Scientific Developments in Human Genetics and Biotechnology

Rev Fischer (Richard) and members of the various communities of believers, I would like to highlight for you this afternoon several key uses of genetic technologies on human beings. The decisions to use and *how* to use these technologies will, now and in the future, need to be going concerns for Christians who believe in the Scriptural mandate of a continuing human stewardship for a fallen world awaiting the final fullness of Christ's Kingdom.

Introduction

The human genome project has opened up a pandora's box of potential change in the way we look, the way be are, the way we live. The chemical identification of the groups of DNA base pairs that constitute a functional gene are but the foundation upon which building blocks of inheritable knowledge will help us understand our complexity as individuals. Along with DNA sequences comes the epigenetic variability that adds yet another level of complexity to the expression of our genes.

With this vast fount of knowledge comes power; the power to heal, the power to create, the power to manipulate the genetic makeup of individual cells, organs, or whole organisms, and indeed successive generations of human beings. Will human beings with such knowledge and power wield that power for good or for evil? Products of this knowledge and their use today are already providing evidence of humankind's selflessness or selfishness, its wisdom or its folly, its loving care or its destructive indifference to fellow humans and to the creation around us.

Procreative Technologies: Making Jack and Jill Go Up the Hill Faster

Almost unbelievable changes in our perception of who we are or who we would like to be as *unborn* human beings have occurred in the last 10 to 15 years. We are now capable of selecting sperm for a genetic make-up that may predict for a child with characteristics more desirable than what might come to be if left to chance or Providence alone. So how are we capable of performing such selection?

Those who engage in procreative technologies are now able to select a pluripotent cell from an eight-celled embryo as young as 3 days old, remove that cell, stain it for various genetic anomalies using different immunochemical and fluorescence staining techniques, and then decide if that remaining 7-cell human creature should continue to develop and be implanted with the expectation of becoming a human infant, *or* should be allowed to die (**slide on preimplantation genetic diagnosis**). You can see on this slide that the removed cell in this case was found to have trisomy 21 shown by the red fluorescent marker. Up to 10 chromosomes can now be evaluated with a battery of fluorescence markers in just one cell. But *even if we believe* that embryos which possess severe genetic anomalies predictive of an infancy with severe deformities, should not be allowed to develop and be born, *who* then *should* be born with *what* degree of the risk of anomalies? *Who* should decide what anomalies are insignificant enough to allow the development of an embryo with such a genetic make-up?

Another question raised by this selection technology is: What constitutes genetic enhancement? At our current rate of knowledge growth, those who desire a child are already beginning to select genetic features to suit their preferences. For some genetic variants or mutations, later phenotypic expression is highly predicable. For most, however, variants or mutations carry with them an unknown chance or degree of expression depending on epigenetic or unknown biological modulations of genetic expression.

Today, different techniques are available that directly assess the DNA itself (**slide2**). In one of these techniques, known as *mutation scanning*, a segment of DNA is screened by a variety of methods to identify variant gene regions. These variant regions are analyzed further to identify any alterations in sequence from the norm. *Target mutation analysis* tests for the presence of a specific type of mutation or set of mutations rather than doing complete sequencing or scanning. *Metabolic tests* can sometimes be used to analyze the genetic absence of key enzymes in a metabolic pathway, as in the case of phenylketonuria (PKU).

So genetic testing is both feasible and for some very desirable. It can prevent severe debilitation in some circumstances but also raises the option to discard embryos or

abort severely deformed fetuses which have undesirable traits or a predictably extraordinarily difficult life.

Pan-genetic Detection

Techniques are now available to test *all chromosomes simultaneously* for various genes. Commercial companies are now springing up world-wide that will test parts or all of your genome for disease risks, bodily traits, and ancestral origins. One company in Iceland, Decode Genetics, does this service if you send in a scraping from the inside of your cheek, and a check for $945! Such pan-genetic testing is achieved by techniques collectively known as microarray technology (**slide3**). The arrays can involve the identification of nucleotide sequences by matching them with known cDNA or oligonucleotides sequences. Single nucleotide polymorphism chips or SNP chips are used. These chips can detect the major points of difference, or polymorphisms, along the entire genome that vary from person to person while ignoring the many DNA sites that are common to us all. More than 900,000 SNPs and a total of more than 1.8 million markers for genetic variation can now be studied with these arrays using the current generation of the technology.

Current applications of this technology include the screening of individuals for acquired or genetically transmitted diseases, the prediction of the genotype of subsequent children, the detection of genetic anomalies in diseases such as cancer, the detection of DNA patterns for determining human ancestry, and use in forensic investigations.

Complementary to this technology is spectral karyotyping or SKY (**slide4**). Using this technique, a 24-color, multi-chromosomal painting assay allows the visualization of all human chromosomes at once. It is highly sensitive in detecting complex chromosomal rearrangements that can be associated with diseases such as leukemias and lymphomas (**slide5**).

With these genetic technologies, complicated algorithms are being constructed to help decide what technologies best suit what purposes.

Epigenetics

Epigenetics has been defined as the study of heritable modifications to genes leading to changes in genome function that occur *without a change in DNA sequence*. This includes: the study of how gene expression changes during the differentiation of one cell type into another, and the effect of environmental factors on the way genes are expressed. In the nucleus of human cells, genomic DNA is highly folded and compacted with histone and non-histone proteins into a dynamic polymer called chromatin. Gene expression, DNA replication, repair, and recombination all act, not on DNA alone, but on this chromatin template. The discovery that enzymes can (re)organize chromatin into accessible and inaccessible configurations revealed epigenetic mechanisms that have considerably extended the information potential of the genetic code. Thus, one genome can generate many 'epigenomes' which help to account for the diversity of cell types in the human body (**slide6**).

Importance in embryonic development

During embryonic development, genome-wide epigenetic reprogramming occurs at stages when the developmental potency of an embryonic cell changes. Already in the earliest stages, embryonic lineages can be distinguished by different epigenetic marks. This epigenetic reprogramming is likely needed for totipotency, the correct initiation of embryonic gene expression, and the early development of distinct embryonic and fetal cell lineages destined to become different organs.

Importance in Oncogenesis

There are far-reaching implications of epigenetic research for agriculture and for human biology and disease, including our understanding of stem cells, cancer and aging. One of the the most studied epigenetic mechanisms, the addition of molecules such as methyl groups, known as methylation, to the DNA backbone, changes the appearance and structure of the DNA and alters how the gene interacts with other interpreting or transcribing molecules in the nucleus of cells. The resultant functional alteration of the epigenome can result in gene expression being turned on or off. Attention to the

epigenomic mechanisms of methylation, histone modifications, and gene silencing are particular foci of the development of new therapeutics in cancer therapy.

These changes also can be inherited for at least a few generations. Studies in identical twins have shown that time spent apart, aging, and differences in lifestyle correlate with variations in their epigenomes. Gene silencing by methylation can alter the normal regulation of cell growth. Cell growth is normally controlled by a balance of genes which suppress growth and ones which amplify growth. Silencing of one or more suppressor genes by DNA methylation or by deacetylation of histones can result in uncontrolled growth leading to a cancer. Inhibitors of histone deacetylation are being developed as cancer therapies and possibly as cancer prevention agents (**slide7**).

<u>As a Mechanism of Plasmodium Invasion of Red Blood Cells</u>

Another application of epigenetic knowledge is the development of malarial prevention and therapy. *Plasmodium falciparum* is responsible for the most severe forms of human malaria. Invasion of host erythrocytes is an essential step of the complex life cycle of this parasite. There is redundancy in many of the interactions involved in this process, such that the parasite can use different sets of receptor–ligand interactions to invade. The parasite can turn off the expression of some of the proteins that mediate the invasion of erythrocytes using chromatin modification resulting in epigenetic silencing. This is far more flexible than direct DNA modification or mutation, and permits fast, reversible adaptation. Turning on or off the expression of these proteins does not affect the capacity of the parasite to invade normal or modified red cells, which suggests that the variant expression of these genes may be used by the parasite to escape immune responses from the host. Parasite proteins that participate in erythrocyte invasion are important vaccine candidates. Determining which proteins can be turned off is important because vaccines based on single antigens of the parasite that can be turned off without affecting its growth would have little chance of inducing protective immunity.

Gene Therapies

Gene therapies were conceived as mechanisms to alter or overcome abnormally functioning genes. In most gene therapy studies to date, a normal or wild-type gene is inserted into the genome so that the abnormal gene is functionally replaced or overridden by the normal gene. To accomplish this, a vector is usually used in order to deliver the gene into the target cell (**slide8**). The most commonly used vector is a virus to which the gene is attached. The cells of the target organ are infected with the virus; once in the cell, the virus releases the gene into the nucleus and the gene begins producing normal functional protein. The types of viruses chosen have properties that allow them to enter the cell and release the gene efficiently while not producing disease related to the virus itself while in the host.

Non-viral approaches to inserting genes into cells include *lipid spheres called liposomes* with carry the gene within the sphere and deliver it through the lipid membrane of the target cell. Using a more novel delivery approach, researchers at the MD Anderson Cancer Center are conducting studies in mice in which two tumor suppressor genes are delivered via lipid-based nanoparticles. Results have thus far shown a reduction in the number and size of human lung cancer tumors implanted in the mice.

Gene therapy has been in clinical testing in humans since 1990 but progress has been slow and several events have set the pace of development back. In 1999, Jesse Gelsinger, age 18, died after receiving gene therapy for an enzyme deficiency. It is thought that his immune system reacted severely to the adenovirus vector. In 2003, the FDA stopped gene therapy trials using retroviral vectors after a child in a French gene therapy trial died of a leukemia-like illness. This child had been successfully treated for a severe immunodeficiency in the previous year. Even if these and other problems are overcome, it must be remembered that most diseases with known causal genetic influences involve multiple gene variants or abnormalities, making it difficult to effectively treat each genetic aberrancy.

The slow progress and the cost and risks of these trials that may benefit relatively few individuals should make us pause to question the wisdom of using such large monetary and human resources that could be used for less costly therapies or preventative measures that could benefit many more individuals.

Ethical Concerns

Ethical concerns that arise from these new technologies include the psychological impact of obtaining knowledge predictive of the development of a specific disease. In cancer diagnosis and therapy, much ethical discussion is already underway regarding the pros and cons of knowing whether one has a gene associated with a high likelihood of cancer. For some tumors, there may be no good screening procedures or no good treatment once the diagnosis is made. In such cases, knowledge of the mutation has questionable merit and may induce considerable psychological harm. Then there is the risk of such information becoming public knowledge, knowledge which employers and insurers may use to deny opportunities and protections to which such person may be otherwise entitled to or qualified for.

As *the way we are* becomes more and more *de*fined and *re*fined in terms of our genetic and post-genetic make-up, the greater will be the risks that we will be perceived as costly liabilities to a society preoccupied with its own concept of health.

What Does it Mean for the Future?

These developments give hope for the diagnosis and prevention of disease where therapies are available. They also provide unprecedented power to health care workers and scientists who want to relieve individuals and patients of genetically-based afflictions but who also may succumb to the desire of individuals to have their progeny in some way advantaged by the enhancement of selected characteristics. Ironically, some individuals possessing what some would call undesirable characteristics would in fact consider life with such characteristics to be the norm such that they feel their children should inherit them. Examples have included some parents with congenital deafness and those with chondroplastic dwarfism. For Christians, it is a time for careful and prayerful discernment as to what the Spirit would have us decide and to do. It is a time that Christian communities need to take time to reflect on what Scripture teaches us about *how* we should deliberate and discern. We must identify and resist the spirits that may lead us down paths of decision-making that will demean our humanity, that would distort rather than redeem ourselves and the creation within which we live. Technology will continue to give humanity more and more power to manipulate the genome and all that it

contains. We not only need Christians with the expertise to understand this technology but to develop effective networks for the exchange of perspectives and for Spirit-led discernment among Christian communities. In this way, all communities of believers can share Spirit-inspired wisdom in order to better counsel its members regarding the promise and pitfalls for genetic technologies for them and for their families. With this same wisdom we can become proactive and formative stakeholders in societal decisions involving genetic technologies.