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Encapsulated islets for diabetes therapy: History, current progress, and critical issues requiring solution ☆

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ABSTRACT

Insulin therapy became a reality in 1921 dramatically saving lives of people with diabetes, but not protecting them from long-term complications. Clinically successful free islet implants began in 1989 but require life long immunosuppression. Several encapsulated islet approaches have been ongoing for over 30 years without defining a clinically relevant product. Macro-devices encapsulating islet mass in a single device have shown long-term success in large animals but human trials have been limited by critical challenges. Micro-capsules using alginate or similar hydrogels encapsulate individual islets with many hundreds of promising rodent results published, but a low incidence of successful translation to large animal and human results. Reduction of encapsulated islet mass for clinical transplantation is in progress. This review covers the status of both early and current studies including the presentation of corporate efforts involved. It concludes by defining the critical items requiring solution to enable a successful clinical diabetes therapy.

Contents

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1. Introduction

1.1. Historic antecedents to islet encapsulation

1.1.1. Diabetic antiquities

As an introduction to his MD Thesis in 1983 and in a later publication, Richard Downing has presented a well-studied history of diabetes and insulin-producing cell transplantation. It is summarized in part here to explain the important developments that resulted in islet encapsulation [1,2]. The signs of diabetes were described in clinical terms in antiquity starting with polyuria and polydipsia in the Ebers Papyrus dated 1500 B.C. [3] followed by Hippocrates (469–399 B.C.), Aritstotle (384–322 B.C.), Celsus (30 B.C.–50 A.D.), and Galen (129–199 A.D.) [4,5]. Aretaeus the Cappadocian (30–90 A.D.) named the disease "diabetes" from the Greek word for "siphon" to describe the polydipsia and polyuria that are a clinical hallmark of that disease [4]. Polyuria was recognized in China in the third century but not recorded in writing as "sweet urine" until the seventh century [3,6]. An Indian physician described a sign of diabetes as "honey urine" in the fifth century [7]. The Arabian physician, Avicenna (980–1027 A.D.) was the first to describe complications of diabetes including gangrene [8]. Pathologic descriptions of glycosuria began with Paracelsus (1493–1541) and Willis (1621–1675) who also added the Latin word for honey, "mellitus", to the name, diabetes [9]. Johan Frank differentiated diabetes mellitus from diabetes insipidus in 1794 [9]. The French chemist Chevreul (1797–1889) showed that the sugar that spilled into the urine in diabetics was actually glucose [10]. While suggestions had been made that sugar may be elevated in the blood in patients with diabetes, it was Chauveau in 1856 who established that hyperglycemia was a hallmark of diabetes and critical in its diagnosis [11].

1.1.2. Clinical diabetes prior to insulin

The pancreas was first implicated in clinical diabetes in 1788 following an autopsy by Cawley of a 34 year old who had diabetes secondary to chronic pancreatitis [12]. Several reports of diabetes secondary to pancreatitis then followed by Bright in 1831, Bouchardat in 1875, and Lancereaux in 1877 [7,13,14]. Paul Langerhans first identified pancreatic islets during his thesis as a medical student in 1869 by careful evaluation of histologic sections of the pancreas observing isolated nests of small, clear cells scattered in the pancreas that he speculated might by lymph tissue [15]. The relationship of his findings to diabetes was not appreciated until suggested by Schafer in 1895 [16]. It was Opie in 1901 who first described hyaline degeneration of the islets in diabetic patients [17]. While Brunner had described the removal of the dog pancreas was followed by polyuria and polydipsia in 1682 [18], its importance was not understood until Mering and Minkowski reported a series of dog pancreatectomies in 1889 that defined diabetes as an absence of some function of the pancreas [19]. Then Laguesse in 1893