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# VCE Biology ¾
## AOS 1 Revision [1.0]
## SAC 4

40 Marks. 5 Minutes Reading. 60 Minutes Writing.

## Section A: SAC Questions (40 Marks)

**CRISPR-Cas9 in Treating Transthyretin Amyloidosis**

In an unprecedented clinical case study, CRISPR-Cas9 gene-editing technology was employed to target transthyretin amyloidosis, a debilitating genetic disorder. The trial involved a novel therapy, where patients received a one-time intravenous treatment designed to disrupt the mutated TTR gene within the liver, the site of the protein's synthesis.

The CRISPR-Cas9 system, delivered through lipid nanoparticles, was engineered to locate and cleave the specific DNA sequence harbouring the mutation responsible for the production of the defective TTR protein. This protein misfolds, and the accumulation of this misfolded protein as amyloid fibrils in tissues leads to systemic organ dysfunction and disease progression.

The trial's participants were closely monitored for efficacy and safety. Remarkably, results indicated a substantial reduction in serum TTR levels, correlating with decreased amyloid deposits. This reduction suggested that the treatment not only alleviated the clinical symptoms but also addressed the pathogenic root of the disease.

This therapeutic intervention represents a significant advance over traditional approaches, which have largely been confined to symptom management and do not modify the underlying genetic defect. Symptom management, it must be noted, has been found to be incredibly successful in providing patients with a relatively symptom-free life at a reduced cost. The success of the therapy in reducing the production of the mutant protein offers hope for a durable and potentially curative treatment.

The clinical trial also established the CRISPR-Cas9 system's safety profile, with most adverse events being mild and transient. Crucially, the study's longitudinal follow-up is assessing long-term outcomes, including any potential off-target effects and the stability of the gene edit over time.

The implications of this case study extend beyond transthyretin amyloidosis, setting a precedent for the use of in vivo gene editing in treating a range of genetic disorders. It underscores the therapeutic potential of CRISPR-Cas9 and opens new avenues for genetic research and medicine.

Moreover, the trial demonstrates the possibility of correcting genetic defects directly within the patient's body, a concept that shifts the paradigm from managing to curing inherited diseases. The success of this gene therapy heralds a new era in precision medicine, where treatments are tailored to the individual genetic makeup, offering a personalised approach to healthcare.

The case study is not only a testament to the power of genetic engineering but also emphasises the importance of ethical considerations in gene editing. With the capability to alter DNA comes the responsibility to ensure that such interventions are safe, ethical, and accessible to those in need.

In summary, the use of CRISPR-Cas9 in this clinical setting has shown that targeted gene editing can have profound effects on treating genetic diseases, potentially offering life-changing benefits to patients with conditions once deemed untreatable. As research progresses, it may pave the way for the approval and adoption of similar gene therapies for other genetic disorders, revolutionising the field of genetic medicine.

**Question 1** (11 marks)

The primary cause of TTR is the result of a misfolded protein – this protein accumulating incorrectly is what leads to fibrosis. Scientists believe this to be the result of a mutation in the gene coding for TTR.

**a.** Explain how a mutation in the TTR gene could lead to changes in the structure of the TTR protein. (2 marks)

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The gene that codes for TTR can code for multiple proteins alongside the malfunctioning TTR.

**b.** Describe ONE reason why this may be the case, and explain how scientists can avoid affecting those proteins in editing for TTR. (2 marks)

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The TTR protein will accumulate in tissues, causing fibrosis.

**c.** Name and describe the role of TWO organelles involved in exporting TTR from hepatocytes. (4 marks)

**d.** Explain, with reference to gene regulation, why the in vivo method of editing the TTR gene is successful in reducing serum TTR levels, as opposed to editing it in an embryo. (3 marks)

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**Question 2** (9 marks)

There are a number of methods that scientists suggested in order to determine the success of gene editing. Frank suggested using PCR to increase the amount of protein and analyse its structure, whereas Josh was backing gel electrophoresis.

**a.** Explain why PCR cannot increase the amount of protein to analyse its structure. (1 mark)

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**b.** Describe the process of PCR. (3 marks)

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**c.** Explain how gel electrophoresis could be used to identify whether an edit has successfully been made or not. (3 marks)

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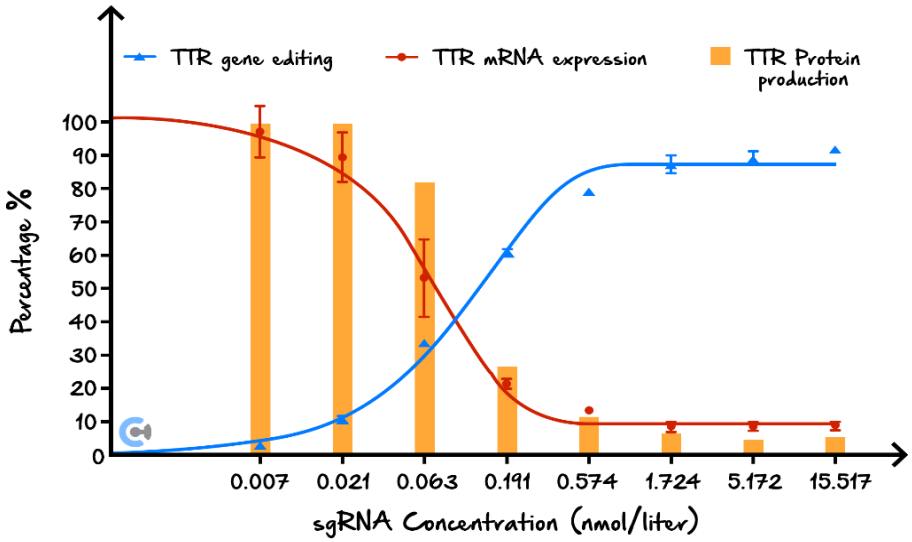
The following were some of the results of this experiment.




**In Vitro Evaluations of the Potency of NTLA-2001**

Shown is the relationship between increasing concentrations of sgRNA and the consequent percentages of TTR editing, as well as TTR mRNA expression and TTR protein production in a single lot of primary human hepato-cytes. The primary indel patterns were a single-nucleotide deletion or insertion at the cut site, inducing a frameshift mutation (data not shown).

**d.** Describe the results and indicate what they mean. (2 marks)

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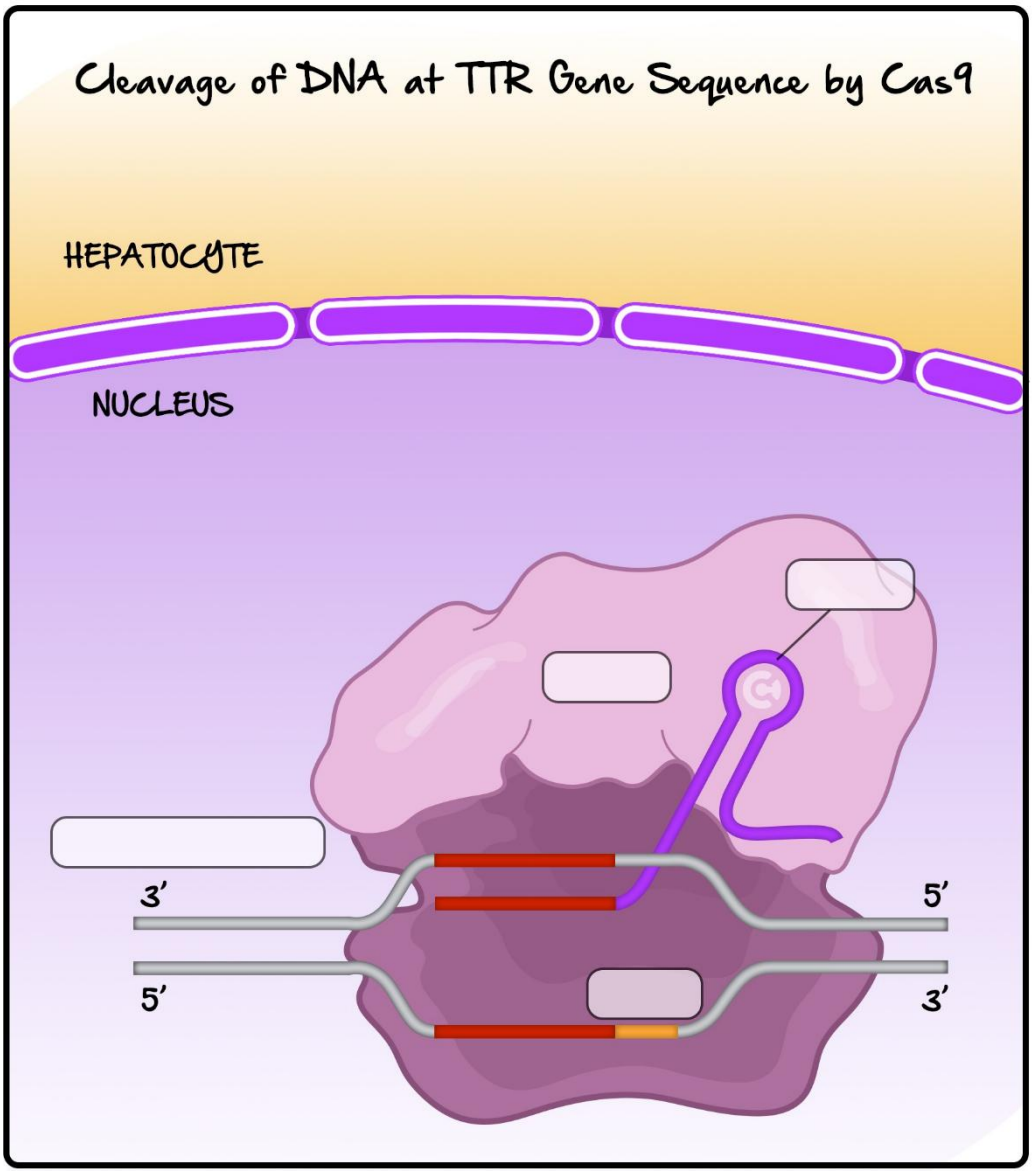
**Question 3** (10 marks)

CRISPR-Cas9 in vivo editing is a revolutionary way to cure TTR.




**a.** Label this diagram. (4 marks)

**b.** Compare the function of the PAM in TTR editing compared to its function in bacteria. (2 marks)

**c.** Name the vector used to deliver the CRISPR-Cas9 complex to the patient in this case, and explain how it is specific to the liver cells. (2 marks)

**d.** Suggest two strategies to reduce the chance of off-target effects when editing using CRISPR-Cas9. (2 marks)

**Question 4** (10 marks)

**a.** Analyse, with reference to justice and integrity, the ethics of editing symptomatic patients with CRISPR-Cas9. (4 marks)

**b.** Discuss the ethical implications of off-target effects in editing for TTR modification, with reference to the principles of respect. (2 marks)

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**c.** What ethical principle must be considered when performing trials for therapies such as CRISPR-Cas9 therapy? Discuss at least 2. (4 marks)

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