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EDITORIAL

# Molecular medicine: Promises and patience

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Knowledge of molecular genetics holds an incredible promise for clinical medicine. As many diseases are based on mutations in DNA, either congenital or acquired, specific interference in this DNA or in the downstream products coming from DNA translation may provide better treatment strategies for a myriad of diseases. The most challenging intervention would be to directly change host DNA, which so far has not been feasible in humans. However, interventions aimed at interference with DNA translation have recently been introduced in clinical medicine. In fascinating experiments in patients with Duchenne's muscular dystrophy administration of small strands of ologonucleotides interfered with mRNA splicing and corrected the reading frame by exon skipping of the mutated part of the dystrophin gene, causing a truncated (but biologically active) gene product rather than the inactive mutant protein. Initial clinical studies showed production of the new protein in boys with Duchenne's disease and a modest clinical improvement.[1] Also, gene therapy, i.e. administration of (viral) vectors containing human DNA encoding for a desired protein, has now entered a new phase with proven efficacy and increased safety, for example in rare lipid disorders or haemophilia B.[2,3] In addition, drugs interfering with defective gene products, translated into proteins that are responsible for dysregulation of cell proliferation and development of malignancies, have shown to be effective in oncology and haematology.[4-6] Lastly, identification of genetic mutations or variation may be used as risk stratifying marker in various diseases, including myeloproliferative disease, severe infections, thrombosis, or pancreatitis.[7-10] Taken together, clinical medicine is starting to experience the advantages that knowledge of molecular genetics may bring to improve clinical management.

However, we may have a very long way to go before we can fully translate even the molecular knowledge that has been accumulated so far into clinically applicable interventions.[11] As previously remarked, even for relatively simple genetic disorders, such as sickle cell disease, affecting hundreds of thousands of people worldwide and a monogenetic affection of which the genetic mutation was elucidated more than 50 years ago,[12] this very precise molecular knowledge has so far no effect at all on clinical management. In fact, despite all genetic preciseness patients with painful sickle cell crises are managed with intravenous fluids and painkillers.[13] Similarly, patients with primary haemochromatosis due to precisely defined gain of function mutations in genes involved in iron absorption are managed with blood letting, a therapy that has been with us since the middle ages.[14] Apparently, the gap between the discovery of the genetic base of a disease and the consequences for clinical management is large and it takes a lot of additional research and time before this gap can be bridged. And the given examples all represent monogenetic and relatively simple diseases, let alone the clinical consequences in terms of management of multigenetic disease, such as atherosclerosis and cancer. Nevertheless, it is clear that molecular genetic applications are seeping through into clinical medicine. In this issue of the Netherlands Journal of Medicine, three additional examples of how molecular genetics may innovate clinical medicine are provided.[15-17] Bins *et al.* demonstrate the utility of DNA vaccination, or genetic vaccination. In DNA vaccination immunity is induced by transfecting host cells with DNA that encodes an antigen instead of traditional vaccination by directly injecting antigens in the form of protein or peptide.[15] Once transfected, cells of the host start producing the protein encoded by the DNA leading to an immune response against this protein along similar lines as responses occur against conventional vaccines. The idea is that with DNA vaccination a more appropriate immune response is evoked. Initial studies have shown that DNA vaccination may be a helpful option for specific infectious diseases or for treatment of malignant disease, such as melanoma. Stroes *et al.* provide an overview on the efficacy and safety of treatment with antisense oligonucleotides.[16] Antisense therapy is based on base-pair hybridisation through which antisense oligonucleotides (ASOs) highly

specifically bind to its complementary mRNA target. Subsequent selective cleavage of the target mRNA leads to a corresponding reduction in target protein. Indeed, several studies, including human studies, have shown that ASOs can potently and selectively inhibit the synthesis of a protein of interest. In the article by Stroes *et al*. the application of antisense drugs in the management of lipid disorders is reviewed, whereas other clinical applications of antisense that are currently being developed are in the area of antithrombotic interventions, oncology and diabetes.[18,19] Lastly, De Graaff *et al*. present an article on the clinical applicability of pharmacogenetics.[17] Indeed, our knowledge on genetic variation as a predictor of drug efficacy but also occurrence of major drug-induced adverse events is rapidly increasing. However, it is not always clear whether this knowledge is clinically relevant. Graaff *et al*. provide data on CYP450 and HLA genotypes relevant to the 100 most commonly used drugs. They discuss the availability and costs of pharmacogenetic testing, show a calculation of the 'number needed to genotype' and, based on these data, they propose a decision model for pharmacogenetic testing by clinicians.

Based on all these new developments, it may be concluded that the steep increase in knowledge on molecular genetics has increasing impact on practical clinical medicine. It also demonstrates that fundamental research is crucial for further development of our insight into normal biology and disease but translational research to bring these results to practical solutions for patients is just as critical and may require major investment and a lot of patience.

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