BISPECIFIC AU NANOPARTICLES FOR THE ENHANCEMENT OF THE NK IMMUNE RESPONSE AGAINST HIV

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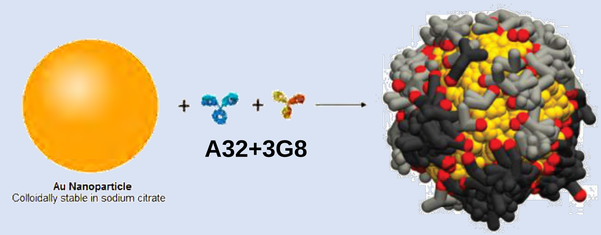
BACKGROUND

- An efficient **immunological synapse** is required for Natural Killer (**NK**) **cells** to kill **viral infected cells**.
- **HIV infection** promotes the appearance of **dysfunctional NK cells**.
- **The A32 antibody reacts against *env* from all HIV clades** and promotes ADCC.
- **The 3G8 clone targets CD16** (low-affinity Fc receptor), molecule which allows NK cells to perform ADCC.
- **Bispecific formats** could help to activate NK cells against HIV infected cells.

Thus, new tools to reinvigorate and redirect the NK-mediated immune effector functions could help to eliminate HIV.

We have developed **BiAb-AuNPs** which are able to:

1) **Promote close contact between HIV-infected and NK cells.**
2) **Trigger a potent cytotoxic NK-mediated response against HIV⁺ cells.**
3) **Enter tonsil blocks and reduce HIV infection in this lymphoid tissue.**
4) **Strongly enhance the killing of reactivated latently HIV-infected cells.**



A32 Ab: IgG **anti-HIV gp120**
3G8 Ab: **anti-CD16**

METHODS

We generated **bispecific multivalent gold nanoparticles (BiAb-AuNPs)** following a novel **cooperative adsorption method** that promotes the ordered distribution in domains of the antibodies.



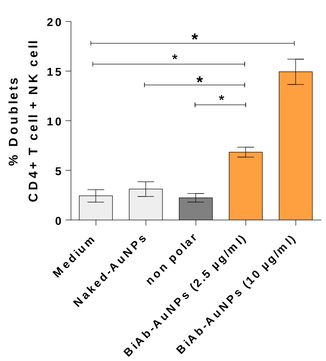
- Validation was performed by TEM, UV-Vis Spectroscopy, Dynamic Light Scattering (DLS) and Zeta-potential measurements.
- Cell contact assays were performed using flow cytometry and confocal microscopy.
- Functional assays:

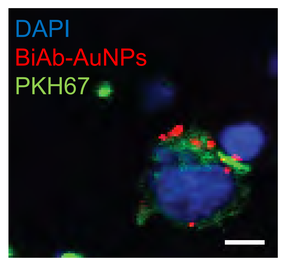
1) Cytotoxicity assays, against cultured cells and tonsil histocultures after *ex vivo* infection with HIV.

2) Killing assays of viral reactivated cells assessed in a primary cell model of HIV latency.

RESULTS

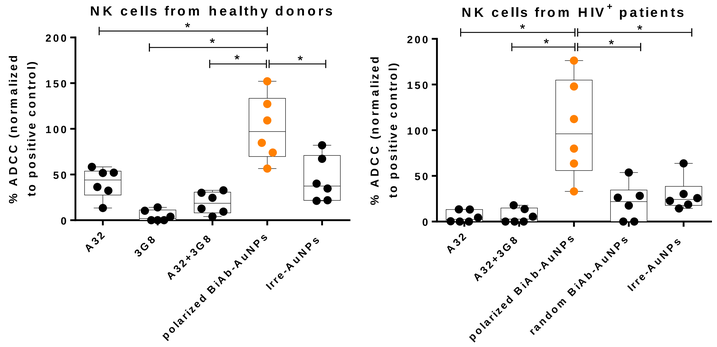
1) Cell-to-cell contact assays





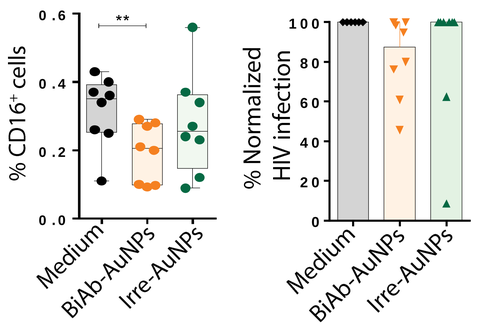
✓ **BiAb-AuNPs enhance specific cell contact between HIV-expressing cells and NK cells by over 7-fold**

2) ADCC assays



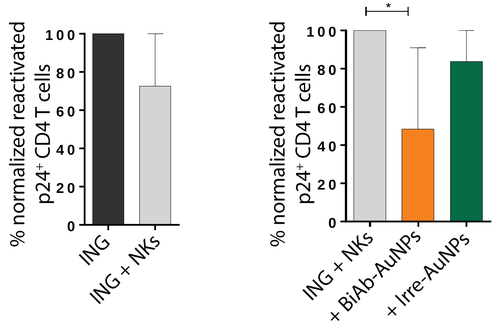
✓ **BiAb-AuNPs promote a highly potent and specific ADCC-like response mediated by NK cells from both, healthy donors and ART-suppressed patients**

3) Tonsil histocultures



✓ **BiAb-AuNPs entered tonsil blocks and reduced HIV infection up to 50%**

4) Primary model of HIV latency



✓ **BiAb-AuNPs enhanced the killing of reactivated latently infected CD4 T cells by a median of 51.5% vs 16.2% in control Irre-AuNPs**

PRESENTED AT CROI 2020
Boston, US