Docket #: S23-129

A high-sensitivity assay for predicting human innate immune responses to rAAV vectors

Stanford researchers have developed a high-sensitivity cell-based assay for predicting the innate immune response to recombinant adeno-associated virus.

Recombinant adeno-associated virus (rAAV) has enabled the development of transformative gene therapies for disorders ranging from spinal muscular atrophy to hemophilia B. However, the use of rAAV is limited by its immunogenicity, which can result in reduced therapeutic efficacy as well as dangerous and even deadly reactions in patients. While rAAV engineering promises less immunogenic vectors, these efforts are hindered by a lack of tools for predicting immunogenicity pre-clinically. Animal models have very different immune systems from humans, while cell-based models are non-physiological and display poor immune responses to rAAV. Assays employing human peripheral blood mononuclear cells (PBMCs) are similarly limited by wide variability between donors and low sensitivity.

To address this challenge, Stanford researchers developed a new tool for predicting innate immune responses to rAAV. rAAV capsids are first opsonized (tagged for recognition by the immune system) with an anti-AAV monoclonal antibody and then incubated with human PBMCs. PBMC immune activation can be measured by cytokine production or the expression of T-cell activation markers. Researchers showed that opsonization enabled immune responses from otherwise unresponsive PBMCs and discrimination between closely related but differentially immunogenic rAAVs.

Stage of Development
In vitro: assay elicits an rAAV-induced immune response in otherwise unresponsive PBMCs that increases with exposure to unmethylated CpGs

Applications

- Tools for rAAV research
- Clinical development of rAAV-mediated vaccines and gene therapies
- Validation of lot-to-lot rAAV consistency during manufacturing
- Basis for human subject inclusion or exclusion in rAAV clinical trials
- Companion diagnostic for evaluating patient suitability for rAAV gene therapies

Advantages

- High sensitivity
- Simple, *in vitro* assay
- Distinguishes immune responses towards closely related rAAV vectors
- Predicts immune responses without the need for animal models
- Overcomes issues with variability between PBMC donors

Publications

- A Human PBMC Assay of Type 1 Interferon Responses to Closely Related AAV Vectors (Meeting Abstract). Molecular Therapy, 4(31), 76.

Innovators

- Bradley Hamilton
- John Wright

Licensing Contact

Cheryl Cathey

Senior Licensing and Strategic Alliance Manager

Email