

Life Sciences News from Scotland's City of Discovery

September 2007

## University of Dundee and Modern Biosciences plc to develop novel cancer drug

The University of Dundee and Modern Biosciences plc have entered into an agreement to develop a new treatment for cancer.

Under the terms of the agreement, the University will grant an exclusive worldwide licence to Modern Biosciences for the development of rimcazole and Modern Biosciences will fund and manage the development programme. Revenues generated through commercialisation of the drug will be shared by Modern Biosciences and the University. Modern Biosciences expects rimcazole to be in clinical trials in patients within a year.



The development of rimcazole for the treatment of cancer has been made possible through the groundbreaking research of Dr Barbara Spruce and her team at the University of Dundee. Dr Spruce's work has focussed on the so-called "sigma-1 receptor", which has been the subject of considerable pharmaceutical research in the field of psychiatric and neurological disorders.

Dr Spruce and her team were the first to show that agents that bind to the sigma-1 receptor (such as rimcazole) cause tumour cells, but not normal cells, to undergo apoptosis. In recognition of her work, Dr Spruce received the inaugural Gannochy Trust Innovation Awards of the Royal Society of Edinburgh in 2003.

Rimcazole represents a highly attractive drug development candidate as it has already been the subject of a clinical trial programme in a different therapeutic area, schizophrenia. The re-profiling of rimcazole for cancer is lower risk than a normal development programme as there is already a considerable amount of pre-clinical and clinical safety data available. These data will allow Modern Biosciences to move into Phase I trials rapidly.

Rimcazole has several features that make it particularly promising for the treatment of cancer:

- It is a small molecule drug that can be taken orally;
- It works via a dual mechanism of action that makes it highly potent – stimulating apoptosis and preventing angiogenesis within tumours;
- It works against a broad range of cancer types, including those that are resistant to existing drugs;
- It has very little toxic effect towards normal, healthy tissues, which means it is likely to have a low side effect profile.

Modern Biosciences plans to initiate Phase I dosing studies in healthy volunteers this year. Phase Ib trials, which will monitor tumour growth and several biomarkers that are indicators of disease progression, are expected to start in 2008. Modern Biosciences believes that proof-of-concept data for rimcazole in cancer could be available within two years.

Modern Biosciences plc was established in 2005 as a specialist drug-in-licensing and development company. Modern Biosciences' business model provides a channel for exciting early-stage drug candidates to reach industry. Modern Biosciences sources drug candidates from partner organisations, funds and manages their development through to proof-of-concept and licenses the resulting programmes to industry for later stage development and marketing.

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## New collaboration to boost brain imaging research

A new collaboration between six of Scotland's Universities is to form the world's first clinical imaging laboratory to research conditions such as strokes, Alzheimer's, disease, schizophrenia and cancer.

SINAPSE (The Scottish Imaging Network: A Platform for Scientific Excellence) will bring together experts from the universities of Aberdeen, Dundee, Edinburgh, Glasgow, Stirling and St Andrews. The £40 million initiative which will focus primarily on imaging of the brain, using technology including magnetic resonance imaging (MRI) and positron emission tomography (PET).

Pooling these resources will allow the partnership to combine the collection of different types of brain information such as structure, function and brain waves, and develop new radioactive tracers for different diseases.

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## Axis-Shield launches Afinion™ ACR ratio test for diabetic monitoring

Axis-Shield (LSE:ASD, OSE:ASD), the international in-vitro diagnostics company recently launched the third marker on its award-winning new point-of-care system Afinion™. The new Albumin/Creatinine Ratio (ACR) test will complement the successful Afinion™ HbA1c assay used for front line monitoring of diabetic blood glucose control in primary healthcare. The new assay measures the ACR in urine and is a measure of renal function and cardiovascular complications that may occur in individuals with poorly controlled diabetes.



These assays provide physicians with two important tests to monitor the efficacy of glucose control in diabetes patients, significantly improving the speed and quality of patient care. It is generally agreed that HbA1c blood levels should be tested four times a year in people with Type 1 diabetes and twice yearly in those with Type 2 diabetes. ACR testing of urine avoids the need for a cumbersome and inconvenient 24 hour urine test and is recommended once a year for all people with diabetes.

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## Board Re-structuring at IDMoS plc

IDMoS plc (AIM:IDO), the specialist in disease detection and monitoring technology, has announced a number of changes to its Board.

Graham Lay was appointed Chief Operating Officer of the Group with immediate effect following the departure of former Chief Executive Stephen Westwood. Graham Lay has extensive experience in the medical devices arena, having spent 18 years with Johnson and Johnson, Inc, ultimately achieving the role of Vice President – Worldwide Research and Development. In this role he was responsible for new product innovation and development, including a significant number of product launches. John Pool has also moved from the role of non-Executive Chairman to the role of Interim executive Chairman.

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## Cyclacel advances clinical and preclinical programmes

Cyclacel Pharmaceuticals, Inc. (Nasdaq: CYCC) recently announced that the company has initiated a multicentre randomised Phase II clinical trial of sapacitabine (CYC682), an orally available nucleoside analogue, in patients with advanced cutaneous T-cell lymphoma (CTCL). Cyclacel plans to conduct several Phase II clinical trials to evaluate sapacitabine's potential in hematological and solid tumours.

The primary objective of the study is to evaluate the tolerability and response rate of high-dose and low-dose regimens in patients with CTCL who have had progressive, recurrent, or persistent disease on or following two systemic therapies. The study uses a selection design with the objective of choosing an optimal dose in the event that both doses are active. Secondary objectives are to assess response duration, time to response, time to progression and relief of pruritus or itching.

Sapacitabine appears to act through a dual mechanism that is unique among nucleoside analogs. It interferes with DNA synthesis by causing single-strand DNA breaks and induces arrest of the cell division cycle at G2 phase. Both sapacitabine and its major metabolite, CNDAC, have demonstrated potent anti-tumour activity in preclinical studies. In a liver metastatic mouse model, sapacitabine was shown to be superior to gemcitabine or 5-FU, two widely used nucleoside analogs, in delaying the onset and growth of liver metastasis.

The study follows four Phase I trials in which sapacitabine has been given as a single agent to approximately 150 patients: three in patients with incurable solid tumours and one in patients with advanced leukaemia's or myelodysplastic syndromes.

In addition, Cyclacel also announced preclinical results from a combination study of seliciclib, an orally-available cyclin dependent kinase (CDK) inhibitor, with epidermal growth factor receptor (EGFR) inhibitor erlotinib (Tarceva®). The study demonstrated that the drugs act synergistically in suppressing tumour growth in models of non-small cell lung cancer (NSCLC). Currently, seliciclib is being evaluated in a Phase IIb randomised double-blinded clinical trial as a single agent in NSCLC. Cyclacel also plans to commence in the second half of 2007 the clinical development of seliciclib as a treatment for patients with nasopharyngeal cancer.

In the first quarter of 2007, Cyclacel raised a further \$36 million through a registered direct financing. This funding will allow the company to pursue clinical trials with the three development-stage candidates, sapacitabine, seliciclib and CYC116, in multiple indications.

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## ITI Life Sciences expands Stem Cell Technologies programme

ITI Life Sciences has recently announced that the University of Dundee is to join the £9.5 million Stem Cell Technologies R&D programme.

The University will join the programme's other research providers, Swedish firm Cellartis AB and the University of Glasgow, in a collaborative effort to develop technologies that will enable automated processes to produce high volumes of high quality human stem cells.

The initial phase of the programme has focused on developing optimal conditions under which human embryonic stem (hES) cells can be screened for their ability to differentiate into specific cells. Having achieved this, the University of Dundee's complementary screening expertise will now be employed in programme to help develop additional technologies towards the programme's ultimate objectives.

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## The emerging epidemic of skin cancer

Skin cancer has two major forms: melanoma and non-melanoma skin cancer (NMSC), both inexorably increasing in incidence in susceptible populations throughout the world, especially in areas of high ambient ultraviolet radiation (UVR) such as Australia and the United States.

NMSC derives from epidermal keratinocytes following; direct DNA damage from UVB; indirect DNA damage by UVA induced guanine oxidation products and UV-induced immunosuppression. Keratinocytes have evolved many UV-defence mechanisms including DNA damage repair, UV induced apoptosis, antioxidant and adaptive responses. Heavily immunosuppressed organ transplant recipients (OTR) are at extremely high risk of developing NMSC and have a higher rate of metastasis and death from these often aggressive tumours. This highlights the critical role of immune surveillance in cancer defence. OTR also develop widespread, persistent viral warts with beta-Human Papilloma Virus genotypes in warts and tumours. In functional studies HPV oncoproteins can abrogate UV induced apoptosis via degradation of Bak.

Cancer susceptibility syndromes predisposing to NMSC such as xeroderma pigmentosa (nucleotide excision repair) and Gorlin's syndrome (Hedgehog signalling pathway), help to elucidate the pathomechanisms of NMSC. The hereditary disease Epidermolysis Bullosa (EB) results from defects in structural proteins of keratinocyte basement membrane or cytoskeleton. Type VII collagen deficiency (RDEB) causes severe skin fragility and scarring with a very high risk of developing SCC. The CR-UK Skin Tumour Laboratory and Debra Skin Cancer programme have both moved to the University of Dundee with the appointment of Professor Irene Leigh. In collaboration with the new Skin Cancer Centre and associated photobiology research in Ninewells Hospital, they will continue to research the molecular mechanisms of skin carcinogenesis in immuno-suppressed, immuno-competent and RDEB patients. This will include basic aspects of keratinocyte biology such as Arnt signalling (A.Panteleyev), AKT signalling and the role of Axl kinase. Research on barrier function will fit well with the work of Professor Irwin McLean on filaggrin, so a Centre for the Diagnosis and Treatment of genetic skin disease will be established in the new Clinical Research Centre.

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## Novel non-genotoxic activators of p53 (Patent pending)

Researchers at the Universities of St Andrews and Dundee have identified a series of compounds activating the p53 tumour suppressor. Data is available showing one of these compounds preferably kills tumour cells expressing normal p53 and reduces tumour growth in a xenograft model.

The p53 tumour protein is a central mediator of cellular stress response and plays a major role in preventing tumour development. Its importance as a tumour suppressor is reflected by its high rate of mutation in human cancer; >50% of adult human tumours bear inactivating mutations or deletions in the TP53 gene. Many current therapies give rise to DNA damage leading to the appearance of mutations in p53 that are associated significantly with poor outcome and drug resistance. Improving the treatment of those cancers in which p53 function is not abolished by mutation may depend on finding novel non-genotoxic activators of the p53 response.

Non-genotoxic activation of the p53 pathway may open the way to long-term cancer treatment including prophylactic treatments where toxicity and resistance are issues. Molecules which are consistent with this requirement may be useful as therapeutic agents for the management of patients with hyperproliferative conditions.

Ref: D293 The University of Dundee is now seeking a commercial partner to further this programme.

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## A novel composition with potent and specific bactericidal action against Staphylococcus aureus and MRSA

**Technology** - Methicillin-resistant Staphylococcus aureus (MRSA) strains cause serious hospital and community acquired infections. Our invention comprises the combination of a cationic peptide with known potency against Gram +ve bacteria, termed Ranalexin, with a bacterially-produced endopeptidase. The combination of these two molecules results in specific inhibition of Staphylococcus aureus MRSA or MSSA (methicillin-susceptible Staphylococcus aureus).

**Applications** - Surface cleaner to prevent spread of MRSA; topical treatment of skin infections or wounds; impregnated into wound dressings, plasters etc.; coating on invasive medical devices, such as catheters, endoprostheses, grafts (including vascular grafts), stents, sutures, replacement joints, pins and plates for fixing bones, stoma devices (including a PEG-device) etc.

The University of St. Andrews has applied for International (PCT) patent protection (No. PCT/GB2007/001157). and would welcome enquiries from commercial parties interested in entering into a licensing arrangement.

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