VIRTUAL FALL MEETING

Wednesday, December 1, 2021
Friday, December 3, 2021

Contents

Agenda....2
Keynote Presentation....3
Expert Panelists:....4
Presentations:....5
Graduate Student Oral Presentation Abstracts (Presenters in bold script)....5
Listing of Poster Titles and Authors (Presenters in bold script)....7
NESOT Officers 2021-2022:....9

Agenda

NESOT Virtual Fall Meeting 2021

DAY 1: Wednesday, December 1

11:00 am EST	**Welcome and Opening Remarks (WebEx)** Joel Cohen, President, NESOT
11:05-12:00	**Graduate Student Oral Presentations (WebEx)**
12:00-1:00	**Student and Postdoctoral Poster Session (Zoom)**

DAY 2: Friday, December 3

11:00 am EST	**Welcome and Opening Remarks (WebEx)** Joel Cohen, President NESOT
11:05-12:00	**Keynote Presentation (WebEx)** Dr. Hungyun “Hank” Lin, Senior Director, Clover BioPharmaceuticals "Nonclinical safety evaluation and the primary driver of toxicities – mRNA, LNP or cationic lipid?"
12:00-1:00	**Undergraduate virtual tour of the Slitt Lab (University of Rhode Island) (Zoom)** **OR** **Graduate Student / Postdoc networking event and expert panel (Zoom)**
1:00-1:15	**Awards Ceremony (WebEx)**

Keynote Presentation

Author:
Dr. Hungyun “Hank” Lin

Bio:
Hank is currently Senior Director, Toxicology at Clover, a global biopharmaceutical company. At Clover, he leads the safety assessments in pre-clinical R&D programs and GLP toxicology studies. In addition, he provides global toxicology strategies in both vaccine and oncology programs; partner with cross-functional R&D teams, in a highly collaborative, global, matrixed environment and as an active member of the preclinical leadership team.
Prior to joining Clover, Hank worked at Translate Bio, a Sanofi Company, as Director of Toxicology where he was responsible for developing regulatory toxicology strategies and providing deep scientific interpretation of nonclinical findings as to their relevance and translation into clinical and regulatory development, has supported multiple mRNA drug and vaccine candidates through early discovery to late development stage (in pulmonary and liver therapeutic area; SARS-CoV2 and Influenza). He has more than 15 years of diverse R&D experiences in small/large molecules and oligonucleotide therapeutic drugs and vaccines, held multiple positions as Head of Toxicology at CSL-Seqirus, Principal Scientist at Alnylam and Pfizer in Cambridge, MA, Scientist at Vaxin (now Altimmune). He is a board-certified toxicologist (DABT), a member of American College of Toxicology (ACT) and Society of Toxicology (SOT). He has published more than 17 manuscripts in basic and applied pathology, molecular toxicology, and endocrinology.
Hank received his M.S. in Toxicology from National Taiwan University in Taiwan and his MS and PhD in Pathology and Laboratory Medicine from University of Rochester Medical School, NY. Most recently he also received MBA from Northeastern University, with specialty in Corp Finance/ International Business.

Title and Abstract:
"NONCLINICAL SAFETY EVALUATION AND THE PRIMARY DRIVER OF TOXICITIES – MRNA, LNP OR CATIONIC LIPID?"

The current COVID-19 pandemic has unprecedentedly expedited vaccine development, to date, more than 20~ COVID-19 vaccines have been approved in the world. Among them, three novel vaccine platforms have been validated including, recombinant adenovirus vaccines, a DNA vaccine and messenger RNA vaccines. The mRNA encapsulated by lipid nanoparticle vaccine was one of the fastest approved and has shown great efficacy against SARS-CoV2. A balance of its inherent innate immune activity from the mRNA-LNP combination and the choices of lipid components, is critical for the efficient generation of neutralizing antibody and cellular immune response, as well as to minimize potential reactogenicity.

Expert Panelists:

Expert	Organization	Role	Sector
Barbara Beck	Gradient	Principal	Consulting
Daniella Pizzurro	Avrobio	Senior Director of Regulatory Toxicology and Preclinical Development	Industry
Milan Prajapati	Brown University	Postdoctoral Researcher	Academia
Larry Thomas	Celldex Therapeutics, Inc.	Vice President, Preclinical R&D and Bioanalytics	Industry

Presentations:

Graduate Student Oral Presentation Abstracts (Presenters in bold script)

1)

A MODULAR SELF-EMULSIFYING DRUG DELIVERY PLATFORM TO ENHANCE CELLULAR UPTAKE ACTIVITY IN TRIPLE-NEGATIVE BREAST CANCER

Nandini Gandhi*1, Shail Modi1, Terrick Andey1

1-Department of Pharmaceutical Sciences, MCPHS University, MA, 01608.

Breast cancer is the most incidental and third leading cause of cancer-related deaths in women in the United States. The triple-negative breast cancer (TNBC) subtype lacks the expression of surface markers including estrogen, progesterone and Her2 receptors, thereby limiting the success of targeted therapies Cisplatin is approved for the treatment of breast cancer, however, tumor resistance, renal toxicity, as well variability in patient response to cisplatin in TNBC limit its clinical use and long-term efficacy. The current study is a proof-of-principle for the successful co-delivery of cisplatin (small molecule, chemotherapy) and siRNA (large molecular, targeted therapy) using an optimized and stable modular self-emulsifying drug delivery (SEDD) platform to enhance drug loading, cellular uptake, and selective cytotoxicity.
SEDD formulations were prepared and optimized using pseudo-ternary phase diagrams to facilitate the formation of water-in-oil-water (w/o/w) emulsions through self- emulsification of an oil phase comprising Labrafac PG, Labrasol, Gelucire 44/14, Compritol ATO 880 and Sorbitan Monoleate 80 Span 80 in water. Optimized formulations of cisplatin and FITC-siRNA were prepared separately and characterized for size, polydispersity (PDI), and surface charge. Cellular uptake studies were performed with (DiIC,DiO) dye-labeled SEDD formulations in TNBC cells (MDA-MB-468) and normal kidney cells (MDCK). Anticancer efficacy of drug-loaded SEDDs was investigated using resazurin-reduction assay and induction of apoptosis was determined by acridine orange-ethidium bromine (AO-EB) staining.
Stable emulsification was achieved with up to 60% (w/w) and 90% (w/w) oil phase for at least 10 days. SEDDs ranged in size, PDI, and surface charge from 174 – 221 nm, 0.153 – 0.207, and -6.87 – -7.29 mV, respectively. SEDDs showed enhanced internalization of and promoted selective TNBC cellular uptake of chemotherapy and siRNA alone. Average cell viability was decreased significantly across dilutions by Cis-SEDDs and were relatively non-toxic to normal kidney cells while inducing apoptosis in TNBC cells.
In conclusion our SEDD formulation approach may be useful in enhancing the anticancer effects of chemotherapeutics such as cisplatin and rescuing from tumor resistance. Additionally, the ability for co-loading of small and large molecule drugs including thermolabile therapeutics such siRNA into SEDDs presents a versatile approach for effective and targeted therapy.

2)

EMBRYONIC PERFLUOROOCTANESULFONIC ACID (PFOS) EXPOSURE INCREASES B-CELL SENSITIVITY TO NITROREDUCTASE-MEDIATED ABLATION IN ZEBRAFISH (DANIO RERIO).

Marjorie Marin (*a,b), Emily S. Marques (a) and Alicia R. Timme-Laragy (a,b)
a)Department of Environmental Health Sciences, University of Massachusetts, Amherst, US
b)Biotechnology Training Program, University of Massachusetts, Amherst, US

Perfluorooctanesulfonic acid (PFOS) is a persistent perfluorinated pollutant that was used in numerous consumer and industrial products. In zebrafish (Danio rerio), embryonic exposure to PFOS induces oxidative stress and pancreatic dysmorphogenesis. Pancreatic β-cells are particularly sensitive to oxidative stress. This study aims to investigate the role of embryonic PFOS exposure on β-cell fragility. Zebrafish embryos expressing a nitroreductase-mCherry transgene that generates reactive oxygen species in a β-cell specific-manner upon challenge with the substrate Metronidazole (MTZ)(Tg(insa:ntr-mCherry)) were exposed to 0 , 4, 8 or 16 µM PFOS from 3 to 72 hours post fertilization (hpf) before challenged with 0 or 10 mM MTZ for 24 hrs. At 4 days post fertilization (dpf), fish were imaged and raised in clean conditions to 15 dpf, where eyes were collected to measure the glycated protein, fructosamine. Length, yolk sac area and β-cell area were measured from blinded images taken at 4 dpf. MTZ challenged embryos were scored for islet loss (mild, moderate, and severe). At 4 dpf, reduced islet area was observed in embryos exposed to 16µM PFOS, and following MTZ challenge, an increase in the frequency of severe islet loss was also observed in embryos exposed to 16µM PFOS, demonstrating increased β-cell fragility. At 15 dpf, the diabetes biomarker fructosamine was elevated in fish exposed to 16µM PFOS. Overall, PFOS increased β-cell susceptibility to ablation during development and may have long lasting effects in the pancreatic β-cells of juvenile zebrafish possibly contributing to the development of diabetes. This work was supported by R01ES025748.

3)

EXAMINING PFOS-INDUCED DYSLIPIDEMIA AND USE OF α-LIPOIC ACID (ALA) AS A POTENTIAL MITIGATION STRATEGY IN ZEBRAFISH (DANIO RERIO)

Madeline C. Tompach*, Alicia Timme-Laragy

Molecular and Cellular Biology Program, Biotechnology Training Program, University of Massachusetts, Amherst, US

Perfluorooctanesulfonic acid (PFOS) is an environmental toxicant found ubiquitously in the aquatic environment and drinking water supply. PFOS exposure has been associated with dyslipidemia in human and animal studies, including zebrafish (Danio rerio) where previous work demonstrates that preconception and developmental PFOS exposure alters uptake of the lipid-rich yolk sac (YS) over the first five days of development. This study investigates how PFOS affects YS uptake of palmitate, the most abundant fatty acid in humans and zebrafish, in the developing embryo and explores the use of a dietary supplement, α-lipoic acid (ALA), in preconception exposures to combat PFOS-induced dyslipidemia seen in the offspring. To assess palmitate uptake, embryos were given a bolus of fluorescently-labeled palmitate via YS injection and imaged daily using fluorescent microscopy. PFOS-exposed embryos showed reduced fluorescence intensity in the YS, indicating increased uptake of palmitate into the body. In preconception studies, ALA, shown to alter lipid profiles in human studies, was investigated as a mitigation strategy against PFOS-induced dyslipidemia. Adult females were treated with PFOS, fed an ALA-supplemented and bred with unexposed males. Embryos from ALA-supplemented, PFOS-treated, and ALA+PFOS-treated females had increased yolk sac area compared to embryos from control females. Embryos from PFOS-treated females had increased length, while length of embryos from ALA+PFOS females was not different from controls. This study demonstrates specific misregulation of palmitate uptake from the YS with PFOS exposure and indicates that ALA supplementation may partially rescue PFOS-induced changes in growth and development. This work is supported by R01-ES028201 and T32-GM135096.

4)

PUTATIVE ROLE OF KERATINIZATION PATHWAY IN CHEMORESISTANCE IN PANCREATIC PATIENTS

Hao Huynh*, Kawther Abdilleh, George Acquaah-Mensah

MCPHS University - Worcester

FOLFIRINOX (Folfox) combination (5-fluorouracil/leucovorin with irinotecan and oxaliplatin) chemotherapy has shown significant efficacy in treating pancreatic cancer. However, there still exists a low response rate due to chemoresistance. To predict factors that predispose patients to treatment responsiveness, an analysis of gene expression profiles of Folfox-responders and -non-responders was conducted.

Data used in this analysis comes from the Pancreatic Cancer Action Network (PanCAN)'s Know Your Tumor program through the PanCAN SPARK platform. We identified a cohort of patients (n=X) with malignant tumors of the pancreas who had been treated with Folfox therapy, and for which outcome (response vs non-response) was available. Differential gene expression (DEG) analysis between these patient groups was conducted using the DESeq2 Bioconductor package. Pathway overrepresentation analysis was conducted using the Reactome database.
There were 333 differentially expressed genes identified between Folfox-non-responders relative to Folfox-responders. The keratinization pathway, formation of cornified envelope, fibrin clot formation, were among the top over-represented pathways among DEGs with elevated expression in the non-responder group.

Notably, the keratinization pathway over-representation does not occur among genes with suppressed expression in non-responders. Although studies on keratinization pathway relative to chemoresistance are limited, studies on keratin molecules, especially keratin 17, have shown its elevated expression to be associated with chemoresistance and shortest survival rate in pancreatic cancer patients. Our results here suggest that the role of keratinization in chemoresistance should be further examined to improve patient outcomes related to treatment response.

Listing of Poster Titles and Authors (Presenters in bold script)

#	Undergraduate Student Posters
1	ESSENTIAL AND NON-ESSENTIAL ELEMENT BIOACCUMULATION, DISTRIBUTION, AND ELIMINATION IN STRANDED ODONTOCETE WHALES IN FLORIDA **Clara Hay***1,2, Wendy Marks2, Steve Burton2, and Annie Page-Karjian2 1Department of Science, U.S. Coast Guard Academy, New London, CT; 2Harbor Branch Oceanographic Institute, Florida Atlantic University, Fort Pierce, FL.
2	WASTEWATER SURVEILLANCE OF COAST GUARD INSTALLATIONS AND SEAGOING MILITARY VESSELS FOR SARS-COV-2 **A. Ruth**, E. L. Langenbacher, C. Hay, A. Krause, G. Hall, E. Page, and J. P. Gray. US Coast Guard Academy, New London, CT

#	Graduate Student Posters
3	IN VITRO ASSESSMENT OF THE ANTICANCER EFFICACY OF ERLOTINIB AND GEFITINIB IN COMBINATION WITH PIPERLONGUMINE IN LUNG CANCER CELLS **Shail Modi***1, Rania Khalil1, and Terrick Andey1 1-Department of Pharmaceutical Sciences, MCPHS University, MA, 01608
4	ANTIMICROBIAL AGENT CETYLPYRIDINIUM CHLORIDE INTERFERES WITH CALCIUM DYNAMICS OF IMMUNE MAST CELLS **Bright Obeng***, Christian M. Potts, Bailey E. West, Sasha R. Weller, John E. Burnell, Marissa S. Kinney, Lucas J. Bennett, Marissa D. Paine, Suraj Sangroula, Julie A. Gosse Department of Molecular and Biomedical Sciences, University of Maine, Orono, ME 04469, USA
5	GENE EXPRESSION CHANGES ASSOCIATED WITH MENOPAUSE IN BREAST CARCINOMAS **Eunmi Kim***, Dr. George Acquaah-Mensah MCPHS University Worcester Pharmaceutical Science Department
6	DAILY VARIATION OF AIR POLLUTANTS NEAR AN ELEVATED HIGHWAY IN SYRACUSE, NY **Shelby Zangari*** and Jaime E. Mirowsky, SUNY College of Environmental Science and Forestry
7	EXPLORING DIFFERENCES IN GENETICS AND COMORBIDITIES IN THE RESPONSE TO FOLFOX IN PANCREATIC CANCER PATIENTS ***Andrew McNiff**, Dr George Acquaah-Mensah, Dr Kawther Abdilleh Massachusetts College of Pharmacy and Health Sciences University
8	MITOCHONDRIAL TOXICITY OF ANTIMICROBIAL AGENT CETYLPYRIDINIUM CHLORIDE **Sasha R. Weller**, John E. Burnell*, Brandon M. Aho, Bright Obeng, Julie A. Gosse, and Samuel T. Hess University of Maine, Orono, ME 04469
9	CHEMICAL EXPOSURES AFFECT INNATE IMMUNE RESPONSE TO SARS-COV-2 **Olatunbosun Kayode Arowolo** Department of Environmental Health Sciences, University of Massachusetts, Amherst
10	BIOMARKERS FOR RESPONSIVENESS TO TWO COMBINATION THERAPIES FOR PDAC Eunmi Kim*, **Tien Van Le***, Dr. George Acquaah-Mensah, Dr. Kawther Abdilleh MCPHS University Worcester Pharmaceutical Science Department
11	DEVELOPMENTAL EXPOSURES TO PFAS MIXTURES IMPAIR ELONGATION OF THE EXOCRINE PANCREAS IN ZEBRAFISH (DANIO RERIO) **Emily Formato***1, Kristina Borys2, Alicia R. Timme-Laragy2 1Molecular & Cellular Biology Graduate Program, 2Department of Environmental Health Sciences, University of Massachusetts

12	THE ROLE OF FATTY ACID BINDING PROTEIN (FABP) IN TOXICOKINETIC PARAMETERS OF PERFLUOROOCTANESULFONIC ACID (PFOS): AN IN VIVO STUDY **Seyed Mohamad Sadegh Modaresi** Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, Kingston, RI, 02881
13	APPLICATION OF PRESATURATION EQUILIBRIUM DIALYSIS BINDING FOR VARIOUS PFAS TO PLASMA, LIVER, AND BREAST MILK **Sangwoo Ryu** University Of Rhode Island
14	IN UTERO AND LACTATION EXPOSURE RESULTED IN A SIGNIFICANT ACCUMULATION OF PFOA, PFOS AND PFHXS LEVELS IN BRAIN TISSUE OF DEVELOPMENTALLY EXPOSED CD-1 MOUSE PUPS AT PND21 **J. Agudelo***, J. Becanova, E. Martell, S. Modaresi SMS, E. Kaye, and A. Slitt. University of Rhode Island, Kingston, RI, United States.
15	DEVELOPMENTAL EXPOSURE TO PFAS MIXTURE: PFOA, PFOS AND PFHXS SIGNIFICANTLY ALTERS THE PUP LIVER PROTEOME **Emily Kaye[1]**, Juliana Agudelo[1], Seyed Mohamad Sadegh Modaresi [1], Emily Marques[2], Angela Slitt[1] [1]University of Rhode Island – College of Pharmacy, Kingston, RI, United States [2]Department of Environmental Health Sciences, School of Public Health and Health Sciences - University of Massachusetts Amherst, Amherst, MA, 01003

#	**Postdoc Posters**
16	SLC39A14 DEFICIENCY IMPAIRS BILIARY EXCRETION OF IRON-RICH FERRITIN IN MICE **Milan Prajapati*,** Heather Conboy, Jared Zhang, Tom Bartnikas Department of Pathology and Laboratory Medicine, Brown University, Providence, RI, 02912
17	NRF2 PROTECTS THE DEVELOPMENTAL REDOX STATUS IN THE LIVER OF THE ZEBRAFISH (DANIO RERIO) EMBRYO **Emily Marques**(*a), Archit Rastogi (b), Emily G. Severance (b), Sarah M. Conlin (a) and Alicia R. Timme-Laragy (a) a. Department of Environmental Health Sciences, School of Public Health and Health Sciences, University of Massachusetts, Amherst, MA 01003, USA b. Molecular & Cellular Biology Graduate Program, University of Massachusetts, Amherst, MA-01003

NESOT Officers 2021-2022:

Position	**Officer**	**Affiliation**
President:	Joel Cohen	Gradient
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Junior Student Rep:	Shelby Zangari	SUNY College of Environmental Science and Forestry
Postdoctoral Rep:	Emily Marques	University of Massachusetts, Amherst