Identification of an adherent cell from human Bon marrow that interacts with malignant cells and inducing chemoresistance

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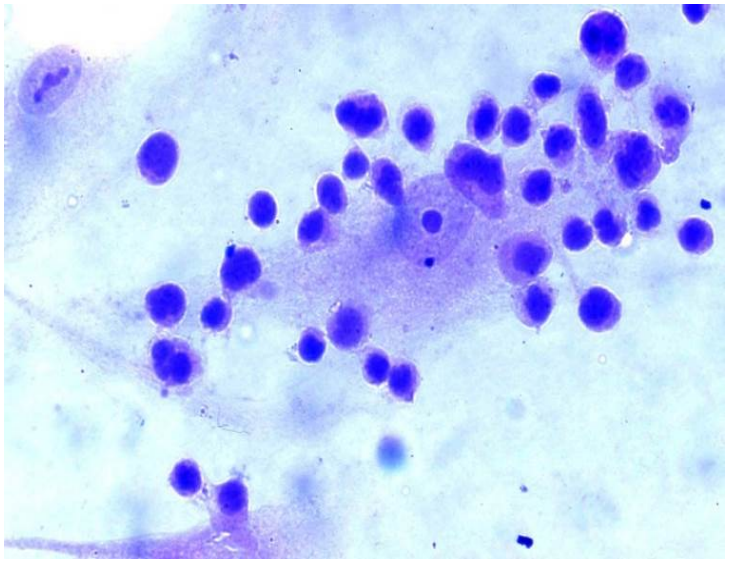
Identification of an adherent cell from bone marrow mononuclear cells that interacts with leukemic cells



Interaction of HL60 with BM adherent cell, named Hospicell

Hospicells are derived from bone marrow (BM) stem cells (CD 34+ or CD 133)

Present spontaneously in the leukemic BM (9 ±4%) and in ascitic fluid of patients with ovarian cancer

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

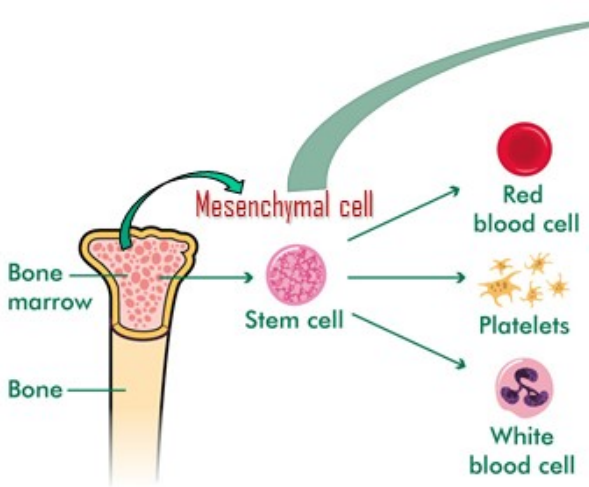
Hospicells = Host cells

What are the functions of Hospicells ??
Study in progress ……

Negative markers:

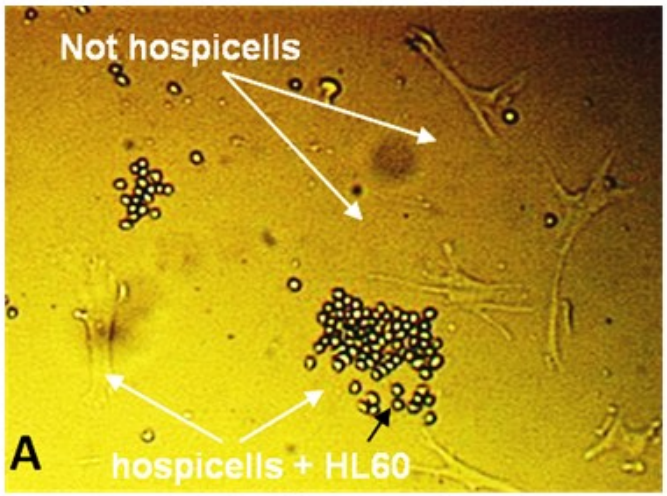
- Endothelial cell
- Smooth Muscular cell
- Hematopoietic cell
- Dendritic cell

Isolation of an adherent cell from bone marrow mononuclear cells that interacts with leukemic cells



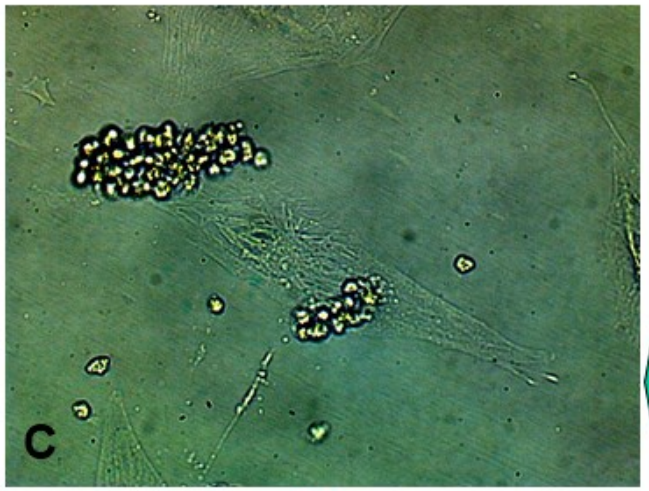
$CD133^{+}/34^{+}$ cells

3 weeks in Conditioned medium



Positive Marker Expression	Negative Marker Expression
CD9	CD3
CD10	CD4
CD29	CD8
CD44	CD14
CD102	CD16
CD105	CD20
CD106	CD25
CD166	CD31
CD90	CD34
	CD45
	CD54
	CD56
	CD117
	CD133

CD Markers



After 48 hours: multiplication of HL-60 in Hospicells

After 3-4 hour, HL-60 fixation on the hospicell

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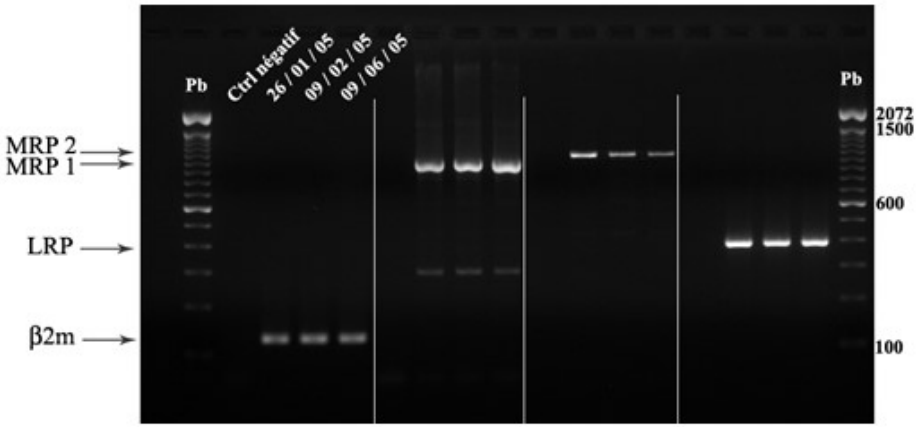
Multi drug resistance proteins on the Hospicells

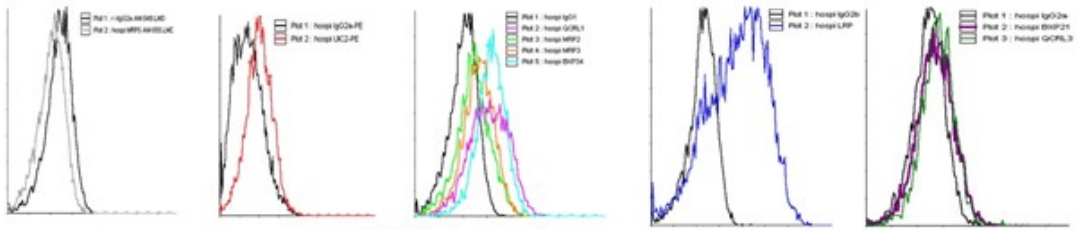
mRNA



Cell type	Hospicell
Markers	Deviation
Pgp (UIC2-PE) ext.	0,34
QCRL1 = MRP1	0,57
QCRL3 = MRP1	0,23
MRP2	0,28
MRP3	0,41
MRP5	0
BXP21 = BCRP	0,16
BXP34 = BCRP	0,7
LRP	0,65

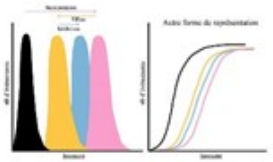
BM Hospicells grown in vitro

Proteins

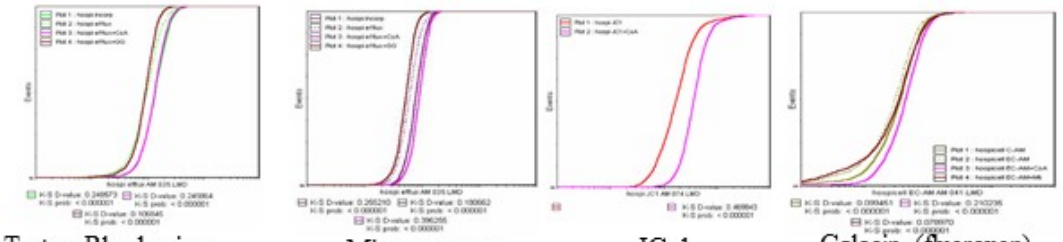


Multi drug resistance on the Hospicells

Functonality



Pompes	Substrat	Inhibitors
Pgp	Rhodamine 123, Calcein, JC-1	Cyclosporin, GG918
MRP	Calcein	MK571
BCRP	Mitoxantrone	Cyclosporine, GG918



Tests: Rhodamine | Mitoxantrone | JC-1 | Calcein (fluorexon)

Functionality tests are based on the study of the incorporation and efflux of fluorescent molecules that are substrates for ABC proteins.

➢ Pgp, BCRP, are functional and MRPs shown less functionality (Hypothesis: glutathione)

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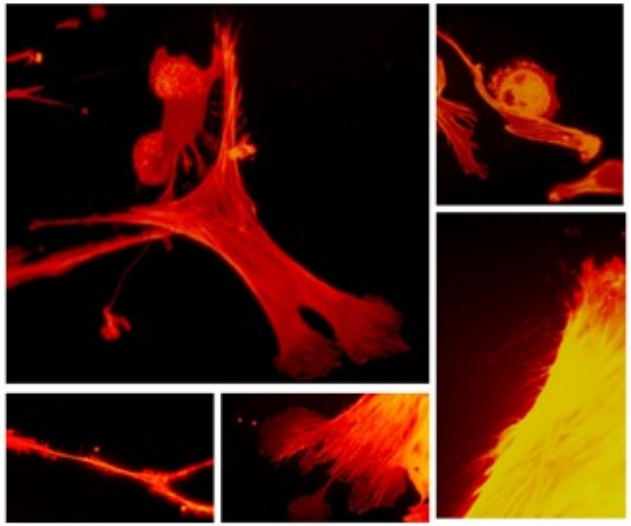
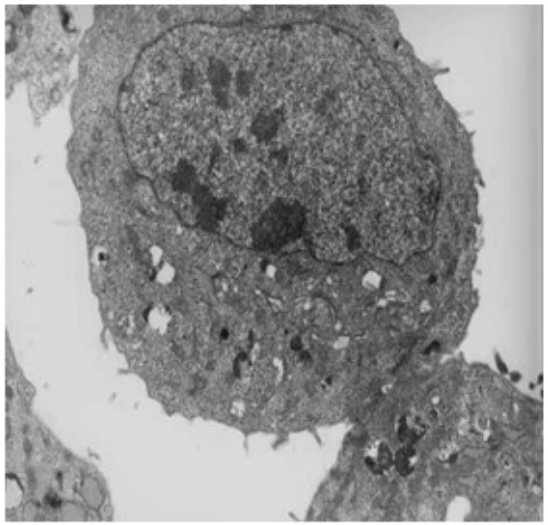
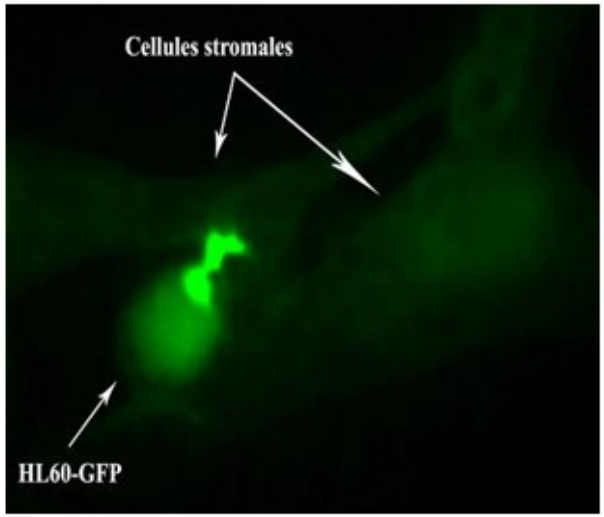
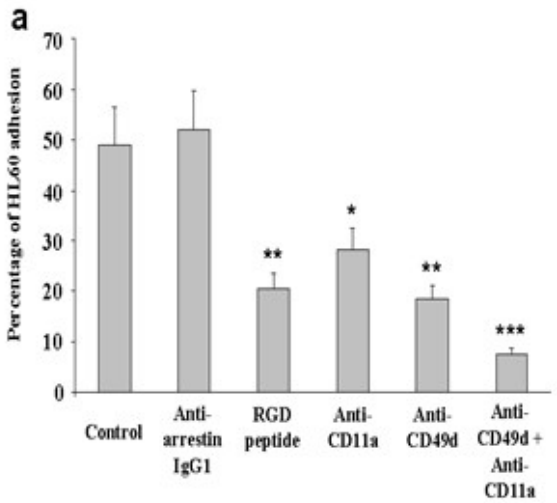
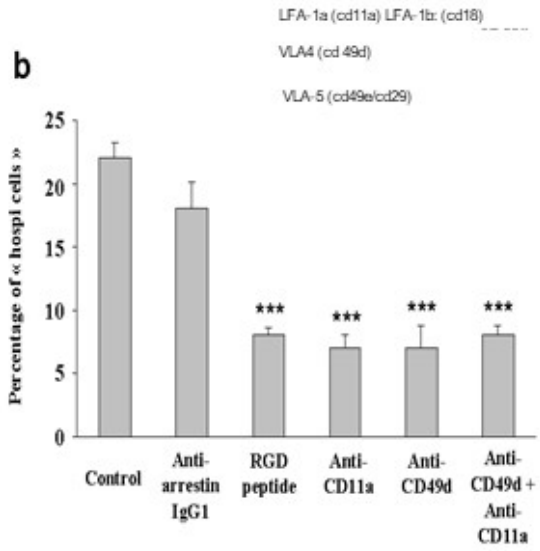
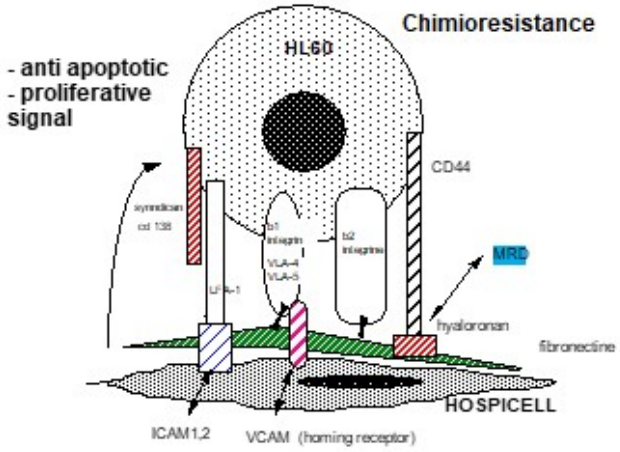






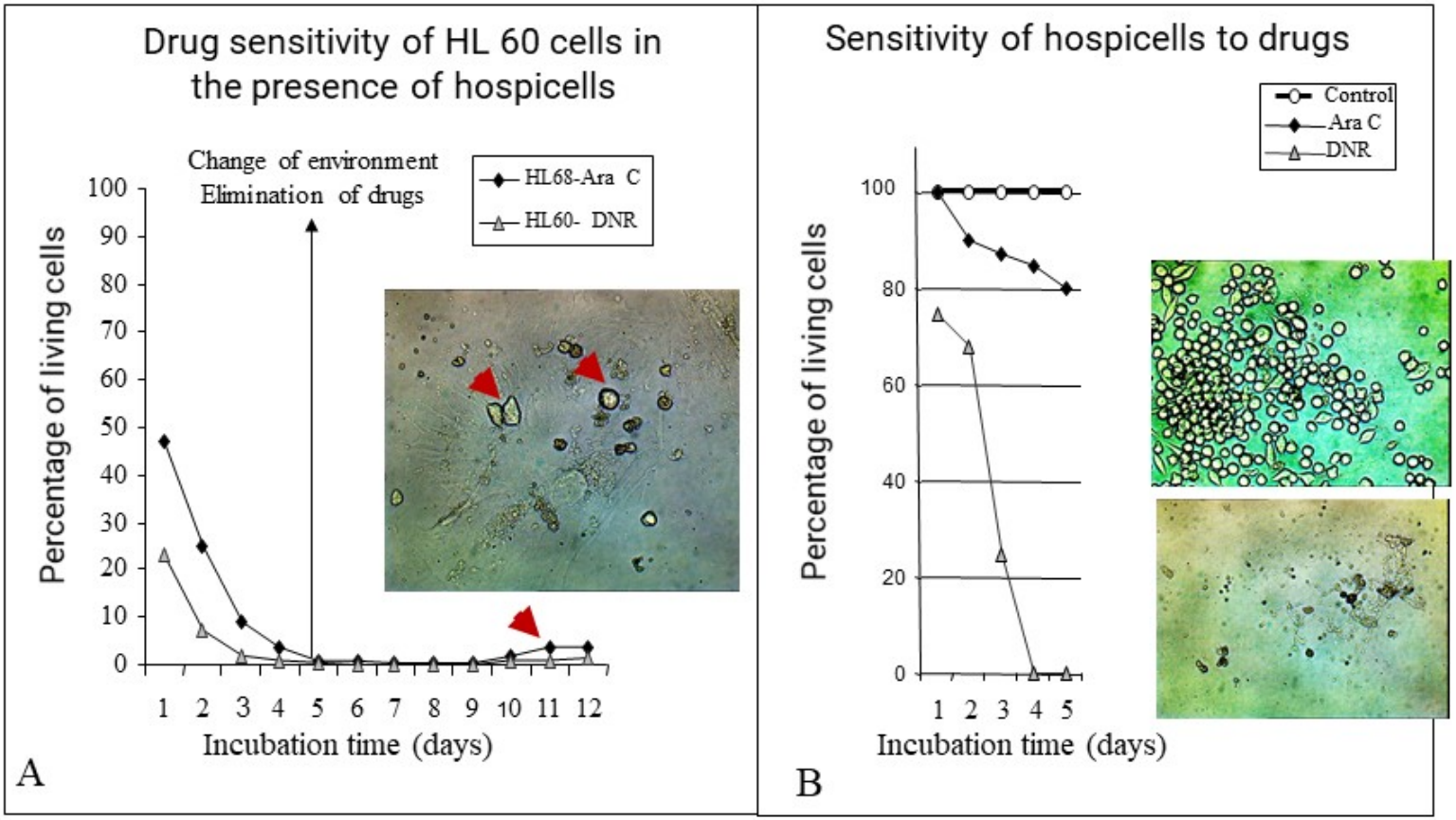




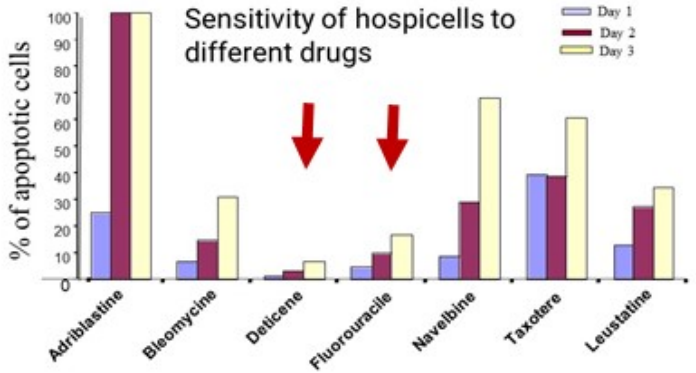


➢ RGD peptide, anti-CD 11a and CD 49d antibodies inhibit HL60 binding to hospicells.

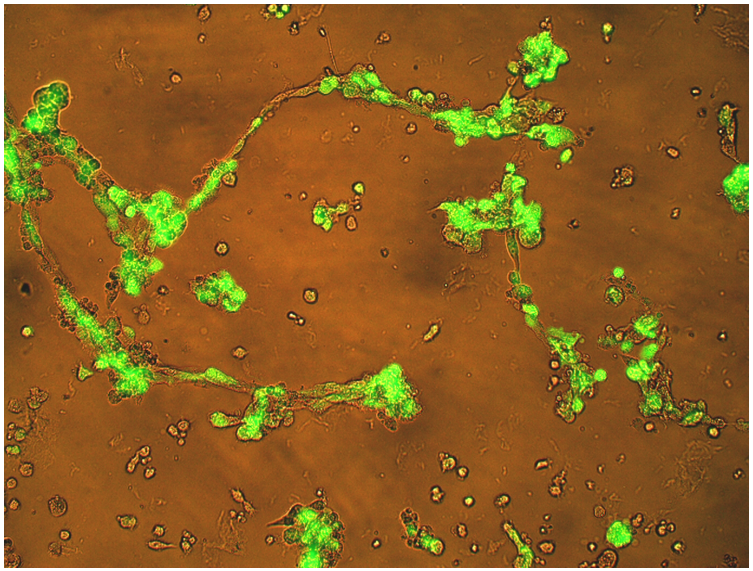
Hospicells protect cancer cells against chemotherapy

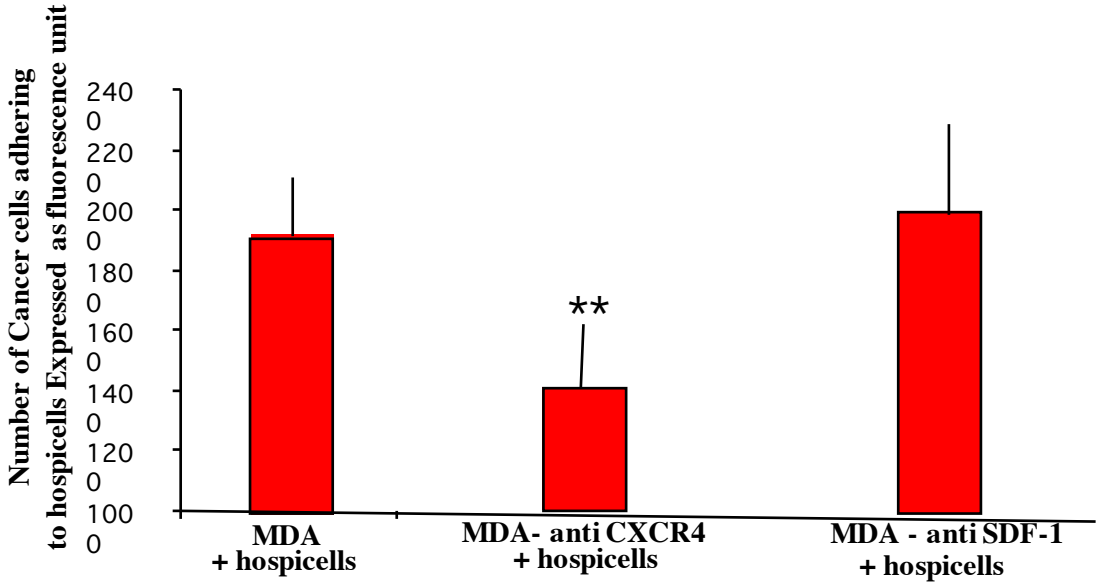


- some cancer cells remain alive on hospicells after AraC treatment



Adherent cells isolated from bone marrow mononuclear cells promotes solid tumor cell adhesion *in vitro*.





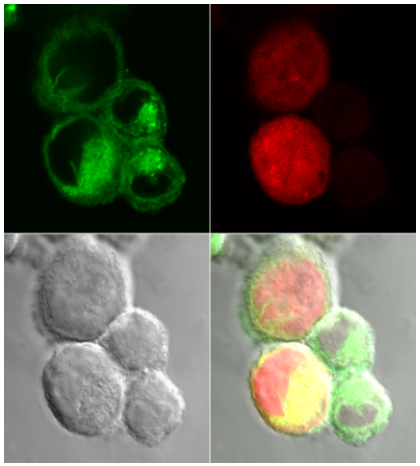
Interaction of Breast cancer cell line-GFP with Hospicells

Inhibition of interaction between hospicell and Rhodamine labelled MDA-MB 231 using an anti CXCR4 Ig

- Possibility of modulation of integrins on cancer cells due to binding of SDF-1 to CXCR4
- These integrins should be susceptible to play a role in the binding of cancer cells to hospicells

Cancer cells can be protected by Hospicells Via induction of:

Chemoresistance acquisition



Hospicell via IGF - JAK2/STAT3 upregulates MDR expression on Leukemic and solid cancer cell line

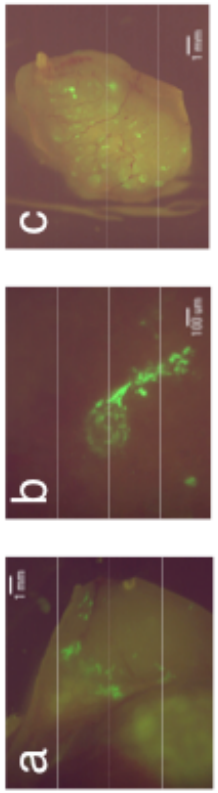
Oncologic Trogocytosis

Rafii et al, 2008, PlosOne

Benabbou et al, 2013 Int. J. Oncol

Benabbou et al, 2014 Int. J. Oncol

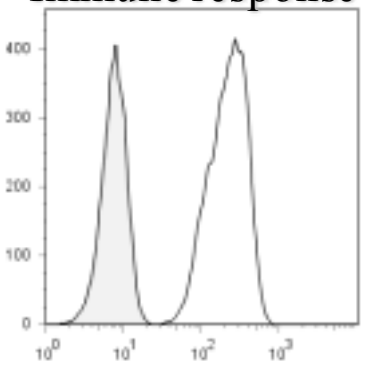
Angiogenesis



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

Immunosuppression

Inhibit T cell Immune response



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

Martinet L et al, 2009, Int. J. Of Cancer

HLA-G Modulation

Ullah et al, 2019 Neoplasia

Conclusion and perspectives

- Human bone marrow contains an adherent cell (Hospicell) that is derived from CD133⁺/CD34⁺ progenitor cells cwinteracting with leukemic cells *in vitro*,
- We have found that malignant cells remain linked to hospicells after chemotherapy and can proliferate, leading to a relapse
- Until now, the proposed test was to evaluate in vitro the effectiveness of a drug against the cancer cell, unsatisfactory process in clinical application.
- We plan to develop an "ONCOGRAM ®": In our test, the toxicity of the drug will be tested at once on cancer cells and hospicells.