DEPARTMENT OF DERMATOLOGY RESEARCH SYMPOSIUM 2025

October 22, 2025

Department of Dermatology
Research Symposium 2025
Agenda

7:00-8:00	**Breakfast**	
8:00-8:05	**Welcome**	Sam Hwang, MD, PhD - Professor and Chair
	Keynote Presentation	
8:05-8:50	Therapeutic Application of CAR T Cells for Cancer and Autoimmune Disorders	Mehrdad Abedi, MD - Professor of Medicine Division of Malignant Hematology/Cellular Therapy, Transplantation Department of Internal Medicine
	Department Highlight	
8:50-9:40	An Introduction to Dermatologic Surgery Research	Daniel Eisen, MD - Professor, Mohs Surgery Director
	Evaluating safety and outcomes of one-week pedicle division in paramedian forehead flap repairs: a single-center retrospective study	Linh Vo, UCD Medical Student, Class of 2028
	One-Week Post-Operative Healthcare Utilization Following Mohs Micrographic Surgery	Aoibhin O'Gorman, UCD Medical Student, Class of 2027
	Hemodynamic Safety of Epinephrine-Containing Anesthesia in Hypertensive and Normotensive Patients Undergoing Mohs Surgery	Linh Vo, UCD Medical Student, Class of 2028
	Influence of Sun Protection on the Aesthetic Outcomes Following Linear Repair of Cutaneous Surgical Defects, a Randomized Split-Wound Study	Linh Tran, UCD Medical Student, Class of 2027
	Q&A	
9:40-9:50	**BREAK**	
	Clinical Research	Victor Huang, MD, Vice Chair of Clinical Research
9:50-10:05	Higher Treatment Intensity Associated with Improved Outcomes in Non-Segmental Vitiligo Phototherapy	Nicholas Le, UCD Medical Student, Class of 2027
10:05-10:20	Topical Timolol as an Adjunct to Standard Care for Diabetic Foot Ulcers: A Randomized Controlled Trial	Janmesh Patel and Pooja Shet, Visiting Assistant Specialists, Rivkah Isseroff Lab
10:20-10:35	Early-Stage Hidradenitis Suppurativa Shows Surface-to-Deep Immune Activation: Spatial and Single-Cell Insights for Early Diagnosis and Therapy	Jongeun Lee, MD, Research Fellow, Jaehwan Kim Lab
10:35-10:45	**BREAK**	
	Basic Science Research	William Murphy, PhD, Professor and Vice Chair of Research
10:45-11:00	A Novel Co-Culture Model of IL-23 Driven Psoriasis: An Efficient Ex Vivo Platform for Cytokine and Therapeutic Studies	Sydney Kenney, Research Fellow, Sam Hwang Lab
11:00-11:15	Viral BCL2 contributes to the survival of KSHV-infected monocytes by regulating the inflammatory response	Somayeh Komaki, MD, Postdoctoral Scholar, Yoshi Izumiya Lab
11:15-11:30	Synergistic Effects of Immunity and Antibiotic Therapy in Reducing Bacterial Infection in Mice	Rajalekshmy Padmakumari, Postdoctoral Scholar, Sasha Shafikhani Lab
11:30	**Closing Remarks**	William Murphy, PhD, Professor and Vice Chair of Research
11:30-12:00	**Poster Presentations**	Sabine Abukhadra, Visiting Assistant Specialist, Kiuru Research
		Deepa Dehari, Postdoctoral Scholar, Sasha Shafikhani Lab
		Wahed Firoz, Graduate Student Researcher, Bill Murphy Lab
		Conan Lee, UCD Medical Student, Class of 2027
		Yoshiaki Matsushima, Visiting Assistant Professor, Sam Hwang Lab
		Anthony Gallegos, Associate Specialist, Rivkah Isseroff Lab
		Angela Soghomonian, UCD Medical Student, Class of 2028
		Getnet Tadege, Postdoctoral Scholar, Sasha Shahfikhani Lab
		Yoshikazu Takada, Professor+A6:C45

UC Davis School of Medicine
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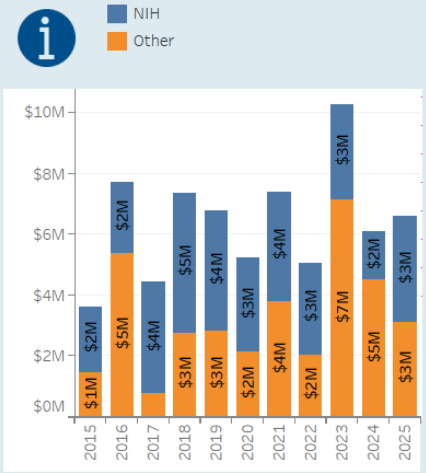
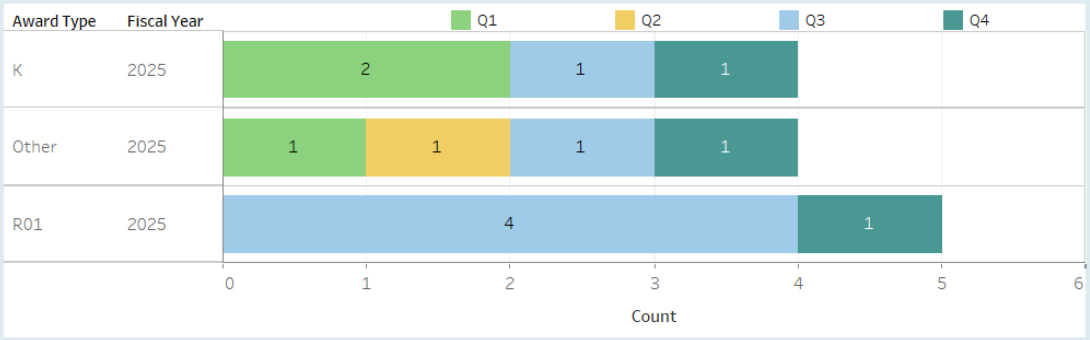
Med: Dermatology	All	2025	All	All	All



NIH Other	2021	2022	2023	2024	2025
NIH	$3,611,580	$2,965,010	$3,140,726	$1,586,494	$3,440,476
Other	$3,809,908	$2,084,127	$7,114,751	$4,520,964	$3,152,032
Grand Total	**$7,421,488**	**$5,049,137**	**$10,255,477**	**$6,107,458**	**$6,592,508**

NIH grants by type



Top 15 funded PIs

PI Name	Total Funding
Izumiya, Yoshihiro	$1,730,538
Shafikhani, Sasha	$1,593,280
Maverakis, Emanual	$1,121,705
Isseroff, Roslyn	$1,100,000
Huang, Victor	$286,017
Awasthi, Smita	$270,622
Hwang, Samuel	$223,398
Kim, Jaehwan	$168,948
Murphy, William	$90,000
Wu, Peggy	$5,000
Melloy, Marin	$3,000
Kiuru, Maija	$0
Zhao, Min	$0

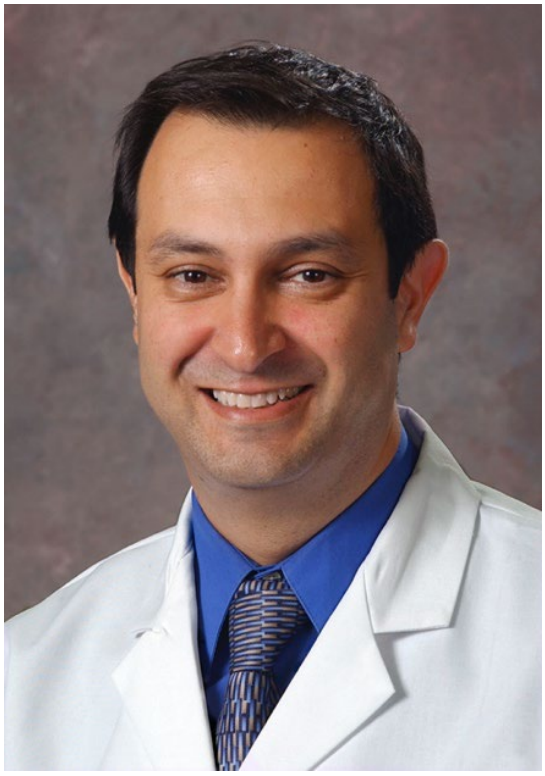
K-awards

PI Name	PI Dept	Type	Total Funding
Kim, Jaehwan	Med: Dermatology	K23	$168,948
Maverakis, Emanual	Med: Dermatology	K24	$187,710

Data up to FY2025 Q4 (June 30, 2025); Project for all SOM Grants analysis update October 1, 2025

KEYNOTE PRESENTATION

Mehrdad Abedi, MD



Dr. Abedi is a Professor of Medicine at the University of California at Davis, a member of the Hematology/Oncology bone marrow transplant team, Director of the Alpha Stem Cell Therapy Clinic, GMP Facility, and Progenitor Lab. As a bone marrow transplant specialist, I spent the beginning of my professional career in laboratories focusing on hematopoietic stem cell transplant and approaches to reduce toxicity. I specifically worked on reduced intensity transplant regimens and the effect of co-stimulation inhibition in the outcome of transplant and graft-versus-host disease. I also worked on stem cell plasticity and its potential on regenerative treatment of muscular and skin injury. A major focus of my clinical research for the last 20 years has been on cellular therapy using CAR-T cells and bispecific antibody armed T-Cells for the treatment of cancer patients and more recently autoimmune disorders.

DEPARTMENT HIGHLIGHT

An Introduction to Dermatologic Surgery Research

Daniel B. Eisen
Professor and Mohs Surgery Director
Department of Dermatology

The dermatologic surgery research program at UC Davis has established itself as a national leader in evidence-based surgical dermatology through an extensive portfolio of randomized controlled trials and outcomes research. The program's research philosophy emphasizes practical, patient-centered investigations that directly challenge surgical dogmas and improve cosmetic and functional outcomes. Numerous peer-reviewed articles have been published, with particular focus on optimizing wound closure techniques, infection prevention, and comparative effectiveness trials. This body of work includes landmark studies on suture spacing, wound eversion, tissue undermining, and various closure methods that have fundamentally influenced dermatologic surgical practice nationwide.

The research program currently maintains an active portfolio of ten clinical trials, ranging from studies on tie-over bolster dressings to novel applications like ethyl chloride spray for pain reduction during local anesthesia. These prospective randomized trials consistently employ rigorous split-wound designs and evaluator-blinding to minimize bias. Additionally, the program conducts multiple retrospective chart reviews examining real-world outcomes, including studies on keystone perforator island flaps, preoperative hypertension screening, and post-operative complications. The program has also contributed significantly to national clinical practice guidelines, participating in guideline development for actinic keratosis, basal cell carcinoma, squamous cell carcinoma, sebaceous carcinoma, extramammary Paget's disease, hidradenitis suppurativa, and microcystic adnexal carcinoma.

Student and Trainee Involvement

Medical students form the foundation of the research program's workforce, including trainees from UC Davis and visiting institutions nationwide. Since 2007, over 30 medical students have participated in research projects, many resulting in publications in high-impact journals including the Journal of the American Academy of Dermatology, Dermatologic Surgery, and JAMA Dermatology. Current student projects span diverse topics including surgical site infections, scalp reconstruction, tranexamic acid use, actinic keratosis treatments, and circulating tumor DNA analysis. Students have won prestigious awards such as the Loren d Carlson Research Award, while others have successfully matched into top dermatology residency programs. The program provides structured mentorship with regular research meetings, manuscript preparation guidance, statistical support, and opportunities for abstract presentations at national conferences, creating a robust pipeline of academically-minded future dermatologists.

Resident and Fellow Contributions

Dermatology residents and Mohs surgery fellows represent the advanced tier of the research program, conducting more complex studies and taking leadership roles in multi-center collaborations. The program has trained 19 Mohs fellows and over 65 dermatology residents since 2003, with many pursuing successful academic careers at institutions nationwide. Fellows and residents receive dedicated research time, access to comprehensive surgical outcome databases, and intensive mentorship in study design and IRB navigation. They have authored numerous first-author publications during training and regularly present their work at prestigious national meetings including the American Academy of Dermatology, American College of Mohs Surgery, and American Society for Dermatologic Surgery. This systematic approach has resulted in trainees winning competitive research awards, securing academic faculty positions, and establishing their own research programs after graduation, thereby perpetuating the culture of evidence-based dermatologic surgery nationwide.

Evaluating safety and outcomes of one-week pedicle division in paramedian forehead flap repairs: a single-center retrospective study

Linh Vo
Medical Student, Class of 2028
University of California, Davis

Authors: Linh N. Vo, BS[1,2*], Marin P. Melloy, BS[1,3*], Jeffrey R. Rajkumar, MD[1], Maha Kazmi, MD[1,4], Daniel B. Eisen, MD[1]
[1] Department of Dermatology, University of California, Davis, Sacramento, CA
[2] School of Medicine, University of California, Davis, Sacramento, CA
[3] University of Minnesota Medical School, Minneapolis, MN
[4] Department of Dermatology, University of Texas Southwestern, Dallas, TX
*Co-first authors with equal contribution.

Purpose of Study
The paramedian forehead flap (PMFF) is the gold standard for reconstruction of complex nasal and facial defects. Traditionally, pedicle division is performed 3–4 weeks after flap creation to allow for neovascularization, but this prolonged interval can cause patient discomfort and functional limitations. Recent reports suggest that earlier division may be feasible, yet prior studies have focused on carefully selected, low-risk profile cohorts with small sample sizes. We aimed to compare outcomes of early (1 week) versus traditional (>3 weeks) pedicle division in a larger, heterogeneous, multi-specialty cohort.

Methods
We performed a retrospective single-center cohort study of patients undergoing PMFF repairs at UC Davis from January 2021 to December 2024. Cases were identified using Epic Slicer Dicer with relevant keywords and CPT codes. Seven attending surgeons were included: six from Otolaryngology (93 cases) and one from Dermatologic Surgery (29 cases). After exclusions, 122 patients were stratified into early (7–11 days, n=23) and traditional (>19 days, n=99) groups. Demographics, comorbidities, defect characteristics, reconstructive details, and perioperative medication use were collected. Primary outcomes were infection, flap necrosis, and surgical revision. Secondary outcomes included rebleeding events and minor postoperative cosmetic interventions.

Results
Among 122 patients, 23 (19%) underwent early division (mean 8.3 days) and 99 (81%) underwent traditional division (mean 38.1 days). Groups were demographically similar except for higher alcohol use in the early cohort (P=.034). Early patients had more cartilage-level and fewer full-thickness defects, and required fewer complex adjunct procedures. Perioperative tranexamic acid use was more common in early cases (P<.001), while systemic steroids were more common in traditional cases (P<.001). Infection (2/23 vs 4/99, P=.32), necrosis (0/23 vs 3/99, P>.99), and surgical revision (3/23 vs 23/99, P=.40) were comparable. ED visits for rebleeding were more frequent in the early group (3/23 vs 1/99, P=.02), though overall rebleeding events did not differ. Minor cosmetic procedures such as dermabrasion and intralesional triamcinolone were more common in the early cohort, but did not cause statistically significant surgical revision, likely reflecting provider practice rather than complications.

Conclusion
Early pedicle division at one week after PMFF was not associated with increased infection, necrosis, or revision compared with traditional division, though ED visits for rebleeding were more common. In a multi-specialty, heterogeneous cohort, these findings suggest early division is relatively safe in appropriately selected patients, particularly with less extensive defects. Larger, prospective studies are needed to refine timing for more complex reconstructions.

One-Week Post-Operative Healthcare Utilization Following Mohs Micrographic Surgery

Aoibhin O'Gorman
Medical Student, Class of 2027
University of California, Davis

Aoibhin O'Gorman, B.S. [1], Linh N. Vo, B.S. [1], Daniel B. Eisen, M.D. [2]
1 School of Medicine, University of California Davis
2 Department of Dermatology, University of California Davis

Background: While Mohs micrographic surgery (MMS) is considered a low-risk outpatient procedure, post-operative complications requiring emergency care can occur. While most complications following MMS are minor, complications leading to emergency department (ED) visits or primary care provider (PCP) encounters remain underreported in the literature.

Our study aims to evaluate the incidence, etiology, and risk factors for emergent follow-up care within seven days of MMS.

Methods: We retrospectively reviewed charts of 295 patients who underwent MMS at a single academic dermatology clinic from 1st January 2014 to 31st December 2024. 60 severely hypertensive patients, defined as systolic ≥160 mmHg and/or diastolic ≥100 mmHg to reflect clinical risk at the upper end of stage 2 hypertension, were included, and 235 normotensive controls were selected using simple random sampling at a 4:1 ratio. All ED visits and PCP encounters within 7 days post-MMS were recorded and categorized by etiology.

Results: MMS-related ED visits occurred in 6 patients (2%): hemorrhage (n=2), infection (n=1), corneal abrasion from sutures (n=1), hypertension (n=1), and chest pain related to coronary artery disease (n=1). Compared to patients without complications, those requiring emergent care were older (mean 79.8 vs 69.1 years) and had larger post-excision defects (mean 7.68 vs 5.4 cm^2). Complications requiring ER visits were higher in hypertensive patients (8.3%) than in normotensive patients (1.7%).

Of the 60 patients presenting with severe hypertension on the day of MMS, 7 (11.7%) were seen by a PCP within 7 days. Mean preoperative blood pressure among these patients was 195 mmHg systolic (182-210 mmHg) and 86 mmHg diastolic (71-110 mmHg). PCP interventions included antihypertensive dose escalation (n=3), medication initiation (n=2), medication discontinuation (n=1), and home BP monitoring (n=1).

Conclusion: Early, emergency healthcare utilization following MMS related to the surgery occurred in 2% of patients. Older age, hypertension, and larger post-excision defect size were associated with increased risk, but larger studies are warranted to validate these associations. Additionally, severe perioperative hypertension prompted PCP follow-up in only around 12% of patients, frequently resulting in medication adjustments. These findings highlight the importance of preoperative risk stratification, patient education, and coordination with primary care for optimal blood pressure management.

Hemodynamic Safety of Epinephrine-Containing Anesthesia in Hypertensive and Normotensive Patients Undergoing Mohs Surgery

Linh Vo
Medical Student, Class of 2028
University of California, Davis

Aoibhin O'Gorman, B.S. [1], Linh N. Vo, B.S. [1], Daniel B. Eisen, M.D. [2]
1 School of Medicine, University of California Davis
2 Department of Dermatology, University of California Davis

Background: Mohs micrographic surgery (MMS) is exceedingly safe, with reported complication rates below 1% [1]. However, concerns persist about the safety and hemodynamic effects of epinephrine-containing local anesthesia in patients with hypertension. Evidence is limited for dermatologic surgery as most existing data have been extrapolated from dental literature [2], which differs in dose and procedural context. Due to the lack of standardization, anesthetic use in patients with elevated blood pressure (BP) varies across dermatologic practices. Our study aims to quantify BP changes associated with local intralesional anesthesia during MMS in both hypertensive and normotensive patients.

Methods: We conducted a retrospective chart review of 295 patients undergoing MMS at a single academic dermatology clinic from 1st January 2014 to 31st December 2024. 60 patients meeting criteria for severe hypertension were included (defined as systolic ≥160 mmHg and/or diastolic ≥100 mmHg to reflect clinical risk), and 235 normotensive controls were selected using simple random sampling at a 4:1 ratio. Local intralesional anesthesia consisting of 0.5-1% lidocaine with 1:200,000-1:100,000 epinephrine, with or without buffering and clindamycin, was administered. Total dose ranged from 3-48 cc (mean 12.1 cc). Systolic and diastolic BP were recorded pre- and post-operatively, demographics were collected, and BP change per cc of anesthesia was analyzed.

Results: Each unit (cc) increase in anesthesia dose was associated with only a 0.09 mmHg systolic change (95% CI: -.20 to +.38; p=0.54) and 0 mmHg diastolic change (95% CI: -0.17 to +0.17; p=0.99). No significant differences in BP change were observed between hypertensive and normotensive patients: systolic -0.56 ± 16.2 mmHg in hypertensive patients versus +2.23 ± 16.6 mmHg in normotensive patients (p = 0.30), and diastolic -0.04 ± 12.2 mmHg versus +0.46 ± 9.1 mmHg (p = 0.80). No statistically significant or clinically meaningful BP changes were observed in response to local anesthesia or surgery, regardless of baseline BP status.

Conclusion: Within this cohort, standard volumes of epinephrine-containing local anesthesia were hemodynamically well tolerated during MMS, with no dose-dependent effects on BP in hypertensive or normotensive patients. These findings support the safe and routine use of epinephrine-containing anesthesia, regardless of baseline BP status, and may help reduce practice variation and alleviate clinician concerns. However, interpretation may be limited by sample size, retrospective study design, and lack of case-control matching pairs, and confirmation in larger cohorts is recommended to confirm these findings.

References:

1. Alam M, Ibrahim O, Nodzenski M, et al. Adverse Events Associated With Mohs Micrographic Surgery: Multicenter Prospective Cohort Study of 20 821 Cases at 23 Centers. JAMA Dermatol. 2013;149(12):1378–1385. doi:10.1001/jamadermatol.2013.6255

2. Bader JD, Bonito AJ, Shugars DA. A systematic review of cardiovascular effects of epinephrine on hypertensive dental patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002;93(6):647-653. doi:10.1067/moe.2002.123866

Influence of Sun Protection on the Aesthetic Outcomes Following Linear Repair of Cutaneous Surgical Defects, a Randomized Split-Wound Study

Linh Tran
Medical Student, Class of 2027
University of California, Davis

Authors: Le, Nicholas T. BS1; Tran, Linh H. BS1; Kim, Keemberly MD2; Lee, Nariko BA3; Xu, Yaohui MD PhD3; Eisen, Daniel B. MD2

[1] *School of Medicine, University of California at Davis, Sacramento, California*
[2] *Department of Dermatology, University of California at Davis, Sacramento, California*
[3] *Department of Dermatology, School of Medicine and Public Health, University of Wisconsin at Madison, Madison, Wisconsin*

Presenting Author: Linh H. Tran Correspondence: Nicholas T. Le
Author Disclosure Information: All the above authors do not have relationships to disclose
Commercial Support Information: No commercial support was involved
Telephone: 916-949-9780 Email: ntyle@health.ucdavis.edu

Background: Ultraviolet radiation is a well-recognized factor that can impair scar formation. Ultraviolet radiation exposure during wound healing disrupts focal adhesion turnover and cytoskeletal dynamics, resulting in delayed healing and hyperpigmentation.1–3

Objective: This study evaluates whether sun protection improves scar outcomes in a split-scar model and provides evidence-based guidance for postoperative care.

Methods: This single-center, randomized, evaluator-blinded, split-wound study included patients undergoing linear repair of cutaneous surgical defects. Surgical wounds were labeled A (left/superior) and B (right/inferior), with randomization determining which side received sunscreen. At three months, blinded assessments included POSAS scoring, colorimetry, scar width measurements, and standardized digital imaging.

Results: Scar width differed significantly between groups (sunscreen mean: 1.10 mm vs. control mean: 0.97 mm, $p = 0.006$). Observer POSAS average sum scores were higher for sunscreen than control (12.52 vs. 11.50, $p < 0.001$), indicating worse scar appearance. Observer overall opinion average scores were slightly worse for sunscreen than control (2.23 vs. 2.05), but the difference was not significant ($p = 0.13$). Patient POSAS average sum scores were lower for sunscreen than control (11.26 vs. 12.22, $p < 0.001$), indicating better patient-rated scar outcomes. Patient overall opinion average scores were also lower for sunscreen than control (2.09 vs. 2.56, $p < 0.001$), indicating better scar appearance.

Conclusions: Sunscreen use after linear facial skin repair was associated with mixed outcomes: it improved patient-rated scar appearance but these results were not mirrored by the blinded observers, who found no significant differences between the two sides. These findings underscore the need for further research to understand discrepancies between patient and observer assessments of scar quality.

References:

1. Veldhuizen IJ, Schroen E, Lee EH, et al. Sun Protection Behavior Following Skin Cancer Resection and Reconstruction. J Cancer Educ. 2022;37(5):1401-1406. doi:10.1007/s13187-021-01971-x
2. Liu H, Yue J, Lei Q, et al. Ultraviolet B Inhibits Skin Wound Healing by Affecting Focal Adhesion Dynamics. Photochem Photobiol. 2015;91(4):909-916. doi:10.1111/php.12462
3. Chadwick S, Heath R, Shah M. Abnormal pigmentation within cutaneous scars: A complication of wound healing. Indian J Plast Surg 2012;45:403-11.

CLINICAL RESEARCH

Higher Treatment Intensity Associated with Improved Outcomes in Non-Segmental Vitiligo Phototherapy

Nicholas Le
Medical Student, Class of 2027
University of California, Davis

Authors: Le, Nicholas T. BS[1]; Huang, Victor MD[2]
[1]School of Medicine, University of California at Davis, Sacramento, California
[2]Department of Dermatology, University of California at Davis, Sacramento, California

Presenting Author/Correspondence: Nicholas Le – Medical Student
Author Disclosure Information: All the above authors do not have relationships to disclose
Commercial Support Information: No commercial support was involved
Telephone: 916-949-9780 Email: ntyle@health.ucdavis.edu

Background: Narrowband ultraviolet B (NB-UVB) phototherapy is a well-established treatment for non-segmental vitiligo. Optimal treatment regimens have not been established, however.

Objective: To evaluate phototherapy parameters associated with response in non-segmental vitiligo in a six-year single-site retrospective study.

Methods: A retrospective review of an IRB-approved REDCap registry included non-segmental vitiligo patients treated with NB-UVB phototherapy at UC Davis (2019–2025). Patients with facial or total VASI data at baseline and within 12 months of treatment completion were analyzed.

Results: Twenty-two patients were included. For facial VASI, responders had higher total sessions (208.07 ± 150.25 vs. 125.50 ± 195.33), weekly visits (1.92 ± 0.75 vs. 1.97 ± 0.44), average dose (622.20 ± 245.00 vs. 448.73 ± 263.55 mJ/cm²), cumulative dose (130,049.30 ± 91,810.70 vs. 63,499.17 ± 87,731.56 mJ/cm²), and maximum dose (1,013.60 ± 359.68 vs. 747.50 ± 517.77 mJ/cm²) than non-responders. For total VASI, responders also had higher total sessions (236.90 ± 168.02 vs. 145.89 ± 164.97), weekly visits (1.94 ± 0.87 vs. 1.78 ± 0.41), average dose (638.39 ± 254.42 vs. 537.31 ± 271.48 mJ/cm²), cumulative dose (144,510.70 ± 91,337.94 vs. 88,179.24 ± 95,964.11 mJ/cm²), and maximum dose (1,088.90 ± 396.67 vs. 825.56 ± 422.67 mJ/cm²).

Conclusions: Vitiligo patients who responded to NB-UVB phototherapy generally received higher total sessions, average doses, cumulative doses, and maximum doses compared with non-responders. These findings suggest that phototherapy regimens be designed to maximize consistency and dosage.

Topical Timolol as an Adjunct to Standard Care for Diabetic Foot Ulcers: A Randomized Controlled Trial

Janmesh Patel and Pooja Shet
Visiting Assistant Specialists
Rivkah Isseroff Lab

Authors:
Pooja A. Shet, BA[1,3]; Janmesh D. Patel, BS[1,3] Rawlings E. Lyle, MAS[1,2]; Mirabel E. Dafinone, BS[1,3]; Johanna Ghebrehiwet-Kuflom MS[1,3]; Pallas Lim, BSN[1,2]; Anuj Budhiraja, BS[1,4]; Alisha Mehta, BS[1,4]; Harrison, Shawa, MD[1], Ramanjot Kaur, MD[1], Catherine Tchanque-Fossuo, MD, MS[1], Sara E. Dahle, DPM, MPH[3,5]; R. Rivkah Isseroff, MD[1,3]

[1] VA Northern California Healthcare System, Dermatology Section, Mather CA
[2] University of California, Davis, School of Medicine, Sacramento, CA
[3] University of California, Davis, Department of Dermatology, Sacramento CA
[4] California Northstate, College of Medicine, Elk Grove, CA
[5] VA Northern California Healthcare System, Podiatry Section, Mather CA

Background:
Diabetic foot ulcers (DFUs) are a major public health concern, often resistant to standard care and linked to disability, high costs, and amputation. Current therapies mainly focus on infection control and offloading. Topical timolol, a beta-blocker, may enhance healing by improving circulation and reducing inflammation.

Methods:
In this randomized, double-blinded, controlled study, patients with chronic DFUs were assigned to standard of care (SOC) alone or SOC plus timolol GFS 0.5%. The primary endpoint was complete wound healing by week 14. Secondary outcomes included healing by week 31, time to closure, wound size reduction, and adverse events. Analyses included Fisher's exact test, Kaplan-Meier survival, and Cox proportional hazards modeling.

Results:
From 2018–2023, 48 patients met inclusion criteria (SOC: n=27; SOC+timolol: n=21). By week 15, healing rates were 38% with timolol vs. 33% with SOC (p=0.77). At week 30, 71% of timolol patients achieved healing vs. 48% of SOC (log-rank p=0.081). Cox modeling showed a significantly higher likelihood of healing with timolol (HR=2.88, p=0.027), with BMI a significant covariate (HR=1.06, p=0.031). Mean time to healing was shorter with timolol (5.8 vs. 9.2 weeks, p=0.015). Wound size reduction was also greater in the timolol group at weeks 14 and 31 ($p<0.05$). VEGF-B and TGF-β1 expression was significantly higher in healed wounds compared to unhealed wounds treated with timolol, suggesting the potential upregulation of these genes. Adverse events were similar, with no cardiac events reported.

Conclusions:
Topical timolol improved healing rates and accelerated closure compared to SOC, supporting its role as a promising adjunct for DFUs with minimal adverse effects.

Early-Stage Hidradenitis Suppurativa Shows Surface-to-Deep Immune Activation: Spatial and Single-Cell Insights for Early Diagnosis and Therapy

Jongeun Lee, MD
Research Fellow,
Jaehwan Kim Lab

Authors: Jongeun Lee, MD[a,b], Jongmi Lee, MD, PhD[a,c], James G. Krueger, MD, PhD[b], Jaehwan Kim, MD, PhD[a,c]

Affiliations:
[a]Department of Dermatology, University of California, Davis, Sacramento, California, USA
[b]Laboratory for Investigative Dermatology, The Rockefeller University, New York, New York, USA
[c]Dermatology Section, Veterans Affairs Northern California Health Care System, Mather, California, USA

Background: Hidradenitis suppurativa (HS) is a chronic, recurrent inflammatory skin disorder that often begins with painful nodules and abscesses. Over time, untreated disease progresses to irreversible dermal tunnels, tertiary lymphoid structures (TLS), fibrosis, and scarring, leading to substantial morbidity and impaired quality of life. Despite the recognition of late-stage immune dysregulation, the early immunologic events that initiate and sustain HS remain poorly defined. Understanding early-stage HS is critical, as current systemic therapies are reserved for advanced disease when irreversible tissue destruction has already occurred.

Objective: To characterize the immune landscape of early-stage HS and delineate the inflammatory transitions that underlie progression from early to late disease.

Methods: Lesional biopsies from early-stage HS (Hurley I; n=10) and late-stage HS (Hurley III; n=8) were analyzed by spatial transcriptomics across epidermis, dermal epithelium, and superficial/deep dermal aggregates, with acne conglobata as a control, which shares follicular occlusion as a common pathophysiological feature with HS. Findings were validated in an independent single-cell RNA sequencing (scRNA-seq) dataset.

Results: Even in the absence of dermal tunnels, TLS, or fibrosis, early-stage HS lesions demonstrated broad and deep immune activation. The dermal epithelium of early-stage HS exhibited increased expression of antimicrobial peptides and neutrophil-associated transcripts (*CD177*, *CXCL1*, *CXCL6*). The superficial dermal inflammatory aggregates of early-stage HS were enriched for B-cell and plasma-cell transcripts with immunoglobulins, while the deep inflammatory aggregates harbored robust Type 17 T-cell (T17) cytokine expression (*IL17F*, *IL21*, *IL22, IL23R, IL26, TNF*), T17-recruiting chemokine (*CCL20*), and neutrophil-enriched transcript (*MPO*). These inflammatory axes intensified in late-stage HS but were already established in the early stage of the disease. scRNA-seq confirmed marked B-cell enrichment in HS compared with psoriasis and controls, with plasma cells expanded from the early-stage. HS B-cells expressed not only antigen-presentation molecules but also pro-inflammatory cytokines (*IL7*, *IL16*), indicating their potential functional roles in sustaining inflammation. Notably, unlike fibroblasts in late-stage HS, T-cells were the primary producers of the B-cell chemoattractant (*CXCL13*) in early disease. Ligand-receptor analysis highlighted B-cell-centered interactions (e.g., *CXCL13*-*CXCR5*), suggesting orchestration of chronic immune activation.

Conclusions: HS is immunologically aggressive from its onset. B-cell enrichment, T17 pathway activation, and neutrophilic infiltration extend into the deep dermis before the formation of dermal tunnels, TLS, and fibrosis. These findings support a clinical framework that views HS as a systemic immune disease from its earliest stages and provide a rationale for testing early systemic interventions that target B-cell and T17 pathways to prevent irreversible progression.

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BASIC SCIENCE RESEARCH

A Novel Co-Culture Model of IL-23 Driven Psoriasis: An Efficient Ex Vivo Platform for Cytokine and Therapeutic Studies

Sydney Kenney
Research Fellow
Sam Hwang Lab

Authors: Sydney Kenney, BA, Xuesong Wu, MD, PhD, and Sam Hwang, MD, PhD

Background: Psoriasis is a chronic immune-mediated disease marked by dysregulated keratinocyte–immune cell interactions, primarily driven by the IL-23/Th17 axis. Murine models have been the cornerstone of psoriasis research, but they are resource-intensive, require large numbers of animals, and necessitate extended treatment timelines. Human-based 3D in vitro systems have emerged but remain costly and technically challenging. There is a critical need for accessible models that faithfully recapitulate psoriasis immunopathogenesis while reducing experimental burden.

Objective: To establish a reproducible, cost-effective, and ethically advantageous in vitro system that mirrors IL-23–driven psoriasis inflammation, responds to FDA-approved therapies, herein, focusing on JAK inhibitors, and provides a bridge to further in vivo validation studies.

Design and Methods: We developed a “Co-Culture Model” by combining murine ear keratinocytes with lymphocytes from cervical lymph nodes, inducing psoriasis via IL-23 stimulation. From a single mouse, ear and cervical lymph node dissections generate up to eight homogenous samples with equally aliquoted lymphocytes. After 24 to 48 hours of co-culture with the stimulator, ear skin samples are washed for RNA extraction and RT-PCR detection of transcription levels of psoriasis-relevant cytokines. Cell-free supernatant is preserved for ELISA to quantify IL-17A protein. Finally, JAK inhibitors including upadacitinib, baricitinib, and tofacitinib are investigated within the model for their therapeutic potential.

Results: The Co-Culture Model reliably reproduced Th17 pathway activation with robust upregulation of IL-17A, IL-17F, IL-22, and inflammatory genes such as S100A8/9. Gene transcription increases were detected by RT-PCR as early as 4 hours. ELISA could identify enhanced protein levels of IL17A after 24 hours of incubation. Addition of JAK inhibitors (baricitinib, tofacitinib, or upadacitinib) respectively in co-cultures demonstrated pharmacologic responses. All three agents inhibited the IL-23-induced inflammation at 1μM dose. When doses were titrated down from 1μM to 100nM, both baricitinib and tofacitinib showed a dose-dependent effect. Unexpectedly, low-dose upadacitinib (100–250 nM) enhanced expression of three characteristic Th17 genes. However, at 1 μM, upadacitinib showed the strongest inhibition, reducing IL-17A nearly to negative control levels (95% vs. 65% with baricitinib and 64% with tofacitinib). Slightly different to Th17 genes, S100A8 and S100A9 were inhibited by all three JAK inhibitors in dose-dependent manner, indicating the existence of diverse cellular and molecular responses to different types of JAK inhibitors.

Conclusions and Relevance: The novel Co-Culture Model represents an efficient and translationally relevant ex vivo model for psoriasis research by replicating IL-23 driven inflammation, responding predictably and paradoxically to targeted therapies, it is able to mechanistically illustrate the complex pathways involved in psoriatic inflammation. This cycle of in vitro development, therapeutic validation, and murine corroboration positions the Co-Culture Model as a practical tool for mechanistic studies, preclinical drug testing, and possibly future patient-derived investigations.

Viral BCL2 contributes to the survival of KSHV-infected monocytes by regulating the inflammatory response

Somayeh Komaki, MD
Postdoctoral Scholar
Yoshi Izumiya Lab

Somayeh Komaki[1], Tomoki Inagaki[1], & Yoshihiro Izumiya[1]
[1] Department of Dermatology School of Medicine, University of California Davis (UC Davis), Sacramento, California US

Gamma-herpesviruses, including Kaposi's sarcoma-associated herpesvirus (KSHV), encode a viral homolog of the BCL-2 protein, which is crucial for viral replication in infected cells. KSHV BCL-2 (vBCL-2), encoded by the ORF16 gene, is expressed during the lytic phase, where it inhibits apoptosis and supports the encapsulation of ORF55 tegument proteins through protein-protein interactions. In MHV68, vBCL-2 prevents the negative selection of infected B cells, thereby facilitating the survival and development of infected B cell populations. Our previous work demonstrated that following primary KSHV infection, vBCL-2 is highly expressed in monocytes but not in endothelial cells, and that vBCL-2 expression is dependent on viral IL-6 expression. We also showed that KSHV preferentially infects monocytes among PBMCs. Here, we investigated the role of vBCL-2 in KSHV monocyte infection.

Our findings demonstrated that:

i) vBCL-2 knockout (vBCL-2/Stop) recombinant KSHV infection to primary monocytes strongly induced pro-inflammatory cytokines (CCL20, CCL18, CCL23, and CCL3L3), whereas the revertant virus (vBCL-2/Rev) prevented such inflammatory responses.
ii) vBCL-2-expressing HeLa cells showed reduced levels of hIL-6 and IL-8 upon TNF-α stimulation, suggesting an anti-inflammatory role for vBCL-2. Decreased hIL-6 appeared to be mediated by inhibition of NF-κB activity demonstrated by NF-κB-luciferase reporter assays in HEK293 cells.
iii) vBCL-2 expression is regulated by PU.1, a key transcription factor for myeloid and lymphoid lineages, which our previous work identified as a downstream target of vIL-6 and involved in gene activation. PU.1 knockdown in THP-1 monocytes significantly reduced KSHV vBCL-2 expression during de novo infection, while PU.1 overexpression rescued vBCL-2 expression from KSHV genome in HEK293 cells.
iv) Infection with the vBCL-2/Rev virus increased monocyte survival, whereas vBCL-2/Stop did not.

Taken together, we propose that KSHV utilizes vBCL-2 to secure its viral reservoir by enhancing monocyte survival, allowing these monocytes to differentiate into longer-lived, dysfunctional macrophages that facilitate immune evasion and support lifelong infection.

Synergistic Effects of Immunity and Antibiotic Therapy in Reducing Bacterial Infection in Mice

Rajalekshmy Padmakumari, PhD
Postdoctoral Scholar
Sasha Shafikhani Lab

Rajalekshmy G. Padmakumari [1], Ruchi Roy [2], Deepa Dehari [1], Getnet Tesfaw [1], Athena M. Soulika [1,3], Roslyn Rivkah Isseroff [1], and Sasha H. Shafikhani [1]*

[1] Department of Dermatology, UC Davis School of Medicine, Sacramento, CA 95817.
[2] UICentre for Drug Discovery, College of Pharmacy, University of Illinois at Chicago, Illinois, USA.
[3] Shriners Hospital for Children, Northern California, Sacramento, California, USA.

BACKGROUND: Antibiotics and host immunity are often considered independent defenses, with antibiotics reducing bacterial load to levels manageable by immune clearance. Yet clinical evidence shows reduced antibiotic efficacy in immunocompromised patients despite pathogen susceptibility. Whether immunity enhances antibiotic action—or antibiotics boost immune responses - remains unclear. Using a *Pseudomonas aeruginosa* wound infection model in immunocompetent (C57BL/6) and immunocompromised (NSG) mice, we hypothesized that tobramycin-mediated bacterial killing releases pathogen-associated molecular patterns (PAMPs) that activate inflammatory pathways and leukocyte recruitment, thereby strengthening infection control. We further postulated that this synergy is impaired in immunocompromised mice, leading to reduced antibiotic effectiveness.

EXPERIMENTAL PROCEDURES: Tobramycin was administered intraperitoneally to immunocompetent (C57BL/6) and immunocompromised (NSG) mice, followed by wound challenge with PA103 (10^6/ wound CFU) (n=4 mice/group). Bioactive LPS levels in wound tissue were measured one hour post-infection using HEK-Blue hTLR4 reporter cells. In parallel experiments, wounds were collected 24 hours after infection and assessed for infection burden by CFU counts, Toll-like receptors mRNA expression by RT-PCR, proinflammatory cytokines production by ELISA and Western blotting, leukocyte infiltration by H&E staining, and activated neutrophil content by MPO analysis by ELISA. To determine whether reduced PAMP levels contributed to impaired infection control in NSG mice, a low dose of LPS (100ng/wound) was topically applied to wounds of tobramycin-treated animals prior to PA103 challenge, and the effects on inflammatory responses and infection burden were evaluated.

RESULTS & CONCLUSIONS: We show that systemic tobramycin enhances immune responses, creating a synergistic feedback loop that improves infection control. In immunocompetent mice, tobramycin-mediated bacterial killing increased bioactive PAMPs, activated TLR signaling, boosted pro-inflammatory cytokine production, and promoted neutrophil recruitment, leading to effective infection clearance. This immune amplification was absent in immunocompromised NSG mice, rendering tobramycin ineffective despite bacteria remaining sensitive to this antibiotic. Importantly, topical application of PAMPs restored inflammatory responses and significantly improved infection control in NSG mice. Together, these findings reveal that antibiotics also function as immune activators, and their efficacy is dependent on host immune competence. These data also highlight the potential of combining antibiotics with innate immune modulators to improve infection outcomes.

POSTER PRESENTATIONS

Presenters will be situated around the auditorium. Please stop by and learn about their research.

Non-invasive Skin Sampling Using Adhesive Patches: Optimization of RNA Isolation and Amplification
Sabine Abukhadra, Visiting Assistant Specialist, Kiuru Research

Immunological and safety profile of CCL3 therapy in diabetic wound: A pre- clinical study
Deepa Dehari, Postdoctoral Scholar, Sasha Shafikhani Lab

CAR T cell products mediate a novel chronic sclerodermatous xenogeneic graft-versus-host disease in NSG mice
Wahed Firoz, Graduate Student Researcher, Bill Murphy Lab

Pharmacokinetics of Topically Applied Timolol for Chronic Wounds: Prospective Pilot Study
Anthony Gallegos, Associate Specialist, Rivkah Isseroff Lab

Characteristics and Outcomes of Patients with Negative Patch Test Results
Conan Lee, UCD Medical Student, Class of 2027

An Analysis of Mouse Model of Pyoderma Gangrenosum Induced by Topical Pyrimidine Synthesis Inhibitors
Yoshiaki Matsushima, Visiting Assistant Professor, Sam Hwang Lab

Mapping the Keratinocyte Microenvironment in Melanoma Using Spatial Transcriptomics
Angela Soghomonian, UCD Medical Student, Class of 2028

Single Cell-RNA Sequencing Revealed Dysregulation of Gene Expression in Neutrophils and Macrophages in an Acute diabetic Wound in a Mice Model
Getnet Tadege, Postdoctoral Scholar, Sasha Shahfikhani Lab

Anti-PF4 (heparin-independent)/PF4 complex induces allosteric activation of integrins αIIbβ3 and αvβ3, a potential mechanism of vaccine-induced thrombotic thrombocytopenia (VITT) and autoimmune diseases
Yoshikazu Takada, MD, PhD, Professor

Non-invasive Skin Sampling Using Adhesive Patches: Optimization of RNA Isolation and Amplification

Sabine Abukhadra[1,2], BS; Laura J. Young[1], BS; Marin Melloy[1,3], BS; Tram Tran[1], BS; John McPherson[4], PhD; Maija Kiuru[1,5], MD, PhD

Departments of [1]Dermatology, [4]Biochemistry and Molecular Medicine, and [5]Pathology and Laboratory Medicine, University of California Davis School of Medicine, Sacramento, CA
[2]Wake Forest University, Winston-Salem, NC
[3]University of Minnesota Medical School, Minneapolis, MN

Introduction

Melanoma is the deadliest form of common skin cancers, responsible for 80% of skin cancer-related deaths.[1] Early detection is crucial for optimal patient outcomes. While biopsy is the current standard of care for diagnosis, only 4% of biopsied lesions are malignant.[2] Biopsies may also lead to complications such as pain, bleeding, infection, and scarring, and patients may prefer non-invasive diagnostic techniques. Therefore, non-invasive techniques have been introduced for melanoma diagnosis.[2] We aimed to optimize a non-invasive RNA isolation and amplification protocol from epidermal keratinocytes using adhesive patches.

Methods

A consecutive series of 20 D101-D-Squame Stripping Discs or ARCare90068 patches were placed on healthy volar forearm skin of a research subject to collect epidermal keratinocytes. The patches were held with pressure for thirty seconds before removal, then cut in half and placed into Eppendorf tubes. RNA was disrupted from the patches using ultrasound sonication or scraping, and isolated using silica-membrane spin column technology. Reverse transcription quantitative polymerase chain reaction evaluated the expression of epidermal keratinocyte genes *KRT10* and *FLG2*, a housekeeping gene *GAPDH*, and a gene expressed in melanoma-associated keratinocytes, *S100A8*.[3]

Results

D101-D-Squame Stripping Discs and RNA disruption via sonication yielded better RNA quality than using ARCare90068 patches or scraping. RT-qPCR analysis showed consistent expression of *KRT10* and *FLG2* and no expression of *S100A8*.

Discussion

The optimized protocol using D101-D-Squame Stripping Discs and RNA disruption via sonication improved RNA isolation from epidermal keratinocytes, with consistent expression of *KRT10* and *FLG2*. Future directions include applying the protocol to the assessment of pigmented lesions utilizing the biomarker S100A8 with the goal of improving the non-invasive diagnostic workup of pigmented lesions.[3]

Immunological and safety profile of CCL3 therapy in diabetic wound: A pre-clinical study

Deepa Dehari, Rajalekshmy Padmakumari, Getnet Tesfaw, & Sasha Shafikhani
Department of Dermatology, UC Davis School of Medicine, Sacramento, USA

Introduction: Diabetic foot ulcers, a serious complication of diabetes, account for 60-75.5% of all lower-extremity amputations and add ~$9–12 billion annually to U.S. healthcare costs and frequently leading to infection and impaired healing. Delayed neutrophil recruitment during the acute phase of injury compromises early infection control, leaving diabetic wounds highly vulnerable to infection. CCL3 (MIP-1α) is a chemokine that recruits neutrophils by targeting CCR1 auxiliary chemokine receptor and enhances innate immune defense. We showed that topical treatment with CCL3 restored neutrophil function, reduced bacterial infection by ~99%, and accelerated wound healing in diabetic mice previously. Understanding the toxicity profile of CCL3 therapy is essential for its FDA approval for use in diabetic wound care.

Strategy: To address this, we conducted a 14-day acute toxicity study using diabetic (db/db) and normoglycemic control (db/+) mice. Mice were randomized into four groups: db/+ + PBS, db/db + PBS, db/db + CCL3 (1 µg, normal therapeutic dose), and db/db + CCL3 (10 µg). On day 0, full-thickness dorsal wounds (5 mm) were created and treated with a single topical dose of PBS or CCL3. Animals were monitored daily for survival, clinical signs, behavior, food intake, and body weight. On day 14, plasma and serum were analyzed for hematological and biochemical parameters (ALT, AST, ALP, BUN, creatinine, electrolytes, glucose, and protein levels) at the UC Davis Comparative Pathology Laboratory. Major organs (liver, kidney, heart, spleen, pancreas) were processed for histopathology, and semi-quantitative scoring for necrosis and inflammation was performed.

Results: We observed that CCL3 had no mortality, abnormal behavior, or adverse clinical effects observed. Food intake and body weights remained stable throughout the study. Hematological and biochemical parameters remained within normal limits, and histopathological examination revealed no additional organ injury in CCL3-treated groups compared to diabetic controls. Intriguingly, diabetic PBS mice exhibited elevated Alanine Transaminase (ALT) and Immunoglobulin G1 (IgG1) levels and histological evidence of hepatic steatosis, ballooning, renal tubular vacuolation and splenic white pulp reduction. Importantly, CCL3 treatment did not exacerbate these findings and, in fact, reduced ALT levels and improved hepatic pathology, indicating hepatoprotective effects.

Conclusion: The study concludes that topical administration of CCL3 at both low (1 µg) and high (10 µg) doses was well tolerated in diabetic mice, with no evidence of systemic organ toxicity. CCL3 reduced hepatic inflammation while maintaining hematological, biochemical, and histopathological safety. These findings provide strong preclinical evidence supporting CCL3 as a safe and effective biologic candidate for diabetic wound therapy and justify its further evaluation in translational and clinical studies.

CAR T cell products mediate a novel chronic sclerodermatous xenogeneic graft-versus-host disease in NSG mice

Wahed A. Firoz, Michael K. Sheng, Pedro Ruivo, Logan V. Vick, Craig P. Collins, Ryan N. Nielsen, Ravi K. Shah, Lam T. Khuat, Ying Xiong, Maneesh Dave, Sean J. Judge, Robert J. Canter, Arta M. Monjazeb, Bruce R. Blazar, Anthony E. Zamora, and William J. Murphy

Background: Although chimeric antigen receptor (CAR) T cells have shown great success against hematological malignancies, they have been associated with long-term adverse effects such as malignant transformation, necessitating long-term study. Xenogeneic graft-versus-host disease (xenoGVHD) resulting from MHC disparity between human and mouse species prevents long-term study. Furthermore, GVHD has been primarily attributed to naïve T cells. Although naïve phenotype is lost during production, human CAR T cells still mediate xenoGVHD in immunodeficient NOD-*scid* IL2Rg^{null} (NSG) recipient mice. Our study aims to characterize the xenoGVHD limitation of the NSG preclinical model while also investigating the immunobiology of the CAR T cell product during GVHD.

Methods: We utilized human lymphoma-bearing NSG mice treated with B cell-targeting CAR T cell products. We assessed both short-term tumor-eradication and long-term effects of CAR T cell transfer in vivo. We performed histopathology to classify xenoGVHD pathology and RNA-sequencing to assess T cell transcriptional profile and TCR-repertoire diversity. Assessment of CAR-positive and negative human T cell populations was also determined over time.

Results: We observed the delayed occurrence of xenoGVHD with kinetics and incidence highly dependent on donor, marked by scleroderma and multi-organ involvement sometimes delayed beyond 100-days, consistent with chronic GVHD, without B cell involvement. Sublethal total-body irradiation conditioning (200cGy) prior to CAR T cell transfer led to faster disease onset with maintenance of chronic xenoGVHD phenotype. Interestingly, despite the consistent expansion of CAR-positive T cells during early tumor-clearance, the emergence of CAR-negative populations during xenoGVHD resulted although this was dictated by production protocol. Sequencing analysis during xenoGVHD demonstrated TCR-repertoire constriction compared to pre-infusion. Finally, the usage of MHCI/II double-knockout (MHC-DKO) NSG mice ameliorated this xenoGVHD but resulted in lack of long-term engraftment.

Conclusions: Our results highlight the xenoGVHD as a major limitation of the NSG mouse for long-term preclinical assessment and potential affecting CAR engraftment. The use of xenogeneic modeling for long-term assessment of CAR T cell effects must consider the potential immunoreactivity of the T cell product to the recipient, as it has implications in both long-term adverse effects and alloreactivity of third-party allogeneic T cell therapies.

Pharmacokinetics of Topically Applied Timolol for Chronic Wounds: Prospective Pilot Study

Authors:
Janmesh D. Patel[1,2], BS, Anthony C. Gallegos[2], BS, Johanna Ghebrehiwet-Kuflom[1,2], BS, MS, Mirabel Dafinone[1,2], MD, Pallas Lim[2], BSN, Neda Afshar[1], MSN, DNP, Chuong Nguyen[2], PhD, Kaitlyn West[1], BS, MS, Pooja A. Shet[1,2], BS, Sara E. Dahle[2,3], MPH, DPM, Rosyln R. Isseroff, MD[1,2]

Affiliations:
[1]Department of Dermatology, VA Northern California Health Care System, Sacramento VA Medical Center, 10535 Hospital Way, Mather, CA, 95655-4200, USA.

[2] Department of Dermatology, University of California Davis Medical Center, 4301 X St, Sacramento, CA, 95817, USA.

[3]Podiatry Section, Surgical Services,VA Northern California Health Care System, Sacramento VA Medical Center, 10535 Hospital Way, Mather, CA, 95655-4200, USA.

Introduction: Chronic wounds impose substantial morbidity and costs. Topical timolol is used off-label to promote healing, but systemic absorption through ulcerated skin is uncertain. We quantified plasma exposure after single-dose application to chronic ulcers to inform safety and monitoring.
Methods: Single-center prospective pilot in veterans with recalcitrant traumatic chronic ulcers (n=1) and diabetic foot ulcers (n=6). Following debridement, timolol gel-forming solution 0.5% was applied at 0.25 mg (<2 cm²) or 0.50 mg (≥2 cm²), then covered with a non-adherent dressing; vitals were monitored. Venous blood was collected pre-dose and at 0.5, 1, 2, 4, 6, 8, and 24 h. Plasma timolol was quantified by validated reverse-phase HPLC (noncompartmental parameters were derived). Correlations among peak plasma concentration (C_{max}), ulcer area, and weight-normalized timolol dose were assessed.

Results: Timolol was well tolerated, no bradycardia, wheezing, or hypotension occurred. C_{max} ranged 0–1.48 ng/mL (mean 0.40 ± 0.56), with at time 0.5–2.0 h (mean 1.0 ± 0.6). The half-life of timolol was 4.00 ± 0.47 h, clearance and volume of distribution were comparable to prior oral/ophthalmic reports. Higher C_{max} was associated with larger ulcer area (P=0.0276) and higher weight-normalized dose (P=0.0181).

Discussion: Single-application timolol to chronic ulcers produced low systemic concentrations with peaks around 1 h, suggesting minimal β-blockade risk in typical outpatients and supporting a 1-hour post-application monitoring window. Findings support dose considerations based on ulcer area and weight. However, small sample size, male-predominant cohort, and single-dose design limit generalizability. Larger, repeated-dose pharmacokinetic studies linking exposure to healing outcomes are warranted.

Characteristics and Outcomes of Patients with Negative Patch Test Results

Conan H. Lee BS[1], Lauren W. Hastings BS[2], Nicholas T. Le BS[1], Olivia Keller BS[3], Christian B. De Guzman BS[1], Sydney Sullivan BS[3], Bruce Abbott MLS[4], Peggy A. Wu MD MPH[3]

[1]School of Medicine, University of California Davis, Sacramento, CA
[2]Des Moines University College of Osteopathic Medicine, West Des Moines, IA
[3]Department of Dermatology, University of California Davis, Sacramento, CA
[4]Blaisdell Medical Library, Sacramento, CA

Abstract

Positive patch test (PPT) results and identification of culprit allergens relevant to patients' dermatitis facilitates allergy avoidance. Patients with negative patch test (NPT) results do not receive this directed counselling, yet their experiences are important to understand. We analyzed and collected data from a patch-tested cohort using an IRB-approved REDCap™ registry from the University of California, Davis (UCD) Contact Dermatitis Clinic. A systematic review of NPT results was conducted for comparison. Of 1001 patients at UCD (769 female, 230 male), 161 (16.1%) had NPTs. Median age, female predominance, race/ethnicity, duration of rash, and number of patches placed was not significantly different between NPT and PPT groups. More patients with NPTs had rashes with leg involvement (p=0.04) and a biopsy performed prior to patch testing (p=0.002). The most common final diagnoses following patch testing were "other" dermatitis (n=123, 42.7%), irritant contact dermatitis, ICD, (n=60, 20.8%), and atopic dermatitis (AD) (n=19, 6.6%). The investigator (Investigator Global Assessment) and patient assessments (Dermatology Life Quality Index, DLQI, Skindex ACD-11) and were significantly improved post patch testing for NPT patients except for the symptoms section of the Skindex ACD-11 scores. In our systematic review, the most prevalent final diagnoses were also "other" dermatitis (28.1%), AD (18.6%), and ICD (18.0%). NPT rates ranged from 16.7-83.1% and number of patch tests placed from 20-102. Seven of 33 studies with demographic information showed higher proportion of females. Commonly affected areas of dermatitis were the hands, with occasional mention of the face and arms. Our study finds a minority of patients have NPT results with no major differences in demographics. NPT patients were diagnosed with "other" dermatitis, ICD, or AD as their primary diagnosis following patch testing. More NPT patients have had biopsies, suggesting an unusual presentation.

An Analysis of Mouse Model of Pyoderma Gangrenosum Induced by Topical Pyrimidine Synthesis Inhibitors

Yoshiaki Matsushima, Xuesong Wu, Hinako Saito, Hideaki Uchida, Sam T Hwang
Department of Dermatology, University of California, Davis School of Med., Sacramento, California, USA.

Background: Pyoderma gangrenosum (PG) is an autoinflammatory disease characterized by progressive skin ulceration. However, its detailed pathogenesis remains largely unclear. Objective: We reproduced a recently established mouse model of PG to investigate its clinical progression and the gene expression profile within the ulcerated tissue, aiming to explore its underlying mechanisms.

Materials & Methods: Following the protocol by Jatana S et al. (2023), we induced a PG-like phenotype in C57B6 mice using the pyrimidine synthesis inhibitors Brequinar and PALA. Ointments containing 0.5% Brequinar or 2% PALA were formulated in Aquaphor. A 5 mm, full-thickness excisional wound was created on the shaved dorsum of each mouse. Wounds were then treated daily with topical Aquaphor alone (control group), 0.5% Brequinar, or 2% PALA. The clinical course of the ulcers was monitored for up to 9 days. Tissues were harvested at several time points across multiple experiments for gene expression analysis by RT-PCR.

Results: From day 4 onwards, control wounds exhibited a clear healing course, whereas wounds in the inhibitor-treated groups progressively worsened. By day 9, control wounds were completely healed, while ulcers persisted in both treatment groups. RT-PCR analysis of the PALA-treated group revealed elevated expression of CCL20, CXCL1, CXCL2, IL-1b, and IL-6 in peri-ulcer skin on day 3. In the Brequinar-treated group, the expression of CXCL1 and CXCL2 increased on day 2, while the expression of CCL20 increased on day 3, respectively, in the peri-ulcer skin. Histologically, the treatment groups showed a more pronounced neutrophil infiltration in and around the ulcers.

Conclusion: This study confirms that a PG-like phenotype can be induced by the local inhibition of the pyrimidine synthesis pathway. We successfully recapitulated the non-healing ulcer phenotype by topically applying these inhibitors to an acute wound. The resulting ulcers showed significant upregulation of pro-inflammatory genes known to be upregulated in human PG tissues.

Mapping the Keratinocyte Microenvironment in Melanoma Using Spatial Transcriptomics

Authors:
Angela Soghomonian[1], BS, Nicholas Love[1], MD, Maayan Baron[2], PhD, Dr. Maija Kiuru[1], MD PhD
[1]Department of Dermatology, University of California, Davis, School of Medicine
[2]Zephyr AI

Abstract: Melanoma, one of the deadliest skin cancers, can be difficult to diagnose due to its clinical and histopathological resemblance to melanocytic nevi (benign moles). This has prompted the use of melanoma-specific biomarkers to improve diagnostic accuracy. Early melanoma originates in the epidermis, and previous research has shown keratinocytes overlaying malignant melanocytes to harbor an altered transcriptional state. However, the exact role of keratinocytes in initiation and progression of early melanoma is poorly understood. Delineating the transcriptomic profile of the keratinocyte microenvironment can lead to a deeper understanding of distinct gene signatures and biological pathways associated with early melanoma. This, in turn, could support the development of less-invasive skin-surface screening methods. In this study, we used the CosMx™ Spatial Molecular Imager (SMI) to profile the in-situ gene expression of ~6000 genes across 7 formalin-fixed paraffin-embedded patient-derived samples (3 invasive melanomas, 1 melanoma-in-situ, 2 dysplastic nevi and 1 basal cell carcinoma. Areas containing both diseased and adjacent normal epidermal tissue were analyzed, revealing a distinct population of activated keratinocytes overlying the tumor microenvironment of melanoma. The damage associated molecular patterns (DAMPs) *S100A7, S100A8,* and *S100A9* and wound-associated keratins (*KRT6B* and *KRT6C*) were among the top differentially expressed genes in this activated keratinocyte group. Additionally, the genes *DSC2*, *DYNLL1, LCN2* and *RAB11A* were uniquely upregulated in the keratinocyte microenvironment of melanoma. Ultimately, these results highlight the potential for single cell transcriptomics to delineate the role of keratinocytes in melanoma progression while simultaneously identifying gene signatures unique to the keratinocyte microenvironment in melanoma.

Single-Cell RNA Sequencing Reveals IL-10 Dysregulation as the Culprit Underlying Impaired Infection Control in Diabetic Wounds

Getnet Tesfaw, Ann Ly, Rajalekshmy Padmakumari, Deepa Dehari, Alexander Merleev, Sasha Shafikhani

Department of Dermatology, University of California Davis, Sacramento, California, USA.

Introduction: Chronic diabetic wounds are characterized by persistent, non-resolving inflammation. However, we demonstrated that in the acute phase, the diabetic wound environment is marked by insufficient production of the proinflammatory cytokines and excessive production of the anti-inflammatory cytokine IL-10, making infection control in acute diabetic wounds particularly challenging. Using single-cell RNA sequencing, we characterized the cell composition and gene expression profiles of acute diabetic wound compared to acute non-diabetic wound.

Methods: We performed scRNA-seq analysis of acute diabetic and non-diabetic wound tissues. We analyzed data using Seurat, retaining cells with 200–10,000 detected genes and <5% mitochondrial reads. Data were log-normalized, and the top 2,000 variable genes were selected for PCA (10 PCs), clustering (resolution 0.5), and UMAP visualization. Cluster markers were identified using FindAllMarkers ($|log2FC| > 1$, adj. $p < 0.05$) and the top 20 markers per cluster. Cell annotations were guided by the STRING Database and curated marker genes from the literature and further refined using GPT-4.1 with cluster-specific marker genes as input.

Results: Higher proportion of cells in diabetic wounds expressed the anti-inflammatory cytokine IL-10 and IL-10Rα/IL-10Rβ. Among all IL-10–expressing cells, neutrophils and macrophages together accounted for more than 75%. We found that acute diabetic wounds were characterized by significantly elevated proportions of neutrophils. Notably, a higher fraction of neutrophils was an anti-inflammatory N2 neutrophil phenotype in the diabetic wound, while proinflammatory N1 neutrophils were predominated in the non-diabetic wounds. Single-cell gene expression analysis of neutrophils revealed downregulation of proinflammatory cytokines and upregulation of anti-inflammatory cytokines in acute diabetic wounds. Interestingly, N1 neutrophils, typically proinflammatory, displayed significant downregulation of proinflammatory cytokines in the acute diabetic wound environment.

Conclusions: Diabetic wounds during the acute phase, early after injury, exhibit an immunosuppressive environment, due to substantially elevated levels of IL-10 and IL-10R-expressing cells, characterized by reduced proinflammatory gene expression and enhanced anti-inflammatory signaling in diabetic wounds, which makes diabetic wounds vulnerable to infection and delayed wound healing. Importantly, therapeutic strategies aimed at targeting IL-10 and IL-10 signaling enhance proinflammatory cytokine production and improve infection control in acute diabetic wounds.

Anti-PF4 (heparin-independent)/PF4 complex induces allosteric activation of integrins αIIbβ3 and αvβ3, a potential mechanism of vaccine-induced thrombotic thrombocytopenia (VITT) and autoimmune diseases

Yoko K Takada[1], Chun-Yi Wu[2], and Yoshikazu Takada (presenter)[1.3]

1. Department of Dermatology, University of California Davis School of Medicine, Sacramento, CA 95817, U.S.A.
2. Department of Neurology, University of California Davis School of Medicine, Sacramento, CA 95817, U.S.A.
3. Department of Biochemistry and Molecular Medicine, University of California Davis School of Medicine, Sacramento, CA 95817, U.S.A.

Previous studies suggest that multiple inflammatory cytokines (e.g., CCL5, CXCL12, CD40L) bind to the allosteric site of integrins (site 2) and induce allosteric integrin activation and inflammatory signals. PF4 is abundantly present in platelet granules, but PF4 levels are very low in plasma. PF4 is released from damaged platelets and is markedly increased in plasma (>1000x) in pathological conditions. PF4 (tetramer) is an inhibitory chemokine, and the specifics of PF4 signaling are unclear. Docking simulation predicted that PF4 monomer binds to site 2, but PF4 by itself did not induce allosteric integrin activation. Anti-PF4 mAb KKO is known to bind to PF4 tetramer and mAb RTO binds to monomer. We discovered that the PF4/RTO complex induced potent integrin activation, but the PF4/KKO complex did not, suggesting that PF4 monomer is active but tetramer is inactive, and RTO converts PF4 from inactive tetramer to active monomer. A PF4 mutant (4E) defective in site 2 binding did not induce integrin activation and acted as a dominant-negative antagonist (patent pending), suggesting that the RTO/PF4 complex is required to bind to site 2 for integrin activation, as predicted. RTO-like autoantibody was detected in plasma of healthy controls, but not in the sera of patients with autoimmune diseases (RA and SLE). We propose that autoanti-PF4 in healthy controls may not be a problem when plasma PF4 levels are very low. When plasma PF4 tetramer is increased, active PF4 monomer is generated by autoanti-PF4 and plays a role in the pathogenesis of inflammatory diseases. Notably, anti-inflammatory cytokine NRG1 and anti-inflammatory ivermectin (IVM) suppressed integrin activation induced by RTO/PF4 complex, suggesting that NRG1 and IVM are useful to suppress PF4/anti-PF4-mediated inflammatory signals.

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