CANCER BIOMARKERS IN CLINICAL DEVELOPMENT

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Clinical trial development is the process through which new medical products are tested for safety and efficacy in patient populations for specific diseases. Medical products undergo three successive phases: Phase I, II and III. Oftentimes, clinical studies are continuously performed for the previous phases, despite having preceding studies finished for that phase. In this study, we explored how clinical trials for a drug clustered overtime and how that may impact the drug approval process. As such, we examined the clinical phase pathways of 750 oncology drugs and the path that individual drugs took toward either failure or regulatory approval. Our study focused on four diseases that use biomarkers: breast cancer, colorectal cancer, melanoma and non-small cell lung cancer. We used the NIH used the database clinicaltrials.gov. to construct the clinical study timelines. For each drug and its relevant combinations, a Gantt chart was used that examined all clinical trials from January 1998 to January 2017. Subsequently, a plausible pathway (coined “forensic reconstruction”) was constructed on top of the cloud of trials to examine the most relevant trials that had an impact on the drug’s pathway of failure or approval. The overall goal of our study was to gain the information necessary for quantifying the risk of failure during the clinical trial process and visualize clinical trial development in a meaningful manner for comparison. This information will provide a reference for developers in the future to statistically examine the success of cancer biomarkers which may improve efficiency of the clinical trial process.

Poster Presentation
C: Physiology & Toxicology

THE DEVELOPMENT OF MYCORRHIZAE IN E151 (*Pssym15*), A PLEIOTROPIC MUTANT OF PEA (*Pisum sativum* L.).

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Majority of terrestrial plants form a mutualistic relationship with arbuscular mycorrhizal (AM) fungi. Many phytohormones have been shown to play a role in the regulation of AM symbioses. In our lab, the phytohormone cytokinin (CK) is of interest because E151 (*Pssym15*), a mutant of wild-type (WT) *Pisum sativum*, generally possesses abnormally high CK levels in its roots and a hyper-mycorrhizal phenotype. Thus, we proposed that CK has a promotive effect on mycorrhizal colonization. This work aims to further investigate our hypothesis by establishing a timeline for E151's mycorrhizal development. WT and E151 plants were grown in soil inoculated with the AM fungus, *Rhizophagus irregularis*. At 5, 10, 15, 20, and 25 days-after-planting (DAP), roots from both pea lines were harvested, stained with Indian ink-vinegar, and assessed for mycorrhizal colonization via a modified magnified intersections technique. The earliest mycorrhizal interaction was observed at 10 DAP; extra-radicular hyphae (ERH) ran along both WT and E151 roots, but E151 displayed longer ERH than the WT. At 15 DAP, WT roots exhibited higher numbers of arbuscules and vesicles than E151. However, this trend reversed at 20 DAP, where E151 roots possessed significantly more fungal structures than WT roots. These results suggest that E151 experiences a delay during early mycorrhizal development, but after mycorrhizae are established AM fungi proliferate more rapidly in E151 than in the WT. Here, we provide additional evidence of CK's promotive effect on mycorrhizal colonization. However, E151's delayed mycorrhizal development suggests that CK's effect is more complex than previously hypothesized.

Abstract for Poster

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DIFFERENTIAL CONNECTIVITY TO THE TEMPORAL AUDITORY CORTX IN EARLY DEAF CATS (*FELIS CATUS*)

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Following hearing loss, cross-modal reorganization in the brain recruits hearing-deprived cortical areas to process visual stimuli. Since it is known that the temporal auditory cortex (area T) is involved in processing conspecific vocalizations in normal hearing animals, I hypothesize that in the deaf, area T is involved visual processing. However, little is known about area T's role in visual processing in the deaf. Researchers recently found a role for area T in enhanced face discrimination in the deaf. They found that this enhancement can be eliminated following deactivation of the left temporal area. However, it is unknown whether the functional hemispheric asynchrony reflects a differential pattern of anatomical connectivity to this region. Thus, for the research I am conducting, the retrograde neuronal tracer biotinylated dextran amine (BDA) was injected into area T of either the left or right hemisphere of a total of four cats. Using Neurolucida Software, neuronal projections were quantified and compared between left and right area T. Since it appears that left area T is responsible for the advantage deaf cats have for recognizing conspecific faces, it is predicted that there will be more neural projections to area T in the left hemisphere from regions of visual cortex involved with facial recognition than in the right hemisphere. The findings of this research can be useful in the development of cochlear implant technologies which are aided by visual processing.

Poster presentation

Group C: Physiology & Toxicology

THE EFFECTS OF 17α-ETHINYLESTRADIOL (EE2) ON THE MATURATION OF MUMMICHOG (FUNDULUS HETEROCLITUS) OVARIAN FOLLICLES

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Early stages of ovarian follicle development in fish are characterized by the production of high levels of 17β-estradiol (E2). E2 produced from the ovarian follicles stimulates liver production of vitellogenin. Following this process of vitellogenesis, MIS (maturation-inducing steroid or 17,20 beta-dihydroxy-4-pregnen-3-one) initiates final follicle maturation, leading to ovulation. In fish, follicular E2 levels generally subside as MIS increases. In mummichog (*Fundulus heteroclitus*), E2 levels remain high even as MIS levels increase. EE2, originating from birth control pills, enters aquatic receiving environments via sewage effluent. EE2 is a synthetic estrogen agonist and has been demonstrated to reduce the reproductive abilities of fish at environmentally-relevant concentrations (≤10ng/L). However, mummichog are able to successfully reproduce in the presence of high EE2 concentrations (>100ng/L), perhaps due to high levels of endogenous E2 continuing through follicular maturation. The goal of this study was to determine the size range of mummichog ovarian follicles that responds to MIS and further, to determine if EE2 hinders the effectiveness of MIS. Follicles in two size classes [<9mm (vitellogenic) and 1-1.3mm (early mature)] were exposed to medium, medium + MIS (100ng/mL), medium + EE2 (100, 1000ng/mL), and medium + MIS + EE2. Follicles <0.9mm increased maturation with MIS addition. Follicles of 1-1.3mm reached maturation without the requirement of MIS. Results from the EE2 experiments are pending. These experiments were designed to further test whether the normal physiological presence of simultaneous ovarian E2 and MIS in mummichog are at least partially responsible for reproductive resistance to high exogenous EE2.

Poster Presentation

C: Physiology & Toxicology

EFFECTS OF INDIUM ON *HYALELLA AZTECA* AND RAINBOW TROUT

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Abstract

Indium (In) is a technology critical element and predominantly used to make indium-tin oxides for liquid crystal displays. Currently there is little information on its concentration in the environment and a poor understanding of its potential impact in aquatic organisms. The goal of this study is to determine the effect of In on a sensitive freshwater invertebrate, *Hyalella azteca*, and on a fish, rainbow trout (*Oncorhynchus mykiss*). Standard test methods (EPS RM 37) were used to determine the toxicity (96 h LC_{50}) of In to *Hyalella azteca*. The LC_{50} value was calculated to be 21.94 mg/L using probit analysis. However, interpretation of toxicity data was complicated because visible precipitation occurred at a pH range of 6.8-7.0 and precipitation at lower pH, although not visible, has not been ruled out as being present. Results suggest that the LC_{50} might be lower as the probit analysis calculated these values using the nominal concentrations. Tests with trout indicate that high concentrations are needed to induce acute lethality. Exposure to sublethal concentrations of 0.25 mg/L and 0.5 mg/L and 1.0 mg/L (nominal mg/L) for a longer duration (up to 10 d) suggests that In is rapidly taken up into the liver by day one and continues to increase. In also accumulates in other tissues, for example gills, muscle, and kidney. The gills show an elevated accumulation by the fourth day. The physiological effects of sublethal exposure were studied in swim performance challenges where time to exhaustion was quantified (Ucrit values). From these challenges, the results suggest that swim performance was affected at lower concentrations (0.25 mg/L) and subsequent testing will involve observing whether growth is affected at this concentration. This research will give more insight into the potential effects of In on freshwater organisms. This research is supported by Environment and Climate Change Canada, the NSERC Strategic Grants Program with contributions from the Ontario Ministry of Environment and Climate Change, Avalon Rare Metals Inc and the International Zinc Association.

Poster Abstract
Physiology and Toxicology

HIDE AND SLCEEKING: LOCALIZATION OF SLC41A1 MAGNESIUM TRANSPORTER ACROSS DIFFERENT TISSUES OF GOLDFISH (*CARASSIUS AURATUS)*

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Diffusive loss of ions is a consequence among fish living in freshwater environments. *Carassius auratus* (goldfish) make use of their osmoregulating organs, the gill and kidney, through influx-efflux systems. Magnesium concentrations in freshwater environments exists in relatively low amounts, making the intestine primarily responsible for maintaining Magnesium levels through dietary uptake. SLC41a1, a solute carrier homologous to the bacterial MgtE Mg^{2+} channel, has been suspected of participating in the regulation of Mg^{2+} levels in fish. In conditions where goldfish have been fed and unfed for 7 days, we investigate the localization of SLC41a1 protein expression in nine tissues of the fish through the use of Western Blot analysis. Contrary to previous findings where mRNA expression of SLC41a1 is greatly detected in the gill, kidney and intestine, SLC41a1 protein expression was primarily expressed in the brain. Subcellular fractionation revealed the solute carrier was confined to the nuclear and mitochondrial membranes. Under conditions of food deprivation, SLC41a1 could participate in the regulation of Mg^{2+} levels within the mitochondria, further assisting in the production of the active form of ATP. In order to sustain growth and development in deficient conditions, Mg^{2+} may be used to stimulate DNA polymerase activation, further allowing for cell cycle progression. The lack of SLC41a1 protein expression in the kidney, gill and intestine suggests a possibility of the inhibition and degradation of SLC41a1 mRNA translation.

Poster Presentation

C: Physiology & Toxicology

AFFECTS OF COLD STRESS ON PARACELLULAR BARRIER PERMEABILITY - *DROSOPHILA MELANOGASTER*

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Body compartments in an organism are separated by paracellular junctions that bind together epithelial cells and maintain chemically distinct body compartments. The structure and function of these junctions are poorly understood in insects but recent evidence suggests that cold stress impacts their stability and permeability. Loss of intestinal barrier function in *Drosophila* is often characterized by leak of a non-absorbable blue food dye from the gut to the hemocoel, rendering the fly blue (termed smurfs). We predicted that flies with leaky junctions in the cold (smurfs) would suffer greater chill injury and recover more slowly from the cold. The proportion of flies that turned blue increased steadily when exposed to 0°C, as flies developed chilling injury. Flies that lost barrier function in the cold (smurfs) tended to die sooner than those that did not, but did not take any longer to recover from chill coma after 12h at 0°C. Thus, cold stress appears to make paracellular barriers in the *Drosophila* gut leaky, and this leak is associated with low temperature injury and death, but not associated with chill coma recovery. Future studies can focus on uncovering the underlying mechanisms of barrier disruption in the cold.

Poster Presentation C:Physiology & Toxicology

TRANSGENERATIONAL EFFECTS OF CARBAMAZEPINE AND GEMFIBROZIL ON THE COURTSHIP AND SPERM MORPHOLOGY OF THE F4 GENERATION OF *DANIO RERIO*

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Gemfibrozil and carbamazepine are both commonly prescribed pharmaceutical drugs being found to enter surface waters in the low µg/L range. Gemfibrozil is a lipid lowering agent and has been found to alter lipid metabolism including the lowering of serum androgen levels in fish. Similarly, Carbamazepine is an anti-epileptic drug that has previously been observed to lower 11-ketotestosterone levels in fish as well as being a histone deacetylase inhibitor. Thus, both of these pharmaceuticals are clearly impacting sexual endocrine function in fish and raises questions as to whether exposure to environmentally relevant concentrations of these drugs have the potential to cause detrimental effects across several generations. Within this study, the F4 generation of zebrafish derived from the F0 generation exposed to 10 µg/L of carbamazepine or gemfibrozil will be assessed in terms of their courtship display and sperm morphological parameters. There are seven different lineages that in order to screen for the possibility of gender specific transfer of altered phenotypes being either female exposed, male exposed or both female and male exposed lineages for both Gemfibrozil and Carbamazepine respectively. It was found that the courtship displays in terms of lead and lateral display were consistently altered across all four generations within the Carbamazepine exposed male and female lineage. Data is still being collected for the sperm morphological parameters of the F4 lineage but it is likely that effects will be seen there as well.

Poster presentation

C: Physiology & Toxicology

ENZYME ACTIVITIES IN DIFFERENT INTESTINAL LAYERS IN CENTRAL STONEROLLER *(CAMPOSTOMA ANOMALUM)* AND GOLDFISH *(CARASSIUS AURATUS)*

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Microbes in the gastrointestinal (GI) tract play an important role in aiding with the breakdown of ingested nutrients. The microbiome of different regions of the GI tract have been widely studied in freshwater fish, however, not much is known about the presence of microbes in the different intestinal layers. In this study, we examined the enzyme activities in the different layers of the intestine in central stonerollers *(Campostoma anomalum)*, an herbivorous species, and goldfish *(Carassius auratus)*, an omnivorous species. PCR was performed to confirm the presence or absence of bacteria in each layer of the intestine. Cellulase and trypsin enzyme assays were conducted to determine the activities of each enzyme in the different tissue layers. It was found that cellulase and trypsin enzyme activities were highest in the chyme of both species, which is abundant in bacteria, and lowest in the muscle and rinsed enterocytes, which have no bacteria. Furthermore, both enzyme activities were higher in central stonerollers compared to goldfish. These results suggest that the presence of bacteria, in addition to having an herbivorous diet, increases enzyme activities in the different layers of the GI tract.

Poster presentation
C: Physiology & Toxicology

ACHETA DOMESTICUS - SPATIAL AND VISUAL LEARNING

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The house hold cricket, Acheta domesticus, is one of the smartest insects, following cockroaches and bees, and has a mamillian hippocampus analogy known as the mushroom body. The purpose of this experiment is to determine if Acheta domesticus is capable of spatial learning. The circkets were individually placed in a T maze and had to escape the maze by turning right. If turned left, the maze is blocked and has to go through the right arm to escape. The crickets were scored out of 6 depending on the frequency of immediately turning right (6 indicates the cricket only made immediate right turns). This experiment suggests that crickets do have spatial memory and have the capacity to learn the T maze.

Poster Presentation
I would like to be judged in physiology