



## HUMANITAS MEDICAL SCHOOL

**Course:** Mechanisms of diseases I

**Year:** 2<sup>nd</sup>

**Period:** 1<sup>st</sup> semester

**Credits:** 9 CFU

**Teachers:** Raffaella Bonecchi, Cecilia Garlanda, Sebastien Jaillon, Alberto Mantovani, professors Hunimed  
Seppo Meri, professor University of Helsinki

### Objectives

The course will offer an integrated introduction to mechanisms of cell, tissue, and organ injury (cellular pathology) and the major microbial agents that cause human diseases (microbiology I), the principal mechanisms of responses to injury (inflammation), and the general processes of the most relevant causes of human diseases (vascular pathology and oncology).

#### **Application of knowledge and understanding:**

At the end of the course students will gain an understanding of:

- how the body reacts to physical and biological agents to recover homeostasis
- general pathological mechanisms leading to cell injury and death
- molecular and cellular basis for inflammatory disease states
- normal functions of the innate immune system
- body's immune reactions to infections
- the general categories of infective agents (bacteria, viruses, fungi, and parasites).
- the pathogenesis of infectious diseases by different types of microorganisms and compare and contrast their pathologic causes.
- The molecular basis for neoplastic disease
- The pathological mechanisms leading to thrombosis, atherosclerosis, ischemia, infarction

#### **Making judgments; Communication skills; Learning skills.**

By the end of the course, students will have

- developed some abilities to communicate and work in team
- acquired some learning skills such as studying in a group, organizing knowledge, revising, and retaining information, select information.

### Prerequisites

To take the exam students must have passed the exams of Principles of the living matter, The Cell: Molecules and Processes, Building bodies: from gametes to organs, and Body architecture.

## Contents

The course is divided into 2 modules: general pathology (cellular pathology, innate immunity and inflammation, vascular pathology, and tumor biology) and microbiology (general microbiology and medical bacteriology). The syllabus is organized by learning outcomes specific to each lecture or for a group of lectures.

### **GENERAL PATHOLOGY:**

#### **CELLULAR PATHOLOGY** (prof Raffaella Bonecchi)

##### **Learning objectives**

At the end of these lectures and activities, students should be able to

- Discuss the pathogenesis of hyperplasia, hypertrophy, atrophy, and metaplasia, and compare and contrast their possible physiologic and pathologic causes.
- Explain causes of cellular injury and describe cellular alterations during injury
- Demonstrate understanding of cellular changes during injury and cell death

##### **Lessons**

#### **1. Mechanisms of cellular adaptation**

- Adaptation of cellular growth and differentiation
- Hypertrophy, hyperplasia, atrophy, metaplasia

*PPP portfolio: Chest pain (cardiac hypertrophy), Abnormal vaginal bleeding (Endometrial hyperplasia)*

#### **2. Cell injury and cell death**

- Causes of cell injury
- Hypoxia exposure and ATP depletion
- Oxidative stress and damage from reactive oxygen species
- Nitrosative stress and damage from reactive nitrogen species
- Mitochondrial damage

#### **3. Programmed cell death**

- Apoptosis
- Necroptosis, pyroptosis, and autophagy

#### **4. Recap on cell pathology**

### **INNATE IMMUNITY AND INFLAMMATION** (prof Raffaella Bonecchi, prof Alberto Mantovani, prof Seppo Meri)

##### **Learning objectives**

At the end of these lectures and activities, students should be able to

- Describe and discuss each of the following cell types in terms of the associated type of inflammation and their role therein: mast cells/basophils neutrophils and eosinophils monocytes/macrophages, NK cells, and dendritic cells
- Describe the classic vascular changes and cellular events of acute inflammation and discuss the receptors and ligands that are responsible for these events.
- Define and use in proper context: abscess, chemotaxis, cytokine, edema, exudate, granulation tissue, granuloma, inflammation, margination, phagocytosis, purulent, pus, pyogenic, resolution, transudate, ulcer.

- Discuss the following chemical mediators of inflammation, in terms of origin (cells vs. plasma) and chief in vivo functions: vasoactive amines, complement system, arachidonic acid metabolites, platelet activating factor, cytokines/chemokines nitric oxide, lysosomal granule contents oxygen-derived free radicals
- Describe the steps involved in the isolation and destruction of an infectious agent by cells of the innate immunity. Describe important molecules involved in the process (opsonins, phagocytic receptors)
- Compare and contrast acute, chronic, and granulomatous inflammation in terms of: etiology, pathogenesis, histologic appearance, laboratory findings, characteristic cells involved, outcome, and systemic effects.
- Describe the phases of tissue repair and cutaneous wound healing, the mechanisms of healing by first intention (primary union) and second intention (secondary union), and possible clinical consequences of abnormal wound healing.

### Lessons

#### 1. **Origin of innate immune cells: hematopoiesis (Bonecchi)**

- The hematopoietic niche
- The hematopoietic stem cells
- Hematopoietic lineages
- Cytokines and growth factors
- The normal blood counts
- Leukocytosis and leukopenia

#### 2. **The acute inflammatory response (Mantovani)**

- Cardinal signs of acute inflammation
- Blood flow alterations and vascular permeability
- The endothelium as a reactive biological structure

#### 3. **Collaborative lesson on cells mediators of inflammation (Bonecchi-Jaillon)**

- Mast cells
- Neutrophils
- Macrophages
- NK cells

#### 4. **Soluble mediators of inflammation (Bonecchi)**

- Molecular mediators active on vessels
- Molecular mediators active on leukocytes
- Primary inflammatory cytokines
- Eicosanoids

*PPP portfolio: fever*

#### 5. **Chemokines and leukocyte recruitment (Bonecchi)**

- Adhesion molecules and cell adhesion
- Migration and chemoattractants

#### 6. **Pathogen recognition in innate immunity (Mantovani)**

- Pathogen-Associated Molecular Patterns
- Structure and signalling properties of Pattern Recognition Receptors
- Structure and signalling properties of opsonic receptors
- Pentraxins

- Genetic defects in pathogen recognition
- Danger-Associated Molecular Patterns and their receptors
- 7. The complement system (Seppo Meri)**
  - Activation pathways
  - Functions
  - Regulatory mechanisms
  - Genetic defects in the complement system
- 8. Pathogen killing (Bonecchi)**
  - Mechanisms of cell-mediated cytotoxicity
  - Phagocytosis and degranulation
  - Oxygen-dependent mechanisms
  - Oxygen-independent mechanisms
  - Opsonic agents
  - Genetic defects in pathogen killing
- 9. Resolution of the inflammatory response (Bonecchi)**
  - Anti-inflammatory cytokines
  - Tissue repair and fibrosis
- 10. Chronic inflammation, fibrosis and tissue renewal (Bonecchi)**
  - Cellular and molecular effectors of chronic inflammation
  - The chronic inflammatory response and immune polarization
  - Fibrosis
  - Stem cells and tissue renewal
  - Growth factors and tissue regeneration
- 11. Acute phase reaction and systemic inflammation (Mantovani)**
  - a. Fever
  - b. Leukocytosis
  - c. Acute phase proteins

*PPP portfolio: Fever; shock, rush*
- 12. Recap lesson on inflammation (Bonecchi)**
- 13. Small groups activity (Bonecchi, Jaillon and Garlanda)**

## **TUMOR CELL BIOLOGY** (prof Sebastien Jaillon)

### **Learning Objectives**

At the end of the lecture course, students should:

- be able to understand and explain the differences between benign and malignant tumors and their relative characteristics.
- be able to understand and explain the hallmarks of cancer.
- be able to understand the molecular and cellular mechanisms that lead to cancer.
- be able to give an overview of the cancer problem, the modern view on what cancer is, from a basic to a clinical perspective (staging and grading systems, cachexia, paraneoplastic syndromes)

## 1. Introduction to tumors

- Definition
- Nomenclature
- Benign and malignant neoplasms
- Epidemiology of cancer

PPP portfolio: Obesity

## 2. Characteristics of benign and malignant tumors

- Differentiation and anaplasia. Metaplasia and dysplasia.
- Local invasion
- Metastasis, pathways of spread

## 3. Molecular basis of cancer 1

- Cellular and molecular hallmarks of cancer
- Genetic and epigenetic alterations
- Oncogenes and proto-oncogenes

## 4. Molecular basis of cancer 2

- Tumor suppressor genes
- Evasion of apoptosis
- Evasion of immune destruction
- Genome instability
- Metabolic alterations

## 5. Clinical aspect of patients with tumors

- Characteristics of neoplastic cachexia
- Paraneoplastic syndromes
- Grading and staging of tumors

PPP portfolio: Abdominal Pain, Chest Pain, Jaundice, Unexplained weight loss, Obesity, Abnormalities of Mood

## VASCULAR PATHOLOGY (professor Raffaella Bonecchi)

At the end of the lecture course, students should be able to understand and explain the

- basic mechanisms and characteristics of the process of angiogenesis and the differences with tumor angiogenesis.
- basic mechanisms and characteristics of the process of hemostasis and coagulation
- the molecular and cellular mechanisms that lead to thrombosis and atherosclerosis.

### 1. Angiogenesis

- Multipotent endothelial cells
- Angiogenesis and vasculogenesis
- Angiogenetic cytokines and their receptors

### 2. Tumor angiogenesis

- Role of angiogenesis to tumor survival and growth
- Soluble angiogenic factors and chemokines
- Endothelial progenitor cells and other relevant bone marrow-derived cells

### 3 Hemostasis and coagulation

- Platelets
- Primary and secondary emostasis

- Coagulation cascade
- Fibrinolytic system
- 4. Thrombotic diseases**
- Thrombus formation and evolution
- Clinical manifestations
- 5. Atherosclerosis**
- Mechanisms of plaque generation
- Risk factors
- Clinical manifestations and complications

## **MICROBIOLOGY and MEDICAL BACTERIOLOGY** (Prof Cecilia Garlanda)

### **Learning objectives**

At the end of these lectures and activities, students should be able to

- Describe the general categories of infective agents including bacteria, viruses, fungi, and parasites.
- Discuss the pathogenesis of infectious diseases by different types of bacterial microorganisms and compare and contrast their pathologic causes.

### **Lessons of MICROBIOLOGY:**

#### **1. Brief history of microbiology and prokaryotic and eukaryotic cells:**

- From the early years of Microbiology to the Golden and Modern ages of Microbiology. Describe how the discovery of the existence of microbes impacted human life and survival.
- Describe cell structure and function in prokaryotic and eukaryotic cells: external structures, cell wall, and cytoplasm of bacterial and eukaryotic cells. To describe the relevance in the pathogenesis of infections.

PPP: fever, shock

#### **2. Microscopy, Microbe classification, Microbial nutrition, and growth**

- Describe major techniques to perform Microscopy and microbial staining
- Describe Microbe classification, Microbial nutrition and growth, metabolism, Growth requirements. Describe how culturing microorganisms.

#### **3. Control microbial growth**

- Describe how we can control microbial growth in the environment through physical and chemical methods, and in the body through antimicrobial drugs. To describe the mechanisms of action of principal classes of antimicrobial drugs and the resistance to antimicrobial drugs.

#### **4. Characterize and classify prokaryotes:**

- Describe general characteristics and modern classification of bacteria relevant in medical microbiology.

#### **5. Characterize and classify eukaryotes:**

- Describe general characteristics of Protozoa and Fungi relevant in medical mycology, Parasitic helminths, and Insects.

#### **6. Characterize and classify viruses, viroids and prions:**

- Describe general characteristics, classification, replication, and culture of viruses. Describe Viroids and Prions.

### 7. Mechanisms of Infection

- Describe mechanisms of Infection, characteristics of infectious diseases, and the principles of epidemiology.

## Lessons of MEDICAL BACTERIOLOGY

### 8. Pathogenic Gram-positive bacteria 1

- Staphylococcus
- Streptococcus

*PPP portfolio: cough, rash, fever, chest pain, shortness of breath, abdominal pain, loss of consciousness, shock, sore throat, diarrhea, headache.*

### 9. Pathogenic Gram-positive bacteria 2

- Enterococcus
- Bacillus
- Clostridium
- Listeria
- Mycoplasmas

*PPP portfolio: cough, fever, chest pain, shortness of breath, abdominal pain, loss of consciousness, shock, diarrhea, dysuria.*

### 10. Pathogenic Gram-positive bacteria 3

- Corynebacterium
- Mycobacterium
- Propionibacterium
- Nocardia and Actinomyces

*PPP portfolio: cough, rash, fever, chest pain, shortness of breath, sore throat, unexplained weight loss.*

### 11. Pathogenic Gram-negative cocci and bacilli 1

- Neisseria
- Anaerobic bacilli: Opportunistic Enterobacteriaceae 1

*PPP portfolio: abnormal vaginal discharge, rash, fever, pelvic pain, loss of consciousness, shock, sore throat, headache, seizure.*

### 12. Pathogenic Gram-negative bacilli 2

- Anaerobic bacilli: Opportunistic Enterobacteriaceae 2: Escherichia, Klebsiella, Serratia, Proteus and others
- Anaerobic bacilli: Truly pathogenic Enterobacteriaceae: Salmonella, Shigella, Yersinia

*PPP portfolio: cough, rash, fever, chest pain, shortness of breath, abdominal pain, shock, diarrhea, dysuria.*

### 13. Pathogenic Gram-negative bacilli 3

- Anaerobic bacilli: Pathogenic Pasteurellaceae
- Aerobic bacilli: Bartonella, Brucella, Bordetella, Burkholderia, Pseudomonads
- Francisella, Legionella, Coxiella
- Anaerobic bacilli: Bacteroides, Prevotella
-



*PPP portfolio: fever, abdominal pain, diarrhea, loss of consciousness, headache, seizure, cough, chest pain, shortness of breath.*

#### **14. Pathogenic Gram-negative Rickettsias, Chlamydias and Spirochetes 1**

- Rickettsias
- Chlamydias: *C. trachomatis*, *C. pneumoniae*, *C. psittaci*
- Spirochetes: *Treponema*

*PPP portfolio: cough, fever, chest pain, shortness of breath, dysuria, abdominal pain, diarrhea.*

#### **15. Pathogenic Gram-negative Spirochetes 2 and Vibrio**

- Spirochetes: *Borrelia*, and *Leptospira*
- Vibrio: *Vibrio cholerae* and others, *Campylobacter jejuni*, *Helicobacter pylori*

*PPP portfolio: cough, fever, chest pain, shortness of breath, dysuria, abdominal pain, diarrhea.*

*Three additional lessons will be inserted in the program: these will be “revision lessons” with questions to student divided in small groups: one of general microbiology, one on Gram positive bacteria and one on Gram negative bacteria.*

## **Teaching Methods**

**Lectures:** the main purpose of lectures is to transfer knowledge to students by guiding them through the most relevant subjects of the disciplines. Collaborative lessons with teachers of the course and recap lessons will be done in order to increase the integration of the different modules. All lectures will be held synchronously, either in presence or using Teams. Students are encouraged to actively participate to the lectures with questions and comments.

**Group work activities/activation of knowledge:** These activities aim to activate and solidify knowledge acquired during lectures and independent study in a collaborative learning setting. For these activities, students will be divided into groups. Participation is mandatory.

**Problem-based learning (PBL).** One PBL will be presented and discussed by tutors with students. Attendance is mandatory and will be evaluated as written below.

**Attendance is mandatory, an absence rate of 25% will be tolerated. For higher absence rates university rules will be followed.**

## **Assessment**

Students' evaluations will be assessed through one multiple choice exam at the end of the course and by evaluation of the PBL activity.

The faculty reserves the possibility to have an oral exam.

**Content of the Exam** (40 questions): general pathology 25q (2q Cell pat, 15q inflammation and innate immunity, 5q tumor biology, and 3q vascular pathology), 15q on microbiology.





**Exam evaluation:** 40 questions, each question 0.75 points.

To pass the test you need to answer at least 24 questions correctly.

A minimum of 60% correct answers in general pathology (15q) and microbiology (9q) must be reached.

**PBL evaluation:** students will be evaluated by tutors and experts following the table below.

For every column of the table, the scale will be: 4= Excellent; 3=Good; 2=Satisfactory; 1= Poor.

Extra points will be added to the exam evaluation following these ranges

Evaluation range 5-9: 1 point; 10-14: 2 points; 15-20: 3 points.

<b>Level of participation</b>	<b>Level of professional behavior in group</b>	<b>Level of small group leadership and initiative qualities</b>	<b>Student's level of desire of feedback and response to criticism</b>	<b>Ability to deal with the process</b>
(Contributes to group process; encourages others)	(Demonstrates respect; shows punctuality; well-prepared)	(Takes initiative; provides leadership; thinks and works independently)	(Asks classmates or tutor for feedback; puts suggestions to good use)	(Identifies problems; suggests hypothesis; provides interpretations of data)

## **Texts**

- Robbins and Cotran, Pathologic Basis of Diseases, 10<sup>th</sup> edition, 2020; Elsevier
- Cellular and molecular immunology 10<sup>th</sup> edition, 2021; Elsevier
- Bauman RW, Microbiology with Diseases by Taxonomy, 6<sup>th</sup> edition, Pearson