263 First in human use of a novel in vivo gene therapy for the treatment of autosomal recessive congenital ichthyosis: Results of a phase I/II placebo controlled clinical trial

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Autosomal recessive congenital ichthyosis (ARC) is a rare, monogenic cornification disorder with erythema, epidermal scaling, ectropion, and impaired skin barrier function. Mutations in TGM1 encoding transglutaminase-1 are the predominant cause of ARC, affecting >5% of US ARC patients. Current therapeutic options for treating ARC provide only symptomatic relief, necessitating the development of targeted therapeutics. KB105 is a novel, convenient, first in class, off-the-shelf disease correcting gene therapy for the treatment of TGM1-deficient ARCI. KB105 poorly penetrates TGM1-deficient epidermis, allowing for localized delivery of TGM1-RNAi silence. In a two dose escalation study for KB105 in ARC patients, demonstrating that application of KB105, the first and only correcting therapeutic candidate for TGM1-deficient ARCI was well tolerated and efficacious. With safety and efficacy in larger target areas and expand enrollment to pediatric subjects in 1H 2020.

264 Interrogating altered enhancer landscapes to decode pathogenic changes in macrophages during chronic inflammatory disease

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Macrophages are key immune cells in dermatologic diseases. This integrated genomics-based approach will yield insights into the mechanisms controlling immune cells in dermatologic diseases.

265 Genome-wide association study of hidradenitis suppurativa in a multi-ethnic cohort

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Hidradenitis suppurativa (HS) is a prevalent inflammatory skin disease. HS patients suffer from deep, painful abscesses that drain malodorous fluid and lead to disfiguring scars that can limit mobility. African Americans and females are at an increased risk. A lack of effective therapies and limited knowledge about HS pathogenesis contribute to unmet needs. Unlike other common inflammatory skin diseases, there has never been a genome-wide association study (GWAS) conducted for HS. Here, we performed a first GWAS for HS using data from the EMERGE network of electronic health record linked biorepositories (project NCT2275758). Our study found robust evidence to identify common and rare variants, with principal component analysis using a set of 40,156 SNPs. Our final cohort consisted of 600 HS cases and 82,611 controls with comparable multi-ethnic ancestry (\(p < 0.05\)). Our cohort recapitulated HS race and gender predictions with genetically African female participants accounting for 35% of cases, but only 10% of controls. Genotype data for 40 million variants was tested for association, adjusting for five principle components. No locus exceeded our threshold for statistical significance. There was no evidence for HLA association supporting classification of HS as inflammatory rather than autoimmunity. Several loci approached the significance threshold, suggesting that a moderate expansion in cohort size may provide adequate power to detect associations. Interestingly, the lead SNP at one of the most significant loci (rs1075745, p = 8x10\(^{-10}\)) is an eQTL for NFAT5, a mediator of NOTCH and WNT signaling pathways.

266 Trichothiodystrophy, a multisystem disorder with early onset debilitating hip degeneration

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Trichothiodystrophy (TTD) is a rare multisystem autosomal recessive disorder of DNA repair and transcription. Cut hair shafts have “tiger tail” banding with polarizing microscopy. Patients have multiple skeletal abnormalities, e.g. short stature, osteosclerosis of the central skeleton with metaphyseal scalloping of the long appendicular skeleton. They have a high risk of death before the age of 10 years, usually from infection. Between 2001 and 2019 we followed a cohort of 39 TTD patients, ranging in age from 1-36 years. Twenty-four had mutations in the X-linked TTD gene, 5 in TTD1, 3 in TTD2, 1 in TTD19, and 6 in unknown genes. Nine had X chromosome deletions with Xp22 mutations developed rapidly progressive, debilitating hip degeneration. Typically, this started at or near age 8 years (range 5-12) as hip pain/leg pain that interfered with walking. In the 9 patients with Xp22 deletions, the mean age of diagnosis was 8 years (range 5-10). Of the 9 affected patients, all had lower extremity contractures/limited extension on clinical examination and 6 had W sitting, suggesting joint laxity. In 6 of the 9 patients similar changes rapidly developed in the other hip, by mean age 10 years (6-17). Only 1 patient of the 9 affected was able to regain ambulation. Following bilateral hip replacements at age 17, he continues to be ambulatory at age 29 years. Three of the 9 died (aged 9, 9, and 15 years), 2 from complications of hip surgery. The average age of the 30 TTD patients without hip degeneration was 14 (range 1-36 years). Seven of these patients died at mean age 10 years (range 2-36): 5 had XPD mutations, 1 TTD1 and 1 unknown. Avascular necrosis may be caused by several collagen abnormalities, e.g., Legg-Calve-Perthes disease (COL1A1 mutations), multiple epiphyseal dysplasia (type IX collagen mutations). The previously reported association of COL6A1 expression and/or overexpression of matrix metalloproteinase 1 in fibroblasts from TTD patients with XPD mutations suggest that collagen abnormalities may contribute to these degenerative hip abnormalities.

267 Mechanisms governing epigenetic regulation of apoptosis in CTCL

Implications for therapy with methotrexate, JAK inhibitors, and resveratrol

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We showed previously that the death receptor ligand pair, FAS/FASL, is silenced at least partially by DNA methylation, and XL1, a selective JAK2 inhibitor, knockdown of DNMT1 and/or 3a, increased FAS/FASL expression in association with decreased promoter methylation. MTX also increased Caspases 3/8 and apoptotic cell death in CTCL lines HH, S24, Hut78, and JTTa. FASL promoter methylation was decreased by MTX, knockdown of DNMT1 and/or DNMT3A in these same CTCL lines with the most significant effects in FAS methylation-high HH and S24. Furthermore, MTX enhanced FASL upregulation induced by knockdown of either DNMT1 or DNMT3A. Using pull-down experiments, we identified STAT1 as a DNMT binding partner for methyl-CpG binding protein (MeCP2) for STAT1 at Tyr-705. The selective JAK2 inhibitor, Fedratinib (FED), was more effective than other mixed JAK inhibitors within IL12B and ATP2C1. We detect novel signals as well as confirm previously detected signals in reducing CTCL viability, spheroid formation, and STAT3 phosphorylation at Tyr-705. Selective JAK2 inhibitor, Fedratinib (FED), was more effective than other mixed JAK inhibitors in reducing CTCL viability, spheroid formation, and STAT3 phosphorylation at Tyr-705.