

Ethical guidelines concerning artificial cells¹

Mark A. Bedau^{*°#¶}, Emily C. Parke[°], Uwe Tangen^{#°§}, Brigitte Hantsche-Tangen[§]

^{*}*Reed College, USA*

[°]*ProtoLife Srl., Italy*

[#]*European Center for Living Technology, Italy*

[¶]*European School of Molecular Medicine, Italy*

[°]*BioMIP, Ruhr-Universität Bochum, Germany*

[§]*Protostream GmbH, Germany*

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Executive summary

Artificial cell technology promises to achieve a revolutionary combination of biotechnology and information technology, which will bring marked social and economic benefits. This new technology also raises significant new ethical issues. This document takes stock of those ethical questions and offers some tentative ethical and socially responsible recommendations about our future with artificial cells.

Artificial cells are characterized as self-assembling and self-reproducing chemical systems, that are created through human artifice but not merely by manipulating a natural living organism, and that produce the following interlocking chemical properties: (1) spatial localization of components by containment, (2) utilization of energy and raw materials from the environment by metabolism, and (3) control of containment and metabolism by chemical information that can be replicated and can mutate. The resulting chemical systems can reproduce themselves, and a population of them could adapt and evolve. Narrower conceptions of artificial cells can be formulated by adding further conditions, such as the *pure bottom-up condition*, according to which the system is constructed without using any materials derived from natural living systems, or the *novel architecture condition*, according to which the system's architecture must be fundamentally different from that of any natural living system, for example, by not employing protein translation from genes. But we believe that the main ethical implications of artificial cells do not depend on these further conditions.

We distinguish five different stages in artificial cell development that require special ethical attention. The five ethical checkpoints are:

- A: Closing the replication loop
- B: Creating the first artificial cell
- C: Potential to survive outside the laboratory
- D: Actual release outside the laboratory
- E: Toxicity or infectiousness

Our recommendations about the responsible and ethical development of artificial cells are listed below. Some are specifically triggered by individual ethical checkpoints.

Communicating with the public

- Recommendation 1: Success at reaching any ethical checkpoint or any major scientific milestone in artificial cell research should be clearly communicated to the public.

Social, cultural, and religious impact

- Recommendation 2: Each of the ethical checkpoints should be accompanied by presentation and discussion of public concerns and worries about the prospect of artificial cells.

New oversight institutions

- Recommendation 3: Before checkpoint B, proper oversight institutions for artificial cells should be established, and these institutions should be re-evaluated at each future checkpoint.

Funding of artificial cell activities

- Recommendation 4: In order to carefully examine the social and ethical implications of artificial cells, even before checkpoint A is reached the sources that fund artificial cell activities should set aside a tiny fraction of all funds for the study of the ethical, legal, and social implications of artificial cell research and development. We recommend that this tiny fraction be set initially to 2%.

Education

- Recommendation 5: Education in the benefits, risks, uncertainties, and best practices of artificial cell research should become a regular part of the artificial cell research curriculum at colleges and universities.

Laboratory containment

- Recommendation 6: Artificial cell research will not require any special regulations until we reach checkpoint A and artificial cells come within technical reach. At that point, oversight institutions should develop a classification of artificial cell safety levels, and a list of best practices and protocols for safely using artificial cells in the laboratory.

Safety mechanisms

- Recommendation 7a: Once checkpoint A is reached and artificial cells are on the horizon, a comprehensive plan for safety mechanisms should be developed.
- Recommendation 7b: Once checkpoint B is reached and artificial cells have been created, a comprehensive and thoroughly vetted set of safety mechanisms should be identified.
- Recommendation 7c: Once checkpoint C is reached and artificial cells could survive outside the laboratory, the vetted set of safety mechanisms should be implemented and thoroughly tested.
- Recommendation 7d: By checkpoint D when artificial cells are released outside the laboratory, thoroughly tested safety mechanisms and quality assurance measures should be deployed. In addition, their success should be continually evaluated so that the safety mechanisms can be adjusted and improved when necessary.
- Recommendation 7e: By the time checkpoint E is reached and toxic or infectious artificial cells exist, we should ensure that our existing social framework of regulations and procedures for handling toxic and infectious agents are providing the proper oversight of artificial cells.

Environmental impact

- Recommendation 8: Oversight institutions should be mindful now of the future environmental impact of artificial cells, and should take concrete steps to evaluate and consider environmental impact as an explicit issue in their oversight once checkpoint C is reached.

Intellectual property

- Recommendation 9: Intellectual property regulations should be re-evaluated with regard to whether they adequately deal with the distinctive properties of artificial cells.

Weaponization

- Recommendation 10: The relatively low likelihood of terrorist or military use of artificial cells should be clearly explained in communications concerning the risks of artificial cells, especially at this early point in the technology.

PART I: PRELIMINARY CONSIDERATIONS

The PACE project is developing a new kind of technology that can be used in the future to create artificial cells (<http://www.istpace.org>). Artificial cells reproduce themselves, and this entails that they autonomously maintain a complex, changing, robust group of behaviors. Artificial cells promise to bring many social and economic benefits, but unlocking these benefits requires that humans be able to program and reprogram them. The technology for programmable artificial cells involves the development of a new approach to information technology. In addition, creating artificial cells raises new ethical questions. These questions have been aired and explored in a series of workshops funded by the PACE project (see Appendix). The purpose of this document is to take stock of those ethical questions and make preliminary recommendations about how to conduct our future with artificial cells in a way that is socially responsible and ethically admirable.

In part I, we describe the motivation behind this document, clarify what we mean by “artificial cell,” and propose a framework in which to situate our recommendations for responsible artificial cell research and development—a series of “checkpoints” in the future of artificial cells which we feel carry social and ethical significance. In part II, we make a series of concrete recommendations, against the background of the framework in part I.

Below, we outline a more detailed understanding of artificial cells, which is broader in scope and implications than the PACE approach. In fact, our discussion is informed by two different broad perspectives on artificial cells, which complement each other. Thus, while this document stems from the explorations of artificial cell technology and its social and ethical implications during the PACE project, it aims to be a more broadly and generally relevant guide for responsible artificial cell research.

There are already a number of existing mechanisms for addressing many of the social and ethical issues raised by artificial cells, including various regulatory institutions and practices on national and international levels. These will be discussed further in part II. In this document we focus specifically on new and distinctive issues that arise specifically for artificial cells. These issues could present new problems and challenges for established mechanisms and institutions, and some might warrant the creation of new mechanisms and institutions. Our goal is not to “reinvent the wheel” but to highlight the novel social and ethical issues raised by artificial cells and to make recommendations about the pursuit of their science and technology.

Our recommendations are influenced and informed by similar recommendations about nanotechnology and synthetic biology. These earlier proposals typically either recommend general and abstract principles that achieve easy consensus (Hagendijk et al. 2005, European Commission 2008), or they are preoccupied with laboratory security and bio-terrorism (Brent 2005, Maurer et al. 2006, Garfield et al. 2007), or they are driven by the social consequences of capitalist biotechnology (ETC Group 2007). Here, we focus on the ethical implications that are distinctive of the

achievements of artificial cell science.

Though artificial cells do not currently exist, we assume and expect that the first ones will be created within the next few years, and that they will be able to survive in the natural environment (that is, outside of the laboratory) within the next ten to twenty years. On that timescale, we expect that they will also be ready for commercial applications, and could become key components of new medical, industrial and informational technology. While the vast majority of work on artificial cells is currently in the basic research stage, the major driving force for their continued development will increasingly be commercial application.

Because artificial cells do not exist yet, the risks of even the most advanced artificial cell research being conducted now are negligible – that is, they are no higher than the risks of any other basic chemical or biochemical research. Nevertheless, we feel it is prudent to take steps now to ensure that due weight is given to scrutiny of ethical issues, risks and regulations as the research progresses.

It should also be noted that, while the actual risk is currently negligible, the perception of risks from artificial cells today is not negligible. Social scientific studies have identified a number of factors that affect risk perception (e.g., how new, readily observed, or controllable the risk is), and artificial cells have virtually all of the factors that make perception of risk high (Cranor, 2009). In the media, at least in the USA and Europe, the prospect of creating artificial cells almost invariably raises worries about scientists playing God and private commercial interests irreparably harming the environment with “Frankencells” that have run amok. So, scientific and commercial realization of the potential benefits of artificial cells will require ethically sensitive and responsible treatment of public perception of risks.

What are artificial cells?

The phrase “artificial cell” lacks a universally known and accepted meaning. So, before we can propose guidelines for artificial cell research and development, we need to agree on what we mean by the term. We also must clarify how artificial cells are like and unlike the products of synthetic biology and nanotechnology.

We will not provide a complete precise definition of artificial cells. Discussions of artificial cells often appeal to distinctions like “bottom-up” vs. “top-down,” or “grounded in chemistry” vs. “grounded in biology.” But these are too vague to delineate the relevant distinctions in a rapidly developing field, and they fail to emphasize artificial cells’ special characteristics. Fortunately, perfect definitions are not needed here because social and ethical implications of artificial cells typically turn on broad conceptions rather than definitional details. Since an exhaustive catalog of different views is orthogonal to our present purposes, we will concentrate only on the main conceptions of artificial cells.

Box 1

Created through human artifice but not by merely manipulating a natural living organism (such as a bacterium), an *artificial cell* is a self-assembling and self-reproducing chemical system, with the following properties:

1. It maintains its identity over time by spatially localizing its components. This spatial localization is a form of containment.
2. It utilizes free energy from its environment and digests environmental resources in order to maintain itself, grow, and ultimately reproduce. This use of energy and materials is a form of metabolism.
3. The containment and metabolism are under the control of replicable and inheritable chemical information that can be “mutated” when the artificial cell reproduces. This informational chemistry functions as a programmable genetic system.

Box 1 contains the general characterization of artificial cells that we will use here.² Characterizing artificial cells along these lines is a near consensus among artificial life scientists. Note that artificial cells are characterized as chemical systems with certain interlocking chemical *capacities* or *functions*. This functional characterization enables the chemistry of artificial cells to differ as much as possible from the chemistry in any existing form of life. For example, containment might be achieved without vesicles formed from bilayer lipid membranes, informational control might be achieved without protein enzymes, and genetic information might be stored without DNA or RNA. See Rasmussen et al. (2008) for a contemporary overall survey of artificial cell science.

The characterization in Box 1 would cover artificial cells on “life support” in an Omega-machine, a key long-term motivation for the PACE project (McCaskill, 2008). In an Omega machine, pre-artificial cell chemistries are complemented by technical devices, such as electronically-driven microfluidic systems. Full autonomy cannot be achieved with such an approach, because the artificial cell depends on the external Omega machine. But it is easy to imagine a step-by-step procedure in which the Omega machine is replaced, chemical function by function, by the right kind of autonomous chemical sub-system that is tightly connected with the rest of the artificial cell’s chemistry. When the whole Omega machine has been replaced, the

artificial cell becomes fully autonomous. At previous stages, the proto-artificial cell was only partially autonomous.

If functionally coordinated in the appropriate way, a robustly self-assembling and self-reproducing chemical system that achieved properly coordinated containment, metabolism, and programmability would have the ability to repair itself, so that it would continue to exist in the face of external perturbations. Here, “repair” might mean simply reproducing a new copy of itself. These properties are important because future applications of artificial cells will require that they be autonomously robust and able to repair themselves, because they will be too small to be repaired or overseen by conventional means (that is, under the direction of some external agency, such as a person). Even if they are “programmed” with external information control systems, this control will be very indirect and quite unlike the existing programming paradigms in computer science.

Note that a chemical system that cannot autonomously reproduce itself is not an artificial cell. For example, what are called “artificial red blood cells” – inert microscopic chemical systems with the capacity to pick up, carry and release oxygen in the blood stream (Shinji, 2005; Orive et al., 2003) – do not meet this conception of an artificial cell. The ability to reproduce autonomously is a fundamental requirement of artificial cells in the present context. A chemical system that produces a container, a metabolism, and some form of genetics but cannot reproduce itself would not be an artificial cell, but an artificial cell *precursor*.

The genetic information that controls an artificial cell’s internal functioning could mutate when an artificial cell reproduces. If different artificial cells contain different genetic information, the resulting behavioral differences could impact their ability to survive and reproduce. Thus, a population of artificial cells will undergo natural (or artificial) selection and, over time, new kinds of artificial cells in principle can evolve. This principle of evolvability is a direct consequence of the closed loop of transcribing “genetic” information and translating it into a functional protein. Slight changes in the informational content of these information-carriers will inevitably change the translation apparatus. Error-free reproduction can be achieved in computer science applications; in chemistry, on the other hand, such reproduction is impossible. Furthermore, it is unwanted because coping with changing environmental conditions requires the ability to adapt and evolve. This evolvability is consistent with the existence of conserved regions in the chemical information, conserved processes, or conserved solutions of vital recipes inside a cell.

Some groups within the artificial cell research community would wish to modify the above conception by adding one of two further requirements. One requirement is motivated by the idea that artificial cells must be made “from scratch” rather than by using the complex cellular machinery extracted from natural life forms. This conception can be captured by adding the following requirement:

- *Pure bottom-up*: the system is constructed without using any materials derived from natural living systems.

This condition would exclude systems that are made by using a whole organism and modifying some of its internal structure. It would also rule out chemical systems that use cell-free extract derived from living cells.³ (Some artificial cell precursors today use cell-free extract to express proteins inside vesicles, e.g., Ishikawa et al., 2004; Noireaux and Libchaber, 2004.) On this pure bottom-up conception, everything in the artificial cell would have to be made by humans or derived from inorganic materials. On the other hand, this conception would allow artificial cells to contain molecules and larger multi-molecular structures found in existing life forms, as long as they were synthesized from scratch. For example, DNA can now be synthesized from nucleotides, and proteins can be synthesized from amino acids. A limitation of this conception is that the meanings of phrases like “from scratch” and “derived from natural living systems” are not completely precise.

Another variant of the artificial cell concept is motivated by the idea that which materials are used is less important than how they are organized. According to this view, in an artificial cell it is not just that the materials used are of non-biological origin, but that the nature of the resulting system is fundamentally different from existing biological systems. Where should we draw the line demarcating a “fundamental difference” from existing life forms? A bacterium that was reengineered to produce proteins that are not found in any existing life form of life might not be thought different enough to warrant the term “artificial cell.” A deeper difference than containing some unnatural substances is having a fundamentally different kind of organization, or “architecture.” So, a conception of artificial cells could capture this by employing the following condition:

- *Novel architecture*: the system’s architecture must be fundamentally different from that of any natural living system at some vital places.

The notion of “fundamentally different” is not precise, and there are different kinds and degrees of architectural novelty. The most distinctive architectural feature of all existing life forms is the translation machinery that produces functional proteins, so lacking this machinery is one of the most natural ways to meet the novel architecture condition. A self-assembling and self-reproducing chemical system that produced proteins using a novel genetic code would be a paradigm case of meeting the novel architecture condition. Some artificial cell designs eschew proteins altogether,⁴ and these would also meet the novel architecture condition.

The pure bottom-up and novel architecture conditions will apply to many of the same systems, though it is easy to imagine hypothetical systems for which they would diverge. In this document we will use the phrase “artificial cell” to cover the basic conception of artificial cells, with or without the addition of the pure bottom-up or novel architecture condition. Each of the resulting conceptions has adherents and can

be defended, and as far as we can tell their social and ethical implications are largely the same. In the discussion below we will call attention to any issues that depend on specific conceptions of artificial cells.

Craig Venter and colleagues are working toward synthesizing a novel biological system, and this effort has generated significant attention in the media. This system involves chemically synthesizing the entire genome of a *Mycoplasma genitalium* bacterium, transplanting the synthetic genome into a living *Mycoplasma* cell, and then getting the cell to express the new genome (Hutchison et al., 1999; Lartigue et al., 2007; Gibson et al., 2008). As with any product of genetically engineering, Venter's creations (when in existence) could legitimately be called "artificial cells," because they are cells that would never exist without intentional human agency. But they do not fit our definition of "artificial cells" here. All conceptions of artificial cells discussed above rule out Venter-style top-down architecture and much of synthetic biology, for these merely subject existing life forms (often, bacteria) to more or less extreme forms of genetic or metabolic reengineering.

The ethical implications of synthetic biology have received considerable attention recently (Cho et al., 1999; Brent, 2005; Maurer et al., 2006; Garfield et al., 2007; ETC Group, 2007; Boldt and Müller, 2008; Balmer and Martin, 2008). So have the ethical implications of nanotechnology (Malakoff, 2003; European Commission, 2008), especially the so-called Nanotechnology-Biotechnology-Information Technology-Cognitive Science (NBIC) convergence (National Academies, 2004; Roco and Bainbridge, 2004; Bainbridge and Roco, 2006; Berloznik et al., 2006; ETC Group, 2003). Artificial cells are related to the constructions produced in both these fields. In fact, artificial cells could be considered one example of NBIC convergence, though they are not the kind of systems typically discussed in that context to date. Among the scope of NBIC convergence, distinctive ethical issues are raised by artificial cells, because of their capacity for autonomous reproduction and the ability to evolve unpredictable new properties.

Synthetic biology attempts to "design and build ('synthesize') novel biological functions and systems" (Wikipedia, 2008). Since artificial cells could fairly be viewed as novel biological systems, they could be thought of as "bottom-up" synthetic biology. However, unlike the construction of artificial cells, the work that now goes by the name "synthetic biology" typically involves just reengineering existing forms of life. Further, synthetic biology emphasizes the suggestion that standardization of parts ("building blocks") for reengineering living systems can be as predictable and reliable as traditional engineering, which, according to the previous explanation, is a sort of illusion. By contrast, research in artificial cells has self-replication as a top priority, as in living systems – and thus a possible resultant unpredictability. Hence, the ethical issues concerning artificial cells differ from those concerning synthetic biology.

However, when synthetic biology leaves the area of semi-static or one-step processes

and incorporates more dynamical control, it must align itself with research in artificial cells and confront the ethical issues raised by unpredictability. The chemical programmability of artificial cells will make them an especially powerful technological advance. Programmable chemical systems would be much easier to fashion into artificial cells, and programmable artificial cells would have much greater social and economic value. But as with all powerful technologies, programmable chemical systems can also be misused or abused. And the unpredictability of chemical programmability raises special concerns. Current programming paradigms and control theory both require full knowledge of the system of interest, which is usually assumed to be linear. We do not know today how to control nonlinear systems governed by unknown parameters, when the systems are as small and complex as the simplest natural cells (Wikipedia on dynamical systems, 2008; Rugh, 1981/2002). Contrary to some of the hype surrounding the human genome project, having the entire “book of life” (genome) for an organism in hand has not meant that we understand all the important details of how that form of life work or can control it (International Human Genome Sequencing Consortium, 2001; Venter et al., 2001).

Investigation of the ethical issues concerning artificial cells has much to learn from commonalities with NBIC convergence and synthetic biology, where they exist. But the critical ethical issues concerning artificial cells are unique enough to require independent investigation. It would help this effort if the disparate artificial cell research efforts were collected into a single scientific community; this community still needs to be built. Artificial cell work has a foot in synthetic biology, nanotechnology, information technology, artificial life, astrobiology, and studies in the origin of life. Each of these other areas of research benefits from well-established scientific communities that are served by conference series and professional journals. Building a scientific community focused on artificial cell research would facilitate focused attention on the broader social implications of creating artificial cells, not to mention promoting the scientific and professional interests and aims of the community.

All conceptions of artificial cells should distinguish certain different kinds of artificial cells and stages in their development. Those details matter in the present context because some ethical issues turn on exactly what properties artificial cells have. Artificial cells which can be conceived as a result of clever breeding or recombinant genetics are not included here. We expect that these entities (genetically modified organisms, GMO) are already subject to existing regulation procedures. The same holds in principle for micro-miniaturized chemical plants which are not able to self-replicate: current regulations for industrial or chemical substances (or both) apply as well.

Five ethical checkpoints

It is useful to distinguish different kinds or stages of artificial cells, depending on exactly what properties they have, because some ethical issues depend on these details. There are various scientific milestones that represent key technical achievements in the path towards artificial cells (Rasmussen, Bedau, McCaskill, and Packard, 2008), and those scientific milestones may overlap our checkpoints. Our goal here, however, is to identify not scientific milestones but rather the points in artificial cell research and development that require special ethical attention, including the evaluation and establishment of social regulations.

The following diagram represents the basic structure of these checkpoints:

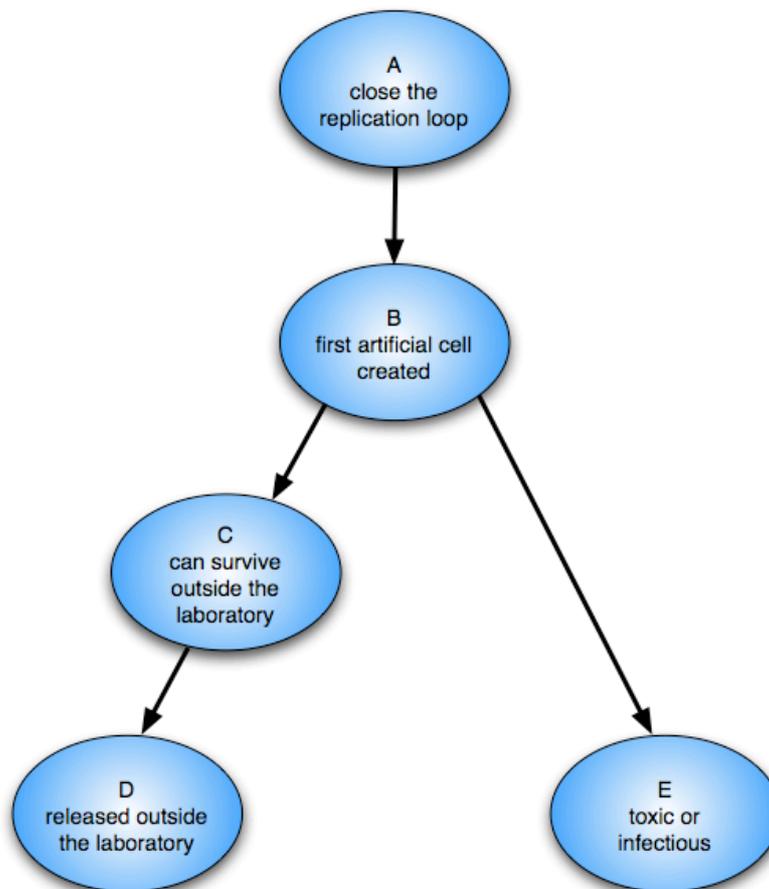


Figure 1. Five ethical checkpoints concerning artificial cells. Time flows down the arrows, but the duration of individual arrows is highly variable and uncertain.

We will briefly describe each checkpoint, and then discuss them all at greater length:

A: Closing the replication loop is the main technical hurdle to creating artificial cells, so it is the only ethical checkpoint that arises before artificial cells actually exist.

B: Creating the first artificial cell in the laboratory would involve creating a self-assembling and self-reproducing chemical system with the properties of containment, metabolism, and programmability. This is the scientific achievement with the single greatest ethical significance.

C: Potential to survive outside the laboratory entails potential to cause great harm to human health and the environment, so potential release in the environment triggers the need to re-assess regulation and containment standards for artificial cells.

D: Actual release of artificial cells (possibly for commercial reasons) in the environment outside of the laboratory has special ethical significance because it puts artificial cells in direct contact with vastly many more forms of life, including people.

E: Toxicity or infectiousness trigger the need for appropriate safety regulations.

The flow of the arrows in Figure 1 indicates the temporal structure of the checkpoints, although the duration between the checkpoints is uncertain and the sequence of some checkpoints could be debated. Arrows branch where the chronological order is especially uncertain. On conceptual grounds, checkpoint A must precede B, and B must precede all subsequent checkpoints. For other obvious reasons, D is a significant ethical checkpoint only after C has been reached.

The checkpoints deserve further discussion. To start with checkpoint A, the mere realistic prospect of artificial cells itself raises ethical issues, but many of these are handled adequately by existing ethical considerations and social institutions. When actual artificial cells are within scientific reach, though, society should prepare for new ethical challenges and difficulties. This prospect is what checkpoint A signals, because closing the replication loop is the main technical hurdle to creating artificial cells. The major bottleneck of current evolutionary biotechnology is the absence of a stable reliable in-vitro translation system. Having to use cell-extracts from pigs, for example, with poor yield of produced proteins, effectively limits the scope of what can be achieved with evolutionary techniques. Transfection of *E. coli* bacteria has other severe disadvantages, including time and cell-toxicity. Until the problem of translation is solved (which might be easier in a non-protein cell), artificial cells will not pose any serious, new ethical problems. When this loop could be closed, all other requirements for artificial cells will either be already available or added in a foreseeable amount of time. This is the only relevant ethical checkpoint before the existence of artificial cells.

The centrality of checkpoint B cannot be overstated. It is in the center of Figure 1 because all subsequent ethical checkpoints depend on artificial cells existing. Since artificial cells do not yet exist, many ethical consequences of artificial cells are not so pressing today. Checkpoint A is relevant only because of the importance of checkpoint B.

It is likely that the first artificial cells created will be dependent on a laboratory environment (i.e., specific environmental conditions, needing careful “feeding” by their creators to survive, etc.). Once created in the laboratory, a next technical hurdle is to enable them to survive outside of the laboratory, an important commercial goal. Checkpoint C is triggered when it becomes technically possible for artificial cells to survive outside the laboratory. Once artificial cells could survive in the environment, new ecological questions become pressing: How quickly do they degrade in different environments, and do they degrade into something harmful? What side effects or collateral damage should be expected?

Checkpoint D concerns the release of artificial cells into the environment outside of the laboratory. Once artificial cells begin to exist outside the lab, the scale of their commercial application will mushroom and their numbers could skyrocket. When artificial cells leave the laboratory, they will go two main places: into the environment (initially in a highly targeted manner, presumably) and into industrial facilities for synthesizing chemicals, improving biochemical processes, etc. Industrial use will raise significantly fewer ethical concerns when the artificial cells are confined to industrial facilities and carefully monitored and controlled.

The ethical importance of the toxicity and infectiousness checkpoint, E, is obvious. Existing tests and regulations for toxicity and infectiousness would apply to artificial cells. However, the novel properties of artificial cells, including their ability to adapt and evolve to suit their own purposes, call for special new actions. The severe new potential hazards of nanotechnology and synthetic biology are an instructive example of what can be expected for artificial cells.

PART II: RECOMMENDATIONS

In this section, we will outline a series of concrete recommendations, against the background laid out in part I. We will group these recommendations in a way that we think is natural, roughly following the chronological order of the checkpoints (though, recall that there is not necessarily a clear chronology among all checkpoints). We will connect our recommendations as much as possible to the checkpoints, with the hopes that those responsible for making decisions about artificial cells in the future will check back in with the key issues raised here well in advance of the achievement of these various steps in the progression of artificial cells.

1. **Communicating with the public.** Advances in artificial cell research are already gaining public attention. This attention will increase, especially as work on

artificial cells begins to transition from the research to the development stage. Thoughtful communication with the public should be one of the earliest concerns on the agenda for socially and ethically responsible artificial cell research. The media and NGOs will each play a major role in the public perception of artificial cell research. Any communication with the public through the media should follow common sense guidelines, such as: provide clear and honest information, acknowledge and address both strengths and weaknesses, acknowledge public concerns as legitimate, avoid hype and misrepresentation, and build trusting relationships with stakeholders so they respect your views.

As checkpoint A approaches, it will be important for these communications to consider the social and cultural concerns (discussed in section (2) below) that arise around artificial cell research. It is also important in these early stages to reinforce to the public that the actual risk of artificial cell research in these very early stages is negligible. The public will be more likely to believe this point if they are supplied with clear information about the actual state of the science, rather than hype about hypothetical prospects for artificial cells many years in the future.

Recommendation 1: Success at reaching any ethical checkpoint or any major scientific milestone in artificial cell research should be clearly communicated to the public.

We cannot anticipate now what new issues will arise as future checkpoints are reached. We can recommend that the artificial cell community as a whole be prepared to anticipate and address these issues in an open, coherent and responsible way, in addition to being clear about the underlying science and realistic about the risks involved.⁵ Currently, individual research groups are communicating with the public via occasional press releases and interviews. When a professional society for artificial cell research is formed, it would become the focal point for communicating with the public through the media and NGOs.

2. **Social, cultural, and religious impact.** The ability to design and engineer entirely new forms of life would generate tension with a number of deep social, cultural, and religious norms and preconceptions (Cho et al., 1999).⁶ Thus, the prospect of artificial cells can be expected to generate widespread unease, distrust, and even hostility in the public at large. The authors of this report are not qualified to speak about the prospect of artificial cells in other cultures in the world, though this would be interesting and important to learn. We can say that in the West (US and Europe) the main public concerns raised by the prospect of artificial cells include at least the following:

- *Conflict with religious doctrines.* Many of the new technologies for manipulating life forms seem to conflict with the doctrines of various religions. In vitro fertilization, reproductive cloning, and embryonic stem cell research are only three of the most recent controversies concerning new biotechnologies in which

religious concerns figure prominently (Kass, 2002; Pallella, 2008). These biotechnologies become controversial mainly when they are applied to human life, so artificial cell technology might escape similar condemnation for the foreseeable future. But religious concerns tend to be raised whenever life is involved, and we need to be aware of the possibility that making artificial cells, even in a research context, might violate someone's deeply held religious doctrines.

- *Violating nature.* The “unnaturalness” of artificial cells unsettles some people, because they feel that creating life from scratch would violate the sanctity or wisdom of life or upset the balance of nature (e.g., Fukuyama, 2002). It must be admitted that artificial cells could be quite unlike any currently existing form of life. However, the boundary between the natural and the artificial is difficult to draw, and artificial cells have the potential themselves to shift the boundaries of what would be considered natural.⁷ Nevertheless, the ethical implications of this boundary are controversial.
- *Playing God.* The worry here is not that only God could create wholly new forms of life, but that only a being with almost God-like understanding and wisdom would have the moral and scientific insight required to properly and judiciously exercise the capacity to create new forms of life (Bedau and Parke, 2008). The force behind this worry comes from the difficulty of predicting and controlling life forms, given their autonomous regeneration and adaptability and their capacity for open-ended evolution. Note that this concern does not depend on believing any particular religious doctrine. It is just common sense, even for atheists.
- *The mechanistic deflation of life.* Constructing artificial cells in the laboratory “from scratch” would blur and perhaps erase the distinction between machines and life forms, and might promote the view that life forms are nothing more than complicated molecular machines. While this view might seem benign to some scientists, it might offend or concern others. Boldt and Müller (2008) emphasize exactly this point: “Calling an object alive is deeply connected, both historically and systematically, with the conviction that the object in question is to be valued as a (more or less) autonomous agent, a status that artifacts do not share,” so the “living machines” vocabulary “identifies organisms with artifacts, an identification that, given the connection between ‘life’ and ‘value,’ may in the (very) long run lead to a weakening of society’s respect for higher forms of life that are usually regarded as worthy of protection” (p. 388). The mechanistic deflation of life raises questions about the wisdom of reengineering the mechanistic details of life, and it might foster the uncongenial view that life forms are commodities with no purpose except serving as instruments for human desire.

Our goal here is to highlight the kind and magnitude of the social, cultural, and religious concerns that are generated in the public mind by the prospect of artificial cells. Many (including the authors of this report) are moved by these concerns, but this report will not address their significance or the response they deserve.

Recommendation 2: Each of the ethical checkpoints should be

accompanied by presentation and discussion of public concerns and worries about the prospect of artificial cells.

3. **New oversight institutions.** As artificial cell research is still in its infancy, to date we have no actual experience with the effects of regulating its activities. Such experience is an invaluable guide to wise action. Thus, it is difficult to have high confidence today about the wisdom of many detailed recommendations for oversight and regulation of artificial cell research. Given this, it is important to identify and create wise institutions and practices and give them the flexibility to adapt to our growing experience with artificial cells and their regulation.

It could be the case that existing oversight institutions provide some or even all of the oversight artificial cells need at present, before artificial cells exist or are even within technical reach. New oversight institutions for artificial cells should be created only after checking whether existing regulations of existing institutions provide adequate regulation. This checking should begin now and should be completed before checkpoint A. As a part of this research process, all existing institutions under whose oversight and regulation artificial cells will fall should be equipped with the relevant knowledge to apply their mandates to this new technology.⁸

Recommendation 3: Before checkpoint B, proper oversight institutions for artificial cells should be established, and these institutions should be re-evaluated at each future checkpoint.

It is conceivable that advances in artificial cell research could reveal unanticipated gaps in regulatory jurisdiction. So, oversight institutions should regularly revisit and revise their recommendations and regulations in the light of new experiences and research discoveries. These institutions should be professional or governmental institutions (e.g., committees). Though there are obvious practical difficulties to surmount, to the extent possible oversight institutions should be coordinated internationally, for the problems artificial cells raise and the scope of their solutions cross national borders.

Oversight institutions should distinguish three different bodies that are subject to recommendations or regulations: (i) the scientific community engaged in artificial cell research, (ii) the governmental agencies responsible for regulating artificial cell research and development, and (iii) companies that produce artificial cells commercially. Regulation of commercial development of artificial cells must address specific concerns about developing and enforcing proper quality assurance standards, such as ISO 9000 (<http://www.iso.org>).

In addition, oversight institutions should distinguish between four different areas in need of oversight:

- scientific research,
- publication (e.g., restrictions on information dissemination or access),

- commercial development of products, and
- intellectual property (e.g., restrictions on patenting new forms of life).

Different regulations might concern different areas, and some might concern multiple areas.

One concrete suggestion for oversight institutions regulating artificial cell technology – whether existing institutions, or ones established for this explicit purpose (see below) – is to model their regulation on the *subsidiarity principle*, which is a basic political principle for decision-making in the EU. This entails putting decisions to be made at the lowest reasonable level in the organizational hierarchy, and involving the scientists and entrepreneurs who are creating artificial cells in decisions about regulating their research and development. This will help to ensure that oversight decisions are informed by the relevant scientific information.

4. Funding of artificial cell activities. Since funding agencies can significantly shape the course and conduct of artificial cell activities, they can be an important constructive force for change. Two major funding institutions in the USA – The Department of Energy (DOE) and the National Institutes of Health (NIH) – devoted 5% of their annual Human Genome Project budgets to studies on the ethical, legal and social issues surrounding the new genetics.⁹ In the EU the European Group on Ethics (EGE) recommended that up to 3% of the nano-medical research budget be devoted to ethical concerns.¹⁰

Recommendation 4: In order to carefully examine the social and ethical implications of artificial cells, even before checkpoint A is reached the sources that fund artificial cell activities should set aside a tiny fraction of all funds for the study of the ethical, legal, and social implications of artificial cell research and development. We recommend that this tiny fraction be set initially to 2%.

Initiatives for funding artificial cell science should follow the lead of the DOE and NIH and set aside a fixed percentage of their funds for the following kinds of activities:

- studies of the ethical, legal, and social implications of scientific research on artificial cells, commercial development of artificial cells, and professional and governmental regulation of artificial cells.
- public education on scientific advances in artificial cell research (to limit hype and misunderstanding, and ensure that sound science informs public perception and social policy).
- public education on the ethical, legal, and social implications of artificial cell activities.

Once checkpoint C is passed, funding agencies should explicitly re-evaluate the risks and environmental issues associated with the eventual release of artificial cells outside

of the laboratory and reconsider the allocated fraction. We expect that at checkpoint C (and at later checkpoints) there will be good reasons for raising the amount set aside for ethical and social issues above 2%. Funding agencies have a special opportunity to assess whether the new issues and risks raised by new research advances are being adequately addressed and regulated by existing institutions, and if not, adjusting or re-allocating portions of their budget to deal with these issues. Candidates for additions to the list of activities above, when we are faced with the possibility of artificial cells existing outside of the laboratory in the near future, include:

- studies of the risks associated with releasing artificial cells outside of the laboratory;
- monitoring the effects of artificial cell products on the environment, on human health, and on society in general.

5. **Education.** A general culture of thoughtful and responsible action should be cultivated in the artificial cell research community. Earlier in this document we discussed the importance of forming a professional society (which does not now exist); this will be a key step towards promoting such a culture. In addition to the public education efforts discussed in section (4) above, education relevant to the social and cultural upshots of artificial cell research as part of academic curricula will contribute to creating a next generation of responsible scientists in the field.

Recommendation 5: Education in the benefits, risks, uncertainties, and best practices of artificial cell research should become a regular part of the artificial cell research curriculum at colleges and universities.

A professional society could exercise oversight in this area, develop and collate pedagogical material, organize training exercises and conferences, and oversee ongoing review and revision of educational efforts. These education efforts should start as soon as possible.

6. **Laboratory containment.** Oversight of artificial cell activities will be able to leverage society's prior experience with regulating genetic recombination in the laboratory. Artificial cell research does not currently merit any special regulation beyond the default for the chemicals and other materials and machines used in the laboratories, and this will remain the case at least until checkpoint A is reached. However, we can start thinking now about what sort of regulation scheme will be appropriate once artificial cells become easily within reach.

There is a standardized system of classifying levels of precaution when handling biological agents, using a scheme of four biosafety levels. We recommend that some analogous classification system be applied to working with artificial cells in the laboratory. Certain features of artificial cells will merit special attention when implementing such a system. Some features can be predicted now, and some will be recognized only after reaching checkpoints C and E. For instance, seemingly harmless features and functions of artificial cells could have a severe impact if they are released

into the biosphere without the proper controls. This illustrates how the mere fact that artificial cells replicate requires additional safety classifications, over and above the four classic biological safety levels.

Recommendation 6: Artificial cell research will not require any special regulations until we reach checkpoint A and artificial cells come within technical reach. At that point, oversight institutions should develop a classification of artificial cell safety levels, and a list of best practices and protocols for safely using artificial cells in the laboratory.

The four existing levels of biosafety can serve as a source of inspiration, but an appropriate classification of artificial cells must be attuned to the most powerful novelties of artificial cells, such as their autonomous reproduction, adaptation, and evolution. Since these features are novel, we cannot assume that traditional biosafety levels developed without special attention to these powerful novelties will be adequate for artificial cells. At each of the subsequent checkpoints, B - E, artificial cell safety classification should be re-examined and revised. This is because at those checkpoints science will understand many more details about the actual safety issues and underlying mechanisms of artificial cells, and these unknown details are the proper basis for resolving details of this classification.

As soon as checkpoints C, D, and E are reached, the efficacy of artificial cell containment and the risks of their release should be carefully analyzed, and this analysis should be informed by the latest scientific advancement at those checkpoints.

7. **Safety mechanisms.** Artificial cells will be able to metabolize material from their environments, reproduce, and evolve. Because they will evolve, there is some chance that they could get out of control and cause problems for human health or the environment. Society has had significant experience providing oversight and regulation with certain kinds of complex and potentially dangerous systems. For example, so-called “dependable” systems in computer science and engineering have resilient, built-in safeguards to prevent erroneous or dangerous behaviour. Making artificial cells similarly “dependable” is a key goal.

Our recommendations about safety mechanisms:

Recommendation 7a: Once checkpoint A is reached and artificial cells are on the horizon, a comprehensive plan for safety mechanisms should be developed.

In addition to relatively standard containment procedures, safety mechanisms might involve engineering “kill switches” that destroy artificial cells or prevent them from reproducing or evolving, or engineering dependence on unnatural food stuffs that only humans can supply, as well as engineering unique “bar codes” that would allow each artificial cell line to be traced to its source of origin. An ideal “kill switches” would target deeply entrenched chemical systems that are so vital to proper cellular functioning that their disruption would destroy the cell. The safety plan could

encourage widespread use of standardized “entrenched vital systems” that would provide nearly universal targets for kill switches. A sufficient number of conserved targets for “kill switches” is vital for ensuring a robust ability to control artificial cells.

Recommendation 7b: Once checkpoint B is reached, a comprehensive and thoroughly vetted set of safety mechanisms should have been identified.

Recommendation 7c: Once checkpoint C is reached and artificial cells could survive outside the laboratory, the vetted set of safety mechanisms should be implemented and thoroughly tested.

The tests should include not just laboratory settings, but should cover the kinds of conditions and environments that artificial cells would likely encounter outside the laboratory.

Recommendation 7d: By checkpoint D when artificial cells are released outside the laboratory, thoroughly tested safety mechanisms and quality assurance measures should be deployed. In addition, their success should be continually evaluated so that the safety mechanisms can be adjusted and improved when necessary.

It seems wise, for example, to ensure that artificial cells in the environment naturally decompose into harmless substances. Otherwise we run the risk of repeating earlier mistakes made with DDT and plastic bags made from PVC.

Recommendation 7e: By the time checkpoint E is reached and toxic or infectious artificial cells exist, we should ensure that our existing social framework of regulations and procedures for handling toxic and infectious agents are providing the proper oversight of artificial cells.

8. **Environmental impact.** Protecting the integrity of the hereditary information of the biosphere in general, and humankind in particular, is a social good. Releasing artificial cells in the environment could threaten this biodiversity, including the genetic repository of human beings. This issue will not become a concrete concern until artificial cells exist outside of the laboratory. It is important not to over-emphasize concerns about environmental impact now, because at the current stage of the research, there are none. When checkpoint C is reached, however, there should be concrete and comprehensive analysis and understanding of the relevant concerns and risks of this issue.

Until we approach checkpoint D, we will not be equipped with enough information to sufficiently evaluate environmental impact. Because artificial cells will be unlike existing forms of life, they might impact the environment very differently, in ways we will better understand once we know more about them (i.e., once the field starts to transition from the research to the development stage). Our experience with existing forms of life can be thought of as a guide – but a very limited, imperfect one – for

starting to think now about how to treat the future environmental impact of artificial cells. We can begin to discuss the issues now in a forward-looking way, provided that we acknowledge our lack of full information, and the need to re-evaluate the situation by checkpoint D. One such issue is the possibility that artificial cells might contain proteins, and thus be biocompatible; this would be a concern comparable to current issues with, e.g., germ-line interference in plants, because “controlled” reverse transcriptases and other enzymes could immediately affect the genomes of living beings. It might well also be the case that artificial cells will not have any proteins in them. Furthermore, their environmental impact might not be limited to direct interactions with other forms of life; they might also directly impact the abiotic environment (e.g., increase or decrease greenhouse gasses), and thus indirectly affect forms of life that depend on that environment.

Our recommendations about the environmental impact of artificial cells:

Recommendation 8: Oversight institutions should be mindful now of the future environmental impact of artificial cells, and should take concrete steps to evaluate and consider environmental impact as an explicit issue in their oversight once checkpoint C is reached.

We assume that there will still be considerable uncertainty about environmental impact. It is extremely difficult to estimate and judge the possible side effects and unintended consequences of introducing into the environment systems as complex as artificial cells. So the evaluation of the environmental impact of artificial cells should incorporate some form of the precautionary principle, presumably one that gives appropriate weight to the potential positive impact of artificial cell technology (see Parke and Bedau, in press).

9. **Intellectual property.** Intellectual property laws have been subjected to significant new criticisms recently. Some of the especially controversial issues concern new informational and biological technologies, such as whether and how algorithms and software should be patented, and whether patents should be granted for genetic material ranging from individual genes to whole genomes. This suggests that the special features of artificial cells will themselves undoubtedly raise new intellectual property challenges (Pottage, 2009).

One concern arises from the fact that artificial cells are a brand new, still emerging technology. Since they are so new, existing intellectual property claims cover very little of the field, so the field is wide open for new claims. Some commentators are concerned that this will give first movers an opportunity to own and control extremely broad swaths of artificial cell intellectual property. Compare, for example, the ETC Group’s concerns (2007) about Venter’s application to patent his modified forms of *Mycoplasma genitalium* (USPTO, 2007).

When one starts contemplating patent applications for specific kinds of artificial cells, the distinctive properties of artificial cells raise further complications. Since artificial cells are self-assembling chemical systems with unanticipated emergent properties,

questions might arise concerning who can be credited as their “inventor.” Further, since artificial cells reproduce themselves, should one be able to ensure intellectual property protection for all the progeny in the resulting lineage? Current regulations concerning the analogous issue for genetically modified organisms might be inadequate for this purpose. In addition, if artificial cells under intellectual property protection start to change and evolve in new directions, their identity over time will become blurred and claims of authorship and ownership will become undermined. This problem is compounded if different strains of artificial cells merge. In general, since artificial cells are a fundamentally different kind of technology, patent examiners will need to navigate uncharted waters with few trusted landmarks to guide them. They might even be compelled to weigh certain social and ethical implications of artificial cells when evaluating patent claims.

Recommendation 9: Intellectual property regulations should be re-evaluated with regard to whether they adequately deal with the distinctive properties of artificial cells.

10. **Weaponization of artificial cells.** There is some chance that artificial cells could be used as weapons by terrorists or other malevolent parties; the synthetic biology community has devoted attention to this threat. Artificial cells could also conceivably be used as bioweapons in the military arsenal, or as vehicles for espionage, or tags for tracking people. We believe that there is some potential for dual use of artificial cells (that is, development for both peaceful and harmful aims), but that the risks of harmful (mis)application are currently overestimated. There are much easier ways to make bioweapons than using artificial cells.

Recommendation 10: The relatively low likelihood of terrorist or military use of artificial cells should be clearly explained in communications concerning the risks of artificial cells, especially at this early point in the technology.

As artificial cell technology advances in the long run, the potential for their use by terrorists or the military could increase. So could their potential use as biosensors and security devices, which could jeopardize individual rights. Whether these developments occur will depend on how the technology develops. Checkpoints B and E will be the appropriate times to determine the real risk of the weaponization of artificial cells.

References

- Bainbridge, W. S., & Roco, M. C. (Eds.) (2006). *Managing nano-bio-info-cogno innovations: Converging technologies in society*. Dordrecht: Springer. Available on the web at <http://www.wtec.org/ConvergingTechnologies/> (accessed May 2008).
- Balmer, A., & Martin, P. (2008). *Synthetic biology: Social and ethical challenges*. Institute for Science and Society, University of Nottingham. Available on the web at http://www.bbsrc.ac.uk/organisation/policies/reviews/scientific_areas/0806_synthetic_biology.pdf#search=%22Synthetic%22.
- Bedau, M. A., & Parke, E. C. (2008). Social and ethical issues concerning protocells. In S. Rasmussen, M. A. Bedau, L. Chen, D. Deamer, D. C. Krakauer, N. H. Packard, P. F. Stadler (Eds.), *Protocells: Bridging nonliving and living matter*. Cambridge: MIT Press. In press.
- Bedau, M. A., & Parke, E. C. (Eds.) (2009). *The ethics of protocells: Moral and social implications of creating life in the laboratory*. Cambridge: MIT Press. Forthcoming.
- Berloznik, R., Casert, R., Deboelpaep, R., van Est, R., Enzing, C., van Lieshout, M., & Versleijen, A. (2006). *Technology assessment on converging technologies*. European Parliament report IP/A/STOA/SC/2005-183.
- Boldt, J., & Müller, O. (2008). Newtons of the leaves of grass. *Nature Biotechnology*, 26 (4), 387-389.
- Brent, R. (2005). *In the valley of the shadow of death*. Draft for NAS committee, 1 Nov.
- Cho, M. K., Magnus, D., Caplan, A. L., & McGee, D. (1999). Ethical considerations in synthesizing a minimal genome. *Science*, 286, 2087-2090.
- Cranor, C. (2009). The acceptability of the risks of protocells. In M. A. Bedau & E. C. Parke (Eds.), *The ethics of protocells: Moral and social implications of creating life in the laboratory*. Cambridge: MIT Press. Forthcoming.
- Deutsche Forschungsgemeinschaft (1998). *Recommendations of the commission on professional self-regulation in science: Proposals for safeguarding good scientific practice*. Available on the web at http://www.dfg.de/aktuelles_presse/reden_stellungnahmen/download/self_regulation_98.pdf (accessed May 2008).
- European Commission (2008). *Commission recommendation of 07/02/2008 on a code of conduct for responsible nanosciences and nanotechnologies research*. Available on the web at ftp://ftp.cordis.europa.eu/pub/nanotechnology/docs/nanocode-recommendation-pe0894c08424_en.pdf (accessed May 2008).
- ETC Group (2003). *The strategy for converging technologies: The little BANG*

theory. Available on the web at <http://www.etcgroup.org/upload/publication/169/01/combang2003.pdf> (accessed May 2008).

ETC Group (2007). Extreme genetic engineering: An introduction to synthetic biology. Available on the web at http://www.etcgroup.org/en/materials/publications.html?pub_id=602 (accessed May 2008).

Fukuyama, F. (2002). *Our posthuman future: Consequences of the biotechnology revolution*. Farrar, Straus and Giroux.

Garfield, M. S., Endy, D., Epstein, G. L., & Friedman, R. M (2007). *Synthetic genomics: Options for governance*. Final report of project funded by the Sloan Foundation. Available on the web at <http://www.jcvi.org/cms/fileadmin/site/research/projects/synthetic-genomics-report/synthetic-genomics-report.pdf> (accessed May 2008).

Gibson, D. G., et al. (2008). Complete chemical synthesis, assembly, and cloning of a *Mycoplasma genitalium* genome. *Science*, 319, 1215-1220.

Hagendijk, R., Healey, P., Horst, M., & Irwin, A. (2005). *Ten lessons for deliberative practice and scientific governance*. STAGE (EU FP5: contract HPSE-CT2001-500003) Final report.

Hutchison, C. A., Peterson, S. N., Gill, S. R., Cline, R. T., White, O., Fraser, C. M., Smith, H. O., & Venter, J. C. (1999). Global transposon mutagenesis and a minimal *Mycoplasma* genome. *Science*, 286, 2165-2169.

International Human Genome Sequencing Consortium (2001). Initial sequencing and analysis of the humane genome. *Nature*, 409, 860-921.

Ishikawa, K., Sato, K., Shima, Y., Urabe, I., & Yomo, T. (2004). Expression of cascading genetic network within liposomes. *FEBS Letters*, 578, 387-390.

Kass, L. (2002). *Life, liberty and the defense of dignity: The challenge for bioethics*. Encounter Books.

Kinkel, S., Friedewald, M., Huesing, B., Lay, G., & Lindner, R. (2007). *Arbeiten in der Zukunft - Strukturen und Trends der Industriearbeit*. TAB Arbeitsbericht Nr. 113. Available on the web at <http://www.tab.fzk.de/de/projekt/zusammenfassung/ab113.pdf> (accessed May 2008).

Lartigue, C., Glass, J. I., Alperovich, N., Pieper, R., Parmar, P. P., Hutchison, C. A., Smith, H. O., & Venter, J. C. (2007). Genome transplantation in bacteria: changing one species into another. *Science*, 317, 632-638.

Malakoff, D. (2003). Congress wants studies of nanotech's "dark side." *Science*, 301, 27.

- Maurer, S. M., Lucas, K. V., & Terrell, S. (2006). *From understanding to action: Community-based options for improving safety and security in synthetic biology*. UC Berkeley School of Public Policy. Draft 1.1, 15 April.
- McCaskill, J. (2008). Evolutionary microfluidic complementation towards artificial cells. In S. Rasmussen, M. A. Bedau, L. Chen, D. Deamer, D. C. Krakauer, N. H. Packard, & P. F. Stadler (Eds.), *Protocells: Bridging nonliving and living matter*. Cambridge: MIT Press, in press.
- National Academies (U.S.A.), National Academy of Engineering (2004). *Emerging technologies and ethical issues in engineering: Papers from a workshop, October 14-15, 2003*. Washington, D.C.: The National Academies Press. Available on the web at http://www.nap.edu/catalog.php?record_id=11083 (accessed May 2008).
- Noireaux, V., & Libchaber, A. (2004). A vesicle bioreactor as a step toward an artificial cell assembly. *Proceedings of the National Academy of Science of the United States of America*, 101, 17669-17674.
- Orive, G., Hernández, R. M., Gascón, A. R., Calafiore, R., Chang, T. M. S., De Vos, P., Hortelano, G., Hunkeler, D., Lacík, I., Shapiro, A. M. J., & Pedrax, J. L. (2003). Cell encapsulation: Promise and progress. *Nature Medicine*, 9 (1), 104-107.
- Pottage, A. (2009). Protocell patents: Property between modularity and emergence. In M. A. Bedau & E. C. Parke (Eds.), *The prospect of protocells: Social and ethical implications of recreating life*. Cambridge: MIT Press. Forthcoming.
- Pullella, P. (2008). Pope says some science shatters human dignity. *Reuters*, 31 January 2008.
- Rasmussen, S., Bedau, M. A., Chen, L., Deamer, D., Krakauer, D. C., Packard, N. H., & Stadler, P. F. (Eds.) (2008). *Protocells: Bridging nonliving and living matter*. Cambridge: MIT Press. In press.
- Rasmussen, S., Bedau, M. A., McCaskill, J., & Packard, N. H. (2008). A roadmap to protocells. In S. Rasmussen, M. A. Bedau, L. Chen, D. Deamer, D. C. Krakauer, N. H. Packard, P. F. Stadler (Eds.), *Protocells: Bridging nonliving and living matter*. Cambridge: MIT Press. In press.
- Roco, M. C., & Bainbridge, W. S. (Eds.) (2004). *Converging technologies for improving human performance: Nanotechnology, biotechnology, information technology and cognitive science*. Dordrecht: Springer. Available on the web at http://www.wtec.org/ConvergingTechnologies/1/NBIC_report.pdf (accessed May 2008).
- Rugh, W. J. (1981/2002). *Nonlinear systems theory: The Volterra/Wiener approach*. Originally published in 1981 by The Johns Hopkins University Press. Published on the web in 2002 at www.ece.jhu.edu/~rugh/214/me/volterrabook.pdf (accessed May 2008).

Shinji, T. (2005). Developmental trend of artificial blood (artificial red blood cells). *Japan Medical Association Journal*, 48 (3), 135-139.

Tamulis, A., & Tamulis, V. (2008). Quantum mechanical design of molecular electronics OR gate for regulation of minimal cell functions. *Journal of Computational and Theoretical Nanoscience*, 5 (4), 545-553.

Turing, A. (1950.) Computing machinery and intelligence. *Mind* 59, 236, 433-60.

USPTO (2007). Patent application 20070122826: Minimal bacterial genome. Published May 31, 2007.

Venter, J. C., et al. (2001). The sequence of the human genome. *Science*, 291, 1304–1351.

Wikipedia contributors, "Biosafety level," *Wikipedia, The Free Encyclopedia*, http://en.wikipedia.org/w/index.php?title=Biosafety_level&oldid=194089921 (accessed March 2008).

Wikipedia contributors, "Dynamical system," *Wikipedia, The Free Encyclopedia*, http://en.wikipedia.org/w/index.php?title=Dynamical_system&oldid=203896397 (accessed April 2008).

Wikipedia contributors, "Synthetic biology," *Wikipedia, The Free Encyclopedia*, http://en.wikipedia.org/w/index.php?title=Synthetic_biology&oldid=199305928 (accessed May 2008).

Appendix: PACE supported five workshops on the social and ethical implications of artificial cells.

- *The social and ethical implications of protocell technology*, ECLT Workshop, 26 February 2005. Speakers: Mark Bedau, Brigitte Hantsche, Per Sandin, Brian Johnson. Organizers: Mark Bedau and Emily Parke.
- *Social and ethical issues in protocell research*, LANL Workshop, 21 July 2005. Speakers: Mark Bedau, George Khushf, David Magnus, Carl Cranor. Organizers: Mark Bedau and Emily Parke.
- *Social and ethical issues in protocell research: Assessing risk and responsibilities in an uncertain world*, ECLT Workshop, 2 October 2005. Speakers: Christine Hauskeller, Mickey Gjerris, Bill Durodié, Jean-Pierre Dupuy. Organizers: Mark Bedau and Emily Parke.
- *Social and ethical issues concerning protocells: Key questions and answers*, ECLT Workshop, 16-17 March 2006. Speakers: Bill Durodié, Brian Johnson. Organizers: Mark Bedau and Emily Parke.
- *Ethical guidelines for artificial cell research*. ECLT Workshop, 13-14 March 2008. Organizers: Mark Bedau, Emily Parke, Uwe Tangen, and Brigitte Hantsche.

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² Some designs for artificial living cells give them a diameter of 5-6 nanometers. This would make them approximately one thousand times smaller than regular living cells, and thus on the scale governed by quantum mechanics. One simple example of quantum mechanical control of minimal cell functions is presented in Tamulis and Tamulis (2008).

³ Those chemical constructions that do employ materials derived from natural living systems fall into a range of cases, depending on to what extent they can survive and reproduce independently of continual external replenishment of critical cellular components. At one extreme, all necessary proteins and the complete translation apparatus must be supplied externally, and only one plasmid or mRNA is translated inside the cell. At the other extreme, all but one component of the translation apparatus can be synthesized by the cell itself, so only and this missing component has to be replenished externally in order for the cell to reproduce. A system's placement in this range will influence some opinions about whether it deserves to be called an "artificial cell."

⁴ See, e.g., the PACE project (<http://www.istpace.org>) and the LANL Protocell Assembly project (<http://protocells.lanl.gov>).

⁵ In 2007 the EGE (European Group on Ethics in Science and Technology) made similar recommendations about public participation concerning nano-medical products. These recommendations included transparency and openness about uncertainties and gaps in knowledge. See the press release at http://ec.europa.eu/european_group_ethics/activities/docs/press_release_op_nano_en.pdf (accessed May 2008).

⁶ The development of artificial cells are one instance of larger social trends involving new technologies, and these larger trends themselves raise a number of social and ethical concerns. According to a study by the German Parliament's Bureau for Technology Assessment (Kinkel et al., 2007), those concerns include company downsizing, decreasing worker control over work schedule, and increasing industrial espionage. The present document focuses only on the social and ethical concerns raised specifically by artificial cells.

⁷ One approach to identifying the demarcation between natural and artificial in this context would be to follow the inspiration of the famous Turing test from artificial intelligence (Turing, 1950), although the most appropriate way to do this is debatable.

⁸ A number of existing oversight institutions might have things to say about

artificial cells and safety, public participation, technology assessment, and regulations and codes of conducts. These exists on many political levels, including the global level (e.g., UNESCO and the ISO, the International Organization for Standards), the EU level (e.g., the European Group on Ethics in Science and New Technologies, and the European Parliament Technology Assessment), and the national level (e.g., in Germany, the Bureau for Technology Assessment of the German Parliament, the Institute of Technology Assessment on Society, and the Network of Technology Assessment).

⁹ See http://www.ornl.gov/sci/techresources/Human_Genome/research/elsi.shtml

¹⁰ See http://www.nks-lebenswissenschaften.de/aktuelles/Newsletter/dtmlInhalt1/wed/Download/dat_/fil_481 and http://ec.europa.eu/european_group_ethics/avis/index_en.htm.