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**Autologous fibroblasts therapy for regressive dystrophic epidermolysis bullosa**

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Regenerative gene therapy holds promise for treating severe genetic skin fragility disorders, including epidermolysis bullosa (EB), which is characterized by the formation of blisters. A recent study has focused on the therapeutic potential of autologous fibroblasts as a treatment option for EB. The researchers used a lentiviral vector to correct a specific genetic defect in the patients' cells. The corrected cells were then transplanted into the patients, with the goal of improving skin integrity and preventing blister formation. This approach demonstrates the potential of gene therapy in treating complex genetic disorders, offering hope for patients with EB and other genetic skin conditions. Further studies are necessary to evaluate the long-term efficacy and safety of this therapeutic strategy.

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**Steady state pharmacokinetics, tolerability and safety of XP23829, a novel fumaric acid ester (FAE) for the treatment of moderate-to-severe plaque psoriasis**

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The objective was to assess the pharmacokinetics (PK), tolerability, and safety of an extended release (ER) FAE formulation after repeated daily dosing. XP23829 is a prodrug of monomethyl fumarate (MMF), the active metabolite of dimethyl fumarate (DMF). DMF is currently licensed in Germany for the treatment of moderate-to-severe psoriasis vulgaris and is in the US for relapsing forms of multiple sclerosis. XP23829 ER has the potential for providing sustained plasma levels of MMF, translating into improved psoriasis control. The study included a single-day, single-dose, randomized, placebo-controlled, oral-dose PK study with healthy adults in sequential cohorts of 12 active and 1 placebo. Each cohort received 7 days of XP23829 at target dose after titration: at 800 mg QD and at 500 mg BID. The PK of MMF was determined on Day 7. Safety was evaluated by monitoring adverse events (AEs), laboratory tests and clinical assessments. Overall, the study demonstrated good tolerability and safety, with no serious AEs reported. The results suggest that XP23829 ER could be a promising therapeutic option for moderate-to-severe plaque psoriasis, offering a potential alternative to existing treatments with improved efficacy and safety profiles.

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**Pentobra: A novel antimicrobial compound with lytic activity against Propionibacterium acnes**

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- *1 Medicine, David Geffen School of Medicine, University of California, Los Angeles, CA, 2 Bioengineering, Department of Bioengineering, UCLA, Los Angeles, CA, 3 Department of Chemistry, and Biological Chemistry, University of California, Los Angeles, CA, 4 California Nanosystems Institute, University of California, Los Angeles, CA, and 5 Department of Dermatology, Greater Los Angeles Healthcare System Veterans Affairs, Los Angeles, CA*

Propionibacterium acnes is a pathogenic bacteria associated with acne vulgaris, which affects over 85% of the global population. The bacteria can cause skin inflammation, redness, and irritation, leading to the formation of acne lesions. Current therapies for acne include topical and oral antibiotics, topical retinoids, and systemic therapies. However, the use of antibiotics has led to the development of antibiotic-resistant strains, posing a significant challenge. A novel antimicrobial compound, Pentobra, has been developed as a potential treatment for acne. In vitro studies showed that Pentobra was effective against P. acnes, with minimal toxicity to human keratinocytes. Moreover, Pentobra demonstrated potent and selective killing of P. acnes in both planktonic and biofilm forms. The compound has the potential to be a viable alternative to current acne treatments, offering improved efficacy and decreased risk of antibiotic resistance.

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**Hamartomatic cell transplantation (HCT) for regressive dystrophic epidermolysis bullosa (RDEB): reduced intensity conditioning (RIC) has a better outcome than myeloablative conditioning (MAC)**

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Hamartomatic cell transplantation (HCT) is a promising therapeutic approach for treating severe genetic skin fragility disorders, such as RDEB. A recent study compared the outcomes of RDEB patients who underwent HCT using reduced-intensity conditioning (RIC) versus myeloablative conditioning (MAC). The findings revealed that RIC has a better outcome than MAC, with lower rates of disease progression and improved quality of life. This suggests that HCT could be a viable treatment option for patients with severe RDEB, offering a potential cure for this debilitating condition. Further studies are needed to confirm these findings and optimize the HCT approach for different patient populations.

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**Novel long-non-coding RNA in melanoma: MIRAT a biomarker of small molecule inhibitor responses**

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Long non-coding RNAs (lncRNAs) have emerged as important regulators of gene expression and cellular processes. In the study, a novel lncRNA, MIRAT, was identified and characterized as a biomarker of small molecule inhibitor responses in melanoma cells. MIRAT was found to be upregulated in response to BRAF and MEK inhibitors, serving as a potential biomarker of response to these treatments. The study also showed that MIRAT knockdown resulted in decreased protein levels of DUSP 6, followed by an induction of pp38, pp53, and p21, suggesting a potential role in the regulation of the MAPK pathway. These findings provide new insights into the mechanisms of small molecule inhibitor responses in melanoma and could have implications for the development of novel therapies.

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**Drug repurposing for dermatomyositis using public expression datasets**

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- *1 Department of Dermatology, Stanford University School of Medicine, Stanford, CA, 2 Division of Systems Medicine, Department of Pediatrics, Stanford University School of Medicine, Stanford, CA, 3 School of Medicine, Stanford University, Stanford, CA, 4 Department of Bioinformatic Informatics, Stanford University School of Medicine, Stanford, CA*

Dermatomyositis (DM) is a rare autoimmune disorder characterized by inflammation of the skin and muscle. Although the cutaneous manifestations of DM can be debilitating, current therapeutics for these conditions in DM are limited, reinforcing the need for a systematic approach to discover novel therapeutic targets. The study used a bioinformatics approach to combine gene expression data of over 47,000 transcripts from 48 lesional DM skin biopsies with gene expression data from over 1,400 U.S. Food and Drug Administration (FDA)-approved drugs to identify potential novel therapeutic targets for the treatment of DM skin. The researchers identified several drug candidates that showed promising activity against DM, including 120 compounds with potential for once-a-day dosing. The study highlights the potential of drug repurposing for treating DM, offering new avenues for the development of effective therapies for this debilitating condition.
A novel therapeutic inhibits Rac1 mediated invasion and metastasis in a newly described in vivo model of human melanoma

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Systemically administered tumor necrosis factor (TNF) inhibitors are highly effective for plaque psoriasis, but are not indicated for most patients because of their cost and associated risks. Novel spherically arrayed oligonucleotide nanoconjugates (SNA) for topical delivery of gene suppressive therapy traverse the epidermis when delivered in a simplified moisturizer, leading to targeted gene knockdown without observed toxicity or immune activation. We hypothesized that SNAs targeting human TNF could reverse the psoriatic phenotype. We engineered TNF nanoconjugates with antisense DNA arrayed around a central 13 nm gold nanoparticle (SNA) or a biodegradable liposomal nanoparticle (L-SNA). SNAs suppressed TNF mRNA and protein expression in human keratinocytes (NHKs) by 82% and 68%, respectively, in comparison with scrambled SNAs or PBS vehicle, while decreasing downstream S100A7 mRNA by 48% and p-DE2FA (β-defensin 2) by 50% (all p<0.001). Knockdown with TNF L-SNAs was similar (89%; 70%; 52% and 56%, respectively; all p<0.001). We then engineered a 3D model of human psoriasis by treating rats 6 days after lifting with 6 days of TNF, IL-17, and IL-22. Psoriasis rats showed many morphologic (parakeratosis, hypergranulosis, and abnormal stratiﬁcation, but no rete ridges) and transcriptomic (increased S100A7 and p-DE2FA, decreased keratin 10 and keratin 19) changes of psoriasis. TNF or scrambled SNAs 50 mN or PBS were applied to the surface of psoriasis or control rats at day 9 and rats were harvested at 12 d. SNAs targeting TNF decreased TNF mRNA by 70%, improved the abnormal differentiation, and reversed the psoriatic transcriptomic proﬁle (SNA reduced S100A7 and p-DE2FA by 51% and 56%, respectively, and IL-SNA by 45% and 42%; SNAs increased keratin 10 and keratin 19 by 45% and 45%, respectively, and L-SNA by 44% and 42%). SNAs and L-SNAs targeting TNF are a promising newly topicalized gene delivery for treating plaque psoriasis.

Electrophilic nitro-fatty acids suppress allergic contact dermatitis in an experimental model

S71

Mycobacterium fungoides (MF) is a subtype of CTCL characterized by long-standing inflammatory skin lesions that contain clonal malignant resident memory T cells. Although various topical therapies can suppress the disease, none are curative. Extremely low-dose irradiation (LDI, 4 gray x 2 treatments) can lead to long-term remissions in even refractory MF. We used high throughput TCR sequencing (HTS) to study malignant T cells in lesional skin before and after LDI. HTS identiﬁed the malignant clone in 14/14 pretreatment samples. 5/5 patients who have completed therapy experienced a complete clearing of the treated lesions. HTS demonstrated complete eradication of the malignant clonal in 3/5 patients, and 99.8% and 81% reductions in the remaining two. Diversity of T cells in skin increased after therapy, numerous benign T cells remained, and tracking of T cell clones present prior to therapy demonstrated these cells survived LDI. In some patients, expanded benign T cells clones after therapy suggested LDI may encourage antitumor immunity. To study the differential sensitivity of malignant versus benign human T cells to LDI, we used immunodeﬁcient mice grafted with human skin containing either benign resident memory T cells or the malignant MF T cell line MAC-1. HTS of treated grafts demonstrated that malignant T cells were markedly more sensitive to radiation than benign T cells. 97% of malignant T cells but only 47% of benign T cells were killed by 7 gray, a biologically close dose to the 4Gy x 2 used in patients. Benign skin T cells were remarkably resistant to radiation, with 30% surviving 11 gray radiation and 19% surviving 15 gray. However, this low-dose efﬁcacy of LDI effectively but spares healthy immunity. Cells that protect against infection and perhaps also recurrence of the cancer. Our results suggest low-dose irradiation may be a defective cure for MF skin lesions that spares healthy immunity.

Regression of cutaneous squamous cell carcinomas induced by topical application of PI3K/mTOR inhibitors

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Cytotoxic squamous cell carcinoma (cSCC) is the second most common human cancer and is associated with activation of Erk 1/2, PI3K/mTOR, Src tyrosine kinases and JAK-STAT. The K14-Fyn Y528F transgenic mouse is a model of cSCC that develops pre-cancerous lesions and cSCCs resembling human lesions. We hypothesized that topically kinase-targeting the PI3K/mTOR pathway could induce regression of cSCCs in K14 Fyn Y528F mice. To test this, cohorts of K14-Fyn Y528F mice were treated with two topical small molecule kinase inhibitors with nanomolar potency against PI3K and PI3K (Alisertib, A0.6 6 gel of DPT-NX7 and a 1.2 6 gel containing NBR1112 were compared to a control gel. The DPT-NX7-treated cohort contained 25 cSCCs, the NBR1112-treated cohort contained 38 cSCCs, while the control cohort contained 28 cSCCs. The size of cSCCs was similar in each cohort (from 8 square mm to 166 square mm) and was measured using calipers every other day for four weeks dramatically inhibited in vivo invasion and metastasis of Rac1MC xenografts (P=0.0001). B001 also inhibited Rac1-mediated invasion in all melanoma cell lines assayed (P<0.05). Overall, our results indicate development of a novel in vivo model of melanoma invasion and metastasis in xenografts that mimics human melanoma. We also demonstrate Rac1 as a relevant therapeutic target across several genetically distinct melanoma subtypes, and introduce B001 as a prototype of a novel class of agents to treat melanoma.

Reactions between nitric oxide, nitrite, and unsaturated fatty acids give rise to electrophilic nitro-fatty acids, which are potent anti-inflammatory mediators and modulate immune responses by inhibiting cytokine secretion. We hypothesized that nitro-fatty acids may be useful for the prevention and treatment of inflammatory disorders. Our goal was to determine if neutral neutralizing antibodies that inhibit nitro-fatty acid formation. Herein, we established that nitro-derivatives of fatty acid exhibit anti-inflammatory properties in vitro and in vivo, and to demonstrate the therapeutic potential of NC-517 in vivo. In contrast, topical application of NC-517 induced no side effects.
Gene Therapy & Clinical Therapeutics

2 target DNA methyltransferase, 4 target HDAC, 1 targets JAK, 1 targets histone demethylases, and histone methyltransferase, 1 targets histone acetyltransferase, 1 targets HIF, 2 target aurora kinase, compounds caused over a 100% increase in CD52 expression, although CD52 negative cells were

CD55 and CD59, were also down regulated, suggesting inhibition of the GPI linkage pathway.

to further treatment. CD52 down-regulation was stable despite the absence of further alemtuzumab

Epigenetic changes in the GPi-linked biosynthetic pathway underlie down regulation of CD52

Site-specific genome editing using CRISPR/Cas9 and TALENs for correction of iPS cells derived from dominant dystrophic epidermolysis bullosa

S Shinkuma, 1 Z Guo 1 and A Christiano 1, 2

we observed complete epidermal regeneration 30 days post grafting with clinically normal skin appearance at 3 and 6 months post transplantation for the first subject and 3 months post surgery for others. Others showed substantial apoptosis or senescence induction. Detailed studies revealed that the combination of IFN-alpha and TNF induced a stable state of senescence in vitro. Senescence was determined by cell cycle analysis, permanent growth arrest, induction of senescence-associated-he
ta-galactosidase (SA-beta-Gal), and senescence-defining p16Ink4a translocation. More importantly, inter-feron-alpha application, intraportal melanoma cells preferentially expressed the senescence marker SA-beta-Gal, whereas the proliferation marker Ki67 was clearly reduced. Simultaneously, melanoma cells became growth-arrested, expressed p16Ink4a and were cleared from the peritoneum. This is the first report showing that immune therapy can, besides killing, induce senescence in melanoma in vivo thereby critically contributing to cancer immune-control.

Cytokine-based immunotherapy induces senescence in human melanomas

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The effects of bisphosphonates on ectopic soft tissue mineralization caused by mutations in the ARCC6 gene: Potential treatment of PEX

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Pseudoachonlamia elastica (PE) and generalized arterial calcification of infancy (GACI) are her-
itables, currently intractable, ectopic mineralization disorders. Most cases of PEX and many cases of GACI harbor mutations in the COL7A1 gene. There is no effective treatment for these disorders. In this study we explored the potential efficacy of bisphosphonates to prevent ectopic calcification caused by ARCC6 using Abcc6 mice, a model of PEX, as a preclinical platform. The mice were fed diet containing calcium (CTDL), 10 and 66 mg/kg/day, or alendronate (AST), 0.53 and 6.36 mg/kg/day, respectively, corresponding to 1x and 12x of the doses used to treat osteoporosis in humans, respectively. The mice were placed on diet at 4 weeks of age, and the degree of mineralization was assessed at 12 weeks by quantitation of the calcium deposits in the dermal sheath of vibrissae, an early and prevalent marker of the mineralization process, by computerized morphometry of histopathologic sections and by direct chemical assay of calcium. We found that ETD, but not AST, at the 12x dosage, significantly reduced mineralization by 50-73%, however, 1x did not have any effect. Considering the low level of absorption of peroral ETD (<1%), subsequent studies tested the mice with subcutaneous injections of ETD, 0.08 and 0.96 mg/kg/day (0.01x and 0.12x).Twice weekly injections of ETD for 8 weeks resulted in a significant decrease in skin mineralization, as determined by calcium chemical assay, by 31 and 63%, respectively. These changes were accompanied by decreased alterations in the trabecular bone microarchitecture, determined by calcium chemical assay, by 31 and 63%, respectively. These changes were accompanied by decreased

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NY, 2 Biomedical Engineering, Columbia University, New York, NY and 3 Genetics and Disease modeling and drug development. Realization of the potential of iPSCs depends on the induction of pluripotent stem cells (iPSCs) can provide an unlimited number of cells for cell therapy, Z Guo, 1 C Shen, 2 K Gledhill, 1 HE Abaci, 1 A Coffman, 1 S Shinkuma, 1 C Higgins, 1
A differentiating endothelial cells from human induced pluripotent stem cells

Differentiating endothelial cells from human induced pluripotent stem cells

Intrinsic resistance to smoothened inhibitors in sporadic basal cell carcinoma

Assessment of amlexanox, an antagonist of nonsense mediated mRNA decay (NMD), for the treatment of RDEB

Intriguingly, 9% of sporadic BCCs harbored SMO mutations with T558 mutations, a highly conserved residue. Both of these mutations cause constitutive activation of SMO likely through the phospho-kinase activation of SMO kinase. Blockade of SMO by small-molecule inhibitors has been shown to induce cell-cycle arrest and apoptosis in BCCs. Several clinical trials have demonstrated the clinical efficacy of SMO inhibitors in BCCs.

BCCs harbored SMO mutations previously shown to confer SI resistance, including SMO p.L412F and SMO p.W535L. Both of these mutations cause constitutive activation of SMO likely through the phospho-kinase activation of SMO kinase. Blockade of SMO by small-molecule inhibitors has been shown to induce cell-cycle arrest and apoptosis in BCCs. Several clinical trials have demonstrated the clinical efficacy of SMO inhibitors in BCCs.

We have previously identified specific mutations in SMO that can confer SI resistance by disrupting drug binding or interfering with SMO autoinhibition. However, it remains unclear if these resistant mutations are acquired during treatment or present prior to the development of resistance. We performed targeted sequencing for SMO, PTCH and TP53 in 58 sporadic untreated BCCs. 66% of patients showed resistance to SMO inhibitors, most commonly due to point mutations in Patched1 (PTCH) or activating mutations in Smoothened (SMO), is a crucial driver of tumorigenesis in basal cell carcinoma (BCC), medulloblastoma, and other cancers. SMO mutations (T558 mutations, a highly conserved residue) are highly prevalent in sporadic BCCs, however, the clinical implications of these mutations are not well understood.

SMO mutations are associated with substantial resistance to SMO inhibitors. A recent study identified SMO mutations in 66% of sporadic BCCs, suggesting that these mutations drive tumorigenesis in sporadic BCCs. We have previously identified specific mutations in SMO that can confer SI resistance by disrupting drug binding or interfering with SMO autoinhibition. However, it remains unclear if these resistant mutations are acquired during treatment or present prior to the development of resistance. We performed targeted sequencing for SMO, PTCH and TP53 in 58 sporadic untreated BCCs. 66% of patients showed resistance to SMO inhibitors, most commonly due to point mutations in Patched1 (PTCH) or activating mutations in Smoothened (SMO), is a crucial driver of tumorigenesis in basal cell carcinoma (BCC), medulloblastoma, and other cancers. SMO mutations (T558 mutations, a highly conserved residue) are highly prevalent in sporadic BCCs, however, the clinical implications of these mutations are not well understood.

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