New understanding of the mechanism of tamoxifen resistance

Researchers suggest that the findings from their study may be useful in the future to predict which patients are likely to respond to tamoxifen

Women who are diagnosed with breast cancer are prescribed tamoxifen for a period of 5 years in order to prevent the disease from returning. However, some patients develop resistance to the drug, meaning that there is a greater likelihood that the cancer will recur. Understanding how tamoxifen resistance occurs will help to combat this problem. It is already known that tamoxifen functions by acting on certain genes to block the production of estrogen, which aids tumor growth in common types of breast cancer; however, the exact mechanism-of-action of tamoxifen has not been completely elucidated, until now. Researchers from the Cambridge Research Institute (Cambridge, UK), have found that tamoxifen blocks a breast cancer gene called *ERBB2* via the paired box 2 gene product (Pax2). Lead investigator, Jason Carroll and his team examined 109 breast cancer tumors, all of which had been treated with tamoxifen. Upon analysis, 68 of the tumors were seen to be PAX2-positive, while 41 were PAX2-negative. Published in *Nature*, the study also revealed that women with PAX2-positive tumors had a 'significantly improved' chance of survival without cancer recurrence in comparison with those who had PAX2-negative tumors. The researchers concluded that PAX2 is a crucial player in controlling ErbB2 activity, as it acts as a switch to repress ErbB2 activity. In addition, resistance to tamoxifen occurs when ErbB2 remains switched on.

Carroll states that the switch for the *HER2* gene is hidden within the gene, and refers to PAX2 as "the handle that keeps *HER2* switched off." In the absence of PAX2, or if PAX2 is forced out by another protein called AIB1, then the switch fails. "It's a tug of war," Carroll explains. "It's a competition between PAX2 and AIB1. The balance between PAX2 and AIB1 determines whether HER2 is switched on or switched off, and this directly dictates whether tamoxifen works or not."

Discussing the implications of the findings, Carroll remarked: "we knew that women developed resistance to tamoxifen but previously our understanding of why this occurred could be compared with trying to fix a broken car without knowing how the engine worked. Now we understand how all the engine parts operate and we can try to think about ways to make repairs."

Carroll believes that the information provided from this study could be used to predict which patients are likely to respond to tamoxifen, and which patients are not likely to respond to the drug. "If we can identify the women who are not going to respond to tamoxifen we can think about alternative therapies, which are probably going to be more effective for these women."

Sir David Lane, chief scientist at Cancer Research, UK, which funded the study, explained the significance of the findings: "Tamoxifen has been a huge success story helping to prevent breast cancer recurring for many women. Understanding why it occasionally stops working is really important because it allows us to identify new targets for drug development and who will need such treatments."

Len Lichtenfeld, deputy chief medical officer of the American Cancer Society, believes that the finding will not have an immediate effect on treatment, but may help direct therapy in the future.

"We have learned a lot about makes a cancer cell a cancer cell, and how it works. We have also learned how to better treat breast cancer. Understanding these mechanisms will inevitably open up new treatment opportunities," Lichtenfeld commented.

Source: Hurtado A, Holmes KA, Geistlinger TR et al.*: Regulation of* ERBB2 *by oestrogen receptor-PAX2 determines response to tamoxifen.* Nature *456(7222), 663–666 (2008).*

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Rosuvastatin significantly reduces the risk of cardiovascular events in healthy individuals

Results from an international clinical trial, JUPITER, has shown that the drug Crestor® (rosuvastatin) significantly reduced the risk of cardiovascular disease among healthy people with normal low-density lipoprotein (LDL) cholesterol levels but an increased level of high-sensitivity C-reactive protein (hsCRP). Steven Nissen of the Cleveland Clinic said "this may be the most important trial we've seen in a decade."

The JUPITER trial investigated whether individuals identified as being at increased cardiovascular risk, due to elevated levels of hsCRP benefited from treatment with rosuvastatin. The randomized, double-blind, placebo-controlled trial was conducted at 1315 sites in 26 countries and recruited 17,802 participants. All study participants were healthy men and women with LDL cholesterol levels of less than 130 mg/dl and hsCRP levels of 2 mg/l or higher. Individuals were randomized to rosuvastatin, 20 mg daily or placebo. The results showed that those who took rosuvastatin had a 47% reduction in the combined risk of stroke, heart attack or cardiovascular death compared with those who took placebo. Furthermore, those who were administered rosuvastatin exhibited a 20% decrease in total mortality and a 50% decrease in LDL cholesterol compared with the placebo group. These results clearly show that administration of rosuvastatin significantly reduced the incidence of major cardiovascular events.

Lead investigator of the study, Paul Ridker, said that the observed benefits "are approximately twice as large as what doctors expect when you use statins in patients with [high cholesterol]." Jacques Genest, of McGill University Health Centre said "we hope that this study will prompt a review of current clinical practices, especially in terms of screening and prevention in adults. However, we still need to do more research to establish specific standards."

AstraZeneca, the manufacturer of the drug, now intends to file the JUPITER data with the US FDA for the prevention of cardiovascular events.

Sources: Ridker PM, Danielson E, Fonseca FA et al.*, on behalf of the JUPITER Study Group: Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein.* N. Engl. J. Med. *359, 2195–2207 (2008). www.astrazeneca.com/pressrelease/5412.aspx*

New evidence shows that antiseizure drug, propofol, could be fatal

Researchers from the Mayo clinic in Rochester (MN, USA) have found that treatment with the antiseizure drug, propofol, may significantly increase morbidity and mortality in patients. Propofol is used as an antiepileptic in patients suffering from refractory status epilepticus (RSE) and is also used as a sedative during surgery.

"Patients with RSE treated with propofol are at high risk for propofol-related side effects because of the high propofol infusion rates and prolonged treatment duration necessary in these patients," said Vivek Iyer, of the Mayo Clinic. "However, it is well described that propofol toxicity can occur even with brief exposure to the drug."

Dr Iyer and his research team wanted to investigate any complications or side effects associated with propofol use, such as propofol infusion syndrome (PRIS). PRIS is a usually fatal complication linked to propofol use and is commonly seen in patients that have been administered propofol at high infusion rates for long periods of time. In the analysis conducted by Dr Iyer and his colleagues, 39 RSE patients were divided into two groups. In group A, 32 of the patients (82%) were treated with propofol for a median of 63 h and a median peak infusion rate of 67 mcg/kg/min, whereas the other seven patients (18%) in group B were administered agents such as midazolam and pentobarbital. Upon analysis, it was found that 30% of patients in the propofol-treated group showed signs of PRIS (seven cases of bradycardia and three cases of sudden unexplained cardiac arrest); however, only one case of bradycardia was reported in group B. Furthermore, group A showed no obvious benefits with regards to seizure control.

The researchers concluded from these results that administration of propofol was linked to a significant increase in mortality and morbidity and, thus, should be used with caution when treating patients with RSE.

"There are several other medications we can turn to in the case of uncontrolled seizures," Iyer stated. "Alternative agents should first be tried for patients with RSE and propofol should only be used after exhausting all other options."

Sources: Iyer VN, Hoel R, Rabinstein AA: Propofol Infusion Syndrome in Patients With Refractory Status Epilepticus: A 10-Year Clinical Experience. Presented at: CHEST 2008, the 74th Annual International Scientific Assembly of the American College of Chest Physicians. *Philadelphia, PA, USA, 25–30 October, 2008 (Abstract AP2328); www.sciencedaily.com/releases/2008/10/081028074315.htm*

Results from the Timing of Intervention in Acute Coronary Syndrome trial offer insight into acute coronary syndrome treatment

Preliminary results from the largest intervention management trial performed to date, have suggested that patients with acute coronary syndromes (ACS), who are treated with early invasive strategies, gain very little advantage over those who underwent a delayed but more invasive strategy.

The Timing of Intervention in Acute Coronary Syndrome (TIMACS) trial identified one exception, this was the group of patients at high baseline risk of myocardial infarction (MI). These patients responded well to angiography within 24 h followed by percutaneous coronary intervention or coronary artery bypass graft, and a significant reduction in death and further recurrent MI and stroke at 6 months when compared with the delayed strategy was observed.

The trial enrolled 3031 patients, from 100 centers in 17 countries, with unstable angina or non-ST-segment elevation MI and set out to determine the optimal timing of percutaneous coronary intervention in ACS. Each patient was randomized to receive either an early invasive strategy involving cardiac catheterization as soon as possible and within 24 h, or a delayed invasive strategy, with catheterization taking place after 36 h.

The primary end points were death, new MI, or stroke at 6 months and occurred in 9.7% of patients who underwent early intervention and in 11.4% of those who underwent delayed intervention. Further end points were statistically significant, all reflecting a lower rate of refractory ischemia in the early invasive group.

> *"Among high-risk patients an early invasive strategy was associated with a significant reduction in the primary end point."*

The authors also identified a significant interaction between treatment strategy and baseline risk. Among high-risk patients an early invasive strategy was associated with a significant reduction in the primary end point. No such effect was evident for patients at low or intermediate baseline risk. Reassuringly, no significant difference in major bleeding or other safety indicators were observed in either strategy.

Sources: Mehta SR et al. Randomized comparison of early vs delayed invasive strategies in high risk patients with non-ST-segment elevation acute coronary syndromes: main results of the Timing of Intervention in Acute Coronary Syndromes (TIMACS) trial. American Heart Association 2008 Scientific Sessions; 10 November, 2008; New Orleans, LA, USA. Late Breaking Clinical Trials Session 2; http://clinicaltrials.gov/ct2/show/NCT00552513

About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in medicine.

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Acyclovir is seen to inhibit HIV replication, but may be risky

Acyclovir is a guanosine nucleoside analog that has been found to potently inhibit replication of the herpes simplex virus. Recent research undertaken at the Johns Hopkins University School of Medicine, Baltimore (MD, USA), has shown that acyclovir can also be used to combat HIV in patients coinfected with herpes and HIV. The study, conducted by Moira McMahon and her research team, used a sensitive infection assay of white blood cells. It was found that acyclovir directly targeted the reverse transcriptase enzyme of HIV, which is responsible for converting the virus' RNA into DNA aiding it's replication. However, 5 days following initial infection, a mutant version of HIV (V75I) emerged spreading to 90% of the viral population within 94 days. The V75I mutation is part of the multidrug resistance pathway and therefore elevates viral resistance to many of the commonly used reverse transcriptase inhibitors approved for the treatment of HIV.

The authors concluded that although acyclovir is able to significantly reduce HIV viral load, its selection of multidrug resistant mutants does mean that this drug could be quite risky if administered to patients coinfected with both herpes and HIV.

Source: McMahon MA, Siliciano JD, Lai J et al.*: The Antiherpetic Drug Acyclovir Inhibits HIV Replication and Selects the V75I Reverse Transcriptase Multidrug Resistance Mutation.* J. Biol. Chem. *283(46), 31289–31293 (2008).*

Drug approvals October/November 2008 (up until December 12th 2008).					
Trade name	**Generic name**	**Indication**	**Region**	**Manufacturer**	**Date approved**
Oncology					
Treanda®	Bendamustine	Indolent B-cell NHL that has progressed during or within 6 months of treatment with Rituxan (rituximab) or a rituximab-containing regimen	USA	Cephalon	November 2008
Erbitux®	Cetuximab	First-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck	EU	Merck Serono	November 2008
Neurology					
Seroquel®	Quetiapine	Treatment of major depressive episodes in bipolar disorder	EU	AstraZeneca	November 2008
Seroquel XR®	Quetiapine extended-release	Treatment of major depressive episodes and moderate-to-severe manic episodes in bipolar disorder	EU	AstraZeneca	November 2008
Banzel™	Rufinamide	Adjunctive therapy of seizures associated with Lennox–Gastaut syndrome	USA	Eisai Medical Research, Inc.	November 2008
Not yet determined	Tapentadol	Moderate-to-severe acute pain in adults	USA	Johnson & Johnson	November 2008
Kuvan®	Sapropterin	Hyperphenylalaninemia caused by phenylketonuria or tetrahydrobiopterin deficiency	EU	Merck Serono & BioMarin Pharmaceutical	December 2008
Nitoman® or Xenazine®	Tetrabenazine	Movement disorders associated with Huntington's disease	Spain	Cambridge Laboratories Ltd	December 2008
Cardiology					
Ranexa®	Ranolazine	Chronic angina	USA	CV Therapeutics	November 2008
Rasilez HCT®/Tekturna®	Aliskiren and hydrochlorothiazide	High blood pressure	Switzerland	Novartis	October 2008
Hematology					
Promacta®	Eltrombopag	Chronic idiopathic thrombocytopenic purpura in patients who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy	USA	GlaxoSmithKline & Ligand	November 2008
Infectious disease					
Selzentry™	Maraviroc	In treatment-experienced adults with CCR5-tropic HIV-1 in combination with other antiretrovirals	USA	Pfizer	November 2008
Zevtera™	Ceftobiprole	Complicated skin and soft tissue infections, including diabetic foot infections	Switzerland	Johnson & Johnson	November 2008
Pegasys®	Peginterferon α-2a	In combination with Copegus (ribavirin) in patients who were not successfully treated with an initial course of interferon-α either as monotherapy or in combination with ribavirin.	EU	Roche	December 2008
Prezista®	Darunavir	In combination with ritonavir and other antiretroviral medicinal products to the treatment of HIV-1 infection in all treatment-experienced adult patients	EU	Tibotec Pharmaceuticals Ltd	December 2008
Boostrix®	Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine, adsorbed (Tdap)	Tetanus, diphtheria and pertussis (Tdap) to include use in adults aged 19–64 years	USA	GlaxoSmithKline	December 2008

Drug approvals October/November 2008 (up until December 12th 2008).

Trade name	Generic name	Indication	Region	Manufacturer	Date approved
Infectious disease (cont.)					
PEGINTRON™ and REBETOL® combination therapy	Peginterferon alfa-2b and ribavirin, USP	For use in previously untreated patients 3 years of age and older with chronic hepatitis C	USA	Schering-Plough Corporation	December 2008
Urology					
Toviaz™	Fesoterodine	Overactive bladder symptoms	USA	Pfizer and UCB	November 2008
Other					
Premarin®	Conjugated estrogens	Moderate-to-severe postmenopausal dyspareunia (painful sexual intercourse)	USA	Wyeth Pharmaceuticals	November 2008
Synthetic conjugated estrogens 0.625 mg/g	Synthetic conjugated estrogens 0.625 mg/g	(1) Treatment of moderate-to-severe vaginal dryness, a symptom of vulvar and vaginal atrophy, due to menopause and (2) treatment of moderate-to-severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause	USA	Duramed Research, Inc.	November 2008
Norditropin®	Somatropin [rDNA origin] injection	For the treatment of short stature in children born small for gestational age with no catch-up growth by age 2–4 years	USA	Novo Nordisk Pharmaceuticals, Inc.	November 2008
Azarga®	Brinzolamide 10mg/ml + timolol 5 mg/ml ophthalmic suspension	Elevated intraocular pressure (IOP) associated with open-angle glaucoma or ocular hypertension in adult patients for whom monotherapy provides insufficient IOP reduction	EU	Alcon, Inc.	December 2008
Acanya™ gel	Clindamycin phosphate 1.2% and benzoyl peroxide 2.5%	Once-daily treatment of acne vulgaris in patients 12 years and older	USA	Arcutis Pharmaceuticals	December 2008