SfRBM – SFRRI 2023 SYMPOSIUM PROPOSAL FORM

SYMPOSIUM TITLE: RNA translation and Redox Biology

DISEASE SECTOR: *Interdisciplinary*

PROPOSER (Name / Institution / Email): Nadine Hempel, PhD / University of Pittsburgh / nah158@pitt.edu

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SYMPOSIUM SUMMARY (Maximum 300 words)

Redox homeostasis is imperative to all living organisms. Upon perturbation of this homeostasis, which is common in the context of disease and in response to extrinsic stress, such as environmental toxicants, cells must rapidly adapt to counter the imbalance between oxidant production and oxidant scavenging. Cells are equipped with stress response signaling pathways that are engaged to increase transcription, *de novo* protein synthesis, and posttranslational modifications of antioxidant enzymes to increase cellular oxidant scavenging. If oxidative stress exceeds the capacity of the antioxidant system, the cellular stress response switches to the initiation of cell death pathways. Over the last several decades, stress-induced transcriptional regulation of antioxidant enzymes has been extensively studied, with a prominent example being the redox sensitive transcription factor Nrf2/*NFE2L2*. However, adaptations to stress often require an immediate response. Transcription, although important for the strength of gene expression, has a considerable lag time until nascent proteins are synthesized. Thus, in addition to transcription, regulation of expression must occur at the posttranscriptional level. RNA translation can initiate rapid changes in protein expression and accommodate prompt adaptation to environmental and cellular cues. The focus of our proposed session will be on translational regulation in the context of redox biology and how this is an important mechanism for cells to maintain redox homeostasis by manipulation of the cell's antioxidant enzyme systems. Cells under stress conditions undergo two important translational adaptations, the attenuation of global protein synthesis to preserve energy, and selective translation of mRNA transcripts necessary for stress adaptation. While this has been extensively studied in the context of the integrated stress response, it is less well known how stress response translational regulation contributes to regulation of the antioxidant system.
In this session, speakers will highlight how RNA modifications (epitranslatome), RNA binding proteins and the translation machinery are altered as a consequence of both intrinsic stress associated with diseases such as metastatic

tumors, and extrinsic stress, such as exposure to environmental toxicants; and illustrate how this specifically translates to cells abilities to deal with oxidative stress. To our knowledge this will be the first plenary session dedicated to translation and RNA biology at the SfRBM / SFRR annual meeting.

SYMPOSIUM CHAIRS

Chair 1 Name / Degree(s): Nadine Hempel, PhD

Institution: University of Pittsburgh

Department/Division: Medicine - Hematology & Oncology, Hillman Cancer Center

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Chair 2 Name / Degree(s): Elena Piskounova, PhD *(Potential Junior Speaker)*

Institution: Weill Cornell School of Medicine

Department/Division: Department of Dermatology, Sandra and Edward Meyer Cancer Center

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SYMPOSIUM SPEAKERS

Presentation Title 1: The epitranscriptome response to environmental stress

Speaker 1 Name / Degree(s): Thomas Begley, PhD

Institution: University at Albany, The RNA Institute

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SPEAKER 1 Abbreviated CV (maximum 300 words)

Environmental and endogenous stressors can cause DNA damage to promote cancer onset, cancer progression and ageing. The overarching theme of Dr. Begley's research program has been the study of cellular, tissue and organismal responses to stress, with an emphasis on alkylating agents and stressors that increase reactive oxygen species (ROS). In addition, he has developed technologies to study and mitigate cellular stress responses. Highlights of research in the Begley Laboratory include (1) the demonstration that epitranscriptomic marks found in the form of RNA modifications play key stress response roles, by regulating the translation of DNA damage and ROS response proteins, including the role of tRNA modifications and the tRNA methyltransferase ALKBH8 in selenocysteine protein synthesis, (2) the development of algorithms and database systems to identify nucleic acid sequences translationally regulated during stress responses, (3) the identification of a new tumor growth suppressor for colorectal cancer, and (4) the development of a mouse model that has increased ROS levels, for use in the testing of potential environmental hazards. The Begley lab has also collaboratively developed several technologies to (1) characterize global changes in RNA modification in response to stress, (2) measure activation of the DNA damage response in patients undergoing diagnostic computerized tomography (CT) scans, and (3) started work to develop single molecule approaches for the analysis of modified RNA nucleosides. Dr. Begley has held several leadership positions including his current role as the Associate Director of The RNA Institute at the University at Albany. Dr. Begley's research is currently funded by several grants from the US National Institutes of Environmental Health Sciences (NIEHS) and he is the PI of a T32 training grant om RNA Science and Technology in Health and Disease.

SPEAKER 1 Publications (maximum 10)

Arsenite toxicity is regulated by queuine availability and oxidation-induced reprogramming of the human tRNA epitranscriptome.

Huber SM, Begley U, Sarkar A, Gasperi W, Davis ET, Surampudi V, Lee M, Melendez JA, Dedon PC, Begley TJ.Proc Natl Acad Sci U S A. 2022 Sep 20;119(38):e2123529119. doi: 10.1073/pnas.2123529119. Epub 2022 Sep 12.

Codon Usage and mRNA Stability are Translational Determinants of Cellular Response to Canonical Ferroptosis Inducers.
Rashad S, Byrne SR, Saigusa D, Xiang J, Zhou Y, Zhang L, Begley TJ, Tominaga T, Niizuma K.Neuroscience. 2022 Oct 1;501:103-130. doi: 10.1016/j.neuroscience.2022.08.009. Epub 2022 Aug 17.

Epitranscriptomic Reprogramming Is Required to Prevent Stress and Damage from Acetaminophen.
Evke S, Lin Q, Melendez JA, Begley TJ.Genes (Basel). 2022 Feb 25;13(3):421. doi: 10.3390/genes13030421.

Disease-associated inosine misincorporation into RNA hinders translation.
Schroader JH, Jones LA, Meng R, Shorrock HK, Richardson JI, Shaughnessy SM, Lin Q, Begley TJ, Berglund JA, Fuchs G, Handley MT, Reddy K.Nucleic Acids Res. 2022 Sep 9;50(16):9306-9318. doi: 10.1093/nar/gkac709.

The epitranscriptomic writer ALKBH8 drives tolerance and protects mouse lungs from the environmental pollutant naphthalene.
Leonardi A, Kovalchuk N, Yin L, Endres L, Evke S, Nevins S, Martin S, Dedon PC, Melendez JA, Van Winkle L, Zhang QY, Ding X, Begley TJ. Epigenetics. 2020 Oct;15(10):1121-1138. doi: 10.1080/15592294.2020.1750213. Epub 2020 Apr 17.

Epitranscriptomic systems regulate the translation of reactive oxygen species detoxifying and disease linked selenoproteins.
Leonardi A, Evke S, Lee M, Melendez JA, Begley TJ.Free Radic Biol Med. 2019 Nov 1;143:573-593. doi: 10.1016/j.freeradbiomed.2019.08.030. Epub 2019 Aug 30.

Lifestyle modifications: coordinating the tRNA epitranscriptome with codon bias to adapt translation during stress responses.
Chan C, Pham P, Dedon PC, Begley TJ.Genome Biol. 2018 Dec 27;19(1):228. doi: 10.1186/s13059-018-1611-1.

tRNA-mediated codon-biased translation in mycobacterial hypoxic persistence.

Chionh YH, McBee M, Babu IR, Hia F, Lin W, Zhao W, Cao J, Dziergowska A, Malkiewicz A, Begley TJ, Alonso S, Dedon PC.Nat Commun. 2016 Nov 11;7:13302. doi: 10.1038/ncomms13302.

Trm9-Catalyzed tRNA Modifications Regulate Global Protein Expression by Codon-Biased Translation.
Deng W, Babu IR, Su D, Yin S, Begley TJ, Dedon PC.PLoS Genet. 2015 Dec 15;11(12):e1005706. doi: 10.1371/journal.pgen.1005706. eCollection 2015 Dec.

Alkbh8 Regulates Selenocysteine-Protein Expression to Protect against Reactive Oxygen Species Damage.
Endres L, Begley U, Clark R, Gu C, Dziergowska A, Małkiewicz A, Melendez JA, Dedon PC, Begley TJ.PLoS One. 2015 Jul 6;10(7):e0131335. doi: 10.1371/journal.pone.0131335. eCollection 2015.

Presentation Title 2: The role of tRNA wobble modifications in stress resistance and metastasis

Speaker 2 Name / Degree(s): Elena Piskounova, PhD

Institution: Weill Cornell Medicine

Department/Division: Meyer Cancer Center

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SPEAKER 2 Abbreviated CV (maximum 300 words)

Metastasis is an inefficient process due to numerous stresses that are encountered by cancer cells at different steps of the metastatic cascade. Dr. Piskounova's postdoctoral research established that high levels of oxidative stress experienced by metastasizing cancer cells are a major barrier for metastatic colonization. Successful metastasizers undergo many different adaptations including transcriptional and metabolic rewiring to increase their antioxidant capacity. However, a rapid response to extrinsic stress requires rapid changes in protein expression through translational regulation. One of the

mechanisms that drives rapid changes in translation under oxidative stress is differential codon usage. The Piskounova lab is specifically interested in the role of distinct tRNA wobble modifications as regulators of codon-dependent translation in the context of oxidative stress resistance. These modifications increase the translational efficiency of specific transcripts with a distinct codon bias, encoding proteins critical for the cellular stress response. Dr Piskounova's laboratory has found that levels of specific tRNA modifications are increased in metastasizing cancer cells. Loss of these modifications sensitizes cancer cells to oxidative stress and blocks metastatic colonization suggesting that they regulate translation of proteins involved in the antioxidant defense. Specifically, one of these modifications occurs on the selenocysteine tRNA and regulates stress-induced translation of selenocysteine-containing proteins. Selenoproteins are central to stress resistance including oxidative and proteotoxic stress. The Piskounova lab has identified and characterized FTSJ1 as the methyltransferase that regulates this modification and enables translation of the metastatic selenoproteome. Overall, this work aims to establish how tRNA wobble modifications and a distinct codon bias reprogram the metastatic proteome as a therapeutically targetable stress response mechanism.

SPEAKER 2 Publications (maximum 10)

Selenocysteine tRNA methylation regulates stress resistance in melanoma metastasis
Nease LI, Church K, Delclaux I, Zerhouni M, Cascio G, Hughes R, Aguirre K, Lewis F, Li Z, Dow L, Dephoure N, Piskounova, E., In Review at Nature

Oxidative stress inhibits distant metastasis by human melanoma cells.
Piskounova E, Agathocleous M, Murphy MM, Hu Z, Huddlestun SE, Zhao Z, Leitch AM, Johnson TM, DeBerardinis RJ, Morrison SJ.Nature. 2015 Nov 12;527(7577):186-91. doi: 10.1038/nature15726. Epub 2015 Oct 14.

Human melanoma metastasis in NSG mice correlates with clinical outcome in patients.
Quintana E, Piskounova E, Shackleton M, Weinberg D, Eskiocak U, Fullen DR, Johnson TM, Morrison SJ.Sci Transl Med. 2012 Nov 7;4(159):159ra149. doi: 10.1126/scitranslmed.3004599.

Lin28A and Lin28B inhibit let-7 microRNA biogenesis by distinct mechanisms.
Piskounova E, Polytarchou C, Thornton JE, LaPierre RJ, Pothoulakis C, Hagan JP, Iliopoulos D, Gregory RI.Cell. 2011 Nov 23;147(5):1066-79. doi: 10.1016/j.cell.2011.10.039.

Lin28 recruits the TUTase Zcchc11 to inhibit let-7 maturation in mouse embryonic stem cells.

Hagan JP, Piskounova E, Gregory RI.Nat Struct Mol Biol. 2009 Oct;16(10):1021-5. doi: 10.1038/nsmb.1676. Epub 2009 Aug 27.

Determinants of microRNA processing inhibition by the developmentally regulated RNA-binding protein Lin28.
Piskounova E, Viswanathan SR, Janas M, LaPierre RJ, Daley GQ, Sliz P, Gregory RI.J Biol Chem. 2008 Aug 1;283(31):21310-4. doi: 10.1074/jbc.C800108200. Epub 2008 Jun 12.

ALTERNATE SPEAKER

Presentation Title Alternate: Translational regulation in stem cell fate and cancer

Alternate Speaker Name / Degree(s): Michaela Frye, PhD

Institution: DKFZ (Deutsches Krebsforschungszentrum)

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ALTERNATE SPEAKER **Abbreviated CV (maximum 300 words)**

The decision of stem cells to self-renew, proliferate or undergo differentiation is initiated by external stimuli that are linked to an intrinsic network of transcriptional, post-transcriptional and translational processes. RNA plays versatile roles in the transcription and translation of genes into proteins. To expand the function of an RNA molecule and to increase its capacity to encode information, each nucleobase can be chemically modified. To date over 150 chemical modifications are known in RNA. Many RNA modifications are functionally indispensable for protein translation because they regulate messenger RNA stability and splicing as well as protein translation efficiency and accuracy. One of the most common chemical RNA modification is methylation. Cytosine-5 RNA methylation for instance, is mediated by a large group of evolutionary conserved enzymes. The correct deposition of a methyl mark at cytosines is required for normal development and aberrant RNA methylation can lead to severe human diseases. Using a combination of novel transcriptome-wide

quantitative analyses and well-established mouse and human in vitro and in vivo differentiation models, the Frye group dissects the roles of RNA methyltransferases and their methylated target RNAs in normal development, human disease and cancer.

ALTERNATE SPEAKER **Publications (maximum 10)**

Mitochondrial RNA modifications shape metabolic plasticity in metastasis.
Delaunay S, Pascual G, Feng B, Klann K, Behm M, Hotz-Wagenblatt A, Richter K, Zaoui K, Herpel E, Münch C, Dietmann S, Hess J, Benitah SA, Frye M. Nature. 2022 Jul;607(7919):593-603. doi: 10.1038/s41586-022-04898-5. Epub 2022 Jun 29.

Sequence- and structure-specific cytosine-5 mRNA methylation by NSUN6.
Selmi T, Hussain S, Dietmann S, Heiß M, Borland K, Flad S, Carter JM, Dennison R, Huang YL, Kellner S, Bornelöv S, Frye M. Nucleic Acids Res. 2021 Jan 25;49(2):1006-1022. doi: 10.1093/nar/gkaa1193.

RNA modifications regulating cell fate in cancer.
Delaunay S, Frye M.Nat Cell Biol. 2019 May;21(5):552-559. doi: 10.1038/s41556-019-0319-0. Epub 2019 May 2.

Stem cell function and stress response are controlled by protein synthesis.
Blanco S, Bandiera R, Popis M, Hussain S, Lombard P, Aleksic J, Sajini A, Tanna H, Cortés-Garrido R, Gkatza N, Dietmann S, Frye M. Nature. 2016 Jun 16;534(7607):335-40. doi: 10.1038/nature18282.