

Faculty of Medicine Department of Cancer Research and Molecular Medicine

# Exam MOL3000 Introduction to Molecular Medicine

# Tuesday 1 June, 2010 9.00am-1.00 pm

# ECTS credits: 7.5

Number of pages (included front-page and MCQ answers sheets): 14

Examination support: English/ Norwegian or Norwegian/ English dictionary

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# Exam results: 14 June, 2010

Examination results are announced on http://studweb.ntnu.no/

#### Question 1 (10 p)

Genetic and environmental factors, including food and life style, are thought to be important in development of disease. Although the mechanisms are complex, cancer is fundamentally caused by mutations due to DNA damage that has not been repaired. Ultraviolet light (UV-light), N-nitrosocompounds and oxidative stress from reactive oxygen species (ROS) cause damage to DNA.

- a) Which are the most common types of damage caused by UV-light? Define them by name and molecular structure.
- b) Which DNA repair mechanism is responsible for repair of the most common type of UV-light damage?
- c) Which type of damage to DNA is caused by N-nitrosocompounds? Give at least one example of an N-nitrosocompound found in the environment and at least one example of a DNA damage caused by such compounds.
- d) Define what is meant by reactive oxygen species (ROS) and give at least one example of a ROS.
- e) Give at least one example of DNA damage caused by ROS.

#### Question 2 (10 p)

Cancer is the second most common cause of death in many countries.

- a) Explain briefly principle characteristics of cancer cells as compared to normal cells.
- b) The protein p53 is mutated or inactivated in a large fraction of human tumours. Outline the mechanisms of action of p53.

#### Question 3 (5 p)

FISH (Fluorescence In Situ Hybridization) can be used to detect genetic translocations in cancer cells. Describe briefly how FISH works.

#### Question 4 (5 p)

Describe briefly clinical characteristics of Sickle Cell anaemia and the most common mutation and the molecular mechanisms underlying the disease. Discuss the possibilities/ challenges using gene therapy in this disease.

## Question 5 (10 p)

Cells have to react upon a wide variety of signals. The term "signal transduction" describes the overall process how cells convert an extracellular signal into a specific cellular response and includes several intracellular signaling pathways. However, there are many common features which are found in most signal transduction pathways.

a) Describe the general features of signal transduction.

Dysregulated signal transduction pathways can have serious consequences for a single cell but also for the whole organism. One example is the ERK MAPK pathway which is linked to cancer: A mutated *RAS* gene is found in many human cancer types. The resulting Ras<sup>D</sup> protein exhibits one amino acid substitution which impairs the GTPase activity.

b) Explain how this mutant Ras<sup>D</sup> protein is cancer-promoting.

# MCQ, each question 1p. One answer is the most correct. Answer the questions on <u>separate MCQ answers sheets</u> enclosed. Only one cross for each question (the best alternative).

## 1.

Oncogenic <i>RAS</i> is found in approx. 30% of all human tumours.		
What is the mechanism of oncogenic activation of <i>RAS</i> ?		
А	Translocation of the gene	
В	Amplification of the gene	
С	Overexpression of the gene	
D	Point mutation in the gene	

## 2.

Activation of an oncogene can take place without point-mutation of the protein-coding sequence.

Wha	What is the most common cause of this?	
А	The mutation in the protein-coding sequence can be silent	
В	The mutation in the protein-coding sequence can be missense	
С	The protein-coding sequence can be translocated	
D	The protein-coding sequence can be deleted	

## 3.

Cancers originating from cells in different stages of the B-cell lineage often have translocations involving the immunoglobulin (heavy- or light-chain) genes.

Why is this?		
А	Immunoglobulins are used in an immune attack on cancer cells	
В	Immunoglobulin genes are rearranged as a part of normal immune defence mechanisms	
С	B-cells are genetically unstable due to amplification of immunoglobulin genes	
D	Immunoglobulin genes exist in many copies in B-cells	

Usually tumour suppressor genes must be inactivated for a tumour to develop.			
Why	Why is inactivation of both alleles of a tumour suppressor gene required?		
А	Inactivation of a tumour suppressor gene represents a loss of function, and both		
	alleles must be inactivated for this to occur.		
В	Inactivation of tumour suppressor gene represents a gain of a new function, and		
	both alleles must be inactivated for this to occur.		
С	The two alleles of a tumour suppressor gene cooperate to suppress tumours.		
D	One allele of a tumour suppressor gene suppresses the expression of the other		
	allele.		

Mutation in the <i>APC</i> gene plays a crucial role in development of Familial Adenomatous Polyposis	
What type of protein is Apc?	
А	Tumor suppressor
В	Proto-oncogene
С	Growth factor
D	Growth factor receptor
Е	Transcription factor

6.

Monogenic inheritable diseases frequently present in childhood. Cystic fibrosis is one such disease, affecting approximately 1 in 2500 individuals.

Which is the correct statement about the genetics of cystic fibrosis:

А	The disease is autosomal dominant and affects both sexes with equal probability.
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В	The disease is X-linked and therefore transmitted from the mother who is ca	rier.
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C The disease is autosomal recessive and affects both sexes with equal probability.

D	The disease is X-linked by	it affects both s	sexes due to triplet e	expansion.
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E The disease is X-linked and therefore affects only males.

# 7.

Cystic fibrosis (CF) is mostly due to mutation in the gene encoding <i>CFTR</i> (Cystic Fibrosis Transmembrane conductance Regulator)		
The molecular mechanisms underlying CF is most precisely described as		
А	Defective cation secretion and excessive sodium reuptake	
В	Defective anion secretion and excessive sodium reuptake	
С	Defective anion secretion with insufficient intraluminal dehydration	
D	Defect in the respons to cAMP leading to constitutive open chloride channels	

8.

Hereditary nonpolyposis colorectal cancer (HNPCC, also called Lynch syndrome) is a disease with a predisposition to develop colon cancer during lifetime.

 Most commonly the patient is born with a mutation in one of the following genes:

 A
 PMS2

- BMLH1 or HJVCAHF or MSH6DMSH2 or MLH1
  - E MSH6 or MLH2

Muta polyp	tion in the APC gene plays a crucial role in development of Familial adenomatous posis
What type of protein is APC?	
А	Tumour suppressor
В	Proto-oncogene
С	Growth factor
D	Growth factor receptor
Е	Transcription factor

# 10.

The protein hepcidin is produced in liver and is required for iron homeostasis.	
The main function of hepcidin is to	
А	Increase the synthesis of heme
В	Increase iron export from intestinal epithelia cells
С	Reduce iron uptake in liver by forming complex with the transferrin receptor
D	Increase storage of iron in liver
Е	Reduce iron export from intestinal epithelia cells

# 11.

In previous years it was debated whether deficient insulin secretion or insulin resistance is the main and primary cause of type 2 diabetes		
Which is the consensus of today?		
А	Deficient insulin secretion is the main causative factor	
В	Deficient sensitivity (= resistance) is the main causative factor	
С	Both A and B are important causative factors.	
D	Neither A nor B are important	

Glucose is the main stimulator of insulin secretion	
Concerning mechanisms of secretion, which statement is true?	
А	Glucose stimulates secretion by binding to extracellular receptors
В	Uptake of glucose stimulates secretion by increasing intraclellular osmolarity
С	Glucose binds to insulin granules thereby transforming them into a releasable state.
D	Glucose is metabolized to ATP and increased ATP in the cytosol triggers secretory events

Maturity onset Diabetes in the Young (MODY) is caused by a single gene mutation	
Which one of the following genes is a MODY gene?	
Α	HNF (hepatic nuclear factor)- 1
В	HIF (hypoxia inducible factor) – 1 alpha
С	GLUT (Glucose transporter) - 1
D	GLUT (Glucose transporter) - 4

14.

People with diabetes run an increased risk of developing foot ulcers.

Which one of the following conditions – known to occur in diabetes - is a recognized risk factor?

А	Neuropathy
В	Hypoglycemic episodes
С	Ketosis
D	Elevated fatty acids

# 15.

Oncoproteins and tumour suppressor proteins are important in cancer development	
What is the best known function of the tumour suppressor p53?	
А	Direct protein interaction
В	Regulation of microRNAs
С	Transcriptional activation of target genes
D	Transcriptional repression of target genes

**16**.

Oncoproteins and tumour suppressor proteins are important in cancer development	
How is p53 activated by expression of oncogenes?	
А	p14ARF binds and inhibits MDM2
В	p14ARF phosphorylates and inhibits MDM2
С	ATM phosphorylates and activates p53
D	p14ARF binds and activates p53

Onco	Oncoproteins and tumour suppressor proteins are important in cancer development	
What describes most precisely the mechanism of p53-dependent cell cycle arrest?		
А	p53 stimulates the expression of p21	
В	p53 stimulates the expression of checkpoint kinase 1 and 2	
С	p53 stimulates the expression of the Cdc25 inhibitor p21	
D	p53 stimulates the expression of the CDK inhibitor p21	

1,2-Diacylglyerol (DAG) and inositol-1,4,5-trisphosphate (IP3) are two important second messengers.	
How do they interfere with the signaling of Ca <sup>2+</sup> ?	
А	IP3 opens IP3-gated $Ca^{2+}$ channels in the plasma membrane and DAG activates $Ca^{2+}$ -dependent protein kinase C
В	IP3 opens IP3-gated $Ca^{2+}$ channels in the ER membrane and DAG activates $Ca^{2+}$ -dependent protein kinase A
С	IP3 opens IP3-gated $Ca^{2+}$ channels in the ER membrane and DAG activates $Ca^{2+}$ -dependent protein kinase C
D	D: IP3 blocks the $Ca^{2+}$ ATPase in the plasma membrane and DAG activates $Ca^{2+}$ -dependent protein kinase C

# 19.

Cholera is an infectious disease caused by the bacterium Vibrio cholera.		
How	How does the cholera toxin (CTX) dysregulate the G-protein coupled receptor	
sign	anng in the nost cen?	
А	CTX modifies the Gs $\alpha$ -subunit which is unable to hydrolyze bound GTP resulting in decreased cAMP level.	
В	CTX modifies the Gs $\alpha$ -subunit which is unable to hydrolyze bound GTP resulting in increased cAMP level.	
С	CTX modifies the Giα-subunit which is unable to hydrolyze bound GTP resulting in increased cAMP level.	
D	CTX modifies the Giα-subunit which is unable to exchange GDP resulting in increased cAMP level.	

Individuals with mutations in the <i>MLH1</i> gene are predisposed to develop colon cancer.	
The MLH1 protein is:	
А	A growth factor
В	A tumour suppressor protein
С	Involved in negative feedback of growth factor-mediated signalling
D	Involved in DNA repair
Е	A kinase mediating growth factor responses

The mitogen-activated protein kinases (MAPK) are important components of mammalian signal transduction pathways. The ERK, JNK and p38 MAPK pathways are among the best explored MAPK pathways.

Which two of them are classically linked to apoptosis?

А	ERK and JNK MAPK
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B JNK and p38 MAPK

C p38 and ERK MAPK

D ERK, JNK and p38 MAPK

# 22.

The ERK MAPK pathway can be activated by growth factors amongst others.

What class of cell-surface receptors do growth factors such as the epidermal growth factor (EGF) commonly activate?

А	G protein coupled receptors
В	Receptor tyrosine kinases
С	Cytokine receptors
D	Ion-channel coupled receptors

# 23.

Communication between cells in a multicellular organism is essential and numerous genes in the human genome are involved in signaling on different levels.

Why is such communication so important for cells?	
А	To be able to coordinate and regulate their activity
В	To be able to secrete signaling molecules
С	To be able to reach all the other cells in the body
D	To be able to proliferate and grow
Е	To be able to benefit from the activity of other cells

# 24.

The adrenal medulla produces and secretes a hormone that is important for the shorttime stress reaction of the body.

What is the name of this hormone?	
А	Gastrin
В	Insulin
С	Epinephrine
D	Cortisol
Е	Thyroxine

Cadherins (*ca*lcium-dependent *adh*esion molecules) are a family of adhesion molecules. Cadherins interact with other cadherins on adjacent cells, and are anchored to the cytoskeleton of the cell, thus forming a mechanical unit.

What is the name of this type of intercellular signaling?	
А	Neuroendocrine
В	Endocrine
С	Paracrine
D	Neurocrine
Е	Contact-dependent

#### 26.

Signalling in response to lipopolysaccaride (LPS) is through TLR4. For the initiation signalling, however, TLR4 utilize two co-receptors.

What is the name of the co-receptors?	
А	CD14 and MD2
В	LBP and CD14
С	MD-2 and LBP
D	LBP and CD14
Е	EEA1 and LBP

## 27.

Toll-like receptors (TLRs) recognize invading pathogens and initiate host responses necessary for pathogen clearance.

In which cellular compartments are the toll-like receptors expressed?	
А	On endosomes and in the cytoplasm
В	On the cell surface and on endosomal compartments
С	On the cell surface and cytoplasm
D	Only in the cytoplasm
Е	Only on the cell surface

28.

Eukaryotes, including humans, have evolutionary conserved mechanisms for pathogen recognition.

Which statement is the most accurate regarding the mechanism of microbe recognition used by the Toll-like Receptors (TLRs)?

Α	Detection of compounds that differ from host
В	Detection of patterns that differ from host
С	Detection of patterns that are common to classes of microorganisms
D	Detection of non-host antigens
Е	Detection of cell damage resulting from pathogen invasion

Blast is a search method that can be used to find similar sequences (protein, DNA) in a database, based on a query sequence. PSI-Blast is a variant of Blast that is particularly suited to finding sequences with relatively low similarity to the query sequence.	
What is the main reason why PSI-Blast is more sensitive than Blast?	
А	PSI-Blast uses Psi-theory to increase the sensitivity of the Blast algorithm.
В	PSI-Blast is iteratively building a search profile which integrates information from several related sequences.
С	PSI-Blast uses a library of iterative search profiles.
D	PSI-Blast uses a more strict significance value than Blast for possible hits.
E	PSI-Blast improves Blast hits through an iterative optimization of each alignment.

# 30.

Blast and PSI-Blast are typically used for searching with a given sequence in a data base to find significantly related sequences, often expressed as an E-value.	
How can the size of the data base affect the estimate of significance?	
А	Results from small data bases require smaller E-values to be significant.
В	Large data bases can easier cause errors in E-value estimates.
С	Size of the data base does not matter.
D	Results from small data bases require larger E-values to be significant.
Е	Small data bases contain too little information to give correct E-values.

A do	A dotplot may be used to compare two sequences (protein, DNA).	
What kind of information can we read from a dotplot?		
Α	A dotplot will directly give us the optimal alignment between two sequences.	
В	A dotplot visualizes similar regions in two sequences as diagonal stripes of dots.	
С	A dotplot shows regions with similar secondary structure in two proteins.	
D	A dotplot shows were the sequences have sequencing errors.	
Е	A dotplot is just a tool for explaining how to find an optimal alignment of two	
	sequences.	

-		
Single nucleotide polymorphisms (SNPs) are considered as normal variants of genes.		
Whi	Which statement about SNPs is the most correct one:	
А	SNPs are associated with specific diseases, but only when in combination with environmental factors.	
В	SNPs may cause disease when associated with copy number variations (CNVs).	
С	SNPs are associated with specific diseases, but with relatively modest increases in odds ratios (OR).	
D	SNPs are associated with clinical and biochemical phenotypic variation, but not with disease.	
Е	SNPs are normal gene variants and are therefore not associated with increased risk of disease.	

## 33.

DNA replication of chromosome ends requires the action of a specific enzyme. This enzyme is important to make cancer cells immortal.

Which enzyme is required for maintenance of chromosome ends?	
Helicase	
Topoisomerase	
Telomerase	
DNA polymerase	
RNA polymerase	

## 34.

DNA in eukaryotic cells is replicated using each of the two DNA strands as a template for the synthesis of a complementary DNA strand. After one round of replication each "new" DNA double helix consists of one parental strand and one new "daughter" strand.

One says that DNA replication is:	
А	Bidirectional
В	Semi-conservative
С	Continuous
D	Discontinuous
Е	Conservative

DNA replication initiates at specific chromosomal sites.	
These sites are termed:	
А	Okazaki fragments
В	Replication forks
С	Replication primers
D	Replication origins
Е	Replication bubbles

#### 36.

In eukaryotic cells different DNA polymerases serve different functions.		
What is the main function of DNA polymerase $\delta$ (delta)?		
А	Mitochondrial replication	
В	Nuclear chromosomal replication	
С	Discontinuous DNA replication	
D	Semiconservative DNA replication	
E	DNA repair replication	

# 37.

Mutations in the human genome can cause hereditary disease and cancer		
Which statement does most accurately describe a point mutation?		
А	A nucleotide change that causes a single amino acid substitution	
В	A deletion, insertion or replacement of a single nucleotide in the genome	
С	A mutation that does not cause a change in amino acid	
D	Any nucleotide change that does not cause shift of reading frame	
Е	Any type of triplet deletion or insertion	

# 38.

Lipoproteins are particles that transport lipids in the blood. One of them is produced in enterocytes lining the small intestinal wall and transports fat from the intestine, via lymph to the blood.

Which lipoprotein transports absorbed fat from the intestine?		
А	HDL	
В	LDL	
С	IDL	
D	chylomicron	
Е	VLDL	

Lipoproteins are particles that transport lipids in the blood. They all contain both triacylglycerols ("triglycerides") and cholesterol, but in different relative proportions. Which lipoprotein is the <u>second</u> most important one for transport of TG, in terms of quantity.

А	HDL
В	LDL
С	IDL
D	chylomicron
Е	VLDL

## 40.

 Lipoproteins are particles that transport lipids in the blood. Two lipoproteins are central in cholesterol transport.

 Which lipoprotein transports cholesterol from peripheral tissues to the liver?

 A
 HDL

 B
 LDL

 C
 IDL

 D
 chylomicron

 E
 VLDL