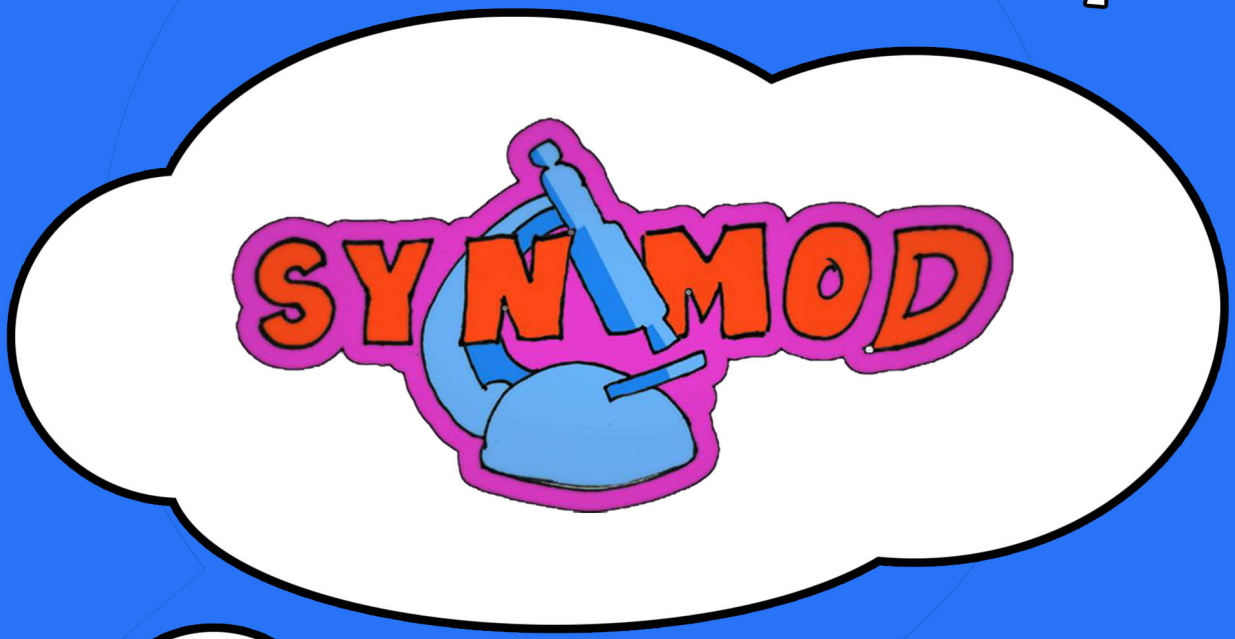
Ethical aspects of



Expert interviews and scientists' feedback

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Procedure and sample

Here we provide a number of ethical issues of the SYNMOD project as seen by an external group of 21 experts (summary: black; original quotations: blue) and responses by the SYNMOD consortium (green). The statements (black) on ethics by the experts as they are presented here are the results of a qualitative content analysis of all interviews. They represent the whole variety of answers to the question: "What ethical aspects of the SYNMOD project do you identify?"

The sample of experts was composed as described in table 1

Table 1. Expertise of the interviewees in relation to synthetic biology

Field of expertise	Number of experts (n=21)
Creative (Bioartist)	1
Funding	4
NGO	1
Ethicist	1
Scientist	7
Entrepreneur	2
Technology assessment	5

Answers and comments

Safety

Within the context of new methods in risk assessment several statements were made:

- There could be incalculable side effects, new resistances or toxic products. Therefore rigorous clinical trials are essential.

  SYNMOD: Clinical trials are always necessary when introducing new drugs. The risks above can be assessed quite well in vitro and in vivo.[1]

- Occupational safety can be at stake in connection with pathogenic[2] *S. carnosus*[3] strains.

  SYNMOD: This would be normal microbiological work with pathogens. For skilled researchers there is no increased risk. However, *S. carnosus* is food-grade and non-pathogenic.

- Horizontal gene transfer[4] of pathogenic traits

  SYNMOD: We will not mix pathogens and there is no DNA involved of the evolved lantibiotics[5], except during screening. After screening potentially pathogenic material is autoclaved[6].

- There is no intended release into the environment

  SYNMOD: Correct

- There are no working models for the risk assessment of new compounds or organisms in the case of synthetic biology. This also concerns SYNMOD products.

  SYNMOD: We will make a list of potential risks (e.g. toxicity of new compounds, allergenic properties, etc.) and take action to test these. Risks in biosafety,

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[1] *in vitro* means in a test tube or another laboratory vessel, *in vivo* means in a living organism.
[2] Pathogenic bacteria cause or are capable of causing diseases.
[3] *Staphylococcus carnosus* is a bacterium that was discovered in 1982. (see also http://ijsb.sgmjournals.org/content/32/2/153.full.pdf). It is part of bacterial cultures in dry sausage fermentation processes. SYNMOD intends to use *S. carnosus* as producer strain for the lantibiotics.
[4] Horizontal gene transfer (also termed lateral gene transfer) refers to the transfer of DNA between different organisms. In contrast, vertical gene transfer denotes the inheritance of genes via reproduction. Horizontal gene transfer is very common among bacteria.
[5] Lantibiotics are peptide-based antibiotics. They consist of chains, and also ring-like modules composed of amino acids. For further information see also the SYNMOD game and video: http://www.biofaction.com/project/synmod-mobile-game/
[6] To autoclave: to put material into a high-pressure-vessel and, after evacuating it, to apply hot and high-pressure steam on it. This serves the purpose of sterilizing (killing all microorganisms) the waste produced in the laboratory.

occupational safety and horizontal gene transfer are not different from general microbiological engineering work.

While the representative of the NGO identified three types of biosecurity issues (no risk assessment possible, worker's safety, horizontal gene transfer of pathogenic traits) one of the scientists said:

Expert 21: "I really cannot see issues, connected to safety, because the bacteria that are involved, are non-pathogenic, the laboratories involved have all types of facilities to handle the manipulation of microbes, and I don't see any scenario by which one of these successful bacteria may escape may produce an evil, let's say, toxin or something, and then it may contaminate a river or something, I mean, all these scenarios, you know, may happen. But this is like if you think that they are going to have an invasion of Martians, you know what I mean. (LAUGHTER) I mean the possibilities are serious but are so remote, that you know. We have to live without them."

SYNMOD: Agree. There is no risk of deliberate release because everything will be autoclaved according to Safe Microbiological Work regulations. Only toxicity of new compounds is something to assess thoroughly.

However, there is the aspect of fear in the public sphere. SYNMOD takes these concerns seriously. All of the research actions are transparent and we also provide summaries for non-scientists in order to engage the public. SYNMOD also fosters dialogue with members of the public via focus group discussions and a dialogue with experts.

Security

Questions of biosecurity were not mentioned. Only one respondent addressed that issue and said that there are no biosecurity concerns for the SYNMOD project.
In the interviews biosecurity was sometimes addressed when talking about synthetic biology in general.

Ethics

Assessing risks and benefits

In the context of ethics the predominant topics were risks and benefits of the project. The key elements of the answers were:

- The context of antibiotic resistances and the correct use of antibiotics
- The risk *not* to make the project
- Medical ethics/ ethics of the use and development of drugs in general
- Risk/benefit assessment in general

Several respondents mentioned that the overuse of antibiotics is a severe societal problem that cannot only be tackled by a technical solution. Experts say, that although the search for new antibiotics is important, the problem also needs a societal solution. One expert states that the analysis of the whole health system could help to understand the threat, but this would go beyond the frame of the SYNMOD project. However, a purely technical solution would just deal with the symptom but not with the cause.

Expert 14: "You know, for us the way to help fight antibiotic resistance is to stop early prescribing certain classes of antibiotics particularly in animal agriculture, and so, kind of that. That is an important question for us. Yes. I guess what, I am sure you, guys, got this question a lot, what methods do you have to ensure that when you come up with, you know, these new types of these lantibiotics, that bacteria don`t grow the resistance to them and end up, you know, kind of a continuous loop of needing to come up with new antibiotics because there is an antibiotic resistance, and you need to come up with new antibiotics."

SYNMOD: Relative to the use of regular antibiotics, lantibiotics show a decreased risk of resistance development because they use lipid II as target and this is an essential compound for cell wall biosynthesis. This receptor molecule can neither change its moiety where the lantibiotic binds (pyrophosphate), nor downregulate its production.[7] Only transient resistance is observed. Also, existing immunity proteins are very specific and have not evolved for new-to-nature compounds (and will be hard to evolve, although not impossible).
As producer organisms we also use bacteria that are regarded as safe and the final idea would be to get a peptide antimicrobial [see also footnote 5] to use in therapeutics, therefore keeping the producer organisms in a confined laboratory/production plant environment.

Indeed, misuse and overuse of antibiotics is a severe societal problem that cannot only be tackled by a technical solution. However, when we consider the consequences if we had not searched and worked on new antibiotics after Fleming's discovered penicillin – it would have been disastrous: where would we be today without tetracycline, rifampicin, erythromycin[8] etc. Soon after the discovery of penicillin it was clear that it is not the panpharmacon[9], as it has been believed at the beginning. This example tells us that we need the continuation of developing new products, no matter whether they are at the end of the day successful or not.

There is no way to produce a novel compound and say with 100% certainty that it is not going to raise resistance when the use is extended. This should not, by any means, discourage the research on novel active compounds (lantibiotics or any other novel compounds with different chemical structure). The necessity of drugs that target

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[7] The lantibiotics make holes in the cell walls of bacteria, which make them leak and die. To be able to do this, lantibiotics first have to bind to the cell walls of the bacteria. They bind at specific sites, namely pyrophosphate groups of lipid II. Lipid II is a precursor for cell wall growth and situated in the outer membrane of bacterial cell walls. Lipids consist of a part attracted to water (hydrophilic) and a part that does not like the contact with water (hydrophobic). The pyrophosphate groups are the hydrophilic part of lipid II and are therefore situated on the outer surface of the cell wall.
This binding mechanism is fool proof, because the bacterium cannot replace lipid II by anything else, and the pyrophosphate groups will always be on the outer surface of the cell wall.
For a scientific article on lipid II as binding site for antibiotics in general, see http://www.nature.com/nrd/journal/v5/n4/abs/nrd2004.html

[8] Tetracycline, rifampicin and erythromycin are antibiotics.
[9] A panpharmacon is a medicine for all diseases.

resistant groups of bacteria of clinical relevance is urgent and the development of a compound for the clinical use takes years. Therefore, scientists should keep working on the research of novel compounds that are needed. Physicians can also work on more efficient uses of antibiotic therapy regimes and do educational work on society showing the correct use of antibiotics (and any other drug). There is no point in choosing one way or the other (novel compounds or better administration of existing ones) when both strategies are necessary and beneficial.

Some experts said that SYNMOD falls under general medical ethics. The production of new antibiotics is comparable to that of insulin. The respondents argue that the ethical aspects are the same as for other projects that deal with the development of new drugs.

Benefits, access and justice

Topics regarding the access to products of SYNMOD discussed by the experts are:

- Patents versus open source
- Access of third world countries to the new products

The following quotations illustrate the discussions around the issue of intellectual property and availability:

Expert 3: "Yes but if that is the way that you envision developing new drugs, and if they are very very costly your ethical issue is to who they will be accessible."

Expert 14: "There is, of course, the more general issue of how, of the way pharmaceutical innovation is translated in marketing products and the availability of that kind of products in terms of price all over the world. And, yes, that I see as a bit more difficult to estimate. At this moment, I think that availability of antibiotics also in terms of price is not a real problem in this world. The availability might be a problem in some parts of the world, but that has to do more, I think, with the general situation of medical care and the infrastructure, than with the price of these antibiotics. And it might be, of course, that this new approaches in developing antibiotics might lead to products, which are much more expensive than we are used to now."

Expert 21: "So the only ethical or questionable issue that I see, but this is one that affects the entire realm of synthetic biology, is intellectual property, OK. So that means that if at some point people involved in these projects discover a super wonderful drug, that, I don't know, kills malaria, or kills diarrhea, or kills whatever, and normally all this infections for the most part afflict underdeveloped countries, then who is going to have access to this you know and to me this is the one ethical issue that is on top of our heads."

SYNMOD: Normally, patents are not really the researchers priority as long as public institutions support the research and development. However, for marketing and particularly to cover the extremely high costs for production, safety control and research, which come downstream of university research, intellectual properties are important. No company would take the risk to make enormous financial investments without protection of some rights.

However, good dissemination of a useful and potent product for all countries at reasonable prices, perhaps supported by governments (like they do for vaccines sometimes) would be desirable.

Public engagement

In terms of public engagement, some experts identify SYNMOD as an ideal project, because the closeness to medical applications touches the interest and understanding of the public.

Other statements

Further statements on ethics were:

- An analysis of ethical aspects of SYNMOD is trivial.
- The ethical aspects are not serious/dramatic.
- There are no specific ethical issues.
- The respondent had not enough information for judging ethical issues.
- The making of promises is an important ethical issue.

SYNMOD: The hypotheses launched by SYNMOD are based on a solid scientific background, but they are still hypotheses that need to be confirmed in the lab. This is applicable to any kind of empirical research. During the elaboration of a project draft some promises (or expectations) appear, but this is intrinsic to the application process itself.
In addition, the 3-year funding period is too short to carry out a project that encompasses more than establishing the basic research tools for the search for new drugs.