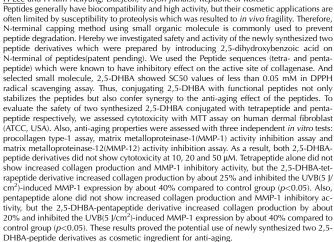
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Assessment of anti-aging properties of novel natural compounds-peptide

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Fascin and Cdk2 are synthetic lethal partners with exceptional potential as joint therapeutic targets in malignant melanoma

SP Smith University of Cambridge, Brinkley, England, United Kingdom Malignant melanoma kills nearly 60,000 people worldwide each year. New targeted treatments have been developed in the last decade which are improving outcomes in late stage disease, but their impact remains limited, and resistance to these new treatments develops quickly in many patients. This study addresses the urgent unmet need for combinations of treatments in melanoma by identifying targets whose expression showed synthetic lethality in clinical melanoma samples. Gene expression was measured by RNA sequencing in melanoma samples (n=445 (TCGA)) and in normal skin (n=558 (GTEx)). Pairs with expression distributions deviant from normal, and which showed no overlap of low expression in melanoma samples were identified. Those with significant synthetic lethality scores were analysed to identify pairs present in functionally redundant pathways. Synthetically lethal partners in melanoma were investigated to identify pairs whose expression was not synthetically lethal in normal skin. These analyses revealed that FSCN1 (Fascin 1) and CDK2 (cyclin-dependent kinase 2) were significantly synthetically lethal, with no samples expressing both genes at low levels in melanoma, but the majority of normal skin samples expressing both at low levels. These genes are directly involved in overlapping and redundant pathways. They have been individually targeted successfully in preclinical trials and demostrate anti-cancer activity. Cdk2 inhibitors have also been tested in stage 3 clinical trials in non-melanoma cancers with good efficacy, but significant toxicity. Along with proprietary small molecules targeting Facsin and Cdk2, this study identified potential drug repositioning candidates. Importantly, independent studies have demonstrated that compounds, including off-patent therapeutic molecules and phytochemicals, can downregulate these genes. Using established targeting compounds which have known safety profiles and PKPD may shorten the development pathway and improve cost effectiveness. Fascin/Cdk2 are potentially synergistic drug targets and may represent a powerful new avenue to treating malignant mela-

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Minipig model of atopic dermatitis: Assessment of in vivo and in vitro activity of recombinant porcine interleukin-4 and interleukin-13

M Jones¹, M Zhong¹, S Johnson¹, D Brocksmith², G Bouchard¹ and A Stricker-Krongrad¹ 1 Sinclair Research Center, Auxvasse, MO and 2 Sinclair Bio Resources, Auxvasse, MO Atopic Dermatitis is a common skin condition that clinically presents as erythematic, dry, pruritic skin. While multiple factors contribute to the pathophysiology of the disease, prominent Th2-mediated immune responses are characteristic of AD. Interleukin-4 (IL-4) and Interleukin-13 may contribute to the pathogenesis of AD. Minipigs are used frequently for toxicity/safety of dermally applied products, and thus a model of AD in minipigs would be beneficial for pre-clinical efficacy tests of such medications. This study assessed sensitivity of Hanford minipigs to recombinant porcine (rp) IL-4 and IL-13. Peripheral Blood Mononuclear Cells (PBMC) isolated from female Hanford minipigs demonstrated approximately a 4 fold increase in STAT6 phosphorylation when challenged with rpIL-4, but not rpIL-13. When female Hanfords received a single intradermal dose of rpIL-4 or rpIL-13, erythema and edema was not different from vehicle control dose sites. However, repeat intradermal injections for a period of five days did elicit increased erythema and edema in rpIL-4 dose sites relative to vehicle control, but not rpIL-13 dose sites. The peak irritation was observed approximately 5 minutes after dose administration, similar to histamine injections in minipigs. Interestingly, perivascular or dermal lymphocytes were observed in ~25-38% of rplL-4 and rplL-13 dose sites, but were not present in the vehicle control sites. Perivascular eosinophils were observed in \sim 25% of the rpIL-4 dose sites, while not observed in vehicle or rpIL-13 dose sites. This suggests that intradermal injection of rpIL-4 and rpIL-13 may recruit lymphocytes to dermal tissues. These findings that rpIL-4 and rpIL-13 appear to have biological activity in Hanford minipigs, and are good candidates for further exploration in developing a porcine model of Atopic Dermatitis.

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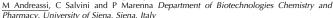
Biomarkers CCL17/TARC and total IgE do not predict clinical response to dupilumab in atopic dermatitis (AD): A post hoc analysis of pooled phase 3



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Dupilumab (DUP), a fully human IL-4Rα mAb, inhibits signaling of IL-4/IL-13, key drivers of Type 2/ Th2 immune diseases such as AD/asthma. CCL17 (TARC) and IgE production are enhanced by IL-4/ IL-13 and correlate with AD severity. This pooled post hoc analysis reports the relationship between baseline (BL) serum CCL17 and total IgE levels and DUP treatment effect in adults with moderateto-severe AD in 2 identical double-blind, placebo (PBO)-controlled phase 3 trials (SOLO 1: NCT02277743 , N=671; SOLO 2: NCT02277769 , N=708). Patients (pts; N=1,379) were randomized (1:1:1) to subcutaneous 300 mg DUP weekly (qw), every 2 weeks (q2w), or PBO for 16 weeks (W). CCL17 and total IgE were measured in serum samples collected between BL and W16 using commercial assays. Efficacy analyses by BL CCL17 tertiles (≤1115; >1115 to ≤4300; and > 4300 pg/mL) and total IgE subgroups (< 150 kU/L and \geq 150 kU/L) were performed for % changes from BL in Eczema Area and Severity Index (EASI) and peak pruritus Numerical Rating Scale (NRS). On study entry, pts with low BL CCL17 (\leq 1115 pg/mL; n=457) or IgE concentrations (<150 kU/L; n=220) had numerically lower BL EASI and pruritus NRS scores than pts with high CCL17 (>4300 pg/mL; n=457) or IgE levels (≥150 kU/L; n=1158). Both DUP dose regimens significantly reduced EASI and pruritus NRS scores from BL at W16 vs PBO in pts with high, mid, or low BL CCL17 or high or low IgE levels (all P<0.0001 vs PBO, except pruritus in the low IgE group [P=0.002/P=0.006; qw/q2w]). The most common adverse events with DUP vs PBO were injection-site reactions and conjunctivitis. BL levels of CCL17 and IgE did not predict DUP treatment response (% reductions in EASI and pruritus NRS), although the smaller n of the low IgE group and lower BL disease activity in the low CCL17 and IgE groups may affect the power of this analysis.

Formulation and evaluation of topical products with Cannabis Sativa oil



This work was aimed to study the stability, and the activity of topical products formulated with Cannabis Sativa oil produced in Italy, in Tuscany (not containing THC). Recent studies have suggested a possible moisturizing and elasticizing activity of Cannabis Sativa oil. For such characteristics Cannabis Sativa oil appears an appropriate ingredient to be used in topical preparations for the treatment of skin hydration. The oil was incorporated into O/W emulsion in a standard formulation at percent concentration of 1%, 3% and 5% respectively of Cannabis Sativa seed oil, one O/W emulsion was preparied without active ingredient as control. The investigation was carried out on 20 healthy male and female volunteers, between the ages of 20 and 40, with normal or dry skin. Each product was applied to the volar surface of the forearm at a dose of 3 mg/cm². As control, the same cream without active ingredient was applied to the other forearm. To evaluate TEWL and skin elasticity, was used the device Aveal 220 (Sylton diagnostic systems). The skin hydration action of the emulsions was evaluated in relation to basal value, and the emulsion without active ingredient, respectively after 15 minutes and 7 days. The skin elasticity was evaluated after 1 h, 8 h and after 7 days. The results showed that the 3 emulsions with Cannabis Sativa oil, compared to the emulsion without active, significantly increase the degree of hydration and elasticity of the skin. The 3% formulation of Hemp oil has a greater power of hydration of the skin compared to other emulsions, both short and long term and is the emulsion that has produced better results.

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Biodegradable bioadhesive nanoparticle delivery of camptothecin for the treatment of PDV squamous cell carcinoma

AK Lee¹, H Suh², E Yin¹, J Lewis¹, W Saltzman² and M Girardi¹ 1 Yale School of Medicine, New Haven, CT and 2 Yale School of Engineering & Applied Science, New Haven, CT Using uniquely coated, biodegradable nanoparticles (NP) as a chemotherapy delivery system, we tested the safety and efficacy of intratumoral injections of NP-encapsulated camptothecin (CPT) in the treatment of squamous cell carcinoma (SCC) in mice. Biodegradable poly(lactic acid)-hyperbranched polyglycerol NPs, biochemically rendered to be either non-adhesive (NNPs) or bioadhesive (BNPs), have been shown to enhance drug delivery with improved solubility and bioavailability within solid tumors. NNPs can be chemically converted into BNPs, which can bind to tumor matrix and cell surface proteins to facilitate sustained drug release. We first tested the ability of dye-loaded NPs to associate with the murine SCC tumor cell line, PDV, in vitro and found that BNPs had increased association compared to NNPs. Injection of dye-loaded NPs into PDV SCC tumors in mice resulted in widespread intratumoral distribution. Having established the ability of dye-loaded NNPs and BNPs to associate with and be taken up by SCC cells and resulting tumors, we therefore assessed the potential therapeutic effects of NNP-encapsulated CPT (NNP-CPT) and BNP-encapsulated CPT (BNP-CPT) on tumors in vivo. PDV SCC tumors were induced in 20 B6TCRβ KO mice, and treated with 2.5mg/kg twice weekly intratumoral injections of NNP-CPT, BNP-CPT, CPT in vehicle (IL-CPT), or intralipid (IL) vehicle. Tumor volumes were monitored over time and tumor histology was performed at termination. Time to reach 1 cm was substantially delayed with NNP-CPT (LD60 at 49d; p=0.0020) and BNP-CPT (LD60 at 59d; p=0.0020), and significantly delayed with IL-CPT (LD60 at 36d; p=0.013) relative to IL (LD60 at 29d). Histologic examination of the tumors at termination revealed the presence of marked necrosis with NNP-CPT and BNP-CPT treatment. Our results suggest that biodegradable NP delivery of CPT offers potential for the efficient treatment of SCC and other skin neoplasms



