

## **Immunosuppressive role of fibrinogen-like protein 2 (FGL2) in CD8+regulatory T cells-mediated long-term graft survival**

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ORAL PRESENTATION

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# Immunosuppressive role of fibrinogen-like protein 2 (FGL2) in CD8<sup>+</sup> regulatory T cells-mediated long-term graft survival

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## Background

We have previously reported that, in a model of cardiac allograft in rat, blockade of CD40-CD40L interaction induces long-term graft survival mediated by CD8<sup>+</sup> CD45RC<sup>low</sup> regulatory T cells (Tregs) [1]. Transcriptomic comparison of Tregs from AdCD40Ig-treated vs naïve rats highlighted the overexpression of FGL2 whose immunoregulatory properties are little known [2].

## Material and methods

A Lewis 1W rat heart is grafted in a MHC-mismatched Lewis 1A rat and infected with 2.10<sup>10</sup> pi of adenovirus recombinant for CD40Ig molecule (AdCD40Ig) the day of the graft. Tregs, effector CD4<sup>+</sup>CD25<sup>-</sup> T lymphocytes (TL), and plasmacytoïde dendritic cells (pDC) from spleen are sorted by FACS Aria for *in vitro* tests. For *in vivo* studies, 4,5.10<sup>11</sup>vg of FGL2-recombinant adenovirus associated virus (AAVFGL2) are intramuscularly or intravenously injected in recipients 30 days before the graft. Splenocytes are transferred to sublethally irradiated rats by *i.v* injection the day before the graft.

## Results

We confirmed FGL2-overexpression in splenic Tregs and in the graft of AdCD40Ig-treated vs non-treated and naïve rats, at mRNA and protein level. FGL2 involvement in Tregs immunosuppressive function was proved by *in vitro* and *in vivo* experiments. Indeed, Tregs from AdCD40Ig-treated rats inhibit TL proliferation in response to allogeneic pDC. This inhibition is abrogated by FGL2-blocking antibodies [3] and can be mimicked by FGL2 protein alone. Moreover, AAV-mediated FGL2

overexpression in rat prolongs graft survival with a median of 18.5 days vs 11 days for controls by *i.m* injection and survival is improved when *i.v* injected. Furthermore, adoptive transfer of splenocytes from an AAVFGL2-treated tolerant rat, to irradiated rats, transmits long-term graft survival iteratively.

## Conclusions

This is the first demonstration that the immunosuppressive molecule FGL2 is able to induce a long-term graft survival and that this tolerance is active and transferable by splenocytes. Work is under progress to identify the population responsible for this infectious tolerance.

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