NEWS

## BILL & MELINDA GATES FOUNDATION ANNOUNCES ADDITIONAL US$50 MILLION PLEDGE TO THE GLOBAL FUND

The Bill & Melinda Gates Foundation announced at the XVth International AIDS Conference in Bangkok that it will contribute an additional US$50 million to the Global Fund to Fight AIDS, Tuberculosis and Malaria, bringing its total contribution to US$150 million.

The Global Fund is a unique global public-private partnership dedicated to attracting and disbursing additional resources to prevent and treat AIDS, tuberculosis and malaria. This partnership between governments, civil society, the private sector and affected communities represents a new approach to international health financing. The Fund works in close collaboration with other bilateral and multilateral organisations to supplement existing efforts dealing with the three diseases.

The announcement was made at an event in Bangkok where Nelson Mandela and UNAIDS director Peter Piot called for full funding for the Global Fund.

A Global Fund spokesman said, 'The Global Fund warmly welcomes this generous contribution as a reaffirmation of the Gates Foundation's continued close relationship with the Global Fund. The Gates Foundation has been one of our very earliest supporters since its June 2001 announcement of an initial commitment of US$100 million, for 2002 - 2003'.

'The fight against the world's most devastating diseases cannot be waged successfully without adequate resources,' said Richard Feachem, Executive Director of the Global Fund. 'We applaud the leadership by the Gates Foundation in making this contribution and signalling its continued support for the Global Fund – especially at this critical moment when increased funding is so important. This will help leverage further funds from additional donors.'

After four rounds of grant approvals since the Global Fund was established in 2002 the total 2-year commitments for funding now stand at $3 billion in 128 countries.

Over the full 5-year terms of all programmes approved to date, the Global Fund is investing over US$8 billion and will finance antiretroviral treatment for 1.6 million people, DOTS treatment for 3.5 million patients, 160 million ACT treatments, 108 million impregnated bed nets, and voluntary HIV/AIDS counselling and testing for 52 million people.

## STRONG RECOMMENDATIONS FROM GLOBAL AIDS FUND'S FIRST PARTNERSHIP FORUM

Two strong recommendations emerged from the Global Fund's first Partnership Forum early in July in Bangkok, attended by more than 400 participants ranging from donor governments to NGOs that have been excluded from Country Coordinating Mechanisms (CCM) membership. The Forum's purpose was to discuss the effectiveness of Global Fund policies and practices and to consider how they can improve.

The first recommendation was that the Global Fund board must launch the Fund's fifth round of grants by early 2005. The second was that several of the 'recommendations' that the board passed last month regarding CCM structure and methods must be strengthened to being 'requirements'. Richard Feachem said that round 5 will have to be launched within days of the board's next meeting in November.

The board's vice-chair, Helene Rossert, said that while civil society and the recipient governments want round 5 to be launched soon, some of the donor governments do not, as they are not yet convinced that the Global Fund should be the main financial vehicle to fight AIDS. 'But I and many others are convinced that it is,' she concluded.

Feachem, in his closing remarks to the Partnership Forum pointed out that, according to a new UNAIDS analysis, the financial cost of fighting the global AIDS pandemic will increase to roughly $12 billion by 2005, and could rise to $20 billion by 2007. Even if the Fund maintains its current pace, fund spending will plateau at around $3 billion a year, not enough, Feachem said, to fill the needs gap that remains after spending from other sources is taken into account.

The board will decide at its November meeting how to respond to the recommendations from the Partnership Forum.

## PERINATAL HIV RESEARCH UNIT CLARIFIES NEVIRAPINE RESISTANCE AND TRANSMISSION ISSUES

Nevirapine (NVP) is the mainstay of preventing mother-to-child transmission (MTCT) in resource-poor settings such as South Africa. One dose of NVP given to the mother once during labour and once to the baby within 72 hours of birth decreases the risk of MTCT by approximately 50%.

Recent studies have demonstrated that the addition of single-dose NVP (for mother and baby) to a zidovudine (ZDV)

regimen starting from 28 weeks of pregnancy dramatically reduces the transmission rate to less than 4%, previously seen only with complex and costly interventions.

Researchers have been concerned that single-dose NVP can induce resistance in HIV-infected mothers and infants. Up to 50% of women have detectable HIV resistance strains within 6 weeks of taking NVP alone or in combination with ZDV. Viral resistance to NVP is mostly found in women with high viral loads and low CD4 counts. This resistance has been shown to decrease over time.

At the Perinatal HIV Research Unit (PHRU), Chris Hani Baragwanath Hospital, South African collaborators and Boehringer-Ingelheim have determined how to minimise this resistance in mothers who have taken single-dose NVP for prevention of MTCT. Resistance is minimised by starting ZDV and 3TC with the NVP dose and by continuing ZDV/3TC for 4 or 7 days after taking NVP. The preliminary results suggest that these short-course regimens could be a feasible and inexpensive way to protect against resistance and prevent MTCT.

## PHASE 1 CLINICAL DATA ON FIRST-IN-CLASS HIV-1 MATURATION INHIBITOR, PA-457

At the XVth International AIDS Conference in Bangkok, Thailand, Panacos Pharmaceuticals, Inc. provided results of a recently completed phase 1 clinical trial of its lead HIV drug candidate, PA-457. PA-457 is the first in a new class of antiretrovirals called maturation inhibitors directed against a novel viral target recently discovered by Panacos scientists.

Because PA-457 has a different target from approved HIV drugs, it retains activity against virus isolates resistant to currently available treatments including reverse transcriptase inhibitors and protease inhibitors. The increasing prevalence of these drug-resistant HIV strains is a major problem for the treatment of HIV infection, driving the demand for the development of novel drugs like PA-457.

In a presentation titled 'The *in vitro* and *in vivo* disposition of PA-457, a novel inhibitor of HIV-1 maturation', Panacos' David E Martin describes the phase 1 results. The safety and pharmacokinetics of PA-457 were examined in uninfected, healthy male volunteers following a single oral dose of 25 mg, 50 mg, 100 mg or 250 mg in a dose escalation protocol. At each dose level, 6 subjects received PA-457 and 2 additional individuals received placebo. PA-457 was well tolerated at all doses, with good oral bioavailability and favourable pharmacokinetics. All doses produced mean circulating plasma levels which exceeded the target therapeutic concentration, and at doses of 50 mg or greater PA-457 levels continued to exceed the target concentration 24 hours after administration. These results suggest that PA-457 will be suitable for once daily oral dosing.

In a related presentation, Dr Carl Wild, Panacos' Chief Science Officer, described a recent study that elucidates PA-457's viral target. The drug candidate specifically blocks a late step in processing of the HIV Gag protein, namely conversion of the capsid precursor to mature capsid protein. Following PA-457 treatment, virus particles released from HIV-infected cells are non-infectious and virus replication is terminated.

## STATEMENT ON STEM CELL RESEARCH ISSUED BY THE JOHNS HOPKINS UNIVERSITY

One of the greatest discoveries in medicine is the potential to use a single undifferentiated cell to help address the severe pain and suffering that numerous diseases, such as heart disease, diabetes, and cancer, inflict every day.

However, the Johns Hopkins University recognises that stem cell research raises significant ethical concerns and that public policy on stem cell research must carefully balance the ethical and medical considerations, yet enable researchers to fulfil the promise of stem cell research for providing medical therapies.

Johns Hopkins strongly supports the use of stem cells for legitimate research and therapeutic purposes. Stem cell research promises to have an enormous impact on human health and quality of life, and also on fundamental biomedical understanding. Stem cells can be obtained from embryonic, fetal, and adult tissues. It is essential that all these sources be investigated to determine which is most likely to fulfil the goals of basic research and lead to the development of new medical therapies.

Johns Hopkins supports the use of the somatic cell nuclear transfer technique (popularly known as 'therapeutic cloning' or 'research cloning') for the purpose of producing stem cell lines that are genetically identical to the person from whom the nucleus was obtained. These stem cell lines are critical to help researchers better understand the pathogenesis of disease and provide information useful in developing therapies for people with a wide variety of diseases and injuries. In addition, stem cell lines produced using somatic cell nuclear transfer could overcome the rejection of tissues following transplantation.

However, Johns Hopkins strongly opposes the use of stem cell technology and somatic cell nuclear transfer for the purposes of creating a cloned human being (popularly known as 'reproductive cloning').

Stem cell research at Johns Hopkins is conducted under strict scientific and ethical guidelines that meet all federally mandated requirements. Johns Hopkins has long been a leader

in the development of new therapies for patients, and stem cells represent a unique and promising approach in the development of new, critically needed treatments. Research at Johns Hopkins on stem cells is supported by the National Institutes of Health, patient-based organisations, partnerships with corporations, and private philanthropy.

*Source:* ***http://www.hopkinsmedicine.org/***

## STUDY: DEMENTIA OFTEN UNDIAGNOSED IN CLINICAL SETTINGS

Many older patients with signs of dementia are not being diagnosed for the progressive brain disorder by their primary care physicians, an Oregon Health & Science University study has found.

The study, published in the current issue of the *Journal of Gerontology: Medical Sciences*, confirms previous research that found dementia often goes undiagnosed in primary care. It points to the need for heightened awareness among primary care physicians of the cognitive functioning of older patients, especially those experiencing adverse events that may be warning signs of dementia. While the study was conducted in the Portland metropolitan area, its results mirror those of previous studies showing the problem is internationally pervasive.

Researchers examined 553 patients of 34 primary care physicians affiliated with three Portland-area managed health care plans. Study subjects aged 75 and older were identified through primary care physicians to be contacted, and the study team assessed their cognitive functioning in their homes. Subjects were divided into three cognitive status groups: normal, mildly impaired and moderately-to-severely impaired. More than 43% were identified as cognitively impaired, including 29.7% classified as mildly impaired and 13.7% as moderately-to-severely impaired.

Researchers studied the medical charts of cognitively impaired individuals for evidence that they were examined, diagnosed or treated for dementia, such as notes about symptoms, exams, discussions with family members, community resource referrals or dementia medication prescriptions.

Charts were analysed for comments about adverse events in the last 3 years, such as medication use errors, problems complying with recommended treatments, increased emergency room visits, falls, family contacts with the doctor about a patient's condition, missed appointments or frequent phone calls by the patient to the doctor. These can, of course, be caused by conditions or factors other than dementia, so unless the doctor carries out a full inquiry into the reasons for these adverse events, he or she may not think to evaluate for possible dementia.

The study found that only 18% of mildly impaired patients and 34.8% of moderately-to-severely impaired patients were clinically evaluated for dementia, and that none of the mildly impaired patients and just 4.3% of the more severely impaired patients were offered dementia medication. Moreover, 61.6% of the mildly impaired patients and 75.4% of the more impaired individuals experienced one or more adverse events. Of those, only 23.7% of the mildly impaired group and 44.2% of the moderately-to-severely impaired group were evaluated for dementia.

According to the study, lagging dementia assessment in primary care could be due to the subtlety of dementia symptoms combined with the constraints of the clinical practice, such as the limited time available for evaluating patients. Other explanations are that physicians considered, but then discounted, that the adverse events should trigger a dementia assessment, or that they didn't find a full clinical evaluation for dementia useful because they believe they could manage the dementia without assessing or identifying the cause.

Early assessment could at least help families prepare emotionally for the tension and confusion that comes in a relationship with a loved one with dementia.

## AGE AT LAST BIRTH HAS SIGNIFICANT IMPACT ON OVARIAN CANCER RISK

The older a woman is when she has her last baby, the lower her chances of developing ovarian cancer.

Compared with women who have never had a child, women who had their last children after the age of 35 had a 51% reduction in risk for ovarian cancer. Women who had 4 or more children had a 64% lower risk than women who had never given birth. Other factors that reduced risk were additional, earlier births and use of oral contraceptives. Earlier ages at natural or surgical menopause were also associated with decreased risk.

Researchers at the University of Southern California interviewed 477 ovarian cancer patients and 660 controls matched for race, ethnicity, age, and neighbourhood. Patients were residents of Los Angeles County between the ages of 18 and 74 who had been diagnosed with ovarian cancer between October 1992 and October 1998.

They identified other factors that increased women's odds of developing ovarian cancer, such as family history and use of genital talc. High body mass index (BMI) was significantly associated with an increased risk of localised ovarian cancer. However, its association with regional or distant disease was not significant.

'The next challenge is to map out the mechanism of the last birth's effect on the ovaries. It would be a major advance in

cancer prevention if, as the authors suggest, these findings lead to the development of a chemoprevention approach for women at high risk for ovarian cancer,' remarked Robert Schenken, MD, President-Elect of ASRM.

(Pike MC, *et al*. Hormonal factors and the risk of invasive ovarian cancer: a population-based case-control study. *Fertility and Sterility* 2004; **82:** 186 - 195.)

*Source:* ***http://www.asrm.org/***

## FDA APPROVES VYTORIN (EZETIMIBE/SIMVASTATIN) – CHOLESTEROL REDUCTION THROUGH DUAL INHIBITION OF THE TWO SOURCES OF CHOLESTEROL IN ONE TABLET

The US Food and Drug Administration has approved Vytorin (ezetimibe/simvastatin; Merck/Schering-Plough Pharmaceuticals) for the treatment of high LDL cholesterol (LDL-C) in patients with primary hypercholesterolaemia or mixed hyperlipidaemia as adjunctive therapy to diet when diet alone is not enough. Vytorin lowered LDL-C by 52% at the recommended starting dose (10/20 mg) and by 60% at the maximum dose (10/80 mg).

Vytorin is the first and only product approved to treat the two sources of cholesterol by inhibiting the production of cholesterol in the liver and blocking the absorption of cholesterol in the intestine, including cholesterol from food. The active ingredients in Vytorin are ezetimibe and simvastatin. The recommended starting dose of Vytorin is 10/20 mg (10 mg ezetimibe/20 mg simvastatin).

'Many patients who continue to have high cholesterol despite diet and other lifestyle modifications may require powerful LDL cholesterol lowering-agents and to do this we frequently look to highly efficacious medicines to provide the reduction they need,' said Christie Ballantyne, director of the Center for Cardiovascular Disease Prevention, Methodist DeBakey Heart Center, Houston, Texas.

In a 12-week multicentre double-blind placebo-controlled clinical study Vytorin lowered LDL-C by 52% at the recommended starting dose (10/20 mg), 55% at the 10/40 mg dose and 60% at the maximum dose (10/80 mg). Vytorin is administered as a once-daily tablet and should be taken in the evening with or without food.

Cholesterol in the blood is derived from two sources – production by the body and absorption from the small intestine. Statins work in the liver to reduce cholesterol production and increase clearance of cholesterol from the bloodstream. Vytorin inhibits absorption of cholesterol in the small intestine, while also reducing cholesterol synthesis in the liver, leading to clearance of cholesterol from the bloodstream.

### Indications and contraindications for Vytorin

Vytorin is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol, LDL-C, Apo B, triglycerides and non-HDL cholesterol and to increase HDL cholesterol in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia. Vytorin is also indicated for the reduction of elevated total cholesterol and LDL-C in patients with homozygous familial hypercholesterolaemia, as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.

Vytorin is a prescription medicine and should not be taken by people who are hypersensitive to any of its components. Vytorin should not be taken by anyone with active liver disease or unexplained persistent elevations of serum transaminases. Women who are of childbearing age (unless highly unlikely to conceive), who are nursing or who are pregnant should not take Vytorin.

### Selected cautionary information for Vytorin

Muscle pain, tenderness or weakness in people taking Vytorin should be reported to a doctor promptly because these could be signs of a serious side-effect.

Vytorin should be discontinued if myopathy is diagnosed or suspected. People taking Vytorin 10/80 mg should receive a liver function test prior to and 3 months after titration and periodically during the first year. Due to the unknown effects of increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, Vytorin is not recommended in these patients. The safety and effectiveness of Vytorin with fibrates have not been established; therefore, co-administration with fibrates is not recommended. Caution should be exercised when initiating Vytorin in patients treated with cyclosporine and in patients with severe renal insufficiency.

*Source:* ***http://www.sch-plough.com***

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