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Widening opportunities in restenosis

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Western society's fondness for chain-smoking, binge drinking and TV dining gives little consideration to the health of its average 21st century dweller. As well as spiralling obesity, diabetes and cancer rates, coronary artery disease remains a prolific killer with an estimated 110,000 deaths per year in England and Wales alone.

Damage to the arterial endothelium caused by elevated cholesterol and triglyceride levels, high blood pressure and cigarette smoke is generally accepted as a precursor to the chronic build-up of atherosclerotic plaque. This plaque mainly consists of calcium, cholesterol, fibrin and other cellular waste products, which eventually develop calcified micro-vessels, causing intra-plaque haemorrhaging and thrombus formation. The accumulation of this plaque is also responsible for narrowing and hardening the artery, decreasing the oxygenated blood supply, potentially causing gangrenous extremities, stroke and myocardial infarction in the unfortunate victim.

Traditionally balloon angioplasty has been the most successful method of unblocking affected arteries. A balloon-tipped catheter is inflated, pushing the atherosclerotic plaque back against the vessel wall. This widens or unblocks the compromised artery to restore myocardial blood flow. However, ~40% of all angioplasty patients experience relapse due to restenosis.

Maladaptive inflammation

Restenosis is the re-narrowing and scarring of the coronary artery after initial angioplasty treatment, identifiable by a lumen diameter diagnosis of <50% at follow-up. The most likely mechanism leading to restenosis is a maladaptive inflammatory response to arterial injury, encouraging tissue proliferation around a balloon angioplasty site. Minute rupturing of the endothelium lining of the artery during balloon catheter inflation is common, initiating an inflammatory cascade of platelets and white blood cells into the injured area. Smooth muscle cells from the wall of the artery migrate and divide in an attempt to repair the wound. These dividing and migrating cells go on to form an overgrown, obstructive scar that leaves the patient no option but to undergo a second surgical procedure.

The solution to this catch-22 situation was the advent of the stent, a tiny wire mesh or scaffold that is inserted after balloon angioplasty to support the weakened artery. Jacques Puel and Ulrich Sigwart were the pioneers of the stent revolution, inserting the first stent into a human coronary artery in 1986, in Toulouse, France. Bare metal stents were approved for use in the USA in 1994. They were so effective they soon became an integral part of modern cardiology. However in-stent restenosis, where the vessel narrows once more (often 'burying' the stent in the vessel wall), occurred in ~20% of patients undergoing these operations.

This provided the incentive to upgrade from the bare metal stent to a device incorporating newly-discovered antirestenosis compounds. These devices would effectively 'leak' an antirestenosis drug into the local area, decreasing the likelihood of in-stent restenosis. Johnson and Johnson and Boston Scientific led the charge with large research initiatives into anti-restenosis stents. The race was on to see who could break into the lucrative American market first. It was Johnson and Johnson that celebrated first with the launch of the Cypher® stent early in 2003, briefly cornering a market now said to be worth a cool US$3 billion.

The Cypher® stent elutes sirolimus (a triene cytostatic immunosuppressent antibiotic from Wyeth) that inhibits the mTOR kinase and blocks the amplification process for T-cells via interleukin 2 (IL2) and non-IL2 pathways. The Cypher® stent was so eagerly anticipated that some patients put off their angioplasty procedures until it became available, causing several unfortunate cardiac events. The launch and approval was conditional on a 2000 patient post-approval study and a three year follow up. However, within a few months of its launch an FDA warning concerning the possibility of an increased risk of subacute thrombosis was issued, dampening the flames of hysteria.

Pharmaprojects includes details of 27 active profiles primarily indicated for restenosis but only three (11%) of the products have been launched to date: an mTOR kinase inhibitor (Cypher®) and two β-tubulin antagonists (TAXUS® Express 2™ and TAXUS® Liberte™) (see Figure 1).

Competition

Boston Scientific launched the TAXUS® Express 2™ in Europe in 2003 and belatedly in the USA in 2004, in collaboration with

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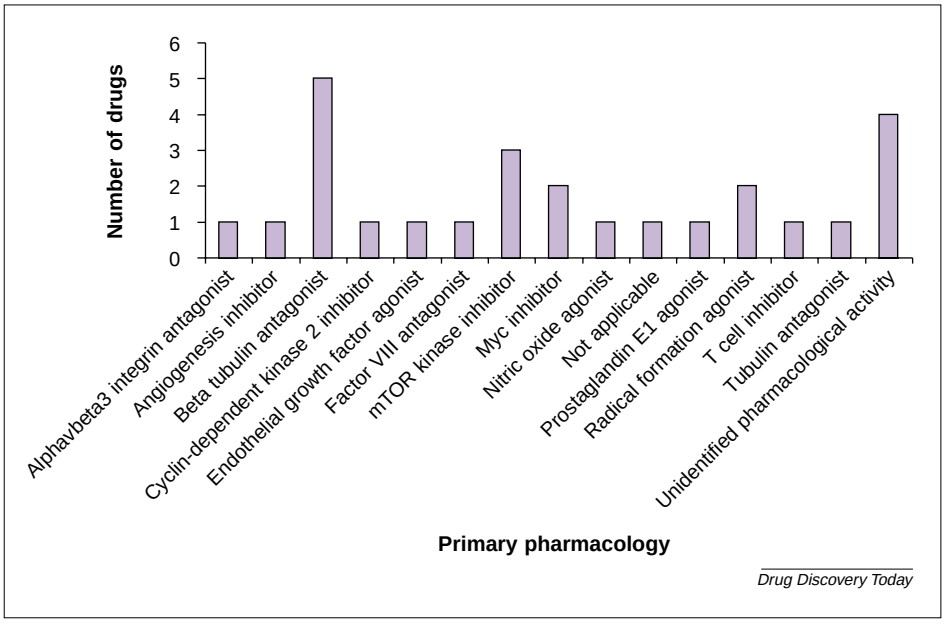

FIGURE 1

Pharmacological activities of active, launched antirestenosis products.

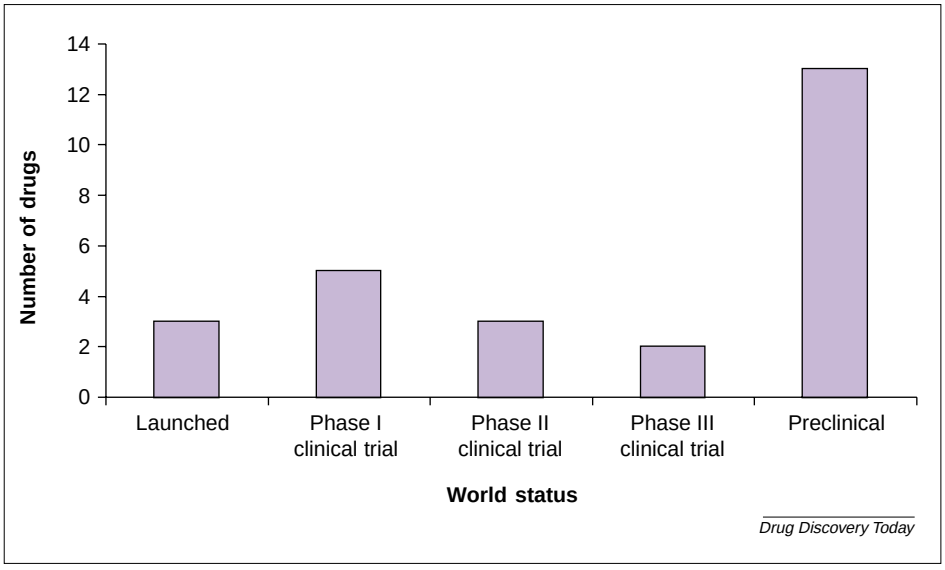

FIGURE 2

Developmental status of antirestenosis products.

Angiotech. It elutes paclitaxel, a β-tubulin antagonist that works by enhancing the assembly of microtubules that interrupt cell proliferation, migration and signal transduction. An additional Japanese launch is planned for 2006. TAXUS® Liberte™ is a second generation version of the TAXUS® Express 2™ stent and it boasts enhanced deliverability and conformality, particularly in challenging lesions. It is currently involved in a multicentre combination trial (ATLAS) in 871 patients at 60 sites across Australia, Canada, Hong Kong, New Zealand, Singapore, Taiwan and the USA. This trial will assess the safety and efficacy of the TAXUS® Liberte™ stent compared with its predecessor system, TAXUS® Express 2™. Preliminary results have shown that the TAXUS® Liberte™ stent has caused fewer major cardiac events and lower rates of both myocardial infarction and stent thromboses.

Rival firm Conor Medsystems are also developing a paclitaxel-eluting stent (COSTAR™) with a pivotal Phase III trial (COSTAR II) in 1700 patients on the horizon.

Following the meteoric success of the TAXUS® Express 2™ and TAXUS® Liberte™ paclitaxel-eluting stents, another Angiotech brainchild, Zilver® PTX™, was developed. This also elutes paclitaxel and has recently entered a pivotal worldwide Phase I trial to determine whether drug-eluting stents can be as effective in treating peripheral arterial disease as they have been at treating heart disease. Zilver® PTX™ is being co-developed with Cook, a firm specializing in medical devices. Also at the Phase I stage is Abbott's candidate ZoMaxx™, a stent eluting ABT-578 (a sirolimus analogue). ABT-578 is licensed to Medtronic under a co-exclusive agreement for use with its drug-eluting Driver™ and Endeavor™ stents.

Figure 2 indicates that 14 (~52%) of all the compounds currently being developed for restenosis are still in the preclinical phase. This is not surprizing considering restenosis is still a relatively new indication, owing to the fact that the first balloon angioplasty procedure was only performed in 1977, by a young German phyisian called Andreas Gruentzig.

Stents for the future

Preclinical candidates include a pimecrolimus drug-eluting stent, being co-developed by Avantec Vascular and Novartis, using Avantec's proprietary Duraflex technology. Clinical trials are expected in 2005.

Drug-eluting stents have been heralded as the dawn of a new era in interventional cardiology. That said, they don't have a complete monopoly over restenosis treatment. BS-1417 is the lead compound in a series of alphavbeta3 integrin antagonists being developed by Dainippon in Japan. It showed significant neointima-formation inhibition in a preclinical rat balloon injury model. Miravant Medical Technologies is using its PhotoPoint® technology, a photodynamic therapy technology that uses photoreactive compounds to destroy diseased cells selectively, thus creating a series of anti-restenosis compounds. MV-0633 and MV-2101 are radical formation agonists and MV-6401 is an angiogenesis inhibitor. All of them are currently in late stage preclinical development.

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However, just like the arteries being treated, the restenosis drug market has plenty of its own scar tissue. *Pharmaprojects* documents the discontinuation of 15 restenosis compounds and a further 45 that are under no active development. Two originally promising candidates, from the AVI Biopharma's NeuGene antisense programme, have become bogged down in the familiar Phase II clinical trial quagmire and are still seeking licensing partners. AVI-4126 and AVI-2221 are both antisense oligonucleotides that inhibit *c-myc* gene expression, with potential in arterial proliferation reduction.

Drug-eluting coronary stents will be increasingly used in the clinical setting despite their high initial outlay because the cost is likely to be compensated for by the reduced need of repeat revascularization. The costs of stents should decrease as more manufacturers enter the market. There are also experiments being conducted into biodegradable stents, especially from Asia, and this will ultimately cut costs. In 2004 >85% (39,000) percutaneous coronary interventions (PCI) performed in the UK involved the placement of a stent and, for the first time, PCIs outnumbered coronary artery bypass graft procedures. The stent has rapidly become popular as a treatment for restenosis, as patients are really taking it to heart.

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Trends in genomic variation: a view of some of the latest technologies

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Capturing information about human genetic variation is a major goal for scientists in several fields. Molecular biologists are constantly developing new ways to explore variation experimentally at the DNA level. Population geneticists are interested in looking at patterns of variation and how different organisms compare in levels of variation. For human genetics and pharmacogenetics, the interest lies in detecting the genetic variations that are associated with clinical outcomes, such as disease and/or drug treatment response.

These topics were discussed at Cambridge Healthtech Institute's Inaugural Conference on *Genomic Variation* on June 15–16 in San Francisco, CA. This event was held in conjunction with *Beyond Genome*, an annual conference held by the Cambridge Healthtech Institute in which several state-of-the-art topics in genome sciences are discussed. The conference on genomic variation will surely become a long standing event in years to come.

The 'one stop shop' for the cutting edge research in genomic variation could be experienced at the 'recent developments in human genomic variation' session. This half-day session covered many of the hot topics in basic science for studying genomic variation to set the stage for the clinical topics that followed for the remaining two days.

Molecular approaches for detecting genomic variation

In recent years, technology has advanced in molecular biology at alarming rates. In the past thirty years, we have seen the development of technology for restriction fragment length polymorphisms, polymerase chain reaction, microsatellite markers or short tandem repeats and variable number of tandem repeat markers, all developed to capture information about variation at the DNA level. However, in the past several years, molecular technology has been advancing even further with the development of genotyping platforms for single nucleotide polymorphisms (SNPs), including many high throughput SNP technologies. Two areas of very recent focus are gene copy number polymorphisms (CNP) and insertion–deletion (indel) polymorphisms.

Charles Lee of the Brigham and Women's Hospital at Harvard Medical School described novel approaches for detecting large-scale gene copy number variants (LCVs) using array-based comparative genomic hybridization. This approach can detect and quantify DNA copy number throughout the entire genome in one analysis, using large DNA clones. He described the arrays developed by Spectral Genomic, which are composed of 2600 large insert clones, spanning 1 Mb intervals. This technology can be used to detect even a single loss or gain in copy number of a particular sequence of DNA. Determining whether these LCVs are important for disease risk and/or drug response will be an enormous task and of great importance. LCVs have been

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