Now that the information revolution is peaking, the next revolution will be biotechnology, with genetic and stem cell treatments for chronic diseases leading the way. The U.S. spends close to $3 trillion every year on health care, of which 75% (over $2 trillion) is for chronic diseases. Over the next two decades, gene therapy and regenerative medicine (stem cell therapy) and their spin-offs are likely to replace a significant portion of that $2 trillion per year, making it very easy to see how investments in biotechnology have the potential to grow like Apple did at the peak of the IT revolution (Apple's world-wide revenue in 2012 was $159 billion). California will be again leading the way just as Silicone Valley led the IT revolution, due to state funding of the California Institute for Regenerative Medicine (CIRM). CIRM has attracted the brightest minds to our universities, but is also collaborating with other leading groups around the world and with biotechnology companies with the capability of translating clinical trials into widely-adopted treatments. Alan Trounson, PhD, who is its president, initially trained me in the new field of in vitro fertilization in 1982 when he was in Australia. I have attended some of his lectures on CIRM research projects (summaries of all the projects are available on the CIRM website) and I review his monthly newsletters on the CIRM website (http://www.cirm.ca.gov/about-stem-cells/presidents-stem-cell-research-picks ). Those summaries of the world's literature are truly mind-boggling in regard to the future potential of this field. Those from the last 12 months are summarized below.

It was originally believed that stem cell therapy would always require cells from human embryos, with the ethical/moral dilemmas and immune rejection of "foreign" tissues having to be overcome. Now it has been shown that various adult cells can be reprogrammed into virtually any tissue in the body and because the resulting tissue is from the same person, rejection is no longer an issue. It also was felt that it would not be possible to produce entire organs for transplant, but by using various tissues as a scaffold (e.g. a pig kidney with its cells removed but its structure retained) and combinations of more than one stem cell type, fully functional organs are expected to be a reality.

Perhaps the most promising stem cell treatment will be an upcoming cure for HIV. This involves producing stem cells from the patient that are able to form immune-competent white blood cells, but which have been modified so they no longer have the cell surface receptor for the HIV virus. It is expected that this stem cell treatment will cure the disease, although not necessarily riding the body entirely of the virus. This would replace the $20,000 annual cost of HIV drugs per individual and also the costs of caring for the various problems due to not having fully functional white blood cells. The lifetime cost for caring for HIV has been estimated to exceed $600,000 per individual and the annual cost of HIV treatment in the U.S has been estimated at $12 billion. A CIRM-funded team at the City of Hope in Duarte, CA is close to initiating a phase 1 clinical trial. A CIRM-funded UCLA team is also planning a trial.

The lifetime cost of juvenile diabetes has been estimated at $300,000 and the annual cost of treatment in the U.S. is about 15 billion. The effect on being able to enjoy a normal life is considerable. Beta cells producing insulin do not have to be placed in the pancreas, which is

quite inaccessible. They will be placed under the skin of the arm. Animal studies have confirmed normal control of blood sugar by stem cell treatment. Other stem cell treatments are being actively studied to retain beta cell function in recent onset juvenile diabetics. This is just one example of the recent use of stem cells as immune modulators in the treatment of autoimmune diseases.

Brain and spinal cord diseases and injuries, for example due to strokes or back and neck injuries, are a major source of long-term health expenditure and disability (one in four Americans will suffer from a neurodegenerative disease). It has been shown that adult stem cells can be programmed to form various types of brain cells. One of the most promising is cells that can restore the nerve insulation (myelin) that is lost in multiple sclerosis, but stem cell treatments of epilepsy, stroke, Parkinson's, and Alzheimers are being very actively pursued. Recently methods have been discovered to restore movement and sensation in animals with spinal cord transection, so restoring function in paralyzed individuals is a very real possibility. Trials in patients with Lou Gehrig's, where the spinal cord undergoes degeneration, are planned soon.

Macular degeneration is the commonest cause of blindness over age 65, affecting 2 million Americans. Stem cell therapy is being very actively applied to these patients, with clinical trials already underway by several research groups. CIRM-funded work has demonstrated restoration of functional vision in an animal model.

Adult stem cells can be programmed to form heart muscle cells that beat in unison with surrounding cells and reduce the abnormal heart rhythm that can be fatal in heart attack victims. Heart failure is a major source of morbidity, mortality and disability that may be remedied by stem cell injections. Several trials are ongoing or planned.

Stem cells have been used to form both liver and kidney tissues, with the possibility that regenerative medicine could replace liver and kidney transplants. In the case of the kidney, the scaffolding of a pig kidney will probably be used. Dialysis for kidney failure is rapidly increasing because of the current epidemic of obesity and resulting diabetes.

Use of stem cells from fetal or adult skin is being actively pursued as a treatment for burn victims. It is foreseen that banks of skin cells that allow matching to the recipient will replace other more cumbersome and lengthy surgical procedures involving skin grafting. The latest advance out of Denmark involves a spray gun to apply a uniform layer of skin cells over a denuded body part.

The study of stem cells can have spin-offs in understanding how tissues function or what specific defect is present in each individual with insufficient function of an organ. An example is the discovery of a new diabetes drug that increases insulin production that will be important as a new approach to adult onset diabetes. Another example is the finding that certain patients with Alzheimer's will benefit from an omega-3 fatty acid, DHA.

Both eggs and sperm can be produced from adult skin cells and in the future may be an alternative when testicular sperm are absent or when a woman has delayed her family until the ovaries are no longer functioning well enough for natural fertility or IVF.

In the case of virtually every tissue in the body, regenerative therapy using stem cells will eventually play a role. Additional examples are cells covering joint surfaces, red blood cells for transfusion, and artificial tissue for replacing body parts such as the trachea (already a reality) termed “tissue engineering”. Even erectile dysfunction due to aging has been shown in animal models to be corrected by stem cell injections. It is easy to imagine that injected stem cells will replace hair transplants and make treatment for baldness much more widely available.

I have not even touched on the use of genetic engineering to treat diseases by altering a specific gene or body function or for more efficient food production. This can be combined with use of stem cells, for example for a new treatment for hemoglobinopathies such as sickle cell disease and Thalasemia. Artificial beef has already been produced from stem cells, through a project funded by the Google co-founder, Sergey Brin. Craig Ventner, the person who sequenced the entire human genome using private means now has a company in California exploring genetically altered algae as a new fuel source. Algae oil has already been shown to successfully fuel commercial airliners and military aircraft to prove its utility. However, he believes that a synthetic cell programmed to produce oil as its only function will be the answer to a commercially successful substitute for fossil fuels.

So, here is my summary of Alan’s monthly newsletters over the last 12 months:

August, 2012

Stanford researchers along with scientists from Harvard and the Salk Institute have discovered a compound that will direct stem cells toward heart cells. Providing large numbers of heart stem cells will allow treatment of a variety of disabling and potentially fatal heart conditions, possibly substituting stem cell injections for extremely expensive and risky options such as heart transplantation.

Researchers in Taiwan and UCSF have developed a scaffold of nanofibers, small enough to be injected, as a matrix containing a hormone that encourages development of new blood vessels. By injecting it into the heart of an animal model of myocardial infarction they were able to see recruitment of stem cells that led to growth of new blood vessels and new heart muscle cells. Injection of scaffolds capable of delivering growth factors as well as providing a matrix for new tissue growth will be crucial in developing various regenerative therapies.

A team at the University of Washington used a heart attack model in guinea pigs to show that injected stem cells beat in rhythm with host cells, improved heart function, and decreased abnormal heart rhythm that tends to occur in damaged hearts. They tagged the stem cells with

fluorescence so that they could then record flashing in concert with the host's electrocardiogram. As with many of these stem cell papers, it appeared in a top journal, Nature.

A Scripps, San Diego team has found a brain stem cell that generates nerves that form the outer shell of the brain responsible for functions such as memory and thought, opening the door to generating large numbers of those cells for therapy.

A team at Harvard was looking for inhibitors of cancer and fell upon an inhibitor of sperm production that was effective and reversible. This is the first indication of a "silver bullet" approach to male contraception. Most likely a related molecule will be found that could function as a long-sought-after male contraceptive that does not disrupt any other male function.

A New York team has developed a method to produce red blood cells from stem cells at a rate 10-100 times as efficient as prior methods. It is likely that stem cell techniques will replace donated blood in the future, providing an unlimited supply.

September 2012

A UC San Diego team has found that neural stem cells from humans and animals will grow across an area of spinal injury when placed in a gel containing growth factors. In a rat model of complete spinal transaction the treatment was able to restore some sensation and movement. Human trials using stem cells for Lou Gehrig's disease are just now being embarked upon. Spinal cord injury is a common cause of severe disability. Christopher Reeves was the most famous victim of such an injury, but he unfortunately died before such research could lead to a cure for his paralysis.

October 2012

In a mouse model, a Japanese team was able to reprogram adult cells to develop into eggs. They used a complex process that required culturing them with ovarian tissue to help them mature. They then fertilized the eggs and produced normal offspring that also were fertile. Although much research remains to be done, this could possibly serve as a source of younger more fertile eggs for women who have put off building a family until their 40's because of their career.

Researchers in Brussels have produced thyroid tissue from stem cells that was able to restore thyroid function. Deficient thyroid function is very common and requires many years of hormone replacement that often is not able to restore the level of well-being that existed before the onset of thyroid deficiency. With stem cell transplant a single treatment could replace many years of hormone measurements and hormone treatment.

A San Francisco team has produced a type of neuron from stem cells in adequate numbers to be used in conditions such as Parkinson's, epilepsy, and Alzheimer's. It is turning out, surprisingly, that the brain is a prime location for stem cell therapy. This opens up a whole new era of treatment for difficult, chronic conditions often causing profound disabilities.

A Stanford team has found that neural progenitor cells secrete a protein that signals other cells to perform their normal functions. Such a finding may explain why neural stem cells appear to aid recovery from stroke in animals without continuing to grow in the damaged tissue. Strokes are another cause of profound disability that is receiving attention of stem cell researchers.

Nov 2012

Reprogramming of adult stem cells is an inefficient process. Researchers found that removing a chemical “lock” covering the chromosomes (a particular histone) allowed the reprogramming to occur more efficiently.

Researchers found that cells developing into the pancreatic beta cells that ultimately produce insulin developed better in a 3-dimensional environment than simply growing in a dish. Cells normally develop in a 3D environment, so this finding is not so surprising.

December, 2012

Teams from the Salk Institute, Scripps, and UC San Diego collaborated to reprogram adult cells such as skin just partway back to form progenitor cells that could be pushed toward a particular adult tissue in large quantity in just a couple of weeks. This could make the process of tissue regeneration much more efficient and practical, whereas forming new tissue from stem cells is currently slow and inefficient.

Heart muscles regenerate at about 5% of their number each year, a rate not sufficient to repair damaged tissue. Researchers demonstrated that this normal process occurs from adult heart cells. Another team found two micro-RNA’s that were able to trigger significant growth of heart cells. Many other groups are of course looking at various stem cells that could be injected into the heart to grow new heart muscle cells in numbers sufficient to repair damaged heart tissues.

The most common type of mental retardation is due to “fragile X”. A group in Tel-Aviv have produced an embryonic stem cell line containing the fragile X mutation, and showed that they matured into neurons having the same defects as those from affected patients. Creation of disease models is a powerful way to study the origins of the disease and thereby design direct cellular fixes for the abnormality. These cells came from embryos biopsied for prevention of fragile X in a carrier of the disease. As increasing numbers of preimplantation diagnosis cases are done in carriers of various diseases, these cell lines can be distributed to researchers looking for cures.

A Toronto team has tracked slow and fast developing colon cancer cells in an animal model. The slow growing cells are not sensitive to chemotherapy and they are working on identifying their genetic make-up and their individual sensitivity to chemotherapeutic agents.

January, 2013

A Boston University team showed that transplantation of tissues derived from adult stem cells did not create any immune reaction when transplanted back into the same animal. Since now it is possible to reprogram various adult cells to form virtually any tissue in the body, transplantation back into that same person will avoid any immune rejection of that tissue.

Researchers were able to reprogram nerve cells to form corticospinal nerves that are the ones that deteriorate in Lou Gehrig's disease (ALS). This is a first step toward being able to replenish those nerves in people suffering from that terrible disease.

One in four Americans will suffer from a neurodegenerative disease. Researchers at UC San Diego working with another team in China were able to reprogram adult cells into neurons using a much simpler technique than a mix of several reprogramming factors.

Cancer researchers were able to reprogram T cells, which are diseased in HIV patients and are insufficiently active in cancer patients, to produce stem cells, and then back again to mature T cells which were more active. The regenerated T cells had more youthful chromosomes, with longer telomeres that allowed them to multiply more robustly. They retained the ability to recognize the HIV virus or cancer cells. T cells have been targeted for an HIV cure, by changing them so they no longer recognize the virus and this technique will provide vigorous immune competent white blood cells to restore these patients' full health.

February, 2013

Adult stem cells were reprogrammed to oligodendrocytes, which are brain cells that form the myelin layer around nerves. These cells were able to replace the missing insulation layer around nerves in an animal model with lesions similar to multiple sclerosis.

Adult stem cells from two patients with Alzheimers were reprogrammed to nerves and supporting cells (astrocytes). Abnormal function in their cells was corrected by an omega-3 fatty acid, DHA. This is an example where cells produced from a patient with a disease may reveal what specific treatment may be targeted to them as an individual.

Blood forming adult stem cells were found to grow much better when grown on a layer of perivascular stem cells. In an animal model these cells were able to restore a fully functioning blood system. They also showed they could obtain these "feeder cells" from fat tissue. This illustrates how certain stem cells may need other supporting stem cells to grow well in the lab to provide the number of cells required for clinical use.

March, 2013

Cells have been found in normal breast tissues that act like embryonic stem cells in forming all tissue cell types.

In a mouse model, liver stem cells obtained from near a liver injury grew much more rapidly, forming large numbers of cells in the lab. Specific chemical pathways appear to be activated in those cells to help them to form the larger number of cells required to be placed into a failing liver.

Beating heart cells were created from the skin of patients with specific causes of poor heart muscle function. Those cells showed the same abnormalities of size, gene expression, and rhythm as seen in those diseases. The cells were then tested with various cardiac drugs targeted to their specific defect.

Another team found that when heart cells created from stem cells are grown for a longer time in the lab, they demonstrate a more mature structure, with better muscle fiber content and contractions. This could make it more workable to replace damaged heart tissue.

“Natural killer cells” are immune cells that have been used to kill residual cancer cells. A research team found that large numbers could be produced from stem cells by adding a protein called a cytokine, potentially making one form of stem cell treatment of cancer a reality.

April, 2013

Stem cell researchers from Harvard discovered a new hormone that stimulates pancreatic cells to produce insulin, demonstrating the power of stem cell research. They scanned beta cells produced from stem cells for genes related to replication of those cells, leading to discovery of the new drug.

Another Harvard team removed soft tissues from a rat kidney and seeded the remaining collagen matrix with two kinds of stem cells to produce a kidney that made urine when transplanted. For kidney transplant for humans probably the scaffolding from a pig kidney will be used (pig heart valves have been used in humans for years without rejection).

An Italian team has produced insulin-producing beta cells from skin cells using a series of chemicals to turn genes off and on. The cells restored normal glucose levels in a mouse model of diabetes. This simplifies the production of beta cells from the patient’s own skin cells, avoiding the immune system rejection from using embryonic stem cells.

Two teams have produced brain cells from skin cells that can produce the myelin coating that is lost around the nerves in patients with MS.

Swedish researchers showed that skin cells can be implanted in the brain and then reprogrammed to form nerve cells and their supporting cells. They inserted the gene modifiers in the lab and then used a common medication to activate the genes within the brain itself rather than to grow the stem cells in the lab. This would potentially simplify the process by using the patient as the incubator.

May, 2013

Oregon researchers took donated eggs, inserted chromosomes from an adult cell and produced embryonic stem cells. There may be some tissues that can't be produced directly from adult cells that would require this technique to avoid rejection by the immune system.

Wisconsin researchers reprogrammed skin cells from Down's syndrome patients to study the resulting neurons. They found decreased connections among those cells and many genes that responded to oxidative stress, illustrating how studying stem cells from patients with diseases could eventually lead to new treatments targeted directly to the underlying disorder.

San Francisco researchers have created thymus tissue from embryonic stem cells, which could eventually lead to dual transplant of both thymus and embryonic stem cell-derived tissues to prevent rejection.

San Francisco researchers have grown inhibitory nerve cells from human embryonic stem cells which, when transplanted into mice with epilepsy calmed the overactive nerves that cause seizures. The cells also reduced the cognitive deficits seen in epilepsy.

June, 2013

Using embryonic stem cells, researchers from Houston removed some of the cell surface antigens responsible for immune rejection as a first step toward creating embryonic stem cell-derived tissues that will not be rejected when transferred.

In a remarkable collaboration, 42 researchers in 4 U.S. states and 4 countries studied factors controlling the expression of over 19,000 genes that direct early development of different tissues in the human embryo. Of the 104,000 factors studied, 32,000 were only active in certain types of cells. This Epigenome Roadmap Project, funded in part by our NIH will add to the understanding of various factors that direct the development of specific types of tissue.

July, 2013

Using a series of chemicals, Beijing researchers demonstrated that adult cells could be programmed to produce stem cells capable of developing into all 3 lines of tissues similarly to embryonic stem cells. More and more research is showing that using various techniques, it may be possible to produce all adult tissues for regenerative medicine from adult cells, avoiding the immune rejection that would occur with embryonic cells, and the ethical objections to using those cells.

Japanese researchers added two supporting cell types (lining cells from blood vessels and connective tissue cells to liver stem cells. The resulting mix produced actual liver tissue which, when transplanted into mice developed connections with its host's blood vessels, produced a protein specific to liver tissue, and metabolized drugs.

A London team had shown that photoreceptor cells could be produced from newborn mice that were capable of restoring vision in blind mice. They are now working on producing those cells from embryonic stem cells.

A CIRM-funded team in Los Angeles has produced blood-forming stem cells from a patient with sickle-cell disease, and altered a gene so that normal hemoglobin was produced. They expect a trial to begin early in 2014 as a cure for this disabling blood disorder where the patient's abnormal hemoglobin causes the red blood cells to sludge in small vessels.