# *In sententiam: occasional commentary and opinion*

## *Archive: February to July 2011*

## Anti-smoking vaccines: out of puff? (uploaded 22nd July 2011)

Like many, I was a "social smoker" in my late teens and early twenties, enjoying the occasional cigarette along with a drink and good company. I was fortunate never to become hooked, although thirty years on, a whiff of cigarette smoke can still kick off a wistful longing. Government health campaigns, smoking bans and societal pressures have thankfully reduced the prevalence of smoking, although rates in the UK have remained at around 20% of men and women aged over 16 years. Despite dedicated campaigns and pharmaceutical support in the shape of nicotine replacement products, nicotine agonists and antagonists, quit rates are low, at around 7% after 20 months.

Nicotine hits the brain within 10 seconds of inhalation, causing dopamine release which in turn hits the pleasure centres. Repeated exposure results in tolerance and withdrawal cravings, leading to physical dependence. Nicotine replacement therapy works by taking the edge of withdrawal symptoms, allowing the quitter to wean themselves off smoking at their own pace. Nicotine agonists reduce uptake of dopamine and norepinephrine which also reduces withdrawal symptoms. Nicotine antagonists compete with nicotine for binding to its receptor but do not cause dopamine release and the consequent pleasurable high. Individual responses to all of these therapies are notoriously variable.

Anti-smoking vaccination is based on the simple concept that nicotine can be efficiently sequestered by antibodies before it can get through the blood brain barrier. Although the principle was demonstrated in animals well over a decade ago, demonstration of meaningful results in human studies has so far eluded substantial commercial and academic effort. Our immune systems are not naturally able to mount a potent antibody response against molecules as small as nicotine, which needs to be chemically linked to large carrier proteins or virus-like protein particles in order to be recognised. Scale up, even to clinical trial batch size can have its problems and at least one product candidate has been scuppered by manufacturing issues. Nicotine-protein conjugates are not strongly immunogenic, requiring multiple booster shots to attain detectable antibody levels and not all individuals are genetically able to mount an anti-nicotine antibody response.

Clinical results obtained with different vaccines have proved to be no better than placebo in reducing the number of cigarettes consumed or benefiting short-term relapse rates. A recent Phase III study performed by NABI Pharmaceuticals in 1000 subjects found no difference in abstinence rates between vaccinated and non-vaccinated individuals. Results from a second Phase III study still need to be analysed but even if there is a glimmer of benefit, this still needs to be stacked up against the finite but established benefit of current drug therapies. Despite the support of government grants and a partnering deal with GSK, NABI's vaccine is unlikely to reach submission stage, but might, at best, assist in the design of future vaccines. It looks like quitters are going to remain dependent on a mixture of pills, patches and gums, sympathy and sheer grit for the foreseeable future.

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## Bugs versus drugs (uploaded 30th April 2011)

April has been a busy month for anyone interested in antibiotic resistance. The WHO's World Health Day message was "Combat drug resistance! No action today, no cure tomorrow", a position echoed in a letter sent to President Obama by the Infectious Diseases Society of America. A number of articles in the popular press were spurred by a report that the NDM-1 gene, a now notorious marker of antibiotic resistance, was readily recovered from sewage and drinking water samples collected in New Delhi.

NDM-1 (New Delhi metallo-beta-lactamase 1) has the unwelcome property of encoding an enzyme which inhibits a broad class of antibiotics, greatly restricting treatment options. While the naming of NDM-1 after the nation's capital drew much fury from the Indian government, there is no denying that its apparent widespread distribution in a city of 14 million people is not good news for anyone, given the potential rate of global spread through travel and migration.

Cries of "the end of the world as we know it" in relation to the threat of antibiotic resistance are hardly new, but the (predictable) appearance of a threat such as NDM-1 does occur at a time when the development of antibiotics with genuinely new mechanisms of action is at an all time low.

The reality is that, even with a current global market of around $42 billion, antibiotic development does not make economic sense for the major pharmaceutical companies. A misplaced belief that there were no new opportunities in the treatment of bacterial infection resulted in a major decline in R&D in the early 1990s, followed by a short-lived renaissance as companies looked to tackle emerging antibiotic resistance, and then a mass exodus, leaving only four or so majors still with an active involvement. Johnson and Johnson announced their strategic exit from the arena this month.

Reasons for abandonment include patent expiry and generic encroachment, low prices for the most commonly used first line drugs, declining antibiotic use in the developed markets and careful husbanding of newer, more expensive agents to delay the emergence of resistance, more demanding regulatory criteria and the consequent increase in development time and cost, plus the sheer difficulty of discovering and exploiting viable antimicrobial targets.

While antibiotic R&D has transferred to the biotech sector, limited resources and the overhanging lack of interest from potential large pharmaceutical partners able to provide the cash and muscle to register and market drugs drastically curtails the ability of small companies to redress the shortage of new agents.

What to do? Good stewardship of our current antibiotics along with active surveillance will buy a little more time but powerful incentives will be needed to bring big pharma back into the battle, particularly a realistic pricing structure for new antibiotics, direct and indirect R&D subsidies, commitments to expedited regulatory review and possibly intellectual property extensions. When to do it? Right now. The WHO "no action today, no cure tomorrow" message is not merely a sound bite. After all, the flight time from New Delhi to London is only around nine hours.

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# PSA screening: Imperfect? Yes, replaceable, no (uploaded 31st March 2011)

All aspects of cancer are emotive and complex, a combination which often conspires to cloud general understanding. For example, while cancer screening would intuitively appear to be a worthwhile strategy for reducing mortality, the technical limitations of testing and the variable course that cancer can take in an individual from first diagnosis significantly lessens the value of large-scale surveillance. This is well illustrated by prostate cancer, whether screening is done using a well-educated and lubricated finger or by measuring blood levels of PSA (prostate-specific antigen), the concentration of which vaguely correlates with the presence of cancer, or both.

Prostate cancer is rare in men under 40 but not uncommon in those aged 70 and over, although its generally slow progression in the latter means that death is far likelier to result from other age related failings: more men die with prostate cancer than because of it. While some advocate annual screening beginning at age 50, the prevalence of prostate cancer in this age group is still low, meaning that many men need to be screened to find even one extra case of prostate cancer and overtreatment of a condition that may never become life threatening.

The value of prostate cancer testing could be boosted by finding a more specific and sensitive marker than PSA, the level of which can rise for a variety of reasons other than cancer and by the use of prognostic markers which can reliably predict the likely rate of disease progression.

A host of potential replacements for PSA are under evaluation, several of which are detectable in urine rather than requiring a blood sample. The most advanced of these markers, PCA3, has been evaluated in a number of large studies. Broadly, PCA appears to be a more specific marker for prostate cancer than PSA, but with a lower sensitivity and a weaker correlation with prostate size and cancer stage. PCA3 looks at best to be a promising adjunct to PSA screening but not a superior replacement.

Reliable prognostic markers are much further away than a better screening test. The ready association of specific genes, gene products or even biochemical metabolites is confounded by the heterogeneity of prostate cancers and the need to follow a substantial number of individuals with prostate cancer for a long period of time to establish outcomes. Lumping of markers may eventual assist in determining whether a continuation of “watchful waiting” or initiation of aggressive chemotherapy is warranted.

Better prostate cancer screening and prognosis will not be with us anytime soon, but it’s worth remembering that PSA screening has been in common use for less than 20 years and as with any diagnostic method, it takes time and substantial clinical usage to get the best out of it. Overall prostate cancer risk prediction is greatly improved when PSA levels are considered in the context of prostate volume, family history, ethnic background and age. Flawed as it is, PSA screening had undoubtedly saved and prolonged the lives of many men and will retain its importance well into the next twenty years.

**Update:** Just after posting the piece above, I became aware of this study http://www.bmj.com/content/342/bmj.d1539 (Open access) which concludes that, based on a 20 years follow up, deaths from prostate cancer were no different among those who had and who had not been screened. These findings reinforce the position that population-based cancer screening is, unfortunately, unlikely to be worth the time and effort to prevent unnecessary deaths at societal level, but this does not mean that current efforts to find reliable means of confirming the presence or absence of prostate cancer in the context of other risk factors (age, prostate size, ethnicity) and in matching clinical management to predicted outcome are not needed.

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## A new light in cystic fibrosis treatment? (uploaded 23rd February 2011)

During the early days of biotech, a cure for cystic fibrosis (CF) was always just around the corner, requiring only the simple step of inserting the right DNA sequence to correct the defective gene. Although the first steps around the corner were taken 18 years ago, gene therapy has yet to deliver, although pursuit of this goal has added hugely to an understanding of the complex genetics involved in CF. Pharmaceutical development in CF treatment has been evolutionary rather than revolutionary, delivering modestly better means to manage symptoms caused by mucus build-up and bacterial infection.

Recent clinical data reported data from Vertex Pharmaceuticals (STRIVE Phase III study) hint that there may be a revolution in CF treatment on the horizon. VX-770 is unique in that it appears to correct a defect in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, although it will work only in individuals with a specific genetic mutation, designated G55ID. Drug treatment resulted in a significant improvement in the lung capacity of treated CF sufferers, with other benefits including fewer pulmonary exacerbations (that is, less episodes of diminished lung function), weight gain and higher chloride levels in sweat (indicating some restoration of chloride ion transport, a function normally compromised in CF patients).

It's still early days, with only 83 people treated in the study, although with few adverse events. A study in children aged between 6 and 11 years and who have at least one copy of the G551D mutation will report later this year. Only around 4% of CF sufferers have this mutation. A second Vertex drug designed to function in those individuals with the more common F508del mutation is in early clinical development.

Even if successful in the majority of CF sufferers, defect correction by drug action will never be a cure. However, safe oral drug treatment would significantly improve the quality of life many thousands of CF sufferers and hopefully extend their relatively short anticipated adult life span (CF suffers have a median survival rate of around 37 years).

VX-770 also serves as a reminder that, while analysis of the human genome has failed as a productive strategy for the development of new medicines, it might still result in odd but significant successes. Vertex's efforts have been largely funded (that's $75 million of large) by the not-for-profit Cystic Fibrosis Foundation, and indicates that if done right, private enterprise and charity can work well together.

***Vertex press release:*** *http://investors.vrtx.com/releasedetail.cfm?ReleaseID=551869*

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# Failed scar-reduction drug could still leave its mark (uploaded 17th February 2011)

The likely outcomes arising from the failure of Renovo's Juvista into show benefit in pivotal clinical studies are sadly all too predictable: another UK biopharmaceutical company in a death spiral and the almost certain abandonment of a once potentially first-in-class drug product.

Juvista's clinical development has been demanding, even by biotech standards. Early clinical studies necessitated a large number of subjects (around 1600) to provide not only essential safety and efficacy data, but to define and validate outcomes and study designs likely to be acceptable to regulatory agencies. Although early clinical studies were not uniformly successful, Renovo were able to attract a credible development and marketing partner, Shire and to embark on a European Phase III clinical study, comparing the benefits of Justiva on scar appearance 12 months after scar revision surgery. Neither clinical investigators nor the patients themselves could discern a significant difference between Justiva or placebo treatment.

Scarring remains a poorly understood process and is the consequence of abnormal deposition and organisation of collagen fibres in the skin. The underlying cause appears to be defects in the regeneration of the normal skin structure after injury, rather than an inherent change in skin composition. It's long been known that foetal tissue has the capacity to self-repair without scarring, a property lost in adult skin, prompting the analysis of differences between foetal and adult wounds to identify potential therapeutic leads. The rationale behind the choice of Justiva (avotermin, recombinant human Transforming Growth Factor Beta 3 or TGFß3) is that this molecule is found in higher concentrations in healing foetal wounds, whereas the related molecules TGFß1 and TGFß2 dominate in adult wounds.

Few other candidate drugs are in clinical development for the reduction of scar formation. A second candidate from Renovo (Prevascar, recombinant human IL10) was, like Justiva, identified through studying foetal wound healing, although whether it has significant clinical utility remains to be established. A small synthetic peptide drug (AZX-100: Capstone Therapeutics) is aimed at disrupting the mechanisms leading to abnormal collagen deposition, although a Phase II pilot study failed to find any benefit in keloid scarring. CoDa Therapeutics has obtained limited, but positive data in chronic leg ulcers with Nexagon, an oligonucleotide which downregulates the expression of a substance known to inhibit healing.

There's now little chance of Juvista reaching the market but as a pioneering product, it has shaped the clinical development and regulatory paths and hurdles for future scar-reduction therapies.

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## "Silence not golden?"(uploaded 9th February 2011)

Biotech would be a dull sector without the promise of truly game-changing technologies and completely new drug classes. A few have even delivered, maybe not often, but spectacularly in the case of therapeutic antibodies and certain targeted small molecule therapies.

For the best part of 10 years, top of the "most promising" list "has been interference RNA, ("RNAi"), a means of exploiting otherwise undruggable protein targets by specifically turning off ("silencing") the genes responsible for their expression through the use of snippets of double-stranded RNA (small-interference RNA- "siRNA "). Biotech can boast few, if any, slam-dunks when it comes to turning concepts into treatments, but a combination of technical difficulty and changing pharmaceutical company priorities appears to be squeezing RNAi drug development particularly hard.

Achieving effective delivery and targeting of RNAi (so far, mainly to tumours) has proved particularly onerous. Injection can achieve local delivery but systemic delivery has proved elusive, although nanoparticle approaches are making some headway. Along with this are challenges posed by the short half-life of siRNA, the need to administer large quantities of siRNA to attain measurable biological effect and that no single delivery technique will target all tissues. Non-specific stimulation of the innate immune system is another headache, both as a potential cause of side effects and a confounding factor when interpreting the significance of treatment responses.

siRNA drugs have a preference for the liver and several RNAi companies are exploiting this propensity to tackle liver cancer or cancers which have spread to the liver. Other solid tumours in the sights of siRNA developers include brain and breast cancers. Systemic delivery of siRNA has been demonstrated in one small clinical study using transferrin as a carrier, being an iron-rich protein for which cancer cells have a particular appetite.

Big pharma's enthusiasm for RNAi does appear to be cooling off, with both Pfizer and Abbott closing their respective development units and Roche, Novartis and Merck no longer throwing cash into RNAi alliances. This may be as much a sign of the times, as drug companies realign and refocus their R&D efforts and not solely growing disenchantment with RNAi progress. In the meantime, certain previously elusive cancer drug targets are proving to be amenable to antibody, small molecule and even antisense approaches (the latter being the granddaddy of RNA based therapeutics).

A well-researched and balanced article in the New York Times[1] describing the ups and downs of RNAi development rightly points out that monoclonal antibodies took the best part of 20 years to make real clinical and commercial impact and that RNAi is not necessarily standing on the cliff edge. As with good comedy, the popular success of RNAi looks to be heavily dependent on delivery.

1. *Drugmakers' Fever for the Power of RNA Interference Has Cooled. Andrew Pollack. The New York Times, February 7, 2011*

(For the music trivialistas out there, "Silence is Golden" was a hit for The Tremeloes on both sides of the Atlantic in 1967. Lyrics were by members of The Four Seasons (of "Rag Doll" fame).