

1. From the Editors

Modern cancer therapeutics are typically developed with the aim of interfering with key pathways and proteins that are critical to the survival and progression of malignant cells. Unfortunately, these drugs are still associated with undesirable side effects due to non-specific toxicity to non-targeted tissues and organs. In recent years, two targeted delivery methods stand out among several approaches. These are nanoparticle (NP) based drug delivery systems and antibody drug conjugates (ADCs).

The development of NPs that carry drugs to tumor tissue in the body have greatly improved the efficacy of traditional therapeutics, while decreasing the associated systemic toxicities. NPs with a diameter of 10-200 nm can selectively target and preferentially home in at the tumor site via the enhanced permeability and retention (EPR) effect. More complex NPs, such as multiple drug carriers (for combination therapy) and coatings of targeting elements for receptors on cancer cells, have also been engineered to improve effectiveness by overcoming problems associated with tumor tissue targeting and penetration, drug resistance, cellular uptake and circulation half-life. Numerous research groups both in industry and academia have been pursuing efforts for the translation of nanoparticle formulations to clinical use. Currently, around 40 nanoparticle formulations are under evaluation at different stages of clinical trials by the FDA, while several more are being developed. Further advantages that NP systems offer include theranostics, where both imaging and therapeutic agents can be used to functionalize within the same NP to report on the progress of the treatment that they deliver.

Another targeted delivery method that has found success in the clinic is the antibody-directed cytotoxic (ADC) approach. In the past two decades, pharmaceutical antibody based therapies for cancers have made significant advancements in terms of both design sophistication and clinical results. As an extension of such antibody treatments, the ADCs combine the targeting efficiency of antibodies with the high potency of chemotherapeutic agents, while reducing their non-specific toxicity and increasing their efficacy. Currently, there are over 120 ADC formulations in clinical trial stages I and II, and most of them, reportedly, are delivering promising results. Despite advances in ADC design and development, there are still limitations to their manufacturing and use including complications with conjugation chemistry, product heterogeneity, tumor penetration and cancer cell specificity. Many research groups are working towards developing methods to overcome these deficiencies, thereby building on the very promising vision for the future of personalized medicine, and prognosis of cancer treatments. One of our highlight articles on targeted drug delivery using ADCs is by Dr Thomas Pillow (Genentech) and co-workers (Nature Chemistry, 2016, doi:10.1038/nchem.2635) and we profile him as this issue's early-career scientist.

Some CICR election news: Drs Vinod Patel (APC Therapeutics) and Julian Blagg (Institute of Cancer Research, ICR) recently stood for election to become CICR

Chairperson-Elect 2017-2018, with the latter winning the election. Here on the editorial board we look forward to working closely with Prof Blagg in the near future while we thank Dr Patel, as always, for his whole-hearted commitment to the CICR community and desire to ensure that chemistry remains a vital pillar stone in cancer research. Prof Blagg brings a wealth of experience and leadership to the CICR Steering Committee. After cutting his teeth on organometallic chemistry (Oxford) and asymmetric synthesis (Geneva), he joined Pfizer in 1988 as a medicinal chemistry team leader. For nearly two decades Prof Blagg worked for Pfizer in both the UK and US, which helped to shape his interest in drug discovery research. Prof Blagg currently serves as Head of Chemistry and Deputy Director of the Cancer Research UK Cancer Therapeutics Unit and Deputy Head of the Division of Cancer Therapeutics at The Institute of Cancer Research. Prof. Blagg will assume this position at the CICR Town Hall Meeting and Reception to be held Sunday, April 2, 2017, 5:30 p.m.-7:00 p.m., Walter E. Washington Convention Center (*room location to be announced*), at the AACR Annual Meeting 2017 in Washington, DC.

There are also a few changes to the CICR editorial board (EB) make-up. Dr Basar Bilgicer, who has contributed to this editorial, is after two years rotating off the EB and on behalf of everyone associated with the EB I would like to pass on our appreciation for all his efforts and contribution to the CICR newsletter. When 2017 kicks in the EB is joined by Drs Alex G. Waterson and Iain Watson from Vanderbilt University and Ontario Institute for Cancer research, respectively, while my own role as editor of the CICR newsletter draws to an end. I got involved in 2012 in an editorial role alongside Dr Billy Day and our brief was to develop a quarterly newsletter. On a personal level, it has been an exciting journey and a great honor to help establish a voice for the CICR community, which now has approximately 2800 members scattered around the globe. I believe over the years we have gradually enhanced the quality of the newsletter although there is still room for further improvement. In particular, I would like to encourage all our members to engage in dialogue and discussion to help the CICR EB in providing a newsletter that caters for all chemical sciences in cancer research. I am very pleased to inform you that Dr George Sheppard from Abbvie Inc, the Editor for 2017, is already working hard behind the scenes to ensure our readers enjoy another year of hearing about undoubtedly exciting chemical innovations. Finally, I hope you all have a successful end to 2016 and I hope to see many of you at the AACR annual meeting in Washington 2017.

with best wishes

Klaus Pors

Editorial co-author: Basar Bilgicer

2. Selected Research Highlights

Stabilized Heptapeptide A7R for Enhanced Multifunctional Liposome-Based Tumor-Targeted Drug Delivery

<http://pubs.acs.org/doi/abs/10.1021/acsami.6b01300>

Ying et al. recently reported enhancement in tumor targeting efficacy and *in vivo* stability of their peptidomimetic (^DA7R) by both qualitative and quantitative analysis. ^LA7R, identified to bind to the overexpressed vascular endothelial growth factor receptor 2 and neuropilin-1 (NRP-1) on glioma cells, has shortcomings of reduced targeting efficacy and stability due to proteolysis in blood circulation. The newly designed ^DA7R by retro-inverso isomerization is not supposedly recognized by proteolytic enzymes, with the advantage of different conformation. It can therefore overcome the problems of ^LA7R. Molecular docking studies and surface plasmon resonance confirmed comparable binding affinity of ^DA7R and uptake studies demonstrated similar uptake efficiency in human glioblastoma cells and human umbilical vein endothelial cells. The more important finding was that ^DA7R was highly stable whereas ^LA7R was significantly degraded under pre-incubation of mouse serum. Moreover, ^DA7R loaded liposome (^DA7R-LS) accumulation in U87 tumors was much greater than ^LA7R loaded liposomes (^LA7R-LS) and plain liposomes (LS). Cytotoxicity studies demonstrated greater cytotoxic effects of ^DA7R-LS as compared to ^LA7R-LS and LS. *In vivo* subcutaneous nude mice studies confirmed unobservable toxicity and greater antitumor efficacy of both the targeting ligand of ^DA7R and doxorubicin loaded liposomes by measuring the size of tumor and body weight. Taken all together, liposomal tumor targeting drug delivery could be enhanced in efficacy by taking advantage of the stabilized peptide of ^DA7R.

Ying et al., *ACS Appl. Mater. Interfaces*, 2016, 8 (21), 13232–13241. DOI: 10.1021/acsami.6b01300

Targeted drug delivery through the traceless release of tertiary and heteroaryl amines from antibody–drug conjugates

<http://www.nature.com/nchem/journal/vaop/ncurrent/full/nchem.2635.html>

Antibody drug conjugates (ADCs) have been increasingly studied over the past years with remarkably favorable results towards treatments for life-threatening conditions such as cancer or immune-related diseases due to the potential of targeted drug delivery. The vast majority of the conjugations have been obtained using p-aminobenzyl carbamate linkers with therapeutic agents that possess primary or secondary amines. However many anticancer and antibacterial drugs present tertiary amines, thus further modifications to their chemical structures are required, leading to a loss in potency, instability and in some cases aggregation. Staben, et al. developed a protecting group-free synthetic method to connect tertiary or heteroaryl amines through a reversible connection with p-aminobenzyl quaternary ammonium salt. Several antibody-conjugates were tested with different protease-cleavable linkers to evaluate their stability and release. *In vitro* experiments demonstrated that under the presence of proteases such as cathepsin, the linkers were cleaved and the drug was easily released. Specific systems were selected as examples for *in vivo* studies to elucidate the efficacy of the chemical method developed by the authors. For the antibody-anticancer drug system, a human lymphoma tumor xenograft in mice revealed that an anti-CD22 - dolastatin 10 conjugate allowed a complete regression for a dose of 8 mg/kg and

cytostasis for 21 days at lower doses. On the other hand, for antibody-antibiotic systems MRSA (Methicillin-resistant *Staphylococcus aureus*) targeting antibody - dmDNA31 conjugate was selected showing a reduction of intracellular bacteria to the limit of detection at very low concentrations (0.4 µg/ml). According to the authors, their findings prove to be important not only for cancer treatment but also for guiding improvements in antibiotic-resistant infection.

Staben et al., *Nature Chemistry*, 2016. Published online 17 October
doi:10.1038/nchem.2635

A New Class of Antibody-Drug Conjugates with Potent DNA Alkylating Activity

<https://www.ncbi.nlm.nih.gov/pubmed/27216304>

Miller *et al.* reports a novel class of antibody-drug conjugates (ADC) with high specificity and potent antitumor activity. However, current ADCs are plagued by a variety of problems, including high *in vivo* toxicity. The authors set out to alleviate these problems by investigating a class of indolinobenzodiazepine pseudodimers (IGN), which contain an imine group allowing for DNA interaction through the minor groove of DNA and crosslink with guanine residues. They first conjugated two IGN molecules to therapeutically relevant antibodies, and evaluated the mechanism of action in preclinical systems. Although the ADC was effective at killing cancer cells *in vitro*, the therapeutic had serious adverse effects in mouse studies. To overcome this lethality in mice, the authors modified their ADC design by reducing the number of crosslinking-reactive functional imine groups and also by introducing the cleavable thiol linker between the antibody and the drug for the best bioavailability. Remarkably, treatment in mice with the improved ADCs containing a cleavable thiol linker resulted in complete tumor regression with no overt toxicity observed. Although recent clinical studies with ADCs have been associated with serious adverse effects, this chemistry-focused rational design demonstrates the promise of ADCs as effective chemotherapeutics with clinical potential.

Miller *et al* *Mol Cancer Ther*: 15(8) 2016

Bioorthogonal two-component drug delivery in HER2(+) breast cancer mouse models

<https://www.ncbi.nlm.nih.gov/pubmed/?term=PMC4828666>

Hapuarachchige *et al.* reports a bioorthogonal two-component, two-step drug delivery system using a functionalized trastuzumab antibody and a drug-loaded albumin nanocarrier. To overcome the mechanistic barrier of a trastuzumab-mediated anti-cancer therapy, the authors first chemically modified FDA-approved trastuzumab (Tz) to introduce the “clickable” bioorthogonal functional group (i.e. trans-cyclooctene, TCO). At the same time, the albumin nanocarrier, which is loaded with paclitaxel, was also developed to have the counterpart of the clickable functional group (i.e. tetrazine, Tt). Using various fluorescence microscopic techniques, the authors were able to track

the sequential steps of their two-component, two-step drug delivery system in cell culture systems as well as *in vivo*. They demonstrated the efficacy of the drug delivery strategy in HER(+) human breast cancer models.

Hapuarachchige *et al.* Scientific Reports (2016) 6, 24298.

Eradication of Acute Myeloid Leukemia with FLT3 Ligand–Targeted miR-150 Nanoparticles

<http://cancerres.aacrjournals.org/content/76/15/4470.long/>

Jiang, et al., have recently described a polyamidoamine (PAMAM) dendrimer-based delivery of an miRNA (miR-150). miRNAs are small non-coding RNAs that can post-transcriptionally regulate gene expression, but successfully utilizing miRNAs requires a targeted delivery system. miR-150, in particular, can regulate the expression of FLT3, which encodes a tyrosine kinase that is overexpressed in some acute myeloid leukemias. By using a ligand for FLT3 (FLT3L), the investigators used a PAMAM dendrimer to FLT3 as a delivery system for miR-150. Through a combination of ex vivo and in vivo approaches, the authors showed that this system may be useful for treating AML.

Jiang et al., Cancer Research, 2016, 76, 4470-80. doi: 10.1158/0008-5472.CAN-15-2949.

Other research highlights

The Genomic Landscape of Male Breast Cancers

<https://www.ncbi.nlm.nih.gov/pubmed/26960396>

Male breast cancer is a rare disease with less than 1% of all breast cancers occurring in men. While substantial attention has been given to characterizing the genomic landscape of breast cancer, these studies have focused primarily on female breast cancer. In a recent study, Piscuoglio et al. sought to understand whether male breast cancers encompass the same somatic mutations in genes as female breast cancers. 59 male breast cancers were selected (all ER positive, 95% HER2 negative) and tumor-normal pairs were collected by tissue microdissection and parallel sequencing was performed to target all exons of 241 genes that have been shown to be frequently mutated in breast cancer or related to DNA-repair. Somatic mutations and copy number variations were compared with female breast cancers. A majority of male breast cancers (71%) were classified as luminal B, with the remainder classified as luminal A. The somatic mutations in male breast cancers somewhat recapitulated ER+/HER- female breast. Differences were noted comparing male and female breast cancers in 16q losses, and *PIK3CA* and *TP53* mutations. Male breast cancers were also found to have more mutations in DNA repair-related genes. These results suggest that extrapolating biological and therapeutic findings from female breast cancer to male breast cancer should be approached with caution.

Piscuoglio et al. Clin Cancer Res. 2016 Aug 15;22(16):4045-56. doi: 10.1158/1078-0432.CCR-15-2840.

Precision glycoalyx editing as a strategy for cancer immunotherapy

<https://www.ncbi.nlm.nih.gov/pubmed/27551071>

Immunotherapy is a promising strategy for cancer treatment. Sialic acids that cover the cell surface of cancer cells are integral to immune modulation and play a key

role in evasion of the immune response. Therapeutic strategies that target cell surface sialic acid on the tumor could potentially provide an effective strategy for antitumor immunity. The Bertozzi Lab has recently reported the development and characterization of antibody-sialidase conjugates that selectively remove sialic acid on the tumor cell glycocalyx as a means to increase tumor cell susceptibility to antibody-based therapy. They demonstrate that sialidase-fused to trastuzumab (a HER2 antibody) was capable of removing sialic acid from tumor cells, reducing binding by NK cell Siglec receptors, and enhancing binding to NK-activating receptor. The conjugate enhanced cytotoxicity against tumor cells with moderate HER2 expression, suggesting potential for treating patients with low HER2 expression or trastuzumab resistance. The study concludes that editing of the glycocalyx with antibody enzyme candidates holds promise for cancer immunotherapy strategies.

Xiao et al. Proc Natl Acad Sci U S A. 2016 Sep 13;113(37):10304-9. doi: 10.1073/pnas.1608069113.

Epithelial–Mesenchymal Transition Is Associated with a Distinct Tumor Microenvironment Including Elevation of Inflammatory Signals and Multiple Immune Checkpoints in Lung Adenocarcinoma.

<https://www.ncbi.nlm.nih.gov/pubmed/26851185>

Immunotherapy strategies in non-small cell lung cancer (NSCLC) have had some success by targeting immune cell check points including PD-1 and PD-L1. Despite these successes, only a subset of patients respond to these treatments. Strategies to identify patients that would benefit from these therapies would provide a clinical benefit. Lou et al. recently published a study where information from three large datasets including the lung cancer TCGA data, as well as two datasets from MD Anderson was integrated – combining information from mRNA gene expression, reverse-phase protein array, immunohistochemistry, and clinical data. Epithelial-mesenchymal transition (EMT) was found to be strongly associated with an inflammatory tumor microenvironment in lung adenocarcinoma, and this association was found to not be dependent on tumor mutational burden. Furthermore, immune activation was found to be correlated with a number of immune checkpoint molecules (e.g. PD-1, PD-L1, etc) and increases in tumor infiltrating cells in lung adenocarcinomas with an EMT phenotype. B7-H3 was also identified as a prognostic marker for NSCLC. The findings in this study suggest that EMT may have the potential to predict immune checkpoint blockade and immunotherapy effectiveness in NSCLC.

Lou et al. Clin Cancer Res. 2016 Jul 15;22(14):3630-42. doi: 10.1158/1078-0432.CCR-15-1434.

Biophysical determinants for cellular uptake of hydrocarbon-stapled peptide helices

<http://www.nature.com/nchembio/journal/v12/n10/full/nchembio.2153.html>

“Stapled peptides” are cyclic, constrained peptides used to inhibit protein-protein interactions, that have been employed against a number of targets, particularly in oncology. Stapled peptides are both conformationally and proteolytically stable,

and in some cases cell-permeable, although the molecular determinants for cell permeability are not fully understood. Walensky and coworkers have recently made a substantial contribution to this end by studying a library of stapled peptides. Their findings indicate that an optimal hydrophobicity and helicity, as well as proper placement of the hydrophobic staple, are critical determinants for cell permeability. These data should be useful to drug discovery scientists interested in delivering stapled peptides to intracellular protein targets.

Bird et al., Nature Chemical Biology, 2016, 12, 845–852. doi:10.1038/nchembio.2153

AZD9496: An Oral Estrogen Receptor Inhibitor That Blocks the Growth of ER-Positive and ESR1-Mutant Breast Tumors in Preclinical Models

<http://cancerres.aacrjournals.org/content/76/11/3307.long/>

The estrogen receptor α (ER α) is the target of several breast cancer drugs, including the selective ER modulator tamoxifen and the selective ER downregulator fulvestrant. Recently, several groups have described mutations to the ligand-binding domain of ER α that render metastatic tumors relatively resistant to existing therapies. A group at AstraZeneca has described AZD9496, an oral selective ER downregulator that functions against wild-type ER α , as well as one of the constitutively active mutants, in a variety of preclinical models. The compound is currently being studied in a Phase 1 clinical trial.

Weir et al., Cancer Research, 2016, 76, 3307-18. doi: 10.1158/0008-5472.CAN-15-2357.

4. Profile of a Young Scientist

	Employment	
	2015-	Senior Scientist in Department of Discovery Chemistry at Genentech
	2009-2015	Scientist in Department of Discovery Chemistry at Genentech
	Education	
	2003-2009	Ph.D. in Chemistry, Stanford University
	1996-2000	B.S. in Chemistry, Trinity University

Dr. Thomas H. Pillow is a senior scientist in the discovery chemistry department at Genentech. He received his bachelor's degree in chemistry from Trinity University in 2000. After a brief stint working as a manufacturing engineer at Sony Semiconductors, he moved to Stanford University for his graduate studies. There he completed his Ph.D in organic chemistry under the direction of Professor Paul A. Wender on the design, synthesis, and evaluation of novel drug delivery methodologies. While at Stanford he received an Eli Lilly Graduate Fellowship and was awarded a Centennial Teaching Award.

Dr. Pillow has a passion for translational research, utilizing synthetic chemistry and chemical biology to explore and develop medicines for cancer and infectious disease. His research focuses on bioconjugation with an emphasis on antibody-drug conjugates (ADCs). Dr. Pillow's group employs ADCs to interrogate the ability of a tumor-specific antibody to selectively deliver small molecule drugs to the interior of a cancer cell with the goal of binding a target, modulating a pathway, and effecting cell death. Another area of focus is utilizing ADCs to eradicate pathogenic bacteria resistant to conventional antibiotics through the use of antibody-antibiotic conjugates (AACs). For both of these areas, the Pillow laboratory investigates the use of novel chemical linkers to provide stable, homogeneous reaction with protein carriers while stably and reversibly connecting small molecules with a variety of functional handles. This interdisciplinary research is carried out in collaboration with scientists from a wide variety of disciplines including cancer and cell biology, antibody engineering, and ultimately physicians as we advance these experimental medicines into patients.

5. Spotlight on World News

FDA approves Bristol-Myers Squibb's Opdivo as first Immuno-Oncology treatment for metastatic squamous cell carcinoma of the head and neck (SCCHN)

<http://www.europeanpharmaceuticalreview.com/45624/news/industry-news/opdivo-fda-bms/>

The FDA has approved Opdivo (nivolumab) for clinical use after the Phase 3 CheckMate-141 trial revealed it to be superior to the comparator arm (investigator's choice of methotrexate, docetaxel or cetuximab). A 30% reduction in the risk of death for patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy was observed.

Source: European Pharmaceutical Review

Life-extending breast cancer drug approved by NICE

<http://www.europeanpharmaceuticalreview.com/45177/news/industry-news/eribulin-breast-cancer/>

The National Institute for Health and Care Excellence (NICE) has issued information that Eisai's eribulin (Halaven) should be an option for people with locally advanced or metastatic breast cancer that has spread after at least 2 chemotherapy regimens (which may include an anthracycline or a taxane, and capecitabine). New evidence based on updated results from the trial used in the original guidance show women taking eribulin lived on average almost 3 months longer compared with women taking other treatments. The drug approval by the appraisal committee was further supported by the fact that the discount available through the patient access scheme represented good value for money.

Source: European Pharmaceutical Review

Next-generation cancer partnership

<http://www.ddn-news.com/index.php?pg=77&articleid=11089>

Boehringer Ingelheim and ViraTherapeutics recently announced a long-term research and development collaboration to co-fund and jointly develop a next-generation oncolytic virus therapy platform and to investigate Austrian-based ViraTherapeutics' lead candidate VSV-GP (vesicular stomatitis virus-glycoprotein) alone and in combination with other therapies. ViraTherapeutics will be responsible for preclinical and clinical testing in Phase 1 trials of their oncolytic virus therapy candidate, which has a shorter replication time and ability to prime and boost an anticancer immune response. Under the terms of the collaboration, Boehringer Ingelheim, one of the world's 20 leading pharmaceutical companies, receives the right to acquire ViraTherapeutics after conclusion of Phase 1 clinical development

Source: Drug Discovery News

Cancer Genetics and BARC launch partnership

<http://www.ddn-news.com/index.php?pg=77&articleid=11097>

Cancer Genetics Inc. (CGI) has launched a partnership with the Bio Analytical Research Corporation (BARC) with the aim of providing clinical trial and companion diagnostics for the oncology industry. An estimated \$5.4 billion is expected to be spent by biotech and pharmaceutical companies in biomarker and genomic testing to support oncology clinical trials from Phase 1 through Phase 4 by 2020. The partnership is focused on an estimated \$5.4 billion expected to be spent by biotech and pharmaceutical companies in biomarker and genomic testing to support oncology clinical trials from Phase 1 through Phase 4 by 2020. The partnership will have an immediate focus on immuno-oncology, hematological cancers and lung cancer and will plan on developing market specific offerings that are collaboratively sold and serviced.

Source: Drug Discovery News

6. Career Forum

<https://cancercareers.org/Pages/default.aspx>

<http://www.nature.com/naturejobs/science/jobs>

<http://jobs.rsc.org/>

<http://chemistryjobs.acs.org/>

7. Conferences

[AACR International Conference on New Frontiers in Cancer Research](#)

January 18 - 22, 2017 | Cape Town, South Africa

[AACR International Conference on New Frontiers in Cancer Research](#)

January 18 - 22, 2017 | Cape Town, South Africa

[AACR Annual Meeting 2017](#)

April 1 - 5, 2017 | Washington, D.C.

[Accelerating Anticancer Agent Development and Validation Workshop](#)

May 3 - 5, 2017 | Bethesda, Maryland

[Hematologic Malignancies: Translating Discoveries to Novel Therapies](#)

May 6 - 9, 2017 | Boston, Massachusetts

[CME Advances in Sarcomas: From Basic Science to Clinical Translation](#)

May 16 - 19, 2017 | Philadelphia, Pennsylvania

American Peptide Society Meeting

<http://aps2017.org>

June 17-22, 2017. Whistler, BC, Canada

8. Other

[**NIH Common Fund glycoscience program funding**](#)

These funding opportunities seek fresh ideas for development of synthetic methods, and tools that will enable researchers in all biomedical fields to study the roles of carbohydrates in health and disease.