

A Hexameric Variant of the Human Contraception Antibody (HCA) Demonstrates Enhanced Contraceptive Activity

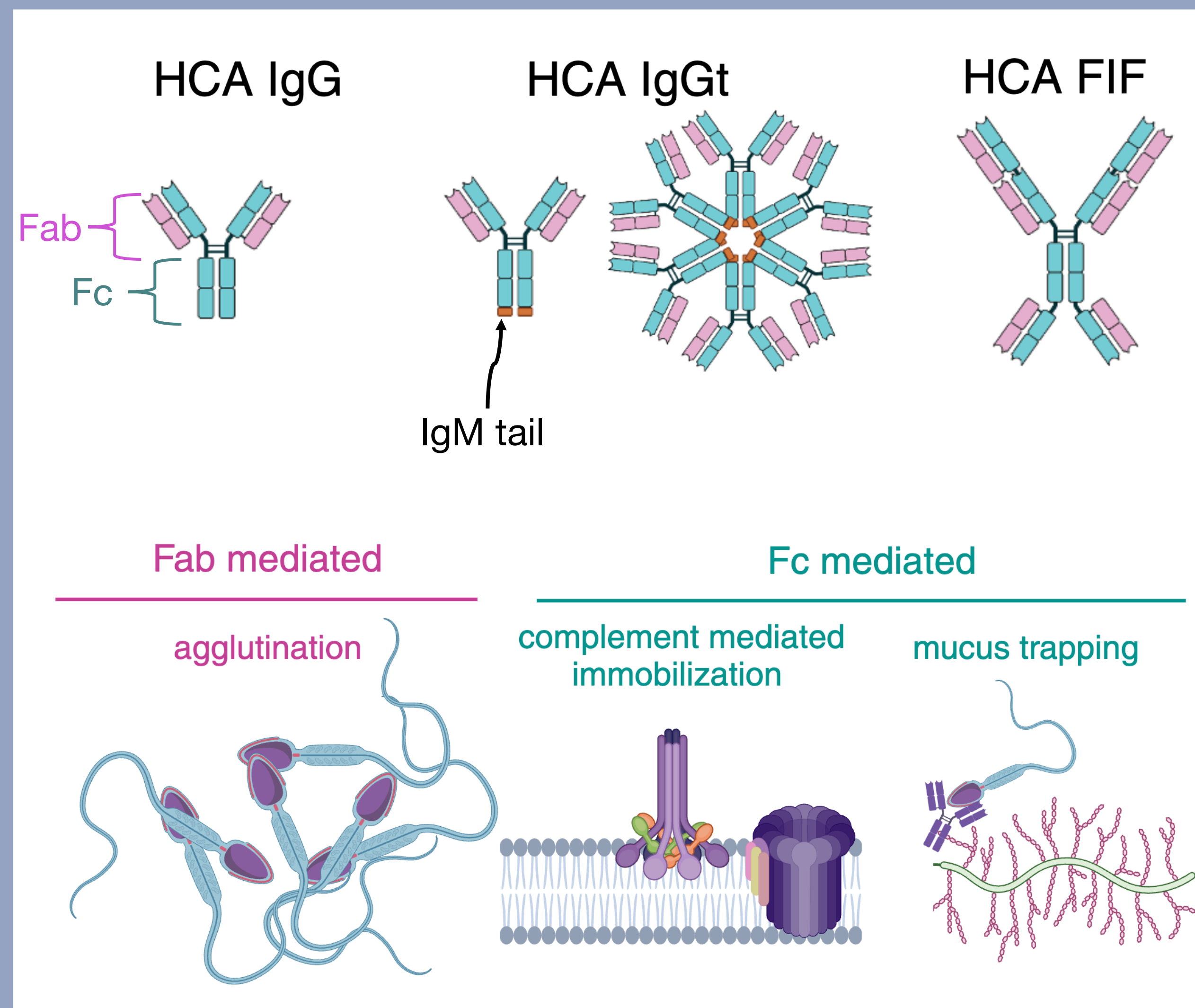
Sarah M. Dohadwala¹, Ellena Nador¹, Emilie Mausser¹, James Doud², Joseph A. Politch², Kevin J. Whaley³, Deborah J. Anderson²

¹Division of Medical Sciences, Boston University Chobanian & Avedisian School of Medicine, Boston, Massachusetts, USA

²Department of Medicine, Boston University Chobanian & Avedisian School of Medicine, Boston, Massachusetts, USA

³ZabBio, Inc., San Diego, California, USA

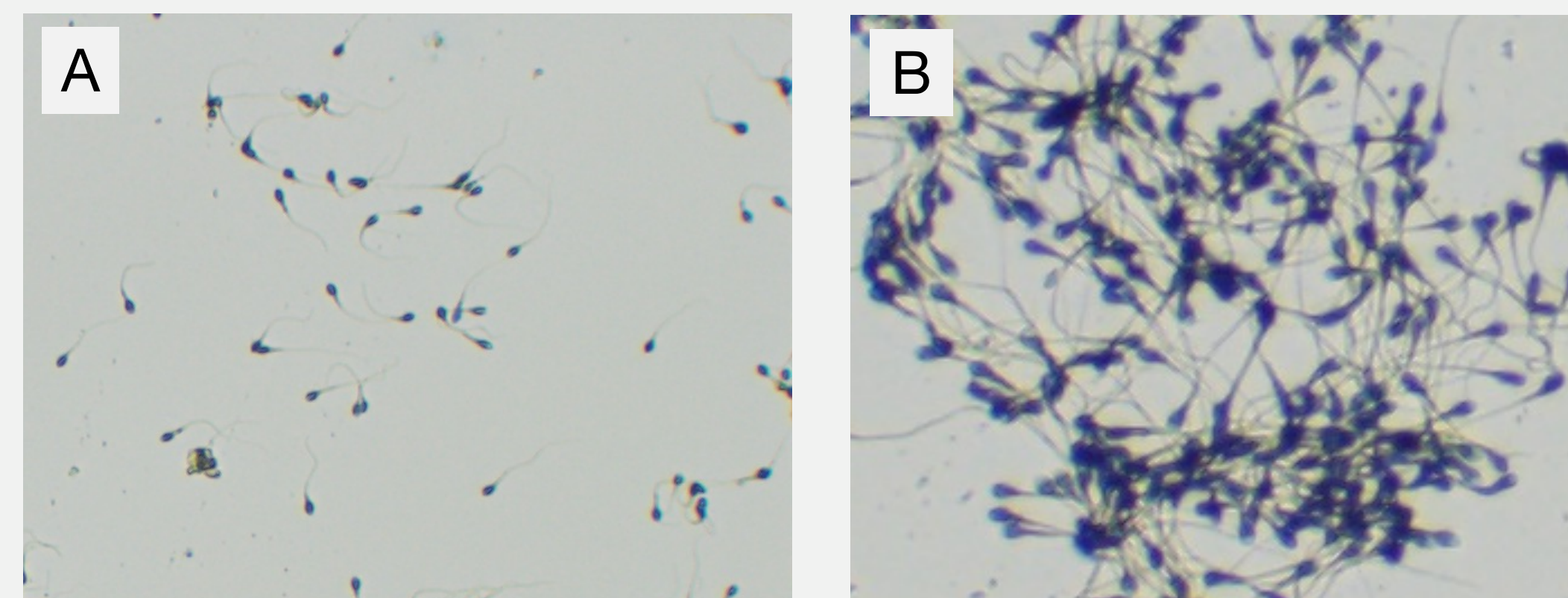
Graphical Abstract



- HCA is an IgG1 monoclonal antibody that binds to a glycopeptide, CD52g, on the surface of sperm
- HCA potently agglutinates sperm and blocks sperm migration through cervical mucus by two Fc-mediated functions: complement-dependent sperm immobilization and mucus trapping
- ZabBio has engineered a hexameric version of HCA comprised of 6 IgG1 antibodies linked together using the IgM tailpiece (IgGt).
- In this study, we compared the activity of the parent IgG1 HCA to the hexameric variant and another HCA multimer, FIF (gift of Sam Lai), in three assays of contraceptive function: sperm agglutination, sperm immobilization and cervical mucus trapping.
- As reported previously, IgG1 HCA agglutinated 100% of sperm in less than 30 seconds at low ug/ml concentrations. The hexameric IgGt achieved the same effect at 10-100-fold enhanced potency.
- Similarly, the IgGt variant had greatly enhanced complement-mediated immobilization activity and more effectively trapped sperm in midcycle cervical mucus than HCA IgG1.
- In contrast, the FIF HCA variant showed strong agglutination activity, but weak Fc-mediated activity (sperm immobilization, mucus trapping).

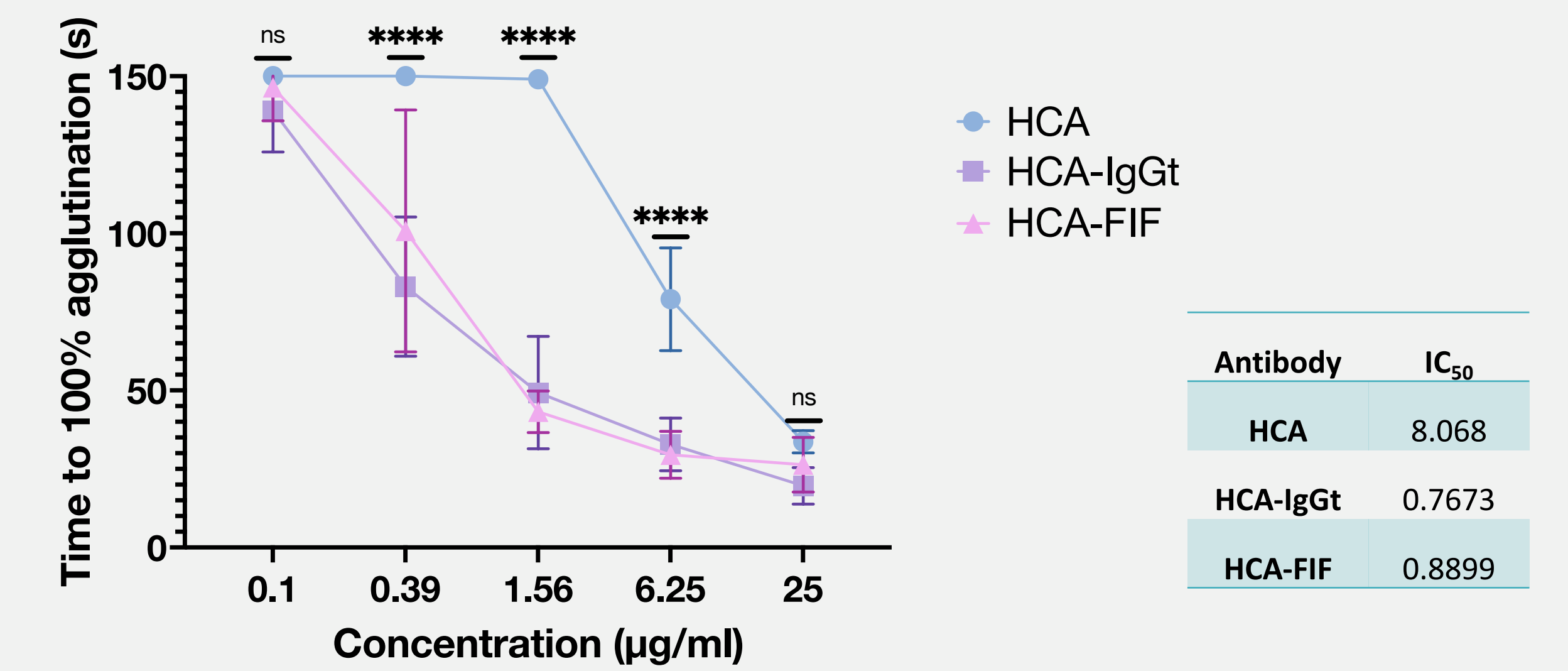
Fab-mediated

Kinetic agglutination assay

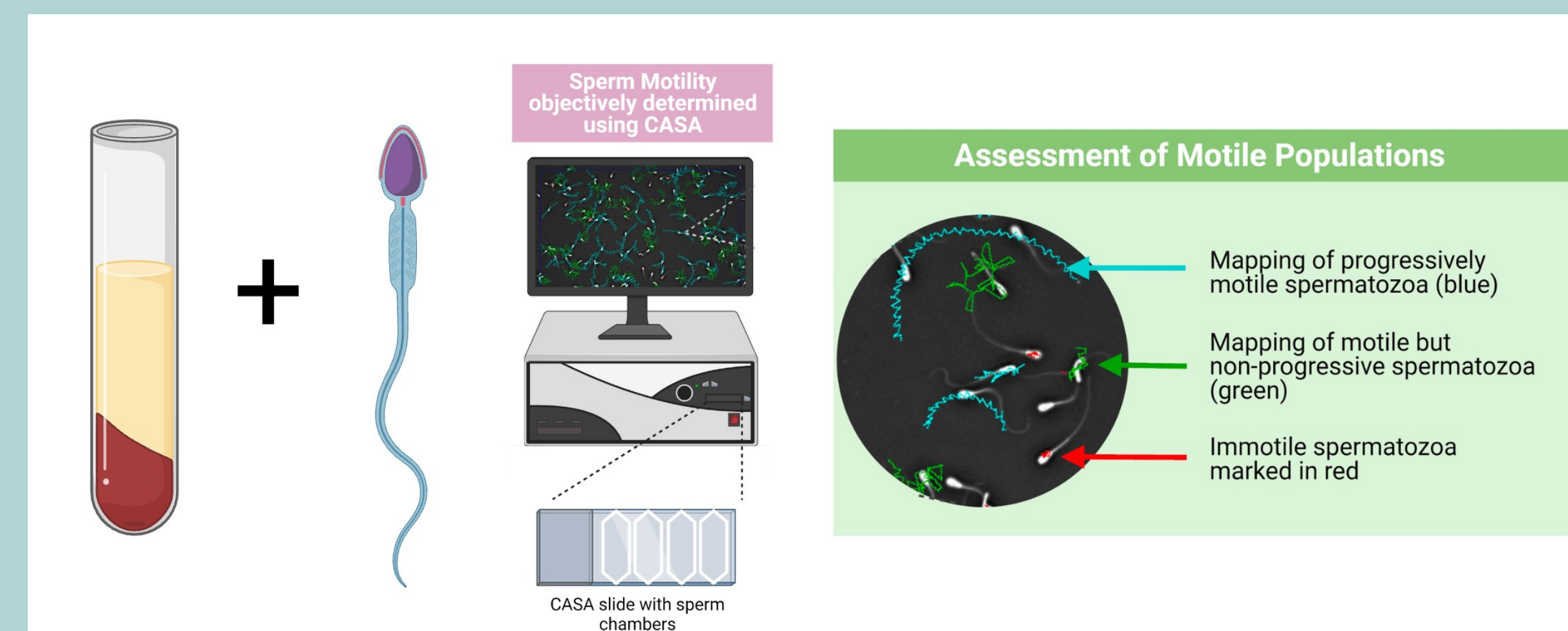


2uL of motile sperm and 2uL of antibody are mixed and visualized at 10x magnification on an inverted light microscope until 100% agglutination is observed. The representative images show nonagglutinated sperm (A) and agglutinated sperm (B). Experiments were performed in triplicate.

Hexameric HCA IgGt and FIF are 10-fold more potent than IgG1 in the sperm agglutination assay



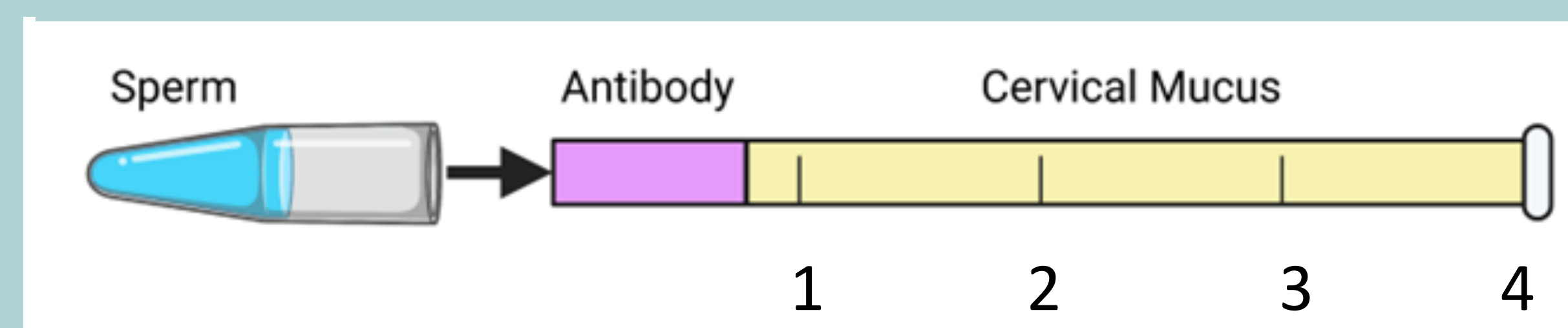
Complement mediated immobilization



Human serum was used as a complement source (C) with heat-inactivated serum (HiC) used as negative control. Washed sperm were mixed with C or HiC, and then diluted antibody was added. Samples were incubated at 32°C for 60 minutes and resulting sperm motility was quantified using CASA software. The data represent the mean of three experiments with different donors.

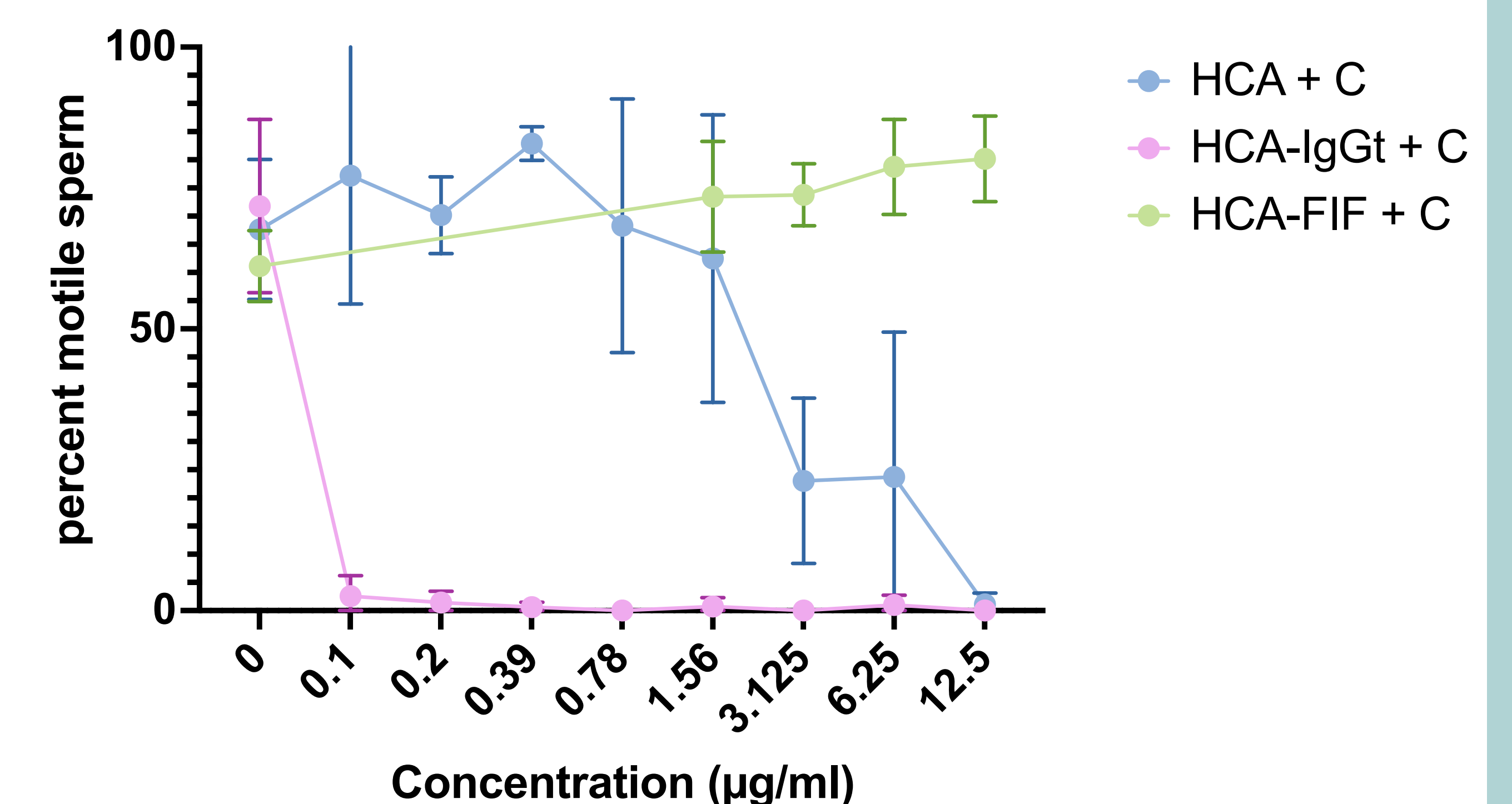
Fc-mediated

Cervical mucus trapping

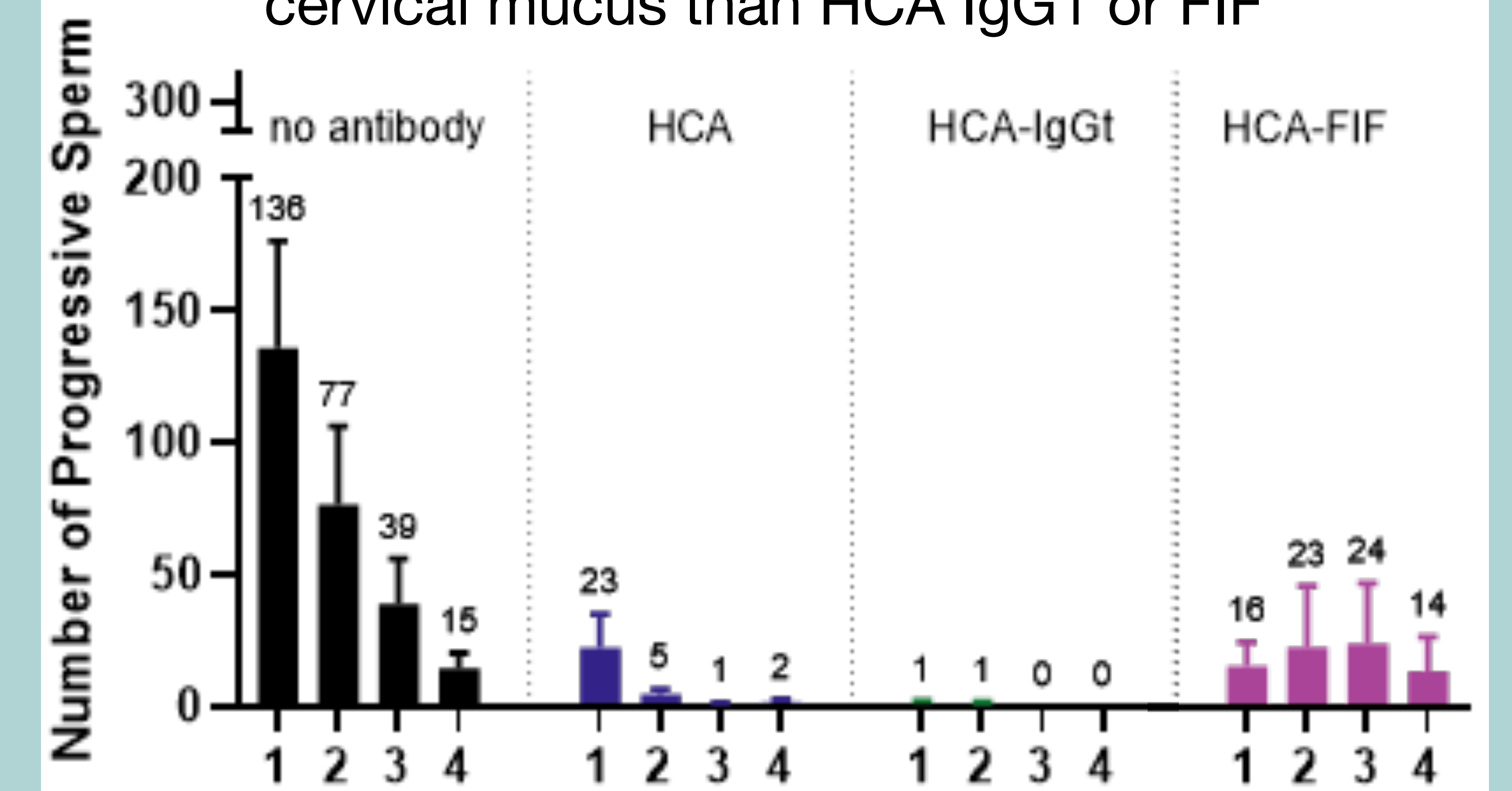


Capillary tubes containing cervical mucus were warmed to 32°C, and media containing antibody was added to fill the tube. The tube was marked at each centimeter for imaging. One end of the tube was sealed, and the open end was inserted horizontally into a tube containing motile sperm. The tubes were incubated for 90 minutes, and the number of motile sperm were quantified on the CASA at four points per cm interval. For some spots, manual counting was used due to the curvature of the tube. Each condition represents three trials with different donors.

Hexameric HCA IgGt is >100-fold more potent than HCA IgG1 and FIF in the sperm immobilization assay



Hexameric HCA IgGt more efficiently traps sperm in cervical mucus than HCA IgG1 or FIF



Conclusions

These results indicate that HCA-IgGt is a promising second generation contraceptive antibody candidate due to its enhanced contraceptive capabilities.

References:

Anderson D et al. *Biol Reprod* 2020.
Baldeon-Vaca G et al. *EBiomedicine* 2021.
Shrestha B et al. *Sci Transl Med* 2021.

Figures prepared in Biorender, and CASA figure is modified from *breeddiagnostics.com*.

This study was supported by NICHD grants P50 HD098957 and R01 HD101562.

Contraception Research Center Website

