

Fibrin deposit on the peritoneal surface serve as a niche for cancer expansion

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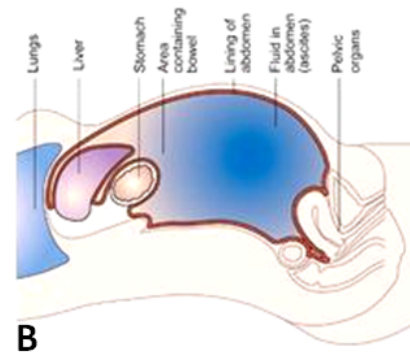
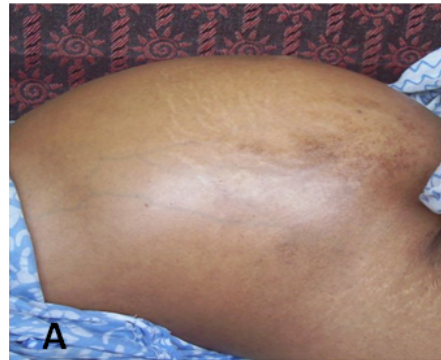
INSERM U965

Carcinose, Angiogenèse et
Recherche Translationnelle
Paris, France

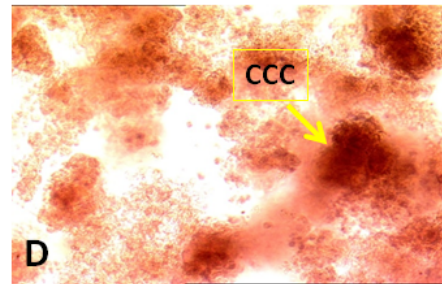


Carcinomatosis and peritoneal fluid

Peritoneal carcinomatosis is a metastatic manifestation of many organ-based malignancies, particularly carcinomas of the gastrointestinal tract and ovary



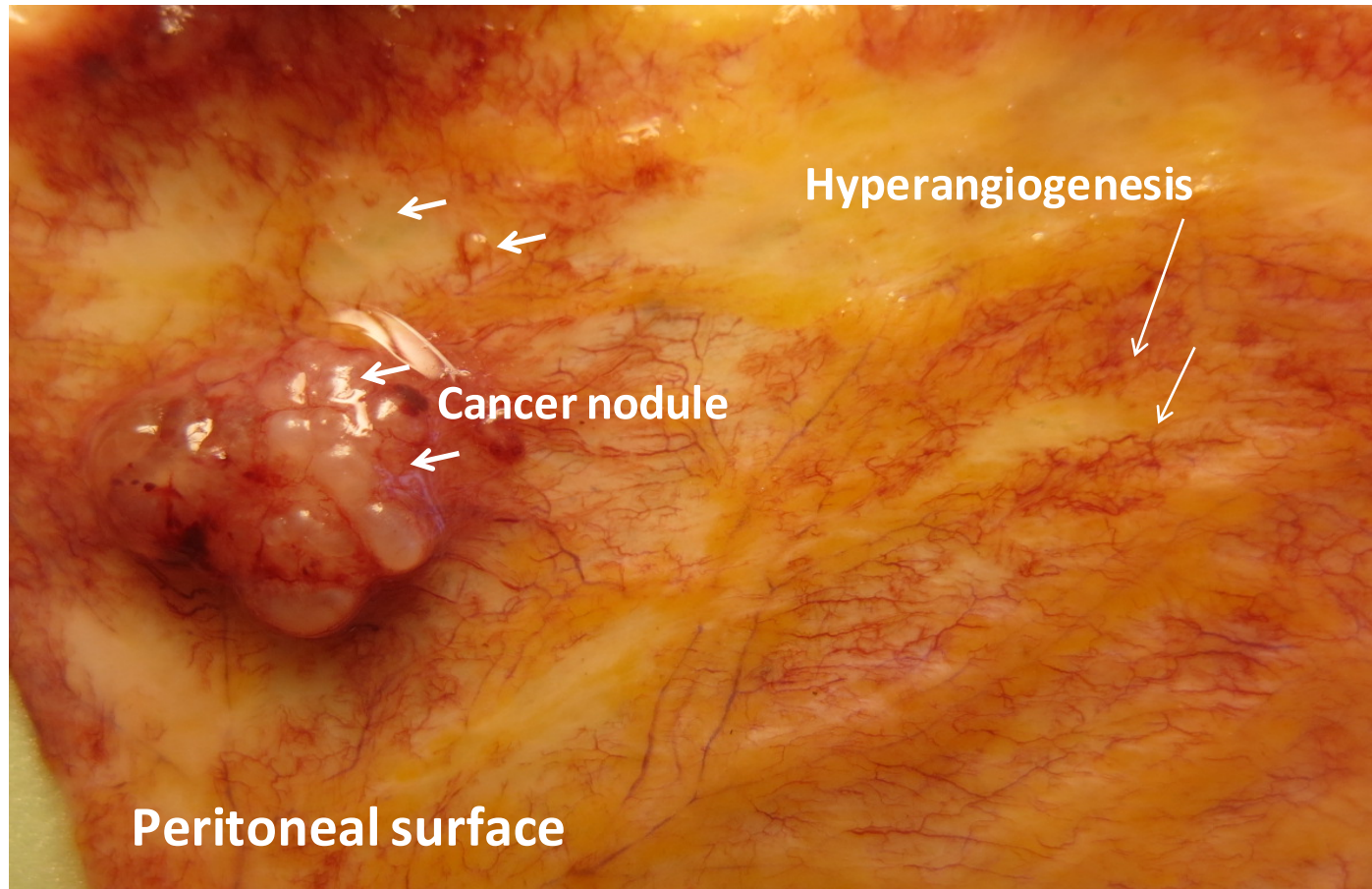
Ovarian Carcinomatosis nodule



Cancer cell cluster

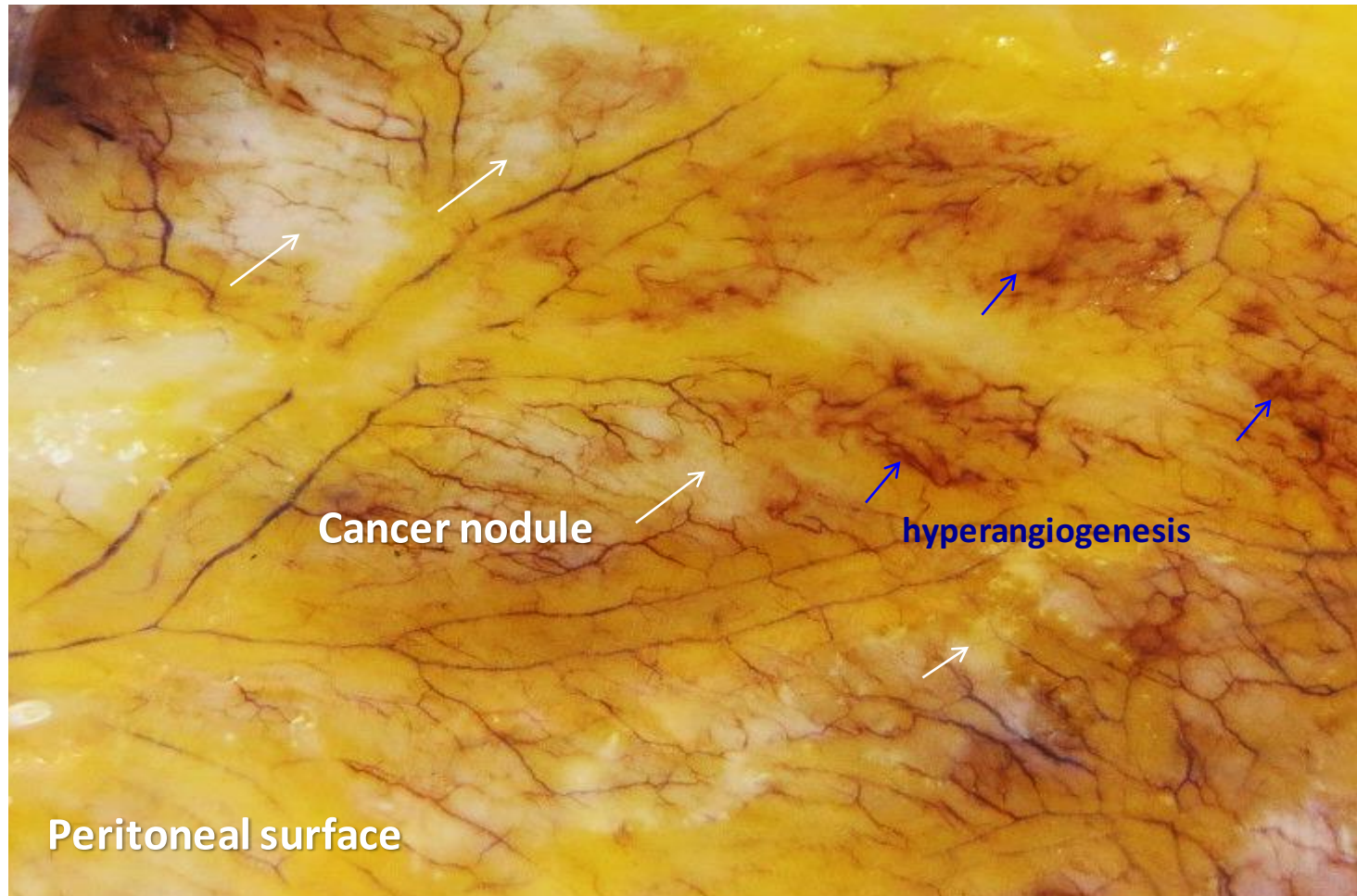
- Peritoneal carcinomatosis is a term used to describe widespread metastases of cancerous tumors in the peritoneal cavity.
 - Peritoneal carcinomatosis is the most common terminal future of abdominal cancers.
- It may occur in two forms: on the peritoneal surface (C) and in the ascites liquid (D)

Human peritoneal carcinomatosis (**macroscopic**)



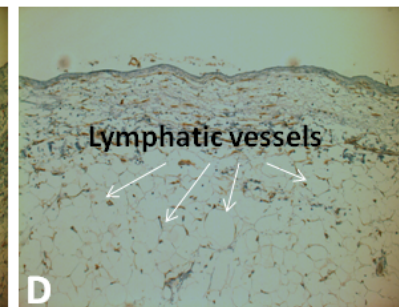
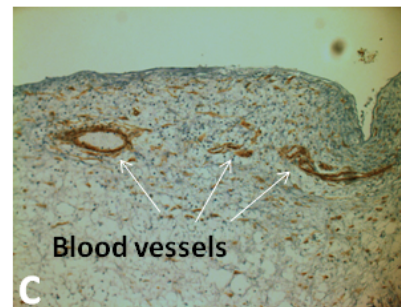
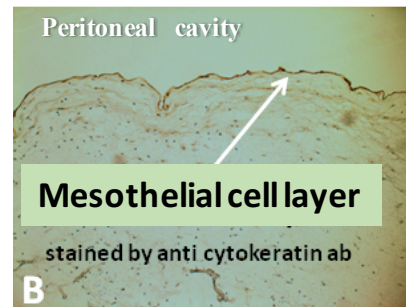
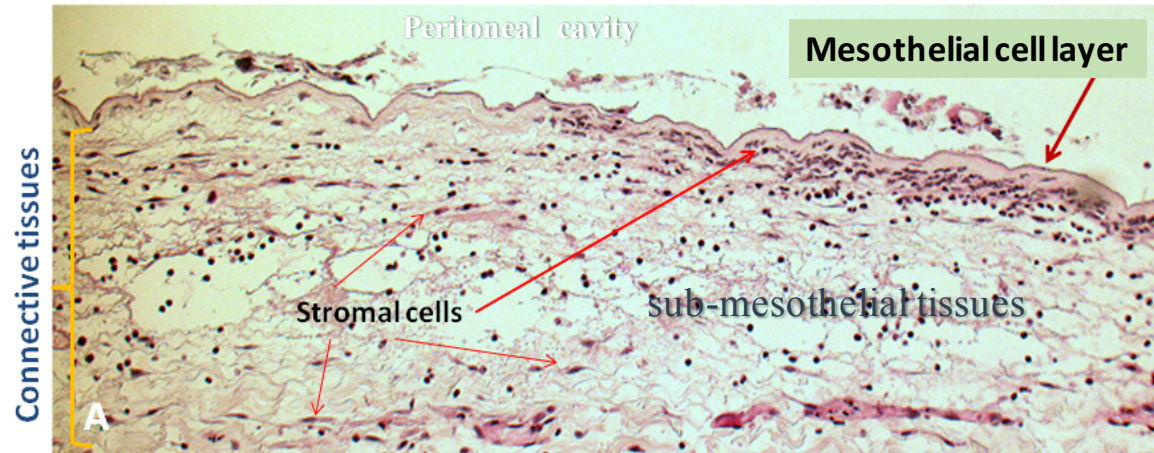
Carinomatosis is a peritoneal mestastasis associated with hyper angio- lymphangiogenesis and is one of the most unfavorable cours of cancer progression (PM)

Human peritoneal carcinomatosis (**macroscopic**)



Sub mesothelial peri-tumoral hyperangiogenesis in peritoneal carcinomatosis

Peritoneum surface and sub-mesothelial tissues (**microscopic**)



- The peritoneum is the largest serous membrane in the body. It consists in two layers which are continuous with each other : the parietal peritoneum and the visceral peritoneum .
- They both consist of a layer of simple squamous epithelial cells, called mesothelial cells that are stained by Cytokeratin (**A and B**).
- There contain blood and lymphatic vessels (**C and D**).

Aim of work

- ❑ To understand the impact of peritoneal microenvironment on
 - **Epithelial Mesenchymal Transition**
 - **Fibrin deposits on the peritoneal surface**

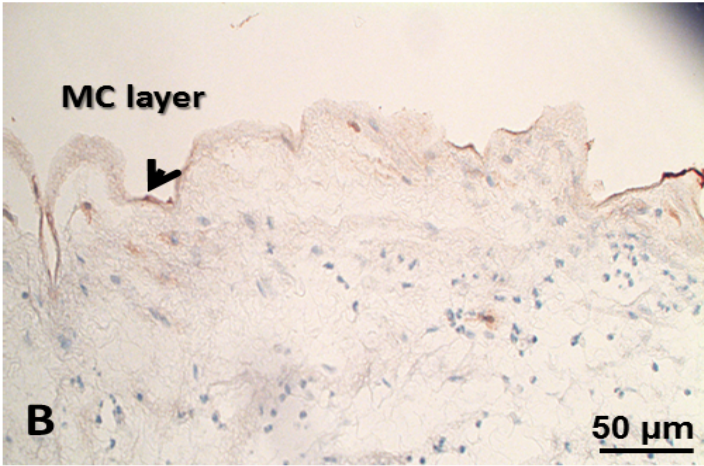
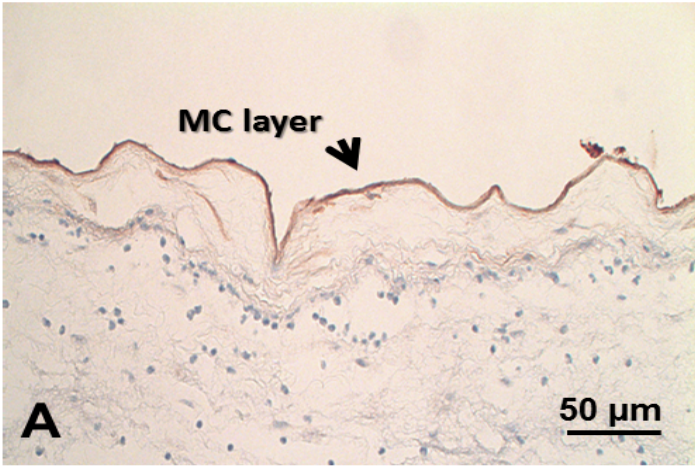
(involved for dissemination of tumor cells in carcinomatosis)

The change of mesothelial cell layer morphology in *ovarian carcinomatosis*

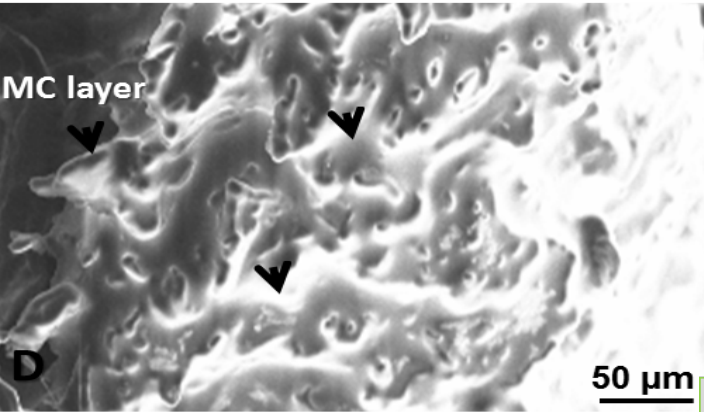
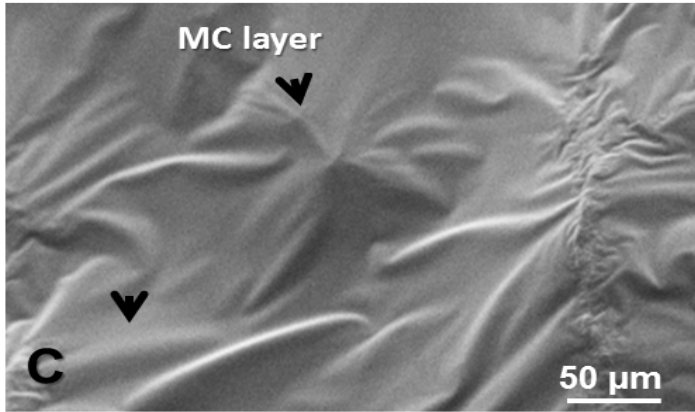
Non Invasive peritoneum

Invasive peritoneum

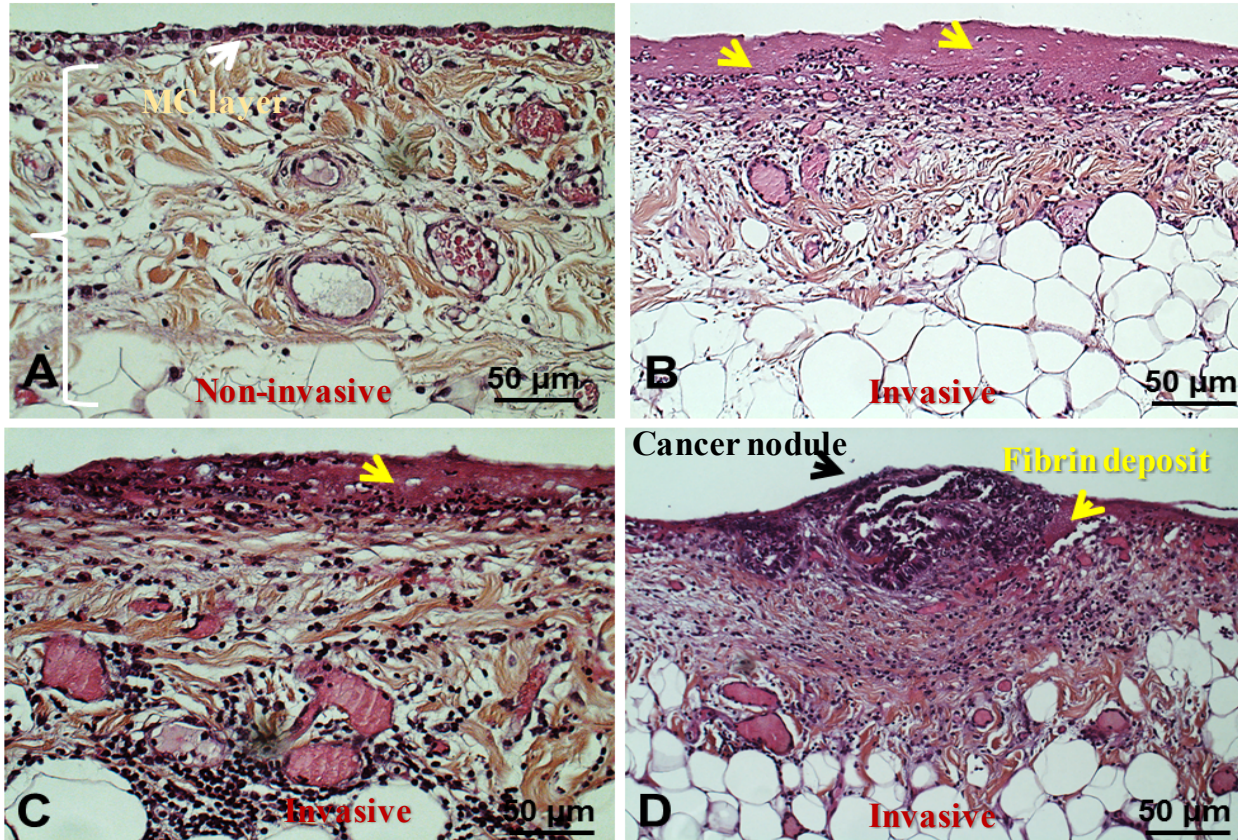
E-cadherin
Immunohistochemistry



Scanning
electron microscopy

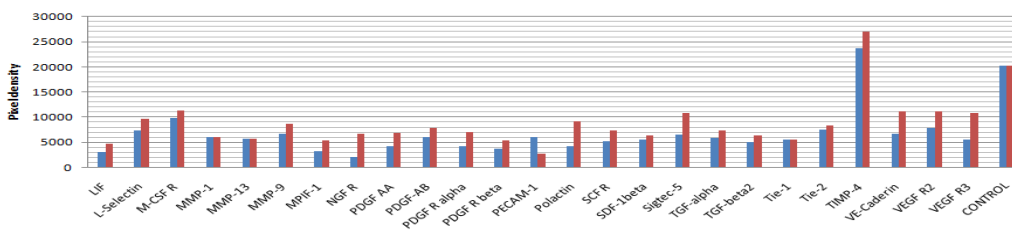
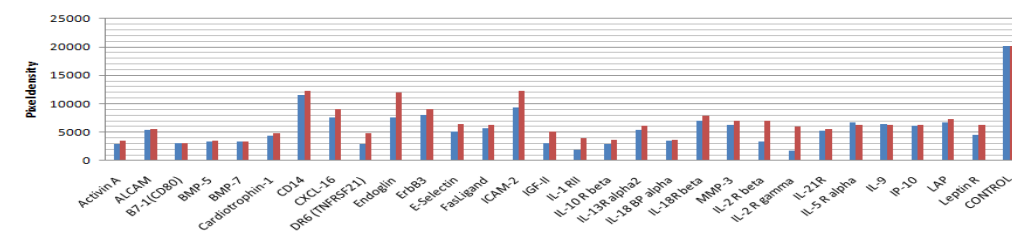
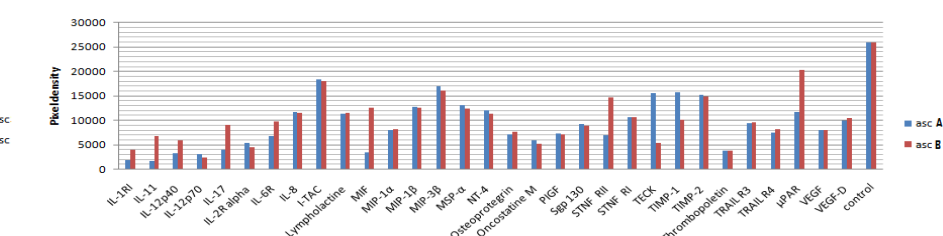
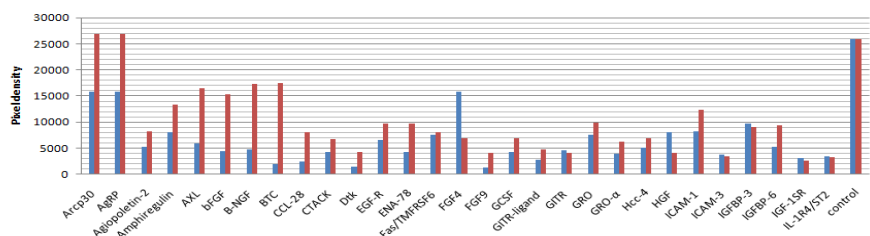
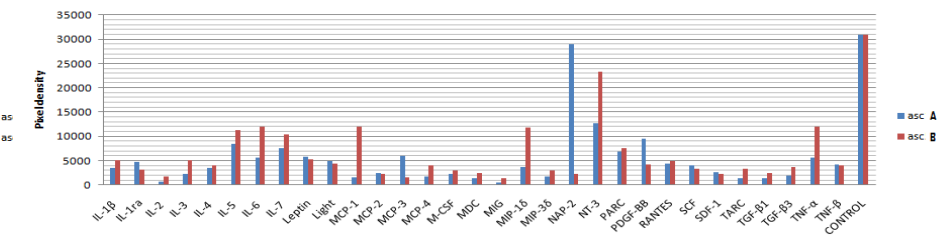
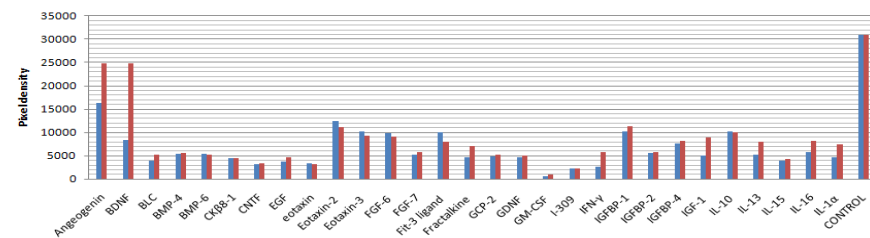


In situ anatomo-pathological study of peritoneal wall stained with hematoxylin and eosin



- **Fibrin deposits as well as cancer nodules found only in invasive part of peritoneal membrane**

Peritoneal fluid contains Chemokines, Cytokines, interleukins and growth factors

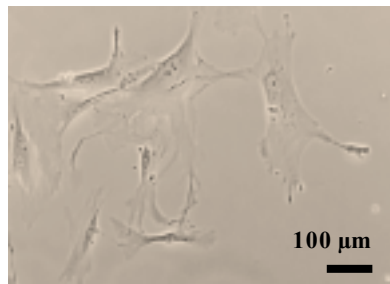


Involved in:

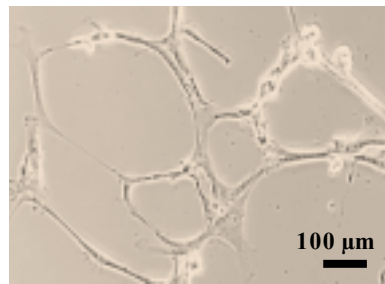
- Cancer cell growth
- Cancer cell progression
- Angiogenic stimulation
- Lymphangiogenic stimulation
- Mesothelial cell activation
- Immune cell activation/ inhibition
- Cell adherence
- Membrane permeabilisation

Peritoneal fluid from ovarian carcinomatosis modified mesothelial cell behavior *in vitro*

1- Modification of mesothelial cell architecture in vitro

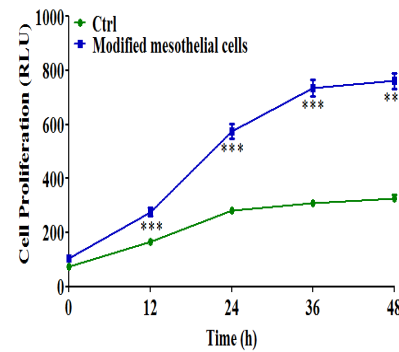


Mesothelial cells (-) ascite
Epithelial shape

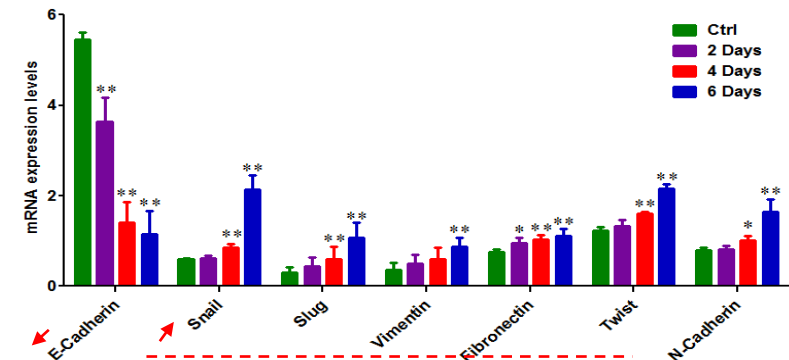


Mesothelial cells (+) ascite
Mesenchymal shape

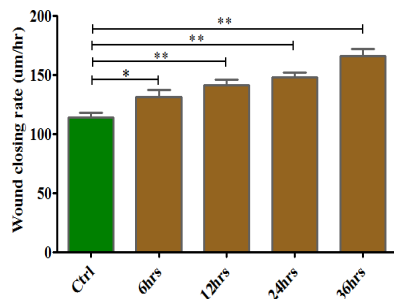
2- Real time Cell proliferation



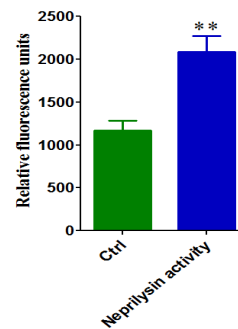
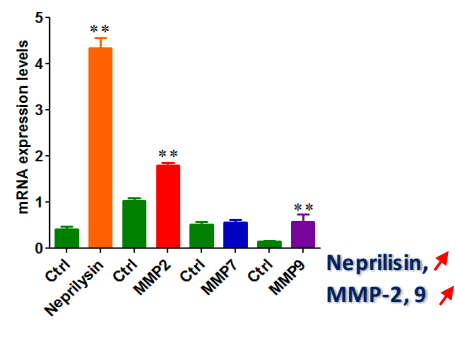
3- EMT markers acquisition (Q-PCR)



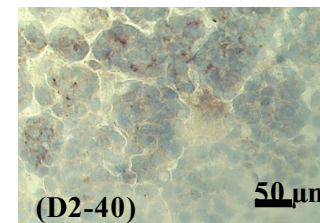
4- Cell migration (WH)



5- Proteolytic expression & activity (Q-PCR)

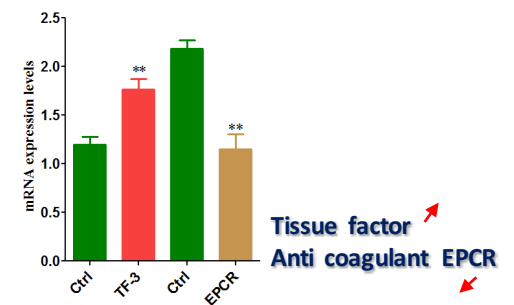


6- Mesothelial cell detachment



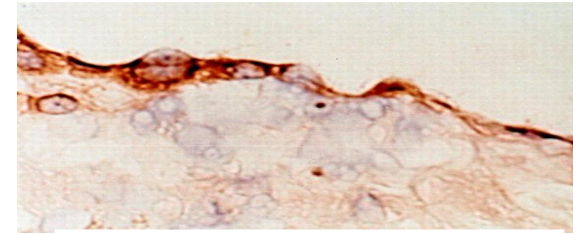
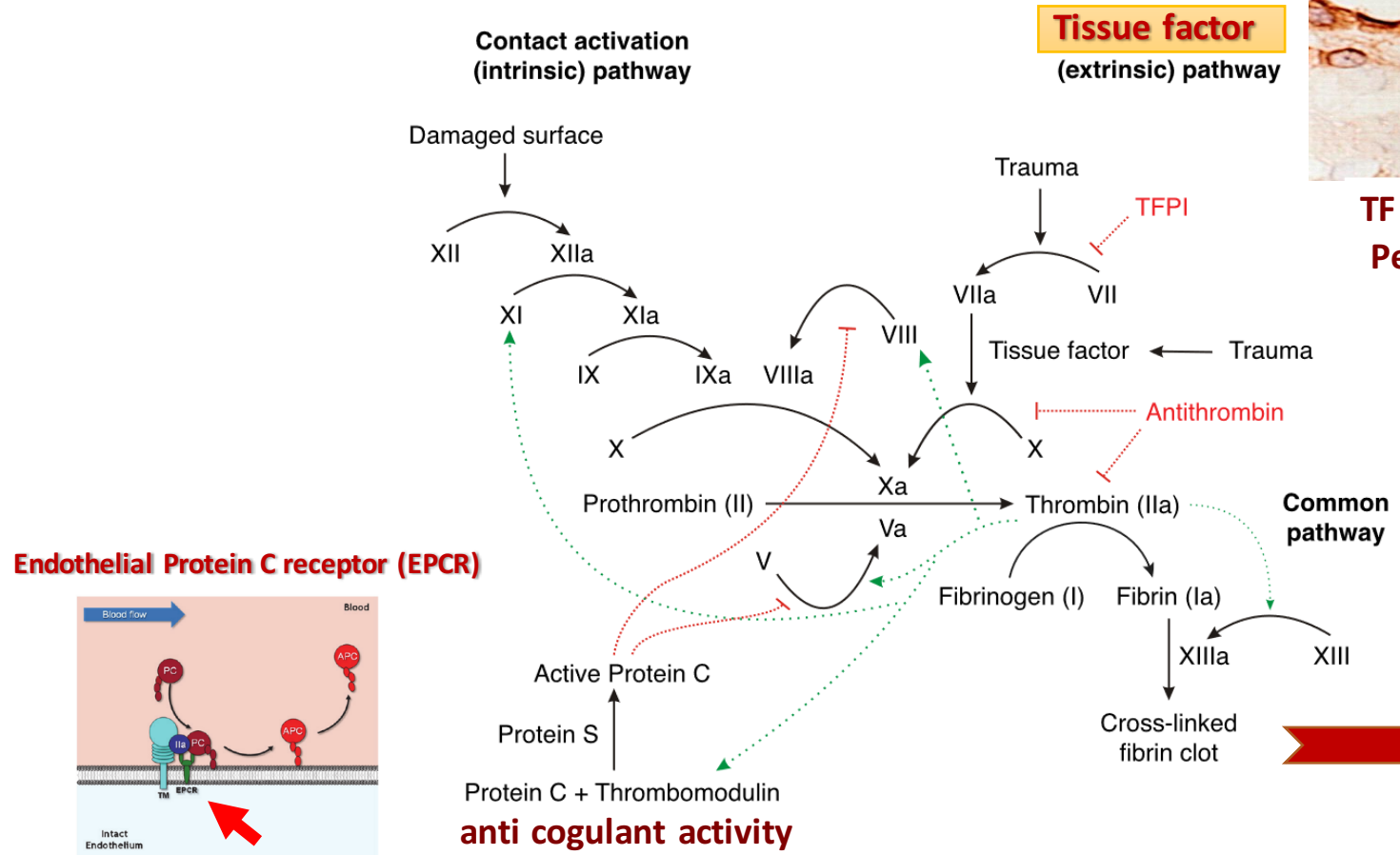
Carcinomatosis cancer cell cluster

7- Procoagulant Factors (Q-PCR)



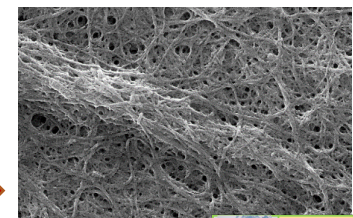
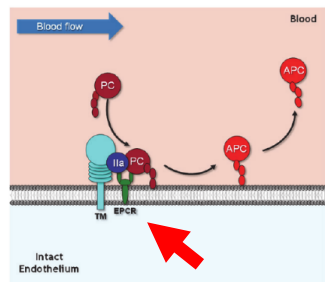
Decrease of EPCR, on meso. Cells down regulate anti-cogulant activity

Increase of Tissue Factor up regulate procoagulant activity



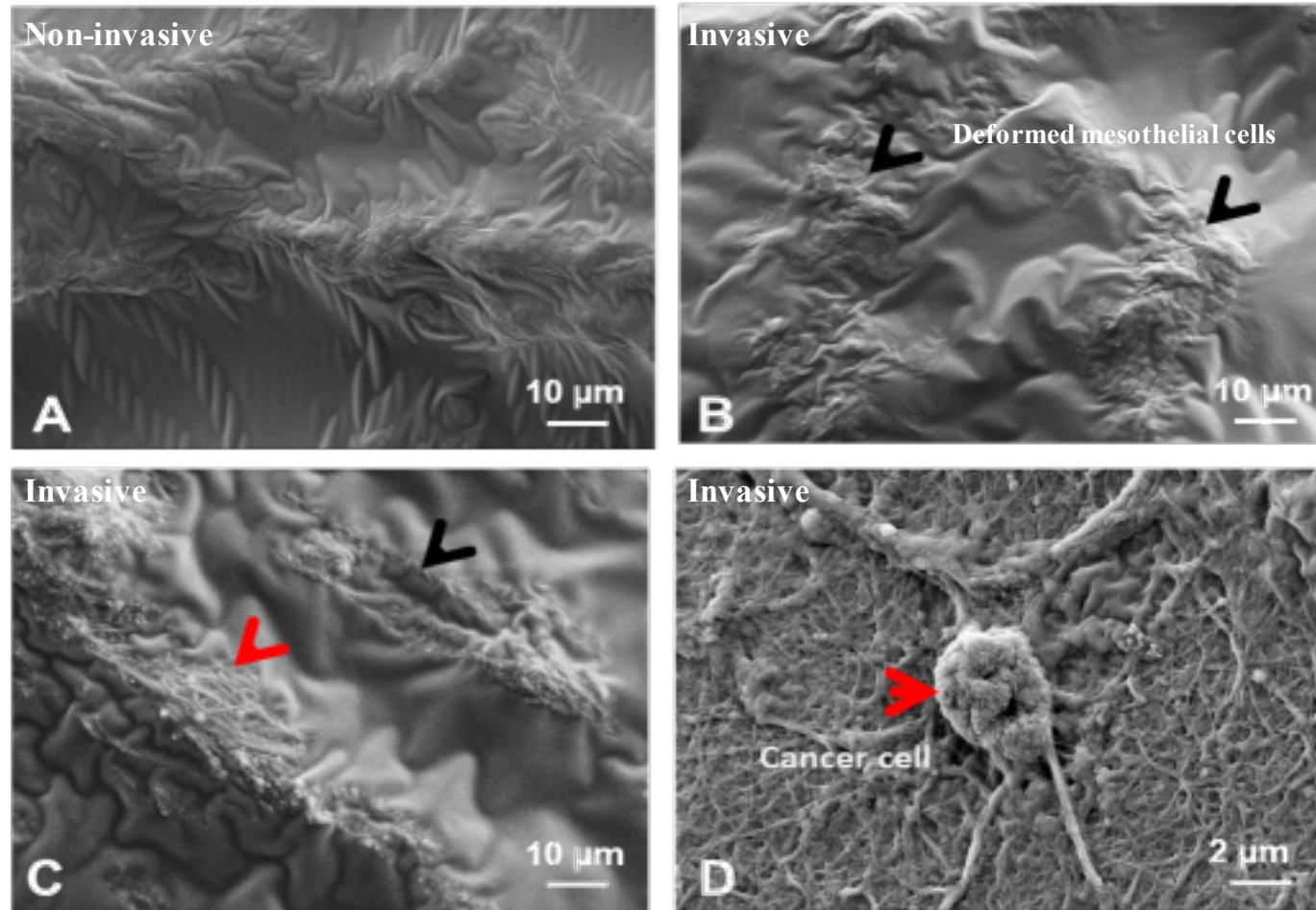
TF immunoreactivity on the Peritoneal mesothelial cell

Endothelial Protein C receptor (EPCR)



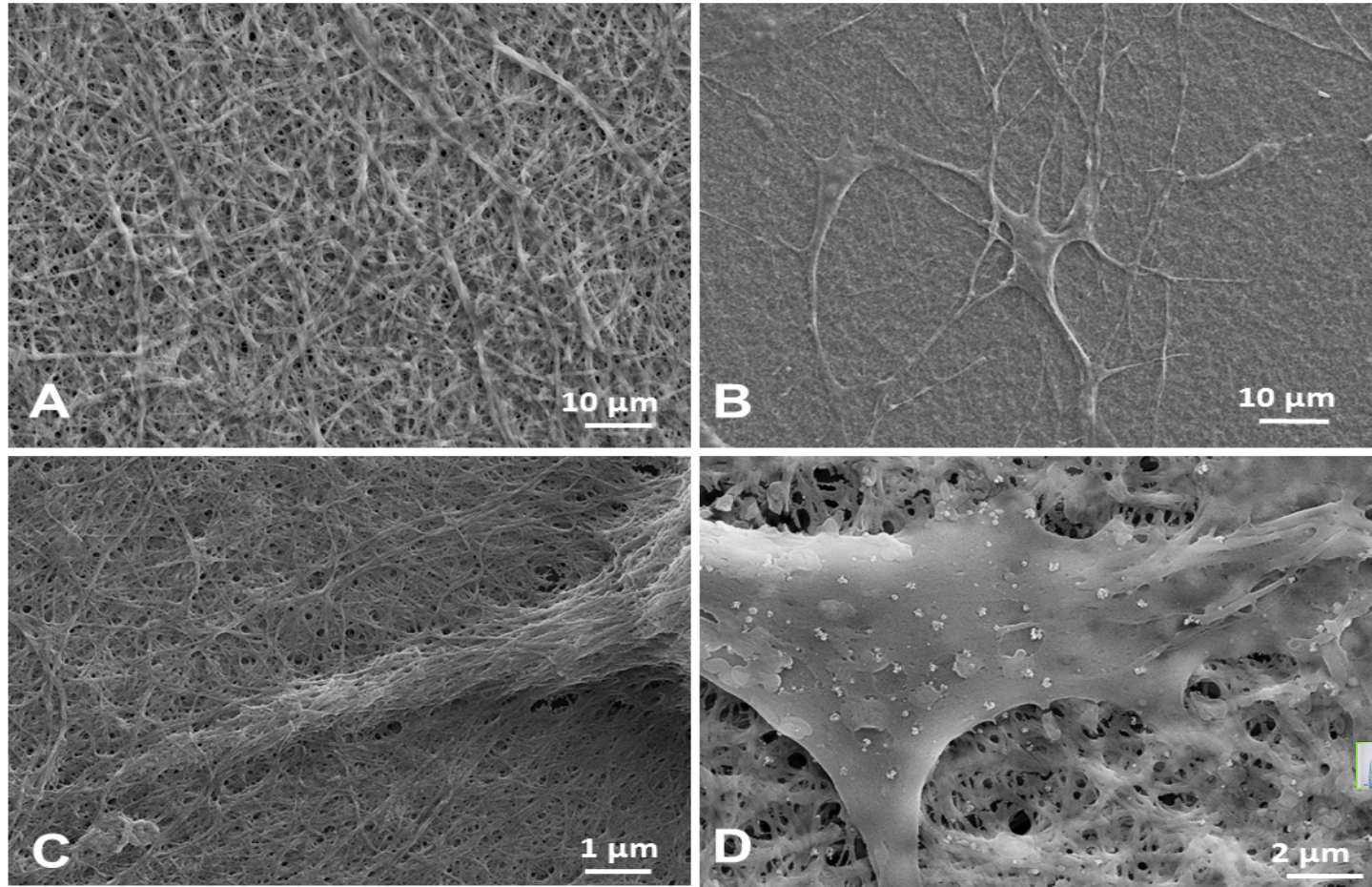
Fibrin

In situ scanning electron microscopic study of peritoneal wall



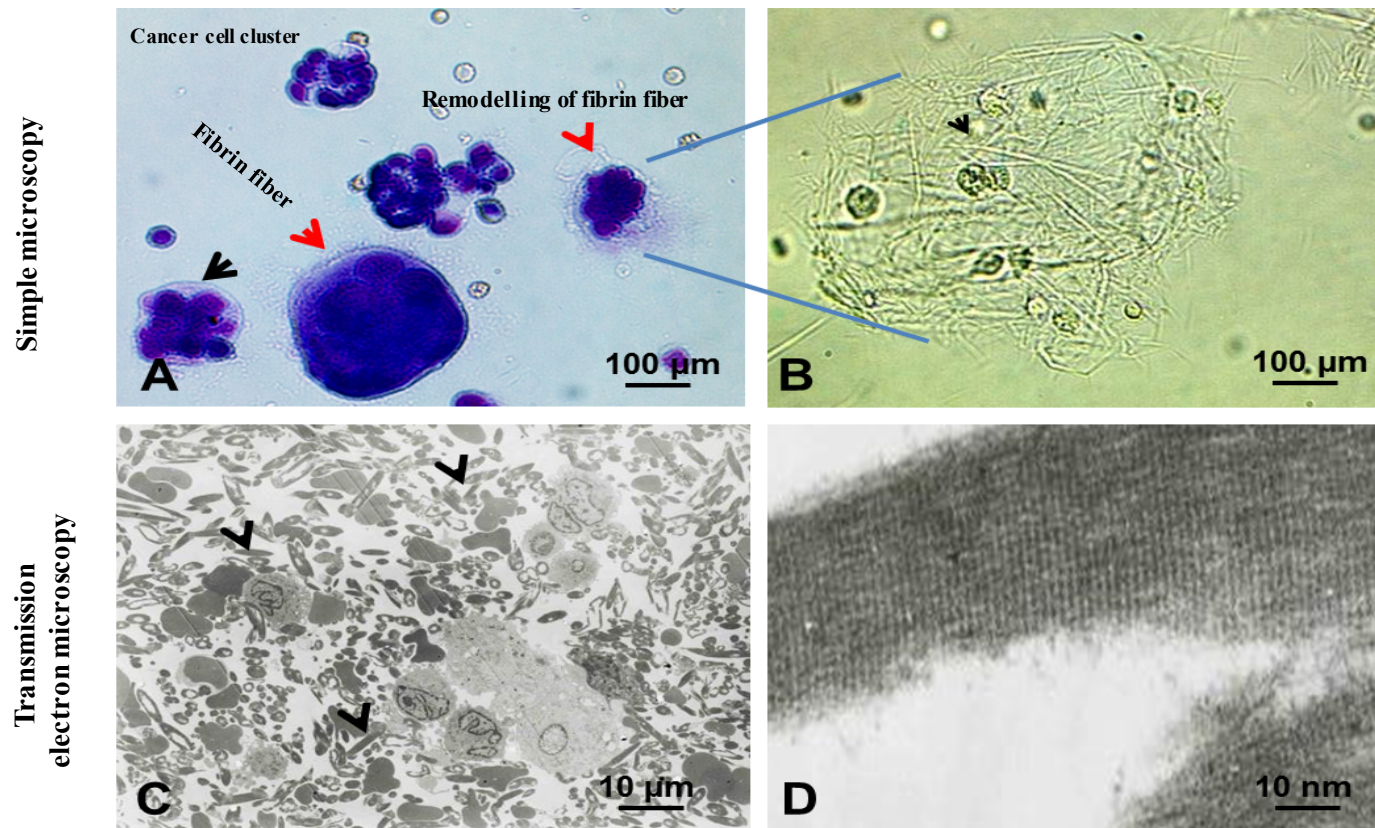
➤ **These results show stages of cancer nodule formation on peritoneal surface**

In vitro study of cancer cell interaction with fibrin clot



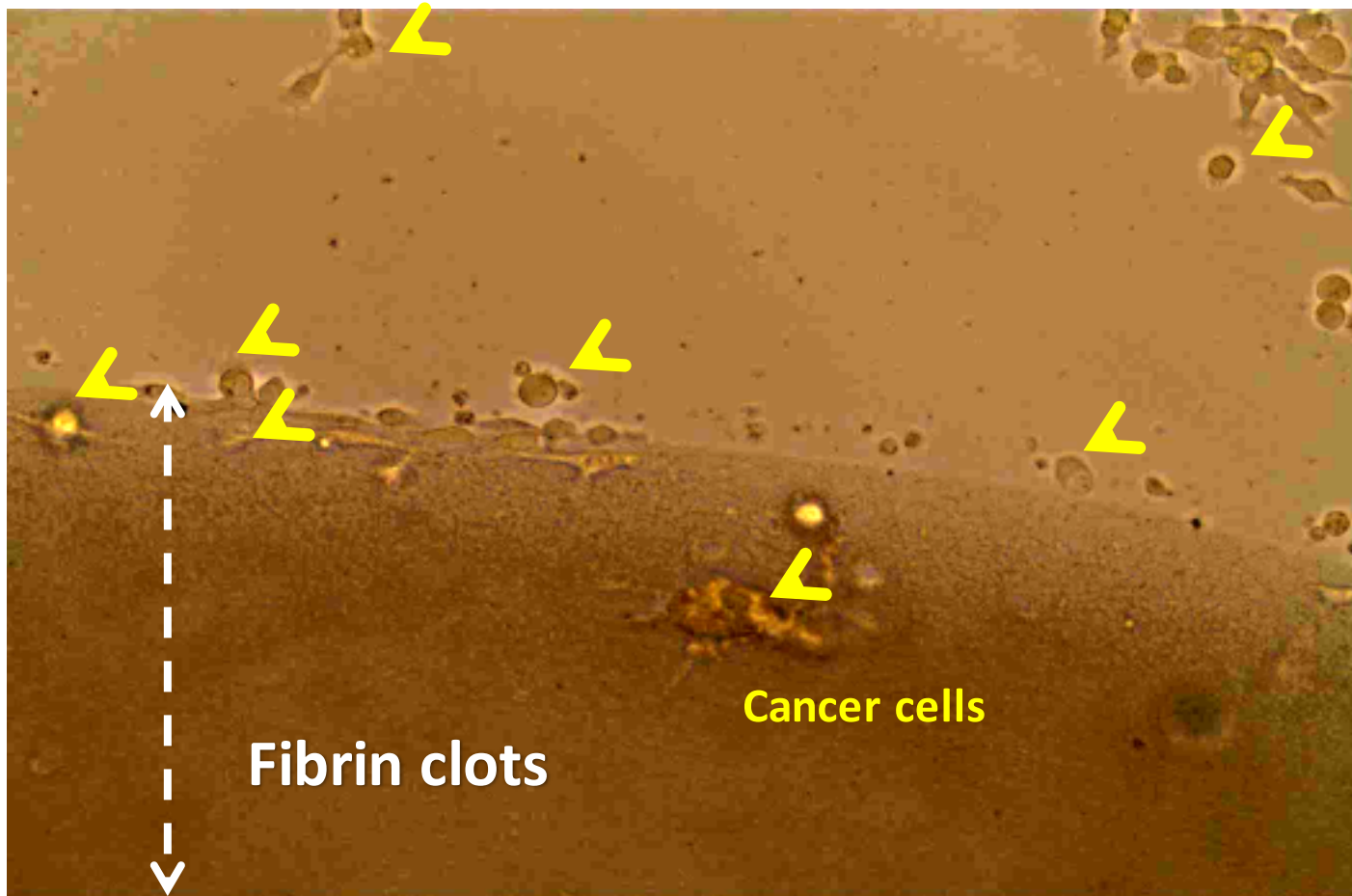
- **These results suggest that fibrin facilitates cancer cell entrapment on peritoneal surface to form nodules**

cancer cell cluster associated with fibrin fiber (in situ)

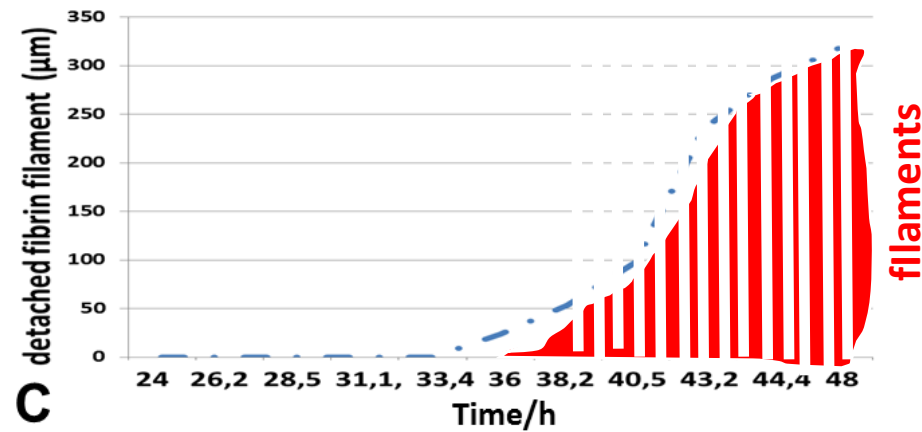
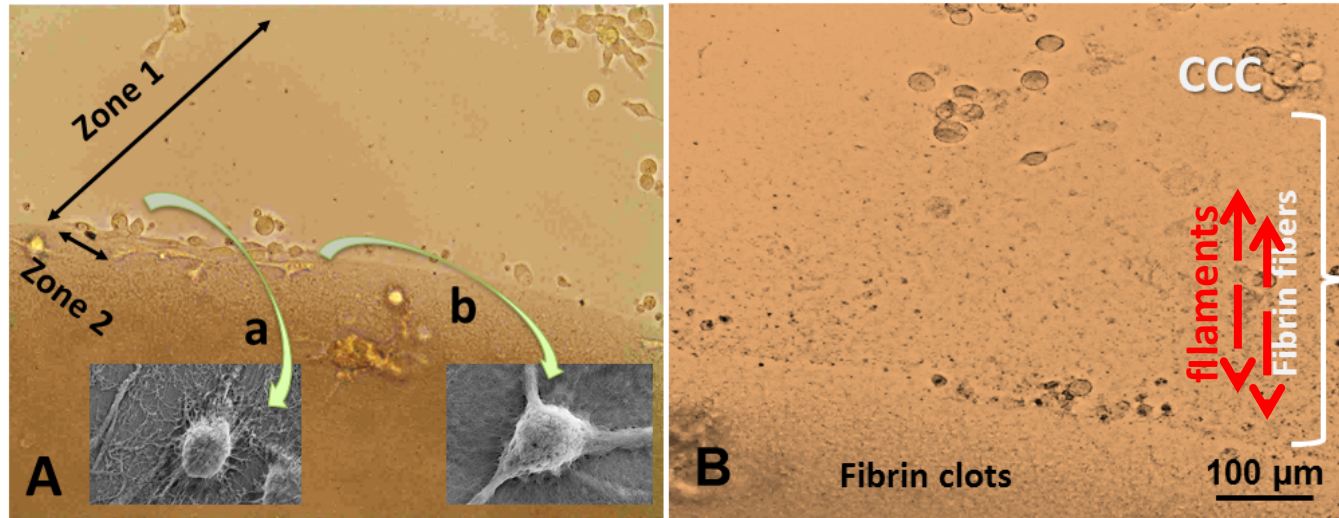


- These results suggest that fibrin can be a support for the cancer cell cluster integrities

Interaction of cancer cells with fibrin clot by Microcinematography

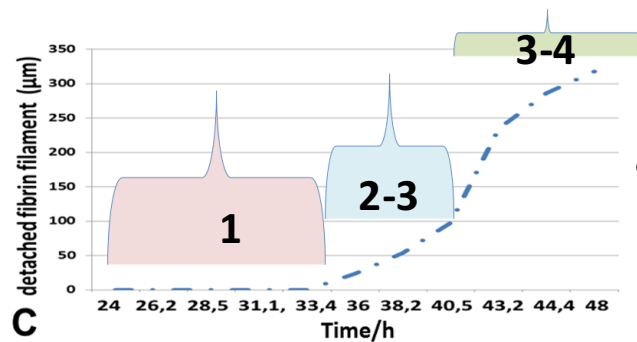


Cancer cell-fibrin clot interaction *in vitro*

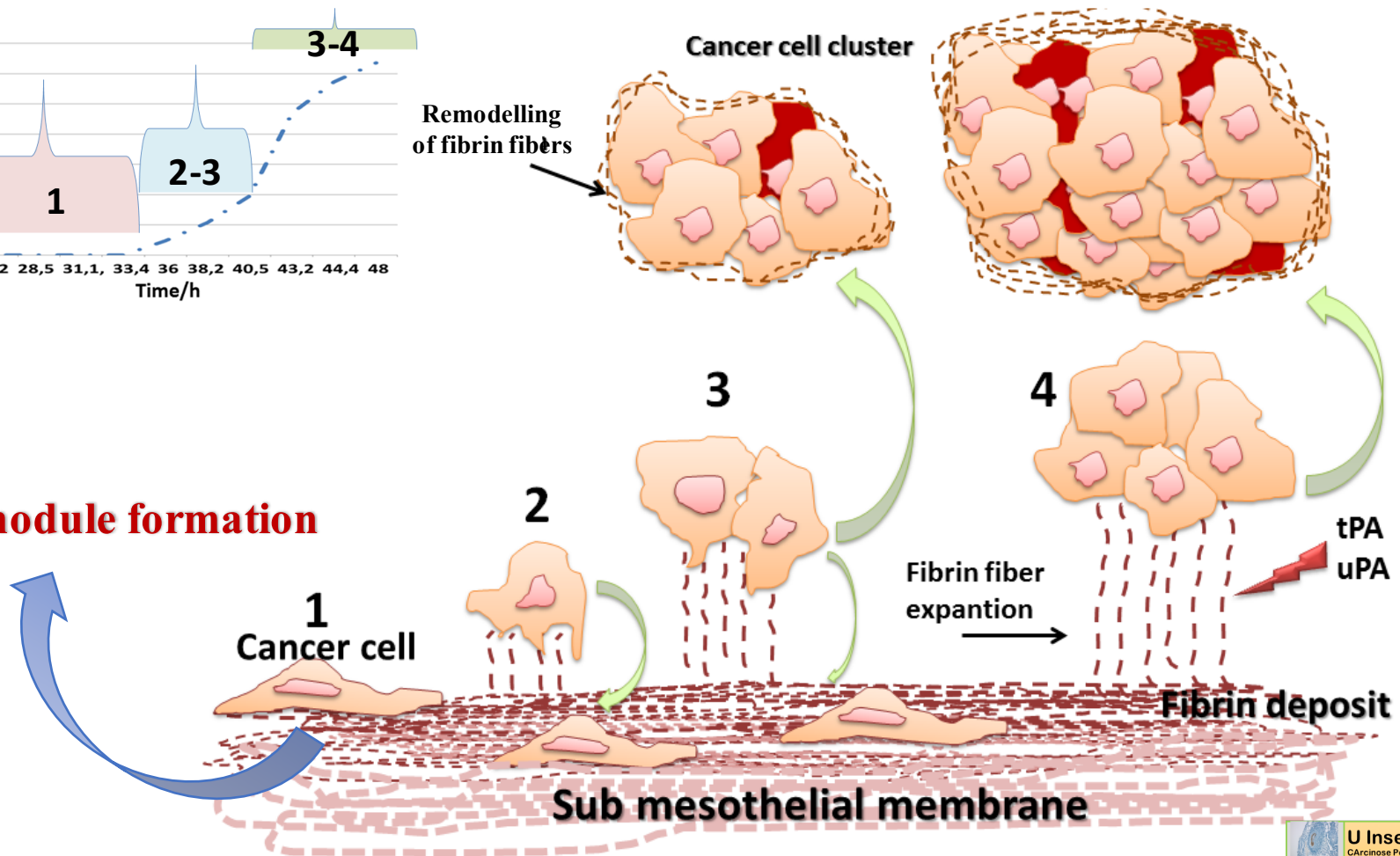


Kinetic of fibrin filaments formation

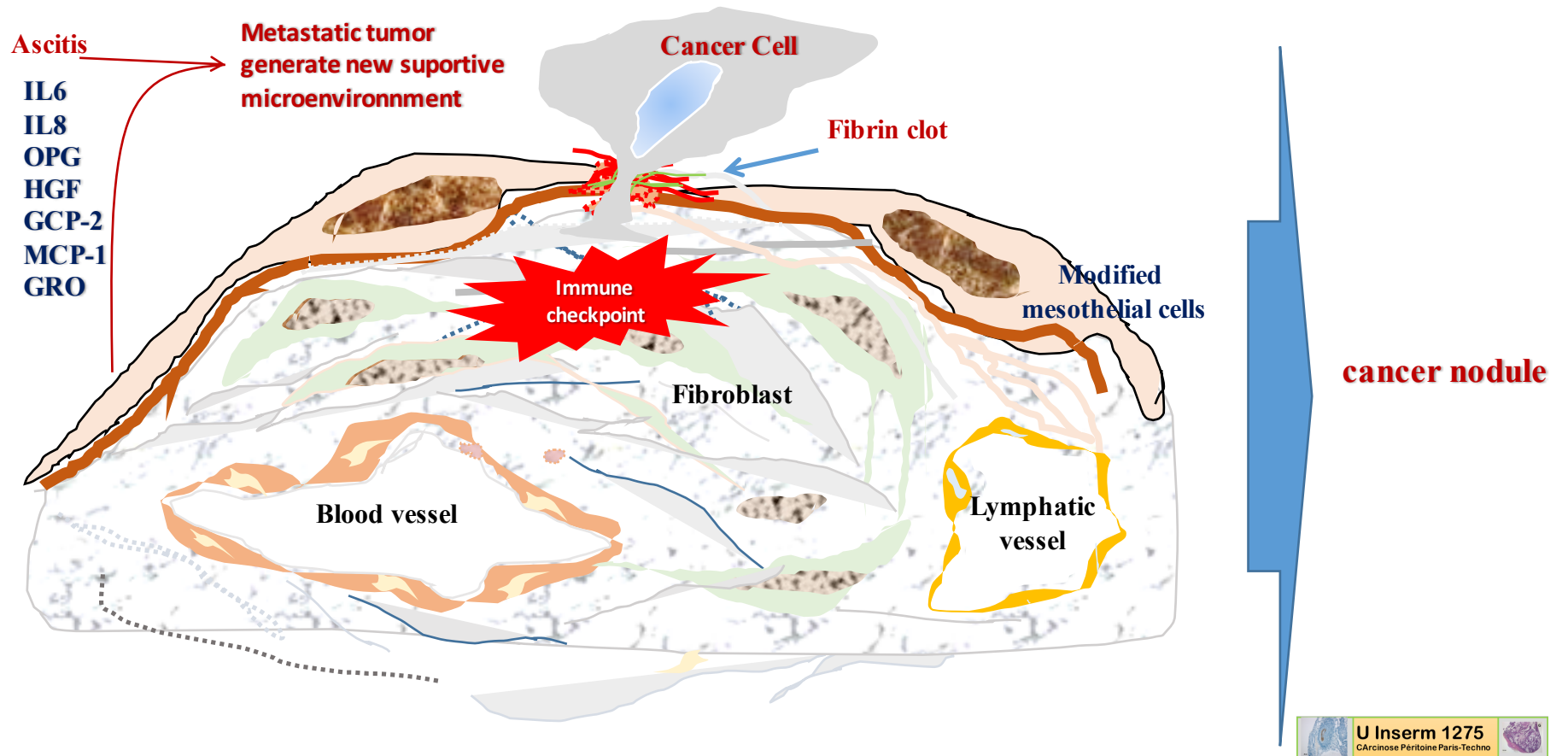
Working model of cancer cell clusters and cancer nodule formation On the peritoneum fibrin deposit



Solid nodule formation



Working model of cancer nodule formation on peritoneal surface



Conclusion

Important role of **fibrin network** on the peritoneal surface

- 1- Micro environment modification of peritoneal mesothelial cells induces an hypercoagulable state responsible for fibrin formation on the peritoneum surface
- 2- Cancer cells bind to fibrin deposits and then penetrate into the peritoneum
- 3- Formation of fibrin filaments that detach from fibrin surface , allowing cancer cells to go /to stay into the peritoneal fluid, where they formed cancer cell cluster



Fibrin deposit on the peritoneal surface serve as a niche for cancer expansion

