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Elevated VEGFR-3 signaling helps to protect neurons during stress

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The metabolic syndrome is driven by the inflammation within obese adipose tissue. By genetically over-expressing the lymphangiogenic factor vascular endothelial factor-D (VEGF-D) specifically in the adipose tissue of mice (Adipo-VD mice), we have previously demonstrated that enhancing VEGFR-3 signaling induced lymphatic vessel expansion, reduced immune accumulation, and preserved insulin sensitivity. VEGF-D is also reported to act as a dendritic arborization maintenance factor and has demonstrated positive effects on neuron morphology and synaptic strength. The potential for VEGF-D to regulate the sympathetic vasomotor tone could, therefore, be critical to adipose pathophysiologic regulation. Our previous Adipo-VD studies also identified an enhanced adrenergic response. We thus hypothesized that VEGF-D may help to preserve neuronal health during tissue stress. We therefore examined whether adipose innervation was preserved or functionally different in Adipo-VD mice during stress in vivo and if VEGFR-3 signaling was specifically neuroprotective to challenged neurons in vitro. We observed reduced stimulus-evoked excitatory sympathetic nerve activity in Adipo-VD mice. Adipo-VD inguinal sympathetic branches demonstrated improved resistance to 6-OHDA dopaminergic denervation, exhibiting higher sympathetic filament branch volume and length than their littermates. In vitro, we found that chronically elevated VEGFR-3 signaling increases synaptic GluN2B localization and upregulates proteolytic conversion of pro-BDNF to mature BDNF, improving synaptic plasticity in cultured neurons. Acute VEGF-D treatment reduced dendritic length but increased dendritic intersections. An upregulation of the m-BDNF-AKT-CREB neuroprotective pathway in acute VEFF-D treated neurons was also prominent in the presence of GluN2B blocker and 6-OHDA induced stress. Targeting the VEGF-D/VEGFR-3 lymphangiogenic pathway thus has a synergistic and positive impact on sympathetic innervation through maintenance of sympathetic tone and neuroprotection.

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The bitter taste of denatonium benzoate in Drosophila larvae

Taste perception is a crucial chemosensory modality essential for feeding. Most animals have functionally distinct population of taste cells, which express taste receptors that are tuned to specific classes of chemicals (both nutritious and harmful). For example, this organizational feature allows mammals and insects, where taste has been studied extensively, to discriminate unadulterated nutritious food compounds (sugars, proteins etc.) from food containing toxic contaminants and execute appropriate behavioral responses, such as feeding or repulsion. In the fruit fly, taste receptors are expressed in primary taste neurons, and depending on the neural circuit these cells are connected to, induce either feeding or avoidance behavior. Drosophila melanogaster use a family of 68 Gustatory Receptors (Grs) to detect such chemicals. Generally, closely related Gr proteins are co-expressed in the same taste neurons, tuned to chemically related compounds and therefore trigger the same behavioral response. Here, we report that closely related Gr proteins of the Gr28 family are expressed in functionally distinct sets of taste neurons, detect chemicals of different valence and trigger opposing feeding behavior. To determine the properties imbued on cells expressing each of the six different Gr28 genes, we expressed the mammalian vanilloid receptor VR1 (sensing the chemical capsaicin to which Drosophila larvae do not respond) in taste neurons marked by individual Gr28 reporter genes and examined larval preference behavior using a two-choice preference assay. We found that when VR1 is expressed in Gr28a neurons, larvae are attracted to capsaicin, whereas expression of VR1 in Gr28b.c neurons triggers avoidance to capsaicin. We also report on rescue experiments by examining the ability of individual Gr28 genes expressed in Gr28b.c neurons to restore avoidance to denatonium benzoate. In summary, our analysis has revealed a complex cellular as well as molecular organization of this highly conserved taste receptor family.

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Larc Implant Use Does Not Exacerbate Bone Loss Associated with Hindlimb Unloading

Combined oral contraceptives (COC; ethinyl estradiol and progestin) reduce exercise-induced gains in bone mineral density (BMD), possibly by suppressing bone turnover. Long-acting reversible contraceptives (LARC; progestin-only) provide many practical advantages over COC and will likely be recommended for female astronauts on long-duration missions; however, the impact on bone health with unloading is unknown. Purpose: To determine if LARC use will blunt loss of bone associated with hindlimb unloading (HU) Methods: Virgin female Sprague-Dawley rats (n=52; 4-mo-old) were singly housed and randomly assigned to placebo (PL) and LARC groups, via an implanted slow-release etonogestrel pellet (0.00ug/d vs. 0.30ug/d). A week later, animals were further randomized to weight bearing (WB) and HU groups (n=13/subgroup) for 6 weeks. Calcein injections were delivered 9 and 2 days prior to termination. Pre/post-HU, proximal tibia metaphysis (PTM) and the tibia mid-diaphysis (TD) were scanned with in vivo peripheral quantitative computed tomography. At termination tibiae were stored for mechanical testing and dynamic/static histomorphometry. Univariate and repeated measures 2-way ANOVA were used. Results: Despite increasing their food intake during HU (p)

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A dual-color, frequency-agile, single-shot CRBS laser system for the measurement of physical properties of neutral particles in weakly ionized plasmas

In this work, a custom-built, dual-color, frequency-agile, single-shot coherent Rayleigh-Brillouin scattering (CRBS) laser system will be presented. CRBS is a four-wave mixing technique in which two pump beams interfere in a medium, generating a moving optical lattice. A third probe beam is Bragg-scattered from the lattice, generating a fourth CRBS signal beam. The system is capable of manipulating energy/pulse duration/frequency of laser pulse and is specifically designed to diagnose neutral particles in weakly ionized plasmas. We restore the velocity distribution function of neutral particles by scanning the velocity of the lattice within a single laser pulse. We adopt a three dimensional and two-color phase-matching scheme to maximize signal-to-noise level in a low-pressure plasma environment, and details of the system will be presented.

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Distributed Projected Subgradient Method for Weakly Convex Optimization

The stochastic subgradient method is a widely-used algorithm for solving large-scale optimization problems arising in machine learning. Often these problems are neither smooth nor convex. Recently, Davis et al. characterized the convergence of the stochastic subgradient method for the weakly convex case, which encompasses many important applications (e.g., robust phase retrieval, blind deconvolution, biconvex compressive sensing, and dictionary learning). In practice, distributed implementations of the projected stochastic subgradient method (stoDPSM) are used to speed-up risk minimization. In this paper, we propose a distributed implementation of the stochastic subgradient method with a theoretical guarantee. Specifically, we show the global convergence of stoDPSM using the Moreau envelope stationarity measure. Furthermore, under a so-called sharpness condition, we show that deterministic DPSM (with a proper initialization) converges linearly to the sharp minima, using geometrically diminishing step-size. We provide numerical experiments to support our theoretical analysis.

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Case-control study with a contaminated case pool

This research deals with case-control studies whose case pools are contaminated by false cases. The true status of the cases are unknown except in a small subset of the case pool. Without assuming any model for the status of a case, we adaptively impute the status with the objective to constructing an unbiased estimating equation for the

target parameter using the whole case pool. A special example with a simple form is considered. We investigate its asymptotic properties and apply it to simulated and real data. The numerical implementation illustrates that our method increases the efficiency of the estimation and is indeed robust to model misspecification.

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A Novel Model to Assess Sulfide Stress Cracking (SSC) Susceptibility of Carbon Steels

NACE TM0177 method D has long been the standard method for estimating SSC susceptibility of carbon steels by directly measuring KISCC. However, the lengthy experimental duration made the generated results unreliable especially in the low H2S concentration environments. Therefore, a new model based on J-integrals obtained from notched tensile slow strain rate test (NTRRST) was established to provide an accurate and universal solution for SSC susceptibility evaluation. In the current research, the J values of two different materials in air, C110 and P110, were calculated using the new model. The effect of the notch ratio was investigated. Finite element analysis (FEA) using Abaqus was performed then to verify the J integrals calculated using the new model. The simulated tensile behavior was compared to the experiment, and the simulated J values were compared with the ones obtained from the new model as well. Good agreement was observed in terms of both the mechanical behavior but also the J values, suggesting the new model provided accurate prediction on the J values in air. In addition, NTRRST experiments of those materials under different H2S concentrations and pH were compared. The results provide further analysis of the successful evaluation of KISSC. Key words: SCC susceptibility, KISCC, Abaqus, Carbon steels, J integrals.

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Psychostimulants influencing Neuro-Epigenetic modification of Class I and II Histone Deacetylase (HDACs): Neuroprotective Role of Nootropic Piracetam

Psychostimulants cocaine, methamphetamine and morphine use have been identified as risk factors for neurodegeneration. In central nervous system (CNS), astrocytes are the primary regulators of energy metabolism and maintains cellular energy homeostasis. Impaired astrocytic energy metabolism may trigger neurodegeneration. Psychostimulants known to interfere with this energy homeostasis and altered epigenetic modification including histone deacetylase (HDAC). The effects of psychostimulants on HDAC class I and II have not been elucidated yet in the contest of energy and metabolic resources. We hypothesize that psychostimulants exposure could impair functions of zinc-dependent mammalian histone deacetylase (HDAC) family of class I and II which comprises of 7 enzymes. Class I and II HDACs have specific and critical functions in histone deacetylation, transcription factor or regulator deacetylation followed by chromatin remodeling and positive or negative outcome regarding transcription initiation. To study our hypothesis, psychostimulants cocaine, methamphetamine (METH) and morphine exposed with human primary astrocytes, either alone or coexposure with “nootropic” drug piracetam on protein modification and gene expression in primary astrocytes. Our study revealed that class I HDAC- 1, 2 and 3 and class II HDAC - 4, 5 and 6 proteins modifications were upregulated when exposed with cocaine, METH and morphine, while coexposure with piracetam reversed the effect of psychostimulants on HDACs compared to control. Similarly, we also observed on class I HDAC1 and class II HDAC 4 gene expression and these effects were significantly restored by piracetam. Interestingly, psychostimulants did not have any effect on HDAC7 protein level. These findings provide evidence that psychostimulants affect astrocyte energy metabolism and epigenetic changes by impairing HDACs activity, which might be a contributing factor to neurodegeneration and perhaps piracetam could be considerate a good candidate to neuroprotective agent. This work was supported by National Institute on Drug Abuse Grant DA044872.

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Evaluation of severity of spinal cord injury and changes in cardiometabolic function

Changes in cardiometabolic function contribute to morbidity and mortality after chronic spinal cord injury (SCI). Despite the advances in the medical care of SCI patients, the cardio-metabolic risk and divergences in severity-related responses remain not well understood. Here, we examined the effects of SCI severity overtime on functional recovery, cardiac and liver function, body composition, and glucose metabolism, following moderate SCI (50kd), or severe SCI (75 kd) contusions (T8) in mice. Functional recovery was assessed by rotarod and BMS, cardiac structure and function were

evaluated by echocardiography, liver function was examined by ultrasound imaging and Masson trichrome staining, body composition was measured by EchoMRI, and glucose metabolism was evaluated by glucose tolerance test (GTT). There was a significant reduction in motor function of the hind limbs and total body fat (%) in all-time points up to 20 weeks post-injury (PI) in both moderate and severe SCI mice. Mice subjected to sever SCI lost significant body weight (g) and total body lean (%) in all-time points up to 20 weeks PI. However, no significant differences were observed in body weight (g) and total body lean (%) in moderate SCI mice compared to sham control. Furthermore, mice subjected to severe SCI showed a significant reduction in left ventricular internal diameters (LVID) and left ventricular volume in (LV) at 20 weeks PI. Interestingly, LVID and LV reduction were associated with increased LV ejection fraction and LV fractional shortening at 20 weeks PI. Severe SCI increased liver echogenicity starting from 12 weeks PI, at the endpoint, there is an increase in liver fibrosis in both moderate and severe SCI. No differences were observed in glucose metabolism at 12 weeks and 20 weeks PI. This data demonstrate that disturbances in cardiometabolic function following SCI vary significantly depending upon the severity of the injury.

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Enhancing community disaster resilience: Probabilistic approach for evaluating the risk of power distribution networks under extreme wind events.

Critical infrastructure systems such as power distribution networks provide essential service to the communities. Evaluation of risk in the power infrastructures, therefore, should take into account not just single utility component failure, but the potential impacts on the community. In this context, this research suggests a probabilistic approach for evaluating the risk of power distribution networks under extreme wind events. Specifically, we regard leaning utility poles as warning signs of potential failures that can affect the power distribution network performance and estimate the failure probability of leaning poles under varying wind loading. The overall concept builds upon the limit state function that describes the performance of a structure by comparing its current resistance and total moments acting on it. We also provide a set of wind fragility functions that consider key design factors including the National Electrical Safety Code (NESC) class, age, height, and leaning angle, span length, and wind speed. The proposed analytics are tested through a case study on the parts of the power distribution network in Houston, TX. The analysis results show that, when Hurricane category 2 comes, 30-degree leaning poles have about 18 % more risk compared to the vertical pole. The proposed method will contribute practitioners by facilitating effective risk-informed decision-making to prioritize maintenance tasks over numerous leaning poles in power distribution networks before hurricane seasons, which helps enhance the community resilience to cascading blackouts.

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Assessing ADL Routine Variability based on High-dimensional Sensing Data using Hierarchical Clustering

Since the irregular patterns of performing Activities of Daily Living (ADLs) can be found when the mental status of the older adults deteriorates (e.g., dementia), an efficient way is required to measure the variability of ADL routines for their healthcare. Various non-intrusive sensors enable us to track and assess ADL performances without bothering the occupant's daily lives. Previous efforts have attempted to recognize the ADLs of the occupants using multiple types of non-intrusive sensors to assess ADL performance. However, these sensor data have all different frequencies and huge amounts of noise so that it causes enormous efforts of human observation and manual annotation for activity recognition. This study develops an unsupervised hierarchical clustering method that works rigorously with high-dimensional data. It captures similar activities as a cluster while allowing to filter the noisy signal to measure the ADL variability by representing the multiple days of ADL logs as an image. The results show that the proposed method can be extended to be capable of using high-dimensional non-intrusive sensing data to capture the variability of ADL routines.

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It’s OK to Go Naked: Transfection of the Respiratory Epithelium with Aerosolized mRNA in Water

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Use of mRNA for vaccines and therapeutics has enormous potential to benefit human and animal health. Synthetic mRNA delivered to tissues can transfect (i.e., be taken into) cells and then be rapidly translated into proteins that can have local or systemic effects. Dogma indicates that transfection agents (chemical carriers that protect mRNA and enhance transfection) are needed for effective mRNA administration. But transfection agents pose problems for added expenses, quality control, and safety. We describe here the first safe and effective transfection of the respiratory tract of a large animal by aerosolizing naked mRNA (i.e, using only water as the vehicle). We first demonstrated in vitro transfection of cultured equine respiratory epithelial cells with aerosolized mRNA encoding enhanced green fluorescent protein (eGFP) using either a commercial transfection agent, Viromer mRNA®, or water. We next aerosolized 250 µg mRNA encoding eGFP to the guttural pouches of 2 foals, using either Viromer or water as a carrier, and used transendoscopic confocal fluorescent microscopy (TCFM) to demonstrate that both carriers resulted in eGFP expression in guttural pouches at 8, 24, and 48 hours post-transfection. Last, we successfully transfected the bronchial epithelium of 2 foals by transendoscopic aerosolization of mRNA in water: eGFP expression in the bronchial epithelium was confirmed by TCFM after 8, 24, 48, 72, and 96 hours. Endoscopic examination of the bronchial tree and histology of mucosal biopsies indicated no gross or microscopic adverse effects of transfection. Our findings of safe and effective transfection of the respiratory epithelium via aerosolization without the need for a transfection agent indicate that it is possible to reduce the costs and complexity of delivering mRNA to the upper and lower respiratory tract for therapeutic or prophylactic purposes in people and animals.

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Testicular Inflammation is Associated with Immune Cell Infiltration and Lymphangiogenesis in L-NAME-Induced Hypertension

Hypertension (HTN) is associated with reduced fertility in men. Although numerous studies report that HTN disrupts hormonal balance in men, less is known about the direct effect of HTN on testes and how HTN influences testicular inflammation and lymphatics. We hypothesized that HTN increases testicular lymphatic vessel density and this is associated with immune cell infiltration and inflammation. Male mice (8 weeks old) were made hypertensive by providing them with L-arginine methyl ester hydrochloride (L-NAME) (0.5 mg/mL) in the drinking water for 3 weeks and control mice received tap water. Testes of hypertensive mice had a significant increase in gene expression of the lymphatic vessel markers Lyve-1, Podoplanin and Prox-1, the lymphangiogenic growth factors VEGF-C and VEGF-D, and their receptors VEGFR-2 and VEGFR-3. There was also a significant increase in the expression of the pro-inflammatory cytokines TNF-a, IFN-g, IL-1b, IL-6, and IL-17. There were also increases in the lymphatic endothelial cell-derived immune cell trafficking chemokines CCL21 and CCL19 and their receptor CCR7, as well as the cell adhesion molecule ICAM in testes of hypertensive mice. Flow cytometry analysis revealed an increased accumulation of F4/80+ macrophages in the testes from hypertensive mice. Together, these data demonstrate that HTN induces inflammation-associated lymphangiogenesis in testes, in association with immune cell infiltration. It is possible that increasing testicular lymphatics may reduce inflammation and improve reproductive function in hypertensive men.

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Uterine bacteria and cytokine profiles prior to artificial insemination between resulting pregnant and open postpartum beef cows

Numerous factors impact reproductive success in beef cattle, however the presence and activity of bacteria in the reproductive tract and its effects on fertility is relatively unknown. The objective of this study was to evaluate the relationship between reproductive tract bacterial communities and cytokine profiles prior to timed-artificial insemination (TAI) and compare between resulting pregnancy status at day (d) 30. Sixty-eight beef cows, 80 ± 2.6 d

postpartum at TAI, were synchronized and subjected to TAI on d 0. Pregnancy was diagnosed via transrectal ultrasonography on d 30. Uterine and vaginal flushes were collected on d -21 and -2 for bacterial DNA extraction to sequence the V1-V3 hypervariable regions of the 16S rRNA gene and to measure pro-inflammatory (interleukin-6 [IL-6]) and anti-inflammatory (transforming growth factor beta [TGFβ]) cytokine concentrations using validated commercial ELISAs. Concentration data were analyzed using repeated measures in PROC MIXED of SAS and correlations were performed in SAS using Pearson correlation. There were no differences in cytokine concentrations by day or status x day. There was no significant difference in uterine IL-6 concentrations (P>0.05). On d -21, tendencies for negative correlations exist between IL-6 and the relative abundance of Proteobacteria (r=-0.81, P=0.10) and Lentisphaerae (r=-0.88, P=0.05) in the uterus of open cows. Additionally, a positive correlation exists between IL-6 and the relative abundance of Bacteroidetes in the uterus of pregnant cows (r=0.92 P=0.03) on d -21. Uterine TGFβ concentrations were overall elevated in pregnant cows compared to open cows (72.6 vs. 13.7 ± 12.1 pg/mL, respectively; P<0.05). On d -2, a positive correlation exists between TGFβ and the relative abundance of Actinobacteria in the uterus of pregnant cows (r=0.93, P=0.02). These data suggest a possible relationship between bacterial communities and cytokines concentrations within the reproductive tract of beef cattle which may affect fertility.

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Post stroke Mir 363-3p treatment reduced stroke-induced cognitive impairment and destruction of forebrain myelin tracts in middle-aged female rats

Stroke is the major cause of death and disability in the USA, and a leading cause of dementia including Alzheimer's disease. Older women are at a greater risk for stroke and stroke associated disability. Recent work in our lab has focused on developing neuroprotectants for this demographic using animal models. The small non coding microRNA mir363-3p, which regulates cell death effectors, reduced infarct volume and sensory motor impairment in the acute stage of stroke in middle-aged females. Here we investigated the effect of mir363-3p on the long-term effects of stroke including cognitive impairment and destruction of white matter tracts in this group. Methods: Middle-aged acyclic rats were subject to middle cerebral artery occlusion (MCAo) via stereotaxic injection of the vasocontrictor endothelin (ET)-1. Four hours later, animals were injected iv with mir363-3p mimics or scrambled oligos. Six months after stroke, animal were tested for novel object recognition task and the Barnes maze to assess non-spatial and spatial learning respectively. At termination, rats were transcardially perfused with saline and 4% paraformaldehyde. Brain were sectioned and stained for Weil myelin stain. Results: Six months after stroke, animals with MCAo displayed cognitive impairment as assessed by the NORT test and the Barnes maze test, as compared to sham animals. However, stroke animals that received mir363-3p shortly after MCAo were no different from sham animals on these measures. The volume of the internal capsule, which connects the fronto-temporal and rostro caudal brain structures, and the corpus callosum, which consists of inter-hemispheric fibers, was significantly decreased in the ischemic hemisphere of scrambled treated rats as to Sham (non-stroke) rats. In contrast, mir363-3p treated rats were no different from shams. Conclusion: These data suggest that mir363-3p treatment, given in the early hours after stroke, may prevent neurodegeneration and cognitive impairment resulting from ischemia.

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Cocaine Influence Mitochondrial Epigenetics in Astrocytic Network: Role in DNA Methylation

Cocaine use have been identified as risk factors for neurodegeneration. Astrocytes are the primary regulators of energy metabolism in the central nervous system (CNS), in which mitochondria maintains this cellular energy homeostasis. Impaired astrocytic energy metabolism may trigger neurodegeneration. Cocaine abuse are known to interfere with this energy homeostasis and could possibly affect mitochondrial DNA (mtDNA) in which DNA methylation an important epigenetic modification has not been elucidated yet. We hypothesize that cocaine exposure could impair DNA methylation by suppressing the function of mtDNA methyltransferase, thereby mediating the mitochondrial genome elicited disease progression. To study our hypothesis, we exposed human astrocytes with cocaine, individually or in combination with energy enhancer drug nootropic piracetam. We then examined the DNA methyltransferases (DNMTs) DNMT-1, DNMT3a, DNMT 3b expression, 5-methycytosine (5-mC) levels and induction of ten-eleven translocation (TET) enzymes in astrocytes. In addition, we also analyzed the mtDNA methylation as well as the targeted genome region D-loop and NADH dehydrogenase subunit 1–6 [ND1-ND6]. Methylation of mtDNA was analyzed by targeted next-gen bisulfite sequencing. We observed a significant decrease in percentage of methylation level in mtDNA of cells which treated with cocaine compared to control. Moreover, mitochondrial methylation levels in the

MT-RNR1, MT-ND5, MT-ND1, D-loop and MT-CYB regions of mtDNA were lower in the cocaine exposed group than in the control group. However, these effects were restored by piracetam coexposure. Our data support the evidence that cocaine affect astrocyte energy metabolism by impairing DNMTs activity, which might be a contributing factor to neurodegeneration, as observed in cocaine users. These effects it might protected by piracetam at least in partially to maintain neuronal function.

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Antimicrobial activity and novel formulation of silver containing non-steroidal anti-inflammatory drugs

Cystic fibrosis (CF) patients suffer from both chronic lung infections and airway inflammation. This inflammation, which precedes and is exacerbated by the lung infections, leads to irreparable tissue damage in the lungs. Combating both infections and inflammation has become a focus in treating CF. Thus, it would be advantageous to develop a new therapeutic that can simultaneously treat these two prevalent issues. The anti-inflammatory, ibuprofen, has been transformed into an efficacious dual therapeutic for this purpose by the synthesis of its silver salt (AgIBU). The antimicrobial activity of AgIBU has been evaluated against several *Pseudomonas aeruginosa* isolates including multi-drug resistant (MDR) isolates from CF patients using standard CLSI protocols. AgIBU has an MIC_{90} of 4 μg/mL and an MBC_{90} of 4 μg/mL, which is comparable to the activity of standard-of-care antibiotics against sensitive isolates. In addition, silver complexes of other common non-steroidal anti-inflammatory drugs (NSAIDs), naproxen and acetylsalicylic acid, have also been synthesized and evaluated for antimicrobial activity, displaying comparable MIC and MBC values (ranging from 4-8 μg/mL and 6-8 μg/mL, respectively). All three of these derivatives are highly lipophilic, with no appreciable aqueous solubility. In order to formulate these silver complexes without the use of DMSO, the excipient 2-hydroxypropyl-β-cyclodextrin has been employed to impart water solubility. Use of this excipient provides a stable solution that does not greatly alter in vitro antimicrobial activity compared to DMSO solutions. This family of silver-NSAID complexes represents a new class of anti-inflammatory and antimicrobial therapeutic options for CF patients.

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Rhodococcus Equi Engages the Cytosolic Dna Sensing Pathway and Induces Type I Ifn Expression

Background: Rhodococcus equi is a common cause of pneumonia in foals younger than 6 months.
Macrophage expression of the type II interferon (IFN), IFN-γ is required for R. equi clearance. Expression of type I IFN, important for antiviral immunity, can be induced by bacterial pathogens to transiently dampen the antibacterial IFN and establish a replicative niche. The balance between type I and type II IFN expression is a critical factor in the host response to bacterial pathogens, however it is unknown whether R. equi induces type I IFN expression in macrophages.

Objective: Determine if R. equi infection induces type I IFN expression in macrophages and by which innate immune pathway.

Methods: Type I IFN expression was measured in murine macrophages infected with R. equi. To determine if the cytosolic DNA sensing pathway is required for type I IFN induction in response to R. equi infection, macrophages deficient in TBK1, STING or cGAS were infected with R. equi, and IFN-β measured by qPCR.

Results and Conclusions: R. equi infected RAW 246.7 and murine bone marrow derived macrophages showed induction of IFN-β and interferon stimulated genes (ISGs) as well as the proinflammatory cytokines TNF-α, IL-1β and IL-6. IFN-β and ISG expression was not dependent on TRIF or MyD88. TBK1, STING and cGAS were required for induction of IFN-β and ISGs. These results indicate that R. equi induced type I IFN expression occurs by engaging the cytosolic DNA sensing pathway in macrophages.

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Potential Applications of Clay-based Therapy to Reduce Human and Animal Exposures from Polychlorinated Biphenyls

Polychlorinated biphenyls (PCBs) have been detected as prevalent environmental contaminants and their accumulation in fatty tissues of fish, shellfish and other animals can be magnified during events such as hurricanes, floods, heavy rain, and storms. During these events, PCB contaminated sediments can be mobilized and redistributed, thus enhancing exposures and adverse health impacts in vulnerable humans and animal populations at the site of disasters. To address this problem, we have developed a broad-acting and highly effective sorbent for PCBs using montmorillonite clays reported to be safe for consumption in humans and animals. In this study, parent clays were processed with high concentrations of acid (APMs) and the sorption of six PCB congeners (PCB 77, 126, 153, 157, 154 and 155) on the surfaces of these APMs were characterized. To predict the in vivo efficacy and confirm the safety of APMs, we used a living organism (Hydra vulgaris) that is sensitive to diverse toxins in the environment. In a novel application of this work, APMs were included in algae-based feed for commerical oysters (Crassostrea virginica) as prophylaxis and treatment against PCB contaminants during disasters and high level exposures. APMs significantly protected hydra against the toxicity of PCBs and common mixtures (Aroclors 1254 and 1260), and reduced PCB uptake and accumulation in oysters when included in the diet. This finding was supported by in vitro studies showing tight binding; high capacity, affinity, and enthalpy; and a low therapeutic dose. APMs have been shown to bind a wide range of PCBs and other environmental chemicals, and can be delivered in food, drinking water and animal feed to mitigate toxin exposures in vulnerable humans and animals at the site of disasters (P42 ES027704).

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Sneezing and asymptomatic virus transmission

The novel coronavirus disease (COVID-19) spread pattern continues to show that geographical barriers alone cannot contain a virus. Asymptomatic carriers play a critical role in the nature of this virus quickly escalating into a global pandemic. Asymptomatic carriers may transmit the virus unintentionally through sporadic sneezing. A novel Computational Fluid Dynamics (CFD) approach has been proposed with a realistic modeling of a human sneeze achieved by the combination of state-of-the-art experimental and numerical methods. This modeling approach may be suitable for future engineering analyses aimed at reshaping public spaces and common areas, with the main objective to accurately predict the spread of aerosol and droplets that may contain pathogens. This study shows that the biomechanics of a human sneeze, including complex muscle contractions and relaxations, can be accurately modeled by the angular head motion and the dynamic pressure response during sneezing. These have been considered as the human factors and were implemented in the CFD simulation by imposing a momentum source term to the coupled Eulerian–Lagrangian momentum equations. The momentum source was modeled by the measured dynamic pressure response in conjunction with the angular head motion. This approach eliminated the need to create an ad hoc set of inlet boundary conditions. With this proposed technique, it is easier to add multiple fixed and/or moving sources of sneezes in complex computational domains. Additionally, extensive sensitivity analyses based on different environmental conditions were performed, and their impact was described in terms of potential virus spread.

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Long Non-Coding RNA DLEU2 alters Sirtuins and Cytochrome C-oxidase: a novel pathway in metabolic regulation

Emerging evidence suggests that long non-coding RNAs (lncRNA) may play critical roles in metabolic regulation. Sirtuins also play roles in metabolic disorders via regulating mitochondrial complexes. However, how sirtuins and mitochondrial complexes are regulated via lncRNA remains to be investigated. One of these lncRNAs, known to be involved in blood cancer, Dleu2, was significantly decreased in the livers of high-fat high-fructose diet (HFD-HF) fed male mouse offsprings (F1) whose mothers (F0) were fed HFD-HF during pregnancy. Hepatic sirtuins (Sirt1-7) were also significantly decreased in these F1 HFD-HF fed mice. In HepG2 cells, DLEU2 siRNA confirmatory studies showed that transcription levels of SIRT1 through 6 and translational levels of SIRT1, 3, 5, and 6 were significantly downregulated under DLEU2 knockdown conditions. Knockdown of DLEU2 also significantly decreased the protein level of cytochrome-c oxidase (complex IV) and increased reactive oxygen species (ROS) levels. These findings show for the first time that the lncRNA DLEU2 can regulate sirtuins and mitochondrial proteins, indicating a potential role of DLEU2 in metabolic disorders.

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Noncompetitive Ligand-coupled Nanoparticles – In Vitro Characterization and Pharmacokinetics Testing in Canine Model

A vast majority, if not all of the receptor-mediated drug delivery systems utilize nanoparticles that are conjugated to physiological mimic ligands, with testing restricted to rodent models. In this report, we use a combination of in vitro and canine models to characterize transferrin receptor 1 (TfR1)-targeted polymeric nanoparticles (abbreviated, P2Ns-GA) that are non-competitive with endogenous transferrin, and serve as a versatile platform for oral drug delivery. Based on endocytosis inhibitors and receptor knockdown, the cellular uptake of P2Ns-GA is clathrin-mediated and dependent on TfR1 expression, but other trafficking mechanisms, particularly those involving caveolae/lipid rafts, can also play a role. The utility of P2Ns-GA in promoting the oral bioavailability of encapsulated compounds is demonstrated with a hydrophobic polyphenol - urolithin A (UA). When compared against plain UA or UA in ligand-free nanoparticles (P2Ns), UA-loaded P2Ns-GA led to markedly higher plasma concentrations among healthy canine, with no adverse health effects observed after oral dosing.