OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

BIOGRAPHICAL SKETCH

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

**A. Personal Statement**

### *Research:* The goal of my laboratory is to elucidate the roles of cadherin adhesion receptors in tissue morphogenesis, differentiation and cancer. I have 35 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. 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 and melanoma cells. 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. I also, serve as Associate Director for Basic Sciences in the Robert H. Lurie Comprehensive Cancer Center and Director of the Skin Tissue Engineering and Morphology Core of the Northwestern Skin Biology and Diseases Resource-based Center.

### *Training and Mentorship:* I am PI of an NCI-funded T32 in Carcinogenesis that has been the primary funding source for Ph.D. training in cancer biology at Northwestern for over 35 years. I serve as Co-Director of the Cancer Biology Cluster at Northwestern University. In addition to providing opportunities for scientific training and discourse, the Cluster nurtures student leadership skills and provides guidance to help students identify careers that are consistent with their skills and goals. In my own lab, I have 35 years of experience training predoctoral students (>20) and postdoctoral fellows and research track faculty (>30), a number who have gone on to establish independent NIH-funded research programs. 15 are in academic faculty positions (including a department chair) and most others are doing research in an industry or academic medicine setting. The 10 Ph.D. students I’ve trained over the last 15 years have published on average 2.7 first author and 6.3 total papers. My mentees have been awarded over 25 fellowships/career development awards. A major goal of both the T32 training program and my laboratory is to promote a diverse and inclusive training environment. For the Carcinogenesis T32, I brought on a Director of Diversity and created a committee that oversees DEI activities, something that did not previously exist in the program. We are proud that students from URGs appointed to the T32 went up from 9% in 2005 to 33% in 2022 and our URG trainees have gone on to faculty and leadership positions nationally. Personally, I support the program by bringing students into my lab who are part of the NCI CURE and NU SROP programs that provide opportunities for URGs to work at the bench.

### Ongoing projects I would like to highlight include:

T32 CA009560-36

Green, PI

7/15/22-7/14/27

R01 CA228196

Green (PI)

2/01/19-1/31/24

Role of Desmoglein 1 in Keratinocyte-Melanocyte Communication and Melanoma

R01 AR043380

Green (PI)

6/1/21-5/31/26

Desmoplakin Assembly and Function in Epidermis

R01 AR041836

Green (PI)

9/01/22 - 08/31/27

Function of Desmoglein 1/Pemphigus Foliaceus Antigen

Leo Foundation

Green (PI)

02/15/21 - 02/14/24

Keratinocyte contributions to inflammatory skin disease

**B. Positions, Scientific Appointments, and Honors**

***Positions***

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

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

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

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

1987-1993 Asst. Prof., Dept. of Pathology, Northwestern University, Chicago, IL

***Selected Honors***

2020 Honorary Member of the European Society for Dermatological Research

2019 Honorary Member of the Society of Investigative Dermatology

2019 Tripartite Legacy Faculty Prize in Translational Science and Education

2018 25th David Martin Carter Mentor Award, American Skin Association

2016 Elected into the German National Academy of Sciences (Leopoldina).

2015-16 Alexander von Humboldt Research Award

2014 Faculty Engagement Award-The Graduate School

2012 Martin and Gertrude Walder Award for Research Excellence

2012-17 Secretary, American Society for Cell Biology

2011 Distinguished Woman in Medicine and Science-Northwestern University

2010 President -Society for Investigative Dermatology

2006 Tanioku Kihei Lectureship, Japanese Society for Investigative Dermatology

2002 William Montagna Lecturer, Society for Investigative Dermatology

2001/03 Gordon Conference on Epithelial Differentiation (Vice-Chair, 2001, Chair, 2003)

2001 Keith Porter Fellow

1999 Fellow of the American Association for the Advancement of Science

1992/94 Gordon Research Conference- Intermediate Filaments (Vice-Chair 1992; Chair 1994)

***Selected Leadership, Peer Review and Editorial:***

2023 Associate Editor-Science Advances

2022- Deputy Editor- Journal of Investigative Dermatology (2002-present: Assoc. Ed./consult.)

2014-18 ACTS Study Section Member and Chair.

2008-11;12-17 American Society for Cell Biology- Council and Secretary (12-17)

2007-10 National Institute of Arthritis, Musculoskeletal and Skin Disease Advisory Council.

2002-present Editor/Deputy Editor in Chief- Journal of Cell Science

2001-06, 09-11 SID Board of Directors

1995-00 NIH, GMA1 Study Section, Member (1995-00) and Chair (1998-00)

**C. Contributions to Science (208 Total Publications; 148 Peer-reviewed)**

1. Desmosome-Intermediate Filament Connection and Cell/Tissue Mechanics: 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 integrating with actomyosin to regulate keratinocyte stratification through delamination, tissue mechanics and the tight junction barrier.

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. PMID: 12101406. (*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. PMC2173978. (cited in *Faculty 1000*)
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. Broussard, J.A., J.L. Koetsier, M. Hegazy and **K.J. Green**. (2021). Desmosomes polarize and integrate chemical and mechanical signaling to govern epidermal tissue form and function. *Curr. Biol.* 31: 3275-91. PMC8355090.

2. Intercellular Junction 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 differentiation-dependent epidermal cadherin, desmoglein 1 (Dsg1) was recently shown to be a cargo for the endosomal recycling complex, the retromer, which is required for positioning on the plasma membrane to promote keratinocyte stratification. Small molecule retromer chaperones were demonstrated to improve the trafficking and function of a human disease associated Dsg1 mutant causing SAM syndrome “Severe dermatitis, multiple Allergies and Metabolic wasting” , raising the possibility that these compounds could be beneficial clinically. 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. We 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 enzymes 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, 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. Godsel, L.M., S.N. Hsieh, E.V. Amargo, A.E. Bass, L.T. Pascoe-McGillicuddy, A.C. Huen, M.E. Thorne, C.A. Gaudry, J.K. Park, K. Myung, R.D. Goldman, L. Chew, and **K.J. Green**. (2005). Desmoplakin assembly dynamics in 4D: multiple phases differentially regulated by intermediate filaments and actin. *J. Cell Biol.* 171: 1045-1060.
2. 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*](http://jcb.rupress.org/content/195/7/1185/suppl/DC2)*)*
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. Hegazy M, J.L. Koetsier, A.L. Huffine, J.A. Broussard, B.M. Godsel, E. Cohen-Barak, E. Sprecher, D.J. Wolfgeher, S.J. Kron, L.M. Godsel\*, **K.J. Green\***. (2022). Epidermal stratification requires retromer-mediated Desmoglein-1 recycling. *Dev. Cell.* Dec 19; 57(24):2683-2698.e8.doi: 10.1016/j.devcel.2022.11.010. (Cover picture)

https://news.feinberg.northwestern.edu/2022/12/09/novel-mechanisms-regulate-inflammatory-skin-diseases/). \*Co-corresponding authors. PMC in process.

3. Desmosomal cadherins in epithelial barrier, immunity 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 of complex tissues and epithelial barrier function. 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. 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. In vitro studies suggest that that this may be a keratinocyte autonomous function of Dsg1, providing a premise for our studies in the role of desmoglein 1 in regulating paracrine signaling. Transcriptomic analysis of a Dsg1 knockout mouse model and SAM patients demonstrates that they share a Th17-skewed inflammatory signature, similar to that exhibited by the common inflammatory disorder psoriasis.

1. 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). (*Recommended in F1000.)* PMC3791825.
2. 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.
3. Raya-Sandino, A., A.-C. Luissint, D.H.M. Kusters, V. Narayanan, S. Flemming, V. Garcia-Hernandez, L.M. Godsel, **K.J. Green**, S.J. Hagen, D.E. Conway, C.A. Parkos and A. Nusrat (2021). Regulation of intestinal epithelial intercellular adhesion and barrier function by desmosomal cadherin desmocollin-2. *Mol. Biol. Cell.* 32: 753-68. doi: 10.1091/mbc.E20-12-0775. PMC8108520.
4. Godsel, L.M.\*, Q.R. Roth-Carter\*, J.L. Koetsier, L.C. Tsoi, J.A. Broussard, G.N. Fitz, S.M. Lloyd, J. Kweon, A.L. Huffine, H.E. Burks, M. Hegazy, S. Amagai, P.W. Harms, J.L. Johnson, G. Urciuli, L.T. Doglio, W.R. Swindell, R. Awatramani, E. Sprecher, X. Bao, E. Cohen-Barak, C. Missero, J.E. Gudjonsson and **K.J. Green**. (2022). Translational implications of Th17-skewed inflammation due to genetic deficiency of a cadherin stress sensor. *J. Clin. Invest.* 132: e144363. doi.org/10.1172/JCI144363. PMC8803337.

4. Dependence of Gap Junctions on Desmosomes: Our work supports the idea that desmosomes help promote gap junction formation and function by regulating trafficking and stability of component connexins. 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 loss of MT cortical capture and failure to form gap junctions. We also identified a novel mechanism by which desmoplakin regulates the post-translational stability of connexin 43, by dampening Ras/MAPK-dependent phosphorylation. We could restore gap junction communication in desmoplakin mutant cardiac myocytes with a novel Ras inhibitor being developed clinically by our collaborator Karla Satchell. Finally, Dsg1 also regulates connexin 43 turnover, and its loss in SAM syndrome is associated with decreased gap junction communication.

1. 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
2. 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/> PMC6123000. *(Recommended in F1000)*
3. Cohen Barak, E., L.M. Godsel, J.L. Koetsier, D. Kushnir-Grinbaum, H. Hammad, N. Danial-Farran, R. Harmon, M. Khayat, R. Bochner, A. Peled, M. Rozenblat, J. Krausz, O. Sarig, J.L. Johnson, M. Ziv, S.A. Shalev, E. Sprecher, **K.J. Green.** (2020). The role of desmoglein 1 in gap junction turnover revealed through the study of SAM syndrome. *J. Invest. Derm.* 140: 556-567. pii: S0022-202X(19)33151-3. doi: 10.1016/j.jid.2019.08.433. PMC7039747.

5. Desmosomes and Cancer: While the role of classic cadherins in promoting and suppressing tumor progression has been well-studied, less is known about how desmosomes participate in tumor growth or metastasis. Our earlier work showed that while Dsg1 suppresses MAPK signaling to promote differentiation, EGFR elevates desmosomal cadherin turnover in head and neck cancer 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. More recently we have shown that Dsg1 has unique properties that position it to be a sensor of environmental stress. While transient Dsg1 downregulation like that occurring in response to ultraviolet radiation (UV) initiates a tanning response in melanocytes, chronic loss stimulates pathogenic pro-inflammatory cytokine production. In the context of melanoma, Dsg1 loss is to the benefit of transforming melanocytes and melanoma cells, as conditioned media from Dsg1-deficient keratinocytes induces signs of senescence bypass in primary melanocytes expressing the BRAFV600E driver oncogene and stimulates melanoma cell migration. Supporting the in vivo relevance of these findings, Dsg1 but not E-cadherin is reduced in keratinocytes next to early stage human melanomas, which we hypothesize creates a pro-tumorigenic inflammatory corona around the developing lesion. Further, we found a reciprocal relationship between keratinocyte Dsg1 expression and local melanoma cell spread. Based on our observations we are testing the hypothesis that melanoma cells hijack normal keratinocyte to melanocyte crosstalk that occurs in response to UV, keeping adjacent keratinocyte Dsg1 expression down to create a pro-melanoma feed forward loop in the developing tumor niche.

1. 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.* 7(5):1195-1206. [PMC6581214](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6581214/)
2. Arnette, C.R., J.L. Koetsier, J.A. Broussard, P. Gerami, J.L. Johnson and **K.J. Green.** (2020). Keratinocyte cadherin desmoglein 1 controls melanocyte behavior through paracrine signaling. *Pigment Cell Melanoma Res.* 33: 305-317*.* doi: 10.1111/pcmr.12826. [PMC7028503](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7028503/). *(Cover picture).*
3. Burks, H. E., J. L. Pokorny, J.L. Koetsier, Q. R. Roth-Carter, C.R. Arnette, J.L. Johnson, P. Gerami, J.T. Seykora, **K.J. Green** (2022). Keratinocyte desmosomal cadherin Desmoglein 1 as a mediator and target of paracrine signaling in the melanoma niche. *bioRxiv.* **doi:** <https://doi.org/10.1101/2022.12.01.518424>. In revision for *J. Cell Biol.,*with favorable reviews.
4. Tong, X., H.E. Burks, Z. Ren, J.L. Koetsier, Q.R. Roth-Carter, **K.J. Green** (2023). Crosstalk in skin: Loss of desmoglein 1 in keratinocytes inhibits BRAFV600E-induced cellular senescence in human melanocytes. *bioRxiv* doi.org/10.1101/2023.02.16.528886

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