Nanotechnology Characterization Laboratory

NCL
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Laboratory

March 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

Prof. Angela Belcher, Department of Biological Engineering, Massachusetts Institute of Technology
We have developed a new class of targeted, bacteriophage-based, imaging nanoprobes, namely: M13 bacteriophage-functionalized single-walled carbon nanotubes (referred to as M13-SWCNT), for early detection and monitoring treatment response in real-time of hard-to-detect, metastatic cancers. This nanoprobe leverages the near-infrared fluorescence emission of SWCNTs in the second near-infrared window (1000-1700 nm), which is ideal for deep-tissue, optical imaging applications due to the low autofluorescence background and reduced tissue scattering in this wavelength domain. One of the target applications for our nanotechnology is in the ability to detect, diagnose and treat Ovarian Cancer. Epithelial ovarian cancer is the most lethal gynecologic malignancy, with over 250,000 cases detected annually worldwide, and ~22,000 cases detected annually in the US. Of these, over 75% are diagnosed at an advanced stage, with a median 5-year survival (across all stages) ~47% in the US. In the first step of treatment, Ovarian Cancer patients undergo debulking surgery. It has been shown that the ability to achieve optimal debulking (reaching the point of no evidence of macroscopic residual disease at the surgical endpoint) is an important prognosticator of patient outcome. The need to improve cytoreductive surgery for advanced-stage ovarian cancer represents a critical challenge for successful management of this disease. By modifying our M13-SWCNT probe with a peptide binding to the SPARC protein, an extracellular protein overexpressed in ovarian cancer, we have demonstrated the utility of this nanoprobe in a guided surgery system. In a preclinical mouse model of orthotopic ovarian cancer, using this nanoprobe coupled with a custom-designed NIR-II imaging system, we have shown that our probe offers > 40% improvement in median survival advantage over the nonguided surgery group. To improve the performance of the M13-SWCNT

The Nanotechnology Characterization Laboratory is operated by Leidos Biomedical Research, Inc. in support of the Frederick National Laboratory for Cancer Research under Contract 75N91019D00024.

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for Cancer Research
sponsored by the National Cancer Institute

Congratulations to this Quarter's Awardees (continued)

nanoprobe, we are simultaneously engineering each of the components, with short phage (inho M13 phage, down to 50 nm) and short SWCNTs (cut using DNA origami, down to 50 nm) to improve the circulation dynamics, and ultra-bright SWCNTs (created using O-doping, with a relative brightness of ~98x compared to commercial SWCNTs) to minimize the amount of fluorophore needed for target detection.

http://belcherlab.mit.edu/

Curadigm SAS

Curadigm SAS, a Nanobiotix Corp spin-off, is an early-stage company that aims to change treatment paradigm for millions of patients by redefining therapeutic bioavailability and toxicity. Curadigm's Nanoprimer technology platform increases therapeutic bioavailability while decreasing unintended off-target effects, specifically liver toxicity. This platform is flexible and thus can be used across multiple therapeutic classes. It utilizes a biocompatible nanoparticle, the Nanoprimer, designed with specific physico-chemical properties to transiently occupying the pathway responsible for therapeutic clearance. Curadigm has demonstrated proof-of-concept for its Nanoprimer technology platform applied to different therapeutic area products. Curadigm has ongoing programs and collaborations across multiple therapeutic classes, disease indications, and target tissues to improved delivery and efficacy. Curadigm is dedicated to bringing broadly applicable solution to patients to increase efficacy in both current & novel therapeutics and improve patient outcomes.

https://www.curadigm.com/

Concarlo Holdings, LLC

Concarlo Holdings, LLC (Concarlo) is an oncology company focused on diagnosing and treating cancer by targeting a unique cellular pathway. Our approach is based on the role of p27Kip1—a key "ON-OFF" switch that modulates the activities of critical proteins involved in many cancers: CDK4, CDK6, and CDK2. Concarlo is developing the product, IpY, a dual CDK4/6 and CDK2 inhibitor to combat drug resistance to CDK4 inhibition (e.g. Palbociclib) in breast cancer and strive toward extending overall survival of treated patients. IpY is comprised of the protein therapeutic encapsulated by liposomes which enable efficient delivery of protein therapeutic to target cells. Concarlo has demonstrated that IpY is delivered to target cells, the protein therapeutic is released and is capable of binding to its target protein, p27Kip1. IpY blocks proliferation in ER+ breast cancer cell lines (MCF7 and T47D), and also is effective in triple negative(TN) (MDA-MB231,HCC70) and TN RB- (MDA-MB-468, BT459) breast cancer lines, which are resistant to Palbociclib, demonstrating its broader activity. In vivo, IpY demonstrates superior efficacy than Palbociclib in breast cancer cell line xenograft models. In our collaboration with NCL, we aim to further characterize IpY for an IND application and subsequent clinical trials.

https://concarlo.com/

Cnano Medicine, Inc.

Imaging and selective drug delivery to cancer cells, regardless of the origin and location, has been a major challenge. To tackle this challenge, professor Louzhen Fan's group at Beijing Normal University has developed a new type of carbon quantum dots (CQDs). Without any modifications, these new CQDs can efficiently penetrate cancer cells but do not penetrate normal cells in vitro, and they selectively accumulate in cancer but not in normal organs in vivo. Our CQDs have a molecular structure that enables near-infrared fluorescence, photoacoustic dual-modular imaging, and efficient chemical loading. Because of this, they have great potential as a universal theranostic platform for caner-selective imaging and drug delivery and vastly improve the clinical management of cancer patients. Cnano Medicine is dedicated to cancer nanomedicine and is working to commercialize the new CQDs.

http://chem1.bnu.edu.cn/fanlz/

Prof. Jeremiah A. Johnson, Department of Chemistry, Massachusetts Institute of Technology and Window Therapeutics, LLC

We are developing a macromolecular prodrug platform that can improve the safety and efficacy of virtually any class of therapeutic agent in a made-to-order fashion. From a library of > 40 prodrugs to date, a bortezomib (Btz) prodrug, one of our most promising candidates, was chosen for our collaboration with the Nanotechnology

Congratulations to this Quarter's Awardees (continued)

Characterization Laboratory (NCL). As the first-in-class proteasome inhibitor, Btz serves as a common front-line therapy for multiple myeloma—a fatal, incurable plasma cell dyscrasia. Nonetheless, since its inception, Btz has suffered from poor pharmaceutical properties, including solubility, pharmacokinetics, stability, and toxicity—factors that have thus far imposed a narrow therapeutic index (TI). To overcome these longstanding challenges and fully exploit Btz's potential, we employed our platform to chemically conjugate Btz through a novel non-natural boronic-ester linkage. The resulting Btz-prodrugs enabled a > 25-fold higher tolerated dose in mice without observable signs of toxicity, as well as efficient tumor accumulation and deep penetration in a subcutaneous mouse model. Additionally, Btz-loaded polymers significantly retarded tumor progression, providing a marked enhancement in survival outcome (> 4-fold increase mean survival times) both in a subcutaneous model and an aggressive orthotopic model of multiple myeloma. In our collaboration with the NCL, we aim to further examine this prodrug candidate in terms of physicochemical characterizations and key in vivo evaluations, gearing towards an IND application and subsequent clinical trials.

http://web.mit.edu/johnsongroup/

SN BioScience, Inc.

SN BioScience Inc. is a nanomedicine R&D company in South Korea, developing cutting-edge platform technology that makes it possible for poorly water-soluble anti-cancer drugs to be intravenously administered. Our proprietary polymeric micelle nanotechnology provides an opportunity for SN-38 (an active metabolite of irinotecan) to be developed as an IV formulation (code name: SNB-101). We have succeeded in manufacturing SNB-101 in scale-up development batches in a GMP facility. In vivo pharmacology studies in xenograft tumor mouse models such as gastric, colorectal, and pancreatic cancers using human cancer cell lines demonstrated greater anti-tumor efficacy of SNB-101 compared to conventional Irinotecan HCl Injection, with a substantial increase in maximum tolerable doses (MTD). With the proven chemistry, manufacturing and control of the novel SN-38 nanoparticle formulation and in vivo efficacy, PK, biodistribution and GLP toxicity studies, SN BioScience will be working closely with NCL to thoroughly characterize SNB-101 for an Investigational New Drug (IND) application and advance into Phase 1 clinical trials for various solid tumors.

http://snbioscience.com

Suntec Medical, Inc.

Suntec Medical, Inc. is developing innovative new drug molecules using our proprietary MINC (Multiple target, Immune modulation, Nanocarrier, Combination therapy) technology. MINC has great potential to treat diseases with inflammation including cancer, autoimmune and CNS diseases. MINC utilizes proprietary bioactive carrier components to form a micelle nanoparticle with encapsulated drugs. Several features of MINC make this nanotechnology distinct from others, including 1) the carrier components have immune modulation functions, 2) the carrier components form combination therapies with the encapsulated drugs, and 3) MINC can deliver various types of drugs including small compounds, proteins and nucleic acid to inflammatory lesions. Currently, we are applying MINC technology to enhance the safety and efficacy of protein drugs for cancer immunotherapy and type I diabetes. Included in Suntec's cancer drug pipeline are STM1 for breast cancer, STM2 and STM3 for a broad spectrum of cancer immunotherapies and STM4 for renal cell carcinoma. Under the collaboration with NCL, we wish to collaboratively address the requirements for IND for one of our cancer therapies.

https://suntecmedical.com/

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 June 1, 2020**.

The company and nanoparticle descriptions herein were supplied by the Awardee.
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