59

Anti-polyethylene Glycol antibodies alter the protein corona on nanoparticles and their fate in vivo

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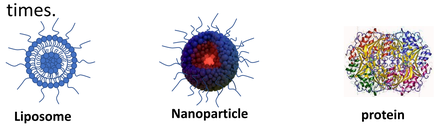
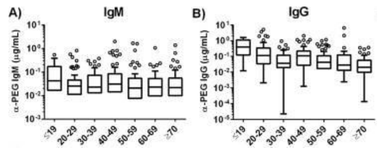
Introduction

- Some nanomedicines and therapeutic proteins employ poly(ethylene glycol) (PEG) to enhance circulation times.



- However, Anti-PEG antibodies could be highly prevalent in the general population.



Anti-PEG IgM and IgG concentration per age group.
Adapted from Qi Yang et al, Anal Chem 2016

- These antibodies can reduce efficacy of PEGylated nanomedicines by reducing their circulation time.
- We developed nanoparticles using PLGA-PEG polymers to assess the importance of anti-PEG antibodies on biological performances of different PEG Architectures.

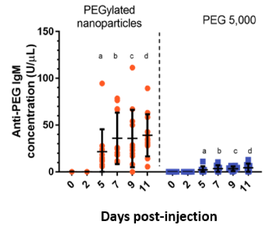
Objective:

1. **Assess the Anti-PEG immune response to polymeric Nanoparticle.**
2. **Evaluate the consequences of these antibodies on the circulation time of different pharmaceuticals vectors.**
3. **Investigate the impact of circulating IgM antibodies on the protein corona at the surface of PEGylated nanoparticles.**

Results

- **An Injection of PEGylated nanoparticles (500µg or, 100 µg of PEG) can trigger an augmentation of circulating levels of anti-PEG antibodies, within 5 to 7 days.**

A. PEG on nanoparticles is more immunogenic than the free polymer



B. Anti-PEG antibodies are mostly from the IgM isotype

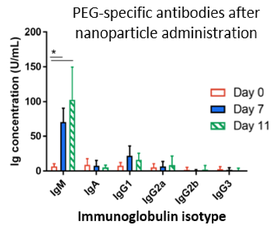


Figure 1 PEGylated nanoparticles show a stronger production of anti-PEG immunoglobulin M (IgM), without affecting the overall concentrations of other antibodies. Values represent individual animals (n = 9-12), a, b, c, d p < 0.05 between each otherValues represent means ± SD (n = 7-8), * p < 0.05.

- **Anti-PEG antibodies alter the compositions of the protein corona found on PEGylated nanoparticles.**

A. All proteins

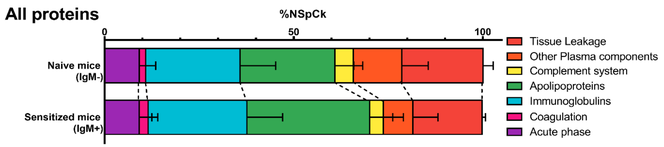


Figure 2 For a given nanoparticle, the presence of anti-PEG IgMs influences the protein corona deposited on nanoparticles. Values represents means ± SD (n = 5).

- **Anti-PEG antibodies reduce the circulation time for PEGylated liposomes and nanoparticles.**

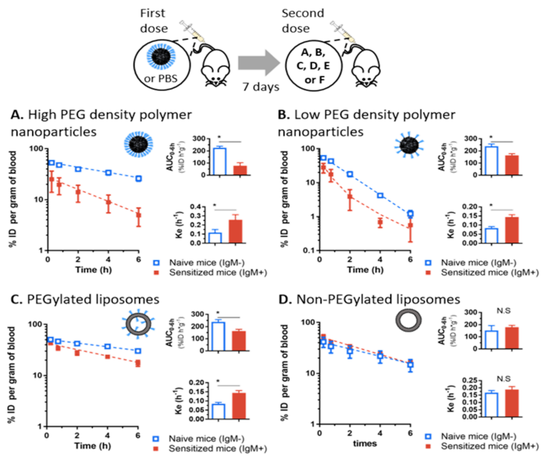


Figure 3 Mice with circulating anti-PEG IgMs clear some PEGylated nanosystems more rapidly than naive mice, but not free polymer and PEG-BSA. Data represents means ± SD (n =4-5), * p < 0.05.

- **PEGylated nanoparticles can trigger complement cascade activation.**

A.

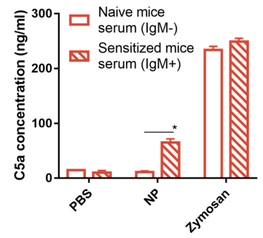


Figure 4 The presence of anti-PEG IgMs potentiates the activation of the complement cascade by PEGylated nanoparticles, but not by PEG-BSA. Values represent means ± SD (n = 3), * p < 0.05.

- **PEGylated nanoparticles injected in sensitized mice with the depletion of complement cascades have a longer circulation time.**

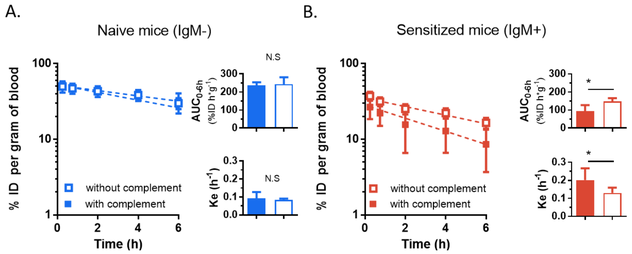
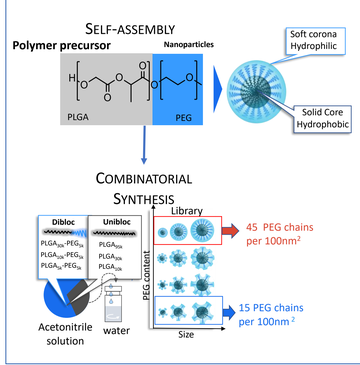


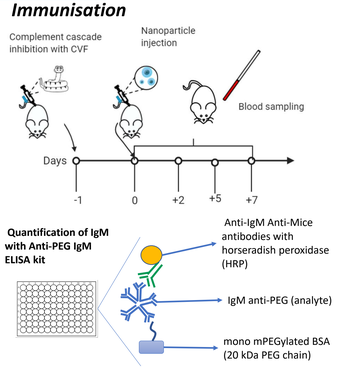
Figure 5 The complement cascade is implicated in the clearance of nanoparticles in the presence of anti-PEG IgMs, but not in naive animals. Data represents means ± SD, * p < 0.05 (n = 5-8).

Methods

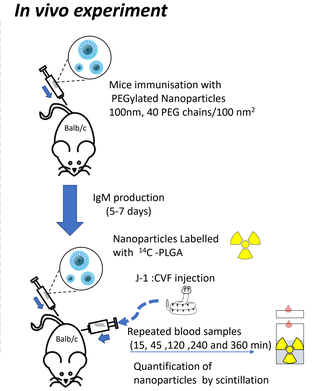
Nanoparticles synthesis



Immunisation



In vivo experiment



Conclusions

- The production of IgM anti-PEG antibodies was triggered in wild type mice Balb/c mice by intravenous injection of PEGylated nanoparticles. These nanoparticles appear to produce higher concentration of anti-PEG IgM than free polymer chains. This is importance because PEG remains a very common material in nanomedicine.
- In animals with circulating IgM anti-PEG, the circulation profile of a second dose PEGylated liposomes or polymeric nanoparticles is reduced.
- Anti-PEG immunoglobulins also alter the deposition of the protein corona on nanoparticles. Notably by increasing the activation of the complement cascade. This work highlights that protein corona also depends on the phenotype of the animal and probably of the patient.
- The Complement cascade appears to be playing an important role in the enhanced clearance observed with IgM anti-PEG. This contrasts with results obtained in naive mice, where abrogation of the complement system did not change the blood circulation.

- For further reading: https://tinyurl.com/y44fvvqy

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