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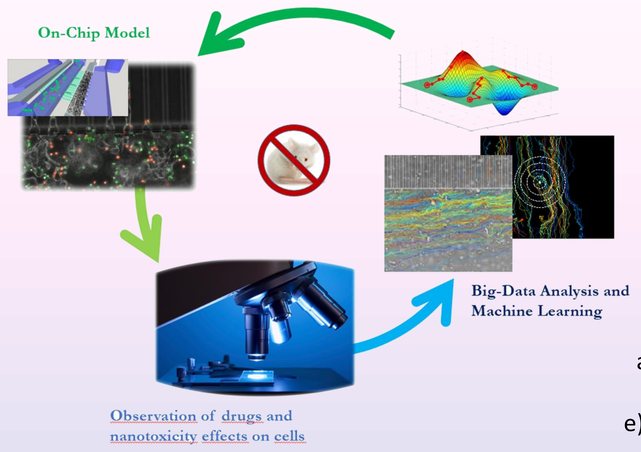


Integrated OOC approach to immuno-oncology: image analysis and microfluidic assays for anti-cancer and immunomodulatory drug evaluation

A. De Ninno[a], F. Bertani[a], A. Gerardino[a], F. Mattei[b], V. Lucarini[b], G. Schiavoni[b], S. Parlato[b], L. Gabriele[b], R. Molfetta[f] R. Paolini[f], E. Martinelli[c], A. Mencattini[c], D. Di Giuseppe[c], C. Di Natale[c], G. Kroemer[d], E. Vacchelli[d], A. Rainer[e], S. Giannitelli[e], and L. Businaro[a]

a) CNR-Institute for Photonics and Nanotechnologies- Via Cineto Romano, 42 00156 Rome, Italy // *b)* Istituto Superiore di Sanità Viale Regina Elena, 299 00161, Rome, Italy
c) Dept. Electronic Engineering, University of Rome Tor Vergata, Rome, Italy // d) Metabolomics and Cell Biology Platforms, Gustave Roussy Cancer Campus; Villejuif, France
e) Università Campus Bio-Medico di Roma - via Alvaro del Portillo, 21 - 00128 Rome // f) Department of Molecular Medicine "Sapienza" University of Rome, 00161, Rome, Italy
e-mail: luca.businaro@cnr.it, adeledeninno@gmail.com, francesca.bertani@ifn.cnr.it

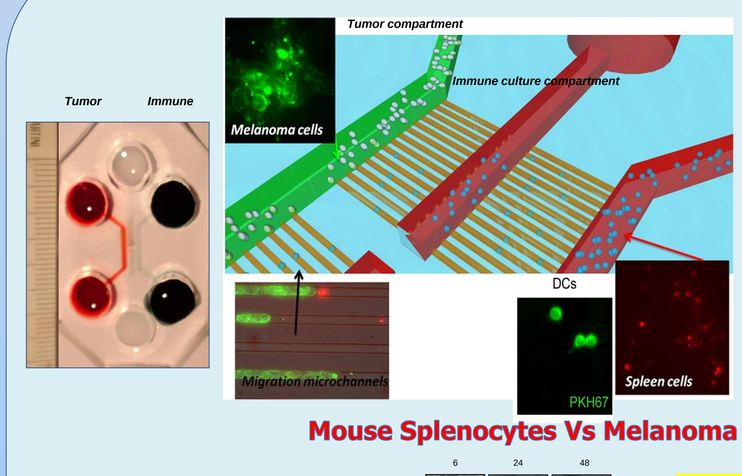
Introduction

The immune system is a striking example of an integrated information system, engaged in coordinated host-protective activities. Organs-on-chip approach (OOC)models allow the direct simultaneous observation of hundreds of different cells, moving, interacting and responding to signals coming from the microenvironment nearby, that give access to a number of parameters describing the system that must be properly measured and elaborated. Combining microfluidics with the ability of cellular imaging enable to collect quantitative data from complex biological systems at a single-cell level.
Reconstitution of the immune-cancer system on chip opens a new window to live observation of the host immune response with or without drug treatments, making OOC a cornerstone for dissecting complex biological phenomena and pre-clinical testing of drugs. Smart implementation of image processing algorithms enable to quantify the simultaneous long-time interactions of huge number of cells and accurately solve the practical problems encountered in multi-cell type context.

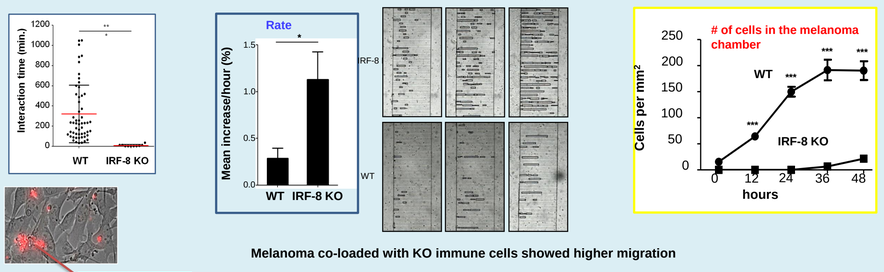
Immuno-Oncology chip 1: 2D microfluidic cocultures and observation of cancer–immune cell motility and interactions

The Starting Idea: What happens if we put the whole pool of immune cells on chip?

Murine Immunocompetent Vs Immunodeficient model



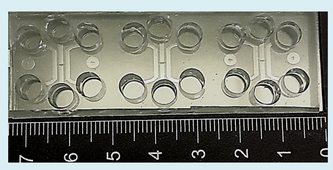
Mouse Splenocytes Vs Melanoma

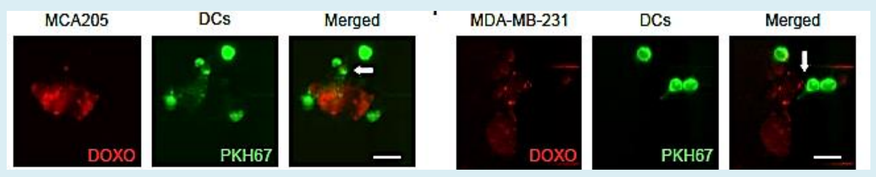


Melanoma co-loaded with KO immune cells showed higher migration

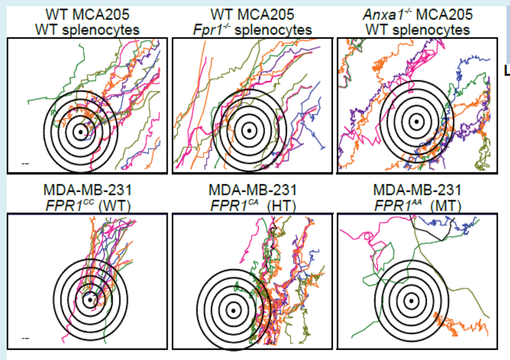
E. Agliari et al.Scientific Reports 2014
F. Mattei et al. Journal of Immunotoxicology 2014
L. Businaro et al .Lab Chip 2013

Chemotherapy – induced anticancer immune response
How dying cancer cell get noticed

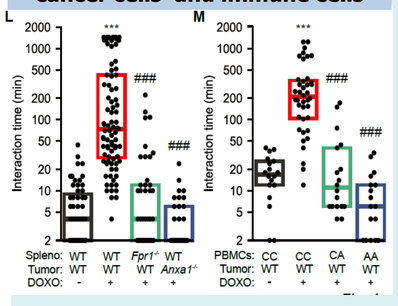




Besides killing tumor cells directly, some chemotherapies, such as anthracyclines, also activate the immune system to kill tumors.



Interaction times between dying cancer cells and immune cells



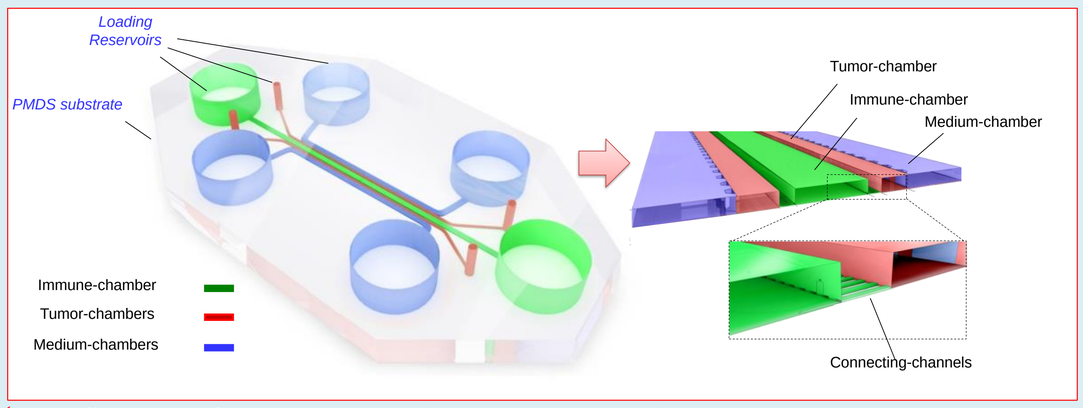
Experiments performed on chip confirmed that FPR1 and its ligand, annexin-1, promoted stable interactions between dying cancer cells and human or murine leukocytes.

Quantification of tracking patterns and approaching of leucocytes against apoptotic tumor cell

E. Vacchelli et al, Chemotherapy-induced antitumor immunity requires formyl peptide receptor. **Science** (2015)

Immuno-Oncology chip 2: 3D cancer–immune microenvironments

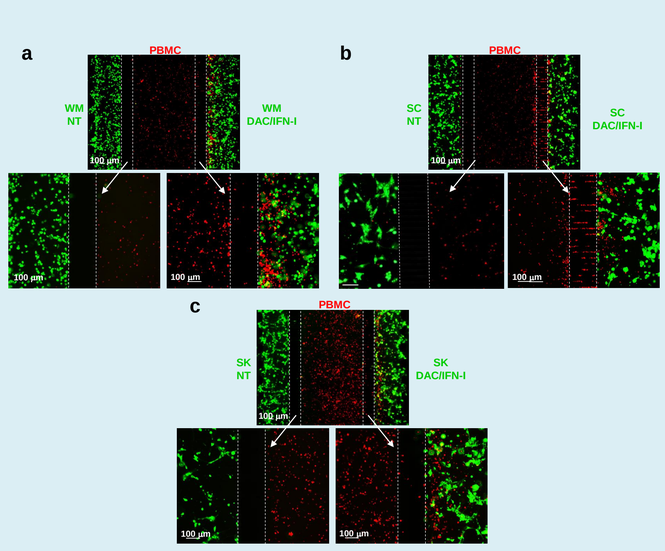
Hydrogel-based microchannel platform

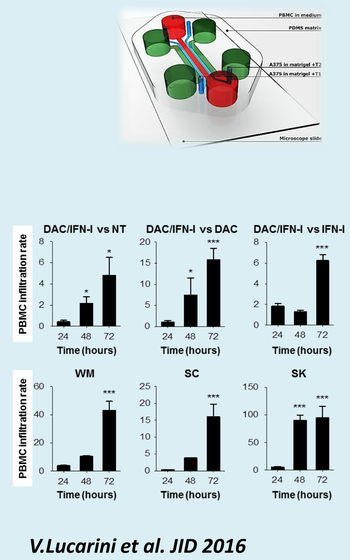


- ✓Microfluidic platform reproduces interconnected 3D immune system and tumor microenvironments with geometrical confinement and biochemical stimuli
- ✓Suitable to study immune-tumor cell interactions by high-resolution time-lapse imaging
- ✓Microfluidic models may enable studying antitumor efficacy of immunotherapeutic treatments

S.Parlato et al. Scientific Reports 2017
V.Lucarini et al. JID 2016

Recruitment of leukocyte exposed to competitive biochemical stimuli



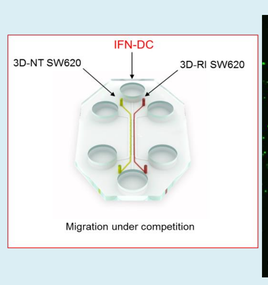


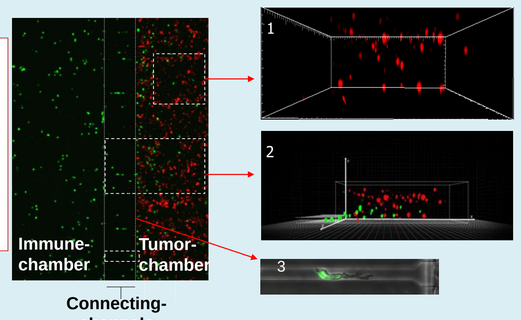
V.Lucarini et al. JID 2016

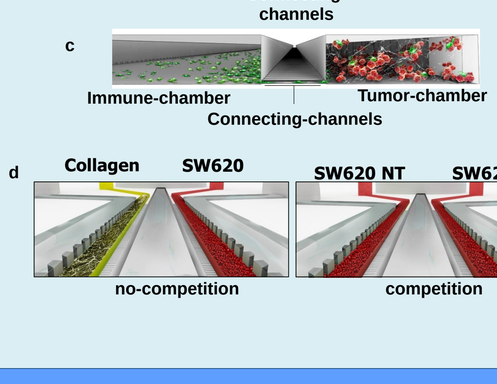
Modulating the Immune response :Testing Anti-cancer and Immunotherapy strategies combination on chip

Immunotherapy relies on the use of therapeutic agents that are able to potentiate immune effector mechanisms also inside the tumor microenvironment (TME). DCs have the specific role of recognizing cancer cells, taking up tumor antigens (Ags) and then migrating to lymph nodes for Ag (cross)-presentation to naïve T cells. Interferon-α-conditioned DCs (IFN-DCs) exhibit marked phagocytic activity and the special ability of inducing Ag-specific T-cell response.

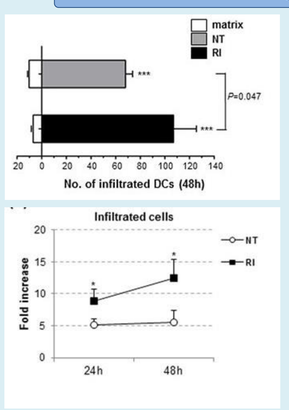
IFN-DC migration toward SW620 colon cancer cells exposed to combined treatment with IFN-α and romidepsin
Within 3D-RI tumor space IFN-DC move establishing contact with cancer cells and execute their effector function of taking-up Ag

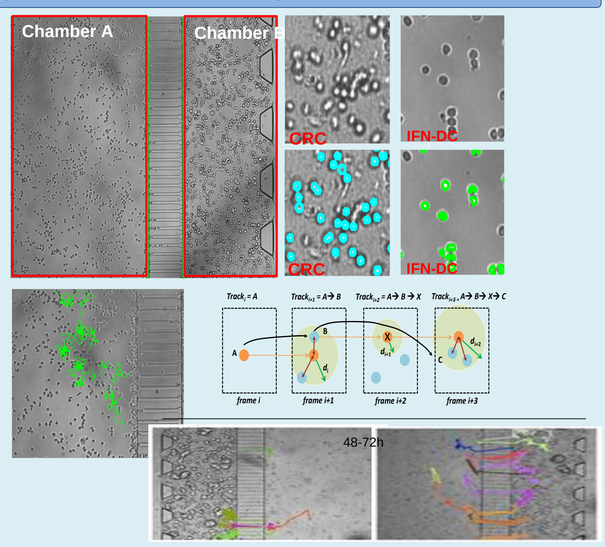




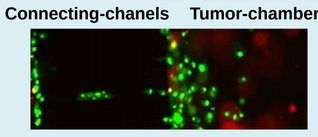


Automatic tracking algorithm of immune migration in 3D matrices

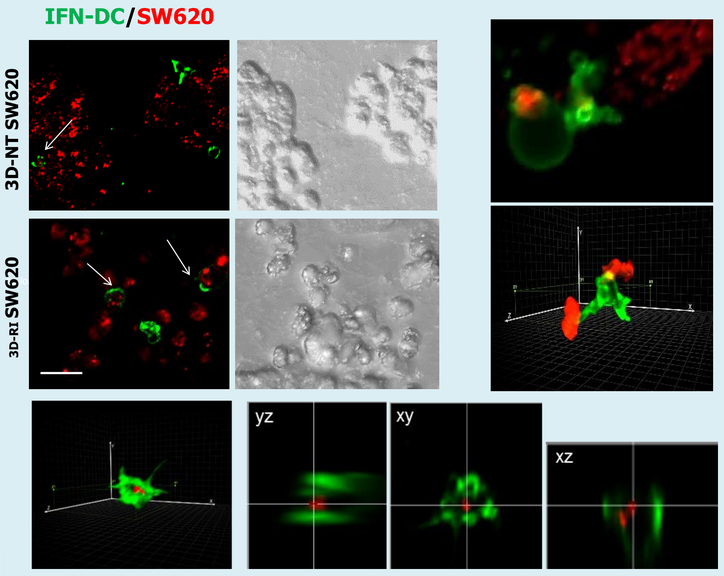




Connecting-chanels Tumor-chamber



Phagocytosis assay in 3D collagen



S.Parlato et al. Scientific Reports 2017

Testing combinatorial therapy to improve therapeutic efficacy