Addiction Vaccines: Promises vs. Reality

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Classical Medications for Drug Users

- Typically small molecule therapeutic drugs.
- They act in the brain.
- Therapeutic drugs are multifunctional and can have significant problematic side effects.
- Vaccines don’t have these brain-based side effects, but could have other side effects.

Vaccination as a Treatment for Drug Addiction

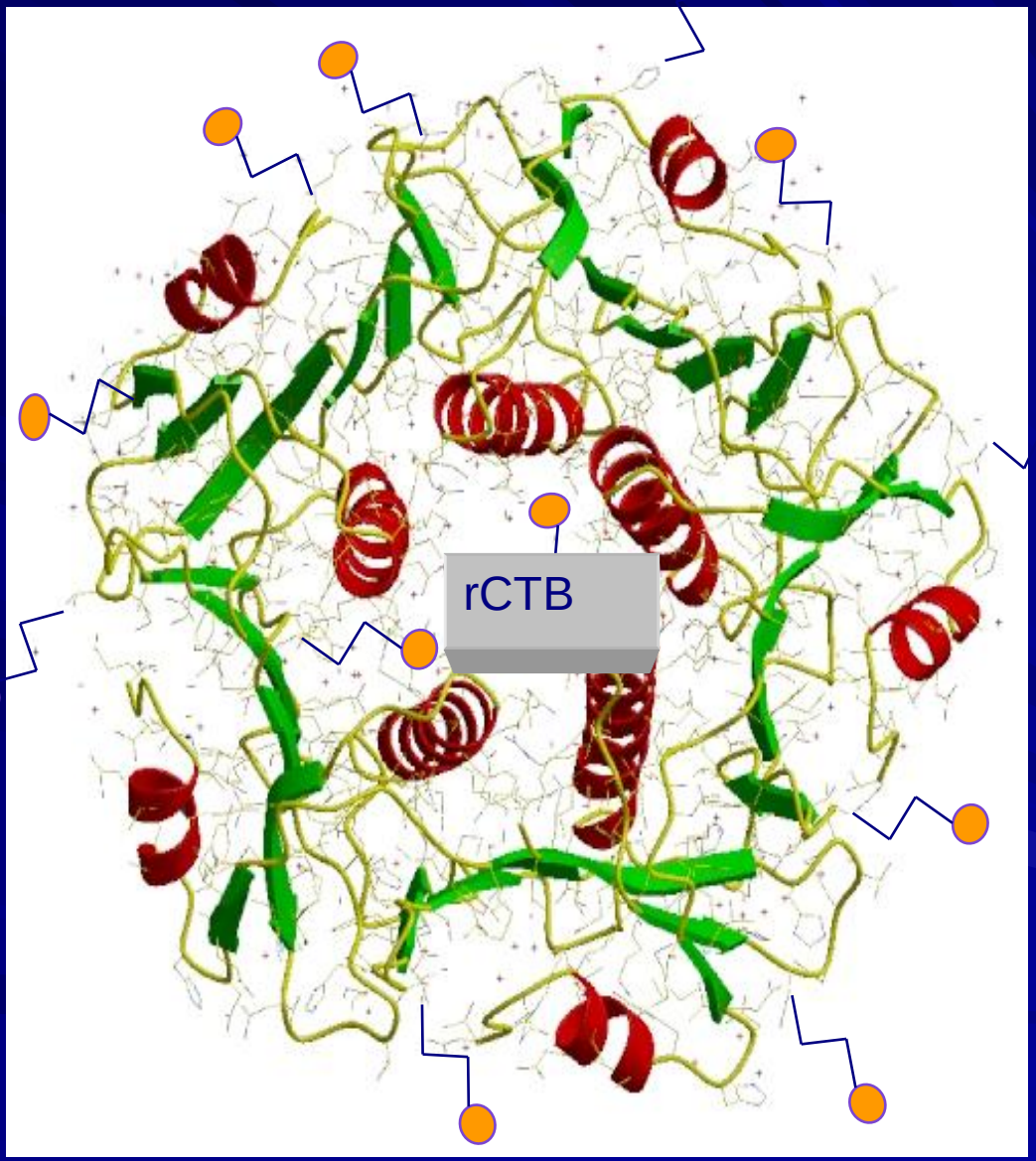
- Potential Advantages
  - Targets the drug in the serum rather than the brain.
  - Vaccines are proven safe and effective without drug-like side effects.
  - Improved compliance (not everyday admin).
- Potential for relapse prevention because antibodies remain in the serum for a long time.
- Combine vaccines with classical treatments

Cocaine Vaccine: What is it?

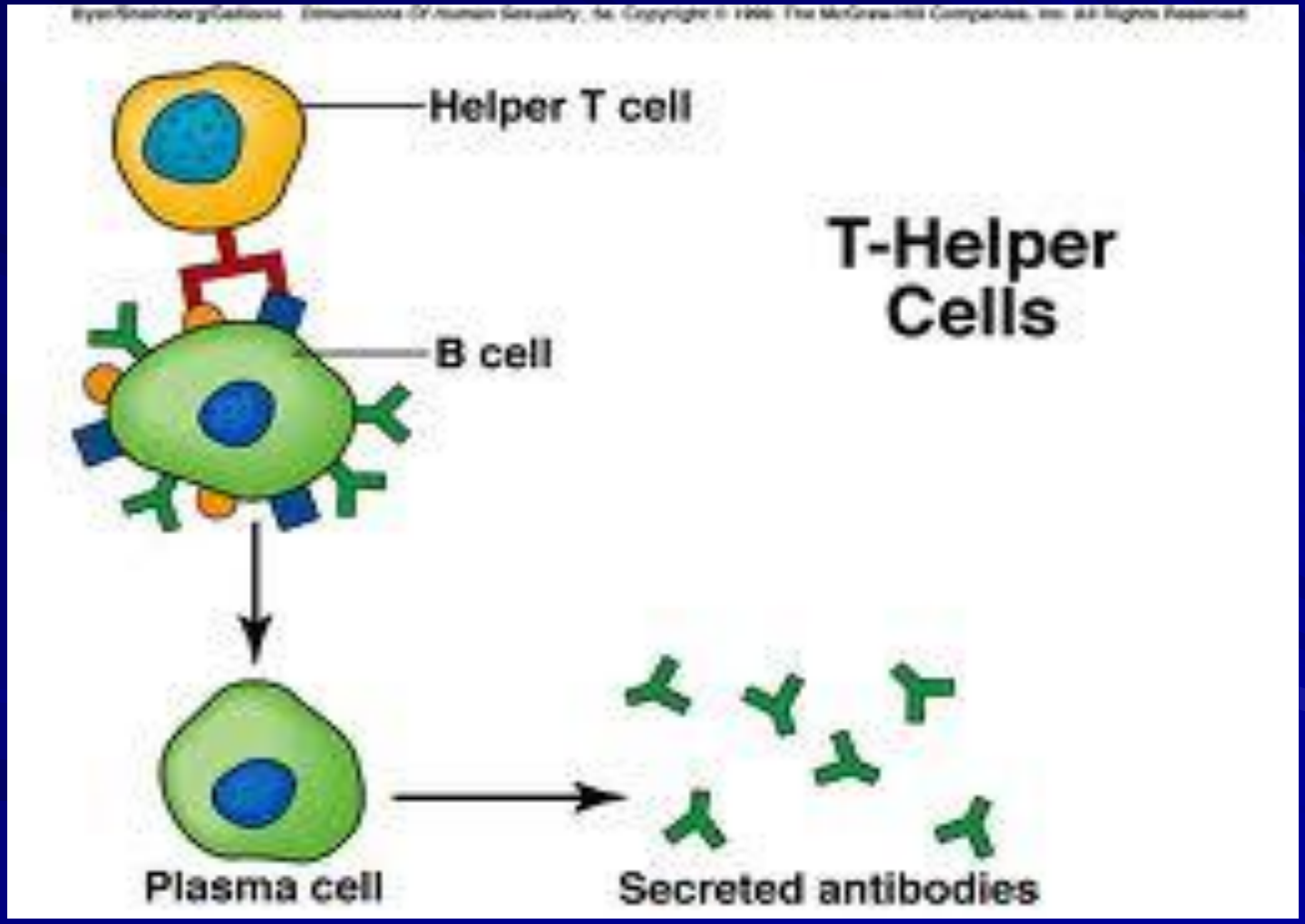
- Active immunisation
- Hapten: Cocaine derivative
- Carrier protein: Cholera toxin B (rCTB)
  - Drug molecules by themselves do not produce antibodies.
- Aluminium hydroxide adjuvant

Cocaine bound to Cholera toxin

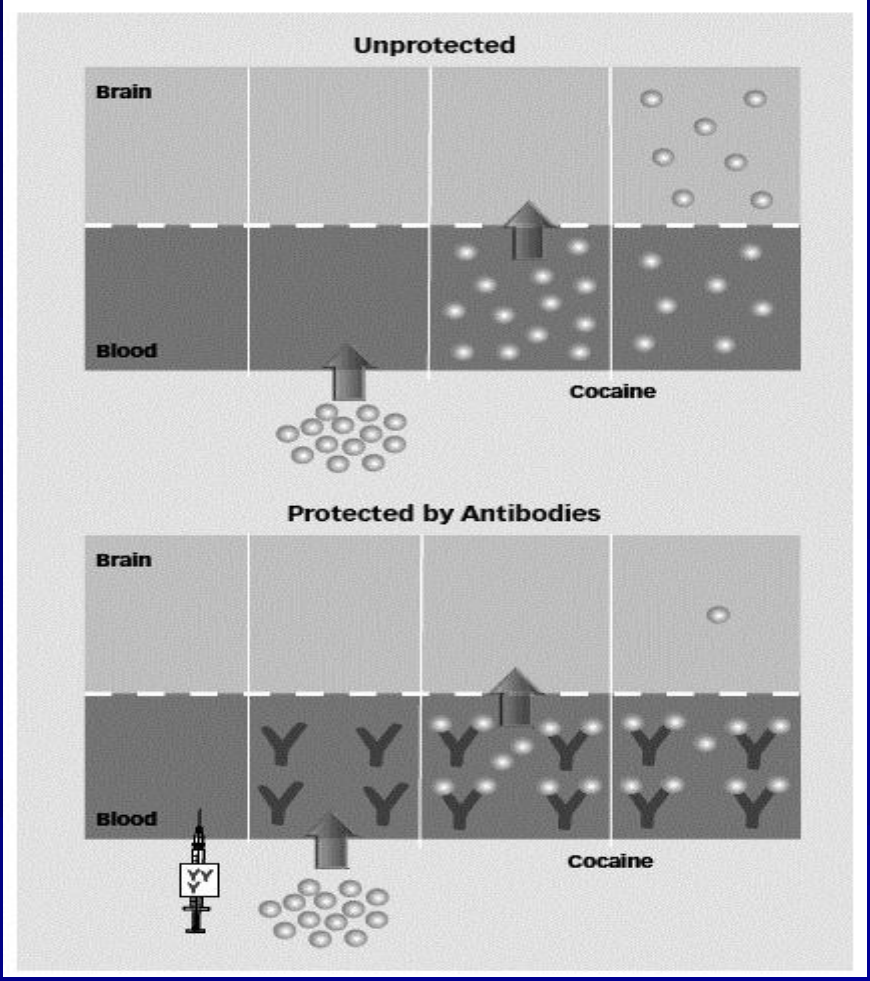
cocaine
derivative



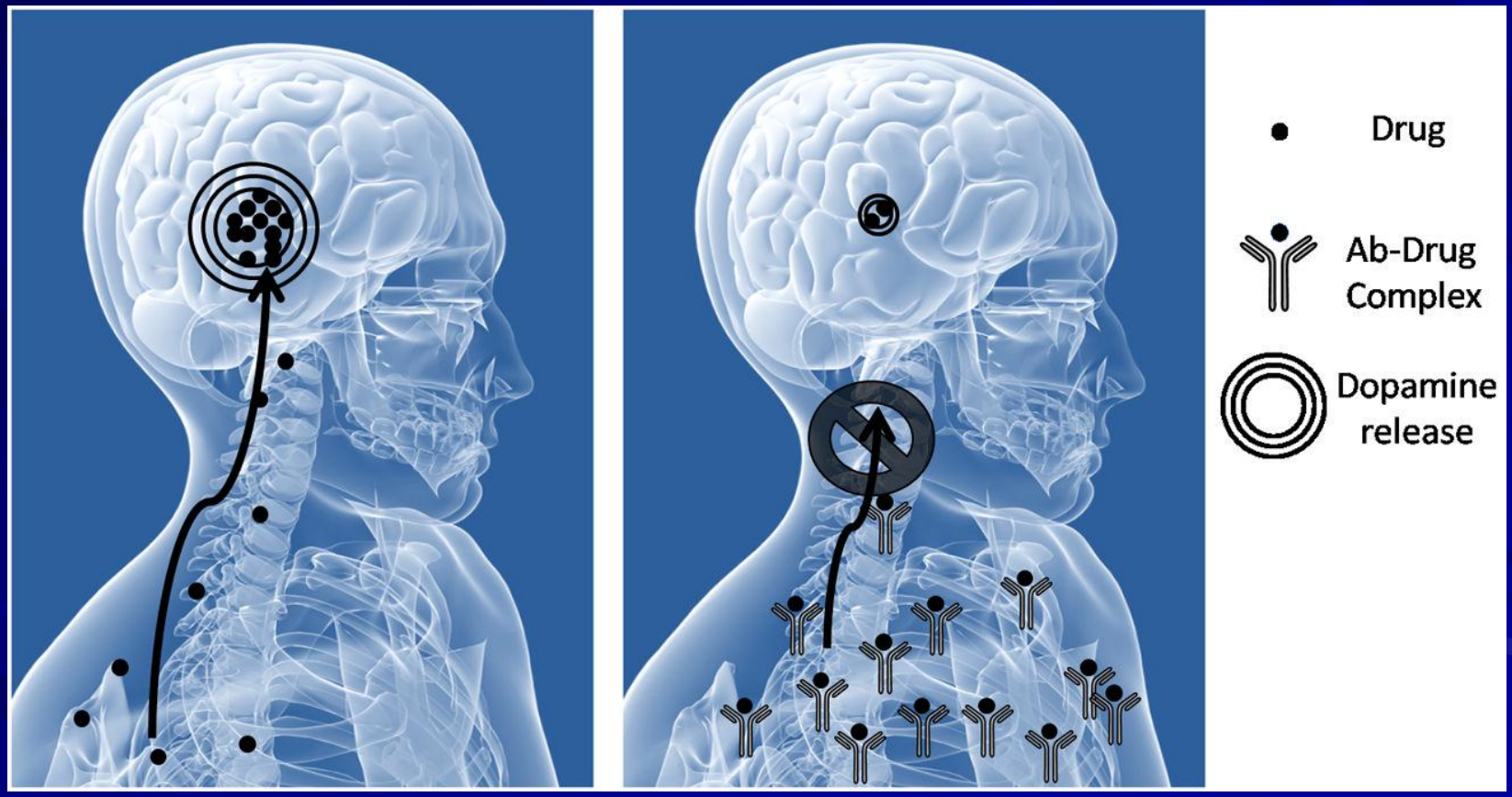
B lymphocytes make ABs



Antibodies keep drugs out of the brain



Antibodies keep drug out of brain

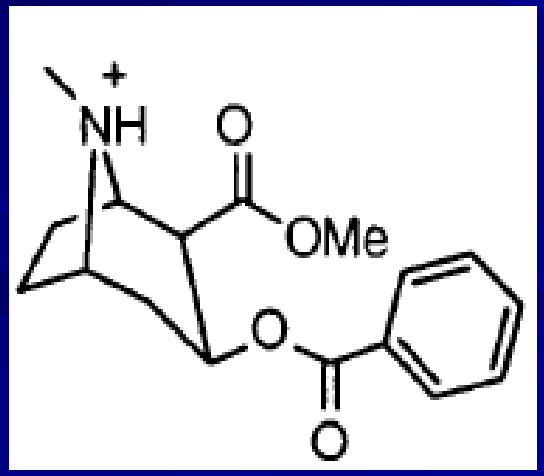


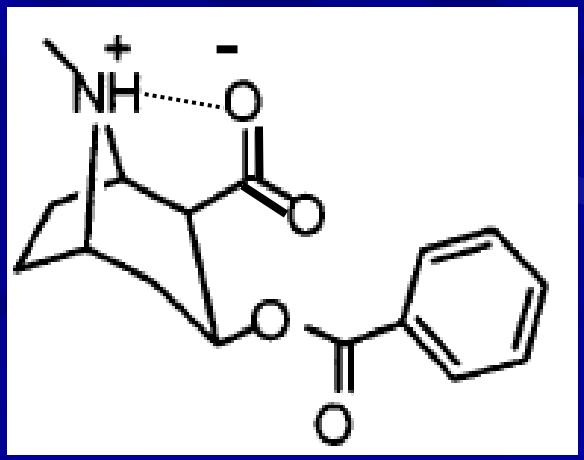
Effects of cocaine vaccine in animals

- Vaccine generated antibodies can bind injected cocaine.
- NO animal toxicity. Even at several times a clinically relevant dose.
- Vaccine decreased cocaine self administration (SA) in rodents.

Antibodies are specific binders

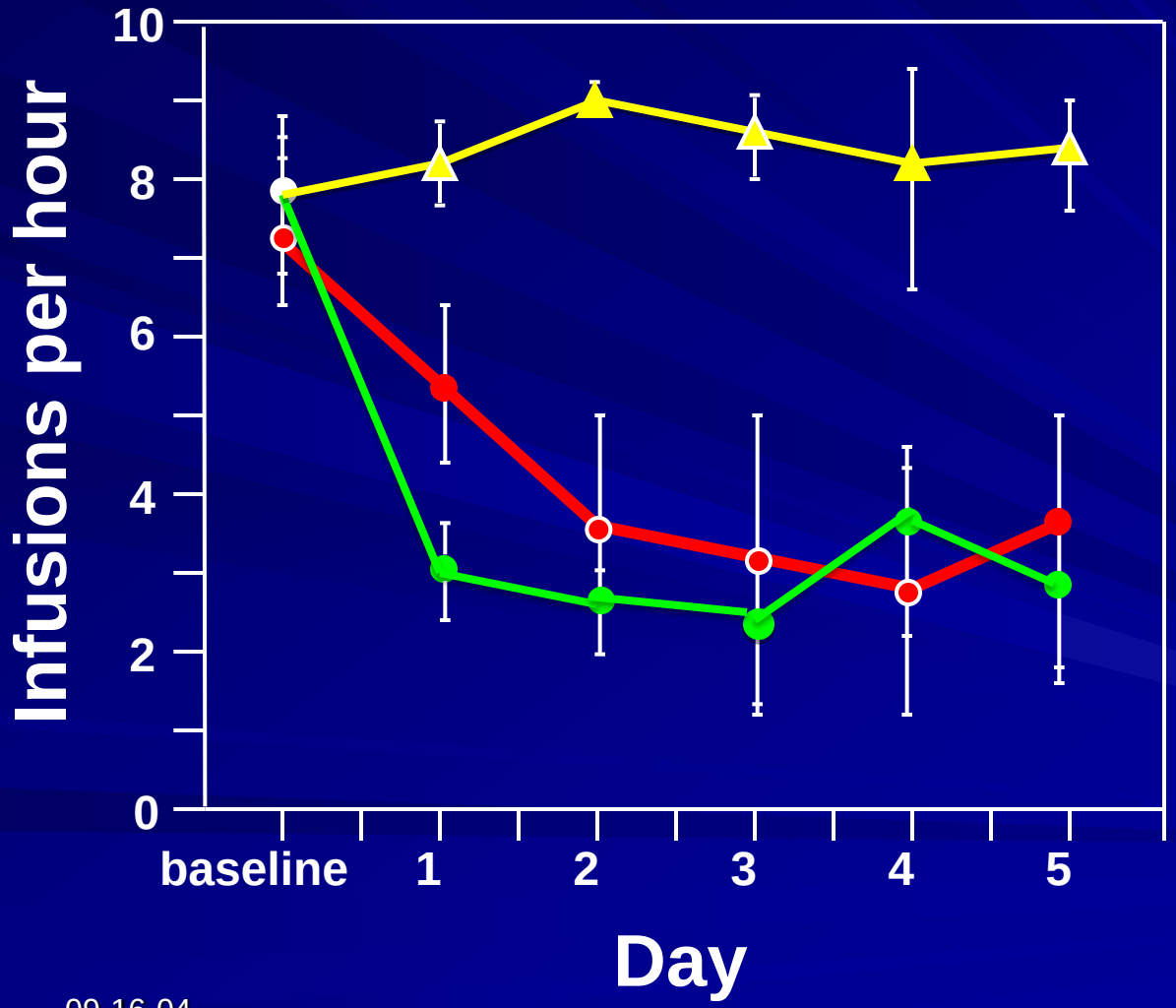
- Antibodies can be very, very specific for a given molecular structure.
- One study showed a 100,000 fold higher binding affinity for cocaine (left) vs benzoylecognine, using serum from mice.





Rodents Self-Administering Cocaine

Cocaine continued each day [yellow], substitute saline for cocaine (red), vaccine + cocaine (green)



AB Response Varies (human data)

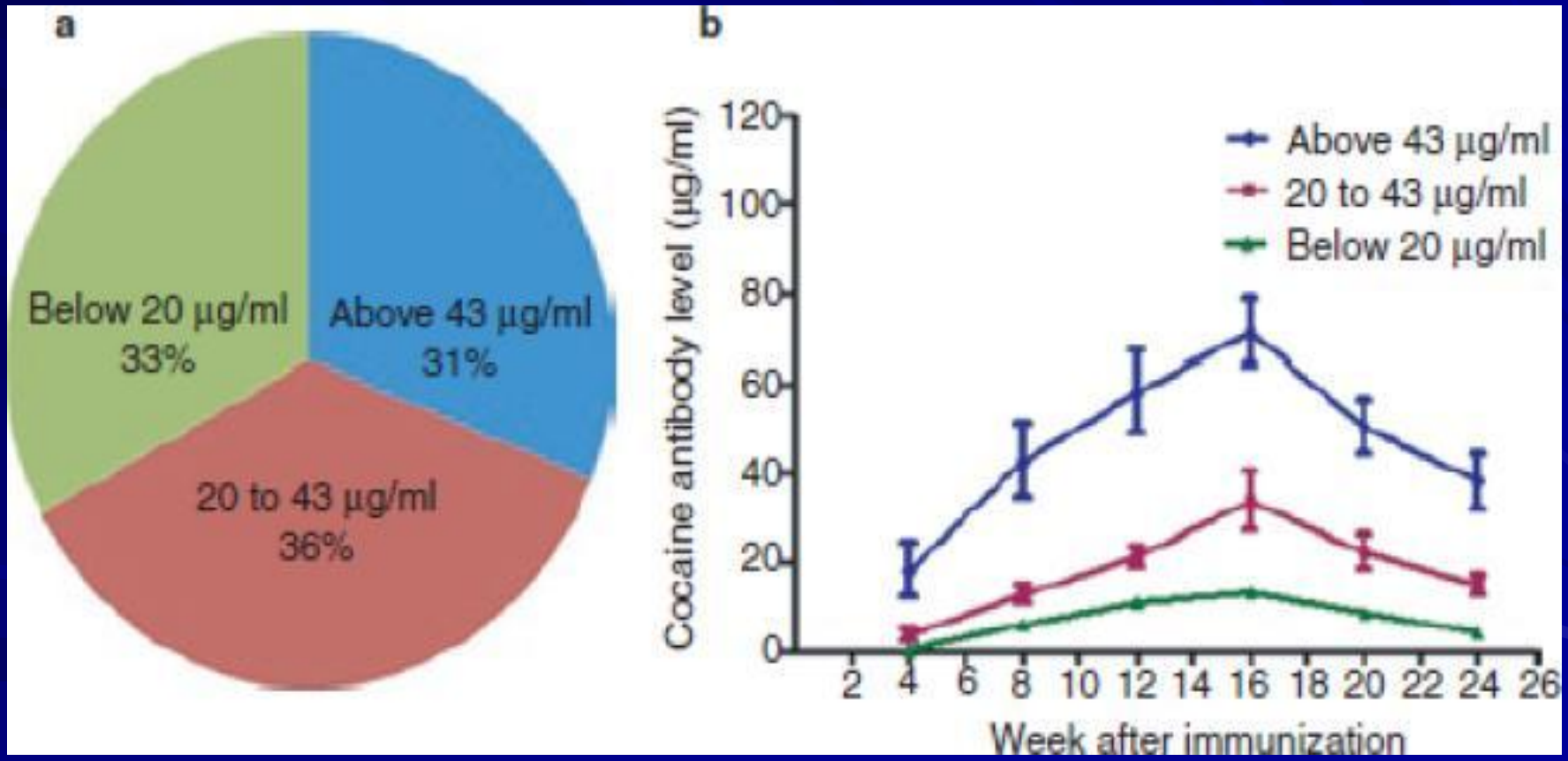


Figure 3

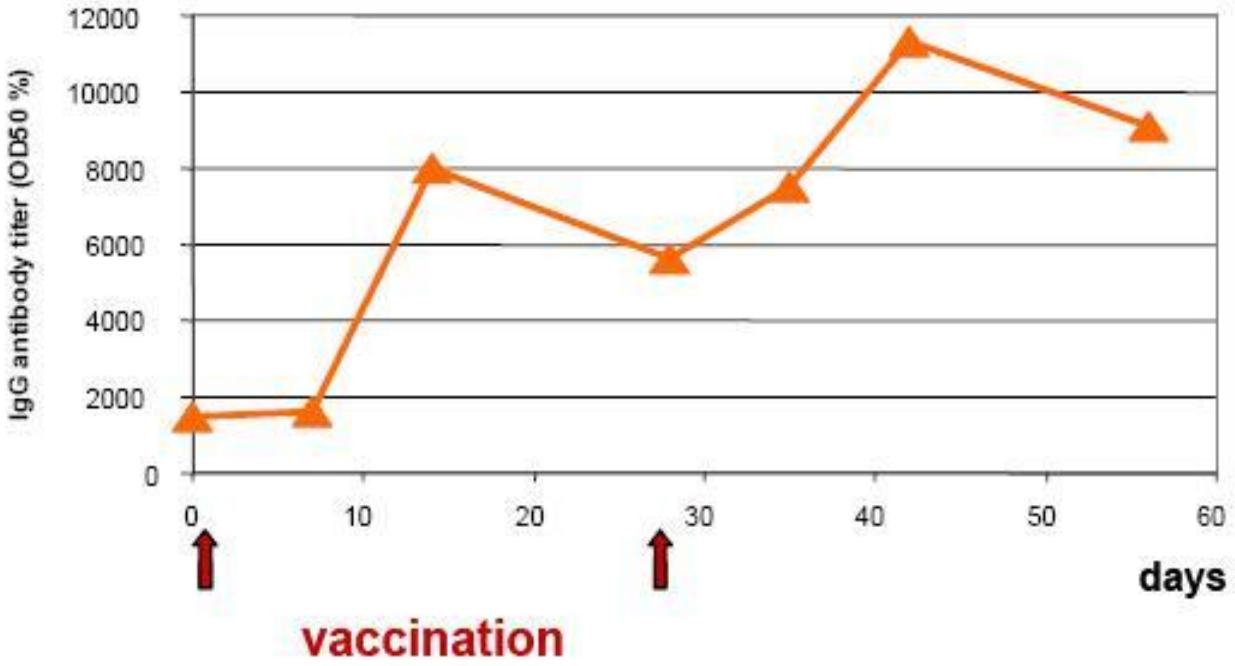


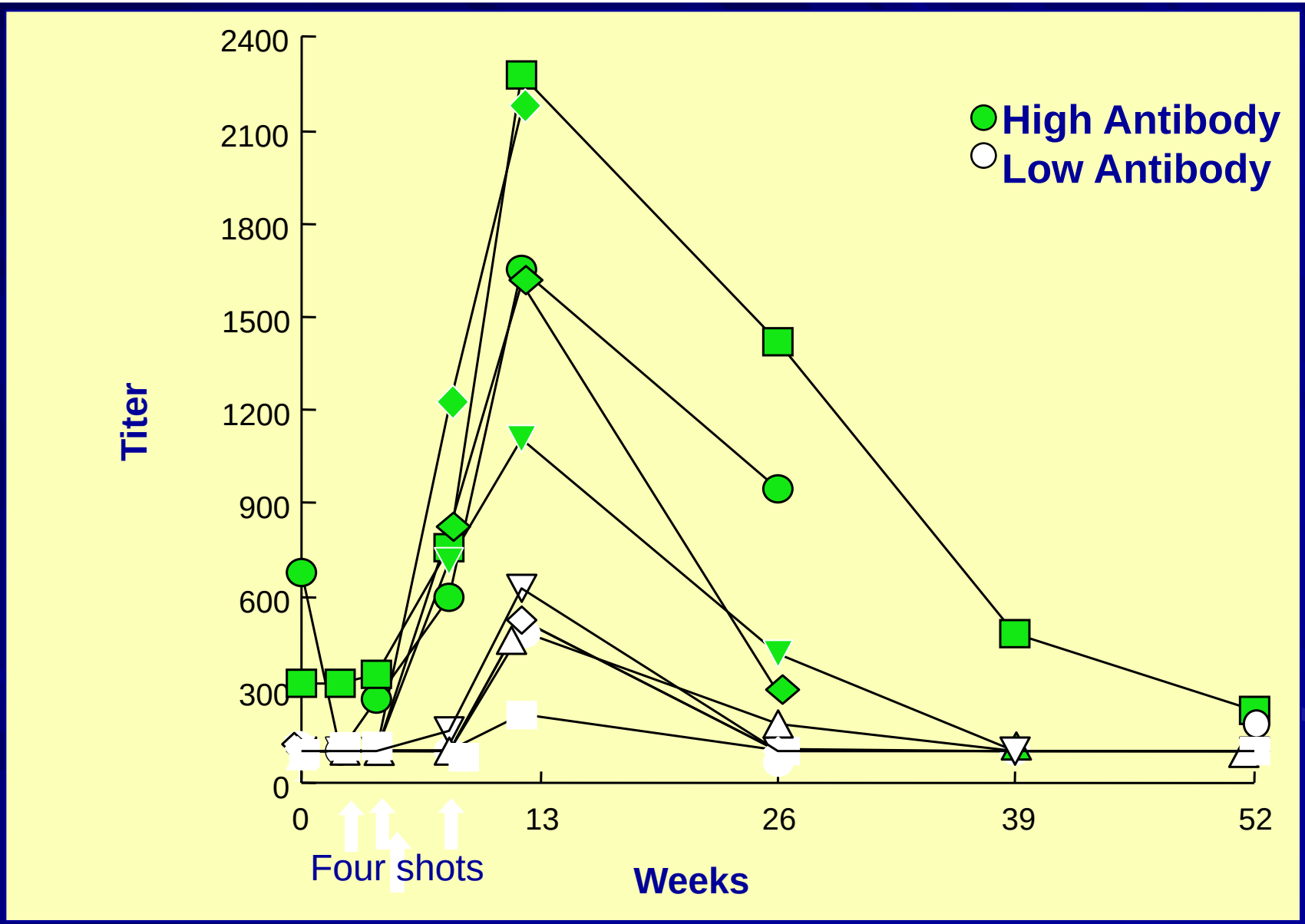
***Figure 3**: Nicotine-specific IgG antibody responses in human volunteers after vaccination with the Immunodrug™ candidate CYT002-NicQb to treat nicotine addiction. Vaccination was performed twice with CYT002-NicQb plus Alum as adjuvant. The graph shows geometric mean nicotine-specific antibody titers of 8 participants per dose regimen as measured by ELISA.*

Human Laboratory Study
Meg Haney – Columbia University

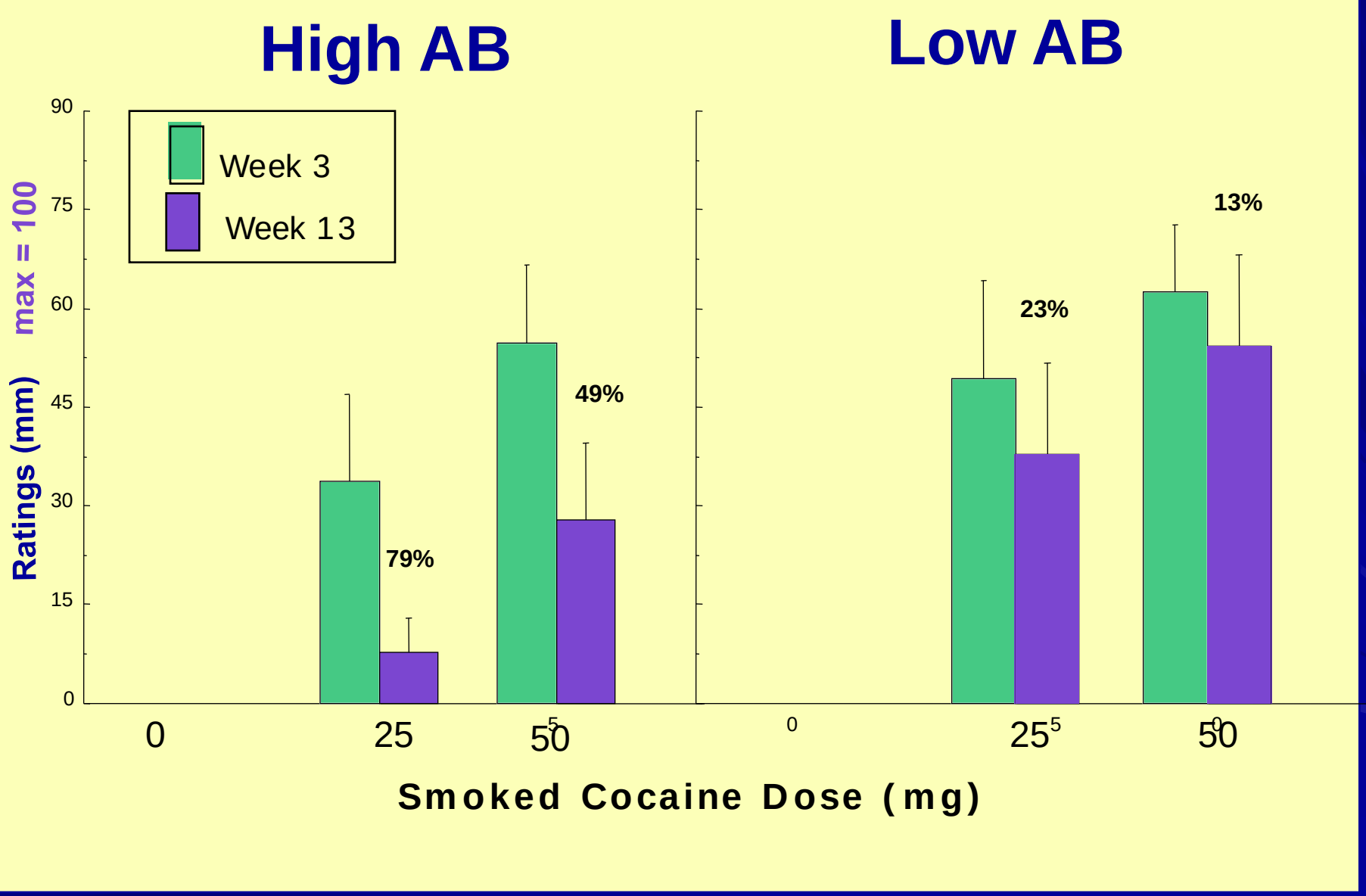
- Determine direct relationship between plasma antibody levels and cocaine's subjective and cardiovascular effects

- Administer smoked cocaine (0, 25, 50 mg) to non-treatment seeking, cocaine-dependent research volunteers pre-vaccine and at 12 weeks post-vaccine

Plasma Antibody (n=10)



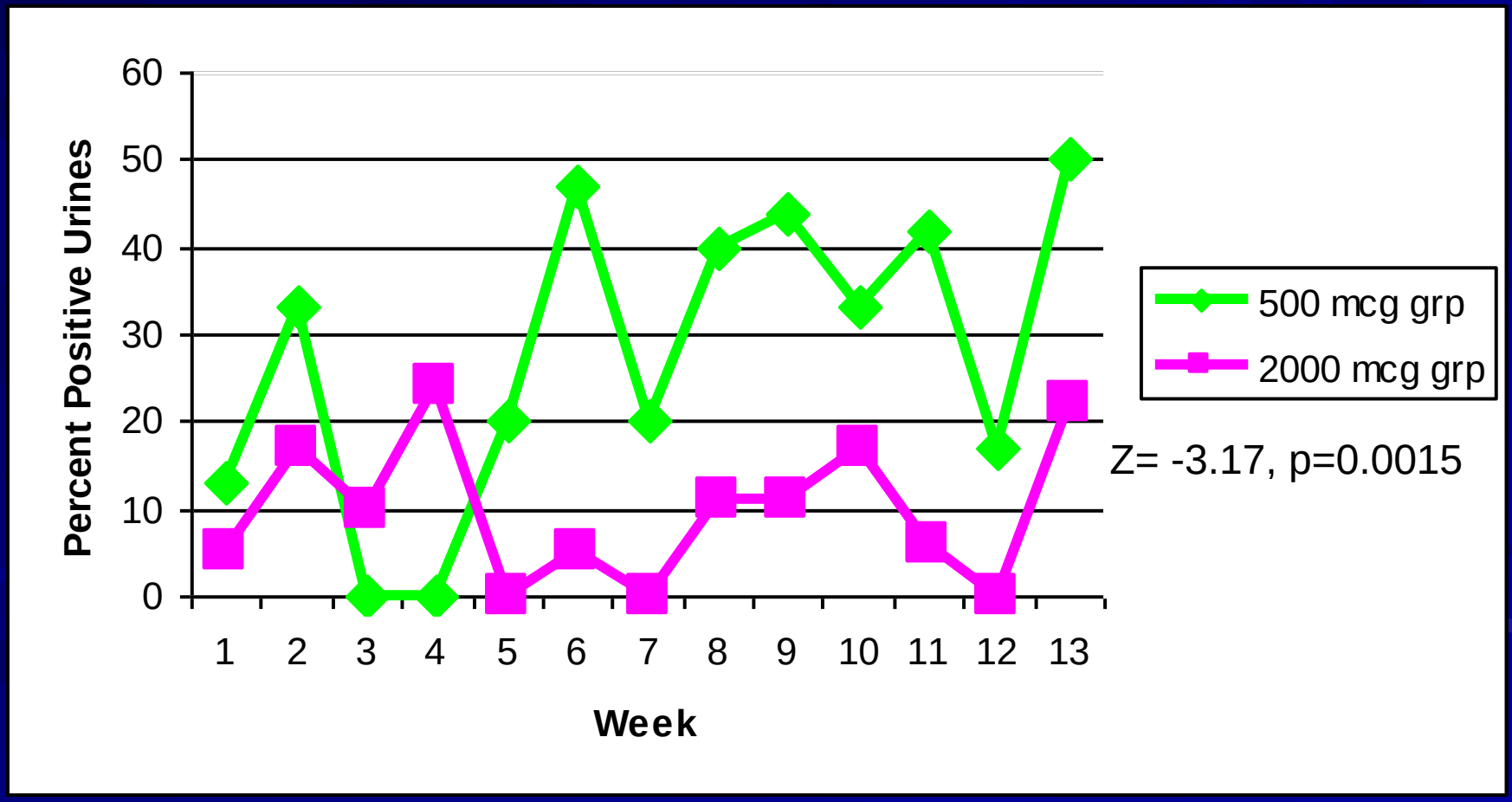
Good Drug Effect



Outpatient cocaine vaccine RCT (randomized clinicaltrials) Efficacy Studies

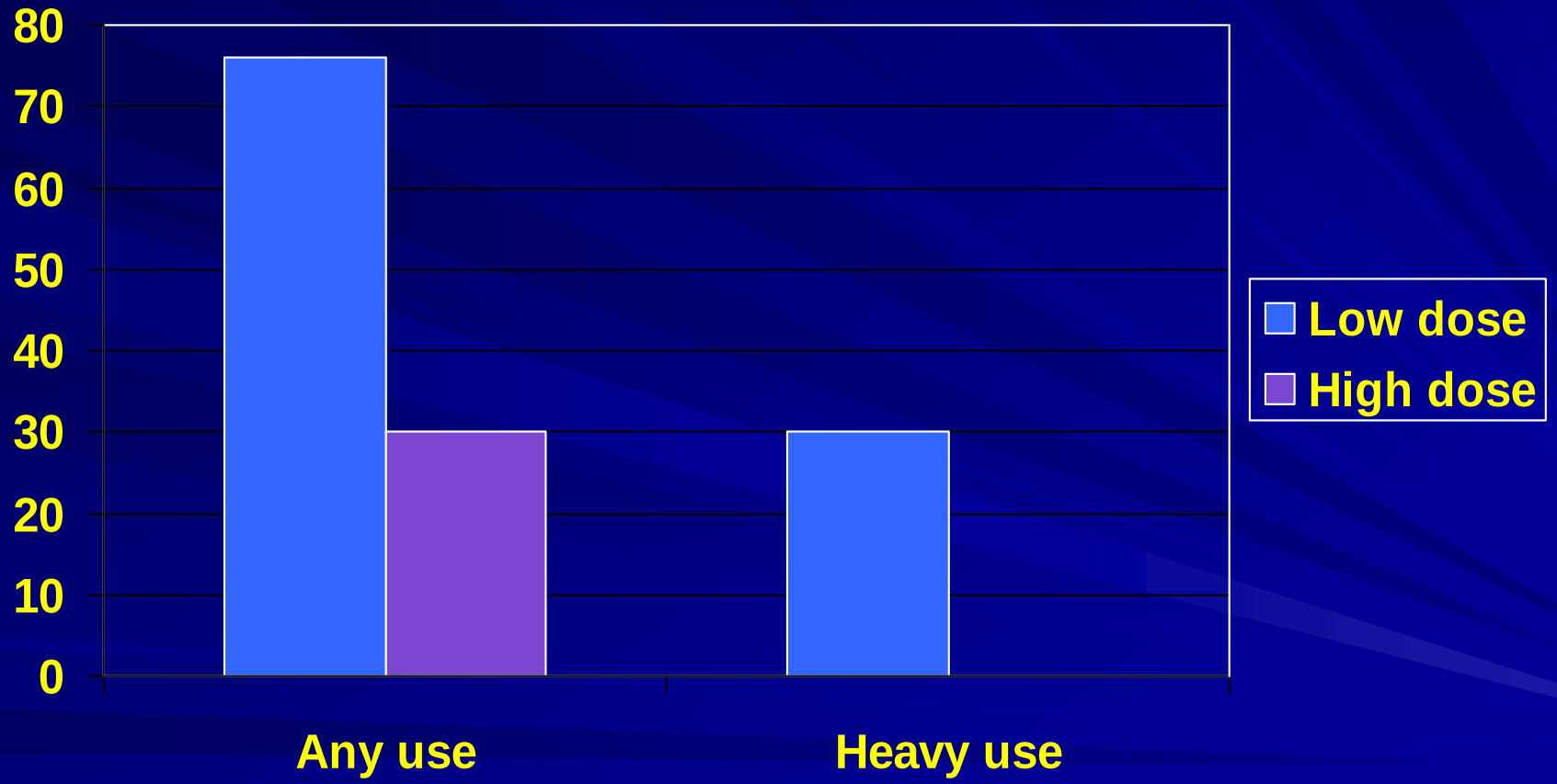
Fewer cocaine urines at higher Vaccine Dose

Vaccination makes antibodies by Week 4 (n=11)

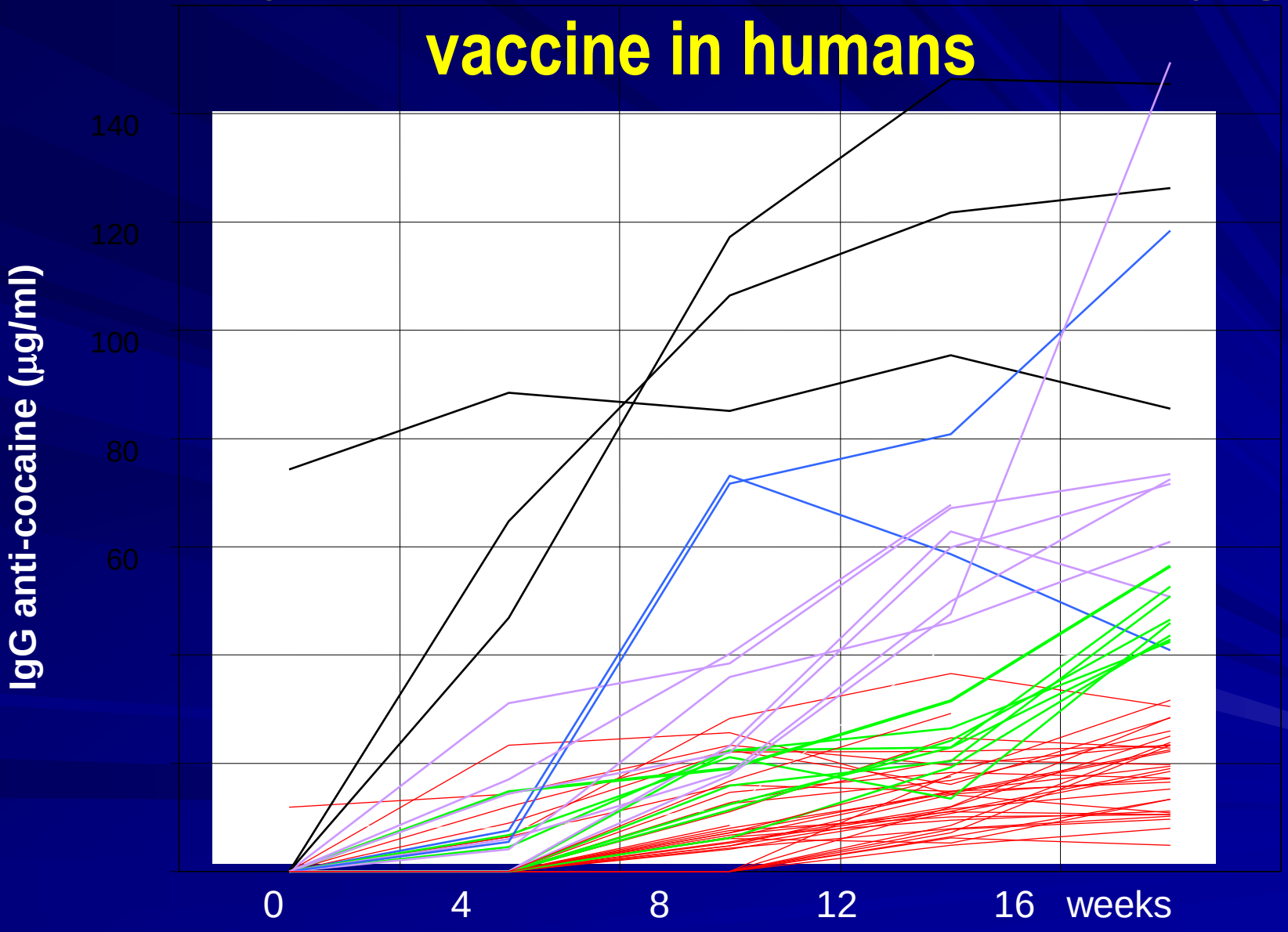


Less relapse to cocaine use with high vs low dose vaccination

(Percent of patients relapsing in each dosage group)

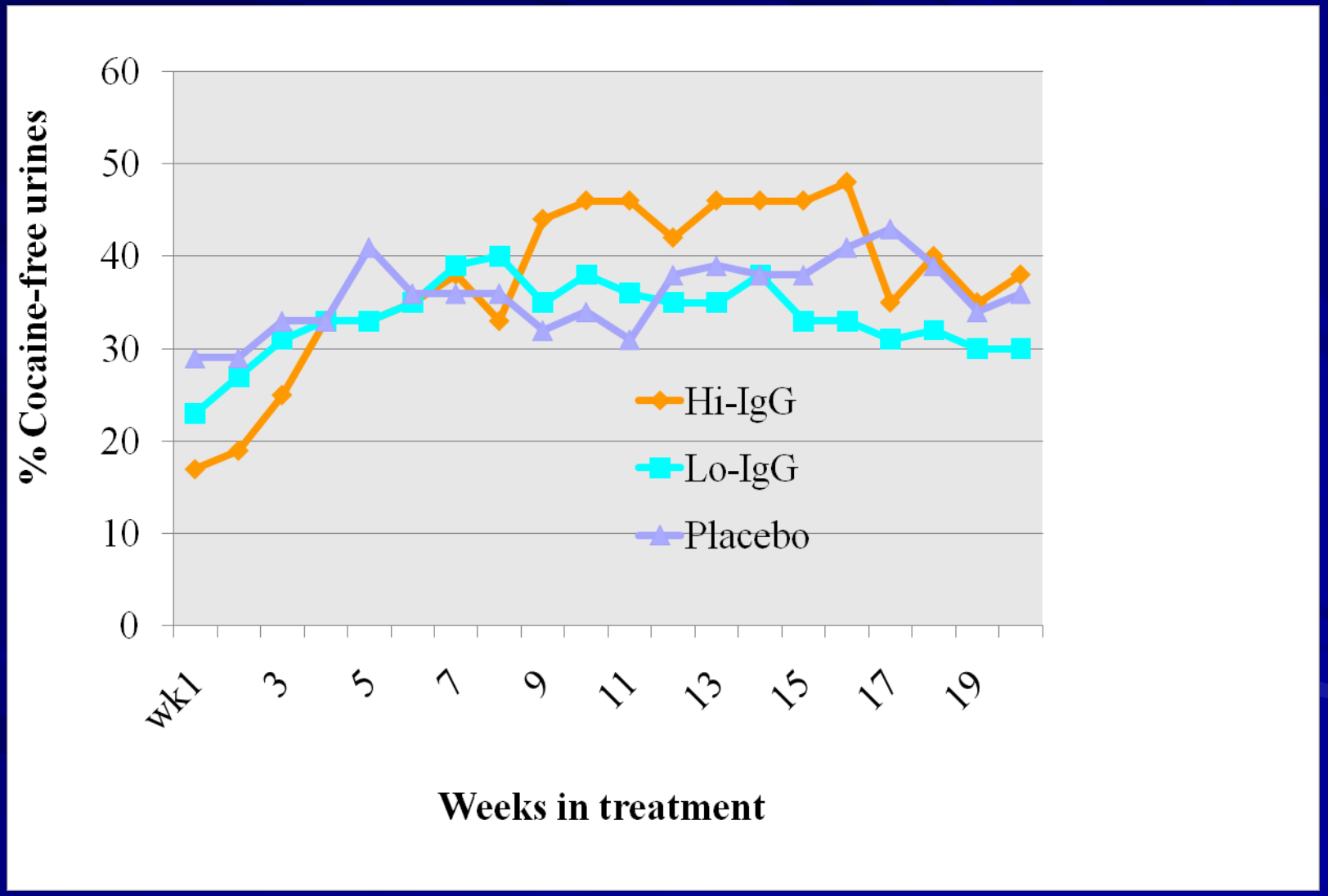


Antibody response to Cocaine-CTB conjugate vaccine in humans



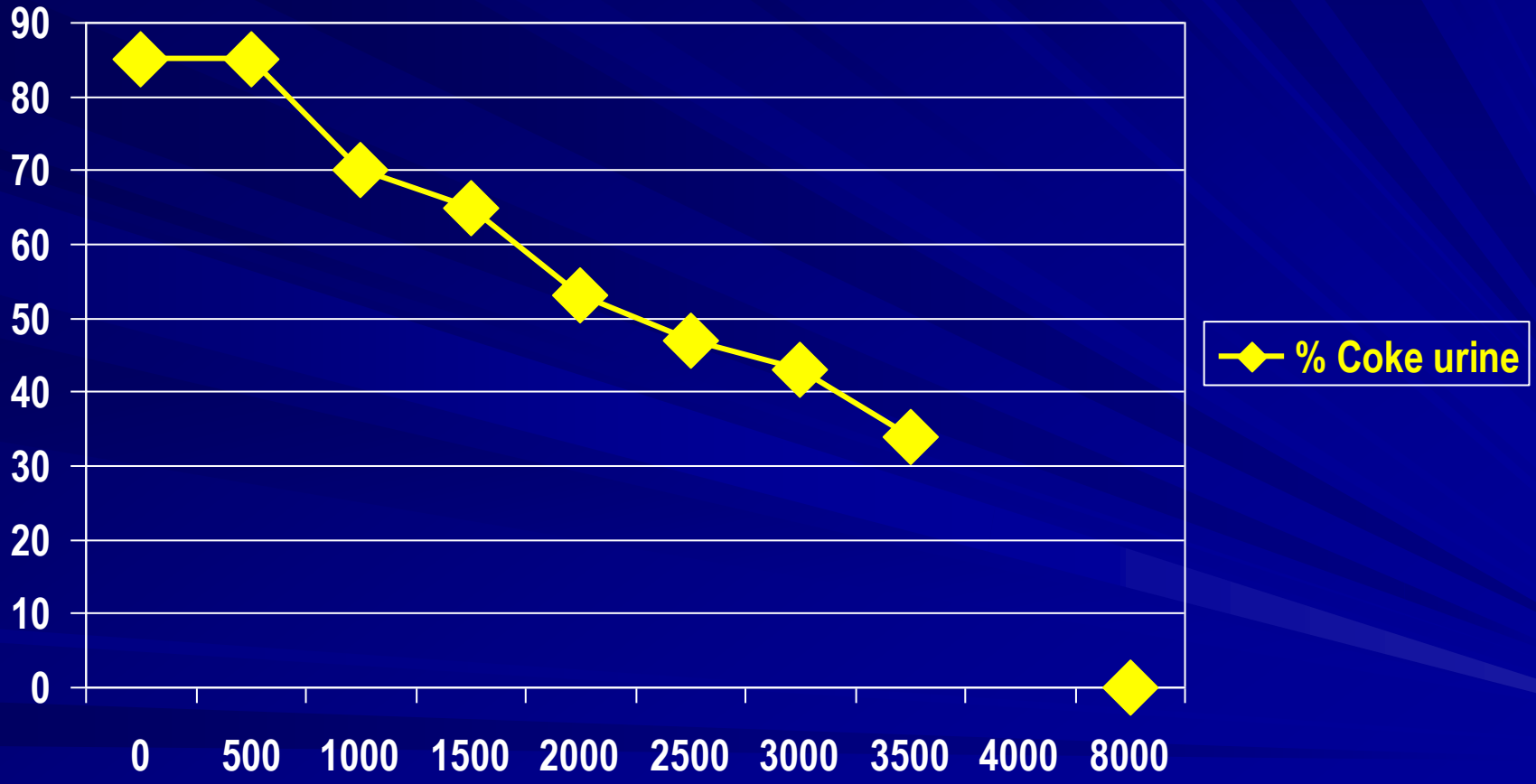
Cocaine-free urines for 20 week trial:

Placebo vs. patients with Hi vs. Lo Anti-cocaine antibodies



Cocaine urines fall as Antibody levels rise

Weeks 1, 4, 8, 12, 16, 20; p<0.0001 (Z= -4.0)



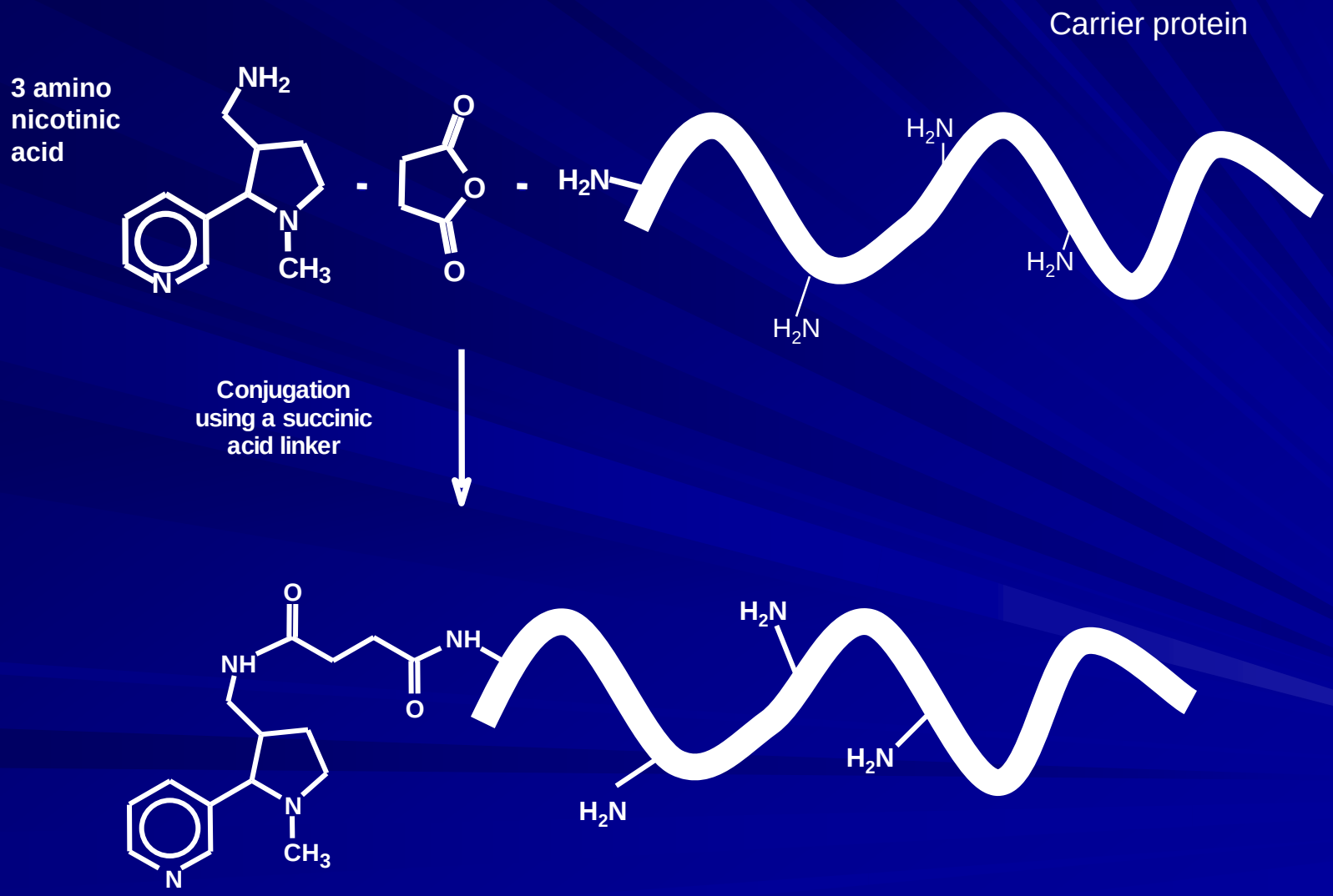
Conclusions from Vaccine RCT

- Cocaine vaccine better than placebo
- Cocaine-free urines increase as AB levels increase
- 75% of patients had effective antibody response
- Vaccine is medically safe, even with 10 times more cocaine use than during baseline
- Better vaccine needed.

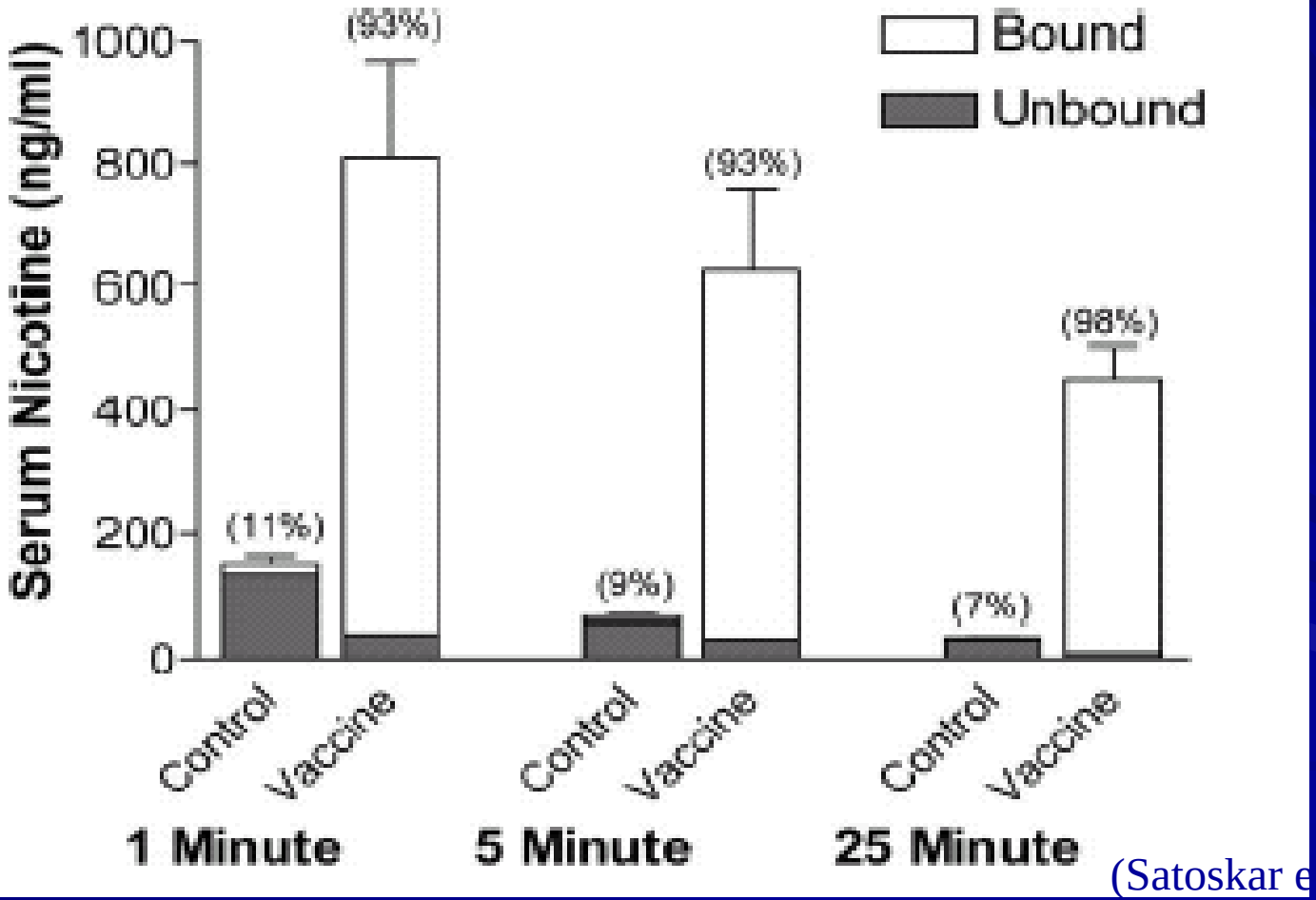
Companies Working on Nicotine Vaccines

- Celtic Pharma (TA-NIC)
- Nabi Biopharmaceuticals (NicVAX)
- Cytos Biotechnology (NIC002)
- Follow progress on their web sites

Synthesis of NicVAX



Effect of Nicotine Vaccine on Serum Nicotine Concentration in Rats



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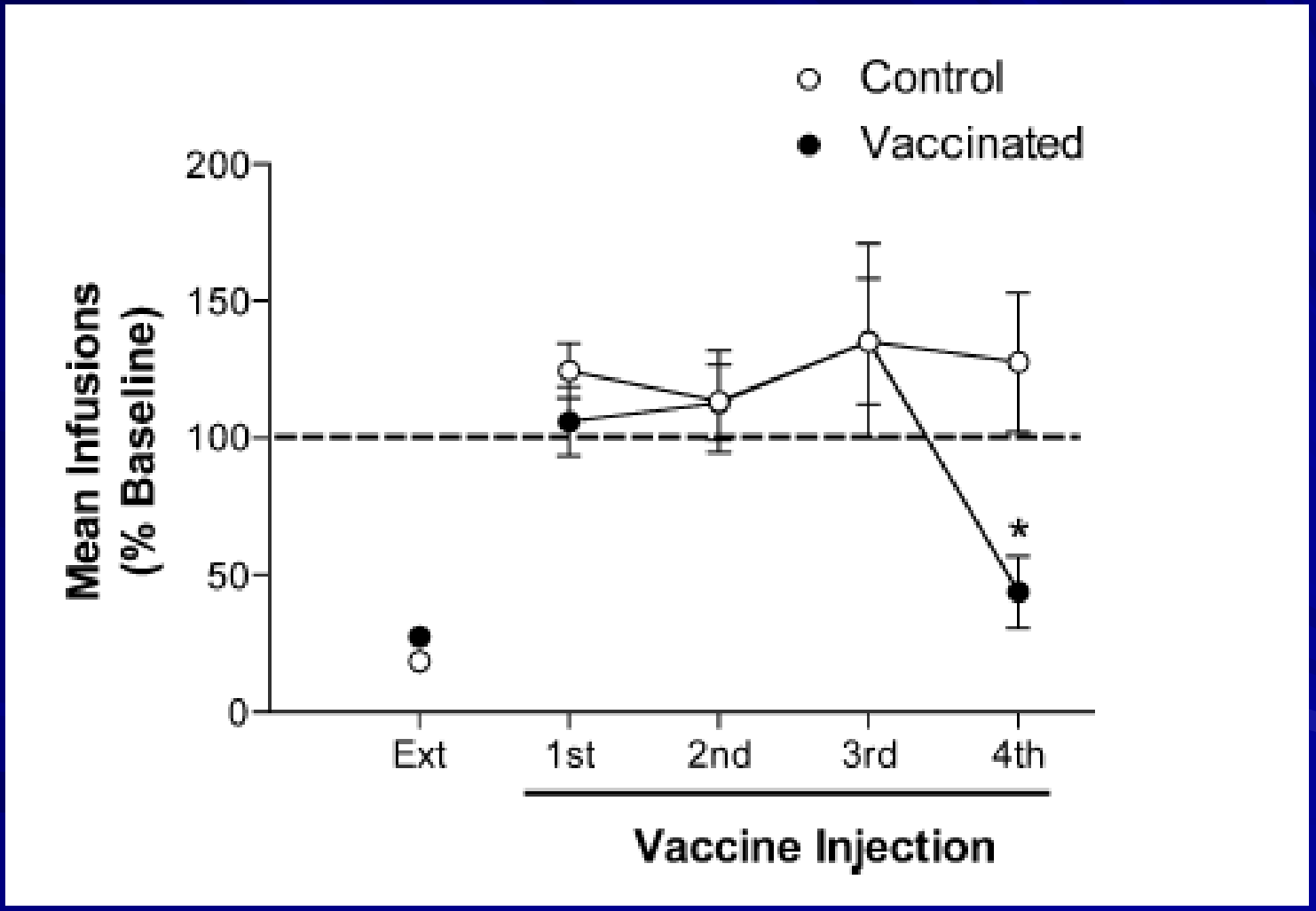
Nicotine Vaccine and Maintenance of Self-Administration



NicVAX ™ is intended to be used:

- As either an aid or stand-alone therapy for smoking cessation (maintenance and relapse)
- As either an aid or stand-alone therapy for smoking reduction (reduced maintenance)
- For the prevention of tobacco/nicotine dependence (acquisition and maintenance)

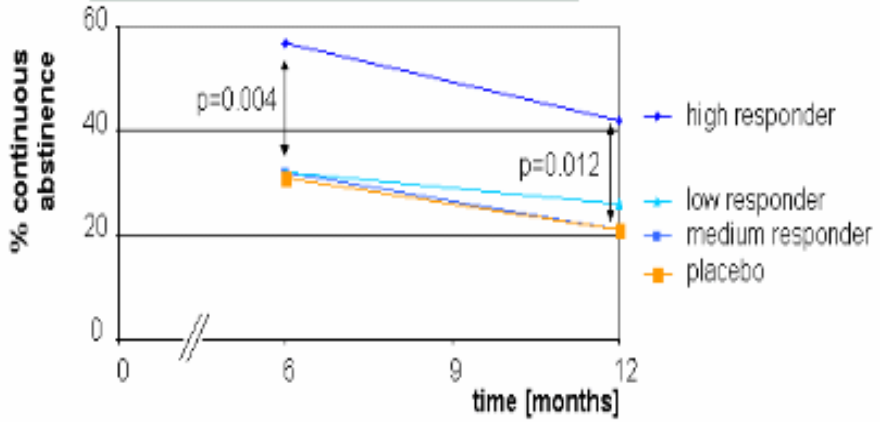
Clinical Trials with NicVAX ™

- Phase I safety study, n = 20 non-smokers. Well tolerated, no SAEs
- Phase I/II trial in the Netherlands to assess the safety of multiple doses and collect data on ab titer, and evaluate abstinence and relapse rate, in 21 smokers and 9 exsmokers
- Multi-site Phase II trial (U.S.) in 63 smokers, to assess immunogenicity and safety in smokers - data analysis showed a 33% quit rate
- New Phase II study underway in the Netherlands in 30 smokers to provide additional data on optimal dose and dosing schedule
- Larger Phase II multi-site efficacy study (n=200) funded through a NIDA grant

Cytos Nicotine Vaccine- Results from their Web Site

CYT002-NicQb Phase II Results

Continuous Abstinence from Smoking (per Protocol)



CYT002-NicQb	6 month*	12 month*
high responder	57% (30 / 53)	42% (22 / 53)
medium responder	32% (17 / 53)	21% (11 / 53)
low responder	32% (17 / 53)	26% (14 / 53)
Placebo	31% (25 / 80)	21% (17 / 80)

* in parenthesis: number of continuously abstinent subjects / total number of subjects in group

Primary Endpoint: Eight-week Continuous Abstinence

Antibody Level vs. Quit Rate

Eight-Week Continuous Abstinence*

Antibody Response	N	% of Drug Treated Patients	Quit Rate
High	61	30%	24.6% 13/61 (p=0.04)
Low	140	70%	10% 14/140
Placebo	100		13% 13/100

***Weeks 19-26 after first vaccination**

Can Someone Smoke Enough to Overcome the Vaccine Titer ? Evidence suggest not.

Conclusions

- Vaccines against nicotine can be safe and well tolerated.
- There is a relationship between high antibody titers and continued abstinence.
- Further trials ongoing.
- FDA approval needed.

Monoclonal Antibodies

- Under development in several labs.
- Instantly useful; not a vaccine!
- Not at the same level of development as the vaccines.
- Targets such as PCP and cocaine that can be a problem in overdose.
- Catalytic ABs have been made.

Ethical Issues

- Use in Children: Informed consent is a problem, and does the benefit (utility) outweigh the risks?
- Legal coercion.
- Prevention? Use of vaccines before a problem exists?
- Not easy for patient to change his/her mind about Tx after vaccination.
- We can’t ignore other proven Txs for drug use and perhaps need to find best combinations of Txs.

Other issues

- Most drug users are multi-drug users. Is the use of multiple vaccines for multiple drugs at the same time acceptable? Probably yes.
- Ethical issues and other issues can be dealt with better as we learn more and gain experience with such vaccines.

Overall Conclusions

- Vaccines have advantages over classical medications.
- Usefulness depends on AB response and quality. Currently, variable responses. Improve vaccines, adjutants and schedules.
- Ethical issues with forced vaccination and underage individuals.
- Vaccines not yet ready for major use and are unlikely to be the final and only answer.

Overall Conclusions - 2

- There is a need to produce better vaccines that produce higher antibody levels that last longer than 3-4 months. Thus, we need improved vaccines, adjuvants, boosters and schedules of inoculation.

Acknowledgements

- Dr Tom Kosten
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