InkBiology

ANSWER BOOK

Pharming, recombinant medicines and synthetic biology

Gene regulation, genomics and biotechnology · Unit B17

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15 questions · 51 marks

NAVY EDITION

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SECTION A · Short, 1 to 2 marks

A1 PS-Q15

B1 pharming is the use of genetically modified organisms, including plants and animals, to produce pharmaceutical substances. **B1** milk is a simpler starting material to purify than cell culture medium, and is collected non-invasively by the routine act of milking. [2]

SECTION B · Standard, 3 to 5 marks

B1 PS-Q1

B1 the biosecurity worry is concrete: poliovirus was assembled from mail-ordered DNA fragments in 2002 and an extinct relative of smallpox was synthesised in 2017 for around one hundred thousand dollars, so recreating a dangerous pathogen needs money and a published sequence rather than rare skill. **B1** against that, the same openness lets a public-health laboratory synthesise a new pathogen's genes within days of its sequence appearing, which is how vaccine development now begins. **B1** the case for patents is that development costs run to hundreds of millions, and a period of exclusivity is what pays for the engineering, the animals and the trials. **B1** the case against is access and displacement: a patented medicine is priced by its owner and the diseases involved are concentrated where patients are poorest, and a fermenter making artemisinic acid competes with the smallholders who grow wormwood for the same drug. **B1** a judgement supported by those points, for example that the service should continue with every order screened against the sequences of known dangerous pathogens and the customer verified, while noting that such screening is voluntary and a fence some suppliers do not build. [5]

B2 PS-Q2

B1 the human gene is joined downstream of the promoter of a milk protein gene, such as the promoter of β-lactoglobulin. **B1** the construct is microinjected into the nucleus of a fertilised egg, or introduced into cultured cells from which an embryo is cloned by nuclear transfer. **B1** the embryo is implanted into a surrogate, and the offspring are tested for the transgene; a transgenic female carries the gene in every cell of her body. **B1** the transcription factors that switch that promoter on are present only in mammary gland cells during lactation, so only those cells transcribe the gene and the protein is purified from milk rather than from blood. [4]

B3 PS-Q3

B1 against: founding the line is inefficient, because microinjection succeeds in only a small percentage of eggs, so each transgenic animal costs many surrogate pregnancies, failed implantations and discarded embryos, and cloning adds its own late pregnancy failures. **B1** against: redesigning an animal's genome so that it serves as production equipment treats a sentient creature as an instrument, whatever its day-to-day conditions. **B1** for: once the founder exists the producing herd is bred normally and milking does not harm the animal, and the commercial need for clean, consistent milk means the animals are housed and fed to a high standard. **B1** for: the alternative sources are pooled human plasma, with the infection record that caused, or mammalian cell culture at a price some health systems will not pay, so the welfare cost has to be weighed against the patients who would otherwise go untreated. [4]

B4 PS-Q8

B1 mammalian cell culture is effective but expensive, requiring the cells to be grown slowly in a rich sterile medium, and typically yielding only milligrams of protein per litre. **B1** a lactating transgenic animal can secrete the protein into its milk at reported yields that vary widely between constructs and species, from milligrams up to several grams per litre. **B1** milk is a simpler starting material to purify than cell culture medium, since routine collection by milking replaces the sterile, continuous maintenance a cell culture demands. **B1** whichever route is used, a claimed yield should be quoted with its source rather than as a general figure, because it varies so widely between different constructs and species. [4]

B5 PS-Q9

B1 before the engineered pathway, artemisinin was extracted from sweet wormwood, a crop whose yield and price varied substantially between years depending on the harvest. **B1** a pathway of enzymes, some from the plant and some derived from yeast's own metabolism, was assembled in brewer's yeast. **B1** the engineered yeast converts sugar into artemisinic acid rather than the finished drug itself. **B1** industrial chemical steps then convert the artemisinic acid into artemisinin, and production at this scale began in 2013, providing a supply that does not depend solely on the harvest. [4]

B6 PS-Q10

B1 for slowing benefit: a patented medicine or process is priced by its owner, and the diseases synthetic biology could treat most cheaply are often concentrated where patients are poorest. **B1** for slowing benefit: fermenter production of a compound such as artemisinic acid competes with existing small-scale producers, such as the farmers who grow wormwood, displacing an established supply rather than only adding a new one. **B1** against, for speeding benefit: patents are the usual justification for development costs running to hundreds of millions, and without a period of exclusivity a company has less reason to fund the engineering, the animals and the trials at all. **B1** the boundary is not fully settled in law either: patenting a single gene is established practice, but whether the overall design of an entire organism can be owned in the same way remains an open question. [4]

B7 PS-Q4

B1 factor VIII is the clotting protein deficient in haemophilia A, the commonest severe haemophilia. **B1** adenosine deaminase is the enzyme missing in ADA-deficient severe combined immunodeficiency. **B1** recombinant factor VIII replaced factor VIII concentrated from donated blood plasma, pooled from thousands of donors per batch, which transmitted HIV and hepatitis C to a large fraction of the people treated in the early 1980s. [3]

B8 PS-Q5

B1 factor VIII is a large glycoprotein: it must be folded with help, have its disulfide bridges formed in the right places, and have sugar chains added in the Golgi apparatus. **B1** a prokaryote can transcribe and translate the human gene but has no endoplasmic reticulum and no Golgi apparatus, so it cannot carry out that post-translational modification. **B1** what accumulates has the right primary structure and the wrong tertiary structure and no glycosylation, so it is inactive, whereas insulin is small enough to need almost none of that modification. [3]

B9 PS-Q6

M1 mass from the goat is the concentration multiplied by the volume of milk, so 2.5 × 800. **A1** 2000 g, which is 2.0 kg of antithrombin a year. **A1** the culture yields 0.050 g per dm^3, so 2000 ÷ 0.050 = 40 000 dm^3 of medium would be needed. [3]

B10 PS-Q7

B1 standard parts are promoters, ribosome binding sites, genes and terminators catalogued with defined, measured behaviour and designed so that any part joins to any other, so a device is assembled from a registry rather than hunted for one sequence at a time. **B1** genome synthesis means whole genomes built chemically from sequence data: a bacterial genome of about a million base pairs was synthesised and installed in a recipient cell in 2010, and the cell ran on it. **B1** an engineered pathway assembles several genes from several organisms so that a cell runs a production line it never had, as in the yeast that ferments sugar into artemisinic acid, a few chemical steps short of the antimalarial artemisinin. [3]

B11 PS-Q11

B1 microinjection of the DNA construct into a fertilised egg can produce a mosaic founder, in which only some of the animal's cells carry the inserted gene. **B1** an animal that is mosaic in the cells relevant to expression, such as the mammary gland, may secrete little or none of the protein even though the construct was successfully introduced. **B1** offspring are therefore tested individually for the transgene, and a confirmed line, descended from an animal shown to express the gene reliably, is established before large-scale production begins. [3]

B12 PS-Q12

B1 milk composition varies with the individual animal, the season and the feed, so a batch collected at one time is not guaranteed to be identical to the last, and each must be purified and tested to prove that it is. **B1** an animal-derived product can carry pathogens the animal itself is infected with, so the herd must be certified free of infections, and of prion disease in particular, that could pass into the product. **B1** both requirements exist because a drug from a living animal poses risks that a batch produced by a sterile industrial process from defined chemical starting materials does not pose in the same way. [3]

B13 PS-Q13

B1 a transgenic goat carries the human gene in every cell of its body and could pass it on to any offspring it breeds with. **B1** if a transgenic animal bred into an ordinary herd, the gene would spread into a population from which it could never be recalled or removed. **B1** containment, keeping the herd closed and its animals tracked individually, prevents that spread while the drug continues to be produced from the certified line. [3]

B14 PS-Q14

B1 the screening is intended to stop a customer using the service to obtain the DNA needed to assemble a dangerous pathogen, such as poliovirus or an extinct relative of smallpox, both of which have been assembled from synthesised DNA fragments. **B1** screening only catches an order if the sequence matches something already in the database, so a novel or disguised dangerous sequence could still be missed. **B1** screening is voluntary and coverage differs between suppliers, so a customer refused by one company could in principle approach a supplier that does not screen orders. [3]

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