Big science for a big problem: ADNI enters its second phase

An initiative to find biomarkers of Alzheimer's disease progression that researchers and industry describe as "a new way to do science" is entering its second 5-year phase. But what makes it so special? Adrian Burton investigates.

Alzheimer's disease (AD) is already a big public health problem, and is set to become much bigger. Worldwide it already affects 1 in 10 people aged over 65 years and nearly half of people aged over 85 years, and the number of patients could double every 20 years as populations live longer. The problem of finding effective treatments before a predicted financially overwhelming epidemic hits is far bigger than any laboratory can tackle in isolation, and our knowledge of AD still falls well short of it making economic sense for drug companies to risk taking on the burden alone. But what if academic laboratories in different countries could come together, shrug off the culture of trying to turn data into patents, use the same protocols so that results would be comparable, make all their results immediately publicly available, and partner with pharmaceutical companies who can provide extra funding and drugdevelopment expertise? Could such utopian "big science" be possible, and would it be big enough to take on AD? Now entering its second major 5-year phase, the Alzheimer's Disease Neuroimaging Initiative (ADNI) is showing that it might just be.

Neil Buckholtz (National Institute on Aging, Bethesda, MD, USA), one of ADNI's founding fathers, explains that the initiative was conceived back in 2003 as a way of accelerating drug research. "Changes monitorable by neuroimaging may occur in the brain long before AD becomes a clinical problem; CSF and blood biomarkers might also change over time. If we knew what [the changes] were, and which of them were reliable predictors of eventual AD, we might be able to understand disease progression better and more quickly test drugs designed

to slow or stop it—and with relatively few patients."

However, such research would require huge collaborative efforts involving laboratories in academia and industry, all producing data that could be easily compared. "For the effort to match the size of the problem, we understood it would mean organising ourselves, inviting collaboration from multiple sources, sharing data openly, and pulling together in a very coordinated fashion", says Buckholtz.

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After rounds of talks to establish such an initiative, ADNI was born in the USA in October 2004 with a budget of US\$67 million, with contributions from the National Institutes of Health, nine pharmaceutical companies, and organisations such as the Alzheimer's Association. 57 centres in the USA and Canada joined the project, making 800 people available for study, including 400 with mild cognitive impairment (MCI), 200 with mild AD, and 200 healthy controls.

"With a 5-year plan ahead of it, one of ADNI's goals was to develop uniform standards for acquiring longitudinal, multisite biomarker data, including MRI, PET, CSF, and blood data for characterising the progression from normality to AD", says Michael Weiner, ADNI principal investigator (University of California, San Francisco, CA, USA). "For data to be comparable, we had to develop a protocol that everyone in the project would use: what type of patients to enrol, their age, how their cognitive status should be measured, and what [criteria there

should be for assignment to different subpopulations, etc. Everyone in ADNI follows this protocol."

Other goals included establishing a database into which the different research groups could immediately log their data. "It's perhaps how we share our data that most sets ADNI apart from other initiatives", explains Weiner. "We certainly could not expect the pharmaceutical industry to wait for months or even years while scientific papers were produced in the normal way. So if we were all going to progress together with speed, we would need to forget holding data back for personal glory and patents. We decided the best way forward was to make a publicly accessible database where all our data goes immediately a quality-control check." Indeed, ADNI researchers do not try to publish in journals first, and then upload their data, but the reverse. And anyone can use their data-non-ADNI researchers can even request CSF and blood samples. The only requirement is that authors state on their publication where the data came from. "At first, some people were concerned that others might take the data they had gathered and beat them to publication", says Weiner, "but it's a sacrifice worth making in order to speed up our reaching other goals, such as testing hypotheses based on biomarker data and developing methods to determine treatment effects in trials."

With some 180 papers already published and 60 more in the pipeline, Weiner believes that speed is being achieved. And the work goes on. ADNI ended its first phase in October 2010, and in 2009 it was awarded a further US\$24 million to enrol patients with early MCI and to do amyloid PET scans

For the **ADNI website** see http://adni.loni.ucla.edu/

on all participants (ADNI-GO). In 2011, it will continue under ADNI II funding of over US\$60 million, with aims that include extending longitudinal studies and enrolling more participants in all subpopulations.

While public-private collaborations are not new, industry hails the unique value of being able to access new data in the ADNI database in real time. "Many cross-functional groups within [our] company benefit from this access, helping them better understand the natural history of early AD, the modelling of future clinical trials, and the utility of biomarkers", says Howard Feldman (Neuroscience Global Clinical Research, Bristol-Myers Squibb, Wallingford, CT, USA). "This builds confidence internally to support greater innovation in steps such as intervening earlier in the disease. Will industry make a profit from its investment in ADNI? Hopefully yes, but all of society will profit from having those treatments developed out of ADNI data."

As a model of collaborative research, ADNI soon became noticed, and other countries showed an interest in joining in. European-ADNI began as a pilot project in 2006 funded by the Alzheimer's Association, with Italy, the Netherlands, Denmark, Germany, Sweden, and France taking part. The peculiar European funding scheme led scientists to secure further funds first for a data repository and infrastructure for computational neuroimaging (neuGRID, funded by the European Commission with €2·8 million), and later for the collection of patient data.

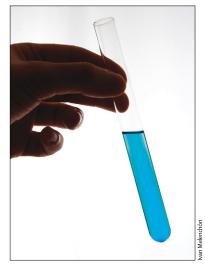
"In Europe, ADNI has been taken up as a technological platform for the harmonised collection of multicentre data", explains Giovanni Frisoni (Centro San Giovanni di Dio-Fatebenefratelli, Brescia, Italy). "A project worth €4.5 million aiming to develop markers to track disease progression has been developed in the context of a larger initiative funded by the European Commission (PharmaCOG). By using the data and image collection protocols of

the original ADNI as a foundation, marker discovery and validation programmes have been developed on candidate serum markers, amyloid imaging with PET, neurophysiological measures, and diffusion, functional, and spectroscopic MR."

The Australian Imaging Biomarkers and Lifestyle Flagship Study of Ageing (AIBL) also contributes data to the ADNI database, and Japanese-ADNI (J-ADNI), which began in 2006, is contributing MRI, PET, and CSF biomarker data from 600 participants. J-ADNI is also about to enter a second 5-year phase of research.

"In the interest of accelerating research findings and biomarker development, it is very important that all participants and stakeholders work on the same platforms, and that these are developed and validated simultaneously around the world", explains Maria Carrillo (Alzheimer's Association, Chicago, IL, USA). "As a global leader in AD research, the Alzheimer's Association drives. facilitates and funds these efforts, for example through our coordination efforts in World Wide ADNI [WW-ADNI, an umbrella organisation for the different countries involved in the initiative], and our project aimed at developing and verifying global standards for the collection and examination of CSF."

Other countries are set to join the initiative: China, South Korea, Taiwan, Thailand, and Argentina are all in the process of signing up. In Argentina the Fundación para la Lucha Contra las Enfermedades Neurológicas de la Infancia (FLENI, which despite its name also does research on neurological problems in elderly people) is the participating institution. "FLENI has decided that participation is a strategic objective for the Institution", says Silvia Vázguez, head of the FLENI Imaging Diagnostics Unit, Buenos Aires. "[We] plan to recruit 50-100 patients per year and believe our brain bank offers an important resource. We hope to start by the end of 2011 or early 2012."



Researchers are also looking for biochemical markers in CSF and blood

For more on the Australian Imaging Biomarkers and Lifestyle Flagship Study of Ageing see www.aibl.csiro.au

For more on the **Japanese ADNI** see http://www.j-adni.org/etop.

China hopes to enrol over 1000 patients to the project, and is now organising work teams and scientific consulting committees, and trying to recruit as many clinicians and researchers from different regions as possible. "All these tasks are underway", says Hongzheng Wang (Secretary General ADNI-China, Beijing, China).

The future could also see the ADNI idea extend into other areas of research. "The free sharing of data shown possible by ADNI could be a model for work in other areas", says Feldman. "Certainly, it lends itself to research in Parkinson's disease, multiple sclerosis and other degenerative diseases." In fact, the Michael J Fox Foundation is already fostering an ADNI-type initiative into Parkinson's disease, the Parkinson's Progression Markers Initiative (PPMI).

Weiner, however, finds another benefit. "It is amazing how so many people in so many different laboratories, from different countries, and alongside industry and foundations, can work together collaboratively and harmoniously towards a common goal. ADNI is teaching us that there is another way to do science."

Adrian Burton

For more on **neuGRID** see http://www.neugrid.eu/pagine/ home.php

For more on the **PPMI initiative** see **Leading Edge** Lancet Neurol 2010; **9:** 1139