“Wellness” Genetics and Regenerative Medicine

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Chronic, dysregulatory and degenerative disease processes have become a major medical problem in the aging populations of our world. The problem is further aggravated by life styles that are out of balance with our genes. Metabolic syndrome (visceral obesity, diabetes, atherosclerosis, and hypertension), cardiovascular problems, neurodegeneration (e.g. Alzheimer’s syndrome) and cancers affect a rapidly increasing number of people.

Massive genotyping of large numbers of human genomes allows association studies, mapping common “illness” and “wellness” gene variants that convey susceptibility or resistance to the dysregulatory and degenerative disease processes. We focus our efforts on finding “wellness” variants associated with adaptation to extreme living conditions (e.g. high altitude Tibetans) or healthy aging of the oldest old (e.g. the Chinese longitudinal healthy longevity survey). The common variants found by traditional GWAS (Genome Wide Association Studies) are of scientific interest, but not very useful, clinically, due to their limited biomedical effect and predictive value. However, the new techniques of whole genome sequencing and assembly can reveal rare, evolutionary recent mutations and even *de novo* aberrations and epigenetic changes of greater significance for the individual patient. Still, genetics is just the first step – functional studies in model systems are necessary.

The pig is an excellent model for medical research as well as for testing new methods and drugs for disease prevention and treatment. The size and longevity of the pig makes it especially useful for the study of chronic disease processes that can be monitored and repeatedly biopsied for long periods of time with and without intervention. We have sequenced the genome of different pig breeds, revealing that the pig is genetically very similar to man - in agreement with the similarities in organ development, physiology and metabolism.

We produce genetically designed model pigs prone to develop disease processes like atherosclerosis, metabolic dysregulation, inflammation, neurodegeneration, and cancer. Primary pig cells are genetically modified in culture. Their nuclei are transferred to pig enucleated oocytes that then can develop into blastocysts for implantation in surrogate sows giving birth to clones of pigs. Our HMC (Hand Made Cloning) technology allows production of genetically designed pigs, without a need for micromanipulation. We can also produce clones of pigs, some disease prone and some fluorescing, and perform experiments in regenerative medicine where the fate of healthy fluorescent cells can be followed in the immunologically compatible, disease prone animals.

The cloned pigs can be bred and crossbred to change the genetic load. Thereby, the pathology might be modified to optimize the possibilities for developing and testing new early diagnostic procedures as well as preventive or regenerative interventions. We have formed a Danish Regenerative Engineering Alliance for Medicine. Our DREAM team focuses on using CRISPR-technology to genetically and epigenetically design and reprogram adult somatic cells to cell types useful for cellular therapy and regenerative medicine.

We envisage a “digital” revolution of medicine, sometimes called “Precision Medicine”, combining detailed genomic and epigenetic knowledge with detailed functional recordings and regenerative interventions. “Digitalizing” our pigs with wireless biosensors and imaging devices in combination with regenerative cell manipulations should help us understand how to clinically apply these fantastic new possibilities.