MOLECULAR BASES OF TUMOR VARIABILITY: MODIFIER GENES OF CANCER SUSCEPTIBILITY AND PROGRESSION

1.- General information					
Code	303012	Plan		ECTS	3
Type	Elective	Course	2026/2027	Periodicity	2nd semester
Language		English			
Department	Cancer Research Center				
Virtual Platform	https://cicloud.dep.usal.es/				

1.1.- Faculty			
Professor Coordinator	Dr. Jesús Pérez Losada		
Research area	Molecular and Genetic Determinants of Cancer Susceptibility, Tumor Evolution, and Treatment Response		
Center	Cancer Research Center		
Office	Laboratory 20		
Tutorials	Monday to Friday, by appointment via email		
URL Web	https://www.cicancer.org/grupo?id=60		
E-mail	jperezlosada@usal.es	Phone	+34 923294820

Professor	Dr. Manuel A. Sánchez Martín		
Department	Department of Medicine. University of Salamanca		
Area	Transgenesis Unit		
Center	Cancer Research Center		
Office	Microinjection Laboratory, basement -3		
Tutorials	Monday to Friday, by appointment via email		
URL Web	https://nucleus.usal.es/es/transgenesis/contacto		
E-mail	adolsan@usal.es	Phone	+34 923294500 Ext. 3015

Professor	Dr. Javier Cañueto Álvarez
Department	Department of Medicine
Area	Dermatology Service
Center	University Hospital of Salamanca

E-mail	jcanueto@yahoo.es	Phone	+34 923 294820

Professor	Dr. Isidro Sánchez-García		
Research area	Experimental and Translational Oncology Laboratory: Stem Cells, Cancer Stem Cells, and Cancer		
Center	Cancer Research Center		
Office	Laboratory 13		
Tutorials	Appointment by email		
URL Web	https://www.cicancer.org/grupo?id=53		
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Professor	Dr. María del Carmen Patiño Alonso		
Center	Medicine Faculty		
Office	Statistics Department.		
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Professor	Dr. Carlos Prieto		
Center	Nucleus. Bioinformatics Unit. University of Salamanca		
Office	Bioinformatics Unit		
URL Web	http://bioinfo.usal.es/		
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Professor	Dr. Marina Mendiburu-Eliçabe		
Center	Cancer Research Center		
Office	Laboratory 20		
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2.- Previous recommendations

None.

3.- Aims of the subject

• To gain an understanding of cancer as a disease characterized by systemic complexity and complex genesis, occurring within a multifaceted organism. As a complex trait, recognize that cancer involves various intermediate or endophenotypes across multiple levels—molecular, cellular, tissue, and systemic—that are integral to its pathogenesis and pathophysiology.

• To grasp the ongoing molecular and physiological interactions between the tumor and its host organism. Cancer disrupts the host's physiological balance, leading to the disease, while the progression of cancer is significantly shaped, and at times dictated, by the host's own physiological processes. This interplay results in clinical variability and differences in disease progression among patients.

• To acknowledge the interactions among various physiological and molecular compartments of the organism, and their impact on the variability in tumor susceptibility and progression.

• To comprehend how various physiological states, such as age and menopause, and pathophysiological states, such as obesity and pro-inflammatory conditions, influence tumor development and progression among individuals.

• To appreciate the principles of Systems Biology and key biostatistical strategies that facilitate the integration of variables at different levels—ranging from DNA and proteins to cells, tissues, and systemic factors—to elucidate complex phenotypes.

• To understand the roles of polygenic control and intergenic interactions in influencing tumor susceptibility and progression. This includes a deep dive into the concepts of Quantitative Trait Loci (QTL) and expression-QTL (eQTL), their importance in cancer susceptibility and evolution, and the influence of cancer-modifying genes on these processes.

• To understand the significance of genetic variants in major impact genes and the concept of low-penetrance genes and their role in modulating tumor susceptibility and progression.

4.- Skills to be acquired / Learning outcomes

Skills

4.1: Basic skills:

4.2: Specific skills:

• **Design and Manage a Mouse Backcross Model**: Develop a genetic and phenotypic variability model using mouse backcrossing techniques. The goal is to investigate the evolutionary dynamics and various pathophenotypes and subphenotypes of tumor variability among different mice, with a focus on identifying Quantitative Trait Loci (QTLs).

• **Analyze Allele-Specific Mutation Studies**: Gain the ability to interpret research involving allele-specific mutations to better understand tumor variability. This involves examining how intrinsic modifier genes affect tumor development and progression.

• **Evaluate Research on Genetic and Molecular Determinants**: Develop skills to critically assess

studies investigating the genetic and molecular factors that influence tumor variability, enhancing understanding of how these determinants impact cancer progression.

4.3: Transferable skills:

5.- Contents (Syllabus)

Theoretical classes

• Lesson 1. Cancer as a complex trait disease I: cancer as a systemic disease within the physiological and pathological framework of the organism. The session covers systems biology, the interaction between genetic background and the environment, polygenic influences on tumor susceptibility and progression, Quantitative Trait Loci (QTL), and the role of intrinsic and extrinsic modifier genes. Duration: 1 hour.

• Lesson 2. Cancer as a complex trait disease II: cancer as the result of genome-environment interactions, strategies to identify genes that modify tumor evolution, and cancer as an evolutionary process shaped by selective pressures. Duration: 1 hour.

• Lesson 3. Mouse models to generate high but controlled genetic variability: genetic background, intercross and backcross strategies, syngeneic mouse studies, genetic standardization, and the collaborative cross. Duration: 2 hours.

• Lesson 4. Advanced biostatistical strategies for integrating multi-level data and analyzing complex phenotypes. Duration: 2 hours.

• Lesson 5. Stem cells and their relationship with tumor variability and cancer origin, including the role of cellular reprogramming. Duration: 1 hour.

• Lesson 6. Strategies to identify genetic and molecular determinants of tumor evolution across multiple levels. Duration: 1 hour.

• Lesson 7. Methods to identify genetic and molecular factors affecting chemotherapy response, including both intrinsic and extrinsic determinants. Duration: 1 hour.

• Lesson 8. Impact of physiological states on cancer susceptibility and tumor evolution, with a focus on aging and cancer. Duration: 1 hour.

• Lesson 9. Integration of semiological, histopathological, and molecular data to assess chemotherapy-induced cardiotoxicity. Duration: 1 hour.

• Lesson 10. Bioinformatics applications in the study of complex phenotypes. Duration: 1 hour.

• Lesson 11. Integration of multi-level data to determine the prognosis of squamous skin cancer. Duration: 1 hour.

Practical sessions

• Practice 1. Design and organization of a backcross experiment to evaluate genotype and tumor phenotype distribution in a breast cancer model. Duration: 2 hours.

• Practice 2. Analysis of multiple phenotype distributions in an Illumina-genotyped mouse backcross cohort, with identification of QTLs. Duration: 2 hours.

Seminars

Selected seminal or especially representative articles will be discussed and presented by students to illustrate the core concepts of the course.

Tutorial meetings

The course coordinator will be available to meet students in Lab 20 at the CIC, preferably by appointment via email (jperezlosada@usal.es).

6.- Teaching methodology

• Language of instruction: The course will be taught primarily in English. When needed to ensure comprehension of complex methodological or statistical concepts, occasional support may be provided in Spanish.

• Theoretical classes: Students are required to attend 13 hours of assessable theoretical sessions. Students are encouraged to prepare these sessions in advance by reading the bibliography and scientific articles indicated by the teaching staff.

• Seminars: Twelve hours will be devoted to seminars in which each student will present a published research article or a current research line related to the course. Presentations will be followed by a critical discussion, which will also contribute to the final assessment.

• Assessable practical sessions: Practical sessions will comprise 4 hours over two days and will focus on the design and evaluation of a backcross and on the identification of Quantitative Trait Loci (QTL). These activities will take place in the laboratory and/or in a suitable computer classroom at the University of Salamanca.

6.1.- 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				
	- Others (specify)				
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**

7.- Materials, other bibliographical, electronic references or any other type of resource

Specific scientific articles and bibliographic resources will be selected and made available to students through CICLOUD.

The course will use updated reviews and original research articles on cancer susceptibility genetics, QTL/eQTL, mouse models, systems biology, biostatistics, bioinformatics, and variability in cancer progression and therapeutic response.

8.- Assessment

8.1: Assessment criteria:

Assessment will evaluate students' understanding of the core concepts of the course, their ability to integrate genetic, molecular, cellular, and clinical information, their critical interpretation of research articles, the clarity of their oral communication, and their active participation in the sessions.

8.2: Assessment systems:

• Research article presentation: Students will present a research article relevant to the field, assigned by the teaching staff. The presentation must not exceed 20 slides. It will be assessed according to the quality of the oral presentation, the clarity of the slides, and the student's ability to interpret the work critically. Key elements include a clear definition of the scientific problem, an introduction that justifies the study, the working hypothesis, the specific objectives, the results, discussion of the findings, possible new questions, and final conclusions. This component will account for 50% of the final grade.

• Attendance and active participation: Attendance and active participation in theoretical classes, practical sessions, and seminars will account for 30% of the final grade.

• Multiple-choice examination: Students will complete a multiple-choice examination designed to assess their understanding of the main course contents. This component will account for 20% of the final grade.

8.3: General considerations and recommendations for assessment and resit:

To pass the course, students must obtain a final grade of at least 5/10. The resit will consist of repeating or improving the component that was not passed, according to the instructions provided by the teaching staff.

9.- Weekly Teaching Schedule

The detailed teaching schedule will be announced through CICLOUD.