|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Macintosh HD:Users:bilodeau:Desktop:logos:template 2017:un.emf | Macintosh HD:Users:bilodeau:Desktop:logos:template 2017:unep-old.emf | **CBD** | | |
| CBD_logo_CMYK_black [Converted] | | | |  | Distr.  GENERAL  CBD/SYNBIO/AHTEG/2019/1/2  6 May 2019  ENGLISH ONLY |

AD HOC TECHNICAL EXPERT GROUP on SYNTHETIC BIOLOGY

Montreal, Canada, 4-7 June 2019

**Considerations on synthetic biology as per decision 14/19**

### Note by the Executive Secretary

# INTRODUCTION

1. In [decision 14/19](https://www.cbd.int/doc/decisions/cop-14/cop-14-dec-19-en.pdf), the Conference of the Parties decided to extend the Ad Hoc Technical Expert Group (AHTEG) on Synthetic Biology with renewed membership, taking into account, inter alia, the work on risk assessment under the Cartagena Protocol, to work in accordance with the terms of reference annexed to that decision. The Conference of the Parties also decided to extend the Open-ended Online Forum on Synthetic Biology to support the deliberations of the AHTEG, and invited Parties, other Governments, relevant organizations and indigenous peoples and local communities to submit to the Executive Secretary relevant information related to paragraphs (a) to (d) of the terms of reference for the AHTEG.
2. In the same decision, the Conference of the Parties requested the Executive Secretary to facilitate the work of the AHTEG by, among other things, collecting and synthesizing relevant information, and convening at least one face-to-face meeting of the AHTEG.
3. In response to the above, the Executive Secretary issued a [notification](https://www.cbd.int/doc/notifications/2018/ntf-2018-103-synthetic-biology-en.pdf), inviting Parties, other Governments, relevant organizations and indigenous peoples and local communities to submit relevant information to the intersessional process on synthetic biology; and called for the nomination of experts to participate in the Open-ended Online Forum.
4. A total of 28 submissions were received by the Secretariat. Among the submissions, 17 were from Parties, 1 from a non-Party, and 10 from organizations. The original submissions are available at <https://bch.cbd.int/synbio/submissions/>.
5. The Open-ended Online Forum on Synthetic Biology was convened from 4 to 31 March 2019. The total number of participants registered for the forum was 400. A total of 109 participants were active, and 338 interventions were made. Out of this total, 188 interventions were made by Parties, 5 by non-Parties, 141 by organizations and 4 by representatives of indigenous peoples and local communities. The discussions under the Open-ended Online Forum on Synthetic Biology are available at <https://bch.cbd.int/synbio/open-ended/discussion/>.
6. A face-to-face meeting of the AHTEG is being convened with the financial support of the European Union. The current document has been prepared to facilitate the deliberations of the AHTEG during its meeting and is organized according to the elements in the terms of reference for the AHTEG which are addressed in sections II through VII below. The information in these sections is drawn from the submissions on synthetic biology, the discussions of the Online Forum and the compilation of literature made by the Secretariat. AHTEG members are encouraged to review the original submissions[[1]](#footnote-1) and online discussions,[[2]](#footnote-2) for further information.
7. In addition, background documents for the meeting containing detailed information to support the AHTEG discussions have also been prepared as follows:
8. Synthesis of submissions on synthetic biology (CBD/SYNBIO/AHTEG/2019/INF/1);
9. Synthesis of discussions of the online forum on synthetic biology (CBD/SYNBIO/AHTEG/2019/INF/2);
10. List of references on synthetic biology (CBD/SYNBIO/AHTEG/2019/INF/3);
11. Information for deliberations on agenda item 3.4 (CBD/SYNBIO/AHTEG/2019/INF/4).
12. In undertaking its deliberations, the AHTEG should bear in mind:
13. The common understanding from the 2015 meeting of the AHTEG that the term “components” (e.g. a naked DNA molecule) refers to parts used in a synthetic process, and that the term “products” (e.g. a chemical fragrance) refers to the resulting output of a synthetic biology process, and to consider “components” and “products” as non-living entities;[[3]](#footnote-3)
14. In decision XIII/17, paragraph 4, by which the Conference of the Parties acknowledged that the outcome of the work of the AHTEG on Synthetic Biology on the operational definition is “synthetic biology is a further development and new dimension of modern biotechnology that combines science, technology and engineering to facilitate and accelerate the understanding, design, redesign, manufacture and/or modification of genetic materials, living organisms and biological systems”, and considered it useful as a starting point for the purpose of facilitating scientific and technical deliberations under the Convention and its Protocols.

# NEW TECHNOLOGICAL DEVELOPMENTS IN SYNTHETIC BIOLOGY

1. In accordance with paragraph (b) of its terms of reference, the AHTEG is to take stock of new technological developments in synthetic biology since its last meeting, in 2017, including the consideration of concrete applications of genome editing, if they relate to synthetic biology, in order to support a broad and regular horizon scanning process.
2. The following list presents examples of new developments in synthetic biology since 2017 that were identified in the submissions and the online forum, although views differ on whether these constitute new technological developments, or new applications of existing technologies. The AHTEG may wish to review the list and revise it as necessary:
   * 1. Creation of yeast with altered chromosome number;[[4]](#footnote-4)
     2. Development of synthetic nucleocapsids that can package their own RNA genome (development of virus-like particles);[[5]](#footnote-5)
     3. Proof-of-concept gene drive system developed for mice;[[6]](#footnote-6)
     4. Development of an efficient gene drive that targets a conserved gene in mosquitos for potential malaria control through population collapse;[[7]](#footnote-7)
     5. Demonstration of a gene drive system for *Drosophila suzukii* population suppression (use of maternal effect dominant embryonic arrest);[[8]](#footnote-8)
     6. Theoretical design and modelling of non-invasive gene drives for altering local populations (daisy type drives);[[9]](#footnote-9)
     7. Proposed gene drive applications to control fall army worm and *Bactrocera dorsalis* pests in sub-Saharan Africa;[[10]](#footnote-10)
     8. Increased photosynthetic efficiency using alternative and synthetic pathways;[[11]](#footnote-11)
     9. The genome project-write (GP-write), an open, international research project that aspires to reduce the costs of engineering and testing of large genomes in cell-lines by 1000-fold;[[12]](#footnote-12)
     10. Construction of an infectious horsepox virus vaccine from chemically synthesized DNA fragments;[[13]](#footnote-13)
     11. Building living systems from scratch using chemical biology and nanotechnology tools;[[14]](#footnote-14)
     12. Cell-free biology, including the synthesis of proteins, environmental sensing, and detecting biomarkers;[[15]](#footnote-15)
     13. Design of a synthetic gene to produce a new synthetic protein in the endosperm of sorghum;[[16]](#footnote-16)
     14. Consistent production of recombinant polyclonal antibodies against snake venom toxins in plants;[[17]](#footnote-17)
     15. Transient expression of transgenes and multistep pathways to produce fine chemicals in leaves without inducing heritable genetic modifications;[[18]](#footnote-18)
     16. The application of synthetically engineered “biologicals” (microbes) to agriculture;[[19]](#footnote-19)
     17. Genetic code based on eight nucleotides (Hachimoji DNA-four natural and four non-natural nucleotides in DNA and RNA);[[20]](#footnote-20)
     18. Insect delivery of modified viruses for the modification of agricultural crops (horizontal environmental genetic alteration agents);[[21]](#footnote-21)
     19. Multiplexed CRISPR-based methods, genetic delivery systems (simultaneous targeting of multiple genes);[[22]](#footnote-22)
     20. The utilization of gene editing for fast and efficient domestication of wild plants;[[23]](#footnote-23)
     21. Use of anti-CRISPR proteins to protect cells against gene editing;[[24]](#footnote-24)
     22. Xenobiological developments for the utilization of non-natural components (e.g. amino acids, nucleotides) and adaptive evolution.[[25]](#footnote-25)

III. SYNTHETIC BIOLOGY APPLICATIONS THAT ARE IN EARLY STAGES OF RESEARCH AND DEVELOPMENT, VIS-À-VIS THE THREE OBJECTIVES OF THE CONVENTION

1. The AHTEG, as per paragraph (e) of its terms of reference, is requested to prepare a forward-looking report on synthetic biology applications that are in early stages of research and development vis-à-vis the three objectives of the Convention by compiling and analysing information, including but not limited to peer-reviewed published literature.
2. The submissions of information and the online forum provided some examples of synthetic biology applications that are in early stages of research and development that could have a potential impact on the objectives of the Convention. These examples are summarized in the list below. The AHTEG may wish to review this list and revise it as needed:
   * 1. Manufacturing using Cyanobacteria (i.e. engineered for the photosynthetic production of fuels and fine chemicals);[[26]](#footnote-26)
     2. Applications of nitrogen fixing gene-edited bacteria and gene-edited bacteria/viruses in agriculture and for biological controls;[[27]](#footnote-27)
     3. Development of artificial organisms, protocells, minimal cells, and self-encoded bio-containment systems;[[28]](#footnote-28)
     4. Applications to produce non-native nucleotides and amino acids inside the cell (novel engineered synthetic pathways);[[29]](#footnote-29)
     5. Development of synthetic virus-like assemblies for drug delivery and vaccine applications (synthetic nucleocapsids);[[30]](#footnote-30)
     6. Design of synthetic biological agents for environmental applications (bioremediation or biodegradation);[[31]](#footnote-31)
     7. Applications of engineer microbes that can excrete compounds that mimic valuable substances;[[32]](#footnote-32)
     8. Gene drive applications (i.e. those directly aiming at conservation objectives and those that could have indirect impacts on conservation).[[33]](#footnote-33)
3. Submissions and contributions to the online forum suggest that potential impacts from synthetic biology applications on the three objectives of the Convention should be considered on a case-by-case basis, considering that there could be multiple scenarios which could lead to different results and impacts. Likewise, the importance of distinguishing between activities in controlled, contained facilities and the environmental release of organisms derived from synthetic biology was pointed out as important in discussing potential positive and negative impacts of synthetic biology.
4. It is noted that similar discussions were held during the previous AHTEG meeting in 2017 (see section 3.1 in the report for more information).

IV. SYNTHETIC BIOLOGY ORGANISMS THAT MAY FALL OUTSIDE THE DEFINITION OF LIVING MODIFIED ORGANISMS AS PER THE CARTAGENA PROTOCOL

1. Paragraph (d) of the terms of reference of the AHTEG request the AHTEG to consider whether any living organism developed thus far through new developments in synthetic biology fall outside the definition of living modified organism as per the Cartagena Protocol.
2. Article 3 of the Protocol contains the following definitions:

(a) “Living modified organism” means any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology;

(b) “Living organism” means any biological entity capable of transferring or replicating genetic material, including sterile organisms, viruses and viroids;

(c) “Modern biotechnology” means the application of:

1. In vitro nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or
2. Fusion of cells beyond the taxonomic family,

that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection.

1. Submissions and contributions to the online forum largely suggested that organisms produced thus far through synthetic biology fall under the definition of a living modified organism (LMO) as per the Cartagena Protocol, with the following exceptions:
   * 1. Organisms whose genomes had been edited without the use of nucleic acids using only protein reagents introduced into the cell;
     2. Virus-like macromolecular assemblies which do not have all functions required for a complete viral life cycle and are not capable of transferring or replicating their genetic material;
     3. Chemically modified organisms that are modified with non-canonical amino acids;
     4. Living protocells;
     5. Living organisms generated by multiplexed DNA free ZFN/TALEN/MN applications.
2. The AHTEG may wish to consider the list of exceptions provided above and to complement or modify the information as necessary.
3. It is noted that similar discussions were held during previous AHTEG meetings in 2015 and 2017 (see section 3.3 in both reports for more information).

V. THE STATE OF KNOWLEDGE ON THE POTENTIAL ENVIRONMENTAL IMPACTS OF APPLICATIONS OF SYNTHETIC BIOLOGY, INCLUDING THOSE APPLICATIONS THAT INVOLVE ORGANISMS CONTAINING ENGINEERED GENE DRIVES

1. The AHTEG, through paragraph (c) of its terms of reference, is to undertake a review of the current state of knowledge by analysing information, including but not limited to peer-reviewed published literature, on the potential positive and negative environmental impacts, taking into account human health, cultural and socioeconomic impacts, especially with regard to the value of biodiversity to indigenous peoples and local communities, of current and near-future applications of synthetic biology, including those applications that involve organisms containing engineered gene drives, taking into account the traits and species potentially subject to release and the dynamics of their dissemination, as well as the need to avoid duplication with the work on risk assessment under the Cartagena Protocol on Biosafety.
2. Submissions and contributions to the online forum pointed out that many synthetic biology applications are still in the initial phase of research and development, and, thus, there may currently be gaps in information on the potential positive and negative environmental impacts of synthetic biology applications. It was also noted that information from other fields (e.g. invasive species, pest management, LMOs) could be relevant in identifying and/or assessing any potential effects.
3. Through the online forum, it was recognized by some that the potential positive and negative impacts from synthetic biology applications has been in some way discussed during previous AHTEG meetings, in particular during the 2015 meeting. Based on this, the background document CBD/SYNBIO/AHTEG/2019/INF/4 presents information from section 3.5 of the 2015 AHTEG report, which has been complemented with information from the literature, the submissions and the online forum, on the potential impacts of current and near-future applications of synthetic biology.
4. The AHTEG may wish to take into account the information in the background document (CBD/SYNBIO/AHTEG/2019/INF/4) to assist in its task of reviewing the current state of knowledge with a view to identifying knowledge gaps in relation to potential positive or negative impacts of current and near future synthetic biology applications.

VI. OPTIONS FOR REGULAR HORIZON SCANNING, MONITORING AND ASSESSING OF DEVELOPMENTS

1. In decision 14/19, the Conference of the Parties agreed that broad and regular horizon scanning, monitoring and assessing of the most recent technological developments is needed for reviewing new information regarding the potential positive and potential negative impacts of synthetic biology vis-à-vis the three objectives of the Convention and those of the Cartagena and Nagoya Protocols (para. 3). The AHTEG, in paragraph (f) of its terms of reference, was mandated to recommend options for carrying out the regular horizon scanning, monitoring and assessing of developments referred to in decision 14/19, paragraph 3.
2. This section presents a summary of the information presented through the submissions and the online forum in this respect. The AHTEG may wish to review the following summary and adapt it as necessary to recommend options for carrying out the regular horizon scanning.
3. The following steps for carrying out the horizon scanning were suggested: information gathering, synthesis and analysis of information and outputs of the horizon scanning.
4. It was suggested that the collection of relevant information for the horizon scanning process could be done through a review of scientific publications, technology surveillance reports, congresses, workshops and activities, networking with key actors, contact with scientists working in this field, and frequent review of the registration of intellectual property rights, such as patent databases.
5. The following tools were identified to facilitate the information gathering process:

(a) Online surveys;

(b) Dedicated space on the clearing house for information sharing on a rolling basis;

(c) Notifications from the CBD Secretariat requesting information;

(d) Online forums convened by the CBD Secretariat;

(e) Participation in related activities (i.e. workshops, symposiums, international meetings, etc.);

(f) Videoconferences;

(g) RSS or Feedly alerts from specialized journals or preprints.

1. The importance of information prioritization for the process was noted, and it was indicated that information could be prioritized based on risk relevance in the near term (<5 years), medium term (5-10 years), and longer term (>10 years).
2. Screening the information to focus on what is relevant for the objectives of the Convention was highlighted as important for this part of the process. The following steps were proposed for the synthesis of information:

(a) Submission of information to an expert mechanism (e.g. an AHTEG or a standing working group on synthetic biology, as further discussed in paras. 36 and 37 below), as well as to an ongoing online forum (if any);

(b) Submission of outputs from the expert mechanism to the Subsidiary Body on Scientific, Technical and Technological Advice;

(c) A recommendation from the Subsidiary Body on Scientific, Technical and Technological Advice to the Conference of the Parties.

1. It was noted that the importance of the horizon scanning process depends on what happens with the output of the process, and it was indicated that there should be a clear procedure to ensure that the information that is collected by a horizon scanning process is reported to the Parties (for decision-making) in a timely manner.
2. The importance of deciding on the timeframe for the process was also noted.

## A*.* Considerations and actors in the process

1. The need for the horizon scanning process to have the right focus and scope was pointed out. There were different opinions on what the focus should be (i.e. limited to listing new technological developments or enabling the identification of emerging trends and clusters of technological developments that require particular governance) as well as on the scope (i.e. tangible applications or developments, or the former plus initial research).
2. It was mentioned that the horizon scanning should engage a wide range of stakeholders in countries around the world and anticipate how different stakeholders might be impacted by, and could feed into the design of, emerging synthetic biology developments.
3. Concerning who could be responsible for carrying out the information gathering, the Secretariat of the Convention on Biological Diversity was identified as an entity that could carry out the process. In this respect, the following challenges for the Secretariat to undertake this task were identified:
4. Identification of information (e.g. from publications, research institutes globally, workshops), due to the high volume of material that could be generated through this process;
5. Synthesis of information, which may require additional staff and expert engagement.
6. In relation to the expert engagement, it was noted that involvement of experts in a permanent process may imply that a permanent expert group or programme under the Convention would be needed, which would need constant and secure funding.
7. In general, the open-ended online forum and expert groups were perceived as useful tools for the assessment; however, the fact that their format is limited (i.e. English only) and that both need to be reauthorized from one meeting of the Conference of the Parties to the next were identified as limitations. Along these lines, the establishment of a standing synthetic biology working group under the Convention was also tabled as an option.

## B*.* Cost-effectiveness

1. In relation to cost-effectiveness of the horizon scanning process, using some of the existing CBD tools (i.e. online forums, Biosafety Clearing-House) and processes (Subsidiary Body on Scientific, Technical and Technological Advice, Conference of the Parties) was identified as a potential useful alternative towards this end. However, it was indicated that not all relevant groups respond to requests for information, which could then imply information gaps.
2. The importance of building on the work done by others (i.e. similar horizon scanning or technology assessment processes) was also noted.

VII. RELATIONSHIP BETWEEN SYNTHETIC BIOLOGY AND THE CRITERIA SET OUT IN DECISION IX/29, PARAGRAPH 12

1. Paragraph (a) of the AHTEG’s terms of reference request it to provide advice on the relationship between synthetic biology and the criteria set out in decision [IX/29](https://www.cbd.int/doc/decisions/cop-09/cop-09-dec-29-en.pdf), paragraph 12, in order to contribute to the completion of the assessment requested in decision XII/29, paragraph 2, building on the preliminary analysis prepared by the Executive Secretary in document [CBD/SBSTTA/22/INF/17](https://www.cbd.int/doc/c/0bc5/ef82/a4da41e530a897de6abc3ca7/sbstta-22-inf-17-en.pdf).
2. Paragraph 12 of decision IX/29 provides that the criteria listed therein should be used for identifying new and emerging issues related to the conservation and sustainable use of biodiversity. Each of the criteria from paragraph 12 of decision IX/29 is presented below along with a summary of considerations raised in the submissions and the online forum.
3. The AHTEG may wish to consider the information arising from the submissions and online forum summarized below alongside the preliminary analysis prepared by the Secretariat.

A*.* Relevance of the issue to the implementation of the objectives of the Convention and its existing programmes of work

1. In decision 14/19, the Conference of the Parties recognized that synthetic biology is rapidly developing a cross-cutting issue, with potential benefits and potential adverse effects vis-à-vis the three objectives of the Convention.
2. In the submissions and the online forum, it was mentioned that organisms, components and products of synthetic biology can have neutral, positive or negative effects on biodiversity, and that their relevance and/or impact must be assessed on a case-by-case basis; generally concluding that synthetic biology is relevant for the implementation of the objectives of the Convention and its existing programmes of work. It was also indicated that synthetic biology falls within the definition of “biotechnology” under the Convention and “modern biotechnology” under the Cartagena Protocol, and is therefore broadly relevant.
3. Two approaches were proposed/discussed to assess the relevance of synthetic biology for the objectives of the Convention: (a) considering only specific applications that are realistically foreseeable; and (b) considering early stages of research and development in addition to specific applications.
4. The importance of the free, prior and informed consent for indigenous peoples and local communities in relation to synthetic biology applications was also highlighted.

B. New evidence of unexpected and significant impacts on biodiversity

1. One of the issues raised in this respect was the lack of evidence that risks associated with synthetic biology organisms and products would be significantly different from those associated with organisms that occur naturally, are the product of conventional breeding techniques, or have been generated by modern biotechnology or industrial chemical products.
2. The fact that, to date, there is no evidence of unexpected or significant impacts on biodiversity resulting from synthetic biology was noted, and it was acknowledged that the current lack of evidence of negative impacts does not mean that there are none.
3. In relation to synthetic biology organisms, it was noted that the fact that, thus far, they are considered LMOs does not mean that their potential impacts are equal to those of organisms produced through classical genetic engineering.

C*.* Urgency of addressing the issue/imminence of the risk caused by the issue to the effective implementation of the Convention as well as the magnitude of actual and potential impact on biodiversity

1. It was pointed out that actual or potential impacts on biodiversity are difficult to predict, and, therefore, the imminence of risk should not be minimized. It was noted that existing regulatory mechanisms that apply to biotechnology/modern biotechnology could serve to assess risks presented by activities related to synthetic biology, and that urgency would be higher for those organisms obtained through synthetic biology that do not fall under the definition of an LMO and that could have a negative environmental effect.
2. In the case of engineered gene drives, it was noted that, currently, no effective technology to control gene drives is available and that the magnitude of actual or potential impacts on the biodiversity should be considered. In addition, and also on engineered gene drives, it was pointed out that the presumed efficiency of gene-drive modified organisms may lead to calls for their release in crisis situations before there is adequate knowledge of their ecological effects, and before mitigation plans for unintended harmful consequences are in place, pointing to the urgency to enhance capacities to assess and monitor the possible effects of synthetic biology.

D. Actual geographic coverage and potential spread, including rate of spread, of the identified issue relating to the conservation and sustainable use of biodiversity

1. It was noted that, to assess such phenomenons as “actual geographic coverage and potential spread”, having a tangible or defined product/organism as the subject of the assessment could be useful. Similarly, it was acknowledged that actual geographic coverage and potential spread, including rate of spread, are likely to be dependent on different factors, such as the genetic structure of the populations (e.g. the presence and frequency of resistance alleles), effective size and geographic spread of populations affected, reproduction times.
2. It was mentioned that the geographic spread of synthetic biology organisms could be similar to that of current LMOs, and it was noted that, in the case of organisms containing engineered gene drives, geographic restriction may potentially be more difficult in comparison with other LMOs. The different types of gene drives that could be used was also considered important when assessing potential spread.

E. Evidence of the absence or limited availability of tools to limit or mitigate the negative impacts of the identified issue on the conservation and sustainable use of biodiversity

1. It was mentioned that, since current and near-future organisms to be released into the environment obtained through synthetic biology could be similar to LMOs, there could be tools available to limit or mitigate negative impacts. Nonetheless, it was pointed out that, even if many of the current tools might be useful, they might not be sufficient for certain cases. An example referred to the fact that, in the future, rapidly replicating and rapidly spreading organisms with engineered gene drives can be released, indicating that tools to mitigate these effects could be limited.

F. Magnitude of actual and potential impact of the identified issue on human well-being

1. It was noted that the magnitude of the potential effects of synthetic biology (positive or negative) cannot be predicted in a generalized manner and must be assessed on a case-by-case basis.

G. Magnitude of actual and potential impact of the identified issue on productive sectors and economic well-being as related to the conservation and sustainable use of biodiversity

1. Similarly to the criterion above, it was noted that the magnitude of these potential effects cannot be predicted in a generalized manner and must be assessed on a case-by-case basis.
2. It was mentioned that synthetic biology is the basis of the “bio-economy”, a broad concept with visions of addressing global challenges, including food security, health, industrial restructuring and energy security, and it was noted that possible impacts could be both positive and negative. It was also mentioned that discussions under criterion (g) might need more attention and engagement from indigenous peoples and local communities in developing countries who might depend on natural products, agriculture and conservation for their well-being.

\_\_\_\_\_\_\_\_\_\_

1. Submissions are available through the Biosafety-Clearing House at <https://bch.cbd.int/synbio/submissions/> [↑](#footnote-ref-1)
2. The discussions under the Open-ended Online Forum on Synthetic Biology are available at <https://bch.cbd.int/synbio/open-ended/discussion/> [↑](#footnote-ref-2)
3. Report of the Ad Hoc Technical Expert Group on Synthetic Biology (UNEP/CBD/SYNBIO/AHTEG/2015/1/3), para. 32. [↑](#footnote-ref-3)
4. Shao, Y. et al. (2018). [doi.org/10.1038/s41586-018-0382-x](file://C:\Users\lefebvre\AppData\Local\Microsoft\Windows\AppData\Local\Microsoft\Windows\INetCache\Containers\com.apple.mail\garforth\AppData\Local\Microsoft\Windows\AppData\Local\Microsoft\Windows\AppData\Local\Microsoft\Windows\AppData\Local\Microsoft\Windows\INetCache\Content.Outlook\AppData\Roaming\Microsoft\Word\synbio%20working%20document%20v2-am307346181248004053\doi.org\10.1038\s41586-018-0382-x) ; Luo, J. et *al*. (2018) doi.org/10.1038/s41586-018-0374-x [↑](#footnote-ref-4)
5. Butterfield, G. L. et al. (2017). <https://doi.org/10.1038/nature25157> [↑](#footnote-ref-5)
6. Grunwald, H. A. et al.(2019). <https://doi.org/10.1038/s41586-019-0875-2> [↑](#footnote-ref-6)
7. Kyrou, K. et al.(2018) <https://doi.org/10.1038/nbt.4245> [↑](#footnote-ref-7)
8. Buchman et al. (2018). <https://doi.org/10.1073/pnas.1713139115> [↑](#footnote-ref-8)
9. Nobel et al.(2019). <https://doi.org/10.1073/pnas.1716358116> [↑](#footnote-ref-9)
10. Ogaugwu et al. (2019) <https://doi.org/10.1016/j.tibtech.2018.07.012> [↑](#footnote-ref-10)
11. South et al. (2019). [doi.org/10.1126/science.aat9077](file://C:\Users\lefebvre\AppData\Local\Microsoft\Windows\AppData\Local\Microsoft\Windows\INetCache\Containers\com.apple.mail\garforth\AppData\Local\Microsoft\Windows\AppData\Local\Microsoft\Windows\AppData\Local\Microsoft\Windows\AppData\Local\Microsoft\Windows\INetCache\Content.Outlook\AppData\Roaming\Microsoft\Word\synbio%20working%20document%20v2-am307346181248004053\doi.org\10.1126\science.aat9077); Shen, BR, et *al*. (2019). doi.org/10.1016/j.molp.2018.11.013 [↑](#footnote-ref-11)
12. Boeke et al. (2016) doi.org/10.1126/science.aaf6850 [↑](#footnote-ref-12)
13. Noyce et al. (2018). <https://doi.org/10.1371/journal.pone.0188453> [↑](#footnote-ref-13)
14. <http://buildacell.io/> ; Liu et al.(2018) <https://doi.org/10.1038/nchembio.2554> [↑](#footnote-ref-14)
15. Benítez-Mateos et al. (2018) doi.org/10.1021/acssynbio.7b0038; Karig, DK. (2017) doi.org/10.1016/j.copbio.2017.01.010 14; Takahashi et al. (2018). doi.org/10.1038/s41467-018-05864-4 [↑](#footnote-ref-15)
16. Liu et al. (2019) <https://doi.org/10.1016/j.jcs.2018.11.001> [↑](#footnote-ref-16)
17. Julve Parreño et al. (2018). <https://doi.org/10.1111/pbi.12823> [↑](#footnote-ref-17)
18. Reed and Osbourne (2018) <https://doi.org/10.1007/s00299-018-2296-3> [↑](#footnote-ref-18)
19. <https://www.wired.com/story/farmers-can-now-buy-designer-microbes-to-replace-fertilizer/> [↑](#footnote-ref-19)
20. Hoshika, et al. (2019). <https://doi.org/10.1126/science.aat0971> [↑](#footnote-ref-20)
21. Reeves et al. (2018). [doi.org/10.1126/science.aat7664](file://C:\Users\lefebvre\AppData\Local\Microsoft\Windows\AppData\Local\Microsoft\Windows\INetCache\Containers\com.apple.mail\garforth\AppData\Local\Microsoft\Windows\AppData\Local\Microsoft\Windows\AppData\Local\Microsoft\Windows\AppData\Local\Microsoft\Windows\INetCache\Content.Outlook\AppData\Roaming\Microsoft\Word\synbio%20working%20document%20v2-am307346181248004053\doi.org\10.1126\science.aat7664) [↑](#footnote-ref-21)
22. Charli and Church (2017) <https://doi.org/10.1038/nrg.2017.59>; Pasin et *al.* (2019) doi.org/10.1111/pbi.13084 [↑](#footnote-ref-22)
23. Zsögön et al. (2018). <https://doi.org/10.1038/nbt.4272>; Li, T., et *al*. (2018). https://doi.org/10.1038/nbt.4273 [↑](#footnote-ref-23)
24. Nakamura et al. (2019). https://doi.org/10.1038/s41467-018-08158-x [↑](#footnote-ref-24)
25. Diwo and Budisa (2019) doi:10.3390/genes10010017; Wannier et *al.* (2018) <https://doi.org/10.1073/pnas.1715530115>; Nickling et al.(2018) <https://dx.doi.org/10.3791%2F57551>; Zhang et *al.* (2017) https://doi.org/10.1073/pnas.1616443114 [↑](#footnote-ref-25)
26. Santos-Merino et al. (2019) https://doi.org/10.3389/fbioe.2019.00033 [↑](#footnote-ref-26)
27. Rogers and Oldroyd (2014) doi.org/10.1093/jxb/eru098; Goold, et al. (2018). doi.org/10.3390/genes9070341 [↑](#footnote-ref-27)
28. Protocells and the potential toxicity of the genetic products and non-natural components on off-target organisms and the potential allergenicity for humans, van Nies et al. (2018) doi.org/10.1038/s41467-018-03926-1; Lee et al. (2018) doi.org/10.1038/s41589-018-0056-x; Zhang et al. (2017). https://doi.org/10.1038/nature24659 [↑](#footnote-ref-28)
29. Hoshika et al. (2019). https://doi.org/10.1126/science.aat0971 [↑](#footnote-ref-29)
30. Butterfield et al. (2017). https://doi.org/10.1038/nature25157 [↑](#footnote-ref-30)
31. de Lorenzo et al. (2018) http://embor.embopress.org/lookup/doi/10.15252/embr.201745658 [↑](#footnote-ref-31)
32. Luo et al. (2019) doi.org/10.1038/s41586-019-0978-9; Carbonell et al. (2018) doi.org/10.1038/s42003-018-0076-9 [↑](#footnote-ref-32)
33. Hayes et al. (2018) doi.org/10.1080/23299460.2017.1415585; Noble et al. (2018) doi.org/10.7554/eLife.33423; Leitschuh et al. (2018) doi.org/10.1080/23299460.2017.1365232 [↑](#footnote-ref-33)