New animal model to study the role of monoclonal immunoglobulins in plasma cell survival

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## Disclosure of Conflict of Interest

- I do not have a relationship with a for-profit and/or a not-for-profit organization to disclose
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Introduction

- Plasma cell development is closely linked to their capacity to cope with **Endoplasmic Reticulum (ER) stress** during massive production of Immunoglobulins.
- Abnormal Immunoglobulins can themselves be stressors and could explain the difference in Proteasome Inhibitors sensitivity.

We want to explore the **direct** effect of different pathogenic immunoglobulins on Plasma Cell proliferation/stress.

- **No mouse model available** to study the toxicity induced by different immunoglobulins in differentiated Plasma Cells.

Use of B-specific promoters (CD19, CD21) → Emerging Plasma cells derive from B-cells that overcome the stress of toxic immunoglobulins → **Selection bias**
First model of plasma cell-specific induction

Knock In (IgJ locus)

Only active in CD138+ cells /secreting cells

Inactive CreERT2 Recombinase

Active CreERT2 Recombinase

Oncogenes (c-MyC, Bcl2)

Pathogenic Ig

Tamoxifen (ERT2 agonist)
First model of plasma cell-specific induction

IgJ-CreERT2 x Tomato Mouse

Plasma cells

B cells
Check the effect of truncated HC on PC while inducing deposits formation in kidney
Monoclonal immunoglobulin effect on PC

Total Spleen Cells - LPS stimulation D4

The truncated Heavy Chain generated causes a difference in stress that kills plasma cells

When PC develops with the truncated Heavy Chain produced from early stages there is no death: PC “selected” during B cell development to tolerate stress levels
Plasma Cell Death

Sorted PCs and B cells - LPS stimulation D3

B cells

Non Treated

Treated 12H

Plasma Cells

Non Treated

Treated 12H

Fixable Viability Stain 780 (FVS780)

B220

CD138

12H OH-Tamoxifen Treatment

CH1+ CH1-
Perspectives

• *In vivo* assays to validate *ex vivo* findings

• Analyse the precise mechanism involved in PC cell death using the *IgJ-CreERT2 x LoxP CH1+ Mouse* as well as others (Light Chain Deposition Disease, Fanconi Syndrome, etc)

• Study of PC that become resistant: molecular mechanisms and proteasome inhibitors sensitivity
Thanks for your attention!