※ 注意：請於試卷內之「非選擇題作答區」標明題號依序作答。

Part A. (6 pts) Read the following story, and summarize precisely its center theme and provide at least 6 take-home messages to it.

1. Why Bacteria are the New Disease Fighters
(https://www.discovermagazine.com/health/why-bacteria-are-the-new-disease-fighters, accessed 1/2022).

The microbial "Ten Most Wanted" list includes some pretty shady characters: *Escherichia Coli, Staphylococcus aureus, Neisseria meningitidis*. Because these and other bacteria can cause serious illness — and even death — they tend to get all the attention. And we tend to think of *all* bacteria as bad guys. But most bacteria aren't harmful, and many are helpful — even necessary — to a healthy life. Without bacteria, we wouldn't be able to digest certain foods or synthesize some crucial vitamins. Some bacteria even eat other microbes that do make us ill.

Even those few that can be dangerous often aren't. And that's a good thing, too. According to the latest count, we have at least as many bacterial cells in our bodies as we have human cells, maybe slightly more. And those tiny critters aren't just passive passengers. Elaine Hsiao is a researcher at UCLA who studies how the microbiota affects the nervous system. In a 2015 YouTube video, she explains that these microbes interact with each other and form communities. "They divide and replicate" and "they even wage wars against each other," she says. This drama is always going on within our bodies; however, we are unaware of most of it.

In many cases bacteria become dangerous only when their populations are disturbed — that is, when the microbial balance of our bodies is out of whack. In his 1974 book Lives of a Cell: Notes of a Biology Watcher, the physician and writer Lewis Thomas put it this way: "Disease usually results from inconclusive negotiations for symbiosis, an overstepping of the line by one side or the other, a biologic misinterpretation of borders."

When bacteria do cause problems, however, those problems are not limited to what you typically think of as infectious disease. Microbes have been linked to a wide array of illnesses, including cancers, autoimmune illnesses, and even cardiovascular disease. But scientists are learning to work with bacteria to keep us healthy and even cure disease — in other words, to enhance those negotiations. As researchers better understand the human microbiome and new technologies enable us to alter individual microbes, it becomes possible to tinker with the microbiome in ways that promote and even restore health.

Nalinikanth Kotagiri is a researcher at the University of Cincinnati. He and his lab are working on a therapy for cancer that adapts the bacterium *E. coli* Nissle (not the strain of *E. coli* that causes illness) so that it secretes a substance that breaks down cancer cells, making it easier for the immune system to destroy the cancer.

These technologies work by engineering bacteria — either tweaking existing proteins or adding engineered proteins — that will reshape the immune system, helping it to do a better job fighting off illnesses such as cancer. "Unlike antibody-based drugs that we take only once we have a diagnosis, these engineered bacteria can be integrated into the microbiome that's already there," explains Kotagiri.

Kotagiri's lab has recently received funding to work on bio-engineering the skin microbiome against environmental damage. This research will explore the feasibility of programming bacteria that naturally live on the skin to provide passive protection to prevent the development of skin diseases.

From Colds to COVID

Bacteria don't have to be altered to be recruited as team members in fighting illness. Several studies looked at using *Streptococcus salivarius* and *Streptococcus oralis* to prevent recurrent upper respiratory tract and ear infections in children. Food

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allergies are also the target of bacteriotherapy research. There have even been clinical trials using oral bacteriotherapy to treat COVID-19.

Perhaps the most startling use of bacteriotherapy is fecal microbiota transplantation (FMT). In this therapy, fecal matter from a healthy person is placed in the colon of a patient whose gut microbiome is unhealthy and causing illness. As the name suggests, this approach essentially transplants the gut microbiome from a healthy person into an ill one. FMT can be accomplished by colonoscopy, enema, or orally (via a pill). While the treatment has had some ups and downs, it is now widely used for recurrent Clostridium difficile infection, a potentially fatal infection that causes severe diarrhea and colitis, and is often the result of antibiotic treatments that have drastically altered the patient's microbiome.

The bacterial communities that interact and wage war inside us usually do a pretty good job of keeping things running smoothly. But when things go wrong, this new research suggests, bacteria can also be important partners in healing.

Part B. (20 pts, 2 pts for each) ANALOGIES (In each of the questions, a related pair of words is followed by five lettered pairs of words. Pick up the lettered pair that best expresses a relationship similar to that expressed in the original pair)

2. Golf: Holes::
   (A) badminton: feather
   (B) football: kick
   (C) baseball: innings
   (D) tennis: net
   (E) swimming: pool

3. Fault: Earthquake::
   (A) death: sorrow
   (B) pain: relief
   (C) delta: river
   (D) lava: volcano
   (E) flower: blossom

4. Neurosis: Psychosis::
   (A) fear: dread
   (B) demise: disease
   (C) aggression: war
   (D) illness: treatment
   (E) nervousness: reaction

5. Acid: Carboy::
   (A) disillusionment: life
   (B) solution: mineral
   (C) water: jug
   (D) discipline: army
   (E) destructiveness: railway

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6. Blueberry: Pea::
   (A) sky: purity
   (B) potato: raspberry
   (C) sky: star
   (D) purity: world
   (E) sky: grass

7. Square: Diamond::
   (A) cube: sugar
   (B) circle: ellipse
   (C) innocence: jewelry
   (D) rectangle: square
   (E) prizefight: baseball

8. Intern: Medicine::
   (A) surgeon: hospital
   (B) custodian: museum
   (C) priest: church
   (D) apprentice: trade
   (E) debutante: party

9. Automobile: Gasoline::
   (A) fire: fuel
   (B) man: energy
   (C) airplane: propeller
   (D) man: food
   (E) disease: germs

10. Sugar: Granular::
   (A) metal: globular
   (B) water: viscous
   (C) salt: savory
   (D) flour: powdery
   (E) dough: flaky

11. Monolithic: Variation::
   (A) unilateral: argument
   (B) ambiguous: explanation
   (C) negative: usefulness
   (D) ephemeral: durability
   (E) intrinsic: addition

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Part C. (24 pts, 1.5 pt for each) Match the vocabulary word with the definition. Write the letter for the definition that matches the word in the blank.

12. Hypothesis ____
13. Conclusion____
14. Procedure____
15. Data____
16. Observation____
17. Materials____
18. Replicate____
19. Investigation ____
20. Scientific Method ____
21. Scientific inquiry ____
22. Control group ____
23. Experimental group ____
24. Independent variable____
25. Dependent variable ____
26. Scientific theory ____
27. Scientific Law ____

A. The steps you take to complete the experiments.
B. The process scientists follow to complete an investigation (question, hypothesis, materials, procedure…).
C. Things you need to complete your experiment.
D. The results of experiment.
E. The information you collect from the experiment.
F. To repeat the experiment.
G. Watching and noticing events that happen during an experiment
H. A prediction about what will happen with the experiment.
I. An experiment design to answer a question.
J. This group shows the effect of the variable being tested.
K. This is the one variable that is changed.
L. A well-tested explanation for experimental results.
M. The many ways in which scientists study the natural world.
N. This describes an observed pattern in nature.
O. This group is left alone and not experimented on.
P. This is the variable that gets measured.

Part D. (36 pts, 3 pts for each) Reading comprehension. Please read each paragraph and answer the following questions.

Cadherin transmembrane proteins are responsible for intercellular adhesion in all biological tissues and modulate tissue morphogenesis, cell motility, force transduction, and macromolecular transport. The protein-mediated adhesions consist of adhesive trans interactions and lateral cis interactions. Although theory suggests cooperativity between cis and **trans** bonds, direct experimental evidence of such cooperativity has not been demonstrated. Here, the use of superresolution microscopy, **in conjunction with** intermolecular single-molecule Förster resonance energy transfer, demonstrated the mutual cooperativity of cis and trans interactions. Results further demonstrate the consequent assembly of large intermembrane junctions, using a biomimetic lipid bilayer cell adhesion model. Notably, the presence of cis interactions resulted in a nearly 30-fold increase in trans-binding lifetimes between epithelial-cadherin extracellular domains. In turn, the presence of trans interactions increased the lifetime of cis bonds. Importantly, comparison of trans-binding lifetimes of small and large cadherin clusters suggests that this cooperativity is primarily due to allostery. The direct quantitative demonstration of strong mutual cooperativity between cis and trans interactions at intermembrane adhesions provides insights into the long-standing controversy of how weak cis and trans interactions act in concert to create strong macroscopic cell adhesions. [Source: PNAS, 2021, 118 (10) e2019845118]

28. Which one is the false statement for cadherin in this paragraph?
(A) cadherin is responsible for cell adhesion
(B) cis-interaction of cadherin greatly prohibits tans-binding
(C) the advanced microscopic technology enables revealing the cadherin interaction
(D) the allosteric cadherin interaction is the key for tissue strength

29. Which title would be the best fit to this scientific paragraph?
(A) cadherin cis and trans interactions are mutually cooperative
(B) roles for cadherin regulation in cancer progression
(C) cadherin switching and cellular proliferation
(D) dynamics in cadherin synthesis and metabolism

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30. What is the meaning of "in conjunction with" in the context?
(A) inferior to
(B) in contrast to
(C) superior to
(D) combined with

31. What is the synonym of "tans" ?
(A) transitive
(B) translate
(C) opposite
(D) via

Osteoarthritis is a common and painful disease caused by damage to our joints. Normally pads of cartilage cushion those spots. But injuries or age can wear it away. As cartilage deteriorates, bone begins to hit bone, and everyday activities like walking become terribly painful.

The best treatments available try to replace the damaged cartilage with a healthy piece taken from elsewhere in the body or a donor. But healthy cartilage is in limited supply. If it's your own, transplanting it could injure the place it was taken from; if it's from someone else, your immune system is likely to reject it. Alternatively, treatments would be to regrow healthy cartilage in the damaged joint itself. Some researchers have tried amplifying chemical growth factors to induce the body to grow cartilage on its own; other attempts rely on a bioengineered scaffold to give the body a template for the fresh tissue. But neither of these approaches works, even in combination.

Recently, a research lab has also been working on cartilage regeneration, and they've discovered that electrical signals are key to normal growth. They designed a tissue scaffold made out of nanofibers of poly-L lactic acid (PLLA), a biodegradable polymer often used to stitch up surgical wounds. The nanomaterial has a neat property called piezo-electricity. When it is squeezed, it produces a little burst of electrical current. The regular movement of a joint, such as a person walking, can cause the PLLA scaffold to generate a weak but steady electrical field that encourages cells to colonize it and grow into cartilage. No outside growth factors or stem cells (which are potentially toxic or risk undesired adverse events) are necessary, and crucially, the cartilage that grows is mechanically robust.

The team recently tested the scaffold in the knee of an injured rabbit. The rabbit was allowed to hop on a treadmill to exercise after the scaffold was implanted, and just as predicted, the cartilage grew back normally. Piezoelectricity is a phenomenon that also exists in the human body. Bone, cartilage, collagen, DNA and various proteins have a piezoelectric response. Such piezoelectric scaffolding is highly clinically translational yet more studies are to be elucidated in evaluating the true potential in cartilage healing. It can, however, pave a new direction toward regenerative engineering as a future medical breakthrough.
[Modified from https://www.sciencedaily.com/releases/2022/01/220112145042.htm]

32. What is osteoarthritis?
(A) a type of cancer disease
(B) a disease that resulted from the overgrowth of bone tissues
(C) a symptom that is caused by bone fracture
(D) a degenerative disease associated with the dysfunction of cartilage

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33. What procedure is "NOT" described as a treatment for osteoarthritis in the paragraph?
(A) autologous cartilage transplantation
(B) allogenic cartilage transplantation
(C) artificial scaffold replacement
(D) drug administration

34. What is the main strategy utilized in treating osteoarthritis in the research?
(A) replacing with healthy human cartilage tissues
(B) replacing with healthy human cartilage and supplementing growth factors
(C) implanting bioscaffolds and supplementing growth factors
(D) implanting piezoelectric bio-scaffolds

35. What is the "NOT" the main advantage of the new replacement technology?
(A) stronger regenerated cartilage tissues
(B) biodegradable scaffold materials
(C) application of external electricity to promote the cartilage regeneration
(D) no outside growth factors or stem cells required

Due to progress in manufacturing and delivery, nucleic acids have **emerged** as an easily scalable and cost-effective vaccination strategy. In addition to applications in protein replacement therapy, nucleic acids are a promising vaccine platform for both infectious diseases, such as COVID-19, HIV, influenza, and rabies, and cancer. Messenger RNA (mRNA) has several advantages as a nucleic acid platform compared to DNA; there is no risk of integration into the host genome, innate sensing can be modulated through base modifications and delivery vehicles, and it is the minimal genetic vector. Furthermore, constructs targeting strain diversity or multiple infectious diseases can easily be combined.

mRNA vaccine is made using a cell-free enzymatic transcription reaction, which allows rapid and scalable manufacturing, as is evident from the swift pursuit of RNA vaccines in the current pandemic. Currently, there are three major types of RNA vaccines: conventional, non-amplifying mRNA molecules (mRNA), base-modified, non-amplifying mRNA molecules (bmRNA), which incorporate chemically modified nucleotides, and self-amplifying mRNA (saRNA or replicons) that maintain auto-replicative activity derived from an RNA virus vector. saRNA is beneficial compared to non-amplifying RNA as it maintains the advantages of mRNA vaccines, such as rapid development, modular design, cell-free synthesis, but requires a lower dose of RNA due to the self-replication. This reduces the burden of manufacturing for both the drug substance and product and is potentially advantageous in the context of pandemic response as it would enable a greater number of the population to be vaccinated. [Source: https://pubs.acs.org/doi/10.1021/acsnano.0c00326; https://www.mdpi.com/2076-393X/9/2/97/htm]

36. What is the main theme of this paragraph?
(A) DNA vaccine manufacturing
(B) COVID-19 pandemic and biopharmaceutics development
(C) RNA vaccine development
(D) the advancement of cancer therapeutics

37. Which type of RNA molecule is NOT listed as the vaccine paradigm?
(A) messenger mRNA
(B) RNA interference

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(C) based-modified RNA
(D) self-amplifying RNA

38. Which one is an invalid statement of RNA vaccine?
(A) economical in manufacturing
(B) mRNA requires less effective does than saRNA
(C) no risks in genetic manipulation
(D) potential in fighting against infectious diseases

39. Which one is most pertinent to the meaning of "emerged" in the paragraph?
(A) materialized
(B) fallen
(C) abstracted
(D) repealed

Part E. (14 pts, Questions 40-42: 4 pts for each, Question 43: 2 pts). Experimental comprehension. Please read and answer the following questions.

Your lab mate is having issues running PCR. Please follow the troubleshooting guide and give some suggestions based on the instruction.

Problem	Causes	Solutions
Low or no PCR product yield	Number of PCR cycles is insufficient	• Increase number of PCR cycles by 5.
	Template is degraded	• Use electrophoresis to check DNA quality.
	Template is contaminated with PCR inhibitors	• Check DNA ratio of absorbance at 260 and 280 nm. • DNA clean-up or ethanol precipitation to remove contaminants.
	Thermocycler program annealing and extension temperatures are not optimal	• Follow general rules of PCR design: Annealing temperature = lowest primer Tm- 5 °C. • Reduce annealing temperature by 6 to 10°C in stepwise fashion.
	Reaction is missing PCR polymerase or other reaction component	• Make sure each component was added to PCR reaction.
	Primer concentration too low	• Check primer concentration; increase concentration if necessary.
	Target sequence is not in DNA template	• Re-extract DNA from source. • Test another region of template.
	Not enough template	• Increase concentration of DNA template.
	Reaction component concentrations not optimal	• Check recommended primer concentrations (normally from 0.05–1 mM) and Mg++ concentrations (normally from 0.2–1 mM).
	Reaction mix components are compromised	• Check expiration date of components. • Aliquot biological components and avoid multiple freeze-thaw cycles.
	Primer design not optimal (causing non-specific annealing, or primer dimer formation)	• Primer design: Length from 18-30 nucleotides, GC content from 40-60% • Avoid stretches of 4 or more of the same nucleotide in repeats. • Avoid self-complementary sequences within primers.

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Problem	Causes	Solutions
Multiple/non-specific products from PCR reaction	Primer design not optimal (causing non-specific annealing, or primer dimer formation)	• Primer design: Length from 18-30 nucleotides, GC content from 40-60% • Avoid stretches of 4 or more of the same nucleotide in repeats. • Avoid self-complementary sequences within primers.
	Template or reaction mixtures are contaminated	• Re-extract template. • Try new reaction mixture.
	Annealing temperature too low	• Incrementally increase annealing temperature.
	Primer concentration too high	• Use less primer.
	Template concentration is not optimal	• For plasmids use 1 pg–10 ng of DNA / 50 µl reaction. • For genomic DNA use 1 ng–1 µg of DNA / 50 µl reaction.

[Source: https://www.genscript.com/pcr-troubleshooting-guide.html]

40. What would you NOT suggest doing if no PCR products are observed?
(A) increase the annealing temperature in the PCR reaction
(B) increase the cycle number of PCR
(C) increase the template quality
(D) increase the primer amount

41. What would you suggest further if the first run of troubleshooting still yields no PCR products?
(A) decrease the amount of primers
(B) decrease the chance of using repetitive sequences in the primers
(C) decrease the PCR reaction volume
(D) decrease the polymerase concentration

42. Which would be the most direct step to troubleshoot if your lab mate obtains two undesirable PCR products?
(A) switch to shorter primers (<15bp in length) to reduce the non-specific interaction
(B) increase PCR cycle numbers
(C) add more DNA template in the PCR reaction
(D) increase the annealing temperature in the PCR reaction

43. Write down the full name of "PCR" in English.

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