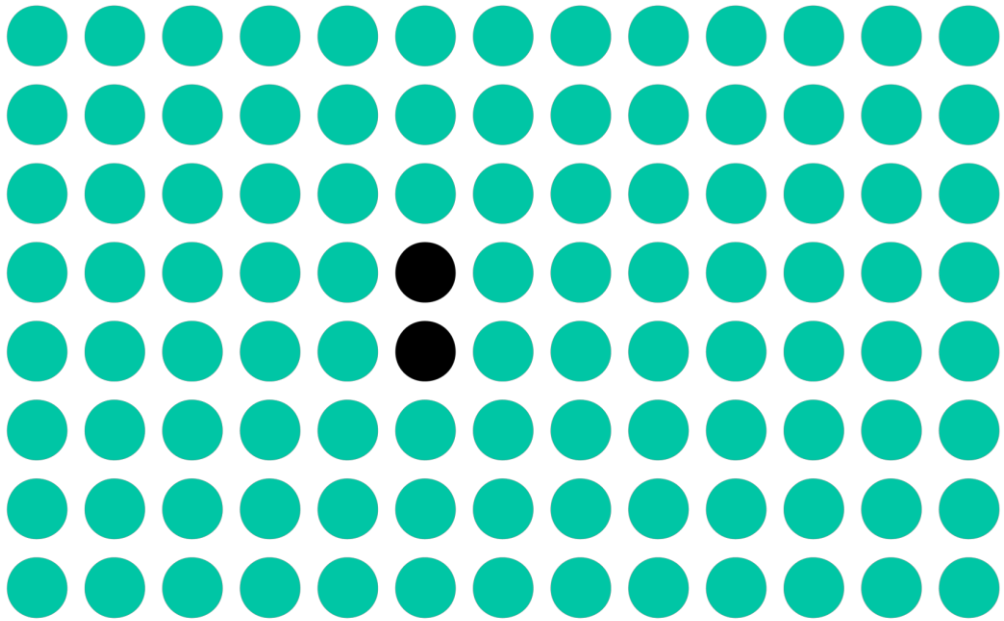
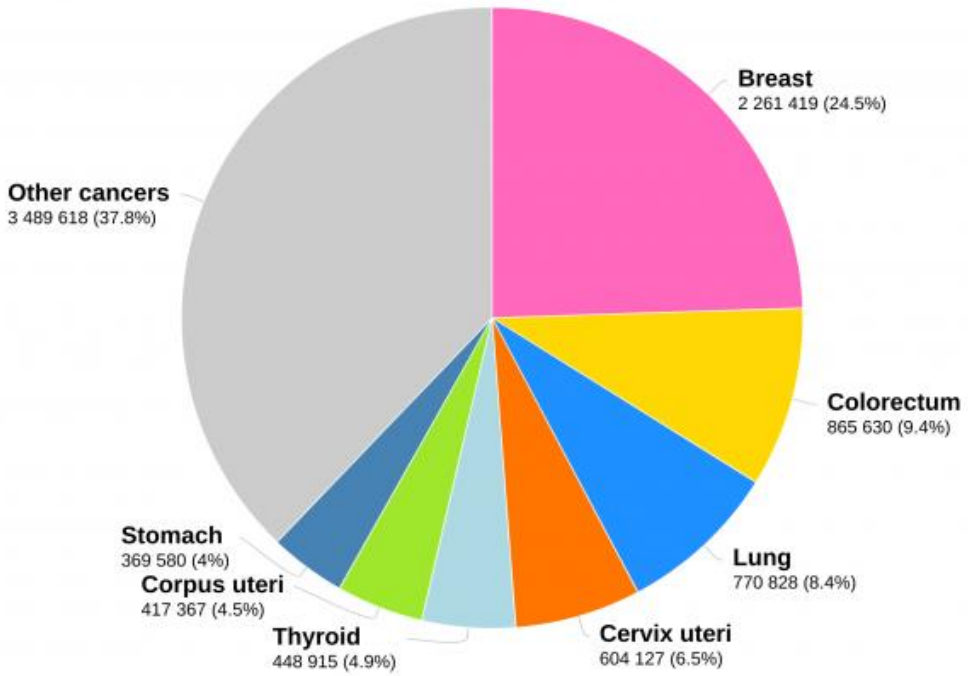
Instituto de Medicina Molecular | João Lobo Antunes



Sérgio Dias

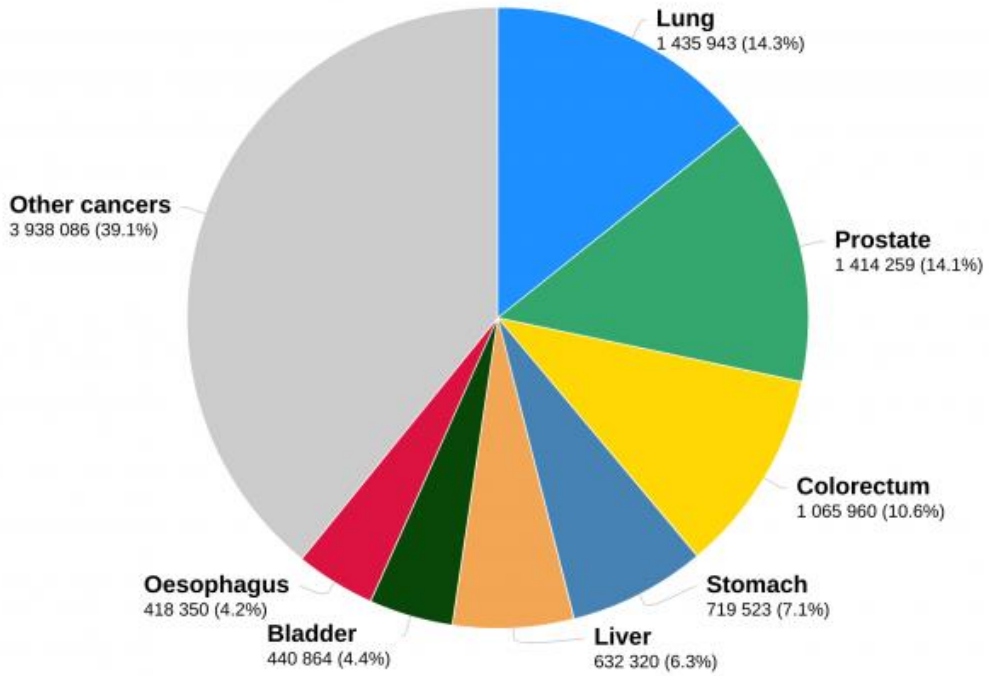
# Why should we study cancer?

Estimated number of new cases in 2020, worldwide, females, all ages




Total : 9 227 484

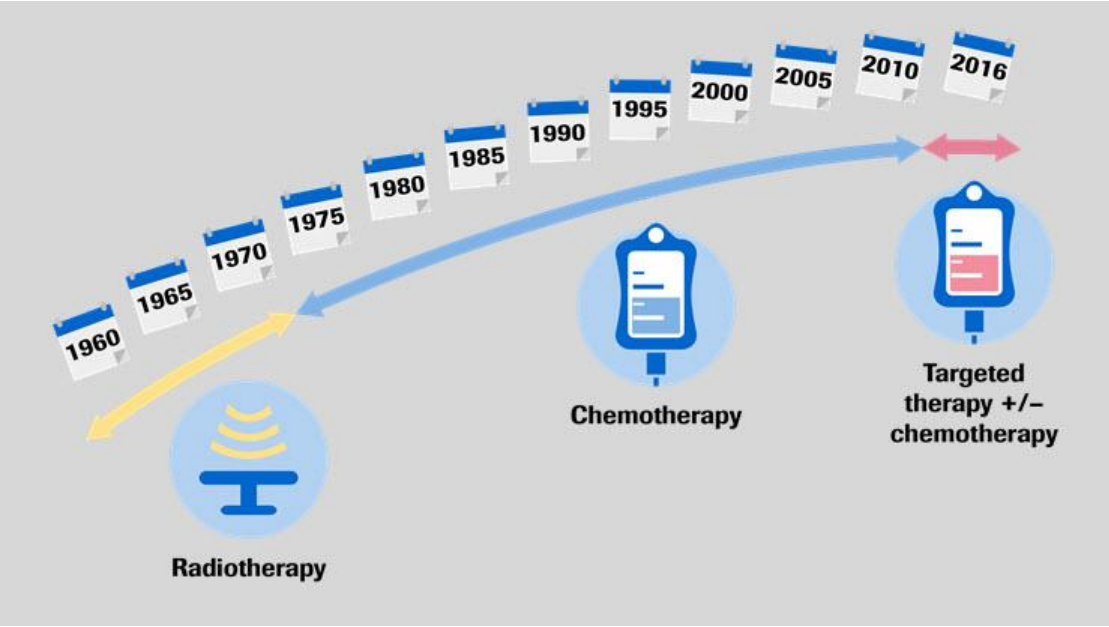
Estimated number of new cases in 2020, worldwide, males, all ages



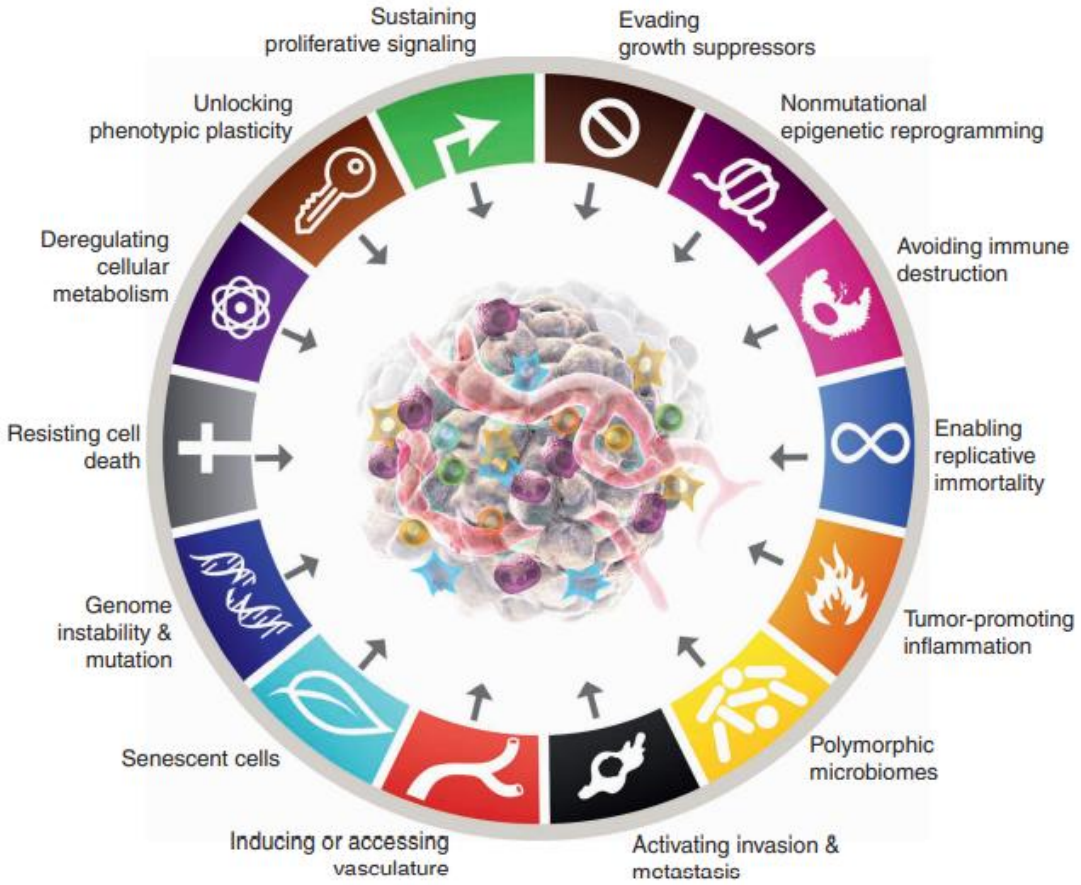

Total : 10 065 305

International Agency for Research on Cancer
World Health Organization

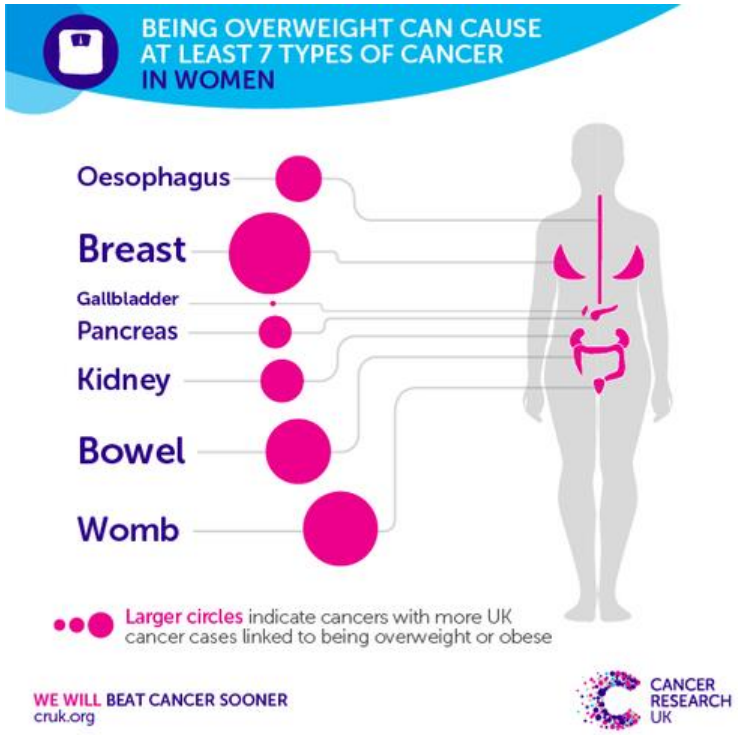
# Why should we study cancer?



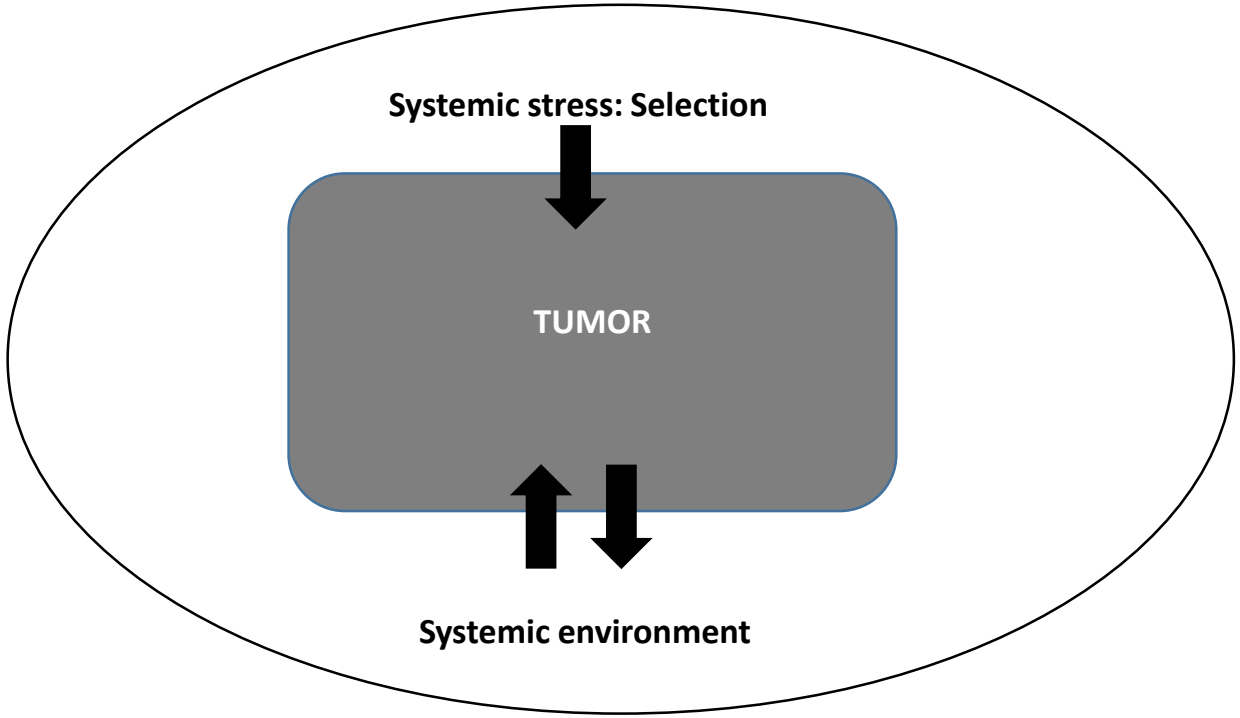
# Updated Hallmarks of cancer (2022)



# Deregulated cellular metabolism: Obesity and cancer incidence



# Can a systemic metabolic stress act as a selective pressure in cancer?



# LDL-cholesterol levels predict BC progression

Rodrigues dos Santos *et al. BMC Cancer* 2014, **14**:132
http://www.biomedcentral.com/1471-2407/14/132

BMC Cancer

RESEARCH ARTICLE Open Access

## Plasma level of LDL-cholesterol at diagnosis is a predictor factor of breast tumor progression

Catarina Rodrigues dos Santos[1,2,5*], Isabel Fonseca[3,5], Sérgio Dias[4,5] and JC Mendes de Almeida[2,5]

**Abstract**

**Background:** Among women, breast cancer (BC) is the leading cancer and the most common cause of cancer-related death between 30 and 69 years. Although lifestyle and diet are considered to have a role in global BC incidence pattern, the specific influence of dyslipidemia in BC onset and progression is not yet completely understood.

**Methods:** Fasting lipid profile (total cholesterol, LDL-C, HDL-C, and triglycerides) was prospectively assessed in 244 women with BC who were enrolled according to pre-set inclusion criteria: diagnosis of non-hereditary invasive ductal carcinoma; selection for surgery as first treatment, and no history of treatment with lipid-lowering or anti-diabetic drugs in the previous year. Pathological and clinical follow-up data were recorded for further inclusion in the statistical analysis.

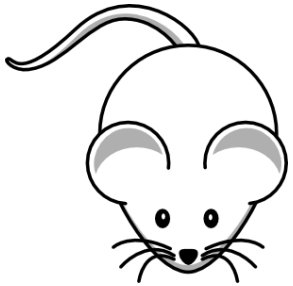
**Results:** Univariate associations show that BC patients with higher levels of LDL-C at diagnosis have tumors that are larger, with higher differentiation grade, higher proliferative rate (assessed by Ki67 immunostaining), are more frequently Her2-neu positive and are diagnosed in more advanced stages. Cox regression model for disease-free survival (DFS), adjusted to tumor T and N stages of TNM classification, and immunohistochemical subtypes, revealed that high LDL-C at diagnosis is associated with poor DFS. At 25 months of follow up, DFS is 12% higher in BC patients within the third LDL-C tertile compared to those in the first tertile.

**Conclusions:** This is a prospective study where LDL-C levels, at diagnosis, emerge as a prognostic factor; and this parameter can be useful in the identification and follow-up of high-risk groups. Our results further support a possible role for systemic cholesterol in BC progression and show that cholesterol metabolism may be an important therapeutic target in BC patients.

**Keywords:** LDL-cholesterol, Breast cancer, Tumor progression

# Experimental model to test how cholesterol may affect tumor growth and progression

Tumor cells



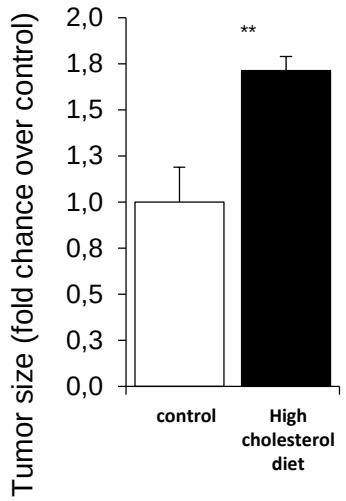
Normal diet

High fat diet

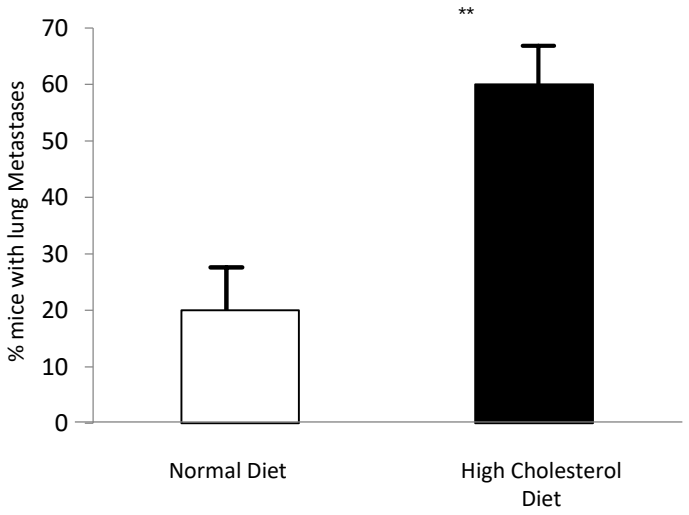
MEDES G, PADEN G, WEINHOUSE S.
**Cancer** Res. 1957 Feb;17(2):127-33.

Instituto de Medicina Molecular | João Lobo Antunes

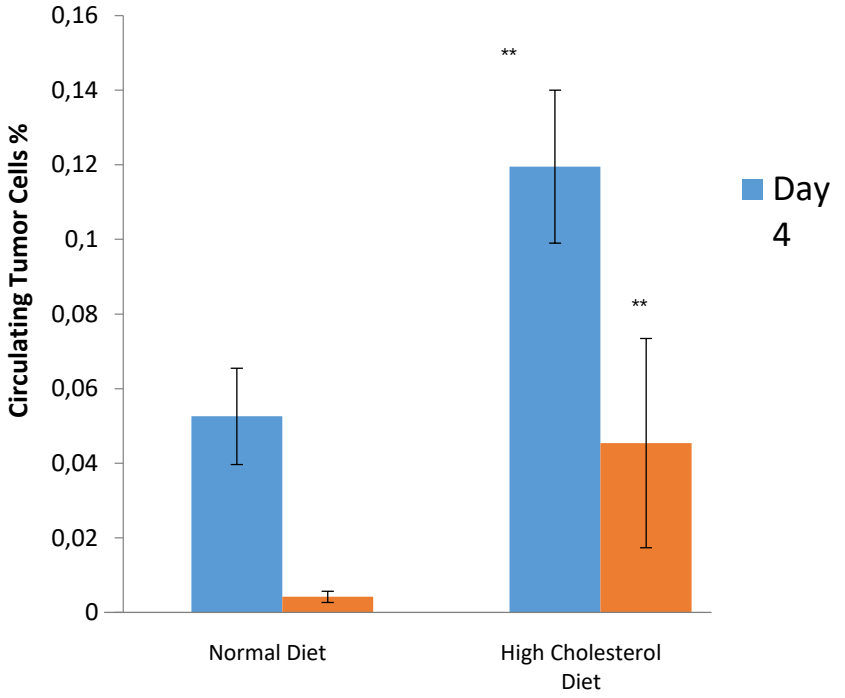
# High cholesterol diet mice show increased breast tumor growth



# High cholesterol diet mice show increased breast cancer derived lung metastases



# High cholesterol diet mice show increased circulating tumor cells



**What are the mechanisms?**

Cell extrinsic (systemic) effects

Cell intrinsic (direct) effects

# LDL cholesterol has direct effects on breast cancer cells

↑ Proliferation

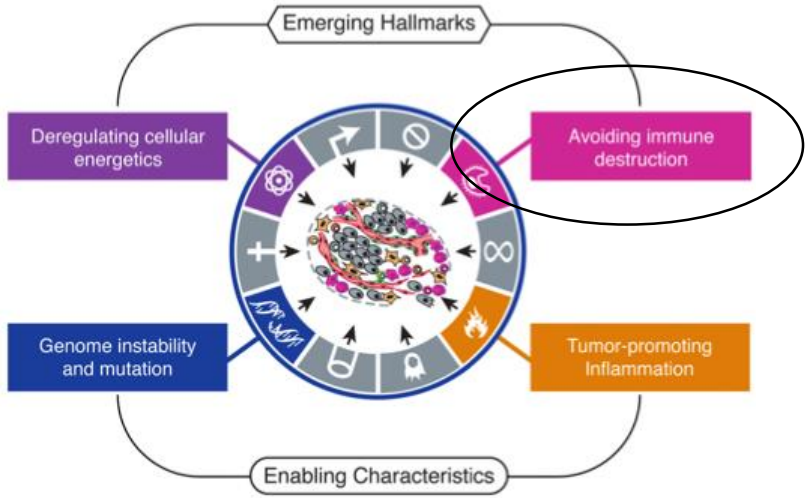
↑ Migration

↓ Adhesion

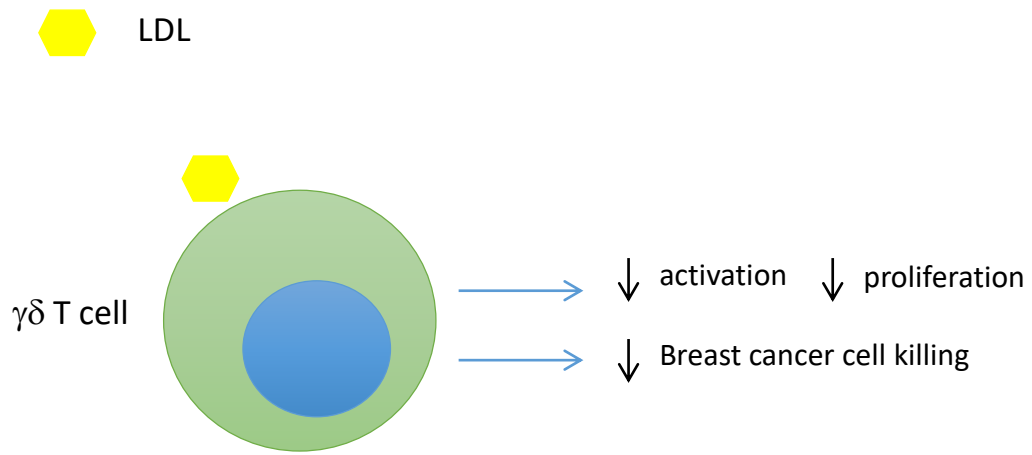
↑ Epithelial to Mesenchymal Transition

Rodrigues dos Santos *et al*., 2014a
Rodrigues dos Santos *et al*., 2014b

# Immune evasion is linked with deregulated celular energetics

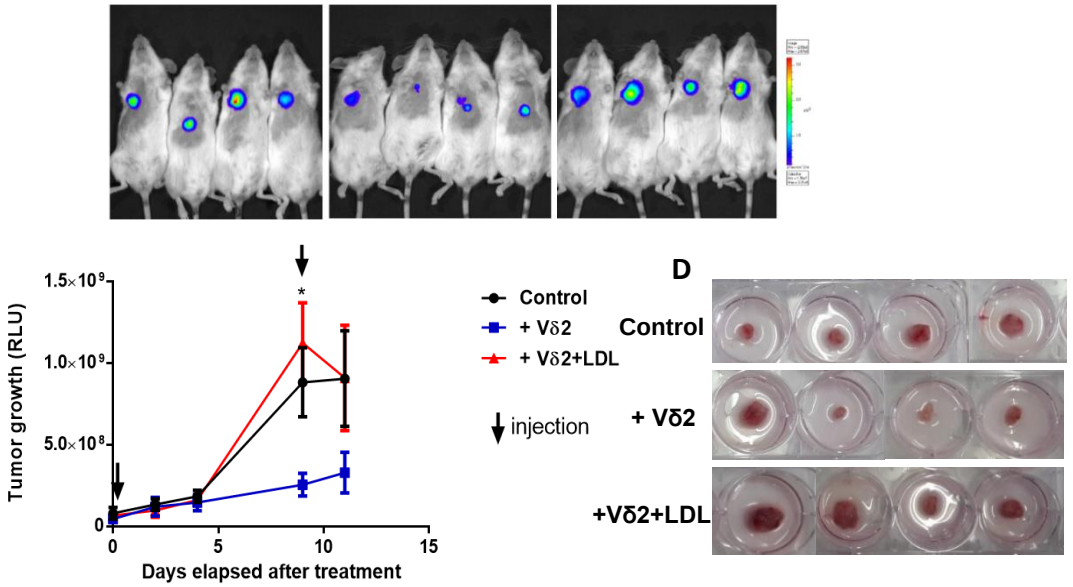


# LDL-cholesterol impairs γδ-T cells response against breast cancer cells




N Rodrigues et al, 2018

# LDL-cholesterol impairs γδ-T cells response against breast cancer cells



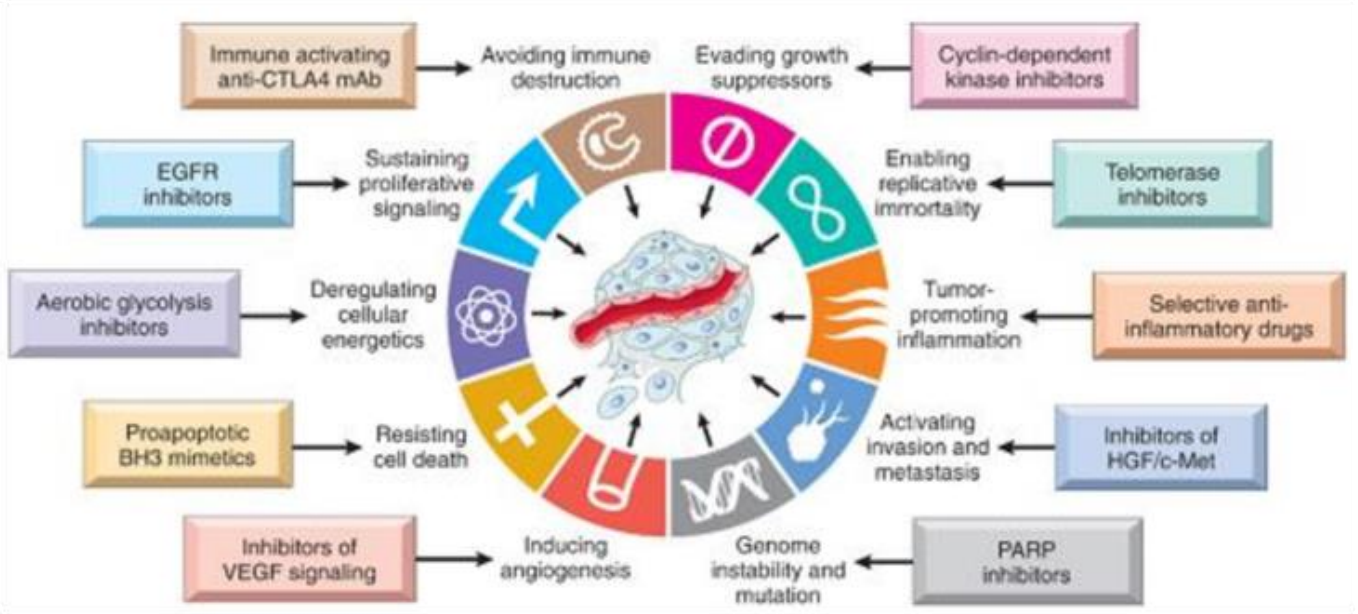

N Rodrigues et al, 2018

**Mechanisms by which LDL-cholesterol promotes breast cancer progression:**

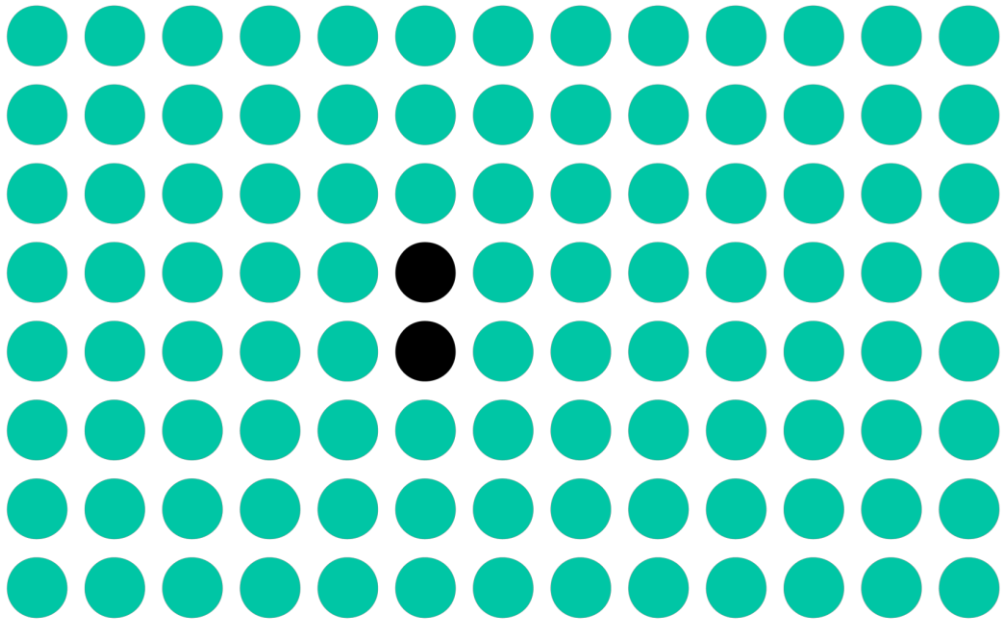
Cell extrinsic (systemic) effects- immune evasion; vascular permeability

Cell intrinsic (direct) effects – proliferation; migration/invasion

# Hallmarks of cancer and targeted therapies



Instituto de Medicina Molecular | João Lobo Antunes



# iMM Laço HUB

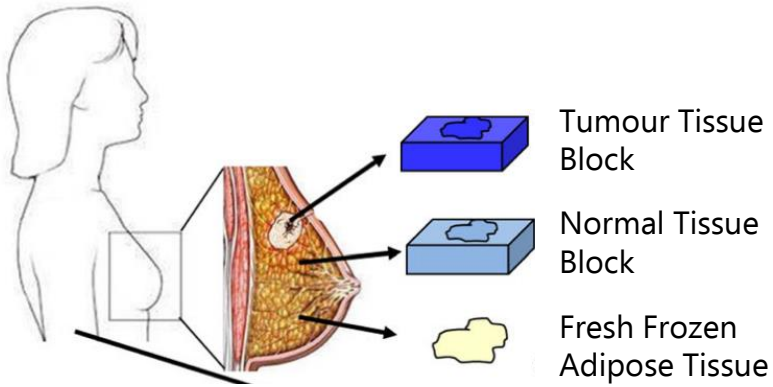
# iMM Laço Hub: scientific challenge with societal support

## Our Key Questions

- How does the GENETIC of the breast cancer affect the cellular microenvironment response?
- What NON-GENETIC factors can affect the microenvironment response in breast cancers?
- Can features of the primary tumour inform on the dynamics of metastasis?

# Breast Cancer Hub: Our proposed approach

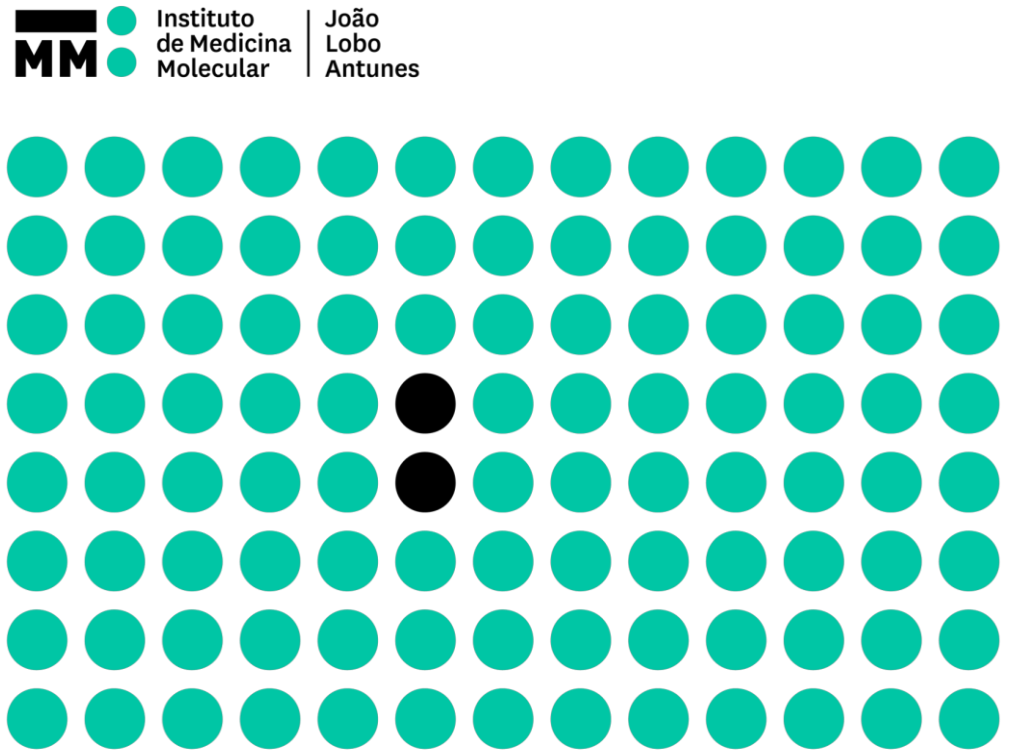
## The disease and the Patients as guides for the research!




## Mapping Tumours in Multiple dimensions

Dissect **genetics**, **transcriptomics**, **cellular composition** and **crosstalks** within the **tumour microenvironment**, using **emerging technologies, involving transcriptomic, genomic and metabolic analyses** that enable a complete cartography of breast cancer.

We anticipate that this approach will provide a deep understanding of how local cellular networks influence responses to cancer treatment and uncover novel therapeutic options.




Sérgio Dias

sergiodias@medicina.ulisboa.pt