In this article we highlight recent advances in cancer nanomedicine. Editorial Board member Dr. Daniel Heller has assembled an overview of the topic.

Nanomedicine advances in cancer

Nanomedicine, the study of medical applications of nanotechnology, includes therapeutic applications such as drug delivery and diagnostics, including biosensors and contrast agents, as well as tools for drug discovery and biological research, such as molecular probes. Drug delivery nanotechnologies are often applied to improve drug solubility or bioavailability, to protect a drug from degradation, to modulate drug pharmacokinetics and biodistribution to increase localization within tumors/disease sites (to improve efficacy), and to reduce exposure to healthy tissues (by abrogating toxicities).

Nanoparticles can modulate drug solubility, pharmacokinetics, and biodistribution, often without modifying the chemical structure of the drug itself. For instance, liposome-formulated drugs (often called liposomal nanoparticles, LNPs) are used in the clinic to modulate drug pharmacokinetics and to obviate side effects. To avoid the cardiotoxicity of doxorubicin, for instance, a liposomal formulation, Doxil (often regarded as the first clinical nanomedicine) was developed to reduce drug exposure
to cardiac tissues. **Abraxane**, a nanoparticle composed of albumin-bound paclitaxel, improves drug solubility and reduces toxicities, including sensitivity to components in the standard formulation of paclitaxel. A Phase II trial using **nanoparticle albumin-bound rapamycin** in treating patients with advanced cancer with mTOR mutations is ongoing.

Recent clinical work has also involved the use of targeted drug delivery vehicles—nanoparticles functionalized to bind to a molecular target. An **Aurora B kinase** inhibitor, **AZD2811** was encapsulated in polymeric nanoparticles composed of poly-D,L-lactide (PLA) and poly(ethylene glycol) (PEG) block copolymers conjugated to a small molecule ligand with affinity for prostate-specific membrane antigen (PSMA). These nanoparticles were shown to accumulate in tumor vasculature, increasing the concentration and duration of exposure of cancer cells to the therapeutic payload. A phase I trial found a favorable safety profile in humans.

Multiple clinical trials have been initiated using RNA therapeutics. Although not an oncologic disease, it is worth noting that a Phase 3 study using **Patisiran**, an siRNA was formulated in lipid nanoparticles to treat amyloidosis, was completed with positive results; FDA approval was granted in August. A phase I/II study of **TKM-080301**, a lipid nanoparticle formulation of PLK1-targeted RNAi, in patients with adrenocortical cancer has been completed; preliminary anti-tumor efficacy was observed. Similarly, a Phase I trial of **MTL-CEBPA**, which is a double-stranded RNA formulated into a SMARTICLES liposomal nanoparticle, has been initiated for the treatment of advanced liver cancer.

New technologies are also needed to translate CRISPR technology for clinical use. Initial results showing delivery of the Cas9 protein along with a guide RNA (sgRNA) **in vivo** have been demonstrated. Examples of materials for this purpose that have shown **in vivo** efficacy include gold nanoparticles, used to bind Cas9 protein and sgRNA into nanoassemblies; lipid-based nanoparticles; cell-penetrating peptides; and 7C1 nanoparticles, which are nanoparticles synthesized via blending C15 epoxide-terminated lipids with low-molecular weight polyethylenimine.

New strategies/vehicles to enhance drug encapsulation are under investigation, including drug nanocrystals, solid lipid-drug pa for instance, machine learning has articles and polymeric nanoparticles. In addition, recent works to improve nanoparticle development **in silico** foretell the emergence of “nanoinformatics,” a new sub-field within nanotechnology. In drug carrier design, for instance, machine learning has been used to predict colloidal aggregation/drug loading, and **in vivo** performance. Barcoded nanoparticles have been developed to use high-throughput experimentation and quantitative analysis to assess biodistribution and drug efficacy.

This issue, dedicated to a novel topic for CICR, highlights the work of a senior investigator as well as an early career investigator in the field. Our senior researcher profile is dedicated to the work of Robert Langer, PhD, of MIT, a luminary in the fields of biomedical engineering and biotechnology.

Dr. Langer’s early work isolated the first angiogenesis inhibitors. The work of his laboratory led to the development of widely-used cancer treatments such as the Lupron Depot, Zoladex, Decapeptyl, and Gliadel. In the early career profile, we highlight the work of Matthias Stephan, MD, PhD, from the Fred Hutchinson Cancer Center. Dr. Stephan’s laboratory is developing nanoparticle-based therapies to reprogram T-cells in situ, potentially obviating the need for adoptive T-cell transfer.
News from the CICR Steering Committee

CICR Chairperson Election

We thank CICR members for participating in the election of the CICR Chairperson Elect for 2019/20 to succeed Dr Andrew Phillips (C4 Therapeutics and Current Chairperson-Elect). Drs. James Audia, PhD, Northwestern University, Chicago, USA and Philip Jones, PhD, Institute for Applied Cancer Science, MD Anderson Cancer Center, USA stood for election, which closed on Wednesday November 15th 2018. We would like to congratulate Dr. Jones on his selection as the next Chairperson-elect.
Selected Research Highlights

Nano-targeted Delivery of Rad6/Translesion Synthesis Inhibitor for Triple Negative Breast Cancer Therapy
Sadaat et al, Mol Cancer Ther September 21 2018
https://doi.org/10.1158/1535-7163.MCT-18-0364

This article, by Saadat, Shekhar, and colleagues at Wayne State University in Detroit, Michigan, USA, features the use of PEGylated gold nanoparticles to overcome the limitations of a previously described small molecule. SMI#9 was initially described by the Skehar group in 2013 as an inhibitor of Rad6B-mediated ubiquitin-conjugating activity. While the compound is capable of affecting breast cancer cell growth alone, a gold nanoparticle-based formulation was previously shown to overcome solubility limitations of the molecule and result in high intracellular concentrations of the compound. In this work, the authors show that conjugation of SMI#9 with the nanoparticle allowed higher exposure and greater persistence in vivo compared with the compound alone. Indeed, efficacy in xenograft models of triple negative breast cancer from systemic dosing was comparable that obtained with intra-tumor injected compound.

Development of multi-layered and multi-sensitive polymeric nanocontainers for cancer therapy: in vitro evaluation
https://dx.doi.org/10.1038%2Fs41598-018-32890-5

Nanocontainers, hollow polymeric shells that can be engineered to open under the influence of specific conditional stimuli, have become a promising drug delivery system. In a recent issue of Scientific Reports, a collaborative team of co-authors from Greece and Italy describe an unusual triple shelled nanocontainer. The shells, arranged from inner to outer, are sensitive to changes in pH, temperature, and redox potential, allowing greater control of the sensitivity of each shell to their respective conditional stimulus. Using daunorubicin, the authors demonstrate delivery of nearly all of the encapsulated compound into cancer cells, with only marginal toxicity displayed by the unloaded nanocontainers. The “burst release” profile in a simulated tumor environment vs a slower controlled delivery under more neutral conditions suggests that this formulation may have promise as means of controlling the release of cytotoxic cancer therapies and thereby lessening the side-effect so often seen with such agents.

High-throughput in vivo screen of functional mRNA delivery identifies nanoparticles for endothelial cell gene editing
https://doi.org/10.1073/pnas.1811276115
The ability to deliver nucleic acid-based therapies, including mRNA, siRNA, and CRISPR technologies, to specific tissues in living organisms remains a barrier to their development into therapeutics. Current technologies allow therapeutic delivery to hepatic tissues, but efficient delivery to other tissues remains difficult. The Dahlman Lab at the Georgia Institute of Technology developed DNA barcoded nanoparticle technology to identify a lipid nanoparticle (LNP) compositions with novel tropisms in vivo. The researchers identified an LNP composition that targets mRNA to endothelial cells and Cas9 mRNA and sgRNA to splenic endothelial cells, allowing gene editing of specific, non-hepatic tissues in vivo.

A modular platform for targeted RNAi therapeutics
https://doi.org/10.1038/s41565-017-0043-5

Although progress has been made in developing siRNA targeted delivery carriers using monoclonal antibodies for targeting, clinical translation is difficult. This is due in part due to problems in production and scale-up. Professor Dan Peer from Tel Aviv University and colleagues developed a modular lipid nanoparticle (LNP) platform that enables the construction of a theoretically unlimited repertoire of siRNA targeted carriers. The platform is based on self-assembly of a membrane-anchored lipoprotein that is incorporated into siRNA-loaded lipid nanoparticles that interact with the antibody crystallizable fragment (Fc) domain. The group showed that a simple switch of eight different mAbs redirects the specific uptake of siRNAs by diverse leukocyte subsets in vivo. The group demonstrated the platform in a mantle cell lymphoma xenograft and inflammatory bowel disease models.
Current T-cell therapies often involve engineering a patient’s own cells, by removing them, reprogramming them, and re-introducing them. The laboratory of Dr. Matthias Stephan is developing nanomedicines to reprogram T-cells inside the patient.

Dr. Stephan is a Laboratory Head and Associate Member at Fred Hutchinson Cancer Research Center and an Associate Professor at the University of Washington. He began specializing in this area as a graduate student at Memorial Sloan-Kettering Cancer Center, where he pioneered auto-costimulation and trans-costimulation as molecular strategies to augment the function of lymphocytes in the microenvironment created by tumors. During his postdoctoral training at the Massachusetts Institute of Technology, Dr. Stephan developed a nanoparticle-based strategy to provide autocrine sources of adjuvant growth factor that support adoptively transferred, tumor antigen-specific T lymphocytes. Much of this work became the intellectual and technical foundation for a Cambridge-based startup company (Torque Therapeutics, Inc.).

The long-term goal of Dr. Stephan’s research at Fred Hutch is to make immunotherapy more practical and widespread by creating unconventional treatments at the interface between materials science and immunology. Sometimes dubbed “Immunobioengineering,” his is an emerging but rapidly growing field originally centered on the creation of synthetic pathogen-mimicking vaccine particles. The field soon introduced a host of innovative materials and new concepts that serve as the basis of novel therapies.

Stephan’s research group recently reported a strategy to program circulating T-cells with tumor-recognizing activities, which avoids the complex laboratory protocols usually used to achieve this transformation for use in patients (Nature Nanotechnology 12 (2017) 813-820). The lab developed DNA-carrying nanoparticles can efficiently introduce leukemia-targeting CAR genes into T-cell nuclei. Stephan's team developed biodegradable poly(β-amino ester)-based nanoparticles targeted to T-cells via f(ab’)2 fragments and to the nucleus via nuclear-localization sequences. The particles were loaded with plasmid DNA encoding the leukaemia-specific 194-1BBz CAR. These particles programmed T-cells in quantities sufficient to bring about long-term disease remission with efficacies similar to adoptive T-cell therapy, demonstrated in mice. With industry partners, his group is currently developing this platform for clinical use.
Robert S. Langer has, by just about every conceivable measure, had an outsized impact on the research and development of biomedical technologies. For two years in a row, he has been cited as the number 1 translational scientist in the world by Nature Biotechnology (36: 798, 2018; 335: 1126, 2017). Langer is one of thirteen Institute Professors (MIT’s highest honors) at MIT, and one of four living individuals to receive the nation’s two highest scientific honors – the United States National Medal of Science (2006) and the United States National Medal of Technology and Innovation (2011). He is the most cited engineer in history (Gura, Science Careers, November 14, 2014) and has an h-index of 260 according to Google Scholar.

Langer has made numerous contributions to cancer research and the development of cancer therapies. At a time when the scientific community did not believe angiogenesis inhibitors existed (Science, 195: 759, 1977), he (with his postdoctoral advisor, Judah Folkman) isolated the first such inhibitors, and developed bioassays (Nature, 263: 797, 1976) that would be used for the isolation of nearly all such inhibitors (Science, 193: 70, 1976) in the future. He also showed that such inhibitors were safe and effective when given systematically (Proceedings of the National Academy of Sciences 77: 4331, 1980).

When Langer first published his research on approaches for controlling the release of macromolecules including nucleic acids and peptides (Nature, 263: 797, 1976), the scientific community reacted with skepticism (Ball, Made to Measure: New Materials for the 21st Century, p. 240, Princeton University Press, Princeton, NJ, 1997; Chemical and Engineering News, 90: 20, 2012). Langer was repeatedly rejected on his grant applications, no chemical engineering department in the country would hire him for a faculty position and when he finally did get a faculty position (this was in a Nutrition and Food Science department), he nearly lost his job (Chemical and Engineering News, 90: 20, 2012; Journal of Biomedical Materials Research, 101A: 2449, 2013; xconomy 6-2014). However, today Langer’s studies are widely recognized as largely creating the field of controlled drug delivery (Nature, 458: 22, 2009) and led to such widely used cancer treatments as Lupron Depot, Zoladex, Decapeptyl and (with Henry Brem) Gliadel.

The original controlled-release materials developed by Langer were generally in the form of microspheres. However, nanoparticles are critical for delivering significant payloads of any drug into cells, particularly potential newer drugs like siRNA and mRNA. Yet, when nanoparticles are injected into the body they are destroyed almost immediately by macrophages, and are unstable because they aggregate. Langer’s lab solved these problems by synthesizing nanoparticles composed of polyethylene glycol (PEG) and any other material (e.g. poly lactic acid), and showed the nanoparticles could circulate for hours in vivo, be stable on the shelf for years, and not
aggregate (Science, 263: 1600, 1994.). These principles are being widely used by many scientists and companies to practice “nanomedicine”. Science magazine has credited Langer's seminal role in this area (Science, 314, 2010). He received both the Rusnano Prize for Nanotechnology and the Kabiller Prize for his work in this area.
Nobel Prize in Physiology or Medicine 2018
On October 1, 2018, the Nobel Prize in Physiology or Medicine 2018 was awarded jointly to James P. Allison and Tasuku Honjo “for their discovery of cancer therapy by inhibition of negative immune regulation.” Read our February editorial for an overview of the topic. See related blog post.

FDA Approval of Cemiplimab-rwic (Libtayo)
On September 28, 2018 Regeneron Pharmaceuticals cemiplimab (Libtayo) was approved to treat cutaneous squamous cell carcinoma (CSCC) by the FDA. The approval marks the third FDA approval of an immune checkpoint PD-1 inhibitor and the sixth FDA approval of a PD/PD-L1 approved antibody after pembrolizumab (Keytruda - Merck, 2014), nivolumab (Opdivo - Bristol-Myers Squibb, 2014), atezolizumab (Tecentriq - Roche Genentech, 2016), avelumab (Bavencio - EMD Serono, 2017) and durvalumab (Imfinzi – AstraZeneca, 2017). The approval marks the first checkpoint approval for CSCC and came just days before the awarding of the 2018 Nobel Prize in Physiology or Medicine to James Allison and Tasuku Honjo for underlying research in cancer immunotherapy. See related blog post.

FDA Approval of Dacomitinib (Vizimpro)
The FDA approved Pfizer’s dacomitinib (Vizimpro) on September 27, 2018 to treat metastatic non-small cell lung cancer (NSCLC). Dacomitinib is an irreversible inhibitor of EGFR, a frequently targeted transmembrane receptor tyrosine kinase. The inhibitor joins a number of other FDA approved inhibitors including generation 1 reversible inhibitors such as gefitinib (Iressa, 2002) and erlotinib (Tarceva, 2004), and irreversible inhibitors afatinib (Gilotrif, 2013), osimertinib (Tagrisso, 2015) and neratinib (Nerlynx, 2017). In particular, the approval is a first-line treatment of patients with EGFR exon 19 deletion or exon 21 L858R substitution mutations as detected by an FDA-approved test. See related blog post.
Source: Pfizer Press Release

FDA Approval of Duvelisib (Copiktra)
The FDA approved Verastem’s duvelisib (Copiktra) on September 24, 2018 to treat relapsed or refractory chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL) and follicular lymphoma. Duvelisib is a dual inhibitor of PI3K isoforms.
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PI3Kδ and PI3Kγ, intracellular signal transducer kinases. The inhibitor is the third approved PI3K inhibitor after copanlisib (Aliqopa, 2017) and idelalisib (Zydelig, 2014), to which it is structurally similar. See related blog post.
Source: FDA

FDA Approval of Moxetumomab Pasudotox-tdfk (Lumoxiti)
On September 13, 2018 AstraZeneca's moxetumomab pasudotox was approved to treat hairy cell leukemia (HCL) by the FDA. The compound is a recombinant anti-CD22 immunotoxin, consisting of a CD22 receptor targeting disulphide-linked antibody fragment (dsFv) fused with an engineered toxin molecule (Pseudomonas exotoxin PE38). See related blog post.
Source: FDA

FDA Approval of Mogamulizumab-kpc (Poteligeo)
The FDA approved Kyowa Hakko Kirin's mogamulizumab-kpc (poteligeo) on August 8, 2018 to treat two rare types of non-Hodgkin lymphoma. The compound is a monoclonal antibody targeting chemokine receptor CCR4. The approval was based on the results of the MAVORIC phase III trial and allows for the treatment of adults who have mycosis fungoides (MF) or Sézary syndrome (SS) two rare cutaneous T-cell lymphomas. See related blog post.
Source: FDA

Boehringer Ingelheim acquires all ViraTherapeutics shares
Boehringer Ingelheim aims to build up its oncology presence with more R&D into next-generation viral-based immuno-oncology therapies, and acquired Austria-based ViraTherapeutics, a biopharmaceutical company specializing in the development of oncolytic viral therapies. ViraTherapeutics, has developed the lead candidate VSV-GP [vesicular stomatitis virus (VSV) with modified glycoprotein (GP)], which is being investigated alone and in combination with other therapies. The total transaction value of €210 million (about $241.8 million) is based on an option and share purchase agreement signed between the companies in August 2016.
Source: Drug Discovery News

Atara and Moffitt announce strategic collaboration focused on multi-targeted CAR-T immunotherapies
Atara Biotherapeutics Inc. already had a collaboration deal signed with Memorial Sloan Kettering Cancer Center around chimeric antigen receptor T cell (CAR-T) immunotherapeutic research. But recently, the company announced that it was furthering its strategy to develop next-generation CAR-T immunotherapies across multiple therapeutic areas—and leverage its off-the-shelf, allogeneic T cell immunotherapy platform—by forming a strategic collaboration with Moffitt Cancer Center as well. In the most recent deal, the aim is to develop multitargeted CAR-T immunotherapies for patients with acute myelogenous leukemia (AML) and B cell malignancies. As part of the collaboration, Atara will gain access to novel CAR-T
targeting and co-stimulation domains designed to improve T cell proliferation and enhance persistence.
Source: Drug Discovery News
Upcoming Conferences and Events

**AACR Annual Meeting 2019**  
March 29 - April 3, 2019, Atlanta, Georgia

**4th International Conference on Drug Discovery, Development and Lead Optimization**  
December 3-5 2018, San Francisco, USA

**11th AACR-JCA Joint Conference on Breakthroughs in Cancer Research: Biology to Precision Medicine**  
February 8 - 12, 2019, Maui, Hawaii

**Fragments 2019: 7th RSC-BMCS Fragment-based Drug Discovery meeting**  
24 – 26 March 2019, Cambridge, United Kingdom (includes pre-conference workshop on 24 March)

**AACR International Conference New Horizons in Cancer Research**  
May 3 - 5, 2019, Shenzhen, China

**Gordon Research Conference in Cancer Nanotechnology: Bridging the Translational Gap in Cancer Nanotechnology**  
June 23 - 28, 2019, Mount Snow, West Dover, Vermont, USA

**EFMC-ACSMEDI: Medicinal Chemistry Frontiers 2019**  
June 10-13 2019, Krakow, Poland
Funding Opportunities

The AACR offers the following opportunities:

**AACR Immuno-oncology Research Fellowships**
Deadline: 12/6/2018

**AACR Lung Cancer Research Fellowships**
Deadline: 12/6/2018

**AACR Lymphoma Research Fellowships**
Deadline: 12/11/2018

**AACR Myeloma Research Fellowship**
Deadline: 12/11/2018

**AACR-John and Elizabeth Leonard Family Foundation Basic Cancer Research Fellowship**
Deadline: 12/12/2018

**Breast Cancer Research Foundation-AACR Career Development Awards for Translational Breast Cancer Research**
Deadline: 12/12/2018

**AACR-AstraZeneca Clinical Immuno-oncology Research Training Fellowships**
Deadline: 12/19/2018

**AACR-AstraZeneca Stimulating Therapeutic Advancements through Research Training (START) Grants**
Deadline: 12/19/2018

**AACR-Bayer Clinical Oncology Research (CORE) Training Fellowship**
Deadline: 12/19/2018