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Drugs of the Future: Personalised Medicines for the Over 65s

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Introduction and Summary

As populations age, the need to find safe and effective treatments for diseases which primarily afflict older people becomes more acute. There are, however, challenges in making this happen, not least the current status of the pharmaceutical industry where a massive investment into drug discovery has been accompanied by a dramatic fall in the number of new therapies introduced per annum. The conference heard about the current state of play in treatments of diseases affecting the elderly, as well as hopes for the future. The morning session focused on Alzheimer's disease and dementia, while the afternoon looked at heart failure. In the evening, exciting potential treatments for age-related macular degeneration – the most common cause of sight-loss in the over-60s – were discussed, along with industry's approach to drugs for dementia and the push towards personalised medicine, tailored to individuals.

Session One: Alzheimer's

Chair: Professor Leslie Iversen, Department of Pharmacology, University of Oxford

Alzheimer's disease is the most common form of dementia and the number of people suffering from it is predicted to increase dramatically as the population ages. There is no cure, but a number of potential therapies are in the pipeline. There are challenges, but personalisation may help provide some answers.

Translational Medicine and the Crisis in Drug Development

Professor Garret FitzGerald, Director, Institute for Translational Medicine and Therapeutics, University of Pennsylvania

Professor FitzGerald called for a new model of drug development, which he said would benefit patients as well as the pharmaceutical industry. This new model would include more partnerships with academia and better investment in 'human capital' – the scientists and clinicians who can bring treatments from the bench to the bedside. He spoke of the crisis in pharma, with only 17 new drugs approved by the FDA in 2007 – the lowest number since 1983. Previously, high prices for prescription drugs have insulated the pharmaceutical industry, but now they recognise that they have a broken business model.

He spoke about the potential benefits of personalised medicine, bringing in the example of Vioxx (rofecobix), which was withdrawn from the market when found to increase the risks of cardiovascular disease. If companies knew which patients would react well or badly to a drug, that knowledge would increase safety and improve effectiveness. He said there is a need to combine quantitative measures of drug response with genetic information, and then relate these to clinical outcome. He described the current 'broken' model as one where there is massive and quite effective investment into drug discovery but poor translation to new products.

There are also two 'cliffs' facing pharma, relating to patents and generic drugs. Some calculate a decline in revenue stream of up to 40 per cent, due to patents expiring. Increased

use of generics – now 60 per cent of prescribed drugs in the US – is also hitting profits. Pharma is trying to cope with these challenges in various ways, including mergers which allow for efficiencies (ie job losses), but Professor FitzGerald suggested some other solutions.

Academia has talented physician scientists with access to patients, but traditionally these have been resource-starved. Often too, they are poorly educated in pharmacology, which may hinder the drug development process. There are few incentives for 'team science' – which brings expertise together – and huge competition for grants, which is helping to keep younger applicants out. On average, physician scientists are now in their 40s before getting the funding which makes them independent, making academia unattractive as a career.

Professor FitzGerald suggests more collaboration between academia and pharma, but also advocates a changed approach to trials. There is pressure to get into Phase 3 trials, at the expense of selecting doses and understanding how a drug works, he said. Currently, Phase 3 trials assume one dose works for everyone, ignoring the potential benefits of personalisation.

He suggests a new discipline which develops quantitative biomarkers which can be used to measure response and use these to come up with the optimal doses for people with different phenotypic responses. He would like academia, industry, funders and regulators to work together to develop a unitary nomenclature and agree core competencies. He'd like funding to be revised and to be focused on longer term and more heterogeneous portfolios. He'd like more emphasis on Phase 2 trials, including on personalised doses, and he would like more people with good knowledge of pharmacology to be at the centre of the process.

The Elderly in Scotland and their Health

Professor John Starr, Department of Geriatric Medicine, University of Edinburgh

Professor Starr gave an overview of the current state of health of older people in Scotland and, based on evidence, made some predictions about the future. Life expectancy is going up and the number of over-65s is increasing. By 2031 the 60–74 age-group will have increased by 40 per cent, while there will be 91 per cent more people aged 75 and over. This is likely to have an impact on health and social care.

Professor Starr looked at what it means to be healthy, including how people feel about their own health and what society says health means. He also described some of the conditions suffered by Scotland's elderly, including osteoporosis, dementia and depression. As the population ages, rates of these conditions are likely to increase.

Professor Starr looked at what's being done now to look after older people. Based on current trends, he said that Scotland's elderly are likely to live longer, spend a longer time with disability (particularly women), and have improving physical, but worsening mental health. Life satisfaction is unlikely to change. Based on a survey carried out in Scotland in 2000, a man aged 65 now can expect to live another 17.2 years and a woman 19.9 years. Both sexes could look forward to about 10 years of good health and a further five years of modest ill health while the remainder of between two and five years would be spent with a considerable incapacity.

Demand for hospital admissions and care at home and in care homes increase when people reach 65, although the number of GP visits remains about the same. Older people use more prescription drugs than younger age groups, but many are prescribed inappropriately. Adults over 60 years have 3.6 times more prescriptions than younger adults and up to 80 per cent of elderly people receive inappropriate treatment, he said, with some being hospitalised due to adverse drug reactions. Importantly, some drugs which are commonly prescribed will have an effect on cognitive abilities.

He concluded that there will be a substantial increase in numbers of older people, living with and without disability; that there will be changing patterns of disease, increasing numbers of prescriptions and increasing risks of adverse drug effects. The impact on health and social services is difficult to measure.

New Drugs for Cognitive Decline

Professor Alistair Burns, School of Medicine, University of Manchester

Professor Burns looked at dementia now and in the future. He summarised current and potential treatment strategies and also considered prospects for prevention.

Dementia affects 700,000 people in the UK and this figure is expected to rise as the population continues to age. Public awareness has never been higher, partly due to a number of official studies and documents which have been publicised and partly as it becomes a pressing political and economical issue. According to a King's Fund report, for example, incidence of Alzheimer's disease (AD) (the most common cause of dementia) will increase by 61 per cent between 2007 and 2026, with costs projected to rise from £14.9 billion to £34.8 billion over the same period.

There are known treatments for AD. These include the cholinesterase inhibitors, (donepezil, (Aricept), galantamine (Reminyl), rivastigmine (Exelon)) and the glutamatergic agent memantine. While the former can be prescribed on the NHS for 'moderate' disease, the latter is only available as part of a clinical trial. Other treatments including anti-depressants, antipsychotics, and novel interventions, including aromatherapy, are also used in the management of dementia. The economic case is difficult to make for these drugs.

A number of drugs are being developed with the aim of slowing down the cognitive decline in dementia. These include those which tackle the amyloid plaques, which develop in a brain with AD, and the tau protein, which is implicated in the neurofibrillary tangles characteristic in AD. There are a number of vaccines and other products in the pipeline, including the possibility of the use of a Rember, which appears to act on tau, although this work has yet to be published.

Other possibilities include the use of a non-selective antihistamine (Dimebon) and even a food supplement, Souvenaid.

Public interest in AD is high and every week, it seems, a new paper is publicised, but nothing definitive has emerged as yet. There is also public interest in prevention of dementia, and there are known risk factors. These include socio-demographic factors, education level, habits, genetics and medical history and treatments in addition to age. Hypertension and high cholesterol levels are risk factors, so it is possible that reducing these might help prevent AD. Keeping the brain active and participating in social networks may also be protective.

Professor Burns concluded that public interest in dementia has never been higher, that current treatments are safe and effective and that there are real and realisable prospects for prevention.

Panel Discussion

There were questions around predicting who would respond to drugs and also around other types of treatment. A woman whose father had died from Alzheimer's wanted to know why there wasn't more emphasis on issues such as diet. Professor Burns agreed that such issues should be considered.

Asked about the possibility of using drugs off-licence, Professor FitzGerald said that safety was pre-eminent, but that it was possible that some drugs might work for different purposes

than originally thought. Professor Starr pointed out that thalidomide – which proved dangerous for its original purpose – was now being used to treat myeloma.

Asked whether individuals could be both clinicians and scientists, Professor FitzGerald said it was a question of aggregating expertise, and that clinician scientists made a unique contribution to the team effort.

Session Two: *Management of Heart Failure*

Chair: Professor Henry Dargie, Department of Cardiology, Golden Jubilee Hospital

Heart failure is a serious condition which affects young and old but is more common in the over-75s. There is a vast array of drugs available, but recent advances have included device therapies, such as implantable defibrillators. It's a common, complex and lethal condition, said Professor Dargie.

Essential Clinical Standards for the Diagnosis, Treatment and Long-Term Management of Chronic Heart Failure

Dr Martin Denvir, Consultant Cardiologist, Royal Infirmary of Edinburgh

As well as being a consultant cardiologist working with patients, Dr Denvir is clinical advisor to NHS Quality Improvements Scotland (QIS) and is involved in drawing up clinical standards for the management of heart failure. This is part of a large body of work, which included Scottish Intercollegiate Guidelines Network (SIGN) guidelines on chronic heart failure published in 2007, and draft standards on the prevention and treatment of coronary heart disease more widely, which were published in February of this year. Dr Denvir described some of the process in drawing up standards and guidelines, and also said that implementation of the SIGN guidelines had been variable. Cardiologists were more familiar with the guidelines than GPs, although the majority of heart failure is treated in primary care.

The clinical standards may be a way of ensuring more consistent implementation of guidelines, which include recommendations on diagnosis, pharmacological treatment, a multi-disciplinary approach to care, the use of device therapies, and supportive and palliative care at end of life. Standards should be clear, measurable and evidence-based, he said. They should be small in number and achievable, but stretching. Dr Denvir accepted, however, that there were many demands on doctors and health boards, so the aim is to make complying with the guidelines, and with audit and monitoring, as streamlined and painless as possible.

Management of heart failure will be continually assessed, however, under the Scottish Patient Safety Programme. The national heart failure audit will include six to ten measures or indicators to show how well patients are being managed.

He concluded by saying that the evidence was out there and the guidance written; the standards of care are agreed and implementation and measurement of the quality of care must be linked in a clear process that everyone understands. They should promote care which is effective, safe, timely, efficient and patient-centred.

The Efficacy of Intracardiac Devices in the Management of Sudden Cardiac Death and Ventricular Dysfunction

Dr Neil Davidson, North West Regional Cardiac Centre, Wythenshawe Hospital, Manchester

As well as drug therapies for heart failure, the meeting heard that other interventions, including specialist nurses and electrical devices such as pacemakers, had made a big difference to treatment, quality of life and survival.

Dr Davidson described the history of implantable devices, talked about their benefits and disadvantages and discussed emerging and possible future technologies. Intracardiac devices have been in use for some 50 years, beginning with the simple pacemaker. More

recent developments have included resynchronisation devices and internal defibrillators. Much of the progress in intracardiac devices has been driven by technical advances outside medicine, as batteries and processors have improved dramatically.

The UK lags behind much of the rest of the developed world in its rate of implantation. There could be a number of reasons for this, including affordability – more devices are implanted in healthcare systems which rely on the number of procedures for payments – and lack of awareness of the benefits among health professionals.

There is also the question of acceptability to patients: some do not like the implantable cardiac defibrillator (ICD), for example, because it works by delivering a ‘shock’ when it senses cardiac arrhythmia in patients at risk of sudden cardiac death due to ventricular fibrillation. Sometimes it is activated in error and there can be psychological side-effects for patients.

While electrical devices show good results, resynchronisation devices, for example, help improve heart function and lead to better quality of life – but they are expensive and aren’t getting cheaper. Resynchronisation devices cost around £6,000; when combined with a implantable cardiac defibrillator, the cost goes up to £15,000. Dr Davidson said that the manufacturers did not focus on producing cheaper models, but instead kept prices constantly high by adding ‘bells and whistles’. He drew attention to the way mobile phones have become ever more complicated but no cheaper.

In the future, he believes there will be further useful refinements. For example, information from the blood flow in the patient’s individual cardiac chambers and major blood vessels (haemodynamic monitoring) using ‘wireless’ devices with no leads might be used to adjust medication.

He concluded by saying that electrical devices had improved quality of life and that they should be used more. In his view, technological advances should be focused on cost-effectiveness.

Which New Medicines Produce Heart Failure and Which Alleviate It?
Professor Allan Struthers, Department of Clinical Pharmacology and Therapeutics, Ninewells Hospital and Medical School, Dundee

There have been a number of successful drugs for heart failure introduced since the 1980s and 90s, including the neurohormonal therapies of ACE inhibitors and beta-blockers. Since then, however, the major advances in treatment have been the use of specialist nurses and of intracardiac devices, such as CRTs and ICDs. Professor Struthers outlined the current strategies for finding new drugs. These include looking for other neurohormones to target, following the success of ACE inhibitors, and there have been trials of a number of possibilities, including testosterone. Another strategy has been to re-examine inotropic drugs, which was where the so-called ‘smart money’ was before ACE inhibitors proved more effective. He described two inotropic drugs which might be promising. Other potential therapies could involve those acting on the cardiac metabolism or antiarrhythmic drugs, such as fish oils.

There is also a suggestion that drugs in use for other conditions, for example Viagra, might have an application in heart failure. The twist, however, is that some drugs, which have been introduced for other diseases, seem to cause heart failure. These include some anti-diabetic drugs and the cancer drugs doxorubicin and herceptin. In the case of herceptin, the heart failure seems to be reversible when the drug is stopped. However, an understanding of the detrimental action of these drugs on the heart muscle might provide clues to potential therapy targets.

Professor Struthers said that there are hopeful new drugs around, but that more research is needed to see if they provided clinical benefit.

Panel Discussion

Questions were asked about management of heart disease, both with drugs and devices, and about the importance of standards. Dr Denvir was asked if putting something in a standard – such as particular methods of diagnosis – could help improve practice. He said that standards were an opportunity and should be seized upon. Asked what developments he'd like to see in devices, Dr Davidson said he'd like them to be more intelligent, for example, so that they could collate data on how the heart was performing and assist in the adjustment of drug dosage.

Asked at what stage in a patient's life devices should stop being implanted (for example, whether a pacemaker should be replaced in someone in their 90s with advanced dementia) Dr Davidson said that it would be a difficult decision to take on ethical grounds because if the pacemaker was keeping them alive, not to replace it would necessarily mean they died. Had the patient signed an advanced directive, the decision would be easier, he said.

Asked about how health boards could meet all standards, Dr Denvir agreed that there were a lot of guidelines and recommendations around. NHS Quality Improvement Scotland, (QIS) was trying to work in a strategic way to make it as easy as possible to push up quality of care and was now engaging more directly with individual health boards.

Session Three: *The Future of Personalised Medicine*

Chairman: Professor David Lawson, Honorary Professor of Medicine and Therapeutics, University of Glasgow

The evening session of the meeting looked at potential therapies for the disease often known as 'Alzheimer's of the eye' because it is so common in older people. It also heard about industry's approach to treatments for dementia, and learned how, in the genomic age, personalised medicine could be coming into its own.

Future of Therapies for Macular Degeneration

Professor Peter Coffey, Ocular Biology and Therapeutics, Institute of Ophthalmology, University College London

Professor Coffey described new and emerging techniques for treating one of the most common and distressing conditions relating to getting older.

Age-related macular degeneration (AMD) is often called 'Alzheimer's of the eye' – not because it has anything to do with the disease, but because of the vast numbers of older people it affects. AMD is the most common cause of sight loss in people aged over 60 and occurs when the cells of the macula become damaged. The macula is in three layers: the retina, the choroid, and, in the middle, the RPE layer (retinal pigment epithelium). It is the RPE cells which seem to age and die first, affecting the retina's ability to 'see'. Professor Coffey is director of the London Project, led by UCL, which aims to find a cure for AMD. This involves using stem cells to halt and reverse loss of sight.

So far stem cells have been used to create healthy RPE cells which have been used to replace those in animal models, most recently in a pig. The possibility of 'personalised' treatment exists because a person's skin could be used to obtain stem cells which could then be used to create RPE cells which could be used in the treatment. This is likely to be an expensive option, however, although the technology might help find new targets for drug treatments.

Stem cell technology is likely to have major advantages over existing treatments. At the moment, the biological drug Lucentis is the main (and controversially expensive) treatment for 'wet' AMD, which accounts for around 10 per cent of cases of AMD (with 'dry' AMD accounting for the other 90 per cent). Treatment with Lucentis involves injecting the patient in the back of the eye every few weeks at a cost of between £1,000 and £1,500 per injection.

There are other possible treatments. Professor Coffey showed videos of patients, one whose central vision had been improved by a surgical technique moving RPE cells from the periphery of the retina to the centre. In another, a retinal flap of healthy cells was rotated to replace the diseased tissue. These techniques take up to three hours, however, so would not be suitable for an outpatient or day-case procedure, compared to 40 minutes for the stem cell operation carried out on the pig. Professor Coffey hopes that techniques using stem cells will be in clinical trials shortly.

Industry's Approach

Professor Leslie Iversen, Department of Pharmacology, University of Oxford

Professor Iversen, who for many years held a senior role with the pharmaceutical giant Merck, described industry's approach to Alzheimer's disease therapy.

Every pharma company is involved in research and development in the area of dementia, which is seen as a huge marketing opportunity by industry, he said. There is a large amount of unmet need, which will grow as the population continues to age, and current therapies are seen by industry to be making large amounts of money. Global sales of Aricept were \$2 billion in 2008.

He described the beta-amyloid hypothesis – essentially that too much of this protein in the brain causes 'plaques' present in the brains of people with dementia – which has dominated scientific thinking about Alzheimer's disease in the last 30 years. It is only now that drugs based on this theory are emerging, and so far, they have not been very successful. There are also, however, known genetic factors which increase the risk of AD. For example, there are mutations which promote formation of beta-amyloid and others such as the nature of Apo-enzyme E alleles 1 to 4 which effect the age of onset and the overall severity of the disease.

Currently cholinesterase inhibitors (such as Aricept) are the only approved medicines. Other approaches in the pipeline include inhibitors of beta-amyloid synthesis, drugs that may prevent or reverse formation of plaques or vaccine or antibody treatments. There has also been a suggestion that inhibiting aggregation of the tau protein (which leads to tangles in the brain associated with AD) might provide an answer. Cholinergic treatments such as Aricept are only moderately effective and many people do not respond. It could be that genetic factors determine who will respond. Beta-amyloid synthesis inhibitors have not proved successful in trials so far, but at least six other drugs are in development.

Vaccines have looked promising but one trial was halted because the drug caused inflammation in the brains of some patients. There are several other vaccines in development. Another novel approach involves using monoclonal antibodies to clear the disease from the brain. Although successful in animal trials, a Phase 2 clinical trial of one antibody (bapineuzimab) showed positive clinical benefit only in a subset of patients (without the Apo-enzyme E4 allele.)

Professor Iversen said it was too early to write off the beta-amyloid hypothesis, although trial results had been disappointing so far. Most of the trials to date have involved moderate to severe AD patients, where it might be more difficult to see a benefit. Personalised medicine may be a way forward, although industry is naturally concerned about the commercial effects of the stratification of disease, each with a different treatment splitting the market for the individual products. Phase 3 trials of bapineuzimab will include patients with and without the Apo-enzyme E4 allele – a form of personalised medicine. Post-hoc analysis of earlier trials which is not accepted as evidence by the regulatory bodies, suggests that this division will show some of the new amyloid attenuating strategies to be successful in those without the E4 allele.

He suggested new approaches to clinical trials, including identifying and including patients at an early state of disease and making better use of neuro-imaging and improved tests for cognitive function.

The goal, he concluded, is to improve quality of life for the future. His hopes for the future include seeing the first effective treatment for AD within ten years, and also the use of stem cell therapy to replace damaged or missing nerve cells in the same timescale. He would also like to see ways of identifying suitable people to treat with preventative medicines.

Personalised Medicines: Coming of Clinical Age

Dr Geoffrey Ginsburg, Director, Centre for Genomic Medicine, Institute for Genome Sciences & Policy, Duke University

Dr Ginsburg began by outlining some of the reasons why we need a different sort of medicine. There are safety issues, with some 6.7 per cent of patients suffering adverse drug reactions in hospitals alone. Serious reactions in small groups of patients have led to drugs being withdrawn, for example Vioxx. And there are efficacy factors: even commonly prescribed drugs are ineffective in a substantial numbers of patients.

There are many reasons for a push towards personalised medicine. These include advances in technology and disease understanding on the one hand – including the mapping on the human genome – but on the other hand also include pressure from consumer demand, demographics, health policy makers and industry. Personalised medicine means getting better at knowing who, how and when to treat, and there are a number of ways of doing this.

You can look at risk factors for disease, said Dr Ginsburg, and make predictions. It's known that risk factors for developing heart disease include smoking, increased cholesterol and high blood pressure, so people with these conditions might be considered for preventative treatment. He cited a paper from 1961, showing that these ideas had been around for some time.

Medicine and biology have moved forward in the last half century from observational to molecular science and, now, to genomic or digital science. The sequencing of the human genome and other advances, such as gene expression profiles, are revolutionising drug discovery and the way we define disease.

Genomics can be used to predict risk and also response to treatment. This is hugely important because it can help develop tailored treatments for diseases which have many forms, for example, breast cancer. Genomics can help us refine prognosis, make better use of available drugs and develop personalised therapies.

Cancer drugs tend to be designed for groups, not individuals, he said, but different people will react differently. For example, although most people who have surgical resection of early stage 1 non-small cell lung cancer will be fine, around 30 per cent will have a recurrence and die. If it was possible to identify that 30 per cent, they might benefit from adjuvant chemotherapy.

A study is being carried out which seeks to use gene expression analysis to predict high risk, with these patients being randomised to chemotherapy or observation (which is the current standard treatment). Gene expression data from tumour samples may also be used to identify which patients will respond to different drugs. Designing clinical trials to do this – so-called trial enrichment – could lead to savings in clinical trials and better identification of the patients who would benefit. The personalised approach to cancer care would therefore involve using genomics to predict recurrence, which would identify whom to treat, and then predict chemotherapy response, showing how to treat.

There is a strong public policy move towards personalised medicine. The Food and Drug Administration (FDA) is behind it, and President Obama, when a senator, introduced a medicine act to 'secure the promise of personalised medicine to all Americans'.

To illustrate how genomics is moving on, Dr Ginsburg shared his own profile, obtained from one of the many companies which will now provide a read-out for a price. There are concerns about the reliability of such information, however, as well as public concerns about ethics, and the fear of discrimination by insurance companies and others.

Much needs to happen to make personalised medicine a reality, including building better infrastructure, improving information-sharing and getting the right workforce in place. Medicine which is science-based is patient-centred, he said, but pharma cannot achieve this in isolation. Academia, health care systems, federal agencies and others will have to contribute and work together.

Panel Discussion

Questions ranged over clinical, economical and religious areas.

Professor Coffey was asked how long new technologies for AMD lasted and was told it was two and a half years so far in small mammals and eight weeks since they had operated on the pig.

He was also asked about the possibility of the stem cells being rejected, but said that the eye was immune-privileged, and therefore more likely to accept transplanted tissue.

Asked about whether religious concerns could hold up the technology, he said that some countries in Europe did not agree with the use of embryonic stem cells, and that he was waiting for a decision at a European level about whether the technology would be approved.

Questions were also raised about the high cost of Lucentis (ranibizumab) and other biologics. Professor Iversen said that current regulations did not permit generic versions of biologics – which enabled companies to keep prices high even after patents had expired – but said it was possible that 'bio-similars' could be introduced which might bring prices down. Professor Coffey said there was a current trial using the colon cancer drug Avastin (bevacizumab), which is marketed in 100mg vials which can be divided up into about 50 or more smaller doses and then used in the same way as Lucentis at proportionally less cost. This is being funded by the NHS, as it isn't in pharmaceutical company interests to fund such a trial. There is also the possibility that Avastin is a better drug. The patents for both biologics are held by the same company.

Asked about the dangers of doctors 'empire building' and working in silos isolated from their colleagues, Dr Ginsburg said that team science was the way forward, and was breaking down traditional disease barriers.

There was discussion over whether insurance companies would use information from genomic testing. Dr Ginsburg said he hadn't told his insurance company about his results and didn't see why anyone would!