Universitat Autònoma de Barcelona

2018/2019

Transgenesis and Gene Therapy: from Animal to Clinic

Code: 42891
ECTS Credits: 9

Degree	Type	Year	Semester
4313772 Advanced Biotechnology	OT	0	1
4313794 Biochemistry, Molecular Biology and Biomedicine	OT	0	1

Contact

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Use of languages

Principal working language: english (eng)

Teachers

Ana Carretero Romay
Marc Navarro Beltrán
Jesús Ruberte París
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Assumpció Bosch Merino
Miguel García Martínez
Anna Maria Pujol Altarriba
Ivet Elias Puigdomenech
Verónica Jiménez Cenzano

Prerequisites

Graduate in the field of life sciences, for example:
Biology, Biochemistry, Biomedicine, Biotechnology, Pharmacy, Genetics, Medicine, Veterinary Medicine.

Objectives and Contextualisation

The student will gain insight into:

- Technologies used to generate transgenic animals overexpressing specific transgenes or mutant models with specific endogenous genes modified (knockout and knockin animal models).
- Application of the aforementioned technologies in biomedicine, biotechnology and livestock.

- Current legislation for animal experimentation
- Mouse anatomy and embryology in order to understand the embryonic development of organs and to analyze

morphological/anatomical abnormalities in genetically modified mouse models.
- *In vivo* and *ex vivo* gene therapy, including characteristics of the different types of vectors (viral and non-viral) used for gene transfer as well as their advantages and disadvantages, administration routes and applications of gene therapy in the treatment of hereditary and non-hereditary human diseases.

Skills

Advanced Biotechnology

- Apply techniques for modifying living beings or parts of these in order to improve pharmaceutical and biotechnological processes and products or develop new products. (Specialisation in molecular and therapeutic biotechnology)
- Communicate and justify conclusions clearly and unambiguously to both specialist and non-specialist audiences.
- Solve problems in new or little-known situations within broader (or multidisciplinary) contexts related to the field of study.
- Use acquired knowledge as a basis for originality in the application of ideas, often in a research context.
- Use advanced biotechnology tools in combination to solve problems in emerging areas of biotechnology.
- Use and manage bibliography and IT resources related to biotechnology responsibly.

Biochemistry, Molecular Biology and Biomedicine

- Analyse and explain normal morphology and physiological processes and their alterations at the molecular level using the scientific method.
- Analyse research results to obtain new biotechnological or biomedical products to be transferred to society.
- Apply techniques for modifying living beings or parts of these in order to improve pharmaceutical and biotechnological processes and products or develop new products.
- Communicate and justify conclusions clearly and unambiguously to both specialist and non-specialist audiences.
- Conceive, design, develop and synthesise scientific and/or biotechnological projects within biochemistry, molecular biology or biomedicine.
- Solve problems in new or little-known situations within broader (or multidisciplinary) contexts related to the field of study.
- Use acquired knowledge as a basis for originality in the application of ideas, often in a research context.
- Use and manage bibliography and IT resources related to biochemistry, molecular biology or biomedicine.
- Use scientific terminology to account for research results and present these orally and in writing.

Learning outcomes

1. Analyse research results to obtain new biotechnological or biomedical products to be transferred to society.
2. Communicate and justify conclusions clearly and unambiguously to both specialist and non-specialist audiences.
3. Describe the foundations of in vivo and ex vivo gene therapy. .
4. Descriure els fonaments de la teràpia gènica in vivo i ex vivo.
5. Distingir les diferents metodologies usades per a obtenir animals transgènics que permeten la sobreexpressió, el bloqueig o la modificació de gens endògens de manera ubiqua o específica de teixit i/o induïble.
6. Explain the characteristics of the different types of vectors used in gene transfer, their advantages and disadvantages, and their use for each disease or tissue.
7. Explicar les característiques dels diferents tipus de vectors usats per a la transferència gènica, els seus avantatges i inconvenients, així com la seva utilitat per a cada malaltia o teixit.
8. Interpret molecular or physiological alterations of a transgenic animal.
9. Interpret the results of gene therapy clinical trials in humans.
10. Proposar un protocol d'utilització de teràpia gènica.
11. Propose a protocol for the use of gene therapy.

12. Show knowledge of the different methodologies used to obtain transgenic animals that allow the global or tissue-specific and/or inducible over-expression, blockage or modification of endogenous genes .
13. Solve problems in new or little-known situations within broader (or multidisciplinary) contexts related to the field of study.
14. Use acquired knowledge as a basis for originality in the application of ideas, often in a research context.
15. Use and manage bibliography and IT resources related to biochemistry, molecular biology or biomedicine.
16. Use and manage bibliography and IT resources related to biotechnology responsibly.
17. Use scientific terminology to account for research results and present these orally and in writing.
18. Visualise morphological changes in a transgenic animal.

Content

PART 1. MOUSE MORPHOLOGICAL PHENOTYPING

By J. Ruberte, A. Carretero, M. Navarro and V. Nacher. Dept. Animal Health and Anatomy, UAB

1. Anatomic Terminology and Regions

2. Development and Placenta

3. Osteology

4. Arthrology and Miology

5. Cardiovascular System

6. Repiratory Apparatus

7. Digestive Apparatus

8. Urinary Organs

9. Male and Female Genital Organs

10. Nervous System

11. Visual Organ

12. Vestibulocochlear Organ

PART 2: TRANSGENIC ANIMALS AND GENE THERAPY

By F. Bosch, A. Pujol, P. Otaegui, E. Riu, F. Mingozzi, S. Frankhauser, V. Haurigot and M. Garcia,

Dept. Biochemistry & Molecular Biology, UAB

Part 2.1. Transgenic Animals:

1. Generation of transgenic animals by pronuclear microinjection.

2. Constitutive and conditional (tissue specific and/or inducible) Knockout/in animals.

3. Generation of *Knockout/in* animals by Genome Edition with *ZFNs, TALENs and CRISPR/Cas9*

4. Cloned animals by nuclear transfer. Aplications.

5. Consortia for genome mutagenesis and mouse phenotyping: Mouse Clinics.

6. Management of transgenic animal colonies. Current legislation on animal experimentation.

7. Aplications of transgenic animal technology in the study of diabetes, obesity, inherited diseases…

Part 2.2. Gene Therapy:

1. Introduction to the gene therapy field.

2. Characteristics of adenoviral vectors. Applications.

3. Characteristics of recombinant vectors derived from adenoassociated viruses. Applications in gene therapy for diabetes mellitus.

4. "Ex vivo" Gene Therapy: retroviral and lentiviral vectors. Applications.

5. Non-viral gene therapy. Applications.

6. Gene Therapy for Hereditary Diseases. Gene Therapy for Mucopolysaccharidosis (MPS).

7. *Invivo" genome editting with Zinc-finger nucleases*.

PART 3. INTRODUCTION AND DESIGN OF GENE THERAPY CLINICAL TRIALS FOR THE TREATMENT OF HUMAN DISEASES

By M. Chillon and A. Bosch, Dept. Biochemistry & Molecular Biology, UAB

Invited speaker: Manel Cascalló, VCN

1-Introduction to clinical trials. Factors to consider in the design of clinical trials of gene therapy. M Chillon

2-Development and production of vectors for clinical trials. M Chillon

3-Regulation on the use of Genetically Modified Organisms. Biosafety level and quality of production (GMP and GLP conditions). M Chillon

4-Clinical trials using non-viral vectors. M Chillon

5-Strategies to improve biosecurity and to reduce the immune response in clinical trials using adenoviral vectors. M Chillon

6-Adenoassociats vectors in clinical trials. Increased tissue specificity using pseudotyped AAV vectors. Immune response. A Bosch

7-Vectors derived from herpes virus in clinical trials. A Bosch

8-Advantages and disadvantages of retroviral and lentiviral vectors in clinical trials. ABosch

9-Ongoing clinical trials for specific diseases: Haemophilia, ß-Thalassemia, Primary Immunodeficiencies, Cystic Fibrosis, Duchenne Muscular Dystrophy, lysosomal storage diseases, neurodegenerative diseases, blindness, cancer, etc. A Bosch, M Chillon

Methodology

Combination of lectures and laboratory practices and presentation of a project supervised by the teacher.

Theory 72%
Laboratory 11%
Supervised work 14%
Tutoring 3%

Activities

Title	Hours	ECTS	Learning outcomes
Type: Directed			
Lectures and lab practices	55	2.2	1, 12, 3, 6, 9, 8, 11, 13, 2, 14, 15, 17, 18
Type: Supervised			
Preparation of oral presentations and lab practices	44	1.76	1, 12, 3, 6, 9, 8, 11, 13, 2, 14, 15, 17, 18
Type: Autonomous			
Literature search and study for exams	120	4.8	1, 12, 3, 6, 9, 8, 11, 13, 2, 14, 15, 17, 18

Evaluation

The evaluation of the module will be based on work done by students, attendance and class participation, practices, oral defence of a scientific paper and the grade of exams at the end of the course.

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.

Important: If plagiarism is detected in any of the works submitted, the student will fail the whole module.

Evaluation activities

Title	Weighting	Hours	ECTS	Learning outcomes
Attendance and active participation in lectures	10%	0	0	12, 4, 3, 5, 7, 6, 9, 8, 10, 13, 2, 14, 16, 15, 17, 18
Attendance to laboratory practices (part 1)	8%	0	0	12, 6, 9, 8, 11, 13, 14, 16, 15, 17, 18
Oral defence of selected papers (part 2)	32%	2	0.08	1, 12, 4, 3, 5, 7, 6, 9, 8, 10, 13, 2, 14, 16, 15, 17, 18
Theorical and practical tests (part 1 and 3)	50%	4	0.16	12, 4, 3, 7, 6, 9, 8, 10, 11, 13, 2, 16, 15, 17, 18

Bibliography

Biblography

Gene and Cell Therapy. Therapeutic and Strategies. 2nd Edition. Edited by Nancy Smith Templeton, 2000.
Molecular Medicine. Edited by R.J. Trent. 3rd Edition. Elsevier Academic Press. 2005.
DNA Pharmaceuticals. Formulation and Delivery in Gene Therapy,
DNA Vaccination and Immunotherapy. Martin Scheef. WiLey-VCH Verlay GmbH &Co.KgaA, 2005.
Gene Therapy Technologies, applications and regulations. From Laboratory to Clinic. Edited by Anthony Meager. John Wiley & Sons, LTD, 1999.
Gene Therapy. Therapeutic Mechanisms and Strategies. Edited by Nancy Smith Templeton, Danilo D Basic. Marcel Dekker, Inc, 2000.
Gene Therapy Protocols. 2nd Edition. Edited by Jeffrey R Morgan Humana Press, 2002.
Human Molecular Genetics 2. T Strachan & AP Read. John Wiley & Sons, Inc., 1999.
Molecular Biotechnology Principles and Applications of Recombinant DNA. Bernard R Glick and Jack J

Pasternak. Washington ASM Press, 1994.
The anatomy of the laboratory mouse. M. J. Cook. Academic Press, 1965
A color atlas of sectional anatomy of the mouse. T. Iwaki, H Yamashita, T. Hayakawa. Braintree Scientific, Inc., 2001.
The atlas of mouse development. M. H. Kaufman. Academic Press, 1995.
Transgenic animals. Generation and use. L.M. Houdebine. Harwood Academic Publishers 1997.
Manipulating the mouse embryo. A laboratory manual. 3rd Edition. A Nagy, et al. Cold Spring Harbor Laboratory Press, 2003.
Mouse genetics and transgenics. A practical approach. Ed. IJ Jackson & CM Abbott. Oxford University Press, 2000.
Gene Targeting. A practical approach. 2nd Edition. Ed. AL Joyner. Oxford University Press, 2000.
Transgenesis Techniques. Principles and Protocols. Edited by: Alan R. Clarke. Humana Press. 2002. (2nd Edition).
Gene Knock-out Protocols. Edited by: Martin J. Tymms and Ismail Kola. Humana Press. 2001.
Embryonic Stem Cells. Methods and Protocols. Edited by: Kursad Turksen. Humana Press.2002.
Human Molecular Genetics2. T. Strachan i A.P. Read. John Wiley & Sons, Inc., Publication. 1999.

Web links

Gene Therapy Clinical Trials Worldwide www.wiley.co.uk/genmed/clinical
Human Genome Project Information
www.ornl.gov/sci/techresources/human_genome/medicine/genetherapy.shtml
The anatomy of the laboratory mouse jaxmice.jax.org/library/notes/498.html
International Society for Transgenic Technologies
www.transtechsociety.org
Transgenesis en mamíferos
www.cnb.uam.es/~transimp/index2.html
EUMORPHIA
www.eumorphia.org
TBASE (The Transgenic/Targeted Mutation Database)
http://tbase.jax.org/
Database of Gene Knockouts
http://www.bioscience.org/knockout/knockhome.htm
BioMedNet Mouse Knockout Database
http://biomednet.com/db/mkmd

Specialized journals

Nature (www.nature.com)
Nature Medicine (www.nature.com/nm/)
Nature Biotechnology (www.nature.com/nbt/)
Nature Genetics (www.nature.com/ng/)
Proc. Natl. Acad. Sci. USA (www.pnas.org)
Journal Clinical Investigation (www.jci.org)
Cancer Gene Therapy (www.nature.com/cgt)
Current Gene Therapy (bentham.org/cgt)
Gene Therapy (www.nature.com/gt)
Gene Therapy & Molecular Biology www.gtmb.org/index_gtmb.html
Gene Therapy & Regulation www.vsppub.com/journals/jn-GenTheReg.html
Human Gene Therapy (www.liebertonline.com/loi/hum)
The Journal of Gene Medicine
www3.interscience.wiley.com/cgi-bin/jhome/10009391
Journal of Molecular Therapy
link.springer-ny.com/link/service/journals/00109
Journal of Controlled Release
www.sciencedirect.com/science/journal/01683659
Journal of Virology (jvi.asm.org)
Molecular Therapy www.sciencedirect.com/science/journal/15250016