A Cure for Type 2 Diabetes?

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Diabetes is a chronic disease that inflicts significant life style changes and reduces life expectancy on the afflicted. In the United States 29.1 million people or 9.3% of the population have diabetes including an estimated 8.1 million who are undiagnosed. The 2012 cost of this disease in the US was $245 billion per annum or approximately $500,000 every minute [1]. Almost 90% of diabetics suffer from type 2 or “insulin resistant” diabetes. Thus any experimental data that indicate a potential treatment pathway for type 2 diabetes should attract the attention of not just health care professionals but also their patients and all those concerned about health care costs. It will certainly attract the attention (and perhaps panic) of the pharmaceutical industry.

Such experimental evidence is presented in this issue of the journal by Giovanni Luca et al. in their paper “Xenografts of microencapsulated Sertoli cells restores glucose homeostasis in db/db mice with spontaneous diabetes mellitus” [2]. In this study the Calafiore group has transplanted microencapsulated porcine Sertoli cells into the subcutaneous fat of 30 type 2 diabetic-prone obese mice (db/db) after they had become frankly diabetic. Ten diabetic mice were injected with empty capsules as controls. Remarkably 60% of the treated mice (18 out of the 30) had their glucose control restored and demonstrated normal glucose tolerance tests. The remaining 40% “failures” all showed improvements as assessed by reduced HbA1c levels. Control mice remained diabetic.
BKS.Cg-Dock7m+/+Leprdb/J mice (db/db) are a specifically developed strain of obese mice which develop type 2 diabetes, going through all the various stages in the development of the disease ending in the requirement for insulin replacement therapy. In humans type 2 diabetes develops when the body becomes “resistant to insulin” which in many cases results in the pancreas stopping the production of insulin. The cause of this “insulin resistance” remains unknown, although genetics and environmental factors, such as diet, excess weight and inactivity, are contributing factors. While no single diabetic mouse model recapitulates all of the features or complications of human diabetes the db/db model chosen by the Calafiore group is certainly one of the best surrogates of the disease.

To those not familiar with the Sertoli cell literature the injection of cells extracted from the testicles of neonatal pigs as a treatment for diabetes sounds more like medieval witch-doctoring than serious medical science. However there is a wealth of published data that has established the immunomodulatory credentials of Sertoli cells and their therapeutic potential. What is unusual about this study is that they have such a profound effect on type 2 diabetes. It has been known for more than 50 years that both allografted and xenografted cells transplanted into the testes are not rejected, a phenomenon called immunological privilege. In a series of innovative studies Selawry and colleagues demonstrated that it was the Sertoli cell which conferred this immunological privilege. The most convincing evidence being when Selawry et al. reported that Sertoli cells and islets of Langerhans co-transplanted under the kidney capsule of diabetic rats were able to survive and reverse the diabetes indefinitely [3]. In an effort to elucidate the mechanism by which the Sertoli cells provided this protection Bellgrau et al. demonstrated a critical role for the membrane expression of CD95 ligand (also known as Fas ligand or Fas-L) by Sertoli cells. Sertoli cells derived from Fas-L expressing mice survived indefinitely when transplanted under the kidney capsule of allogeneic recipients, whereas Sertoli cells derived from mutant gld mice, which express non-functional ligand, were rejected. The conclusion of
these studies was that the Fas-L expression interacting with Fas-expressing T cells activated by the graft antigens induced apoptotic cell death of these T cells thus halting the rejection process [4].

It had been assumed that cell-cell contact was critical for the induction of this Fas/Fas-L induced apoptosis. Since in this study of type 2 diabetes the Sertoli cells are microencapsulated such cell-cell contact cannot occur. However soluble Fas-L can also induce apoptosis, and so this process cannot be excluded as a possible explanation for the results reported by Luca et al. There is in vitro evidence that Sertoli cells can produce soluble Fas-L [5]. In addition Sertoli cells produce a number of other immunomodulatory factors, specifically complement inhibitors, cytokines, and cytotoxic lymphocyte inhibitors [6]. In total Sertoli cells secrete 47 different proteins many of whose functions are still unknown [7].

In the absence of evidence to the contrary, it is reasonable to accept the interpretation provided by the authors of this paper that it is the immunomodulatory properties of the Sertoli cells which are responsible for the reversal of the type 2 diabetes reported here. In support of this conclusion they demonstrate an up-regulation of CD11c-negative CD206-positive F4/80-positive macrophages and a down-regulation of CD11c-positive F4/80-positive macrophages in treated mice compared to control mice. They also demonstrate significant changes in the B-lymphocyte populations of their treated mice. These observations are consistent with a number of recently published studies associating adipose inflammation with obesity and the development of insulin resistance. This current publication however is the first study to demonstrate that immunosuppression can reverse the type 2 diabetic state. While it is universally accepted that autoimmune destruction of pancreatic beta cells is the effector cause of type 1 diabetes [8], the possibility that autoimmunity is also the primary cause of type 2 diabetes represents an important paradigm shift. While not intuitive it is difficult to draw any other conclusion from the data presented here. These results are all the more remarkable because the restoration of glucose
control was achieved with no changes in the body weight of these obese mice.

This study also poses a number of important questions that need to be addressed. Undoubtedly the experiments published here will be repeated by others. It will also be important to establish if similar results can be achieved in other species. There are a number of large animal models of type 2 diabetes including obese primates. It would seem an important next step to test the effectiveness of xenotransplantation of Sertoli cells into some of these models. In this study the Sertoli cells were injected subcutaneously directly into the adipose tissue. Would the same results have been achieved if the microcapsules had been injected into the peritoneal cavity? The dose used in these experiments was 1 million per gram (1 billion per Kg!). The dose is based on previous studies by the Calafiore group into the treatment of type 1 diabetes [9]. Given the local administration of the microcapsules compared to the systemic treatment required for type 1 treatment is it possible that a smaller dose would be as effective in treating type 2 diabetes? The Sertoli cells were microencapsulated because of (excessive?) safety concerns over the clinical therapeutic use of viable porcine cells. Would the results have been improved by administering the Sertoli cells without encapsulation? Perhaps the most difficult question to be addressed is how do the Sertoli cells induce the reversal of the type 2 diabetic state? Sertoli cells secrete a complex cocktail of known immunomodulatory molecules and probably some that have yet to be identified. Dissecting which molecule or combination of molecules are responsible for the results reported here is going to be a major challenge which will take many years of hard work to unravel. In the interim porcine testicles are in plentiful supply and the results reported here by Luca et al. should encourage much more research into the therapeutic value of Sertoli cells, in the treatment of type 2 diabetes. Hopefully clinical trials will not be too long delayed.

This paper offers up the possibility of a simple, safe, clinically applicable treatment that results in type 2 diabetics recovering normal glucose homeostasis.
There are still questions that have to be addressed before this possibility is confirmed. Perhaps it is worthwhile expending 10 minutes worth of those US diabetes treatment dollars to find out the answers.

References
2. LUCA G, ARATO I, CALVITTI M et al. Xenografts of microencapsulated Sertoli cells restores glucose homeostasis in db/db mice with spontaneous diabetes mellitus. Xenotransplantation 2016; this issue.