Universitat Autònoma de Barcelona

2019/2020

Gene Therapy

Code: 100901
ECTS Credits: 6

Degree	Type	Year	Semester
2500252 Biochemistry	OT	4	0

Contact

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Use of Languages

Principal working language: catalan (cat)
Some groups entirely in English: No
Some groups entirely in Catalan: Yes
Some groups entirely in Spanish: No

Teachers

Miguel García Martínez
Ivet Elias Puigdomenech
Verónica Jiménez Cenzano

Prerequisites

There are no prerequisites to attend this course. However, to facilitate the student's understanding of the subject matter and the achievement of the learning goals proposed, it is advisable that the student has previous knowledge on Cellular Biology, Genetics, Molecular Biology and Recombinant DNA technology.

It is also advisable that the students have basic knowledge of English, so that they can use the information sources of the field, which are mostly in this language.

Objectives and Contextualisation

The objective of the subject "Gene and Cell Therapy" is to provide the students with up-to-date knowledge in the methodologies available for the genetic engineering of cells for therapeutic purposes. Thus, the content of the subject will cover the following topics: Description of *in vivo* and *ex vivo* gene therapy; Study of the different vectors used for viral and non-viral gene transfer and their respective advantages and shortcomings; study of the possible routes of administration of the vectors and the applications to the treatment of hereditary and non-hereditary human diseases. Description of cell therapy. Transplant of fully differentiated somatic cells (pancreatic islets, hepatocytes, and bone marrow). Transplant of pluripotent stem cells (embryonic and adult). Sources of cells for cell therapies. Therapreutic applications of cell therapies. Biosafety, ethics and legal aspects associated to the use of cell therapies in humans.

Competences

- Apply general laboratory security and operational standards and specific regulations for the manipulation of different biological systems.
- Apply the legal and ethical principles that govern the development and application of molecular life sciences.

- Apply the principal techniques used in biological systems: methods of separation and characterisation of biomolecules, cell cultures, DNA and recombinant protein techniques, immunological techniques, microscopy techniques, etc.
- Be able to self-evaluate.
- Collaborate with other work colleagues.
- Combine research and and the generation of knowledge with problem-solving in one's own field, showing sensibility to ethical and social questions.
- Describe the structural, physiological and biochemical characteristics of the different types of cells and explain how their properties fit in with their biological function.
- Interpret experimental results and identify consistent and inconsistent elements.
- Make an oral, written and visual presentation of ones work to a professional or non-professional audience in English and understand the language and proposals of other specialists.
- Read specialised texts both in English and ones own language.
- Show a capacity for leadership.
- Show initiative and an entrepreneurial spirit.
- Stay abreast of new knowledge of the structure, organisation, expression, regulation and evolution of genes in living beings.
- Take responsibility for one's own learning after receiving general instructions.
- Think in an integrated manner and approach problems from different perspectives.
- Use ICT for communication, information searching, data processing and calculations.

Learning Outcomes

1. Apply general laboratory security and operational standards and specific regulations for the manipulation of different biological systems.
2. Be able to self-evaluate.
3. Collaborate with other work colleagues.
4. Combine research and and the generation of knowledge with problem-solving in one's own field, showing sensibility to ethical and social questions.
5. Describe the fundamental principles and the applications of cell therapy.
6. Describe the fundamental principles of in vivo and ex vivo gene therapy.
7. Interpret experimental results and identify consistent and inconsistent elements.
8. Make an oral, written and visual presentation of ones work to a professional or non-professional audience in English and understand the language and proposals of other specialists.
9. Perform a protocol for using gene therapy.
10. Read specialised texts both in English and ones own language.
11. Recognise the ethical, legal and biosafety-related aspects of cell therapy in humans.
12. Show a capacity for leadership.
13. Show initiative and an entrepreneurial spirit.
14. Take responsibility for one's own learning after receiving general instructions.
15. Think in an integrated manner and approach problems from different perspectives.
16. Use ICT for communication, information searching, data processing and calculations.

Content

Knowledge on the following topics will be imparted during the theoretical classes:

TOPIC 1

Molecular basis of Gene Therapy. Gene therapy *in vivo* and *ex vivo*. Introduction to Cell therapy.

TOPIC 2

Retroviral vectors derived from murine leukaemia virus. Retroviral replicative cycle. Production of retroviral vectors. Retrovirus-mediated gene expression. Applications.

TOPIC 3

Lentiviral vectors (LV). Genomic organization of lentiviruses. Production of lentiviral vectors. Properties. Applications.

TOPIC 4

Adenoviral vectors (Ad). Structure and genomic organization of adenoviruses. Production of adenoviral vectors. Properties. Applications. Production of less immunogenic later generation adenoviral (HD-Ad). Oncolytic adenoviral vectors.

TOPIC 5

Adeno-associated viral vectors (AAV). Biology of adeno-associated viruses. Production of adeno-associated virus-derived recombinant vectors. Properties. Applications.

TOPIC 6

Non-viral vectors (I). Use of cationic liposomes in gene therapy. Gene transfer with cationic polymers. Receptor-mediated gene transfer.

TOPIC 7

Non-viral vectors (II). Transfer of plasmidic DNA in solution to the muscle. Electrotransfer. Transfer of plasmidic DNA in solution to the liver through hydrodynamic procedures. Applications.

TOPIC 8

Interference RNA (siRNA). Gene therapy based on the use of siRNA. Applications.

TOPIC 9

Genome editing. Different types of nucleases: Meganucleases, Zinc-finger nucleases, TALENs, CRISPR Technologies. Applications in the field of Gene Therapy.

TOPIC 10

Ex vivo gene therapy; hematopoietic stem cells.

TOPIC 11

Introduction to Embryonic Stem Cells (*ES cells*). Differentiation of *cells*. Clinical Applications of *ES cells*.

TOPIC 12

Adult stem cells and their applications.

TOPIC 13

Reprogramming and *Induced Pluripotent Stem Cells (iPS*).

TOPIC 14

Gene therapy for hereditary monogenic diseases: Immunedeficiencies. Lysosomal diseases. Cystic fibrosis. Eye diseases. Haemophilia. Muscular dystrophies. Other diseases.

TOPIC 15

Gene therapy for cancer. Immunotherapies. Use of suicide genes. Antiangiogenic gene therapies. Use of tumour suppressor genes. Use of antisense sequences. Other therapeutic strategies.

TOPIC 16

Gene therapy for diabetes mellitus. Gene therapy for cardiovascular diseases. Gene therapy for neurodegenerative diseases.Gene therapy for infectious diseases (AIDS, hepatitis). DNA vaccines.

TOPIC 17

Cell therapies for the regeneration of bone and cartilage.

TOPIC 18

Cell therapies for the regeneration of skin. Cell therapies for the regeneration of eye diseases.

TOPIC 19

Cell therapies for Parkinson disease and other Central Nervous System diseases.

TOPIC 20

Cell therapies for diabetes mellitus and cardiovascular diseases.

TOPIC 21

Cell and Gene Therapy Clinial protocols. Phases of a clinical trial. European regulatory bodies, American regulatory bodies. Ethical aspects of gene and cell therapies.

Three exercises are proposed for the laboratory practice classes. The first assignment is the design of a gene or cell therapy strategy for a given disease, from design of the gene or cell product to proof-of-concept studies and translational studies that allow a clinical trial in humans.This exercise is proposed as a review of all the concepts introduced in the theory classes. The second proposed activity allows students to acquire experience in the use of laboratory animals in gene and cell therapy studies. Finally, in the third proposed activity we show students how to perform a partial hepatectomy for gene therapy approaches directed to the liver.

Content of the laboratory practice classes:

- Design of a gene or cell therapy strategy; discussion of the different options.

- Introduction to the use of laboratory animals in gene and cell therapy studies.

- Methods and routes of administration of viral and non-viral vectors.

Methodology

The subject "Gene and Cell Therapy" consists of theory and laboratory classes, and tutored oral presentations of relevant literature. The formative activities of the subject are complementary.

Theoretical classes

The contents of the theoretical classes will be imparted by a Professor in a series of master classes supported by audio-visual material. The slides used by each professor in each class will be available to the students through the subject'sCampus Virtual/Moodle. These master classes will constitute the main form of transfer of theoretical contents. Students are advised to periodically consult the books and links suggested in the Bibliography section of this document and at the Campus Virtual/Moodle to consolidate and clarify, if necessary, the contents explained in class.

Laboratory practice classes

The laboratory practice classes have been designed to help students get familiarized with the methodologies used in the field of gene therapy and have a direct experience in the handling of laboratory animals for gene therapy studies. We expect that, during these laboratory practice classes, students will be able to experience a

"real world" experimental situation. We would like students to experience the excitement associated to research in the field of gene therapy.

The laboratory practice classes are composed of 3 sessions of 4 h each (from 3PM to 7PM), during which students will work in groups of 2 people under the supervision of an experienced professor. The dates assigned to each laboratory practice group will be published in the subject's Campus Virtual/Moodle with sufficient anticipation.

Attendance to laboratory practice classes is mandatory.

The laboratory practice guide willbeavailable through the Campus Virtual/Moodle. Students must bring their own lab coat, a waterproof marker and the Laboratory Practice Guide to each laboratory practice class.

Oral presentations of selected papers

Students will analyse and discuss in an oral presentation in front of the whole class a selected recent scientific publication on gene or cell therapy published in a recognized international scientific journal. To this end, students will pair with a fellow classmate. During the process of analysis of the paper's content and preparation of the oral presentation, students will be tutored by researchers with experience in the field of gene and cell therapy. Students will have 10 minutes for the oral presentation, equally divided amongst the members of the group, plus 5 minutes for questions (total of 15 minutes). The objective of this evaluating activity is that students get used -under the supervision of a tutor- to the process of searching, reading and understanding of scientific literature, and if necessary, develop a critical view on the figures, tables and results described in the publication. On the other hand, with this activity students will increase their knowledge of the current applications of gene and cell therapy technologies.

Tutoring

The oral presentations of selected papers will be tutored. In addition, upon request from the students, individualized tutoring will be available throughout the course. The objective of this sessions will be to help the student resolve doubts and review basic concepts and to provide them with advice on sources of information and the best way to discuss scientific results in public.

Activities

Title	Hours	ECTS	Learning Outcomes
Type: Directed			
Oral presentations	8	0.32	16, 3, 5, 6, 7, 10, 15, 11, 8, 14, 2, 12, 13
Practical lessons	12	0.48	1, 3, 7, 15, 9, 11, 4, 14, 2, 12, 13
Theorical lessons	34	1.36	3, 5, 6, 7, 10, 15, 11, 4
Type: Supervised			
Tutorials	6	0.24	3, 7, 15, 11, 8, 14
Type: Autonomous			
Individual study time	74	2.96	16, 5, 6, 7, 10, 15, 11, 4, 8, 14, 2, 12, 13
Oral presentations	10	0.4	16, 3, 6, 7, 10, 15, 11, 4, 8, 14, 13

Assessment

To pass the course, students must achieve a final score of 5 points (over a total of 10 points) and must attend the laboratory practice classes. The evaluation activities are:

1.- Final examination of theoretical classes

Accounts for 50% of the final score (5 points out of 10). Assessment will consist of a written examination, under the format of a True or False test, on topics explained during the theoretical classes. A score greater than 2.5 in this examination is required to pass the course.

There will be a Second Chance/Recovery Exam, under the same format as the original exam.

2.- Examination of Laboratory classes

Accounts for 15% of the final score (1.5 points out of 10). Assessment will consist of a written examination, under the format of a True or False test, on topics explained during the practical classes. It will be held at the end of practical classes period.

Attendance to practical sessions (or field trips) is mandatory. Students missing more than 20% of programmed sessions will be graded as "No Avaluable.

3.- Self-study exercise

Accounts for 10% of the final score (1 point out of 10). Assessment will consist of an exercise that the student will have to develop on their own. Details will be posted online in the "Campus Virtual" at the end of April.

4.- Oral presentations of selected research papers

Accounts for 15% of the final score (1.5 points out of 10). Students will be evaluated individually, both on their performance during the oral presentation of the selected paper and on the audio-visual material that they prepared to support their group presentation.

5.- Attendance to the oral presentations of research papers

Accounts up to 10% of the final score (1 point out of 10). Both attendance and participation in the scientific discussions of the sessions will be evaluated, following the scale:

Attendance 90-100% = 1 point

Attendance 80-89% = 0,8 points

Attendance 70-79% = 0,7 points

Attendance 60-69% = 0,6 points

Attendance 50-59% = 0,5 points

Attendance 0-49% = 0 points

To be eligible for the retake process, the student should have been previously evaluated in a set of activities equaling at least two thirds of the final score of the course or module. Thus, the student will be graded as "No Avaluable" if the weighthin of all conducted evaluation activities is less than 67% of the final score.

Assessment Activities

Title	Weighting	Hours	ECTS	Learning Outcomes
Attendance to the oral presentations of research	10%	0	0	16, 3, 7, 10, 15, 11, 4, 14, 2, 13

papers				
Exam of theorical lessons	50%	3	0.12	16, 1, 5, 6, 7, 10, 15, 9, 11, 4, 8, 14, 2, 13
Examination of Laboratory classes	15%	1	0.04	16, 1, 3, 5, 6, 7, 10, 15, 9, 11, 4, 8, 14, 2, 12, 13
Oral presentations of selected research papers	15%	1	0.04	16, 1, 3, 5, 6, 7, 10, 15, 11, 4, 8, 14, 2, 12, 13
Self-study exercise	10%	1	0.04	16, 1, 3, 5, 6, 7, 10, 15, 9, 11, 4, 8, 14, 2, 12, 13

Bibliography

1- Gene and Cell Therapy. Therapeutic Mechanisms and Strategies. 2nd Edition. Edited by Nancy Smyth Templeton. Marcel Dekker, Inc. 2004.

2- Gene Therapy technologies, aplications and regulations. From Laboratory to Clinic. Edited by Anthony Meager. John Wiley & Sons, LTD. 1999.

3- Gene Therapy Protocols. 2nd Edition. Edited by Jeffrey R. Morgan. Humana Press. 2002.

4- Human Molecular Genetics 2. T. Strachan i A.P. Read. John Wiley & Sons, Inc., Publication. 1999.

5- Cell Therapy. D. Garcia-Olmo, J.M. Garcia-Verdugo, J. Alemany, J.A. Gutierrez-Fuentes. McGraw-Hill Interamericana. 2008.

6- Gene and Cell Therapy. Therapeutic Mechanisms and Strategies. Second edition, Revised and Expanded. N.S. Templeton. Marcel Dekker, Inc. 2004.