

Targeting the Brain in Type 2 Diabetes: Therapeutics to Induce Remission

Dr Jarrad Scarlett, MD, PhD

TARGETING THE BRAIN IN TYPE 2 DIABETES: THERAPEUTICS TO INDUCE REMISSION

Type 2 diabetes (T2D) is among the most impactful and costly biomedical challenges confronting society. Current treatment regimens for T2D rely upon daily drug dosing and frequent glucose monitoring to normalise blood glucose levels. However, these medications can only delay disease progression and frequently have undesired side effects including hypoglycaemia and weight gain. Growing evidence supports a key role for the brain in glucose homeostasis and diabetes pathogenesis. **Dr Jarrod Scarlett** and his research team at the University of Washington and Seattle Children's Hospital are working on the development of novel pharmaceuticals to target the brain to induce sustained remission of T2D.

Fibroblast Growth Factor 1 and the Brain

Fibroblast Growth Factor 1 (FGF1) is a growth factor and signalling protein that is involved in a wide range of biological processes. While the mechanisms of action of FGF1 in the brain remain to be elucidated, Dr Scarlett and his team have proposed that the brain is capable of initiating full remission of Type 2 diabetes (T2D) via the Fibroblast Growth Factor (FGF) receptor that is expressed on brain glucoregulatory neurocircuits.

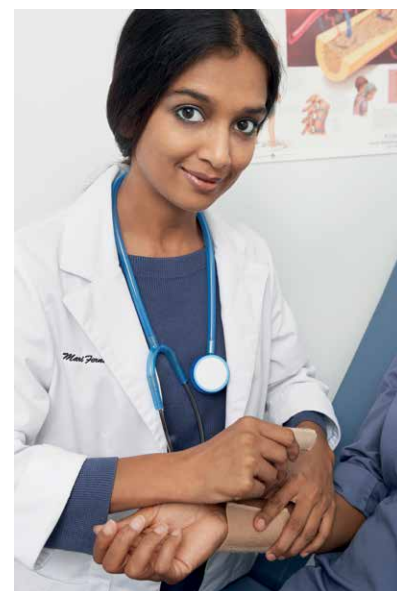
To test this proposal, Dr Scarlett and his team compared the effects of central administration of FGF1 through injection into the brain with peripheral administration that was injected into the body. Tests in both mouse and rat models of T2D showed that a single central administration of FGF1 – at a dose only 10% of the peripheral dose – resulted in sustained remission of T2D. The data confirmed that a fall in the

level of glucose in the blood resulted from the action of FGF1 binding to receptors specifically located in the brain.

The low dose used in these tests negated the negative side effects associated with the currently prescribed anti-diabetic drugs, namely low blood glucose (hypoglycaemia). As such, the FGF receptors in the brain are believed to be viable targets for pharmacological solutions for diabetes in humans.

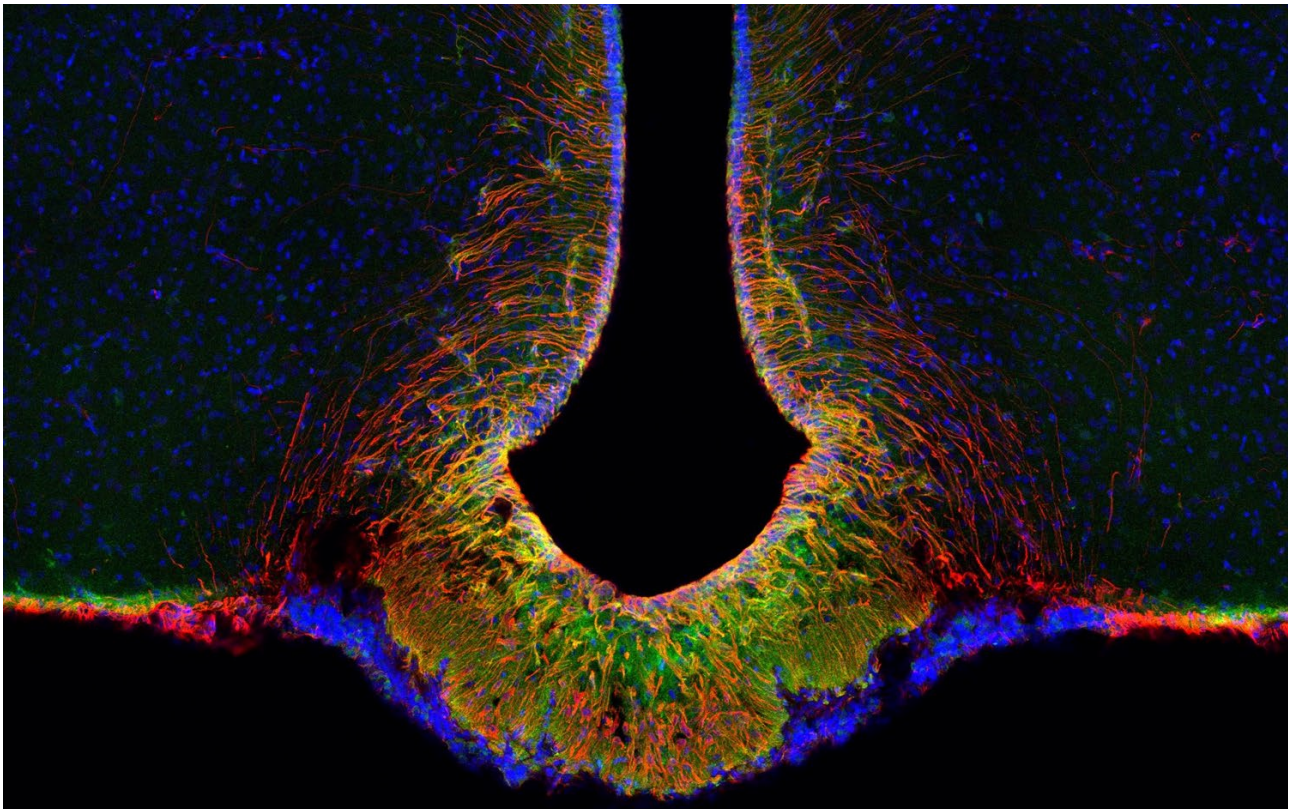
Sustained Remission of T2D

To determine whether this treatment may have longer-term effects and the potential to induce remission in T2D, Dr Scarlett and colleagues tested animals over a period of 18 weeks following a single low dose of FGF1 administered into a lateral cerebral ventricle using an implanted device, known as the ICV route. Blood glucose levels remained at normal levels in both fasted and fed

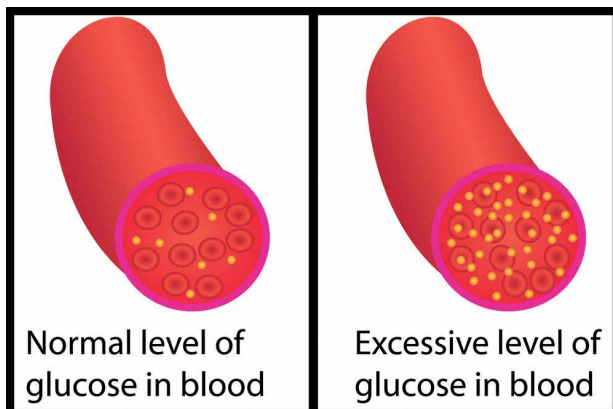


T2D mice over this extended period. This outcome indicated that sustained remission of hypoglycaemia due to T2D is attainable, at least in the animal models tested.

It is important to note that these changes did not reflect variations



Fibroblast Growth Factor in the hypothalamus. Credit Jarrad Scarlett.



in either insulin or glucagon, the agents responsible for balancing glucose levels in the blood, and thus the mechanism involved is not related to either of these blood glucose control mechanisms. Instead, Dr Scarlett and his team found that central FGF1 action in the brain promoted the sustained lowering of blood glucose by a novel mechanism that doubled the clearance of glucose from the blood in the basal, pre-fed state.

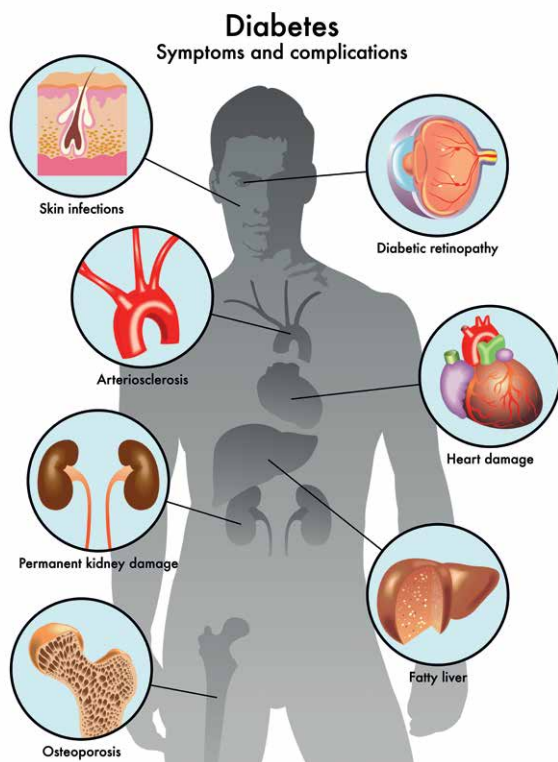
Proposed Mechanism for FGF1 Action in the Brain of T2D Mice

Dr Scarlett and his team propose a mechanism of action that leads to the sustained remission of T2D via an enhanced clearance of glucose from the body. That is, some organs and muscles remove glucose more efficiently from the

blood in response to FGF1 action in the brain. Dr Scarlett and his colleagues provide evidence to support this putative mechanism by demonstrating that there is no change to the base level of glucose production by the liver, nor is there any change to glucose tolerance, as denoted by insulin sensitivity, the acute insulin response to glucose, and by insulin-independent glucose disposal. Instead, they found that central FGF1 action produces a significant increase in glucose uptake by skeletal muscle and the liver.

The third ventricle of the brain, in which FGF1-responsive cells are located, is lined with cells known as tanycytes. These cells respond to both blood glucose and FGF1, and Dr Scarlett and his team investigated the importance of these cells in inducing remission of high blood glucose in T2D animal models. To do this, they compared the effects of two different types of FGF, namely, FGF1 and FGF19, and they found that while FGF1 induced remission in T2D mice, FGF19 did not.

In determining the effects of FGFs directly on tanycytes using specific tests for cell activation and expression, Dr Scarlett and colleagues found high levels of activation in response to FGF1 whereas no corresponding effect on the tanycytes was observed on exposure to FGF19. These results support the likelihood of a relationship between the tanycytes of the third brain ventricle and FGF1 in inducing remission in T2D.



Targeting the Brain

Given Dr Scarlett's key focus on translating research findings into useful therapeutics for T2D and other metabolic conditions, the team devised a protocol to determine the optimal brain area to target with the FGF1. Using a rat model of T2D, the team compared two regions of the hypothalamus (a specific area within the brain), and concluded that the arcuate nuclear-median eminence is the desired target area as sustained remission of high blood sugar is delivered on exposure to the FGF1-therapy, while injection of FGF1 into the paraventricular nucleus of the hypothalamus showed no effect with regards to hyperglycaemic remission.

Furthermore, this work demonstrated that a key marker protein, following FGF1 injection, was highly concentrated in glial cells, specifically tanycytes and astrocytes, which surround and support the brain neurons, and which the team has already proposed a putative role for in the initiation of remission of T2D.

Peripheral Changes in Response to Central FGF1 Administration

In humans, following the onset of high blood glucose levels, there is a progressive loss of cell function in the pancreas, which results in lowered insulin production. Recently, using a rat model which closely parallels this key aspect of human T2D, namely, the degradation of cell function in the pancreas, Dr Scarlett and colleagues investigated the peripheral processes that are induced and likely to contribute to the

prolonged remission of hyperglycaemia observed when FGF1 is administered to the rat brain.

The team found that hyperglycaemic remission is supported by two processes. First, injection of FGF1 into the rat brain delays the progressive failure of the pancreatic cells that produce insulin and is likely to be a critical aspect for human T2D-remission inducing treatments, and second, by stimulating an increase in uptake of glucose from the blood by the liver.

The Brain, Glucose Management, and Diabetes

While it is clear that the brain has the potential to affect blood glucose levels, it remains unclear as to whether these capabilities are important on a day-to-day basis for glucose control. The influence of the brain is partially managed through fast, highly coordinated adjustments to both insulin sensitivity and secretion.

Dr Scarlett and colleagues propose that alterations in this brain-system, including high levels of blood glucose, contribute to the development of T2D under hypoglycaemic conditions, that is, when blood glucose levels are low. Some researchers have demonstrated the presence of glucose regulatory nerve circuits (neurocircuits) in the brain; however, there is no evidence as yet to indicate that there are similar neurocircuits in normal glucose conditions, only in T2D disease pathology.

Pivotal to this discussion is the finding by Dr Scarlett and colleagues that the brain is capable of reverting diabetic hypoglycaemia to a normalised state, that is, this process is not simply lowering blood sugar but, rather, remodelling dysfunctional glucoregulatory neurocircuits so to restore normoglycemia in a sustained manner.

Future Work

Delivering a pharmacological solution that induces remission of T2D is critical. T2D is a costly condition for health care providers by causing significant damage to patients and perpetuating damage to the pancreatic cells. Furthermore, the currently available drug treatments for T2D have significant side effects, including hypoglycaemia and weight issues.

Understanding of the damage inflicted on both adults and children by T2D has driven Dr Scarlett to focus his efforts on this scientifically controversial and innovative area. His work exploring longer-term remission of T2D, whereby treatment appears to have only minimal side effects, may last weeks or months. Dr Scarlett aims to translate his current work into viable pharmacological treatments for patients. This will necessitate an extensive programme of work including pre-clinical and clinical trials; however, the gains in the treatment of T2D will be many-fold.



Meet the researcher

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Dr Jarrad Scarlett is currently an assistant professor at the University of Washington and an attending paediatric gastroenterologist at Seattle Children's Hospital. After completing his PhD in neuroscience and MD at Oregon Health and Science University in 2009, he subsequently completed a residency in paediatrics and a fellowship in paediatric gastroenterology and hepatology. During his fellowship under the mentorship of Dr Michael Schwartz, Dr Scarlett focused his studies on the mechanisms whereby the brain-centred glucoregulatory system regulates blood glucose in response to neural and hormonal signals. Dr Scarlett has now established an independent research programme within the Diabetes Institute at University of Washington conducting translational research on the pathophysiology of diabetes and metabolic disease. As a ground-breaking physician-scientist, Dr Scarlett has received several young scientist and early career awards and has published multiple high-impact manuscripts.

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FURTHER READING

JM Scarlett, K Muta, JM Brown, et al, Peripheral mechanisms mediating the sustained antidiabetic action of FGF1 in the brain, *Diabetes*, 2019, 68, 654–664.

JM Brown, JM Scarlett, ME Matsen, et al, The hypothalamic arcuate nucleus-median eminence is a target for sustained diabetes remission induced by fibroblast growth factor 1, *Diabetes*, 2019, 68, 1054–1061.

Brown JM, Scarlett JM, Schwartz MW, Rethinking the role of the brain in glucose homeostasis and diabetes pathogenesis, *Journal of Clinical Investigation*, 2019, 3035–3037.

JM Scarlett, JM Rojas, ME Matsen, et al, Central injection of fibroblast growth factor 1 induces sustained remission of diabetic hyperglycemia in rodents, *Nature Medicine*, 2016, 22, 800–809.

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