Australian Government

Department of Health

Office of the Gene Technology Regulator

MINUTES OF THE
GENE TECHNOLOGY TECHNICAL ADVISORY COMMITTEE
6 June 2016 Meeting

About these Minutes

These minutes are intended to summarise discussion during the Gene Technology Technical Advisory Committee (GTTAC) 6 June 2016 meeting. They reflect key elements of the discussion, outcomes, matters agreed and actions arising, and are not intended to be a verbatim record of the meeting.

Attendance

Members
- Professor John Rasko AO (GTTAC Chair)
- A/Prof Jason Able
- E/Prof Craig Atkins
- Prof Ross Barnard
- Prof Gabrielle Belz
- Dr Graham Bonnett
- Ms Laura Fell
- Prof Ian Godwin
- A/Prof John Hayball
- Dr Rodney Mahon
- Dr Michael Michael
- Dr Gabrielle O'Sullivan
- Prof Marie Ranson
- Prof Kevin Smith
- A/Prof Jason Smythe
- Dr Diane Webster
- Prof Paul Young

Apologies
- Prof Jacqueline Batley
- Dr Kelly Shaw

Guests
- Dr Jane Cook (A/g Gene Technology Regulator)
- Dr Michael Dornbusch (GTTAC Secretary)
- Ms Judy Jones (Chair of the Gene Technology Ethics and Community Consultative Committee)

Presenters
- Dr Louisa Matthew
- Dr Dennis Dowhan
- Dr Peter Thygesen
- Dr Anne-Sophie Dielen

Secretariat
- Mr Greg Barber
- Dr Gillian Colebatch
- Mr Dimitri Kun
- Ms Lill Sclater

The meeting commenced at 09:30am (AEST)

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Agenda Item 4. New Technologies

Dr Louisa Matthew gave a presentation and sought GTTAC's advice on the technical aspects of new technologies, including site-directed nuclease (SDN) techniques[1], to inform the Regulator's technical review of the Gene Technology Regulations 2001 (the Regulations). The Chair thanked Dr Matthew for providing a very clear presentation of a complex topic.

The Chair reminded members that the discussion paper they had been provided cannot be circulated until it is made public, which will be after the outcome of the federal election is known.

The following five questions were put to the committee:

1. Are the risks posed by organisms altered by non-homologous end joining to repair DNA cleavage (i.e. SDN-1) any different to naturally mutated organisms?
2. Does SDN-2 or oligo-directed mutagenesis (ODM) pose any risks that are different to natural mutations, conventional breeding or mutagenesis?
3. Could successive rounds of modification using SDN-2 or ODM give rise to any new risks?
4. Do the potential off-target effects of SDNs or ODM pose different risks to the intended effects of these techniques?
5. What is the evidence base available to support the assessment of the above risks?

Members queried the positions of other governments and regulatory authorities regarding the risks to the health and safety of people and the environment posed by new technologies. Dr Matthew advised that there was a lot of discussion going on internationally but no clear decisions had been made. She informed members that in the United States, Cibus' Rapid Trait Development System™ is not regulated as gene technology, but a review of the US regulatory scheme is underway. Dr Graham Bonnett commented that the current regulatory scheme in the US has a different trigger than in Australia.

The Chair suggested that early discussions around human clinical trials, antisense techniques, oligonucleotides as therapeutics and other techniques when they emerged may provide some precedent for how new techniques are considered. He commented that Australia's gene technology regulatory scheme has worked well to date but does need reviewing to clarify the regulatory status of new technologies. Prof Paul Young referred to a very recent publication on an RNA-targeting CRISPR system, and asked whether such a new tool could be also considered in the review of the Regulations.

Prof Ross Barnard and Dr Matthew agreed that ODM was not a new technique, rather it was in use when the Act came into effect. Dr Matthew added that clarity around its regulatory capture would still be useful. Prof Barnard observed that off-target effects were neither new nor unique to the new technologies, for example using restriction enzymes, or some of the other longstanding, routinely used mutagenesis or cloning methods, can also result in off-target effects. Prof Young added that all changes made by chemical and radiation-induced mutagenesis were untargeted. Prof Ian Godwin suggested that off-target effects from new technologies may be less likely because the changes are so targeted, but the presence of multi-gene families might mean the effect is greater.

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1 Site-directed nuclease (SDN) techniques:

- SDN-1: non-homologous end joining repairs DNA cleavage, which can result in random insertions, deletions and substitutions, often of only a few nucleotides.
- SDN-2: homology-directed repair of DNA cleavage is guided by a supplied template, incorporating changes to one or a few nucleotides.
- SDN-3: homology-directed repair of DNA cleavage is guided by a supplied template, inserting a new gene or genetic element.

Dr Bonnett clarified that SDN-1 can be used to produce sequence deletions, which Dr Matthew confirmed. Prof Godwin observed that his experiments in sorghum using SDN-1 produced a range of sequence changes, including variations in the number of nucleotides deleted.

The Chair referred to the first question being asked and Prof Marie Ranson, Prof Barnard and Prof Godwin agreed that the risks posed by organisms altered by SDN-1 are unlikely to be any different to naturally mutated organisms. Dr Michael suggested that the answer might be different if human embryos are being considered. Dr Matthew advised that, in some cases, genetic modification of humans may be regulated under the Act, but the NHMRC also regulates research involving human embryos and human cloning.

Addressing Question 2, members discussed what types of sequence changes could be achieved using SDN-2. Dr Matthew advised that generally modifying one or a few nucleotides were associated with use of SDN-2, and larger changes were generally associated with use of SDN-3. Dr Gabrielle O'Sullivan noted that the size of the change is not always important, since even changing a single amino acid has been shown to increase the pathogenicity of some organisms.

The Chair invited Ms Fell to comment. Ms Fell suggested that not everyone will distinguish these techniques from traditional genetic modification techniques, and the Chair and Dr Dornbusch agreed. Dr Dornbush informed members that public consultation will take place after this technical input and some indication of public perceptions of these technologies may be gauged as a part of the consultation process.

The Chair asked members whether the risks from SDN-2 or ODM are different to natural mutations, conventional breeding or mutagenesis. A/Prof Jason Smythe considered that risks are unlikely to be different when the techniques are used once (as in Question 2), but may be different when they are used to make successive rounds of modifications (as in Question 3).

Prof Kevin Smith commented that the techniques suddenly becoming accessible is another issue additional to the technical risks being discussed today. The Chair commented that these new technologies do not result in any changes that were not achievable from older, more expensive techniques – the difference is that everyone can access them. A/Prof Smythe suggested a minor difference is that the new technologies have the potential to deliver more specific, targeted changes.

Referring to Question 3, Dr Diane Webster asked whether successive rounds of modifications in one gene using SDN-2 could result in the sort of change that SDN-3 causes, and A/Prof Smythe said that it could. Prof Smith commented that using SDN-2 at a number of different sites in the genome would be similar to multiple rounds of mutagenesis, but that if the same site was targeted then the result may be like SDN-3 or inserting a gene. Dr Dornbusch summarised that therefore successive rounds of SDN-2 may pose risks similar to inserting a gene.

The Chair referred to Question 4 and suggested that the potential off-target effects of SDNs or ODM do pose risks different to the intended effects, and members agreed. Moving to Question 5, the Chair commented that the evidence base for new technologies is large and rapidly growing. Dr Dornbusch requested that members with any relevant references forward them to the OGTR. The Chair added that Australia has a number of experts that could be called on, including Prof Ryan Lister, Dr Marco Herold, Prof Peter Waterhouse, and Prof Paul Thomas, who all have specific experience with this technology.

Prof Godwin raised a concern that changes made now to the Regulations may not keep up with the rapidly evolving technology. Dr Bonnett commented that the approach of other regulators such as FSANZ may complicate the issue. Dr Matthew responded that FSANZ has a different focus so their approach does not necessarily need to match the OGTR's. That aside, the OGTR is in regular

contact with FSANZ on this topic and the two agencies keep each other up to date with developments.

The Chair reminded members that the committee's focus is on the science, and it is not a question for GTTAC how this could be legislated. Dr Matthew advised that the next steps will be public consultation on options for updating and improving the Regulations in relation to new technologies.

GTTAC provided the following advice to the Regulator:

Resolutions:

1. Risks posed by organisms altered by SDN-1 are unlikely to be different to naturally mutated organisms.
2. SDN-2 and oligo-directed mutagenesis are unlikely to pose risks that are different to natural mutations, conventional breeding or mutagenesis.
3. Successive rounds of modifications using SDN-2 and oligo-directed mutagenesis may pose risks similar to inserting new genes or SDN-3.
4. Off target effects do pose risks different to the intended effects.
5. Members recommended some experts and will send relevant evidence.

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