PROGRAM OF PHARMACEUTICAL BIOLOGY
2016-2017

7 Credits

Prof.ssa Beatrice Macchi

Description and Aims:
The course aims are to provide basic knowledge on drugs and   their principal targets, general principles on mechanisms regulating interaction between drug and its target. Emphasis will be placed on recent research on biological targets and their application in the design of novel therapeutics.

General principles on drug discovery. *Rational drug design and druggable targets, drug discovery and development.*

How drugs act: general principles*: Evaluation of drug –receptor interaction: Agonist, partial agonist, antagonist, allosteric potentiation, allosteric inhibition, inverse agonist*

How drug act: molecular aspects on   drug targets: *Target for drug action, types of drug targets. Membrane targets: Ionotropic receptors (Nicotinic receptors for Acetylcolin, GABA A), Metabotropic receptors (Muscarinic receptor for Acetylcholine, GABA B receptors), Tyrosine kinases receptor (Insulin, EGF receptor) Tyrosine associated receptors (cytokine receptors). Membrane transporters, Adhesion molecules. Ion channels Intracellular targets: Acid retinoic receptor, glucocorticoid receptors*

Biopharmaceuticals and drug targets:

Therapeutic monoclonal antibodies: classification, IgG structure, Fab and Fc functions, generation of monoclonal antibodies (hybridoma method, recombinant antibodies: transgenic mice, phage display, human memory cell immortalization), differences between murine, chimeric, humanized and human monoclonal antibodies); mechanisms of action [antibody dependent cellular cytotoxicity (ADCC), complement dependent cytotoxicity (CDC); neutralization of secreted growth factors or cytokines, interaction with receptors and block of signal transduction, induction of apoptosis); naked and conjugated monoclonal antibodies targets and mechanism of action, side effects, toxicity.

RNA target: RNA interference: siRNA and microRNA; comparison with oligonucleotide antisense; isoform specific siRNA and allele specific siRNA; modified siRNA to improve efficacy; targeted siRNA; off-target effects of siRNA; clinical trials and siRNA (anti-VEGF: bevasiranib; anti-keratin, anti-VEGF; anti-tat of HIV, anti-tenascin, anti-ribonucleotide reductase); clinical trials with miRNA: microRNA-122.

The proteasome pathway:
General properties; proteasome inhibitor [bortezomib (velcade)]: principal consequences deriving from proteasome inhibition: stabilization of p53, inhibition of NF-kB and inhibition of cell cycle regulators.

Cell cycle checkpoints:
general properties; DNA damage and cell cycle arrest (ATR and ATM kinases); targeting cell cycle kinases for cancer treatment: cycle dependent kinases (CDKs) inhibitors, ATM inhibitors; inhibitors of mitosis: inhibitors of microtubule polimerization (vinca alkaloids), agents inducing microtubule stabilization (taxanes), aurora and polo kinase inhibitors.

Apoptosis : principle of apoptotic mechanisms: Drugs promoting and inhibiting apoptosis.

Mitochondria:
general properties; mitochondria and apoptosis; inhibitors of Bcl2 (obatoclax), anti-sense anti bcl-2 (oblimersen); BH3 mimetic agents; inhibition of the IAP surviving; mitochondria and reactive oxygen species (ROS); anti-oxydant defences and mithocondria protection; targeting mitochondria for Alzheimer disease with MitoQ; mitochondria in ischemia/reperfusion damage and cardioprotection; mitochondria and senescence, mitochondria damage and cardiotoxicity of anthracyclines.

Metabolism:
drug targets in metabolism: glycolysis, 5'-AMP-activated protein kinase, mTOR system, lipids

Interferon . classification. Interferon type I and III: Biological effect and characterization of targets. Jak/Stat pathway.

Epigenetic-enzymes:
general principles; histone acetyltransferase (HAC) and histone deacetylase (HDAC); HDAC inhibitors: mechanisms of action; HDAC inhibitors and retinoic acid for acute promyelocytic leukemia; DNA methylation by DNA methyltransferases (DNMT), inhibitors of DNMT.

Telomere structures and telomerase:
general principles; telomerase inhibitors for cancer treatment (example: imetelstat); telomere damaging agents (G-quadruplex ligands).

DNA: nuclear receptors; DNA damaging agents: principal mechanisms of actions (alkylating agents, antimetabolites, inhibitors of topoisomerase I or II, inhibitor of ribonucleotide reductase)
DNA repair enzymes:
principal DNA repair systems; inhibitors of O^6-methylguanine DNA methyltransferase (MGMT) and the methylating agent temozolomide; poly(ADP-ribose) polymerase (PARP) inhibitors

Genome Editing: The CRISPR/Cas system

Drug Targets in Neurodegeneration:
protein folding: general properties. Protein misfolding in neurodegeneration. Beta amyloid: generation, APP metabolism, folding, toxicity. β-secretase, γ-secretase: structure, function. Inhibitors of β-secretase, and γ-secretase complex. Inhibitors of amyloid aggregation. (GSK3β).

Tau protein, metabolism, folding, toxicity. Inhibitors of Tau. Models to study drug targeting in neurodegenerative diseases. Authophagy and mTOR system.

Principal suggested readings:

J. L. Medina-Franco, M. A. Giulianotti,G.S. Welmaker, R. A. Houghten. Shifting from the single to the multitarget paradigm in drug discovery. Drug Discovery Today. 2013. 18: 495-501.
-Beck A, Wurch T, Bailly C, Corvaia N. Strategies and challenges for the next generation of therapeutic antibodies. Nat Rev Immunol. 2010 May;10(5):345-52.
-Rask-Andersen M, Almén MS, Schiöth HB. Trends in the exploitation of novel drug targets. Nat Rev Drug Discov. 2011Aug 1;10(8):579-90.
- Gashaw I, Ellinghaus P, Sommer A, Asadullah K. What makes a good drug target? Drug Discov Today. 2012Feb;17 Suppl:S24-30.
-Watts JK, Corey DR. Silencing disease genes in the laboratory and the clinic. J Pathol. 2012 Jan;226(2):365-79.
De Strooper B, Iwatsubo T,Wolfe MS. Presenilin and Ý-secretase: Structure,Function and Role in Alzheimer disease. Cold Spring Harb Perspect Med 2012Jan 2(1):a006304.

Further bibliography will be supplied for the subjects not exhaustively described within the suggested texts.

Recommended Textbooks:

Rang and Dale's Pharmacology Eighth edition (2016), HP Rang, MM Dale, Ritter JM, Flower RJ, Henderson G. Elsevier

The Cell: A Molecular Approach, 6th Edition (2013) Geoffrey M. Cooper and Robert E. Hausman, ASM Press and Sinauer Associates, Inc.