Part A. (30 pts, 10pts for each) Read the following stories, and summarize precisely their center theme and provide at least 5 take-home messages per story to the readers.

1. **Pregnancy, Interrupted - A new device can replicate the placenta, bringing hope for babies born premature (http://discovermagazine.com/2017/oct/pregnancy-interrupted, accessed 1/2018).**

While that's still the stuff of fantasy, there have been serious attempts to create artificial wombs dating back to the 1960s. Most fell far short of the warm embrace of a real placenta. Scientists keep trying, partly because pregnancy is so complex, and, like anything else human, childbirth can go wrong, with consequences that affect a child's entire life. Premature births occur in more than 10 percent of pregnancies and can result in heightened risks for lung diseases, cerebral palsy and developmental disorders.

For extremely premature babies, those born before 28 weeks of pregnancy, the statistics are grim: Thirty to 50 percent die, and up to half of those who survive experience some sort of health issue. The best we can do for preemies today is place them in a heated, humid incubator and pump in nutrients through IVs and tubes. Though we may not feel comfortable abdicating procreation just yet, humanity could clearly use some help.

The earliest attempts at fake wombs failed to sustain animal fetuses for longer than a few days. With improved technology, that marker was pushed back, but animals weaned on such systems still emerged with major birth defects — if they survived at all. The latest step forward comes from researchers at the Children's Hospital of Philadelphia (CHOP), who successfully gestated premature lambs in an artificial placenta for a month. The lambs — removed from their mothers at the human equivalent of 22 weeks — developed normally inside the fake womb. They were born nearly indistinguishable from lambs birthed normally.

The device, called a Biobag, is basically a clear plastic bag filled with an electrolyte fluid. The fetus's own heart pumps blood through an external oxygenator to avoid dangerous pressure differences. The lamb's umbilical cord pulls in nutrients, and external heaters maintain a healthy temperature. The researchers even plan to pipe in recordings of the mother's heartbeat as a soothing soundtrack. Their results were published in April in Nature Communications.

The Biobag addresses a crucial concern for fetuses: lung development. Once a baby's budding lungs are exposed to air, there's no going back, no matter what stage of maturation they may be in. The fluid environment of the fake womb, however, lets lung development continue unhindered.

Although the Biobag does mark a significant step forward for artificial womb technology, it's not ready for human fetuses yet. For one thing, human babies are smaller, and downsizing the device could bring unforeseen complications. The scientists also have to find the right electrolyte fluid mix, and figure out how to connect to human umbilical cords. These problems are surmountable, however, and the researchers say that they expect human trials in three to five years. Beyond saving preterm infants, the greatest benefit may be lowering life-altering birth defects by letting babies continue growing in a womb.

The looming prospect of gestation outside a woman's body has some ethicists raising concerns, such as women being compelled to use the device to shorten pregnancy leaves. Dena Davis, a professor of bioethics at Lehigh University, sees this concern as overwrought.

"I don't think anyone's going to force a woman to have a C-section and use this thing," she says.

Davis focuses instead on the potential benefits the technology could bring. "I actually think this could be a fabulous thing," she says. "The absolute worst place for a preemie is a neonatal ICU." The units can be bright, noisy and stressful. Marcus Davey, a

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Biobag team member and developmental physiologist at CHOP, stresses that the device isn't meant to reinvent pregnancy. He still doesn't think it will work for babies born earlier than 23 weeks — a crucial window for development. And they don't plan on trying. "The main goal is to offer an alternate therapy for these infants born at 23 to 25 weeks," he says. "The current standard of care is putting them on a ventilator and giving them a high level of oxygen. We've been doing that for 25 years, and mortality and morbidity rates in these infants, it really hasn't shifted."

2. The CRISPR Antidote - Scientists hacked the machinery of cellular warfare to splice genes. Now they've found a way to guard against it, too (http://discovermagazine.com/2017/dec/the-crispr-antidote, accessed 1/2018)

An arms race is playing out inside your body. It's part of an invisible war that's raged for billions of years. When viruses hunt and infect bacteria, the bacterial survivors store pieces of their vanquished foes — DNA snippets — within their genomes so that next time, they can detect and defend against the attack. In response, viruses evolve their own counterattack.

The bacteria's natural defense system is called CRISPR-Cas9. And in 2012, biochemist Jennifer Doudna, together with French microbiologist Emmanuelle Charpentier, upended genetics with an ingenious idea. What if scientists could exploit CRISPR as a gene-editing tool? Since then, Doudna and others have hacked these cellular weapons in an effort to treat diseases and create stronger crops. Now scientists are attempting another task: avoiding unintended mutations resulting from their gene edits.

To grasp the tool's precision, imagine the letters of a genome — G, A, T, C — typed into a stack of books dozens of stories high. A guide RNA shepherds Cas9 — which acts like a pair of DNA scissors — to the right spot, where it zooms in on just 20 letters and lets scientists change a few.

"CRISPR-Cas9 lets you find the right spot," says Joseph Bondy-Denomy, a microbiologist at the University of California, San Francisco. "That's a big deal."

Indeed, a global gene editing revolution is underway. Lawyers battle over patent rights. CRISPR startups are selling stocks on the NASDAQ. And in a milestone this year, Oregon Health and Science University researchers used CRISPR to successfully correct heart disease-causing genes in human embryos. It was the first U.S. CRISPR experiment on humans.

But despite its track record, sometimes CRISPR brings unintended consequences — gene edits in undesired locations. Scientists call these "off-target effects." Cas9's scissors don't always stop once the targeted cuts are made. Sometimes the scissors will roam for another day or two, cutting other sites that resemble the target but aren't quite a perfect match.

"If left to their own devices, over time, [CRISPR proteins] might have the ability to cause trouble," says Doudna, who is also a University of California, Berkeley, professor.

In May, a group of ophthalmologists and others sounded the alarm bells in a letter published in Nature Methods. The team used CRISPR to fix a blindness-causing gene in mice. But when they re-examined the mice, they found hundreds of unintended genetic mutations. Headlines about off-targets ensued, and CRISPR stocks tanked.

Doudna challenges the group's methods and thinks that, in general, the off-target fear is overblown. Scientists knew about these mutations, and the technology is more than accurate enough for academic research purposes. The problems begin only as scientists move CRISPR into complex clinical trials.

Bondy-Denomy, the UCSF micro-biologist, appears to have found a "natural" way to combat these off-target effects. His research focuses on the arms race between bacteria and viruses, and last year, Bondy-Denomy started testing out a hunch. If

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bacteria defend against viruses using CRISPR, he reasoned, then viruses likely have a response to counteract it. He was right. Viruses do produce "anti-CRISPR" proteins that grab Cas9 and impair its gene-editing ability. He published his results in Cell in January 2017. "This is basically an off switch," he says.

By summer, Doudna, Bondy-Denomy and their collaborators had used this viral counterpunch to reduce off-target effects. In Science Advances, the team detailed how they used CRISPR to make edits and then deployed anti-CRISPR to stop the Cas9 scissors from running amok.

The technique could help CRISPR move from the lab toward more therapeutic applications where absolute precision is required, Doudna says. Other teams are exploring different ways to avoid off-target effects, too. For example, the team that edited human embryos earlier this year saw no off-target effects, thanks to prep work aimed at keeping CRISPR on a shorter leash.

However, this gene-editing antidote could have another important use. Security experts, including former Director of National Intelligence James Clapper, worry that CRISPR makes things easier for would-be bioterrorists. Bondy-Denomy says if someone launched a CRISPR attack on humans or our crops, anti-CRISPR could work as an antidote. DARPA, the U.S. military research agency, liked the idea enough to give Doudna and Bondy-Denomy a grant to continue making Cas9 safer.

While Bondy-Denomy doubts CRISPR will ever be deployed in a human battle, he can at least be confident in knowing anti-CRISPR has already proven itself in the cellular arms race.

3. **Fast-tracking T-cell therapies with immune-mimicking biomaterials - A new approach to amplify patient-specific T cells outside the body could increase the efficiency of cancer immunotherapies (https://www.sciencedaily.com/releases/2018/01/180115120555.htm, accessed 1/2018)**

Immunologists and oncologists are harnessing the body's immune system to fight cancers and other diseases with adoptive cell transfer techniques. In a normal immune response, a type of white blood cell known as T cells are instructed by another kind of immune cell called an antigen-presenting cell (APC) to expand their numbers and stay alive. Adoptive cell transfer procedures are mimicking exactly this process in a culture dish by taking T cells from patients, multiplying them, sometimes genetically modifying them, and then returning them to patients so that they can, for example, locate and kill cancer cells. However, these procedures often take weeks to produce batches of therapeutic T cells that are large and reactive enough to be able to eliminate their target cells.

A team led by David Mooney at Harvard's Wyss Institute for Biologically Inspired Engineering and John A. Paulson School of Engineering and Applied Sciences (SEAS) is now reporting in Nature Biotechnology an alternative material-based T-cell-expansion method that could help surmount these obstacles. With an APC-mimetic biomaterial scaffold, the researchers achieved greater expansion of primary mouse and human T cells than with existing methods; and they demonstrated the approach's potential in a mouse lymphoma model treated with chimeric antigen receptor-expressing T cells (CAR-T cells) that are engineered to home in on and destroy lymphoma cells.

"Our approach closely mimics how APCs present their stimulating cues to primary T cells on their outer membrane and how they release soluble factors that enhance the survival of the T cells. As a result, we achieve much faster and greater expansion. By varying the compositions of lipids, cues, and diffusible factors in the scaffolds, we engineered a very versatile and flexible platform that can be used to amplify specific T cell populations from blood samples, and that could be deployed in existing

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therapies such as CAR-T cell therapies," said Mooney, Ph.D., a Core Faculty member at the Wyss Institute and leader of its Immunomaterials Platform. Mooney is also the Robert P. Pinkas Family Professor of Bioengineering at SEAS.

To engineer an APC-mimetic scaffold, the team first loaded tiny mesoporous silica rods (MSRs) with Interleukin 2 (IL-2) -- an APC-produced factor that prolongs the survival of associated T cells. The MSRs were then coated with lipids that formed a thin supported lipid bilayer (SLB), which resembles the outer membrane of APCs and that the researchers then functionalized with a pair of T cell-stimulating antibodies that remain mobile in the lipid layer and can bind to receptor/co-receptor molecules on the surface of T cells. In culture medium, 3D scaffolds spontaneously formed through the settling and random stacking of the rods, forming pores big enough to allow the entry, movement, and accumulation of T cells, thereby signaling them to multiply.

In a series of side-by-side comparisons, Mooney's team demonstrated that APC-mimetic scaffolds performed better than methods involving commercially available expansion beads (Dynabeads), which are currently used in clinical adoptive cell transfer approaches. "In a single dose, APC-mimetic scaffolds led to two- to ten-fold greater expansion of primary mouse and human T cells than Dynabeads. As another advantage, APC-mimetic scaffolds enabled us to tune the ratios of subpopulations of T cells with different roles in the desired immune responses, which in the future might increase their functionality," said David Zhang, the study's second author and a Graduate Student working with Mooney.

Building on these findings, the researchers demonstrated the utility of their T cell expansion platform in a therapeutic model. "Prompted by recent breakthroughs in CAR-T cell therapies, we showed that a specific CAR-T cell product expanded with an APC-mimetic scaffold could facilitate treatment of a mouse model of a human lymphoma cancer," said first author Alexander Cheung, Ph.D., who started the project in Mooney's team and now is a scientist at UNUM Therapeutics in Cambridge, Massachusetts. An APC-mimetic scaffold that was engineered to activate a specific type of CAR-T cell was able to generate higher numbers of the modified T cells over longer periods of culture than analogously designed expansion beads, and the resulting cells were similarly effective in killing the lymphoma cells in the mice.

After successfully using the material to expand all T cells present in a sample, the team demonstrated that APC-mimetic scaffolds could also be used to expand antigen-specific T cell clones from a more complex mixture of cells. Such T cell clones are constantly developed by the immune system to recognize small specific peptides contained in foreign proteins. To this aim, the researchers incorporated molecules into the scaffolds that are known as the major histocompatibility complex (MHC) and that presented small peptides derived from viral proteins to T cells.

"Based also on studies in which we showed that APC-mimetic scaffolds also have superior potential to specifically enrich and expand rare T cell sub-populations from blood, we strongly believe that we created an effective platform technology that could facilitate more effective precision immunotherapies," said Cheung.

"The bioinspired T cell-activating scaffolds developed by the Wyss Institute's Immunomaterials Platform could accelerate the success of many immunotherapeutic approaches in the clinic, with life-saving impact on a broad range of patients, in addition to advancing personalized medicine," said Wyss Institute Founding Director Donald Ingber, M.D., Ph.D., who is also the Judah Folkman Professor of Vascular Biology at HMS and the Vascular Biology Program at Boston Children's Hospital, as well as Professor of Bioengineering at SEAS.

In addition, Sandeep Koshy, Ph.D., who worked as a Graduate Student on Mooney's team and now is an Immuno-oncology Researcher at the Novartis Institutes for BioMedical Research in Cambridge, Mass., is an author on the study. The work was supported by the Wyss Institute for Biologically Inspired Engineering at Harvard University, the National Institutes of Health, and the National Science Foundation.

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Part B. (10 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)

4. **COLOR : SPECTRUM ::**
   - **(A) tone: scale**
   - **(B) sound: waves**
   - **(C) verse: poem**
   - **(D) dimension: space**
   - **(E) cell: organism**
5. **SEDATIVE : DROWSINESS ::**
   - **(A) epidemic: contagiousness**
   - **(B) vaccine: virus**
   - **(C) laxative: drug**
   - **(D) anesthetic: numbness**
   - **(E) therapy: psychosis**

6. **BLUEBERRY : PEA ::**
   - **(A) sky: purity**
   - **(B) potato: raspberry**
   - **(C) sky: star**
   - **(D) purity: world**
   - **(E) sky: grass**

7. **CURIOSITY : KNOW ::**
   - **(A) temptation: conquer**
   - **(B) starvation : eat**
   - **(C) wanderlust : travel**
   - **(D) humor : laugh**
   - **(E) survival : live**

8. **TREE RESIN : AMBER :: CARBON :**
   - **(A) Car**
   - **(B) Bonbon**
   - **(C) Cuts**
   - **(D) Diamond**
   - **(E) Burns**

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Part C. (10 pts, 1 pt for each) Match the vocabulary word with the definition. Write the letter for the definition that matches the word in the blank.

9. Hypothesis ____
10. Variables____
11. Conclusion____
12. Procedure____
13. Data____
14. Observation____
15. Materials____
16. Replicate____
17. Investigation ____
18. Scientific Method ____

1. The steps you take to complete the experiment.
2. The process scientists follow to complete an investigation (question, hypothesis, materials, procedure…).
3. Things you need to complete your experiment.
4. The results of the experiment.
5. The information you collect from the experiment (usually in numbers).
6. To repeat the experiment.
7. Watching and noticing events that happen during an experiment.
8. A predication about what will happen with the experiment.
9. An experiment designed to answer a question.
10. Parts of an experiment that can be changed and can affect the results of an experiment.

Part D. Please read the following article and answer the questions [source: Nature Reviews Drug Discovery 16, 669 (2017) & Nature Reviews Clinical Oncology 15, 47–62 (2018)].

Chimeric antigen receptor (CAR) T cells are an ex vivo form of gene therapy, in which T cells are removed from cancer patients, genetically modified to express cancer-cell seeking receptors, and re-infused into patients. It is rapidly emerging as a promising new treatment for haematological and non-haematological malignancies. CAR-T-cell therapy can induce rapid and durable clinical responses, but is associated with unique acute toxicities, which can be severe or even fatal. Cytokine-release syndrome (CRS), the most commonly observed toxicity, can range in severity from low-grade constitutional symptoms to a high-grade syndrome associated with life-threatening multiorgan dysfunction; rarely, severe CRS can evolve into fulminant haemophagocytic lymphohistiocytosis (HLH). Neurotoxicity, termed CAR-T-cell-related encephalopathy syndrome (CRES), is the second most-common adverse event, and can occur concurrently with or after CRS. Intensive monitoring and prompt management of toxicities is essential to minimize the morbidity and mortality associated with this potentially curative therapeutic approach.

19. What aspects are irrelevant to CAR-T cells? (4%)
(A) cell therapy (B) genetic engineering (C) disease treatment (D) chemotherapy

20. What is the main message conveyed in this paragraph? (4%)
(A) CAR-T therapy is used for treating CRS and CRES
(B) CAR-T therapy has no benefits over other cancer treatments
(C) CAR-T therapy is among the standardized cancer therapies
(D) CAR-T therapy could cause immune-associated toxicities

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Part E. Please read the following article and answer the questions [source: Nature 553, 86–90 (2018)].

The mammalian microbiome has many important roles in health and disease, and genetic engineering is enabling the development of microbial therapeutics and diagnostics. A key determinant of the activity of both natural and engineered microorganisms in vivo is their location within the host organism. However, existing methods for imaging cellular location and function, primarily based on optical reporter genes, have limited deep tissue performance owing to light scattering or require radioactive tracers. Here the authors introduce acoustic reporter genes, which are genetic constructs that allow bacterial gene expression to be visualized in vivo using ultrasound, a widely available inexpensive technique with deep tissue penetration and high spatial resolution. These constructs are based on gas vesicles, a unique class of gas-filled protein nanostructures that are expressed primarily in water-dwelling photosynthetic organisms as a means to regulate buoyancy. Heterologous expression of engineered gene clusters encoding gas vesicles allows Escherichia coli and Salmonella typhimurium to be imaged noninvasively at volumetric densities below 0.01% with a resolution of less than 100 μm. The study demonstrates the imaging of engineered cells in vivo in proof-of-concept models of gastrointestinal and tumour localization, and develop **acoustically** distinct reporters that enable multiplexed imaging of cellular populations. This technology equips microbial cells with a means to be visualized deep inside mammalian hosts, facilitating the study of the mammalian microbiome and the development of diagnostic and therapeutic cellular agents.

21. What is the technological feature of this research? (4%)

(A) generation of an optical free system for in vivo microbiome detection
(B) establishment of an engineered microbial system with gas vesicles
(C) detecting resolution less than 100 μm
(D) all of above

22. Can you suggest an appropriate title for this research? (4%)

(A) tunable thermal bioswitches for in vivo control of microbial therapeutics
(B) acoustic reporter genes for noninvasive imaging of microorganisms in mammalian hosts
(C) localization of microscale devices in vivo using addressable transmitters through magnetic spins
(D) in vivo imaging and tracking of host-microbiota interactions via metabolic labeling of gut anaerobic bacteria

23. What is the term "acoustically" relevant to? (4%)

(A) vision (B) odor (C) sound (D) touch

Part F. Please read the following article and answer the questions [source: Nature 552, 214–218 (2017)].

Progress towards the integration of technology into living organisms requires electrical power sources that are biocompatible, mechanically flexible, and able to harness the chemical energy available inside biological systems. Conventional batteries were not designed with these criteria in mind. The electric organ of the knifefish Electrophorus electricus (commonly known as the electric eel) is, however, an example of an electrical power source that operates within biological constraints while featuring power characteristics that include peak potential differences of 600 volts and currents of 1 ampere. An electric eel-inspired power concept has been introduced here that uses gradients of ions between miniature polyacrylamide hydrogel compartments bounded by a repeating sequence of cation- and anion-selective hydrogel membranes. The system uses a scalable stacking or

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folding geometry that generates 110 volts at open circuit or 27 milliwatts per square metre per gel cell upon simultaneous, self-registered mechanical contact activation of thousands of gel compartments in series while circumventing power dissipation before contact. Unlike typical batteries, these systems are soft, flexible, transparent, and potentially biocompatible. These characteristics suggest that artificial electric organs could be used to power next-generation implant materials such as pacemakers, implantable sensors, or prosthetic devices in hybrids of living and non-living systems.

24. What is the topic of this article? (4%)

(A) environmental conservation (B) biological evolution (C) biomaterials development (D) animal physiology

25. What does the biomimicry concept originate from? (4%)

(A) firefly (B) spider (C) gecko (D) fish

Part G. Please read the following article and answer the questions [source: Frontiers in Cell and Developmental Biology 4, 89 (2016)].

Fluorescence in situ hybridization (FISH) is a macromolecule recognition technology based on the complementary nature of DNA or DNA/RNA double strands. Selected DNA strands incorporated with fluorophore-coupled nucleotides can be used as probes to **hybridize** onto the complementary sequences in tested cells and tissues and then visualized through a fluorescence microscope or an imaging system.

The majority of FISH probes target to specific chromosomal and genomic abnormalities in the human genome. Rapid phylogenetic identification of single microbial cells was achieved using fluorescently labeled oligonucleotides complementary to 16S ribosomal RNA (rRNA). Some segments in the 16S rRNA are invariant in all organisms but phylogenetic group-specific 16S rRNA in different groups of organism can be used as oligonucleotide FISH probes (length 17–34 nucleotides) to identify infectious agents in clinical samples. For example, FISH probes complementary to specific sequence of 16s rRNA can detect malaria infection in blood samples. The Plasmodium Genus (P-Genus) FISH assay has a Plasmodium genus specific probes that detect all five species of Plasmodium known to cause the disease in humans. The sensitivity of this FISH assay is better than the Giemsa staining method. A LED light source may be an available device to read FISH result, which can extend the clinical application of FISH especially in the resource-limited areas. Since rRNA has a short life and is present in a live organism with plenty of copies, FISH should be done in the live pathogens.

26. What biomolecule is the primary target that FISH detects? (4%)

(A) nucleic acids (B) proteins (C) sugars (D) lipids

27. What does "hybridize" mean in the main context? (4%)

(A) snap (B) incorporate (C) bend (D) glue

28. Which statement is NOT true for FISH in this paragraph? (4%)

(A) FISH is applicable for pathogen detection

(B) PCR can enhance the signal detection

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(C) 16S rRNA can be used as a probe

(D) FISH requires a fluorescence microscopy or imagine system

Part H. Please read the following article and answer the questions [source: Gut Microbes 1, 1-16 (2017)].

Exercise reduces the risk of inflammatory disease by modulating a variety of tissue and cell types, including those within the gastrointestinal tract. Recent data indicates that exercise can also alter the gut microbiota, but little is known as to whether these changes affect host function. In the study, a germ-free (GF) animal model to test whether exercise-induced modifications in the gut microbiota can directly affect host responses to microbiota colonization and chemically induced colitis. Donor mice (n=19) received access to a running wheel (n=10) or remained without access (n=9) for a period of six weeks. After euthanasia, cecal contents were pooled by activity treatment and transplanted into two separate cohorts of GF mice. Two experiments were then conducted. First, mice were euthanized five weeks after the microbiota transplant and tissues were collected for analysis. A second cohort of GF mice were colonized by donor microbiotas for four weeks before dextran-sodium-sulfate was administered to induce acute colitis, after which mice were euthanized for tissue analysis. We observed that microbial transplants from donor (exercised or control) mice led to differences in microbiota β-diversity, metabolite profiles, colon inflammation, and body mass in recipient mice five weeks after colonization. We also demonstrate that colonization of mice with a gut microbiota from exercise trained mice led to an attenuated response to chemical colitis, evidenced by reduced colon shortening, attenuated mucus depletion and augmented expression of cytokines involved in tissue regeneration. Exercise-induced modifications in the gut microbiota can mediate host-microbial interactions with potentially beneficial outcomes for the host.

29. What is the main conclusion relevant to this study? (4%)

(A) Diet will change the ecology of gut microbiome

(B) Workout can alter body weights

(C) Exercise shows no evidence of controlling body cholesterol

(D) Physical activities might shape the gut microbiome of hosts

30. What is the facility accessible to the mice for exercise? Please answer in English (6%)

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