Exploring Genome Editing: Actors, Arenas, and Attitudes towards Governance

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1st Annual Conference on Governance of Emerging Technologies

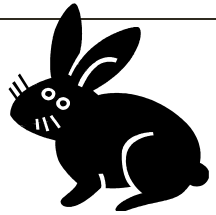
May 20, 2013

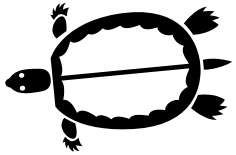
HUMPHREY SCHOOL OF PUBLIC AFFAIRS

UNIVERSITY OF MINNESOTA

Research Questions

Genetic engineering is changing rapidly

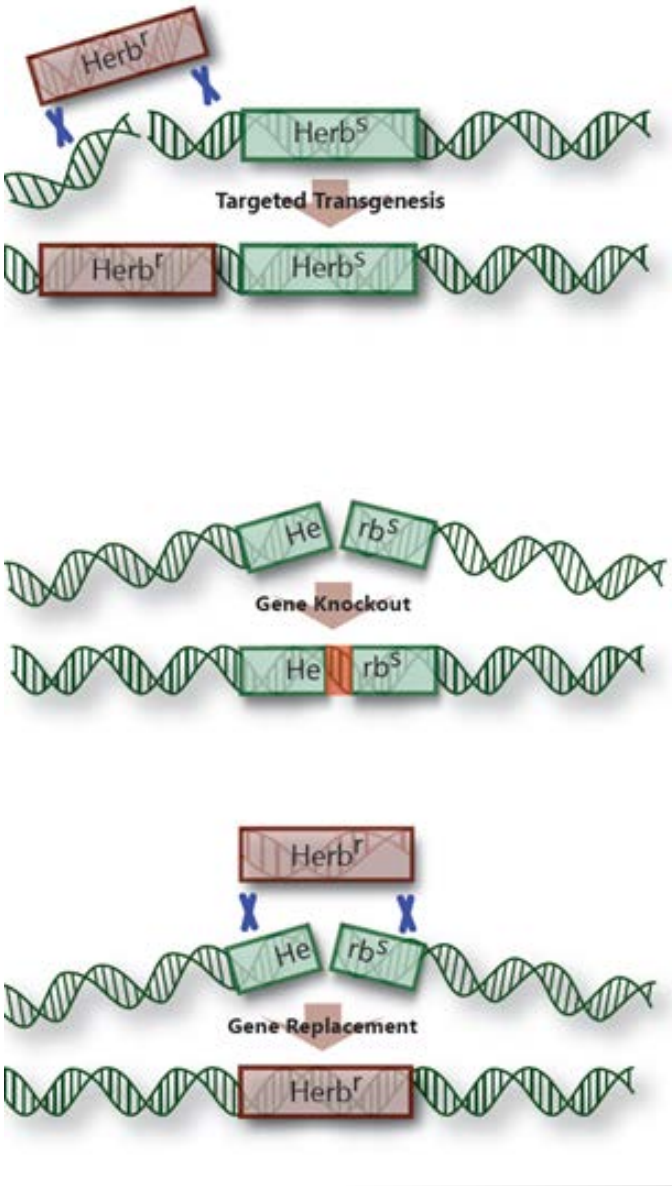




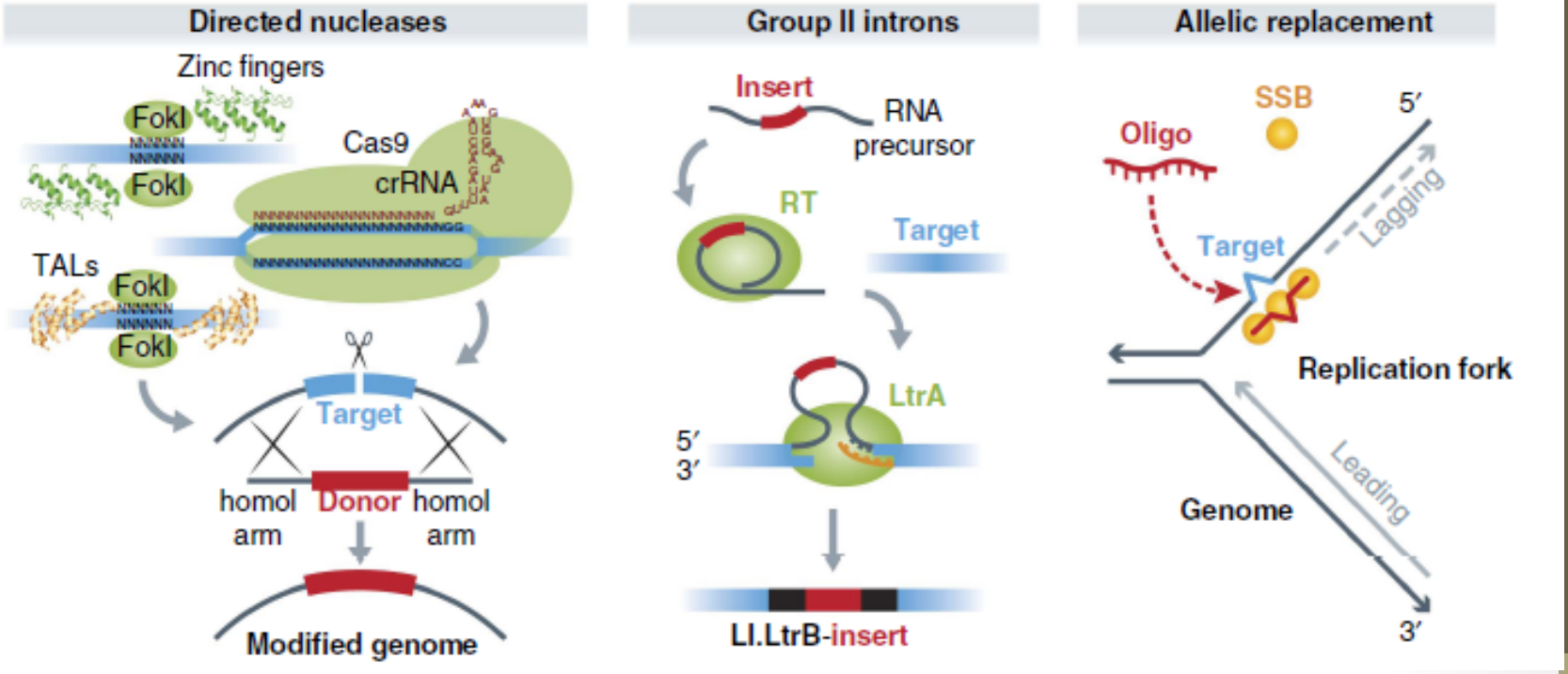
- What is the landscape of this change?
- What does this mean for governance?
- How do expert-stakeholders understand new targeted modification technologies and oversight?
- How do these understandings compare to last generation GM methods?

Targeted genetic modification

- Mutate genes, Swap gene sequences, insert foreign DNA, or delete genes
- Targeted sites in host DNA
  - Creates double-strand DNA breaks
  - Exploit cell's own repair mechanisms
- More stackable - can insert or delete multiple genes more quickly
  - For currently used traits & organisms
  - For new traits & organisms presently not feasible

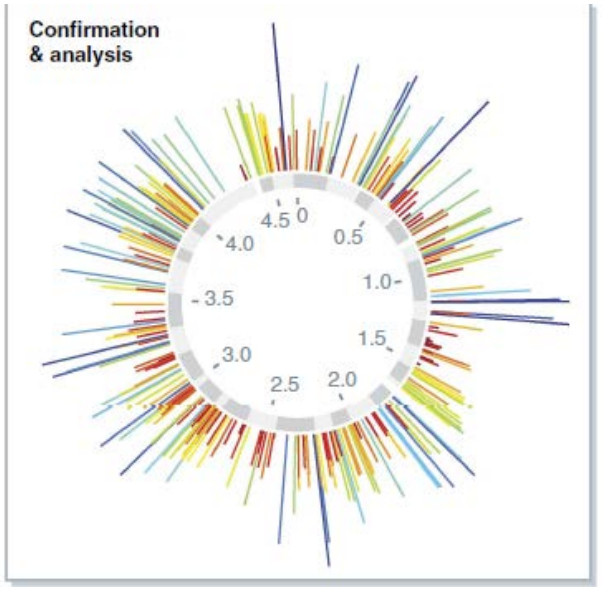


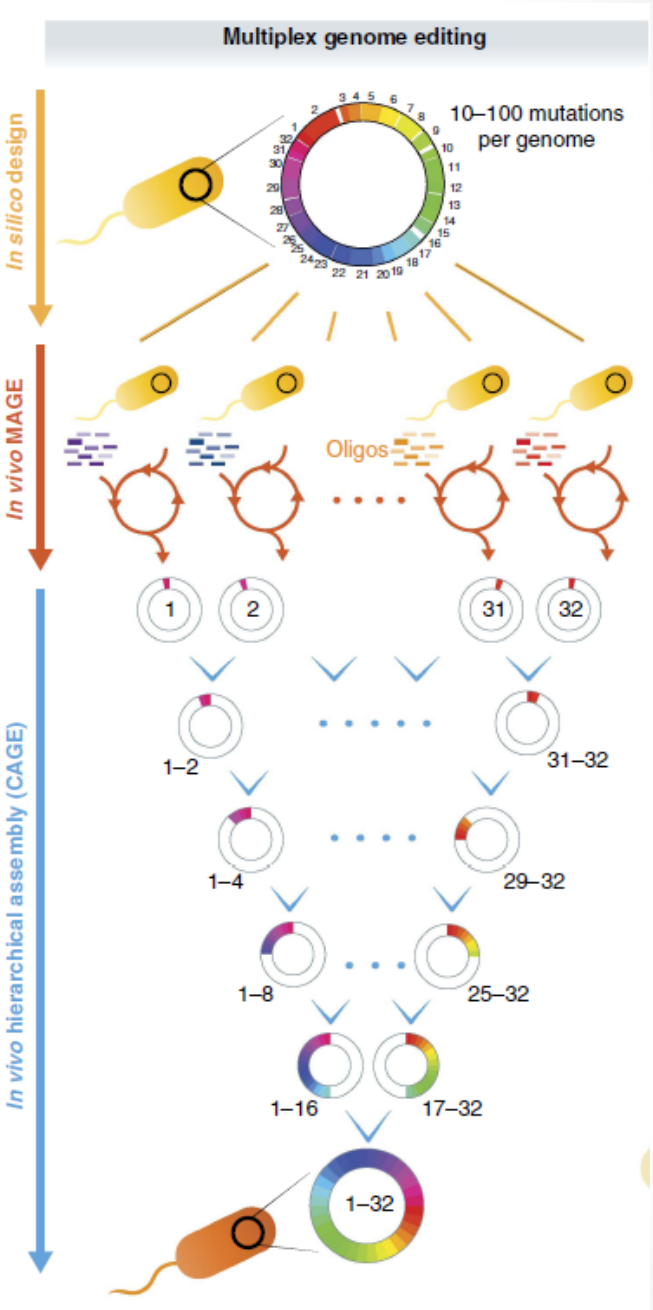
TagMo—genome editing



Multiplex Automated Genome Editing

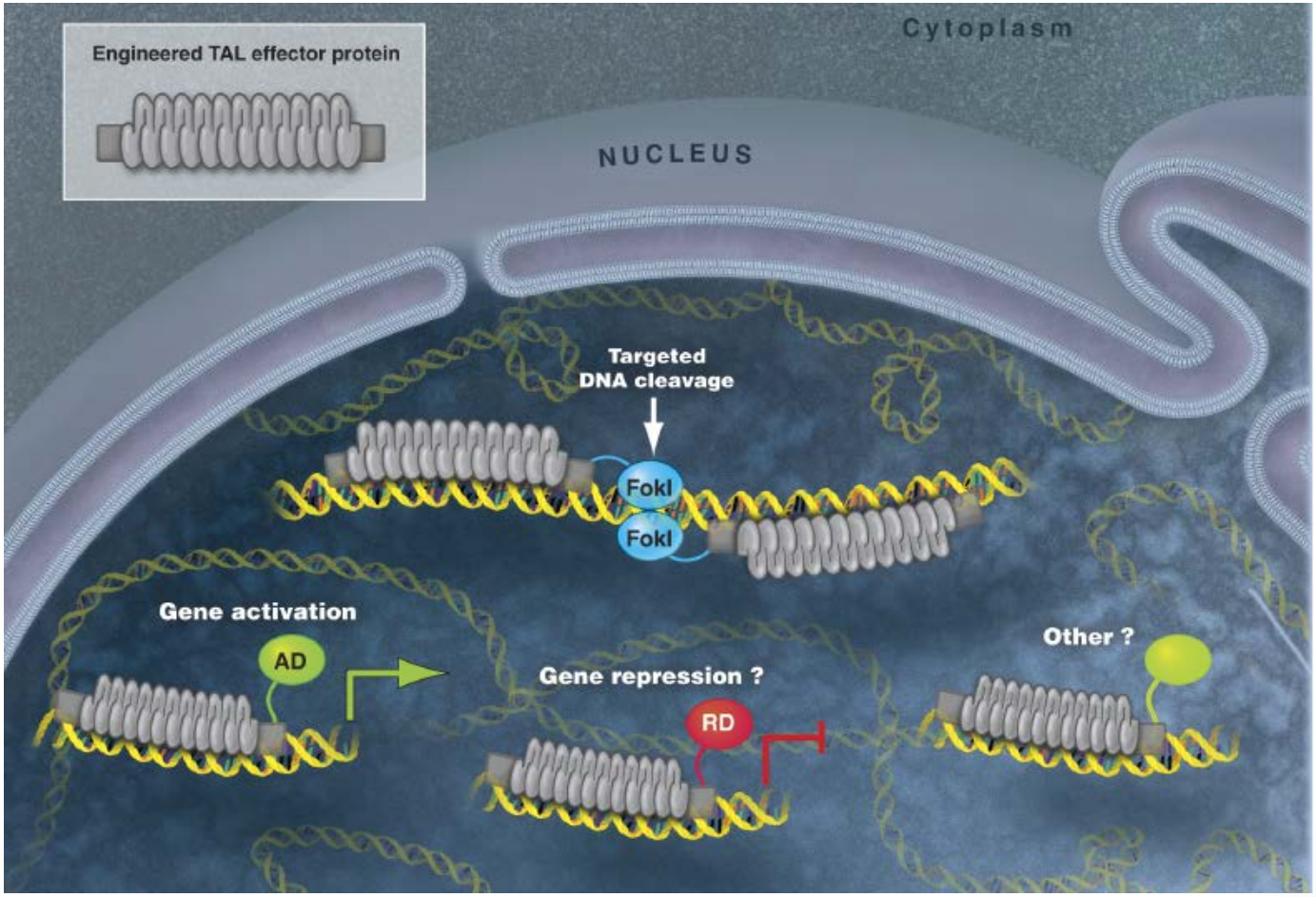
Esvelt & Wang 2013





TALEN--TagMo

Bogdanove & Voytas 2011



WHO OR WHAT IS INVOLVED IN GENOME EDITING?

Methodology

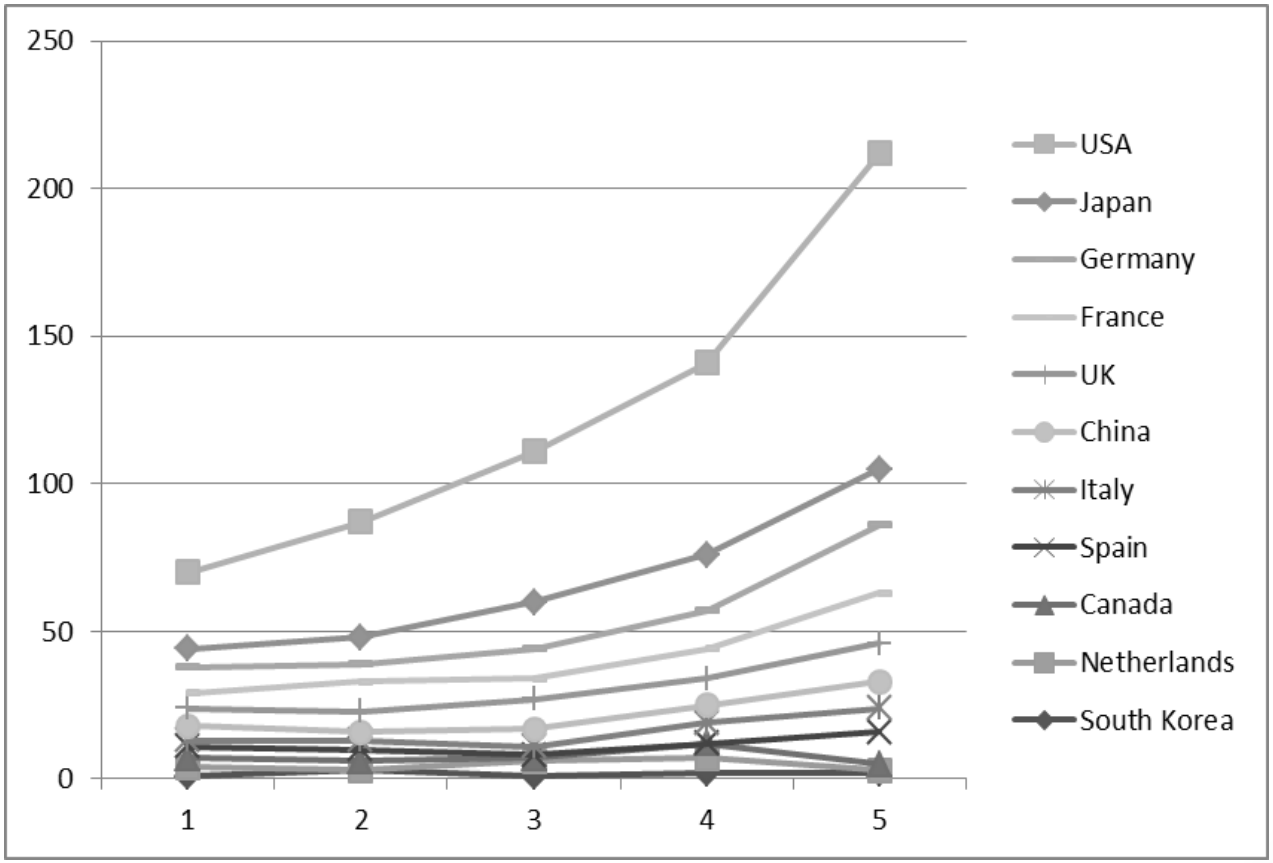
- Who and What?
- Networks of co-authorship as evidence of collaboration

- Bibliometric Studies with “Tech Mining” approach
  - E.g. Porter & Cunningham (2004)

- Developed keywords with experts from U of MN in iterative process
- Searched Web of Science
- Vantage Point analysis of actors, institutions, and co-authorship

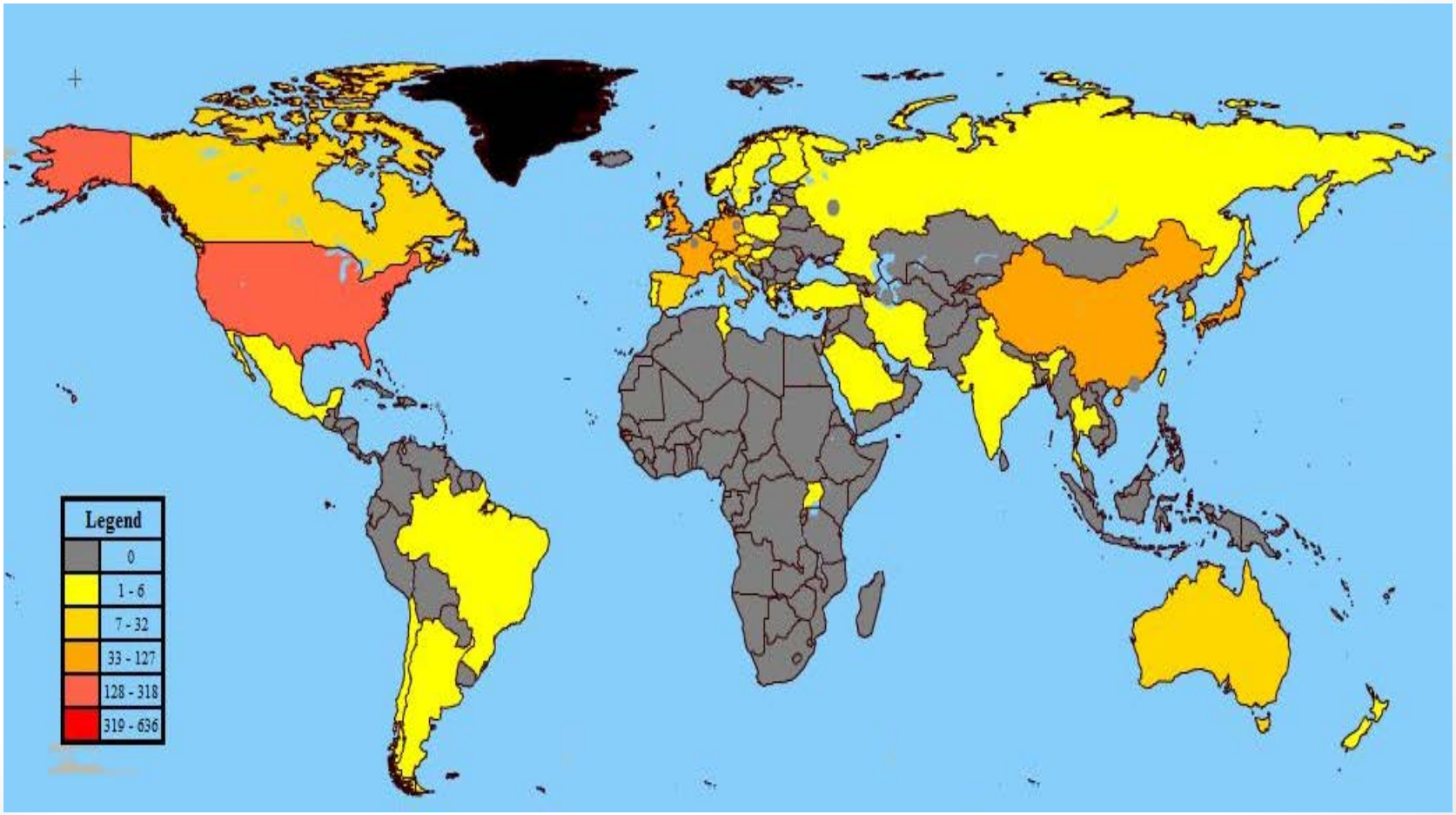
Genome editing in early exponential growth?

- Articles by year (07-12)

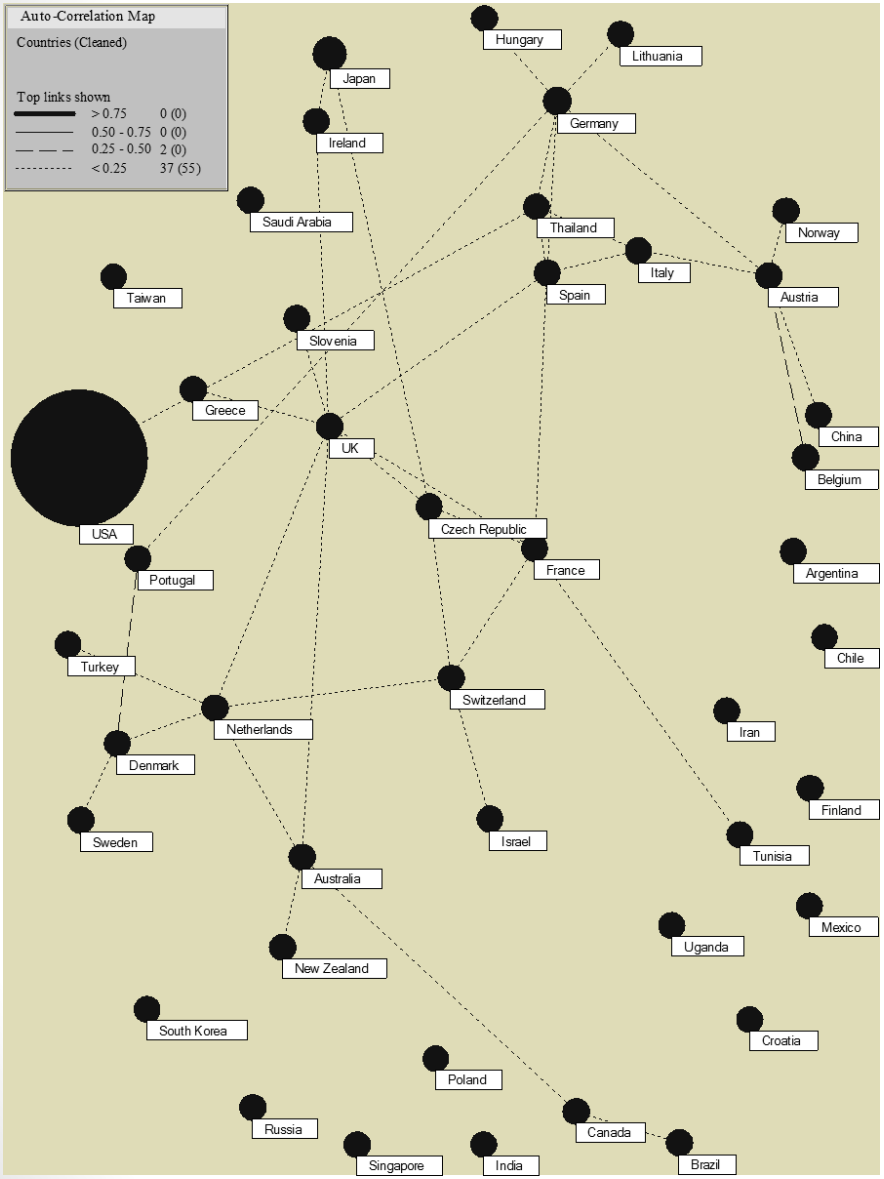


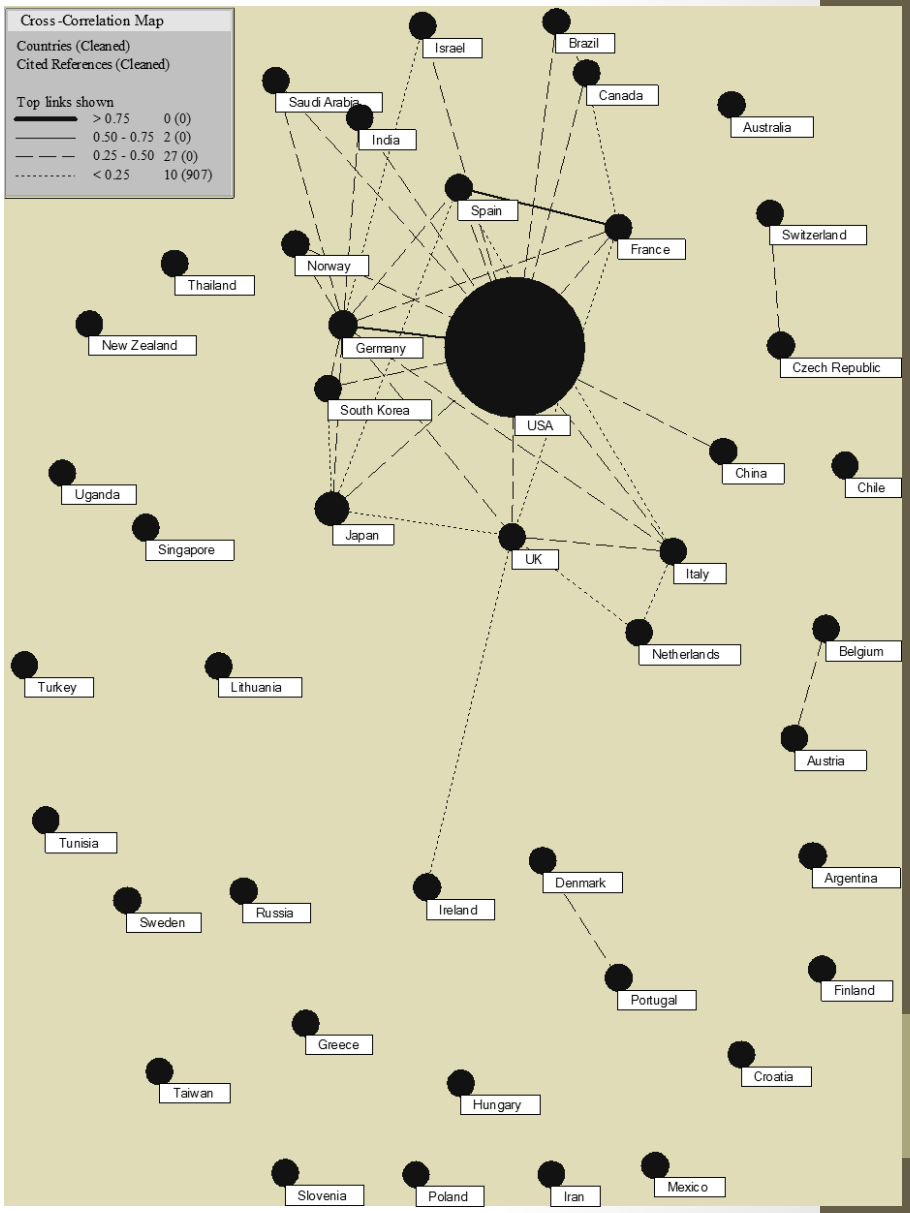
Geographic distribution of genome editing articles

- Kuzhabekova and Kuzma *(in review)*

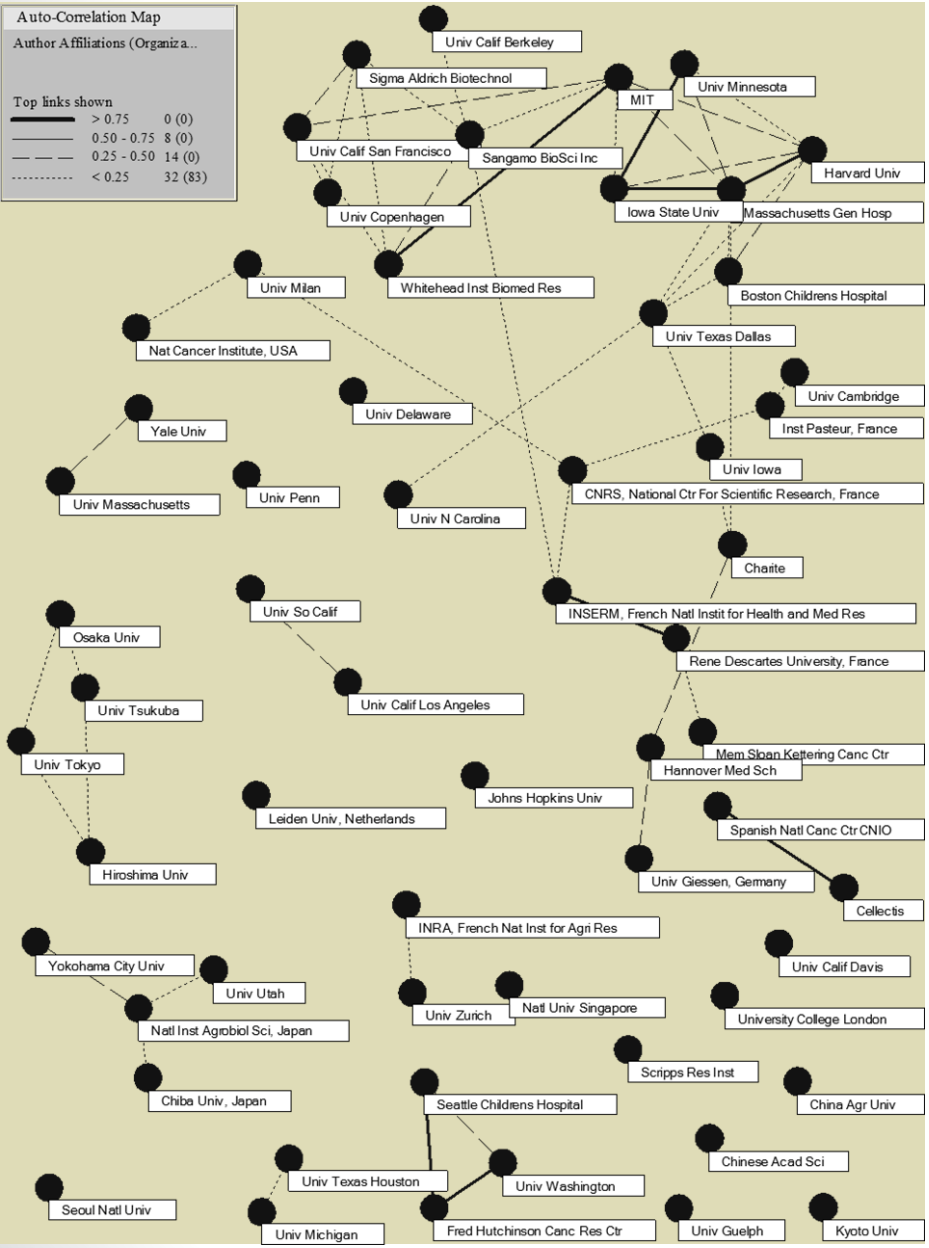


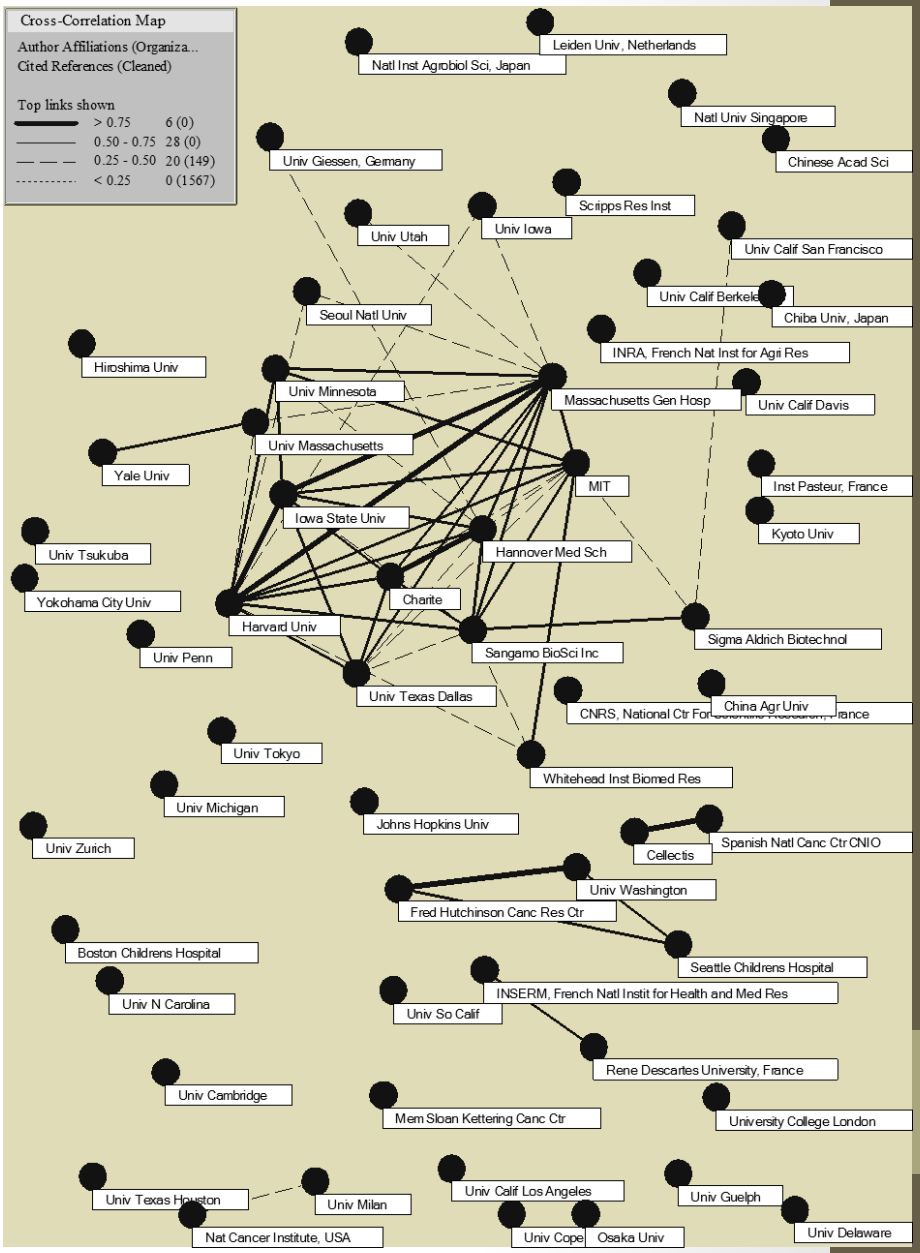
US dominance--Isolates in LDCs



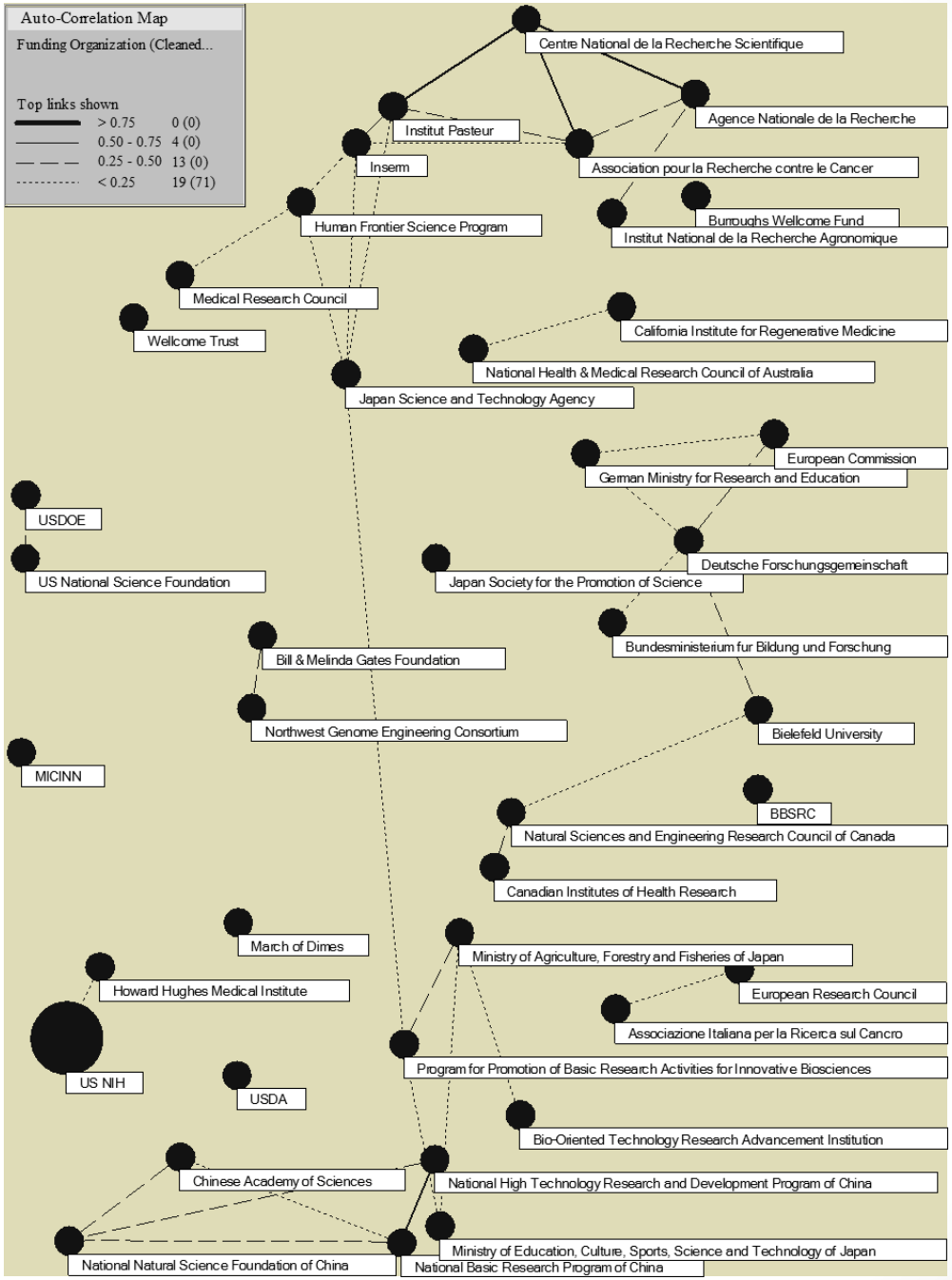


Institutional networks





Funding orgs Co-funding



Top first authors' affiliations

13 of 24 from Sangamo

18 of 24 from USA (3 from Harvard, 2 U Mass, 1 U of MN)

Number of records	Affiliation	Country
36	Sangamo BioSciences Inc.	USA
23	Sangamo BioSciences Inc.	USA
22	Sangamo BioSciences Inc.	USA
19	Sangamo BioSciences Inc.	USA
18	Sangamo BioSciences Inc.	USA
17	Harvard University	USA
16	Hannover Medical School	Germany
16	Sangamo BioSciences Inc.	USA
14	Cellectis	France
12	Harvard University	USA
12	Sangamo BioSciences Inc.	USA
10	Sangamo BioSciences Inc.	USA
9	Cellectis	France
9	University of Minnesota	USA
9	Sangamo BioSciences Inc.	USA
8	Sangamo BioSciences Inc.	USA
8	University of Massachusetts	USA
7	Yokohama City University	Japan
7	Sangamo BioSciences Inc.	USA
7	Cellectis	France
7	Sangamo BioSciences Inc.	USA
7	Harvard University	USA
7	Kyoto University	Japan
7	Sangamo BioSciences Inc.	USA

Monopolies?
closed vs. open source

2005

Table 1 Selected recent patents issued to Sangamo

Title	Patent number	Year of issue	Year of expiration
Regulation of endogenous gene expression in cells using zinc finger proteins	6,824,978	2004	2019
Iterative optimization in the design of binding proteins	6,794,136	2004	2020
Selection of sites for targeting by zinc finger proteins and methods of designing zinc finger proteins to bind to preselected sites	6,785,613	2004	2019
Functional genomics using zinc finger proteins	6,777,185	2004	2019
Nucleic acid binding proteins (zinc finger proteins design rules)	6,746,838	2004	2018
Screening system for zinc finger polypeptides for a desired binding ability	6,733,970	2004	2019
Regulation of endogenous gene expression in cells using zinc finger proteins	6,607,882	2003	2019
Functional genomics using zinc finger proteins	6,599,692	2003	2019
Methods of using randomized libraries of zinc finger proteins for the identification of gene function	6,503,717	2003	2020

2011

Table 1 Cost of designer nucleases

Source	Resource	Price	Time required
ZFNs			
Sigma (Sangamo)	Premade or custom ZFNs	$25,000 custom; $12,000 premade	2 months
Zinc Finger Consortium and Addgene	OPEN Protocols, reagents, including plasmids and bacterial strains	$5,000 for hundreds of Zfns	6 months–1 year
Zinc Finger Consortium	CoDA	Not available as a kit; $600–900 to assemble reagents for one Zfn	1 month
Addgene	Modular assembly	$650 for hundreds of Zfns (not all work)	2 months
TALENs[a]			
Cellectis	Premade or custom TALENs	$5,000 custom; $10,000 mammalian cell validation	1.5 months
Addgene	Golden Gate method cloning kit	$350 for full kit (one-time cost)	1 week

[a]Life Technologies is a licensed provider of TAL effectors. As *Nature Biotechnology* went to press, the company was not making them broadly available.

Source: Dave Segal, UC Davis

What is landscape?

- Concentrated –U.S. universities and a few companies
- Focusing on biomedical problems of DCs (money makers?)
- Few partnerships with LDCs
- Different foci in DCs and LDCs
- Little Collaboration among U.S. funders
- Will we repeat problems of agricultural biotechnology?

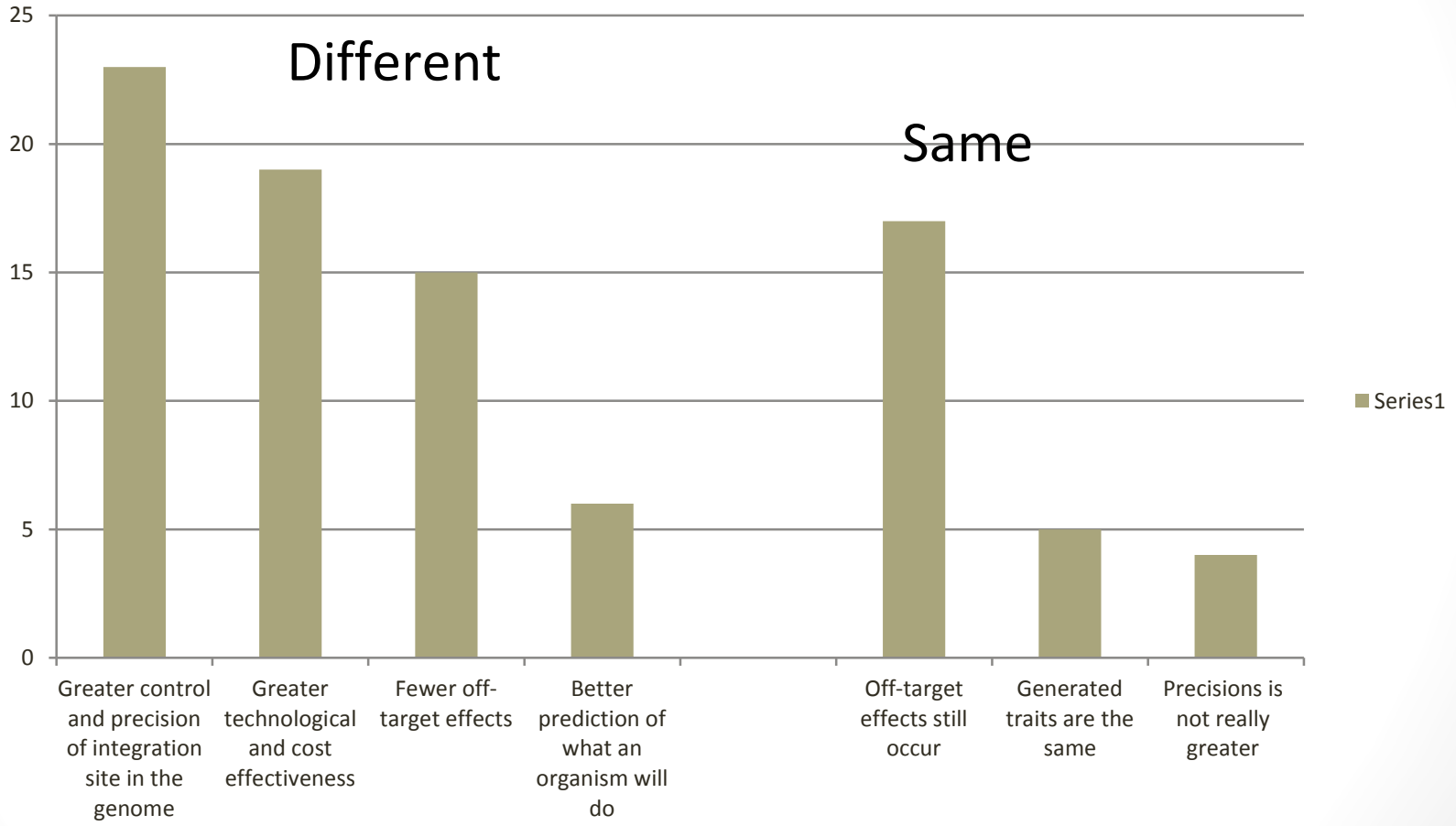
WHAT CHANGES DO TAGMO AND GENOME EDITING BRING FOR GOVERNANCE?

Governance studies

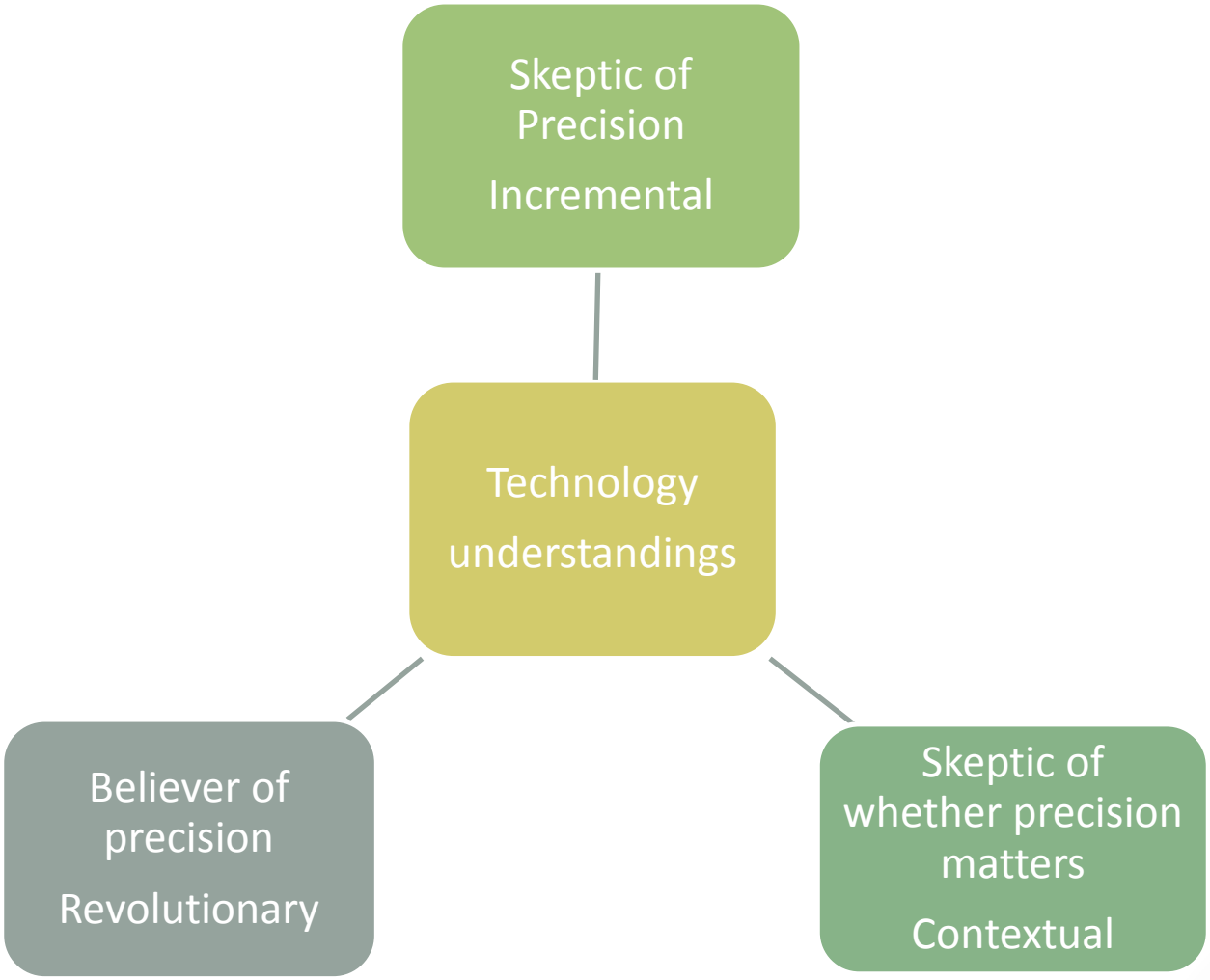
- Interviews
  - 31 qualitative, semi-structured, ~ 1 hour each
  - Oct 2010 to Feb 2011, TagMo and GMOs experts-stakeholders
  - Academe, Industry, NGOs, Government
  - Policy, Biology, Law, Philosophy, Social Science, Business, History
- Internet post surveys
  - 28, qualitative and quantitative
- Qualitative analysis, thematic coding & frequency, narratives
  - Atlas Ti
  - Nvivo
  - Two coders

QUESTION A: TO WHAT EXTENT IS TAGMO THE SAME OR DIFFERENT FROM TRADITIONAL GM IN THE MINDS OF EXPERT-STAKEHOLDERS?

TagMo technology: similar or different from 1st generation GMO technology?



Technology understandings



Technology as tool for reducing environmental risk

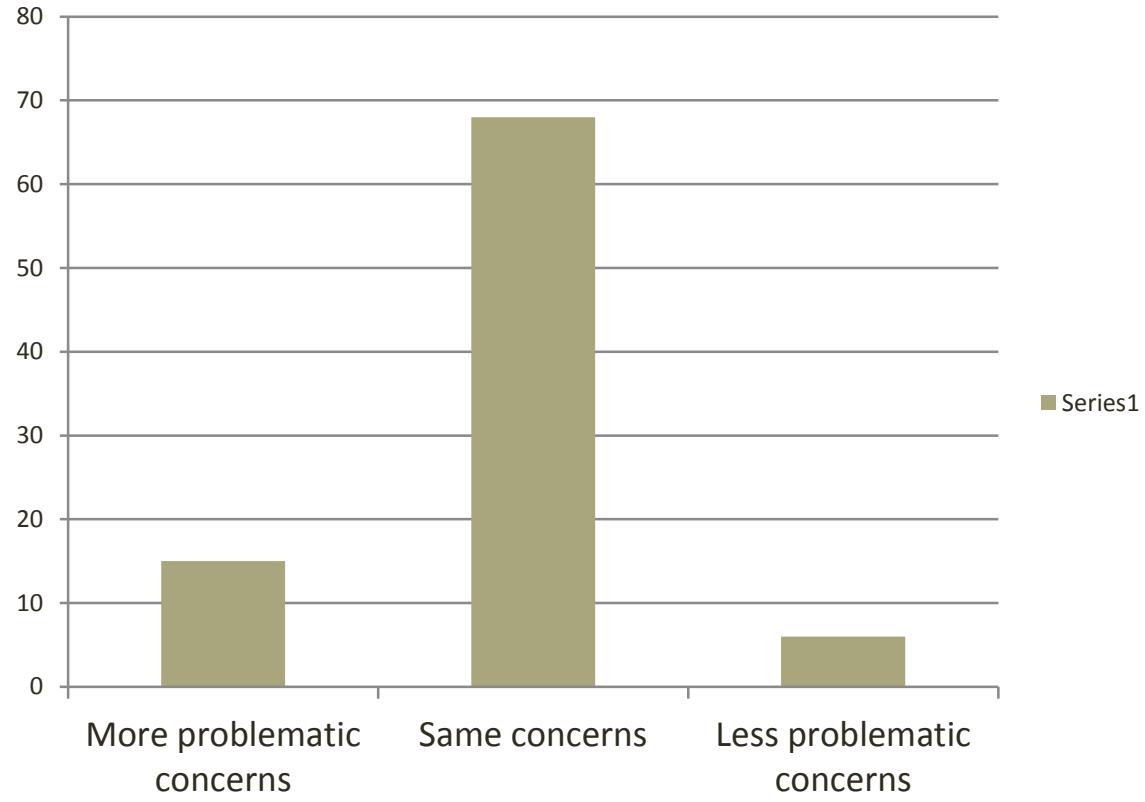
"By reducing some of the uncertainty associated with traditional recombinant DNA engineering, I think it helps to remove some of the concerns that have been raised about the potential risks of the technology by allowing us to be more comfortable with predictions about how the plant will in fact behave and perform in the environment."

"I think we're actually going to see some more positive impacts environmentally from targeted technologies largely because the targeted technologies are making it easier to control gene flow in the wild.

So, for example, by knocking out genes involved in pollination, that's something that's relatively easy to do with a nuclease…I mean the environmental impact of having a GM plant that can't produce pollen is pretty obvious."

QUESTION B: TO WHAT EXTENT DOES TAGMO AFFECT CONCERNS ABOUT GOVERNANCE IN CONTEXT OF TRADITIONAL GM?

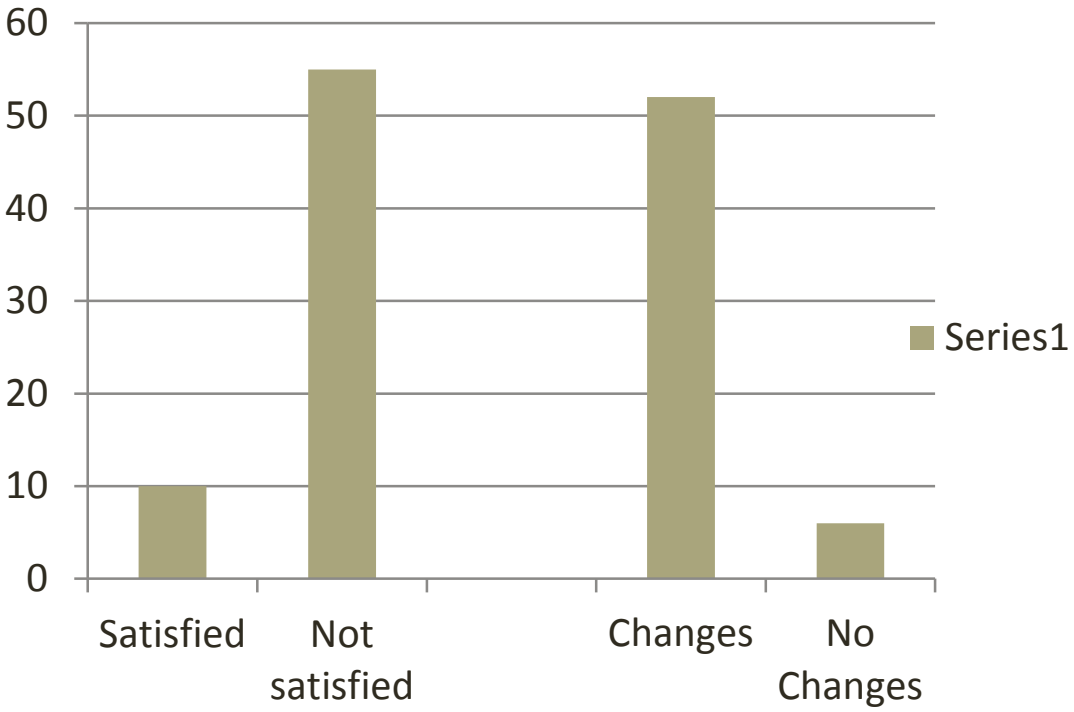
Concerns


80
70
60
50
40
30
20
10
0
More problematic concerns
Same concerns
Less problematic concerns
Series1

CONCERNS ABOUT OVERSIGHT	Number of references
More problematic concerns	
-communication and public understanding	5
-greater public distrust due to negative experiences with GM	3
-security issues may become more problematic	2
-ethical oversight	2
-fair distribution of benefits	1
-fascination with TagMo may overshadow safety concerns	1
Less problematic concerns	
-Animal welfare concerns	2
-environmental safety	2
-toxicity	2
Same concerns	
-international harmonization of regulation	17
-fair distribution of benefits	8
-public understanding and acceptance	8
-regulatory capacity building in developing countries	5
-maintaining crop variety	3
-ownership of germplasm banks	2
-IPR-related-impact on competition	9
-impact on public research	8
-impact on access in developing countries	4
-impact on research relevant to the needs of developing countries	4

QUESTION C: HOW WILL TAGMO AFFECT CURRENT OVERSIGHT?

Are you satisfied with current oversight in context of TagMo? Will TagMo challenge oversight?



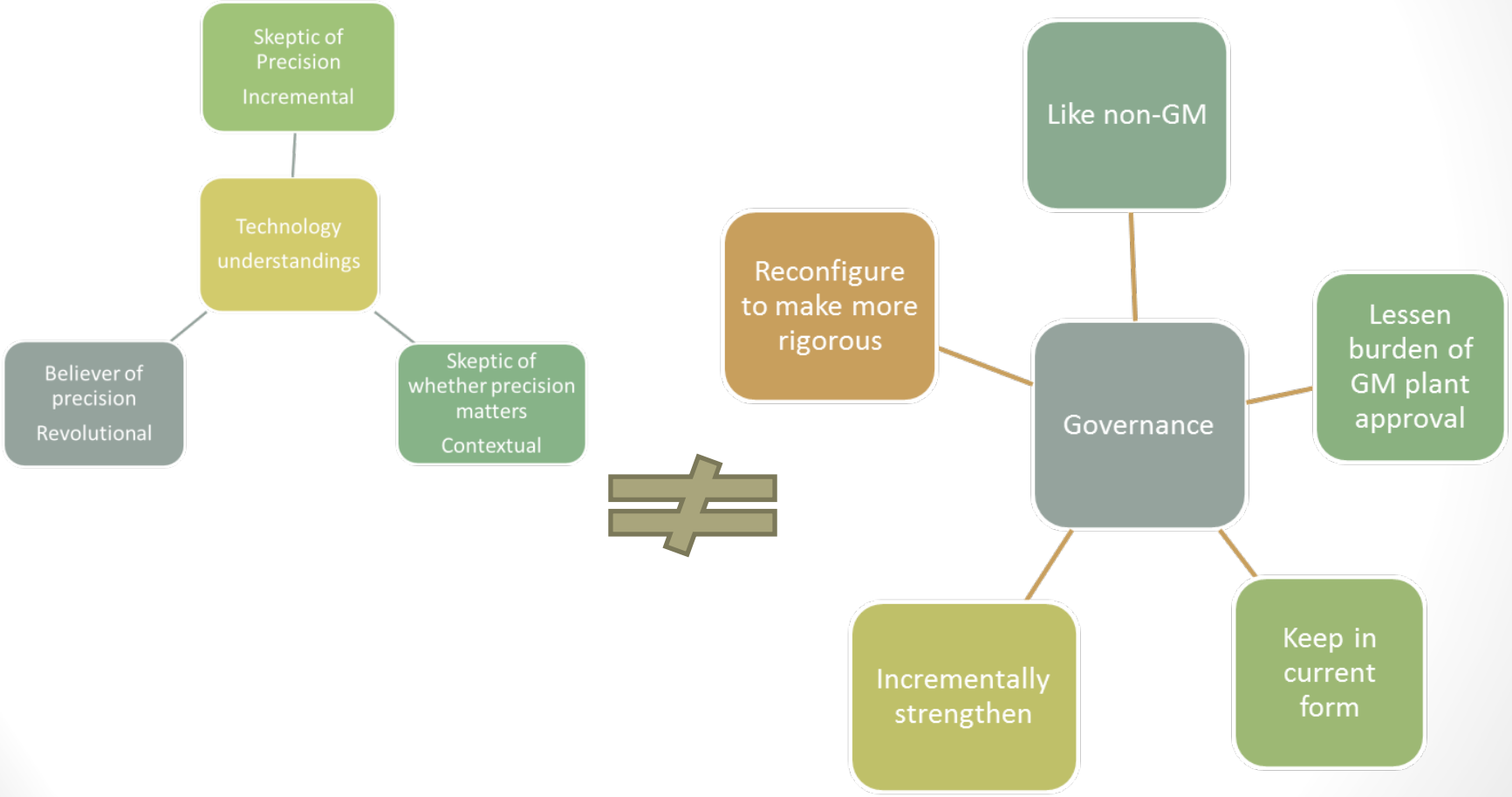
Problems with current oversight

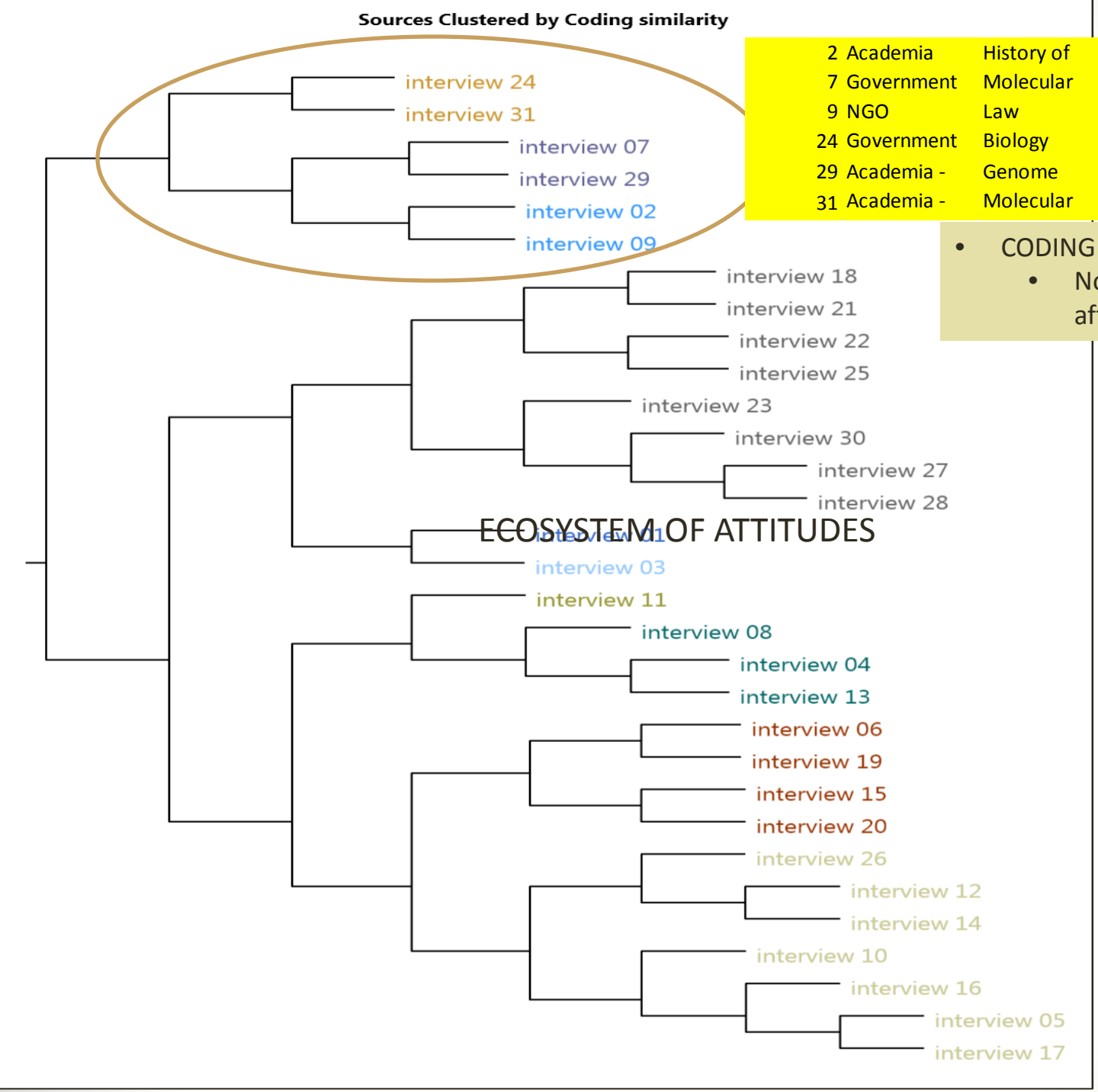
Opinions about current approach	Number of references	Number of quoting individuals
Not satisfied with current approach	55	47
-Confusing	8	7
-Piecemeal	7	5
-Unable to adequately address safety	6	5
-competition and conflict between agencies	5	5
-Holes in the system	5	5
-Favoring big companies	5	5
-Slow approval process	4	4
-Overall approach	4	4
-Lack of scientific rigor	4	4
-poor enforcement of compliance	3	3
-lack of transparency and public participation	2	2
-lack of postmarket monitoring	2	2

How will TagMo affect oversight

	Number of references
There will be changes	52
Greater speed of development, adoption, production may overwhelm the regulatory system	14
Faster approval process	11
Greater variability in traits and products may not be successfully handled by the oversight system	11
New definition of GM will be necessary	5
Greater access to technology will present issues for regulatorty regimes and their coordination	3
Will fail the old process approach	3
Regulators will start to encourage the technique	2
New ethical concerns	1
New scientific capacity will be required from regulators	1
Less testing will be necessary	1

Technology understandings do not map neatly onto governance policy preferences





ECOSYSTEM OF ATTITUDES

2	Academia	History of	Social studies of science
7	Government	Molecular	Risk assessment
9	NGO	Law	Biosafety
24	Government	Biology	Biology (Molecular Biology)
29	Academia -	Genome	Genome engineering
31	Academia -	Molecular	Molecular Biology

- CODING THEMES
  - Not a strong correlation with affiliation/expertise/degree

Narratives of governance change

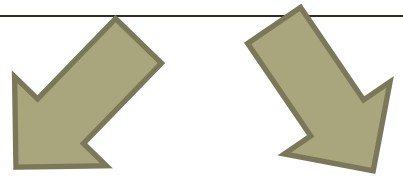
TagMo is an Incremental Technology --

- Maybe TagMo doesn't change technology concerns dramatically
- It doesn't FORCE a governance change, but gives us OPPORTUNITY to re-examine and change governance.

Opportunist

TagMo is Revolutionary Technology

- TagMo is a dramatically different technology that forces a change in governance: How?



Relaxes need for oversight

Hype-Hypo

Intensifies need for oversight

Systems context

Revolutionary—systems view

- "As we're able to…have more and more powerful techniques to modify these plants, we will be able to modify these plants more and more from their standard configurations. Especially with gene addition, we can completely rewire a number of these plants… The one concern I have is that if we're creating plants before we really know what the sorts of products are."
    - *- TagMo researcher*

However….

Genetic engineering

GM or not GM? That's the question

Cath O'Driscoll

A $10m funding boost from the Bill & Melinda Gates Foundation announced in July 2012 will help scientists at the UK's John Innes Centre in Norwich to transfer the valuable nitrogen fixing ability of peas and other legumes to cereal staples, so freeing them from the need for costly fertiliser inputs. But controversial GM technologies such as this may one day be superseded by novel gene editing approaches that achieve similar results without the need to introduce foreign DNA, researchers say.

And, depending on legislation now being hammered out by regulators, the resulting products may not be classed as

a genetics expert at the Sainsbury Laboratory and co-inventor of the newest of the gene editing technologies called TAL effector nucleases. 'Gene editing technologies can only modify something that's already there but can't add something new, and so are limited by the organism's genome.'

Many of the necessary genes to carry out the same transformations already lie dormant or repressed in plant or animal genomes as they have become redundant over the course of evolution, Schornack explains. Gene editing technologies are a way of activating or restoring those latent functionalities.

Technologies such as zinc finger nucleases, meganucleases and TAL effector nucleases work by binding to specific DNA sequences and cutting or nicking them ready for subsequent editing or removal. They are much more precise or targeted than conventional

to develop products faster, better and more affordable. The big question is whether or how they will be regulated.' A recent study by McDougall suggests that it now takes 13.1 years and $136m on average to bring a biotech crop to market, Rudgers pointed out (see page 36). However, 37% of the time taken and 26.1% of the cost is concerned with the regulatory process.

In Europe, the jury is still out on whether gene editing technologies should be considered as GM, Rudgers said – although in December 2011, the German Central Commission for Biological Safety (ZKBS) issued a position statement backing non-GM status. In the US, the US Department of Agriculture (USDA) does not regulate on GM status but rather on whether the product is a 'plant pest', with gene edited products to be viewed on a case by case basis.

Speaking at the recent BIO meeting in Boston, US, Dow AgroSciences' Gary Rudgers commented: 'We already know that these new technologies can help us to develop products faster, better and more affordable. The big question is whether or how they will be regulated.'

Classifying products as GMO simply based on the technique used would subject these technologies and products to the same costly and lengthy regulatory hurdles as seen with transgenic approaches. As a result, the classification would unjustifiably stigmatise the technology; inhibit innovation; limit use of these applications to high-value crops; and delay, or even inhibit, uptake of the technology. With the urgency for solutions to

Hype-hypo-regulation

Comparison of impacts	Number of references
More positive social impacts	61
-greater public acceptance of the technology	11
-lower cost and greater efficiency of production	7
-new solutions to hunger problem	6
-increased food safety	5
-greater variability in traits	4
-more opportunity for research in developing world	3
-greater energy independence	2
-less concentration of R&D in large companies	2
-animal welfare issue will be less of a concern	1

But no different from conventional plants from regulatory perspective

Complex attitude toward technology & governance

- All you've done is taken a few bases out, **which fundamentally changed the physiology**, but there's no clear regulatory pathway by which that plant would or would not be considered genetically modified. So I think we'll probably see **significantly streamlined approval processes**. And actually, **one thing that we're hoping for as a business is that the regulatory hurdles will actually be raised for GM plants that are not made using technologies like ours**."

Broader governance narratives for TagMo

- A public deficit of knowledge will lead society to view this technology as similar to first generation GM plants, thereby not understanding the true potential of plant TagMo and hampering its potential development
- Intellectual property rights considerations and licensing agreements will lead researchers to not share their scientific findings, thereby hampering the advancement of the plant TagMo science
- Oversight systems that are too burdensome will stifle the development and use of plant TagMo
- Commercial interests will lead to only profitable traits being pursued with plant TagMo, hampering the potential of plant TagMo to impact the societal good
- Plant TagMo will further entrench the biotechnology paradigm of plant science, to the detriment of agricultural system health

POINTS OF AGREEMENT—POST SURVEY

- *Against voluntary, self-regulation (20 out of 27)*

9. The field of plant targeted genetic modification should be self regulated and subject to voluntary oversight.

		Response Percent	Response Count
Strongly disagree		25.9%	7
Disagree		**48.1%**	**13**
Neutral		22.2%	6
Agree		3.7%	1
Strongly agree		0.0%	0
		answered question	**27**

- *TagMo should be overseen prior to market release*
- *(25 of 27)*

21. At what point should regulatory action, including safety studies, take place?

	Response Percent	Response Count
During the development and before the application for product release	**55.6%**	**15**
As a part of the application for product release	37.0%	10
After release of the product	3.7%	1
No regulatory action should take place	3.7%	1
	answered question	**27**

Important of inclusion

13. It is important to include stakeholders in the decision making and regulatory process surrounding targeted genetic modification.

		Response Percent	Response Count
Strongly disagree		0.0%	0
Disagree		3.7%	1
Neutral		14.8%	4
Agree		**63.0%**	**17**
Strongly agree		18.5%	5
		answered question	**27**

FOIA request response—Oligonucleotide-mediated Mutagenesis—no authority ZFN deletion for low phytase corn--not a plant pest

USDA

United States Department of Agriculture

Animal and Plant Health Inspection Service

Marketing & Regulatory Programs Business Services

4700 River Road
Riverdale, MD
20737

March 25, 2004

(b)(6)
Cibus Genetics, LLC
14 Chesapeake Landing
Annapolis, MD 21403

Dear (b)(6)

APHIS BRS has determined that under our current regulations, the agency has no authority to regulate products created by mutagenesis techniques such as Genoplasty. Therefore it is not necessary under current USDA-APHIS regulations to file a notification to conduct a field trial for a product created by this technology

Sincerely,

Neil E. Hoffman
Director, Regulatory Programs
Biotechnology Regulatory Services

USDA

May 26, 2010

(b)(6)
Global Regulatory Leader - New Ventures
Dow AgroScience LLC
9330 Zionsville Road
Indianapolis, IN 46268

Re: APHIS review as to whether *Zea mays* plants with the IPK1 gene deleted u
nuclease technology is regulated by APHIS.

Dear (b)(6)

As described by Dow during the March 18, 2010 presentation, no plant pest was used to create the ZFN-12 maize plants, which contain deletions at the IPK1 gene. There is no reason to believe that *Zea mays* containing an IPK1 deletion is a plant pest or is likely to pose a plant pest risk. Therefore, the ZFN-12 maize plants with induced deletions due to the use of zinc finger nuclease technology are not considered regulated articles.

What have we learned for genome editing governance?

- What have we learned from two decades of GMO governance?
- What have we learned from STS and STP scholars?

  - upstream dialogue and oversight assessment?
  - post normal science and need for diverse participation?
  - conflicting messages of “powerful, fast technology” and “less regulation/lower risk concerns”?
  - reactions/distrust of control on technology?
  - focus on Western (Northern) problems?
  - international collaboration?
  - interagency cooperation?

Responsible Research & Innovation

- *Von Schomberg (forthcoming 2013). "A vision of responsible innovation". In: R. Owen, M. Heintz and J Bessant (eds.) Responsible Innovation. London: John Wiley.*

- "I categorise here four types of irresponsible innovation: Technology push, Neglectance of fundamental ethical principles, Policy Pull, and Lack of precautionary measures and technology foresight."

- *"Responsible Research and Innovation is a transparent, interactive process by which societal actors and innovators become mutually responsive to each other with a view to the (ethical) acceptability, sustainability and societal desirability of the innovation process and its marketable products(in order to allow a proper embedding of scientific and technological advances in our society)."*

Acknowledgments

- NSF Award NSF DBI 0923827 2009-2013
- Precise Engineering of Plant Genomes using Zinc Finger Nucleases Societal implications

  Voytas, Dobbs, Kuzma, Wang

Adam Kokotovich, Ph.D. student

Aliya Kuzhabekova, Post-doc

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