



Oralject Technology Summary

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This Summary has been prepared by PerOs Systems Technologies and is being furnished to provide an introduction to PerOs' Technology

The Oralject technology

The controlled delivery of bioactive substances via non-parenteral routes to a wide range of species has received considerable attention. In particular, efforts have focused on methods to orally deliver therapeutic compounds past the stomach of monogastric animals (and past the abomasum of a ruminant) in order to bypass gastric digestion and deliver the intact compound of interest to the site of absorption in the small and/or large intestine(s). To date, a large proportion of this work has centered on developing encapsulation strategies using a range of polymers to protect the compound of interest. These polymer systems may simply modulate the release of a specific compound in a predetermined fashion, or may use specific physiological determinants (e.g. pH, temperature etc.) to trigger the delivery of the encapsulated material. There are, however, several drawbacks related to the utilization of such polymer systems with the net effect that few reliable systems have been developed and none have found their way into commercial application on a broad scale. Additional challenges have arisen including cost, difficult characterization of encapsulation systems, and the composition of certain encapsulating materials being such that regulatory approval of these systems is a long and risky process.

PerOs Systems Technologies Inc is employing a different strategy. Feeding a bioactive compound along with a cocktail of antinutritional factors to temporarily suppress digestive enzyme function and products that augment intestinal absorption, PerOs has demonstrated the ability to effectively bypass or neutralize the enzymatic process, thus permitting intestinal uptake of the compound to achieve the desired biological effect. This technology has been patented and is undergoing commercial development for a variety of applications under the trade name Oralject™

One component of the Oralject™ technology is to reduce the effects of an acidic environment and the detrimental effects of a number of key proteolytic enzymes. By combining specific compounds to temporarily increase gastric pH, as well as compounds to buffer the effects of additional endogenous gastric acid secretion, two key objectives are addressed. First, the direct hydrolyzing effect of gastric acid secretion is neutralized, both on the bioactive compound of interest and on the hydrolysis of the inactive proteolytic enzyme precursor pepsinogen to its active form pepsin. Secondly, pepsin activity is significantly reduced as the induced elevated gastric pH depresses the activity of pepsin (pH optimum of 1.5-2). Furthermore, the reduced activity of pepsin has more profound effects during the continued passage of the biological agent through the digestive system. Pepsin is the key enzyme that, along with gastric acid, initiates the degradation of proteins, allowing other pancreatic proteolytic enzymes to act on the partially-digested proteins. Thus by limiting the activity of pepsin and reducing gastric acidity, the overall gastric digestive capacity is limited.

The addition of specific and non-specific anti-proteases provides a second line of enzyme inhibition by combining a number of potent inhibitors of protease activity. Two key intestinal proteolytic enzymes in particular are rendered inactive. Enterokinase and trypsin are important catalytic

initiators that activate a number of more specific proteases. By targeting these specific enzyme systems, the normal activation cascade is temporarily interrupted, thus shutting down a large number of proteolytic enzymes. Combining all of the above products greatly reduces, on a temporary, targeted basis, gastric and intestinal digestive capacity, allowing the delivery of bioactive compounds to sites of interest within the small intestine.

The intestinal mucosa provides a formidable barrier, allowing only specific products to pass into the general circulation. A variety of naturally-occurring products have been identified that increase significantly the permeability of the intestinal mucosa to a variety of compounds, thus increasing subsequent circulating concentrations. The combination of specific factors to reduce overall digestive capacity along with those to increase intestinal absorption provides a novel method to transport bioactive compounds intact to the sites of intestinal absorption and increase intestinal uptake. This method has the potential to efficiently deliver wide range of compounds to a variety of monogastric animals.

The intensification of livestock production and the increase in stocking densities has created the need for intervention at critical time points to assure the health and performance of the animal while taking into consideration the need to provide for a healthy, nutritious source of protein for the global human population as well as management of diseases which threaten both animals and humans. The increasing management of animal resources has led to a better understanding of the disease challenges faced by the animal and allowed a targeted approach to intervention. However, the challenge has been to deliver the intervention at the correct point with minimal stress on the animal and least disruption of the growth cycle.

Oral administration of vaccines and other bioactive substances for livestock industries is by far the most sought after method of delivery. Oral vaccine delivery requires no change in normal animal husbandry or handling; thus, eliminating the stress associated with other methods of administration. Oral vaccination is a method suitable for the rapid and simultaneous mass immunization of bioactive compounds to a large population; which is essential for the prevention and control of disease outbreaks.

Oral vaccination has been hindered by seemingly insurmountable biological and technical limitations. Oralject™ is an answer to the ongoing quest for methods of providing the safe and non-invasive delivery of treatments for multiple diseases and other therapeutic applications. Oralject™ permits the oral delivery of therapeutic molecules including antigens vaccines, peptides and nutraceuticals without costly and complicated encapsulation systems.

There is a potential to combine Oralject™ with a large variety of therapeutic applications, and PerOs is constantly developing new applications, for different aquatic species such as tilapia, salmonids, sea bass, and shrimp. In tests conducted Canada, USA, Chile, and Norway, the Oralject™ system has been used to successfully deliver a range of bacterial and viral vaccines to a variety of species, including gastric and agastric fish (Shoemaker, C. et al.2006. Aquaculture. 255:151-156; Desormeaux, A., et al. 2005. European Association of Fish Pathologists. Copenhagen Sept 9-12 2005.)

Oralject™ does not require any specialists or specific skills to administer the desired intervention; a single meal is simply replaced with Oralject™, thus opening the door to effective mass

inoculation. However, the key advantage of this technology is its cost effectiveness. Traditional parenteral injection not only requires specialists and equipment, the disruption from the necessary handling can also generate significant indirect costs for producers (estimated to be as high as the direct costs) as a result of animal stress, mortalities, adhesion, necrosis and eating disorders. With no needles and a simple administration procedure, Oralject™ technology provides a straightforward, cost-effective solution that requires only minimal human labor. The Oralject™ technology is very flexible and adaptable with specific formulations being developed for specific biological agents and combinations. - The Oralject™ delivery platform can be applied to a wide range of bioactive compounds in monogastric species including vaccines, peptides, proteins, and antibodies. This versatility makes Oralject™ the ideal solution for a large variety of applications.

In vitro and clinical studies employing Oralject to deliver vaccine orally have demonstrated antigen stability following incorporation in the formulation. Oral delivery of vaccines using Oralject has induced a variety of immune responses including systemic and gut associated mucosal responses important in the protection of the mucosal surfaces from infection. Specific components of the Oralject formulation have been demonstrated to have the ability to target particular cell types in the gastrointestinal tract, thus permitting the possibility of custom formulation based on antigen type and target species. Finally, investigation of the ability of combining antigens within the Oralject formulation along with novel extrusion and processing methods is on-going in order to fully optimize oral vaccine delivery to a range of monogastric animals.

Patent Summary

- Composition for Intestinal Delivery: 1 250 056, 150818, 241484, 200223464, 90560/30, 520238
- Composition for Modulating a Physiological Reaction or Inducing an Immune Response: 101249
- Immunoactive Compositions for Improved Oral Delivery of Vaccines and Therapeutic Agents: 60/894.563