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Permeon reveals discovery of Intraphilins as new approach to intracellular biologic drugs

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Permeon Biologics, a biopharmaceutical company pioneering a novel class of intracellular protein biologics, today announced the discovery of an entirely new class of naturally occurring human supercharged proteins called Intraphilins™. The sequence and structure of these naturally supercharged human proteins enable biologic drugs to penetrate and function inside of mammalian cells. This new class of proteins is the foundation of Permeon Biologics' novel Intraphilin™ Technology Platform and provides an innovative approach to develop intracellular protein biologic drugs, such as intracellular monoclonal antibodies and enzyme replacement therapies. Intraphilins enable functional proteins to act inside cells to treat disease, impacting over 1,500 intracellular target proteins currently considered undruggable with available technologies.

The data were published online today in the journal *Chemistry & Biology* in a seminal paper by David R. Liu, Ph.D., professor of chemistry and chemical biology at Harvard University and investigator at the Howard Hughes Medical Institute, and his colleagues. The findings represent natural scaffolds for developing potent human intracellular biologic drugs, and also raise the possibility that some of these supercharged proteins may penetrate cells as part of their native biological functions. The ability of human Intraphilins to penetrate cells to enable intracellular protein biologics has not been previously reported.

"The data show that naturally supercharged Intraphilin proteins already exist within the human body and can enable the delivery of protein biologics into mammalian cells in vivo," said Dr. Liu, Permeon's

scientific founder and scientific advisory board chairman. "Intraphilins are now being developed as a new class of human protein therapeutics to access previously undruggable intracellular target proteins and pathways."

The study sought to determine if this class of proteins could provide a natural platform for intracellular protein biologics in vivo. Dr. Liu and his colleagues tested the ability of Intraphilins to enable active enzymes in adult mice to function in cells of three tissues of therapeutic interest – the retina, pancreas and white adipose tissues. Intraphilins were fused to Cre recombinase, an enzyme that mediates DNA splicing inside the nuclei of cells, then injected into the mice.

Following a post-injection incubation period, each Intraphilin-Cre recombinase fusion protein tested exhibited DNA splicing activity in the nuclei of living cells in each of the tissues tested. These study results collectively establish that Intraphilins enable protein biologics to function inside a variety of living mammalian tissues in vivo. The paper shows that Intraphilin-Cre-injected retinae exhibited large areas of recombined cells in the eyes of treated mice. In contrast, retinae injected with Cre recombinase protein by itself did not show activity in vivo, highlighting that protein biologics are typically unable to enter cells. Of importance, the Intraphilins tested were able to mediate internalization of fused proteins with up to 40-fold higher potency than cell penetrating peptides, which have been used previously to develop intracellular biologics.

"This potent ability to target and treat the source of disease within the cell cytoplasm and other intracellular compartments holds promise to address a vast new spectrum of intracellular disease targets," said Alex Franzusoff, Ph.D., president and board director of Permeon Biologics. "First-generation approaches to intracellular biologics, such as cell-penetrating peptides, have not realized their full potential due to limited

uptake of larger macromolecules into cells and limited tolerability. This paper shows for the first time that we can leverage natural human proteins to enable intracellular protein biologics, such as humanized intracellular monoclonal antibodies, to address clinically important targets of interest which were previously undruggable."

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