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Developing a Reflexive, Anticipatory, and Deliberative Approach to Unanticipated Discoveries: Ethical Lessons from iBlastoids

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Title page

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Developing a Reflexive, Anticipatory, and Deliberative Approach to Unanticipated Discoveries: Ethical Lessons from iBlastoids

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Abstract: In this paper, we explore the recent creation of 'iBlastoids,' which are 3-D structures that resemble early human embryos prior to implantation which formed via self-organization of reprogrammed adult skin cells. We explore some of the ethical, philosophical, social, and regulatory issues related to this research, with focus particularly on what it means to 'anticipate' research outcomes when using novel methods or when serendipitous discoveries are made. We defend the need for reflexive, anticipatory, and deliberative ethical and conceptual work by researchers working in emerging and contentious research domains, in collaboration with interdisciplinary scholars, as well as regulators, funders, and publics.

Keywords: stem cell research; cloning; research ethics; regulatory issues

Dans les champs de l'observation le hasard ne favorise que les esprits préparés.
In the field of observation, chance favors only the prepared mind. (Pasteur 1854)

Introduction

Study of early human development is essential for continued understanding of pregnancy including effects of environmental toxins and gene mutations on development, and for studying fertility problems and refining assisted reproductive technologies. Although difficult to measure and hotly debated, recent estimates indicate that for women of reproductive age, losses between embryo implantation and clinical recognition of pregnancy are approximately 10–25%; although considerably lower than older estimates which ranged from 30–70%, this rate is still non-trivial (Jarvis 2017). But research on these developmental stages has been accompanied by considerable challenges in many locales related to ethical, social, and legal constraints on the availability of human embryos for research purposes. Hence developing *in vitro* models of human development (particularly three-dimensional [3-D] models that are scalable and versatile) has been a priority amongst developmental biology researchers.

Several recent papers detail different methods used to create 3-D structures that resemble early human embryos prior to implantation. We focus on research by Liu et al. (2021) which used cells reprogrammed from adult skin tissue and which were induced to self-organize in a dish to form what they term 'iBlastoids.' This research raises intriguing ethical, philosophical, social, and regulatory issues, particularly in association with how to innovate responsibly in this domain. It also allows us to unpack what it means to 'anticipate' research outcomes when using novel methods or proceeding with research in previously uncharted territory. We explore questions raised by this research, and defend the need for reflexive, anticipatory, and deliberative ethical and conceptual work by researchers working in emerging and potentially contentious domains of research, in collaboration with interdisciplinary scholars, as well as regulators, funders, and publics.

Emerging technologies such as those explored in this article typically fall into what has been termed an "institutional void" (Hajer 2003) or at the very least "tentative governance" (Kuhlmann, Stegmaier, and Konrad 2019). There are few agreed structures to govern them, and the definitions and concepts underlying them may not have been thoroughly considered or settled. We argue for the need for transparent and reflexive processes that will support more robust regulatory outcomes and more adequate ethical and social consideration of new methods and novel research outcomes, rather than reliance on outmoded or inadequate definitions and rules that do not provide clear or relevant guidance. We also contend that it is critical to engage in constant reflection on and debate about regulatory processes, rather than attempting to force ambiguous or outdated regulation to fit emerging contexts.

Making Blastoids

In less than a week, a fertilized human egg develops from a single cell to a cluster of around 240 cells referred to as a blastocyst. Studying early stages of human development, including the various cell types in the blastocyst, has always been difficult. Animal models provide some insights but key differences in how embryos form and develop limit their relevance (Rossant and Tam 2017). While it is possible to study the cellular and molecular interplay underpinning blastocyst formation and implantation using donated human embryos, their use is limited due to technical, legal, and ethical concerns. Thus researchers have sought to generate models that recapitulate different aspects of early human development in order to shed light into this process. These models rely on human pluripotent stem cells–embryonic stem cells (ESC) or induced pluripotent stem cells (iPSC)–to explore the formation and development of human embryos (known as embryogenesis). While researchers have been able to use pluripotent stem cells to create 3-D structures *in vitro* that mimic how organs such as the eye, brain, kidney, and liver develop for many years (broadly termed 'organoids,' which provides part of the etymology for the neologism 'iBlastoid') (Lancaster and Knoblich 2014), extending directed differentiation of pluripotent stem cells to mimic the earliest stages of human development has only been pursued in recent years.

Previous models have focused on specific post-implantation landmarks, such as allocation of cells to structures destined to form the fetal tissues or identifying what gives rise to some of the support tissues essential to establish and maintain a pregnancy. Although these models are likely to prove very useful for our understanding of specific stages of early human development, they only recapitulate a specific landmark event rather than more generalizable cellular and molecular aspects of the process. However, various research groups have now generated 3-D structures, dubbed blastoids, that provide alternative models for exploring human embryology.[1]

The approach to generating 3D structures that we focus on here took adult human skin cells (fibroblasts), and cultured these in the laboratory over several weeks in conditions designed to

[1] Coinciding with these publications in *Nature*, two other groups reported 3-D models of human blastocyst development on a preprint server (Fan et al. 2021; Sozen et al. 2021); we do not explore these in any detail as they have not yet undergone peer review.

induce them to change or be reprogrammed into more primitive cell states (Liu et al. 2021; see Figure 1). The concept of reprogramming involves converting somatic cells, such as those found in adults which have a fixed and specialized function, into cells similar to those found in early embryos and capable of developing into a range of cell types. While the usual outcome of reprogramming is the derivation of iPSC which can be used for various therapeutic purposes, the aim of this research was to understand the molecular mechanisms underpinning this reprogramming and thus to better control and replicate these processes associated with cell fate, rather than simply to generate these cells.

<INSERT FIGURE 1 with caption "A: The fertilization process leading to human blastocyst; B: the process leading to human iBlastoids generated from skin cells. Image courtesy of the Polo lab.">

During the research process, the intermediate state of the cells was analyzed, and different types of cells were observed: some had gene expression patterns similar to epiblast (the type that eventually become fetal cells), which was expected since iPSC represent that cellular state. However, the research team also observed cells with patterns similar to trophectoderm, the layer of cells surrounding the blastocyst that supply the embryo with nourishment and which later form the major part of the placenta (these findings were originally published in Liu et al. 2020). Further interrogation of those intermediate states revealed that some of those cells undergoing reprogramming also expressed genes of the primitive endoderm (yolk sac). Given this finding, the researchers decided to place the cells undergoing reprogramming into a 3-D culture system to see how they would behave and interact in order to better characterize the cells. They found that after 6 days, cells self-assembled into aggregates; to their surprise, around 10% of these cellular clusters had a cavity reminiscent of that observed in a blastocyst, which prompted them to further characterize these structures. After a comprehensive molecular and functional analysis, the researchers concluded that they had generated what appeared to be blastocyst-like structures that they termed 'iBlastoids' (short for 'induced blastoids'). A critical point here is that these structures were derived from reprogramming adult human skin cells rather than being generated from existing pluripotent stem cells.

The generation of these iBlastoids opens a window into the second week of human development. Although some cells found in the iBlastoids seem not to be found in blastocysts (more research is required on this point), iBlastoids do appear to provide valuable 3-D models of the architecture, spatial localization, and molecular make-up of the blastocyst. They also are able to mimic implantation, as the iBlastoids were shown to be able to attach to the surface of a culture dish and develop over an additional period of 5 days in a similar manner to human blastocysts. It seems likely that iBlastoids can be generated at scale and manipulated using molecular techniques, allowing researchers to investigate the complex molecular and cellular interactions occurring in this stage of development which previously were very difficult or impossible to study.

Assuming the work is reproducible, and noting that the research that resulted in the creation of iBlastoids is at a very early stage, the researchers hope that the model can provide new insights into critical differentiation events and how cell fates are determined, allowing interrogation of gene expression patterns at a level not previously possible. While comparative studies with donated human embryos may be required to further benchmark reproducibility, in principle this approach could lead to creation on demand of iBlastoids and ultimately less need for donated human embryos. Even if iBlastoids only allow focus on the first 7 days of development, they clearly have the potential to be important models for early development.

The Ethics Review Process

The iBlastoid research was undertaken at Monash University and hence was subject to Australian regulatory oversight. As detailed in the "Ethics Statement" included in the methodology of the published research article, the research was performed first under the oversight and approval of the Monash University Human Research Ethics Committee (HREC). Initially the research was not subject to the special review processes required in Australia in conjunction with human embryo research (Australian Commonwealth, *Research Involving Human Embryos Act* 2002). The researchers stated that the additional ethics review processes did not apply because the research was focused on functional and molecular characterization of human fibroblasts undergoing reprogramming using different culture conditions and did not involve the use of human embryos, embryonic material, or gametes, nor did it involve performance of *in vitro* fertilization.

However once molecular and functional data demonstrated that blastocyst-like structures had been generated, the researchers contacted their HREC and the Australian National Health and Medical Research Council (NHMRC) Embryo Research Licensing Committee (ERLC), which is the national regulatory authority for human embryo research. The ERLC advised that processing and analyzing of non-living material (such as fixed specimens, lysed cells, and so on) and data collected until that point did not require an embryo research license, and so could continue. However, the ERLC also advised that the researchers should stop the production of iBlastoids while the ERLC considered the regulatory path forward for future iBlastoid work in Australia.[2]

The research group also initiated a new ethics application process to their HREC specifically to cover the generation and the molecular and functional characterization of iBlastoids. They noted that this review process was "bolstered by the expertise of embryo and ethics specialists" and was in accordance with international guidelines for research involving embryo-like structures (notably ISSCR 2016). Furthermore, they acknowledged the existing "national and international consensus" about these issues, and specifically that the

[2] On the day that the Liu et al. iBlastoid paper was published, the NHMRC issued a statement that they considered iBlastoids to meet the definition of a human embryo in the *Research Involving Human Embryos Act 2002*, and that future work on iBlastoids would require an appropriate licence (NHMRC 2021).

International Society for Stem Cell Research (ISSCR) Guidelines do not permit research that involves culturing human embryos or embryo-like structures beyond 14 days post-fertilization and/or formation of the primitive streak, whichever occurs first.[3] Researchers found interpretation and application of the 14-day rule to *in vitro* models of early development to be "not clear" when there is no fertilization event to effectively start the timer. The researchers stated that "to be cautious," they decided to allow the iBlastoids only to develop for a maximum of an additional five days during which they examined cell function and behavior in their implantation model. They also tracked the expression of key genetic markers related to primitive streak formation and noted that all experiments were terminated 4.5 days after iBlastoid attachment, with no morphological or molecular evidence of the appearance of the primitive streak detected at any point in the process.

But is an iBlastoid an embryo, a clone, or what?

An immediate question that arises based on the above account of the research is whether iBlastoids (or blastoids in general) should be considered to be human embryos, as this definition has clear legal and ethical implications, including in Australia where the research occurred. While the Australian regulators have since clarified that in their view iBlastoids fulfil the definition of a human embryo and require higher-level review including licensing (NHMRC 2021), how this type of research will be viewed in different jurisdictions will depend on existing legislation pertaining to human embryo research and how a human embryo is legally defined (Hyun et al. 2020; Matthews and Moralí 2020). Given that laws covering human embryos in research and/or cloning were written more than a decade ago in many locales, well before reprogramming and the use of pluripotent stem cells to model human embryo development was even envisaged, there may be uncertainty around which regulations could or should apply, and how they should be interpreted.

In the first instance, the definitional question can be explored from a strictly biological and ontological point of view, in which case it might be argued that an iBlastoid is a model of development that simulates conditions in an embryo but which is not wholly equivalent to a traditional sperm-egg embryo. There are notable differences in the iBlastoid, including that it is not created via fertilization and also it includes cells not usually found in the blastocyst (though it is yet to be determined what this extra material is and what it does), despite considerable structural, genetic, and functional similarities. The iBlastoid is effectively a genetic copy of its (skin) donor (a clone), whereas a sperm-egg embryo has a unique genetic composition. Cloning is permitted in Australia for non-reproductive purposes (so-called therapeutic cloning) so long as a license is issued by the ELRC.

[3] In May 2021, the International Society for Stem Cell Research released updated Guidelines (ISSCR 2021). While research involving the creation of human stem cell-based embryo models that "represent integrated development of the entire embryo" such as that seen in iBlastoids remain permissible following comprehensive scientific and ethical review, the requirement to limit culture to 14 days has been removed. The revised recommendation is to culture the models for "the minimum time necessary" to achieve the study's scientific objectives.

However, there is an important stress in Australian regulations on the 'potential' to form a full organism. In a NHMRC Discussion Paper (2006) to clarify the definition of a human embryo from a biological standpoint, the following key characteristics are noted: the entity must (i) have an integrated organization and (ii) have a self-directed active disposition to mature to the next stage of development; and (iii) genetic identity should be established from the beginning. It is stressed that this includes not only the first mitotic division when fertilization of a human oocyte by a human sperm is complete (standard sperm-egg embryos) but also any other process that initiates organized development of a biological entity with a human nuclear genome or altered human nuclear genome that has the potential to develop up to, or beyond, the stage at which the primitive streak appears and has not yet reached eight weeks of development since the first mitotic division (see also Findlay et al. 2007). A subsequent review of the Australian legislation that was first introduced in 2002 resulted in refinements to the definition of a human embryo in the relevant Acts to include "a discrete entity" that has also arisen from "any other process that initiates organised development" and that has the potential to "develop up to, or beyond, the stage at which the primitive streak appears" (Australian Commonwealth 2002). Hence although the potential of iBlastoids to give rise to the primitive streak was not determined, it is conceivable that (with considerable effort) the right conditions may be found and iBlastoids could eventually meet the criteria to be considered to be human embryos, given the emphasis in the legal definition both on potential as well as the explicit inclusion of any other process that initiates organized development and not just fertilization.

Discussions of these types of arguments (e.g., Hyun et al. 2020) often stress that this definition creates a sort of 'chicken and egg' problem: this type of developmental or 'organismic' potential is problematic in the human because the definitive experiments to prove (or disprove) full human developmental potential are not possible under accepted ethical standards. While blastoids created in mouse studies did not support the development of 'bona fide' embryos, they were able to initiate clear signs of implantation in the uterus of surrogate mice (Rivron et al. 2018). However data obtained from other species may not be applicable in humans (Fu, Warmflash, and Lutolf 2021). Hence regulations require knowing how to define particular types of entities but establishing a definition depends on doing research which is not permitted. Furthermore, the word 'potential' as used within developmental biology denotes certainty that under the right conditions the expected function can indeed happen. Thus approaching iBlastoids or other blastoid models from their 'potential' necessarily leads to confusion as their 'potential' will depend on conditions not yet established and experiments that cannot be conducted, and also to the conclusion that they should not be explored any further without higher levels of ethical review or licensing.

We need better agreement on some key concepts surrounding the iBlastoid model, including what the model is seeking to do, particularly in terms of what stage of development is being modelled. There have recently been a number of developmental models focused on particular modelling a discrete set of anatomic structures, such as aspects of embryogenesis (formation of the embryo) and gastrulation (formation of the initial body plan) (e.g., Moris et al. 2020; Zheng et al. 2019). In contrast to the iBlastoid and blastoid work, these models do not attempt

to generate integrated cells capable of developing into all of the cell types required to establish and maintain a pregnancy and therefore lack human organism potential (e.g., ISSCR 2016). Hence it might be argued that it is less about what the entity models or does and more about what it could do or become, or what stages of development can be modelled (e.g., under the conditions that the iBlastoids have been placed, they can only model the preimplantation stage and the initial implantation stage which are much earlier stages of development than some of the other models discussed).

When considering the status and proper definition of the iBlastoid, we might also consider why the iBlastoid was created: rather than being made for the purposes of reproduction, the intent is to model and understand development, and hence it could be claimed that this makes it distinct from blastocysts and embryos derived from fertilization. Recall that in Australia among other jurisdictions, it is illegal to create an embryo for research; sperm-egg embryos originally created for infertility treatment but now surplus to requirements can be used for research purposes. This argument parallels that made in the context of somatic cell nuclear transfer (SCNT), where reproductive cloning is claimed not to be ethical, but therapeutic cloning is thought to be ethical and legally permitted under certain conditions (e.g., in Australia subject to licensing by the ELRC: see e.g. Sinclair and Schofield 2007). However relying on this sort of definition (i.e., focusing on the purpose for which something has been created) would require a high level of oversight and transparency in research processes from the start and throughout their development, as well as robust regulatory and/or licensing procedures in the jurisdiction in question. It also would require a certain reflexivity on the part of the researchers particularly to understand how to engage with these regulatory and oversight processes (as we argue below).

Reflexive, Anticipatory, and Deliberative Processes are Needed

Many research ethics frameworks, including those centering on responsible research and innovation (RRI), emphasize that being able to anticipate ethical issues in advance of the commencement of research can be a powerful way of fostering early discussion, consultation, and regulatory consideration that can be helpful for both researchers and stakeholders (e.g, Stilgoe, Owen, and Macnaghten 2013). There is some previous literature in bioethics fields on using anticipatory approaches in related areas (e.g., Harvey and Salter 2012 on anticipatory approaches to human/animal chimeras), the need for more attention to social implications and public engagement particularly on stem cell related research (e.g., Scott 2015), and on 'speculative bioethics' (Schick 2016), but anticipatory approaches have largely not gained traction specifically in bioethical domains. Science and technology studies (STS) policy scholar David Guston (2014) has argued that anticipatory governance, which he describes as "a broad-based capacity extended through society that can act on a variety of inputs to manage emerging knowledge-based technologies while such management is still possible" (219), should be a pillar of any systematic ethical approach to research. By defining anticipatory governance in this broad way, anticipation is extended across a range of actors, including researchers, funders, regulators, and publics, among others.

Alfred Nordmann (2014) has helpfully raised the question of whether anticipation is actually anticipation of the future, or something else, and outlines a range of types of anticipation. In the case of iBlastoids, the researchers note that there was no initial intention to make blastocyst-like structures from reprogramming intermediary cells, and that the creation of such structures was not "foreseeable." Although researchers or labs may have particular goals and not intend other outcomes from their research, they might do well to anticipate (in the sense intended in the RRI literature) a wide range of possible outcomes. In its simplest sense, the concept of anticipation asks that researchers and others involved in the research process such as regulators ask 'what if. . .?' questions (Ravetz 1997) about what is known, what is likely, what is plausible, and what is possible. Anticipation involves developing more systematic thinking about opportunities and risks particularly in emerging research fields. It is clearly distinct from prediction in that anticipation requires recognition of many complexities and uncertainties involved in the scientific process, particularly in the context of societally important or contentious research (Barben et al. 2008). Anticipation hence is fundamentally different from the routine, everyday considerations associated with scientific methodologies and their associated uncertainties. Anticipation is particularly valuable and necessary when potential outcomes must be considered within their broader context of their ethical, social, and legal implications.

Reflexivity is also critical: it involves a combination of practices of reflection and critical imagination, in order to improve researchers' abilities to anticipate future phases of their work, understand and address oppositional views from other researchers and publics, and encourage the creative and critical thinking that drives innovation. Scholars in science and technology studies and RRI have stressed that these processes need to be embedded in scientific practices within communities (Sample et al. 2019), and must include not only researchers but also regulators, research funders, and other institutions involved in science governance and communication to develop a shared understanding of reflexivity and more adequate capacities for engaging in reflexive considerations (e.g., Salmon, Priestly, and Goven 2017; Schuurbiers 2011). Such processes also should be deliberative, and seek to make values and arguments underlying research more transparent in order to shape regulation and public policy to make it legitimate, rather than merely informing or communicating to members of various publics (Dodds and Ankeny 2018).

Australia has some history of encouraging reflexivity on practices in this domain, at least amongst scientists and regulators, as occurred in the extensive 2005 review process to examine Commonwealth legislation regulating human embryo research (known as the Lockhart Review after its chair, see Harvey 2008). However public engagement in this process was much more limited than was desirable and arguably not truly deliberative though some values associated with deliberative processes were incorporated (Ankeny and Dodds 2008; Dodds and Ankeny 2006). Subsequent opportunities for reflection and deliberation in this domain have been limited to a less extensive review in 2010 (known as the Heerey Review, see Skene 2012) which did not extensively engage publics nor did it result in any

changes to legislation, and a recent targeted consultation around the research and clinical use of mitochondrial donation which is currently prohibited under Australian legislation.[4]

Thinking systematically and reflexively about anticipation is becoming increasingly important in this era of 'mission-based' science, where many funding regimes and the research programs associated with them are increasingly larger-scale and broad in intent as well as being goal oriented and funneling fundamental research toward particular ends. The idea of mission-based science, ranging from the moonshot of the Apollo program to the war on cancer, is characterized by its propensity for spin-offs or spillovers from the science and innovation of the mission. The idea is that mission-based science and innovation is an "open-ended way of framing a problem" which can initiate "new types of risk-taking in many different sub-projects" (Mazzucato 2021, 87–8). This type of risk-taking in emerging areas of science is likely to create a perfect context for serendipitous discoveries.

The iBlastoid work explored in this paper fits this model of mission-based research and its potential spin-offs. It is part of a much larger set of historical efforts to understand development (a 'mission'), a form of what used to be called 'basic' research which now is highly valued because of its potential applications particularly for human health and well-being, or what is termed 'translational' research (Maienschein et al. 2008). What can be anticipated in this context lies on a continuum and is relative: while iBlastoids might be considered to be imaginable or relatively near on a continuum of anticipation, other outcomes such as ex utero cultures may arguably be further down the continuum (and may never be possible, although recent work in mouse on artificial wombs might provide a starting point: see Aguilera-Castrejon et al. 2021). The point here is that scientists can and should be encouraged to envision possible futures and different outcomes from various scenarios, including key ethical and social considerations. However, envisioning or anticipating these possibilities does not mean that the science is out of control, particularly if possibilities are considered in concert with reflection on relevant ethical, legal, and social issues, and the implications of these issues for regulation and law, ideally along with stakeholders in a deliberative manner. The textual evidence that we have from the iBlastoid paper and the way in which researchers and regulators interpreted each other's actions should give us cause for some hope for researchers and regulators working together in the future in timely ways, at least is model of some initial steps toward fostering reflexivity.

There remains an important distinction between unintended and unanticipated outcomes in iBlastoid (and other emerging technology) research. The concept of mission-based science may also be helpful in parsing some of the differences between what one researcher might 'intend' and what those looking from the outside of a mission might anticipate. As Samantha Copeland (2019) notes, "Serendipity is a category used to describe discoveries that occur at the intersection of chance and wisdom...it requires both luck and skill, and is both

[4] Legislation to allow mitochondrial donation, *Mitochondrial Donation Law Reform (Maeve's Law) Bill 2021*, has recently been introduced to Parliament with a vote anticipated in the coming year.

unpredictable and yet can be cultivated" (2386). Bringing frameworks and tools from RRI into this context, such as the concepts of serendipity, intention, anticipation, and reflexivity along with the processes necessary to foster them, reveals underlying values associated with research and creates dialogues that permit us to better address surprises as they occur in a wise and responsible manner. For instance in the iBlastoid case, the published article notes that careful attention was paid to the requirements of institutional ethics clearance processes together with national guidelines and laws; however these do not appear to have encouraged or aided the researchers to consider the range of possible outcomes and their potential ethical, social, and legal implications.

The broader community needs to be brought into discussions about these sorts of issues of anticipation in the domain of emerging and potentially contentious scientific research, and ideally in a manner that is deliberative, involving respectful and informed debate, and clear and justifiable policy recommendations. There are at least two points in this research at which publics could be involved: one is associated with the consent processes relating to the sources of material and expectations about what it will be used for. In this case, the skin cells used were obtained from a commercial provider, but this type of research finding raises more general issues about how we might understand and better use blanket or broad consent processes (Tomlinson 2013) in domains where we might not intend certain outcomes and where participants are likely to have deeply held values for instance about ethical permissibility of some types of research and concerns about others, such as creation of immortal cell lines or even what some might view as creation of life itself. We need to foster more explicit discussions about what researchers do not know and cannot anticipate, along with consideration of what is intended within the scope of research.

A second issue that warrants attention by publics as raised in this research related to transparency about the complex processes associated with science including unanticipated findings: if approached thoughtfully, increased understanding and engagement with the complexities of scientific practices could result, as well as demystification of how science works (Shapin 1992). Such framing would be considerably more constructive than the imagery of 'Frankenstein' and scientists 'out of control' that accompanied some of the popular media coverage of this research. The general public should hear more about research that does not result in the findings that were anticipated (including scientific 'failures') and most importantly, what regulatory and other procedural mechanisms are in place to assist researchers when their research proceeds in unexpected ways. Furthermore, there needs to be more public attention drawn to regulatory mechanisms that do place limits on research (such as in this case the need for licenses to conduct embryonic research of certain types and the 14-day rule), including making the reasoning behind such mechanisms more transparent through public discussion and debate.

Toward an Ethics of the Unintended and Unanticipated

But how can researchers ask 'what if' questions where they might risk making transparent to themselves and others that they could discover or create something unintended and ethically problematic? We contend that this risk is in fact an opportunity: it is critical to promote more

explicit discussion and frameworks for articulating these considerations particularly in these contentious domains. The ethics statement contained in the Liu et al. (2021) iBlastoid paper and its detailed account of the processes used to consider and reconsider the research (as summarized above) is an opening bid at how such a dialogue associated with unanticipated discoveries might occur.

But to fully embrace the unexpected or serendipity in science and make it both more productive and ethical, we must encourage researchers and their broader communities to create spaces and processes through which they expose their epistemic and other expectations, and probe the concepts, intentions, and values underlying their research, in part to help shape public policy in deliberative ways. These spaces should include laboratories, institutions, oversight bodies, ethicists, regulators, and professional organizations, which as we see in the context of the iBlastoid work included the HREC as well as the key national regulator, NHMRC ERLC in concert with consultation and interpretation of what was then the current ISSCR guidelines (2016). In particular, regulatory authorities should be part of the dialogue on an ongoing basis; the published paper hints that such a process did occur between the investigators and the ELRC, and we would encourage such exchanges also occur on an anticipatory basis, along with continued community engagement and consultation in these spaces. Transparency about this form of consultation would help to further dialogues between researchers and regulators, and assist with viewing the regulatory authorities as more than hoops to jump through. Such an approach also would allow regulations and laws to be more thoughtfully and productively applied in novel and emerging contexts, rather than simply abandoning all hope for regulatory oversight in rapidly emerging domains as has been suggested by some commentators (Savulescu 2021).

Such an approach is likely to have other positive results: as Copeland (2019) notes, awareness of the potential for serendipity results in a democratization of knowledge-production, by widening the scope of expectations about potential sources of knowledge, beyond the specific community within which the research is occurring and perhaps even more broadly to various publics. Discourses of intention and anticipation have both expert and lay interpretations, and the latter warrant more excavation. Scientific communities who seek to learn from their experiences with the unexpected arguably also will be more adaptive to the broader needs of society, and generate more timely and effective responses to new problems (Michener et al. 2009).

Of course, there is a cautionary note about stories of serendipity. The history of science is replete with positive examples of serendipitous discovery: penicillin, Viagra, and X-rays are usually cited as such examples. However, there is less said on suspect, discarded, or worrisome findings, particularly where their ethical standing is less immediately obvious (and discovery accounts are themselves misleading, as noted in the classic Woolgar 1976 paper). It may well be that stories of serendipitous findings that are unintended or unanticipated and do not fit into larger narratives of scientific advancement, or which are negative findings, just do not get told. It may also be that researchers do not have traditions of talking about them, but doing so could help them to be more anticipatory and help to shift public expectations about

science. More attention to the processes rather than merely the products of science would assist us in reconstructing these incomplete sorts of accounts of how science works. Again, the ethics declaration in the iBlastoid publication makes the processes of unintended discovery more visible and promotes consideration of how researchers have negotiated local and general norms in that context.

Need for interdisciplinary dialogues and starting the conversation

iBlastoids, and blastoids in general, raise a series of issues including consideration of the ethical dimensions of their ontic state (e.g., there are likely to be disagreements about whether they are embryos, clones, or models), how to understand intention and anticipation in serendipitous and novel discoveries, and the ethical and social implications of the mission-based context in which this research is embedded. These issues can only be understood and unpacked by interdisciplinary teams working together from the early stages of research and throughout the research process. Such teams can bring diverse skills that permit identification of these types of issues particularly in areas of contentious science, allow development of understanding of the regulatory processes that govern this science including both what is explicit and what may be intended but currently be unclear or unaddressed, and help to anticipate potential future impacts. This type of engagement allows development of the broad-based capacities that Guston describes when articulating what RRI could do for scientific research, and also can ground deliberative processes which can contribute to regulation and public policy.

Researchers typically do not set out to create contentious issues or ethical breaches; collaboration with an interdisciplinary team can create space for dialogue and the rich context necessary to foster reflexivity, thus allowing the envisioning of future possibilities together with more anticipatory practices and greater attention to multiple perspectives on the research. Hence we contend that it is critical not just to build, model, create, and discover but to reflexively engage with interdisciplinary scholars, regulators, funders, and various publics on an ongoing basis, in order to facilitate innovative and transformative scientific research in these sorts of rapidly changing domains and prepare our minds for chance.

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