ABSTRACTS

**LB1571**

**Effects of SB414 cream on S. aureus and tissue cytokines in an atopic dermatitis mouse model**

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Atopic dermatitis (AD) is a chronic inflammatory skin disease where >90% of AD patients exhibit Staphylococcus aureus (SA) colonization of their lesional skin. The density of SA colonization has been correlated with both severity of AD lesions and the degree of cutaneous inflammation. A filaggrin-defect atopic dermatitis mouse model (FG5 transgenic mice) has been used previously to correlate the depth of SA skin penetration with upregulation of IL-4, IL-13 and other cytokines. Using this model where mice are first sensitized by ovalbumin and then exposed to 1 x 10^6 colony forming units (CFU) SA, a pilot study was conducted to identify the time course of peak cytokines levels (48 hrs) after cutaneous infection with SA and determine the optimal, treatment window (initiate dosing at 24 hrs). In a second study, animals were treated topically after the 24 hr SA incubation period, and again 8 hrs later, with vehicle or 6% SB414, a cream that releases nitric oxide. At 48 hrs, mice were euthanized and biopsied for SA counts and tissue cytokines levels in all treatment groups (IL-4, IL-13, TSLP, IFNγ, IL-17a). Upregulation of individual cytokines in the untreated group ranged from 3 to 18-fold. All cytokine levels in the SB414-treated group, except IL-17a, were statistically indistinguishable from the unaffected, baseline tissue cytokine values. IL-4 was reduced by 67% and IL-13 by 76% compared to placebo treated mice. TSLP, an initiator of the atopic response and a sensitive marker of chemical irritation, was not elevated in SB414-treated infected or uninfected mice, demonstrating the local tolerability of the nitric oxide releasing cream. SA levels in mice were measured to be <0.63 x 10^10 CFUs, representing a >90% reduction over untreated and vehicle treated mice. Importantly, the anti-staph effects of SB414 were not driven by increased IFNγ tissue cytokine levels. Collectively, these data demonstrate the ability of topically applied 6% SB414 to reduce key Th2 cytokines like IL-4 and IL-13, and to reduce SA burden in an atopic dermatitis mouse model.

**LB1572**

**Evaluation of a novel therapy and identification of uncertainties critical to efficacy and competitive differentiation in a Psoriasis PhysioPD® Platform**

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The efficacy of SNA-125, a first-in-class topical selective kinase inhibitor (including JAK3/C212) was applied once daily for 10 days on ears and shaved backs to induce PSO. SNA-125 (5% or 10%) or vehicle (25% transcutol P; 75% propylene glycol) was applied twice daily to ears and backs (2 and 8 hrs post-IMQ) for 10 days. When the positive control was applied once daily (clohexol 0.05%; 2 hrs post-IMQ), the PSO clinical score (sum of component erythema [0-4], plaque [0-5], and punctate redness/scabbing [0-3] scores) was assessed daily. Ear thickness was measured on days 0, 4, 6, and 10. On day 4, PSO-associated cytokine levels were measured on ear punch biopsies for IL-17F. On day 10, spleen weight was measured. Both doses of SNA-125 resulted in significantly greater improvement in PSO clinical score relative to vehicle (5%): p<0.01 for days 5, 8, and 10 and p<0.05 for day 9; (10%): p<0.01 for days 4, 8, and 10. Specifically, SNA-125 demonstrated a dose-dependent increase in erythema, with the 10% dose demonstrating a significantly greater increase in erythema than vehicle. These data suggest that SNA-125 is an effective treatment for psoriasis, with the highest dose showing the most promise for clinical efficacy.

**LB1573**

**A novel small molecule STK899704 reveals anticancer activity and prevents skin carcinogenesis in vivo**


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Skin cancer is the most common type of cancer worldwide. Both prevention and protection against skin cancer is a global issue, and an advanced therapy with convenient accessibility and low side effects would be in high demand. In an effort to discover anticancer agents, we identified a novel tubulin inhibitor STK899704, which structure is distinct from other microtubule-binding agents such as colchicine, vinca alkaloids, and taxanes. STK899704 inhibited microtubule polymerization leading to the cell cycle arrest at mitosis, and repressed the proliferation of cancer cell lines from various origins. Moreover, our preclinical evaluation of the novel compound STK899704 revealed both the prevention and regression of tumors using in vivo skin carcinogenesis model. Interestingly, almost 80% of the tumors treated with STK899704 were regressed with tumor size reduced to one fifth of the initial tumor volume. The efficacy of STK899704 was two times higher than that of 5-fluorouracil, a widely used skin cancer therapeutic. Our results demonstrate the potential of STK899704 to be a promising anticancer chemotherapy and an alternative candidate for existing therapies, particularly for the treatment of skin cancer.

**LB1574**

**Novel small molecule LB1576 reveals anticancer activity and prevents skin carcinogenesis in vivo**

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Skin cancer is the most common type of cancer worldwide. Both prevention and protection against skin cancer is a global issue, and an advanced therapy with convenient accessibility and low side effects would be in high demand. In an effort to discover anticancer agents, we identified a novel tubulin inhibitor STK899704, which structure is distinct from other microtubule-binding agents such as colchicine, vinca alkaloids, and taxanes. STK899704 inhibited microtubule polymerization leading to the cell cycle arrest at mitosis, and repressed the proliferation of cancer cell lines from various origins. Moreover, our preclinical evaluation of the novel compound STK899704 revealed both the prevention and regression of tumors using in vivo skin carcinogenesis model. Interestingly, almost 80% of the tumors treated with STK899704 were regressed with tumor size reduced to one fifth of the initial tumor volume. The efficacy of STK899704 was two times higher than that of 5-fluorouracil, a widely used skin cancer therapeutic. Our results demonstrate the potential of STK899704 to be a promising anticancer chemotherapy and an alternative candidate for existing therapies, particularly for the treatment of skin cancer.

**LB1575**

**SNA-125, a novel selective kinase inhibitor, improves clinical symptoms in a mouse model of psoriasis**

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The efficacy of SNA-125, a first-in-class topical selective kinase inhibitor (including JAK3/C212) was applied once daily for 10 days on ears and shaved backs to induce PSO. SNA-125 (5% or 10%) or vehicle (25% transcutol P; 75% propylene glycol) was applied twice daily to ears and backs (2 and 8 hrs post-IMQ) for 10 days. When the positive control was applied once daily (clohexol 0.05%; 2 hrs post-IMQ), the PSO clinical score (sum of component erythema [0-4], plaque [0-5], and punctate redness/scabbing [0-3] scores) was assessed daily. Ear thickness was measured on days 0, 4, 6, and 10. On day 4, PSO-associated cytokine levels were measured on ear punch biopsies for IL-17F. On day 10, spleen weight was measured. Both doses of SNA-125 resulted in significantly greater improvement in PSO clinical score relative to vehicle (5%): p<0.01 for days 5, 8, and 10 and p<0.05 for day 9; (10%): p<0.01 for days 4, 8, and 10. Specifically, SNA-125 demonstrated a dose-dependent increase in erythema, with the 10% dose demonstrating a significantly greater increase in erythema than vehicle. These data suggest that SNA-125 is an effective treatment for psoriasis, with the highest dose showing the most promise for clinical efficacy.

**LB1576**

**Applying a novel computational drug-repurposing system to psoriasis**

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Psoriasis is the most common chronic immune skin condition, impacting roughly 125 million people worldwide. The pathogenesis is not wholly understood, though an assumed complex interplay between environmental factors, immune dysregulation and genetic susceptibility suggests that an autoinflammatory pathway contributes to the skin disease. We previously reported the activation of immune cells in the skin leading to a dysregulated pro-inflammatory response. This response triggers secretion of IL-12 and IL-23, causing migration and differentiation of Th17 and Th1 cells. These cells release cytokines such as IL-22 and IL-17AT driving proliferation of keratinocytes and epithelial cells. It has become increasingly important to model this disease, in immune competent animals such as rats. To this end, MD Biosciences has optimized two psoriasis models in the rat. IMQ mimics a pathogenic insult to the skin, eliciting a robust Th17 immune response leading to plaque formation. IMQ is applied to the shaved backs and ears of naive rats, and disease progression and skin thickening is monitored. Diseased animals exhibit erythema and plaque formation shortly after the start of the study and progress through terminations accompanied by increased biomarkers, IL-12, IL-17A and IL-17E. IL-23 is the main pathogenic cytokine in the initiation of psoriasis disease progression and has become a target for the clinical treatment. Exogenous IL-23 can be delivered directly to the dermis of rats to induce a downstream cascade of inflammatory biomarker upregulation, erythema and epidermal hyperplasia, similar to what is seen in human psoriatic plaques. The IMQ- and IL-23-induced psoriasis models are robust pre-clinical models to help develop therapeutics, as both models mimic specific disease pathologies. These models can be used to assess efficacy of candidate drugs for pathogenic pathway targeting such as Th17 and Th1-23IL-17. The versatility of the models and the benefits of the rat as a host organism make these models ideal for pre-clinical drug development for psoriasis or other Th17/IL-17 dependent diseases.