Exercise 1 (5 points) Neurofibromatosis Type 1

Neurofibromatosis type 1 is an autosomal hereditary disease which is manifested by the appearance of lightly pigmented spots at the level of the skin and malformations at the level of skeleton.

Neurofibromatosis type 1 is related to a protein called Neurofibromin1, symbolized by NF1. This protein is indispensable for the regulation of cell division.

The synthesis of NF1 protein is controlled by a gene called NF1 which exists in two allelic forms.
A research is performed to determine the genetic origin of this disease.

Document 1 presents a fragment of the transcribed strand of the normal allele of gene NF1 in a healthy individual and that of the abnormal allele in an individual affected by neurofibromatosis type 1.

Number of triplet :	1	2	3	4	5	6
Normal allele:	AAA	ACG	AAA	CTG	TAG	GAA
Abnormal allele:	AAA	ACG	AAC	TGT	AGG	AA

Reading direction

Document 1

1.1- Compare the two fragments.
1.2- Draw out the position and the type of mutation that took place.

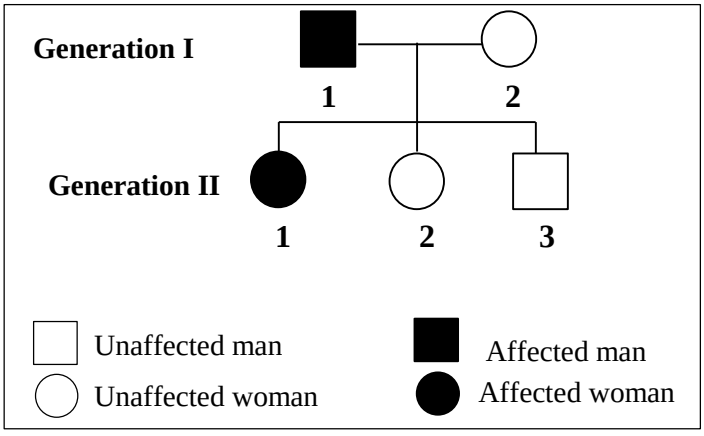
Document 2 presents a part of the genetic code table.

Codons	UAA UAG	UCU UCC	ACA ACG	AUU AUC	GAU GAC	CUU UUG	UGU UGC	UUU UUC
Amino acid	**(Stop)**	**Ser**	**Thr**	**Ile**	**Asp**	**Leu**	**Cys**	**Phe**

Document 2

2- Write, based on documents 1 and 2, the mRNA and the amino acid sequences corresponding to each of the normal allele and the abnormal one.
3- Explain how the modification of the nucleotide sequence of the normal allele leads to the appearance of the symptoms of neurofibromatosis type 1.

Document 3 presents the pedigree of a family where some members are affected by neurofibromatosis type 1.
It is given that individual I_2 is homozygous.



Document 3

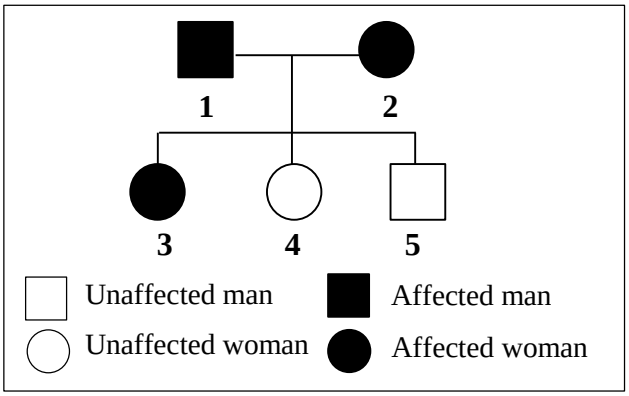
4- Show that the allele responsible for the disease is dominant.
5- Determine the probability of couple I_1 - I_2 to have an affected child.

Exercise 2 (5 points) **Familial Hypercholesterolemia**

Familial hypercholesterolemia or HF is an autosomal dominant hereditary disease characterized by a high level of LDL (carrier of cholesterol) circulating in the blood. This hypercholesterolemia is due to a mutation of a gene responsible for the synthesis of a protein which plays the role of an LDL membrane receptor at the level of liver cells.

Let D represents the symbol of the mutant allele and n the symbol of the normal allele.

Document 1 presents the pedigree of a family where some members are affected by HF.



Document 1

1- Choose the correct answer. Justify the choice.

1.1- the genotype of individual 2 is:

a- D//n

b- D//D

1.2- the genotype of individual 4 is:

a- D//D

b- n//n

Familial hypercholesterolemia or HF has two origins:

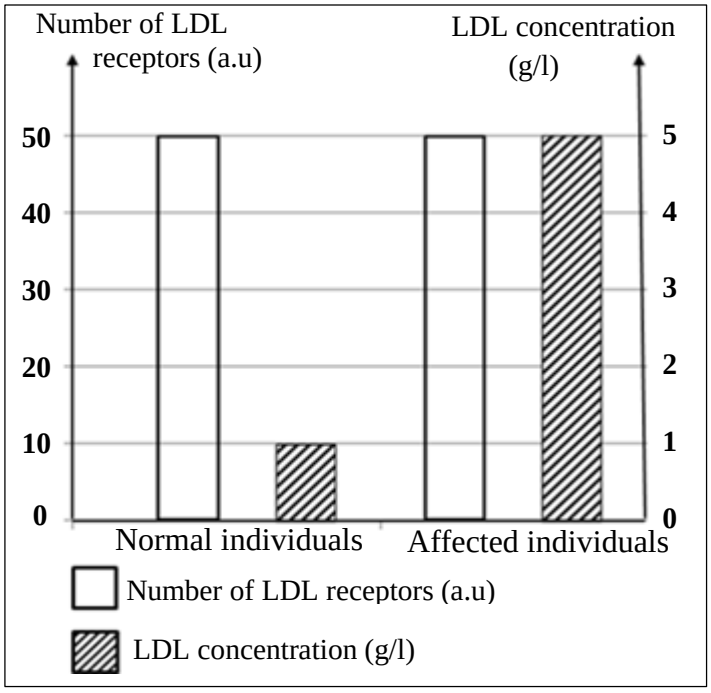
Origin 1: A mutation leading to the production of a limited number of LDL receptors at the level of the liver.

Origin 2: A mutation leading to the production of abnormal LDL receptors at the level of the liver.

In order to determine which of these two origins is responsible for HF in a family A, the LDL concentration and the number of LDL receptors in liver cells are measured in normal and affected individuals in family A.

Note that the fixation of LDL on its receptor leads to a decrease in its concentration in the blood.

The obtained results are presented in document 2.



Document 2

2- Construct a table representing the results of document 2.

3.1- Compare the obtained results.

3.2- Conclude the origin of HF in family A.

The results of the same measurements in individuals affected by hypercholesterolemia belonging to another family B show that these individuals have an LDL concentration of 5g/l and a number of LDL receptors in liver cells of 3 a.u.

4- Draw out the origin of HF in family B.

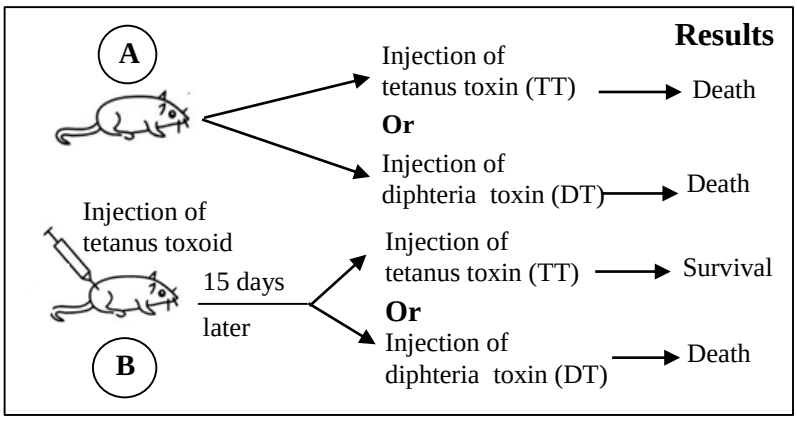
Exercise 3 (5 points) Immune Response Against Bacteria

Tetanus and diphtheria are two diseases caused by the invasion of the organism by bacteria. These bacteria release tetanus toxin and diphtheria toxin respectively in the body.

In order to study the immune response against these bacteria, several experiments are carried out.

Experiment 1:
An experiment is carried out on two guinea pigs A and B. The experimental conditions and the results are given in document 1.

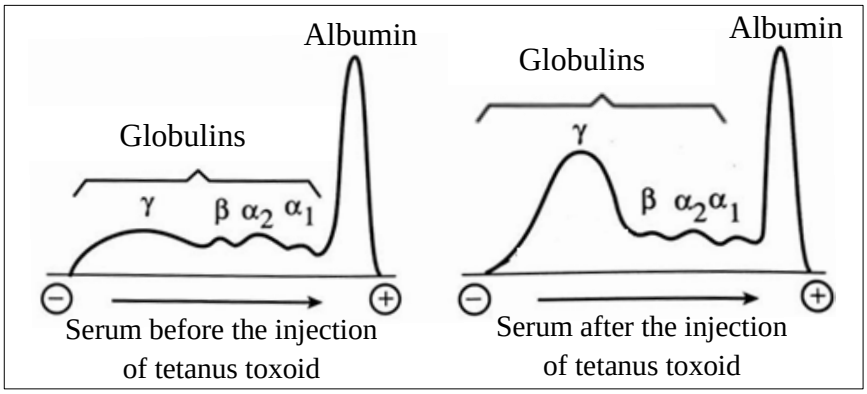
1- Interpret the obtained results.
2- Draw out a characteristic of the immune response.



Document 1

Experiment 2:
Serum from guinea pig B is taken before and after the injection of tetanus toxoid. The analysis of the proteins found in this serum is done. The results are shown in document 2.

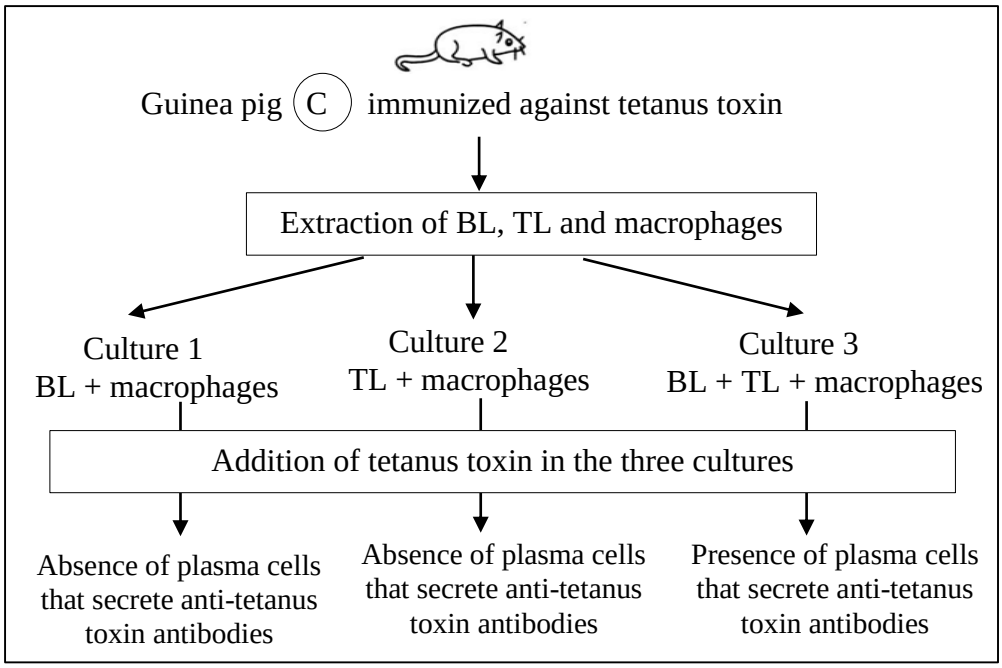
3- Specify the nature of the immune response triggered against tetanus toxin.



Document 2

Experiment 3:
Scientists seek to identify the cells involved in the immune response against tetanus toxin.
Document 3 presents the experimental conditions as well as the results obtained.

4- Deduce the necessary condition for the production of anti- tetanus toxin antibodies.
5- Name the molecule indispensable for the differentiation of BL into plasma cells.



Document 3

Exercise 4 (5 points) **Immune Response against a Virus**

In order to determine the nature of the immune response against an infection by a virus X, three experiments were carried out.

Experiment 1: In mice infected with virus X, we study the evolution of the blood concentration of virus X and that of the number of LT8 specific for virus X as a function of time. Document 1 presents the obtained results.

Time (days)	1	4	6	7
Blood concentration of virus X (a.u.)	10^7	10^6	10^4	0
Number of LT8 specific for virus X ($x10^3$)	0	100	300	120

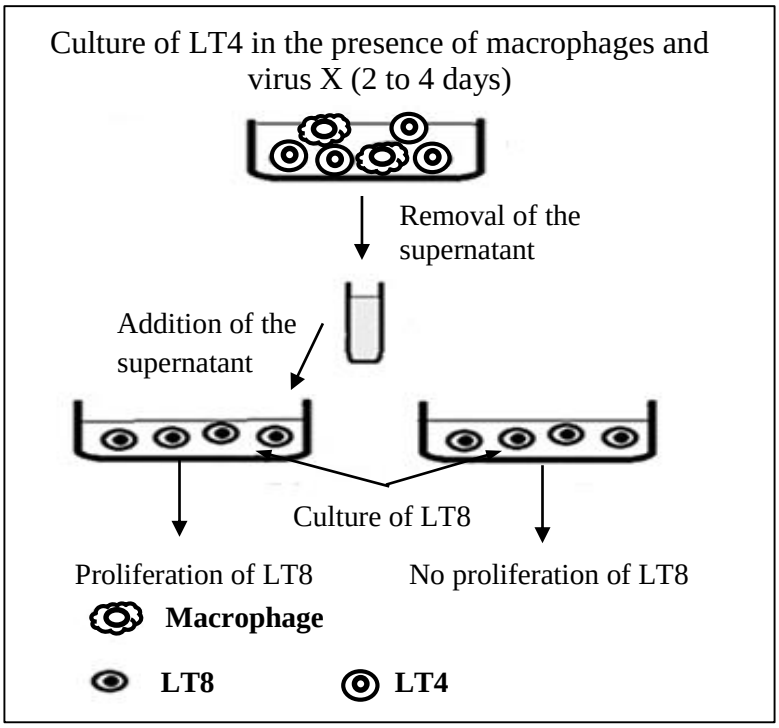
Document 1

1- Analyze the obtained results.
2- Name the type of the specific immune response triggered against virus X.

Experiment 2: LT4 are cultured in the presence of macrophages and virus X. The experimental conditions as well as the results are represented in document 2.

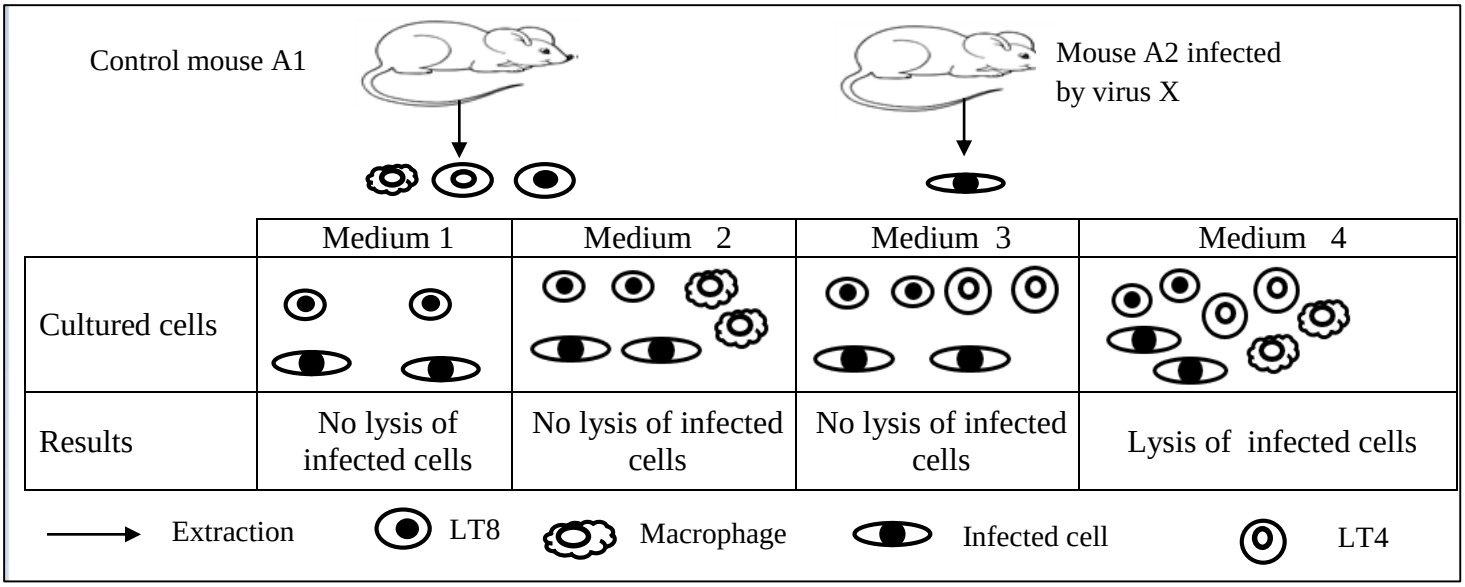
3.1- Analyze the results of experiment 2 (document 2).
3.2- Draw out the role and the mode of action of the involved LT4.

Experiment 3: An experiment is carried out on two mice of the same strain. Cells infected by virus X are extracted from mouse A2.



Document 2

Then, cells are added to the culture medium containing different immune cells extracted from the control mouse A1. The experimental conditions as well as the results are shown in document 3.



Document 3

4- Determine from document 3 the condition necessary for the lysis of the infected cells.
5- Explain, referring to acquired knowledge, the mechanism of lysis of infected cells by LT8.

علوم الحياة
أسس التصحيح

الاسم:
الرقم:

1	**Exercise 1 (5 points) Neurofibromatosis Type 1**	**Grade**
1.1	The first two triplets are identical in both alleles, but the number of total triplets in the fragment of the abnormal allele is 5 triplets in addition to 2 nucleotides (or 17 nucleotides) which is less than the number of triplets in the fragment of the normal allele which is 6 (or 18 nucleotides).	0.5
1.2	The mutation is at the level of one of the nucleotide (A) in the third triplet It is a point mutation by deletion.	0.5
2	Normal allele: Transcribed strand AAA ACG AAA CTG TAG GAA mRNA UUU UGC UUU GAC AUC CUU Amino Acids Phe - Cys - Phe - Asp - Ile - Leu Abnormal allele: Transcribed strand AAA ACG AAC TGT AGG AA mRNA UUU UGC UUG ACA UCC UU Amino Acids Phe - Cys - Leu - Thr - Ser	1
3	The mutation by deletion of the nucleotide A at the level of the third triplet will cause a modification at level of transcribed mRNA leading to a change at the level of the translated amino acid sequence. This new amino acid sequence affects the three-dimensional form of NF1 which becomes inactive (non-functional). As this protein is indispensable for the regulation of cell division, the symptoms of the disease, lightly pigmented spots at the level of the skin and malformations at the level of the skeleton, will appear.	1
4	Woman I2 is healthy and homozygous which means that she can only transmit the healthy allele to her children but her daughter II 1 is affected and inherits the normal allele which is not expressed and masked by the allele determining the disease. OR If the allele determining a normal phenotype was dominant, then woman I2 who is homozygous would be of genotype NN thus obligatory transmitting allele N to all her children who would be unaffected but this is not the case.	1
5	Mother I2 is unaffected of a recessive phenotype, her genotype is thus. Mother I2 of genotype n//n can only transmit one allele n. Thus, the phenotype of the child depends on the allele inherited from his father. Since the father is heterozygous, the probability to produce a gamete carrying the allele D is ½. Father I1 of genotype Dn can transmit two alleles, allele D and ½ allele n. Thus, the probability of the couple I1 and I2 to have an affected child = ½.	1

<table>
<tr><th>Part</th><th>Exercise 2 (5 points) Familial Hypercholesterolemia</th><th>Grade</th></tr>
<tr><td>1.1</td><td>Genotype of individual 2 is D//n, since the disease is autosomal dominant and woman 2 is affected but has 2 unaffected children 4 and 5 who must have inherited the normal allele which is masked by the mutant one. Thus woman 2 is heterozygous.</td><td>0.5</td></tr>
<tr><td>1.2</td><td>Genotype of individual 4 is n//n, since she is an unaffected girl and the normal allele is recessive thus it is only must be expressed in the homozygote state.</td><td>0.5</td></tr>
<tr><td>2</td><td><table><tr><td>Individual</td><td>Normal</td><td>Affected</td></tr><tr><td>Number of LDL receptors (a.u.)</td><td>50</td><td>50</td></tr><tr><td>LDL Concentration (g/L)</td><td>1</td><td>5</td></tr></table>Variation in LDL receptor number (a.u.) and LDL concentration (g/L) in normal and affected individuals</td><td>2</td></tr>
<tr><td>3.1</td><td>The number of LDL receptors is the same and equal to 50 a.u. in both normal and affected individuals. However, the concentration of LDL in affected individuals is 5 g/l which is greater than that in normal individuals equals to 1 g/l.</td><td>1</td></tr>
<tr><td>3.2</td><td>The origin of HF in family A is a mutation leading to the production of abnormal LDL receptors at the level of the liver.</td><td>0.5</td></tr>
<tr><td>4</td><td>The origin of HF in family B is a mutation leading to the production of a limited number of LDL receptors at the level of the liver.</td><td>0.5</td></tr>
</table>

Part	Exercise 3 (5 pts) Immune Response against Bacteria	Grade
1	The death of guinea pig A is due to its injection by TT or by DT, this indicates that TT and DT are fatal. On the other hand, the injection of tetanus toxoid in the guinea pig B before 15 days of its injection by TT causes its survival or the injection of the guinea pig B by DT causes its death. This indicates that tetanus toxoid protects the guinea pig against TT and not against DT.	**1.5**
2	The immune response against tetanus toxin is specific.	**0.5**
3	The immune response is a specific humoral immune response since antibodies are the effector molecules of the humoral response and following the injection of guinea pig B with tetanus toxoid, the concentration of δ globulins which are antibodies increases in the serum.	**1**
4	Since only in medium 3 containing LB, LT and macrophages, the presence of plasma cells secreting anti-tetanus toxin antibodies is obtained after the addition of tetanus toxin, hence the cooperation between macrophage, LB and LT is necessary for the production of anti-tetanus toxin antibodies.	**1.5**
5	Interleukin 4 (IL4).	**0.5**

Part	Exercise 4 (5 pts) Specific Immune Response	Grade
1	From day 1 to day 7, following the infection of mice by virus X, the number of LT8 specific to virus X increases from 0 to $300x10^3$ on d=6, then decreases to 120 $x10^3$ at day 7; however the blood concentration of virus X decreases from 10^7 a.u. to null.	**1**
2	The immune response is a specific cell-mediated immune response.	**0.5**
3.1	There is proliferation of LT8 only upon the addition of the supernatant liquid taken from a culture of LT4 in the presence of macrophage and virus X. However, there is no proliferation of LT8 in the absence of the supernatant.	**1**
3.2	LT4 stimulate the multiplication/proliferation of the LT8 lymphocytes by the secretion of a chemical substance/chemical messengers. (Interleukins)	**0.5**
4	No lysis of infected cells is obtained in medium 1,2, and 3 despite the presence of LT8 in medium 1 or LT8 with macrophages in medium 2 or LT8 and LT4 in medium 3. On the other hand, the presence of macrophages, LT4 and LT8 in medium 4 causes the lysis of infected cells. This indicates that the cooperation between macrophages and LT4 is necessary to activate LT8 thus inducing the lysis of infected cells.	**1**
5	The TCR of LT8 performs double recognition by binding to the MHC Class I - viral peptide complex on the target cell. It then secretes perforin which form a polyperforin channel on the plasma membrane of the target cell, then it releases granzymes which cross the polyperforin channel and enter the target cell, causing the degradation of its DNA and subsequently leading to its destruction by apoptosis.	**1**