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: Kathleen J. Green

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

POSITION TITLE: Joseph L. Mayberry Professor of Pathology Professor of Dermatology

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
Pomona College, Claremont, CA.	B.A.	1977	Biology
Washington University, St. Louis, MO.	Ph.D.	1982	Cell, Dev. Biol.
Northwestern Univ. Med. School, Chicago, IL	Post-Doc	1987	Cell, Mol. Biol.

A .Personal Statement. The goal of my laboratory is to elucidate the roles of cadherin adhesion receptors in tissue morphogenesis, differentiation and cancer. I have over thirty years of experience in defining functions of cell-cell junctions called desmosomes, which anchor intermediate filaments at sites of strong cell-cell adhesion to maintain tissue integrity, particularly in skin and heart. We were the first to recognize the existence of the plakin family and one of the first to demonstrate that desmogleins belong to the cadherin superfamily of cell-cell adhesion receptors. Our adaptation of live cell and high-resolution optical imaging techniques revealed important aspects of desmosome structure and trafficking dynamics. We showed that in addition to their critical role in adhesion, desmosomes serve as signaling scaffolds that dictate cell behavior and promote stratification and differentiation of complex tissues. Our recent work indicates that one of these adhesion receptors, desmoglein 1, controls keratinocyte cytokine expression and regulates paracrine signaling between different cell types in the epidermis, including melanocytes. We use in vitro, 3D organotypic and in vivo (mouse and human) models of epidermal differentiation, cardiac disease and melanoma initiation and progression to address how these novel functions control tissue development and disease progression. I am currently Director of the Skin Tissue Engineering and Morphology Core that provides standardized materials, methods, service and training for investigators who use skin cell cultures and engineered skin tissue. I also serve as Associate Director for Research in the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

Training and Mentorship: I have had longstanding leadership roles in training programs at Northwestern University. I am PI of a National Cancer Institute-funded T32 in Carcinogenesis that has been the primary source of funding for advanced Ph.D. training in cancer biology at Northwestern for the past 30 years. I previously served as PI of a NIAMS T32 that supports postdoctoral trainees in Cutaneous Biology. I currently serve as Co-Director of the Cancer Biology Cluster of the Northwestern University Life and Biological Sciences Ph.D. Program. As Associate Director for Basic Sciences in the R.H. Lurie Comprehensive Cancer Center, I am actively involved in developing cancer-related programs that contribute to enrichment and career development activities. With respect to mentoring in the laboratory, I have 30 years of experience training predoctoral students (>20 Ph.D. students), postdoctoral fellows and research track faculty (>25 postdoctoral fellows/research track faculty), a number who have gone on to establish independent NIH-funded research programs. 14 are in academic faculty positions and most others are doing research in an industry or academic medicine setting. Mentees in the Green lab have been awarded 25 fellowships/career development awards to support their research.

B. Positions and Honors.

Positions

1987-1993 Asst. Prof., Dept. of Pathology, Northwestern University, Chicago, IL
1993-1997 Assoc. Prof., Depts. of Pathology and Derm., Northwestern University, Chicago, IL

1997-present Prof., Pathology and Dermatology, Northwestern University, Chicago, IL

2009-present Director/Co-Director, Northwestern University Skin Disease Research Center Skin Tissue Engineering and Morphology Core

2014-current Associate Director for Basic Sciences, RH Lurie Comprehensive Cancer Center

Honors

1977	Phi Beta Kappa
1988-91	March of Dimes Basil O'Connor Award
1990-93	Am. Cancer Soc. Junior Faculty Research Award/Faculty Research Award (93-98)
1992/94	Gordon Research Conference- Intermediate Filaments (Vice-Chair 1992; Chair 1994)
1992-94	J&J Focused Giving Award
1999	Fellow of the AAAS
2001	Keith Porter Fellow
2001/03	Gordon Conference on Epithelial Differentiation (Vice-Chair, 2001, Chair, 2003)
2002	William Montagna Lecturer, Society for Investigative Dermatology
2006	Tanioku Kihei Lectureship, Japanese Society for Investigative Dermatology
2010	President -Society for Investigative Dermatology
2011	Distinguished Woman in Medicine and Science-Northwestern University (2011)
2012-17	Secretary, American Society for Cell Biology
2012	Martin and Gertrude Walder Award for Research Excellence
2014	Faculty Engagement Award-The Graduate School
2015	Kligman Frost Leadership Award-The Society for Investigative Dermatology
2015-16	Alexander von Humboldt Research Award
2016	Elected into the German National Academy of Sciences (Leopoldina).
2018	25th David Martin Carter Mentor Award, American Skin Association
2019	*Tripartite Legacy Faculty Prize in Translational Science and Education (to be awarded 4/4/19)*

Selected Leadership, Peer Review and Editorial:

1995-00	NIH, GMA1 Study Section, Member (1995-00) and Chair (1998-00)
2001-06, 09-11	SID Board of Directors
2002-cur	Editor/Deputy Editor in Chief- Journal of Cell Science
2002-cur	Associate Editor/Editorial Consultant- Journal of Investigative Dermatology
2004-05	American Society for Cell Biology (ASCB) Program Committee
2006	ASCB-E.B. Wilson Award Selection Committee
2007-10	National Institute of Arthritis, Musculoskeletal and Skin Disease Advisory Council.
2008-11;12-17	American Society for Cell Biology- Council and Secretary (12-17)
2014-18	ACTS Study Section Member and Chair (2016-18).

C. Contribution to Science (Total 185 publications; 130 peer-reviewed).

Desmoplakin Structure and Function: Insights into Human Disease: During the early 90's my lab cloned and characterized several core desmosome molecules. Analysis of the one of these, the intermediate filament (IF) anchoring protein desmoplakin, led us to recognize the existence of a gene family, now known as "plakins", members of which have widespread functions in organizing the cytoskeleton. Later, we collaborated with William Weis (Stanford) to determine the high-resolution crystal structure of the desmoplakin intermediate filament (IF) binding domain, the first for an IF-associated protein. These findings provided a foundation for a series of studies that provided experimental demonstration for functions of desmoplakin domains and their binding partnerships (e.g. for plakophilins). Work from our lab facilitated the identification of the first of many mutations resulting in disorders that have been dubbed "Desmoplakinopathies", including perinatal lethal skin disease caused by a virtual loss of desmoplakin protein. Our work demonstrated for the first time the importance of the IF-desmosome link in regulating tissue mechanics.

1. Choi, H-J, S. Park-Snyder, L.T. Pascoe, **K.J. Green** and W.I. Weis. (2002). Structures of two fragments of the intermediate filament binding protein desmoplakin reveal a unique repeat motif structure. *Nature Struct. Biol.* 9 612-620, pub online July 8, 2002. (*highlighted in. News & Views*).
2. Huen, A.C., J.K. Park, X. Chen, L.M. Godsel, L.J. Bannon, E.V. Amargo, T.Y. Hudson, A.K. Mongiu, I.M. Leigh, D.P. Kelsell, B.M. Gumbiner, and **K.J. Green**. (2002). Intermediate filament-membrane attachments function synergistically with actin-dependent contacts to regulate adhesive strength. *J. Cell Biol.* 159: 1005-1018. (cited in *Faculty 1000*)

3. Dubash, A.D.*, C.Y. Kam*, B. Aguado, D. Patel, M. Delmar, L. Shea and **K.J. Green** (2016). Plakophilin-2 loss promotes TGF-β1/p38 MAPK-dependent fibrotic gene expression in cardiomyocytes. *J. Cell. Biol.* 212: 425-38. PMC4754716. * Equal contribution.
4. Broussard, J.A., R. Yang, C. Huang, SSP. Nathamgari, A.M. Beese, S L.M. Godsel, M. H. Hegazy, S. Lee, F. Zhou, N.J. Sniadecki, **K.J. Green***, and H.D. Espinosa* (2017) The desmoplakin/intermediate filament linkage regulates cell mechanics. *Mol. Biol. Cell.* 28: 3156-64. *Co-corresponding authors. PMC5687018.

The desmosomal cadherin, desmoglein 1, as a signaling scaffold in epidermal morphogenesis and disease: We showed that in addition to playing a critical role in adhesion, desmosomal cadherins serve as scaffolds for signaling and cytoskeletal remodeling to promote the morphogenesis and differentiation of complex tissues. For instance, desmoglein 1 (Dsg1), attenuates EGFR and MAPK signaling to promote epidermal differentiation by interfering with Ras-Raf coupling through its association with an ERBIN-Shoc2 complex. At the same time Dsg1 scaffolds an actin remodeling complex to promote cell delamination from the underlying matrix and thus formation of a multi-layered stratified tissue. With geneticist Eli Sprecher we showed that loss of Dsg1 in patients with the skin disorder Striate Palmoplantar Keratoderma (SPPK) have elevated MAPK signaling associated with increased proliferation and loss of differentiation. This work has implications for understanding "RASopathies" associated with cutaneous defects as well as a common malignant skin tumor, basal cell carcinoma. Along with Dr. Sprecher, we reported a new disease entity termed SAM syndrome "Severe dermatitis, multiple Allergies and Metabolic wasting" caused by loss of membrane-associated Dsg1. This disease is associated with loss of cell-cell adhesion and barrier function, but also increased expression of genes encoding allergy/inflammation-related cytokines. Using an in vitro model we can recapitulate the observed increases in cytokine expression, indicating that this may be a cell autonomous function of Dsg1. This work provides the premise for our studies in the role of desmoglein 1 in regulating paracrine signaling, including in the tumor microenvironment.

1. Harmon, R.M., C.L. Simpson, J.L. Johnson, J.L. Koetsier, A. Dubash, N. Najor, O. Sarig, E. Sprecher, and **K.J. Green** (2013). Desmoglein-1/Erbin interaction suppresses Erk activation to support epidermal differentiation. *J. Clin. Invest.* 123: 1556-70. PMC3613912. (*Commentary by Hammers, C.M. and J.R. Stanley. Desmoglein-1, differentiation, and disease. Highlighted in F1000)*
2. Samuelov, L., O. Sarig R.M. Harmon, D. Rapaport, A. Ishida-Yamamoto, O. Isakov, J.L. Koetsier, A.Gat, I. Goldberg, R. Bergman, R. Spiegel, O. Eytan, S. Geller, S. Peleg, N. Shomron, C.S.M. Goh, N. J. Wilson, F.J.D. Smith, E. Pohler, M.A. Simpson, W.H. I. McLean, A.D. Irvine, M. Horowitz, J.A. McGrath, **K.J. Green*** and E. Sprecher*. (2013). Desmoglein 1 membranal deficiency results in severe dermatitis, multiple allergies and metabolic wasting. *Nat. Genet*. 45: 1244-8. (*Co-corresponding authors). PMC in process. (*Recommended in F1000.)* PMC3791825.
3. Nekrasova, O., R.M. Harmon, J.A. Broussard, J.L. Koetsier, L.M. Godsel, G.N. Fitz, M. Gardel and **K.J. Green**. (2018). Desmosomal cadherin association with Tctex-1 and cortactin-Arp2/3 drives perijunctional actin polymerization to promote keratinocyte delamination. *Nat. Commun.* 9 (1): 1053. Doi: 10.1038/s41467-018-03414-6. PMC5849617.
4. Polivka, L., S. Hadj-Rabia, E. Bal, S. Leclerc-Mercier, M. Madrange, Y. Hamel, D. Bonnet, S. Mallet, H. Lepidi, C. Ovaert, P. Barbet, C. Dupont, B. Neven, A. Munnich, L.M. Godsel, F. Campeotto, R. Weil, E. Laplantine, S. Marchetto, J.P. Borg, W.I. Weis, J-L. Casanova, A. Puel, **K.J. Green,** C. Bodemer and A. Smahi. (2018). Epithelial barrier dysfunction in desmoglein-1 deficiency. *J. Allergy Clin. Immunol*. 142: 702-706. PMC6078820.

Intercellular Junction Assembly and Dynamics in Homeostasis and Disease: Our lab advanced the use of optical imaging methods to evaluate desmosome dynamics in living cells, and to establish how these dynamics are altered by human disease mutations and in tumor cells to mediate functional differences in adhesion strengthening. We determined that in keratinocytes, desmogleins and desmocollins traffic independently on microtubules via kinesin-1 and -2 respectively, towards sites of cell-cell contact. The plaque components that associate with the cytoplasmic tails of the cadherins, on the other hand, are assembled into non-membrane bound precursors that translocate in an actin-dependent manner to sites of junction assembly where they associate through plakophilins with the transmembrane complex. Using a combination of imaging and biochemistry, we determined how inherited mutations in desmosome molecules cause human skin and heart disease, including Arrhythmogenic Cardiomyopathy (AC), which causes sudden death in young individuals. We identified the microtubule (MT) plus tip protein, end binding protein 1 (EB1), as a novel binding partner of the desmoplakin N-terminus, a "hot spot" for disease causing mutations. Mutations in this region interfere with EB1 binding, resulting in a loss of MT cortical capture and a failure to form gap junctions. More recently, we identified

a novel mechanism by which desmoplakin regulates the post-translational stability of connexin 43, by dampening Ras/MAPK-dependent phosphorylation, ubiquitination and turnover of connexin 43. We could restore gap junction communication in desmoplakin mutant cardiac myocytes with a novel Ras inhibitor being developed clinically by our collaborator Karla Satchell. We also identified arginine methylation as a novel posttranslational modification in the IF binding domain of desmoplakin. We showed that phosphoserines generated because of processive phosphorylation via GSK3beta cooperate with arginines to recruit kinases and methyltransferases critical for regulating desmoplakin's dynamic association with IF. An AC mutation in one of these sites interferes with DP's dynamic association with IF, delaying its assembly into desmosomes, and leading to features of AC in a transgenic mouse model. These data implicate desmoplakin as a signaling scaffold that positions and regulates the activities of enzymes important for junction dynamics and, more broadly, cell behavior in remodeling tissues.

1. Nekrasova, O.E., E.V. Amargo, Smith, W.O. Smith, J. Chen, G.E. Kreitzer, and **K.J. Green.** (2011). Desmosomal cadherins utilize distinct kinesins for assembly into desmosomes. *J. Cell Biol.* 195: 1185-203. PMC3246898. *(Highlighted in Biosights video: "A Twin-Track Approach to Building Desmosomes" http://jcb.rupress.org/content/195/7/1185/suppl/DC2; featured in Journal Club http://jcb.rupress.org/content/195/7/1185/suppl/DC3).*
2. Patel, D, A. Dubash, and G. Kreitzer and **K.J. Green** (2014). Disease mutations in desmoplakin inhibit Cx43 membrane targeting mediated by desmoplakin-EB1 interactions. *J. Cell Biol.* 206: 779-97. *(Featured in JCB Biobytes).* PMC4164953
3. Albrecht, L.V., L. Zhang, J. Shabanowitz, E. Purevjav, J.A. Towbin, D.F. Hunt, and **K.J. Green**. (2015). Methylation-mediated modulation of desmoplakin-cytoskeletal interactions and cardiocutaneous disease. *J. Cell Biol.* 208: 597-612. (Cover photo; highlighted in "In this Issue". Desmoplakin's tail gets the message. *J. Cell Biol.* 2015. 208: 494.) PMC4347645
4. Kam, C.Y., A.D. Dubash, E. Magistrati, S. Polo, K.J.F. Satchell, F. Sheikh, P.D. Lampe, **K.J. Green**. Desmoplakin maintains gap junctions by inhibiting Ras/MAPK and lysosomal degradation of connexin-43. (2018). *J. Cell Biol.* 217: 3219-3235. doi: 10.1083/jcb.201710161. Featured in: http://news.feinberg.northwestern.edu/2018/08/mechanisms-driving-inherited-heart-disease/

Desmosomes and Cancer: While the role of classic cadherins in both promoting and suppressing tumor progression has been well-studied, less is known about how desmosomes participate in tumor growth or metastasis. Our work has shown that in head and neck cancer, desmosomal cadherins participate in bi-directional signaling with receptor tyrosine kinases. While Dsg1 suppresses MAPK signaling to promote differentiation, EGFR elevates desmosomal cadherin endocytosis and turnover in tumor cells to attenuate cadherin signaling functions, reduce adhesion strength and promote migration. The loss of Dsg1 in cancers of the head and neck has been associated with poor patient prognosis, possibly due to loss of its functions in promoting differentiation and suppressing cytokine production. UV exposure specifically reduces expression of Dsg1, but not E-cadherin or other desmosomal cadherins, associated with reduced binding of p63 to previously undescribed enhancer regions in the Dsg1 gene. The resulting shift away from differentiation may create an environment permissive for progression of SCCs and melanoma. The desmosomal armadillo proteins plakoglobin, PKP2 and PKP3 also participate in regulation of cell motility and adherens junction assembly status in tumor cells, through regulation of tyrosine kinase and small Rho GTPases.

1. Klessner, J.*, B. Desai*, E.V. Amargo, S. Getsios and **K.J. Green**. (2009) EGFR and ADAM17 Cooperate to Regulate Shedding and Endocytic Trafficking of the Desmosomal Cadherin Desmoglein 2. *Mol. Biol. Cell.* 20(1):328-37 **Authors contributed equally to this work.*
2. Johnson J, Koetsier J, Sirico A, Agidi A, Antonini D, Missero C, **Green KJ.** (2014) The desmosomal protein desmoglein 1 aids recovery of epidermal differentiation after acute ultraviolet light exposure. *J. Invest. Derm.* 134: 2154-62. PMC4102640.
3. Najor, N.A., G.N. Fitz, J.L. Koetsier, L.M. Godsel, L.V. Albrecht, R.M. Harmon, and **K.J. Green**. (2017). Epidermal growth factor receptor neddylation is regulated by a desmosomal-COP9 (constitutive photomorphogenesis 9) signalosome complex. *Elife.* DOI:10.7554/eLife.22599. PMC5663478.
4. Valenzuela-Iglesias, A., H.E. Burks, C.R. Arnette, A. Yalamanchili, O. Nekrasova, L.M. Godsel, and **K.J. Green.** (2019). Desmoglein 1 regulates invadapodia by suppressing EGFR/Erk singaling in an erbin-dependent manner. *Mol. Cancer Res.* Jan. 17. Doi: 10.1158/1541-7786. MCR-18-0048. [Epub ahead of print].

Link to My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/kathleen.green.1/bibliography/40768970/public/?sort=date&direction=ascending

D. Research Support

R37 (MERIT) AR043380-21 (Green, PI) 4/1/11 - 3/31/21
Desmoplakin Assembly and Function in Epidermis
The goals of this project are to determine how the DP C-terminal "signaling hub" regulates IF binding, adhesion and differentiation, determine how desmosomes orchestrate keratinocyte differentiation and assembly of junctional complexes through RhoGEFs, and to define role of desmosome-IF interactions in mechanotransduction and regulation of the contractile actin machinery.

R01 AR041836-24 (Green, PI) 09/01/17 - 08/31/22
Function of Desmoglein 1/Pemphigus Foliaceus Antigen
The major goals of this project are to determine the mechanism of Dsg1 targeted delivery the plasma membrane, elucidate the contribution of Dsg1 to a mechanosensitive cortical cytoskeleton required for epidermal morphogenesis and barrier formation, and determine how Dsg1 works with Erbin to promote epidermal differentiation by dampening EGFR signaling.

R01 CA228196 (Green, PI) 12/01/18-11/30/23
Role of Desmoglein 1 in Keratinocyte-Melanocyte Communication and Melanoma The goals of this project are to determine how desmoglein 1 loss in KCs alters MC behavior through paracrine signaling and to establish how a desmoglein-deficient KC:MC unit is established and promotes melanomagenesis. *(Slated for funding 12/18).*

Liz and Eric Lefkofsky Innovation Research Awards (Green, PI) 03/01/17 – 5/30/19
Surrounded by Bad Neighbors: Do Keratinocyte "Cancerization Fields" Promote Melanoma Development?
Major goals are to test the concept that alterations in perilesional keratinocytes will be predictive of pigmented nevi that are likely to convert to malignant melanoma, and to understand the biology underlying this conversion.

R01 AR044016-2 (Troyanovsky, PI) 9/1/16 - 7/31/21
Inter-junctional signaling in epithelial junctional complex
The goal of this proposal is to determine the mechanisms coordinating different adhesive structures in the epithelial junctional complex. It will test our hypothesis that the changes of the cytoskeleton induced by adherens junctions trigger formation of tight junctions, nectin junctions, and desmosomes. Dr. Green is Co-I of this project, which is to determine the mechanism by which remodeling of the actin cytoskeleton and its associated proteins directs the ordered assembly of nectin junctions, tight junctions and desmosomes. Role: Co-I

T32 CA009560-31 (Green, PI) 7/1/12 - 6/30/22
Carcinogenesis Training Program
The major goal of this project is to provide training for predoctoral students in investigations of the mechanisms of tumorigenesis and carcinogenesis.

P30 CA60553 (Platanias, PI) 8/1/18 - 7/31/23
The Robert H. Lurie Comprehensive Cancer Center
The goals of this Cancer Center Support Grant are to conduct and support cancer research and to integrate cancer-related research throughout the university; to coordinate and integrate cancer-related activities of the University including community outreach initiatives; to develop and conduct cancer education programs; to promote and participate in state-of-the-are care of cancer patients at the affiliated hospitals of the McGaw Medical Center of Northwestern University and; to develop and implement the initiatives in cancer prevention and control research. Role: Associate Director for Basic Sciences

P30 AR057216 (Paller, PI) 08/01/14 - 07/31/19
Northwestern Univ. Skin Disease Research Core Center
Dr. Green is the Tissue Engineering Core Co-Director (Core B), the major goal of which is to provide cells and instruction related to investigations in cutaneous biology research at Northwestern.
Role: Core B Associate Director

Completed Research Support

Leducq Foundation Jalife & Hatem (PIs) 10/1/09-9/30/15
Structural Alterations in the Myocardium and the Substrate for Cardiac Fibrillation

This Transatlantic Research Network proposes research towards improving mechanistic insight into arrhythmogenesis and ultimately developing and clinically testing novel approaches for the prevention and treatment of cardiac arrhythmias. Role: Core Member.