STEM CELL DEVELOPMENT AND THE PATHWAY MODEL: SCIENTIFIC PUZZLES AND BIOETHICAL ISSUES

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This thesis examines various scientific puzzles and bioethical issues that are related to the pathway model of stem cell development. This model has been criticized in the bioethics and philosophy of science literature by those who claim that it: (1) oversimplifies development in ways that misrepresent scientific understanding,[1] (2) leads to poorly informed scientific and clinical decision-making,[2] and (3) lacks appropriate justification.[3] Robert et al (2006) rely on these points to claim that scientists who rely on this model are acting "unethically," because the model inaccurately oversimplifies development and suggests unrealistic future therapies.[4] In this project I provide an analysis of the rationale that underlies the pathway model in the context of hematopoietic stem cell biology. I suggest that this model is representative of current scientific understanding and that it can be used to appropriately inform decision-making. In order for this model to appropriately figure in various decision-making processes, the assumptions and reasoning strategies that it depends on must be appreciated, as these clarify the scope and limits of the model.

[1](Robert, 2004).
[2](Robert, Maienschein, and Laubichler, 2006).
[3](Oyama, 1998; Oyama, Griffiths, and Gray, 2001).
[4][23](Robert et al., 2006).

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1.0 INTRODUCTION

In the bioethics and philosophy of science literature, the claim that biological phenomena are causally complex has become somewhat of a truism. For any biological phenomenon of interest, there often seem to be a multitude of causal factors that work together to produce it. However, when scientists explain and discuss biological outcomes, they do not always cite or appeal to a large amounts of causal detail and they seem to simplify characterizations of the causes at work. One example of such a simplification, is the pathway model of stem cell development–a model that represents a linear sequence of developmental steps, where few causal factors are represented as controlling each of these steps.[1][2] Recently, this model has come under attack in both the bioethics and philosophy of science literature, which claim that it: oversimplifies the developmental process in ways that misrepresent our best scientific understanding (Robert, 2004), leads to poorly informed scientific and clinical decision-making (Robert et al., 2006), and lacks appropriate justification (Oyama, 1998; Oyama et al., 2001). The attention that this model draws in stem cell biology and the public sphere warrants taking a closer look at these criticisms. What is our best scientific understanding of stem cell development and how does this model capture, or fail to capture, this work? What rationale, if any, underlies the ways that this model simplifies the causal complexity of development? Finally, how should this model influence decision-making in

[1]Discussion of stem cells in the bioethics literature has typically focused on ethical issues related to their extraction and grown from human embryos (Shapiro, 1999; McLaren, 2001; Lo and Parham, 2009). As recent developments have allowed scientists to cultivate pluripotent stem cells without using human embryos–cells referred to as induced pluripotent stem cells–it has been argued that many ethical debates focused on human embryos are or will become outdated (Hurlbut and Robert, 2012). In either case, this paper focuses on another topic related to stem cells and stem cell development, viz. the simplification complex processes like development and how these relate to bioethical issues.

[2]An example of this model, from the context of hematopoietic stem cell biology, is displayed in Figure 1 of chapter 2.

various contexts like medical research and clinical practice?

This project examines the rationale behind the pathway model of stem cell development and it explores how this model should influence decision-making. My analysis in this thesis focuses on hematopoietic stem cells, which give rise to the cellular components of the blood. This cell type provides a useful example to analyze, because hematopoietic stem cells are viewed as "a paradigm" for understanding adult mammalian stem cell biology,[3] they have influenced the creation of "basic concepts" in stem cell biology,[4] and they are the most well-understood stem cell system.[5]

The rest of this thesis is outlined as follows. In the second chapter, I examine criticisms of this model in more detail, in particular, criticisms from the perspectives of bioethics and philosophy of science. A significant portion of this chapter is devoted to providing a positive analysis of the reasoning behind the content and use of this model. This analysis relies on Woodward's (2003) interventionist account of causation and further distinctions I suggest among types of causal factors. I argue that the simplifications inherent to this model are justified by a principled and appropriate rationale, but that these simplifications depend on assumptions that should be make explicit when the model is used to explain development. The third chapter of this thesis examines how the pathway model of hematopoietic stem cell development should figure in medical decision-making. This chapter focuses on clarifying the limits and scope of this model. I examine three main features that constrain the use of this model in decision-making. These constraints include (1) the type of stem cells under consideration, (2) the surrounding environment of the stem cells, and the (3) form of stem cell treatment being discussed.

This thesis explores a connection between distinct projects that have taken place in the domains of bioethics and philosophy of science. My work is motivated by the view that ethical considerations associated with the pathway model are helpfully informed by an understanding of the scientific reasoning that supports the model. An additional motivation is that for whatever methods and strategies are employed in scientific contexts, reflection

[3] (Li and Li, 2006) (Orkin and Zon, 2008, 641), (Ema, Kobayashi, and Nakauchi, 2010, 2).

[4](Ema et al., 2010, 2).

[5](Blank, Karlsson, and Karlsson, 2008, 492),(Orkin and Zon, 2008, 641),(Rosenbauer and Goodell, 2014, 65).

on associated ethical issues is valuable and provides an important larger picture view of scientific practice. In short, there are good reasons to view connections between bioethics and philosophy of science as important and worth exploring.

2.0 PATHWAY MODEL: RATIONALE

2.1 INTRODUCTION

In the bioethics and philosophy of science literature an increasingly common claim is that scientists over-simplify complex biological phenomena in problematic ways. These claims have targeted discussions of development[1] and the monocausal model of disease,[2] which both appear to privilege very few causal factors, while leaving many other causes unaccounted for. In these cases, it has been claimed that scientists simplify biological phenomena in ways that: (a) misrepresent our best scientific theories and understanding,[3] (b) lead to poorly informed scientific and clinical decision-making,[4] and (c) lack appropriate justification.[5] More recently, these claims have been extended to the particular context of stem cell biology, where concise linear pathways are used to represent stem cell development, which is the process by which stem cells differentiate into various cell types. In this chapter I focus on these pathway models[6] of stem cell development, the criticisms they have faced in the literature, and what reasoning, if any, underlies their use in stem cell biology.

An example of one of these pathway diagrams is shown in Figure 1, which represents the differentiation (or development) of hematopoietic stem cells.[7] Hematopoiesis refers to the development of a particular precursor stem cell (a multipotent hematopoietic stem cell) into various cellular components of the blood (e.g. erythrocytes, lymphocytes, monocytes,

[1] (Oyama, 1998, 2000).
[2] (Alex Broadbent, 2009; Griffiths, 2006; Kitcher, 2003; Kendler, 2012).
[3] (Robert, 2004).
[4] (Robert et al., 2006).
[5] (Oyama, 1998, 2000; Oyama et al., 2001).
[6] This type of model is also called models are also called a " 'classical' hierarchy diagram "(Orkin and Zon, 2008, 641).
[7] I will discuss hematopoiesis and this pathway diagram in more detail later on in the paper.

platelets, and granulocytes). In this model an early precursor stem cell is located upstream, while the variety of cell types that the precursor can form are located downstream.[8] The cell types are connected by arrows, where factors that control or support each step are represented along each arrow. This type of pathway model is the focus of recent criticisms in the bioethics literature. Robert et al (2006) support the claim that these pathway characterizations are merely a "tongue-in-cheek" model, which scientists do not support or fully endorse.[9] These authors claim that scientists who use this model "are behaving unethically, because this particular way of simplifying the science suggests promises for therapeutic applications that we know to be extremely improbable" (23). Finally, Robert et al (2006) maintain that the pathway model "badly informs scientific and clinical decision making" (21). They suggest that one reason for this, is that the model incorrectly suggests that particular factors control or drive development, in the way that we might simply drive a car along a road. The authors view this model as overly simplified in the sense that it (1) only cites a subset of all of the causes involved in development and (2) naively suggests that these few factors have "control" over the development process. The authors suggest that a more realistic and scientifically grounded understanding of development supports a "holistic" and "dynamic" view of this process, where many causal factors interact in complex ways to orchestrate a developmental process. This dynamic process is not amenable to the identification of few causal factors with control over development, as the pathway model suggests.

These criticisms of the pathway model in stem cell biology lead to a number of puzzles. If this model is a gross misrepresentation of our best scientific understanding of stem cell biology, why do scientists in this field continue to use it? If this is merely a tongue-and-cheek model, why do scientists seem to suggest that this model is both accurate and valuable? In this chapter I argue that there are principled and justified reasons for employing pathway characterizations in explanations of stem cell development. However, I will suggest that these characterizations rely on particular assumptions and goals that need to be appreciated in order to understand the limits and scope of such characterizations, and how they should inform decision-making. In this chapter I focus on providing an analysis of the rationale

[8] In Figure 1 the upstream cells are located at the top of the page, while the downstream cells are located at the bottom of the page.

[9] (Robert et al., 2006, 21).

that underlies the pathway model, while in the following chapter I further examine how the assumptions, scope, and limitations of this model clarify how it should be used in decision-making. My analysis in these chapters will focus on a particular type or lineage of stem cells, which are referred to as hematopoetic stem cells (HSC). This cell type provides a useful example, because they are viewed as "as paradigm" for understanding adult mammalian stem cell biology,[10] they have influenced the creation of "basic concepts" in stem cell biology,[11] they are the most well-understood stem cell system,[12] and they are "the only stem cells routinely used in the clinic."[13]

2.2 THE PATHWAY MODEL OF STEM CELL DEVELOPMENT:

The pathway concept is very common in biology and biomedicine. Scientists discuss metabolic pathways, cell-signaling pathways, gene expression pathways, developmental pathways, and pathways from genotype to phenotype.[14] The use of this concept in stem cell biology has similarities to its use in these other biological contexts. I will mention some of these similarities throughout my analysis, insofar as they help clarify the reasoning behind this concept in stem cell biology. In the following section, I will suggest that the pathway model involves at least three main features: (1) a sequence of ordered steps, (2) where some phenomenon or trait is represented at each step, and (3) where these steps are caused by controlling or regulatory factors. After clarifying these features, the rest of my analysis will focus on the three main questions: What are the main features that characterize the pathway model in stem cell biology? How do scientists rely on this concept in their explanations of development? In particular, if development is a causally complex process how and why do pathway models contain such sparse causal detail?

A significant focus of stem cell biology is on the development or differentiation[15] of stem

[10] (Li and Li, 2006) (Orkin and Zon, 2008, 641), (Ema et al., 2010, 2).
[11](Ema et al., 2010, 2).
[12](Blank et al., 2008, 492),(Orkin and Zon, 2008, 641),(Rosenbauer and Goodell, 2014, 65)
[13](Rosenbauer and Goodell, 2014, 65).
[14]For further discussion of the pathway concept in biology, see (Schaffner, 2008).
[15]I use these terms interchangeable, following the scientific literature.

cells. While scientists are interested in understanding and explaining many features of stem cells (e.g., their ability to self-renew), it is their capacity for *differentiation* that motivates the use of the pathway model. Differentiation in this context, refers to a set of changes in the state or phenotype of a biological system over time. These changes are understood as taking place in a sequential fashion, where one state precedes a second state, the second state precedes a third state, and so on. The sequential nature of these changes is one important motivation for the pathway model—a path or sequence of steps is used to represent the ordered changes that stem cells undergo. With respect to the pathway model for stem cell development, the sequential steps are represented with arrows that connect upstream and downstream factors. Sometimes these sequences are represented in a strictly linear fashion, sometimes they are cyclical,[16] other times they branch with many earlier states leading to the same final state, or one earlier state leading to many final states. These features of the pathway concept are common to its other uses in biology. In biochemistry, metabolic pathways refer to sequential changes in metabolites as they are modified, in biochemical genetics, gene expression pathways involve step-wise molecular changes that transmit various signals, and in embryology, developmental pathways characterize the set of changes that an organism undergoes overtime. In all of these cases, the ordered sequence is significant in the sense that getting from an earlier state on the pathway to a later state necessitates moving though the steps or intermediates that span these states. In other words, the only way to get from an earlier state X to a later state Y, is by progressing through the intermediates that link these states, unless there is an alternative pathway or route in between these states.

While the sequential or step-wise nature of changes is one important feature of the pathway model, a second important feature involves that actual states, traits, or phenotypes that are changing and how they are represented. In the case of stem cell biology, the steps along the pathway connect up particular stem cell types–types that all derived from the original multipotent stem cell. These stem cell types are distinguished on the basis of exhibiting different cell surface and intracellular proteins, structural features, and functional roles (Kiel, Yilmaz, Iwashita, Yilmaz, Terhorst, and Morrison, 2005). For example, consider

[16] An example of a cyclical pathway is the Kreb's cycle a metabolic pathway involved in energy breakdown and production (Bechtel and Abrahamsen, 2005; Bogen and Machamer, 2010; Bechtel, 2011).

platelets and erythrocytes, which are downstream products of early multipotent stem cells. Platelets are colorless cell fragments involved in blood clotting, while erythrocytes are red disc-shaped cells that primarily serve in oxygen transportation. The different cell receptors that are used to distinguish stem cell types are referred to as "phenotypic markers" (Wognum and Szilvassy, 2015). Other downstream products of the early multipotent stem cell also vary significantly with many playing different roles in immune system functions. So each step along the pathway represents a particular cell type and the types are lined-up on the basis of which come before and after others in the developmental process.

A third feature of the pathway model is that for each step in the pathway, particular factors are viewed as causing or controlling each step. For example, consider one of the first steps from the original hematopoietic stem cell (HSC) to the common myeloid progenitor (CMP) cell, on the upper left of the diagram 1. At this step two factors are listed along the arrow that connects the HSC to the CMP–these two connecting factors are stem cell factor (SCF) and the hormone thrombopoeitin (Tpo). Scientists claim that SCF and Tpo "regulate" the proliferation of CMP from HSC and that they are factors that "promote expansion."[17] In this manner, the factors listed at each step in the pathway model are viewed as having types of control over the outcome of each step.

I have discussed three main features of the pathway concept as it figures in explanations of stem cell development. These pathways involve: (1) a sequence of ordered steps, (2) where some phenomenon or trait is represented at each step, and (3) where these steps are caused by controlling or regulatory factors. The sparse causal information in the pathway model raises a number of questions. If developmental processes are complicated and involve, in some sense, a large number of causally relevant factors, how do these pathway models characterize such processes while containing so few factors and such an economy of information? Why do scientists represents such few factors as controlling development and what does it mean to attribute control to these factors? I turn to these questions in the next section by first introducing the interventionist account and analyzing the pathway model within the framework of this account.

[17]For more on this, see: http://www.ebioscience.com/resources/pathways/hematopoiesis-from-multipotent-stem-cells.htm.

2.3 CAUSAL REASONING AND THE PATHWAY MODEL.

In this section I provide an analysis of the causal reasoning behind the pathway model. As my analysis relies on Woodward's (2003) interventionist account of causation, I first discuss this account then examine how it can be used to understand the use of pathway models in explaining stem cell development.

2.3.1 Interventionist account.

Woodward's interventionist account of causation is motivated by the view that causal relationships are relationships that are potentially exploitable for purposes of manipulation and control (Woodward, 2003). On this account, the relata of causal relationships are variables, which represent properties or entities of interest, e.g. genes, phenotypes, etc. These properties can take on different values, which represent different states of the property in question. For example, variable C might represent the phenotype "eye color," where this variable can take on different values (0, 1, 2,...n), which in this case might refer to different eye colors (blue, green, brown, etc.). On this account, to say that a variable C is a cause of variable D means that, given some background circumstances, an ideal intervention that alters the value of C results in a change in the value of D (Woodward, 2003). To say that this intervention is "ideal" means that it only alters the value of C, and that this causes a change in the value of D, through C and not through any other route. The notion of an ideal intervention is represented in Figure 2 and it is intended to capture the notion of an unconfounded experimental manipulation of C with respect to D. An ideal intervention on C with respect to D (i) should not be associated with a variable Y that can cause D, (ii) it should not directly change the values of D without going through C, and (iii) it should not directly change the values of any of the intermediate variables that span C to D, without going through C first.

The causal relationship between these variables can be characterized by a pattern of counterfactual dependance that captures how specific changes in the value of C would result in specific values of D. Consider another case where the variable C represents a gene where

different values of this variable represent different gene variants {variant 1, variant 2...}. Additionally, D is a variable representing a trait where this variable can take different values representing different versions of the trait {trait 1, trait 2...}. To say that C causes D means that changing C to a specific variant (e.g. variant 1) will cause D to take the value of a specific trait (e.g. trait 1). For example, suppose that variable C represents the Huntington's disease gene and that variable D represents Huntington's disease. C can take on a range of values (0, 1, 2, ...) that represent different numbers of trinucleotide repeats in this gene and D can take on two values (0 or 1), which represent the absence or presence of the disease. To say that this gene causes Huntington's disease means that, hypothetically, *if* there were an ideal intervention on this gene that changed the number of trinucleotide repeats it contains, this *would* control or "make a difference" to whether the patient acquires the disease or not. Woodward's account relies on a *hypothetical*–as opposed to an actual–notion of intervention. In other words, the intervention need not be one we can actually perform with current technology, but one that we can hypothetically consider and evaluate. This feature makes sense of the fact that scientists often cite factors as causes even when they cannot actually intervene on them. The suggestion is that, when they engage in causal reasoning they consider the outcomes of hypothetical interventions, or hypothetical changes in the values of candidate causes with respect to particular effects. This makes sense of the fact that scientists claim that genes cause various traits and disorders, despite the fact that current technology is limited in allowing for genetic interventions in humans. The idea is that, when scientists claim that a gene is the cause of a trait, they mean that if there were some intervention that changed the gene in particular ways, that this would make a difference to the manifestation of the trait. Of course, even when scientists cannot actually perform an experimental manipulation, they may gather other sources of information that provide evidence of causal relationships.[18]

[18]One example of this is a natural experiment, which refers to a situation where natural changes set up conditions that can be studied as if they were controlled experiments. For example, in the late 19th century scientists were unable to identify an animal model to use in studying cholera (and they were unable to experiment on humans due to ethical considerations). At this time scientists used cholera outbreaks in human populations to study the disease. These outbreaks were a type of natural experiment in the sense that they involved natural changes or interventions that resulted in disease and that could be used to better understand disease in humans. In many of these outbreaks the cholera bacilli was identified and, ultimately, this bacilli was viewed as an important cause of this disease.

This reveals the importance of hypothetical control in causal reasoning–causes are factors, such that, *if* those factors were manipulated they *would* provide control over the outcome of interest. On face value, this makes sense given goals in this context–scientists want to identify factors that control or guide development. Identifying these factors is viewed as providing an understanding of how this process unfolds in addition to important information about how to potentially control it, for the purposes of treatment and prevention. For example, to say that the *huntingtin* gene is a cause of Huntington's disease, means that if this gene variant were manipulated in humans, this would change the occurrence of the disease. In other words, this gene variant is a kind of light switch for the disease–turning this switch on or off would change whether the disease was present or absent. Our understanding that this gene has control over this disease, is partly what explains why efforts at devising treatments focus on changing this gene variant, or its downstream products. My point here is that assessing which factors are causes of some outcome involves considering whether these factors, when manipulated, would provide control over the outcome.

2.3.2 Analysis of the pathway model with interventionist framework.

Recall that the pathway model of stem cell development involves three main features– (1) a sequence of ordered steps, (2) where some phenomenon or trait is represented at each step, and (3) where these steps are caused by controlling or regulatory factors. My analysis in this section will focus on clarifying the reasoning behind these features of the model and the role they play in explanation.

First, each cell type along the causal pathway can be understood as an outcome or phenotype that scientists are interested in explaining. Any particular cell type on the pathway can be singled out as an effect or outcome to be explained. Furthermore, to provide an explanation, in this context, involves citing the causes of the outcome of interest (where causes are understood along the lines of the interventionist approach). Consider one of the first steps on the pathway again, from the HSC to the CMP cell type. In this case, the downstream CMP cell type represents the explanatory target. The causes that explain this target are the immediately upstream factors listed on the pathway model–both the original hematopoietic

stem cell (HSC) and the two controlling factors, SCP and Tpo (which are listed along the arrow). What does it mean to say that these are the causes of the CMP cell? It means that each of these factors is a kind of "switch" that, when manipulated, provides control over whether the CMP cell is produced, or not. The original HSC cell can be represented as the variable X_1, which can take on one of two values (0,1), which represent the absence or presence of this cell. In order for the CMP cell to be produced, the HSC cell needs to be present, which is represented by X_1 taking on the value (1). If the HSC cell were absent, no downstream CMP cells could be produced. So manipulating X_1 such that it takes on either value provides control over whether the downstream cell is produced–in the sense that the presence and absence of the HSC cell makes a difference to whether the CMP cell outcome occurs.

Of course, just the presence of the HSC cell is not enough to reliably produce the downstream CMP cell: there are other factors that interact with this cause to increase the likelihood that the downstream cell is produced. Furthermore, most criticisms of the stem cell model are unlikely to take issue with the claim that an upstream stem cell is, in some way, causally relevant to production of a downstream cell. What is usually at issue–at least with respect to the criticisms I focus on–is that there are too few causal factors represented and that these factors are viewed as "causing" or as having "control" over the developmental trajectory, where no factors could possibly have such control. These criticisms are motivated by the view that there are surely numerous causally relevant factors for development, where no small set of factors can be accurately characterized as "controlling" the developmental process. Back to our example at hand, in addition to the upstream stem cell, pathway diagrams list two other causally relevant factors for the development of CMP from HSC. Why have scientists listed these factors as controlling this developmental step? What do they mean by viewing them as causes and why have they not listed other causal factors?

Suppose the original stem cell (HSC) is present, in a living organism or in vitro. When scientists claim that SCP and Tpo cause HSC to develop into CMP they mean that they are causes in an interventionist sense–they mean that changes in SCP and Tpo "make a difference to" whether the CMP cell type develops. More specifically, consider an ideal intervention that changed the value of SCP: changing whether SCP is present or absent in

the current environment. Under such an intervention, when SCP is present this increases the likelihood that the HSC cell will develop into CMP. It doesn't make the outcome of CMP development %100 (or even %90) likely, but it makes the CMP outcome much more likely to occur than it would otherwise be in the absence of SCP. This type of causal relationship involves what I call probable causal control. This causal control refers to the *probability* with which each outcome of the contrastive focus is produced when selected factors are manipulated. Consider a light switch C, which can take the values 'up' or 'down' and a light E, which can take the values "on" or "off." In the first case, turning the switch "up" results in a 99% probability of the light bulb being "on" and turning the switch "down" results in a 99% probability of the light bulb being "off." In a second scenario, turning the switch "up" has only a 60% probability of causing the light to turn "on" and turning the light switch "down" only has a 60% probability of turning the light "off." In both cases the switches have some causal control over the state of the light, but their control differs with regard to how *probable* each outcome of the contrast is with interventions on the switch.[19]

When scientists identify and search for causes of stem cell development, they might prefer causes that have a high degree of probable control, but they are often still willing to view a factor as a cause if it has a lower degree of probable control. In an effort to understand and identify factors that influence developmental outcomes, scientists are willing to include any factor with even a small amount of causal control. One problem with common criticisms of the pathway model of stem cell development, is the following. When a scientists cites a cause of stem cell development, these criticisms interpret this as a claim that the causal factor has a high degree of probable control–that this factor provides complete control over the stem cell outcome in the way that we have complete control over driving a car along a highway (Robert et al., 2006). This is not the right way to interpret scientist's claims in this context: they are not suggesting that these factors have complete or highly probable control over development, but just that they have at least some control in the sense of a low degree of probable control over the outcome. It makes sense that they value factors with a low degree of probable control, in comparison to how they regard factors without control at

[19]This notion of probable causal control shares similarities with the suggestion by Lu et al. that we look for causes with high "power" (Lu, Yuille, Liljeholm, Cheng, and Holyoak, 2008).

all, because these are factors that would allow for control over the outcome if manipulated.

What about all of the other seemingly causally relevant factors that are not represented in the pathway model? Surely there are many other factors with probable causal control over the outcome–factors like oxygen, nutrients, and other sustaining constituents. Why are these left out of the simplified pathway diagram? Again, the interventionist account of causation clarifies why scientists do not cite these factors as causes. Many of these factors do not meet a minimal interventionist standard because they do not "make a difference" to the explanatory target that scientists are interested in. In explanations of stem cell development, scientists want to explain a particular contrastive focus, which includes the presence or absence of a downstream stem cell. In the case under discussion, the effect variable Y is the CMP cell, where this variable takes on two particular values of interest–presence (1) or absence (0) of the CMP cell. I have already suggested three factors that meet this minimal interventionist standard: the precursor HSC cell, SCF and Tpo. Aren't there many factors that make a difference to this contrastive focus? Consider factors like oxygen, nutrients, other factors required for life in various organisms. Why aren't these factors cited or represented in the pathway diagram? These are factors that don't "make a difference" to which outcome of the contrast is obtained, because they are required for *both* outcomes. These factors are necessary to consider developmental processes–they don't take place in humans without oxygen for example–but they are not factors that control whether various steps unfold or not.

If we consider a hypothetical intervention of these factors, they make a difference to whether an organism lives or dies–if they are manipulated (and set to various levels) they can either kill an organism or sustain life. Scientists do not cite these factors as causes of stem cell development, because they don't provide control over the developmental steps they are focused on. The contrastive focus of interest is whether a downstream cell is produced or not *in a living organism.* Thus, given this contrastive focus, scientists assume a situation where factors required for life are present. They want to know what causes and controls development in living organisms. Many necessary factors, like oxygen and nutrients, do not provide this control, although it is the case that they are "causally relevant" in the sense that they must be present to consider developmental processes in the first place. Thus,

by specifying a narrow explanatory target, i.e., one that takes place in a living organism, and by focusing on causes that provide particular types of control, as understood within the interventionist framework, scientists justifiably exclude from their explanatory model many factors that one might think of as causally relevant. As it turns out, their selective process of identifying causes is valuable and reasonable, because it identifies factors that, if manipulated, would provide control over the progression of stem cell development.

Although scientists are only citing a few factors at each of these steps, this does not mean that they think that these are the *only* causally relevant factors at each step. In many cases, they are still searching for additional causal factors and when they are found, the pathway model will be updated. In this manner, the pathway diagram isn't intended as a comprehensive or final account of development, but as one that captures what is currently known about the factors that control development.

2.4 CONCLUSION

This chapter provides an analysis of the pathway model as it is used in explanations of stem cell development. I have suggested that this model has three main features, which include (1) a sequence of ordered steps, (2) where some phenomenon or trait is represented at each step, and (3) where these steps are caused by controlling or regulatory factors. Scientists' identification of these factors as causes can be well-understood with the interventionist account of causation. More specifically, these are factors that would change or produce an outcome if they were manipulated in a particular way. The factors represented as causes in the pathway model are not meant to be exhaustive; they are not viewed by scientists as the complete set of causal factors that fully explain this developmental process. However, they are viewed as some of the most important factors that science has thus far identified, because of the fact that they provide a kind of probable control over the explanatory targets that scientists focus on. As research continues to reveals other causes of stem cell development, scientists will likely revise and update the pathway model. It will be interesting and important to continually evaluate how they construct and rely on this model in explanations

of development.

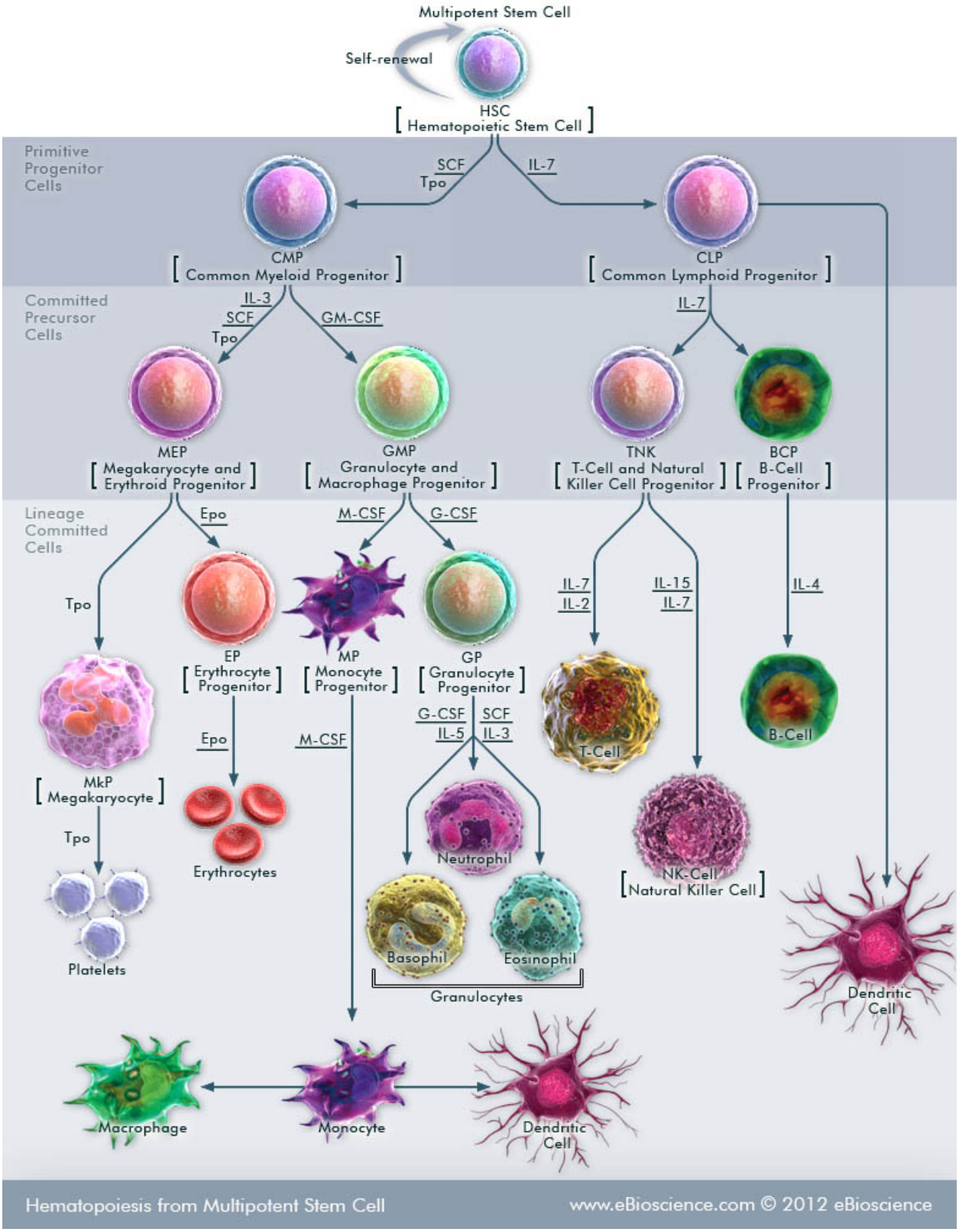

Figure 1: Pathway diagram representing differentiation of hematopoeitic stem cells: http://www.ebioscience.com/resources/pathways/hematopoiesis-from-multipotent-stem-cells.html

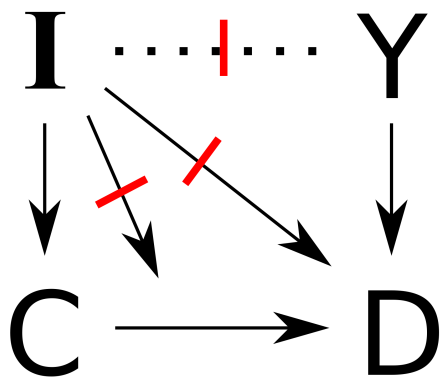

Figure 2: Interventionist account causation (Woodward 2003): notion of an ideal intervention

3.0 PATHWAY MODEL: SCOPE AND LIMITS

In the last chapter I explored the reasoning and rationale behind the pathway model of stem cell development, in particular, the use of this model for hematopoietic stem cells. The current chapter focuses on how this model should figure in various types of decision-making and how we should best understand its limits and scope. A main focus of this analysis addresses recent criticisms in the bioethics and philosophy of science literature, which claim that the oversimplified pathway model badly informs medical decision making and that those who endorse this model are "behaving unethically" because they rely on a model that supports the development of stem cell therapies that are unlikely to come to fruition (Robert et al., 2006, 23). I build on my analysis in the previous chapter to provide a positive account of when the pathway model can well inform decision-making and when it over steps reasonable limits.

3.1 PRELIMINARY CONSIDERATIONS

In many ways, it is unsurprising that the discovery of stem cells and their potential has created so much excitement, particularly with respect to novel disease treatments. The ability to restore and grow specific types of healthy cells, tissues, and organs would be an incredible feat that could potentially allow for curative treatments of numerous devastating and deadly diseases (Kamenova and Caulfield, 2015). Healthy cells might be introduced into patients with neurodegenerative disorders, like Parkinson's or Alzheimer's (Lindvall and Kokaia, 2006); various types of cancers, like leukemia and lymphoma; or blunt force injuries that destroy functioning of vital cells, tissues, or organs. The ability to create

cellular products from precursor stem cells of individual patients would have the potential to provide a specific treatments, with a higher likelihood of being accepted by the patient's immune system without deleterious consequences. These potential treatments contrast with common donor transplantations procedures where patients receive donor products–like blood transfusion and organ donation–and incur a risk of product rejection, host-graft reactions, and immune suppression side effects. Such donor procedures involve onerous challenges for developing successful treatments, in part, because of the complications associated with the acceptance and growth of foreign donor products in patients. Amid longstanding challenges in modern medicine and an awareness of common, plaguing ailments, stem cells can provide an intriguing and irresistible hope. This hope has surely influenced their representation in the media and scientific contexts, which often engage in hyperbolic discussion and expectations. Stem cells have been touted as a providing technology that will "revolutionize the future" of medicine and provide "panaceas for every imaginable disease" (Bongso and Richards, 2004, 827, 828). While most statements on the potential for stem cell treatments have not been this optimistic (or exaggerated), most early and current views on stem cell research have been highly positive.[1]

However, while stem cell research has contributed to medical understanding and (as I will discuss shortly) particular medical treatments, it has yet to supply the groundbreaking advancements that many hoped it would deliver. These perceived shortcomings have contributed to the view that medical researchers have misrepresented the nature of stem cell development and their ability to harness this development for medical use. In the wake of these claims, the pathway model of stem cell development has become a target for criticisms. Robert et al (2006) claim that this model is "misleading" in because promotes a picture of development that is more simplified, controllable, and fixed that it actually is (Robert et al., 2006). These authors have associated such a fixed view with a "mechanistic" framework–or orientation to biological topics–that encourages dividing up biological systems into discrete parts, which interact in predictable ways to produce some outcome of interest.[2] Robert et

[1]For example, see: (Segers and Lee, 2008; Baksh, Song, and Tuan, 2004; Reya, Morrison, Clarke, and Weissman, 2001).

[2]This mechanistic paradigm is alive and well in the philosophy of science literature, particularly in the areas of biology and neuroscience. This current mechanistic framework is often viewed as having originated from a seminal paper by (Machamer, Darden, and Craver, 2000), which has received significant attention

al (2006) have associated the fixed, decomposable nature of the mechanistic framework with the tendency to view stem cell development as controllable, and divisible into discrete causal components. Instead, they support a view of development as a dynamic and holistic process that is not easily divisible into causes or component parts. To support such a mechanistic view in this context, is to suggest unlikely future stem cell therapies. These authors use this line of criticism to claim that scientists who use the pathway model are acting "unethically," because they purposefully misrepresent the current state of this research and its future potential. Robert et al (2006) state:

> Those scientists who publicly endorse a simplistic mechanistic metaphor (often by simplifying their own scientific understanding of the complexities of the biological system) are behaving *unethically*, because *this particular way of simplifying the science suggests promises for therapeutic applications that we know to be extremely improbable.* (Robert et al., 2006, 23, emphasis added)

Are scientists who endorse this model acting unethically? How should the pathway model of stem cell development influence decision-making about research funding, if at all? Does this model suggest treatments that we know will not come to fruition or, alternatively, does it suggest treatments that we have good reason to expect and pursue through scientific research? Addressing these questions matters for a number of reasons. First, the resources we have for scientific research are limited; we want to make sure that they are directed towards projects that can better medical practice and patient lives. Furthermore, the ways that scientists communicate current scientific research influences patients, patient's families, and societal understanding of ailments and expectations for medical care. If these populations expect newly emerging medical treatments because scientists suggest that they are around the corner, the lack of such developments could lead to a mistrust of the biomedical community. Finally, misleading communication of scientific research can place patients and others at risk if such practices encourage clinical trials that are not based on sound research and involve unknown or unappreciated harms. Being able to clarify how the pathway model

in philosophy of science. For example, dominant views in these fields maintain that most or all of the explanations in biology and neuroscience are mechanistic (Kaplan and Craver, 2011; Craver, 2007, 2006) and that "the concept of a mechanisms generates the clearest picture of molecular biology's history, concepts, and case studies utilized by philosophers of science" (Tabery, Darden, and Piotrowska, 2015). The mechanistic paradigm has become the mainstream account of explanation and understanding in philosophy of biology and neuroscience.

of stem cell development should inform medical decision-making and allocation of research funding are non-trivial topics that deserve further attention.

The rest of my analysis in this paper focuses on the following questions: What conclusions or decisions can current scientific understanding of stem cells support? How does understanding of the causal reasoning involved in the pathway model translate into assessments of likely (or unlikely) future therapies? This chapter focuses on three main features that clarify constraints on decision-making that is influenced by or reliant on the pathway model. These constraints include (1) the type of stem cells under consideration, (2) the surrounding environment of the stem cells, and the (3) form of stem cell treatment being discussed.

3.2 THE PATHWAY MODEL: LIMITS AND SCOPE

As suggested in the previous chapter, scientists use the pathway model of stem cell development to identify and discuss factors that cause or provide causal control over developmental outcomes. Robert et al (2006) are correct in claiming that scientists select factors as controlling development. However, I view this selection of factors with causal control as backed by a principled rationale. Scientists select factors as causes when these factors, after being manipulated, would provide control over the outcome of interest.[3] In this section I consider what more can be said about how this reasoning should bear on assessments of the future therapeutic potential of stem cells.

First, what, if anything, gives us reason to think that the pathway model of stem cell development is accurately predictive of the future development of therapies? One reason to view the pathway model as a reliable indicator of the potential for future treatment, is that the causal factors it identifies are currently used in treatments that provide control over therapeutic outcomes. In other words, some of the causal factors that scientists localize on the pathway model of hematopoietic stem cell development are already targeted to successfully control cellular development. Consider the pathway diagram again (Figure 1),

[3]For more on this see chapter 2.

from chapter 2. On the left-hand side, near the middle lower portion of the diagram there is a causal link between an erythrocyte progenitor cell and an erythrocyte (or red blood cell). The factor that links the upstream progenitor cell and the downstream erythrocyte is erythropoietin (EPO), a glycoprotein hormone that stimulates red blood cell production. EPO is routinely administered to patients to stimulate production of red blood cells. This treatment is provided to patients with anemia or certain forms of cancer that diminish red blood cell levels. In addition to this, EPO has been used as a performance enhancing drug in many sports, as increased red blood cell count confers a cardiovascular advantage (Juul and Felderhoff-Mueser, 2007; Lodewijkx and Brouwer, 2011). Scientists state that EPO "controls the production of erythrocytes in mammals," which is a causal claim that is well-interpreted with the interventionist account. Specifically, intervening on and changing levels of EPO results in changes in levels of red blood cell production (Koury and Bondurant, 1992, 649). The fact that some causal factors on the pathway model are related to actual, successful treatments indicates that it is incorrect to view this model as suggesting therapeutic promises that we know to be unlikely, as Robert et al (2006) claim. EPO supplementation is not the only medical therapy that demonstrates the principles of the pathway model of stem cell development. Another example of a successful stem cell therapy is transplantation of hematopoietic stem cells. I discuss this treatment modality more in subsection 3.2.3., where I consider various forms of stem cell therapies. My point here is simply that, before considering the limitations of the pathway model, it is important to note that we have evidence that the pathway model accurately depicts causal reasoning based on experimental findings.

3.2.1 Stem cell type

Part of understanding how the pathway model should influence decision-making about the allocation of research resources requires clarifying the scope and limits of the claims it can support. In particular, assessing the likelihood of future stem cell therapies depends on the (1) particular type of stem cell, (2) environment of stem cell development, and (3) form of therapy. My analysis of the pathway model has focused on hematopoietic stem cell research– the most extensively studied and understood stem cell type. In considering assessments of

stem cell therapies, our scientific understanding of hematopoietic stem cells should be viewed as most directly relevant to assessing the potential of therapies with *hematopoietic cells*, as opposed to other stem cell types. Just because current experimentation has identified factors that control hematopoietic stem cell development, does not indicate that such factors will also be found for other stem cells, for example, stem cells in neural, cardiac, or hepatic tissues. This point might seem obvious or trivial, but it is easy (and exciting) to consider the many diseases that might have treatments if all stem cell types had features we know to be common to hematopoietic cells. The ability to regenerate patient specific tissues, organs, and cell types is a very intriguing treatment modality, which is easy to relate to various conditions that are devastating, fatal, or currently lack treatments.[4] However, current understanding of features of hematopoietic stem cell development does not yet provide clear-cut information about other stem cells. If claims about future therapies with other cells are made by drawing on hematopoietic research, some rationale or justification for the connection should be provided. Otherwise, extending claims that are accurate about hematopoietic stem cells to non-hematopoietic cells is one way in which the pathway model can be extended beyond its limits to provide conclusions that are unwarranted.

3.2.2 Stem cell environment

A second constraint of the pathway model is that it depends on a particular environment or set of background conditions, which is not always made explicit. Experimentation with hematopoietic stem cells involves setting up environments where many external conditions are held fixed or controlled in various ways, while the value of some candidate cause is varied to test for its relationship to an experimental outcome. For example, factors like temperature, availability of nutrients, and even genetic make-up of an animal model can be set fixed at particular values. An advantage of controlling factors in this way is that it can provide reliable evidence for causal relationships. If multiple factors or variables are changing within

[4]If it were possible to create patient specific hepatic, cardiac, or neural cells, for example, we might have the ability to combat diseases that are common or have few successful treatments. The possibility to provide healthy patient-specific cells for diseases that irreversibly damage tissues and organs–like brain cancer or sever liver failure–is difficult to ignore given how hard it is to successful cure and alleviate suffering for patients with such conditions.

an experiment, it can be difficult to assess which of these variables is causally relevant to an outcome. For example, if we wanted to test whether EPO is causally relevant to increased red blood cell production, we could vary EPO levels in mouse models, where EPO levels are the only difference across the models. If we vary EPO levels in these mouse models, in the sense of an ideal intervention discussed in chapter 2, and we see differences in red blood cell production, we have good evidence that this change is due to EPO levels as opposed to some other candidate cause. This is because the mice either do not have differences across other identifiable candidate causes, or if they do, the intervention is such, that it is not correlated with changes in these factors. However, the ways in which we control factors in experimentation often differs from how we control factors in human patients, which is the population to which we are often interested in extended experimental claims. Even though experimentation with animal models indicates that EPO has causal control over red blood cell production in mice, it may be the case that there are other causal variables that also influence red blood cell production, but that we have not identified yet, perhaps because we have (unknowingly) held them constant in the experimental set up or failed to measure them altogether.[5]

Identifying and studying a causal factor in such an experiment, is relative to an environment where many other potential candidate causes are held fixed. We may not be able to hold these external causal factors fixed in other situations–e.g. in other animal models, experimental settings, or even in human patients, where we ultimately aim to develop treatments. In this manner, the pathway model of stem cell development–and the causal factors it identifies–are dependent on assumptions about holding various external factors constant.

[5]Recent work on hematopoietic stem cells suggests that there many more factors with roles in controlling development than scientists previously thought. Scientists are starting to refer to stem cell "niches" as sets of causal factors that make up micro-environments, which influence development(Li and Li, 2006). These niches are related to both bone and vascular areas, and are thought to involve various signaling factors that regulate development (Chotinantakul and Leeanansaksiri, 2012; Zhang, Niu, Ye, Huang, He, Tong, Ross, Haug, Johnson, Feng, Harris, Wiedemann, Mishina, and Li, 2003). Experimental work with stem cell niches is relatively new, and these complex micro-environments are much more difficult to control and measure than other single factors like EPO. Thus, although it may be the case that such a niche concept well-characterizes some features of stem cell development, current developmental understanding and the pathway model do not assume such a context or environment. To export causal claims made with the pathway model to stem cell development in other environments (like a complex microenvironment of causal factors or niche) is currently premature, and scientists are often qualifying their causal claims about stem cells to particular environments, within which these causal relationships are studied and supported by research.

To say that EPO is a cause of red blood cell production, means that when EPO is manipulated with an ideal intervention, in a context where other factors are held constant, that this results in a change in red blood cell production. If scientists attempt to export this causal claim to situations where these assumptions do not hold, further justification for the claim should be provided. This point clarifies another way in which the pathway model can be extended beyond its limits. The causal reasoning of the pathway model is guided by experimental work, which relies on various assumptions, including the assumptions about simplified experimental situations. Thus, the conclusions about future stem cell therapies that are drawn from the pathway model are importantly dependent on assumptions inherent to the experimental work on which the model relies. This relativity of causal claim to a set of background conditions is standard for causal claims made in scientific fields. For example, when a scientist claims that saturated fat causes heart disease, she does not mean that saturated fat is the only cause of this disease or that it causes this disease in every person, no matter what other extenuating circumstances are present. There are many other extenuating circumstances that can significantly change whether a person gets this disease while eating a high diet in saturated fat. For patients who eat a high diet in saturated fat, some factors can make acquiring heart disease more likely (e.g., lack of exercise, increased sugar consumption, etc.) and other factors can make the likelihood of this disease much lower (e.g., sufficient exercise, antioxidants, other medications, etc.). When scientists make this causal claim, they usually assume a particular set of background conditions, where other causal factors are held fixed in some range of values, so as to not influence the causal relationship in question. Of course, scientists are not claiming that saturated fat is the only cause of heart disease, or that other factors don't influence this relationships, but just that in a particular standard background context the causal variable provides causal control over the effect variable, in the interventionist sense discussed in chapter 2.

3.2.3 Stem cell therapy

A final consideration that clarifies how the pathway model should be used to support claims about stem cells, involves the *type* of stem cell therapy that is considered. Different forms of

stem cell treatments can vary in difficulty of implementation, relation to current understanding in stem cell biology, and relative likelihood of success given current scientific knowledge. While the pathway model identifies a variety of causal factors and causal relationships that characterize development, there are different ways that these factors can be exploited in medical treatments. One example of a particular stem cell treatment, is hematopoietic stem cell transplantation, which is a treatment currently in use in biomedicine where multipotent hematopoietic stem cells are transplanted into a patient. This treatment is used in patient's with cancers like multiple myeloma or leukemia,[6] where cells in the blood or bone marrow are defective. In these patients, the defective store of immune cells are destroyed with irradiation and healthy hematopoietic cells are introduced via transplantation.[7] This procedure relies on the ability of the healthy precursor hematopoietic stem cells to develop into all necessary downstream cells. This treatment involves a fairly low degree of technical control, as healthy precursor cells are introduced and left to develop in the patient's body without any further guidance or manipulation on the part of the researchers or therapy. The patient's body dictates downstream development of the precursor cell. In this treatment, our understanding of the step-wise development of hematopoietic cells and the factors that play a role in guiding this development does not translate into a focused target of controlling factors or treatments that single out the causes of development. Instead, the model captures the step-wise process of differentiation that transplanted cells follow: the model is entirely compatible and suggestive of this stem cell therapy, which has been successfully used to treat patients with these disorders. Commentators like Robert (2006) et al. should not claim that the pathway model of stem cell development inappropriately suggests the likelihood of successful transplantation therapies, because such therapies are already in use and successful in treating various diseases. However, not all of these therapies rely on using the identified causal factors in the pathway models as targets that we might exploit in treatment. Instead, healthy stem cells are introduced into a patient and the normal factors present in the patient

[6] Additional disorders that involve this treatment include acute myloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, Hodgkin lymphoma, Non-Hodgkin lymphoma, Neuroblastoma, Ewing sarcoma, Multiple myeloma, Myelodysplastic syndromes, glioma, thalassemia, sickle cell anemia, aplastic anemia, immune deficiency syndromes, and inborn errors of metabolism.

[7] These can be stem cells harvested from the patients that are treated (e.g, autologous transplantion) or they can be mixed stem cells, which are derived from both the patient and a donor (allogeneic transplantion) (Schuster, Stupnikov, Ma, Lai, Ma, and Aguila, 2012).

guides development of the cells.

Part of what this example shows, is that there are many ways in which stem cells can figure in treatments, and determining how the pathway model figures in discussions of future therapies depends on what particular therapies are under for consideration. To say that this model supports confidence in developing one medical treatment (like transplantation or EPO-based therapies) is not to say that it can or should be used to support confidence in any imaginable type of treatment. For example, this model is less likely to support confidence in treatments that require highly fine-grained control over stem cell differentiation, because the pathway model does not identify factors with such control. To use this model to support claims of the imminent future development of stem cell treatments with fine-grained control, is to use this model inappropriately. If a scientist makes this claim without providing any kind of further rationale beyond the model itself, this might raise concerns about the motivation behind such claims and what negative consequences they may have, if taken seriously. What kinds of further rationale might be provided here? In many cases, the best kind of evidence is experimental work that reveals a type of control or therapeutic outcome that a future treatment would involve. Experiments which demonstrate the ability to control developmental outcomes with therapeutic measures, in particular, with animal models, would provided some of the best reassurance of likely future therapies in humans. In discussing the potential for future neural stem cell therapies, Lindvall and Kokaia (2006) state:

> It would be premature to launch clinical trials to use stem cells to treat neurological disorders. However, steady progress supports the hope that stem-cell-based therapies to restore and preserve function in the brain and spinal cord can be developed...Before we apply stem-cell therapies to patients, we must be able to control the proliferation and differentiation of stem cells into specific cellular phenotypes and to prevent tumour formation. Furthermore, the efficacy of stem cells and their mechanisms of action should be demonstrated in animal models with pathology and symptomatology resembling the human disease.... Finally, we must remember that however exciting the neurobiological mechanisms might be, the clinical usefulness of stem cells will be determined by their ability to provide patients with neurological disorders with safe, long-lasting and substantial improvements in quality of life. (Lindvall and Kokaia, 2006, 1096)

This statement reveals a number of helpful points. First, it indicates that many scientists who are interested in identifying stem cell therapies (in areas beyond just the hematopoi-

etic system) stress the importance of experimental evidence before viewing such therapies as attainable or appropriate for clinical trial testing. Gaining evidence of successful control in animal models is an important step in achieving stem cell therapies. Second, this statement reveals the care with which scientists can take claims about particular stem cells–in these case neural stem cells and their ability to treat various neurodegenerative disorders. Although hematopoietic treatments are available and used, some scientists are careful not to immediately export these results to neural stem cells, without appropriate rationale. Finally, as suggested at the end of the quotation, the aim of developing stem cell treatments is not just to display control over a complex developmental process, but to afford patients long-term enhancements in their quality of life.

There are many different ways in which we can conceive of using stem cells in novel treatments of human disease. Some of these treatments will be more difficult to carry out than others, some will be more straightforwardly achievable, and others will be more similar to experimental work that is already underway (and successfully used to counteract disease in animal models). Whether the pathway model supports the likelihood of developing successful therapies depends on exactly what therapies are considered. To make the general claim that this model fundamentally suggests treatments that we know to be unattainable is clearly incorrect–successful stem cell therapies are already in use and their method of functioning is clarified by the pathway model. However, it is clear that this model alone cannot reasonably indicate the likelihood of developing just any kind of future stem cell therapy–the particular therapies it most straightforwardly suggests involve those that target the causal factors it identifies or that rely on step-wise formation of cells after transplantation of precursor cells.

3.3 BIOETHICAL CONSIDERATIONS

What claims about stem cell therapies would it be unethical for scientists to make, when drawing on the pathway model of stem cell development? What makes them unethical? I have suggested that scientist's claims should be importantly constrained by (1) stem cell type, (2) stem cell environment, and (3) stem cell treatment. When claims about potential

stem cell therapies are not constrained by these features, further rationale should be provided and claims should be more carefully examined. In this section I further examine why these claims are unethical and what can motivate or pressure scientists into making them.

One clear reason that scientists may exaggerate the promise of future stem cell therapies, is that their own research may benefit from such claims. The ability to secure research grants, other sources of funding, and attention in social and scientific settings is often aided by the perceived potential for a research program to translate into life-saving or enhancing care. Such perceptions of life-saving potential often allow research programs and labs to be much more competitive in securing funding and other resources[8] and justifying the continued value of their research. In a university and private sector climate where scientists are under pressure to secure grants, it is easy to understand their motivation to err on overselling the potential therapeutic outcomes of their work, even if such therapeutic outcomes are still more of a pipe dream. Gannet (1999) discusses scientists tendency to do this as being driven by their "professional interest" and the fact that they have a"professional stake" in the matter (Gannet, 1999, 359). The inability to gain funding or attention can jeopardize their own career and job security, and can encourage them to inaccurately characterize their own work. Such mischaracterization of scientific research is often considered a form of scientific misconduct. As Macrina states:

> "[scientists] can fall prey to self-deception, rationalizing their actions in ways that mislead themselves and others. The term "sloppy science" is frequently used to describe some behaviors, but the distinction between sloppy science and scientific misconduct can be nebulous. Those seeking clear-cut answers commonly invoke the idea of deliberate deception as the defining element in misconduct." (Macrina, 2005, 2)

These misrepresentations of scientific work are not just problematic because of the false nature of the information or the intent of scientists to purposefully mislead others. These misrepresentations can have significant consequences that (1) place patients in harms way, (2) waste limited resources for medical research, and (3) degrade trust in the medical community, by giving patients, patients' families, and society false hopes for therapeutic breakthroughs. Exaggerating the potential for stem cell therapy breakthroughs could encourage clinical trials and steps towards clinical use of a research modality before there is sufficient reason to do

[8]For example, resources like lab space at a university, graduate students, faculty, and assistants.

so. One worry is that this rushed treatment implementation in patients, exposes them to increased risks as the treatment has not been adequately evaluated.

In addition to potentially placing patients at risk, exaggerated claims about the potential for stem cell therapies can funnel limited resources away from research that may positively benefit patients. Even if stem cell research was not rushed into clinical trials on the basis of exaggerated claims, it could stagnate on its way to this step while nevertheless drawing resources away from other projects that could have resulted in successful therapies or scientific breakthroughs. The scarcity of resources and immense advantage that successful treatments can afford patients, make issuing inaccurately positive claims about stem cell therapies unethical. Such claims increase the likelihood of wasting precious resources that, if employed differently, could significantly better patient lives. Finally, if scientists continually make promises about future treatments that fail to pan out, the broader public may lose trust in their claims and in biomedicine in general. This might result in reduced funding of scientific research, increased questioning of physicians and medical researchers in clinical, research and other settings, and a degrading of the relationship between science researchers and the broader public. Of course, there is always an element of uncertainty when scientists make predictions about future treatments. We should want scientists to strive for treatments and even be creative and hopeful in their aims to achieve new treatment goals. Nevertheless, the predictions they provide should be carefully grounded in current research, experimental evidence, and scientific understanding. The three topics discussed in this chapter–(1) stem cell type, (2) stem cell environment, and (3) type of stem cell therapy–provide dimensions along which their predictive claims should be assessed.

One important theme that this analysis raises is how scientists communicate their research to others, e.g. their peers, patients, and the broader public. Instead of just assuming that there are issues with the pathway model, it should be carefully studied and understood. In particular, the pathway model should be viewed as a helpful and important medium for communicating scientific ideas to various audiences. Research has shown that illustrations and diagrams are helpful tools for conveying complex scientific information (Maddalena, 2013). This suggests a helpful role for the pathway model in communicating causal information about developmental processes. As has been discussed in this project, this model

involves important assumptions that must be clarified to understand the information it conveys. Relying on this model to communicate information requires appreciating and acknowledging these assumptions, in addition to the limits and scope of the model. Further work on the reasoning and limits of pathway models of stem cell development would be welcome as stem cell research continues to develop and gain attention.

4.0 CONCLUSION

Causal complexity appears to be ubiquitous in biology. For many biological phenomena, there are numerous causally relevant factors. This multiplicity poses an interesting challenge for efforts to explain and understand biological phenomena. If the causes of biological outcomes are so numerous, it is difficult to see how we could possible cite them all, or communicate such information to our peers or society at large. Depending on their goals and interests, scientists often find ways of prioritizing some causal factors over others and abstracting from significant amounts of causal detail in the explanations they provide. The factors that scientists choose to privilege in their explanations of scientific phenomena matter. The factors they privilege can receive more attention in research, clinical, and social settings, and can be viewed as targets for developing medical treatments. If biological phenomena are extremely causally complex, then scientists will often need to prioritize some causes over others in their explanations. Future work in bioethics and philosophy of science should work to better understand how scientists reason in these situations, whether and how such reasoning practices are justified, and the ethical implications of their reasoning practices, and whether such practices.

The pathway model represents a select set of causal factors, which scientists view as importantly characteristic of stem cell development. The notion of a pathway is common in biology and it typically involves at least three main features: (1) a sequence of ordered steps, (2) where some phenomenon or trait is represented at each step, and (3) where these steps are caused by controlling or regulatory factors. The pathway steps usually represent some biological state of interest and additional factors are represented as factors that control the unfolding of these steps. I have suggested that when scientists identify and cite causes of stem cell development, they are identifying factors that, when manipulated, "make a

difference" to the occurrence and non-occurrence of these steps. These are factors that, when hypothetically manipulated, increase the probability of producing the outcome of interest.

Finally, the pathway model should be viewed as a useful current model, but not one that is in its final or complete form. As scientists gain more information about the causes of stem cell development, they will revise and modify this model. As these revisions take place, it will be important for us to consider why scientists are characterizing development in the ways that they do, what experimental work underlies their characterizations, and how their characterization influences our expectations for future medical breakthroughs.

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