The future for clinical immunology

The last ten years has seen a tremendous increase in our understanding of the molecular basis of different disorders. Clinical immunology is a specialism which is currently developing in different ways, some of which are highlighted here. This discipline has a responsibility to provide a complete array of analytical measurements for the diagnosis and treatment of patients with dysfunction of the cellular and humoral immune system. Immunologists are working towards novel approaches to therapy in clinical immunology and the future is promising. The driver is to find less invasive means of diagnosis and treatment for life-threatening disorders and to improve patient morbidity and mortality.

Early diagnosis of cancer

According to epidemiological studies pancreatic cancer is the fourth leading cause of cancer-related death and the tenth most commonly diagnosed cancer in the United States. Exocrine tumors are the most frequent type of pancreatic cancer where pancreatic ductal adenocarcinoma (PDAC) accounts for 80 percent of malignant tumors of the pancreas. Most patients with pancreatic cancer present with advanced stage disease because patients with early-stage pancreatic cancer frequently do not have symptoms. Distribution of this tumor to distant sites in early stages with lack of effective markers for initial diagnosis and ineffective treatments for later stages of this tumor result in a poor prognosis for patients with pancreatic cancer. Within five years, prognosis for this disorder could be improved by discovering a way to detect microRNA biomarkers in blood for an early diagnosis of this disorder which will result in increased survival rate of patients.

Treatment of Cancer

About 50 percent of human malignancies are known to be due to mutations in the *TP53* gene leading to alterations inp53protein which makes the latter a potential target for cancer immunotherapy. It has already been found that adoptive transfer with p53-specific $CD4^{+}$ T-helper and cytotoxic T – lymphocytes (CTL) eliminatep53over-expressing tumors in mice. p53is immunogenic as antibodies and specific CTLs can be detected in cancer patients. Based on this, clinical trials were initiated to review the clinical and immunological response ofp53-vaccines for immunotherapeutic treatment of cancer patients. Different vaccination strategies varying from dendritic cells, short- and long- peptide fragments and viral vectors have been used. The results from initial clinical trials were disappointing. There is a need to improve the immunogenicity of the above potentiators by enhancing the robustness of the induced effector T-cell responses or by simultaneously targeting additional tumor antigens. It is highly likely that in future the addition of multiple antigens top53-vacinne will make it applicable in many cancer patients.

Disease markers in Breath

Human breath contains over 200 different volatile organic compounds (VOCs). Some diseases, including cancer, are associated with an increase in oxidative stress which generates a specific pattern of VOCs in the breath, known as the breath methylated alkane contour (BMAC). Changes in the BMAC are unique to different diseases allowing the potential identification of disease via the breath. Menssana Research has developed a BreathLink testing system for early diagnosis of breast cancer from the collection and

analysis of VOCs. Together with gene profiling this could help detect otherwise asymptotic tumors.

Cell-free Circulating DNA

Cell-free circulating DNA (cf-DNA) has been reported as a biomarker in acute cardiovascular pathologies and as a mortality predictor in myocardial infarction. Jylhava et al. (2014) investigated whether the baseline cf-DNA concentration could indicate increased levels of early atherosclerosis and cardiovascular risk. The study population consisted of 1337 participants (aged 46–77 years) in the Health 2000 Survey. cf-DNA was quantified directly in plasma using the fluorescence-based Quant-iT™ high-sensitivity DNA assay kit. Increased cf-DNA levels paralleled a group of cardiometabolic risk factors, such as high blood pressure, unfavorable lipid metabolism profile and systemic inflammation in both sexes. In addition, higher cf-DNA levels indicated decreased arterial elasticity and glucose intolerance in women not using hormonal replacement therapy (HRT). The cf-DNA level was also observed to be an independent determinant for Young's elastic modulus but not for carotid artery compliance or beta stiffness index in the women not using HRT. Hence, it was concluded that cf-DNA could serve as an auxiliary biomarker in cardiometabolic risk assessment and as an indicator of arterial stiffness in women not using HRT.

Brain Tumour Markers

Glioblastoma (GBM) is the most common malignant primary brain tumor. Present treatment options for this tumor include chemotherapy, radiation and surgical resection. Its clinical outcome is poor due to its existence in the

body which makes it difficult in imaging. Magnetic resonance imaging is generally utilized to follow patients for tumor recurrence but it is challenging for a neurologist to distinguish between tumor regrowth and treatment effect. Therefore, clinical decisions frequently require a tissue diagnosis by means of surgical biopsy. A major disadvantage of biopsies is that they give an inaccurate picture of the presence of tumor due to inherent heterogeneity. The complex pathophysiology of brain tumors joined with a requirement for improved markers of prognosis and therapy response emphasize the necessity for clinically useful biomarkers that would exactly reveal the complete tumor.

Recently published research (2012) has revealed a microarray-based technology called ‘ immunosignaturing’. By using this technology the type of disease could be established, normally before symptoms were manifest, by capturing the dynamics of circulating antibodies. Antibodies are good biomarkers because of their abundance, high affinity and specificity to their complementary antigen (epitopes), and they have high stability in serum. The benefit to the technique that Stafford employed is that it is inexpensive, simple, and highly sensitive to alterations in the antibody repertoire. Immune surveillance happens constantly and is fairly sensitive to changes in circulating proteins, for example, the introduction of cancer-specific chimeras such as BCR-ABL. From previous findings it is known that cancer cells elicit a detectable humoral immune response. According to Stafford et al, 2012., the precise antigens that may elicit an immune response in gliomas is not known therefore Stafford et al produced a single-use microarray which consisted 10, 000 diverse random peptides in order to

determine the pattern of antibody binding instead of examining single antibodies to a cancer antigen. These microarrays provide information about partial binding therefore by changing the length of time that an antibody is given to interact with these random peptides. A great deal of kinetic and thermodynamic information can be obtained. That is how Stafford et al. 2012 classified blinded glioma patient samples into precise groups that matched the tumor pathology and a molecular biomarker, MGMT promoter methylation. In the future this technique could be utilized to differentiate treatment efficacy and tumor recurrence.

Dengue Virus and Immuno-Inflammatory Pathologies

According to an epidemiological study by the World Health Organization about 50 million people get infected by dengue virus and around 2. 5 million people are at risk. Severe dengue fever can manifest as dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) with complex complications. There are three known immune components that interact with each other to produce DHF/DSS. This virus first contaminates immature dendritic cells via the mediation of dendritic cell specific intercellular adhesion molecule-3 (ICAM-3) binding to non-integrins which result in production of cytokines and metalloproteases. This, in turn, leads to activation of T-cells which result in activation of effector cells and leakage from blood vessels. Antibody enhancement is facilitated by Fc receptors that are found on the cell surface membrane of mature dendritic cells. Antibodies effect the replication of dengue virus – antibodies to viral epitopes cross react with a cell protein which results in production of cytokines and anaphylatoxins due to activation of CD8 effector cells. Anaphylatoxins are generated in two ways – through

viral proteins or by forming an antibody-complement complex. The anaphylatoxins result in the altered activity of T-cells and hence to the pathogenesis of dengue virus fever.

There are very few constituents of the immune system that are unaffected by viruses. There are many unanswered questions on the spread of viruses. Such research will not only impact on the hemorrhagic viruses, but HIV, and the masters of disguise, the influenza viruses.

Gene Therapy

There will be further substantial advances in gene therapy. Not only will new genes be identified, but new techniques to modify or ablate their expression will be identified. These will target all levels of the genomic translation cascade, from DNA to protein. Genomics and proteomics will interface here. The greatest potential will arise from the identification of genes that either cause disease or lead to a susceptibility to disease. The expression of such genes is already achievable in experimental animals, and it is only a matter of time before this technology can be introduced into humans. For example, gene therapy has been effectively utilized to express chimerical antigen receptors (CARs) which give T cells their ability to identify tumor-associated antigens without the necessity for presentation by the MHC complex. Recent research by Singh, et al, 2013 made an attempt to modify the *sleeping beauty* (SB) gene system to lower manufacturing costs linked with transducing T-cells with recombinant viral vectors.

[1517 words].