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NEW INSIGHTS IN NON-INVASIVE MARKERS FOR REJECTION IN LUNG TRANSPLANTED PATIENTS

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OBJECTIVES
Easily accessible and non-invasive markers of rejection after lung transplantation need to be identified. We tested soluble immune-check-points in plasma and extracellular-vesicles in bronchoalveolar-lavage.

METHODS
Plasma samples were collected from 20 patients at 72-hours and at 3, 6, 12 and 17 months after lung-transplant. Soluble immune-checkpoints (Galectin9, TIM3, PD1 and PDL1) were evaluated by ELISA at each time points; surveillance transbronchial-biopsy were performed at 3, 6, 12 months for diagnostic purposes and clinical parameters were recorded. At the same time as the transbronchial-biopsy, we do the bronchoalveolar-lavage. Extracellular-vesicles were isolated from bronchoalveolar-lavage and were phenotyped using the ExoView platform and antibodies against CD45, EpCam and CD68.

RESULTS
At 18 months, plasma Galectin9 was significantly reduced in patients with rejection compared to those without rejection ($p<0.05$). More in detail: patients with acute rejection have Galectin9 reduction starting from 3 months up to 18 months ($p<0.05$). In patients with chronic rejection a similar trend was observed from 6-month. Similar behaviour was observed for other soluble immune-checkpoints. Note that PD1 was highly expressed on biopsy tissue.
Sixty-five per cent of extracellular-vesicles from bronchoalveolar-lavage expressed the CD45 antigen on their surface, suggesting a lymphocyte origin. Intriguingly, the exposure of bronchial recipient cells to extracellular-vesicles from patients with chronic rejection induced expression of the Aryl-Hydrocarbon-Receptor gene, a transcription factor involved in differentiation of T-cells in Th17 (a subset of pro-inflammatory T-cells defined by their production of interleukin-17).

CONCLUSIONS
Since the identification of soluble markers of rejection would be of great importance in supporting the clinical management of patients with lung transplant, our pilot study opens a new scenario dedicated to soluble immune-check-points. Early results seems to promote Galectin9 as a possible rejection marker. In addition, we found that extracellular-vesicle

isolated from broncoalveolar-lavage could be another marker do to their property of activate the pro-inflammatory differentiation of T-lymphocytes.

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