



Interleukin-1 β is an important HLA-G inducing factor in ovarian carcinomatosis

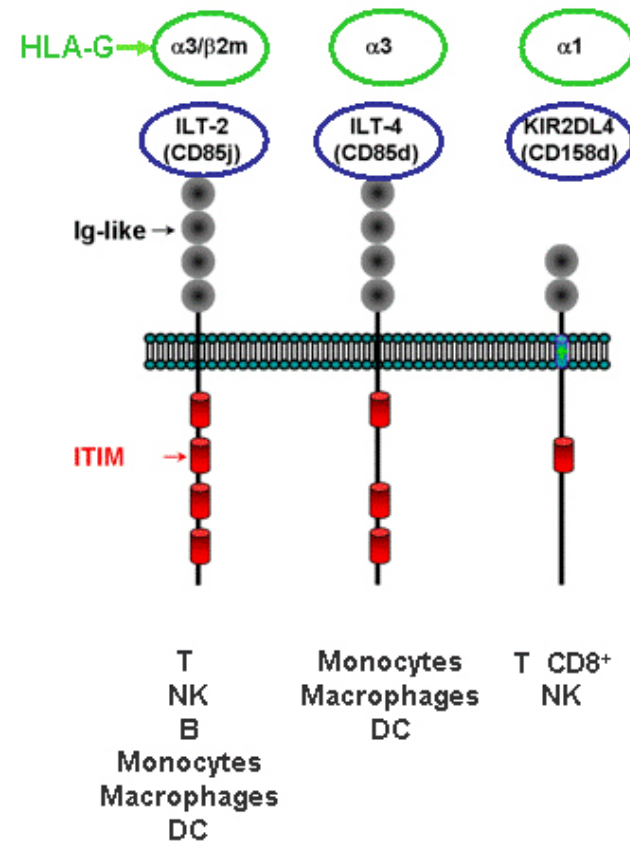
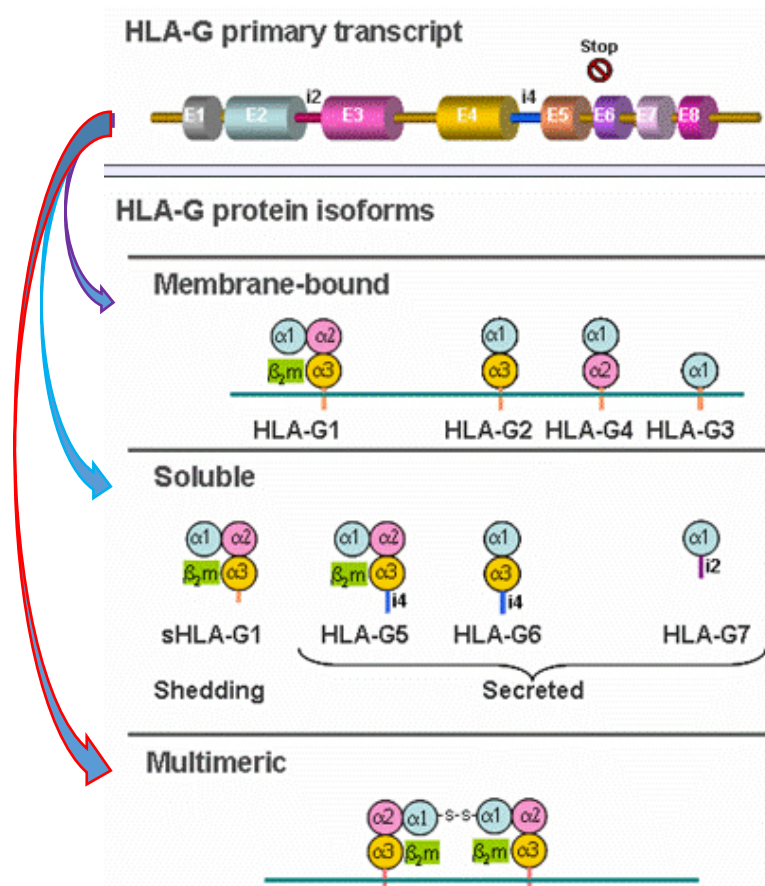
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Human Leukocyte Antigen G (HLA-G)

- ❖ is a regulator of immune system responsible for immunosuppression or immune tolerance.
- ❖ **HLA-G** was described for the 1st time by Ellis et al. in 1990 as class-I and physiologically expressed on trophoblasts and thymus.
- ❖ During embryogenesis, HLA-G via trophoblast cells inhibits Natural Killer cells and prevents attack on fetus by the maternal immune system and It allows the foetus implantation in uterus
- ❖ Surprisingly, expression of elevated HLA-G also was found during development of different pathologies.
- ❖ **In cancer patients** HLA-G was associated with **malignant, invasive** or **metastatic** status and **poor prognosis**.
- ❖ HLA-G is mainly expressed in the case of cancer **ovarian** (54%), gastric (40%) and breast (6%)

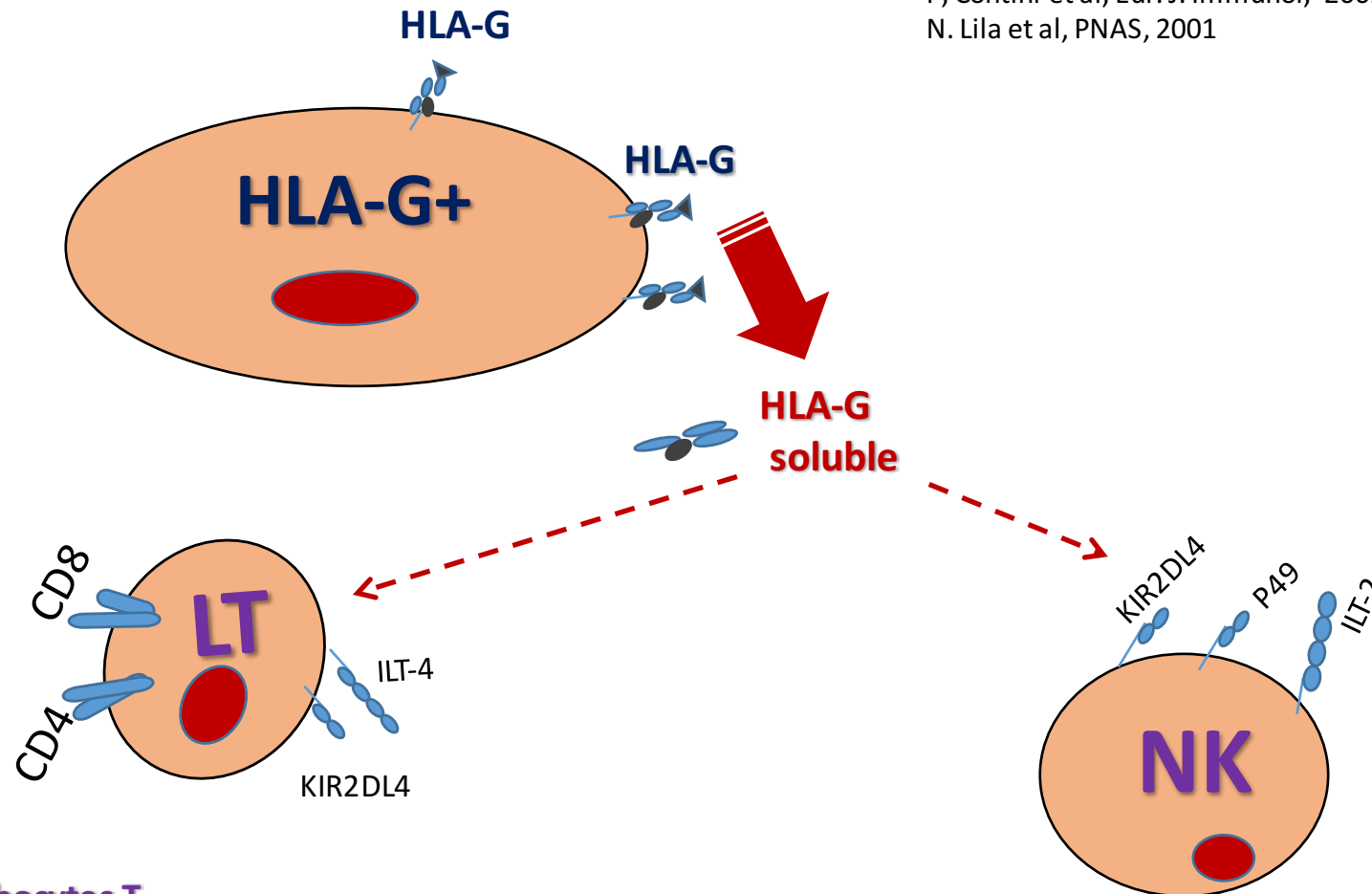
HLA-G isoforms and their receptors



➤ In this study, we investigated the presence of HLA-G1 and HLA-G5

Action of HLA-G in the cellular immune response

P, Contini et al, Eur. J. Immunol, 2002
N. Lila et al, PNAS, 2001



On lymphocytes T

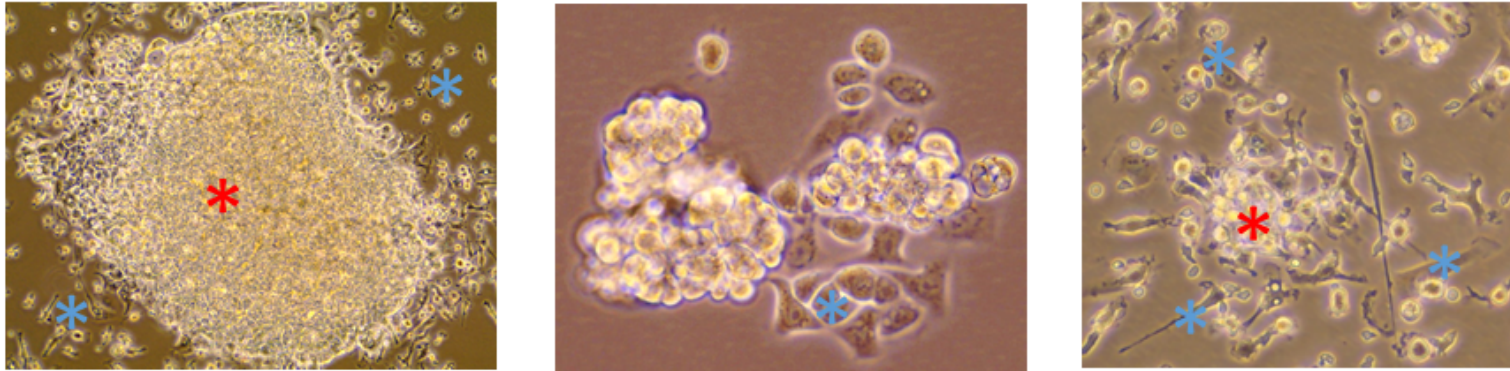
- Inhibition of cytolytic activity antigen specific
- Apoptosis of activated lymphocytes T CD8+
- Production of cytokines type Th2
- Inhibition of proliferative response of lymphocytes T CD4+.

On NK cells:

- Inhibition of cytolytic activity of NK cells
- Inhibition of transendothelial migration of NK cells

Presence of Hospicells, Cancer cells and Immune cells In Ovarian Ascitic Cell Clusters.

A



Day 1

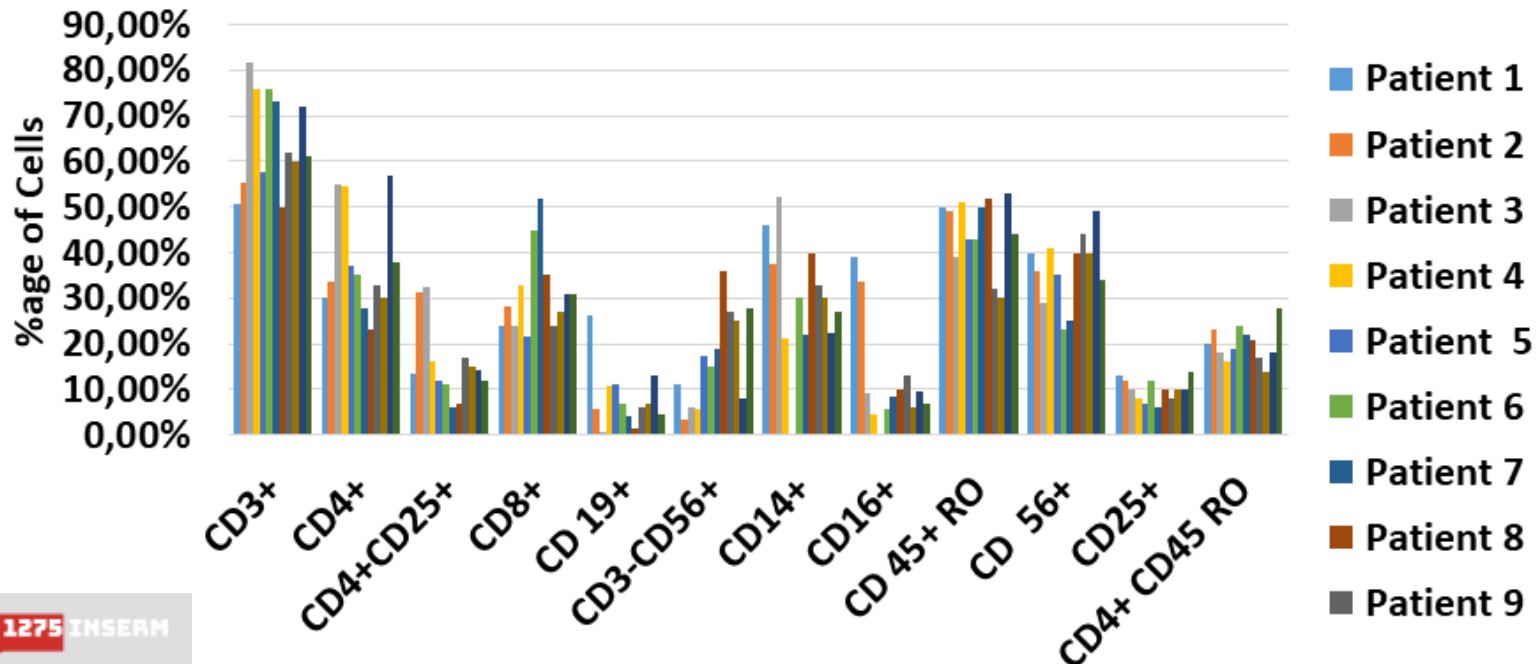
Day 3

Day 7

* Hospicells (Stromal cells)

* Cancer Cells

B

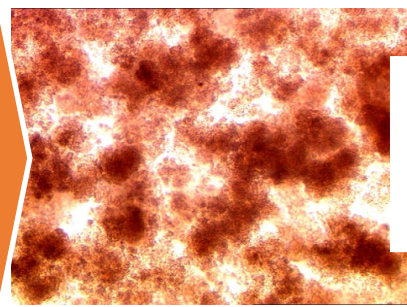


What is an hospicell?

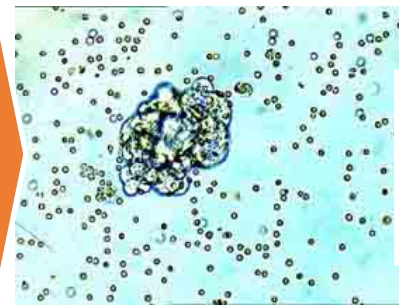
Is an stromal cell that identified in ascetic cancer cell clusters from patients with ovarian cancer & in pleural fluids from patients with breast cancer.



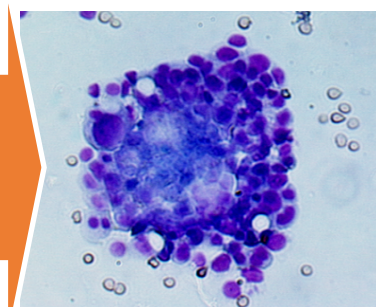
Carcinomatosis



Peritoneal fluid contains cancer cell clusters



Primo-cancer cell cluster



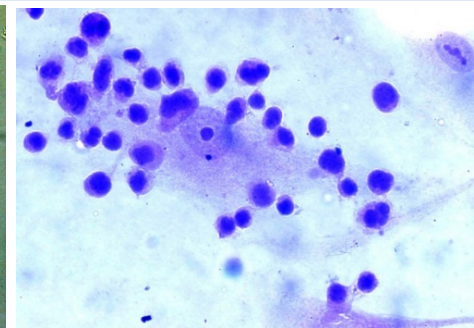
HES cancer cell cluster



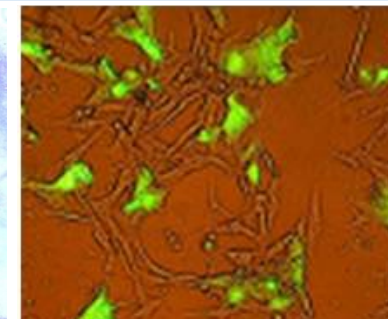
cancer cell cluster in culture medium



Stromal (Hospicell) Bind leukemic HL60 cells



HES : HL60 bind to Hospicell

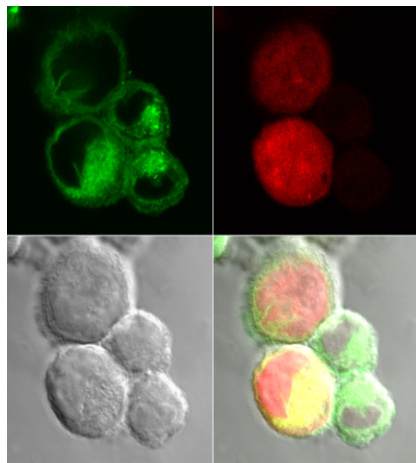


MCF-7 (GFP) bind to Hosaicell

Cell of great size which is characterized by its property to bind leukemic and cancer cells (progenitor cells)

Cancer cells can be protected by Hospicells Via induction of:

Chemoresistance acquisition



Oncologic Trogocytosis

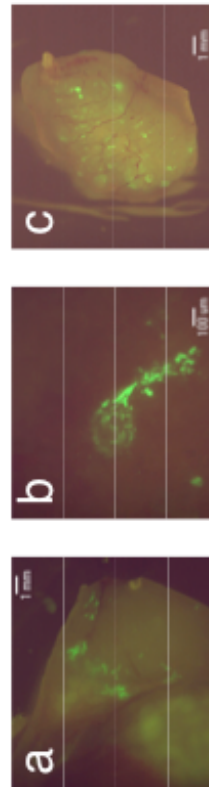
Rafii et al, 2008, PlosOne



Hospicell via IGF - JAK2/STAT3 upregulates MDR expression in Ovc3 cells

Benabbou et al, 2013 Int. J. Oncol
Benabbou et al, 2014 Int. J. Oncol

Angiogenesis

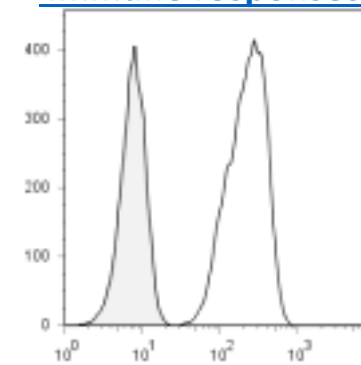


Pasquet M., et al, 2009, Int. J. Of Cancer

Immunosuppression



inhibit T cell immune responses.



NO production by iNOS is the main factor responsible for CD8+, CD4+ T cell inhibition by Hospicells.

Martinet Let al, 2009, Int. J. Of Cancer

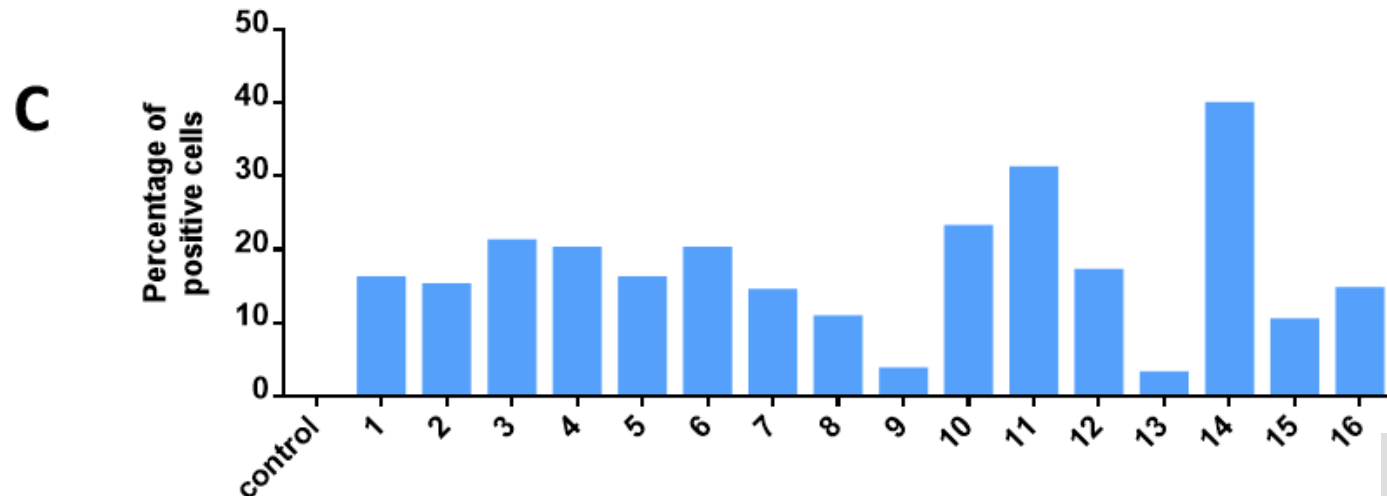
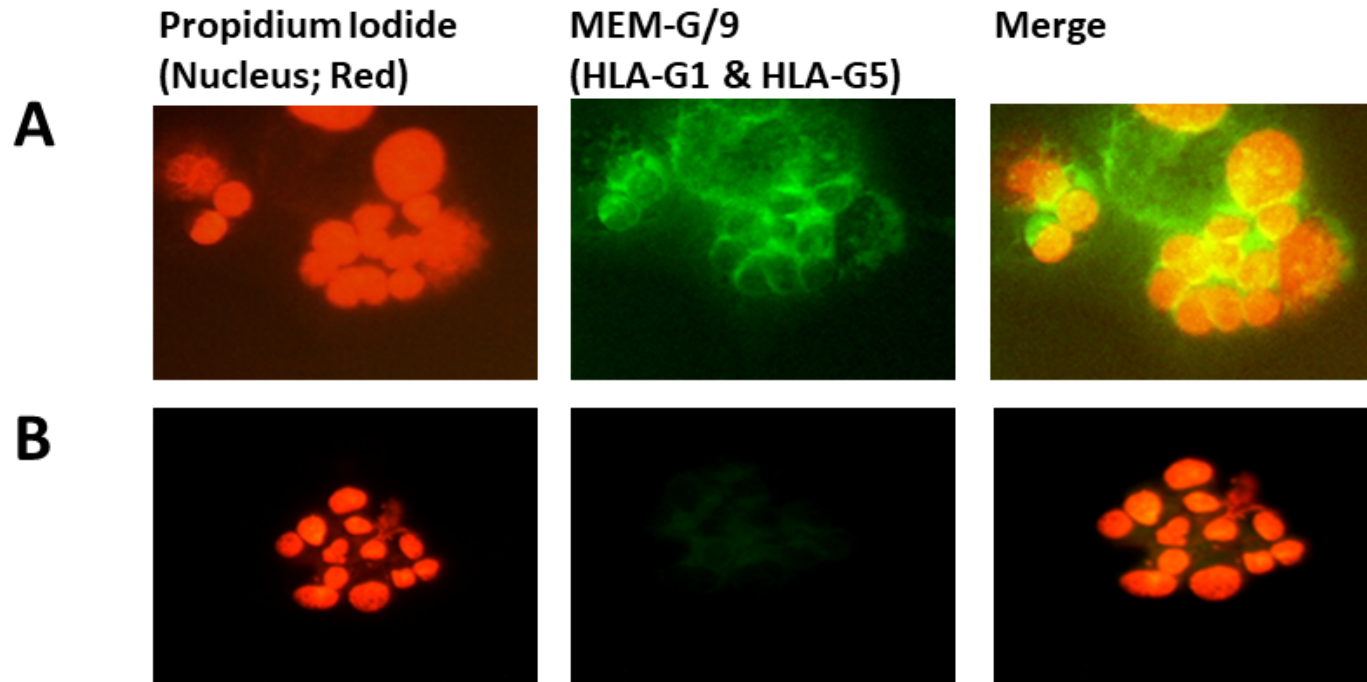


HLA-G Modulation



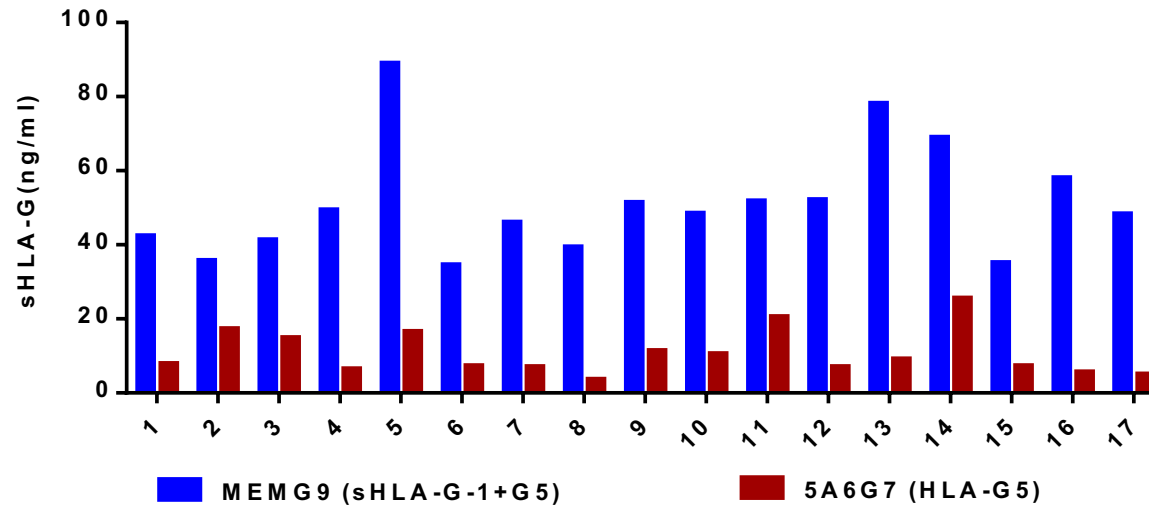
Ullah et al, 2019 Neoplasia

Immunofluorescence staining of HLA-G in cell clusters derived from ascites of patients with ovarian cancer.

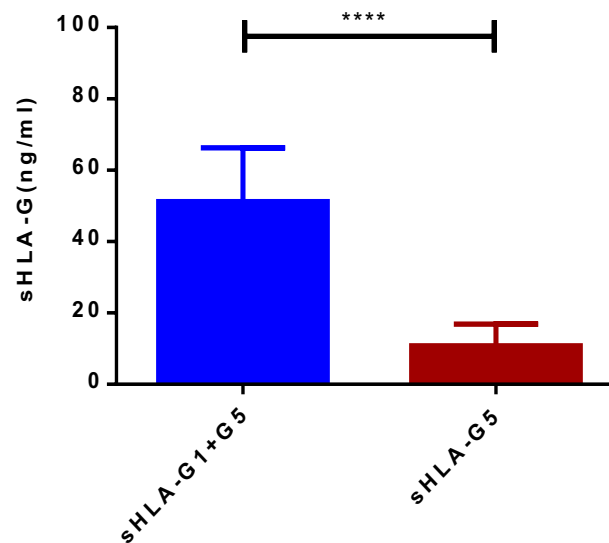


Detection of sHLA-G1 & G5 in ascitic fluids of patients with ovarian cancer

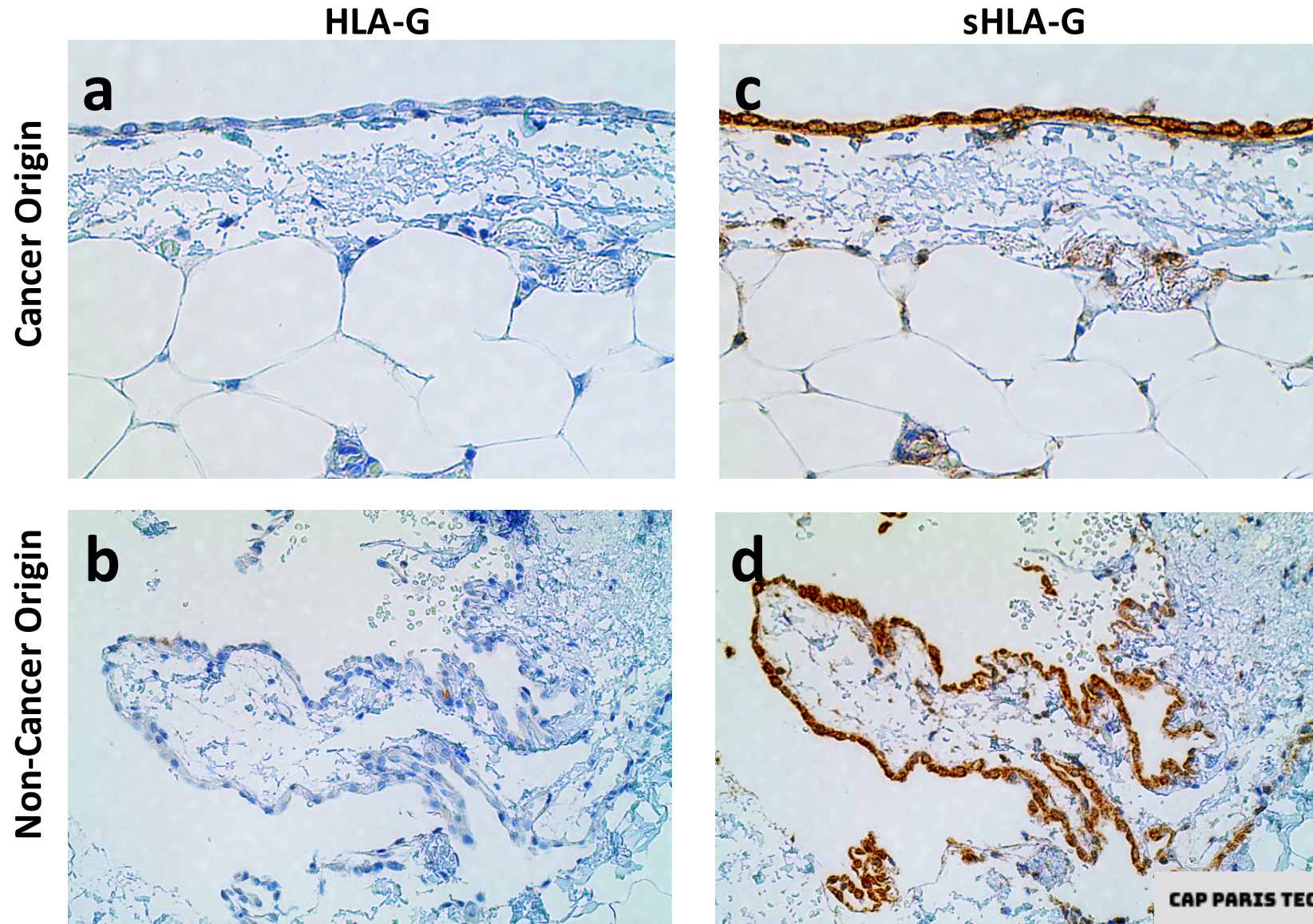
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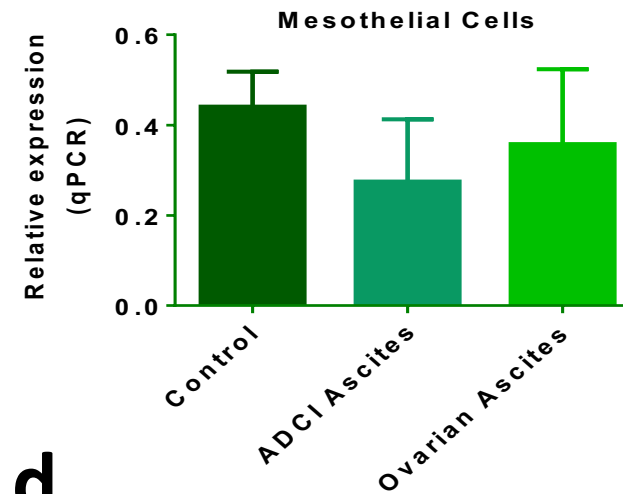
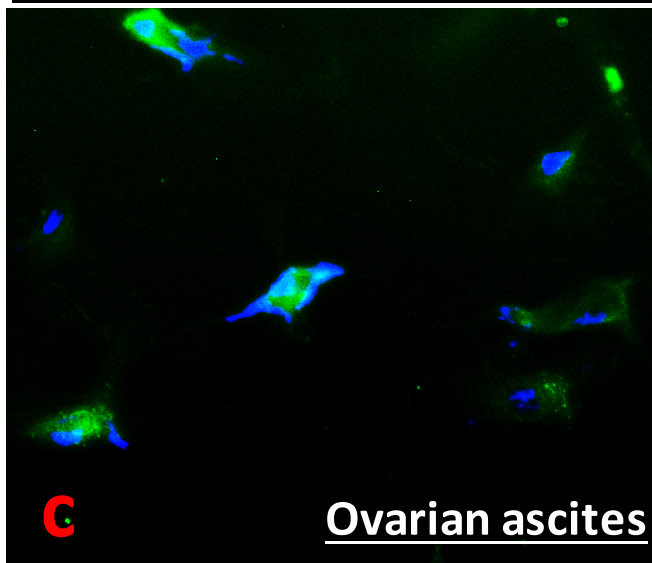
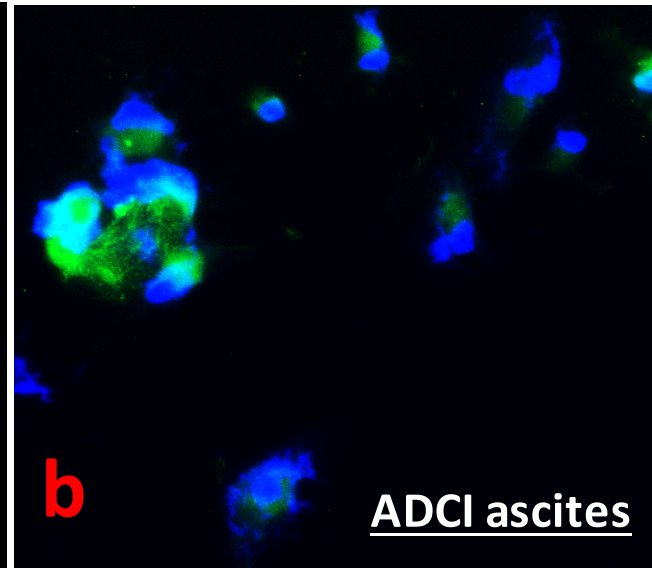
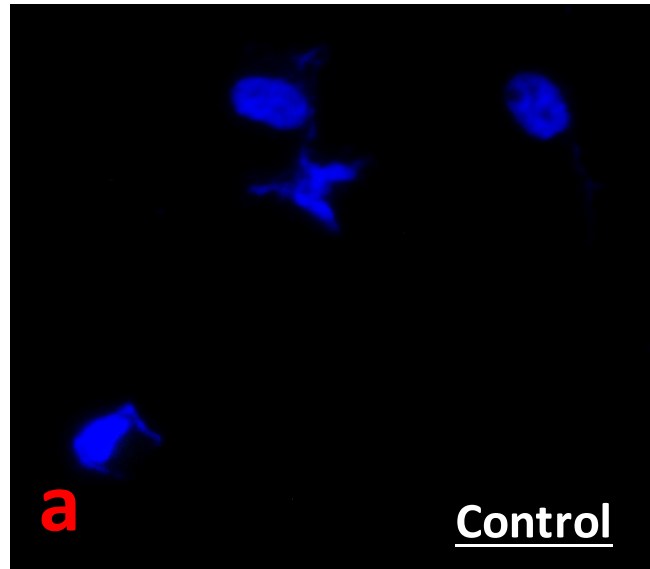
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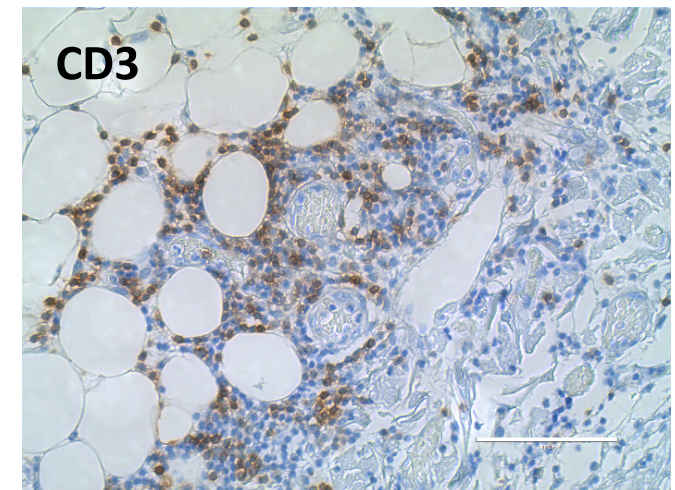
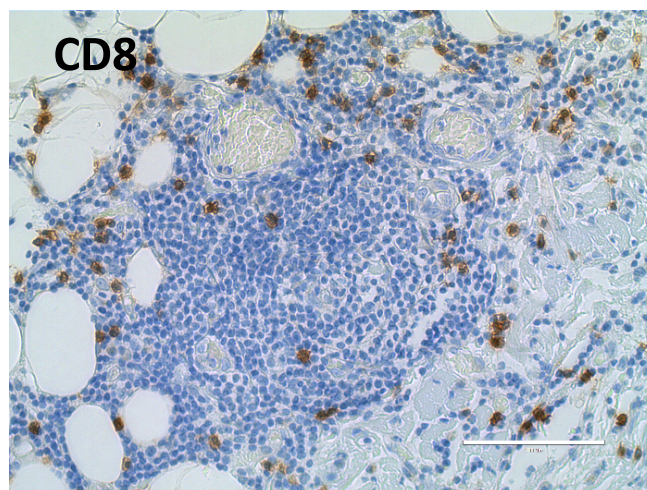
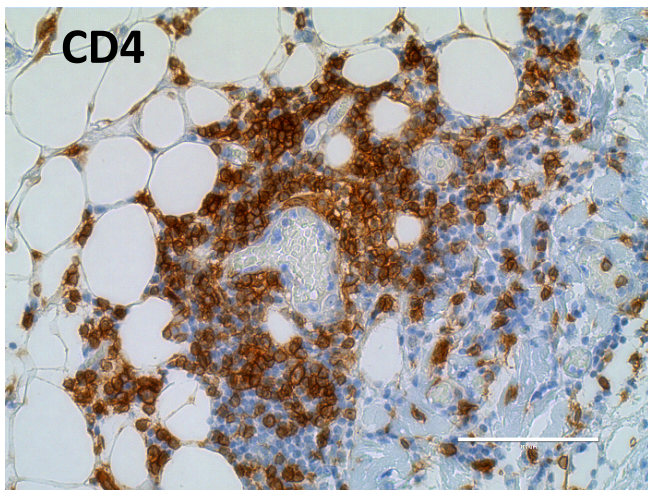
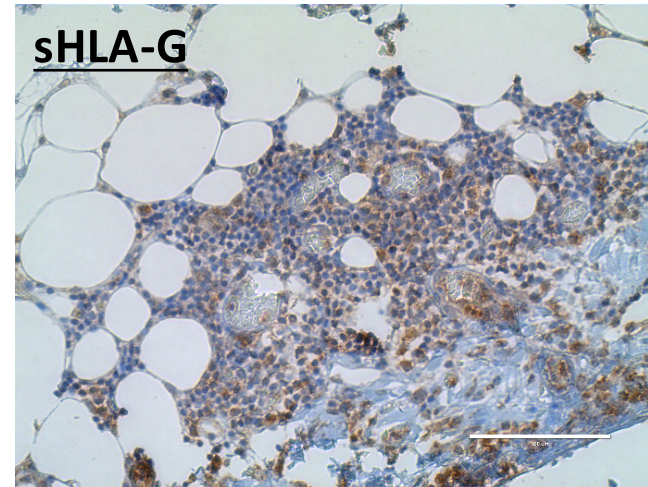
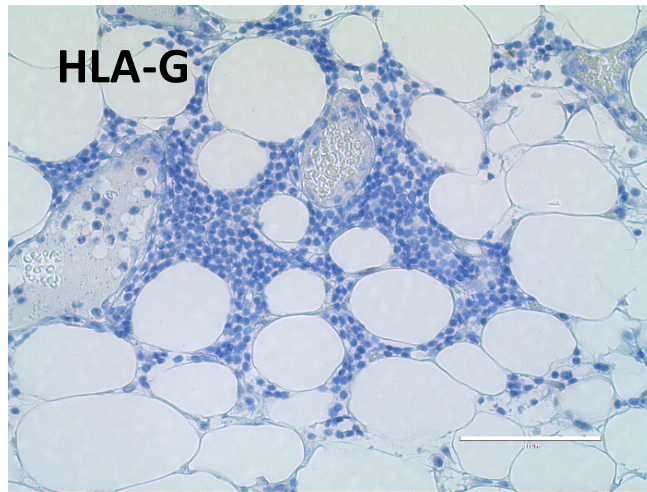
sHLA-G was detected in inflammatory condition on the mesothelial cells (MC), Absence of HLA-G expression by MC in vivo



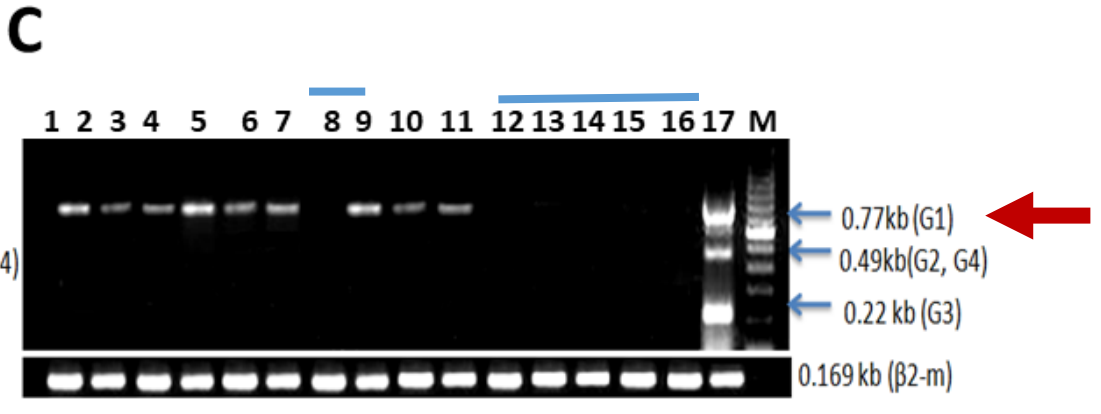
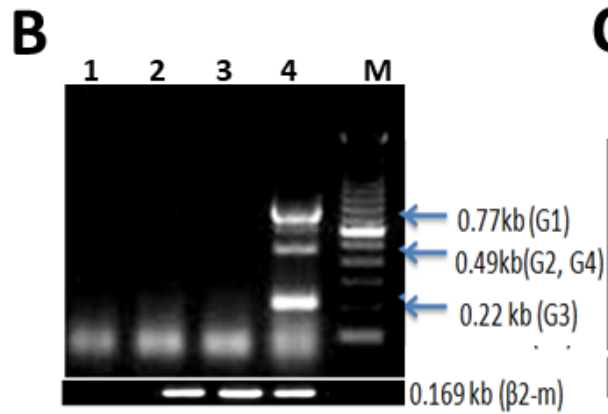
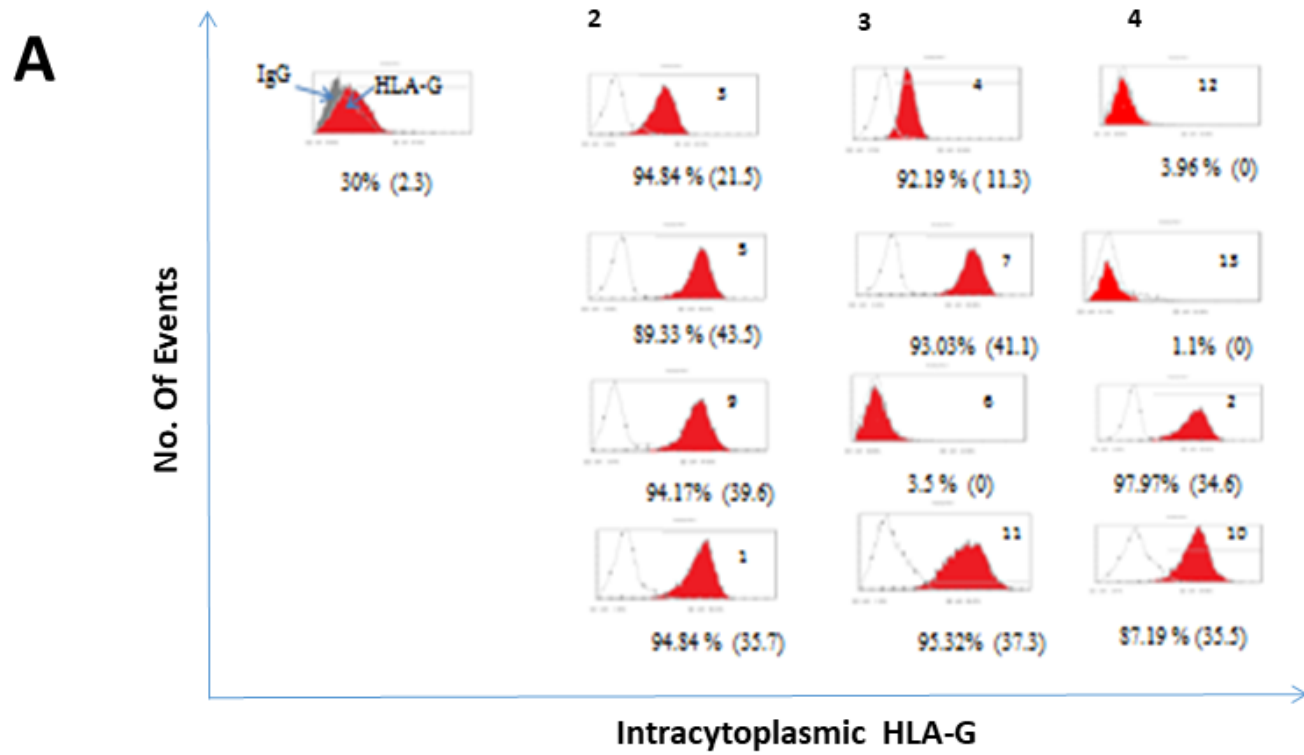
HLA-G captage from carcinomatosis ascitis by mesothelial cells in invitro



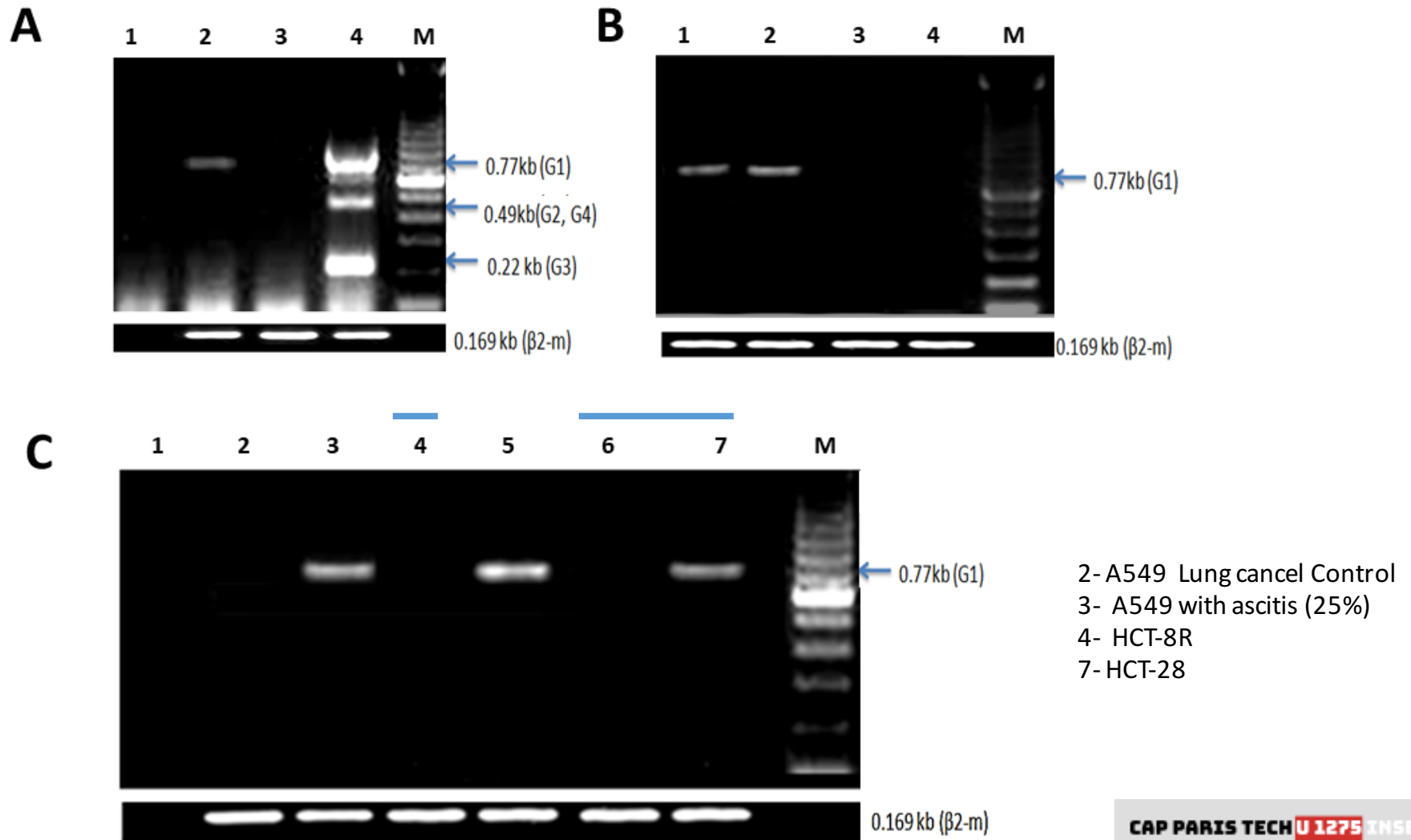
Absence of HLA-G expression by immune cell
in peritoneal Immune cell infiltrate (in-situ),
sHLA-G co localisation



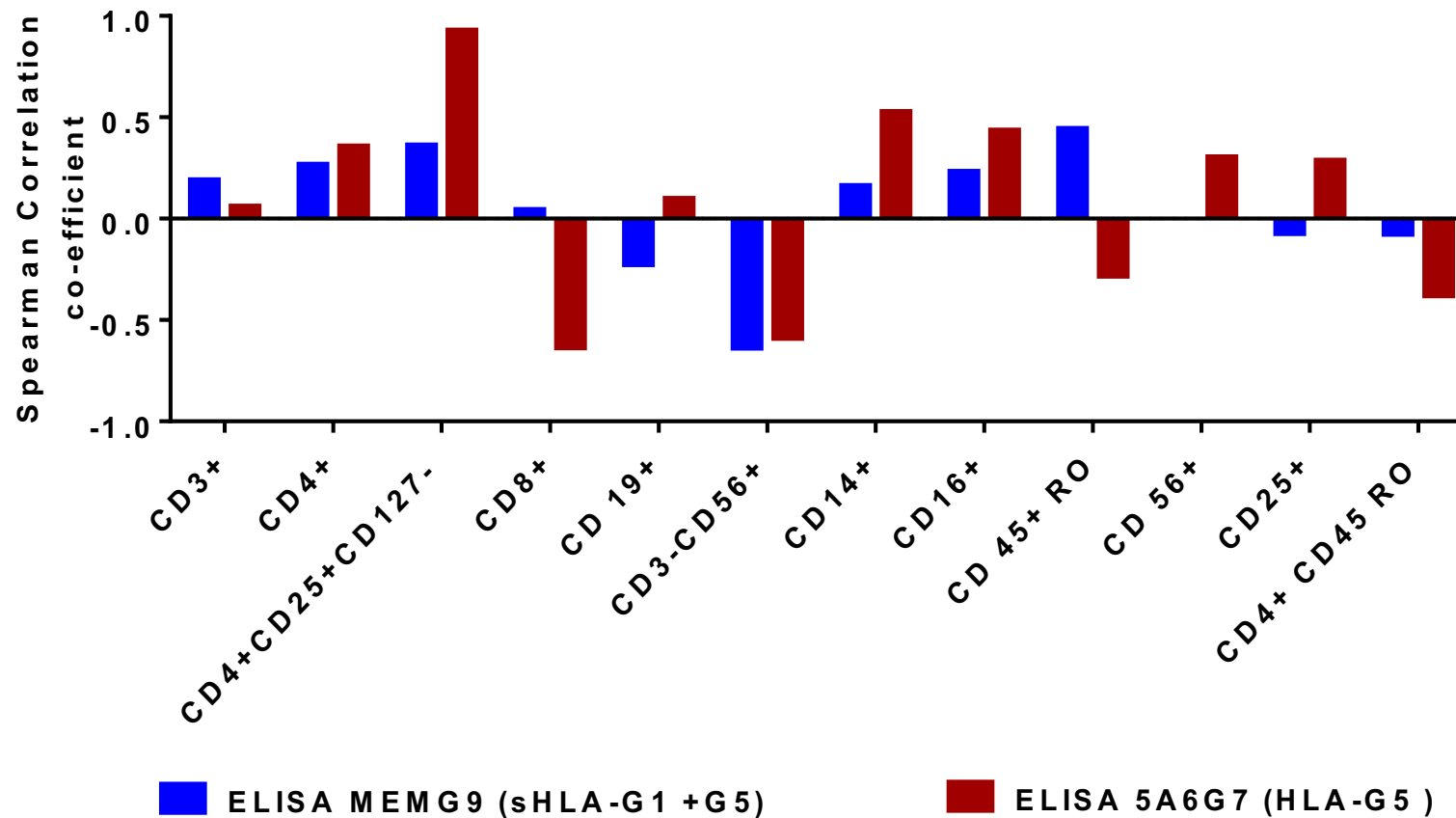
HLA-G expression by Hospicells



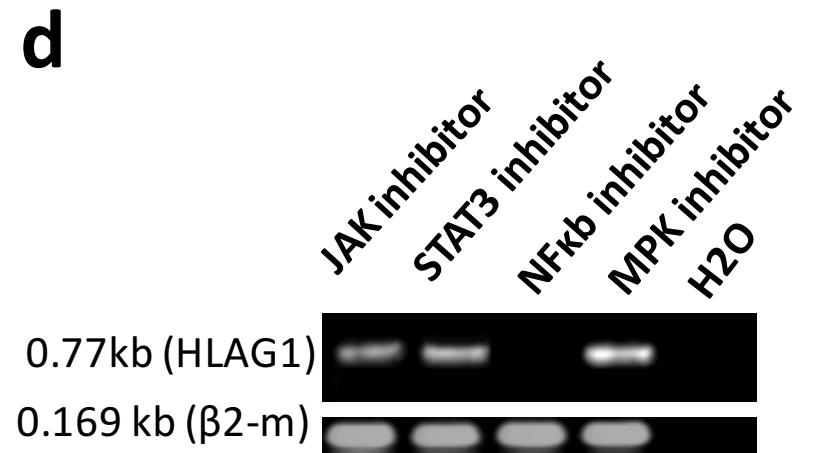
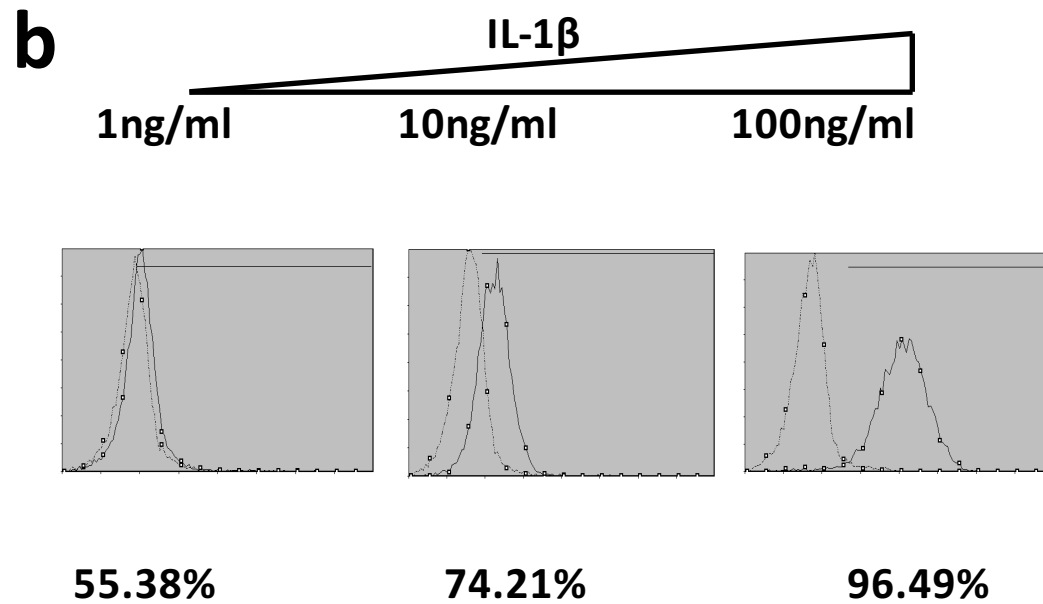
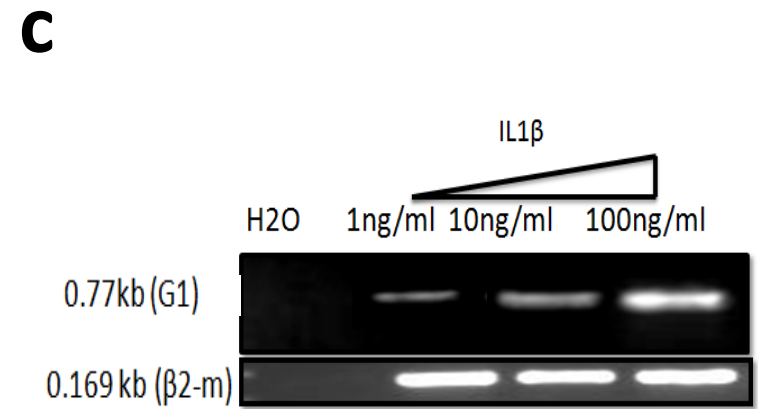
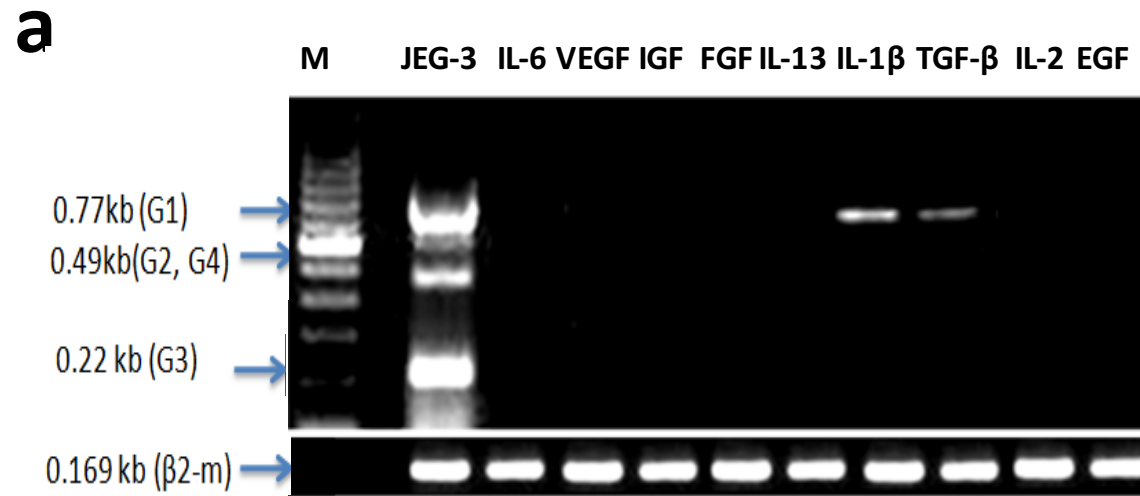
HLA-G expression by cancer cell lines before and after culture with ascites supernatant or serum



Correlation between HLA-G levels in ascites carcinomatosis and composition of immune cell population in ascitic clusters



HLA-G inducing factors in ascitic fluids



Conclusion

- ❑ In pathological situations, HLA-G produced by the interaction of stromal cells, immune cells and cancer cells, generate an immunosuppressor microenvironments in peritoneum cavity,
- ❑ The production of HLAG by IL-1 β is associated with microenvironment immune tolerant cells such as T-reg and through diminution of NK and memory T cells.
- ❑ This phenomena help the expansion and implantation of tumor nodules by neutralization of anticancer immune responses
- ❑ **Canakinumab** is a human monoclonal antibody targeted at IL-1 β , and approved in many countries for treatment of cryopyrin-associated periodic syndromes. (systemic inflammation and clinical symptoms involving skin, joints, central nervous system and eyes)

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High Expression of HLA-G in Ovarian Carcinomatosis: The Role of Interleukin-1 β



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