CRISPR/Cas9 based gene drives for fighting malaria: aspects of prospective technology assessment

Univ.Prof. Dr. Wolfgang Liebert
Institute of Safety and Risk Sciences (ISR)
University of Natural Resources and Life Sciences (BOKU) Vienna

“Fighting Malaria with CRISPR/Cas9: Ethical Implications”
Medical University of Vienna, 7 Sept. 2016

Prospective Technology Assessment

- Analysis of scientific-technological development **at an early stage** anticipating what might be relevant for science-based mid-term assessment and for (participatory) discourse inside and outside science
- Assessment of **intentions**/visions, **potentials**, **risks** and unintended **consequences**, realistic potentials versus unrealistic visions and **promises**, **uncertainties** (and ignorance)

  [partly impossible without analysing the scientific-technological core]
- Analysis/assessment of **opportunities for shaping** science and technology and technical or **socio-technical alternatives**

  [partly impossible without analysing the scientific-technological core]
- Reflection on **normative issues**, values and interests involved.

- 1. Intentions
- 2. Potentials of research and development risks related to (homing-based) gene drives
- 3. Risks, consequences, and uncertainties
- 4. Alternatives
- 5. Shaping opportunities
- 6. Normative questions, values and interests involved
- 7. Why early stage assessment and discourse?

Intentions

In general, research aiming to realizing CRISPR-Cas9-based gene drives to conquer malaria seems to be justified.
Our compassion with the malaria victims worldwide (mainly several African regions) cannot allow to stand idly by.

However: Malaria is not only a naturally occurring phenomenon! Social, political and economic factors are also of great importance when fighting malaria:

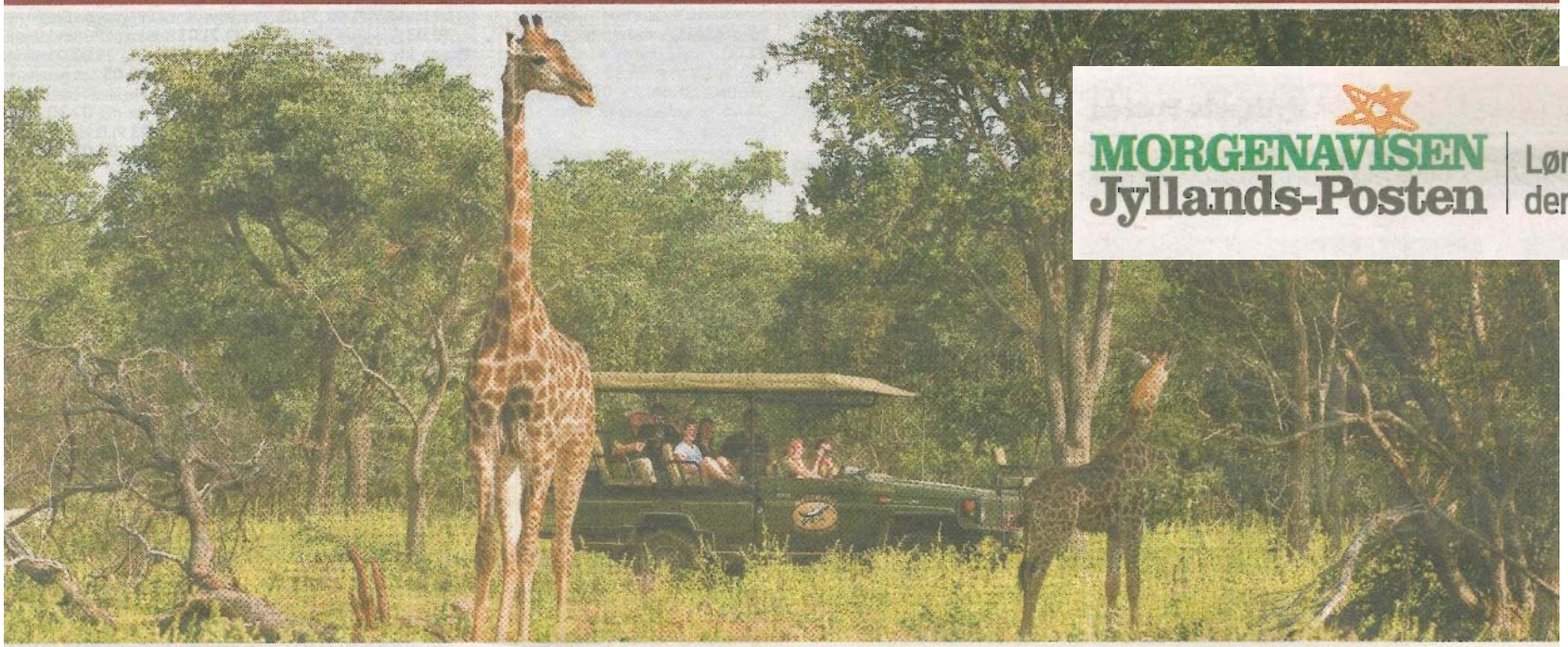
- social organisation and behaviour
- access to modern healthcare
- functioning health care system in regions concerned
- access to preventive and curative measures
- availability and affordability of suitable means.

What we currently observe is an unjust societal and global divide with respect to the malaria burden. (Example: advertisement in a the leading Danish newspaper…)

Awful social stratification of the malaria burden has almost nothing to do with new high technological approaches to fight against malaria

MALARIA-FRI LUKSUS-SAFARI I SYDAFRIKA

MORGENAVISEN Jyllands-Posten | Lørdag den 23. juli 2016



Matswani Safari lodge ***, afrejse hver tirsdag f.eks 2/8, 30/8, 6/9, 20/9, 4/10 og 22/11 2016, fra Aalborg, Kastrup og Billund, 10 dage/8 nætter**

Potentials of research and development risks related to gene drives

Mutagenic Chain Reaction (MCR)/Gene Drives (GD) in 4 organisms in the lab:

- fruit fly *Drosophila melanogaster* (Gantz/Bier 2015)
- yeast (DiCarlo et al. 2015)
- malaria mosquito *Anopheles stephensi* (Gantz et al. 2015)
- malaria mosquito *Anopheles gambiae (*Hammond et al. 2016)

→ Toning down of chain reaction after a few generations

Doubts that gene drives in mosquito wild populations will be feasible:

- Competition between Non Homologous End Joining (NHEJ) after a cleavage of targeted DNA Homology Directed Repair (HDR) essential for the GD
- development of resistance against a drive are expected by mating with wild exemplars
- Intrinsic limits to stabilize gene drives in the wild

→ **Development risks** are numerous; **BUT imagine it could work…..**

Risks, consequences, and uncertainties I

Suppression drives aim at dramatically reducing or eradicating malaria transmitting species regionally or globally.

Modification/manipulation drives strive to genetically modify or manipulate mosquitoes in a way that malaria infection of humans is reduced or enabled.

Risks, consequences, and uncertainties II

Questions arising related to suppression drives:

- Efficient Mutagenic Chain Reactions will eventually go across all national borders → who decides and regulates?
- What, if modified mosquito genes mutate and evolve further on, unwanted variants emerge and reproduce themselves uncontrolled?
- Is it possible that after the genetically engineered fight against *Anopheles gambiae* *Plasmodium* (and other malaria parasites) finds a way to change its currently dominating host mosquito?
  → more and more gene drives unleashed on nature?
- Could the eradication programme jump over to other species?
- What, if unintended consequences for ecosystems are generated? (there are examples, but great ignorance about that)

Risks, consequences, and uncertainties III

Questions arising related to modification/manipulation drives:

- Again: What, if modified mosquito genes mutate and evolve further on, unwanted variants emerge and reproduce themselves uncontrolled? (Role of off-target effects?)
- It is well known that parasites (like Plasmodium) evolve (quickly) in relation to their host organisms.
  Provokes that the engineering of another gene drive attempt –
  and after the next one an over next?

Lot of uncertainties and ignorance

Risks, consequences, and uncertainties IV

Many fundamental problems and questions emerge (1):

- Any single release of a GD modified organism with “wrong” or detrimental characteristics could have irreversible consequences.
  There is not something like a tolerable limited release.
- A dual-use potential of GDs seems to be obvious.
- Mutagenic chain reactions increase massively the enormous depth of intervention by humankind into natural processes.
  Irreversible unintended changes could be the result.
- Engineering gene drives to fight malaria could turn out as a harbinger of much more. What is next? Gene drives against other mosquitoes, insects or rodents transmitting infectious diseases? Probably: against so-called pest animals, various fruit flies or plague locust? So-called invasive species? Neophytes can be attacked, eventually eradicated…

Risks, consequences, and uncertainties V

Many fundamental problems and questions emerge (2):

- What starts with the fight against malaria could end in a nature under complete management of humankind having a tool to steer evolution deliberately. However: huge ignorance of the complex, non-linear interactions in genetic transfer, living cells and organisms, populations, ecosystems, sensitive global life connections
- Intrinsic logic of gene drives fighting malaria: a chain reaction of mutagenic chain reactions, prone to human errors and ignorance??
- Gene drives are engineered selfish genetic elements designed to operate autonomously in nature. Is a new form of technology emerging? "*Late-modern technology*" (Jan Schmidt) with intrinsic limits in respect to predictability and controllability
- How all that can be regulated? The well adapted integrity of life on earth, which is the result of the self-organized "interplay of evolution" over millions of years could possibly be distorted.
  But only national authorities (if existing) can act…

Alternatives

Ideas **for technical alternatives to GDs** are currently discussed and researched:
- infection of malaria mosquitoes with *Wolbachia* bacteria
- release of genetically modified mosquitoes passing on dominant lethal factors to their offspring

Global malaria elimination programme:
- UN "2030 Agenda for Sustainable Development – Transforming our World" --
- WHO "Global Technical Strategy for Malaria 2016-2030":

- **vector control** (LLIN, IRS, screening, education,…)
- **prevention** (pregnant women and children under 5 in many Africa,…)
- better access/use of **diagnostics** and medical **treatmen**t (ACT…)

Minimally functional health care system and durable and affordable access to diagnostics and medicaments is crucial as well as educating and empowering communities so that their can reduce the risk themselves

- Past (successful) elimination campaigns had also very harmful side effects by massive use of DDT
- Role of socio-cultural or techno-economic change by rapid increase of plastic consumption or by scrap tyres providing mosquitoes with ideal breeding grounds
- Socio-economic conditions of origin besides natural-scientific causes for malaria

Shaping opportunities

Engineering "**reversal drives**" have been proposed to undo bad consequences of a drive. However, a fundamental irreversibility of GDs has to be admitted. A "reversal" GD could only be a second drive which again could be ill-targeted.

Self-limiting drives have been proposed ("daisy-chain drives").
However, just theoretical models not reflecting the actual complex dynamics in real life. Furthermore, seems to be more a test-bed approach, where drives at first (hopefully) are locally and timely restricted. Later on the full-fleshed global release is intended.

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Assessment necessary: which procedure for malaria elimination seems to be promising, associated with low risk, and globally, societally and ethically acceptable?

Obvious that the **WHO strategy cannot be replaced by anything else**.
(Maybe additional measures or tools could be helpful, if acceptable.)

Normative questions, values and interests involved I

Criteria for normative orientation in the field of science and technology development:

- Hans Jonas´ **principle of responsibility** related to a "heuristic of fear"
  → **"preservation principle"**
  ("conservative" preservation of our life world)
- Ernst Bloch´s utopian **principle of hope** addressing the "open horizon" of the future
  → **"unfolding principle"**
  ("alliance technology" which serves humankind and is concurrently in harmony with nature)

Often advocated purely **utilitarian** position "risk has to be balanced against benefit"

versus

the **precautionary principle** deduced from the preservation principle

in combination with developing

alliance technology in harmony with nature aiming at a positive and socially just further development of humankind deduced from the unfolding principle

Normative questions, values and interests involved II

The whole fabric of risks, uncertainties and ignorance, possible dramatic consequences of mutagenic chain reactions will (and must) have a massive influence on ethical discourse

The perceived role of humans in nature is highly relevant:

- **humankind as manager of all life on earth** or
- **humankind embedded into nature** and as partner of life on earth
  principle *respect for live (Albert Schweitzer):*
  "I am life that wants to live in the middle of life that wants to live".

Interests are involved related to gene drive research, e.g. Gates Foundation or OXITEC company

Why early stage assessment and discourse? I

“First let us research and develop technology, thereafter we will see, thereafter society can decide”.
The example of gene drive R&D demonstrates (again) that this is not anymore tenable.

When a gene drive technology fighting malaria seems to be mature it is too late. Then it is barely possible anymore to deny its use in a region with serious malaria burden.

Science and (global) society at the crossroad:

There is a need to seriously enable a broad discourse where the direction and the normative orientation of the scientific-technological progress is scrutinized before it takes place.

Why early stage assessment and discourse? II

Kevin Esvelt (MIT researcher – heavily involved in gene drive R&D):

"We need to recognize that the answer to the question whether we should use a gene drive in a particular instance - `no´ has to be an acceptable answer." (Nature Biotechnology 2015)

"Scientists must accept the possibility that society could say no, halting gene drive research entirely." (Harvard Magazine, May-June 2016).

Yes, I agree, that has to be debated, now.

An early and broad discourse inside an outside science is necessary.