Arkansas Nanomedicine Center (ANC)

Four major benefits for the State of Arkansas which will be derived from the formation of the Arkansas Nanomedicine Center (CAN) :

Research benefits: Advanced nanomaterials will be tested as potentially active agents for bio-nano-science and the treatment of many diseases such as cancer, infections, and cardiovascular disorders. Other applications will include tissue engineering (plant and animal), drug delivery, nano-bio-sensors for low dose radiation dosimetry and environment toxicity monitoring.

Educational benefits: The ANC together with NCTR will extend the opportunities to develop novel and model educational programs that have been proposed in discussion with the FDA commissioner. Further, the universities that are fully engaged in providing outstanding education for students in the fields of Nanomedicine will focus on interdisciplinary graduate student programs.

Economic benefits: It is expected that the research results generated by the ANC and the support of the resources of NCTR provide an unusually favorable opportunity for significant economic impact on the region. Spin off and technology companies will be formed around the ANC and located in the central part of Arkansas and will attract companies to the Central Arkansas Research Park to be built near UAMS. UAMS Bio-ventures is already incubating several spin off businesses that are engaged in nanomedicine applications.

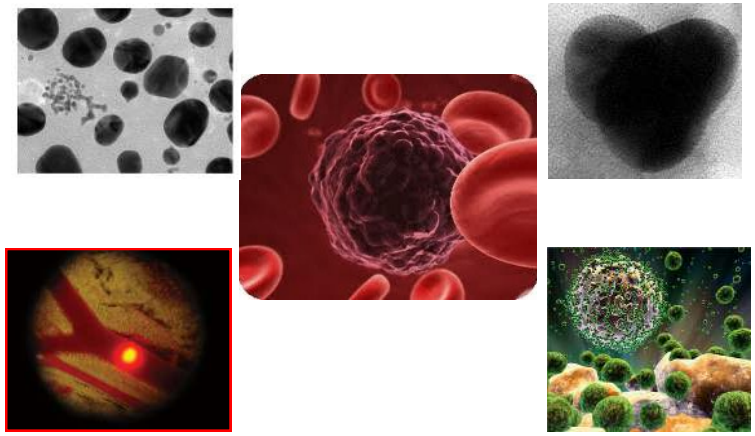
Healthcare benefits: New early diagnosis approaches and advanced treatments developed at ANC will first benefit all Arkansans. The Nanomedicine technologies will be expected to have a national and international impact. This will be reflected in a large number of patients coming to Arkansas resulting in a significant economic impact.

UAMS
COLLEGE OF MEDICINE
UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES

UAMS College of Medicine Series

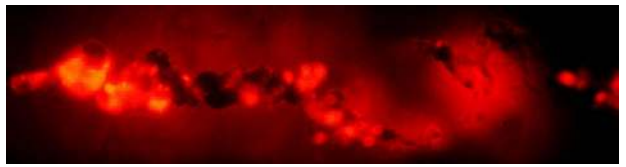
Showcase of Medical Discoveries:

A Focus on Nanomedicine



A Wine and Cheese Reception Featuring UAMS Investigators Discussing their Research and Discoveries.

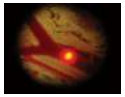
Winthrop P. Rockefeller Cancer Institute
10th Floor Rotunda



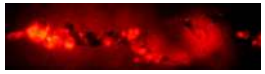
Wednesday, February 27, 2013

4:00—5:30 p.m.

Poster #1



Arkansas Nanomedicine Center (ANC) at the University of Arkansas for Medical Sciences



Background: Nanomedicine is an offshoot of nanotechnology, and refers to highly specific medical research and applications at the molecular scale for curing disease or repairing damaged tissues.

Gathering nanomedicine efforts and resources from within the University of Arkansas for Medical Sciences (UAMS) and statewide collaborators under one umbrella, UAMS announced in 2012 the creation of the Arkansas Nanomedicine Center (ANC) in the College of Medicine as a virtual hub at UAMS

Goal: The goal of the Arkansas Nanomedicine Center (ANC) is to bring revolutionary Nanotechnology advances from Bench to Bedside. The mission of the ANC is to establish collaborations with UAMS departments and institutes including the Winthrop P. Rockefeller Cancer Institute; the Jackson T. Stephens Spine & Neurosciences Institute, the Myeloma Institute, the Translational Research Institute (TRI), and many clinical and basic science departments of the College of Medicine and at state institutions and centers with abundant expertise in nanotechnology.

Arkansas Nanomedicine Center (ANC) Scientific Directions

Nanotheranostics
Phillips Classic Laser and Nanomedicine Laboratories
Director: Vladimir P. Zharov, PhD
Dept. of Otolaryngology Head & Neck Surgery

Anti-cancer Nanomedicine
Leader: Robert Griffin, PhD
Professor & Director, Radiation Oncology

Molecular Nanoimaging
Leader: Michael Borrelli, PhD
Professor of Radiology, Physiology and Biophysics
Dept. of Radiology

Nanotoxicity
Leader: Alexei Basnakian, MD, PhD
Professor & Director
DNA Damage & Toxicology Core Center
Dept. of Pharmacology & Toxicology

Nanogenetics
Leader: Anna Radominska-Pandya, PhD, Professor,
Department of Biochemistry and Molecular Biology

Nanopharmacology
Leader: Eric C. Peterson, PhD
Assistant Professor
Dept. of Pharmacology & Toxicology

ANC Director
Vladimir Zharov, PhD DSc

ANC Associate Director
Michael Borrelli, PhD

ANC Associate Director
Robert Griffin, PhD

Poster #12

Characterization of Carbon-Based Nanomaterials Using Innovative Analytical Photothermal and Photoacoustic Techniques In Vitro and In Vivo

Dmitry A. Nedosekin, Ekaterina I. Galanzha, Vladimir P. Zharov

Background: Carbon-based nanomaterials (CBNs) have been proposed for various biomedical applications including gene therapy, biological sensing and imaging, creation of biocompatible scaffolds for cell cultures, drug and siRNA delivery and even photothermal therapy. Numerous composite materials containing carbon nanotubes and graphene family nanomaterials were created for energy technology (fuel cells, batteries), sensors and catalysis. Biocompatibility, unique optical properties, high specific are, electric conductivity, mechanical strength and simple derivatization of carbon groups increase potential of these nanomaterials in various areas including medical applications. Thus, further widespread use of CBNs in technology and biomedicine increases the importance of studying safety of these materials. However, the quantification of CBNs consisting mostly of carbon and oxygen atoms is challenging, especially, in biological carbon reach matrixes. For the successful interpretation of nanotoxicity data nanoparticle uptake should be quantified at each step including knowledge of distribution at a subcellular level, volume uptake by different cells, uptake by small model organisms (nematodes or zebrafish), and pharmokinetics in blood and lymph circulatory of small rodents.

Results: In this presentation we discuss innovative photothermal and photoacoustic techniques and the novel methodology tailored for characterization of CBNs in biological systems. Combination of conventional nanotoxicology approaches with innovative methods for quantification of nanomaterials in carbon reach matrixes provides a reliable correlation between uptake and toxicity. We discuss applications of super-resolution confocal photothermal microscopy, *in vivo* photoacoustic microscopy, *in vivo* and *in vitro* flow cytometry with fluorescence and photoacoustic detection schematic, and photothermal nanohistology for characterization and quantification of various exogenous nanomaterials.

Poster #11

Novel DNA fragmentation-based technology for the assessment of nanomaterial toxicity in vitro and in vivo

Eugene O. Apostolov, Tariq Fahmi, Todd Fite, Alena Savenka, Xiaoying Wang, Anna Stewart, Oleg Karaduta, Daesong Jang, Dmitry Zhdanov, and Alexei G. Basnakian

Background: Rapid development of nanotechnology requires new methods, which would be universally applicable to study toxicity of new nanomaterials to assess their safety and predict potential adverse reactions. We have developed an innovative technology, which has a promise to be the first direct "marker of harm" that is capable of quick evaluation of nanomaterials cytotoxicity in live cells and animals. Important advantage of this technology is its universality, which makes it applicable for various types of cell death mechanisms, species, and variety of toxic agents, including all kinds of nanomaterials and drugs. It is a non-invasive and quantitative approach that can be easily combined with other quantitative imaging methodologies as well as existing methods of toxicity assessment. The technology is based on the measurement of DNase-mediated DNA fragmentation, which is the only marker of *irreversible* (final) cell death, and a hallmark of all types of cell death regardless of their mechanism. We have developed a novel DNase activity probe to measure DNase activity *in vitro* and *in vivo*. It is a cell-penetrating, DNase-activatable, self-quenching near infra-red fluorescent (NIRF) reporter probe named AB259.3. The probe is applicable for *in vitro* or *in vivo* use, visualization and quantification of DNase activity in solutions (as a high throughput assay), in live cells, previously frozen tissue biopsy samples, or live animals. It is universal, not specific to any particular DNase, cell type, tissue, species or type of cell/tissue injury.

Results: After intravenous administration in mice, the unprotected probe accumulated in kidney, while the probe packed in cationic liposomes was distributed in all organs with predominant accumulation in the liver, lung, spleen, pancreas, intestine and heart. In tissues like kidney, where the majority of DNase activity is provided by DNase I, the probe measures this endonuclease. The NIRF signal in live animals can be measured using an Intravital Imaging System (IVIS) instrument. For cells, a fluorescence plate reader or microscope equipped with quantification software can be applied. Cell penetration by the probe can be visualized in organs isolated from injected animals, or in cultured cells. Importantly, tissue injury *in vivo* is associated with the increase of the signal intensity. Similarly, cultured cells exposed with nanoparticles or toxic agents like cisplatin or camptothecin demonstrated marked increase of the signal. The increase of the NIRF signal inside the cells was associated with apoptosis starting with very early stages and reaching maximum at apoptotic nuclear shrinkage (pyknosis) phase.

Poster #2

High-Frequency Ultrasound (HIFU) Mapping of Tumor Vascular Hypoxia as a Targeting Modality for Focused Ultrasound Ablation to Complement Ionizing Radiotherapy

Nathan A. Koonce, Xin Chen, Sunil Sharma, David Y-W. Lee, James A. Raleigh, and Robert J. Griffin

Background: We have discovered a new approach to image the amount of oxygen in the cells that make-up blood vessels in tumors. With our new technique we are hoping to uncover new aspects of predicting and monitoring the success of therapy against various types of solid tumors. Because the cells being detected are in contact with the circulation, we are also creating a target for advanced drug delivery. In this regard, we are developing new nanomedicine compounds with gold and other nanomaterials to deliver high doses of potent drugs to the tumor blood vessels.

Hypoxia is a well-studied physiological barrier to radiation and chemotherapy, and we hypothesize that tumor hypoxia attenuates sterotactic radiation therapy (SRT) response. PET/MRI-guided focused ultrasound with ^{18}F-misonidazole for detection of regional tumor hypoxia and selective ablation of these areas proved that a rationale for combined HIFU and radiotherapy exists. However, this approach is inefficient in spatial resolution of tumor hypoxia and cumbersome for clinical translation. A recent development by our lab for imaging tumor vascular hypoxia prompted proposal of an alternative approach to selective ablation by HIFU. This ultrasound metabolic imaging technique combined with HIFU may complement SRT if imaging criteria for ablation can be achieved as surviving endothelial cells have been proposed to play a crucial role in revascularization of recurrent tumors.

Results: This study captures the first appraisal of non-invasive detection of tumor vascular hypoxia using targeted microbubbles. Perfused tumor vessels at oxygen levels resistant to radiation and chemotherapy were detected with targeted microbubbles. The specificity of these microbubbles was found to be 17-fold higher in targeted tumors than the negative control tumors, mean$\pm$SEM (110.8$\pm$23.64 vs. 6.25$\pm$2.842, p=0.0118). Ongoing efforts are toward 3D contrast-enhanced ultrasound mapping of the $MB_{pimonidazole}$ binding pattern as a template for treatment planning with HIFU to destroy these areas as an adjuvant to chemo/radiotherapy.

Poster #3

Nanotechnology: A Tiny Solution to Huge Problems in Infectious Disease?

Karen Beenken, Ekaterina Galanzha, Vladimir Zharov, and Mark Smeltzer

Background: Antibiotic resistance is a growing problem in all forms of infectious disease, with many bacterial pathogens being more problematic now than at any time since the pre-antibiotic era. Among these is *Staphylococcus aureus*, which has been designated one of the ESKAPE pathogens given its prominence as a cause of human infection and its increasing ability to "escape" the effects of antibiotic therapy. Many forms of *S. aureus* infection are also characterized by formation of a biofilm, which consists of multiple layers of stationary bacterial cells encased within some form of protective extracellular matrix. In effect, the biofilm serves as a "fort" capable of protecting the associated bacteria from both antibiotics and host defenses. For this reason, the treatment of biofilm-associated infections requires, in addition to long-term antibiotic therapy, and assuming an appropriate antibiotic is available, surgical intervention to remove infected tissues and/or indwelling devices. In effect, you have to remove the fort to gain access to the offending bacteria, and even after doing so far too many patients suffer recurrent bouts of infection and ultimately experience therapeutic failure. Typical surfaces involved in biofilm-associated infections include native and prosthetic heart valves, vascular assist devices, vascular grafts, native bone and cartilage, and indwelling medical devices including catheters and orthopaedic implants.

The use of such indwelling devices is of paramount importance in the treatment of patients suffering many forms of disease, including cancer, thus putting patients at increased risk of an infection that cannot be treated using conventional antimicrobial therapy at precisely the time when they are least able to fight back on their own. We are working to overcome this growing problem by developing novel methods for the treatment of *S. aureus* biofilm-associated infection. This includes studies to define the mechanism by *S. aureus* builds its fort to gain the relative safety of a biofilm. We have identified what can be viewed as key structural components of the biofilm, and in this project we are taking advantage of antibodies targeting these components to exploit the therapeutic promise of nanotechnology in this context. Because it offers the opportunity for the targeted physical destruction of biofilm-associated bacteria, our approach has the potential to overcome both the intrinsic resistance (e.g. the fort) that characterizes these infections and the acquired antibiotic resistance responsible for the ESKAPE status of *S. aureus*. Indeed, until now, nanotechnology has been exploited almost exclusively in the context of cancer, but in our view biofilms and tumors share two common properties. First, both are growths within the human body that have pathological consequences and therefore must be destroyed without damage to the surrounding healthy tissues. Second, it is very difficult to achieve this objective using conventional therapeutic strategies, which in the case of infection are focused on the use of conventional antibiotics.

Results: Taking advantage of our knowledge of *S. aureus* biofilm formation, and the technical expertise of the Zharov laboratory in nanotechnology and laser biophysics, we have confirmed we can use antibody-based methods to selectively deliver golden nanorods to the surface of *S. aureus* cells in sufficient quantity to generate lethal photothermal (PT) effects. We have confirmed the utility of this approach both in vitro and in vivo in the context of bloodstream infections and in an established biofilm. Much remains to be done to optimize this approach for therapeutic use in humans, and this is the current focus of our work.

Poster #10

Photothermal nanodrugs: potential of functionalized TNF-gold nanospheres for cancer theranostics

Dr. Griffin's Staff

Dr. Zharov's Staff

Robert J Griffin, Jingwei Shao, Ekaterina I. Galanzha, Jin-Woo Kim, Nathan Koonce, Jessica Webber, Dmitry A. Nedosekin, Alexandru Biris, Vladimir P. Zharov

Background:

Nanotechnology has been extensively explored for imaging, therapy, and drug delivery. Here, we introduce the concept of a nanodrug whose mechanism is based on synergy between physical and biological effects which are photothermally activated in nanoparticle-drug conjugates. To prove this concept, we utilized tumor necrosis factor-alpha coated gold nanospheres (Au-TNF) heated by nanosecond laser pulses. To enhance photothermal nanodrug efficiency in the near-infrared window of tissue transparency where nanospheres have off-resonance weak plasmonic absorption, we explored slightly ellipsoidal nanospheres and the occurrence of nanosphere clustering in tumor tissues providing a red-shift in plasmonic resonances. In addition, laser–induced dynamic nanoparticle modification and nanobubble formation led to amplification and spectral sharpening of the red-shifted photothermal resonances. Using a murine carcinoma model, we demonstrated higher photothermal therapy efficacy of Au–TNF conjugates compared to laser and Au–TNF alone or laser with TNF-free gold nanospheres. The photothermal activation of Au–TNF conjugates, which are in phase II trials in humans, with a laser approved for medical applications opens new avenues in the development of clinically relevant photothermal nanodrugs and a means to create synergistic antitumor action.

Results:

Functionalized gold nanoparticles can be heated with NIR lasers. Unique effects from the destruction of the particles upon laser exposure may contribute to improved tumor response. Clustering of the nanoparticles in and around cells leads to enhanced absorption, heating and synergistic effects on tumor control.

Poster #9

A Novel Strategy for Targeted Drug Delivery to the Tumor Vasculature by Radiation-Induced Receptor Expression on Endothelial Cells

Meenakshi Upreti, Azemat Jamshidi-Parsian, Eldin Swindell, Scott Apana, Marc Berridge, Nathan Koonce, Thomas V. O'Halloran and Robert J. Griffin

Background:

One of the primary goals of a successful cancer treatment regimen is to deliver an effective combination of radiation and/or drugs to tumors while minimizing damage to normal tissues. Tumor growth is considered to be directly dependent on its blood supply. Several unique proteins functionally important to tumor vessel growth and formation, termed angiogenesis, are expressed on tumor vessel cells and can serve as potential targets for drug delivery to solid tumors. Targeting the tumor vasculature is a strategy that can therefore allow targeted delivery to a wide range of tumor types. A major challenge in this approach is in defining the optimal targeting agent or agents to selectively transport chemotherapy to the tumor/tumor stroma. The present study demonstrates the specificity and efficacy of an anti-angiogenic peptide in targeting therapeutic liposomes to the tumor vasculature by radiation amplified Galectin-1 expression.

Results:

The present study works toward establishing the use of anginex as a targeting approach for delivering liposomes carrying therapeutic/cytotoxic agents to the tumor vasculature by radiation-induced amplification of its target, the galectin -1 receptor.

Poster #4

Biodegradable Starch Nanoparticles are an Effective and Safe Adjuvant for Sonothrombolysis Especially for more Fibrin Rich, Aged and Rigid Clots.

Michael Borrelli, PhD **Ajay Malshe, PhD**

Kaleb Smithson, Dheeraj Ahluwallia, Ajay Malshe, Eric Hamilton, Laura J. Bernock, and Michael J. Borrelli

Background: Ultrasound is used to lyse clots that obstruct blood vessels via a process called sonothrombolysis. Medical applications for sonothrombolysis include treating vascular occlusion diseases like stroke, myocardial infarct (MI), deep venous thrombosis (DVT), pulmonary embolism, etc. More fibrous, rigid and aged clots are more difficult to lyse, even when tissue plasminogen activator (tPA- a thrombolytic molecule) and microbubbles are used as adjuvants to promote the sonothrombolysis process. Consequently, we combined nanoparticles with ultrasound and microbubbles, postulating that the nanoparticles would serve as an abrasive to hasten sonothrombolytic break down of blood clots. The concept is that as the microbubbles oscillated in response to the ultrasound they would project the nanoparticles into the clot to facilitate sonothrombolysis, in a manner similar to the process of sandblasting. We used biodegradable starch nanoparticles to avoid any potential toxicity that might be associated with non-biodegradable nanoparticles made of iron, gold, etc.

Results: Surprisingly, using just the biodegradable starch nanoparticles with ultrasound produced effective sonothrombolysis, especially for more fibrin-rich and rigid clots. Combining the starch nanoparticles with microbubbles produced even more effective sonothrombolysis. Thus, the biodegradable starch nanoparticles are an effective and nontoxic agent to promote sonothrombolysis efficacy, and they are synergistic with microbubbles to provide even higher levels of sonothrombolysis. The potential clinical impact is that the biodegradable starch nanoparticles would yield more rapid and safe lysis of clots, especially the more fibrous and rigid clots that are more resistant to lysis by tPA and other, current treatments. This is particularly desirable for cases of stroke or pulmonary embolism where faster clot breakdown can save lives and reduce disease-associated disabilities.

Poster #5

Developing Novel Nanotherapies for the Treatment of Methamphetamine Addiction

Nisha Nanaware-Kharade, Emily E. Reichard, Shraddha Thakkar,
Guillermo A. Gonzalez III, Reha Celikel, Kottayil I. Varughese, Eric C. Peterson

Background: Methamphetamine (METH) abuse is a serious problem in the US and worldwide, with associated devastating socioeconomic consequences for individuals, families, and communities. There are no FDA-approved medications available for treatment. Methamphetamine acts on multiple sites in the brain, and efforts to design drugs that protect against the effects of METH have not been successful. Thus, current METH abuse treatment is mainly limited to supportive behavioral therapy with no pharmacological aid to help patients avoid relapse to drug use. Unfortunately, most patients do relapse to METH use at some point. Thus, discovery of new treatments that could help patients avoid relapse, or blunt the rewarding effects from reinitiating drug use is of primary importance.

Results: We are currently accomplishing this goal through two projects in the laboratory. In the first project we are combining antibody therapy and nanotechnology to generate an adaptable range of anti-METH medications that will have applicability to important therapeutic treatment (e.g., a short-acting medication for overdose and a long-acting, low volume of distribution medication needed for chronic treatment of addiction). We are accomplishing this through the use of nanotechnology and advanced protein modification with inert polymers. These studies will provide the first detailed information on the necessary design features and molecular principles required to create advanced new generations of novel nanotherapeutics for the treatment of drug abuse. In a second collaborative project with researchers in the UAMS Department Physiology and Biophysics, we are using x-ray crystallography to determine the molecular structures of our highest activity anti-METH antibodies. We are using the resulting structural data and recombinant molecular technologies to engineer a new generation of antibodies with enhanced efficacy against METH.

Poster #8

Real-Time Monitoring of Nanoparticle and Drug Nanocarrier Pharmokinetics with Ultra-Fast Photoacoustic Flow Cytometry

Mustafa Sarimollaoglu, Dmitry Nedosekin, Ekaterina I. Galanzha,
and Vladimir P. Zharov

Background: The rapidly growing development and application of nanotechnology-based drug and gene carriers has placed an urgent demand on monitoring their dynamic interactions with blood cells and clearance rates in the vessels of various locations. No clinically relevant method has been developed to address this problem adequately. As most contrast agents and drug carriers have intrinsic or enhanced optical absorption, photoacoustic flow cytometry (PAFC) is an almost ideal tool for real-time, label-free monitoring of their pharmacokinetics. We present here a new multicolor PAFC using a high pulse repetition laser array with different wavelengths (e.g., 532 n, 671 nm, 820 nm, and 1064 nm) to monitor the pharmokinetics of liposomes, nanoparticles coated with drug (e.g., gold-TNF-alpha), nanoparticles with empty core (e.g., golden carbon nanotubes), and conjugated microbubbles.

Results: We discovered that after injection of drug carriers or contrast agents, PAFC provides two typical signal trace patterns: an increase in the baseline level above blood background, and strong fluctuations above baseline. The first pattern is associated with homogenous random distribution of nano-objects in circulation, while the second pattern is related with the presence of their aggregates which provide a stronger localized absorption. The clearance rate of most nanoparticles depending on their surface properties was in the range of 0.5-4 hours, while liposomes demonstrated a long term circulation of up to a few days. We revealed dynamic aggregation of nanoparticles in blood flow during and immediately after injection, while prior to injection they demonstrated homogenous, non-clustered patterns. The proposed technique can be useful for the routine evaluation of possible influence of the natural properties of drug careers, the protective materials, and the coating procedures on their clearance. It also allows the minimization of the number of animals used, in contrast to *ex vivo* methods where periodical blood sampling is required.

Poster #7

Human UGTs: A Novel Role in Modulating Cytotoxicity in Cancer

Anna Radominska-Pandya, Tariq Fahmi, FeAna FrancisDevaraj, Centdrika R. Dates,
Aleksandra K. Greer, Sebastian J. Pyrek, and Stacie M. Bratton

Background: Drug-metabolizing enzymes, such as human UDP-glucuronosyltransferases (UGTs), are involved in not only the metabolism and detoxification of xenobiotic and endogenous compounds but also the regulation of steady state levels of cellular lipids and ligands that affect growth, homeostasis, and differentiation of cells. Glucuronidation of lipophilic ligands such as androgens, estrogens, corticoids, farnesyl, and retinoids can terminate signals conveyed by nuclear receptors. This suggests that UGTs may have naturally evolved to play an important role in the regulation of steady state levels of low molecular weight effectors, such as transcription activating ligands and secondary messengers that are important in growth and development. It is also documented that cancer cells have the capacity to synthesize their own supply of biologically active lipids, independent of the signals that down-regulate their synthesis in normal cells. Increased concentrations of such compounds may result from inefficient regulatory mechanisms, such as down-regulation of UGT-mediated glucuronidation, controlling their levels in the cell and destabilizing cell homeostasis. This also would expose cells to elevated levels of mutagens and carcinogens.

The present studies were initiated to test the hypothesis that the levels of specific UGTs are altered in cancer cells. Our original work has shown that UGT2B7, which glucuronidates steroids, farnesyl, bile acids, fatty acids, and retinoids, is down-regulated in ovarian and breast cancer cells. In ovarian tumors, we see an accumulation of cellular lipids, which has been linked to cancer development and metastasis. Stable transfection of primary ovarian cancer cell lines with UGT2B7 dramatically reduces the lipid content and mediates growth arrest in these cells in a concentration dependent manner. This suggests that UGT2B7 down-regulation may be directly involved in the development of ovarian cancer and its function in normal cells may be compared to tumor suppressor genes. In 6 breast cancer cell lines (MCF7, MDA231, MDA468, MCF10, T47D, and ZR75), we have used Real Time RT-PCR to measure the levels of mRNA for 15 UGT isoforms from the 1A and 2B families. No UGT2B7 expression was seen in any of these cell lines, and low levels of UGT2B4 and UGT2B15 were seen in most cell lines. Experiments with MCF-7 cells chemically transfected with UGT2B15, UGT2B7, and UGT2B4 were carried out to investigate the influence of the individual UGTs on cell viability and up to 50% reduction in cell proliferation was seen after the reintroduction of UGT2B4 and UGT2B7 expression.

Results: Interestingly, many of the UGT1A isoforms, especially UGT1A7, show very high levels of expression in these cells and these levels are highest in the T47D and ZR75 cell lines. Increased expression of these UGTs could lead to enhanced drug toxicity and/or more rapid excretion leading to drug resistance. Therefore, the full understanding of the complex regulation of UGT levels in cancer cells may be therapeutically advantageous since many drugs are eliminated *via* this pathway. These preliminary data support the role of UGTs as potential anticancer agents and novel agents for nanodelivery. (NIH-GM075893, DoD-W81XWH1110795)

Poster #6

Repeated Doses of Dodecafluoropentane Emulsion, a Nanodroplet, Provide Neuroprotection Up to 24 Hours Following Cerebral Artery Occlusion in Rabbits

Sean D. Woods, Robert D. Skinner, Aliza T. Brown, Aaron M. Ricca, Univ of Arkansas for Medical Sciences, Little Rock, AR; Jennifer L. Johnson, Evan C. Unger, NuvOx Pharma LLC, Tucson, AZ; Michael J. Borrelli, John D. Lowery, William C. Culp, Univ of Arkansas for Medical Sciences, Little Rock, AR

Background: Neuroprotective strategies in ischemic stroke include oxygen delivery to sustain penumbra and prevent hypoxic cell death. Hyperbaric oxygen, blood substitutes, and liquid fluorocarbon-based oxygen carriers have often failed in treatment of stroke and other ischemic disorders. Dodecafluoropentane emulsion (DDFPe, boiling point 29°C) shifts to quasi-gas phase at body temperature, which allows absorption and transportation of very high levels of oxygen. Exceptionally small particle size, 250-300 nm, may allow oxygen delivery even through occluded vessels, by diffusion into hypoxic tissue unreachable by whole blood. In a preliminary stroke study in rabbits, DDFPe reduced infarct volumes in the immediate 4 and 7 hours post-ischemia.

Results: Percent infarct volume means significantly decreased for all DDFPe treated groups compared with controls (Table 1).

Group No.	DDFPe Dosage	Sacrifice Time (h)	N	Infarct Volume (%) ± SE	P-value (vs. Control)
1	Control	7	6	3.88 ± 1.41	-
2	0.1 ml/kg	7	7	0.58 ± 0.21	0.004
3	0.3 ml/kg	7	9	0.59 ± 0.25	0.003
4	0.6 ml/kg	7	8	1.03 ± 0.69	0.009
5	Control	24	16	3.39 ± 0.94	-
6	0.1 ml/kg	24	9	0.51 ± 0.14	0.008

Intravenous DDFPe begun 1 hour after stroke onset protects the brain from ischemic injury in the rabbit model of permanent embolic stroke. Decreased infarct volumes represent salvaged brain tissue. This effect can be observed for 24 hours with repeated doses.