Translational Scientist

DECEMBER 2017



Upfront

From MS to AMR

A 20-year-old drug used to treat symptoms of MS could be repurposed to treat infections in cystic fibrosis patients

December 2017

A 20-year-old drug used to treat symptoms of MS could be repurposed to treat infections in cystic fibrosis patients

The immunomodulator glatiramer acetate (GA) has been used to treat multiple sclerosis patients for over 20 years. The drug is well tolerated by most patients, can be administered systemically – but why would it be effective in the fight against antibiotic resistance? We spoke to co-author of a study into its antimicrobial effects (1), Thomas Vorup-Jensen, professor at the Department of Biomedicine, Aarhus University, Denmark, to find out more...

Why did you choose to investigate glatiramer acetate as a potential antimicrobial agent?

We have worked for many years on the effects of GA in multiple sclerosis, and we noted that its biochemical properties are similar to the so-called antimicrobial peptide, LL-37. In spite of their name, antimicrobial peptides often exert a modulatory effect directly on the immune system without the involvement of microbes. In a previous paper (2), we compared the effects of GA and LL-37 on human immune cells and concluded that certain effects of LL-37 were also found in GA, suggesting that GA affected the immune system in ways mimicking the evolutionary highly conserved LL-37.

Then we asked the question that is central to this more recent study: if GA mimics the immunomodulatory effects of LL-37, could it also mimic the antimicrobial effects?

And the answer?

GA efficiently kills Gram-negative bacteria, in particular Pseudomonas aeruginosa, which is a crucial finding, as we lack antibiotics/antimicrobials that target these organisms; many Gram-negative organisms develop multiresistance to conventional



antibiotics. As GA is already in use, we have the opportunity to repurpose it as an a new treatment of Gram-negative infections. Finally, we argue that the Gram-positive organism Staphylococcus aureus, presumably by shedding fragments of its thick cell wall, generates a type of nanoparticulate decoy that may deviate the attack of GA or LL-37, which may explain why S. aureus is better at surviving treatment with GA and LL-37 than the Gramnegative organisms.

Where could GA have the most clinical impact?

Cystic fibrosis patients in particular have trouble clearing bacterial infections from their lungs, very often infections with Pseudomonas. We hope that our discovery will help fight these infections in a more effective way.

What's next?

We want to understand the mechanisms of GA killing better. We also want to investigate the effects of GA on other bacteria, with the aim of hopefully expanding the number of clinically significant infections which can be treated with this compound.

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Think Small

Nanotechnology helps track down micrometastases missed by MRI

December 2017

What?

Tracking tiny tumors in real time could soon be a reality, thanks to a new nanotechnology-based approach for following the spread of micrometastases (1).

Who?

A team of researchers from Rutgers University and Cancer Institute of New Jersey, USA, and Singapore University of Technology and Design.

Why?

Current imaging methods cannot spot tumors in the early stages of metastases, confounding cancer staging and treatment decisions – and the "Achilles heel" of surgical management, say the authors.



Figure 1. In the study, human breast cancer cells in a mouse model were "chased" with novel rare earth nanoscale probes injected intravenously. When the subject is illuminated, the probes glow in an infrared range of light that is more sensitive than other optical forms of illumination. In this image, the probes show the spread of cancer cells to adrenal glands and femur bones. Image credit: Harini Kantamneni and Professor Prabhas Moghe, Rutgers University New Brunswick

How?

Light-emitting nanoparticles are injected intravenously and reveal lesions that can't be detected using contrastenhanced MRI, allowing real-time surveillance of cancer spread in a mouse model (see Figure 1).

When?

According to the authors, the technology could be available in the clinic within five years, and lead to more accurate cancer monitoring.

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Innovation Versus Exnovation

Sometimes, we need to go backwards to go forwards in medicine

December 2017

Innovation drives translational science forwards – but what happens after an innovation has been adopted? Sometimes, advancing medical practice means taking note of new evidence and moving in the opposite direction, according to Kimon Bekelis, a professor at the Dartmouth Institute for Health Policy and Clinical Practice, New Hampshire, USA – and first author of a recent study on the importance of deadoption – also known as exnovation (1).

"The process by which innovations enter everyday use has been studied extensively in many disciplines. But the process by which physicians scale back the use of medical practice has received much less attention", says Bekelis.

Understanding the process of deadoption – why medical practices fall out of favor – is important when it comes to ensuring that low-value treatments, such as those that have little effect or those that are prohibitively expensive, are reduced in everyday practice, explains Bekelis.

Using carotid revascularization – a surgical procedure that has become controversial (2) – as an example, Bekelis and his colleagues looked into the factors that caused a decline in its use. They found that more experienced surgeons were likely to scale back their use of the procedure more quickly – but, on the other hand, surgeons who used the procedure more often were more likely to keep using it. "Reliance on some procedures for financial reasons might deter physicians and organizations from integrating new evidence into clinical practice," adds Bekelis.

Next, the authors plan to find out whether their findings can be applied to other procedures and settings – and they believe that more should be done to ensure that interventions that are not supported by strong evidence are more quickly scaled back in the clinic. "Specialty societies should more aggressively disseminate practice guidelines, and national registries should aid in quality control and benchmarking," says Bekelis.

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Pain and Vision Gain

An analgesic is helping researchers explore new drug targets for sight-threatening diseases

December 2017

Pentazocine is an opioid most commonly used to treat pain – but could it also be used to save sight? A team of researchers from Georgia, USA, previously found evidence that pentazocine can protect the cones of the retina – and have received a US\$1.14 million grant from the National Eye Institute to explore the connection further. Ultimately, they hope to find new drug targets to treat causes of sight loss, including glaucoma and retinitis pigmentosa (1).

Pentazocine apparently binds to the sigma 1 receptor (S1R), activating a transcription factor - nuclear factor erythroid-derived 2-like 2 (NRF2) - which increases the expression of detoxifying and antioxidant genes. Last year, the team demonstrated that activation of S1R via administration of pentazocine could combat cone cell loss, using a mouse model of retinal degeneration (2), and they suspect that its ability to modulate NRF2 levels is the reason for its protective effect. Building on this discovery, they conducted a study exploring how S1R activation and inhibition affects the survival of optic nerve head astrocytes, and found that S1R activation - again using pentazocine - protects cells from oxidative stress (3).

As oxidative stress is implicated in retinal degeneration, and has been previously linked with cone cell death (4), S1R becomes a promising drug target. Next, the team plan to further study how pentazocine affects NRF2 expression, and to see if the protective effects in the retina last over time.

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A Deadly Combination

Diabetes and obesity often go hand-in-hand, with devastating effects on public health

December 2017

Obesity and diabetes represent two significant – but also potentially preventable – sources of human death, disability and disease. But what damage are they doing when united? A recent study has found that together, the two conditions contributed to 792,600 cases of cancer in 2012 – or 5.6 percent of new cases (1). "While obesity has been associated with cancer for some time, the link between diabetes and



cancer has only been established quite recently. Our study shows that diabetes, either on its own or combined with being overweight, is responsible for hundreds of thousands of cancer cases each year across the world," said Jonathan Pearson-Stuttard, lead author of the study and a Clinical Fellow at Imperial College London, UK (2).

For the study, the authors defined a BMI of 25 or over as "high", and did not distinguish between type I and type II diabetes (a potential limitation when considering preventative measures). They hope that the results will highlight the toll obesity and diabetes are having on public health, and call for more to be done to tackle the problem. "Both clinical and public health efforts should focus on identifying effective preventive, control and screening measures to structurally alter our environment, such as increasing the availability and affordability of healthy foods, and reducing the consumption of unhealthy foods", said Pearson-Stuttard. "In the past, smoking was by far the major risk factor for cancer, but now healthcare professionals should also be aware that patients who have diabetes or are overweight also have an increased risk of cancer," he added.

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Cancer Types (Men) Liver 126,700 Colorectal 63,200 Kidney 37,400 Cancer Type Pancreas 31,900 Gallbladder 12,800 Oesophagus (adencarcinoma) 9,100 Stomach 6,400 Multiple myeloma 4,500 Thyroid 3,900 0 20,000 40,000 60,000 80,000 100,000 120,000 140,000 Cancer Cases (n) Cancer Types (Women) Breast 147,400 Endometrial 121,700 Liver 60,900 Colorectal 58,600 Cancer Type Pancreas 30,100 Kidney 25,200 Gallbladder 19,400 Thyroid 14,800 Ovarian 9,100 Multiple myeloma 4,400 Stomach 2,900 Oesophagus (adencarcinoma) 2,200 100,000 120,000 0 20,000 40,000 60,000 80,000 140,000 160,000

600,000 544,300 500,000 Cancer Cases (n) 400,000 280,100 300,000 200,000 Diabetes 100,000 0

Risk Factor

Cancer Cases: Men Versus Women

Cancer Cases: Obesity Versus Diabetes



Dark Fields and Diagnostic Disks

New devices for detecting tuberculosis may speed up diagnosis and improve treatment

December 2017

Tuberculosis (TB) is the eighth most common cause of death in lowand middle-income countries (1) and a challenging disease on many levels. To begin with, it's difficult to diagnose - symptoms like fever, weight loss and coughing apply to a wide range of illnesses, and many tests are inconclusive or subject to a high percentage of false positive and negative results, especially in patients with additional health problems. To reach a conclusion, doctors require a medical history, a physical examination, and a variety of tests, including skin tests, chest X-rays, sputum smears and microbiological cultures. Even after diagnosis, the battle isn't over; treatment is long, arduous, and side effects are common - and antibiotic resistance compounds these problems. But the longer patients go undiagnosed, the worse the odds of survival become – and it is more likely that they will spread the disease to others.

Tony Hu and his colleagues from the Arizona State University's Biodesign Institute decided to tackle the problem of diagnosis by developing a nanotechnology-based method of detecting and quantifying TBspecific proteins in circulation (2): an antibody-conjugated nanodisk that improves detection by high-throughput MALDI-TOF mass spectrometry. The disk first binds target peptides CFP-10



and ESAT-6, and then enhances the MALDI signal to allow quantification of the peptides at low concentrations. In the group's proof-of-concept study, the disks were highly sensitive and specific, successfully diagnosing culture-positive and extrapulmonary tuberculosis even in HIV-positive patients. The specificity was similarly high in healthy and high-risk patient groups. And during treatment, the nanodisks were able to quantify serum antigen concentrations to assess how well patients were responding.

It seems the new test has everything – speed, sensitivity, specificity, and the ability to offer conclusive results from a single, low-volume blood draw. But it's not the Hu group's only TB diagnostic; they've also developed another proof-of-concept device for use in resource-limited settings (3), which takes the form of a simple dark-field microscopy system with an LED light source, a dark-field condenser, a 20x objective lens, and

the user's smartphone. It's small, light, and cheap at under US\$2,000 – but the researchers aren't done yet, setting their sights on higher sensitivity, less weight, and a fraction of the cost.

The goal is to make high-quality TB care – and eventually, broad-range infectious disease diagnosis – available to every patient, regardless of location, health status, or resource availability.

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Believe in RNAi

The gates for gene and cell therapies are open – and RNAi technology could be a serious contender for the therapy of the future.

By Geert Cauwenbergh, President and CEO of RXi Pharmaceuticals, MA, USA.

December 2017

The discovery of RNA interference (RNAi) was regarded by the scientific community as a crucial advance evidenced by the selection of RNAi as Science journal's 2002 "Breakthrough of the Year" and the fact that its codiscoverers, Andrew Fire and Craig Mello, were awarded the 2006 Nobel Prize in Medicine. RNAi has high specificity for targeted genes and high potency - and because of its ability to silence genes, RNAi is being investigated as a platform for the development of novel therapies by many researchers, including those in our company (co-founded by Mello).

"I truly believe that RNAi-based therapeutics will be the next generation of medicine."

Much like antibodies transformed medicine, I truly believe that RNAibased therapeutics will be the next generation of medicine. In fact, I believe that 20 years from now, RNAi-based therapeutics will be at the forefront of approved treatments over antibodies. The exciting aspect of RNAi compounds is that they can potentially be designed to target any one of the thousands of human genes - many of which, such as transcription factors and targets that act by protein-protein interactions, are undruggable by other modalities. The overexpression of certain proteins plays a role in many diseases, so the ability to inhibit gene expression with RNAi is a powerful tool. RNAi drugs also offer key safety advantages in that they can achieve their effects without the need for permanent, and potentially dangerous, gene modifications.

But what is needed to help the field flourish? RNAi is a complex and challenging field of research. Although there has been significant progress in the clinical development of RNAi products, none have yet reached the commercial stage. RNAi needs a "first" to convince the market that previously identified roadblocks for successful RNAi therapy can be resolved. One of the most significant challenges has been the appropriate delivery of RNAi compounds into the cell type of interest. Chemically stabilized small interfering RNAs have been well explored but have demonstrated limited clinical efficacy. Some companies have used encapsulation in a lipid-based particle, such as a liposome, to improve circulation time and cellular uptake, but there are also compounds being developed with built-in delivery properties that do not require a delivery vehicle for local therapeutic applications. Our company is exploring the latter approach as we seek to develop RNAi-based therapeutics.

RXi's first clinical candidate, RXI-109, targets connective tissue growth factor, a critical regulator of fibrosis. A phase II clinical trial is underway to evaluate RXI-109's ability to reduce the formation of hypertrophic scars after revision surgery. An additional clinical trial is evaluating treatment with the same compound in patients with subretinal fibrosis associated with advanced wet age-related macular degeneration.

"I eagerly await the day when the first company – whoever that may be –



gets an RNAi product approved."

We have also initiated an immunooncology program that will initially focus on cell-based therapies for the treatment of cancer. This approach builds on well-established methodologies of adoptive cell transfer, in which immune cells are isolated. expanded and processed to optimize their anti-tumor activity. We have developed an approach for the ex vivo treatment of adoptively transferred cells to silence immune checkpoint genes, and make the cells more effective in the immunosuppressive tumor microenvironment. We can target multiple immune checkpoints in a single cell-based therapeutic treatment that will hopefully come with fewer of the side effects associated with combination antibody treatments, while potentially providing similar efficacy.

I eagerly await the day when the first company – whoever that may be – gets an RNAi therapeutic approved. Whoever reaches the finish line first will stand in the media spotlight but, more importantly, will signal to the rest of the biomedical community that a new era in drug development has arrived.

Collaborating for the Clinical Win

Sitting Down With... Ron Heeren, Director of Maastricht MultiModal Molecular Imaging Institute (M4I), Distinguished Professor and Limburg Chair at Maastricht University, the Netherlands.

December 2017

Is there a common theme to your career?

Change and passion. I always told myself that every ten years I would do something different. I was trained as a physicist, became a professor in chemistry, and now I am working in a molecular imaging institute housed in a medical department. I stay enthused about what I am doing by making it worthwhile – and changing my environment and research topics helps to keep my passion for science alive. **So, what motivates you?**

Curiosity, enthusiasm, passion – wanting to be an explorer. I'm very lucky to have been able to set up this wonderful institute within the University of Maastricht. A collaborator of ours said to me recently, "I feel like a kid in a candy store!" And that's exactly the environment that we wanted to create – it encourages people to do great analytical science and great molecular imaging. Here, I get to define the questions I'd like to ask and the best tools for answering those questions, and so explore the world around me. How much better does it get?

Tell us about your current research...

Our major focus is using molecular imaging based on mass spectrometry to assess the molecular content of tissues, so we can provide clinicians and medical researchers with feedback on the cellular phenotype. Say a surgeon operates on a patient and removes a tumor; it's sent to a pathologist, who takes a section for hemotoxylin-eosin staining and inspection, and we take an adjacent section for mass spec imaging analysis. Half an hour later, we aim to provide the surgeon and pathologist with our findings and see how they match. In a second clinical research project - intraoperative diagnostics - we are analyzing the smoke from laser surgery to give surgeons the information they need in real time. Most of our research is biomedical, but we also use MS imaging to study new biomaterials, regenerative medicine, drug distribution and metabolism, forensics, and even historical paintings.

And recent findings?

In a study on cholangiocarcinoma we identified several peptides, proteins and lipids that distinguish transient neoplastic tissue (on its way to becoming a tumor) from full-blown tumor cells and healthy tissue. In other words, we can assess a single piece of tissue and define different cellular tissue phenotypes, which helps us to assess how clean the surgical margin of a tumor is; has the surgeon removed enough? Is there any cancerous or precancerous tissue remaining?

How close are these tools to the clinic?

We've developed technology and methods for a number of diseases. The next step is validation – we need to work with large patient cohorts to make sure that the markers we have found in ten organs are stable and robust in 100 organs or 1,000 organs. That's one reason the group is based in Maastricht, which gives us access to a dynamic clinical environment with a large volume of samples.

To establish a validated clinical diagnostic test, several major clinical studies and a lot of administrative and legal paperwork are needed. It's difficult to predict how long it will take, but I hope that within 3-5 years some of these tests will be routinely available. For now, they are still in the research phase.

What is the role of analytical scientists in clinical collaborations?

Typically, the analytical scientist provides the technology and data needed to make a clinical assessment. The analytical scientist also needs to understand the questions or challenges faced by medical practitioners, and how new techniques could fit into the clinical workflow. They are the axle in the wheel – a project manager, analytical scientist and communicator all in one. As an analytical scientist, you are too often forced into the role of a service provider, and that's not the way we work. Our ethos is CORE – collaborative, open research and education.

What's the secret to successful collaboration?

Crucial to the success of this type of multidisciplinary research is a willingness to give something up to ultimately gain a lot more. Sometimes we generate great results, but rather than presenting them at an analytical science conference ourselves, we ask the surgeons on the team to present them at a surgery conference. We may give up a



little visibility in our own community but, in the long term, we have a much bigger impact in the clinical field – where it really matters.

How important have your communication skills been in your career?

Absolutely crucial. Without good communication, it is impossible to start new projects or to motivate other researchers to move in the same direction. To my mind, communication is nothing more than showing how passionate you are about what you're doing, how much fun you're having while doing it, and how good the results are. It's also important for me to showcase and emphasize the importance of the work of my (younger) colleagues, without whom I would be dead in the water.

What does the perfect team look like?

I believe in heterogeneous teams. My current group has a very international flavor and is 50 percent female - and that makes it a very culturally diverse group. Diversity in passions and interests is also crucial for the success of any team - we have specialists in everything from clinical science to bioinformatics. But they all share one thing: a passion for research. The enthusiasm of young researchers really helps with building such an institute. We aim to come up with new and fresh ideas, and that characterizes my staff: young, willing, enthusiastic, eager, and impassioned by their research.

What are your career highlights, so far?

From a research perspective, the best thing has been seeing how the ideas we had ten years ago are being realized in the clinical environment. I've always believed our work would make a difference for patients, and seeing that start to happen is wonderful. Talking about it at TEDxMaastricht recently was an absolute highlight for me, personally. Molecular structure plays a much bigger role in disease than we previously thought, and being able to visualize that with the technology we've developed is fantastic. It's also great to have the chance to improve the instruments we all rely on, by collaborating with the companies who make them.

Trimming the Fat

Could intensive weight management replace medication as the first line of treatment for type II diabetes?

December 2017

At a Glance

- Diabetes has long been regarded as a lifelong progressive condition – and often, medication and intervention must increase over time
- A recent study has found that significant weight loss could put diabetic patients into remission, removing the need for other treatments
- The next challenge is to help patients lose weight in a primary care setting – and to maintain a lighter weight over time
- If weight loss proves to be a successful strategy in the long term, it could potentially replace medication as the first option for patients

Type II diabetes is a big contributor to disease and disability around the world, and can result in a range of side effects, from loss of limbs, to coma and death. Medicine can be prescribed to manage it, but should drugs be the first port of call? A recent UK study has found that weight management – already recommended for those with diabetes – could have an even bigger effect than previously thought, even years after disease onset. In the trial, participants went on a meal replacement formula diet of 825–853 calories per day for several months, followed by gradual reintroduction of food. Over half of the 306 people who took part achieved remission from their diabetes (1). We spoke to Roy Taylor, Professor of Medicine and Metabolism at Newcastle University, to find out more.

How did you get involved in this research?

I have been looking after people with diabetes since 1976, and since 1981 have been researching the causes of type II diabetes, which has always been regarded as a lifelong and inevitably progressive disease. More and more tablets are required, and eventually insulin injections. This appears to be caused by the insulin producing cells of the pancreas slowly dying over time.

But in 2006, blood sugar levels in people with type 2 diabetes were shown to fall to normal within seven days after bariatric surgery (2). And because research at that time was revealing the link between excess fat in the liver and the failure of insulin effects on the liver, the explanation for the normalized sugar after bariatric surgery seemed obvious. The people undergoing surgery would suddenly have to stop eating - nil by mouth. That would rapidly deplete liver fat. Then the liver would respond properly to insulin, and stop pumping sugar into the blood.

But could this also explain the problem with the pancreas? Excess fat in the liver causes excess fat in the blood, and excess fat delivered to the pancreas. Some early studies had shown that this long term exposure to fat would cause the insulin producing cells to stop working.

I published these ideas as the Twin Cycle Hypothesis (3) (one vicious cycle in the liver interacting with a second vicious cycle in the pancreas). And now we had a hypothesis to test.

My first test of the Twin Cycle Hypothesis was published in 2011. It showed that a 700 calorie diet (achieving 15 kg weight loss in eight weeks) would return blood sugar to normal within seven days because of a fall in liver fat; we also showed that over eight weeks the level of fat in the pancreas gradually fell, and the insulin producing cells steadily returned to normal function. The outcomes were all the more remarkable as the tablets used to control blood sugar had been stopped on day one of the diet.

Next, we set about testing whether the reversal would last after returning to normal eating. It did!

And whilst that study was underway (and once we had already seen that the effect was long term, provided weight was not regained), we asked our next question: Could a simple but effective weight loss program be delivered in primary care? And the DiRECT study was born, funded by Diabetes UK.

Did you expect weight loss to have such a dramatic impact?

In short, yes! In view of our work on small groups over the last decade, we expected a dramatic impact – but only if the practice nurses involved could effectively deliver the program. By using the low calorie diet, people feel better very rapidly. Within a couple of weeks they are delighted by their weight loss, running upstairs and getting up without a struggle. The commonest



comment is "I feel 10 years younger!" – which is a great incentive for people to continue with the program.

What are the challenges when working with patients to achieve and maintain weight loss?

It is really important to emphasize that substantial weight loss can only be achieved by decreasing food intake, and that additional exercise should actually be avoided during weight loss - which may seem counterintuitive. Misinterpretation of epidemiological data has led to widespread advice to take up exercise and eat less if you want to lose weight, and that is a recipe for failure because of compensatory eating (partly conscious, and partly unconscious). The impressive weight loss in all of our studies is achieved solely by cutting down food intake. However, it is also important to add that for long term avoidance of weight regain, daily increased physical activity as part of everyday life is very useful, along with modest food limitation.

But what support is most effective in helping people avoid regaining the weight they've lost? That's the really important question. Somehow, we must find a way to work with and regulate food companies, who spend huge sums persuading the population to eat between meals, to eat unsatisfying prepared portions, and who are offering unreasonable portions sizes at bargain prices. In a democracy, it's a tough challenge.

From a research perspective, we also we need to know much more about the insulin producing cells (beta cells) and their de-differentiation.

What's next?

We are at a watershed moment for type II diabetes understanding and management. We have shown that this disease can be reversed to normal by substantial weight loss, and we describe a practical way to achieve that weight loss. The first step in managing type II diabetes on diagnosis must now be to explain to the individual that they have a choice – a lifetime with diabetes, tablets and complications – or substantial weight loss and longterm avoidance of weight regain. Drugs should no longer be the first line.

Ongoing research will answer the

questions of whether diabetes stays away long term, and a formal health economic analysis will determine the cost savings. As prescription of tablets to control blood sugar cost over £1 billion annually in the UK alone, and as the number of blood pressure tablets required is halved for patients on this program, the potential savings are huge. But the greatest savings will come in the form of better health outcomes for patients: less blindness, less amputation and less kidney failure.

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Distribution:

The Translational Scientist, is published by Texere Publishing Ltd and is distributed in the US by UKP Worldwide, 3390 Rand Road, South Plainfield, NJ 07080

Periodicals postage paid at South Plainfield, NJ

POSTMASTER: Send US address changes to (Title), (Publisher) C/O 3390 Rand Road, South Plainfield NJ 07080.

Single copy sales £15 (plus postage, cost available on request *tracey. nicholls@texerepublishing.com*)

Annual subscription for non-qualified recipients $\pounds 110$