In February of this year, the Faculty of Pharmacy, Kuwait University, held its 5th bi-annual international conference for the advancement of pharmacy and pharmaceutical sciences. This meeting was devoted to cancer-related issues focusing on novel therapeutic strategies, in particular to overcome drug resistance. Several plenary sessions and preferred presentations, as well as posters discussed recent progress in both basic research and clinical management in oncology.
**MILESTONES IN ONCOLOGY**

- **Smoking linked to Cancer** (1950’s)
- **Chemotherapy cures Hodgkin’s Lymphoma** (1965)
- **Benzene cause of cancer** (1988)
- **First targeted cancer drug rituximab** (1997)
- **Gleevec transforms treatment for rare Leukemia, GI Cancer** (2001)
- **EGFR targeted drugs for Lung Cancer; erlotinib, gefitinib** (2003)
- **Vaccine to prevent Cervical Cancer** (2006)
- **ipilimumab improves survival in advanced Melanoma** (2010)
- **Nab-Paclitaxel and Gemcitabine improves survival in metastatic Pancreatic Cancer** (2013)
- **Crizotinib improves DFS in patients with advanced Lung Cancer** (2014)
- **1st Chemotherapy drug for Hodgkin’s Lymphoma** (1949)
- **New drugs for Testicular Cancer Advent of mass breast screening** (1977)
- **Tamoxifen for Breast Cancer** (1986)
- **1st targeted anti-Breast Cancer drug, trastuzumab (Herceptin) has major impact on care** (1998)
- **Study links household radon exposure to lung cancer** (2000)
- **Human genome sequenced** (2003)
- **First "anti-angiogenic" drug bevacizumab** (2004)
- **NCI, NHGR launch Cancer Genome Atlas** (2005)
- **CT scanning reduces Lung Cancer deaths among heavy smokers** (2010)
- **Adding palliative care to standard chemotherapy improves survival in advanced Lung Cancer** (2010)

The drug
Researchers have found a new way to modify cell-killing agents to make them selectively poison cancer cells, while avoiding healthy cells, according to a paper published in Nature Communications (N. Ueki et al. doi:1038/ncomms3735, 2013). The researchers deactivated a toxic agent, puromycin, by adding an acetylated lysine residue to it. The resulting compound, called Boc-KAc-Puro, is a pro-drug-the compound is biologically inactive until it interacts with enzymes produced by the cancer cells it targets. The proposed activating enzymes include histone deacetylases (HDACs) and the protease cathepsin L (CTSL), which are more abundant in cancer cells. To activate the drug, the HDACs first deacetylate the lysine residue. Only after the deacetylation can CTSL remove the lysine from the puromycin, freeing it to kill any nearby cells by interrupting protein synthesis. The paper proposes a clever way of making sure that the anticancer drug gets activated only in designated tumors by targeting two distinctive enzymes over-expressed in cancer cells.

What’s new
Tumor-targeting pro-drugs are not a new concept and have been developed for several decades. The novel aspect of Boc-KAc-Puro is that it uses HDACs as triggering enzymes, and unleashes its toxicity in two steps rather than one. Having HDAC alone will not activate the drug as both HDAC and cathepsin L is required. The two-step triggering process makes it less likely that a non-cancerous cell could activate the drug’s toxicity. As the pro-drug activates and demonstrates toxicity only after having the two unique enzymes in cancer cells, the system demonstrates increased specificity and safety compared to conventional pro-drugs targeting a single enzyme. The researchers found that Boc-KAc-Puro was able to kill a variety of cancer cells in vitro, and reduce tumour growth in mice injected with human colon cancer cells. Meanwhile, non-cancerous cells were significantly less affected, both in vitro and in the mice.

Importance
Cancer researchers aim to target malignant cells selectively while leaving healthy cells unharmed. But most cancer cells operate using the same set of enzymes and cellular machinery as normal cells, and drugs designed to kill cancer cells frequently harm normal cells as well. Much work has gone into creating pro-drugs activated by proteases expressed at high levels in cancer cells, but these pro-drugs are often unstable and become toxic in the presence of healthy cells. Additionally, researchers are working to slow cancerous growth by inhibiting HDACs. But HDAC inhibitors can also stymie the necessary work of the enzymes in normal cells. This technique could aid in the development of cancer drugs that kill more malignant cells and fewer benign ones. Acetylated lysine could be added to a broad range of cancer-killing drugs. According to the lead author, they just proved one example by using puromycin, and theoretically, they can use this small substrate to attach to other drugs to give them tumour selectivity. They also hope that the drug will work for diverse malignancies beyond colon cancer, since HDACs and CTSL are elevated in many types of cancer cells. Boc-KAc-Puro appeared to selectively kill pancreatic, cervical, and liver cancer cells in vitro.

Examples of pro-drugs and their active metabolites

<table>
<thead>
<tr>
<th>Prodrug</th>
<th>Active Drug</th>
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<tr>
<td>Protonsil</td>
<td>Sulfanilamide</td>
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<tr>
<td>Levodopa</td>
<td>Dopamine</td>
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<tr>
<td>Talampicillin</td>
<td>Ampicillin</td>
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<tr>
<td>Cyclophosphamide</td>
<td>Phosphoramide mustard</td>
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<tr>
<td>Diazepam</td>
<td>Oxazepam</td>
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<tr>
<td>Azathioprine</td>
<td>Mercaptopurine</td>
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<tr>
<td>Cortisone</td>
<td>Hydrocortisone</td>
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<tr>
<td>Dipivefrin</td>
<td>Adrenaline</td>
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<tr>
<td>Prednisone</td>
<td>Prednisolone</td>
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<tr>
<td>Enalapril</td>
<td>Enalaprilat</td>
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<tr>
<td>Ampicillin</td>
<td>Pivampicillin</td>
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Stealth drugs - the next generation

<table>
<thead>
<tr>
<th>Drug</th>
<th>HDAC</th>
<th>CTSL</th>
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<tr>
<td>Ueki et al Nature Comm 4, 2735</td>
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Needs improvement

However, the authors of the study emphasize that much work needs to be done before Boc-KAc-Puro makes it to the clinic. They continue to make modifications to the pro-drug to make it more cancer-cell selective. Additionally, the system should be confirmed by treating animals when cancers reach a later stage or have spread in the body. Some experts question how Boc-KAc-Puro is converted to puromycin, and how it achieves its selectivity. Although they think it’s an interesting concept, it’s very unclear how the thing works “mechanistically”. In particular, they noted that there is insufficient evidence to definitively say CTSL is cleaving lysine from puromycin.

The authors made their case for CTSL’s role by producing fluorescent probes modified with lysine or acetylated lysine and using them to tag cancer cells. The probes fluoresced when exposed to the cancer cells, but in the presence of CTSL inhibitors, they showed little activity. The probes also showed little activity in non-cancerous cells. Although some experts stated that the inhibitors used in the study were not necessarily specific to CTSL and could have altered the activity of any number of proteases, the lead author of the study argued that two out of three inhibitors used had shown CTSL specificity in previous studies. They believe that a more definitive way to test CTSL’s role in the unmasking of Boc-KAc-Puro would be to genetically silence CTSL and see whether the drug’s toxicity was altered. Even so, they are convinced that Boc-KAc-Puro does somehow selectively kill cancer cells.

Source:

FDA approved drugs for Oncology in 2014

January 10: accelerated approval for the combination of trametinib (Mekinist) and dabrafenib (Tafinlar); GSK, for treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600 K mutation, as detected by an FDA-approved test.

February 12: accelerated approval to Pharmacyclics for ibrutinib (Imbruvica) for treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.

April 17: approved atumumab (Arzerra) in combination with chlorambucil for previously untreated patients with CLL, for whom fludarabine-based therapy is considered inappropriate.

April 21: approved ramucirumab (Cyramza) from Eli Lilly for use as a single agent for treatment of patients with advanced or metastatic, gastric or gastroesophageal junction (GEJ) adenocarcinoma with disease progression on or after prior treatment with fluoropyrimidine- or platinum-containing chemotherapy.

April 23: approved siltuximab (Sylvant) for the treatment of patients with multicentric Castleman disease who are HIV and human herpes virus negative.

April 28: approved an oral suspension of mercaptopurine (Purixan) for the treatment of patients with acute lymphoblastic leukemia as part of a combination regimen.

April 29: accelerated approval to Novartis for ceritinib (Zykadia) for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic non-small-cell lung cancer (NSCLC) with disease progression on, or who are intolerant to, crizotinib.

July 3: accelerated approval to Spectrum Pharmaceuticals for
belinostat (Beleodaq) for treatment of patients with relapsed or refractory peripheral T-cell lymphoma.

**July 23:** approved Zydelig (idelalisib) from Gilead for the treatment of patients with relapsed CLL, in combination with rituximab, for whom rituximab alone would be considered appropriate therapy due to other comorbidities, follicular B-cell NHL and small lymphocytic lymphoma.

**August 14:** approved bevacizumab (Avastin) solution for intravenous infusion for treatment of persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan.

**September 4:** accelerated approval to Merck for Pembrolizumab (Keytruda) for treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

**October 10:** approval to Helsinn for Akynzeo (netupitant and palonosetron) for prevention of chemotherapy-induced nausea and vomiting.

**November 5:** expanded the indication of ramucirumab (Cyramza) to include its use in combination with paclitaxel for treatment of patients with advanced gastric or GEJ adenocarcinoma.

**November 14:** approved bevacizumab solution for intravenous infusion in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for the treatment of patients with platinum-resistant, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.

**December 3:** accelerated approval to Amgen for blinatumomab (Blincyto) for treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia.

**December 4:** approved ruxolitinib (Jakafi) for treatment of patients with polycythemia vera who have had an inadequate response to, or are intolerant of, hydroxyurea.

**December 12:** approved ramucirumab (Cyramza) for use in combination with docetaxel for treatment of patients with metastatic NSCLC with disease progression on or after platinum-based chemotherapy.

**December 16:** approved lanreotide (Somatuline Depot injection) for the treatment of patients with unresectable, well or moderately differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumours to improve progression-free survival.

**December 19:** accelerated approval to AstraZeneca for olaparib (Lynparza), a new drug for women with advanced ovarian cancer associated with mutant BRCA genes, as detected by an FDA-approved test.

**December 22:** accelerated approval to Bristol-Myers Squibb for nivolumab (Opdivo) for treatment of patients with unresectable or metastatic melanoma who no longer respond to other drugs.
The 5th KIPC focused on Cancer, with plenary sessions presenting current research and clinical practice in the general areas of cancer therapeutics, drug delivery and chemo-resistance, and pharmaceutical care.

A keynote lecture by Gary Yee, reviewed both the successes and challenges in combating various cancers, with promise of new strategies in the post-genomic era, echoed by Fahd Al Mul-la who described the use of new high throughput technologies to individualise patient treatment.

Stephan Grupp presented impressive data on immune mediated T cell therapy using chimeric antigen receptors to treat pediatric leukaemia.

A broader perspective of clinical trials data with promising new agents was presented by Jo Anne Zujewski and Jasem Al Barak.

The emerging recognition of EMT and microRNA both in tumour progression as well as their involvement in drug resistance was discussed in several talks by Fazlul Sarkar, Yunus Luqmani and Maitham Khajah.

William Elmquist and Arwyn Jones elaborated on drug uptake through various transporter mechanisms that include endocytotic pathways, while Abdelbary Elhissi described proliposome and nano-emulsion delivery systems.

The theme of herbal-derived medicinals by John Pezzuto was followed up in several proffered papers.

Several workshops dealt with automation in neoplastic preparations (Zubeir Nurgat), the increasing role of immuno-oncology in patient management (Sherif Mohamed) and an audience participating session on patient counseling.

Poster viewing sessions were held each day, and some were selected for podium presentation; prizes were awarded.

A public awareness campaign organised with the assistance of the Kuwait Pharmacy Students Society directed at informing high school children and members of the public about cancer care and the role of pharmacists met with considerable enthusiasm, and was well attended.
How are we doing in the war against cancer?

Professor Gary C. Yee (Keynote Speaker)
College of Pharmacy, University of Nebraska, USA

In the early 1970s, the “war against cancer” became a national issue in the United States. The President of the United States signed the National Cancer Act in 1971 promoting the National Cancer Institute. Funding for the National Cancer Institute increased. What progress has occurred over the last 40+ years? Little change in cancer incidence and mortality occurred initially. Beginning in the early 1990s, however, the cancer-related death rate began to decline. Over the last 20 years, the cancer-related death rate in the United States has declined by about 20%, which translates into more than 1.3 million fewer cancer deaths. The decline in cancer-related death rate is due to advances in cancer prevention, detection, and treatment. The most exciting new cancer therapies are a result of advances in our understanding of cancer biology, particularly genomics. Studies of the cancer genome have identified mutations in certain genes that allow cells to become cancer. Targeted drugs against these “driver mutations” offer the potential to selectively target cancer cells while largely sparing normal cells. Over 20 targeted drugs are currently available to treat various hematologic malignancies and solid tumors. However, except for a few cancer types, these targeted drugs have not resulted in major improvements in survival. Although these targeted drugs cause less damage to rapidly proliferating normal tissues, they are often associated with unusual and sometimes serious adverse effects. Another group of exciting new cancer therapies is immune checkpoint inhibitors. Most of these new therapies are very expensive, with many costing over $100,000 US per year. Cancer costs are currently rising faster than other sectors in medicine, and some policy makers recommend more formal consideration of the value (e.g. cost-effectiveness analysis) of new therapies. Since most of these new targeted therapies are orally administered, pharmacists working in all practice settings should be prepared to provide care for cancer patients.

Cell Therapy for leukaemia crosses the activity threshold

Professor Stephan A. Grupp
Department of Pediatrics, University of Pennsylvania, USA

Chimeric antigen receptors (CARs) combine a binding fragment (scFv) of an antibody with intracellular signaling domains. We have previously reported on CTL019 cell therapy expressing an anti-CD19 CAR. Infusion of these cells results in 100 to 100,000 x in vivo proliferation, durable anti-tumor activity, and prolonged persistence in patients with B cell tumors, including sustained complete responses (CRs) in adults and children with acute lymphoblastic leukemia.

Trial results (from ASH 2014): 30 children median age 10y (5-22y) with CD19+ ALL were treated. 25/30 patients had detectable disease on the day before CTL019 cell infusion, while 5 were minimal residual disease (MRD)(-). A median of 3.6 x10⁶ CTL019 cells/kg (1.1-18x10⁶/kg) were infused over 1-3 days. There were no infusional toxicities >grade 2, although 9 patients developed
fevers within 24 h of infusion and did not receive a planned 2nd infusion of CTL019 cells. 27 patients (90%) achieved a CR, including a patient with T cell ALL aberrantly expressing CD19+. 3 did not respond. MRD was negative in 23 responding patients and positive at 0.1% (negative at 3m), 0.09%, 0.22%, and 1.1% in 4 patients. With median follow up of 9 m (up to 30 m), 16 patients have ongoing CR, with only 3 patients in the cohort receiving subsequent treatment such as donor lymphocyte infusion or stem cell transplantation (SCT), 6-month event free survival (EFS) measured from infusion is 63% (95% CI, 47-84%), and OS is 78% (95% CI, 63-95%). CTL019 cells were detected in the CSF of 17/19 patients and 2 patients with CNS2a disease experienced a CR in CSF. 10 patients with a CR at 1m have subsequently relapsed, half with CD19(-) blasts. 2/5 patients who relapsed with CD19(-) disease had previously been refractory to the CD19-directed therapy blinatumomab, and subsequently went into CR with CTL019.

All responding patients developed grade 1-4 cytokine release syndrome (CRS) at peak T cell expansion with marked increase of interleukin 6 (IL-6) and interferon gamma. Treatment for CRS was required for hemodynamic or respiratory instability in 37% of patients and was rapidly reversed in all cases with the IL6-receptor antagonist tocilizumab, together with steroids in 5 patients. Although T cells collected from the 21 patients who had relapsed after allo SCT were median 100% donor origin, no graft-versus-host disease (GVHD) has been seen. Grade 4 CRS was strongly associated with high disease burden prior to infusion and with elevations in IL-6, ferritin (suggesting macrophage activation syndrome) and C reactive protein after infusion. Persistence of CTL019 cells detected by flow cytometry and/or QPCR, and accompanied by B cell aplasia, continued for 1-26 m after infusion in patients with ongoing responses. QPCR showed very high levels of CTL019 proliferation. B cell aplasia has been treated with IV Ig without significant infectious complications. Probability of 6 m CTL019 persistence by flow was 68% (95% CI, 50-92%) and relapse-free B cell aplasia was 73% (95% CI, 57-94%).

We conclude that CTL019 cells can undergo robust in-vivo expansion and can persist for over 2y in patients with relapsed ALL, allowing for the possibility of long-term response without subsequent SCT. This approach also allows for a salvage therapy for relapse after allo-SCT with a GVHD. CTL019 therapy is a significant CRS that responds rapidly to IL6-targeted anti-cytokine treatment. CTL019 cells can induce potent and durable responses for patients with relapsed/refractory ALL CTL019 therapy has received Breakthrough Therapy designation from FDA in both pediatric and adult ALL, and phase II multicenter trials have been initiated.
A novel approach for overcoming drug resistance in cancer

Professor Fazlul H. Sarkar
Karmanos Cancer Center, School of Medicine, Wayne University, USA

Combined annual mortality from pancreatic cancer (PC) and colon cancer (CC) is estimated at 88,170 deaths surpassing the toll from breast and prostate cancer combined (72,280 deaths), and represents the second leading cause of death after lung cancer (157,300 deaths), with no cure in sight, in part due to both intrinsic (de novo) and extrinsic (acquired) resistance to conventional therapeutics.

This disappointing outcome is in part due to our inability to kill cancer cells that have undergone the Epithelial-to-Mesenchymal Transition (EMT) reminiscent of cancer stem/stem-like cells (CSCs) which are resistant to conventional therapeutics. The aggressiveness of PC, and recurrence of CC (affects nearly 50% of patients treated by conventional therapeutics), is in part due to the re-emergence of chemotherapy-resistant CSCs.

We tested our hypothesis in preclinical (in vitro and in vivo) studies using both PC and CC cells with our newly developed small molecule CDF, derived from a natural agent-curcumin. We also investigated whether specific microRNAs (miRNAs) may in part be responsible for the killing of drug resistant cells by CDF alone or in combination with conventional therapeutics.

We found that CDF could up-regulate the expression of miR-200 (low expression is the “hallmark” of CSCs and drug resistance) and reduced the expression of miR-21 (high expression is the “hallmark” of CSCs and drug resistance associated with tumour aggressiveness) in gemcitabine-resistant PC cells. Down regulation of miR-21 by CDF resulted in the induction of PTEN, an endogenous negative regulator of Akt signaling. We also found decrease of EZH2 and increased expression of a panel of tumour-suppressive miRNAs (let-7a, b, c, d, miR-26a, miR-101, miR-146a, and miR-200b, c that are typically lost in PC) by CDF. Mechanistic investigation showed that the re-expression of miR-101 by CDF led to decreased expression of EZH2 and the killing of CSCs. CDF in combination with 5-fluorouracil and oxaliplatin (5-FU + Ox) were able to kill the CSCs derived from CC cells.

Moreover, expression of miR-34a and miR-34c was down-regulated in CC specimens compared to normal colonic mucosa and the loss of expression was consistent with data from CC cell lines.

Our results suggest that deregulation of miRNAs and their targets by CDF is mechanistically associated with overcoming drug resistance in both PC and CC. Moreover, CDF could become a novel demethylating agent for restoring the expression of miR-34 family and potentially other miRNAs, and thus CDF could become a newer therapeutic agent for the treatment of both PC and CC, which could be largely due to the killing of CSCs, resulting in overcoming drug resistance and tumour recurrence.
Proliposomes: A novel anticancer generator for the treatment of brain tumour

Dr. Abdelhary Elhissi
College of Pharmacy, Qatar University, Doha, Qatar

Proliposomes have emerged as smart technologies to evade the instability manifestations exhibited by liposomes. Proliposomes are phospholipid formulations that generate liposomes upon addition of aqueous phase and shaking. Paclitaxel (PTX) is an anticancer drug with wide activity against many types of cancer such as ovarian carcinoma, prostate cancer, lung cancer, breast cancer, head and neck cancers and AIDS-related Kaposi’s sarcoma. Taxol® is a commercially available formulation of PTX consisting of the drug dissolved in ethanol and Cremophor EL® (polyoxyethylated castor oil) and ethanol (50:50 v/v). Unfortunately, the serious toxic effects caused by Cremophor EL® (nephrotoxicity, neurotoxicity, hypersensitivity, etc.) means that finding alternative vehicles is highly in need. In this study, we investigated proliposomes as potential vehicles for PTX. Ethanol-based proliposomes consisting of soya phosphatidylcholine (SPC), hydrogenated soya phosphatidylcholine (HSPC), or dipalmitoyl phosphatidylcholine with equi-mole ratio of cholesterol were prepared to act as vehicles for PTX added in a range of concentrations. Aqueous phase was added followed by probe-sonication. Liposomes were characterized in terms of size, zeta potential and morphology using dynamic light scattering, laser Doppler velocimetry and transmission electron microscopy (TEM) respectively. The entrapment efficiency of PTX was determined. Cytotoxicity study was conducted using U87-MG (grade 4 glioma) and SVG-P12 (normal glial) cell lines.

Small unilamellar liposomes were successfully generated from the proliposome formulations, which was confirmed by size analysis and TEM study. Zeta potential of the vesicles was neutral or slightly negative, and the surface charge tended to increase slightly by increasing the drug concentration. DPPC liposomes exhibited the highest drug entrapment (70-85%), followed by SPC liposomes (46-75%) and HSPC liposomes (26-67%). Cytotoxicity studies have shown cell viability to be dependent on formulation and cell type. PTX-DPPC liposomes had higher cytotoxicity against U87-MG cells compared to PTX-SPC and PTX-HSPC formulations. Moreover, the viability of the malignant cells was much lower than viability of normal glial cells, indicating that proliposomes have generated liposomes with desirable targeting properties. Ethanol-based proliposomes are appropriate vehicles of PTX and the resultant liposomes demonstrated promising anticancer properties against glioma cell lines.
Endocytic pathways of cells as doorways for therapeutic macromolecules targeting cancer

Professor Arwyn T. Jones
School of Pharmacy, Cardiff University, UK

The possibility of targeting a disease process inside a cell has attracted widespread interest in the drug delivery community. The attraction is further strengthened when one considers the number of individual intracellular targets that are available. This is particularly the case for cancer where most often aberrant network processes of signalling mediated by specific proteins interfere with cell function to promote cell division and inhibit apoptosis.

The concept of targeting cancer through a macromolecular therapeutic entity introduced the design and characterisation of a wide range of non-viral drug delivery vectors including those that are based on peptides, proteins, polymers and lipids. These are, most often, complexed with membrane impermeable therapeutics to deliver them, following administration, to disease sites such as tumours. The vector is then required to promote cell entry of the therapeutic and allow it to gain access to distinct intracellular locations such as the nucleus - intracellular targeting.

Endocytosis is a process encompassing several mechanisms by which reorganisation of, and budding from, the plasma membrane of cells allow for uptake of fluid and also plasma membrane components. Cell biology research has highlighted the complexity of endocytosis as almost all cell types utilise several different endocytic pathways that are each regulated by distinct proteins and lipids. For drug delivery research these pathways offer significant opportunities for internalisation of therapeutic macromolecules.

Our research is focused on studying endocytosis and specifically on designing methods to analyse individual endocytic pathways to characterise how therapeutic macromolecules enter cells. As vectors we have paid particular attention to cell penetrating peptides and have studied their capacity to not only interact with and enter cells but also how they and their cargo reach the cytosol.

In this lecture I describe work we have performed that focuses on design and characterization of methods to study endocytosis of drug delivery vectors such as cell penetrating peptides, with the goal to improve the delivery of biopharmaceuticals across major biological barriers of the intestine, lung, blood brain barrier, and skin.
Natural products as a vital source for the discovery of cancer chemotherapeutic and chemopreventive agents

Professor John Pezzuto
Daniel K. Inouye College of Pharmacy, University of Hawaii at Hilo, Hawaii

Early diagnosis and definitive tumour eradication through radiation therapy or surgical resection offer greatest hope. For metastatic disease, it is generally necessary to resort to chemotherapy; many of the most useful agents have resulted from the systematic investigation of nature. Notable examples include taxol, vinblastine, and camptothecin; isolation from natural sources is the only plausible method that could have led to their discovery. In addition to terrestrial plants as sources for starting materials, the marine environment (e.g., bathymodiolamides A and B, bryostatin, eceinascidin 743, kahalalide F, salinosporamide A), microbes (e.g., bleomycin, doxorubicin, staurosporin), and slime molds (e.g., epiptilone B) have yielded remarkable cancer chemotherapeutic agents.

Cancer chemoprevention, by use of synthetic or natural agents to inhibit, retard, or reverse carcinogenesis, is another important approach for easing the formidable public health burden. Several seminal clinical trials have demonstrated prevention of breast cancer with tamoxifen and raloxifene, and aromatase inhibitors. Finasteride has shown promise for prevention of prostate cancer.

Natural products play an important role in cancer chemoprevention. Through serendipity or epidemiological observations, dietary phytochemicals such as sulforaphane and phenethyl isothiocyanate (cruciferous vegetables), epigallocatechin-3-gallate (green tea), curcumin (turmeric), sulfur-containing compounds and selenium (the genus Allium), and lycopene (tomatoes) are considered positively for cancer prevention.

Using activity-guided fractionation with a battery of state-of-the-art in vitro assays, we have monitored the natural product purification process, to isolate the most active agents in their pure form. New biological targets have been developed, as well as sophisticated new techniques involving LS/MS/MS. Once purified, the structures of the molecules are determined using advanced NMR, mass spec and X-ray crystallographic methods. Our group has discovered active substances from a variety of structural classes such as alkaloids, flavonoids, coumarins, triperpenoids, and withanolides. Some of the compounds such as the rotenoid, deguelin have shown promise for clinical trials. We have also concentrated on the discovery of marine microorganism-based cancer chemopreventive agents. It logically follows that synthetic organic chemistry is an integral component the program, and some semi-synthetic compounds such as 4’-bromoflavone, oxomate (a relative of sulforaphane), and 3-amino-6-(3-aminopropyl)-5,6-dihydro-5,11-dioxo-11H-indeno[1,2-c]isoquinoline have shown promise.

One of our most notable discoveries, stilbene (resveratrol), a constituent of grapes originally reported by us to mediate cancer chemopreventive activity, has been entered into clinical trials for the prevention of colon cancer. We investigated the absorption and metabolism of resveratrol and, through crystallographic analysis, observed its interaction within the arachidonic acid binding site of cyclooxygenase. In addition, a series of resveratrol derivatives have been produced capable of demonstrating responses with much greater potency and specificity.

Given the unfathomable diversity of nature, it is reasonable to suggest that chemical leads can be generated that are capable of interacting with most or possibly all therapeutic targets. With the advent of high-throughput screening, a large number of potential starting materials can be readily evaluated, for unearthing prototype ligands worthy of further development as therapeutic agents. (edited from original)
Role of drug transporters in cancer chemotherapy

**Professor William F. Elmquist**  
*College of Pharmacy, University of Minnesota, Minneapolis, USA*

One of the major problems in successfully treating cancer is the development of resistance. Resistance to therapy can occur by many mechanisms, particularly through target mutation and changes in regulatory pathways. Another important resistance mechanism that has been extensively studied is “multidrug resistance” due to the active efflux transport of chemotherapeutics out of the cancer cell, thereby lowering the intracellular concentrations, leading to treatment failure. Many efflux transporters have been identified; especially those in the ATP-binding cassette superfamily (ABC transporters). These transport systems can influence specific intracellular concentrations of chemotherapeutics in tumour cells (such as the “cancer stem cell” phenotype) that overexpress these transporters; however efflux transport can particularly influence the systemic pharmacokinetics of certain anti-tumour agents. One important aspect of this is the distribution of chemotherapeutics into the central nervous system across the blood-brain or blood-CSF barriers. This talk will review the history of multidrug resistance mechanisms and the early attempts to use adjuvant therapies that inhibit the active efflux transport of cytotoxic agents, like doxorubicin. Also discussed will be how we can still make use of such adjuvant therapies in the current use of more molecularly-targeted agents, such as the kinase inhibitors, which are primarily cytostatic. The presentation will briefly touch upon the role influx transporters may play in delivery of very hydrophilic anti-cancer agents, such as the antifolate antimetabolites and the organic cation anti-tumour agents. Finally, the talk will discuss the redundancy and regulation of certain transport systems in critical tissue barriers, using the blood-brain barrier as a prototypical illustration.

Effect of pH on endocrine resistant breast cancer cells

**Dr Maitham Khajah**  
*Faculty of Pharmacy, Kuwait University, Kuwait*

Resistance to endocrine-based therapies in breast cancer occurs in parallel with cell transition from epithelial to mesenchymal phenotype (EMT), which is associated with enhanced proliferative and invasive potential, and presents a significant therapeutic challenge. The pH surrounding the tumour microenvironment is thought to be acidic, and play a role in enhancing cell invasion and metastasis, and it has been claimed that alkaline-based therapy can reduce tumour size and metastasis. In our laboratory, we have established several endocrine insensitive breast cancer cell lines by shRNA induced depletion of estrogen receptor (ER) by transfection of MCF-7 cells, which all exhibit EMT. In examining the behaviour of these cells under different pH conditions, we have observed that brief exposure of specifically ER-ve breast cancer cells to extracellular alkaline (but not acidic) pH results in cell rounding and segregation (termed contractolation), formation of bleb-like actin-rich structures on the outer membrane, and enhanced invasive potential. Our finding suggest that the effect of pH on the microenvironment of endocrine resistant breast cancer cells maybe be different when compared to other tumours, and caution against indiscriminate application of alkalinising drug therapy.
Endocrine resistance in breast cancer

Professor Yunus A Luqmani
Faculty of Pharmacy, Kuwait University, Kuwait

Although an essential hormone, estrogen becomes a woman’s worst enemy when she develops a breast malignancy, causing tumour growth and proliferation, through increased transcriptional activation effected through an overexpressed estrogen receptor (ER). Current therapeutic strategies are two-fold: i), reduction of circulating ovarian estrogen (in case of premenopausal women) by ovariectomy or chemical blockade of pituitary stimulation (with LHRH analogues such as goserelin), or of peripherally produced estrogen (in postmenopausal women) with aromatase inhibitors (such as anastrazole and letrozole) and ii), application of selective estrogen receptor modulators (SERMS), such as tamoxifen, raloxifene and fulvestrant for pharmacological receptor blockade.

The success of these interventions, which are significantly superior to the less-specific alternatives of general cytotoxic agents, is limited by the variable but persistent onset of acquired resistance, and also by intrinsic refractiveness which manifests despite adequately expressed levels of the target ER, in about 50% of patients with advanced metastatic disease. Loss of functional ER has been shown in cell lines to lead to endocrine insensitivity, loss of cellular adhesion and polarity, and increased migratory potential due to a transdifferentiation of the epithelial cancer cells into a more motile mesenchymal-like phenotype (EMT). Multiple mechanisms contributing to this therapeutic failure have been proposed, the most likely of which are i), loss or modification in ER expression including by epigenetic mechanisms ii), agonistic actions of SERMS that may be enhanced through increased expression of ER co-activators iii), attenuation of tamoxifen metabolism through expression of genetic variants of P450 cytochromes that leads to more or less active metabolites iv), increased activity of growth factor signaling pathways particularly of EGFR/erbB2 including MAPK, PI3K and mTOR v), interaction of protein kinase/c-junNH2 complex to increase transcriptional activity vi), activation of pathways involving KGF, PDGF/abl and NFƙB.

In addition to these mechanisms, the small non-coding microRNAs, that have been recently recognized as critical gene regulators, have been found to exhibit differential expression in tamoxifen sensitive vs resistant cell lines, and are now the subject of intense scrutiny. In consequence of the heterogeneity of mutated phenotypes as well as the multiplicity of factors controlling cellular proliferation, identification of a common underlying cause of endocrine resistance, if indeed such exists, is still proving elusive. The goal of re-sensitising tumour cells, with the aim of re-gaining efficacy of endocrine agents, may be re-orientated to reversing the aggressive metastatic phenotype by reversal of the EMT.

Changing paradigms in breast cancer therapeutics 2000-2015

Dr. Jo Anne Zujewski
Center for Global Health, National Cancer Institute, Maryland, USA

Breast cancer is the leading cause of cancer in women worldwide. In 2000, the United States NCI conducted an NCI consensus conference on the adjuvant treatment of breast cancer. At that time, it was recommended that most women diagnosed with early stage breast cancer should receive combination chemotherapy. Those who had tumours that were hormone receptor positive should also receive hormonal therapy. Since that time, it has been recognized that breast cancer can be characterized into at least 5 different molecular subtypes based upon the gene expression profile in the tumour (luminal A, Luminal B, HER-2 enriched, basaloid, and normal). Each subtype also exhibits marked heterogeneity. In addition molecular diagnostic tools have been developed to identify subgroups of patients
for whom chemotherapy is not likely to be of benefit. In addition, major breakthroughs have occurred in the development of therapeutics targeted against Her-2. Ongoing research is focused on understanding the mechanisms of drug response and drug resistance, as well as developing agents targeted towards these aberrant pathways. In 2015, the treatment of early stage breast cancer requires a tailored approach, considering the characteristics of the tumour, host factors, and patient preferences.

**The evolution of systemic therapy in metastatic colorectal cancer**

*Dr. Jasim Al-Barak*
*Kuwait Cancer Center, Kuwait*

The past decade has witnessed unprecedented advances in the treatment of metastatic colorectal cancer (mCRC). Although mCRC is a rarely curable entity and the treatment is mainly of palliative intent, systemic therapy can have a remarkable impact on patients’ quality of life and survival. The main classes of drugs with significant anti-tumour activity in mCRC include: Chemotherapeutic agents (Fluoropyrimidines, Irinotecan and Oxaliplatin), Antiangiogenesis therapy (Bevacizumab, Aflibercept, Regorafenib) and Anti-Epidermal Growth Factor Receptor (EGFR) therapy (Cetuximab and Panitumumab). Testing tumours for the RAS mutational status permits the selection of individuals with unmutated or “wild-type RAS” tumours who are expected to benefit from Anti-EGFR therapy. Identifying biologic and molecular markers predictive of response to conventional chemotherapy and antiangiogenic agents and the optimal way of combining and sequencing active systemic therapy agents remain to be an active area of research.

In our modern era, an approach that emphasizes an individualized treatment strategy and exposure to all applicable active drugs has resulted in a significant impact on clinical outcomes and over-all survival that exceeds two years has been observed.

**Pharmaceutical care of cancer patients: from the genomic medicine point of view**

*Professor Fahd Al-Mulla*
*Faculty of Medicine, Kuwait University, Kuwait*

Similar diseases behave differently and respond variably to treatment in different patients. Perhaps the most important milestone of recent time is the deciphering of the human genome and the realization of its complexity. The utilization of high throughput technologies, such as microarrays, proteomics and complex functional techniques has allowed us to explore reasons behind the variations seen in disease expressivity and treatment responses. Moreover these technologies and advances are allowing us to identify genetic and epigenetic causes of complex diseases in an impressive speed and ingenuity. We gained complex tools to match and decipher complex disorders, which enhanced our diagnostic and therapeutic efficacies tremendously. In my talk, I will introduce the term ‘Genomic Medicine’ and present evidence of it clinical utility and validity. I will also discuss how our collaboration with the Kuwait Medical Genetics Center and Kuwait Cancer Center supporting the use of Next generation sequencing (NGS) improved disease prediction, diagnosis and treatment. I will emphasize the importance of local and international collaboration in providing evidence-based reports. Caveat of NGS will also be highlighted.
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