BIOGRAPHICAL SKETCH

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NAME: GREEN, RACHEL

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

POSITION TITLE: Bloomberg Distinguished 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
University of Michigan, Ann Arbor, MI	BS	1986	Chemistry
Harvard University, Cambridge, MA	PHD	1992	Biological Chemistry
University of California, Santa Cruz, CA	Postdoctoral Fellow	1998	Biochemistry

A. Personal Statement

My laboratory has studied the molecular mechanism of translation for the past 20 years. While our initial focus had been on the detailed molecular mechanics of the various steps of elongation in bacterial translation using pre-steady state kinetic approaches, in recent years we have substantially expanded our horizons to multiple eukaryotic systems. We have established an in vitro reconstituted system for yeast translation and have defined key steps in the termination and recycling process. We have made key connections between these core events and eukaryotic mRNA quality control systems such as No-go decay (NGD) and Non-stop decay (NSD) and, more recently, Nonsense-mediated-decay (NMD). We have developed and substantially enhanced ribosome profiling methodologies for high-resolution, global analysis of translation in multiple different systems (E. coli, yeast and mammalian cells). These studies are allowing us to follow translation in live cells with unprecedented clarity thus revealing fundamental processes of translation and mRNA surveillance. Our ribosome profiling projects are synergizing beautifully with ongoing mechanistic biochemistry and will serve as our core strength for the foreseeable future. An excellent example of this synergy is found in our recent publication defining the role of an essential elongation factor (eIF5A) using in vitro biochemistry and ribosome profiling. In addition to our studies in yeast, we have recently expanded our efforts to multiple projects in mammalian cells centered around the lifetime of an mRNA, mRNA surveillance, translational control and questions related to ribosome homeostasis. My principle role for the laboratory is in guiding the general focus of the group, looking at data and guiding subsequent experiments, in helping those in the lab to see synergies where they exist, and in communicating our work to the outside world.

1. Mills EW, Green R. Ribosomopathies: There's strength in numbers. Science. 2017 Nov 3;358(6363)PubMed PMID: 29097519.
2. Schuller AP, Green R. The ABC(E1)s of Ribosome Recycling and Reinitiation. Mol Cell. 2017 Jun 1;66(5):578-580. PubMed PMID: 28575655.
3. Young DJ, Guydosh NR, Zhang F, Hinnebusch AG, Green R. Rli1/ABCE1 Recycles Terminating Ribosomes and Controls Translation Reinitiation in 3'UTRs In Vivo. Cell. 2015 Aug 13;162(4):872-84. PubMed PMID: 26276635; PubMed Central PMCID: PMC4556345.
4. Shoemaker CJ, Eyler DE, Green R. Dom34:Hbs1 promotes subunit dissociation and peptidyl-tRNA drop-off to initiate no-go decay. Science. 2010 Oct 15;330(6002):369-72. PubMed PMID: 20947765; PubMed Central PMCID: PMC4022135.

B. Positions and Honors

Positions and Employment

1982 - 1986 B.S., University of Michigan, Honors in Chemistry, Ann Arbor, MI

1984 - 1986 Undergraduate Researcher, University of Michigan, Chemistry , Synthesis of heterocyclic anti-filarial compounds, Ann Arbor, MI

1986 - 1992	Ph.D., Harvard University, Biological Chemistry, Thesis: An In Vitro Genetic Analysis of the Group I Self-splicing Intron, Cambridge, MA
1993 - 1998	Post-doctoral Fellow, University of California, Santa Cruz, Biochemistry, Santa Cruz, CA
1998 - 2003	Assistant Professor, Johns Hopkins University School of Medicine, Molecular Biology and Genetics, Baltimore, MD
2000 - 2005	Assistant Investigator, Howard Hughes Medical Institute, Johns Hopkins University School of Medicine, Baltimore, MD
2003 - 2007	Associate Professor, Johns Hopkins University School of Medicine, Molecular Biology and Genetics, Baltimore, MD
2005 -	Investigator, Howard Hughes Medical Institute, Johns Hopkins University School of Medicine, Baltimore, MD
2007 -	Professor, Johns Hopkins University School of Medicine, Molecular Biology and Genetics, Baltimore, MD
2017 -	Bloomberg Distinguished Professor, Johns Hopkins University School of Medicine and Krieger School of Arts and Sciences, Baltimore, MD

Other Experience and Professional Memberships

2007 -	Editorial Board, Molecular Cell
2007 -	Editorial Board, RNA Journal
2008 - 2009	Editorial Board, Journal of Biology
2010 - 2014	Board of Directors, RNA Society
2011 - 2012	chair, NIH Study Section MGA
2011 - 2012	Chair, NIH Study Section MGA
2012 -	Member, National Academy of Sciences
2012 - 2013	President, RNA Society
2014 -	BRE, eLife
2014 -	Board of Advisors, NCCBI-NLM
2015 -	Member, Director Search Committee, NCI-Frederick
2016 -	Member, Moderna Therapeutics Scientific Advisory Board
2017 -	Member, National Academy of Medicine
2017 -	Chair, Damon Runyon Post-doctoral Fellowship Committee
2018 -	Member, Stowers Institute Board of Directors

Honors

1982 - 1986	Undergraduate Academic Scholarships, University of Michigan
1987 - 1990	Predoctoral Fellowship, National Science Foundation
1993 - 1996	Damon Runyon Walter Winchell Postdoctoral Fellowship, Damon Runyon Foundation
1996 - 2001	Burroughs Wellcome Career Award, Burroughs Wellcome Foundation
1996	Postdoctoral Fellowship, American Cancer Society, California Division
1999	RPI/RNA Award for Young Scientists, RPI/RNA
1999 - 2002	Searle Scholarship Award, Searle Foundation
2000	David and Lucile Packard Fellowship Award, Packard Foundation
2000	Howard Hughes Medical Institute Assistant Investigator Award, Howard Hughes Medical Institute
2005	Teacher of the Year, Johns Hopkins University, School of Medicine
2012	Elected Member, National Academy of Sciences
2017	Elected member, National Academy of Medicine

C. Contribution to Science

1. Mechanistic studies of core events in translation in bacteria: High-resolution structures of the ribosome were first published as I began as a faculty member at Johns Hopkins. A core focus of my group during the

first 10 years was on defining the molecular mechanisms of the fundamental steps in translation elongation and termination. Using pre-steady state kinetics and approaches to purify mutant ribosomes from E. coli, we made substantial contributions to defining the role of universally conserved nucleotides in the peptidyl transferase and decoding centers of the ribosome. We continue to use this high-resolution biochemical system to explore features of translation elongation, termination and recycling and quality control mechanisms that modulate these steps. Additionally, in collaboration with a senior scientist in my group, Allen Buskirk, we are using ribosome profiling approaches to complement our biochemistry; as in eukaryotes, we find the synergy to be powerful.

a. Cochella L, Brunelle JL, Green R. Mutational analysis reveals two independent molecular requirements during transfer RNA selection on the ribosome. Nat Struct Mol Biol. 2007 Jan;14(1):30-6. PubMed PMID: 17159993.
b. Cochella L, Green R. An active role for tRNA in decoding beyond codon:anticodon pairing. Science. 2005 May 20;308(5725):1178-80. PubMed PMID: 15905403; PubMed Central PMCID: PMC1687177.
c. Woolstenhulme CJ, Guydosh NR, Green R, Buskirk AR. High-precision analysis of translational pausing by ribosome profiling in bacteria lacking EFP. Cell Rep. 2015 Apr 7;11(1):13-21. PubMed PMID: 25843707; PubMed Central PMCID: PMC4835038.
d. Youngman EM, Brunelle JL, Kochaniak AB, Green R. The active site of the ribosome is composed of two layers of conserved nucleotides with distinct roles in peptide bond formation and peptide release. Cell. 2004 May 28;117(5):589-99. PubMed PMID: 15163407.

2. Discovery of post-peptidyl transfer quality control in bacteria: In biochemical studies that grew from our exploration of core events in translation elongation, we discovered a novel and wholly unanticipated form of quality control during protein synthesis in bacteria. In brief, ribosomes that incorporate errors during elongation or frame-shifting are recognized as aberrant, and a premature termination reaction is triggered. This unusual event depends specifically on a non-essential translational GTPase, RF3, which appears to be specifically involved in this quality control event. More detailed biochemical studies defined the mechanism by which the fidelity of termination (and elongation) is sensed and modulated, thus further informing us on the molecular mechanisms of decoding on the ribosome. The process of discovery for this project was perhaps the most exciting of my scientific career.

a. Zaher HS, Green R. A primary role for release factor 3 in quality control during translation elongation in Escherichia coli. Cell. 2011 Oct 14;147(2):396-408. PubMed PMID: 22000017; PubMed Central PMCID: PMC3415990.
b. Zaher HS, Green R. Kinetic basis for global loss of fidelity arising from mismatches in the P-site codon:anticodon helix. RNA. 2010 Oct;16(10):1980-9. PubMed PMID: 20724456; PubMed Central PMCID: PMC2941106.
c. Zaher HS, Green R. Quality control by the ribosome following peptide bond formation. Nature. 2009 Jan 8;457(7226):161-6. PubMed PMID: 19092806; PubMed Central PMCID: PMC2805954.

3. Biochemical characterization of ribosome rescue in eukaryotes: During the past 10 years we have established an in vitro reconstituted translation system with S. cerevisiae components to probe eukaryotic ribosome function. Our first major discovery identified a novel role for the proteins Dom34 and Hbs1 (homologs of eRF1 and eRF3, respectively) in a codon-independent subunit splitting reaction. Subsequent biochemical studies with the ATPase Rli1 demonstrated that Dom34:Hbs1 and eRF1:eRF3 work together with Rli1 to promote rescue (on aberrant mRNAs) and recycling (on normal stop codons). We have recently developed high throughput sequencing methodologies for classic chemical modification protection approaches (DMS-Seq and BABE-Seq) and have met with considerable success. These initial insights into the function of quality control factors on the ribosome motivated many subsequent and ongoing studies with other factors having potential roles on the ribosome including Upf1, eIF5A, PABP, Asc1, and others. This in vitro reconstituted system will remain a core feature of ongoing studies in our lab aimed at deciphering molecular mechanisms of translation.

a. Koutmou KS, Schuller AP, Brunelle JL, Radhakrishnan A, Djuranovic S, Green R. Ribosomes slide on lysine-encoding homopolymeric A stretches. Elife. 2015 Feb 19;4PubMed PMID: 25695637; PubMed Central PMCID: PMC4363877.

b. Schuller AP, Green R. The ABC(E1)s of Ribosome Recycling and Reinitiation. Mol Cell. 2017 Jun 1;66(5):578-580. PubMed PMID: 28575655.

c. Schuller AP, Zinshteyn B, Enam SU, Green R. Directed hydroxyl radical probing reveals Upf1 binding to the 80S ribosomal E site rRNA at the L1 stalk. Nucleic Acids Res. 2017 Dec 14;PubMed PMID: 29253221.

d. Shoemaker CJ, Green R. Kinetic analysis reveals the ordered coupling of translation termination and ribosome recycling in yeast. Proc Natl Acad Sci U S A. 2011 Dec 20;108(51):E1392-8. PubMed PMID: 22143755; PubMed Central PMCID: PMC3251084.

4. Ribosome profiling to define mechanisms of ribosome rescue in living cells: High throughput methods emerged in a seminal paper by Ingolia and Weissman in 2012 as a method to observe the action of ribosomes in living cells with codon level resolution. We are using ribosome profiling to address a wide range of mechanistic questions centered around translation and its control. In a series of publications during the past 5 years, we have used ribosome profiling to explore the roles of various recycling and rescue factors in multiple different systems including E. coli, S. cerevisiae, S. pombe and mammalian cells. Together, these studies have defined in vivo roles for several factors (including Dom34, Hbs1 and Rli1) in unstressed and stressed cells and have defined the pathways for mRNA degradation involved in NGD and NSD. More recently, these studies have guided us to thinking more broadly about ribosome homeostasis in yeast and in mammalian systems where we continue to use our much improved ribosome profiling methodologies. These broad approaches will serve as a core feature of our work for the foreseeable future.

   a. Guydosh NR, Kimmig P, Walter P, Green R. Regulated Ire1-dependent mRNA decay requires no-go mRNA degradation to maintain endoplasmic reticulum homeostasis in S. pombe. Elife. 2017 Sep 25;6PubMed PMID: 28945192; PubMed Central PMCID: PMC5650469.

   b. Mills EW, Wangen J, Green R, Ingolia NT. Dynamic Regulation of a Ribosome Rescue Pathway in Erythroid Cells and Platelets. Cell Rep. 2016 Sep 27;17(1):1-10. PubMed PMID: 27681415; PubMed Central PMCID: PMC5111367.

   c. Woolstenhulme CJ, Guydosh NR, Green R, Buskirk AR. High-precision analysis of translational pausing by ribosome profiling in bacteria lacking EFP. Cell Rep. 2015 Apr 7;11(1):13-21. PubMed PMID: 25843707; PubMed Central PMCID: PMC4835038.

   d. Young DJ, Guydosh NR, Zhang F, Hinnebusch AG, Green R. Rli1/ABCE1 Recycles Terminating Ribosomes and Controls Translation Reinitiation in 3'UTRs In Vivo. Cell. 2015 Aug 13;162(4):872-84. PubMed PMID: 26276635; PubMed Central PMCID: PMC4556345.

Complete List of Published Work in My Bibliography:
http://1.usa.gov/1lB5xwg

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

R37 GM059425-15
GREEN, RACHEL (PI)
05/01/99-08/31/19
Molecular mechanisms of ribosome pausing and the cellular response
Role: PI

U54 GM105816-04
ELCOCK, ADRIAN Hamilton (PI)
06/10/13-04/30/18
Interactions Regulating Translation and Protein Biogenesis in Vivo
Role: PI

N/A, Howard Hughes Medical Institute
GREEN, RACHEL (PI)
09/01/00-01/01/20
Molecular Mechanisms of Translation and Their Implications for Gene Regulation
This source of funding supports the remainder of work in the Green laboratory including studies in E. coli, in human tissues (platelets and tissue culture cells) and in yeast, aimed at deciphering molecular mechanisms of translation elongation, termination and recycling. We also work broadly on translational control by proteins such as Dhh1 in yeast, and how this relates to miRNA-mediated translational repression in higher eukaryotes. Again, biochemistry and ribosome profiling are synergistically allowing us to adress increasingly sophisticated questions about the ribosome function in these systems.
Role: PI

124760, Cystic Fibrosis Foundation
GREEN, RACHEL (PI)
11/01/16-10/31/18
Defining readthrough drug specificity for CF therapeutic development
Mutations in the CFTR gene are known to cause cystic fibrosis (CF), and nonsense mutations in CFTR have few available therapeutic options. We aim to study a class of drugs known as nonsense-suppression therapeutics to treat this class of mutations. These drugs force the ribosome to "read through" nonsense mutations thereby ignoring the early termination signal and producing a functional protein. By studying how these drugs force the ribosome to read-through nonsense mutations and if these drugs interact directly with the ribosome, we anticipate knowledge gained from this study can direct personalized treatment of nonsense mutations in CF.
Role: PI

Completed Research Support

R01 GM059425-13
GREEN, RACHEL (PI)
05/01/99-08/31/14
The role played by the RNAs and tRNAs in translation
Role: PI

R01 GM062128-13
GREEN, RACHEL (PI)
09/11/00-03/31/14
Kinetic Dissection of Eukaryotic Translation Initiation
Role: PI