# Course unit name: MOLECULAR BASES OF TUMORAL VARIABILITY: MODIFIER GENES OF THE SUSCEPTIBILITY AND EVOLUTION OF CANCER

## 1.- General information

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| Code | 303012 | Plan | | ECTS | 3 |
| Type | Elective | Course | 2023/2024 | Periodicity | 2nd Semester |
| Department | Cancer Research Center | | | | |
| Virtual Platform | Platform: | CICLOUD | | | |
| | URL de Acces: | http://cicloud.dep.usal.es/index.php/s/Gp0vghR305Y6glo/authenticate | | | |

## Faculty

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| Professor Coordinator | Dr. Jesús Pérez Losada | | |
| Research area | Genetic determinants of the cancer susceptibility, evolution, and treatment response | | |
| Center | Cancer Research Center | | |
| Office | Laboratory 20 | | |
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| Professor | Dra. Mª Purificación Galindo Villardón | | |
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| Professor | Dr. Manuel A. Sánchez Martín | | |
| Department | Medicine | | |
| Area | Medicine | | |
| Center | Faculty of Medicine, Medicine Department. | | |
| URL Web | https://nucleus.usal.es/es/transgenesis/contacto | | |
| Office | Lab. Transgenic, Basement -3, CIC. | | |
| Tutorials | 16.00-18.00 | | |
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| Professor | Dr. Javier Cañueto Álvarez | | |
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| Professor | Dr. Isidro Sánchez-García | | |
| Research area | Experimental and Translational Oncology Laboratory: Stem Cells, Cancer Stem Cells, and Cancer | | |
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| Professor | Dr. Carlos Prieto | | |
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## 2.- The course in the context of the Master's Program

| Training Module |
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| The fifth block (out of five) of master program organization. |

## 3.- Previous recommendations

No prior requirements.

## 4.- Aims of the subject

-To understand cancer as a systemic and complex genesis disease, which develops in the context of a complex organism. As a complex trait, cancer has multiple intermediate phenotypes or endophenotypes at different levels (molecular, cellular, tissue, and systemic) that participate in their pathogenesis and pathophysiology.

-To comprehend the molecular and physiological crosstalks between the tumor and the organism in which it is generated. Cancer destabilizes the physiology of the organism producing the disease, and, simultaneously, the evolution of cancer is greatly influenced and sometimes determined by the organism's physiology. These facts contribute to the generation of clinical variability and the evolution of disease among patients.

-To recognize the concept of interaction between different compartments of the organism (physiological and molecular ones) and its role in the variability of tumor susceptibility and evolution.

-To understand the relationship between different physiological states (e.g., age and menopause) and pathophysiological (e.g., obesity and pro-inflammatory states.) and different

tumor evolution among patients.

-To realize the concept of Systems Biology and the main Biostatistics strategies that allow integrating of variables of different levels, including DNA, protein, other molecules, cells, tissues, and systemic factors, and explain a complex phenotype.

-To understand the concept of polygenic control and intergenic interaction in tumor susceptibility and evolution, together with the concept of Quantitative Trait Loci (QTL) and expression-QTL (eQTL) and its role in the different cancer susceptibility and evolution. To understand the concept of cancer-modifying genes and their role in susceptibility and tumor evolution.

To comprehend the role of genetic variants of higher impact genes and the idea of low-penetrance and low expressive genes (polygenes) and their role in tumor susceptibility and evolution.

## 5.- Contents

**Theoretical classes**

•Lesson 1. Cancer as a complex trait disease (I): Cancer is a systemic disease in the context of the physiology and pathology of the organism. Systems Biology and cancer. Interaction between the environment and the genetic background. Polygenic influence of susceptibility and tumor evolution. Quantitative Trait Loci (QTL). Modifier genes: allelic forms of higher-effect, low-penetrating genes. Intrinsic or autonomous-cellular and extrinsic or non-self-contained-cellular modifier genes. Duration: 1 hour.

•Lesson 2. Cancer is a complex trait disease (II). Cancer as a result of the interaction between the genome and the environment: Strategies for identifying genes that modify tumor evolution. Cancer as an evolutionary and adaptive process under selection pressure: Intrinsic modifier genes of tumor evolution. Allele-specific mutations. Intrinsic modifier genes, according to the intracellular functional compartment. Duration: 1 hour.

•Lesson 3. Mouse strains for the generation of models of high but simplified genetic variability in the mouse. Genetic background. Intercross and backcross concepts. Studies in syngeneic mice. Genetic standardization. Collaborative cross. Duration: 2 hours.

•Lesson 4. Main biostatistics strategies to integrate variables of different levels and explain complex traits. Duration: 4 hours. This lesson will be taught in Spanish.

•Lesson 5. Involvement of extrinsic compartments to the tumor cell in the growth and spread of the tumor. Duration: 1 hour.

•Lesson 6. Stem cell and origin and tumor variability. Role of reprogramming at the source of cancer. Duration: 1 hour.

•Lesson 7. Strategy for identifying genetic and molecular determinants of tumor evolution at different levels, including molecular, cellular, tissue, and systemic. Identification of part of the missing heritability. Duration: 1 hour.

•Lesson 8.Strategies to identify intrinsic and extrinsic genetic and molecular determinants of response to chemotherapy. Duration: 1 hour.

•Lesson 9. Influence of physiological states on the susceptibility and tumor evolution: Identification of genetic and molecular determinants of cancer and aging. Duration: 1 hour.

•Lesson 10. Different semiological, histopathological, and molecular levels are integrated to

define cardiotoxicity by chemotherapy in a model of breast cancer. Duration: 1 hour.

•Lesson 11. Integration of different semiological, histopathological, and molecular levels to define the prognosis of squamous skin cancer in patients. Duration: 1 hour.

**Practices**
Practice 1. To design and organize a backcross database. To evaluate the distribution of genotypes and tumor pathophenotypes in a backcross cohort that develops breast cancer.

Practice 2: To analyze the distribution of different phenotypes in a backcross cohort of mice genotyped by the Illumina platform. Identification of QTLs.

**Seminars**
The articles for discussion and presentation by the students will be chosen from the classic works of the field, which best illustrate the course's concepts.

**Tutorial meetings**
The course tutor will be available to students in the CIC, Lab 7, preferably by email appointment

## 6.- Skills to be acquired

| Specific skills |
| --- |
| -To design and organize a genetic and phenotypic variability model with a mouse backcross. The purpose is to analyze tumor evolutionary and pathophenotypes and subphenotypes of tumor variability between mice. Identification of QTLs.<br><br>-To interpret studies of allele-specific mutations in tumor variability for the analysis of intrinsic modifier genes.<br><br>-To interpret the manuscript where genetic and molecular determinants of tumor variability are studied. |

## 7.- Teaching methodology

-The classes will be taught totally or partially in English.

The student must attend the evaluable theoretical classes of the course (13 hours), having read and understood the recommended bibliography.

-The student must attend the seminars (12 hours) in which each student will present a published research work related to the course. An evaluable critical dialogue will be established.

To assist in the evaluable practices (4 hours, organized in 2 days), evaluate a backcross, and identify QTL. The practice will take place in a computer classroom.

## 8.- Estimated learning time

| | | Hours tutored by the teacher | | Individual work (hours) | TOTAL HOURS |
|---|---|---|---|---|---|
| | | Attendance required (hours) | Distance learning (hours) | | |
| Lectures | | 13 | | 20 | 33 |
| Practices | - In classroom | | | | |
| | - In laboratory | 2 | | | 2 |
| | - In computer classroom | 2 | | | 2 |
| | - Countryside | | | | |
| | - Visualization classroom | | | | |
| Seminars | | 12 | | 12 | 24 |
| Work presentations and debates | | | | | |
| Tutorials | | 5 | | | 5 |
| Online activities | | | | | |
| Work preparation | | | | 8 | 8 |
| Other activities | | | | | |
| Exams - evaluation | | 1 | | | 1 |
| TOTAL | | **35** | | **40** | **75** |

## 9.- Materials

Books

Other bibliographical, electronic references, or any other type of resource

## 10.- Assessment

Assessments of the performance of the student

-Presentation of a research article in the field by PowerPoint (20 slides maximum): the quality of the display and exposure will be evaluated. It is essential to be able to understate the scientific problem that is intended to be solved, preceded by the introduction that justifies it, the working hypothesis, with what objectives the hypothesis is designed to respond to, the results, and its discussion with a focus on new questions, conclusions (50% of the final qualification).

- Attendance and participation in theoretical sessions, practices, and seminars (30% of the final qualification).

- Exam: test type (20% of the final grade).

Recommendations