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Feasibility, rationale and prospects for therapeutic cocaine vaccines

NDARC Technical Report No. 168

FEASIBILITY, RATIONALE AND PROSPECTS FOR THERAPEUTIC COCAINE VACCINES

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ISBN: 1 877027 56 1

THIS REPORT WAS FUNDED BY THE AUSTRALIAN GOVERNMENT DEPARTMENT OF HEALTH AND AGEING

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EXECUTIVE SUMMARY

Cocaine dependence is a highly treatment-refractory condition. Cocaine is a potent and efficient drug that acts rapidly on the brain's reward pathways to deliver the cocaine high. To-date there have been no pharmacological treatments recognised as more effective than placebo in initiating and maintaining abstinence in cocaine dependent patients (Shearer & Gowing, 2004) while the success of psychosocial interventions has been modest (Simpson et al., 2002). This is in contrast to heroin, nicotine and alcohol dependence where a range of effective pharmacological treatment modalities exist. This unmet treatment need has prompted a search for novel approaches such as vaccines. Cocaine vaccines are designed to stimulate antibodies that target cocaine molecules in the bloodstream and thereby reduce the amount of cocaine reaching the brain. They differ from other pharmacological approaches that have targeted neurotransmitter sites within the brain. The potential advantages of an effective cocaine vaccine include assured compliance, fewer side effects than CNS-acting drugs and an effective therapy where none has previously existed.

The harnessing of the body's natural immune system to protect against illness and disease represented an historic advance in modern medicine. Recent developments in biotechnology have extended vaccines from their traditional protective role to therapeutic uses in diseases including HIV/AIDS, cancer, allergies and the prevention of organ transplant rejection. Addiction vaccines extend the use of this technology to a complex disorder with physiological, psychological and behavioural aspects. There are three main approaches to cocaine vaccination: (1) active immunisation seeks to stimulate the immune system to produce cocaine antibodies that recognise and bind to cocaine molecules or the active metabolites with resultant cocaine-antibody complexes that are too large to cross the blood brain barrier; (2) passive immunisation does not seek to elicit an immune response but rather directly loads in monoclonal antibodies that have been produced in the laboratory; and (3) passive immunisation with catalytic antibodies that seek to increase the rate of cocaine metabolism rendering cocaine inactive before it can reach the brain. The effectiveness and duration of these approaches vary - most are unlikely to be permanent. Potential therapeutic applications of vaccines include the management of overdose, detoxification and as a pharmacological supplement to relapse prevention.

Pre-clinical studies have shown that cocaine vaccines block the effects of cocaine in animal models reducing cocaine self-administration and protecting against lethal doses (Bunce et al., 2003). This review has identified four potential candidate vaccines for cocaine disorders. One of these has progressed to phase II trials in humans with three still in pre-clinical development. Human trials of one vaccine, TA-CD, have found that it was well tolerated and provoked an immune response to cocaine that peaked at about 3 months (Kosten et al., 2002). However, there are technical, economic and ethical challenges for the development of immunotherapy for cocaine. Technical barriers include underlying behavioural pathology, craving, drug substitution and inadequate duration of effective antibody levels. There may also be risks of overdose should users attempt to override vaccines with high doses of cocaine. Vaccines are associated in the public mind with prevention or protection and responses to a 'vice' vaccine have been alarmist and cynical. However, the effects of the therapeutic vaccines under investigation have been temporary and do not offer long-term protection from cocaine effects. Rather, they offer the potential to provide cocaine users with a valuable and rare

therapeutic window or respite to engage with psychosocial therapy and make the lifestyle and personal changes central to relapse prevention.

The cost associated with the production of cocaine vaccines is considerable and several vaccine candidates have failed due to difficulties in achieving commercial scale production. The burden of disease in Australia associated with cocaine-related disorders may not be sufficient to justify the substantial investment required to conduct large scale original research studies into cocaine vaccines. Research into vaccines targeted towards other drugs of dependence such as nicotine may be more viable in the Australian context. It will be many years before a clinically useful cocaine vaccine becomes available. Earlier availability through clinical trials or special access may occur although this may be limited by substantial manufacturing costs. Vaccines are unlikely to completely block cocaine effects or act as stand-alone treatments, but they may be a valuable additional therapeutic pathway in conjunction with psychosocial and pharmacological approaches.

ACKNOWLEDGEMENTS

The authors thank Kathleen Kantak, Campbell Bunce, Chris Doran, Linda Gowing, Ingrid van Beek and Alex Wodak for their comments on earlier drafts of this report. This report was funded by the Australian Government Departmetn of Health and Ageing.

1. BACKGROUND TO COCAINE USE

1.1 Prevalence of cocaine use

Cocaine is a potent stimulant drug derived from the coca plant cultivated at high altitudes in the South American Andes. Cocaine is illegally imported into Australia in powder form and is usually consumed by snorting or injecting; the use by smoking of crack cocaine is very rare. Cocaine powder is expensive relative to other drugs with a stable street price of AUD$200 per gram (Darke et al., 2002). Cocaine induces feelings of euphoria, well-being, energy and alertness through elevation of synaptic monoamine neurotransmitters including dopamine, serotonin and noradrenaline. Cocaine effects are intense but short-lived (half-life of 20 minutes) often leading to binge use and costly habits. Life-time reported use of cocaine among Australian adults has remained steady at 4.4% or around 700,000 (AIHW, 2002). Approximately 16% of cocaine users who used in the past year (over 30,000 users) could be classified as regular users (frequency of use monthly or greater). Although males were more likely to report lifetime use of cocaine, females who had recently used cocaine were more likely to be frequent users.

Concerns in the 1980s that Australia could experience a cocaine epidemic as experienced in the United States did not eventuate although cocaine use has rapidly escalated in Europe over the 1990s (Corkery, 2002). Research into prevalence and patterns of use of cocaine conducted in the late 1980s and early 1990s found that cocaine use among recreational Australian drug users was typically of low frequency and appeared to be associated with low levels of harm (Moosburger et al., (1990); Mugford (1994); Hando et al., 1997). Further, cost and availability mitigated against a high potential market for cocaine (Hall et al., (1991); Spooner et al., (1993); Homel et al., (1990)). The social and geographic concentration of cocaine use in Australia may have reduced the visibility of use and harms (Hando et al., 1997). The Illicit Drug Reporting System, an early warning drug use monitoring system, concluded that cocaine use in Sydney had increased substantially over the period 1996 to 2000 and had become entrenched in the Sydney illicit drug market (Darke et al., 2002). In the 2001 survey, 29% of injecting drug users reported daily cocaine use compared to 9% in 2000 although these findings should be understood in the light of sharp reductions in the availability of heroin in that period.

1.2 Nature of cocaine harms

There are a range of physical, psychological and social harms associated with both acute and chronic cocaine use. Cocaine use has been implicated in serious cardiovascular (Vasica and Tennant, 2002; Lange & Hillis, 2001), neurological (Neimann, Haapaniemi & Hillbom (2000); Pettiti et al., 1998), gastrointestinal and respiratory problems (Warner, 1993). Various routes of drug administration present their own problems including ulceration and perforation of nasal passages and aggravation of respiratory conditions such as asthma (Warner, 1993). Injecting use can lead to vein damage particularly due to the vasoconstrictive effect of cocaine. Compulsive binge behaviour, frequent and frenetic injecting due to the short activity of cocaine can aggravate vein damage leading to severe ulceration and infections such as endocarditis. Cocaine injection has also been associated with elevated risk of acquiring blood borne viral infections such as HIV and hepatitis C (Chaisson et al., 1989; Darke et al., 2002; van Beek et al., 2001). Social problems can include violent, reckless criminal or other anti-social behaviour (van Beek

et al., 2001; Darke at el., 2002). The psychological effects of long term high dose cocaine use often manifest in a transient but serious psychosis marked by paranoid ideation. Dependent patterns of cocaine use are characterised by regular use (daily or several times per week), injecting use, long histories of use, physical tolerance to high doses, the presence of withdrawal symptoms such as intense cravings, mood swings and sleep disturbance, binge patterns of use and persistent histories of relapse to cocaine use. Finally, chronic users may exhibit symptoms suggestive of depression or attention deficit disorder (Gawin & Kleber, 1984).

The proportion of people presenting to drug and alcohol services with cocaine problems in Australia has been stable at under one percent between 1995 and 2001 (Shand and Mattick, 2002). Adverse effects associated with acute cocaine toxicity are very rare events in Australia. Very few deaths have cocaine as an underlying cause: more often cocaine is mentioned in connection with opiate related deaths (Degenhardt et al., 2003). This is in contrast to the US experience where the rating of cocaine has increased as a major cause of emergency department visits and deaths (DAWN, 2002). The disparity with the US experience could be explained by the restricted availability of cocaine as reflected in its expense ($200 per gram) and possibly purity. Among injecting drug users, cocaine use is uncommon outside heroin users in Sydney. Cocaine use problems in Australia are generally associated with chronic use such as dependence and blood borne viral risks rather than acute problems of cocaine overdose and mortality.

1.3 Treatment for cocaine use disorders

To date, there have been no pharmacological treatments recognised as more effective than placebo in initiating and maintaining abstinence in cocaine dependent patients (Shearer & Gowing, 2004) while the success of psychosocial interventions has been modest (Simpson et al., 2002). Psychosocially-based therapies including cognitive-behavioural therapy (relapse prevention, motivational interviewing), community reinforcement, individual and group counselling have clinically demonstrated benefits although an enduring challenge is to attract and retain problematic cocaine users (Platt, 1997). This is in contrast to heroin, nicotine and alcohol dependence where a range of effective pharmacological treatment modalities have been developed in conjunction with psycho-social interventions. No pharmacotherapeutic agent has been identified that can either effectively block or mimic the action of cocaine at the receptor site in the human brain without unacceptable side-effects. A recent systematic review of 45 different studies of pharmacological treatments for cocaine dependence including many commonly prescribed anti-depressants, anti-convulsants and dopamimetics found no evidence for efficacy as measured by the presence of cocaine metabolites in urine (de Lima et al., 2002). Recent health and social welfare needs assessments undertaken by two inner city health services (van Beek., et al 2002; Adam et al., 2003) both identified a need for cocaine-specific detoxification services (residential and ambulatory).

2. INTRODUCTION TO COCAINE VACCINES

2.1 General principles of immunotherapy

Immunisation is an approach to the prevention and treatment of illness based on inducing immune system resistance to disease-causing agents also known as antigens. Exposure of an individual to deactivated antigens contained in a vaccine triggers the immune system to recognise the antigen and produce specific antibodies that bind and deactivate the target antigen. The advent of vaccines was an important breakthrough in the prevention of infectious diseases. The first vaccines induced immunity to disease-causing micro-organisms such as cowpox, polio, smallpox and rubella. Immune system based treatments have extended beyond disease prevention to the treatment of conditions including cancer, organ transplant rejection, HIV/AIDS, allergies and contraception (Metens & Monteyne, 2002).

Addiction vaccines further extend immunotherapy to a disorder that has physical, psychological and behavioural manifestations. Drug development in addiction medicine has largely been based on small molecule technology that crosses the blood-brain barrier to act at neuroreceptors implicated in drug dependence either to block drug effects (antagonists) or substitute drug effects (agonists) or a combination of these actions. Vaccination or immunotherapy, based upon large molecule technology, does not seek to cross the blood-brain barrier but rather targets drug molecules in the circulatory system through the use of antibodies or enzymes. Small molecules, such as cocaine and its active metabolites, are too small to be recognised by the immune system. In order to induce a cocaine-specific antibody, the cocaine molecule must be attached to a carrier protein that can be recognised by the body's immune system. Sometimes this can be a deactivated or weakened pathogen (such as cholera) or antibodies derived from other animals.

Early research into heroin vaccines in rhesus monkeys was discontinued as effective antibody levels did not last beyond a few weeks and the heroin blockade could be overcome when higher doses of heroin were available (Bonese et al., 1974). In addition, other pharmacotherapies for heroin dependence were reporting excellent results including the opioid antagonist, naltrexone, which could achieve 100% opioid receptor blockades. Advances particularly related to the proteins to which the cocaine derivatives are attached, appear to have largely overcome the earlier problems of unstable or saturated antibody levels experienced with heroin vaccination. Indeed, recent success in the development of cocaine vaccines has prompted new interest in developing heroin vaccines (Kantak, 2003).

2.2 Rationale

A major incentive to develop cocaine vaccines has been the failure to identify effective pharmacotherapies in the treatment of cocaine related disorders. No effective pharmacological agents have been found that can either mimic (agonise) or block (antagonise) cocaine effects without unacceptable side effects. A cocaine vaccine offers the potential advantage of few side effects since neuroreceptors are not targeted, and also the important advantage of enhanced compliance due to a longer duration of action. Vaccines targeted towards cocaine may offer respite from the effects of cocaine and

provide a therapeutic window for patients to make the lifestyle and other personal changes necessary to protect against relapse in the longer term. Treatment objectives include relapse prevention, reductions in cocaine use, overdose and reduction of brain and cardiac toxicity (Kantak, 2003).

2.3 Mechanism

Three main methods of immunisation have been studied for use in cocaine disorders: 1) active immunisation; 2) passive immunisation and 3) immunisation with catalytic antibodies (Sparenbourg et al., 1997). Active immunity seeks to trigger a natural antibody response or resistance to cocaine through inoculation with a vaccine. This method can be effective for a few months or years. Passive immunisation involves inoculation with monoclonal antibodies, a single species of molecule produced from laboratory cultured cells. Monoclonal vaccines tend to have a highly specific affinity for target drugs but are also very short-lived. Catalytic antibodies are specific types of monoclonal antibodies that can increase the natural metabolism of cocaine into inert fragments by weakening or cleaving cocaine molecules.

2.4 Preclinical evidence

Animal models, most often involving rat self-administration experiments, have provided support for the proposed mechanism of action of anti-cocaine antibodies through limiting the access of cocaine to brain reward centres. These studies have shown: 1) cocaine vaccines induce an immune response through production of cocaine-specific antibodies (Kantak et al., 2000; Carrera et al., 2001); 2) the antibodies arise even during periods of chronic cocaine administration (Kantak et al., 2001); 3) antibody generation and reduction in cocaine in the brain are correlated (Fox et al., 1996); 4) vaccine pre-treatment prevents the reacquisition of cocaine-seeking behaviour (Carrera et al., 2000); 5) the effect of vaccines may not be over-ridden by increasing the available dose of cocaine (Kantak et al., 2001) and that 6) vaccines have been highly specific to cocaine with no other drug or biological interactions (Bunse et al., 2003). To be effective, cocaine vaccines must not only be specific to cocaine and its active metabolites but also have a high degree of affinity. This is important because the drug-induced reward is related both to the amount of the drug (dose) and the speed with which it achieves the drug effect or "high". Pre-clinical animal model work has supported the treatment rationale and mechanism of action of cocaine vaccines, however, effective antibody levels in humans can ultimately only be established in clinical trials.

2.5 Challenges

Potential disadvantages include the delay to achieving adequate immunogenicity, the risk of autoimmune responses, site reactivity, reversibility requirements, individual responses, the need for intact immune systems and the need for intra muscular injection. Cocaine reaches the brain in only a few seconds and reaches the peak subjective high within minutes when smoked or injected, more slowly when snorted (15-20 minutes) (Volkow et al., 2000). Thus, the immunogenicity (a measure of the strength of the body's immune response to any particular vaccine variant) for addiction vaccines will need to guarantee that antibodies have high affinity for the target cocaine molecules (i.e. find them and bind

or cleave them) and also display persistently high circulatory levels. Unless patients are well motivated and supported there may be a risk of relapse or attempts to overwhelm the vaccine with high doses of cocaine. Further, even a completely effective blockade may be circumvented by moves to other stimulant or sedative drugs.

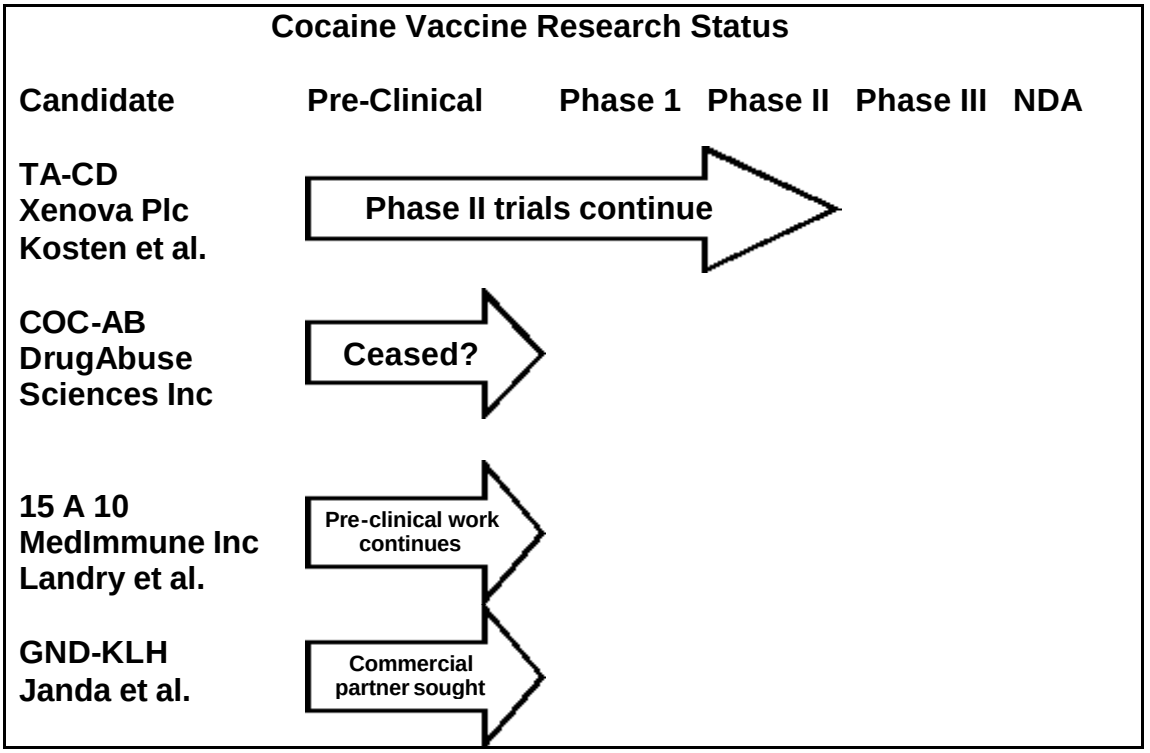
2.6 Development process

Mettens & Monteyne, (2002) suggested four evaluation criteria to test the feasibility of cocaine vaccines: 1) The target cocaine molecules must be accessible to the immune system; 2) The target needs to be identified and neutralised; 3) An unmet treatment need exists due to ineffective medications; and 4) The disorder should be chronic to achieve maximum benefit from a vaccine. The development process for vaccines is comparable to that of other pharmacotherapies which take on average 11 years from pre-clinical testing through the three major phases of clinical trials to Food and Drug Administration (FDA) approval in the USA (Nies & Spielberg, 1996). The local requirements of the Therapeutic Goods Administration (TGA) may extend this time line for final approval for general use in the Australian market. Potential antigens and carrier proteins must be identified and bonded. Animal proteins must then be purified for use in humans. Animal models are then used to test safety, strength and duration of the immune response, effectiveness of suppression of circulatory cocaine and cocaine taking behaviour. This process includes making the vaccine non-toxic to humans and manufacturing development to produce viable quantities. Phase I trials are then needed to assess safety, drug interactions and immunogenicity in healthy volunteers. Phase II trials in selected subjects, such as abstinent patients and current users, evaluate optimal inoculation regimes, dose escalation and indicators of therapeutic efficacy. Phase III trials of safety and efficacy in large samples of patients allow for definitive evidence of benefits and risks of the vaccine candidate.

3. CANDIDATES

3.1 Summary

Four potential cocaine vaccine candidates were identified and their research progress is summarised below. TA-CD, developed by Xenova Plc of the UK, is currently being investigated by Thomas Kosten at Yale University and is by far the most advanced having successfully negotiated phase I and phase II trials. The other three candidates do not appear to have entered phase I mainly due to difficulties in manufacturing viable quantities of vaccine or securing commercial support.



3.2 TA-CD

Vaccination type and mechanism: TA-CD is a therapeutic cocaine vaccine composed of a cocaine derivative (succinylnorcocaine) coupled to an inactive recombinant cholera toxin B carrier protein. Using active immunisation, it is designed to induce cocaine-specific antibodies capable of binding free cocaine in the blood thereby preventing it from reaching the brain. TA-CD-generated antibodies have been shown to decrease self-administration of cocaine in immunised rats (Kantak et al., 2000). The vaccine has been designed for use in relapse prevention and is not effective in overdose as it is an active immunity that takes between 4 to 8 weeks to produce effective antibody levels.

Research status: Phase I human trials have been successfully completed (Kosten et al., 2002). Phase II human trials are underway (Kosten, 2003). A marketable vaccine is not expected to be available until 2009 at the earliest.

Progress: TA-CD has undergone successful phase I safety and immunogenicity testing in 34 abstinent cocaine users in drug-free rehabilitation (Kosten et al., 2002). The vaccine was shown to be well tolerated at all dose levels (13, 82 and 709ìg) and generated cocaine-specific antibodies. Vaccinations were administered at 0, 4 and 8 weeks. A dose-related response was achieved in all subjects. The first detectable antibodies appeared on day 28 which corresponded in time with the initial reductions in cocaine self-administration observed in rats. Peak antibody levels were achieved at 3 months and remained at this level for 4 months and then declined rapidly. There was substantial inter individual variability in the size of the antibody response. Subjects were followed for 12 months after which antibody levels returned to baseline.

A second phase I study was undertaken, in outpatient cocaine users, using an accelerated four-doses schedule (0, 2, 4 and 8 weeks). Patients were enrolled into a cognitive-behavioural program and were required to be cocaine-free for the two weeks prior to vaccination. The vaccine was again well tolerated systemically and locally. Antibodies were detected sooner using the accelerated schedule. Several subjects reported anecdotal evidence of altered perception when using cocaine following administration of the vaccine. Side effects were mild and of brief duration and included slightly raised temperature, sore throat, injection site tenderness, swelling and redness.

Two phase II trials are underway. The first is a dose optimisation study examining immunogenicity of the vaccine in outpatient cocaine users using a four (0 2 4 8-weeks) and five (0 2 4 8 12-weeks) injection dosing schedule. Six shots were found to be optimal in the TA-NIC anti-nicotine vaccine. Reversion to cocaine use after about 12 months appears to be correlated with antibody levels. Results from this second phase IIa dose escalation trial were reported by Thomas Kosten at CPDD in June 2003 (Kosten, 2003). 13 patients received up to 5 injections over 12 weeks using doses up to 360ìg. The vaccine was safe and well tolerated with a dose-related immune response. Twelve subjects completed the treatment course, eight lapsed at some stage and four remained cocaine-free. A total of 30 subjects were enrolled in the phase II trials. A significant number reported reduced cocaine effects during post-treatment relapses to cocaine use (Xenova Plc press release 17th June 2003; Kantak, 2003; Bunce et al., 2003).

The second phase II trial is a cocaine administration study among cocaine users not wishing to quit. In this study, cocaine (0, 25 or 50 mg) will be administered pre- and post-vaccination and physiological and psychometric assessments will be made. The potential for overriding depends whether a 100% blockade is achieved. No problems have been noted in subjects to date however only subjects committed to abstinence have been selected for studies. This question will be further examined in the cocaine administration study.

3.3 GND-KLH

Vaccination type and mechanism: The vaccine consists of a modified cocaine derivative conjugated with keyhole limpet haemocyanin (KLH). The availability of both active and passive immunisation offers treatment potential in both cocaine dependence and overdose.

Research status: The vaccine is ready to move to phase I clinical trials but is delayed until a suitable commercial partner is found (Professor Kim Janda, personal communication July, 2003).

Progress: GND-keyhole limpet hemocyanin (GND) is a second generation cocaine vaccine that has been shown to suppress the psychomotor effects of cocaine for 12 days in rats (Carrera et al., 2001) The effect was enhanced in repeated cocaine challenges and prevented priming-induced reinstatement in abstinent rats trained to self-administer cocaine. The study also showed a dramatic increase when active and passive immunisation were administered concurrently. This appears to be the optimal therapy (combined active/passive with boosters). GND superceded GNC which was not successful when rats had unlimited access to cocaine (Johnson & Ettinger, 2000).

3.4 15 A 10

Vaccination type and mechanism: Catalytic antibodies have been modelled on the cocaine-metabolising properties of the human enzyme butyrylcholinesterase (BChE). Cocaine is an ideal candidate for a catalytic antibody because it can be deactivated by a simple cleavage reaction that yields two inactive products, benzoic acid and ecgonine methyl ester. This is in contrast to cleaving heroin which produces morphine. An enzyme already exists in human blood (butyrylcholinesterase) that does this but at a rate too slow to make any difference to peak cocaine concentrations in plasma that are the basis of cocaine's high. Catalytic antibodies are specific types of monoclonal antibodies that destabilise cocaine molecules causing them to break down into non-toxic or non-psychoactive fragments (Mets et al., 1998).

Another advantage of catalytic antibodies has been that they are not broken down after facilitating the break down of their target cocaine molecules. Thus they are less prone to being overwhelmed by large amounts of cocaine and may be effective for much longer than other types of antibodies. Indeed, their ability to break down cocaine molecules can be quite phenomenal – up to 40 reactions or turnovers per second (Landry et al., 1997).

Research status: Preclinical. There are no current clinical trials (Bernard Landry, Director, Clinical Operations, MedImmune Inc, personal communication July, 2003).

Further research: Continued work developing more effective catalytic antibodies. Catalytic antibodies need to be delivered passively and while this can be achieved using monoclonal antibodies their duration of effectiveness (up to one month) requires booster shots. The effectiveness of varying levels of blockade need to be investigated. Landry continues to synthesise analogues of cocaine hydrolysis, immunise mice and generate antibodies that hydrolyse circulatory cocaine. One has achieved the activity needed for preclinical studies and has been demonstrated to prevent lethal doses in rats (15 A 10) (Baird et al., 2000). However, all 15 A 10 levels returned to pre-treatment levels after 48 hours and as such 15 A 10 will not be effective in cases of repeated high doses of cocaine (Kantak, 2003).

3.5 COC-AB

Vaccination type and mechanism: COC-AB is a passive horse-derived polyclonal cocaine antibody. It is created by challenging horses with an immunoconjugate that

includes a cocaine-like molecule, then purifying the resulting antibodies to remove equine properties. Overdose may be best managed by passive immunisation which loads in antibodies rather than waits for the body to produce them. The vaccine antibodies attach to free cocaine in the blood and act as an osmotic pump drawing cocaine out of the brain, heart, muscles and tissues.

Research status: Preclinical stopped due to commercial reasons. Preclinical development in France stopped in 2001 prior to entry to phase 1 due to problems in achieving commercial levels of antibody production (Prof Jean Michel Schermann, director Laboratoire de Pharmacocinetique at the University Rene Descartes (Paris V), personal communication, April 2003). The company no longer exists in France.

4. RESEARCH ISSUES

4.1 Ethical issues

In the public mind, vaccines remain strongly associated with disease prevention or protection. When combined with headlines describing vaccines against drugs of dependence as "vice vaccines" (Cohen, 2000), this may lead to emotive or alarmist reactions from health professionals and the general community or in some cases an unrealistic and somewhat totalitarian joy at the prospect of behavioural control via inoculation. Hall and Carter (2002, 2003) recently reviewed the ethical implications of developments in cocaine vaccines. The free and informed consent of voluntary patients was a key concern. Such consent is particularly important as cocaine users may be vulnerable to financial inducements or other social pressure to trial participation. It is also likely that immunotherapy will not be effective alone as vaccines do not prevent withdrawal, craving or treat behavioural aspects of cocaine dependence. Thus, patients must be offered the highest levels and quality of psychosocial intervention available. Privacy concerns were also critical with the potential for discrimination against individuals positive for cocaine antibodies. This potential was much less for "passive" immunisation where antibodies disappear from the body within weeks. These concerns are also reduced in "active" immunotherapies such as TA-CD where antibodies have also been found to be short-lived (up to 12 months) and there are no assays available to detect immune memory cells. The temporary nature of the vaccines so far developed overcome some of these ethical concerns but as Hall and Carter noted more permanent or longer-lived vaccine antibodies may be developed. Equitable access to a potentially expensive treatment may also be an issue for government. The use of vaccines in overdose situations to mop-up excess circulatory cocaine may be less ethically contentious but technically more difficult given the speed with which cocaine reaches the brain. Finally, the development of preventative vaccines for non-cocaine users or coerced use are the most ethically contentious uses that could only be considered after extensive experience in the treatment of voluntary patients.

4.2 Funding Issues

4.2.1 Economic evaluation

Economic modelling would be an important first step to assess the potential value of a cocaine vaccine by estimating the economic and social costs of cocaine use and the costs of vaccines and ancillary treatment. A similar proposal to model the potential impact of a nicotine vaccine on smoking abstinence rates and associated burden of disease has been submitted for funding (Chris Doran, personal communication August 2003). Although cocaine vaccines are likely to be expensive at the unit level, they most probably will be at least equivalent in cost to maintenance therapies that require daily medication compliance. However, it is likely that combined therapy may be the most optimal approach which diminishes this cost advantage. Cost effectiveness analysis provides another framework to compare the relative effectiveness of interventions for cocaine disorders, however, currently it would be problematic to compare a vaccine with other interventions as none are recognised as effective in attracting or retaining patients with good outcomes.

4.2.2 Research and development costs

The estimated costs of conducting clinical research into cocaine vaccines in Australia are prohibitive. Vaccine manufacture, monitoring and immunological assays comprise the major part of clinical trial costs. Presently only one UK company, Xenova Plc, appears able to produce viable quantities of vaccine. The production costs of TA-CD vaccine (including monitoring and immunological assays) for a single Australian pilot study were estimated at GBP1 million (John St Clair-Roberts, Xenova Plc, personal communication November 2002). Previously Yale University received a US National Institute on Drug Abuse grant of US$760,000 to develop TA-CD (Anon, 2000). The other major cost involved in clinical trials is salaries for research and clinical staff. Based on recent NHMRC grant applications for pharmacotherapy pilot studies in cocaine dependence, this cost would be in the region of AUS$250,000 for a 2 year study. Therefore, the total cost of a pilot study involving 30 subjects at current exchange (AUD$2.5:GBP1) would be approximately AUD$2,750,000. It is unlikely proposals for Australian trials would be successful until the cost of vaccine manufacture and associated safety analyses are substantially reduced or shared across a number of international study sites.

4.3 Design and measurement issues

4.3.1 Study populations

Current TA-CD trials have recruited among abstinent cocaine users in rehabilitation. The rationale has been that optimal benefits may be best observed in patients motivated and supported to maintain abstinence especially if the vaccine blockade is not total or can be overcome with high or continuous cocaine doses. This work will be extended to non-treatment seeking cocaine users in a dose administration study that will examine the blocking effects of the vaccine. A further potentially valuable treatment population may be current non-abstinent users seeking treatment. Vaccines targeted towards cocaine may offer respite from the effects of cocaine that could provide a therapeutic window for

patients to make lifestyle and other personal changes necessary to protect against relapse in the longer term. In Australia two potential treatment populations of dependent cocaine exist; cocaine injectors (predominantly poly drug users) and heavy cocaine snorters (higher socio-economic status). The only cocaine treatment trial conducted in Australia to-date predominantly targeted the former involving 30 injectors mainly female sex workers and concurrent methadone patients (Shearer et al., 2003). Cocaine vaccines targeted towards emergency room overdose have not entered phase I trials and in any event, emergency presentations for overdose are rare in Australia.

4.3.2 Adjunctive psychosocial and medication treatments

The initial indication for most vaccines other than those specifically targeted towards overdose has been for relapse prevention in abstinent cocaine users. No vaccines prevent cocaine craving or withdrawal (Kantak, 2003). Shearer & Gowing (2004) recently reviewed pharmacotherapies for psychostimulant dependence and found that anti-depressants, anti-convulsants, dopamine agonists and antagonist were generally not effective in cocaine dependence. Agents demonstrating potential in early studies included the opioid antagonist naltrexone (Schmitz et al., 2001), the aversive agent, disulfiram (George et al., 2001; Petrakis et al., 2000), dexamphetamine substitution therapy (Grabowski et al., 2001; Shearer et al., 2003) and the wake promoting agent modafinil (Dackis et al., 2003).

Naltrexone plus relapse prevention significantly reduced cocaine use compared to placebo plus drug counselling (Schmitz et al., 2001) however induction and compliance difficulties with concomitant opioid and cocaine dependence may limit its use. Kosten (2002) suggested that disulfiram, an aversive agent for alcohol, may be a suitable adjunctive medication for the TA-CD vaccine. Two placebo controlled studies have reported positively on the effect of disulfiram in promoting cocaine abstinence in 20 buprenorphine maintained patients (George et al., 2001) and 67 methadone patients (Petrakis et al., 2000) - in both studies alcohol use was minimal.

Agonist approaches through attenuating cravings, may enhance compliance and prevent relapse during the 8 to 12 week inoculation period when antibody levels and the cocaine blockade is sub-optimal. Dexamphetamine has also been investigated for cocaine dependence in two studies. A 13-week controlled study (n=128) of sustained release dexamphetamine (placebo, 15-30 mg/day and 30-60 mg/day) found dose-related changes in retention and cocaine use in favour of dexamphetamine treatment with no serious adverse events or cardiovascular complications. Findings were limited by high study attrition. An Australian 14-week placebo controlled study (n=30 cocaine injectors) of dexamphetamine 60 mg/day found outcomes (cocaine use, crime, cocaine craving and severity of dependence) favoured treatment with no improvement in the placebo group. Modafinil promotes wakefulness, vigilance and alertness and may therefore have value in the management of psychostimulant withdrawal symptoms such as hypersomnia, poor concentration, and low mood (Dackis et al., 2003).

While cocaine pharmacotherapies remain experimental, psychosocial interventions have demonstrated promise where patients can be attracted and retained in treatment. Controlled evaluation of cognitive behavioural therapy for amphetamine users has yielded positive results in Australia (Baker et al., 2001). Cocaine specific protocols are also available (Carroll, 1998).

4.3.3 Study design and measures

A double blind randomised placebo controlled trial is the gold standard in treatment evaluation. The feasibility of conducting such a trial is well established in TA-CD. The use of adjunctive therapy such as cognitive behaviour therapy and medication to blunt cravings such as dexamphetamine or modafinil may further protect the study blind and ensure recruitment and follow-up. Validated and reliable measures of cocaine use and related harms are available. Regular urinalysis or hair analysis allows objective measurements of cocaine use over time while self-report can supplement these data and add a quantitative measure. Cocaine dependence is a chronic relapsing condition and the most sensitive measure of treatment outcome should yield continuous or quantitative data. A completely successful vaccine induced cocaine blockade may cause patients to switch to other drugs such as amphetamine, benzodiazepines or heroin, thus testing for other drugs is indicated. Adverse events must be systematically monitored including those peculiar to immunotherapy such as autoimmune responses, injection site problems and immunological assays of effective protection. Overdose risk through attempts to override the vaccine blockade should be carefully monitored. The psychological and behavioural components of dependence make recovery a slow process and the question of clinical end-points is always problematic in addiction medicine. A component of long term follow up would be important.

4.3.4 Potential collaborators

The directors of two inner city treatment centres (Kirketon Road Centre, Sydney Hospital, Director Ingrid van Beek and Rankin Court, St Vincent's Hospital, Director Alex Wodak) commented on earlier drafts of this report. Both directors believed trials of cocaine vaccines would be supported as a logical step in the process of developing treatments, however, they cautioned that numbers of interested patients may be quite small. Most clients with cocaine problems were also opioid dependent.

5. OTHER DRUG TARGETS FOR VACCINES

5.1 Nicotine

Three vaccines are currently in phase I/II human trials although results have yet to be published in peer reviewed journals. TA-NIC has a similar structure to the leading cocaine vaccine, TA-CD, and has been developed by the same UK biotechnology company, Xenova Plc. TA-NIC was found to be safe and well tolerated in a dose-escalation study involving 50 adult smokers and 10 non-smokers with a specific anti-nicotine response (St Clair Roberts et al., 2002; Bunce et al., 2003). NicVAX developed by US biotech Nabi Pharmaceuticals has also shown promise with phase I results in 20 healthy non-smoking volunteers showing a sustained immune response to a single dose with no serious adverse events. Further studies are planned at the University of Maastricht with the aim to recruit 21 smokers and 9 former or non smokers. Nic-VAX development is partially supported by a US NIDA grant DA-13327. Nabi Pharmaceuticals announced the start of Phase II clinical trials at 3 sites in the US (Nabi, Press Release August 5, 2003). Three dosage levels will be evaluated in 3 groups of 21 patients in a collaborative study involving the Universities of Nebraska, Minnesota and Wisconsin in the US. Nicotine-Qbeta, developed by Swiss biotech Cytos Biotechnology AG, successfully completed phase I trials in 40 non smoking adults. The vaccine was found to be well tolerated and produced high levels of nicotine-specific antibodies. A

phase II efficacy study was planned for late 2003 (Cytos Biotechnology, Press Release July 1, 2003). For further discussion of the prospects of immunotherapy in smoking cessation see Hall, 2002 and Kantak, 2003.

5.2 Amphetamine

Given the relatively higher and more general prevalence of methamphetamine-related problems in Australia, vaccines targeted towards methamphetamine, particularly overdose, are of interest. Vaccines targeting circulatory methamphetamine have been tested in rodent models but are some time away from human trials (Brynes-Blake et al., 2003). MAP-AB, a vaccine targeted towards methamphetamine overdose related to COC-AB, was being developed by DrugAbuse Sciences Inc.

6. ENZYMATIC APPROACHES

An alternative approach to vaccination has been focused on Butyrylcholinestrase (BChE) - a naturally occurring human enzyme that metabolises cocaine in plasma but too slowly to reduce the effects of cocaine. BChE has been the model for the previously discussed catalytic vaccine. According to Gorelick (1997) BChE administration offers several advantages 1) it is a safe, natural compound 2) success is not dependent on a functioning immune system 3) only inactive metabolites are produced. Disadvantages are 1) a very short half-life requiring repeated administration every few days at best and 2) limited effectiveness in smoked cocaine. There are no current plans to test anti-cocaine enzyme formulations in humans.

7. CONCLUSIONS

Immunotherapy is a promising approach in the treatment of cocaine-related disorders. Animal studies have demonstrated that vaccination can allow the immune system to recognise and neutralise cocaine molecules. Early trials in humans of one vaccine, TA-CD, have shown that this anti-cocaine vaccine was well tolerated, generated persistent and specific anti-cocaine antibodies and appeared to block cocaine-effects. These trials have concluded that further studies of the effectiveness of cocaine vaccines in humans are warranted.

There are several technical, economic and ethical challenges to the development of effective anti-cocaine vaccines. The effectiveness of vaccines may be impaired by underlying behavioural pathology, cocaine craving, switching to other drugs and the risk of the blockade being overcome by high doses of cocaine. The cost associated with the production of cocaine vaccines is considerable and several vaccine candidates have failed due to difficulties in achieving commercial scale production. The burden of disease in Australia associated with cocaine-related disorders may not be sufficient to justify the substantial investment required to conduct large scale original research studies into cocaine vaccines. Research into vaccines targeted towards other drugs of dependence such as nicotine may be more viable in the Australian context.

Cocaine is a potent drug that efficiently blocks neural dopamine re-uptake within moments of administration. These efficient biological characteristics underpin its addictive liability and its attraction to humans. Cocaine vaccines are likely to be only weakly effective in blocking the effects of such a powerful and effective drug. Optimal outcomes may require an integrated approach incorporating immunotherapy, psychosocial support and pharmacotherapy targeted towards symptomatic relief and craving suppression. Immunotherapy is an important and rational contribution to the range of treatment options available for patients experiencing cocaine disorders.

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GLOSSARY

Antibody

Antibodies are proteins produced by the immune system that attach to, destroy or otherwise disarm specific drugs at the molecular level in the blood thereby preventing them crossing the blood brain barrier.

Therapeutic immunotherapy/vaccination

Vaccines effective in patients who are already infected or ill. Alternative terms include pharmazines, therazines.

Preventative immunotherapy/vaccination

Vaccines effective in patients who are disease naïve or unexposed.

Passive immunity

Passive immunity may be achieved by inoculation with monoclonal/polyclonal antibodies created outside the body in laboratory cell cultures. Such antibodies may be very short-lived. Monoclonal antibodies are identical while polyclonal antibodies are a group of antibodies that can recognise different targets on the antigen. Polyclonal antibodies are generally much longer lived than monoclonal antibodies.

Active immunity

Active immunity may be achieved by inoculation with a vaccine, consisting of a drug linked to a protein, causing the immune system to respond by producing antibodies to lock onto the drug. Typically immunity may last from several months to several years.

Combined active/passive immunity

Combinations of active and passive approaches allow drug effects to be blocked immediately by powerful monoclonal antibodies while active antibodies are boosted to effective levels.

Catalytic antibodies

These are specific types of monoclonal antibodies that destabilise cocaine molecules causing them to break down into non-toxic or non-psychoactive fragments.

Immunogenicity

The immunogenicity of a vaccine refers to its ability to produce an immune response. The measurement of immunogenicity is an important aspect of vaccine trials both in terms of the strength of the immune response that is achieved and its duration.

Adjuvent

The adjuvent in a vaccine refers to the protein group which is recognised by the immune system. Often this is an inactivated viral protein. Varying adjuvents may produce superior immune responses.

Antigen

The antigen in a vaccine refers to the target molecule for which we hope antibodies will be produced. In the case of cocaine these are derivatives of the cocaine molecule and its active metabolites.

Phase I Clinical Trial – Safety and Pharmacology

The first administration of a drug in normal healthy humans. The main aims of phase I studies are to establish safety, dose ranges and pharmacokinetic data such as absorption, distribution, metabolism, other drug interactions and excretion of the compound.

Phase II Clinical Trials – Clinical Efficacy

The first administration of a drug in small samples of selected patients to test efficacy, safety, adverse events, therapeutic range and tolerated dose.

Phase III Clinical Trials – Comparative efficacy

The administration of a drug in larger samples of selected patients to evaluate the drug through comparison with existing therapies. Confirmation of clinical benefit and safety (side effects, contra indications).

Preclinical Testing

Studies in animals or *in vitro* (at the benchtop) conducted prior to experiments in humans.

Phase IV Clinical Trials

Studies in new patients groups and new indications. Evaluation of long term risks and benefits.