

1. From the Editors

Pancreatic cancer statistics makes for depressing reading (cf. CA Cancer J Clin 2011, 61, 69-90 and CA Cancer J Clin 2014, 64, 9-29). Worldwide, the incidence of all types of pancreatic cancer (85% of which are adenocarcinomas) ranges from 1 to 10 cases per 100,000 people. In 2014, in the United States alone, pancreatic cancer is estimated to develop in 46,000 people, and 40,000 people (87%) are expected to die from it. Pancreatic ductal adenocarcinoma is the most lethal common cancer as it is usually diagnosed at an advanced stage and is resistant to therapy (N Engl J Med. 2014, 371, 1039-49). Whether the dismal prognosis of patients with pancreatic cancer compared to patients with other types of cancer is a result of late diagnosis or early metastasis to distant organs is not known. In a ground-breaking study a few years ago (Nature, 2010, 467, 1114-7), Christine A. Lacobuzio-Donahue and colleagues showed for the first time that primary pancreatic cancers contain a mix of geographically distinct sub-clones, each containing large numbers (hundreds of millions) of cells that are present within the primary tumour years before the metastases become clinically evident. They proposed a pancreatic cancer model that predicted an average of 6.8 years between the birth of the cell giving rise to the parental clone and the seeding of the index metastasis. Unfortunately, the vast majority of patients are not diagnosed until the last 2 years of the entire tumorigenic process, which is too late for clinicians to effectively treat patients with conventional drugs. In this issue, we discuss recent advances in combating and understanding pancreatic cancer and explore the advances and progress in chemical sciences that may offer new innovative solutions in early detection, biomarker identification or discovery of new targeted therapeutics to tackle this disease. In this issue, we also report on Dr. Costas A. Lyssiotis, our profile of a young scientist, whose work focuses on unraveling metabolic pathways in the pancreatic tumor microenvironment that may be key to tumorigenesis and could be ultimately targeted by small molecules for therapeutic intervention.

Focusing on a specific field of chemistry in cancer research or a particular type of cancer as in this issue is an effort by the editorial board to enhance the content of the CICR newsletter in a constructive way. We are working to deliver to you the most current and relevant information in cancer research and procreate a source of inspiration for the CICR community as well as debate on the progress of chemical sciences in understanding and combating cancer. Are we succeeding? If we are not, please do let us hear your opinion on how the CICR newsletter content should be enhanced. You can contact us at cicr@aacr.org.

Before signing off, a reminder to our readers that the abstract submission deadline for the [AACR Annual Meeting 2015](#) is 3 December, 2014 and the early registration deadline is 19 December 2014. For more information:

2. Selected Research Highlights

Pancreatic adenocarcinoma (Review)

This is an excellent review on pancreatic adenocarcinoma which discusses the most recent advances in four focal points: (i) epidemiology and risk factors, (ii) biologic features of pancreatic cancer, (iii) new insights into cellular metabolism and (iv) clinical presentation, diagnosis, and staging.

The complex landscape of pancreatic cancer metabolism (Review)

Pancreatic ductal adenocarcinoma (PDA) cells have the ability to adapt their metabolism to the particular environment to which they are exposed by utilizing diverse fuel sources depending on their availability and efficiently recycling various intermediate metabolites through activation of different salvage pathways such as autophagy and macropinocytosis. These diverse metabolic adaptations allow PDA cells to survive and thrive in harsh environments that may lack nutrients and oxygen. In a review recently published on Carcinogenesis, Cristovão Marques Sousa and Alec C. Kimmelman summarize the metabolic landscape of PDA tumors and discuss how such information can be exploited for future diagnostic and therapeutic approaches.

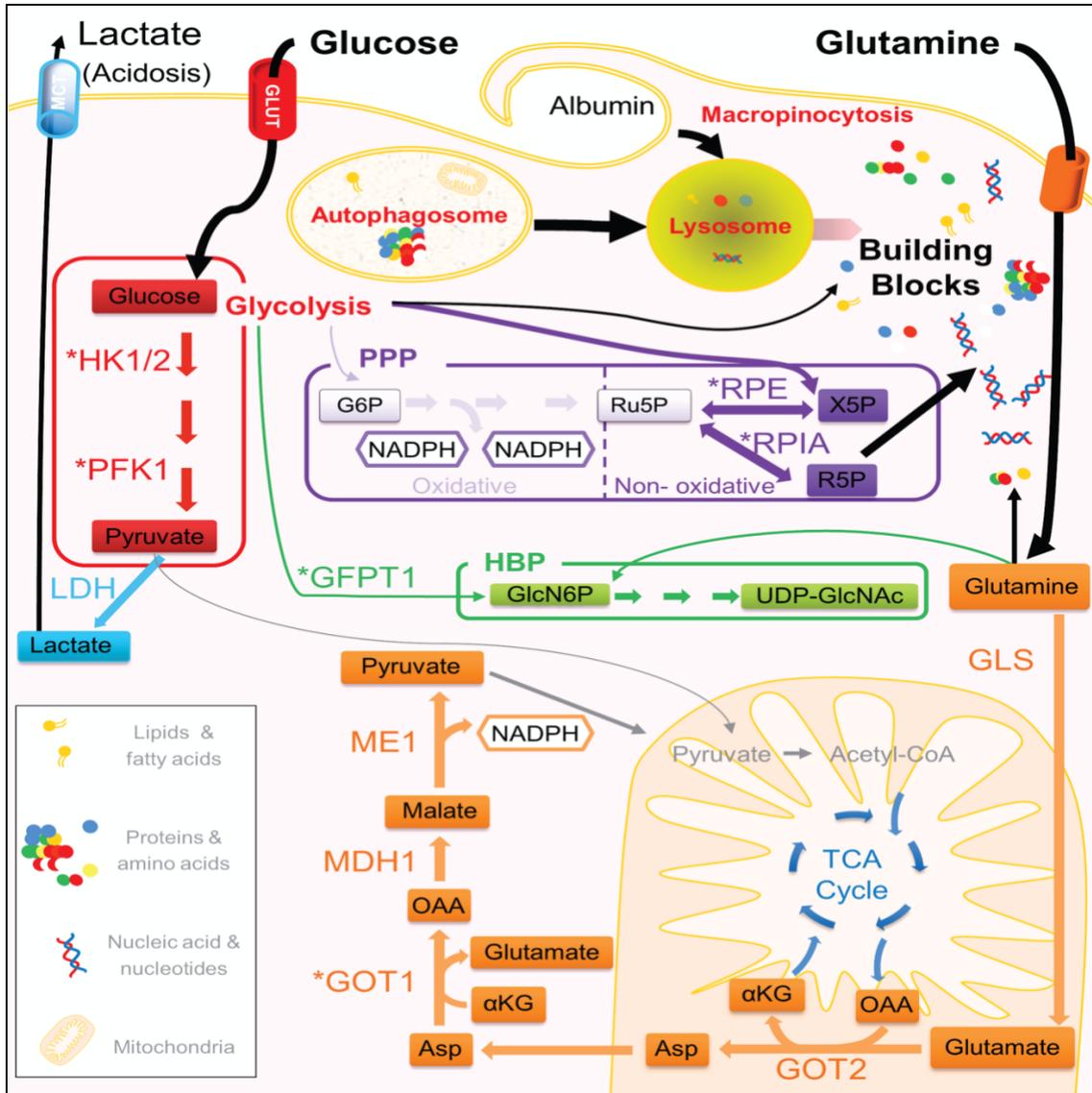


FIGURE 1 A typical PDA cell is depicted showing schematics of representative metabolic pathways that are altered in the disease in response to oncogenic Kras. Enzymes whose expression is increased by Kras are indicated with an asterisk. Reprinted with permission. Sousan and Kimmelman, *Carcinogenesis* 2014, 35 (7), 1441–1450.

Metabolic profiles are principally different between cancers of the liver, pancreas and breast

A recent study by Budhu et al. investigated metabolomic differences between liver, pancreatic, and breast cancers. Metabolic profiling on paired tumor and non-tumor liver, breast and pancreatic tissue specimens allowed the research teams in the National Cancer Institute (MD) to concisely differentiate between the cancers. Briefly, 43, 35 and 106 metabolites in liver, pancreas and breast tumors, respectively, were identified as cancer type-specific molecules relative to the paired non-tumor tissues. Based on the biochemical distribution of the metabolites, lipid and amino acid pathways were distinctly altered in pancreatic and breast cancers. At the same time, the authors also discovered metabolite

profiles that are differentially altered in early stage tumor versus non-tumor tissues of liver, pancreas and breast. While several metabolic pathways were altered in these tumors, the largest alteration in early stage liver and pancreatic cancers occurs in lipid pathways, while amino acid pathways were predominantly perturbed in early stage breast cancers. Collectively, the authors reveal unique biochemical biomarkers of liver, pancreas and breast cancers, which may aid in more accurately defining the molecular determinants of each cancer type.

Elevation of circulating branched-chain amino acids is an early event in human pancreatic adenocarcinoma development.

New non-invasive diagnostic methods are a holy grail in pancreatic cancer and desperately needed to detect early stage pancreatic cancer, when the disease is more treatable. A recent metabolomics study investigated whether metabolites in pre-diagnostic pancreatic cancer plasma samples and matched controls could diagnose pancreatic cancer in four different patient cohorts. Elevated levels of three natural branched-chain amino acids (leucine, isoleucine, and valine) were found to be associated with a greater than two-fold risk of pancreatic cancer. In this study, elevated levels of these amino acids were also identified in mice with early-stage pancreatic cancers driven by mutant Kras expression, but not in mice with Kras-driven tumors in other tissues. These results suggest that circulating branched-chain amino acids may have diagnostic utility although further studies are warranted in additional cohorts and patients with severe pancreatitis, which is a risk factor for developing pancreatic cancer.

Heterogeneity of pancreatic cancer metastases in a single patient revealed by quantitative proteomics

The vast majority of pancreatic cancer patients bear metastases at the time of diagnosis due to late discovery of the disease. Genetic studies have shown that there is significant molecular heterogeneity in clonal populations of the primary tumor and metastases at different organs are the result of different subclones; however, little is known about the evolution of pancreatic cancer at the protein level. This study describes a Stable Isotope Labeling by Amino acids in cell Culture (SILAC)-based proteomic profiling strategy to investigate the proteome and tyrosine phosphoproteome to explore a model system consisting of cells from a single patient isolated from three different metastatic sites. Differences in both protein expression and tyrosine kinase activities were identified across the different metastatic lesions. This study suggests that patients with multiple organ metastases could potentially benefit from therapies targeted to different disease subclones.

Using a highly faithful mouse model of pancreas cancer help to discover early stage biomarkers

Due to the frequently asymptomatic character of pancreatic ductal adenocarcinoma (PDA) at early stages, diagnosis generally occurs only after locally advanced or metastatic spread, and the majority of patients therefore present with unresectable disease. Mouse models that accurately recapitulate

the human condition allow disease tracking from inception to invasion and can therefore be useful for studying early disease stages when surgical resection is possible. A group at Fred Hutchinson Cancer Research Center led by Drs. Paul D Lampe and Sunil R Hingorani used KPC mouse model of PDA and a high-density antibody microarray containing ~2500 antibodies to investigate the pancreatic tissue proteome at pre-invasive and invasive stages of disease. They found seven upregulated proteins, thus distinguishing PDA from normal pancreas. Particularly, the levels of serine/threonine stress kinase 4 (STK4) increased between pre-invasive and invasive stages suggest its potential as a tissue biomarker and possibly its involvement in progression from precursor pancreatic intraepithelial neoplasias (PanIN) to PDA. Immunohistochemistry of STK4 in a panel of human pancreas cancers confirmed that STK4 levels were increased in tumor epithelia compared to normal tissue. Overall, the integrated approach yielded several tissue markers that could serve as signatures of disease stage including early (resectable), and therefore clinically meaningful, stages.

[Oncogene ablation-resistant pancreatic cancer cells depend on mitochondrial function](#)

Viale et al. explored pancreatic tumor recurrence by characterizing tumor cells surviving oncogene ablation. The researchers from Texas MD Anderson Cancer Center demonstrate that a subpopulation of dormant tumor cells surviving the genetic and pharmacological ablation of oncogenic pathways (i.e. surviving cells) possesses the characteristics of cancer stem cells. In addition, their transcriptomic and metabolomic analyses reveal that surviving cells metabolically rely on oxidative phosphorylation for survival. Accordingly, the authors anticipate that mitochondrial respiration would be an attractive target that may eliminate surviving cells and thus prevent tumor relapse in pancreatic cancer.

[Therapeutic effects of an anti-Myc drug on mouse pancreatic cancer](#)

Mouse models faithfully simulating human cancer are valuable for genetic identification of potential drug-targets but, among them, the most advantageous for practical use in subsequent preclinical testing of candidate therapeutic regimes are those exhibiting rapid tumor development. Considering that a KRAS mutation (predominantly in codon 12, such as KRASG12D; KRAS*) occurs with high frequency (~90%) in cases of human pancreatic ductal adenocarcinoma (PDA), Stellas et al. sought to develop a mouse PDA model that would exhibit high tumor incidence and short latency by ectopic overexpression of Kras*. This transgenic modification caused by 2 weeks postpartum the appearance of pancreatic intraepithelial neoplasia (PanIN), which evolved into invasive PDA within a week later and resulted in a moribund condition at one month. Interestingly, however, this aggressive form of pancreatic tumorigenesis was effectively prevented by genetic ablation of Myc specifically in the pancreas. On the basis of this observation, causally demonstrating that Kras* oncogenicity fully depends on unperturbed Myc activity, these investigators evaluated the therapeutic potential of an orally administered anti-Myc drug. Daily treatment of

moribund PDA-bearing mice with Mycro3, a small-molecule inhibitor of Myc-Max dimerization, resulted in the survival of animals until these were sacrificed after two months for further analysis. PET/CT image analysis demonstrated marked shrinkage of PDA, while immunohistochemical analyses showed an increase in cancer cell apoptosis and reduction in cell proliferation. Tumor growth was also drastically attenuated in Mycro3-treated NOD/SCID mice carrying orthotopic or heterotopic xenografts of human pancreatic cancer cells. These results provide strong justification for eventual clinical evaluation of anti-Myc drugs as potential chemotherapeutic agents for the treatment of PDA.

MMP-9 responsive PEG cleavable nanovesicles for efficient delivery of chemotherapeutics to pancreatic cancer

In this article, the authors exploit biochemical differences between the microenvironments of healthy and tumor tissues and in particular the activity of the enzyme matrix metalloproteinase-9 (MMP-9) and glutathione levels. Kulkarni et al. synthesized gemcitabine-loaded liposomes functionalized with a MMP-9 sensitive lipopeptide and PEG conjugated to a reduction sensitive ligand. PEG protects the liposomes until it reaches a tumor site in which high glutathione levels reductively remove PEG. MMP-9 is also present in the tumor microenvironment and cleaves the sensitive lipopeptide, disrupting the liposomal integrity and ultimately releasing gemcitabine. The authors demonstrate the validity and efficacy of this novel nanovesicle drug delivery system in vitro and in vivo using pancreatic ductal carcinoma cells.

3. Profile of a Young Scientist

	<p>Employment 2013-present</p>	<p>Pancreatic Cancer Action Network-AACR Pathway to Leadership Postdoctoral Fellow, The Cancer Center, Dept. of Medicine, Weill Cornell Medical College, New York, NY</p>
<p>Costas A. Lyssiotis</p>	<p>2010-2013</p>	<p>Damon Runyon Cancer Research Foundation Postdoctoral Fellow, Dept. of Systems Biology, Beth Israel Deaconess Medical Center, Division of Signal Transduction, Harvard Medical School, Boston, MA</p>

	2010	Postdoctoral fellow, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland
	Education	
	2010	Ph.D. in Chemical Biology, The Scripps Research Institute, La Jolla, CA
	2004	B.S. Chemistry and Biochemistry, University of Michigan, Ann Arbor, MI

Costas A. Lyssiotis is currently a postdoctoral fellow in the department of medicine at Weill Cornell Medical College, under Prof. Lewis Cantley's supervision. Upon graduating with distinction and highest honors in chemistry from the University of Michigan, Ann Arbor, he went on to pursue a PhD degree with Prof. Peter Schultz at Scripps Research Institute. His thesis entitled "Insight into the reprogramming of cell fate with small molecules" describes a collection of his PhD work on selective activation and deactivation of various cellular signal transduction pathways such as apoptosis, embryonic stem cell differentiation, and developmental plasticity in oligodendrocyte precursor cells using small molecule agonists and antagonists. After a brief postdoctoral stint at Swiss Institute for Experimental Cancer Research in Switzerland, he worked as a Damon Runyon Cancer Research Foundation Postdoctoral Fellow in Beth Israel Deaconess Medical Center, where his initial introduction to pancreatic cancer transpired. He investigated manipulation of pancreatic cancer cells by regulating the anabolic glucose metabolism. He furthered his studies on various cell cycles that support proliferation and survival of pancreatic cancer cells, and identification of compounds and methods to manipulate them. In the future, he is dedicated to utilize his expertise in small molecule activated manipulation of metabolic dependencies of pancreatic cancer cells. The recent Pancreatic Cancer Action Network-AACR Pathway to Leadership Award will allow him to further his studies on pancreatic cancer.

4. Spotlight on World News

[The Institute of Cancer Research and the Wellcome Trust, UK to collaborate with Merck Serono to develop anticancer drugs](#)

Some of the most promising advances in cancer research have been small-molecule inhibitors that inhibit the activity of poly (ADP-ribose) polymerase (PARP) enzyme family, which includes the enzyme tankyrase. ICR and Merck Serono aim to identify inhibitors of tankyrase towards clinical development for anti-cancer drugs. At the end of the collaboration period, Merck Serono will take over full responsibility for the selected clinical development candidate, with the goal of bringing a new cancer therapeutic drug to patients. The collaboration will be jointly funded by Merck Serono and the Wellcome Trust. The existing drug discovery program at the ICR is supported by a Wellcome Trust Seeding Drug Discovery Award. Source: Wellcome Trust

[Pfizer and Merck team up to evaluate novel anti-cancer combination regimen](#)

Pfizer Inc. and Merck & Co. Inc. (also known as MSD) have partnered to explore the therapeutic potential of the combination of Pfizer's crizotinib (XALKORI®) with Merck's investigational anti-PD-1 antibody pembrolizumab in a Phase 1b clinical study evaluating the safety and tolerability of the combination in patients with anaplastic lymphoma kinase (ALK)-positive advanced or metastatic non-small cell lung cancer (NSCLC). XALKORI is a kinase inhibitor indicated for the treatment of patients with metastatic non-small cell lung cancer, whose tumors are ALK-positive. Pembrolizumab (MK-3475) is an investigational, humanized, monoclonal antibody against PD-1 designed to reactivate anti-tumor immunity. Pembrolizumab exerts dual ligand blockade of the PD-1 pathway by inhibiting the interaction of PD-1 on T cells with its ligands PD-L1 and PD-L2. Source: Drug Discovery News

[NIH launches the "Exceptional Responders to Cancer Therapy" initiative](#)

The Exceptional Responders Initiative aims to investigate the molecular factors of tumors associated with exceptional treatment responses of cancer patients to drug therapies and was launched in September 2014 by the National Cancer Institute (NCI). Under this Initiative, scientists will attempt to identify the molecular features of tumors that predict whether or not a particular drug or class of drugs will be beneficial. Investigators will examine tumor specimens from patients in clinical trials who achieved an exceptional response relative to other trial participants, or other patients who achieved an exceptional and unexpected response to a non-investigational therapy. The output of this initiative might include a list of plausible mutations, possible mutations, or simply all the mutations found in the exceptional responder cases. Researchers hope other investigators will seek to build on the data generated by this study by testing hypotheses on specimens from a trial that used a particular drug, or by comparing their own dataset with the shared data. Questions from investigators, physicians, and hospitals looking to contribute tumor samples can be sent by email to the Exceptional Responder's email box at NCIExceptionalResponders@mail.nih.gov. Source: Cancer.gov

[Lung cancer death rates continue to fall according to the NCI Annual Report](#)

The Annual Report to the Nation on the Status of Cancer, covering the period 1975–2010, showed that death rates for lung cancer, which accounts for more than one in four cancer deaths, is dropping at a faster pace than in previous years. The recent larger drop in lung cancer deaths is likely the result of decreased cigarette smoking prevalence over many years, and is now being reflected in mortality trends. The lung cancer death rate decline, as well as declines in colorectal, breast, and prostate cancer death rates, has also helped drive decreases in death rates for all cancers types combined, a trend that began about 20 years ago. The decreased death rates for these four cancers accounted for more than two-thirds of the overall reduction in cancer death rates in the period 2001-2010. The report showed, however, that death rates increased for some cancers, including cancers of the liver and pancreas for both sexes, cancers of the uterus in women, and, in men only, melanoma of the skin and cancers of the soft tissue in this 10 year period.

Source: Cancer.gov

5. Career Forum

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

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

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

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

6. Conferences

[Tumor Immunology and Immunotherapy: A New Chapter](#)

December 1-4, 2014, Orlando, FL, USA.

[World Cancer Congress](#)

December 3-6, 2014, Melbourne, Australia.

San Antonio Breast Cancer Symposium

December 9 - 13, 2014, San Antonio, TX

[MYC: From Biology to Therapy](#)

January 7-10, 2015, La Jolla, CA, USA.

[Keystone Symposium on Epigenetics and Cancer](#)

January 25-30, 2015, Keystone, CO, USA.

[Translation of the Cancer Genome](#)

February 7 - 9, 2015, San Francisco, CA.

[Computational and Systems Biology of Cancer](#)

February 8 - 11, 2015, San Francisco, CA

[Gordon Research Conference on Stem Cells & Cancer](#)

February 15-20, 2015, Ventura, CA, USA.

[32nd Annual Miami Breast Cancer Conference](#)

February 26 - March 01, 2015, Miami Beach, FL, USA

[Tumor Angiogenesis and Vascular Normalization: Bench to Bedside to Biomarkers](#)

March 5 - 8, 2015, Orlando, FL.

[American Association for Cancer Research Annual Meeting 2015](#)

April 18-22, 2015, Philadelphia, PA, USA

[Metabolism and Cancer](#)

June 7 - 10, 2015, Bellevue, Wash.

[The 5th Conference on Notch targeting in cancer](#)

June 24-26, 2015, Mykonos, Greece.

7. Other