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Atherosclerosis groups bid for fresh funds

Leading atherosclerosis research laboratories in the US are gearing up to compete for the biggest single grants available in the field. The Donald W. Reynolds Foundation is offering $24 million over four years to each of two new Cardiovascular Clinical Research Centers. The funding represents around 11% of the annual atherosclerosis budget of the National Heart, Lung and Blood Institute, which was $211 million in 2001. Winners will be announced in May 2003.

The new centers will join two existing cardiovascular groups that have received recent support from the Reynolds Foundation. A team including, Helen Hobbs, Ron Victor, Scott Grundy and Eric Olson at the University of Texas Southwestern Medical Center was funded in 1999, and Mark Hlatky, Tom Quetermous, Steve Fortmann and Rick Myers at Stanford University received backing in 2000.

Several atherosclerosis research groups are already known to be planning to bid for the new money. R. Sanders Williams led the successful UT Southwestern application, and has since transferred to become the new Dean of Duke University Medical School where he will direct an application by Pascal Goldschmidt and Rob Califf. Duke's program correlates statistical analyses of multiple changes in gene expression with the intensity of atherosclerotic lesions in aortas of human heart donors. "Presumably, these genes represent components of interacting pathways and it is the sum total of expression of these genes that results in cardiovascular disease," says Goldschmidt. Once patterns of gene expression that distinguish atherosclerosis are understood, these data can be combined with "classic genetic studies on [siblings] and proteomic and metabolic approaches, such that the gene make-up of atherosclerosis can be unveiled."

A group from Harvard University and Brigham and Women's Hospital will also seek funding, according to Peter Libby, Chief of Cardiovascular Medicine at Harvard Medical School. Libby's group studies the control of smooth-muscle cell proliferation, and the immune and inflammatory functions of cells in blood-vessel walls. Reynolds funding aims to give researchers freedom to go beyond traditional protocols. "The type of work undertaken by the Reynolds Centers affords a major opportunity for speeding translation of bench research insights into clinical practice, and ultimately public benefit. Traditional peer-review mechanisms for allocation of research funds do not always favor funding of high-risk or exploratory initiatives," says Libby.

Also sure to apply for Reynolds funding is a research group at the University of Pennsylvania, which includes Garret Fitzgerald and which studies quantitative biomarkers of oxidative damage to DNA, proteins and lipids, and the effects of oxidative and antioxidative conditions on proteins in mouse models and human tissue. Other possible, but unconfirmed, contenders include the research group led by Steven Schwartz at the University of Washington in Seattle, which studies the clonal nature of atherosclerotic plaques and the properties of the arterial intima that contribute to atherosclerosis; MacRae Linton's team at Vanderbilt University, which uses genetically altered macrophages delivered by bone-marrow transplantation as vehicles for cellular gene-therapy of atherosclerotic lesions in mice; and Alan Tall's department at Columbia University, which studies cellular cholesterol efflux and its regulation by the LXR transcription factors.

A strong bid is expected from Jan Breslow's group at Rockefeller University, which studies the role of the *apoE* gene family in atherosclerosis mouse models, as well as lipoprotein metabolism in humans. Recent work with *apoE* -deficient mice has revealed numerous genes that may contribute to the disease. For example, mice lacking the *Acat2* gene, which codes for a cholesterol esterification enzyme, show resistance to diet-induced hypercholesterolemia through a reduced capacity to absorb cholesterol (*Nature Med.* **6**, 1341; 2000). The putative role of ACAT2 in hypercholesterolemia makes it an appealing therapeutic target. CCR2, a receptor for the chemokine MCP-1, is thought to have a role in early atherosclerotic lesion formation (*Nature* **394**, 894; 1998). And the adipocyte fatty-acid-binding protein gene, *aP2*, appears to protect against atherosclerosis by reducing the ability of macrophages to accumulate cholesterol esters, thereby reducing the accumulation of foamy cells associated with atherosclerotic plaques (*Nature Med.* **7**, 699; 2001).

Caitlin Smith, Oregon

Resurrecting the resurrection drug

Over the past decade, the pharmaceutical industry has been steadily increasing its investment in lifestyle drugs (see next page). Although this effort is geared more toward capturing revenue from the developed countries of the West, there can occasionally be a positive outcome for developing nations. Eflornithine is one such example and its development also illustrates just how far public-private partnerships have come.

AP Photo/Javier Bauluz

Incidence of sleeping sickness has risen sharply

Eflornithine is used to treat advanced human African trypanosomiasis (HAT), or sleeping sickness, the incidence of which has increased nearly a 100-fold in the last 40 years, returning to levels similar to those in the 1950s. But the compound originated from a depilatory product marketed to women in North America by Bristol Myers Squibb (BMS). So how did a cosmetic product recently become a life-saving drug for a parasitic disease?

Originally developed in the 1970s as an anti-cancer molecule called difluoro-methyl-ornithine (DFMO), the

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agent failed in trials, but had the same hair loss side effect associated with other chemotherapy drugs. During this period, Cyrus Bacchi, from Pace University, New York, noticed that DFMO showed marked anti-trypanosome activity in animals, and in 1983, Belgian physician Henri Taelman used the renamed eflornithine to treat a comatose woman in Antwerp. She began to revive within a day, earning eflornithine the soubriquet "the resurrection drug."

However, set against the backdrop of war, economic deterioration and collapse of rural health infrastructure in countries such as Angola, Congo and Sudan, the potential of eflornithine to mitigate HAT suffering languished. This, combined with eflornithine's difficult administration procedure—it requires two-week hospitalization and continuous IV infusions, requirements difficult to satisfy in HAT-endemic regions—means that the compound had no real revenue value for pharmaceutical companies. In 1995, Aventis halted its production, along with that of two other drugs for HAT. Simultaneously, Bayer AG threatened to stop making a fourth anti-HAT drug, suramin, leaving a growing number of patients in Africa bereft of treatment for their disease after the three-year stock ran out.

Anticipating the calamity, health agencies such as the World Health Organization (WHO) and the Centers for Disease Control and Prevention, and non-governmental organizations

Médecins Sans Frontières (MSF) and Epicentre, began looking for a way to persuade pharmaceutical companies not only to resume production, but to provide the drugs free or below cost. Jean Jannin of WHO's Department of Communicable Disease Surveillance and Response in Geneva, was instrumental in the lobbying effort. "We established a special network to try to find a solution. The first step was to have Aventis give WHO a license and transfer the technology to produce the drug."

But there were two problems: WHO and MSF are not drug manufacturers, and because eflornithine is difficult and expensive to make, alternate producers were not easy to find. Second, availability of drug in itself was not enough. Equally important were surveillance and screening, training of health workers and rehabilitation of clinics.

It was with the appearance of Vaniqa that a solution began to take shape. As Aventis was threatening to drop its panel of HAT drugs, BMS was examining new uses for failed drug candidates and found that DFMO in a cream preparation enabled hirsute women to eradicate facial hair. Topical application eased the problems of administration in a resource-poor setting and existing production facilities could be used as the source. Jannin's group persuaded BMS to donate the drug for five years, and additional lobbying triggered Aventis and Bayer to continue producing the other HAT drugs, and donate US $5 million a year for five years for monitoring, treatment and research and development.

The result is current widespread access to a much-needed drug. 55 million people are exposed to HAT in 36 countries, with only 4 million of those under surveillance. There are half a million new cases a year, with perhaps 60,000 deaths, according to estimates by the World Health Organization (WHO). By contrast, the rate of disease in 1960 was 1 or 2 per 10,000.

Potter Wickware, San Francisco

Lifestyle drug market booming

Lifestyle drugs—medicines that treat conditions associated with lifestyle such as weight-loss tablets, anti-smoking agents, impotence therapies and hair restorers—are now a major research and development area for the pharmaceutical industry. In fact, companies have invested over $20 billion in research into such drugs since the 1990s. The reason why is clear: the market lifestyle for drugs is forecast to rise to over $29 billion by 2007 from its current $20 billion.

The market is driven predominantly by Western countries, where an image-conscious, aging society is prepared to pay high prices for compounds that promise to slow the aging process, improve mental agility, reduce weight gain and rejuvenate sexual function.

AP Photo/Barbara Mather

Perhaps the first lifestyle drugs were Viagra for erectile dysfunction (ED) and the anti-depressant, Prozac, whereas newer products include the anti-wrinkle agent, Botox. Although the sector is far from saturated, competition is already tight. For example, in the area of ED, new products include Abbot's Uprima (apomorphine), which was launched in Europe in May 2001, and Lilly ICOS's Cialis (tadalafil), which is expected to receive marketing authorization in the EU later this year. Both are considered to offer advantages over current therapies such as faster onset of action and duration of efficacy and will undoubtedly cannibalize Viagra's share of the ED market—worth an estimated $2 billion in 2001.

Weight-loss drugs also represent a potentially large and profitable market as only two prescription medicines are currently available (Xenical and Reductil/Meridia). Novel products such as Regeneron's Axokine and Phytopharm's P57 are expected to show great promise as new and efficacious anti-fat drugs. Pharmaceutical companies will doubtless be showing keen interest in newly discovered properties of the leukemia drug, Geevec. Apparently the compound restores color to gray hair (*NEJM* **347**, 446; 2002).

In other areas of lifestyle drugs, smoking cessation drugs include GlaxoSmithKline's GW468816 (glycine receptor), which is currently in phase 1 trials, and Roche's Tempium (lazabemide) in phase 3 trials. GlaxoSmithKline's Zyban (bupropion) is currently the only available drug to assist in smoking cessation and had sales of $174m in 2000. For full details see www.reutersbusinessinsight.com.

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