Oral tolerance to AAV-delivered antibodies

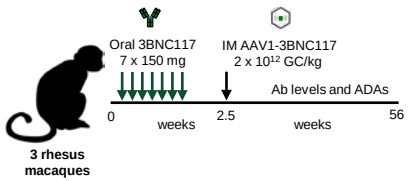
Jose M. Martinez-Navio[1], Sebastian P. Fuchs[1], Desiree E. Mendes[1], Claudia P. Ramos Muniz[1], Michel C. Nussenzweig[2], Eva G. Rakasz[3], Guangping Gao[4] & Ronald C. Desrosiers[1]

[1] Department of Pathology, Miller School of Medicine, University of Miami, Miami, Florida, USA. [2] Laboratory of Molecular Immunology and HHMI, The Rockefeller University, New York, NY, USA. [3] Wisconsin National Primate Research Center, University of Wisconsin, Madison, WI, USA. [4] Gene Therapy Center, University of Massachusetts Medical School, Worcester, MA, USA.

Background

Vectored delivery of broadly neutralizing antibodies has the potential to a) achieve stringent and durable suppression in HIV individuals and b) be a successful and robust prophylactic approach[1-5]. The use of recombinant adeno-associated virus vectors (AAV) for such delivery applications is ideal in many respects[6-8]. AAV has an outstanding safety record in clinical trials[9] and, as long as the delivered protein is viewed as self[10], it can result in continuous durable expression of the transgene product for years[11]. Unfortunately, due to years of affinity maturation, broadly neutralizing antibodies exhibit unusually high levels of somatic hypermutation and may have uncommon features that can be seen as 'non-self' by the recipient's immune system[12]. In fact, despite showing the huge promise of this approach, monkey trials from our group and others have revealed that antibody responses to the delivered antibodies can severely limit their concentration and functionality[10,13,3,5]. Building up on our previous monkey trials, what we propose here is to induce immune tolerance to the delivered antibodies prior to AAV inoculation so that optimal concentrations can be consistently achieved in circulation. To achieve this, our plan is to exploit the tolerogenic potential of the oral route: it is well known that orally ingested antigens can become tolerized[14]. In fact, the gastrointestinal mucosa is specialized in maintaining a balanced response to innocuous antigens, pathogens and the microbiome. Overall, our intention is to perform experiments in monkeys that will inform and guide development of the AAV-antibody concept for use in people.

Methods



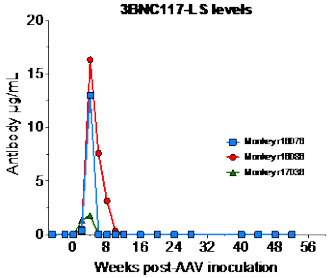
In a pilot experiment, 3 Indian-origin rhesus macaques received 1 g of recombinant, purified, broadly-neutralizing anti-HIV antibody 3BNC117 by oral gavage (7 doses of 150 mg, spaced 2-3 days) prior to receiving intramuscular administration of recombinant AAV vector expressing 3BNC117. Antibody and ADA levels were measured by ELISA.

Abstract

Background: Long-term delivery of monoclonal antibodies using adeno-associated virus (AAV) holds promise for the prevention of HIV infection. However, host antibodies (anti-drug antibodies or ADAs) raised against the AAV-delivered antibodies can jeopardize the applicability of this approach by decreasing their concentration and functionality. Here we explore the oral route to generate tolerance to the AAV-delivered antibodies prior to their delivery.
Methods: In a pilot experiment, three Indian-origin rhesus macaques received 1 g of recombinant, purified, broadly-neutralizing anti-HIV antibody 3BNC117 by oral gavage (as 7 doses of 150 mg/each and spaced 2-3 days) prior to receiving intramuscular administration of recombinant AAV vector expressing 3BNC117. Antibody and ADA levels were measured by ELISA.
Results: All monkeys successfully expressed AAV-delivered 3BNC117. Peak levels in serum ranged from 1.8 to 16.3 µg/ml at week 4. Strong ADA responses to 3BNC117 were detected after week 4. Afterwards, 3BNC117 levels dropped drastically and became undetectable by week 12 in all three animals. Notably, comparison with our prior monkey studies showed a delay in the emergence of ADAs to 3BNC117.
Conclusions: While the ADA problem was not solved in our experimental conditions, our data show promise in the use of the oral route to prevent transgene responses when delivering antibodies via AAV. Eradicating or minimizing ADA responses is crucial to make the AAV-delivery of antibodies a consistent and reliable approach against HIV.

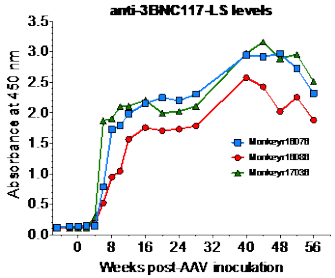
Results

1. AAV-delivered antibody levels



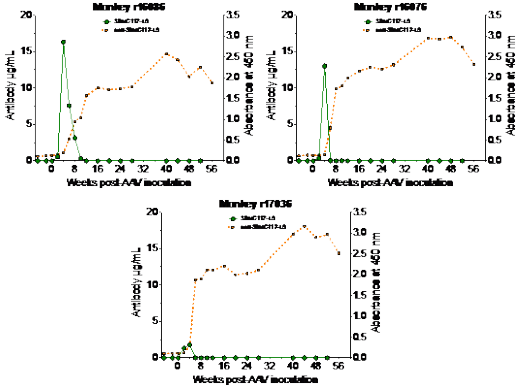
All three monkeys successfully expressed AAV-delivered 3BNC117. Serum levels of 3BNC117 peaked at week 4 post-AAV administration (range 1.8 to 16.3 µg/ml). Afterwards, 3BNC117 levels dropped drastically and became undetectable by week 12 in all three animals.

2. Anti-drug antibodies (ADAs)



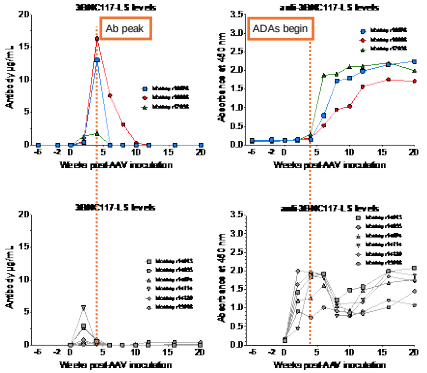
Anti-3BNC117 levels in serum were measured over time in the three recipient monkeys. Strong ADA responses to 3BNC117 were detected after week 4 post-AAV administration.

3. Overlays (antibody levels vs ADAs)



Data overlay shows that 3BNC117 levels dropped coincidentally in time with the rise of the anti-3BNC117 antibodies (ADAs) in all three monkeys.

4. Comparison with historical data



AAV-delivered 3BNC117 peaked later (week 4 vs week 2) and higher (average of 10.4±7.6 µg/ml vs 2.1±2.1 µg/ml) when compared with historical data of monkeys that did not receive oral 3BNC117 prior to the AAV (left panels). Notably there was also a 4-week delay in the apparition of ADAs to 3BNC117 (right panels).

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Conclusions

While the ADA problem was not solved in our experimental conditions, our data show promise in the use of the oral route to prevent transgene responses when delivering antibodies via AAV. Eradicating or minimizing ADA responses is crucial to make the AAV-delivery of antibodies a consistent and reliable approach against HIV.