Australian Government
Department of Health
Office of the Gene Technology Regulator

OGTR Perspective on Gene Editing

Presentation at the *CSIRO Gene Editing of Crops Workshop*
28-30 November 2017

Dr Andrea Robold
Regulatory Practice Section
Office of the Gene Technology Regulator

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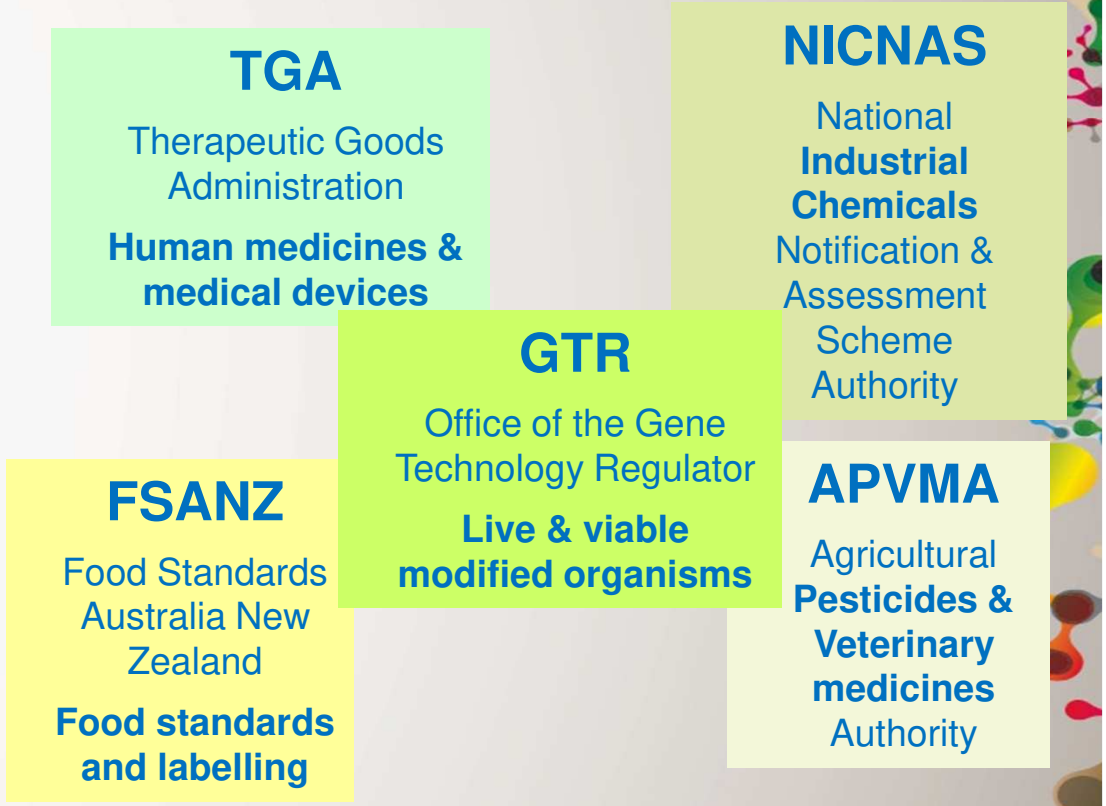
Integrated regulation of GMOs & GM Products

- GTR regulates GMOs
- avoid duplicating regulation
- align decision making as far as possible.



What challenges do new technologies pose for the Gene Technology Regulator?

- New methodologies and applications
  - How do these fit with legislative definitions?
- New techniques that utilise natural processes
  - Are there risks that warrant regulation?
  - How different are the resulting organisms to natural mutants?
  - Should these organisms be regulated as GMOs?

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What is a GMO?

Section 10 of the *Gene Technology Act 2000*:

Gene technology is any technique for the modification of genes or genetic material

the Regulations can declare techniques not to be gene technology

A **GMO** is

a) an organism that has been modified by gene technology or

b) inherited traits that occurred because of gene technology

the Regulations can also declare things to be GMOs or not GMOs

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GT Regulation in the year 2000

not gene technology

natural mutations

mutagenesis

inserting transgenes

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Science – technical advances

2000

35S | gene | nos

transgenics

2015

RNAi

oligo-directed mutagenesis (ODM)

site specific nucleases, mutations (SDN)

cisgenesis, intragenesis

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Technical review of the Regulations
What is the problem?

- Technology has changed since the definitions of 'GMO' and 'gene technology' were last amended
- It's unclear whether organisms modified by some new technologies are GMOs
- New technologies are being used increasingly in research and development, and are moving towards commercialisation

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Review of the Regulations

Primary aim:

Bringing the lists of exclusions in the Regulations up to date with current science to provide clarity

Main consideration:

Regulation should be commensurate with the risks posed by gene technology

An important constraint: can't alter the policy settings

- E.g. process trigger

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Review progress to date

First round of consultation was in 2016

- 4 options for how new technologies could be regulated
- options paper and submissions are on the OGTR website

Public consultation

- on draft amendments to the Regulations
- open until February 2018

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Site-directed nucleases

CRISPR/Cas9, TALENs, ZFN, etc, makes a targeted double-strand break

non-homologous end joining

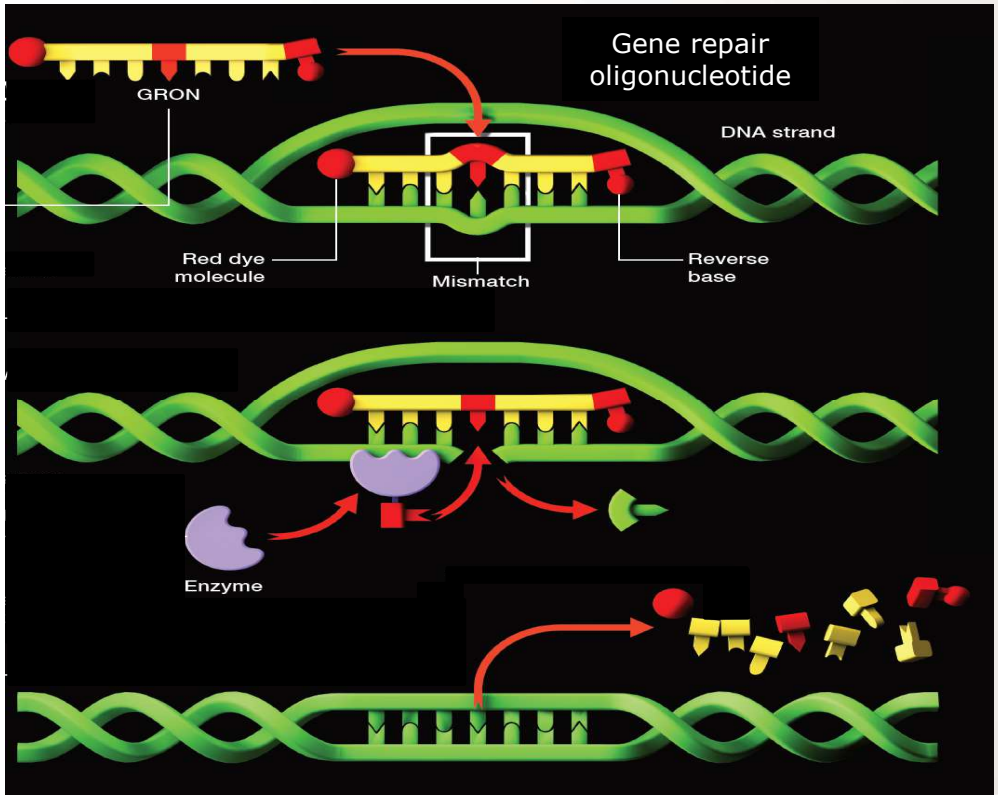
random indels
SDN-1

homology-directed recombination guided by an added template

short template with one or several nt difference
SDN-2

long template with a new sequence
SDN-3

Oligo-directed mutagenesis



Cibus' Rapid Trait Development System

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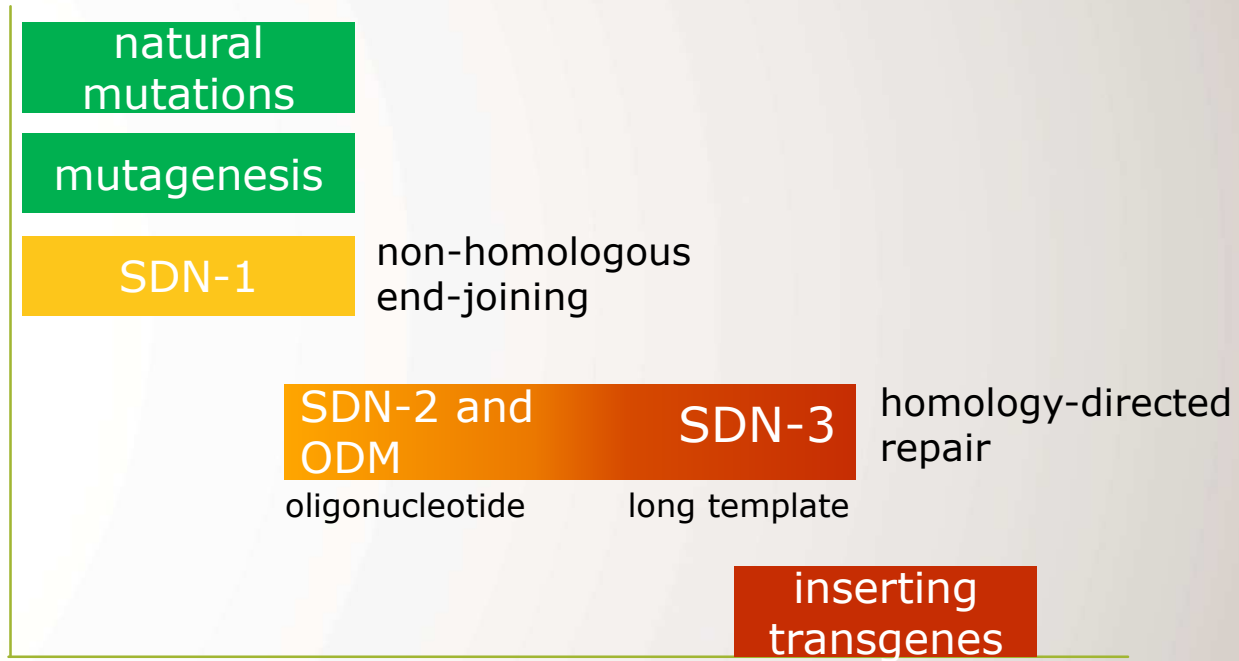
Some new technologies fit 'in-between'

not gene technology



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New technologies proposal

Amendment proposal for public consultation – subject to change

natural mutations

mutagenesis

SDN-1

Regulate template-guided changes

Any organism with its genome modified by SDN-2, ODM and SDN-3 will be regulated, whether or not it also contains other genetic modifications, such as a DNA insert for delivery of the technology.

Exclude SDN-1 from regulation

SDN-2 and ODM

SDN-3

inserting transgenes

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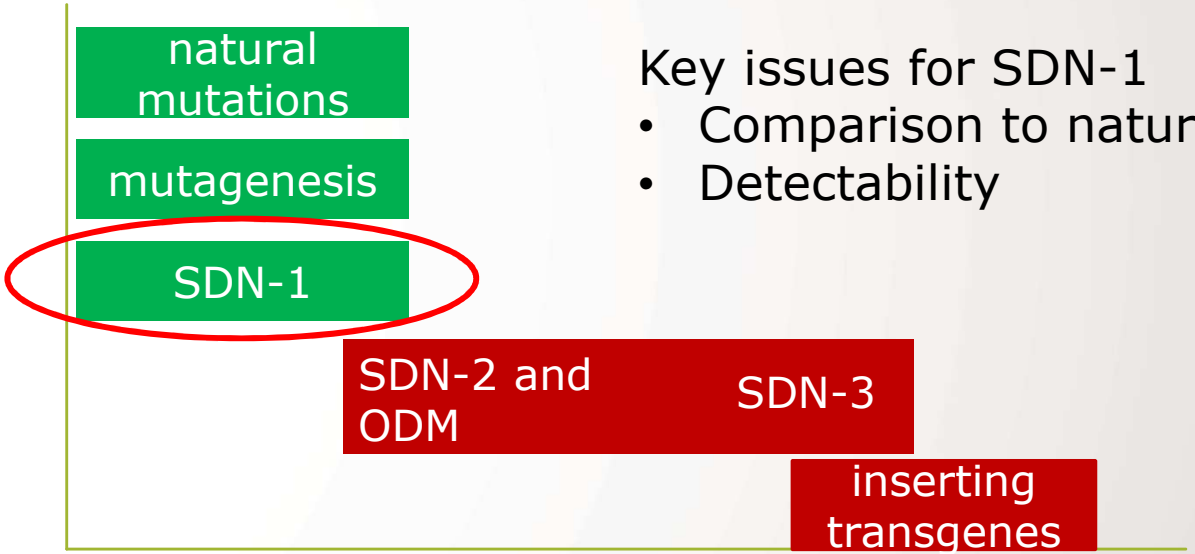
New technologies proposal

Amendment proposal for public consultation – subject to change



Key issues for SDN-1

- Comparison to natural mutations
- Detectability

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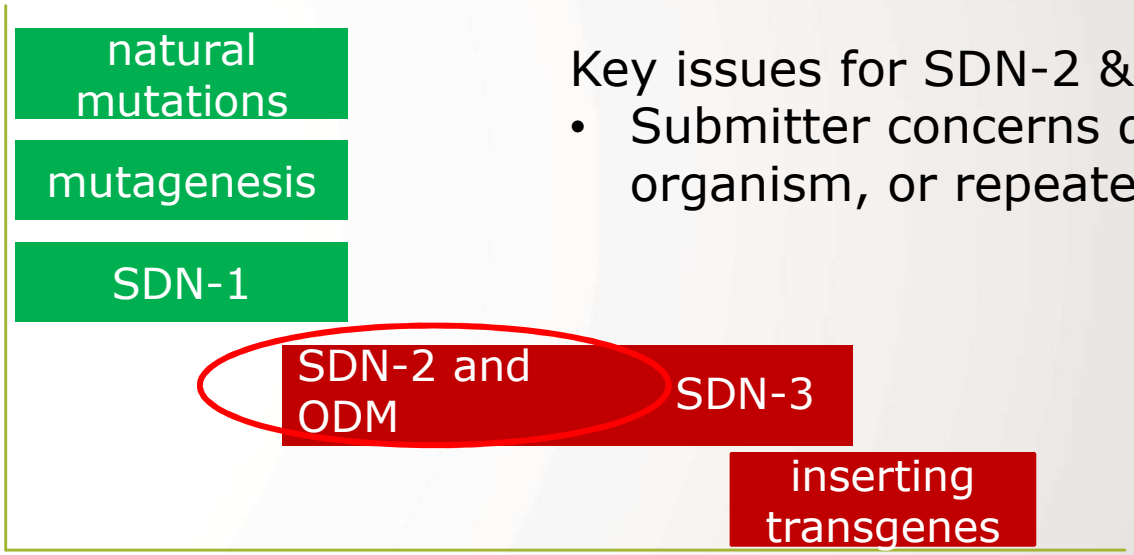
New technologies proposal

Amendment proposal for public consultation – subject to change



Key issues for SDN-2 & ODM:

- Submitter concerns depending on parent organism, or repeated use of technique

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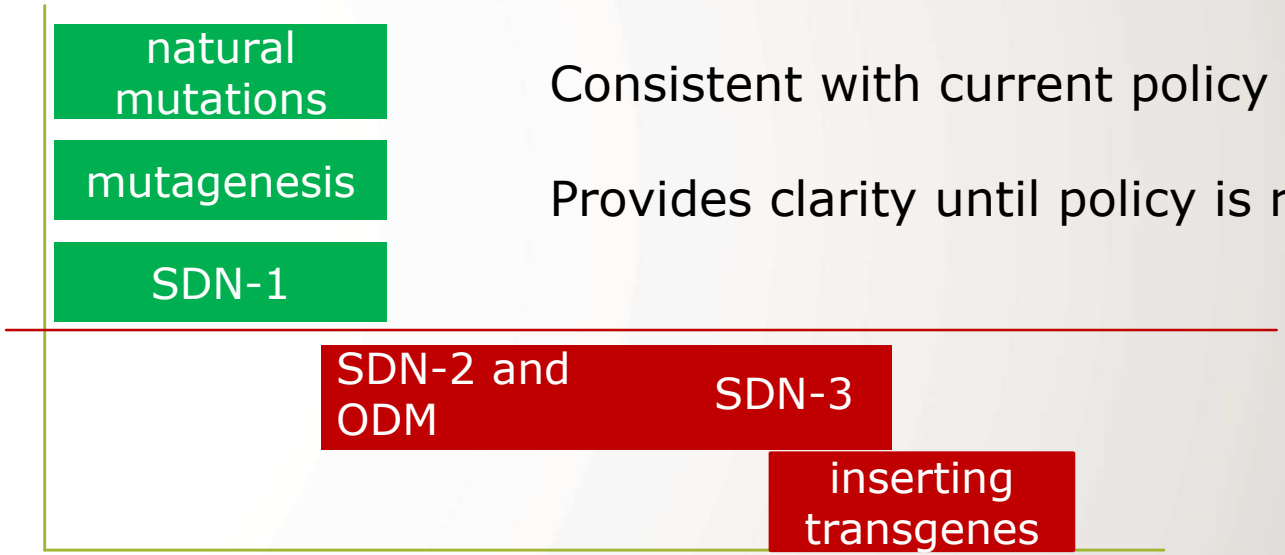
New technologies proposal

Amendment proposal for public consultation – subject to change



Consistent with current policy settings

Provides clarity until policy is reviewed

Gene drives

- Gene drives are preferentially inherited genetic elements
- 'drive' a trait into a population – including deleterious traits
- Many possible uses have been speculated, including:
  - Disease control, eg virus transmission by mosquitoes
  - Invasive species control, eg rodents, cane toads
  - Agricultural applications, eg fruit fly control, herbicide-resistant weeds, pesticide-resistant insects
- Research is in an early phase: recent proof of concept laboratory experiments in yeast, Drosophila and mosquitoes

Regulatory status of gene drives

- Engineered gene drives involve stable integration of modified genes – these organisms are GMOs

- **Currently**: general plant and animal NLRD categories would include most contained gene drive work

- **Amendment proposal** for public consultation – subject to change: case-by-case assessment of all contained gene drive work (DNIR licence)
  - to be reassessed at the next Regulations Review

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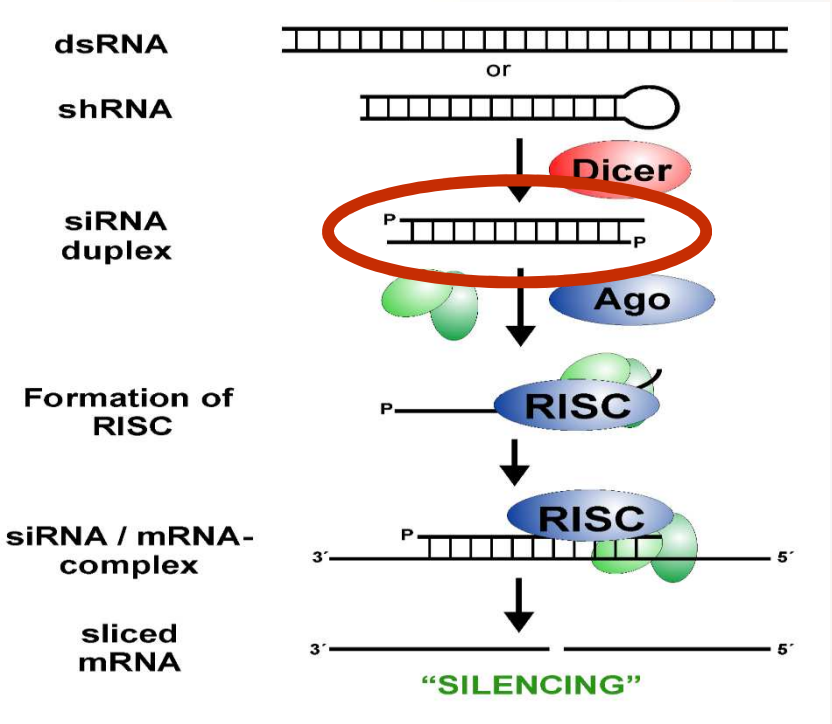
RNA interference



Gene-specific small interfering RNAs may lead to:

- mRNA degradation
- inhibition of mRNA translation
- DNA methylation (represses transcription)

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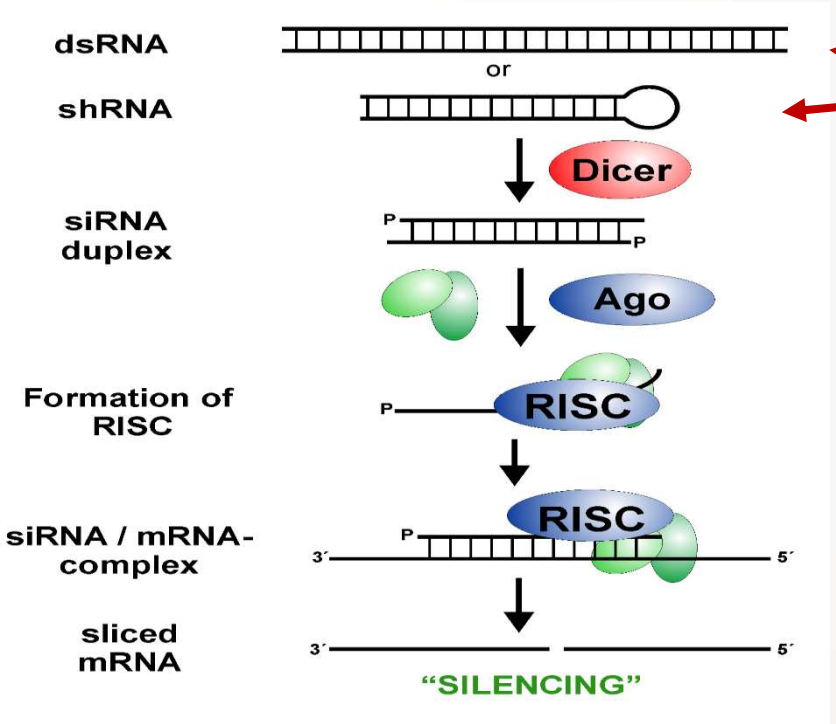
RNA interference



Permanent effects:
integrated transgene

Short-term effects:
Viral vector

Applied as RNA

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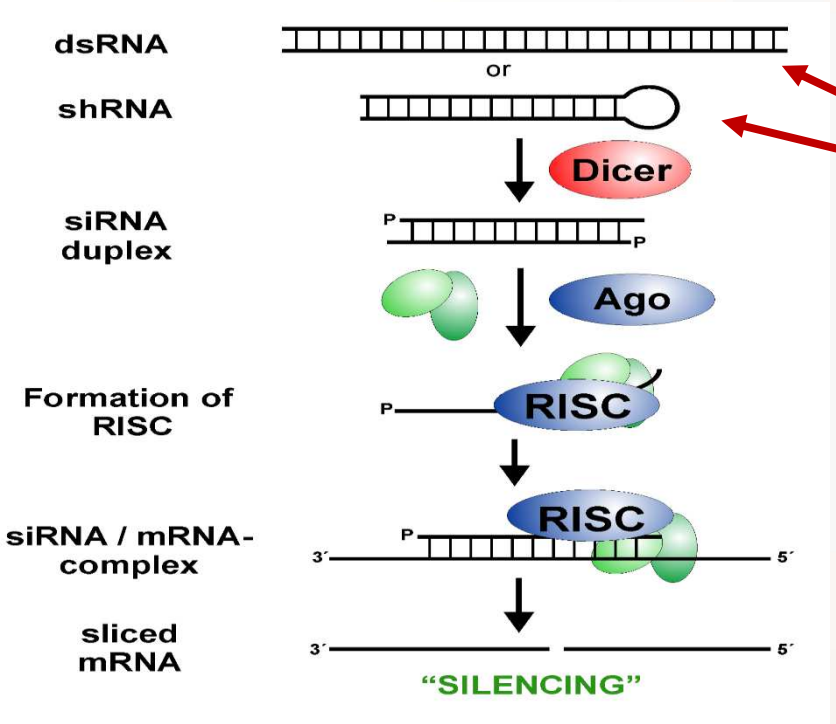
RNA interference



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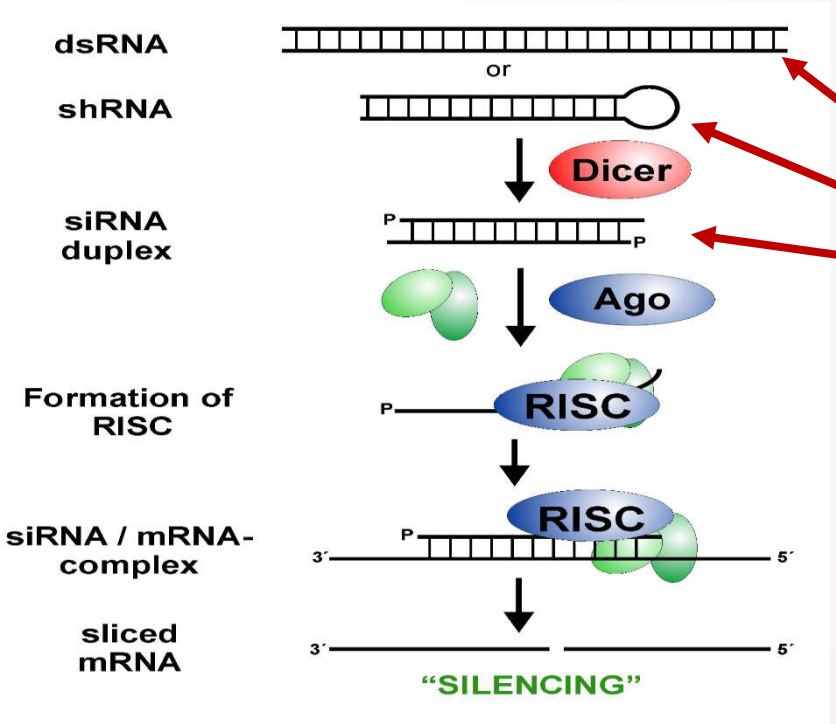

Permanent effect:
integrated transgene

Short-term effect:
Viral vector

Applied as RNA

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RNA interference proposal

Amendment proposal for public consultation – subject to change

RNAi techniques involving direct application of RNA will **not** be gene technology if they

- do not cause changes to genomic sequence
- do not allow translation of novel proteins
- do not cause formation of an infectious agent

e.g. directly applying siRNAs and dsRNA

RNAi techniques that will remain gene technology involve:

- inserting sequences into the genome and
- vector delivery.

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What's next?

- Public consultation until February 2018 on
  - drafted amendments
  - paper outlining the directions
- Finalise amendments, taking submissions into account
  - **proposals may be modified**
- State and Territory approvals, Australian Government Regulation-making process
  - **amendments would <u>not</u> commence before 2019**

Do <u>not</u> act on any of these proposals now.
Always apply the current legislation!!!

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How can you contribute?

Technical review consultation aims to:

- fine-tune the amendment wording for best clarity and
- help us understand the impacts of these proposals.

Get involved in the Review of the National Gene Technology Scheme at

https://consultations.health.gov.au/health-systems-policy-division/genetechreview2017/

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Department of Health
Office of the Gene Technology Regulator

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[redacted]

From: Institutional Biosafety Committee IBC [redacted]
Sent: Wednesday, 20 May 2015 12:32
To: MITCHELL, Heidi
Cc: Iain Searle
Subject: RE: Query_Regulation of non-transgenic progeny derived from a transgenic plant [SEC=No Protective Marking]

Hi Heidi

Iain fine with you contacting him directly.
Contact details Dr Iain Searle
http://www.adelaide.edu.au/directory/iain.searle
http://biological.adelaide.edu.au/research/searle/
[redacted]

Regards
Virginia

From: MITCHELL, Heidi [mailto:[redacted]
Sent: Wednesday, 13 May 2015 5:19 PM
To: Institutional Biosafety Committee IBC
Subject: RE: Query_Regulation of non-transgenic progeny derived from a transgenic plant [SEC=No Protective Marking]

Hi Virginia,
Thanks for the response. I had just found the same information from his web page. He may be looking for epigenetic effects? Are you happy if I contact him directly?

Thanks

Heidi

Dr Heidi Mitchell | Director | Plant Evaluation Section | Evaluation Branch | Office of the Gene Technology Regulator | MDP 54 | GPO Box 9848 | CANBERRA ACT 2601 | AUSTRALIA | tel. [redacted] fax. [redacted] |
[redacted]

From: Institutional Biosafety Committee IBC [mailto:[redacted]
Sent: Wednesday, 13 May 2015 5:27 PM
To: MITCHELL, Heidi
Subject: FW: Query_Regulation of non-transgenic progeny derived from a transgenic plant [SEC=No Protective Marking]

Hi Heidi

Thank you for the phone call re the query.
I am about to go on leave for a few days so you will get a vacation message coming up. Back at work on the 20 May.

The researcher is Dr Iain Searle
http://www.adelaide.edu.au/directory/iain.searle
http://biological.adelaide.edu.au/research/searle/

[redacted]

His research according to the research link is:
We are interested in understanding the molecular mechanisms underlying reproductive development and currently focus on non-coding RNAs (miRNAs, siRNAs, long non-coding RNAs) and post-transcriptional RNA modifications.

So you may be right in deducing that it may be genetic modifications involving RNA. But it would be nice to know why he wants to propagate the non-GM plant.

Regards
Virginia

--
Virginia Furness
Research Compliance Officer (Gene Technology)
Secretary IBC
Office of Research Ethics, Compliance and Integrity, Research Branch
The University of Adelaide, AUSTRALIA 5005
[redacted]
Ph : [redacted]
Fax : [redacted]
e-mail: [redacted]

http://www.adelaide.edu.au/ethics/genetech/

From: Institutional Biosafety Committee IBC
Sent: Monday, 11 May 2015 4:02 PM
To: 'ogtr@health.gov.au'
Subject: Query_Regulation of non-transgenic progeny derived from a transgenic plant

University of Adelaide IBC is seeking advice on the following proposed research and whether it requires regulation under the GT Act.

Are non-transgenic plant (in this case canola) progeny still required to be regulated under an IBC dealing? More information, if we have a heterozygous transgene in a canola plant, self pollinate the plant and identify progeny that do NOT contain the transgene, can we release these non-transgenic plants from PC2 containment? Ultimately I would like to release the non-transgenic plants to canola breeders.

Regards

Virginia

--

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The University of Adelaide, AUSTRALIA 5005
[redacted]
Ph : [redacted]
Fax : [redacted]
e-mail: [redacted]

http://www.adelaide.edu.au/ethics/genetech/

CRICOS Provider Number 00123M

[redacted]

From: MATTHEW, Louisa <[redacted]
Sent: Wednesday, 14 September 2016 11:25
Subject: RE: Agenda for OGTR meeting on Monday [SEC=UNCLASSIFIED]

Hi Peter,

There's no need to go into SPT or accelerated breeding – techniques resulting in null segregants have a well-established place outside the gene technology regulatory scheme, and that's not up for review. The techniques the review will focus on are oligo-directed mutagenesis and site-directed nuclease techniques (utilising either non-homologous end-joining or homology-directed repair).

Does that sound okay to you?

Louisa

From: Peter Langridge [mailto:[redacted]
Sent: Wednesday, 14 September 2016 11:16 AM
To: MATTHEW, Louisa
Subject: RE: Agenda for OGTR meeting on Monday [SEC=UNCLASSIFIED]

Dear Louisa,
Can I just check on the technologies you would like me to cover in the presentation; was the meeting just planning to look at gene editing techniques or did you also want me to cover SPT and accelerated breeding techniques?
Cheers
Peter

From: MATTHEW, Louisa [mailto:[redacted]
Sent: Tuesday, 13 September 2016 3:23 PM
To: [redacted] <[redacted]>; Peter Langridge <[redacted]>
Subject: Agenda for OGTR meeting on Monday [SEC=UNCLASSIFIED]

Dear [redacted] and Peter,

Please find attached the agenda for the meeting at OGTR on Monday. I look forward to seeing you then,

Kind regards,
Louisa

Louisa Matthew
Assistant Director, Regulatory Practice Section
Regulatory Practice and Compliance Branch

Office of the Gene Technology Regulator
Australian Government Department of Health
T: [redacted] E: [redacted]
Location: Pharmacy Guild House, 15 National Circuit, Barton ACT 2600

MPD 54, GPO Box 9848, Canberra ACT 2601, Australia

The Department of Health acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to elders both past and present.

[redacted]

From: Iain Searle <[redacted]>
Sent: Sunday, 31 May 2015 19:45
To: MITCHELL, Heidi
Subject: Re: Query_Regulation of non-transgenic progeny derived from a transgenic plant [SEC=No Protective Marking]

Dear Heidi

The parent would be transformed with a T-DNA by using Agrobacterium tumefaciens.

In this scenario, the T-DNA would be transformed into Brassica rapa and the T-DNA would contain a common plant selectable marker (BAR) and a plant promoter driving the production of dsRNA targeted to induce RNA silencing against an endogenous plant (host) gene. The trait conferred upon this transgenic parent would be the ability to produce viable hybrid seed when crossed to Brassica oleracea. When this seed is germinated, the hybrid plant is sterile as the two parents had different chromosome numbers unless we double the chromosomes by using a conventional chemical treatment. The segregating progeny (seeds) that contain the transgene would be discarded. Non-transgenic seed would not have the trait mentioned above. Please not these plants are actually synthetic Brassica napus (canola). If this is not clear I am happy to explain it further.

Best Regards,
Iain

http://www.genetics.org.au/2015-conference/

Dr. Iain Searle
Group Leader & ARC Future Fellow
****
Dr. Iain Searle
The University of Adelaide
School of Biological Sciences
School of Agriculture, Food and Wine
[redacted]
Adelaide, SA 5005, Australia
E- [redacted]
****

From: , Heidi <[redacted]>
Date: Wednesday, 27 May 2015 1:20 pm
To: Iain Searle <[redacted]>
Subject: FW: Query_Regulation of non-transgenic progeny derived from a transgenic plant [SEC=No Protective Marking]

Dear Dr Searle,
Virginia Furness from the University of Adelaide IBC passed your query on to me about whether non-transgenic progeny are regulated as GMOs.

Please could you provide me with some more information about the process that you used to transform the plants, the introduced DNA and the trait that is present in the GM plants (and whether this is passed onto the non-transgenic progeny). This additional information will enable me to provide a response back to the IBC.
Kind regards
Heidi
Dr Heidi Mitchell | Director | Plant Evaluation Section | Evaluation Branch | Office of the Gene Technology Regulator | MDP 54 | GPO Box 9848 | CANBERRA ACT 2601 | AUSTRALIA | tel. [redacted] fax. [redacted]
[redacted]

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Regards

Virginia

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[redacted]
Ph : [redacted]
Fax : [redacted]
e-mail: [redacted]
http://www.adelaide.edu.au/ethics/genetech/
CRICOS Provider Number 00123M

[redacted]

From: MITCHELL, Heidi
Sent: Monday, 29 June 2015 13:45
To: 'Iain Searle'
Cc: [redacted]
Subject: RE: Query_Regulation of non-transgenic progeny derived from a transgenic plant [SEC=No Protective Marking]

Dear Iain,
My apologies for the delay in responding to your query.

For the scenario that you have explained below, the segregating seeds which do not contain any transgenes would not be regarded as a GMO under the *Gene Technology Act 2000* (the Act).

The relevant legislative provision is the definition of genetically modified organism (GMO) in the Act. Section 10 of the Act defines a GMO as:

genetically modified organism means:

(a) an organism that has been modified by gene technology; or

(b) an organism that has inherited particular traits from an organism (the ***initial organism***), being traits that occurred in the initial organism because of gene technology; or

(c) anything declared by the regulations to be a genetically modified organism, or that belongs to a class of things declared by the regulations to be genetically modified organisms;

but does not include:

(d) a human being, if the human being is covered by paragraph (a) only because the human being has undergone somatic cell gene therapy; or

(e) an organism declared by the regulations not to be a genetically modified organisms or that belongs to a class of organisms declared by the regulations not to be genetically modified organisms.

It is my opinion that these seed which do not contain the genetic material that was introduced into the parent plant, do not fall within the definition of GMOs in section 10 of the Act. This is because these are not organisms which have themselves been modified by gene technology (paragraph (a) of the definition of a GMO) nor are they organisms that have inherited particular traits that occurred in an initial organism because of gene technology (paragraph (b) of the definition).

However the parent plant, or seed carrying any part of the genetic modification from the parent line, are GMOs and must not be imported or used in Australia without appropriate authorisation under the Act.

Please note that this response to your enquiry represents my view based on a review of the information before me at this time. It is not to be considered legal advice.

Thank you for your engagement with the regulatory system.

Kind regards

Heidi

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[redacted]

From: Iain Searle [mailto:[redacted]
Sent: Sunday, 31 May 2015 7:45 PM
To: MITCHELL, Heidi
Subject: Re: Query_Regulation of non-transgenic progeny derived from a transgenic plant [SEC=No Protective Marking]

Dear Heidi

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In this scenario, the T-DNA would be transformed into Brassica rapa and the T-DNA would contain a common plant selectable marker (BAR) and a plant promoter driving the production of dsRNA targeted to induce RNA silencing against an endogenous plant (host) gene. The trait conferred upon this transgenic parent would be the ability to produce viable hybrid seed when crossed to Brassica oleracea. When this seed is germinated, the hybrid plant is sterile as the two parents had different chromosome numbers unless we double the chromosomes by using a conventional chemical treatment. The segregating progeny (seeds) that contain the transgene would be discarded. Non-transgenic seed would not have the trait mentioned above. Please not these plants are actually synthetic Brassica napus (canola). If this is not clear I am happy to explain it further.

Best Regards,
Iain

http://www.genetics.org.au/2015-conference/

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Group Leader & ARC Future Fellow
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Adelaide, SA 5005, Australia
E-[redacted]
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Date: Wednesday, 27 May 2015 1:20 pm
To: Iain Searle <[redacted]>
Subject: FW: Query_Regulation of non-transgenic progeny derived from a transgenic plant [SEC=No Protective Marking]

Dear Dr Searle,

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Kind regards

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Virginia

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[redacted]
Ph : [redacted]
Fax : [redacted]
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http://www.adelaide.edu.au/ethics/genetech/

CRICOS Provider Number 00123M

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communication is strictly prohibited. If you receive this transmission in error please notify the author immediately and delete all copies of this transmission."

[redacted]

From: ROBOLD, Andrea [redacted]
Sent: Tuesday, 5 December 2017 8:52
Subject: RE: CSIRO Gene editing of crops Kiama workshop - feedback requested and pdfs available on website [SEC=UNCLASSIFIED]
Attachments: Kiama 2017 OGTR.pptx

Follow Up Flag: Follow up
Flag Status: Flagged

Dear Steve

Thank you again for putting together this workshop – it was very interesting from a research point, but also felt that it was well rounded because you included people from regulatory agencies and social scientists.

I apologise for the delay in giving permission to upload my presentation.
I have made a change to slide no 13 which explains the directions we had at the time on how SDN technologies are proposed to be regulated. I did so, because I was unsure if people understood me correctly and it is important that regulatory requirements are clear to everyone. Could you please make the attached presentation available to the attendees of the workshop?

Regards
Andrea

From: Steve.Jobling[redacted][mailto:[redacted]
Sent: Monday, 4 December 2017 4:48 PM
To: [redacted]

Subject: CSIRO Gene editing of crops Kiama workshop - feedback requested and pdfs available on website [SEC=No Protective Marking]

Dear participants, I hope you all enjoyed the workshop as much as we did and you all got home safely, especially the overseas visitors.

As was said at the end of the meeting, we would be grateful for feedback on the event especially on topics such as:

- Quality of speakers
- How well the meeting performed as a forum for making new contacts and potential collaborations
- How the Q&A sessions were received both from a regulatory/ethics and science/technical perspective
- Feedback from the regulators and departmental officials would be especially welcomed as a key reason behind the workshop was to discuss issues and inform them of developments in the gene editing field.
- Should we hold the event again perhaps in 2-3 years?

PDFs of the presentations are now uploaded to the website https://research.csiro.au/gene-editing-workshop/ along with a couple of photos from the workshop. If anyone has other photos they think would add to the appearance of the website please forward them and we may add them – perhaps in a separate page?

Please remember that the website has a list of contact details so we can help build a gene editing community in Australia and New Zealand.

On that note, if participants are willing to share the vectors and experience they have in gene editing, then please send us the details and we will upload to the website. Please include ;

- Vector name (Agro/biolistic)
- Species transformed and approx. efficiency of editing
- sgRNA system (source of U3/U6 promoters, single multiple cassettes etc
- conditions of use (MTA etc).

Please note that CSIRO requires a signed MTA before any material is exchanged with a CSIRO party.

Regards

Steve Jobling
Filomena Pettolino
Ming Luo

The organising committee