BIOGRAPHICAL SKETCH

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NAME: Alon, Assaf

eRA COMMONS USER NAME: assafalon

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE	FIELD OF STUDY
Tel Aviv University, Tel Aviv	BS	08/2005	Biotechnology
Weizmann Institute of Science, Rehovot	PHD	03/2012	Structural Biology
Weizmann Institute of Science, Rehovot	Postdoctoral Fellow	03/2015	Computational biology and protein design
Whitehead Institute, Cambridge, MA	Postdoctoral Fellow	12/2015	Structural Studies of immune receptors
Harvard Medical School, Boston, MA	Postdoctoral Fellow	11/2022	Structural and Pharmacological studies of membrane protein receptors

A. Personal statement

I was appointed as an Assistant Professor in the Department of Pharmacology at Yale University School of Medicine in December 2022. My laboratory investigates receptors and enzymes involved in sterol synthesis, regulation, and homeostasis, with the overarching goal of linking molecular mechanisms to therapeutic opportunities in cardiometabolic disease. We use an interdisciplinary toolkit of receptor pharmacology, structural biology, and drug discovery to define how receptor–ligand interactions shape lipid metabolism and to identify points of therapeutic intervention.

As a postdoctoral fellow at Harvard Medical School, I identified and characterized the sigma-2 receptor (TMEM97), an enigmatic membrane protein whose role in cholesterol biology had remained elusive for decades. By determining its structure and ligand-binding properties, I provided the foundation for exploring how sigma-2 regulates cholesterol flux and sterol homeostasis. Building directly on this work, my laboratory now investigates the molecular mechanisms by which sigma-2 controls sterol metabolism through protein–protein interactions, and how small molecules can modulate these processes. These studies have broad implications for cardiovascular disease, given the central role of cholesterol regulation in atherosclerosis and lipid-driven pathologies.

We are also expanding to other members of the EXPERA family. Of particular interest is TM6SF2, a protein critical for VLDL lipidation and secretion. Because it harbors a ligand-binding pocket, TM6SF2 represents a promising therapeutic target for hyperlipidemia and metabolic dysfunction–associated steatotic liver disease (MASLD). Using a combination of structural biology, pharmacology, and computational approaches, my group seeks to uncover how EXPERA proteins integrate into cholesterol and lipoprotein regulation and how their activities can be harnessed for therapeutic benefit.

Alongside my research, I have maintained a strong commitment to mentoring and teaching. At the Weizmann Institute of Science, I supervised graduate and undergraduate students, guiding them in experimental techniques and scientific communication. At Harvard Medical School, I extended this mentorship to experimental design, data interpretation, and career development. As an independent investigator, I remain dedicated to training the next generation of scientists in an interdisciplinary environment at the intersection of structural biology, pharmacology, and cardiovascular science.

1. Lyu J†, Kapolka N†, Gumpper R†, Alon A†, Wang L†, Jain MK, Barros-Álvarez X, Sakamoto K, Kim Y, DiBerto J, Kim K, Glenn IS, Tummino TA, Huang S, Irwin JJ, Tarkhanova OO, Moroz Y, Skiniotis G,

Kruse AC, Shoichet BK, Roth BL
Science. 2024. DOI: 10.1126/science.adn6354

2. **Alon A**, Lyu J, Braz JM, Tummino TA, Craik V, O'Meara MJ, Webb CM, Radchenko DS, Moroz YS, Huang XP, Liu Y, Roth BL, Irwin JJ, Basbaum AI, Shoichet BK, Kruse AC. Structures of the σ_2 receptor enable docking for bioactive ligand discovery. ***Nature***. 2021 Dec;600(7890):759-764. DOI: 10.1038/s41586-021-04175-x
3. **Alon A**, Schmidt HR, Wood MD, Sahn JJ, Martin SF, Kruse AC. Identification of the gene that codes for the σ_2 receptor. ***Proc Natl Acad Sci U S A***. 2017 Jul 3;114(27):7160-7165. DOI: 10.1073/pnas.1705154114
4. Ilani T, **Alon A**, Grossman I, Horowitz B, Kartvelishvily E, Cohen SR, Fass D. A secreted disulfide catalyst controls extracellular matrix composition and function. ***Science***. 2013 Jul 5;341(6141):74-6. DOI: 10.1126/science.1238279
5. **Alon A**, Grossman I, Gat Y, Kodali VK, DiMaio F, Mehlman T, Haran G, Baker D, Thorpe C, Fass D. The dynamic disulphide relay of quiescin sulphydryl oxidase. ***Nature***. 2012 Aug 16;488(7411):414-8. DOI: 10.1038/nature11267

B. Positions, scientific appointments and honors

Positions and scientific appointments

2007 – 2012	Graduate Research, Weizmann Institute of Science, Rehovot
2013 – 2015	Postdoctoral Fellow, Weizmann Institute of Science, Rehovot
2016 – 2022	Postdoctoral Fellow, Harvard Medical School, Boston, MA
2022 – present	Assistant Professor, Yale University School of Medicine, New Haven, CT

Honors

2025-2029	Lois E. and Franklin H. Top, Jr. Yale Scholar, Yale University School of Medicine
2023	Rudolph J. Anderson Endowed Postdoctoral Fellowship
2017	The Merck Postdoctoral Fellowship, Merck
2016	Outstanding Postdoc Fellow Award, Harvard Medical School
2013	Biochemistry Dean postdoctoral award, Weizmann Institute of Science
2005	Dean's honor list, Tel Aviv University
2003	Dean's honor list, Tel Aviv University

Professional societies and public advisory committees:

2013 – 2016	Member – RosettaCommons
2014 – present	Member – The Protein Society
2022 – present	Member – The American Society for Pharmacology and Experimental Therapeutics (ASPET)
2022 – present	Member – American Society for Biochemistry and Molecular Biology (ASBMB)
2016	Reviewer – *Protein Science*
2017	Reviewer – *Scientific Reports*
2020	Reviewer – *Communications Biology*

Teaching and mentoring experience:

In my laboratory, I have mentored trainees from diverse backgrounds and at multiple career stages, including high school volunteers, Yale undergraduates, graduate students, postgraduate scholars, first-year rotation students, and postdoctoral fellows. Training is a core mission of my lab, and I emphasize developing both technical expertise and scientific communication skills.

My mentorship extends beyond research projects to structured activities such as group meetings and journal clubs, where I guide trainees in analyzing literature, presenting research, and writing effectively. I provide

individualized feedback on figure design, poster preparation, and manuscript writing to ensure that students learn to communicate their science with clarity and impact.
At Yale, my teaching includes a seminar-style course in which students present assigned research papers and develop their own research proposals. I also contribute to the Pharmacology Department's drug discovery course, where I share my expertise in in silico drug discovery and computational methods, integrating real-world research experience into the classroom.

C. Contribution to science

1. Postgraduate work:

The σ_2 receptor – from a pharmacological mystery to structure- based drug discovery

During my postdoctoral training in the laboratory of Andrew Kruse at Harvard Medical School, I solved the decades-long mystery of the sigma-2 receptor (σ_2). The σ family was identified in the 1970s, with σ_1 cloned in 1996, but the molecular identity of σ_2 remained unknown. This gap precluded the use of modern molecular biology to investigate σ_2 function despite its implication in cancer, pain, and neuropsychiatric disorders.

I cloned the σ_2 receptor from calf liver tissue using classical biochemical fractionation and radioligand binding, identifying it as TMEM97, a four-helix ER-resident protein. Functional assays demonstrated that TMEM97 is both necessary and sufficient for σ_2 activity, establishing its molecular identity.

I then turned to structural biology to define ligand recognition at the atomic level. Using advances in lipidic cubic phase crystallography, I purified and crystallized TMEM97, determining structures in complex with cholesterol, the schizophrenia drug candidate roluperidone, and the tool compound PB28. These structures revealed how ligands are recognized and explained the long-standing overlap in pharmacology between σ_1 and σ_2, despite their distinct folds.

To expand ligand discovery, I collaborated with Jiankun Lyu and Brian Shoichet to virtually dock half a billion small molecules, identifying novel σ_2 ligands. Crystal structures confirmed the accuracy of the predicted binding poses, and subsequent in vivo work with Allan Basbaum demonstrated that these compounds are brain-penetrant and exert anti-allodynic effects in a mouse model of neuropathic pain.

This body of work transformed σ_2 from a pharmacological mystery into a structurally defined, druggable receptor, laying the foundation for therapeutic targeting in pain and neuropsychiatric disease.

1. **Alon A**, Lyu J, Braz JM, Tummino TA, Craik V, O'Meara MJ, Webb CM, Radchenko DS, Moroz YS, Huang XP, Liu Y, Roth BL, Irwin JJ, Basbaum AI, Shoichet BK, Kruse AC. Structures of the σ_2 receptor enable docking for bioactive ligand discovery. ***Nature***. 2021 Dec;600(7890):759-764. DOI: 10.1038/s41586-021-04175-x
2. **Alon A**, Schmidt HR, Wood MD, Sahn JJ, Martin SF, Kruse AC. Identification of the gene that codes for the σ_2 receptor. ***Proc Natl Acad Sci U S A***. 2017 Jul 3;114(27):7160-7165. DOI: 10.1073/pnas.1705154114
3. **Alon A**, Schmidt H, Zheng S, Kruse AC. Structural Perspectives on Sigma-1 Receptor Function. ***Adv Exp Med Biol***. 2017;964:5-13. DOI: 10.1007/978-3-319-50174-1_2

4. Postgraduate work:

Using computational protein design to switch antibody species preference

As a graduate researcher in the laboratory of Sarel Fleishman at the Weizmann Institute of Science, I developed computational methods for antibody design. My work was motivated by a cancer therapeutic antibody that bound human QSOX but not mouse QSOX due to self-tolerance, preventing its use in preclinical mouse models.

To overcome this barrier, I designed algorithms to switch the species preference of antibodies. I generated computationally redesigned variants, screened them experimentally, and solved crystal structures of two high-affinity binders. These structures highlighted both the strengths and limitations of the design algorithm, enabling me to propose improvements to the method.

Beyond this specific case, I extended the approach to develop a general framework for antibody humanization across species. This work provided a foundation for rationally adapting antibodies for therapeutic development and preclinical testing.

1. Lapidoth GD, Baran D, Pszolla GM, Norn C, **Alon A**, Tyka MD, Fleishman SJ. AbDesign: An algorithm for combinatorial backbone design guided by natural conformations and sequences. ***Proteins***. 2015 Aug;83(8):1385-406. DOI: 10.1002/prot.24779

5. Graduate work:

Structure, dynamics, and inhibition of a secreted disulfide catalyst

My graduate research in the laboratory of Deborah Fass at the Weizmann Institute of Science focused on the disulfide catalyst quiescin sulfhydryl oxidase (QSOX). Unlike canonical disulfide bond formation in the endoplasmic reticulum, which requires sequential action of PDI and EroI, QSOX uniquely fuses an oxidoreductase and a sulfhydryl oxidase into a single polypeptide and functions downstream of the ER, including in the extracellular matrix (ECM).

I solved the crystal structure of QSOX in its resting state and, through mutagenesis and purification strategies, trapped an intermediate conformation with a mixed disulfide bond. By integrating crystallography with FRET and cross-linking mass spectrometry, I showed that QSOX's two catalytic modules are linked by a flexible tether and undergo large-scale conformational sampling to enable intramolecular electron transfer.

Given QSOX's overexpression in prostate and pancreatic cancers and its secretion into the ECM, I hypothesized that its activity could influence tumor progression. To test this, I generated and screened monoclonal antibodies, identifying a potent inhibitory clone with nanomolar affinity that completely blocked catalytic activity. Using this tool, I demonstrated that QSOX regulates laminin incorporation into the ECM and impacts cell migration.

This work provided fundamental insight into the structural dynamics of a unique disulfide catalyst and delivered the first inhibitory antibodies against QSOX, establishing both mechanistic understanding and therapeutic potential in cancer biology.

1. Grossman I, **Alon A**, Ilani T, Fass D. An inhibitory antibody blocks the first step in the dithiol/disulfide relay mechanism of the enzyme QSOX1. ***J Mol Biol***. 2013 Nov 15;425(22):4366-78. DOI: 10.1016/j.jmb.2013.07.011
2. Ilani T, **Alon A**, Grossman I, Horowitz B, Kartvelishvily E, Cohen SR, Fass D. A secreted disulfide catalyst controls extracellular matrix composition and function. ***Science***. 2013 Jul 5;341(6141):74-6. DOI: 10.1126/science.1238279
3. **Alon A**, Grossman I, Gat Y, Kodali VK, DiMaio F, Mehlman T, Haran G, Baker D, Thorpe C, Fass D. The dynamic disulphide relay of quiescin sulphydryl oxidase. ***Nature***. 2012 Aug 16;488(7411):414-8. DOI: 10.1038/nature11267
4. **Alon A**, Heckler EJ, Thorpe C, Fass D. QSOX contains a pseudo-dimer of functional and degenerate sulfhydryl oxidase domains. ***FEBS Lett***. 2010 Apr 16;584(8):1521-5. DOI: 10.1016/j.febslet.2010.03.001

Complete List of Published Work in My Bibliography:
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