# Computational deconvolution of the dengue immune response complexity with identification of novel broadly neutralizing antibodies

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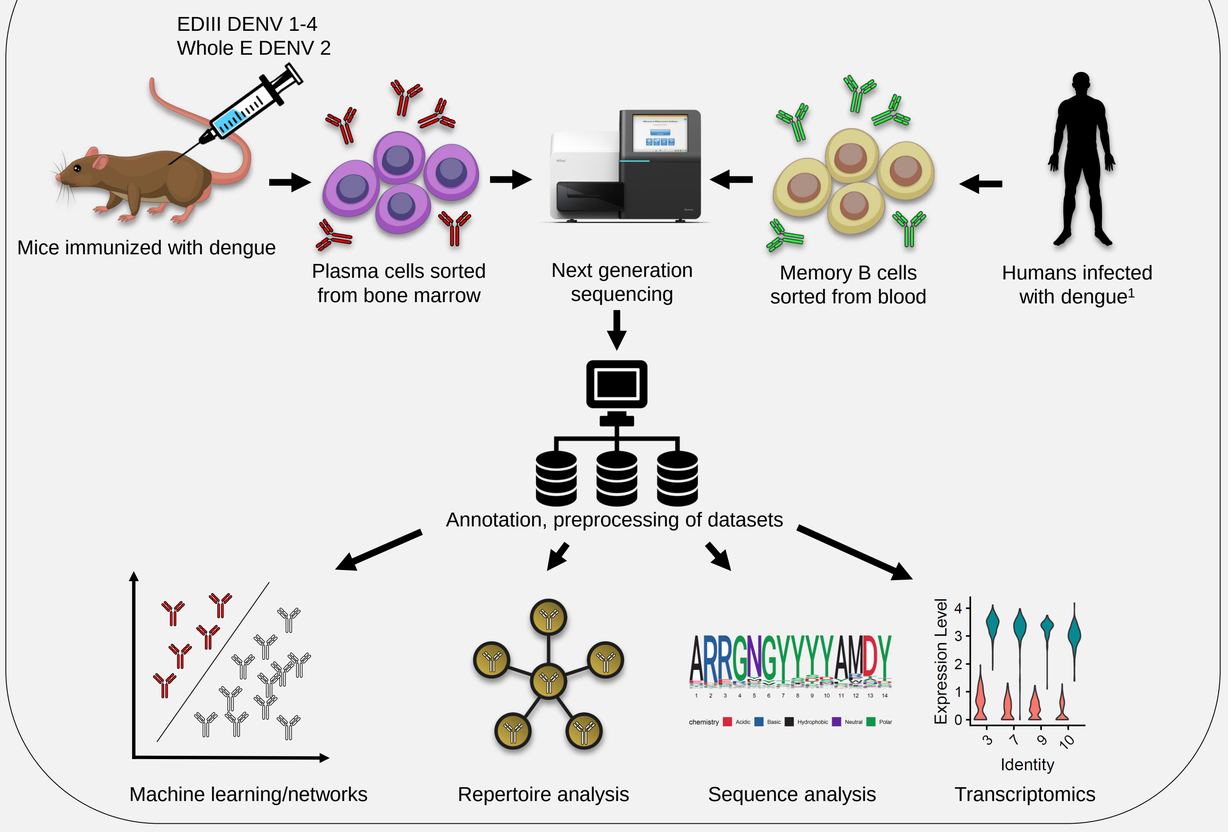
## Abstract

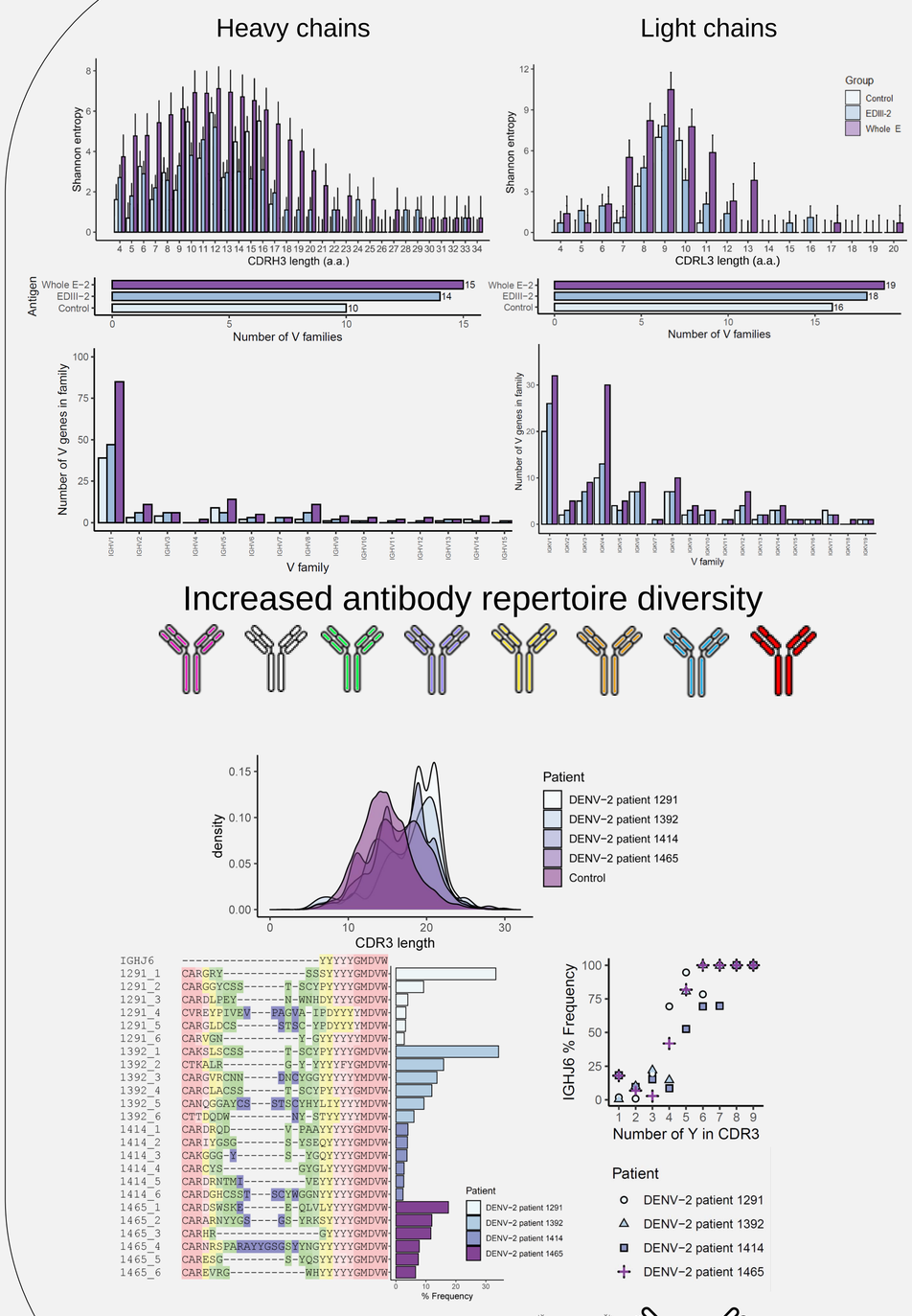
Dengue virus poses a serious threat to global health as the causative agent of the dengue fever. Currently, there is no approved therapeutic, and broadly neutralizing antibodies recognizing all four serotypes may be an effective treatment. High-throughput immune repertoire sequencing and bioinformatic analysis enable in-depth understanding of the immune response in dengue infection. Here, we use these technologies and apply machine learning to identify rare and underrepresented broadly neutralizing antibody sequences through investigation of antibody response in dengue. We observed challenging the immune system with dengue elicits the following signatures on the antibody repertoire: (i) an increase of the diversity in the CDR3 regions and the germline genes; (ii) a change in the architecture by eliciting power-law network distributions and enrichment in polar amino acids of the CDR3; (iii) an increase in the expression of transcription factors of the JNK/Fos pathways and ribosomal proteins. Moreover, our work demonstrates the applicability of computational methods and machine learning to high-throughput antibody repertoire sequencing datasets for neutralizing antibody candidate identification. Further investigation with antibody expression and functional assays is planned to validate the obtained results.

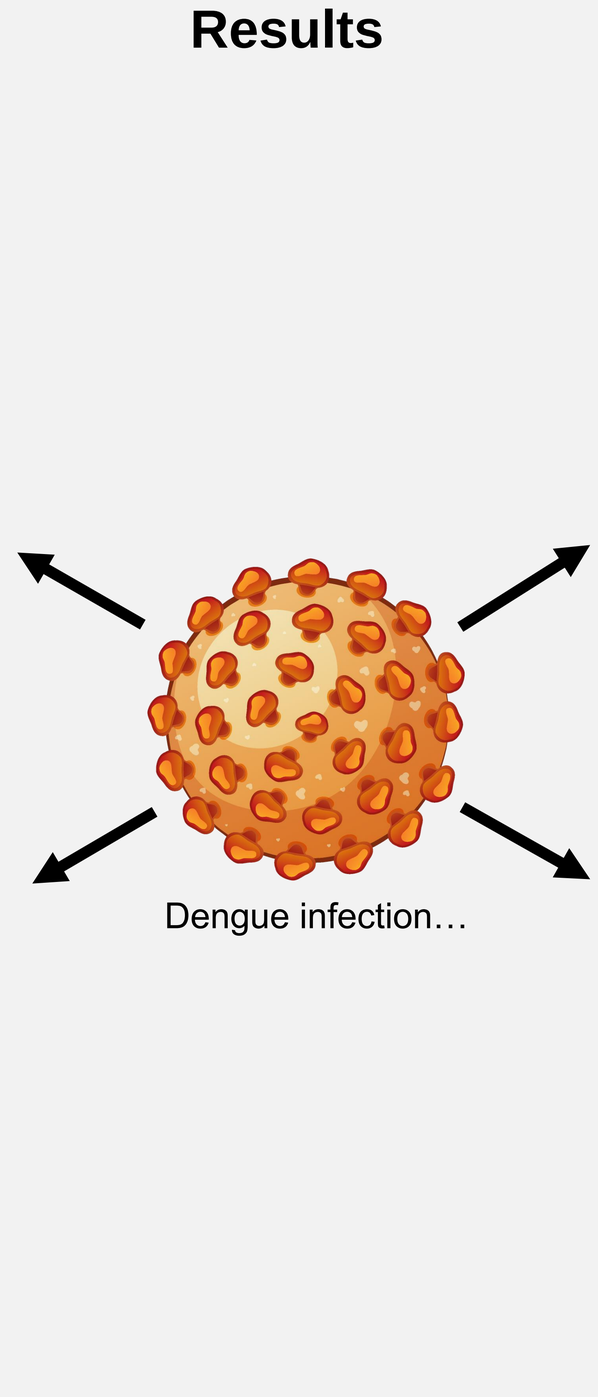
Key question: how can we identify novel dengue immunotherapeutics with computational approaches?

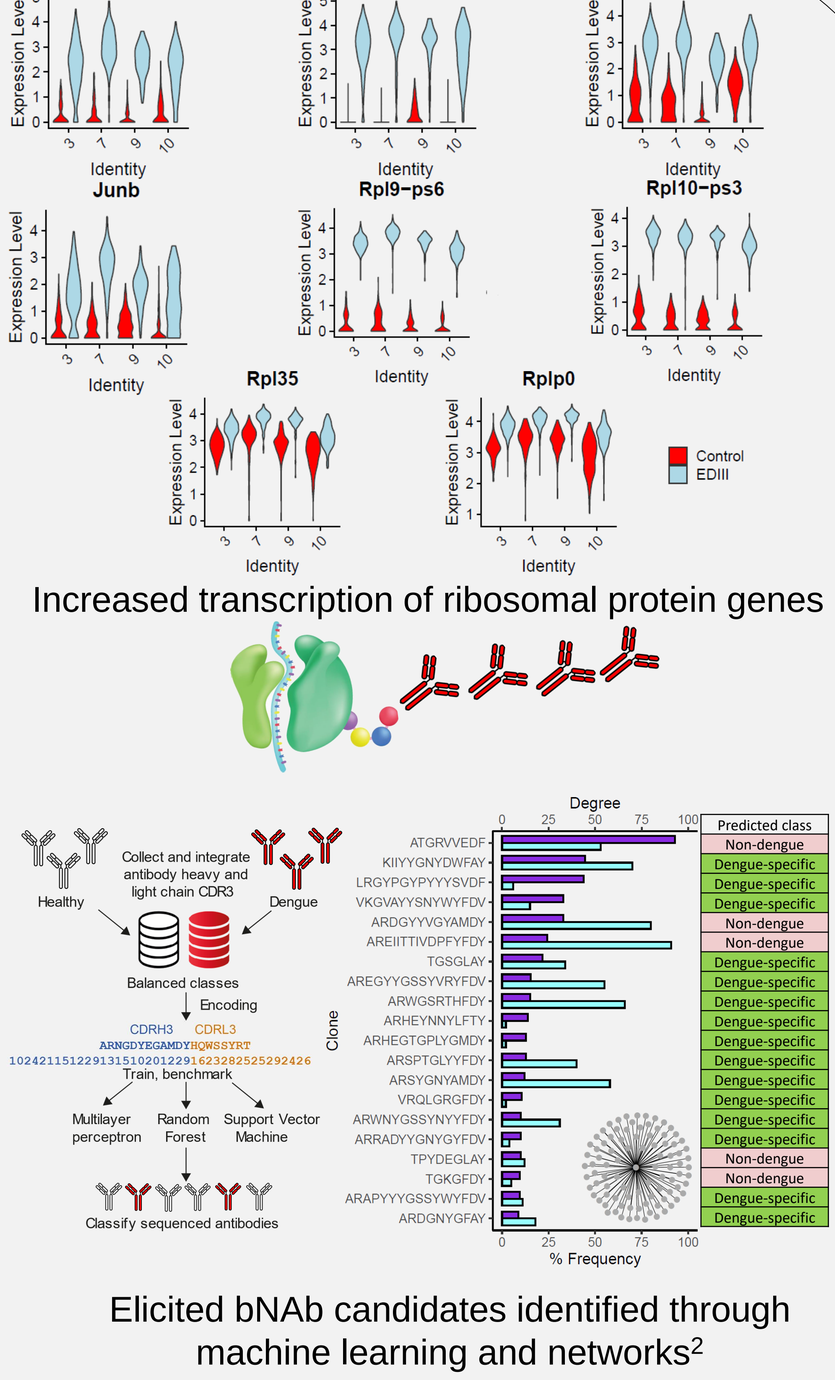
## Methods




## Results




## Conclusions

Identification of broadly neutralizing antibody clones has been historically a long, laboratory-intensive process in which large collections of recombinant antibody libraries or B-cell secreted antibodies must be tested for binding to an antigen. Given the enormous diversity of the B cell repertoire, only few clones usually bind to the desired antigen and most clones are excluded. Conversely, our antibody discovery approach starts from deep sequencing of the antibody repertoire and implements computational tools which allow selection of top candidates before expressing the antibodies and testing them, narrowing down the binding screening steps to only a few top clones. Through the implementation of these tools, we were able to identify 20 antibody top clone candidates which could be broadly neutralizing antibodies. Moreover, we have characterized the effects of dengue on the long-lived plasma cells in the bone marrow, finding that it elicits an increase of the diversity of the antibody repertoire in this compartment, imprinting antibodies with long CDR3 or CDR3 with repeated Tyrosines. Moreover, dengue enhanced expression of ribosomal protein genes and transcription factors of the more upstream Jun and Fos pathways.

References

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