Halakhic Issues Related to Synthetic Biology

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Synthetic biology is an emerging field of research that investigates the design and construction of novel artificial biological pathways, organisms or devices, or the redesign of existing natural biological systems. In this article, we address important halakhic implications arising from developments in the field of synthetic biology. Yet, before doing so, we first present some of the most conventional and controversial technologies that have emerged so far from the field of synthetic biology.

Synthetic Biology & Innovative Technologies

The expansive nature of synthetic biology[1] can be daunting, yet there are many research platforms that are already seen as conventional, and whose research has proven to be beneficial. One example of a conventional application of synthetic biology research is the development and use of "simple cells" (SimCells).[2] Scientists at MIT removed native chromosomes from natural cells and replaced them with synthetic genetic circuits,

1 Coradini, et al., "Building genomes to understand biology," *Nature Communications*, 11:6177, 2020.

2 Fan C, Davison PA, Habgood R, Zeng H, Decker CM, Salazar MG, Lueangwattanapong K, Townley HE, Yang A, Thompson IP, Ye H, "Chromosome-free bacterial cells are safe and programmable platforms for synthetic biology," *Proceedings of the National Academy of Sciences*, 2020 Mar 24;117(12):6752-61; Rampley CP, Davison PA, Qian P, Preston GM, Hunter CN, Thompson IP,

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to re-program these cells to deliver a potent anticancer drug in a timely fashion in the treatment of a variety of cancers. However, these bio-circuits are not limited to cancer therapy. They can also be programed to "sense" the presence of a serious virus, like SARS-CoV2 (the COVID-19 virus), or the presence of toxic materials in humans or in the environment. Scientists have also genetically engineered bacteria to dissolve organic toxins from the body or from the atmosphere. These bacteria can be engineered to isolate and purify specific metals, such as gold and silver, from computers and cell phones.[3]

A more controversial technology would be the recent creation of synthetic DNA bases. There are only four natural genetic bases or nucleotides, i.e., adenine (A), cytosine (C), guanine (G), and thymine (T). However, scientists have recently been able to expand nature's universal genetic four-letter alphabet. They have synthesized four new letters of the genetic code and created bacteria that utilize, reproduce, transcribe, and translate these new synthetic genetic letters as part of a new 8-letter genetic code.[4] While scientists are using the expanded genetic code to develop powerful bio-computers,[5] this technology also opens the door to rewrite our genetic code—the letters that defines our species.

Another example of a controversial synthetic biology technology is the development of synthetic or artificial embryos.[6] The creation of these types of embryos are the next step in stem cell technology where specific stem cells can be obtained from skin or blood to transform them into artificial human embryos that can mimic the early development of a human embryo. Based on U.S. governmental regulations, human embryos

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Wu LJ, Huang WE, "Development of SimCells as a novel chassis for functional biosensors," *Scientific reports*, 2017 Aug 3;7(1):1-0.

3 Kwok R, "Inner Workings: How bacteria could help recycle electronic waste," *Proceedings of the National Academy of Sciences*, 2019 Jan 15;116(3):711-3.

4 Lee KH, Hamashima K, Kimoto M, Hirao I, "Genetic alphabet expansion biotechnology by creating unnatural base pairs," *Current opinion in biotechnology,* 2018 Jun 1;51:8-15; Hoshika S, Leal NA, Kim MJ, Kim MS, Karalkar NB, Kim HJ, Bates AM, Watkins NE, SantaLucia HA, Meyer AJ, DasGupta S. Hachimoji, "DNA and RNA: A genetic system with eight building blocks," *Science,* 2019 Feb 22;363(6429):884-7.

5 Zhou C, Geng H, Wang P, Guo C, "Programmable DNA Nano Indicator-Based Platform for Large-Scale Square Root Logic Biocomputing," *Small,* 2019 Dec;15(49):1903489; Katz E, editor. "DNA-and RNA-Based Computing Systems," *John Wiley & Sons*, 2020 Dec 22.

6 Zhang PY, Fan Y, Tan T, Yu Y. "Generation of artificial gamete and embryo from stem cells in reproductive Medicine," *Frontiers in Bioengineering and Biotechnology,* 2020;8.

created from sperm and eggs are permitted to be maintained in the laboratory for only 14 days of development.[7] However, the creation of "artificial human embryos" using stem cells would not fall under these federal regulations, since they are currently not deemed to be in the same category as embryos created from sperm and eggs. Artificial human embryos can, therefore, be maintained for several weeks in the laboratory so that researchers can use them as a model system to understand normal embryology and pathological conditions that lead to miscarriages and embryo defects.

Scientists now also have the capacity to remove specialized cells from many adult organs, to generate stem cells. These stem cells are precursor cells that can differentiate into any human cell type, such as muscle, pancreas, blood, heart or brain. Scientists can implant these stem cells with the right chemical signals into a biological scaffold to generate synthetic organs, or organoids, that mimic eyes, livers, skin and muscle. This technology is referred to as 3D cellular printing.[8] One exciting potential application of this technology is to isolate stem cells from healthy individuals and insert them into patients with disabling diseases so that they generate healthy tissue and organs. This technology serves as the next generation of regenerative medicine.

Currently, many scientists also are using 3D cellular printing to generate brain organoids—neural networks—that include motor neurons, sensory neurons, oligodendrites, astrocytes, and microglial cells. These brain organoids serve as experimental models to study normal physiological development as well as pathological development of diseases such as autism and Alzheimer's disease. Brain organoids are also being implanted into mice and eventually will be implanted into monkeys in order to create human-animal neural chimeras.[9] The purpose of these procedures would be to develop better animal models to study neurological diseases or to better understand human speech and intelligence.

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7 Williams K, Johnson MH, "Adapting the 14-day rule for embryo research to encompass evolving technologies," *Reproductive Biomedicine & Society Online,* 2020 Jun 1;10:1-9.

8 Tian X, Zhou K, "3D printing of cellular materials for advanced electrochemical energy storage and conversion," *Nanoscale,* 2020;12(14):7416-32; Dogan E, Bhusal A, Cecen B, Miri AK, "3D Printing metamaterials towards tissue engineering," *Applied materials today*, 2020 Sep 1;20:100752.

9 Crane AT, Voth JP, Shen FX, Low WC, "Concise Review: Human-Animal Neurological Chimeras: Humanized Animals or Human Cells in an Animal?" *Stem Cells*, 2019 Apr;37(4):444-52.

Another recent application of stem cell technology is the creation of artificial ovaries.[10] Many women who are diagnosed with cancer can become infertile from radiation or chemotherapy. Scientists can now create artificial ovaries for these cancer patients by implanting female adult generated stem cells onto an ovary scaffold. These scaffolds are prepared using mild detergents to remove any cells from the ovary. Stem cells, obtained from women who have recovered from their cancer, are then added to this ovary scaffold to create an artificial ovary. After cancer treatment, the ovary can be transplanted into the arm of the woman and will respond to her cyclic hormones to generate one oocyte every month, mimicking normal menses. The arm is an ideal target location for the artificial ovary because it can easily be monitored by ultrasound for oocyte maturation and follicle retrieval. When the woman wants to conceive, physicians would remove several of her oocytes from the artificial ovary, fertilize the eggs *in vitro*, and then implant one pre-embryo into the woman's uterus.

A final example of synthetic biology in the realm of reproductive technology is the creation of artificial placentas.[11] While the ultimate purpose of artificial placentas may be to gestate a fetus from conception to birth, they will be used first to incubate premature babies and preserve their health during development.

Jewish Ethics and Halakhic Implications

While all of the above biotechnologies are recent developments, Jewish ethics and Halakhah have precedents upon which to rely to understand the ethical implications of these new technologies.

Question 1: Is the development of these technologies morally/halakhically sound?

The Jewish tradition explicitly and repeatedly asserts that God created the world as an unfinished product so that human beings can be partners in the creation process, by developing technologies that make use of natural

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10 Dolmans M, Amorim CA, "Construction and use of artificial ovaries," *Reproduction* 158 F15–F25.

11 De Bie FR, Davey MG, Larson AC, Deprest J, Flake AW, "Artificial placenta and womb technology: Past, current, and future challenges towards clinical translation," *Prenatal Diagnosis*, 2020 Sep 1; Fassihi A, Radovanovic ML, inventors; Amnion Life LLC, assignee. "Systems, methods, and devices for artificial placenta and amniotic bed incubators," United States patent application US 16/555,525. 2020 Jan 30.

resources for the purpose of human and social use.[12] The primary Biblical source that justifies this position is identified as "And God blessed them, and God said to them, 'Be fruitful and multiply and fill the earth and *subdue* it, and rule over the fish of the sea and over the fowl of the sky and over all the beasts that tread upon the earth.'"[13] It is also supported by the verse, "And God blessed the seventh day and He hallowed it, for thereon He abstained from all His work that God created *to do*."[14] The italicized expression in this latter verse is interpreted to mean that God's sole work in creation was completed in the first week. The moral responsibility to partner with God in creation in ways that align with the values that the Torah commands is further supported by the verse, "Now the Lord God took the man, and He placed him in the Garden of Eden *to work it and to guard it*."[15] This italicized expression implies that human beings have a responsibility to preserve the earth that God created including the land, sea, environment, plant and animal life.[16] Finally, the verse, "The heavens are

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12 The following midrash provides an example of how humans use technology to improve the natural world as follows:

> Once Rabbi Ishmael and Rabbi Akiva were strolling in the streets of Jerusalem along with another man. They met a sick person who said to them, "Masters, can you tell me how I can be healed?" They said to him, "Take such-and-such until you feel better." The man strolling with the two rabbis turned to them and said, "Who made this man sick?" "The Holy Blessed One," they replied. "And you presume to interfere in an area that is not yours?" the man remarked. "God has afflicted and you heal?" "What is your occupation?" they asked the man. "I'm a tiller of the soil," he answered, "as you can see from the sickle I carry." "Who created the land and who created the vineyard?" "The Holy Blessed One." And they said, "And you dare to move into an area that is not yours? God created these and you eat their fruit?" He said to them, "Don't you see the sickle in my hand?" the man asked. "If I did not go out and plow the field, water it, fertilize it, weed it, no food would grow!" Fool," the rabbis said, "have you not heard that the days of people are like a harvest. Just as a tree that is not fertilized and weeded and pruned does not grow, and if it grows and does not drink (or take fertilizer) it does not live and dies, so too the body is a tree—the medicine is the fertilizer and the doctor is the farmer."

13 Genesis 1:28.

14 Genesis 2:3.

15 Genesis 2:15.

16 The Talmud uses the expression, "partners with God in the work of creation," in a context of implementing social justice in the following passage, "Any judge who judges a true judgment truthfully, even if he sits in judgment only one hour, the verse ascribes to him as if he became a partner to the Holy One, Blessed be He, in the act of Creation. This conclusion is derived by means of a verbal analogy [*gezerah shavah*]: It is written here: 'And the people stood over Moses from

heavens of the Lord, but the earth He gave to the children of men,"[17] is interpreted to imply that God has granted man dominion over the world and over the species that are co-inhabitants of that world. In other words, man has been given almost an unrestrictive license—limited only by the values and norms that God commands humans to obey—to apply his intellect, ingenuity, and prowess in developing the world. With this license also comes the responsibility for humans to use their intellect to learn biology, chemistry, and physics to develop technologies to improve the world by creating a safe, healthy, and just environment for human—and all—existence.

Rabbi Chaim of Volozhin places the license and responsibility to "improve the world" through technological advancement in human beings' intrinsic nature. In his *Nefesh Ha-Ḥayyim*,[18] he writes that the term "Elokim" denotes God's power to rule over Creation. Therefore, when the Torah writes that humankind was created in the likeness of "Elokim," i.e., *tzelem Elokim*, it means that human beings were endowed with the power to rule over God's Creation as a mini-"Elokim." This gives humans the ability and the permission to create new worlds through innovative technology. This perspective parallels that presented by Maharal who points out that human creativity is part of the creation of the world and should be properly utilized to make the world more amenable to its inhabitants.[19]

Again, the directive of partnering with God in Creation is not without boundaries. The development of new technologies must have purpose and concrete objectives to fulfill the moral role of being partners in the creation process. Thus, the translational objectives must be focused on improving the environment, the wellbeing of animals, and/or the human condition. Human beings do not have unrestricted rights to engage in any technology for any purpose. This last principle is shared by secular bioethicists.[20] To ensure that technological development fulfills this purpose rabbis are required to master the underlying science before responding to Jewish legal questions associated with innovative technology. There are

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the morning until the evening.' And it is written there, in the act of Creation: 'And it was evening and it was morning, one day' (Genesis 1:5)." See BT *Shabbat* 10a.

17 Psalms 115:16.

18 *Nefesh Ha-Ḥayyim*, gate one, chapters 4-6, translated by Rabbi Avraham Yaakov Finkel.

19 Rabbi Judah Luria of Prague (Maharal Me-Prague), *Be'er Ha-Golah,* pp. 38-39 (Jerusalem 5731).

20 Silverman E, "The 5 most pressing ethical issues in biotech medicine," *Biotechnology healthcare,* 2004 Dec;1(6):41.

many examples of contemporary rabbis with degrees in medicine, biology, and physics who adjudicate Jewish law. If possible, rabbis should see the actual technology before adjudicating the question.

The development of organoid technologies is viewed favorably in Halakhah, provided the research objectives in using these technologies are designed to better understand human neurological development and neurocircuitry, to develop systems or platforms to examine drug toxicity using these organoids and to use these platforms to better understand neurological diseases such as Alzheimer's, synucleinopathies, ALS, SMA, autism, and Huntington's disease.

Scientists recognize that studying animal models of human diseases has benefits and challenges. Many animal models of human diseases cannot be adequately translated into successful human clinical trials. Nonetheless, scientists have learned a lot of biology about these diseases from animal models. It is precisely the scientific value and knowledge gained by these platforms that is the reason why Halakhah permits their use in the laboratories. It is important to emphasize that the scientific objectives of human organoids, artificial human embryos, or human-animal chimera are not to create a new species or to create a synthetic human being. Rather, the goal is to learn more about neural health and disease.

Question 2: What are the moral/halakhic responsibilities of researchers to research subjects (i.e., animals, organoids)?

The Jewish tradition values the sanctity of all life forms and not simply human life. There are many laws directed to preserve plant species and to ensure that animals do not suffer. For example, the halakhah requires that we feed our animals before we sit down to eat ourselves. The importance of these halakhot is to ensure that animals do not suffer but does not imply that animals are moral agents. Yet, it does imply that they are moral subjects. A moral agent has a responsibility to act morally. A moral subject, on the other hand, is someone or something to which a moral agent must act morally. There is a specific prohibition, i.e., *tza'ar ba'alei ḥayyim*, which, by the semantics of the terms, seems to apply to all life forms that can experience pain, not just animal life. This means that researchers must be cognizant of the potential experience of suffering that they may incur upon research animals or even organoids, and conduct their research in ways that minimize such suffering.

Question 3: How should we consider organoids and chimera morally/halakhically—are they human or something else?

As we have discussed elsewhere,[21] Jewish tradition provides certain categoric descriptions that pertain to how human beings are different from other life forms. However, as recognized through the prohibition to sow mixed seeds together (*kilayim*) or crossbreed animals, Jewish law also has category distinctions between other species as well.

Essentially, a living organism must have the capacity to: 1) reproduce, 2) undergo metabolic homeostasis (that includes regulating growth and movement in response to both internal and external stimuli) and 3) mutate, adapt, and evolve their phenotypes. With respect to what distinguishes human beings from other species or life forms, Biblical and Talmudic sources derive two critical biological criteria for identifying a human being. A human being is (1) created using human gametes,[22] and (2) the resulting embryo emerges from a woman.[23] With respect to the latter criteria, emerging from a woman's uterus entails that the embryo spent a certain gestational period in the uterus as well. Moreover, even though these two criteria naturally go together, with the rapid growth of reproductive technological innovations, it is no longer necessary to conceive of these two requirements as connected.

This development, results in the following emerging question: Which criteria is primary? This inquiry is specifically related to the question of who should be considered the mother in situations when the ovum donor is different from the gestational surrogate.[24] Jewish law has evolved to have three different threads of resolution. Either the gestational mother is the actual mother, the ovum donor is the mother, or—either due to

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21 Loike, J.D. and Tendler, M.D., "Creating Human Embryos Using Reproductive Cloning Technologies," *Journal of Halacha and Contemporary Society*, 367:37-60, 2014.

22 While human gametes generally implies sperm and ova, Jewish law considers the product of human cloning that reaches embryological maturation to be human.

23 A potential Biblical source for this definition is that even though God created Adam and Eve with neither the use of sperm or egg nor with the embryos gestating in a woman, once created, God declared in the Bible that these two lives were indeed defined as human beings. However, in the future, other human beings would procreate through human gametes and gestation in a human being.

24 Loike, J.D. Tendler, M.D., "Halachic Perspectives of Gestational Surrogacy," *Hakirah*, 16:115-132, 2013; Loike, J.D. Tendler, M.D, "Becoming a Surrogate for an Infertile Jewish Couple," *Journal of Halacha and Contemporary Society*, 66:5-21, 2013.

doubt or the belief in matrilineal flexibility—both the ovum donor and the surrogate would be considered the mother of the newborn.

We would argue that the same reasoning should apply to the present question, with certain limitations, as described below. In other words, for life forms that are created using stem cell-generated human gametes from woman should be treated as human beings.[25] Their obligations as moral actors will depend on their capacity to perform moral duties that pertain to human beings in general, yet they possess the status of human moral subjects who are due respect and dignity in accord with their humanity.

Limitations to this suggestion relate primarily to chimera and life forms created with synthetic DNA who are not born, emerging from a woman's uterus.[26] For these beings, the moral/halakhic status of these beings will depend on whether natural human DNA or synthetic "human" DNA is the dominant genotypic influence on their phenotype. If it is, they should be accorded the status of human being. This is in line with the following Talmudic passage:

> Rabbi Yasa states in the name of Rabbi Yoḥanan: If [a creature] has a human body but its face is of an animal, it is not human; if [a creature] has an animal body, but its face human, it is human. Yet suppose it is entirely human, but its face is animal-like, and it is learning Torah? Can one say to it, "Come and be slaughtered"? [Rather one cannot]. Or, consider if it is entirely animal like, but its face human, and it is plowing the field [acting like an animal] do we come and say to it, "Come and perform levirate marriage [*yibum*] and divorce [*halitzah*]"? [Rather, one cannot.][27]

The principle is that when dealing with a being that does not fit within the category of being born of a human mother, it may nevertheless be deemed human by virtue of its cognitive abilities and human-like conduct.

This creature that possesses an animal-like face but learns Torah is different from the classical example of the Golem who is oftentimes used as the prototype for discussions on artificial human beings. The Golem,

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25 Loike, J.D. and Tendler, M.D., "Creating Human Embryos Using Reproductive Cloning Technologies," *Journal of Halacha and Contemporary Society*, 367:37-60, 2014.

26 Loike, J.D. and Tendler, M.D., "Tampering with the Genetic Code of Life: Comparing Secular and Halakhic Ethical Concerns," *Hakirah*, 18: 41-58, 2014.

27 JT *Niddah* 3:2.

who was created through incantations, could not speak.[28] Therefore, it was not deemed to be human and its destruction was not considered to be murder. The cognitive capabilities of chimera and life forms created with synthetic DNA mirror the cognitive abilities of humans and, therefore, can be considered as falling under "the image of God" or *tzelem Elokim*, even if only by analogy (as an image of an image).

This categorization would provide chimera and life forms created with synthetic DNA who are not born, emerging from a woman's uterus, with the recognition that they also possess freedom of thought and action, which should be directed through *yirat Shamayim*. Rambam[29] takes the term *yirat Shamayim* to refer to all activities where human beings exercise their freedom of choice. This is also in line with Rashi and Radak, who state that the term *tzelem Elokim* refers to special intelligence that is unique to human beings.[30] According to Onkelos, it includes speech. Rabbi J.B. Soloveitchik writes that the term *tzelem Elokim* refers to creativity in thought and in action. Just like their human counterparts, these creations should take on moral and almost Divine responsibilities in their thoughts and actions.[31]

Most likely, rabbinical scholars would need to observe such creations first hand to better assess their nature before issuing a halakhic decision. To be clear—we do not condone the creation of new species or to create a synthetic human being. The goal of research using these technologies should be to learn more about neural health and disease. However, in the unfortunate event that scientists engage in moral trespass and create a new species or a synthetic human being, the above is meant to clarify how and what they should be deemed. At the end, it is important to recognize the limits of God's directive to be partners in the creation of His world. ☙

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28 There is some discussion in the *meforshim* whether the capacity of speech is an indication that God has infused his *tzelem Elokim* into an organism but this is beyond the scope of this discussion.

29 *Hilkhot Teshuvah,* Laws of Repentance 5:1.

30 See Rabbi Michael Rosensweig, "Man's Creation Betzelem Elokim" https://www.torahweb.org/torah/2010/parsha/rros_breishis.html.

31 Rabbi J.B. Soloveitchik, *The Lonely Man of Faith*, Three Leaves Press -Doubleday, New York, p. 11).