TA-CD – the anti-cocaine vaccine

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Summary

- Cocaine addiction is a serious problem in the US and EU.
- There are currently no pharmacotherapies to help addicts to quit.
- TA-CD is a novel approach to treatment, targeting cocaine in circulation.
- Proof of concept established in preclinical studies.
- Phase I and II studies have shown:
  - Vaccine is safe and well tolerated.
  - Promising indications of efficacy.
- Phase IIb study (132 patients, randomised, placebo-controlled) is due to report June 2006.
Vaccine may help addicts kick the habit

Vaccine helps smokers and cocaine users to quit

Vaccine could end drug abuse

Anti-addiction vaccine offers hope to quitters

JAG TO STOP ADDICT KIDS
Cocaine Addiction – the problem

- **US**
  - 2m regular cocaine users in US\(^1\)
  - 25% Americans between ages 26-34 used cocaine\(^2\)
  - 33.9m Americans age >12 reported lifetime use of cocaine\(^3\)
  - 500,000 emergency hospital visits annually\(^2\)

- **EU**
  - Up to 10% lifetime prevalence in 15-34 age group\(^4\)
  - 4% recent prevalence in UK and Spain\(^4\)

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\(^1\) Office of Applied Studies, 2002 National Survey on Drug Use and Health
\(^2\) Drug-Rehab.org
\(^3\) NIDA, figures for 2002
\(^4\) EMCDDA, 2004
The A-Z (almost!) of cocaine treatment so far

amantadine
baclofen
cabergoline
disulfiram
fluoxetine
fluoxetin
isradipine
Java
ketoconazole
lamotrigine
modafinil
ondansetron
pergolide
sertraline
risperdol
tiagabine
UC2Jokes
venlafaxine

w x y z to follow!
Features of cocaine addiction

- Addiction is a chronic relapsing disorder
- When cocaine is taken, it is transported rapidly to the brain
- Speed of transport depends on how cocaine is taken
- It is the quantity and speed of delivery of cocaine into the brain that is important in generating the high
- “Priming” is associated with this effect, often leading to binging
A strategy for cracking cocaine addiction

- Addiction is a chronic relapsing disorder
- It is very unlikely that an addict will quit unless highly motivated
- It is expected that a patient will lapse during treatment
- Priming contributes to turning a lapse into a binge
- Priming is a function of the rate and extent of cocaine entry into the brain
- Blocking the priming effect can keep a lapse from becoming a full blown relapse
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:coke complexes cannot cross the blood-brain barrier. The amount of cocaine reaching the brain and also the speed of delivery are thus reduced.
- This reduces or prevents the high and the associated priming effect
Vaccines of Addiction - Product Concept

Before vaccination

Cocaine

Blood:brain barrier

“reward”

After vaccination

Cocaine

Antibodies produced by immune system

Brain

no “reward”
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
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
Immunogenicity of TA-CD in mice

![Graph showing the immunogenicity of TA-CD in mice]

- **Y-axis:** O.D. 450 nm
- **X-axis:** 1/Dilution

- **Legend:**
  - TA-CD immunised
  - Non-immune
Duration of antibody response in mice

Mice bled on days 25, 42, 70, 113, & 196.
Specificity of immune response

Concentration (µM)

OD 450 nm

- cocaine
- norcocaine
- cocaethylene
- benzoylecgonine
- ecgonine methyl ester
- procaine
- cocaine-HEL conjugate
Loss of cocaine from brain in immunised mice

![Graph showing the loss of cocaine from brain in control and immunised mice over time.](image)
Effect of TA-CD on cocaine self-administration in rats (i)

- Graph showing the effect of Alum (left) and IPC-14,551 with alum (right) on total infusions during baseline, immune, and no cocaine conditions.

- Data points indicating changes in cocaine self-administration across different conditions.
Effect of TA-CD on cocaine self-administration in rats (ii)

![Graph showing the average inter-infusion interval (min) for baseline, immune, and no cocaine conditions with or without alum and IPC-14,551.](image)
TA-CD: Clinical Studies Summary

• **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)
Phase I study design

- Placebo-controlled double blind study
- 30 cocaine abstinent subjects in in-patient facility
- Endpoints
  - Safety
  - Immunogenicity
- 3 dose levels
  - 13 μg, 82 μg, 709 μg

- Newtown Ct, USA, Prof Tom Kosten
TA-CD Phase I study - safety

- Vaccine well tolerated
  - Mild injection site reactions, also found in placebo group
  - No vaccine-related serious adverse events
- No significant difference in adverse events between placebo and active groups
TA-CD Phase IIa Study Design

- Two studies
  - Relapse Prevention (8 evaluable patients)
  - Abstinence Initiation (12 evaluable patients)
- Endpoints
  - Safety
  - Immunogenicity
- Two dose levels
  - 82 µg, 360 µg
TA-CD Phase IIa

- **Safety**
  - Vaccine well tolerated
  - No vaccine-related serious adverse events
  - Some patients experienced mild injection site reactions

- **Immunogenicity**
  - Patients produced anti-cocaine antibodies in response to the vaccine
  - Higher dose generally resulted in higher antibody levels
  - Booster injection increased antibody levels which had dropped
Phase IIa – Immunogenicity

Mean Responses in 82µg and 360µg groups

Week

Antibody titre

360µg

82µg
TA-CD - Phase IIa - efficacy

- **Relapse prevention:**
  - 6/8 maintained abstinence during 12 wk study

- **Abstinence initiation:**
  - 7/12 achieved & maintained abstinence during 12 wk study
  - 5/12 remained cocaine free after 6 months

- **Indication that higher antibody response correlates with reduced likelihood of using cocaine**

- **Some of those patients who relapsed post vaccination reported a reduction in euphoric effects of cocaine**
TA-CD - Phase IIb

- **Study design**
  - 132 methadone dependent cocaine addicts
  - Placebo controlled, randomized, double blind study

- **Primary end point**
  - Quit rate as determined by at least 3 consecutive weeks of negative urine samples between weeks 8-20

- **Supported by NIDA**

- **Results due June 2006**
TA-CD – Future plans

- **If Phase II data are positive...**

- **Plan to move rapidly into**
  - Phase III US
  - Phase III EU

- **Challenges**
  - Treatment of cocaine addicts varies from country to country
    - medically
    - healthcare system
  - **Success depends on patient receiving full course of vaccinations**
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- Phase I and II studies have shown
  - vaccine is safe and well tolerated
  - promising indications of efficacy
- Phase IIb study (132 patients, randomised, placebo-controlled) is due to report June 2006
- Positive data will trigger a rapid move into Phase III studies