TA-CD, a vaccine for cocaine addiction

- an update

Verona, 20th December 2006

Vaccination – a novel approach to cocaine addiction

- **Vaccinate the patient**
- **Patient makes antibodies**
- **Antibodies remain in circulation for several months**
- **If the patient takes cocaine, it is bound by circulating antibodies**
- **Antibody:cocaine complexes cannot cross the blood-brain barrier. The amount of cocaine reaching the brain and also the speed of delivery are thus reduced.**
- **This prevents or reduces the "high" and the associated priming effect**

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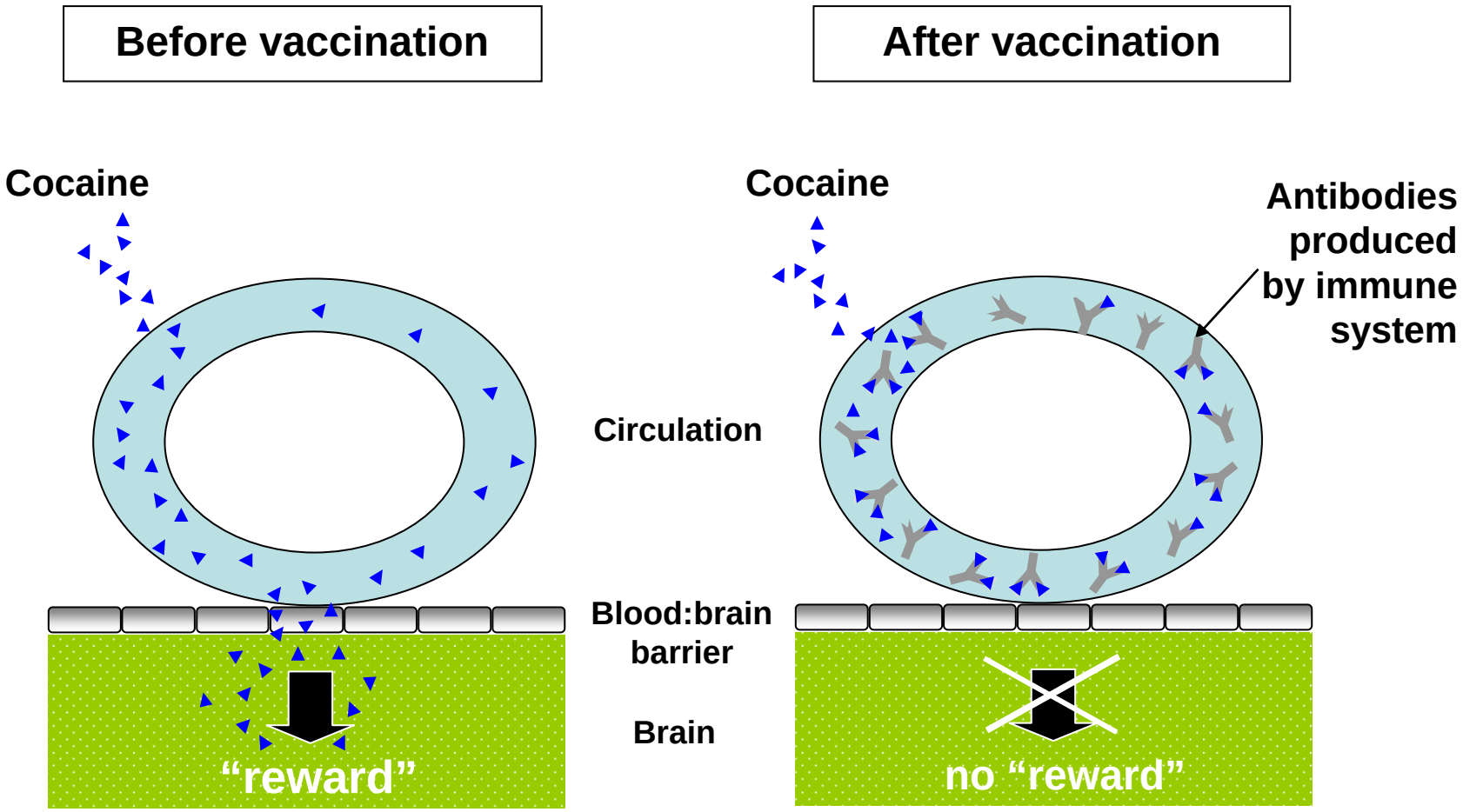
Vaccines of Addiction - Product Concept



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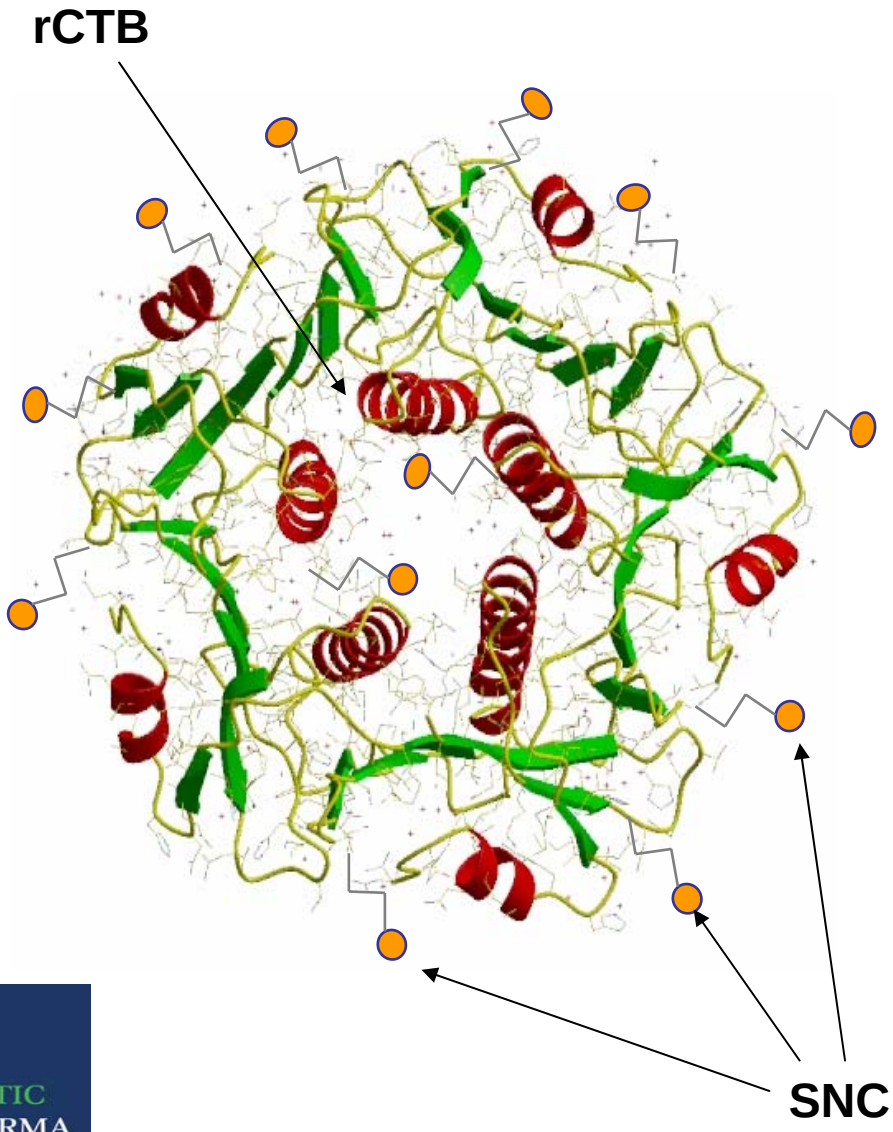
TA-CD Product Description



- Cocaine derivative (succinyl norcocaine) coupled to recombinant cholera toxin B (rCTB)
- Linked by a stable covalent bond
- Aluminum hydroxide adjuvant added
- Given by intramuscular injection to upper arm

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TA-CD – Preclinical Studies

- **Proof of concept established in pre-clinical models**
  - **Vaccine induces cocaine specific antibodies**
  - **Antibodies reduce levels of cocaine in brain**
  - **Vaccination leads to a significant reduction in cocaine self administration in addicted rodents**

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TA-CD: Clinical Studies Summary (June 06)

- **Completed:**
  - **Phase I: TA-CD/01 - Safety and Immunogenicity (n=30)**
  - **Phase IIa: TA-CD/03 - Relapse Prevention (n=9)**
  - **Phase IIa: TA-CD/06 - Abstinence Initiation (n=13)**
- **In progress:**
  - **Phase IIa: TA-CD/04 – Cocaine Challenge (n=11)**
  - **Phase IIb: TA-CD/08 – Efficacy (randomised, double-blind placebo-controlled; n=132)**

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TA-CD/04

- Dr Meg Haney, Columbia University
- Study design
  - 13-week investigator study
  - Multiple vaccinations over 8 weeks
  - Inpatient: 2 nights/wk for 13 wks
    - 3 cocaine sessions/week
    - Each session tested one dose of smoked cocaine (0, 25, 50 mg) administered 2x/session

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Participants - Completers

- **10 males (6 black, 3 white, 1 hispanic)**
- **39 ± 1 yrs of age**
- **Cocaine-dependent (no other drug dependencies apart from nicotine)**
- **Smoked cocaine: 4 ± 1 days/wk, $279 ± 86**
- **Years of smoked cocaine use: 13 ± 3**
- **HIV-ve**
- **Not interested in treatment for cocaine dependence**

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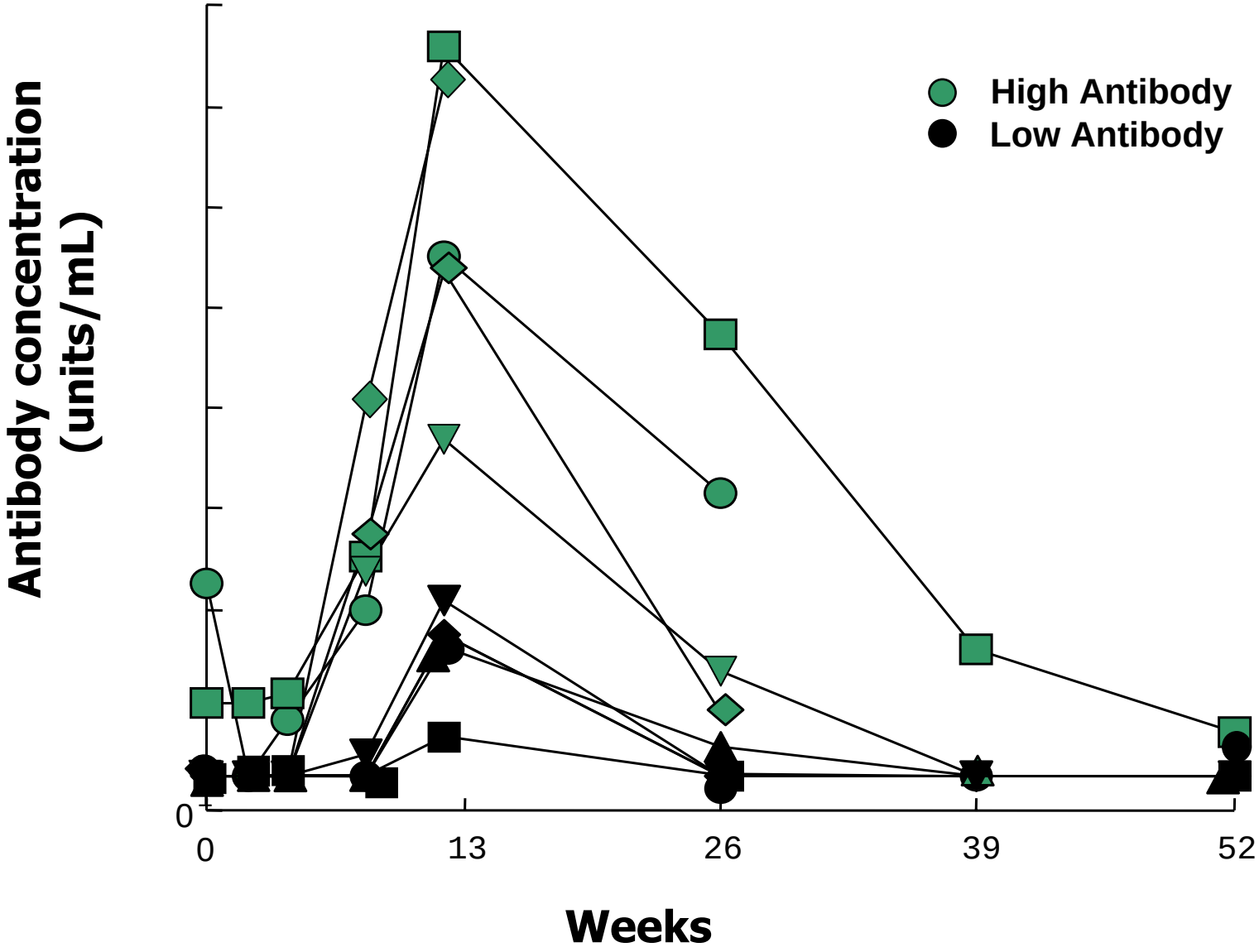
Plasma antibody levels (n=10)



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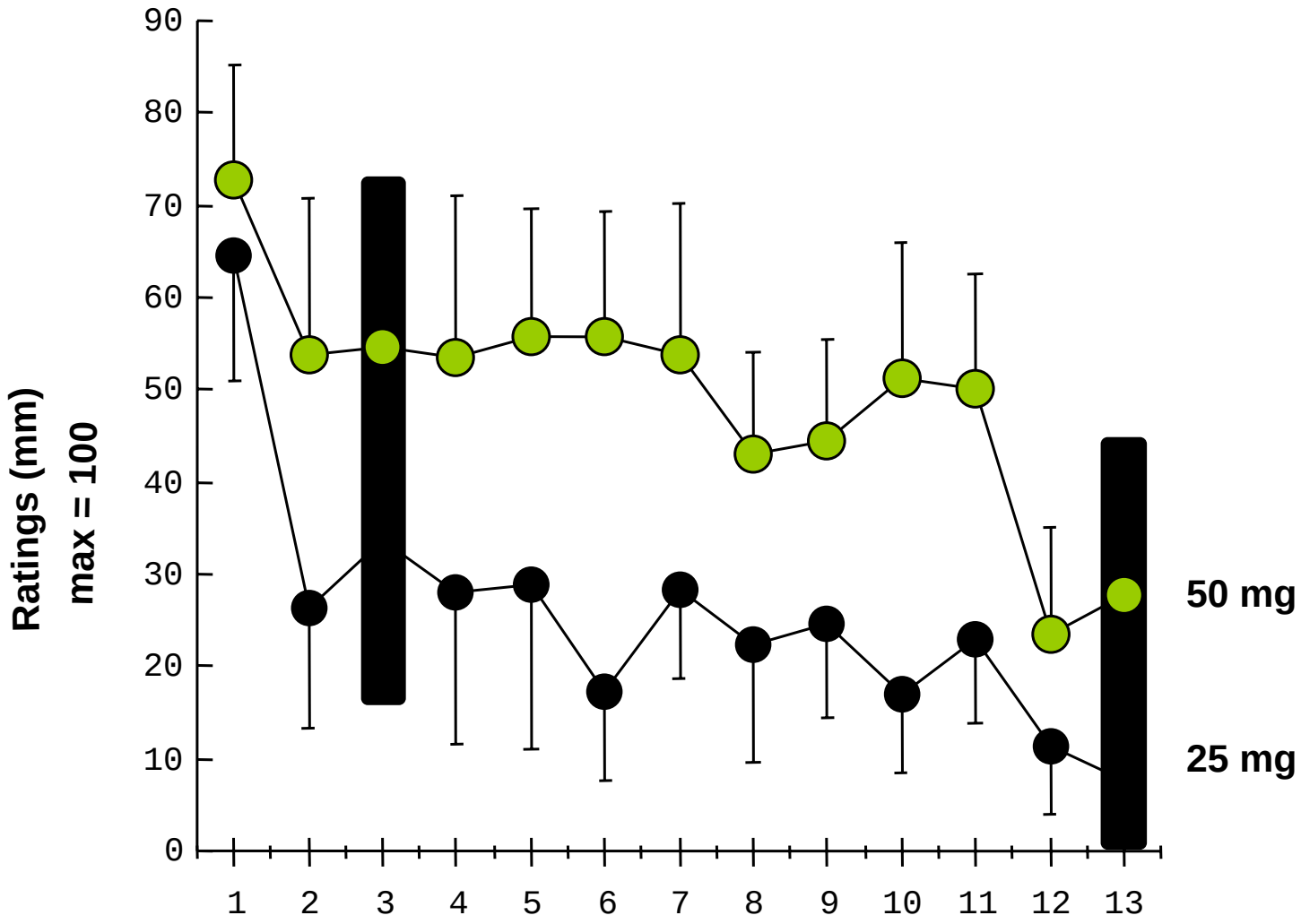
Good Drug Effect: High Ab



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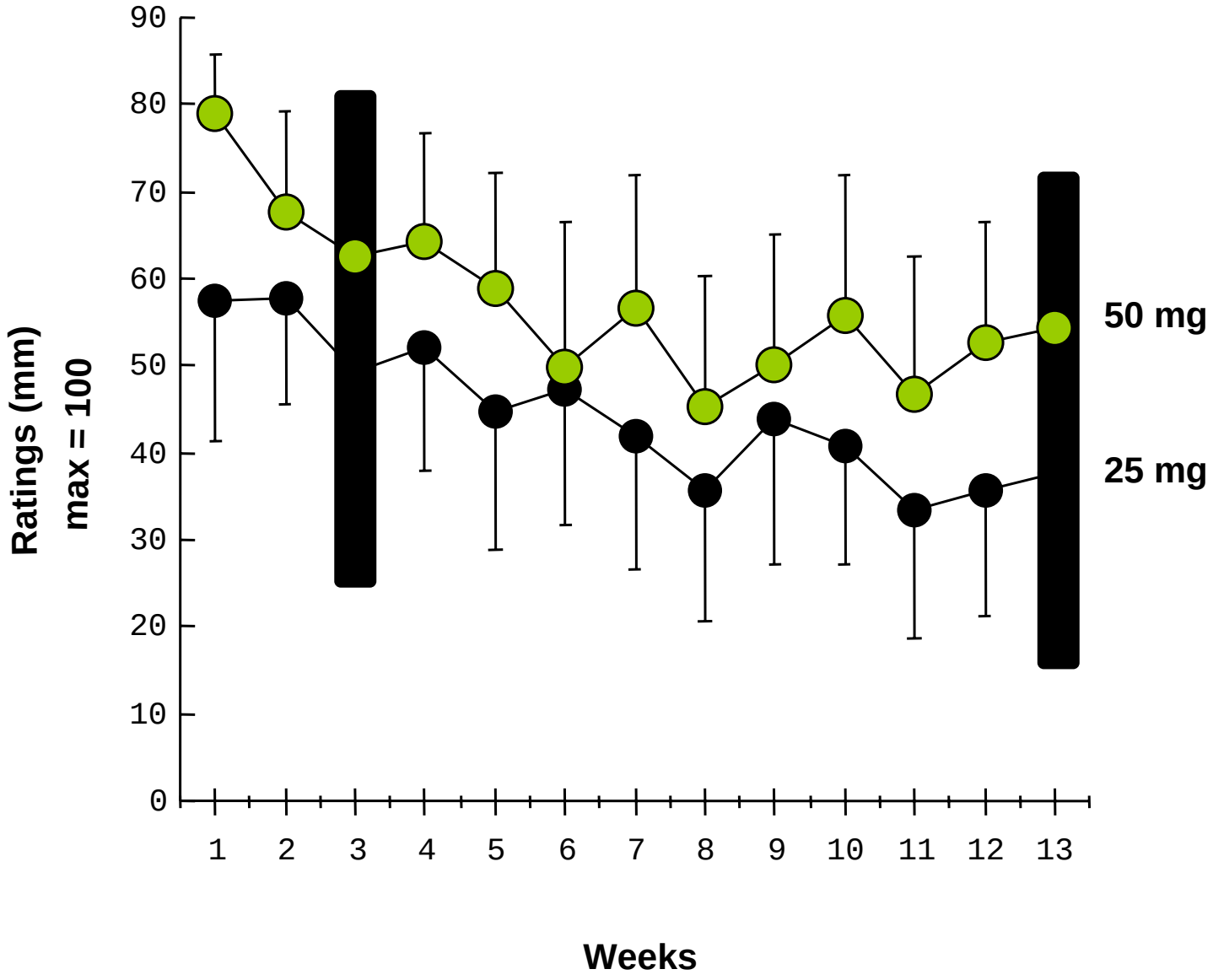
Good Drug Effect: low ab



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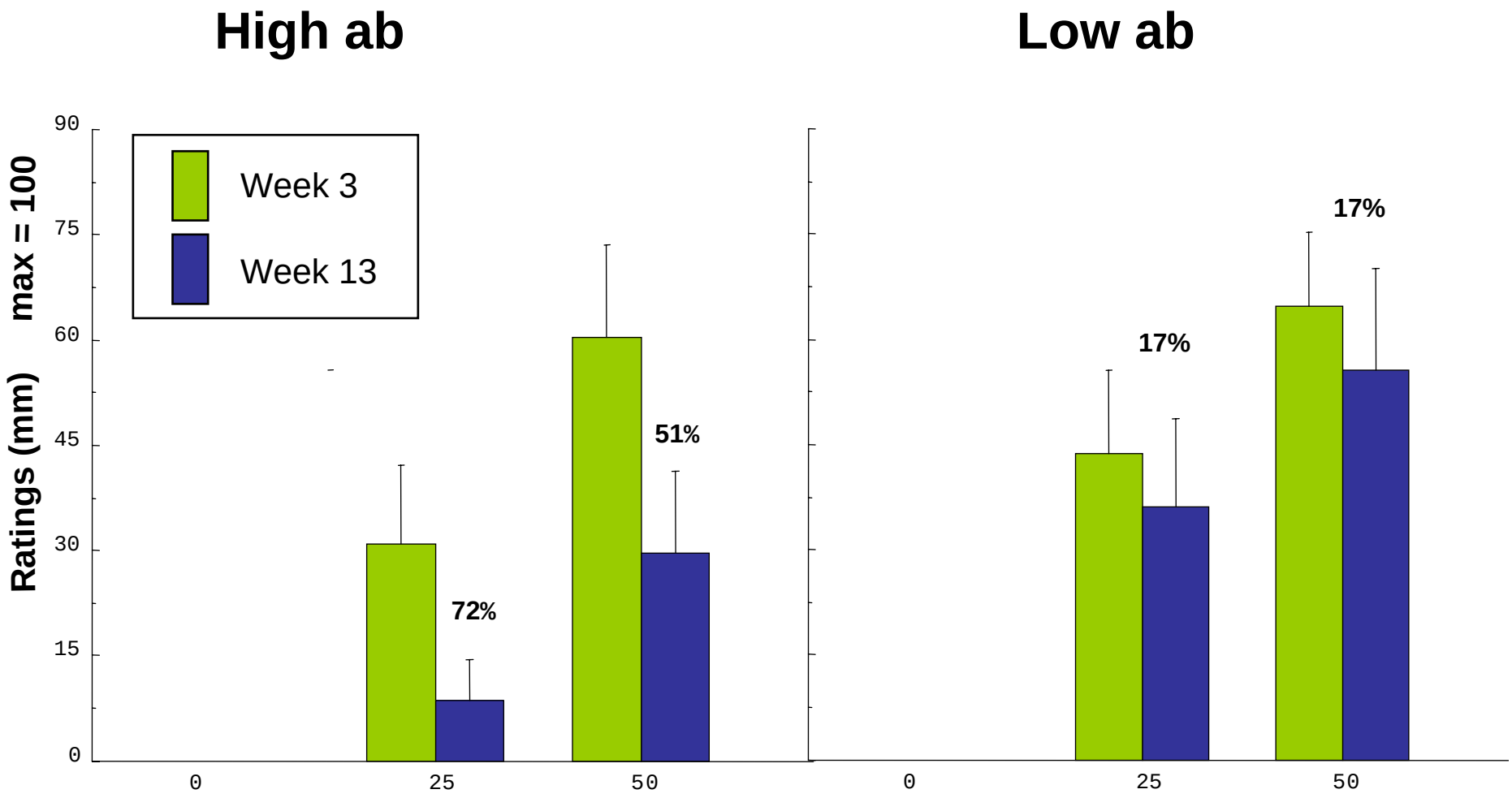
Dose Potency



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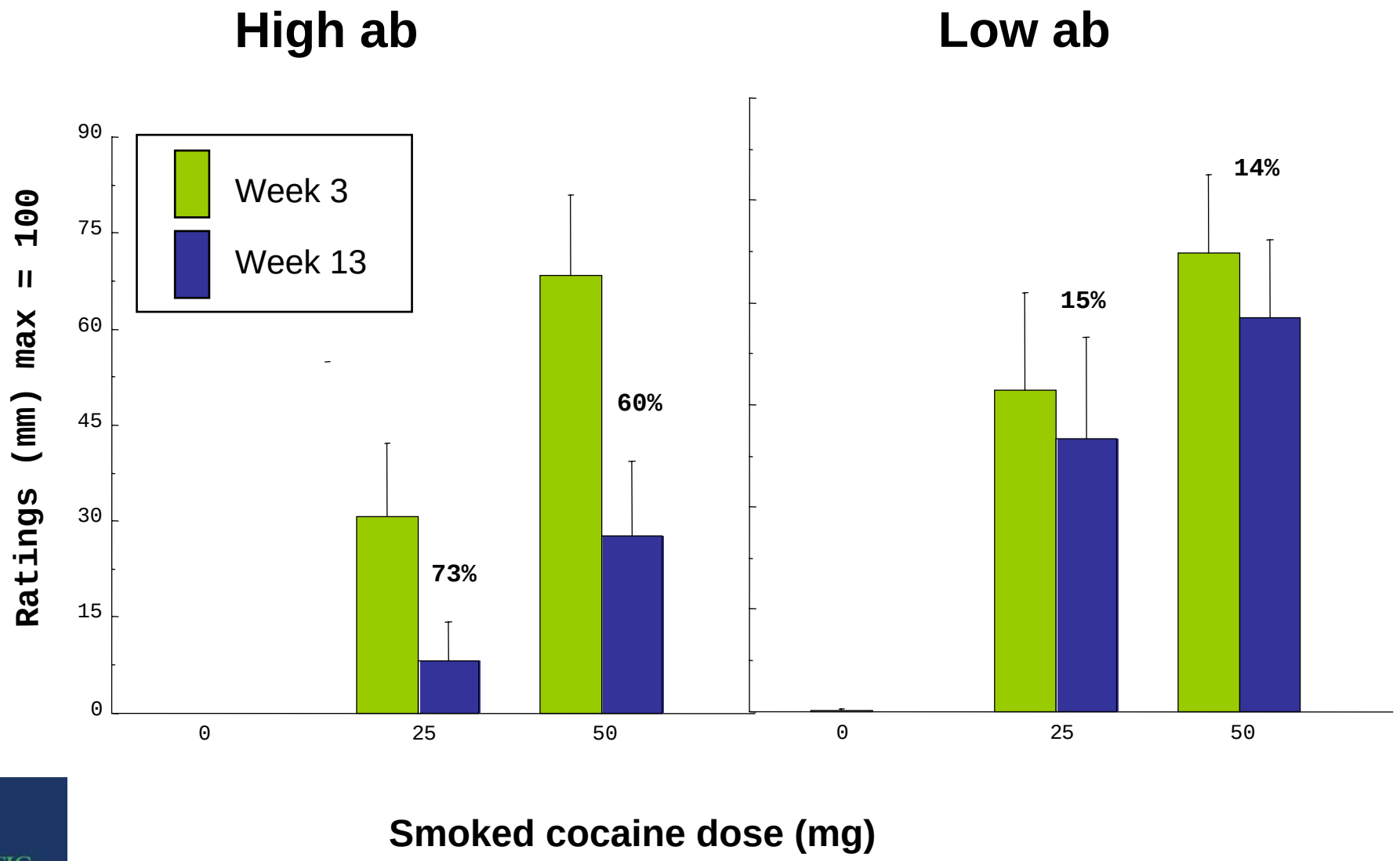
Like Dose



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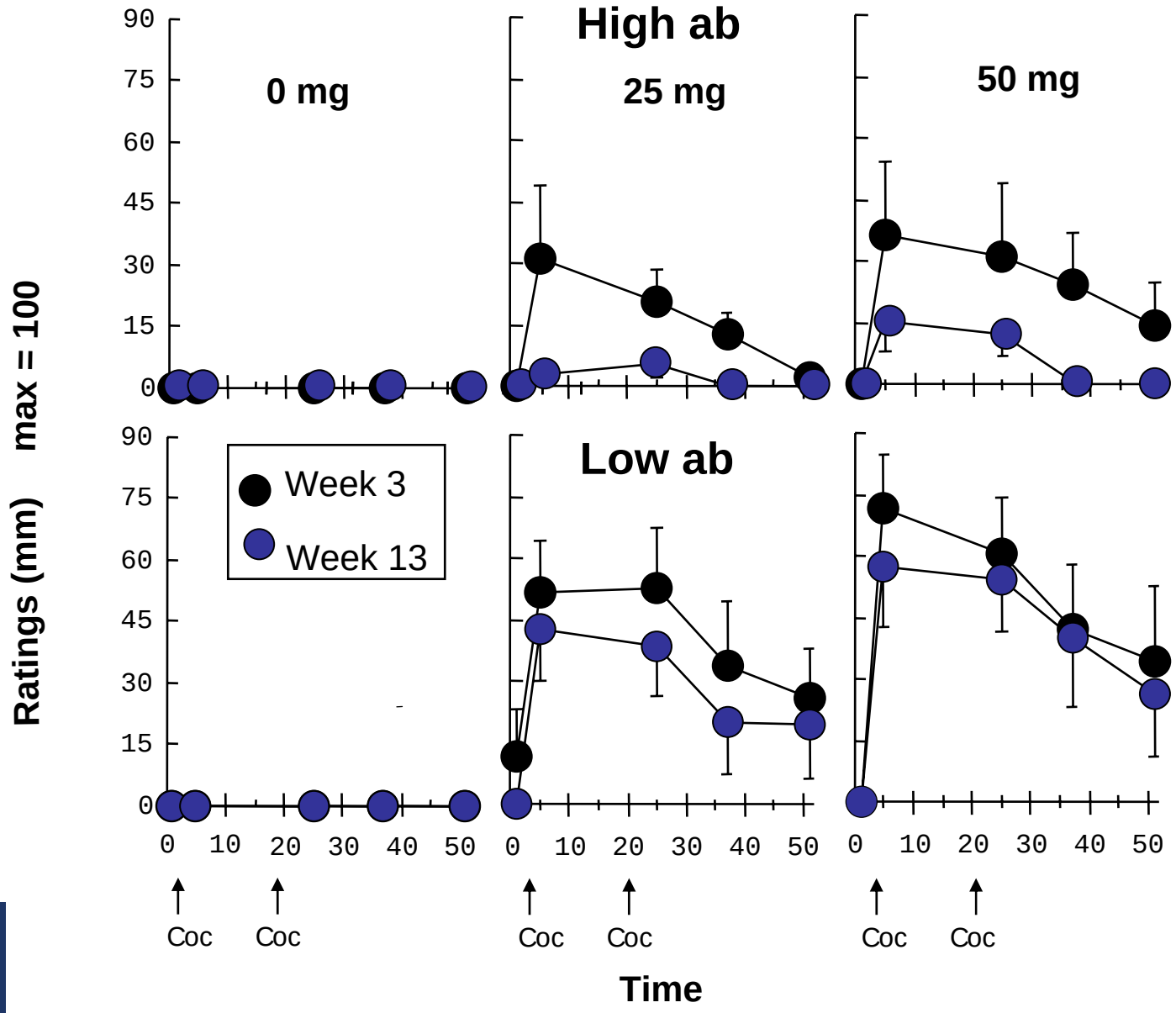
Stimulated



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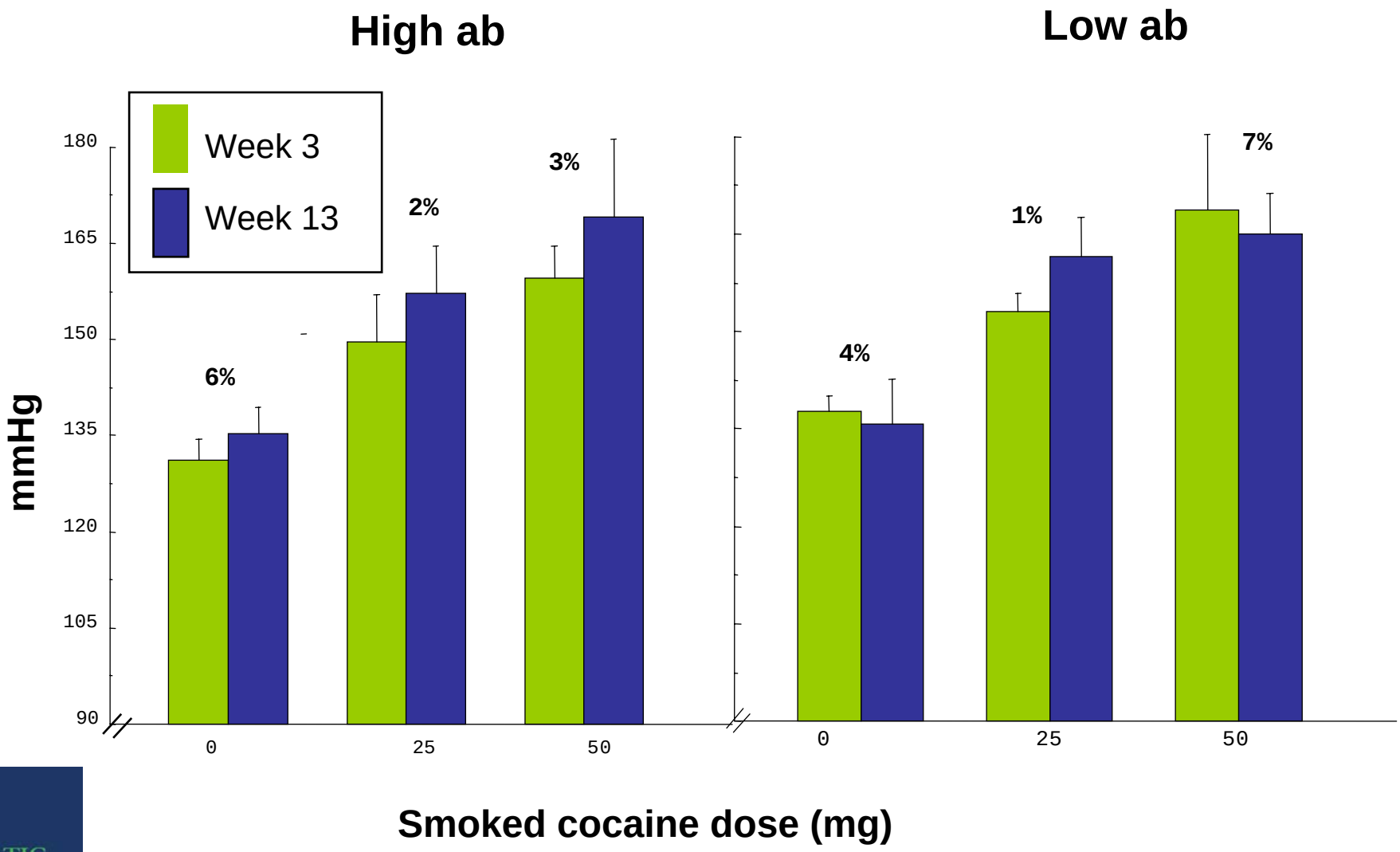
Systolic Pressure



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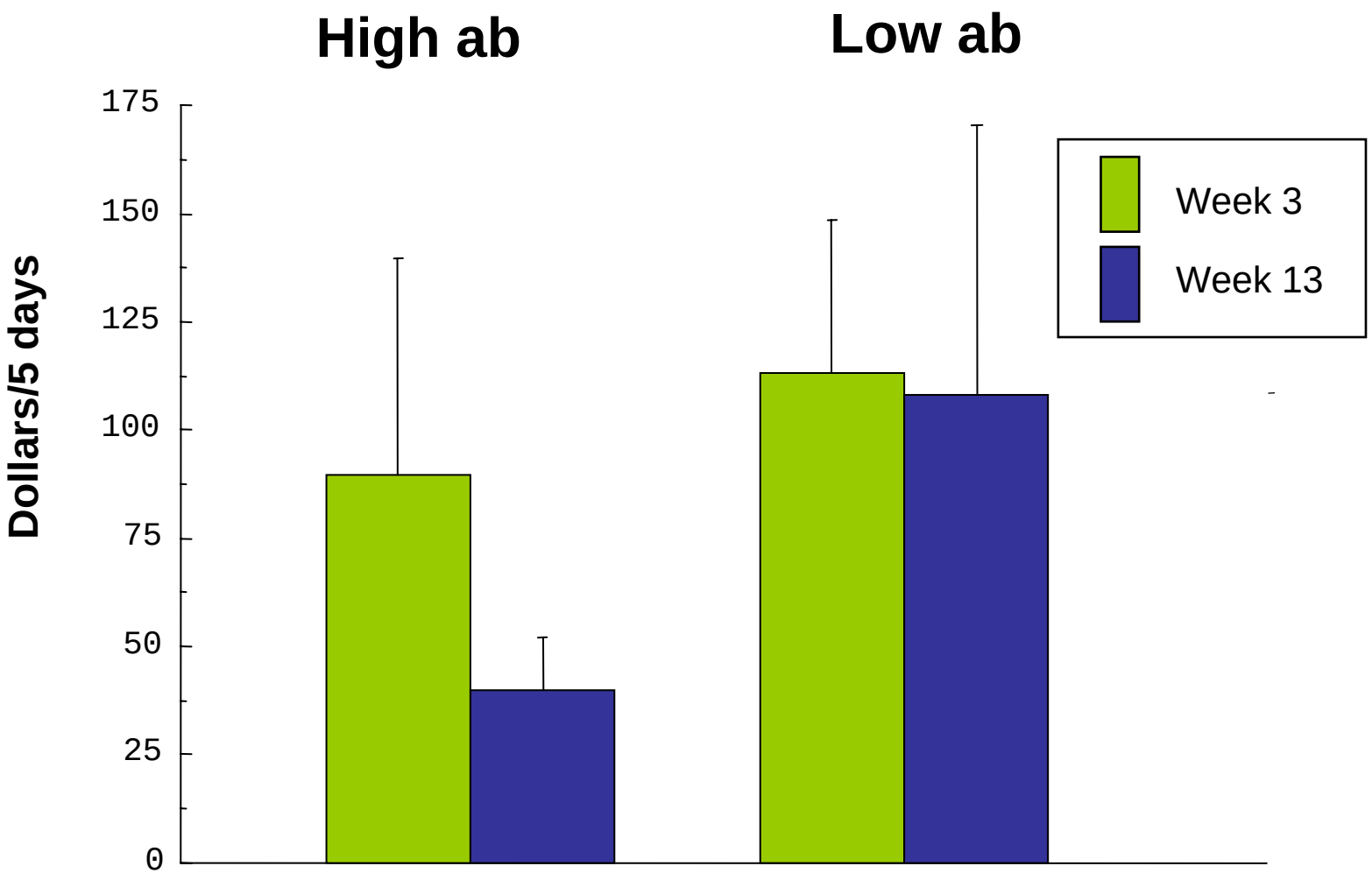
Self-reported Cocaine Use



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TA-CD/04 – summary

- **Vaccine well tolerated; safe in combination with cocaine**
- **No evidence that participants attempted to surmount effects of vaccine by using more cocaine**
- **Those participants who produced high antibody levels showed a substantial decrease in cocaine intoxication**

Pharmacological efficacy demonstrated in addition to safety

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TA-CD/08

- **Prof Tom Kosten, Yale University**
- **Study Design**
  - **Double blind placebo-controlled randomised clinical trial**
  - **114 methadone-maintained cocaine dependent patients**
  - **Vaccinated with TA-CD over 12 weeks**
  - **Urine toxicology 3x/week**
  - **Serum antibody levels assessed throughout study**
  - **Intent to treat analysis**
  - **Primary endpoint – 3 weeks' cocaine abstinence between weeks 8 and 20**

Primary endpoint was not met

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TA-CD/08

But that is not the whole story!

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TA-CD/08 – what have we learned? (i)

- **Very high retention rate in this patient population (95% at week 12)**
- **High placebo effect (~35%)**
- **No significant protocol violations**
- **Significant proportion of patients "clean" throughout study or "dirty" throughout study**

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TA-CD/08 - what have we learned? (ii)

- **Vaccine safe, even at high doses of cocaine**
  - **>110 pts treated in 5 studies with no vaccine-related serious adverse events**
- **Vaccine stimulated production of anti-cocaine antibodies**
- **Methadone-dependent population contains a variety of patient types, including:**
  - **patients not motivated to quit**
  - **patients able to quit without vaccine**
  - **patients motivated to quit, but unable to quit without support**

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TA-CD/08 – what have we learned? (iii)

- **During the initial 12 weeks of study, vaccine was more effective than placebo**
  - **defined as ≥50% reduction in cocaine use from baseline**
  - **28% success for vaccine vs 14.5% for placebo**
  - **based on 3x weekly urine toxicologies**

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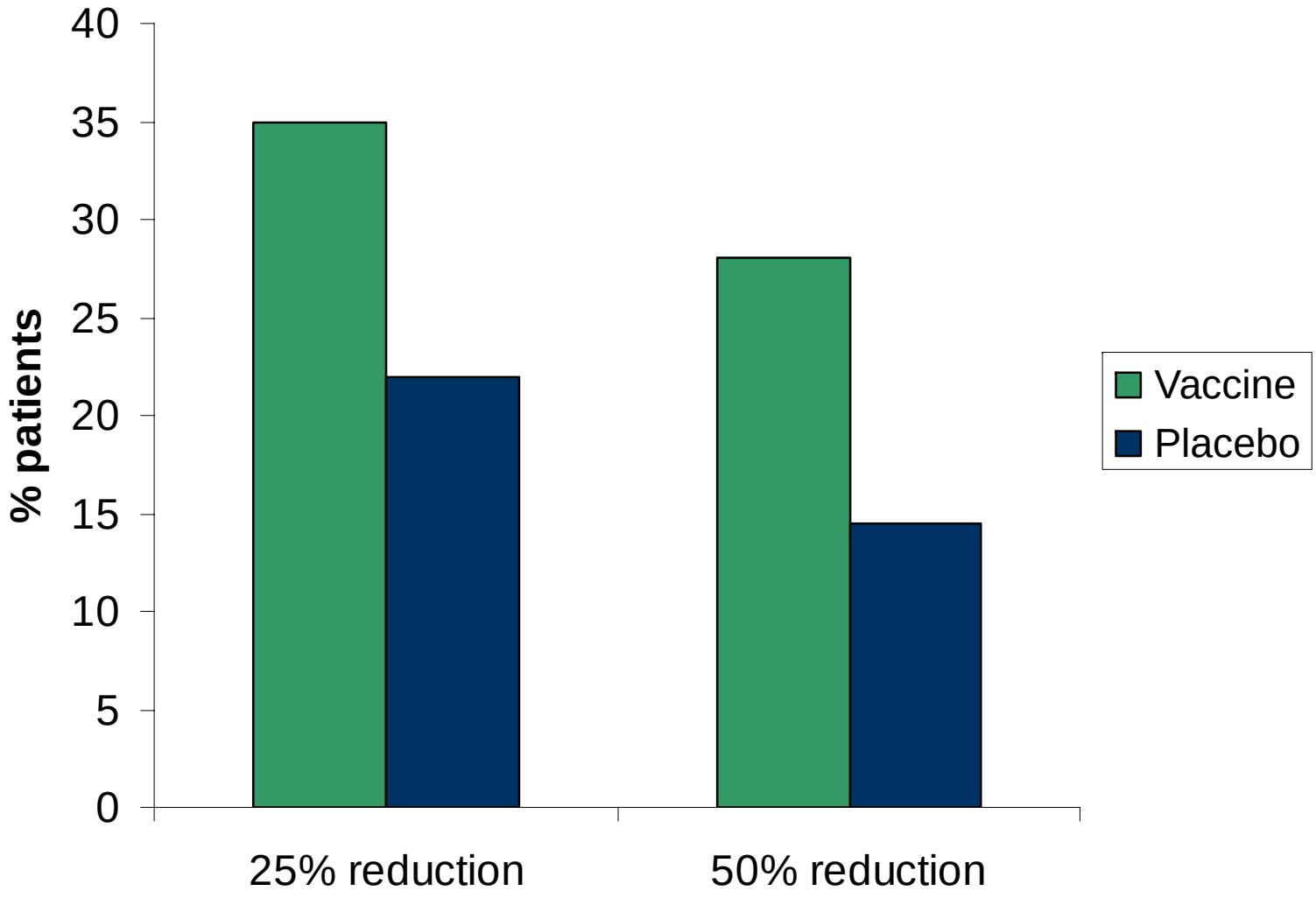
TA-CD/08 – what have we learned? (iv)



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TA-CD/08 – what have we learned? (v)

- **Other studies have shown that early abstinence is a good prognostic indicator**
- **When a baseline of cocaine use is established for each patient (number of clean urines during first 4 weeks)**
  - **clear relationship between this number and likelihood of meeting the primary endpoint**
  - **data adjusted for this measure of "motivation", shows a superiority of vaccine over placebo**

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Summary of new clinical data

- **Small, highly controlled study showed reduction in cocaine intoxication in subjects with high antibody levels**
- **Larger study in methadone-dependent subjects did not reach primary endpoint**
- **Effect of vaccine (primary endpoint) was seen when baseline cocaine use was accounted for**
- **Vaccine also apparently effective during early stage of the study**

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Where do we go from here?

- **Future clinical work**
  - **New Phase II study needed**
  - **Use non-methadone-dependent subjects**
  - **Make baseline assessment of cocaine use**

- **Potential issues/discussion points**
  - **How can we ensure patient retention throughout the study?**
  - **How can we collect adequate quantitative urine toxicology data?**
  - **Can we use reduction in cocaine use as an endpoint rather than abstinence?**

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