Cloning and stem cells

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Introduction

Abbreviations: ESC = embryonic stem cell(s). iPSC = induced pluripotent stem cell(s). Note: usage varies as to whether the C is included with the abbreviation for stem cell terms. That is, some people will say ESC and some will say ES cells.

Why are cloning and stem cells shown as one topic? Because they are closely related in some ways. Both involve dealing with the progress of cells as an organism develops. A fertilized egg cell develops into a complete organism; that egg cell has the capability to replicate -- and to "differentiate" (change) into different kinds of specialized cells (e.g., heart and kidney). These specialized cells are typically unable to replicate much, if at all.

Stem cells are cells that can replicate and can turn into any of some variety of cells. Potentially, stem cells may be useful in replenishing missing or defective cell populations in an organism.

Cloning (in this context) involves growing a new organism from a single cell of an old organism. In part, this requires that the cell used for cloning be able to revert to the "primitive" state typical of an egg cell -- able to replicate and differentiate. This is particularly a challenge if the cell used for cloning is already differentiated. The common form of cloning that is discussed involves "nuclear transfer"; only the nucleus of the cell to be cloned is used, and it is transferred to an egg cell that has been deprived of its own nucleus. That same nuclear transfer procedure has been used in some procedures for making stem cells -- specifically for making embryonic stem cells.
The word "cloning" has various meanings in biology. The general meaning is to make an identical copy of something. Some organisms, such as bacteria, normally reproduce by cloning; they get bigger, then divide in two, producing two identical daughter cells. Some plants can reproduce from pieces of an old plant -- a type of cloning. Those working with DNA refer to cloning a gene -- making many copies of it outside its normal environment. Note that the "nuclear transfer" type of cloning actually does not clone the donor cell, but only its nucleus.

Overview: The view in 2003

This topic was discussed in the BITN class, Fall 2003. This overview section summarizes the class presentation. The original web materials were designed as a supplement to that class presentation. Although the field has advanced -- spectacularly in some cases -- this overview still seems useful. Much of the basic outline is still germane, and it is fun to compare the current scene with this one from only a few years ago.

We started with a general perspective on what stem cells, regeneration, and cloning are about. We discussed how a single cell, a fertilized egg cell, develops into a complex organism, by the dual processes of cell division and differentiation. Both of these processes are highly regulated. It is as important that cells stop dividing as that they divide. We showed an example of how growth factors interact with a receptor that spans the cell membrane to regulate cell growth. (In fact, such a growth factor receptor is the target of the cancer drugs Gleevec and Herceptin, which we discussed last time.) It is a useful generality that cells tend to lose the ability to divide as they become differentiated. Stem cells are a supply of undifferentiated (or partly differentiated) cells that can still divide. Thus stem cells can replenish missing differentiated cells. That happens naturally. The goal of stem cell work, broadly, is to allow us to use stem cells for medical treatment. We discussed one example of stem cell work, which has turned out to be less positive than the initial results suggested. It is important to realize that we are very early in stem cell work. The negatives we talk about do not diminish the potential of the field, but they should make you cautious about simplified summary headlines about stem cell work.

Some of the figures I showed are from Lodish et al, Molecular Cell Biology (4th edition, 2000), or are similar to figures from that book. This book is available online at the PubMed Bookshelf: http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books. Relevant figures include: Fig 8-32 (Preparation of embryonic stem cells); Fig 14-7 (Production of differentiated cells from stem cells; diagram); Fig 24-8 (Formation of differentiated blood cells from hematopoietic stem cells in the bone marrow). For more about this site, which includes a number of free books, see my Internet - Misc: Books section. (If you are already at the PubMed site, choose Books.)

The big news story of the week was the nuclear transplant work from China, done to circumvent a type of infertility due to cytoplasm problems. The basic procedure here is similar to that used for cloning, although "common cloning" uses nuclei...
from adult cells. A student brought another example of the use of gene chips (arrays) to classify cancer, in this case, breast cancer.

We discussed more of the complexity of the real world of stem cells. We spent much of our time on two examples of how very promising work reported with stem cells has turned out to be more complicated than one might have guessed from the initial report, and certainly from the headlines about the initial report. I emphasize again that I do not mean my presentation on stem cells to be negative about their potential. But I do hope I have de-hyped the work some. There is very little that is well accepted yet, in this rather new field. There is much that is fascinating and exciting.

We then discussed cloning. The area of interest is cloning of mammals from adult cells. We outlined the general procedure of nuclear transfer. We then discussed some recent work which showed problems with cloning. Gene function in developing clones is abnormal, apparently due to failure to achieve proper reprogramming of the transferred adult cell nucleus. Cloning of primates has failed so far; most work has been with rhesus monkeys. Recent work has shown that cell division in this case is quite abnormal, and that this problem is due to certain proteins being missing. These proteins are normally found in the egg nucleus in primates -- and this nucleus is discarded. This same problem is thought to occur with humans; thus we predict that human cloning would not work with current technology. Note that things identified as problems may at some point be solved.

**Terminology**

Stem cells are commonly classified two ways: by their origin, and by their potency (capability).

Stem cell origin. The most common terms, perhaps, have long been embryonic stem cells and adult stem cells. These terms clearly point to the origin of the cells. The term embryonic stem cells usually refers to a specific procedure for getting stem cells from a particular stage of embryonic development -- one that has been shown to work well. In contrast, the term adult stem cells is general, and encompasses a variety of types of cells. For example, hematopoietic (blood-forming) stem cells and nerve stem cells are both examples of adult stem cells. As these examples illustrate, the "origin" terms are fairly straightforward descriptors. The caution is that the term per se does not imply the characteristics, and we must always be careful to remember that our common views of them may or may not be completely correct. In particular, we should not expect various kinds of adult stem cells to behave similarly.

Stem cell potency. This type of term describes what the cells can do. Common terms include pluripotent, multipotent, and unipotent. These terms represent a hierarchy, from having a wide range of capabilities to having only one possible fate. Pluripotent stem cells can become most anything. Unipotent stem cells are restricted to becoming only one special type of cell. Multipotent cells are somewhere in between. As an example, hematopoietic stem cells may become any of various kinds of blood cells, but not other types of cells.

Relationship between origin and potency. The common view is that embryonic stem cells, from early in development, are undifferentiated, and therefore pluripotent. As development continues, cells differentiate to one or another fate, and become of lower potency. Thus adult stem cells are generally thought to have restricted potency, being either multipotent or unipotent, depending on the specific case.
Differentiation. The broad view in biology is that an organism starts as an undifferentiated (unspecialized) cell (the fertilized egg). As development proceeds, individual cells become progressively more differentiated (specialized). Differentiation is usually thought to be primarily unidirectional, especially in higher organisms. Dedifferentiation refers to the process of becoming less specialized; this is probably uncommon in real life, but we will see that it is an important process in stem cell work. Trans-differentiation refers to the hypothetical process in which a cell that is specialized to be one type changes to become specialized of another type. Whether trans-differentiation actually occurs, either in the animal or in the lab, is a controversial issue.

Caution. Stem cells terms are descriptive. Do not take them as definitive. For example, we have said above that adult stem cells have restricted potency. This fits with our general understanding of how differentiation occurs, and agrees with most of our experiences. But it would be improper to conclude that it must always be so. In fact, people are still exploring and debating the properties of adult stem cells -- in part because there are many types. As always in biology, we must take care to not get trapped in our terminology. Biological phenomena often do not classify as cleanly as we would like, or as early work might suggest.

Gene therapy and stem cells: How are they related?

The short answer is that they are distinct techniques, but they can be combined. Gene therapy involves changing the genetic information in a cell. Stem cells are cells that can divide and differentiate into the desired cell type. It is possible to do gene therapy on stem cells. One approach used in the work on treating muscular dystrophy in dogs was of this type. That work is described below: Muscular dystrophy in dogs.

This section is included on both my pages for stem cells (this page) and for gene therapy.

Induced pluripotent stem cells (iPSC)

The hot new kid on the stem cell block is the induced pluripotent stem cell (iPSC). To understand why this development is so exciting, we need to look at the pro and con of embryonic stem cells (ESC). The big plus of ESC is their versatility -- their pluripotency. They can become any kind of cell -- naturally in ordinary development of the embryo into an adult animal, or in the lab. The big minus is that they are hard to get. Getting ESC requires getting a young embryo or newly fertilized egg. In humans, this is technically demanding, and ethically controversial.

So what are iPSC? Briefly, they are cells with ESC capabilities (pluripotency -- the plus side of ESC), but produced without an egg or embryo (thus avoiding the minus side of ESC).

How are iPSC made? The basic idea is to take cells from an adult -- fully differentiated cells such as skin cells, grow them in the lab and treat them, to induce them to dedifferentiate to an ESC-like state.
Why did people think to try that? Because we know it works. Procedures such as the cloning that created Dolly the sheep do something like this. The nucleus of an adult cell is transferred into an unfertilized egg. The new hybrid cell develops into a new organism, a clone of the animal that donated the nucleus. This process is called somatic cell nuclear transfer (SCNT). We understand that the adult nucleus must first have dedifferentiated into an embryonic-like state. If it can happen in an egg, then maybe we can make it happen outside of an egg -- in the lab.

How is it done? And how did people figure it out? Well, the first thing they did was to examine gene expression in ESC. This gave some hints about which genes were likely to be important. Those genes were then checked more carefully. Turns out, adding about four gene products to the adult cells induces them to become ESC-like -- what we now call induced pluripotent stem cells, or iPSC. It's all fairly new, and there are various procedures that work. People are now trying to refine the procedures.

The original procedures used to make iPSC were not particularly efficient, and some aspects of the procedures were undesirable. For example, one of the genes used to induce iPSC was an oncogene -- a gene known to cause cancer. Interestingly, the initial reports from different labs used somewhat different procedures. So, despite the weaknesses, the procedure seems better than isolating ESC from embryos. Even in the few months since the initial reports of iPSC, there have been reports of work on understanding why it works, why it is inefficient, and developing improved procedures.

Are iPSC really just like ESC? That is still an open question. They seem to be quite similar. In particular, they can be made to produce many cell types, as with ESC. On the other hand, they do not seem exactly like ESC when their gene expression patterns are examined. Remember, not all ESCs are the same. It is probably best at this point to be very cautious. The development of iPSC is an exciting new development, but its potential remains to be seen.

Bottom line, are induced pluripotent stem cells the magic answer we have all been waiting for? Whoa. Patience. It is too early to know. We know only a little about them so far. As noted above, they do seem to have some key characteristics of ESC, but are not identical to ESC. The significance of the differences remains to be understood. Further, one of the early procedures for making iPSC used one gene product that may well cause cancer. Better ways to make them are needed -- and are being worked out. So, let's take this as an exciting development, a good story to follow.

Here are a few papers from the iPSC field. They are in reverse chronological order; if you want to read this group of references in historical order, start at the end of this section.

The difference between iPSC and ESC. Although iPSC show many of the key characteristics of "true" ESC, they usually show some differences, and are variable. This paper does a detailed comparison of iPSC and ESC, and shows that transcription of a particular chromosome region is key to the difference, and that this difference is due to imprinting. This would seem to open the door to understanding the iPSC process better, and also to recognizing "better" iPSC lines. A news story: Gene Silencing May Be Responsible for Induced Pluripotent Stem Cells' Limitations (Science Daily, 4/29/10); http://www.sciencedaily.com/releases/2010/04/100425151134.htm. The paper is M Stadtfeld et al, Aberrant silencing of imprinted genes on chromosome 12qF1 in mouse induced pluripotent stem cells. Nature 465:175, 5/13/10.

Making human iPSC that cure a disease. They take skin cells from patients with a genetic defect, cure the genetic deficit, and make iPSC. They then show that these stem cells can form hematopoietic (blood forming) cells. They do not yet carry out the final step, showing that these can be used to treat the patient. Press release from the Salk Institute:

Making iPSC using only one factor. A German group has shown that a single factor seems to be both necessary and sufficient for making induced pluripotent stem cells -- in one particular case. This is a good step forward both in its practical implications (simplicity, and in avoiding the oncogene factors), and in understanding. Its generality remains to be seen. A news story: Single Factor Converts Adult Stem Cells Into Embryonic-Like Stem Cells. February 5, 2009. http://www.stemcellresearchnews.com/absolutenm/anmviewer.asp?a=1571&z=9. The paper is J B Kim et al, Oct4-Induced Pluripotency in Adult Neural Stem Cells. Cell 136:411, 2/6/09.

Disease-specific stem cells. A group at the Harvard Stem Cell Institute (HSCI) used the iPSC technique to make stem cell lines from a number of individuals with a range of genetic diseases, both simple and complex. For now, these lines will be for research. But of course, the dream is that some day it may be possible to make therapeutic cell lines based on disease-specific, or even patient-specific, stem cell cultures. Their press release is: Daley and colleagues create 20 disease-specific stem cell lines - Lines to be part of new HSCI iPS collection available to researchers. August 7, 2008. http://news.harvard.edu/gazette/story/2008/08/daley-and-colleagues-create-20-disease-specific-stem-cell-lines-2/. The paper is I-H Park et al, Disease-specific induced pluripotent stem cells. Cell 134:877, 9/5/08. The PubMed listing, with abstract, is at http://www.ncbi.nlm.nih.gov/pubmed/18691744; a copy of the final manuscript is freely available there.

Understanding and improving the process of making iPSC. The procedure for making iPSC certainly has advantages over the original procedure for making ESC. However, it has its own problems. It is inefficient, and at least some versions of the procedure use a gene that may cause cancer. So, there has been an active effort to understand what is going on during reprogramming, and to find improved procedures. Work at Harvard has made progress. The ease of making iPSC at all has certainly facilitated the work. In this work, they examined the state of the genome and its expression during the reprogramming. As a result of their explorations, they try using a particular drug to aid with the formation of iPSC -- and indeed find that it improves the efficiency. This is rather complex stuff, not easy to read. The main point -- and simple bottom line -- is that they are making progress improving the iPSC procedure. That is very encouraging. Their press release is: Genomic analysis gives new insights into cellular reprogramming - Research uncovers critical events on reverse path from adult to stem cell state. May 28, 2008. http://news.harvard.edu/gazette/story/2008/05/genomic-analysis-gives-new-insights-into-cellular-reprogramming/. The paper is T S Mikkelsen et al, Dissecting direct reprogramming through integrative genomic analysis. Nature 454:49, 7/3/08. There is an accompanying news story by J F Costello, p 45. The PubMed listing for the paper, with abstract, is at http://www.ncbi.nlm.nih.gov/pubmed/18509334; a copy of the final manuscript is freely available there.

Stem cells from skin -- human. The item below this one is about making a type of stem cell with properties similar to those of embryonic stem cells (ESC) starting with skin cells. With mice. Now, similar results have indeed been reported with human skin cells. One group reporting this is the lab of human stem cell pioneer James Thomson, Univ of Wisconsin. Their press release is: UW-Madison scientists guide human skin cells to embryonic state, November 20, 2007. http://www.news.wisc.edu/14474. A news story in Science discusses the Thomson work, plus the similar work from the Yamanaka lab at Univ Kyoto, which was one of the labs that did the mouse work in the next item: G Vogel & C Holden, Developmental biology: Field leaps forward with new stem cell advances. Science 318:1224, 11/23/07. The paper: J Yu et al, Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells. Science 318: 1917, 12/21/07. http://www.sciencemag.org/content/318/5858/1917.abstract.
Stem cells from skin. An announcement that has attracted much attention: three groups reported that they can make a type of stem cell with properties similar to those of embryonic stem cells (ESC) starting with skin cells. If this holds up, it would allow production of the versatile ESC without use of embryos. But a big caution... The work is with mice, and no one yet knows whether it will work with humans. Further, it remains to be seen how well these skin-derived cells really work. That is, the work reported here is an exciting finding, but it is only a "step 1" in what is inevitably a long and complex process. One of the news stories reporting this work: Scientists Use Skin To Create Stem Cells - Discovery Could Recast Debate. June 7, 2007. http://www.washingtonpost.com/wp-dyn/content/article/2007/06/06/AR2007060601345.html.

**Trans-differentiation**

The idea of trans-differentiation was introduced in the section above on Terminology. Briefly, it refers to converting one type of differentiated cell directly to another type of differentiated cell. I also noted there that it is controversial. Interestingly, in the month or so since I wrote that section, it has perhaps become less controversial -- in one way.

There is no problem with the idea of trans-differentiation. It is only a matter of showing that it has occurred. And frankly, until recently, preliminary reports of trans-differentiation just did not seem to hold up.

So, what is new? In the previous section, on Induced pluripotent stem cells (iPSC), we noted that they were developed by a specific procedure. The first step was to explore gene expression in the two cell types of interest. In that case, they were the adult cell used to start and the embryonic stem cell, which was the goal. This analysis then prompted some specific work to see which of the differences observed were key to making the cell change from one to the other. A similar approach seems to have led to trans-differentiation. They analyzed gene expression in the two cell types of interest: the starting type of differentiated cell and the desired final type of differentiated cell. They then tested to see which of those differences were key. It worked.

This seems to be an exciting development. However, some cautions are in order -- beyond the simple obvious one that this is a first report, and needs to be confirmed.

* Lest the procedure discussed above sound simple, I should caution that it is not. The list of gene expression differences is not short or simple. It is a lot of work, some of it trial and error, to sort out what is important. Still, the list of gene expression differences is a huge step compared to knowing nothing about the two cell types. Further, as experience is gained, people will begin to predict which differences are more likely to be critical.

* The specific problem addressed was perhaps a simple one: the two cell types involved were related: both pancreatic cells. It remains to be seen how well the approach extends to other cases. On the other hand, the case dealt with here is quite interesting and hopefully useful.

Blood stem cells (bone marrow, cord blood)

One type of stem cell therapy has been around for a while. Bone marrow transplantation involves treatment with stem cells from the hematopoietic (blood-forming) system, to form a new blood-forming system in the recipient. In modern terminology, this is a use of adult stem cells -- stem cells not only taken from an adult, but which are partly specialized: they are stem cells for the blood system, and they do not change that basic character in this treatment. The method is not without problems, mostly related to the role of the immune system, but it is a long-standing and well-accepted use of stem cells. The work on developing bone marrow transplantation was recognized in the awarding of the 1990 Nobel Prize in Physiology or Medicine to E Donnall Thomas (along with Joseph E Murray) "for their discoveries concerning organ and cell transplantation in the treatment of human disease". See the Nobel site: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1990/index.html.

Cord blood. One source of blood stem cells that is becoming very interesting is the umbilical cord. Harvesting of blood from the umbilical cord (or placenta) at birth may provide a source of blood stem cells that the individual can use later in life. These stem cells may also be useful in treating other individuals. One source of good information about cord blood is the National Cord Blood Program Website, from the New York Blood Center. http://www.nationalcordbloodprogram.org/.

Cancer stem cells

Stem cells, broadly, are cells that can divide and then go on to become "something else". Could one have "cancer stem cells" -- cells that can divide, and which are destined to go on to become cancer cells. This possibility is being considered, and is now thought likely to be true for at least some cancers. One implication is that successful treatment must, somehow, remove not only the cancer but the cancer stem cells -- those cells not yet part of the cancer, but destined to take that route. The picture is complicated; some -- but not all -- cancers do seem to have stem cells. And there is some evidence that the presence of stem cells does affect treatment.

A news article about some aspects of cancer stem cells... "Killing Cancer Stem Cells - A new screening method identifies drugs that selectively target these elusive cells in tumors. " (8/13/09.) http://www.technologyreview.com/biomedicine/23222/.

NIH: Educational sites and reports

Creating a Cloned Sheep Named Dolly -- an introduction to Dolly and to cloning, from the NIH Science Education pages: http://science-education.nih.gov/home2.nsf/Educational+ResourcesTopicsGenetics/BC5086E34E4DBA0085256CCD006F01CB?OpenDocument&Highlight=0,dolly. The page also discusses cloning...
monkeys from embryonic cells -- a result announced at about the same time as Dolly. There are flow charts showing the main steps in the two cloning procedures. For the monkey cloning, the flow chart shows the donor nucleus coming from embryonic cells. The key difference with Dolly is that the donor nucleus came from a cell from an adult animal. The general flow of the cloning procedure is otherwise the same. However, use of adult cells turns out to be a major difference, because of the differentiated state of these cells.

Stem Cell Information -- The National Institutes of Health resource for stem cell research. An educational site on stem cells, from the NIH. http://stemcells.nih.gov/. To start, you might choose Info Center from the top menu bar, near left; then choose Stem Cell Basics.

There are also two NIH Reports listed at the Info Center noted above:

* Regenerative Medicine, 2006. "Written by experts in stem cell research, this report describes advances made since 2001 and outlines the expectations for future developments. It discusses current stem cell biology, not limited to NIH-funded research. Authors explain research using cells from embryos, fetal tissue, and adult tissues."
* Stem Cells: Scientific Progress and Future Research Directions, 2001. Basic background, and discussion of how stem cells might be used.

Human cloning?

In January 2004 we once again hear reports claiming to have cloned humans, or that such work is in progress.

In my opinion, it is extremely unlikely that any of these reports are correct. Further, I believe that is the broad view of the biomedical community.

Why do we take reports of human cloning with such disbelief?

First, as scientists, we find that absolutely no evidence has been presented that any such cloning has occurred. Scientific work progresses by presenting and analyzing evidence. News conferences are not scientific reports. It would be a relatively simple matter to show that a child is a clone of a specified individual, by analysis of the genome. No such analysis, at any level, has been offered.

Second, there are many scientific reasons why cloning work on humans is unlikely. Although several mammals have been cloned, it is still a very difficult process. It is not that the actual operations are difficult, but rather that it is difficult to obtain success. Overall, only around 1% of cloning attempts are successful. Further, cloned animals often show some degree of abnormality. The low efficiency of success and high frequency of abnormalities combine to mean that the chances of producing a normal clone, in any mammal, are extremely low. They also tell us that we lack understanding of some key parts of the process.

In particular, attempts to clone other primates (monkeys) -- still have had only limited success.
Overall, it seems that cloning is a high risk procedure, with more barriers in primates. With that background, it is extremely unlikely that cloning would work with humans (using current procedures). Further, most scientists would argue that there is no basis for even attempting such work with humans.

The idea of human cloning raises ethical questions. It is important to note that there really are two distinct ethical questions here. One is the general question of whether one should clone humans at all. The second is whether there is sufficient knowledge about cloning at this point to allow extension of the procedure to humans. My usual approach at this site is to emphasize the scientific issues, not the ethical issues. However, a reasonable interpretation of my discussion above of the scientific background is that it would be inappropriate to do cloning experimentation on humans at this point, given what we know about the process.

Human cloning: can it be made safe? An article by S M Rhind et al, Nature Reviews Genetics 4:855, 11/03. An overview of issues concerning human cloning; the authorship includes Ian Wilmut, head of the pioneering team that made Dolly. Some of the content is too technical for the general audience, but browsing it should yield much that is accessible and of interest. It includes some nice figures, including a flowchart comparing therapeutic cloning and reproductive cloning.


Human Cloning and Human Dignity: An Ethical Inquiry. Report from The President's Council on Bioethics (the Kass commission, on stem cell research); July 2002. Now archived at: http://bioethics.georgetown.edu/pcbe/reports/cloningreport/


Book. Leon Kass (then head of President Bush's bioethics commission; see above) has written a book: Life, liberty and the defense of dignity - The challenge for bioethics. Encounter Books, 2002. ISBN 1-893554-55-4. I have not seen the book, but there is a review of it in Science 298:2335, 12/20/02, by O'Neil. The review gives an idea of the issues that Kass presents. For those with subscription access, the review is online at http://www.sciencemag.org/content/298/5602/2335.1.summary.

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**Miscellaneous (books, web sites, comments)**

I have thought about trying to subdivide the following collection. But the topics are so interrelated that it is really hard to do so. So, browse! Stem cell work is mixed here with cloning work -- and some involves both. Some resources here emphasize scientific issues, some emphasize ethical issues, and many consider both.
Most books listed here are also listed on my page Books: Suggestions for general reading.

Book. Michael Bellomo, The Stem Cell Divide: The facts, the fiction, and the fear driving the greatest scientific, political, and religious debate of our time. Amacom, 2006. ISBN 978-0-8144-0881-0. A short overview of the stem cell issues. The emphasis is on the broad picture, both in terms of the biology and the social perspective. The book is new enough to deal with the California Stem Cell Initiative and the fall of Hwang. This may be a good place to start for some people looking to get a sense of the stem cell landscape. Also see Sott, 2006 (next item), for more, especially on the biology.

Book. Christopher Thomas Scott, Stem Cell Now - From the Experiment That Shook the World to the New Politics of Life. Pi Press, 2006. ISBN 0-13-173798-8. A stem cell primer, for the general audience. It starts with basic biology, and describes the types of stem cells. It then describes some of the types of work being done with stem cells, and finally the moral and political debate. Scott is obviously an advocate of stem cell work, but strives for balanced presentation of controversies. The best part of the book, for many, will be the basic biology in the first chapters. Also see Bellomo, 2006 (just above); Bellomo may be a less technical introduction to stem cells.

Book. Ian Wilmut & Roger Highfield, After Dolly: The Uses and Misuses of Human Cloning. Norton, 2006. ISBN 0-393-06066-7. Ian Wilmut was the head of the team that cloned Dolly the sheep. Here Wilmut teams with a science journalist to tell two interwoven stories. One is the story of how Dolly came to be, and the other is Wilmut's views of the social issues he has encountered -- and those that are in front of us, especially with regard to human cloning. The story of Dolly is superb -- told by a person who was at the center of it. Wilmut includes the historical background on which the Dolly work built. I found Wilmut's discussion of the social issues somewhat less interesting. He raises good questions, but tends to provide the simple pat answers one might expect from a scientist who is pioneering in the field. That's fine, but it does not add much. Certainly one should not go away simply accepting Wilmut's answers -- or those of any single individual. Perhaps his views will stimulate serious thought on the matter by some. Fortunately (for me), the bulk of the book was on the Dolly story and its background. The level is suitable for general reading.

Book. Stephen S Hall, Merchants of Immortality - Chasing the dream of human life extension. Houghton Mifflin, 2003. ISBN 0-618-09524-1. This is a book by a journalist, not a scientist. It tells the story -- or is it stories? -- of developments in the related fields of aging (especially the hype about telomerase), cloning and stem cells. Much of it focuses on Michael West and a couple of his companies -- including the Bay Area company Geron, a pioneer in aging work. The book has little scientific depth, but the science is rather good so far as it goes. The subject matter of the book has been major grist for news over recent years, and the social issues remain unresolved. In fact, the scientific issues largely remain unresolved. Hall takes the story into 2001 and even 2002. I think this book can be a good introduction to cloning and stem cells, with a little science and a good sense of the public debate. This book is also noted in the section for the topic Aging.


An informational site on stem cells from the Univ of Michigan. The tutorials will introduce you to the types of stem cells, and to potential applications. http://www.umich.edu/stemcell/
Upon the death of Dolly, Nature put up a special "web focus" site, Dolly the sheep. It includes all relevant publications in Nature journals. [http://www.nature.com/nature/dolly/index.html](http://www.nature.com/nature/dolly/index.html)

Nature also has special web sites on stem cells.

[http://www.nature.com/nature/focus/stemcells/index.html](http://www.nature.com/nature/focus/stemcells/index.html). Riches in stem-cell niches: Bone marrow niches, Neural stem cell niches, Drosophila germ cells. (June 2005)
[http://www.nature.com/nature/stemcells/index.html](http://www.nature.com/nature/stemcells/index.html) (June 2002)

Access to Nature web sites may be incomplete, unless you have a subscription (perhaps through your university). In any case, even partial access is probably "useful".

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Do No Harm, from The Coalition of Americans for Research Ethics. A site from an organization opposed to research on embryonic stem cells. [http://www.stemcellresearch.org](http://www.stemcellresearch.org)

Tissue engineering - and stem cells. Tissue engineering is the construction of artificial tissues. Stem cells might be one source of cells for getting started. There is a nice intro to this in The Scientist for Oct 6, 2003 (Vol 17 #19): A Constans, Body by science, p 34. [http://classic.the-scientist.com/article/display/14154/](http://classic.the-scientist.com/article/display/14154/)

Then, on Oct 28 the following news story showed up in my daily news feed, Science in the News, from Sigma Xi:

STEM CELLS GROWN INTO TISSUES from The Boston Globe

MIT scientists today reported the first known success in using human embryonic stem cells to grow primitive versions of human organs and tissues. They say this represents a promising step toward the development of lab-engineered tissues that could one day eliminate some organ shortages.

The researchers, led by Robert Langer, created structures resembling young cartilage, liver, and neural tissues by growing cells on biodegradable polymer scaffolds -- spongelike structures that resemble the shape of the organ to be created. The scientists also exposed the cells to several hormones that normally stimulate the growth of these organs during embryonic development.

The newly forming tissues were implanted in mice whose blood vessels began to grow into the lab-made tissues, supplying oxygen and nutrients needed for further growth. [http://www.boston.com/news/nation/articles/2003/10/28/stem_cells_grown_into_tissues/](http://www.boston.com/news/nation/articles/2003/10/28/stem_cells_grown_into_tissues/)

California Institute for Regenerative Medicine, California's new home for stem cell research not supported by the usual procedures of federal funding: [http://www.cirm.ca.gov/](http://www.cirm.ca.gov/). (The CIRM was established by the voters of California, in Proposition 71, November 2004.)

Vet-Stem.Inc, a company for "Regenerative Veterinary Medicine"; they provide stem cell treatments for horses. [http://www.vet-stem.com](http://www.vet-stem.com). I post this as something of a curiosity, without any judgment on how well documented their technologies are. They do post a reference list, with abstracts, but I have not tried to evaluate how close their services are to what has been shown to be useful.


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**Recent items, briefly noted**

CAUTION. A single report does not a truth make. Stem cells are an area of active work. Many people are trying many things. I will note here some interesting reports. But these are not final answers. Sometimes such reports turn out to not be reproducible, or not due to what the original authors thought. Or even if true, they may not work in humans. Etc etc. This is all part of the normal process of developing new things. Each breakthrough begins with a simple preliminary step. Some of these hold up, some do not. So, here are some news stories -- of various steps along the way.


Cloning of an extinct animal. Cloning can be done from a dead animal -- if genetic material is available. Simplest is to have well-preserved cells from the donor. In this case, the animal was not only dead, but extinct. The donor cells were from the last known specimen of the animal; samples had been taken the year before its death. Cloning "worked"; a live specimen was born. However, it died a few minutes after birth, due to a birth defect. Such defects are not uncommon in cloning, and are probably due to imperfect reprogramming of the genome during the cloning process. Nevertheless, the work is symbolically of interest. News story: Extinct ibex is resurrected by cloning -- An extinct animal has been brought back to life for the first time after being cloned from frozen tissue. Feb 4, 2009. [http://www.telegraph.co.uk/science/science-news/4409958/Extinct-ibex-is-resurrected-by-cloning.html](http://www.telegraph.co.uk/science/science-news/4409958/Extinct-ibex-is-resurrected-by-cloning.html).

Cloning of prize horses. A Texas company, ViaGen, in collaboration with Texas A&M University, has cloned a prize show horse. The clone will be used as stud, not as a performer. Thus the clone will pass on the genes of the prize horse. An interesting development. (Apparently, use of clones is forbidden for thoroughbred race horses, by regulation.) News story: Cloned horses could offer insight into DNA possibilities; January 2009. It appeared originally in The Philadelphia Inquirer, and is now available at [http://www.physorg.com/news152115527.html](http://www.physorg.com/news152115527.html).
Myelination of nerve cells. Myelin is the coating around nerve cell axons; it serves as a type of insulation. Numerous diseases, in man and mouse, involve defective myelin formation. Here, they treat mice that have a myelin deficiency with a special population of nerve stem cells, isolated from human fetal tissue. The treated mice show improvement at two levels. At the cellular level, there is myelin formation. However, even more importantly, at the animal level, there is improved survival of the mice. The survival is an improvement over previous such work, and they attribute the improvement to various specific technical improvements. Still, fewer than 1/4 of the treated mice survived. Thus the work shows both improvement and limitation; much more is to be done before trials with human children. A press release from the University of Rochester, June 4, 2008: Human Stem Cells Show Promise Against Fatal Children’s Diseases. http://www.urmc.rochester.edu/news/story/index.cfm?id=2025. The work is published: M S Windrem, Neonatal Chimerization with Human Glial Progenitor Cells Can Both Remyelinate and Rescue the Otherwise Lethally Hypomyelinated Shiverer Mouse. Cell Stem Cell 2:553-565, 6/08.

Insulin-producing cells. An obvious target for stem cell work has long been to make insulin-producing cells to treat Type 1 diabetes. But it has proved difficult. Here, a group at Novocell (now ViaCyte) reports significant progress: they use insulin-producing cells derived from human embryonic stem cells to successfully treat mice, in a model system. As always, it remains to be seen whether this work translates to real humans. Their press release is: Novocell Reports Successful Use of Stem Cells to Generate Insulin in Mice, February 20, 2008. http://www.viacyte.com/news/press/2008-2-20.html. The work is published: E Kroon et al, Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells in vivo. Nature Biotechnology 26:443, 4/08.

Jose Cibelli, Developmental biology: A decade of cloning mystique. Science 316:990, 5/18/07. A nice overview of the field, on the occasion of the tenth anniversary of Dolly. For those with subscription access, it is online at http://www.sciencemag.org/content/316/5827/990.summary. A general conclusion is that the process is still very inefficient and often produces animals with abnormalities; we don’t know why.

Mice with neurodegenerative disease. The work here is on Sandhoff disease -- or rather a mouse model of it. This is a serious neurodegenerative disease, of the type commonly called lysosomal storage diseases. In the mouse model, they show that mouse neural stem cells provide some benefit to the mouse patient. They also show that human neural stem cells, ether primary or based on embryonic stem cells, work in the mice. A news story: Burnham team is successful in stem cell study, http://legacy.signonsandiego.com/uniontrib/20070312/news_1m12stem.html. The work was published: J-P Lee et al, Stem cells act through multiple mechanisms to benefit mice with neurodegenerative metabolic disease. Nature Medicine 13(4):439, 4/07.

Muscular dystrophy in dogs. Duchenne muscular dystrophy is a muscle weakness, caused by loss of functional dystrophin protein. A dog model of the disease is available. A European collaboration, led by Dr Giulio Cossu of the Univ of Milan, has shown some promising results treating the dogs with stem cells. They use a special type of stem cell, isolated from blood vessels, that is capable of differentiating into muscle cells. They take two approaches. In one approach, they use stem cells from a healthy donor; in this case, the stem cells contain a normal copy of the dystrophin gene, but immunosuppression is required. In the other approach, they use stem cells from the afflicted dog, and use gene therapy to provide these stem cells a new dystrophin gene. The latter approach avoids the problem of immunological rejection. However, the dystrophin gene is huge, and it is currently possible by gene therapy to provide only a fragment of the protein; that fragment has only partial function. Both approaches show some encouraging results -- and limitations. Logically, the approaches might reasonably work with humans, but that remains to be tested. A news story... Muscular Dystrophy: Stem Cell Help? Stem Cell Treatment Shows Potential in Lab Tests on Dogs. http://www.webmd.com/
Stem Cell Experiment Yields Heart Valves. "Scientists for the first time have grown human heart valves using stem cells from the fluid that cushions babies in the womb - a revolutionary approach that may be used to repair defective hearts in the future. The idea is to create these new valves in the lab while the pregnancy progresses and have them ready to implant in a baby with heart defects after birth." The procedure uses fetal stem cells isolated from the amniotic fluid. From Simon Hoerstrup, University of Zurich. Press release, November 17, 2006, based on a meeting presentation: http://www.nytimes.com/2006/11/18/health/18stem.html?ex=1321506000&en=87eaf77ec605f0ef&ei=5090&partner=rssuserland&emc=rss. The work was later published as: D Schmidt et al, Prenatally fabricated autologous human living heart valves based on amniotic fluid-derived progenitor cells as single cell source. Circulation 116:I-64, 9/11/07.

Stretching bone marrow stem cells pushes them towards becoming blood vessels, a UC Berkeley press release (Oct 23, 2006) about work from the lab of Dr Song Li and his students, in the Dept of Bioengineering and Center for Tissue Engineering. Their goal is to take stem cells and get them to differentiate in vitro into muscle tissue, which can then be used to repair damaged blood vessels. They explore the effect of physical stresses on the fate of stem cells. In particular, they show that the direction of stretching forces can affect how the cells develop. The press release is at: http://www.berkeley.edu/news/media/releases/2006/10/23_stretch.shtml. The publication referred to is K Kurpinski et al, Anisotropic mechanosensing by mesenchymal stem cells. PNAS 103:16095-16100, 10/31/06. Online at: http://www.pnas.org/content/103/44/16095.abstract.

A fascinating story about repair of damaged hearts has been developing over the last few years. This may be a good stem cell story -- or it may not be. Briefly... Injection of bone marrow cells (stem cells from the blood-forming system) into a damaged heart leads to a small improvement in heart function. Results from work with model animals were sufficiently encouraging that trials with humans have been done. One interpretation is that the bone marrow cells are changing to become heart muscle cells (more precisely, are changing to allow heart muscle cells to develop). Unfortunately, attempts to show that this happens have all failed. Yet the effect remains -- maybe. It is a very small effect, and is not seen in all experiments. So we have a tantalizing mystery. There seems to be something good happening -- though even that is not entirely for sure. And why it is happening is not clear at all. The following article is an editorial accompanying three reports of clinical trials in humans: A Rosenzweig, Cardiac Cell Therapy - Mixed Results from Mixed Cells. N Engl J Med 355:1274, 9/21/06. Free online at: http://www.nejm.org/doi/full/10.1056/NEJMe068172.

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