A Novel Class of Multi-Functional Anti-Inflammatory Drugs (MFAIDs) for the Treatment of Inflammatory/Allergic Diseases

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Inflammatory/allergic diseases affect billions of people worldwide, and treatments for these conditions are a major focus of the pharmaceutical industry. The most common drugs used to treat these numerous diseases are corticosteroids, which are potent but can have severe, even devastating side effects. For the past three decades, non-steroidal alternatives (NSAIDs, biologics) have been the focus of the pharmaceutical industry. Frustratingly, these have produced unsatisfactory results: synthetic NSAIDs are less potent and have their own serious side effects; biologics are costly, hard to administer, and often have severe side effects.

While inflammatory diseases often present different symptoms affecting different organs (e.g., skin inflammation, airway injury and allergy [asthma, cystic fibrosis, ], atherosclerosis and cancer metastasis) - they share key biochemical processes. One such process is the phospholipase A₂ (PLA₂) enzymatic hydrolysis of cell membranes which provides the precursor for a cascade of inflammatory lipid mediators (ILMs). Among them is the COX pathway, which was assumed to be a major pro-inflammatory determinant, hence developing COX inhibitors has been a major therapeutic target in the pharmaceutical industry. However, this approach has yielded unsatisfactory results, with some high-profile drugs being withdrawn from the market due to safety concerns.

In our lab, we have designed and developed an entirely novel generation of PLA₂ inhibitors acting as multi-functional anti-inflammatory drugs (MFAIDs). The MFAIDs were shown to be safe and efficient in treating diverse inflammatory conditions in animal models, using different modes of administration. The MFAIDs technology has been licensed by the Hebrew University to Morria Biopharmaceuticals PLC, which is currently developing these drugs to treat inflammatory diseases of the airways (hay-fever, asthma, cystic fibrosis), skin (eczema), gut (Crohn’s disease) and the eye (conjunctivitis).
Mitochondria are intracellular organelles that play a critical role in cellular homeostasis. Participating in intracellular signaling, programmed cell death and performing numerous biochemical tasks, the most crucial task of which is regulating cellular energy metabolism. Any defect in one of the numerous mitochondrial proteins can cause a mitochondrial disorder. These disorders usually manifest as systemic metabolic dysfunctions, affecting primarily high-energy demanding tissues such as the liver, muscles, and central nervous system. Mitochondrial defects affect about 1:8,000 live births and many other inborn errors of metabolism are localized to the mitochondria. Modern medicine offers no cure for mitochondrial metabolic disorders. Conventional treatment is limited to symptomatic care and involves administration of vitamins, cofactors, and antioxidants, to postpone or mitigate the massive damage caused by the overproduction of free radicals, the accumulation of toxic metabolites, and the low rate of energy production.

We developed a novel approach for restoring the activity of a mitochondrial protein, even when part of a multicomponent-protein complex, by replacing one mutated component with the normal protein. Our approach for Cell- and Organelle-Directed Protein Replacement Therapy (C/O-DPRT) entails the fusing of a normal mitochondrial protein with a delivery system (a small peptide), which is capable of rapidly crossing biological membranes, thereby allowing the fused protein to be delivered into cells and their mitochondria where it can replace the mutated endogenous protein and restore its biological activity. Our approach was examined with two different mitochondrial proteins and was proven to restore successfully the activity of a defect mitochondrial protein in primary patients’ cells as well as in an animal model for a mitochondrial disease. Moreover, these fusion proteins were able to reach the brain.

A key advantage of this new C/O-DPRT approach is its ability to deliver the fusion proteins into virtually all cells with no specificity, reaching mainly high-energy demanding tissues, which are usually affected the most in these types of disorders. Another major advantage is its ability to cross the blood-brain barrier, making it a promising means for developing novel, more efficient molecules to treat metabolic disorders involving the central nervous system. In these types of disorders, there is no need to restore protein activity back to 100%. It is sufficient to partially restore protein activity above a certain energetic threshold, which can differ from patient to patient. As we have shown, in this kind of therapy this goal can be achieved relatively easily. Moreover, in the clinical context, our results suggest that even a single application of such a fusion protein may be sufficient for rescuing patients from life-threatening episodes, which last sometimes up to 24 h. This promising approach is now being developed for clinical use for the treatment of human diseases.

This novel approach of C/O-DPRT may be applied to the numerous other mitochondrial diseases, in which the damaged mutated protein involved is known. The new approach may open new inroads in the management of many incurable mitochondrial diseases, as well as other metabolic disorders.
Generation of Anti-NKp46 mAb for the Treatment of Type 1 Diabetes

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Type 1 diabetes mellitus (T1D) is one of the most common chronic diseases in children and adolescents. Approximately 1 million Americans have T1D and it is estimated that by 2030, this number will be doubled. T1D is associated with a high morbidity and mortality and with numerous microvascular and macrovascular complications. The disease is currently incurable and is mainly treated by daily injections of insulin. In rare situations, human islet transplantation is considered as possible treatment. However, in almost all cases, more than 90% of the islets are rejected within a short period of time.

T1D is considered to be an autoimmune disease in which autoreactive T cells attack the pancreatic beta cells. About a year ago we showed that Natural Killer (NK) cells also actively participate in T1D development. NK cells belong to the innate immune system and kill various hazardous cells by using an array of activating NK cell receptors. Among these, NKp46 is considered to be one of the most potent NK killer receptors.

We have found that the killer receptor NKp46 specifically recognizes pancreatic beta cells and that this recognition leads to NK cell killing of beta cells. We further revealed that blocking of NKp46 activity, in a murine model of T1D, prevented diabetes development. Recently, we have expanded our observations and demonstrated that human beta cells that are intended to be used for transplantation also expressed a ligand for NKp46 receptor and are killed in an NKp46-dependent manner.

These combined findings demonstrate the importance of the NKp46 receptor in diabetes development and emphasize the therapeutic potential of the anti-NKp46 mAb as a new treatment modality for T1D. Based on these results, a patent was filed and, together with BiolenRX Company, we are now in the process of developing a blocking anti-NKp46 mAb for the treatment of Type 1 Diabetes.