

Bladder tissue engineering through nanotechnology

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The field of tissue engineering has developed in phases: initially researchers searched for “inert” biomaterials to act solely as replacement structures in the body. Then, they explored biodegradable scaffolds – both naturally derived and synthetic – for the temporary support of growing tissues. Now, a third phase of tissue engineering has developed, through the subcategory of “regenerative medicine.” This renewed focus toward control over tissue morphology and cell phenotype requires proportional advances in scaffold design. Discoveries in nanotechnology have driven both our understanding of cell-substrate interactions, and our ability to influence them. By operating at the size regime of proteins themselves, nanotechnology gives us the opportunity to directly speak the language of cells, through reliable, repeatable creation of nanoscale features. Understanding the synthesis of nanoscale materials, via “top-down” and “bottom-up” strategies, allows researchers to assess the capabilities and limits inherent in both techniques. Urology research as a whole, and bladder regeneration in particular, are well-positioned to benefit from such advances, since our present technology has yet to reach the end goal of functional bladder restoration. In this article, we discuss the current applications of nanoscale materials to bladder tissue engineering, and encourage researchers to explore these interdisciplinary technologies now, or risk playing catch-up in the future.

Vitamin D deficiency in children with chronic kidney disease: Uncovering an epidemic

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BACKGROUND: Vitamin D deficiency in children adversely affects bone development by reducing mineralization. Children with chronic kidney disease are at risk for altered bone development from renal osteodystrophy and concomitant vitamin D deficiency. The pediatric Kidney Disease Outcomes Quality Initiative guidelines suggest measuring serum 25-hydroxyvitamin D (25[OH]D) levels if serum parathyroid hormone levels are above the target range for chronic kidney disease stages 2 and beyond, but the magnitude of vitamin D deficiency in children with chronic kidney disease is not well studied. **OBJECTIVES:** The purpose of this work was to determine whether children with chronic kidney disease had vitamin D deficiency, to evaluate whether the prevalence of vitamin D deficiency changed over time, and to examine seasonal and ethnic differences in

25(OH)D levels. **METHODS:** 25(OH)D levels in children with chronic kidney disease (stages 1–5) were measured over a 10-year period from 1987 to 1996. Data were also collected for a contemporary group of patients from 2005 to 2006. **RESULTS:** The prevalence of vitamin D deficiency ranged from 20% to 75% in the decade studied. There was a significant trend for decreasing 25(OH)D levels over the decade, both at the group and individual levels. Seasonal variation was noted. In our contemporary population with chronic kidney disease, the mean 25(OH)D level was 21.8 ng/mL; we found a prevalence of vitamin D deficiency of 39%. Black and Hispanic patients had lower levels of 25(OH)D than white patients. **CONCLUSIONS:** Children with chronic kidney disease have great risk for vitamin D deficiency, and its prevalence was increasing yearly in the studied decade. Contemporary data show that vitamin D deficiency remains a problem in these children. Sunlight exposure and ethnicity play a role in levels of 25(OH)D. Our data support the recent pediatric Kidney Disease Outcomes Quality Initiative guidelines for measurement of 25(OH)D levels in children with chronic kidney disease and secondary hyperparathyroidism.

Familial aggregation of food allergy and sensitization to food allergens: A family-based study

Tsai HJ, Kumar R, Pongracic J, Liu X, Story R, Yu Y, Caruso D, Costello J, Schroeder A, Fang Y, Demirtas H, Meyer KE, O’Gorman MR, Wang X.
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BACKGROUND: The increasing prevalence of food allergy (FA) is a growing clinical and public health problem. The contribution of genetic factors to FA remains largely unknown. **OBJECTIVE:** This study examined the pattern of familial aggregation and the degree to which genetic factors contribute to FA and sensitization to food allergens. **METHODS:** This study included 581 nuclear families (2,004 subjects) as part of an ongoing FA study in Chicago, IL, USA. FA was defined by a set of criteria including timing, clinical symptoms obtained via standardized questionnaire interview and corroborative specific IgE cut-offs for > or =95% positive predictive value (PPV) for food allergens measured by Phadia ImmunoCAP. Familial aggregation of FA as well as sensitization to food allergens was examined using generalized estimating equation (GEE) models, with adjustment for important covariates including age, gender, ethnicity and birth order. Heritability was estimated for food-specific IgE measurements. **RESULTS:** FA in the index child was a significant and independent predictor of FA in other siblings (OR=2.6, 95% CI: 1.2-5.6, P=0.01). There were significant and positive associations among family members

(father-offspring, mother-offspring, index-other siblings) for total IgE and specific IgE to all the nine major food allergens tested in this sample (sesame, peanut, wheat, milk, egg white, soy, walnut, shrimp and cod fish). The estimated heritability of food-specific IgE ranged from 0.15 to 0.35 and was statistically significant for all the nine tested food allergens. **CONCLUSION:** This family-based study demonstrates strong familial aggregation of FA and sensitization to food allergens, especially, among siblings. The heritability estimates indicate that food-specific IgE is likely influenced by both genetic and environmental factors. Together, this study provides strong evidence that both host genetic susceptibility and environmental factors determine the complex trait of IgE-mediated FA.

Cathepsin L inhibition suppresses drug resistance in vitro and in vivo: A putative mechanism

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Cathepsin L is a lysosomal enzyme thought to play a key role in malignant transformation. Recent work from our laboratory has demonstrated that this enzyme may also regulate cancer cell resistance to chemotherapy. The present study was undertaken to define the relevance of targeting cathepsin L in the suppression of drug resistance in vitro and in vivo and also to understand the mechanism(s) of its action. In vitro experiments indicated that cancer cell adaptation to increased amounts of doxorubicin over time was prevented in the presence of a cathepsin L inhibitor, suggesting that inhibition of this enzyme not only reverses but also prevents the development of drug resistance. The combination of the cathepsin L inhibitor with doxorubicin also strongly suppressed the proliferation of drug-resistant tumors in nude mice. An investigation of the underlying mechanism(s) led to the finding that the active form of this enzyme shuttles between the cytoplasm and nucleus. As a result, its inhibition stabilizes and enhances the availability of cytoplasmic and nuclear protein drug targets including estrogen receptor-alpha, Bcr-Abl, topoisomerase-IIalpha, histone deacetylase 1, and the androgen receptor. In support of this, the cellular response to doxorubicin, tamoxifen, imatinib, trichostatin A, and flutamide increased in the presence of the cathepsin L inhibitor. Together, these findings provided evidence for the potential role of cathepsin L as a target to suppress cancer resistance to chemotherapy and uncovered a novel mechanism by which protease inhibition-mediated drug target stabilization may enhance cellular visibility and, thus, susceptibility to anticancer agents.

Three times weekly tacrolimus ointment reduces relapse in stabilized atopic dermatitis:

A new paradigm for use

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OBJECTIVE: Long-term, safe and effective therapeutic options for managing the chronic relapsing nature of atopic dermatitis are essential for improving patient quality of life. To minimize the risks of continued topical corticosteroid usage and potentially reduce the incidence of flares, we tested the efficacy and safety of a rotational paradigm of initial brief application of topical corticosteroid followed by long-term intermittent application of non-steroidal tacrolimus ointment to previously inflamed sites of dermatitis. **METHODS:** In this 2-phase study, patients who were 2 to 15 years of age and had moderate to severe atopic dermatitis were randomly assigned to 4 days of twice-daily double-blind therapy with either alclometasone ointment 0.05% or tacrolimus ointment 0.03% (Phase I acute), followed by up to 16 weeks of twice-daily open-label tacrolimus ointment 0.03% (Phase I short-term). Patients whose disease stabilized underwent new randomization to double-blind tacrolimus ointment 0.03% or vehicle applied once daily, 3 times per week to clinically normal-appearing skin for up to 40 weeks (Phase II). Corticosteroid use was prohibited. **RESULTS:** Of 206 randomly assigned patients, 152 completed Phase I; 105 of 152 were randomly assigned into Phase II (68 tacrolimus ointment and 37 vehicle). There were no differences in adverse events between alclometasone and tacrolimus (Phase I) or between tacrolimus and vehicle (Phase II). In the acute period, alclometasone-treated patients showed greater improvement in atopic dermatitis signs and symptoms; thereafter, when all patients applied tacrolimus ointment (short-term), there were no differences. In Phase II, tacrolimus-treated patients had significantly more disease-free days compared with vehicle, significantly longer time to first relapse, and significantly fewer disease relapse days. **CONCLUSIONS:** For patients with stabilized moderate to severe atopic dermatitis, long-term intermittent application of tacrolimus ointment to normal-appearing but previously affected skin was significantly more effective than vehicle at maintaining disease stabilization, with a safety profile similar to vehicle.

Massage therapy in outpatient pediatric chronic pain patients: Do they facilitate significant reductions in levels of distress, pain, tension, discomfort, and mood alterations?

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BACKGROUND AND OBJECTIVES: This study was designed to look at the efficacy of adjuvant massage therapy in children and adolescents who presented to a chronic pediatric pain clinic for management. **METHODS:** After Institutional Review Board approval and informed consent and assent was obtained, all pediatric patients who presented to the outpatient chronic pain clinic at Children's Memorial Hospital from July 2006 to May 2007 were invited to participate in a study that offered massage therapy as an adjunct to conventional pain treatment. Patients (n = 80 sessions, 57 patients) were asked to rate their levels of distress, pain, tension, discomfort, and degree of upset mood on a scale of 1-5 (e.g. for distress 1 = very calm; 5 = very distressed) before and after massage therapy. Paired t-tests were used to compare pre- and postmassage ratings and probability values were corrected for multiple comparisons using the Bonferroni procedure. **RESULTS:** After massage therapy, patients reported highly significant improvement in their levels of distress, pain, tension, discomfort, and mood compared with their premassage ratings (all t-values >6.1, ****P < 1 x 10(-8)). To control for the possible effects of patients reporting improvements simply as a result of rating their symptoms, we collected control ratings before and after a comparable 'no intervention' time period in a subset of 25 patients. The 'no intervention' time period typically took place in the treatment room with the therapist present. Approximately 60% of the control ratings were obtained before the intervention and 40% were obtained after the massage therapy. None of the differences between the pre- and postratings associated with the 'no intervention' control time period were significant. In these same patients, the difference between the pre- and postmassage ratings were significant, all t-values >3.8, **P < 0.001.

Methods of investigation and management of infections causing febrile seizures

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The management of febrile seizures is reviewed, with emphasis on methods of investigation and treatment of associated infections. Records of 100 consecutive febrile seizure patient-visits were examined retrospectively at an East Carolina University-affiliated hospital. Causes of fever and infection, viral and bacterial studies, antipyretic, antibiotic, and antiviral treatments, and indications for lumbar puncture were analyzed. Febrile seizures were first episodes in 64, simple in 76, and complex in 23 (prolonged, at 30-60 minutes, in 4). The mean age was 20 months. Viral studies in 26 patients were positive in 9 (35%). Bacterial cultures in 100 were positive in 5%, none from CSF. Antibiotics were prescribed in 65%, and antipyretics in 89%. Lumbar puncture was performed in 14 patients; 11 had complex seizures, and 3 simple. Of simple seizure patients, none was aged <12 months, and only 1 was aged <18 months at time of lumbar puncture. Clinical manifestations and complex seizures are the principal indications for lumbar puncture, and not patient age. Viral infection is the most common cause of fever, and bacterial infection is infrequent. Early viral diagnosis should lessen the emphasis on bacterial cultures, and lead to reduced use of empiric antibiotics.

Nitric oxide and beyond: New insights and therapies for pulmonary hypertension

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Persistent pulmonary hypertension of the newborn (PPHN) contributes significantly to the morbidity and mortality associated with meconium aspiration syndrome. This review article discusses new insights into the vascular abnormalities that are associated with PPHN, including the recent recognition of the importance of oxidant stress in its pathogenesis. Recent data are presented showing that treatment with high oxygen concentrations may increase production of oxygen free radicals. The rationale for the use of inhaled nitric oxide, and strategies for enhancing nitric oxide signaling are discussed. Finally, the rationale for new treatment approaches is reviewed, including inhibition of cyclic guanosine monophosphate-specific phosphodiesterases and scavengers of reactive oxygen species.