

AplaGen announces publication of a patent application for a novel technology that increases half-life of proteins in vivo

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Baesweiler, Germany, December 7, 2009 - AplaGen GmbH announced today the publication of a patent application describing an innovative method for increasing the half-life of complex and/or multifunctional proteins in human and animal circulation in order to reduce infusion rates and increase patient quality of life. Large proteins that undergo high levels of interaction with other components in the body – e.g. coagulation factors, neurotoxins, and matrix molecules – are best positioned to benefit from this new technology that was developed in cooperation with a large European pharmaceutical company.

The patent application describes an innovative formulation for elongation of the half-life of recombinant factor VIII used in hemophilia. Treatment of bleeding disorders like hemophilia traditionally involves infusions of polypeptides to replace the natural polypeptide that is defective or missing. However, the use of polypeptide therapeutics like coagulation factors is handicapped by certain drawbacks, including short circulating half-life, immunogenicity and proteolytic degradation. One solution for increasing the half-life of these proteins is covalent attachment to a polymer like polyethylene glycol (PEG) or hydroxyethyl starch (HES). Unfortunately while covalent conjugation to a polymer increases the half-life, it also decreases the ability of the protein to interact with other proteins, decreasing its effectiveness.

This crucial dilemma of conjugation technology was solved with a novel strategy that results in an increase in the half-life of the therapeutic protein, increasing efficiency and reducing the amount of the therapeutic proteins received by the patient. Aside from the increased quality of life resulting from fewer treatments, it also reduces the cost of the treatment. Unlike traditional conjugation strategies, the new method does not build on muteins (mutated recombinant proteins) for successful site-specific conjugation. Instead, the protein – factor VIII in this case – is bound non-covalently via a selective and strong-binding linker molecule to the HES carrier. This HES-linker entity is added to the protein formulation and reversibly inhibits elimination of the protein, and as a result, increases the circulation half-life in vivo. This non-covalent technology provides the advantage that proteins used in therapy do not have to be chemically modified in order to prolong their half-life. Instead the conjugates are incorporated into the existing pharmaceutical composition in order to exert their function. This also creates a regulatory benefit because there is no change to the active pharmaceutical ingredient (API), only the formulation of the product.

HES Conjugation Technology

Hydroxyethyl starch (HES) is a highly water-soluble derivative of naturally occurring starch (amylopectin & amylose) and is degraded in the body over time. HES exhibits advantageous biological properties and it is widely used as a stand-alone API in blood volume replacements (plasma expander) and in hemodilution therapy. HES is the most commonly used plasma expander in Europe today, a position it has enjoyed for a number of years. During that time, it has shown neither toxicity nor immunogenicity.

AplaGen's technology allows covalent and non-covalent conjugation of HES to a variety of existing API molecules either as monovalent or multivalent polymeric drug carrier. The monovalent concept is optimal for medium-size and larger molecules,

like proteins, peptides, and oligonucleotides. The multivalent technology allows the clustering of small to medium-size drug molecules, like small molecules or peptides. Both strategies result in improved pharmacokinetic and pharmacodynamic effects.

AplaGen GmbH is a biopharmaceutical company focused on discovery, design, synthesis, and development of peptides. It has extensive experience and an impressive track record in the fields of peptide lead discovery and peptide lead optimization. AplaGen has successfully created a portfolio of its own products with independent patent protection for major indications and markets, including the anemia market and the thrombocytopenia market. In parallel to developing its own pipeline products, the company engages in “Innovation Partnerships”, collaborations with pharmaceutical and biotech companies, which aim at significant long-term value generation by unique strategic positioning of drugs controlled by its partners. AplaGen’s Innovation Partnership services include both HES conjugation and peptide development capabilities, resulting in novel solutions for product differentiation and for enabling superior pharmacological profiles and life-cycle management opportunities.

For more information about AplaGen please visit the company’s website: www.aplagen.com.

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