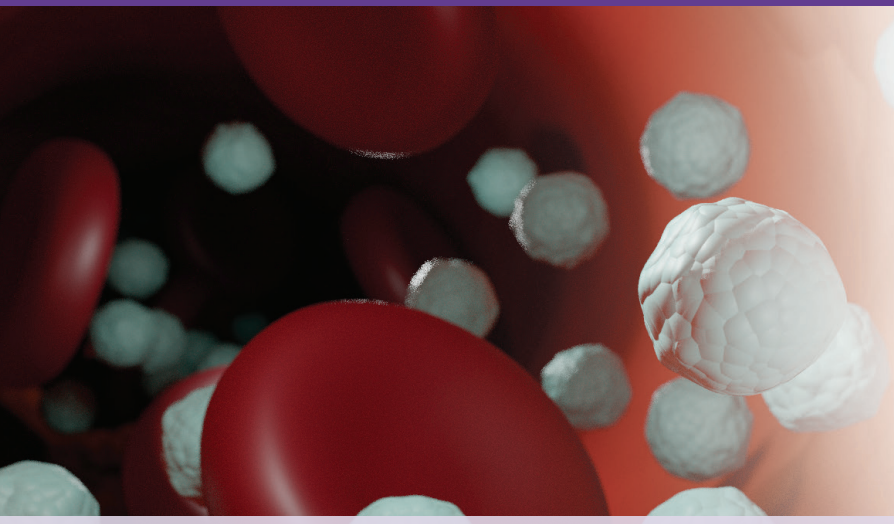
Nanotechnology Characterization Laboratory



NCL
Nanotechnology
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July 2020

Each quarter the NCL accepts the most promising cancer nanomedicine candidates into its Assay Cascade characterization and testing program. Nanomedicines accepted into the program will undergo a rigorous evaluation that may include sterility and endotoxin testing, physicochemical characterization, in vitro hemato- and immunotoxicity, and in vivo studies to evaluate safety, efficacy and pharmacokinetics. The studies are tailored to each individual nanomedicine and are designed to promote the clinical translation of these novel therapies. **All studies are conducted free of charge for Awardees**.

Congratulations to this Quarter's Awardees

Y. Barenholz, Hebrew University
Nano-mupirocin is a PEGylated nano-liposomal formulation of the antibiotic mupirocin. Mupirocin is a unique mode of action antibiotic limited to topical use due to its rapid metabolism in vivo and high protein binding. By encapsulating in nano-liposomes, the parenteral activity of mupirocin was enabled resulting in a parenteral new mode of action antibiotic. The unique characteristics of Nano-mupirocin fits well targeting tumor microbiome as: 1) it is accumulated in tumors due to the EPR effect; 2) it is active against bacteria known to promote cancer progression; 3) there is no activity of the free drug in the circulation, and therefore it is not expected to affect gut microbiome upon long-term use. Diverse gut microbiome was found to improve outcomes in many cancer types; and 4) a unique mode of action--not expected to produce cross-resistance with commonly-used antibiotics. Nano-mupirocin may therefore present a selective and efficacious treatment for desired tumor microbiome modification.

Antonio Costa, Department of Pharmaceutical Sciences, School of Pharmacy, University of Connecticut and DIANT Pharma Inc.
At UConn, in the lab of Dr. Diane Burgess, we have developed a high-throughput and scalable continuous manufacturing system to make nanoparticles such as liposomes, lipid nanoparticles, polymeric micelles, etc. Our system uses a turbulent jet in co-flow, coupled with process analytical technology, to accurately control and monitor the nanoparticle formation process. This system incorporates multiple modules, providing a flexible pharmaceutical processing approach including particle formation, concentration, particle modification and bioburden reduction. Accordingly, our manufacturing platform has been designed to be GMP-ready. In our collaboration with NCL, we aim to examine liposomal doxorubicin with different intra-liposomal, doxorubicin crystal structures. This work will provide an in-depth physicochemical characterization of our material and important in-vivo evaluations.

https://burgess.lab.uconn.edu

www.diantpharma.com

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Frederick National Laboratory
for Cancer Research
sponsored by the National Cancer Institute

Congratulations to this Quarter's Awardees (continued)

ZR Lu, Case Western Reserve University
We are developing a multifunctional nanoparticle platform technology that can specifically regulate novel but "undruggable" targets like oncogenic long non-coding RNAs (onco-lncRNAs) for human triple-negative breast cancer (TNBC) therapy. For heterogenous cancers like TNBC, onco-lncRNAs are attractive therapeutic targets, owing to their ability to regulate the transcriptome, proteome, and epigenome, and their highly specific temporal and spatial expression. Efficient RNAi of onco-lncRNAs by tumor-specific delivery of therapeutic siRNA into the cytosol of target cells via systemic administration is indispensable for effective cancer therapy. To this end, we have developed a safe, effective, and highly versatile targeted RGD-PEG-ECO/siRNA nanoparticle technology. At the core of this nanoplatform is the amino lipid carrier, (1-aminoethyl)iminobis[N-oleicylsteinyl-1-aminoethyl)propionamide] (ECO), which self-assembles with negatively charged therapeutic cargo like siRNA to form stable nanoparticles, which can be customized with targeting moieties like PEG for biocompatibility and tumor-targeting ligands like the RGD peptide. After systemic delivery, the nanoparticles undergo endocytic uptake, followed by pH-sensitive amphiphilic endosomal escape and cytosolic release of the therapeutic siRNA cargo in tumor cells. Our preliminary proof-of-concept studies with RGD-PEG-ECO/siDANCR nanoparticles (bearing siRNA to the onco-lncRNA DANCR) have demonstrated sustained silencing of DANCR (80-90% silencing for up to 7 days) and significant suppression of invasion, migration, proliferation, and survival of TNBC cells and tumor xenografts in 2 independent models. We have also uncovered several pleiotropic effects of DANCR silencing on oncogenic signaling moieties like AKT and on epigenetic factors like EZH2. Our ongoing research is focused on optimization of several aspects, including formulation stability, scalability, and enhanced tumor-targeting of the nanoparticle platform, as well as conducting pre-clinical PK/PD, ADME, and toxicity assays for its clinical translation.

https://engineering.case.edu/groups/cbm

Dr. Bruce A. Shapiro, RNA Biology Laboratory, RNA Structure and Design Section, National Cancer Institute
Our technologies are based on the design and usage of nucleic acid nanoparticles consisting of all RNA, or RNA/DNA hybrid architectures having controllable shapes consisting of multiple stand assemblies (e.g. 30 strands) which we have shown via several sets of experiments to have therapeutic value. We have demonstrated that these particles have significant capabilities in cell culture studies involving, for example, induced apoptosis in a variety of cancers (e.g. colon, lung, thyroid and breast cancer) and knockdown of viruses (e.g. HIV). In addition, we have shown their ability to reduce tumor growth in mouse models by synergistically targeting multiple genes, and via a differently designed construct to produce tumor cures in immune competent mice using a form of immunotherapy, thus demonstrating the versatility inherent in their designs. In addition, we have demonstrated that when applying our constructs to activate the RNAi pathway they were able to produce enhanced knockdown of targeted genes when compared with comparable concentrations of siRNAs alone. The constructs are relatively simple to make since they consist of only nucleic acids and don't require sophisticated conjugation chemistry. The particles can be constructed to be multivalent and to simultaneously contain fluorescent dyes for tracking.

http://ccr.cancer.gov/RNA-Biology-Laboratory/bruce-a-shapiro

If you are interested in learning more about the NCL's services, please visit our website, https://ncl.cancer.gov, or contact us for more information, ncl@mail.nih.gov. **The next application deadline is September 1, 2020**.