Issues with synthetic biology

M Mclaren BNut & Diet

A brief summary of some studies and papers

To contribute to issues for Open Consultation for the Third Review of the National Gene Technology Scheme

DNA is live dynamic powerhouse, and making a DNA cocktail is possible (proof or concept) but will it further humanity or cause multiple problems if allowed to continue unfettered (no scientific safety testing).

As a Dietitian it is concerning to me that scientific standards seems to have dropped to roll out these technologies, albeit at the expense of public health. Just like with GM foods, no one can clearly make an informed choice for the risks of consuming the GM product, - if **ALL** the possible outcomes are not fully elucidated.

As we only grow two crops in Australia commercially, - do not forget that the food brought from O/S may contain GM ingredients as no labelling is required, or the majority of GM ingredients fall through loop holes, which means GM is rarely stated on products. Also, the food producers think it will be detrimental to sales to admit to gene changes in food stuffs thus we all remain in the dark and are not free to opt out of GM food.
http://www.foodstandards.gov.au/consumer/gmfood/labelling/Pages/default.aspx

With far too much focus on genetic factors and ignoring environmental factors which work on the DNA and cause it to express different genes depending what is required in the environment (poisons in our environment also act on the DNA and can cause mutations) Most diseases have multiple genes involved and this complex interplay could not but controlled externally, you can't have a gene turned on constantly especially if changing environmental factors would ordinarily turn off regulation of the gene.

Injecting a few CRISPR cells will not change expression of the germ line and thus 'if it works' this whole gene cocktail seems to be more a patch requiring constant 'fixes' and an ongoing dependence likened to a drug addiction and a persistent financial noose for the client.

Damage to the gut and gut flora from GM food maybe causing organ problems as early independent evidence suggest (Judy Carmen 2013- link below). Now with the advent of CRISPR the industry claims they can cure all ales- including problems from the original (recently admitted by the industry) **random** GM technique food creations.

Synthetic Biology should be halted and banned until 30 years of randomised control trials have no demonstrated problems (thus if the profit incentive is removed it may dent the zealous rollout of the technology) and then highly regulated to monitor problems with the technology.

UNESCO panel of experts calls for ban on "editing" of human DNA to avoid unethical tampering with hereditary traits

http://en.unesco.org/news/unesco-panel-experts-calls-ban-editing-human-dna-avoid-unethical-tampering-hereditary-traits

A 2013 article was very detailed about GM foods and called for a GM food ban https://ban-gmos-now.com/ (see links at end- a lot of info)

The following framework could be used to inform Australia's regulations for CRISPR and beyond.

US example of Synthetic Biology Regulation Protocol

The Principles for the Oversight of Synthetic Biology

The Principles for the Oversight of Synthetic Biology is an important tool to help people reign in these new technologies." – Vandana Shiva
https://www.wilsoncenter.org/sites/default/files/principles_for_the_oversight_of_synthetic_biology.pdf

Problems, concerns, issues or possible problems with CRISPR

1) **More developed marketing than the technology itself**

The arrogance and confidence in this show does not marry with the problems with the technology
Medicine's Big Breakthrough: Editing Your Genes | Guide - SBS
https://www.sbs.com.au/guide/.../medicines-big-breakthrough-editing-your-genes
Apr 4, 2017 - '*Medicine's Big Breakthrough*: Editing Your Genes' shows us a future where we'll be able to pick and choose our children's traits. But will that ...
Repeated around the 1/10/17

Australian TV and radio including news broadcasts talk about this topic daily with a very infomercial style which has forced me to stop listening to radio national as the propaganda was deafening.

2) **The phase II of GM cleaving claims to be more accurate than phase I, however with many off target mutations created, this is questionable**

CRISPR gene editing causes hundreds of unintended, off-target mutations:

A new study finds that the revolutionary CRISPR-Cas9 gene editing technique can cause large numbers of unwanted insertions and deletions of genetic material, writes Jana Howden. 30 May 2017
https://cosmosmagazine.com/biology/crispr-gene-editing-causes-hundreds-of-unintended-off-target-mutations

".. looking at the full genomes of the mice, they also found that two of the mice treated with CRISPR technology had undergone 1500 unintended single nucleotide mutations, as well as more than 100 large deletions and insertions of genetic material. "

CRISPR Gene-Editing Might Cause Thousands of Unintended Mutations

The popular genetic engineering tool could cause hundreds or thousands of unwanted mutations, potentially creating random side effects. By Avery Thompson May 30, 2017
http://www.popularmechanics.com/science/health/a26693/crispr-causes-thousands-of-mutations/

"When scientists want to edit a gene with CRISPR, they use techniques to select a specific gene sequence to edit. But selecting a single region in an entire genome is not easy, and often CRISPR will target other regions in the genome as well. Researchers believed they could predict most of these

"off-target effects," but a new study in Nature Methods suggests they probably can't." (1. link below)

"Off-target effects have been known about for some time, and to combat them, researchers can use computer algorithms to predict where the mutations will occur. Scientists using CRISPR could test to make sure any off-target mutations aren't harmful before using the technology on animals or humans. But the new research suggests that potentially hundreds or thousands of off-target mutations are unaccounted for by these algorithms, meaning that any use of CRISPR could be potentially dangerous."

"But considering that human trials with CRISPR are already underway in China and only a year away in the United States, it's worth taking the time to ensure we're not accidentally introducing new genetic problems while trying to fix older ones."

CRISPR controversy raises questions about gene-editing technique: A new controversial research study is causing a stir with scientists Ian Haydon, The Conversation
https://www.salon.com/2017/06/03/crispr-controversy-raises-questions-about-gene-editing-technique_partner/

"A central promise of CRISPR-based gene editing is its ability to pinpoint particular genes. But if this technology produces dangerous side effects by creating unexpected and unwanted mutations across the genome, that could hamper or even derail many of its applications.

Several previous research articles have reported off-target effects of CRISPR, but far fewer than this group found." (2. link below)

…"The Cas9 enzyme in the CRISPR system is what actually cuts DNA, leading to genetic changes. Unusually high levels of enzyme activity could account for the observed off-target mutations — more cutting equals more chances for the cell to mutate its DNA."

"…Lluis Montoliu says…"He believes the authors used suboptimal molecular components in their injected CRISPR therapies — specifically a plasmid that causes cells to produce too much Cas9 enzyme — likely leading to the off-target effects they observed."

"Researchers have known for a few years now that off-target mutations are likely given certain CRISPR protocols. More precise variants of the Cas9 enzyme have been shown to improve targeting in human tissue the lab."

"As scientists continue to hone the gene-editing technique, we recognize there's still a way to go before CRISPR will be ready for safe and effective gene therapy in humans."

CRISPR gene editing can cause hundreds of unintended mutations May 29, 2017
https://phys.org/news/2017-05-crispr-gene-hundreds-unintended-mutations.html
"We feel it's critical that the scientific community consider the potential hazards of all off-target mutations caused by CRISPR, including single nucleotide mutations and mutations in non-coding regions of the **genome**," Stephen Tsang, MD, PhD,

Nature

Doubts raised about CRISPR gene-editing study in human embryos
Alternative explanations challenge whether technique actually fixed a genetic mutation as claimed.
https://www.nature.com/news/doubts-raised-about-crispr-gene-editing-study-in-human-embryos-1.22547
" Doubts have surfaced about a landmark paper claiming that human embryos were cleared of a deadly mutation using genome editing. In an article[1] posted to the bioRxiv preprint server on 28 August, a team of prominent stem-cell scientists and geneticists question whether the mutation was actually fixed."

"Egli and Jasin raise that issue in their paper. They suggest that Mitalipov's team was misled into believing that they had corrected the mutation by relying on a genetic assay that was unable to detect a far likelier outcome of the genome-editing experiment: that CRISPR had instead introduced a large deletion in the paternal gene that was **not picked up** by their genetic assay. The Cas9 enzyme breaks DNA strands, and cells can attempt to repair the damage by haphazardly stitching the genome together, often resulting in missing or extra DNA letters."

'Chemical surgery' used to mend harmful mutations in human embryos
Scientists have used the technique, also known as 'base editing', for the first time in human embryos to change a single letter in a faulty gene
https://www.theguardian.com/science/2017/sep/28/chemical-surgery-used-to-mend-harmful-mutations-in-human-embryos-base-editing

"In 2015, scientists led by Junjiu Huang at Sun Yat-sen University in Guangzhou, China, tried to use Crispr to correct abnormal beta thalassemia genes in human embryos without much success. In the latest breakthrough, the same team turned to base editing instead."

"Writing in the journal Protein and Cell, the researchers show that the new procedure worked to some extent. Humans carry two copies, or alleles, of every gene and in many cases both versions have to be "healthy" to avoid disease. In the study, base editing sometimes repaired only one faulty gene rather than both, creating so-called mosaic embryos"

The Chinese team has not suggested that the procedure is ready to use in humans, especially as they found that it **sometimes created mutations instead of fixing them.**

CRISPR, the disruptor
A powerful gene-editing technology is the biggest game changer to hit biology since PCR. But with its huge potential come pressing concerns. Heidi Ledford 03 June 2015
Clarified: 08 June 2015
https://www.nature.com/news/crispr-the-disruptor-1.17673

"The sentiment is widely shared: CRISPR is causing a major upheaval in biomedical research. Unlike other gene-editing methods, it is cheap, quick and easy to use, and it has swept through labs around the world as a result. Researchers hope to use it to adjust human genes to eliminate diseases, create hardier plants, wipe out pathogens and much more besides."

"But although CRISPR has much to offer, some scientists are worried that the field's breakneck pace leaves little time for addressing the ethical and safety concerns such experiments can raise."

GMO Reports: New Plant Breeding Techniques (NPBTs) February 10, 2017

https://ban-gmos-now.com/2017/02/10/gmo-reports-npbts/
"CRISPR (often referred to as a type of "gene editing" – an association that critics say is inaccurate and misleading)"

Ethics
How Gene Editing Could Ruin Human Evolution Jim Kozubek Jan 10, 2017
http://time.com/4626571/crispr-gene-modification-evolution/
"CRISPR may be used to repair a gene that has a deficient product, such as an enzyme or receptor, or alter code that merely suggests of risk. Ideas on how to use it change hourly. The method is here to last. The ethics will only get more fraught. But there is a bigger obstacle to the emergence of "designer babies" and *Gattaca*-type dystopian futures: the principles of evolution."

CRISPR STUDIES

1) Nature Methods

Unexpected mutations after CRISPR–Cas9 editing *in vivo*

Kellie A Schaefer, Wen-Hsuan Wu, Diana F Colgan, Stephen H Tsang, Alexander G Bassuk & Vinit B Mahajan Affiliations Corresponding authors Nature Methods 14, 547–548 (2017) doi:10.1038/nmeth.4293 Published online 30 May 2017 Updated online 14 June 2017 Corrected online 25 July 2017
"…. However, concerns persist regarding **secondary mutations** in regions not targeted by the single guide RNA (sgRNA)[2]."

2) Nature Methods

Off-target mutations are rare in Cas9-modified mice

Vivek Iyer, Bin Shen, Wensheng Zhang, Alex Hodgkins, Thomas Keane, Xingxu Huang & William C Skarnes Affiliations Corresponding authors Nature Methods 12, 479 (2015) doi:10.1038/nmeth.3408 Published online 28 May 2015
"Previously, we reported cotransmission of a Cas9-**induced mutation** in the X-linked *Ar* gene and an off-target mutation to offspring of founder animals from pronuclear injection of Cas9 mRNA"

GM FOOD STUDIES

A long-term toxicology study on pigs fed a combined genetically …
https://www.organic-systems.org/journal/81/8106.pdf by JA Carman - Cited by 85 - Related articles

Seralini and Pusztai also did studies with adverse effects if GM crops (I'm sure your up with this?)

Some excellent YouTube to watch (Jeffery smith is the guy who discuss GM roundup resistance transferred to gut bacteria)

GMO Side Effects with Jeffrey Smith - YouTube
▸ 28:38
https://www.youtube.com/watch?v=uwX2xTf9i-I
Jan 12, 2017 - Uploaded by Dr. Josh Axe
Learn more about *genetically modified organisms* and *GMO* side effects here: ...

The Real Truth About GMOs by Jeffrey Smith - YouTube
▸ 1:22:14
https://www.youtube.com/watch?v=sLIcvPtBACU
Feb 25, 2016 - Uploaded by The Real Truth About Health
Expert Panel Host: *Jeffery Smith* (A podcast version of this video is available on iTunes.) • Expert Panel Host ..

Great Minds - Jeffrey M. Smith - Are GMOs Safe? - YouTube
▸ 12:58
https://www.youtube.com/watch?v=fZ0raBO-oos
May 27, 2015 - Uploaded by The Big Picture RT

***Jeffrey* M. *Smith*, Institute For Responsible Technology/Seeds of Deception/Genetic Roulette: The Gamble of ...**

The Truth About GMO's, Lecture at UCSB by Jeffrey Smith ... - YouTube
▸ 1:13:59
https://www.youtube.com/watch?v=0cgbDhKs_Os
Oct 12, 2012 - Uploaded by Bryan Rosen

Lecture by bestselling author *Jeffrey Smith* about the dangers of *genetically modified organisms* (*GMO's*) in ...

Jeffrey M. Smith: The GMO Threat (Full Length • HD) - YouTube
▸ 59:49
https://www.youtube.com/watch?v=oPvkZv5MfRw
Jan 16, 2011 - Uploaded by infokriegerBerlin
http://www.infowars.com/ http://infowars.wordpress.com/ *Smith* documents how consumption of *genetically* ...

Jeffrey M. Smith: Monsanto, GMO Seeds of Destruction - YouTube
▸ 1:03:23
https://www.youtube.com/watch?v=LSDEkoPwMfk
Jul 18, 2012 - Uploaded by The Alex Jones Channel
"Outrageous! That's what you'll say over and over again when you read how the biotechnology companies ...

…and many more videos

Dr. Stephanie Seneff presentation on harmful effects of ... - YouTube

▸ 56:38

https://www.youtube.com/watch?v=MqWwhggnbyw

Oct 24, 2013 - Uploaded by Wellesley Public Media

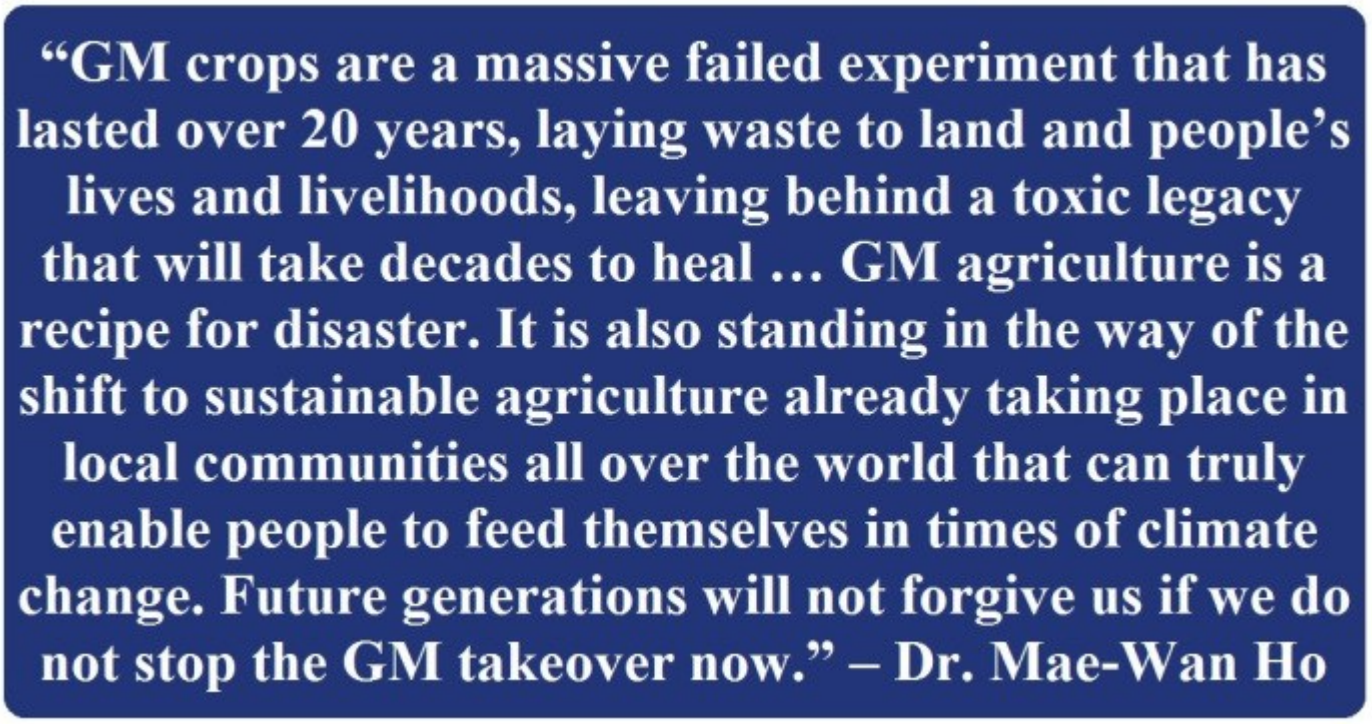
In her presentation entitled "Roundup: The Elephant in the Room," Dr. *Seneff* outlines adverse health and

Ban GMOs Now

https://ban-gmos-now.com/

The name of this website was inspired by a report of the same name, "**Ban GMOs Now –** Health and Environmental Hazards, Especially in Light of the New Genetics," by Dr. Mae-Wan Ho and Dr. Eva Sirinathsignhji, Institute of Science in Society; July 2013 (52 pages).

https://ban-gmos-now.com/ or see http://www.i-sis.org.uk/Ban_GMOs_Now.php



Dr. Mae-Wan Ho (1941-1916) "**In Memory of Dr. Mae-Wan Ho**," by Jeff Kirkpatrick, Ban GMOs Now; May 20, 2016)

There some working posts on this blog that are updated periodically:

(1) "**GMO Reports**," by Jeff Kirkpatrick, Ban GMOs Now

Also see: "**GMO Reports: New Plant Breeding Techniques (NPBTs)**," by Jeff Kirkpatrick, Ban GMOs Now

(2) "**Why Glyphosate should be Banned**," by Jeff Kirkpatrick, Ban GMOs Now

(3) "**GMOs are not necessary to feed the World**," by Jeff Kirkpatrick, Ban GMOs Now

(4) "**GMO Law Review Articles (Including Notes and Comments)**," by Jeff Kirkpatrick, Ban GMOs Now

Regulation

Two days ago there has been a call to regulate new breeding techniques.

Anti-GM groups criticise OGTR proposal regarding gene technology

Gregor Heard@grheard 16 Dec 2017, 6:30 a.m.

http://www.farmonline.com.au/story/5124399/anti-gm-groups-criticise-ogtr-proposals/

Problems with CRISPR

Mosaic problem stands in the way of gene editing embryos:

The first results of gene editing in viable human embryos reveals it works better than we thought, but that there's another big problem blocking the way News & Technology 15 March 2017

https://www.newscientist.com/article/mg23331174-400-mosaic-problem-stands-in-the-way-of-gene-editing-embryos/

Although very optimistic this paper discusses the problems of the new gene editing techniques And shows how infantile this industry is and should not be considering patents or marketing until years down the track if they think they can overcome the blueprint of life-at least 10 years of study is needed and then only if no problems or side effects from gold standard randomised control trials.

However the inherent actions of DNA cannot be held down- what we know is DNA will work to overcome mutations etc and if all somatic cells are written one way how does injecting something change all of these cells in the body? It seems like these ideas are not based in science. The new system is set up to constantly drip money to get treatment- due to being tethered to the drug for life.

CRISPR and off target mutations

CRISPR Gene Editing Controversy: Does It Really Cause Unexpected Mutations?

Steven Salzberg , Contributor Jul 10, 2017 @ 08:00 AM

https://www.forbes.com/sites/stevensalzberg/2017/07/10/crispr-gene-editing-problems-does-it-really-cause-unexpected-mutations/#1c8351b66a1a

This study discusses CRISPR and talks about 100's of off-target mutations.

He quotes Stephen Tsang "We feel it's critical that the scientific community consider the potential hazards of all off-target mutations caused by CRISPR."

Accectability of gene changes

With known low acceptability of gene modification why would the industry continue to advance before testing the first generation of GM? And complicate gene modification more and never ask people if they would trust gene modified- IVF babies before spending billions on creating a product most likely to be refused by the customers. Especially, if there is no security the product is safe- as DNA is dynamic- it would be arrogant, and simplistic to believe it is as easy as suggested and demonstrates ignorance and naivety to human molecular biology and biochemistry, thinking that changes to the DNA wouldn't have unintended consequences.

Labelling and acknowledging gene changes

It is a concern if medical procedures with CRISPR changes the way IVF is done without telling people it is gene changed and we haven't proven it is safe. And potentially the parents may need to care for disabled children so they should be informed. People must be informed thus for integrity of the

industry more thorough TESTING MUST PRECEDE before regulation and rolling out the erratic technology.

Changes to medical procedures or treatment must be in line with the medical oath to do no harm. Thus and gene changed treatments being suggested must be fully tested up to the standard of current medical therapies. This is not the time to **water down regulation** and by doing so **water down the quality of therapies and Medicine**- we do not need to enter into the dangerous territory that some 3rd world countries that are known for their botched medical procedures.

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If one changes and thus modifies the genes of the DNA of any species then one can't argue that the product is not changed or gene modified- that would be a direct lie and an attempt to mislead and misdirect people from the facts, which puts profit before public health- which is not how Australia should regulate gene changes.

As the industry is in its Infancy more testing is needed, before rigorous regulation and then labelling and informing people of every vaccine or antibiotic or IVF or any drug or any product which has gene changes and will need to tell the public about that change. This is to help people with drug interactions or allergies and for the industry to maintain credibility in the medical profession- who will be encouraged to prescribe these treatments and to avoid massive public health disasters thus strong regulation will keep the industry strong.

Study : example of problems with CRISPR

The Cytokine storm from TGN1412- that damaged subjects was dubbed the elephant man trial.
The human trial had a faster dose administration than in monkey models even though it was around 100x more dilute than that study and subjects still had a massive acute reactions and unknown long term effects.
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This report goes in detail into the subject and the paper considers the way trials are being run, informed consent and subject rights, and questions the collapse of standards of science and ethics in the new "knowledge economy".

Regulation before litigations

The Australian regulatory bodies overseeing GMO's should not allow dodgy products and trials like the one that nearly killed people in England and the company and those involved that ran the trial were passing the buck. It is not ok to create products and not prove safety and then not own up to your slackness when there is a problem with the product. Therefore to protect companies from legal assaults we must follow the precautionary approach and check safety, regulate first then let them produce and sell a labelled product.

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http://www.independent.co.uk/news/world/asia/philippines-dengue-fever-vaccine-children-immunisation-dengvaxia-sanofi-pasteur-a8088561.html

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http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/dir148/$FILE/Questions%20and%20Answers%20on%20licence%20decision.pdf

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CRISPR and off target mutations

CRISPR Gene Editing Controversy: Does It Really Cause Unexpected Mutations?

Steven Salzberg , Contributor Jul 10, 2017 @ 08:00 AM

https://www.forbes.com/sites/stevensalzberg/2017/07/10/crispr-gene-editing-problems-does-it-really-cause-unexpected-mutations/#1c8351b66a1a

This study discusses CRISPR and talks about 100's of off-target mutations.

He quotes Stephen Tsang "We feel it's critical that the scientific community consider the potential hazards of all off-target mutations caused by CRISPR."

Accectability of gene changes

With known low acceptability of gene modification why would the industry continue to advance before testing the first generation of GM? And complicate gene modification more and never ask people if they would trust gene modified- IVF babies before spending billions on creating a product most likely to be refused by the customers. Especially, if there is no security the product is safe- as DNA is dynamic- it would be arrogant, and simplistic to believe it is as easy as suggested and demonstrates ignorance and naivety to human molecular biology and biochemistry, thinking that changes to the DNA wouldn't have unintended consequences.

Labelling and acknowledging gene changes

It is a concern if medical procedures with CRISPR changes the way IVF is done without telling people it is gene changed and we haven't proven it is safe. And potentially the parents may need to care for disabled children so they should be informed. People must be informed thus for integrity of the

industry more thorough TESTING MUST PRECEDE before regulation and rolling out the erratic technology.

Changes to medical procedures or treatment must be in line with the medical oath to do no harm. Thus and gene changed treatments being suggested must be fully tested up to the standard of current medical therapies. This is not the time to **water down regulation** and by doing so **water down the quality of therapies and Medicine**- we do not need to enter into the dangerous territory that some 3rd world countries that are known for their botched medical procedures.

Regulation: Gene changed is not the same as not gene changed.

If one changes and thus modifies the genes of the DNA of any species then one can't argue that the product is not changed or gene modified- that would be a direct lie and an attempt to mislead and misdirect people from the facts, which puts profit before public health- which is not how Australia should regulate gene changes.

As the industry is in its Infancy more testing is needed, before rigorous regulation and then labelling and informing people of every vaccine or antibiotic or IVF or any drug or any product which has gene changes and will need to tell the public about that change. This is to help people with drug interactions or allergies and for the industry to maintain credibility in the medical profession- who will be encouraged to prescribe these treatments and to avoid massive public health disasters thus strong regulation will keep the industry strong.

Study : example of problems with CRISPR

The Cytokine storm from TGN1412- that damaged subjects was dubbed the elephant man trial.
The human trial had a faster dose administration than in monkey models even though it was around 100x more dilute than that study and subjects still had a massive acute reactions and unknown long term effects.
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This report goes in detail into the subject and the paper considers the way trials are being run, informed consent and subject rights, and questions the collapse of standards of science and ethics in the new "knowledge economy".

Regulation before litigations

The Australian regulatory bodies overseeing GMO's should not allow dodgy products and trials like the one that nearly killed people in England and the company and those involved that ran the trial were passing the buck. It is not ok to create products and not prove safety and then not own up to your slackness when there is a problem with the product. Therefore to protect companies from legal assaults we must follow the precautionary approach and check safety, regulate first then let them produce and sell a labelled product.

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1) The research needs to precede the release and monitoring unlike your diagram
2) Intentional release should be avoided for now-too risky
3) Need to be careful introducing these techniques in schools due to the unreliability and infancy of the industry and potential problems for the kids

4) Vested interests that recommend reducing regulation to facilitate their industry is a conflict of interest and as there is about 60% from industry contributing to this review vs 45 individual submissions. You wording and direction tend towards a bias to roll out this technology before we have regulated to stop it until it is proven safe and thus protect everyone: humans, animals, plants, mozzies (which are an import food source for animals) etc and industry. Then we can trust products - if this rolls out people will just stop buying products and if more vaccine damage like in the Philippians lately it will sabotage the medial industry too,

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Please regulate first, before our children are permanently damaged- like the Philippine kids with dengue!

Regulation

Two days ago there has been a call to regulate new breeding techniques.

Anti-GM groups criticise OGTR proposal regarding gene technology

Gregor Heard@grheard 16 Dec 2017, 6:30 a.m.

http://www.farmonline.com.au/story/5124399/anti-gm-groups-criticise-ogtr-proposals/

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