MOLECULAR BASES OF TUMORAL VARIABILITY: MODIFIER GENES OF THE SUSCEPTIBILITY AND EVOLUTION OF CANCER

1.- General information					
Code	303012	Plan		ECTS	3
Type	Elective	Course	2025/2026	Periodicity	2st 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	Genetic determinants of the cancer susceptibility, 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		
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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		
URL Web	http://www.cicancer.org/uploads/master/Optativas/1Semestre/modelos_cancer_ratones.pdf		
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Professor	Dr. Javier Cañueto Álvarez		
Department	Medicine		
Center	University Hospital of Salamanca		
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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		
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Professor	Dra. Mª del Carmen Patino Alonso		
Center	Medicine Faculty		
Office	Statistics Department.		
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Professor	Dr. Carlos Prieto		
Center	Nucleus.Bioinformatics Unit. University of Salamanca		
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Professor	Dr. Marina Mendiburu-Eliçabe		
Center	Cancer Research Center		
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2.- Previous recommendations

No needed.

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: Exploring Cancer as a Complex Trait Disease (I): Discussion on cancer as a systemic disease within the physiological and pathological framework of an organism. The session covers Systems Biology, the interaction between genetic backgrounds and the environment, the polygenic impacts on tumor susceptibility and progression, Quantitative Trait Loci (QTL), and the role of modifier genes including high-impact and low-penetrance alleles, both intrinsic and extrinsic to cell autonomy. Duration: 1 hour.

• Lesson 2: Cancer as a Complex Trait Disease (II): This lesson delves into the genomic and environmental interactions that influence cancer, with a focus on strategies for identifying genes that affect tumor evolution. It also examines cancer as an evolutionary and adaptive process influenced by selective pressures, and explores intrinsic modifier genes specific to cellular compartments. Duration: 1 hour.

• Lesson 3: Utilization of Mouse Models for High but Controlled Genetic Variability: This class introduces genetic background considerations, the concepts of intercross and backcross, studies in syngeneic mice, genetic standardization, and the collaborative cross. Duration: 2 hours.

• Lesson 4: Key Biostatistics Strategies for Integrating Multi-level Variables: This comprehensive session discusses methodologies to analyze complex traits across various biological scales. Duration: 4 hours. (Note: This session will be conducted in Spanish.)

• Lesson 5: Examining the Role of Extrinsic Compartments in Tumor Growth and Spread. Duration: 1 hour.

• Lesson 6: Stem Cells: Their Role in the Origin and Variability of Tumors and the Impact of Reprogramming on Cancer Genesis. Duration: 1 hour.

• Lesson 7: Approaches to Identify Genetic and Molecular Determinants of Tumor Evolution Across Multiple Levels: Molecular, Cellular, Tissue, and Systemic. The session includes discussions on unearthing missing heritability components. Duration: 1 hour.

• Lesson 8: Techniques to Determine Genetic and Molecular Factors Influencing Chemotherapy Response, covering both intrinsic and extrinsic determinants. Duration: 1 hour.

• Lesson 9: How Physiological States Affect Tumor Susceptibility and Evolution: Focus on the Interplay Between Aging and Cancer. Duration: 1 hour.

• Lesson 10: Integration of Semiologic, Histopathologic, and Molecular Data to Assess Chemotherapy-Induced Cardiotoxicity in Breast Cancer Models. Duration: 1 hour.

• Lesson 11: Combining Various Data Types to Forecast the Prognosis of Squamous Skin Cancer. Duration: 1 hour.

Practical Sessions

• Practice 1: Design and organization of a backcross experiment to evaluate the genotype and tumor pathophenotype distribution in a breast cancer cohort.

• Practice 2: Analysis of phenotype distribution in a genotyped mouse backcross cohort using the Illumina platform, focusing on the identification of QTLs.

Seminars

Articles selected for discussion and presentation will exemplify fundamental concepts of the course, chosen from seminal works in the field.

Tutorial Meetings

The course tutor will be available to meet with students in Lab 20 at the CIC, primarily via email appointments.

6.- Teaching methodology

• **Language of Instruction**: Classes will be conducted entirely or partially in English to enhance language proficiency in a professional academic setting.

• **Theoretical Classes**: Students are required to attend 13 hours of assessable theoretical classes. Prior to these sessions, students should have thoroughly read and understood the recommended bibliography to fully engage in the learning process.

• **Seminars**: Over 12 hours, each student will present a piece of published research work that is relevant to the course topics. These presentations will be followed by a critically evaluative discussion, which will also contribute to the overall assessment.

• **Practical Sessions**: Students must participate in 4 hours of assessable practical work, organized across 2 days. These sessions will involve evaluating a backcross and identifying Quantitative Trait Loci (QTL). The practical work will be conducted in a designated computer classroom.

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

8.- Assessment

8.1: Assessment Criteria:

8.2: Assessment Systems:

• **Research Article Presentation: S**tudents will present a research article related to the field using PowerPoint, limited to a maximum of 20 slides. The evaluation will focus on the quality of the presentation and the ability to effectively communicate the content. Key elements include clearly defining the scientific problem addressed by the research, providing an introduction that justifies this focus, detailing the working hypothesis, outlining the objectives that address this hypothesis, presenting the results, discussing these findings with an emphasis on posing new questions, and summarizing the conclusions. This component will account for 50% of the final grade.

• **Attendance and Active Participation:** Consistent attendance and active participation in all theoretical classes, practical sessions, and seminars are required. This engagement will constitute 30% of the final grade.

• **Examination:** Students will be assessed through a test-type examination, which will determine 20% of the final grade.

8.3: General Considerations and Recommendations for Assessment and Resit:

9.- Weekly Teaching Schedule