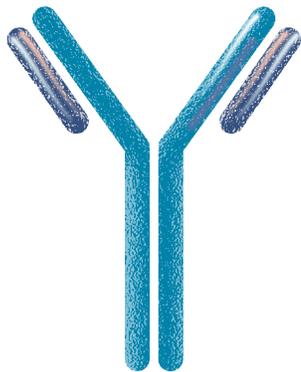
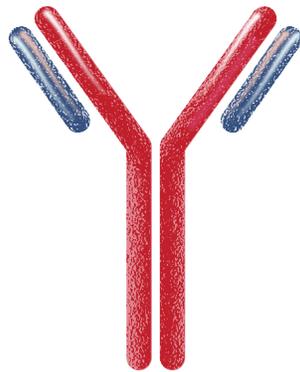


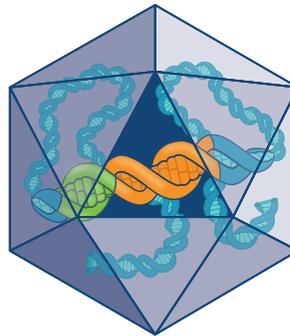
The importance of antibodies and their role in adeno-associated virus (AAV)-based gene therapy



Antibody



Pre-existing neutralizing antibody (NAb)



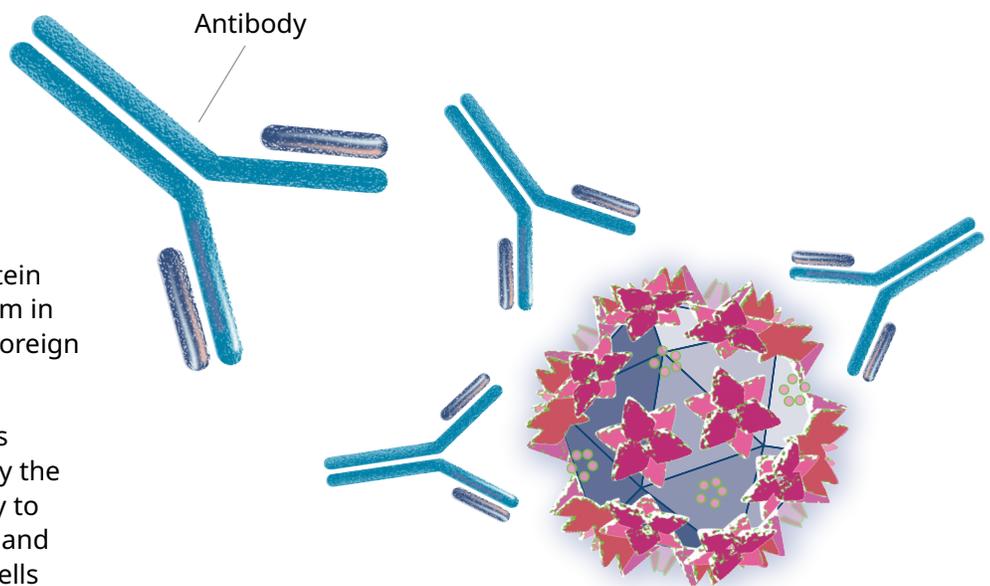
AAV vector protein shell

Antibodies are important to understand when investigating gene therapy in clinical trials. At uniQure we are studying neutralizing antibodies (NAbs) and their impact on the efficacy and safety of AAV-based gene therapy.

What are antibodies?

Antibodies are responsible for defending cells from foreign substances, like viruses. They are naturally produced by the body as part of the antibody-mediated immune response.

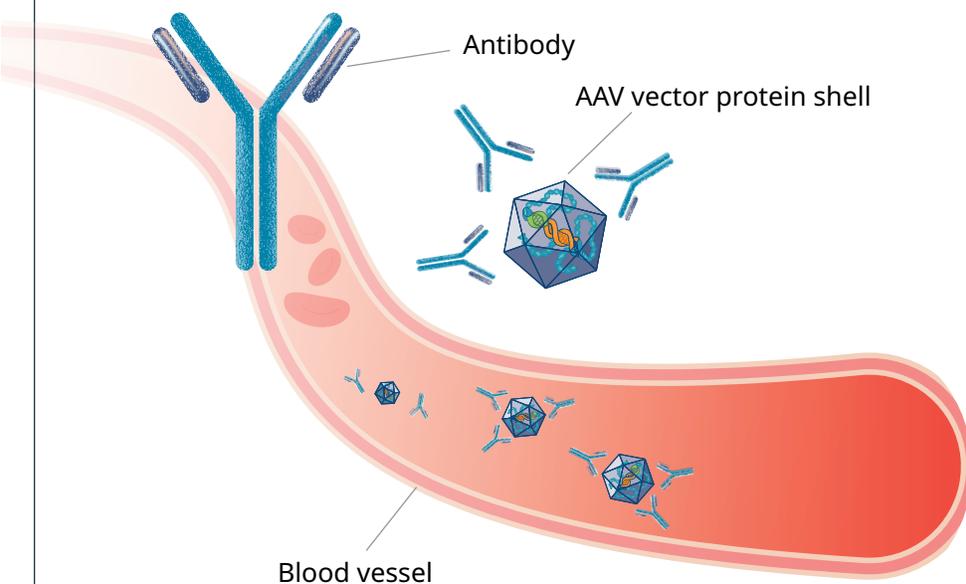
- An antibody is a protective protein produced by the immune system in response to the presence of a foreign substance, like a virus
- One example of how antibodies function is that they are used by the immune system to bind directly to foreign substances like viruses and interfere with virus entry into cells



Adeno-associated virus (AAV)

What is antibody-mediated immunity?

Gene therapies have the potential to trigger the immune system. AAV-based gene therapy has been reported to activate antibody-mediated immunity in clinical trials.^{1,2}

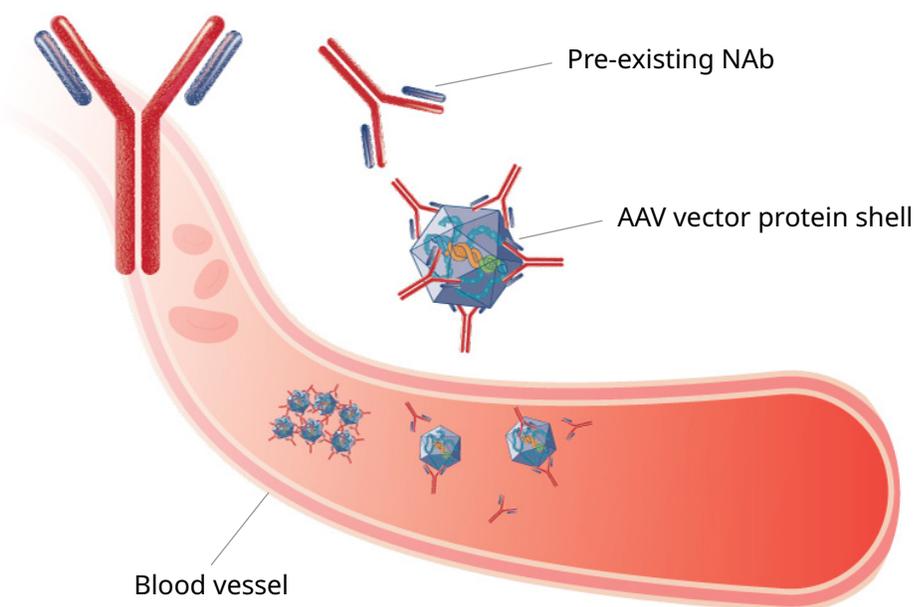


- Antibody-mediated immunity is mediated by a special immune cell known as a B cell
- These cells produce proteins called antibodies that circulate in the blood and bind to a foreign substance, like a virus

What is the relevance of pre-existing NABs to AAV-based gene therapy?

Most adults have been naturally exposed to AAVs resulting in antibody formation.³ Pre-existing antibodies may interfere with AAV-based gene therapy and are called NABs.⁴

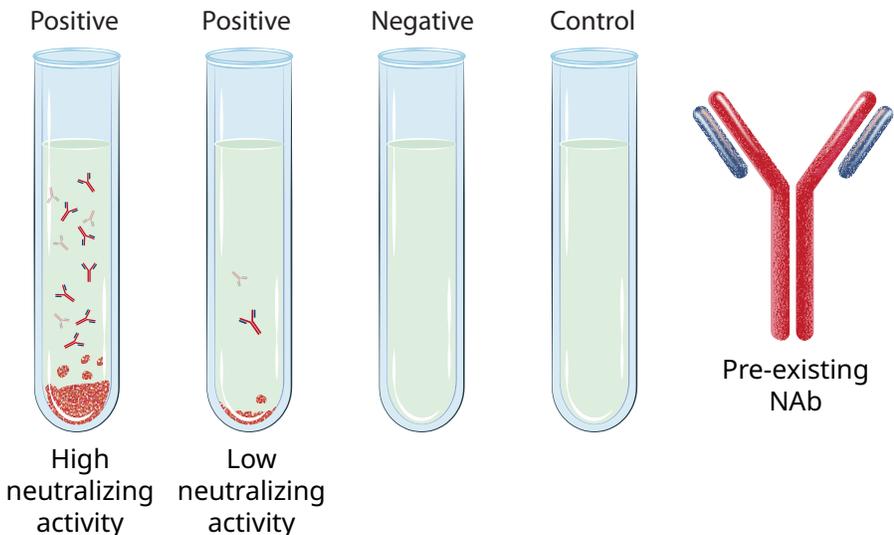
- There are different types of AAVs³
- Up to 60% of adults have been naturally exposed to different types of AAVs in the environment³
- AAV-based gene therapies use protein shells from AAVs to deliver a functional gene to target cells⁴
- Some people have pre-existing anti-AAV NABs to the specific AAV protein shell being used in the treatment, which can prevent the AAV vector from delivering gene therapy⁴



Are there tests to measure the amount of neutralizing activity for pre-existing NABs?

Pre-existing anti-AAV NABs may reduce the effect of AAV-based gene therapy.⁴ Because of this, NAB assessment is an important part of clinical trial development for gene therapy.

Test to detect and measure antibody activity

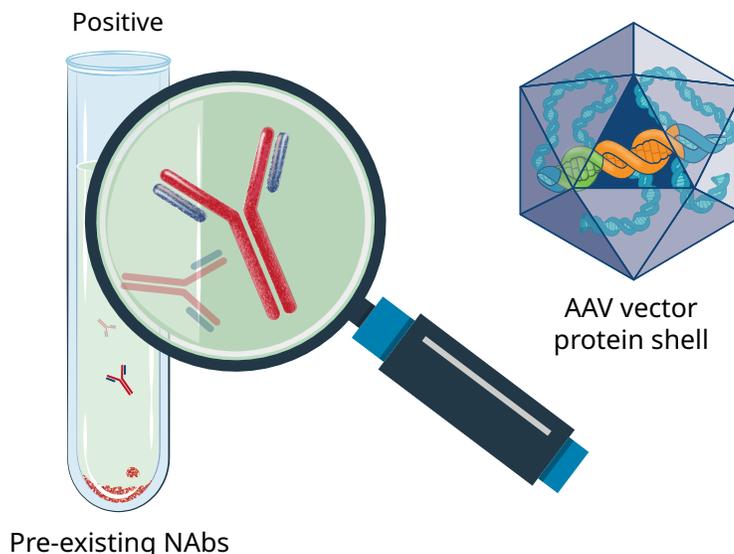


- Current AAV-based gene therapy trials are measuring levels of neutralizing activity of pre-existing NABs to help understand if these values are important^{5,6}
- There are no standardized tests to measure neutralizing activity of NABs and so values from different trials and laboratories cannot always be compared⁷

Will pre-existing NABs impact the ability to receive AAV-based gene therapy?

Pre-existing NABs may impact patient ability to receive AAV-based gene therapy.⁴ To increase eligibility, trials are assessing if and how much NAB activity affects gene therapy delivery.^{5,6}

- Certain activity levels of pre-existing NABs may or may not prevent the delivery of AAV-based gene therapy⁴
- It is also possible to develop NABs after a single administration of AAV-based gene therapy, which may impact future gene therapy using the same type of AAV protein shell
- Current gene therapy clinical trials are assessing the impact of pre-existing NABs to provide greater depth of insight into the safety and efficacy of AAV-based gene therapy^{5,6}



Illustrations by Virginia Ferrante-Iqbal

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