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Team-Based Learning and Threshold Concepts in Biological Security and Dual-Use: Toward a Transformative Biological Security Pedagogy—The Game Changing Implications of CRISPR/Cas and the Design of a Novel Methodology for Influencing the Culture of Life and Associated Science through Awareness Raising and Education

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Abstract

CRISPR (clustered regularly interspaced short palindromic repeats) gene editing technologies appear to be a game-changer and suggest great potential for genome manipulation and for developments in next-generation therapeutics. Ethical, legal and social concerns have been raised in light of recent applications in humans. Concern also arises in relation to the potential of such developments for misuse. In addressing the post-COVID19 challenges raised by responsible research innovation and in confronting what to do about the vexed question of "dual-use", we contend that awareness-raising and education concerning the ethical, legal and social implications of scientific research innovation represents a welcome and empowering alternative to top down regulatory responses that may serve to stifle innovation. The design and subsequent implementation of a novel transformative pedagogy combining Team-Based Learning and Threshold Concepts yields both empirical evidence-based metrics for real-time learning. As well as generating novel empirical data-sets for the identification of subject-specific threshold concepts across discrete specialisms in the life sciences, we argue that this hybrid methodology can be used to engage science professionals and students alike in meaningful and much-needed dialogue about developments relating to genome manipulation. We demonstrate how evidence-based threshold concepts can inform the design of bespoke subject-specific training as we suggest was the case from our deployment of team-based learning and threshold concepts during our proof of concept application, prior to the pandemic, during the course of two European Union Human Brain Project training programmes undertaken in 2017 and 2018, with experts in neuroscience research at the Karonlinska Institutet, Stockholm, Sweden.

Keywords

CRISPR, Gene Editing, Ethical, Legal, Social, Responsible Research Innovation, Dual-Use, Pedagogy, Neuroscience, Team-Based Learning, Threshold Concepts

1. Introduction

Overview and Argument

Against a backdrop of condemnation (Normile, 2018) in December 2018 that followed the announcement by a Chinese scientist that gene-editing technologies have been used to manipulate the human germ-line, this paper advances a novel methodology for a transformative Biological Security and Dual-Use Pedagogy and, consistent with security concerns around the potential that benignly-intended innovation might be misused, it outlines advanced practice in teaching and training on the ethical, legal and social implications of innovation in life and associated science research. It does so via an original epistemologically-informed constructivist analysis for harvesting original empirical data-sets from the identification of "threshold" concepts in biological security and dual-use. It is the contention of the authors that this suggests an approach to teaching and learning that is methodologically novel and innovative, as well as theoretically, and pedagogically informed. The approach is concerned with a pedagogy that is student-centred, as well as evidence-based. We argue that our approach 1) Facilitates the production of learning-outcome-related metrics that generate original empirical evidence of improvements in knowledge and understanding of biological security and dual-use in learners in real-time. 2) That this approach represents a methodology for identification of threshold concepts in biological security and dual use. 3) That threshold concepts identified make a significant and original contribution to research on pedagogy in this area. 4) That the methodology is replicable and can be used by others.

Overall, we argue that the approach successfully takes questions of security beyond the confines of the laboratory into the wider areas of "biological security" and "dual-use" where learners develop a critical appreciation of how improvements to professional development and practice might be understood as strengthening ethical, legal and social aspects of life and associated science research. Moreover, we consider if this approach might allow for an understanding of how change might be brought about concerning a culture in life science that has been shown by Dando & Rappert (2005) to overlook this important area of social responsibility. We further ask if this approach might help in understanding the mitigation of the potential for misuse of benignly-intended research in the wider fields of science, technology and engineering.

Overall the paper adopts the following approach. The next section, section two relates germ-line research and practical application in China to the story of gene-editing technologies, notably, the discovery by Doudna and colleagues (Doudna & Sternberg, 2017), of a technique that would become known as CRISPR/Cas9. the discussion locates questions of biological security and dual-use in terms of significance and context with this section highlighting concerns and dilemmas relating to contemporary scientific and technological developments in gene editing.

In the third section definitional issues are addressed regarding the concepts of "biological security" and "dual-use". We identify where calls for awareness and education came from in the field of biological security.

In the fourth section we outline the contours of a transformative biological security and dual use pedagogy. This is underpinned by the design of a novel methodology that incorporates threshold concepts into Team-Based Learning. Addressed in this section are a range of methodological considerations used including: the anti-positivistic, socially constructed context in which transformative learning is conceived of, and takes place, the theory and practice of Team-Based Learning, as well as the notion of so-called "Threshold" Concepts.

In the fifth section we demonstrate the application of this methodology to, and results that arose from, two team-based learning sessions conducted with neuroscience professionals under the auspices of the EU Human Brain Project, both conducted at the Karolinska Instisutet, Stockholm, first in July 2017, and then second in November 2018.

In the sixth section an interpretive methodology for analysis of qualitative data by way of a discourse analysis was utilised for this part of the methodology where we present discussion and conclusions relating to threshold concepts and empirical evidence.

2. CRISPR/Cas

At an international conference in late November 2018 the Chinese scientist He Jiankui announced that he had made hereditable modifications to human beings using CRISPR/Cas technology. The Chinese scientist maintained that he was proud of his benignly-intended work, but fellow scientists criticised him for what was widely seen as unethical conduct and of bringing the scientific community into disrepute (Sataline & Sample, 2018). We agree with both of these criticisms but think that civil society could reasonably ask whether the scientific community could have done more to prevent the unethical conduct in the first place. We think that at least it could have taken effective measures to ensure that the dangers of such misuse were widely understood within the scientific community and therefore have provided reassurance to civil society that it had taken measures to avoid such dangerous research. We illustrate our argument here in regard to the vexed question of "dual use" whereby the dangerous possibility exists that others could deliberately take the results of benignly-intended CRISPR/Cas research and use it for hostile purposes.

In her 2017 book titled *A Crack in Creation: The New Power to Control Evolution* Professor Jennifer Doudna, one of the people who discovered CRISPR/Cas genome editing, gives a 246-page essentially chronological account of her experience over the last few years following the discovery of this revolutionary technology. On page 90 she reports being on a plane in 2013 thinking that "the genome would become as malleable as a piece of literary prose at the mercy of an editor's pen" and that "I could hardly believe how quickly things had evolved." By page 111 she expresses her exhilaration as "just a few dozen scientists at first, then hundreds, then even thousands…adopted CRISPR tools." This is not at all surprising when the power and simplicity of this novel technology is understood.

Yet, by page 139 she registers her unease as the technology was applied to genes implicated in neural disorders in monkeys, and by page 197, as she contemplates possible hereditable changes being made to human genomes she notes that "I wasn't used to asking myself these sorts of questions in my day-to-day life as a professor and biochemical researcher." And she goes on to describe her efforts to engage others in helping to decide what might best be done to regulate CRISPR/Cas technology in civil society. However, it is only on page 217 of the book that Professor Doudna comes to describe her encounter with the *game changing dual-use implications* of CRISPR/Cas technology. As she puts it:

> "American spy agencies seemed rattled by the experiments too. I was shocked when the next Worldwide Threat Assessment… described genome editing as one of the six weapons of mass destruction and proliferation that nation states might try to develop, at great risk to America."

She then quotes the assessment as stating that: "Biological and chemical materials and technologies, almost always dual use, move easily in the globalized economy," and defines dual use as "a term of art for technologies that can be used for both peace and war". Again, none of this is very surprising as State Parties to the Biological and Toxin Weapons Convention (BTWC) have worried about the possibility of genetic manipulation of biological weapons agents for decades and indeed had decided in 2017 to pay specific attention to current advances in genome editing at their meetings in 2018. Moreover, it has been obvious, at least since the early 2000s, that many practicing scientists in relevant fields of civil science have little knowledge of the possibility of dual-use of their benignly-intended research (Dando & Rappert, 2005) despite many calls for their awareness to be increased

(IAP, 2016). Crucially however, there has been little research on the structure of the thinking of these scientists and of how their awareness might best be changed so that they appreciate the dangers of dual use and what they might be able to contribute to in reducing these dangers.

Professor Doudna suggests that, even early on, her mounting concerns about the societal impacts of her discovery were causing her subconscious to "offer up answers in the form of nightmares." On page 199 she describes one such nightmare in which a colleague asks her if she will teach someone how the technology works and the person who wants to understand the uses and implications of the amazing technology turns out to be Adolf Hitler. This must have been a particularly unpleasant experience for a scientist who had the sole intention of producing research that would benefit society.

As we can certainly expect, many more amazing discoveries in the life and associated sciences in coming decades (Nixdorff et al., 2018), it raises the question of whether there is a more efficient and effective way to raise the awareness of biological security and of dual use and to promote effective engagement amongst the scientific community so that others may not be subject to similar experiences and society can be more prepared for dealing with these issues because scientists are engaged from early on in debates about how important new technologies can best be anticipated and if necessary even regulated.

3. Definitions: Biological Security and Dual-Use

3.1. Biological Security

Table 1. Definition of biological security.

Biosecurity and Biosafety (and Biorisk Management) make vital contributions to a wider concept of "biological security" that is made up of a web of integrated and complementary elements that reinforce each other… [This] refers to a "web of prevention" that locates biosafety and biosecurity in the context of a range of "biological security" measures that go beyond the laboratory door and include: *international and national prohibitions, disease detection and prevention, effective threat preparedness, export controls, oversight of life science activities, and bio[logical]security education and codes on conduct*, the latter ensuring that all those engaged in the life sciences whether in government, industry or academia are aware of their responsibilities to protect their work from misuse to counter the threats to humans, animals, and plants posed by states, non-state actors or other entities.

Graham Pearson (Pearson, 1993) refers to a "web of prevention" that locates laboratory biosafety, biosecurity and biorisk management in the context of a range of biological security measures that take our appreciation of biological security beyond the laboratory door. This range of measures include: international and national prohibitions, disease detection and prevention, effective threat preparedness, export controls, oversight of life science activities, codes of conduct, ethics and practice, as well as "biological security" education and awareness raising, the latter ensuring that all those engaged in the life sciences whether in government, industry or academia are aware of their responsibilities to protect their work from misuse to counter the threats to humans, animals, and plants posed by states, non-state actors or other entities (**Table 1**).

The awareness and education disconnect identified above is also a characteristic of discussions concerning the notion of dual-use, and controversy surrounding scientific and technological innovations made in the early years of this century has seen a flurry of activity prompting high level reviews (mainly in the US) and discussion and debate across a range of popular media outlets.

3.2. Dual-Use

Early definitions of dual-use were offered by the US Office of Technology Assessment and subsequent to that by the US National Research Councils and later the National Science Advisory Board for Biosecurity (NSABB) (Forge, 2013). Focus was initially on research in the physical sciences and engineering and related to security concerns about scientific research that had both civil as well as military applications. Publication in the open scientific literature of what became biological security "paradigm cases" saw attention widen to include so-called experiments of dual use concern, namely Mouse-Pox (Jackson et al., 2001) experiment Spanish Influenza (H1N1) virus (CDC, 2019) and Polio Virus (Cello & Wimmer, 2002). Recent attention has focused on so-called "gain of function" (Selgelid, 2016) experiments with attention switching in December 2018 to address the problem of gene editing. A burgeoning literature thus began to emerge with academic and policy activity taking place across a range of academic sub-disciplines. For the purpose of this discussion, "dual use" is defined as "research results that have both civilian and military applications" (National Research Council, 2004).

3.3. Where Have Calls for Awareness and Education Come From?

Institutional calls for improvements in awareness raising and education have arisen from negotiations to strengthen the 1975 Biological Weapons Conventions. The Biological Weapons Convention prohibits on an entire class of weapons. Review Conferences taking place every five years subsequent to entry into force of the Convention facilitate the Article by Article review of implementation of the Convention and under Article IV States Parties review the implementation of "necessary measures" to "…prohibit and prevent the development, production, stockpiling, acquisition, or retention of biological weapons". Subsequent to the Second, Third, and Fourth Review Conferences, States Parties noted the importance of the inclusion "…in textbooks and in medical, scientific and military education programmes of information dealing with the prohibitions contained in the Biological Weapons Convention and the Geneva Protocol of 1925". By the Seventh Review Conference (BWC, 2012) in 2011 States Parties agreed to complement regulatory and oversight measures with outreach, education and awareness-raising measures relating to national implementation under Article IV of the Convention. The Review Conference in 2013 called for the "consideration" of "…appropriate arrangements to promote awareness among relevant professionals in the private sectors…", and it also called upon States Parties to "…promote the development of training and education programmes for those granted access to biological agents and toxins relevant to the Convention…" as well as the, "…promotion of a culture of responsibility amongst relevant national professionals…"

4. Methods

In this study a range of concepts and practical considerations informed the research design including: constructivism, team-based-learning, threshold concepts and application.

4.1. Constructivism and Transformative Pedagogy

From the perspective of learning and teaching it is important not to lose sight of insights and theories from pedagogy that recognise the importance of context, particularly in relation to awareness raising and education that has transformative potential. In this connection, we suggest that an understanding of the post-positivistic, socially-constructed context in which transformative learning is situated is needed and its relevance to pedagogy acknowledged. An example of what is meant by "transformative" is the statement in 2017 UK Higher Education Academy paper (HEA) (2017), *Transforming Teaching Inspiring Learning: Reflecting on threshold concepts: an introductory tool*, of the "…need for critical reflection on a "disorienting dilemma" to bring about a deep and significant shift in perspective followed by a reintegration of the new way of thinking into a wider understanding." In accordance with constructivist approaches, we view biological security and dual-use learning, as socially and historically situated, contextualised, and as an active process that centres around the construction of knowledge and meaning through student experiences and through learner reflection (Cooper, 1993). Constructivism underpins a range of transformative approaches (Cooper, 1993) to learning and teaching that place the student at the centre of the learning experience. In line with constructivist learning theory (Hrynchak & Batty, 2012), TBL is learner-focused and student-centred where the role of the teacher is to facilitate. The latter facilitates problem-solving via self-directed learning. Learning arises from dialogue with and interaction between other learners and via shared experience. And reflection allows for accommodation and assimilation of new understandings with existing knowledge. A range of transformative approaches have been developed including problem-based and online learning, class-based, and virtual academic and continuing professional development (CPD) courses. Informed by decision making models, in this article, we argue that transformative learning on biological security and on dual use can be conceived of via a student-centred learning approach that combines use of Team-Based Learning with threshold concepts (Meyer & Land, 2005)

4.2. Team-Based Learnimg (TBL)

According to Sweet (2011), Team-Based Learning (TBL) is "a special form of collaborative learning using a special sequence of individual work, group work and immediate feedback to create a motivational framework in which students increasingly hold each other accountable for coming to class prepared and contributing to discussion". Emerging from approaches to learning and teaching in the field of business management, TBL is now widely used all over the world across a wide range of academic disciplines. Sweet continues, the essential skills imparted from this synergistic approach to learning and teaching in teams consists of the following elements: 1) A critical thinking attitude. 2) The ability to use specific critical thinking skills. 3) The ability to apply those skills in new contexts. 4) Habits of reflection upon one's own thinking. He also notes that standardly in a university setting TBL consists of a fixed four-stage process that includes: a) Instructor-formed teams (strategically formed and permanent). b) a readiness assurance process (RAP) comprising: individual pre-class preparation via an advanced assignment; a short individual summative test followed by an identical team test to incentivise pre-class preparation; an appeals process where student teams can develop evidence-based appeals that challenge the answers or wording of questions; and, a clarification teacher-led discussion to provide a focused follow-up on where any identified weaknesses in student understanding may have emerged during the tests. c) Application exercises that focus on problem-solving, collaborative decision-making and a teacher-facilitated inter-team discussion and debate whereby student teams verbalise and defend their decisions. These application exercises follow a 4S structure (*Significant* or challenging task, all teams work on the *same* exercise to optimize learning and future discussion, teams make a *specific* choice i.e. make a decision to defend, and finally teams *simultaneously* reveal their decision to prevent answer drift), to promote deeper approaches to learning through facilitated inter-team discussion and debate. d) A formative and summative student-to-student peer evaluation. TBL grading includes contributions from individual marks, team performance, and peer evaluation (see **Figure 1**).

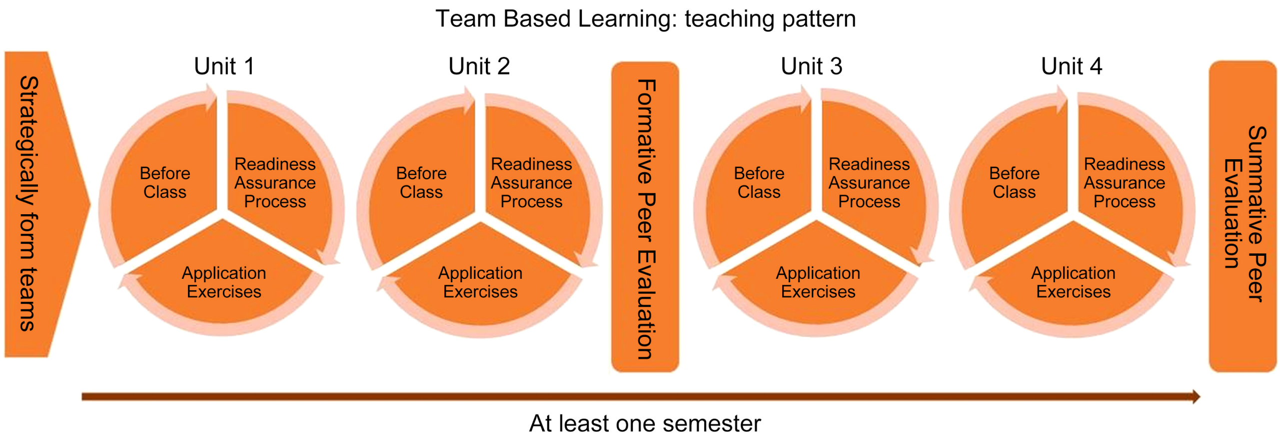

Figure 1. Team based learning: teaching pattern.

4.3. Threshold Concepts

In their paper: "Identifying Threshold Concepts: From Dead End to a New Direction", Shinners-Kennedy & Fincher (2013), in relation to their own discipline of computer science, highlight the drawbacks of existing methodological approaches to the classification of threshold concepts. As they note, methodological approaches have been developed in order to generate empirical evidence of threshold concepts and common methodologies have typically involved data generation from discipline experts and "would-be discipline experts" alike, and their own initial approach (Critical Incident Technique) involved the creation of a series of semi-structured interviews designed to facilitate the identification of the "transformative" quality of threshold concepts. As they note, threshold concepts have remained elusive in spite of the range of methodological approaches that have been devised to identify them. Our own approach to the identification of threshold concepts departs from those identified above, in that, as a way of generating empirical evidence, by way of the inclusion of a dedicated application exercise, our methodology incorporates the notion of threshold concepts as conceptualized by Meyer and Land, into the structure of Team-Based Learning.

Meyer & Land (2003) recognised that certain concepts are often central to the mastery of a subject. "Threshold concepts", as they have become known, are used in curriculum design and in teaching, and are associated with the above appreciation of a conceptual approach to understanding. They allow teachers to focus on aspects of curriculum design and teaching that seem central and often difficult to grasp by most learners. Their identification in curriculum design, it is argued, also helps to avoid an "over stuffed" curriculum, and often leads to a "less is more" approach to curriculum design. Since their introduction a decade or so ago, threshold concepts are increasingly being used to inform curriculum design and to inform the way teachers teach in higher education on a world-wide basis. Threshold concepts are also useful in the design of active and Team-Based Learning (TBL) approaches to curriculum design and teaching. Meyer and Land's work describe Threshold Concepts as "akin to a portal, opening up a new and previously inaccessible way of thinking about something… [as] a transformed way of understanding, or interpreting, or viewing something without which the learner cannot progress." "Threshold" concepts, they argue, have common characteristics in that they are: transformative, troublesome, irreversible, integrative, bounded, discursive, reconstitutive, and liminal. To elaborate regarding the above, according to Barradell (2013), threshold concepts are: (likely to be) transformative, (probably) irreversible, (contain the capacity to be) integrative and bounded, and (be potentially and possibly inherently) troublesome.

In other words, threshold concepts are likely to be:

1) Transformative: Once understood, a threshold concept changes the way in which the student views the discipline.

2) Troublesome: Threshold concepts are likely to be troublesome for the student, in that knowledge can be troublesome e.g. when it is counter-intuitive, alien

or seemingly incoherent.

3) Irreversible: Given their transformative potential, threshold concepts are also likely to be irreversible, i.e. they are difficult to unlearn.

4) Integrative: Threshold concepts, once learned, are likely to bring together different aspects of the subject that previously did not appear, to the student, to be related.

5) Bounded: A threshold concept will probably delineate a particular conceptual space, serving a specific and limited purpose.

6) Discursive: Meyer & Land (2003) suggest that the crossing of a threshold will incorporate an enhanced and extended use of language.

7) Reconstitutive: "Understanding a threshold concept may entail a shift in learner subjectivity, which is implied through the transformative and discursive aspects already noted. Such reconstitution is, perhaps, more likely to be recognised initially by others, and also to take place over time".

8) Liminality: Meyer and Land have likened the crossing of the pedagogic threshold to a "rite of passage" (drawing on the ethnographical studies of Gennep and of Turner in which a transitional or liminal space has to be traversed; "in short, there is no simple passage in learning from "easy" to "difficult"; mastery of a threshold concept often involves messy journeys back, forth and across conceptual terrain.

As set out above, one observation from the evidence generated by analysis of the expert level literature is that the notion of "biological security" and the notion of "dual-use" appear to be so-called "core concepts". However, here we argue that our research design facilitated the systematic comparison of such "core" concepts with "threshold concepts" and that distinctions between the two could be comprehended from the incorporation of threshold concepts into TBL, the latter we argue resulting in a methodology for the design of a novel transformative biological security and dual-use pedagogy.

5. Threshold Concepts in Biological Security and Dual-Use—Stockholm 2: Toward a Transformative Pedagogy

5.1. Overview of the TBL in Stockholm in 2018

Team-Based Learning exercises take time to design and test, but once this has been done successfully they have proved to be an effective method of conveying key concepts in many educational fields Hrynchak & Batty (2012). They are also efficient as they are easily replicated for large groups of people. The designer of a TBL unit has to define what it is intended that participants should be able to do (in terms of learning outcomes) at the end of the unit and then to work backwards to produce resources to achieve this outcome within a standard pedagogically-informed methodology.

We had three main objectives for this TBL workshop for a relatively small test group of participants:

1) To design and run TBL exercises focused on dual-use applications of the

novel CRISPR/Cas technology in order to determine the extent that it could be effective in raising the participants' awareness of the dangers of dual use.

2) To obtain feedback from the participants on the design of the resources and running of the TBL workshop in order to improve it for future use. And,

3) To make an initial attempt to apply a methodology that would allow us to gain a better understanding of the participants' thinking and of how it might be changed more effectively.

The whole of the meeting in Stockholm was intended to introduce the concept of biological security and the problem of dual use and all of the participants had given their written consent to taking part in the TBL workshop and for the facilitators to use of the result of the exercise.

In the standard methodology participants are asked to study a small amount of pre-reading as an advanced assignment. Before they started the exercise, the participants were placed into different teams around separate tables. Then individual participants are asked to complete a short test comprising a number of multiple-choice questions related directly to the pre-reading material. This is termed the individual readiness assurance test (iRAT). Each team is then required to complete the same test again as a team. This is termed the team readiness assurance test (tRAT). The results of the iRATs and the tRATs are relayed back to all participants and discussed by everyone involved in the exercise. It is expected that this mechanism will help to incentivise preparation and ensure a generally high level of understanding of the pre-reading material and prepare all participants to take part effectively in the subsequent application exercises. This strategy allowed the teams to apply their new knowledge to make a decision, which they visually display and defend to promote discussion amongst all of the participants. Facilitators call upon each team in turn to defend and verbalise their decisions to promote debate. A fundamental point is that the organisers of the exercise act as facilitators for the participants to engage in discussions with the subject issue and *not as instructors* telling them what they should learn. These discussions are also very useful in refining the exercise to make it more interesting and effective, particularly in the first trial runs such as the exercise we describe here. The timings used in the exercise in Stockholm are set out in **Table 2**.

The participants in the exercise in Stockholm were expected to have quite diverse backgrounds as modern neuroscience draws on many different disciplines. We therefore carefully constructed the pre-reading in three parts: a simple introduction to CRISPR/Cas technology in a set of power point slides that we had constructed so that everyone had at least a basic knowledge of the technology, and two recent papers which dealt with the societal implications of the use of the technology. The first of these papers dealt with the civil implications of the technology (Kang et al., 2017) and the second dealt specifically with the problem of dual use of the technology (Reeves et al., 2018). We also suggested that it would be helpful if the participants watched the video of the TBL workshop that we facilitated in Stockholm in 2017 as this was concerned with the question of dual use more generally. Our participants ranged from postgraduate students through to professional scientists with slightly more men than women taking part. We split the participants into three teams of four people and one team of three people.

Table 2. Timings for the Stockholm TBL.

Introduction: 1:25
iRATs: 1:40
tRATs: 1:50
Marking (of iRATs and tRATs) Break: 2:00
Feedback and Discussion: 2:20
Application Exercise 1: 2:30
Discussion of Application 1: 3:00
Coffee Break: 3:30
Application Exercise 2: 4:00
Discussion of Application Exercise 2: 4:30
Application Exercise 3*: 5:00
Roundup Discussion 5:15 - 5:45

*Participants written comments collected but not discussed.

All the participants had received a one-page briefing on the background to our previous work on biological security, dual use and on TBL exercises so that we could keep the introduction short. In this introduction, we stressed our concern not just with laboratory biosafety and laboratory biosecurity but with security issues well beyond the laboratory door. We defined this concept as B*iological Security* and presented it along side our definition of dual-use in the power point slide shown in **Table 1**.

As shown in **Table 2**, this short introduction led straight into the iRATs and tRATs being completed and then into the application exercises.

In a development from the standard methodology, in order to help us better understand the impact of the exercise on participants' "appreciation" (Novossiolova et al., 2018) of the problems of biological security and of dual use, before we went into the final discussion at 5:15 pm, we asked participants if they would individually take a look at some of the ideas that have been put forward about how concepts might be formed in TBL exercises and write down their reflections on these ideas (Application Exercise 3 in **Table 2**). We collected in these contributions from participants prior to the final wrap up discussion.

The question that we wanted to answer was exactly what participants had learned in the exercise and how did that match up to our aim of getting them to understand the profound change that CRISPR/Cas seems to have introduced into concerns about biological security and dual-use? In Application Exercise 3 we drew on key pedagogy papers on TBL exercises that have considered what kinds of concepts might be conveyed in learning and teaching in order to attempt to answer that question. According to Shinners-Kennedy (2016), acquisition by the learner of threshold concepts may cause "knowledge integration" transforming the "learners view of their discipline and possibly even their world". In short, we wanted to know to what extent such a transformation had occurred amongst our participants? Did they now appreciate the very dangerous dual use possibilities opened up by CRISPR/Cas technology and see the need increased life science involvement in the mitigation of the misuse of benignly-intended research?

Meyer & Land (2005) have been at the forefront of the threshold concepts debate and whilst numerous methodologies have been designed and deployed in their identification, little or no work research been done carried out on the role of such concepts in the subject areas of biological security and dual-use. On the basis of the issues raised in the iRATs/tRATS and in Application Exercises 1 and 2, we sought in Application Exercise 3, to invite the participants to submit reflections which related to each of Meyer's and Land's concepts.

5.2. Facilitating the TBL workshop

The iRATs and tRATs had seven questions and each question suggested four possible answers. These questions related to the power point slides that we had prepared for participants. The questions, however, were deliberately not straightforward: some, for example, asking what was false instead of just asking what was correct (**Table 3**). In total the responses to the iRAT questions were 80% correct, and as expected, this rose to 90% correct answers for the tRATs as the different groups debated the possibilities. In the discussion some questions were raised about two of the sets of answers and adjustments have been made to these in order to avoid any ambiguity.

Table 3. Example of an iRAT/tRAT Question.

Question 1. According to the powerpoint presentation provided, which of the following is false?
1) The CRISPR-Cas9 system consists of two key molecules that introduce a change into DNA?
2) CRISPR-Cas9 is long established technology that enables geneticists and medical researchers to edit parts of the genome?
3) The Cas9 enzyme acts as a pair of "molecular scissors" that can cut the two strands of DNA at a specific location in the genome?
4) These two key molecules are an enzyme called Cas9; and a piece of RNA called guide RNA (gRNA)? (REF here please)

Application Exercise 1 related specifically to the pre-reading paper by Kang and colleagues and had the following instructions:

> "As a Team, discuss each question and agree on an answer to the question. Write your answers on the flipchart provided; and, be prepared to provide clarifications and rationale for selecting your answers.
> 1) Table 1 [of the paper] represents a 'summary of genetic correction using CRISPR/Cas9 technology in cell therapy, agriculture, antimicrobials, and anti-viral treatment from 2013 onwards', in so far as genetic correction has been applied in human, animals and plants. Order this list as a hierarchy indicating, in order of importance, and identify from the list, the 'genetic correction' that your team feel is most ethically, legally and socially problematic.
> 2) Scientists have identified the technical challenges associated with the development and use of CRISPR technology that 'hinder it' from being 'clinically used.' Identify three such challenges described by the authors of the above article.
> 3) 'CRISPR/Cas9 technology…can be regularly and more efficiently performed in several species of organisms, ranging from insects and plants to rodents and primates.' According the authors, 'It can also be carried out in… stem cells and in human somatic cells for the purposes of basic research'. Make a list of challenges and problems that arise when considering the use of CRISPR technologies for manipulation of genes in the human germline and decide on the most important issue? What is the most important benefit and the biggest risk?
> 4) According to the authors this technology has 'revolutionised genomic research.' However, they also note that there, 'remains the risk of improper use' of this technology. What is the most important governance/oversight recommendation you would be recommend in order that human germline/embryo gene modification could take place? And what is the most important governance/oversight you would recommend to mitigate the potential for its misuse?"

All four teams produced interesting and detailed answers to these questions on their flipcharts and a vigorous debate ensued again with suggestions about how the instructions might be improved.

In Application Exercise 2 we focused directly on the problem of dual use in the paper by Reeves and his colleagues by describing a fictitious scenario and asking teams to decide how to deal with the situation. The exercise instructions were:

> "Read the (Scenario) Passage below and agree what the MOST IMPORTANT actions you, as a team of scientists, could take to address the situation described in the scenario.
> Write your answer on the flipchart. You need to prepare a justification for your answer and be ready to respond to questions and clarification requests from the floor.

SCENARIO: As an Agricultural Geneticist you know that vertical modification of chromosomes in plant science takes time since modified chromosomes must be vertically inherited from one generation to the next. This can take many growing seasons. However, as a team of scientists working on the development of novel 'biocontrol' agents, you come across a technique that facilitates horizontal modification of chromosomes that allows for the editing of crop chromosomes directly in fields. You and your team believe that the regulatory, biological, economic, and societal implications of dispersing such horizontal environmental genetic alteration agents (HEGAAs) into ecosystems are profound. The technique that you have developed in order to disseminate (HEGAAs) in the environment is via insect-based dispersion. Your technique involves a CRISPR system that is engineered to be part of a virus that allows for the modification of plant chromosomes, in other words, this technique would facilitate plant chromosomal editing by means of virally encoded CRISPR proteins that are delivered directly to plants by aphids, that will result in increased plant resilience to environmental challenges and/or herbicides."

As with the previous exercise the groups had intensive discussions and detailed flip charts were presented and discussed by the teams. The obvious dangers of the work described in the scenario being used to produce a novel biological weapon as suggested in the Reeves paper and these considerations featured in the presentations and discussions.

5.3. Results: Threshold Concepts and Empirical Evidence

We then asked for the answers to the questions in Application Exercise 3 to be written down and these answers were collected in. This then led on to a wide-ranging discussion of the exercise in the context of the whole meeting on biological security and dual use in which it seemed that the participants had enjoyed the exercise and found it useful.

In relation to each of the concepts articulated by Meyer & Land (2018) the number of written responses we received from the 14 participants were as follows: Transformative (11), Troublesome (12), Irreversible (13), Integrative (12), Bounded (6), Discursive (8), Reconstitutive (9), and Liminal (9). A short synthesis of a representative sample of the respondents' remarks is set out below:

Table 4. Selected significant impacts from different participants.

Question 1: Transformative

Participant 15: "Responsible science needs to be open and ethical concerns should be integrated into science."

Question 2: Troublesome

Participant 6: "The possibility/reality that powerful tools like CRISPR/Cas can be used for hostile purposes and maybe not being able to prevent misuse/dual use as a scientist."

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Question 3: Irreversible
Participant 10: "CRISPR/Cas as a potent biological weapon and not at all harmless, interesting technology."
Participant 12: "The importance of discussing dual use responsible research and innovation."
Question 4: Integrative
Participant 1: "More awareness, knowledge and practice in thinking about dual use."
Question 5: Bounded
Question 6: Discursive
Participant 1: "international and legal regulatory measures."
Question 7: Reconstructive
Participant 8: "Yes, I believe it will be harder for me in the future to conduct research without really thinking ethical questions through. That includes team research and therefore all my future colleagues."
Participant 13: "Yes definitely. Most of my colleagues do not know of the "need" to consider responsible research or dual use."
Question 8: Liminality
Participant 9: "It sure can be hard to navigate but the focus of such workshop and TBL helps confine the topics and actual issues and real life examples."
Participant 14: "It involves messy journeys back and forth."

As illustrated in **Table 4**, Selected Significant Impacts from Different Participants, data from participants included the following insights. In relation to the Transformative category (changed the way you view responsible science), a view of one participant (4) was the need to integrate ethical considerations into science. Another (2) noted that the exercise helped in focusing on the responsibilities of individual scientists. Another (8) noted that the exercise underlined the "hard question" of devising action plans and policies. Another (11) observed that responsible science was "…much more intricate" than the first thought. According to one participant (6), a Troublesome (counter-intuitive, alien or seemingly incoherent) aspect of biological security and dual use was that possible hostile misuse may not be possible for scientists to mitigate against. One participant (2) singled-out the idea of hostile environmental modification as counter intuitive. Regarding the (difficult to unlearn) Irreversible quality of (anything discussed/learned today), one participant (10) noted the realisation that science and technology was not at all harmless and this is one of the reasons that the participant found discussion of the technology interesting. Another (12) concluded, as follows, that discussions about dual use, responsible research and innovation, were therefore important. One observation (1) concerning the Integrative quality of the topic (that was likely to bring together different aspects of the subject together), identified more awareness, knowledge and practice as a desirable outcome of the exercise. Another (4) identified: horizontal exchange between experts and public/different disciplinary backgrounds. Another (12) identified the connections between biochemical research and dual-use. In terms of the Discursive category (extend your use of language about this subject), one participant (12) identified knowledge of/language about the chemical and biological conventions as well as their implementation. Another (1) identified extended use of language concerning international legal and regulatory measures. In terms of the Reconstructive category (set you apart/recognition from others/influence your professional practice) one participant (8) noted that it would "…be harder for me in the future to conduct research without really thinking ethical questions through. That includes team research and therefore all my future colleagues." Another (13) noted "Yes definitely. Most of my colleagues do not know of the 'need' to consider responsible research or dual use." And finally in terms of Liminality (the crossing of the pedagogic threshold "where transitional or liminal space has to be traversed"), according to one participant (9): "It sure can be hard to navigate but the focus of such a workshop and TBL helps confine the topics and actual issues and real life examples." And another (14) observed that "the experience involved…messy journeys back and forth."

This process of mapping responses to threshold concepts therefore resulted in a series of insights into participants experience in taking part in the TBL and we regard such responses as making a contribution to our understanding of subject-specific threshold concepts that may inform and improve the design and application of TBL training in this area in future, particularly in regard to backward design, and in regard to constructive alignment between course aims and objectives and learning outcomes.

The data generated under application Exercise 3 was then coded and organised in relation to relevance to the themes of biological security and dual use. Coding and tagging of the data generated by the Threshold Concept exercise in this stage of the process allowed for the categorisation and distribution of participant responses in relation to three key themes: biological security, dual use, and ethics, with 35% of participants responses falling under the biological security theme, 60% of participants responses falling under the dual use theme, and 5% of responses falling under the theme of ethics. Our overall contention, and a significant contribution of our work—is, we argue, that incorporation of the threshold concepts framework into team based learning facilitates the identification of subject-specific threshold concepts and that a discourse analysis of participants observations suggests the need, in our training, for closer alignment between biological security, dual use and ethics.

From our point of view the exercise clearly indicated that, while the participants may not have had enough background knowledge of the history of biological weapons and the debates over the last two decades on biological security and on dual use to fully appreciate the game changing nature of the discovery of CRISPR/Cas technology, there can be little doubt from the responses that participation in the workshop and exercise had an impact on their thinking about the issue.

6. Discussion and Conclusion

6.1. Discussion

Our methodological approach allowed us to design an epistemologically informed transformative pedagogy for teaching and learning in a constructivist context. This allowed for the inclusion in the design of the TBL workshop of questions framed to guide participants to consider consequences, duty and virtue and other relevant normative ethics approaches and facilitated fruitful observations about real-word scientific and technological dilemmas and problematics, some of which highlighted ethical dilemmas whilst some highlighted practical dilemmas.

Our methodology facilitated the generation of learning-outcome-related metrics showing first that TBL participants' scores increased throughout the course of the CRISPR/Cas individual and team readiness assurance tests, and second, that original empirical evidence of contentions and observations regarding threshold concepts of relevance to biological security and dual use thus followed from a process of mapping these onto Meyer's and Land's categories. Coding and tagging of participant observations subsequently verified the mapping of the latter onto the definitions that we had advanced for biological security and dual use, and the mapping exercise suggested that one outcome of the TBL workshop was there was a case to be made for stronger convergence of, and linkage to be forged between, biological security, dual use, and ethics. We, therefore, contend that the above methodology provides important information about how TBL courses in this area can be continuously improved and refined.

It is our hope that the approach could result in further research in this area and the validation of a novel methodology would emerge for approaching awareness raising and education that meets the expectations set for the promulgation of training in this area. And that this may lead to the possible development of a creative bottom-up process of empowerment of scientific and civil society actors (Walther, 2013) engaged in the management of security issues related to life and associated sciences, contributing significantly to the mitigation of risks deriving from the potential for misuse.

6.2. Conclusion

In relation to the three objectives we had, it seems clear that the participants enjoyed and engaged in the exercise over the entire 4-hour period, and that they provided very useful feedback on the iRAT/tRAT questions and the instructions for Application Exercises 1 and 2. Thus, one overall conclusion is that this TBL exercise could easily be repeated in other contexts and would be useful in raising awareness of biological security, dual use and ethics, and the problem of the manifold future applications of this novel CRISPR/Cas technology. That, of course, would not solve the problem of improving biological security and mitigating against dual use, but we would argue that it is the first necessary step in the achievement of that objective. For example, it seems to us that if Professor He Jiankui and his colleagues at Southern University of Science and Technology in Shenzhen Cyranoski & Ledford (2018) had had a course on biological security, dual use and ethics involving discussions of the misuse of the modern life sciences including TBL exercises of the kind described here, someone might have had the sense to raise questions about his research at a much earlier stage and he would have avoided the likely coming destruction of his career and the damage he has done to the credibility of the scientific community.

Moreover, it is clear from Application Exercise 3 that for a large percentage of the participants the exercise may have had a significant impact on their thinking. Yet one might reasonable ask what had really changed and how long would any such change last in the rush of everyday work in the laboratory. In the original work cited above, it was found that the vast majority of practicing scientists had little idea of the possibility that their work could be relevant to the notion of biological security and dual use and was worthy of ethical consideration, and there is much evidence that the same situation pertains still worldwide. The first threshold that has to be crossed by most life and associated scientists is to become aware of the possibility that their work could later be used by others to create new biological and also chemical weapons. Once that door opens they can begin to think about what responsibilities they might have to help prevent such dual use applications of their work.

Yet without further information about the wide range of things that they might do they could very easily decide that there is little that they can do. Clearly that next step could be assisted by familiarity with the range of exercises that have been developed with that wider objective in mind. Crossing that threshold could open up possible avenues for action such as insisting that there is a proper course in biological security, dual use and ethics within the institution where they work or that their professional association sees the Chemical and Biological Weapons Conventions as their Conventions and that the association has part of the responsibility to take care of these and other relevant international agreements. We might then be less likely to be in the present situation where the 2018 Meeting of States Parties of the Biological and Toxin Weapons Convention could do little about the CRISPR/Cas dual use problem it had on its agenda because it had to spend so much time trying to find ways to ensure that State Parties paid their financial contributions on time; and, fruitful discussions could have taken place regarding the related problem of chemical security and of chemical dual-use at the 4th Five Year Review Conference of the Chemical Weapons Convention that ended without agreement.

But perhaps the biggest problem we have in finding ways to effectively and efficiently help life and associated scientists through these portals into a wider and effective understanding of their responsibilities is to gain a better understanding of what we are trying to do and how to do it. We hope our study makes a modest contribution to that end.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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