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Anti-(+)Methamphetamine Monoclonal Antibody Antagonists Designed to Prevent the Progression of Human Diseases of Addiction

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Introduction

Anti-(+)-methamphetamine monoclonal antibodies (mAbs) have the potential to reduce the devastating behavioral and societal effects of the worldwide epidemic of (+)-methamphetamine (METH) addiction while transforming the treatment paradigm for diseases of addiction. These novel protein-based medications could play a vital role in the initiation and continuation of abstinence from METH abuse, in a way similar to that played by insulin therapy in the initiation and continuation of diabetes therapy.

METH addiction as a disease target

The use of anti-addiction mAb medications for the medical indication of preventing relapse to METH use is promising for several reasons. First, the anti-METH murine mAbs, from which the human mAb medications are developed, have undergone extensive *in vitro* characterization and preclinical testing in addiction models.^{1–3} Second, the most important characteristics for therapeutic potential in humans reside within the mAb variable site binding regions. These key immunochemical binding properties can be transferred intact to a mouse/human chimeric mAb (anti-METH ch-mAb) for administration to humans.⁴ Third, the feasibility of using an anti-addiction antibody therapy to block drug effects has been partially demonstrated in early phase clinical trials of a cocaine vaccine in humans.⁵ Fourth, unlike active vaccines for cocaine⁵ or nicotine⁶ that require time for effective anti-drug antibody concentrations to develop, rapid attainment of high therapeutic concentrations is possible with mAbs. Furthermore, effective mAb concentrations can be more easily sustained for long periods of time, which is needed to achieve long-lasting behavioral modification in addicted patients (*e.g.*, at least 6–12 months). Fifth, the antibodies have a unique mechanism of action (see next paragraph), are not addicting, and could be used safely in combination with small molecule medications. As with all current mAb therapies the major limitations are the high cost of protein production and the eventual antigenicity of chimeric, humanized or fully human mAbs with prolonged use.⁷

Conflict of Interest Statement

S.M.O. serves as the Chief Scientific Officer and W.B.G serves as the Chief Medical Officer and both have financial interests in IntervXion Therapeutics, LLC, a pharmaceutical biotechnology company developing vaccines and monoclonal antibodies for the treatment of human diseases, including drug abuse.

Designing a long-lasting mAb antagonist to prevent reinforcement of METH's addictive effects

Cook *et al.*⁸ suggest that the rapid onset of METH's subjective effects following smoking or iv injection, is a factor in the reinforcing and addictive power of the drug. Indeed, the rapid perception of the effects of many drugs of abuse is believed to contribute to their addictive properties. Oldendorf⁹ suggests "The more immediate the effect after intake, the more addicting the substance is likely to be." METH is rapidly acting because it can quickly cross the blood barrier and it is highly lipid soluble in critical tissues like the brain.¹⁰

This onset rate-driven theory of behavioral reinforcement is demonstrated in human studies evaluating patients' perceived drug effects following different rates of drug administration. For example, the euphorogenic¹¹ and reinforcing effects¹² of a fixed *iv* cocaine dose increases as the duration of infusion decreases. Furthermore, de Wit and colleagues¹³ report that for similar peak concentrations of pentobarbital, subjective ratings of the "high" and craving are greater when the drug is given as a single *iv* bolus as opposed to six divided doses over 3 hrs.

We hypothesize that blocking or slowing the rate of METH entry into the brain with sustained blood levels of high affinity anti-METH mAbs will have substantial beneficial therapeutic effects (Figure 1). While rate of onset of CNS effects is a known determinant of addiction liability, it is underappreciated as a potential disease target for developing new pharmacological treatments.

Anti-drug antibody medicines have a distinct mechanism of action compared to small molecule receptor agonists or antagonists because they do not rely on binding to CNS receptors. MAbs bind their target molecules with high affinity and confine them mainly to the extracellular fluid space, which includes the blood stream. Because of their large molecular size, mAbs do not pass through the tight junctions of the CNS vesicular blood-brain barrier¹⁴ and do not enter the brain. This mechanism of mAb action is categorized as a pharmacokinetic antagonism because mAbs alter target drug disposition, and effectively prevent the addictive drugs from reaching their sites of action. MAbs also have of an excellent safety record in humans, and are unlikely to be addictive like many small molecule agonist medications for treating addiction (*e.g.*, methadone).

Determinants of successful antibody function and safety

There are several key determinants of anti-drug antibody function. These include but are not limited to antibody affinity for its target ligand, the molar ratio of the antibody:ligand, the route and timing of immunotherapy administration, and the antibody pharmacokinetic profile.^{1,15} We hypothesize that use of an antibody with a very low dissociation constant (K_D value) for METH will have the best chance for therapeutic success. Preclinical studies in rats suggest that anti-METH mAbs with K_D values for METH in the range of <10–20 nM could be adequate.¹⁶

A frequent scientific criticism of the use of immunotherapy for treating drug abuse is the concern that a highly addicted patient could escalate METH use until they overcome the binding capacity of the antibody, and then suffer a disastrous medical outcome. There is preclinical and clinical evidence to suggest this is not likely for METH and other stimulant drugs of abuse. Preclinical studies in rats with a high-affinity anti-PCP mAb show attempts to overwhelm the capacity of the antibody does not result in increased toxicity, in fact the mAb protects from lethality. For these studies, rats were continuously infused with a dose of PCP (18 mg/kg/d) that is lethal in ~25% of the animals.¹⁷ One day after beginning the PCP

infusion, they were given a single dose of the mAb with a binding capacity that was equal to one-third the mole equivalent amount of PCP in the rat. Three days later, the controls and mAb-treated animals were given a 1 mg/kg intravenous dose of PCP, a dose which typically results in increased locomotor activity for about 45–60 min in normal rats. Following the iv PCP bolus dose two of the placebo treated animals almost died from respiratory failure, while the mAb-treated animals only exhibited mild hyperactivity.

In other preclinical studies with an anti-nicotine active vaccine, rats were immunized against nicotine until significant anti-nicotine titers were achieved.¹⁸ They were then given a one-week constant infusion of nicotine subcutaneously followed by a single iv bolus dose large enough to provoke seizure activity. Compared to a control group of animals that had not been immunized against nicotine, the immunized animals had significantly less seizure activity.

In a human study of the effects of an anti-cocaine vaccine in combined cocaine-heroin addicts, the subjects were immunized and followed for 24 weeks.⁵ While only 38% of the total subjects generated a significant anti-cocaine antibody immune response for about 2 months, over 50% of these subjects significantly increased their duration of abstinence, compared to 23% of subjects treated with cognitive behavioral therapy alone. Several of these subjects who generated high titers attempted to overcome the effects of the vaccine by self-administering cocaine, but there was no increase in cocaine-related adverse events including hospitalization and overdose.

In these studies with PCP, nicotine, and cocaine, antibody capacity was substantially less than the body burden of the drug, yet major adverse effects did not occur. Because beneficial effects were observed even when antibody capacity was substantially exceeded by the target ligand concentrations, these findings also show antibody capacity for its target ligand is not the primary determinant of immunotherapy efficacy.

Our preclinical studies suggest that high-affinity anti-PCP or anti-METH mAbs can produce and maintain a sustained equilibrium shift of PCP or METH, respectively, from the brain into the blood serum where the mAb resides. We hypothesize this is accomplished by the combination of an extremely small volume of the vascular cerebral space relative to the general circulation, the beneficial presence of a blood–brain barrier that restricts mAb but not PCP or METH to the vasculature, and the extremely small fraction of the total administered METH dose localizing to the brain (only 0.1–0.2% for METH³). These data suggest temporary greater drug-mAb occupancy in the brain than in the general systemic circulation with each pass through the brain.

It is not clear how mAb therapies alter receptor binding rates to effect changes in perceived effects, or whether the on- or off-rate of receptor binding is more affected (Figure 1). This remains an important question with regard to understanding the pharmacological interactions of anti-drug antibodies and their target ligands, which can only be answered when anti-METH ch-mAbs are tested in humans.

Scaling preclinical studies in rats to humans

Given the excellent safety record of the many mAbs now on the market, the use of anti-drug mAbs should be safe in humans, even with the possibility that a clinically manageable immune response against the anti-METH mAb could occur. A major hurdle that still exists is determining the effective human dose and dose regimen. Because mAb medications are expensive to produce, the doses must be as low as possible to minimize costs to the patient and a widespread adoption of the therapy. Animal data and animal scaling simulations suggest that effective doses will be low enough to be feasible in humans. We analyzed the

total monthly doses of 15 current mAb medications used by the hospital pharmacy of the University of Arkansas for Medical Sciences for treating cancer, autoimmune disease, and other diseases. We found the highest doses for mAb therapies were approximately 30–45 mg/kg/month. We anticipate that effective anti-METH mAb doses will be in this range.

Preclinical data in rats suggest the protection from adverse stimulant drug effects can be achieved with anti-METH mAb doses that result in METH binding capacity that is significantly less than the amount of METH used by the subjects.³ Our most comprehensive findings on this subject are from studies of anti-PCP mAb protection against chronic PCP use.^{17,19} In these studies, a single anti-PCP mAb dose as low as 15 mg/kg was effective in preventing adverse health effects from PCP, including weight loss and death from PCP overdose. This 15 mg/kg mAb dose was only 1/100th the body burden of PCP, and was given as a single iv dose, while the PCP was continuously administered for two weeks.

Pharmacokinetic modeling of steady-state concentrations of mAb in rats and humans indicates that human mAb concentrations will be about 2.5 times higher in the human at the same mAb doses, when the mAb is dosed once every half-life for each species (see Figure 2). These data also suggest that effective rat mAb doses will likely significantly overestimate the dose of mAb that will be needed for human treatments. This is important given that Roiko *et al.*²⁰ suggested that it is the steady-state levels mAb that ultimately predict functionality, and that they suggested that an effective steady-state concentration for anti-nicotine mAbs in rats is > 40 µg/ml. While these studies were not designed to determine a ‘threshold’ level for mAb action, these data strongly suggest that such a level exists.

Summary and Conclusions

A major reason for failure of current METH addiction therapies is the inability to protect patients against impulsive, episodic relapse to METH use, especially during the initiation of therapy. Medical protection from METH effects during these vulnerable periods could be obtained with a long-lasting anti-METH chimeric mAb pharmacokinetic antagonist. We hypothesize that medicines with less frequent demands on dosing and patient compliance will increase the addict’s probability of successful outcomes. Thus, these long-acting mAb medications (possibly 2–4 weeks in duration) could be viewed as an around-the-clock protective sentry for a patient’s will power and vulnerability, when they are not actively in behavioral counseling or support groups.

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Figure 1.

The balance of events in the brain needed to achieve therapeutic success for anti-METH mAb therapy for addiction. In this artist conception, the antibody (mAb) circulates through the brain confined to the vasculature in the blood serum compartment. The mAb binds tightly, but reversibly to the METH (yellow filled circle) and thereby reduces the rate at which METH crosses the blood brain barrier. Normally, the rate of METH entry into the brain is much faster than the rate of exit. Inside the central nervous system, METH enters and leaves CNS nerve terminals and binding sites such as the dopamine transporter. The mAb-induced reduction in the amount of METH in the brain and the rate at which METH crosses the blood brain barrier leads to significantly reduced METH CNS effects.

Figure 2.

Species scaling of pharmacokinetic data from rat IgG_{2b} and human IgG₂ for use in predicting “equivalent” doses and duration of protective effects in the two species. Simulations of serum IgG₂ concentrations are shown for 3 days (upper graph) and 105 days (lower graph) in the rat and human. Two-compartment pharmacokinetic models were constructed based on the pharmacokinetic parameters published by Joos *et al.*²¹ for a human IgG₂ mAb ($t_{1/2}$ = 21 d) and by Laurenzana *et al.*³ for a mouse IgG_{2b} mAb in the rat ($t_{1/2}$ = 6.9 d). For these simulations of mAb concentrations, mAb doses were administered over a 2 hr period in both models. The red dashed line on both graphs is drawn at ~40 $\mu\text{g/ml}$, which

is a reported effective concentration of anti-drug polyclonal antibodies in trials of a cocaine (human) and nicotine (rat) active vaccine.^{5,20}