majid Siddiqui award, Dept. of Biochemistry, AMU
2012 - 2014 M.Sc. Builder fellowship, Department of Biotechnology (DBT) Govt. of India

C. Contribution to Science

Postdoctoral research: My postdoctoral research is focused on understanding the structural mechanism of protein aggregation in disease. In transthyretin amyloidosis, a protein, transthyretin, misfolds, and forms amyloid fibrils that deposit in multiple organs and tissues, leading to a systemic form of amyloidosis. ATTR amyloidosis has a wide range of phenotypic variability, making early disease diagnosis difficult. My primary aim is to understand the mechanism and implications of these phenotypic variabilities through a structural perspective. To this end, I use cryo-election microscopy to study the structure of amyloid fibrils extracted from patient tissues. Structural heterogeneity of transthyretin amyloidosis (ATTR) fibrils using cryo-electron microscopy. In our recent study, we observe that structural polymorphism exists in ATTR amyloidosis both at the patient level as well as at the mutation level, suggesting that several factors, including the mutation and the patient body environment, play a role in the formation of specific polymorphs in ATTR. These results were recently accepted for publication in Nature Communications (a) where I share a first co-authorship. We are now exploring structural polymorphism in a larger sample size of mutations and patients to determine the correlation between disease phenotype and specific structural morphologies. We are also exploring how these changes occur at the organ level by looking at ATTR fibrils extracted from different organs of ATTR patients. In the proposed work, we will expand on this focus to understand the molecular mechanism of ATTR aggregation in the brain. Additionally, we are leveraging the mechanistic and structural information from these fibrils to design structure-specific detection tools. We have discussed these and other strategies for inhibition of protein aggregation in our recent review article (b). Additionally, in collaboration with other groups we have contributed to the mechanistic understanding of amyloid formation of α-synuclein (c).

a. Nguyen BA*, Singh V*, **Afrin S***, Yakubovska A, Wang L, Ahmed Y, Pedretti R, Fernandez-Ramirez MD, Singh P, Pękała M, Cabrera Hernandez LO. Structural polymorphism of amyloid fibrils in ATTR amyloidosis revealed by cryo-electron microscopy. Nature communications. 2024 Jan 17;15(1):1-2.
b. Fernández Ramírez M*, **Afrin S***, Saelices L*. Conformational inhibitors of protein aggregation. Current Opinion in Structural Biology. 2023 December; 83:102700-. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0959440X23001744 DOI: 10.1016/j.sbi.2023.102700
c. Balana AT, Mahul-Mellier AL, Nguyen BA, Horvath M, Javed A, Hard ER, Jasiqi Y, Singh P, **Afrin S**, Pedretti R, Singh V. O-GlcNAc forces an α-synuclein amyloid strain with notably diminished seeding and pathology. Nature Chemical Biology. 2024 Feb 12:1-0.

2. **Graduate research:** As part of my early graduate work, I studied how cardiovascular drugs, specifically antiplatelet drugs ticlopidine and dipyridamole interact with transport protein serum albumin. The binding of a drug to serum albumin affects its pharmacological properties; therefore, an optimum binding affinity of drug to serum albumin is essential for its therapeutic efficacy. Moreover, drugs that bind to a common binding site on serum albumin can compete for the binding site and alter their therapeutic efficacy. I determined the binding affinity and site of ticlopidine and dipyridamole on serum albumin. Additionally, I characterized the thermodynamic parameters of the interaction. My studies also suggested that ticlopidine, at its therapeutically relevant doses, may displace bilirubin from serum albumin, which may be one of the mechanisms through which ticlopidine induces hyperbilirubinemia. I also collaborated on the study that characterized the binding site and affinity of gastrointestinal disorder drugs pirenzipine and nizatidine on serum albumin.

   a. **Afrin S**, Rahman Y, Alhaji Isa M, Ahmed S, Tabish M. Biophysical insights into the binding characteristics of bovine serum albumin with dipyridamole and the influence of molecular interaction with β cyclodextrin. J Biomol Struct Dyn. 2020 Jul;38(10):3046-3058. PubMed PMID: 31366288.
   b. Rahman Y, **Afrin S**, Alhaji Isa M, Ahmed S, Tabish M. Elucidating the molecular interaction of serum albumin with nizatidine and the role of β-cyclodextrin: multi-spectroscopic and computational approach. J Biomol Struct Dyn. 2020 Mar;38(5):1375-1387. PubMed PMID: 30955446.
   c. **Afrin S**, Rahman Y, Tabish M. Elucidating the interaction of ticlopidine with serum albumin and its role in bilirubin displacement in vitro. J Biomol Struct Dyn. 2019 Mar;37(4):863-876. PubMed PMID: 29513159.

d. Rahman Y, **Afrin S**, Tabish M. Interaction of pirenzepine with bovine serum albumin and effect of β-cyclodextrin on binding: A biophysical and molecular docking approach. Arch Biochem Biophys. 2018 Aug 15;652:27-37. PubMed PMID: 29908138.

3. My research also explored the repurposing potential of antiplatelet rug ticlopidine by studying its interaction with DNA. Small molecules such as drugs interact with DNA mostly by binding within the grooves of DNA helices or by interacting within the base pairs. As part of a repurposing study, ticlopidine was found to inhibit Methicillin-resistant Staphylococcus aureus in synergism with antibiotics by decreasing the expression of TarO gene. My preliminary research suggested that ticlopidine, like distamycin, binds to the minor grooves of DNA in the AT-rich regions and, therefore, may disrupt transcription factor-DNA complexes, and this may explain the decrease in gene expression observed. I also collaborated on studying the interaction between diflunisal and DNA using a similar approach. Moreover, I contributed to a study on the toxicity of iron oxide nanoparticles and its attenuation by thymoquinone both invitro and in vivo. I assessed how iron oxide nanoparticles, which have a wide range of applications, interact with DNA as well as the genotoxic implications of the interactions. My research on drug DNA interactions has contributed to developing a fundamental body of thermodynamic and structural information that can be used for the rational design of DNA binding drugs.

   a. Ansari MO, Parveen N, Ahmad MF, Wani AL, **Afrin S**, Rahman Y, Jameel S, Khan YA, Siddique HR, Tabish M, Shadab GGHA. Evaluation of DNA interaction, genotoxicity and oxidative stress induced by iron oxide nanoparticles both in vitro and in vivo: attenuation by thymoquinone. Sci Rep. 2019 May 6;9(1):6912. PubMed Central PMCID: PMC6502885.
   b. **Afrin S**, Rahman Y, Sarwar T, Husain MA, Ali A, Shamsuzzaman, Tabish M. Molecular spectroscopic and thermodynamic studies on the interaction of anti-platelet drug ticlopidine with calf thymus DNA. Spectrochim Acta A Mol Biomol Spectrosc. 2017 Nov 5;186:66-75. PubMed PMID: 28614751.
   c. Rahman Y, **Afrin S**, Husain MA, Sarwar T, Ali A, Shamsuzzaman, Tabish M. Unravelling the interaction of pirenzepine, a gastrointestinal disorder drug, with calf thymus DNA: An in vitro and molecular modelling study. Arch Biochem Biophys. 2017 Jul 1;625-626:1-12. PubMed PMID: 28558964.

D. Scholastic Performance

Aligarh Muslim University graduate courses are graded P (pass) or F (fail).

YEAR	COURSE TITLE	GRADE
	ALIGARH MUSLIM UNIVERSITY	
2015	Biotechniques and Research Methodology	P
2015	A course designed for each candidate related to his /her area of research	P

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Lorena Saelices Gómez

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

POSITION TITLE: Assistant 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 Seville, Spain	B.Sc.	10/2005	Biology
University of Seville, Spain	Ph.D.	12/2010	Biochemical Sciences
University of California, Los Angeles	Postdoctoral Training	05/2014	Structural Biology
ETH Zürich, Switzerland	Postdoctoral Training	05/2015	Structural Biology

A. Personal Statement

My personal goal is to combine multidisciplinary techniques to delve deeply into fundamental molecular mechanisms that link protein structure to protein function and ultimately to disease phenotypes. During my training period, I worked with a diverse range of national and international collaborators to employ cutting edge techniques in cell biology, genetics, biochemistry, molecular biology, protein engineering, spectroscopy, crystallography, cryo-electron microscopy (cryo-EM), mass spectrometry, clinical assays, and *in vivo* studies in flies and mice. These experiences enable me to carry out innovative work and will provide the tools and foundations for the proposed studies. I have also extensive experience teaching and mentoring, as I detail below.

In my early training as a graduate student with Dr. Florencio (University of Seville, Spain), I studied protein-protein interaction using biochemical analysis and x-ray crystallography. As a Marie-Curie postdoctoral fellow with Dr. Roland Riek (ETH Zurich, Switzerland), I studied amyloid-beta assemblies using NMR and solution biophysics. My postdoctoral experience in the laboratory of Prof. David Eisenberg (UCLA) was focused on biophysical studies of amyloid-beta and ATTR recombinant fibrils using X-ray crystallography and cryo-electron microscopy (cryo-EM) and the design of structure-based peptide inhibitors of protein aggregation. When I came back to UCLA as a scientist, I designed structure-based peptide tools, trained on structure determination of recombinant amyloid fibrils by cryo-EM, and generated a mouse model of ATTR amyloidosis.

I started my independent laboratory at UTSW in June 2020. We use cryo-EM to determine the structures of amyloid fibrils extracted from the organs of patients, and to develop structure-based tools for the study of disease biology and detection of pathology. Our initial results have been published by *Nature Communications* (Nguyen et al. 2024) and accepted for publication in *Circulation* (Pedretti et al., 2024, in press).

As a Hispanic female scientist, I am fully committed to facilitating and mentoring a diverse community of scientists. Throughout my professional career, I have mentored and taught >30 students and postdocs, including female, immigrant, Latino, Hispanic, Black, and first-generation college students and postdocs. My past mentees are now pursuing their career choices, including grad school or postdoctoral positions in academia (University of Yale, UCLA, UC Davis, UCSD, ETH Zurich, Columbia University, Duke University, among many others) or industry. I am proud to have a laboratory of 12 people, in which 8 are women, 5 are first-generation college students, 1 is Black Latino, 1 is Hispanic, and 7 are immigrants. My goal as a mentor is to enrich their scientific and professional development and I aim to do so by cultivating a mentor-mentee relationship that profoundly advances their capabilities as independent scientists, providing close guidance in their research by meetings

and presentations, and providing opportunities to establish collegial relationships in the scientific community that are instrumental toward building their professional networks. I deeply care about mentoring in a diverse and inclusive environment.

Citations with direct relevance to the proposed project:

a. **Saelices** L, Chung K, Lee JH, Cohn W, Whitelegge JP, Benson MD, Eisenberg DS (2018). Amyloid seeding of transthyretin by ex vivo cardiac fibrils and its inhibition. *Proc Natl Acad Sci U S A* 115, no. 29: E6741–50 PMID: 29954863

b. **Saelices L**, Nguyen BA, Chung K, Wang Y, Ortega A, Lee JH, Coelho T, Bijzet J, Benson MD, Eisenberg DS (2019). A pair of peptides inhibits seeding of the hormone transporter transthyretin into amyloid fibrils. *J Biol Chem*, 294:6130-6141. PMID: 30733338

c. Nguyen BA, Singh V, Afrin S, Yakubovska A, Wang L, Ahmed Y, Pedretti R, Fernandez-Ramirez MDC, Singh P, Pękała M, Cabrera Hernandez LO, Kumar S, Lemoff A, Gonzalez-Prieto R, Sawaya MR, Eisenberg DS, Benson MD, **Saelices L.** (2024) Structural polymorphism of amyloid fibrils in ATTR amyloidosis revealed by cryo-electron microscopy. *Nat Commun*. Jan 17;15(1):581. PMID: 38233397

d. Pedretti R, Wang L, Hanna M, Benson M, Grodin JL, Tang WWH, Masri A, **Saelices L** (2024). Detection of circulating transthyretin amyloid aggregates in plasma: a novel biomarker for transthyretin amyloidosis. *Circulation*. https://doi.gov/10.1161/CIRCULATIONAHA.123.067225 [In Press]

Ongoing projects that I would like to highlight include:

- NIH New Innovator Award - DP2-HL163810-01
  Saelices Gómez (PI) - 09/01/2021-08/31/2026
  "Closing the gap between structural biology and translational science for amyloid diseases". This grant is focused on the structural study of amyloid fibrils from ATTR wild-type amyloidosis, the development of a cell-based model for the study of ATTR aggregation, and the structure-based design of peptides for its inhibition. The proposed study does not overlap with this grant.

B. Positions, Scientific Appointments, and Honors

Positions

2022-present	Peter O'Donnell Jr. Brain Institute Investigator, UT Southwestern Medical Center
2020-present	Assistant Professor, Amyloid Diseases, Center for Alzheimer's and Neurodegenerative Diseases, UT Southwestern Medical Center
2018-2020	Associate Project Scientist, Amyloidosis, Transthyretin, UCLA
2015-2018	Asst. Project Scientist, Structural Biology, Amyloid (David Eisenberg), UCLA
2014-2015	Postdoc, Structural Biology, Amyloid (Roland Riek), ETH Zürich
2012-2014	Postdoc, Structural Biology, Amyloid (David Eisenberg), UCLA
2011-2012	Postdoc, Enzymology, Structural Biology, Biochemistry, (Fco. Javier Florencio Bellido), University of Seville, Spain

Honors and awards

2022	Welch Foundation Research Award
2021	Distinguished Researcher Award from the President's Research Council
2020	NIH New Innovator Award
2019	Molecular Biology Institute Productivity Award
2019	The Company of Biologist Award for Scientific Meetings to organize the 2019 FASEB NextGen
2019	FASEB NextGen Award
2018	UCLA Clinical and Translational Science Institute (CTSI) Voucher Award
2018	Travel Award for The XVIth International Society of Amyloidosis 2018 Symposium.

2018 Recognized for outstanding Research and Contributions in the Subject of Neurobiology of Disease
2017 Amyloidosis Foundation David C. Seldin, MD, Ph.D. Memorial Research Grant, 2017 and 2018
2016 The Company of Biologist Award for Scientific Meetings to organize the 2016 Gordon Research Seminar
2016 Amyloidosis Foundation Research Grant, 2016
2016 Travel Award for The XVth International Society of Amyloidosis 2016 Symposium.
2016 Presentation Prize at The XVth International Society of Amyloidosis 2016 Symposium.
2012 Marie-Curie Fellowship for Postdoctoral Studies from People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme (FP7/2007-2013)
2009 Travel Fellowship for Ph.D. studies, awarded by the Government of Spain
2007 Travel Fellowship for Ph.D. studies, awarded by the Government of Spain
2006 FPI Fellowship for Ph.D. studies, awarded by the Government of Spain
2005 Honorary Collaborator of the Dept. of Genetics of University of Seville, Spain
2004 Fellowship for Undergraduate Research Training, awarded by the Government of Spain
2001 Yearly Scholarships for Undergraduate Studies, awarded by the Government of Spain

C. Contributions to Science

Full list of my published work:
https://www.ncbi.nlm.nih.gov/myncbi/lorena.saelices%20gomez.1/bibliography/public/

1. **UNDERGRADUATE STUDIES. Identification of the gene responsible for cleavage of torulene in the carotenoid pathway of *Neurospora crassa*.** My undergrad studies focused on the molecular mechanisms that control the production of secondary metabolites of biotechnological interest in fungi. I was assigned to lead a small research project focused on the regulation of carotenoid biosynthesis in the ascomycete *Neurospora crassa*, and its connections with the production of other secondary metabolites. This study resulted in the publication of my first paper (paper *a*), which describes the identification of *cao2*, the gene responsible for the cleavage of torulene in the carotenoid pathway. Carotenoids have attracted the attention of the industries and researchers because of their versatility. The characterization of the genetic pathway responsible for the production of carotenoids is of critical importance for future biotechnological applications, such as production of vitamin A precursors, food coloring, and antioxidants. My work described in paper *a* marked the beginning of subsequent studies such as the one described in paper *b*, and it was included in many other manuscripts such as the review *c.*

    a. **Saelices L**, Youssar L, Holdermann I, Al-Babili S, Avalos J. (2007). Identification of the gene responsible for torulene cleavage in the Neurospora carotenoid pathway. *Mol Genet Genomics,* 278(5), 527-37. PMID: 17610084
    b. Estrada AF, Youssar L, Scherzinger D, Al-Babili S, Avalos J. (2008). The ylo-1 gene encodes an aldehyde dehydrogenase responsible for the last reaction in the Neurospora carotenoid pathway. *Mol. Microbiology,* 69(5), 1207-20. PMID: 18627463
    c. Avalos J, Estrada AF. (2010). Regulation by light in Fusarium. *Fungal Genetics and Biology,* 47(11), 930-8. PMID: 20460165

2. **GRADUATE STUDIES. Characterization of the enzymatic regulation of glutamine synthetase by protein-protein interaction in cyanobacteria.** During my predoctoral period, my interest focused on enzymatic regulation by protein-protein interaction in cyanobacteria. Glutamine synthetase is a key enzyme of the metabolism of nitrogen that is finely regulated by up to two inactivating factors IF7 and IF17 in cyanobacteria. In paper *a,* we identified the binding site in IF7 and IF17 responsible for the GS regulation in *Synechocystis*. This work was followed up by paper *c,* a structural and biochemical analysis of the enzyme that describes the identification and characterization of the regulatory core of glutamine synthetase. With the support of a travel award during my Ph.D., an exhaustive training in structure analysis by x-ray crystallography in the lab of Prof. David Eisenberg at UCLA resulted in the determination of the atomic structure of the GS from *Synechocystis*, included in paper *c*. In paper *b,* we analyzed the inactivating factor IF17 by NMR and

found it to be partially unfolded in its native state. This work was followed up by the biophysical study of both IF7 and IF17 in the presence of the enzyme, as shown in paper *d.* The analysis of IF7 and IF17 by NMR revealed that these unfolded proteins fold upon binding to the GS. For more publications, please visit my NCBI bibliography in the link above.

a. **Saelices L**, Galmozzi CV, Florencio FJ, Muro-Pastor MI. (2011). Mutational analysis of the inactivating factors, IF7 and IF17 from Synechocystis sp. PCC 6803: critical role of arginine amino acid residues for glutamine synthetase inactivation. *Mol Microbiology,* 82(4), 964-75. PMID: 22023175.
b. **Saelices L**, Galmozzi CV, Florencio FJ, Muro-Pastor MI, Neira JL. (2011). The inactivating factor of glutamine synthetase IF17 is an intrinsically disordered protein, which folds upon binding to its target. *Biochem,* 50(45), 9767-78. PMID: 21992216
c. **Saelices L,** Robles-Rengel R, Muro-Pastor MI, Florencio FJ. (2015). A core of three amino acids at the carboxyl-terminal region of glutamine synthetase defines its regulation in cyanobacteria. *Mol Microbiology,* 96(3), 483-96. PMID: 25626767
d. Pantoja-Uceda D, Neira JL, **Saelices L**, Robles-Rengel R, Florencio FJ, Muro-Pastor MI, Santoro J. (2016). Dissecting the Binding between Glutamine Synthetase and Its Two Natively Unfolded Protein Inhibitors. *Biochemistry*, *55*(24), 3370-82. PMID: 27232663

3. **POSTDOC AND INDEPENDENT STUDIES. Structural studies of ATTR fibrils and structure-based design of specific peptide-inhibitors.** My most recent studies aim to characterize the mechanism of protein aggregation that leads to the formation of amyloid fibrils by TTR causing ATTR amyloidosis. ATTR amyloidosis is characterized by the abnormal formation of amyloid fibrils mainly made of TTR, which accumulates in almost every organ thereby leading to organ dysfunction and death. Paper *a* describes the identification of the TTR segments responsible for the formation of amyloid fibrils. Based on the crystal structure of these segments in their amyloid form, we were able to design efficient inhibitors. We discovered that fibrils present in the organs of ATTR patients can catalyze, or *seed*, fibril formation of soluble TTR, thereby accelerating deposition. Our peptide inhibitors inhibited this seeded aggregation, whereas TTR stabilizers used currently in the clinic do not hinder this process. We studied these peptide inhibitors in two Drosophila models of ATTR amyloidosis, showing a significant reduction of TTR deposition and an improvement of overall mobility. Our peptide inhibitors represent a novel therapeutic strategy that fills a gap in the field of amyloidosis, by targeting amyloid seeding, and are included in International Patent - Application No. PCT/US17/40103. Using a similar design pipeline, we have developed structure-based peptides that detect TTR aggregates in blood of patients even prior to showing symptoms. These results have been accepted for publication in *Circulation*. We will expand on these studies in the present proposal. Finally, our recent cryo-EM study reveals unprecedented structural polymorphism of amyloid fibrils extracted from ATTR amyloidosis patients, now published in *Nature Communications*.

a. **Saelices** L, Chung K, Lee JH, Cohn W, Whitelegge JP, Benson MD, Eisenberg DS (2018). Amyloid seeding of transthyretin by ex vivo cardiac fibrils and its inhibition. *Proc Natl Acad Sci U S A* 115, no. 29: E6741–50 PMID: 29954863
b. **Saelices L**, Nguyen BA, Chung K, Wang Y, Ortega A, Lee JH, Coelho T, Bijzet J, Benson MD, Eisenberg DS (2019). A pair of peptides inhibits seeding of the hormone transporter transthyretin into amyloid fibrils. *J Biol Chem*, 294:6130-6141. PMID: 30733338
c. Nguyen BA, Singh V, Afrin S, Yakubovska A, Wang L, Ahmed Y, Pedretti R, Fernandez-Ramirez MDC, Singh P, Pękała M, Cabrera Hernandez LO, Kumar S, Lemoff A, Gonzalez-Prieto R, Sawaya MR, Eisenberg DS, Benson MD, **Saelices L.** (2024) Structural polymorphism of amyloid fibrils in ATTR amyloidosis revealed by cryo-electron microscopy. *Nat Commun*. Jan 17;15(1):581. PMID: 38233397
d. Pedretti R, Wang L, Hanna M, Benson M, Grodin JL, Tang WWH, Masri A, **Saelices L** (2024). Detection of circulating transthyretin amyloid aggregates in plasma: a novel biomarker for transthyretin amyloidosis. *Circulation*. https://doi.gov/10.1161/CIRCULATIONAHA.123.067225 [In Press]

4. **OTHER INDEPENDENT STUDIES AND COLLABORATIONS. Structural and molecular studies of amyloid precursors associated with neurodegenerative diseases.** I am committed to the study of the molecular and structural basis of protein aggregation and its detection and inhibition. In an early study as an

independent researcher, I explored the inhibition of aggregation of amyloid-beta peptides by naturally occurring peptides, derived from neuroprotective molecules, such as the human protein transthyretin (TTR). As explained above, TTR is an amyloidogenic protein that causes systemic ATTR but can also serve as a neuroprotective agent in the brain. Previous studies have shown that TTR binds to amyloid-beta, inhibits its aggregation, and exerts neuroprotection in animal models. In our studies, we found that the tetrameric functional form of TTR needs to dissociate into monomers to exert such protection. Based on structural analysis, we identified the minimum segment of TTR that can mimic its inhibitory effect. Additionally, in collaboration with other groups, we have contributed to the understanding of amyloid fibril formation of α-synuclein, tau, and SARS-CoV-2 amyloids, using cryo-EM and peptide design.

a. Cao Q, Anderson DH, Liang W, Chou J, **Saelices** L. (2020). The inhibition of cellular toxicity of amyloid-beta by dissociated transthyretin. *JBC*, 295(41):14015-14024. PMID: 32769117
b. Li L, Nguyen BA, Mullapudi V, Li Y, **Saelices L**, Joachimiak LA. (2023). Disease-associated patterns of acetylation stabilize tau fibril formation. *Structure*, 31(9):1025-1037.e4. PMID: 37348495
c. Tayeb-Fligelman E, Bowler JT, Tai CE, Sawaya MR, Jiang YX, Garcia G Jr, Griner SL, Cheng X, Salwinski L, Lutter L, Seidler PM, Lu J, Rosenberg GM, Hou K, Abskharon R, Pan H, Zee CT, Boyer DR, Li Y, Anderson DH, Murray KA, Falcon G, Cascio D, **Saelices L**, Damoiseaux R, Arumugaswami V, Guo F, Eisenberg DS. (2023) Low complexity domains of the nucleocapsid protein of SARS-CoV-2 form amyloid fibrils. *Nat Commun.* 14(1):2379. PMID: 37185252
d. Balana AT, Mahul-Mellier AL, Nguyen BA, Horvath M, Javed A, Hard ER, Jasiqi Y, Singh P, Afrin S, Pedretti R, Singh V, Lee VM, Luk KC, **Saelices L**, Lashuel HA, Pratt MR. (2024). O-GlcNAc forces an α-synuclein amyloid strain with notably diminished seeding and pathology. *Nat Chem Biol.* https://doi.org/10.1038/s41589-024-01551-2. Online ahead of print. PMID: 38347213