The Challenge and Approach of Developing a Novel Anti-Nicotine Vaccine

Heather L. Davis, PhD
Pfizer Vaccine Immunotherapeutics
Ottawa, Canada
Disclaimer

This work was funded by Pfizer and was conducted solely by Pfizer employees or contractors.

All data presented is non-clinical. Pfizer’s anti-nicotine vaccine is not approved for human use.

Animal studies were conducted under approval of local Institutional Animal Care and Use Committee (IACUC) and in accordance with the guidelines of the Canadian Council on Animal Care (CCAC) and the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC).
Anti-Nicotine Vaccines Potentially Offer Unique Mechanism of Action for Smoking Cessation

• Nicotine must bind to receptors in brain for experience of “reward”
• Putative mechanism of action of anti-nicotine vaccines
  – Blood-brain barrier allows small (e.g., nicotine) but not large (e.g., Ab) to enter brain tissue
  – Anti-nicotine Ab should reduce brain nicotine to levels that don’t induce reward – may help in quit attempt and help prevent relapse (if no reward during a “lapse”)
• Other potential features
  – Slowly rising Ab may mimic gradual weaning off
  – Long lasting Ab quit should help prevent relapse over prolonged period
Two vaccines tested as monotherapy in randomized controlled Phase 2 trials

- NicVax (Nabi) and NicQb (Cytos) showed similar results
- Did not achieve efficacy in ITT, but sub-group analysis showed subjects with top 1/3rd anti-nicotine Ab had significantly better quit rates at 1 year (2x placebo)

Antibody (Ab) function depends on both amount of Ab (titer) and quality of Ab (avidity), but it appears both vaccines were developed to induce high titers

Why haven’t vaccines worked to date?

Might Abs with NicVax and NicQb be low avidity?
NIC7 Anti-Nicotine Vaccine Design Features

- Goal was to select antigen and adjuvant formulation that induces anti-nicotine antibodies of high titer, avidity and function

- Approach
  - Screen in mice and non-human primates (NHP) using functional assays
  - Compare to a mimetic of NicQb

- Antigen
  - Nicotine must be conjugated to a carrier protein for immune recognition, as well as to provide T-help
  - Tested many conjugates
    - Most induced equally high titers in mice
    - However many antigen properties affected avidity and function
      - Carrier, hapten, conjugation chemistry, linker, hapten density

- Adjuvant(s)
  - Required to induce high titers of antibodies
  - Can also influence Ab avidity
  - Selected aluminum hydroxide + CpG (TLR9)
In Vivo Functional Assay:

- $^3$H-nicotine IV challenge 2-4 wks after last vaccine dose
- Perfuse animal 5 mins later and remove brain to measure radioactivity
- Calculate % reduction of $^3$H-Nic in brain relative to non-vaccinated control
**Effect of High Molecular Mass Species in Conjugate on Anti-Nicotine Antibody Function in Mice**

*In Vivo Functional Assay:*
- $^3$H-nicotine IV challenge 2-4 wks after last vaccine dose
- Perfuse animal 5 mins later and remove brain to measure radioactivity
- Calculate % reduction of $^3$H-Nic in brain relative to non-vaccinated control

NIC7 adjuvanted with CpG (TLR9) + AIOH
NicQb contains TLR7 agonist and adjuvanted with AIOH
Key Questions for Developing an Anti-Nicotine Vaccine

Q1. How much nicotine needs to be kept from the brain to prevent reward?

⇒ Estimate 50% based on studies administering nicotine IV and asking subjects if they “feel” or “like” it.  

Q2. How much nicotine must be bound in the vascular space to achieve a 50% reduction in the brain?

⇒ Estimate 95% based on modeling data including brain levels in NHP after IV administration of radiolabeled nicotine with and without vaccination.

Q3. What is the likelihood that an anti-nicotine vaccine can achieve this?

⇒ In NHP, NIC7 vaccine with alum + CpG adjuvants reduced nicotine in brain by >80% compared to <10% for NicQb mimetic.
How can we assess this in humans? Relationship Between Nicotine Binding in the Blood and Nicotine in the Brain

- Standard 2-compartment kinetic model for distribution of small molecules, modified to account for:
  - Delivery by lung
  - Retention of nicotine in blood by anti-nicotine Abs
  - Largely unidirectional movement of nicotine from blood to brain

- NHP data used to establish model
  - PK after single IV dose nicotine (0.05 mg/kg)
  - Brain levels of radiolabeled nicotine in vaccinated and placebo NHP
  - Kinetics of distribution of nicotine to brain (published)

- Model indicates:
  - Binding up to 80% of nicotine in blood has very little impact on brain levels
  - To have 50% reduction in brain requires binding 95% of nicotine in blood
FIH Clinical Study with NIC7 Vaccines

- Randomized, double-blind, placebo controlled, repeat dosing study - ongoing
- Explores both antigen and adjuvant dose response
- Outcome measurements
  - Safety and tolerability
  - Immunogenicity
    - Ab titer, avidity
  - Function
    - *Ex vivo* nicotine binding capacity
    - *In vivo* nicotine PK (using nicotine gum) allows calculation of % binding in blood and modelling of % reduction in brain
- Exploratory smoking assessments

### Time (weeks)

- 0
- 4
- 8
- 12
- 16
- 20
- 24
- 28
- 32
- 36
- 40
- 44
- 48
- 52

### Dosing days

- **Immunogenicity measures**

### Target Quit Period

- Weeks 6-12

### Smoking Assessments

- 7 Day PP and CAR at Key Time Points