Course unit name: LEUKEMIC NICHE AND IMMUNE-EFFECTOR CELLS

1.- General information

Code	303030	Plan		ECTS	3
Type	Elective	Course	2024/2025	Periodicity	2nd Semester
Department	Cancer Research Center and Department of Medicine, USAL				
Virtual Platform	Platform:	CICLOUD			
	URL de Acces:	https://cicloud.dep.usal.es/			

Faculty

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2.- The course in the context of the Master´s Program

Treaning Module

Fifth block of the academic year of the five into which the academic year is divided.

Second quarter.

General aim of the subject

The subject will allow the Master's student to know the biological, physiological and methodological bases of the involvement of the bone marrow microenvironment and its diverse progenitor cells in the physiopathology of malignant hemopathies and other tumors. Other aspects related to the use of these cell types for therapeutic purposes will also be addressed.

Professional specialization

The subject aims to provide students with basic theoretical and practical knowledge for the design of pre-clinical and clinical studies that evaluate the role of the bone marrow microenvironment in cancer.

3.- Previous recommendations

It is recommended that students have previous knowledge of cell culture biology and basic methodology.

4.- Aims of the subject

Understand:

1. The concept of stem cell and the different types of stem cells that exist in the bone marrow: hematopoietic, mesenchymal, endothelial.
2. The mechanisms involved in the regulation of hematopoiesis. The role of the bone marrow microenvironment and the hematopoietic niche.
3. The role that these cells and their microenvironment play in the development of hematological malignancies and other neoplasms.

To know:

1. The usual methodologies used in a Cell Culture and Cell Therapy laboratory.
2. What are they and how are the different assays carried out for the study of hematopoiesis (e.g. clonogenic studies, long-term cultures, etc.). Analysis of the interrelation between hematopoietic cells and the microenvironment.
3. How mesenchymal cells are manipulated and expanded. What are the main sources of procurement. Characterization and its therapeutic potential.
4. How endothelial progenitors are obtained. Characterization and clinical use.
6. What are the main animal models to assess bone marrow cell engraftment in the context of cell therapy.
7. The main biosafety and quality control procedures used in a cell therapy laboratory.

5.- Contents

Master classes:
Topic 1. History of the knowledge of hematopoiesis and methods of study.
Topic 2. Hematopoietic transplantation as a basis for the development of cell therapy.
Topic 3. Structure and regulation of hematopoiesis.
Topic 4. The mesenchymal stromal cell: multipotent and immunomodulatory capacity.
Topic 5. Preclinical studies to evaluate the immunomodulatory capacity of MSCs.
Topic 6. Animal models for the evaluation of graft-versus-host disease, engraftment and inflammation.
Topic 7. iPS: concept, development and importance.
Topic 8. Extracellular vesicles: concept and applications. Role in the development and maintenance of tumors. Biomarkers.
Topic 9. The marrow microenvironment in myelodysplastic syndromes.
Topic 10. The marrow microenvironment in other hemopathies.
Topic 11. Cellular immunotherapy: concept and applications.
Topic 12. CAR cells: practical applications, approved indications, adverse effects.
Topic 13: Preclinical studies to evaluate CAR cells.
Topic 14. Cellular immunotherapy. Concept and applications
Topic 15. European regulations for cell therapy. Concept of GMP Lab. Importance of quality control and biosafety in cell therapy.

Practical lessons*:
Practice 1. Hematopoiesis assays using in vitro cultures. Clonogenic assays and long-term culture.
Practice 2. Expansion of MSC from different sources. Characterization by flow cytometry. MSC Differentiation.
Practice 3. Animal models for the study of cell engraftment and graft-versus-host disease.
Practice 4. Immunotherapy. Methods of study in the laboratory.
Practice 5. GMP facilities: construction, tuning and management.

*In case it would not be possible to give the practical teaching at the University Hospital due to different circumstances (e.g. COVID-19), the following "training microvideos" of our Unit will be used (which in any case will be uploaded to Studium during the period corresponding to the subject):
- Video 1: Introduction to the Cell Culture laboratory.
- Video 2. Cell-line chimerism and Bone marrow harvest.
- Video 3: MSC Culture and Expansion
- Video 4. Characterization of MSCs by flow cytometry.
- Video 5. Cell differentiation of MSCs
- Video 6: Mineralization of differentiated MSCs
- Video 7: Clonogenic and co-culture assays
- Video 8: MTT assay
- Video 9: Obtaining CD34+ cells from apheresis
- Video 10: Obtaining EVs from plasma and cell cultures
- Video 11: Murine models of GVHD
- Video 12: Inoculation pathways in mice
- Video 13: GMP production of MSCs
- Video 14: Management and handling of CAR-T cells

Seminars:
Some relevant articles will be selected and discussed in an open forum, prepared by the students.

6.- Skills to be acquired

Basic skills

-To know the concept of stem cells and their different types, with their main characteristics, their potential therapeutic uses and their role in the physiopathology of tumours.

-Understand the methodological basis for conducting preclinical studies that evaluate the role of microenvironmental cells in tumors.

-To know the latest therapeutic strategies in cancer based on cell immunotherapy, with emphasis on cell production and regulation.

Specific skills

-Understanding the role of bone marrow as a cellular source and knowing why hematopoietic stem cell transplantation has laid the foundation for other cellular therapy application and modern cellular immunotherapy.

-To be able to differentiate the characteristics of embryonic cells, cells obtained by somatic nuclear transfer, induced reprogrammed cells (iPS) and adult cells.

-To know the properties and methods of isolation and characterization of mesenchymal stromal cells (MSC).

-To know the properties and methods of isolation and characterization of endothelial progenitor cells (EPC).

-To know the role of all these cell types in the physiopathology of tumours, especially in hematological malignancies.

-To know the concept of extracellular vesicles are and their potential in the diagnosis and monitoring of cancers, and their implications for their physiopathology.

-To learn the current regulation, processes and methodology of the production of modified cells used in cellular immunotherapy (immunoefector cells).

Transversal skills

-To know the basic procedures of a cell culture, haematopoiesis and cell therapy laboratory.

-To know the requirements of sterility and biosafety of work in Cell Production Units and GMP laboratories.

7.- Teaching methodology

Theoretical classes: The student must attend the theoretical sessions of the course (16 hours). During these sessions, powerpoint presentations will be used and participation will be stimulated through the discussion of previously recommended bibliography.

Practical classes: Attendance to the evaluable practices (20 hours in two groups organized in 5 days), that will take place in the laboratory of Cell Therapy of the University Hospital of Salamanca or in the Animal Care Facility of the University of Salamanca.

Seminars: Organization of the students in work groups that will consist of less than 5 students per group and that will have to prepare the seminars on the most relevant works on the subjects of the course and their presentation on the part of the students and their critical discussion. This participation will be evaluable for the final grade.

Tutorials: face-to-face or not at a time to be agreed upon and with the full availability of the teaching staff to guide and resolve doubts.

Autonomous work of the student: To extend information, to study, to solve problems and to prepare the seminars.

Evaluation: There will be a written multiple-choice test which will be 40% of the grade. The remaining 60% will be evaluated from assistance and participation in classes, practices and seminars through continuous evaluation

8.- Estimated learning time

		Hours tutored by the teacher		Individual work (hours)	TOTAL HOURS
		Attendance required (hours)	Distance learning (hours)		
Lectures		15		5	20
Practices	- In classroom	5		2,5	7,5
	- In laboratory	5		2,5	7,5
	- In computer classroom				
	- Countryside				
	- Visualization classroom				
Seminars		4		20	24
Work presentations and debates					
Tutorials		7			7
Online activities					
Work preparation					
Other activities					
Exams - evaluation		1		8	9
TOTAL		**37**		**38**	**75**

9.- Materials

Books

Atala A. Principles of Regenerative Medicine (3rd Ed.). Elsevier, 2019.

Baronzio G. Cancer Microenvironment and Therapeutic Implications: Tumor Pathophysiology Mechanisms and Therapeutic Strategies. Springer, 2010.

Warburton D. Stem Cells, Tissue Engineering and Regenerative Medicine. World Scientific, 2015.

Normas de Correcta Fabricación, Medicamentos de uso humano y uso vetenerinario (4ª edición). Agencia Española de Medicamentos y Productos Sanitarios, Ministerio de Sanidad, 2011.

Balkhi M. Basics of Chimeric Antigen Receptor (CAR) Immunotherapy. Elsevier, 2019.

Other bibliographical, electronic references or any other type of resource

RICORS de Terapias Avanzadas, ISCIII. https://www.redterav.es/

International Society for Cellular Therapy. http://www.celltherapysociety.org/

International Society for Stem Cell Research. http://www.isscr.org/

Mesenchymal Cell News. https://www.mesenchymalcellnews.com/

10.- Assessment

Assessments on the performance of the student

Evaluation of assistance and participation in theoretical sessions, practical sessions and seminars (continuous evaluation) (60 % of the final grade)

Written evaluation of the course (multiple-choice test) (40% of the final grade).

Recommendations

Continuous evaluation: asistance and active participation.