Reply to 'One for the money'

To the editor:

Your June news feature, 'One for the money' by Apoorva Mandavilli, and accompanying editorial question the US National Institutes of Health (NIH) Center for HIV/AIDS Vaccine Immunology (CHAVI) on two grounds: first, its cost, which may be on the order of $300 million over seven years; and second, its reliance on competitive bidding for leadership of the initiative, which has temporarily self-sorted the AIDS vaccine research field into at least four competing multidisciplinary teams—contrasting this to using these public research funds for a large number of RO1-type peer-reviewed investigator-initiated research grants.

The US government, through the NIH and National Institute of Allergy and Infectious Disease, has consistently funded the vast bulk of AIDS vaccine research, an amount that has increased from about $100 million per year when the AIDS Vaccine Advocacy Coalition (AVAC) was founded in 1995 to $530 million today, still only 20% of its AIDS research portfolio. This increase is justified by the enormous value a preventive HIV vaccine would have toward controlling an out-of-hand global catastrophe and because of a consensus that such a vaccine is feasible. In the process, they and others have spent at least a few billion dollars funding every reasonable idea and approach, bringing us to our current situation of testing vectored vaccines for cellular immunogenicity and efficacy. Should these fail or, more predictably, prove less than perfect in the next few years, it is hard to know where we would look next for better approaches. Hence CHAVI, a group effort to reduce that nagging uncertainty.

No one should be willing to give up on the prospect of an AIDS vaccine. And no one would underestimate the value of investigator-initiated research. But the NIH should not be criticized for trying something bigger, and new. The funding for CHAVI, $300 million over seven years, works out to be about 8% of this year's AIDS vaccine expenditures, which can be expected to increase in the coming years. Any government program has to be competitively bid, and already the competition to run CHAVI has generated surprisingly broader thinking than heretofore. And if the selected leaders don't engage the whole research community as CHAVI moves forward, that would be surprising. It will also be a terrific way to recruit new investigators into a very difficult and risky field with some coordination and leadership. That is the aim of the Global HIV Vaccine Enterprise, which may or may not succeed as an organizational solution to an intractable scientific problem. But not trying and hoping more of the same would give a different outcome would be foolishness for the scientific community and for humankind.

Bill Snow for the AIDS Vaccine Advocacy Coalition

AIDS Vaccine Advocacy Coalition
101 West 23rd Street, #2227,
New York, NY 10011, USA.
e-mail: wm.snow@comcast.net

Killing pain, not neurons

To the editor:

In their recent paper, Kukar *et al.*[1] studied the effects of a number of drugs on beta-amyloid (Aβ) production in wild-type mice and a mouse model of Aβ deposition. They conclude that there are therapeutic agents that may augment Aβ42 production and thereby increase the risk of Alzheimer disease in individuals on long-term therapy with such drugs. Celecoxib (Celebrex) is among the agents suggested to raise Aβ42 levels. Here we review evidence that celecoxib therapy in individuals with Alzheimer disease does not lead to increased levels of Aβ42 in a clinical trial and, therefore, is unlikely to be of relevance to individuals taking recommended doses of Celebrex.

In view of the increasing weight of epidemiological evidence that chronic therapy with anti-inflammatory agents such as NSAIDs could decrease the risk of Alzheimer disease, Searle and Pfizer sponsored clinical trials with celecoxib in individuals with Alzheimer disease, examining numerous biomarkers and cognitive outcomes. In a 28-day study designed to monitor Aβ42 as a cerebrospinal fluid (CSF) biomarker[2], individuals with probable Alzheimer disease ($n = 5$ per group) were treated with placebo, celecoxib 50 mg twice daily, 200 mg twice daily or 400 mg twice daily. The two higher doses are twice the recommended daily prescribed amount for osteoarthritis and rheumatoid arthritis, respectively[3]. CSF samples were collected to measure Aβ42 and plasma and CSF samples were collected to measure drug exposure at baseline and after 28 days of treatment. At all doses tested, there were no significant differences in Aβ42 concentrations in the CSF when compared to baseline. These conclusions were not only true for the mean Aβ levels for each treatment group but also when data points from individual subjects were evaluated[2].

To examine the potential impact of Celebrex on clinical efficacy in Alzheimer disease, a 1-year placebo-controlled, double-blind study of celecoxib (200 mg twice daily) was conducted in individuals with Alzheimer disease[4]. No differences were observed between placebo- and celecoxib-treated groups in terms of disease progression as measured by changes in the Alzheimer's Disease Assessment Scale-Cognitive Behavior composite score and the Clinician's Interview-Based Impression of Change Plus score. So although there was no indication of modifying disease progression, enhanced clinical decline was not evident, as might be predicted if Aβ42 levels were augmented.

Although the data presented by Kukar *et al.*[1] are intriguing, the differences in the human and mouse studies could be explained by the disparity between celecoxib exposures in these two studies. In the Kukar study[1], mice given 50 or 100 mg/kg/day, doses that consistently