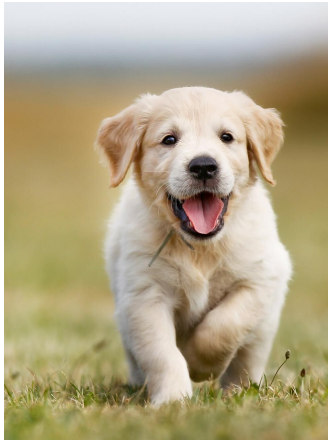
Treatment Windows for Obesity-Induced Type II Diabetes with GLP-1 Agonist Drugs

By Eli Bullock-Papa

Quiz: What is something that looks cute but is extremely dangerous?



Quiz: What is something that looks cute but is extremely dangerous?

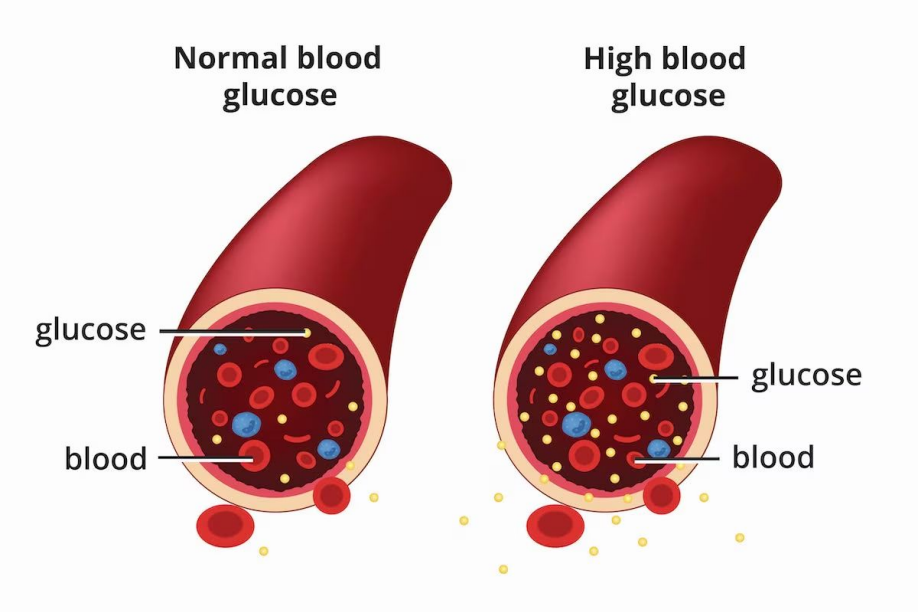
In this presentation:

1. What is diabetes
2. Overview of how it forms
3. A more complete model and why we think it’s accurate
4. How the model has been used
5. What is missing from existing work and my research plan

What is Diabetes?

Diabetes Overview

Complex condition **diagnosed** by having **too much glucose in your blood**



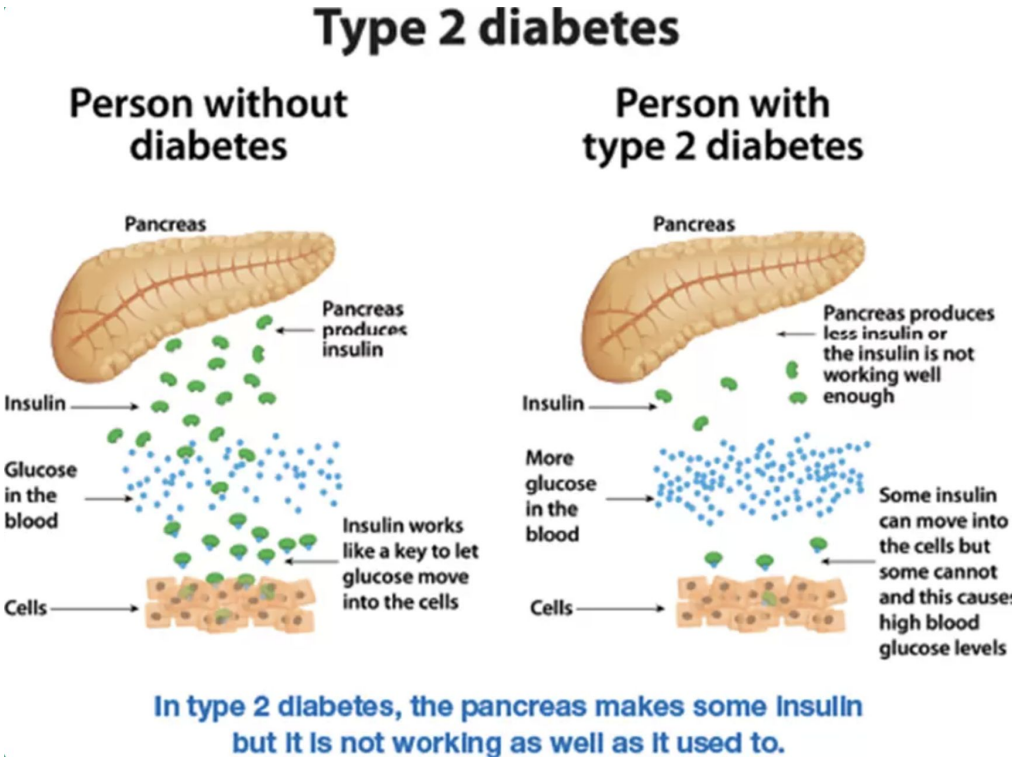
Major Components Overview

Blood Glucose: sugar your body produces when you eat.

Insulin: a hormone produced to tell cell they should absorb glucose from the bloodstream.

Beta cells: cells in the pancreas that produce insulin.

Type 2 Diabetes



How does it develop?

Diabetes Development and Obesity

Views have **changed over time** but this is the modern overview of **how we think Type 2 Diabetes (T2D) is developed in youth** (people under 40):

1. Due to the combination of diet and lack of exercise, a person starts to **gain excessive weight**, potentially leading to obesity.
2. In response to high blood sugar levels, the **pancreas produces more insulin** than normal to try to lower blood sugar levels.

Diabetes Development and Obesity

3. The body **begins to develop insulin resistance as a protective response**. It's theorized that this resistance helps shield the body's cells from excessive sugar intake and the stress of high insulin levels
4. The insulin resistance means that cells aren't taking up all of the blood glucose, and **blood sugar remains high** even with high insulin levels.
5. High blood sugar levels **keep beta cells producing insulin levels in overdrive**.
6. Over long stretches of time, this overwork causes **beta cells to begin dysfunctioning or even die**.
7. This plus continued insulin resistance means **blood glucose levels continue to spiral upwards**

A more complete model

Model source:

iScience. 2023 Nov 17; 26(11): 108324.
Published online 2023 Oct 23. doi: 10.1016/j.isci.2023.108324

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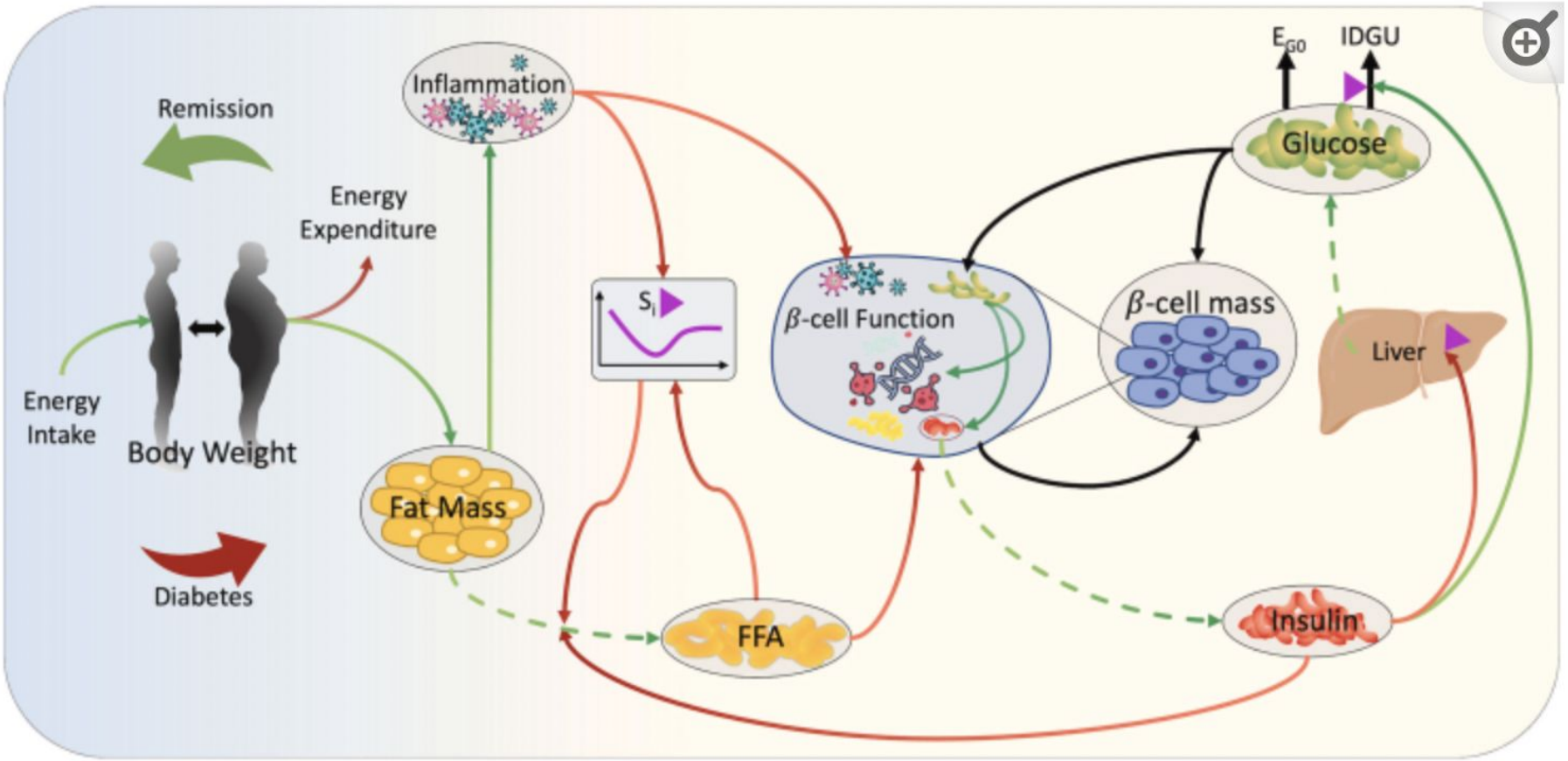
PMID: 38026205

Journal Article

A data-driven computational model for obesity-driven diabetes onset and remission through weight loss

Vehpi Yildirim,[1,2,9,*] Vivek M. Sheraton,[2,3,4] Ruud Brands,[5,6] Loes Crielaard,[1,2] Rick Quax,[2,3] Natal A.W. van Riel,[7,8] Karien Stronks,[1,2] Mary Nicolaou,[1,2] and Peter M.A. Sloot[2,3]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β-cell Function
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Body Weight
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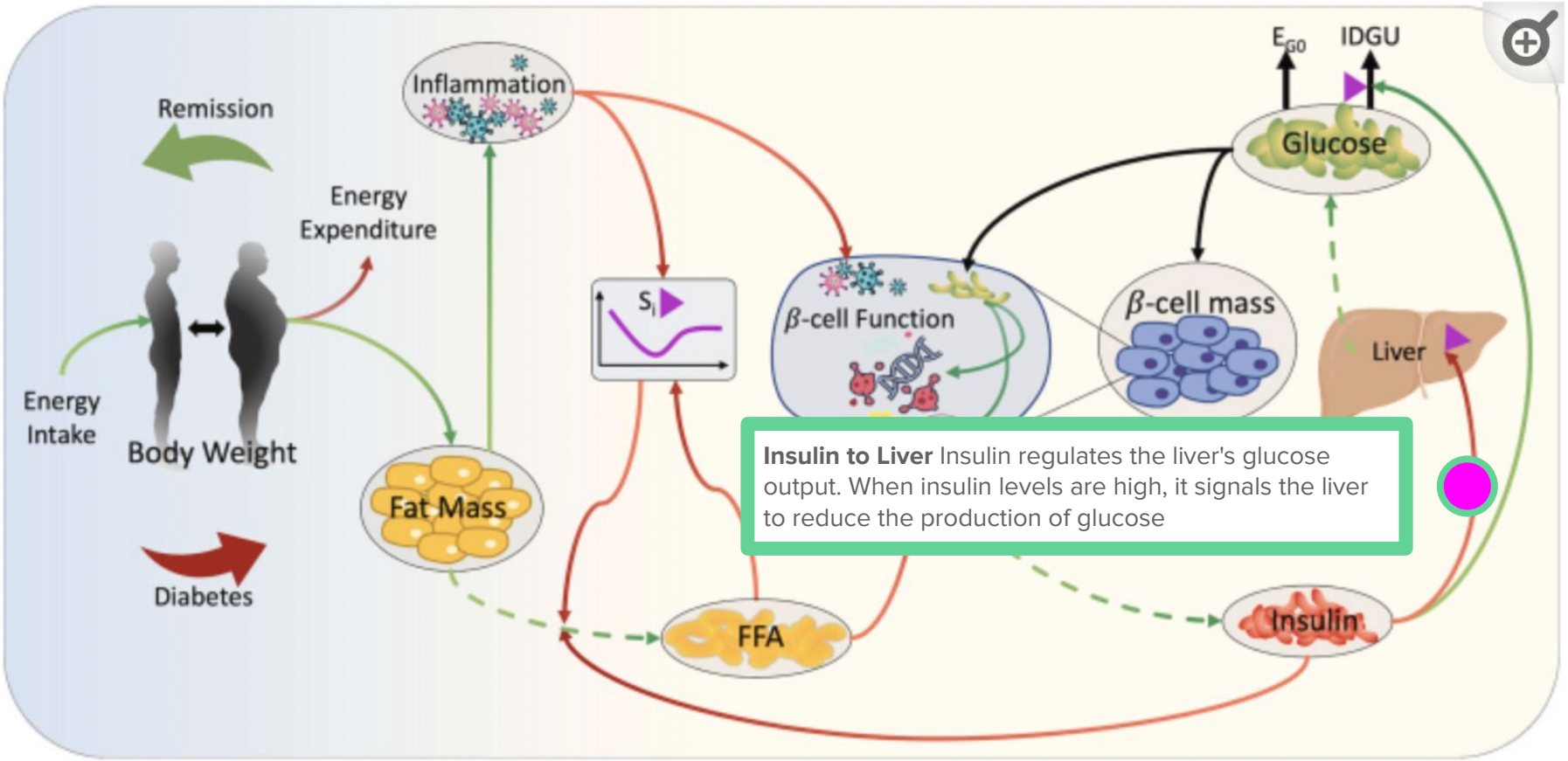
FFA
Insulin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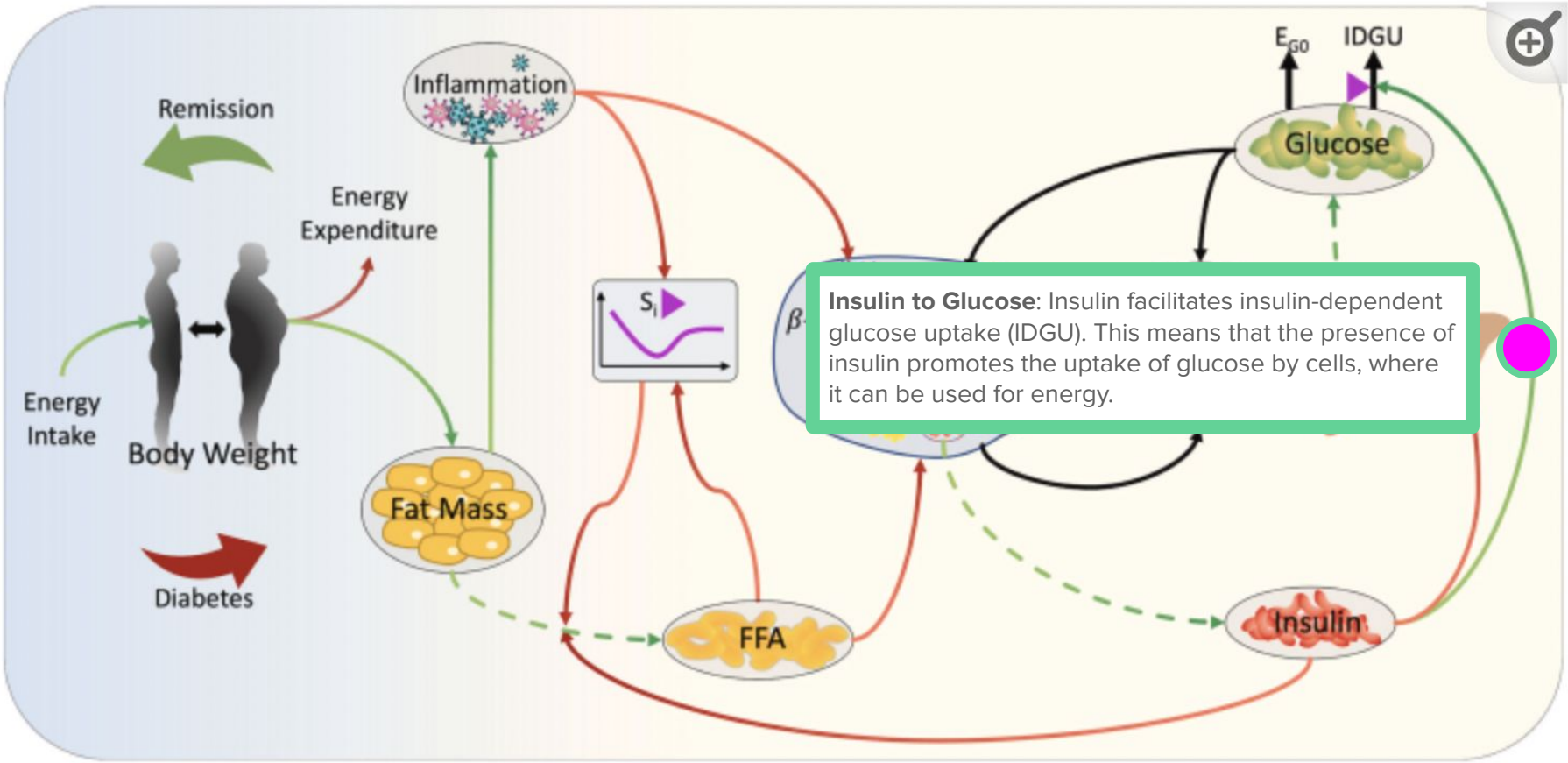
Insulin to Liver Insulin regulates the liver's glucose output. When insulin levels are high, it signals the liver to reduce the production of glucose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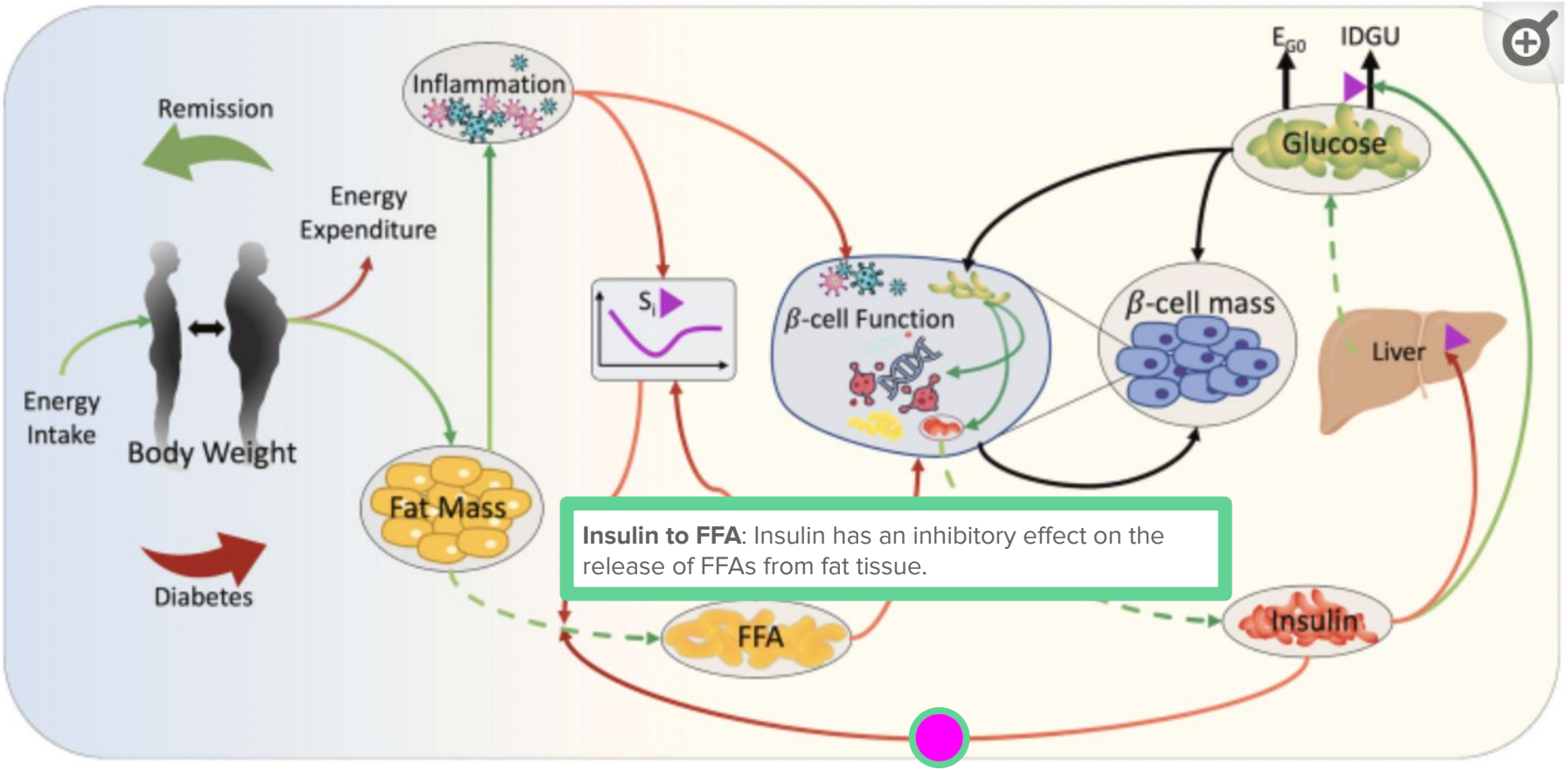
Insulin to Glucose: Insulin facilitates insulin-dependent glucose uptake (IDGU). This means that the presence of insulin promotes the uptake of glucose by cells, where it can be used for energy.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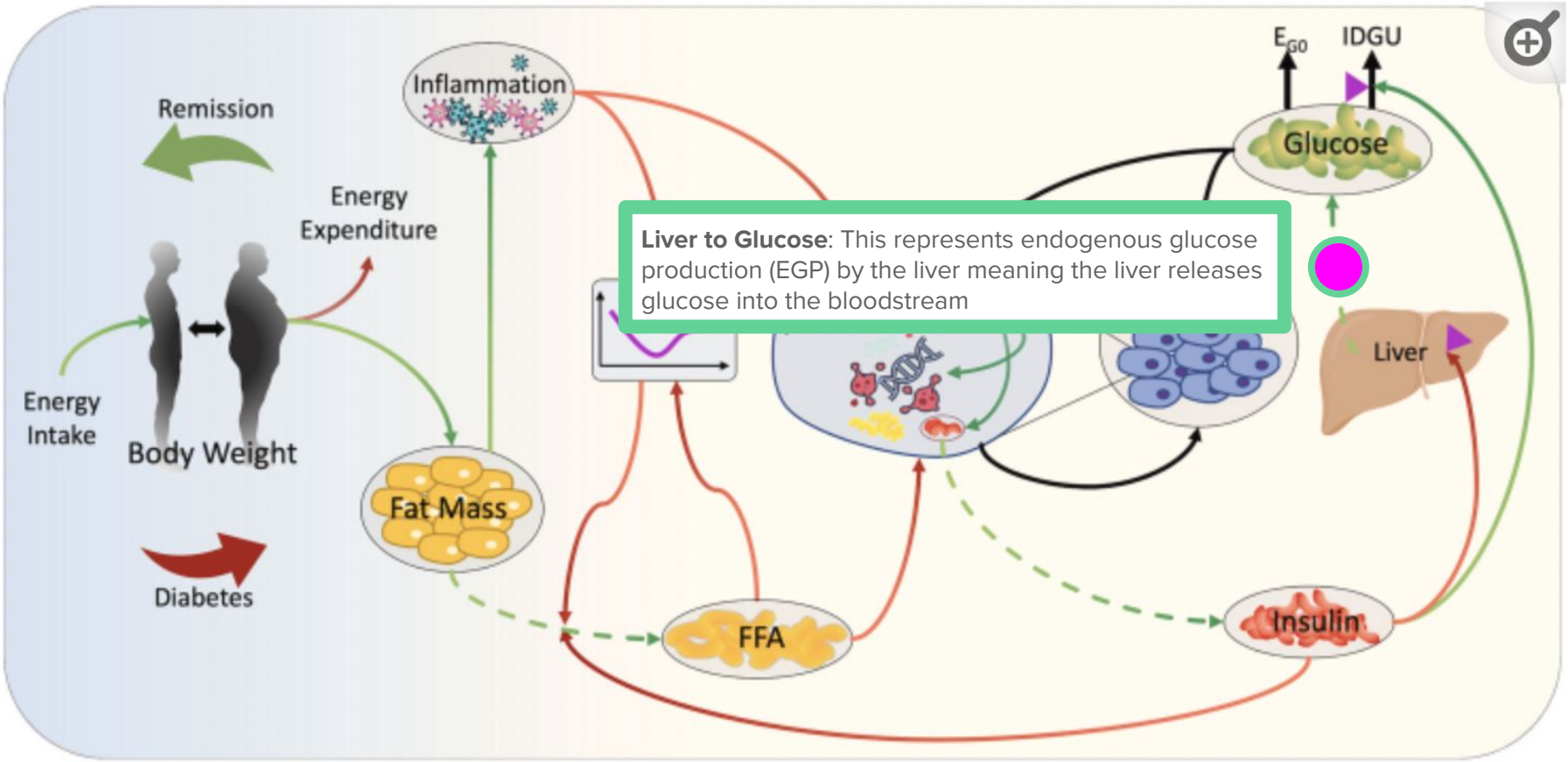
Insulin
Insulin to FFA: Insulin has an inhibitory effect on the release of FFAs from fat tissue.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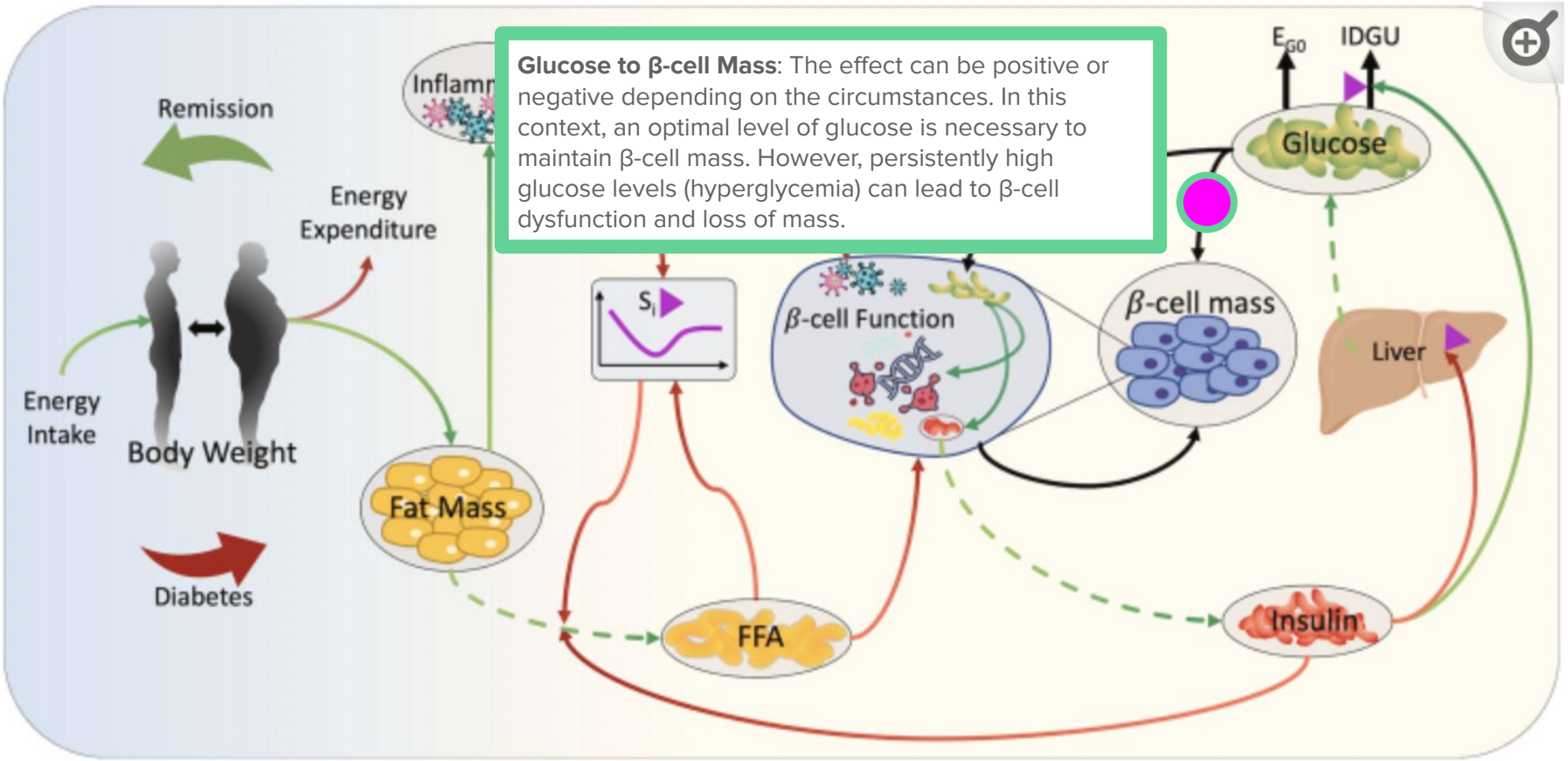
Liver
Liver to Glucose: This represents endogenous glucose production (EGP) by the liver meaning the liver releases glucose into the bloodstream


Glucose to β-cell Mass: The effect can be positive or negative depending on the circumstances. In this context, an optimal level of glucose is necessary to maintain β-cell mass. However, persistently high glucose levels (hyperglycemia) can lead to β-cell dysfunction and loss of mass.
Remission
Energy Expenditure
Energy Intake
Body Weight
Diabetes
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Fat Mass
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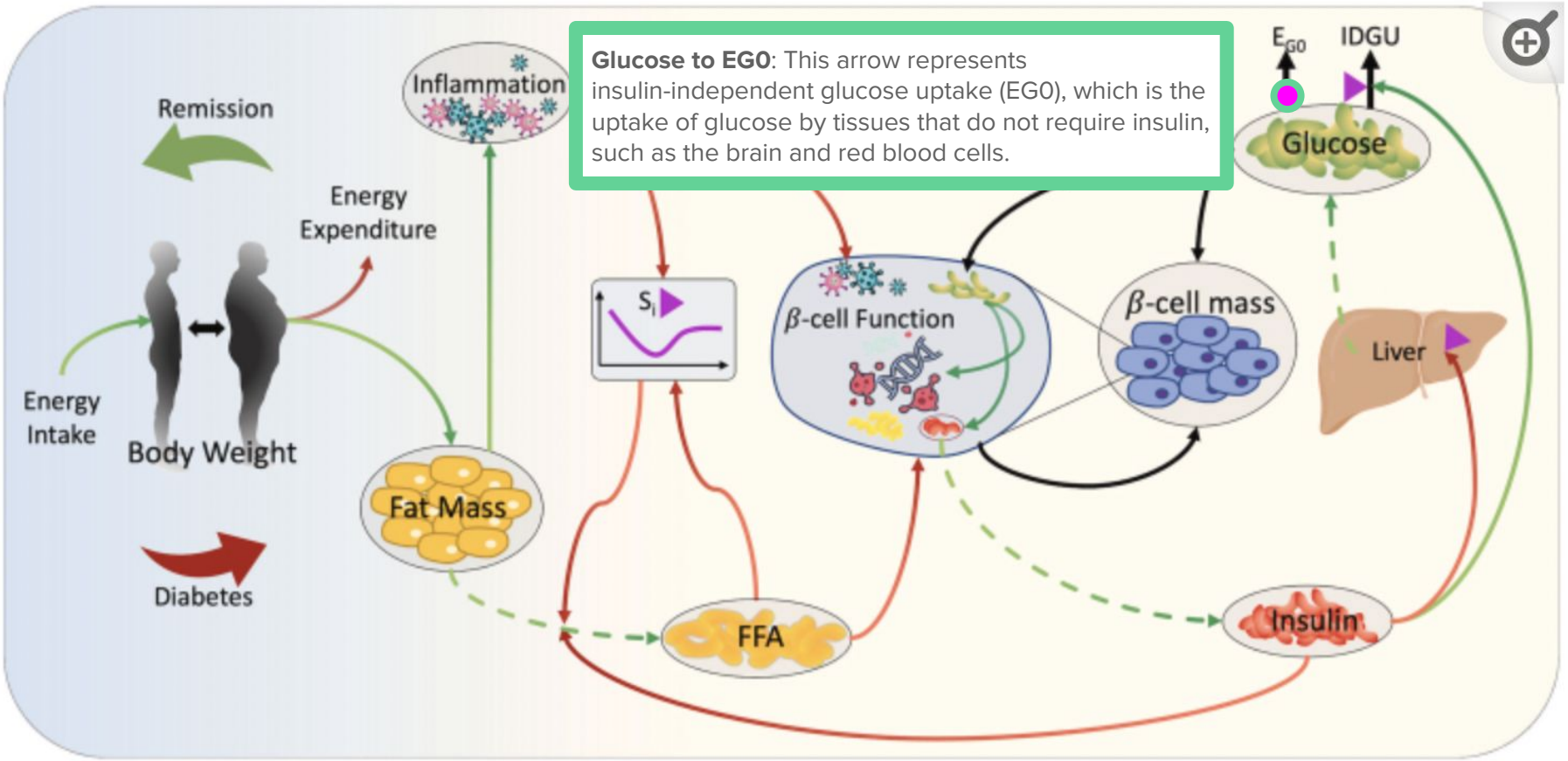
Glucose to EG0: This arrow represents insulin-independent glucose uptake (EG0), which is the uptake of glucose by tissues that do not require insulin, such as the brain and red blood cells.
Remission
Inflammation
Energy Expenditure
Energy Intake
Body Weight
Diabetes
Fat Mass
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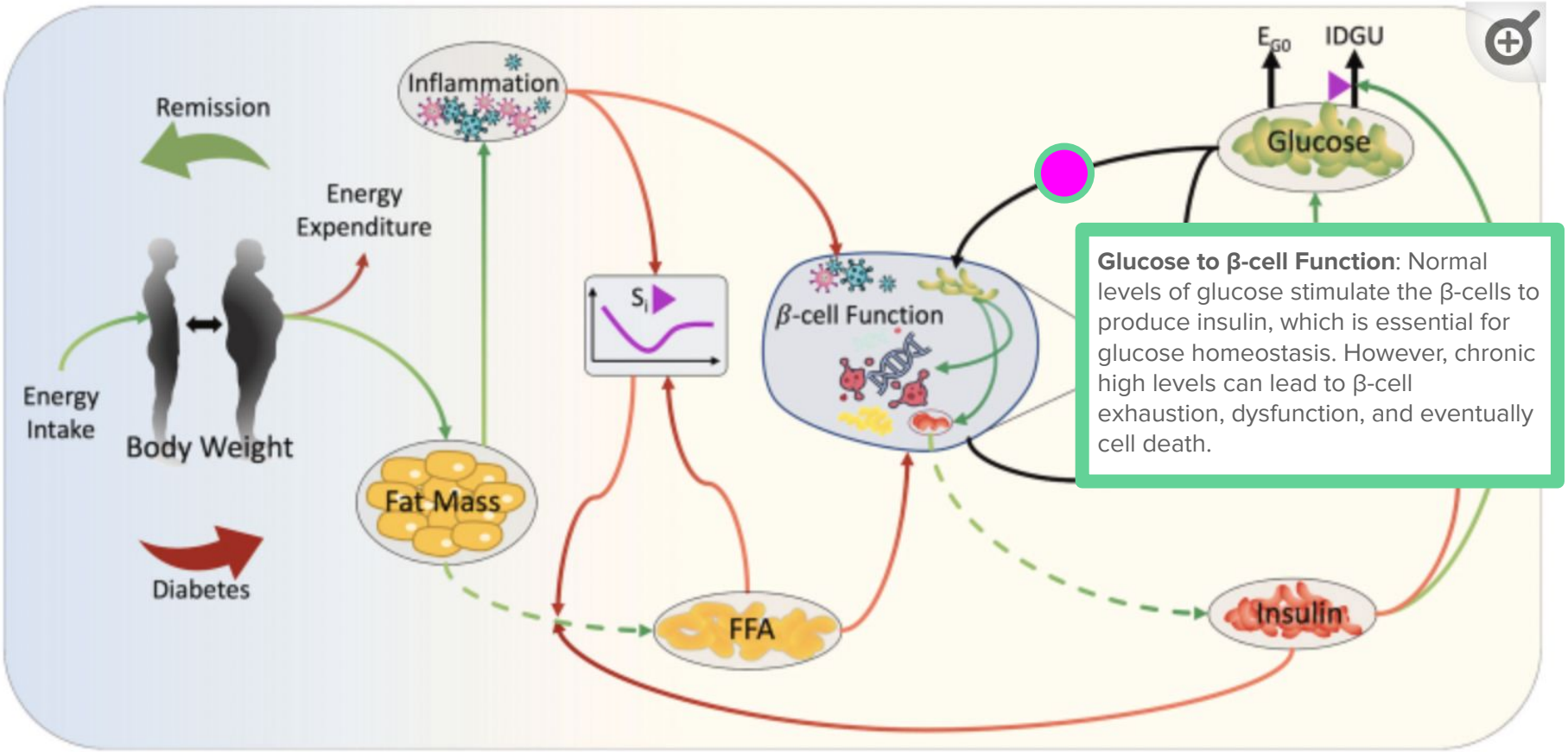
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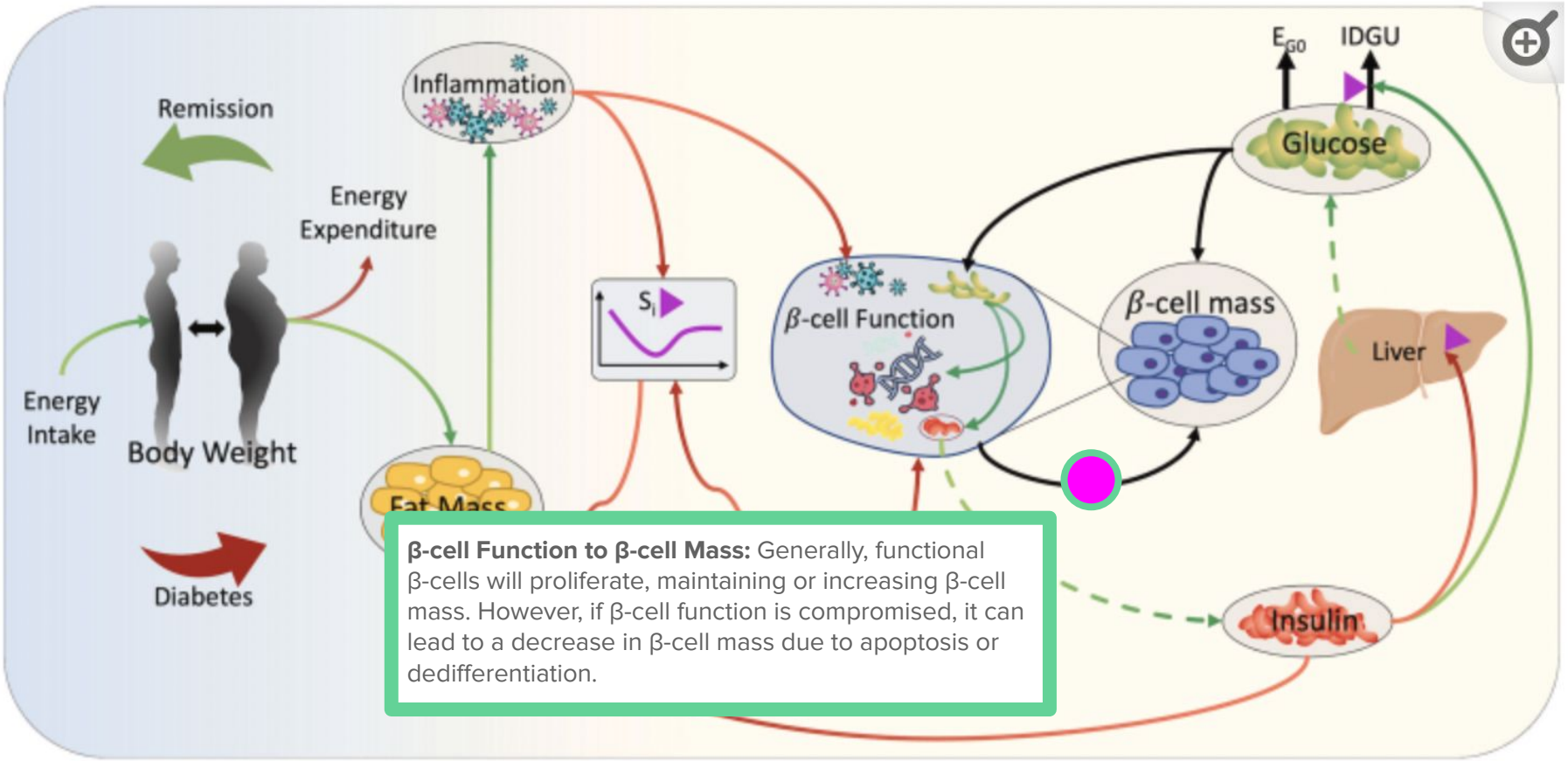
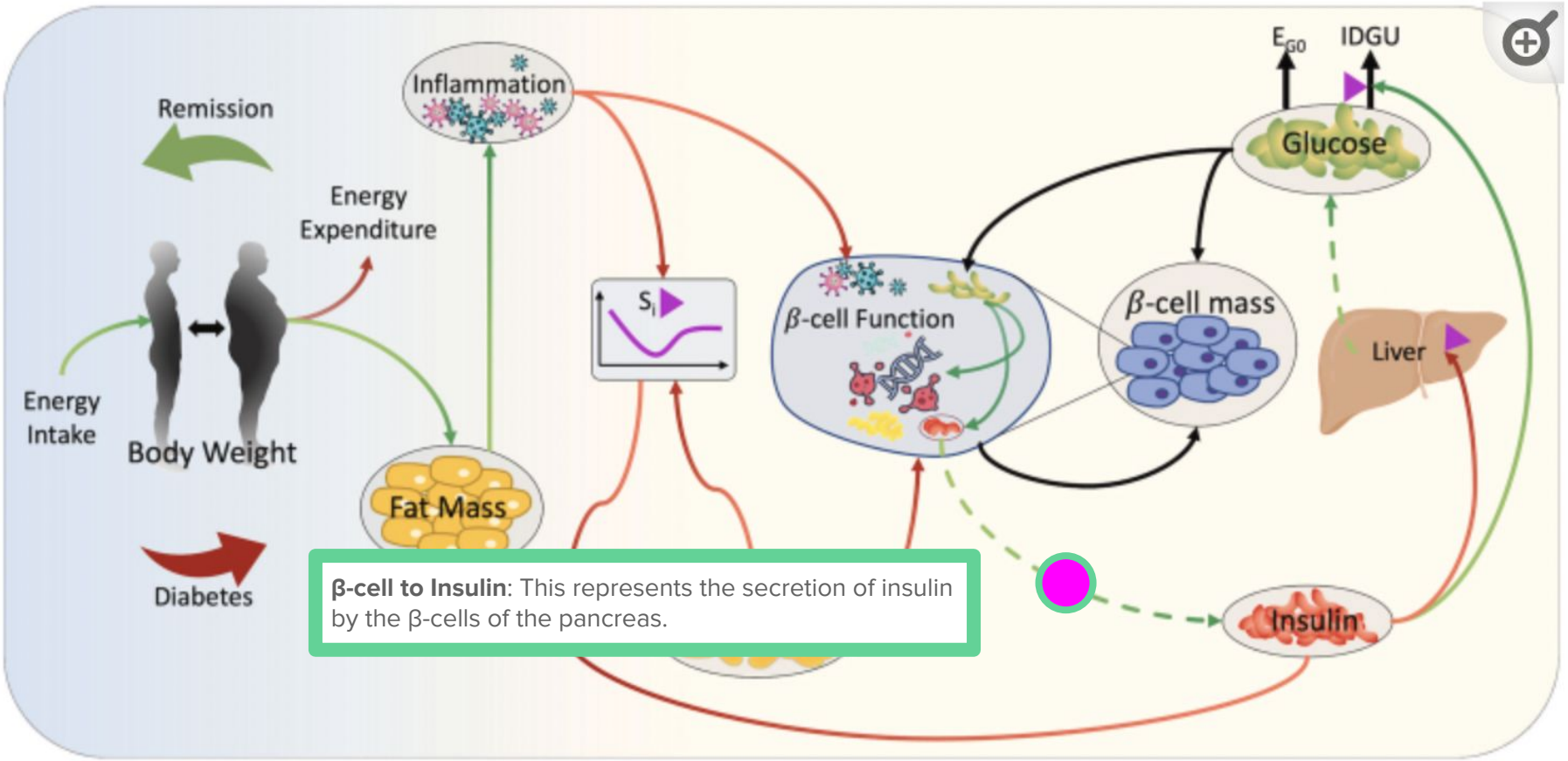
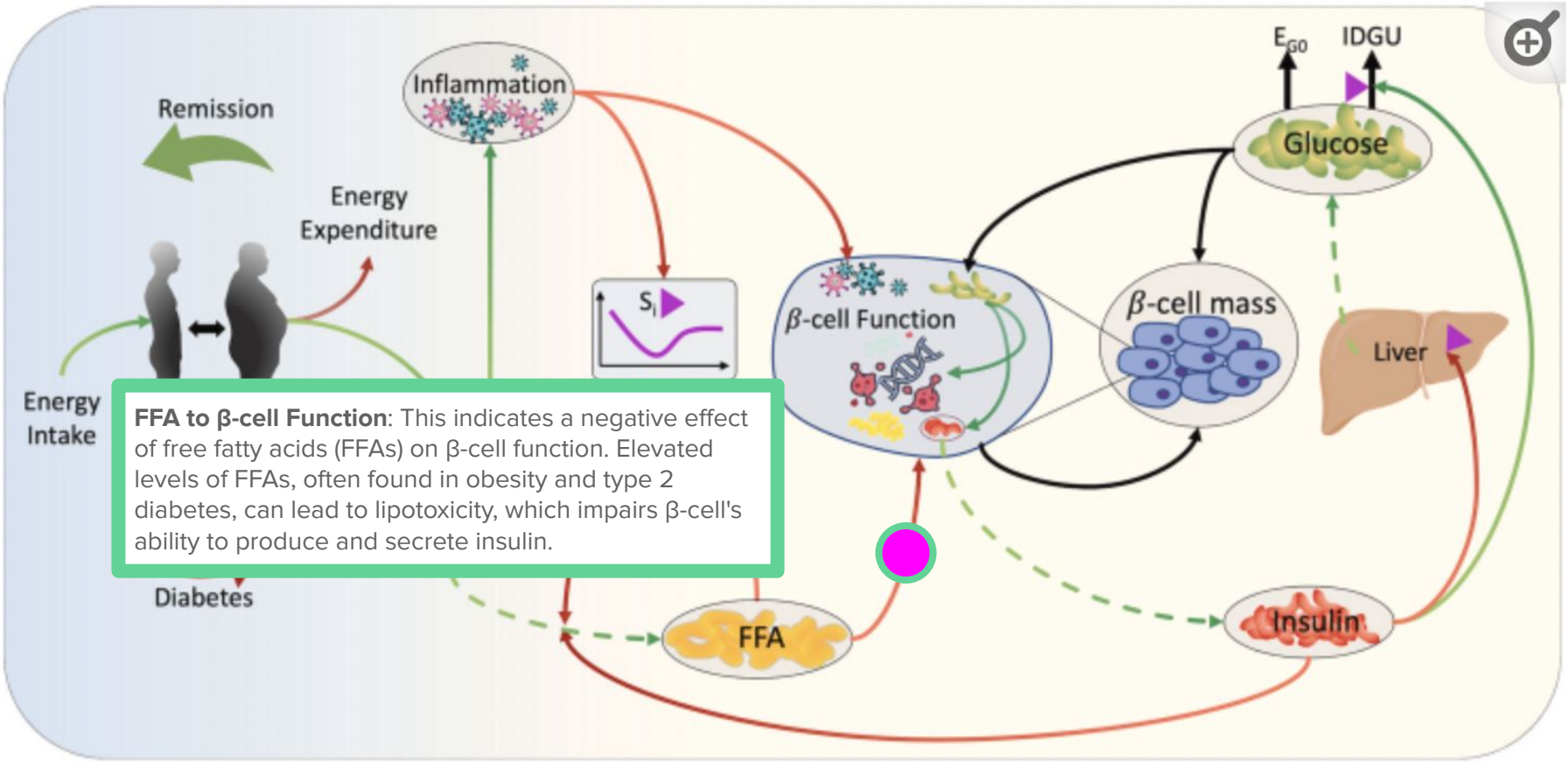
Glucose to β-cell Function: Normal levels of glucose stimulate the β-cells to produce insulin, which is essential for glucose homeostasis. However, chronic high levels can lead to β-cell exhaustion, dysfunction, and eventually cell death.



β-cell Function to β-cell Mass: Generally, functional β-cells will proliferate, maintaining or increasing β-cell mass. However, if β-cell function is compromised, it can lead to a decrease in β-cell mass due to apoptosis or dedifferentiation.



β-cell to Insulin: This represents the secretion of insulin by the β-cells of the pancreas.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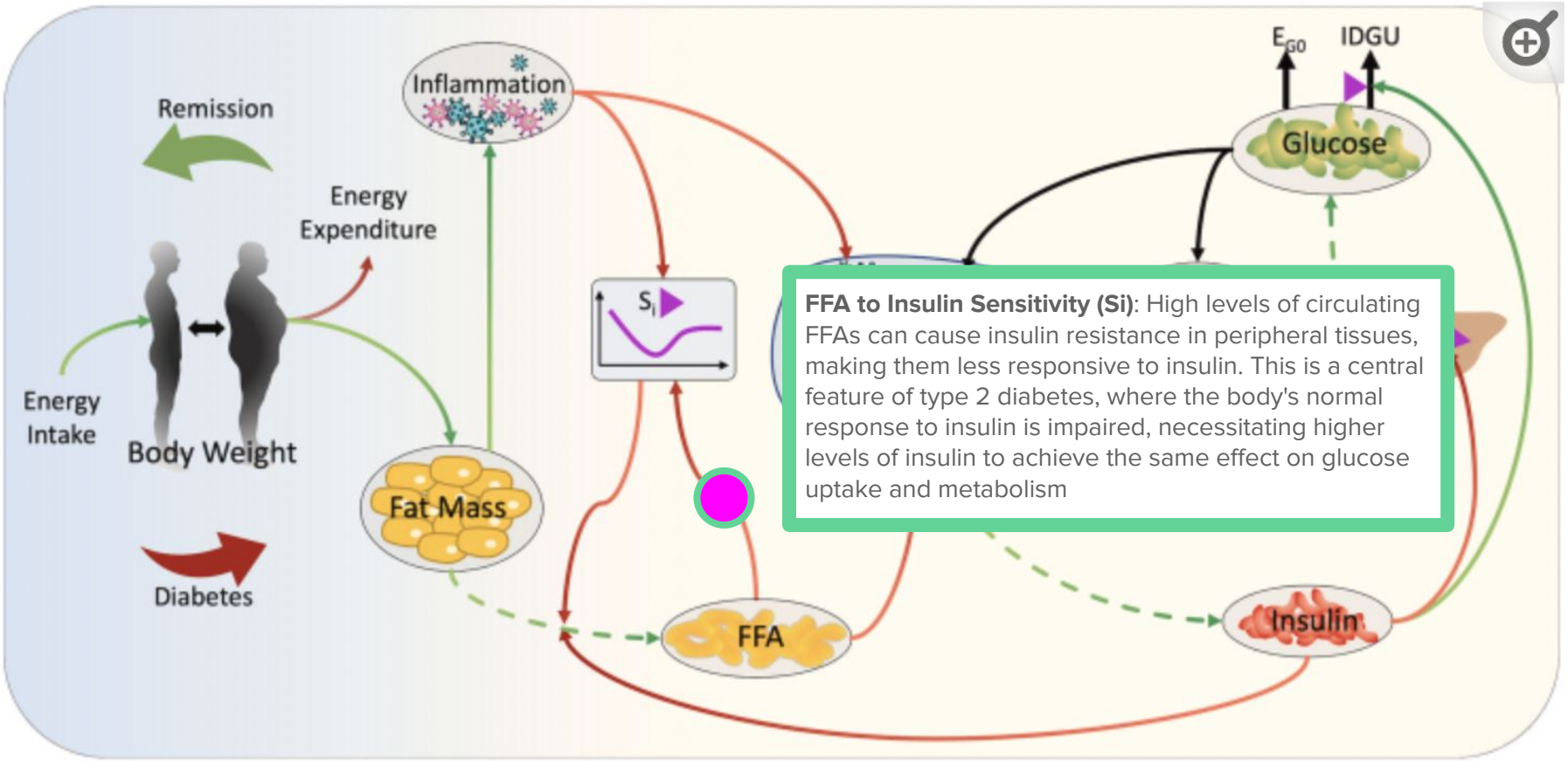
FFA to β-cell Function: This indicates a negative effect of free fatty acids (FFAs) on β-cell function. Elevated levels of FFAs, often found in obesity and type 2 diabetes, can lead to lipotoxicity, which impairs β-cell's ability to produce and secrete insulin.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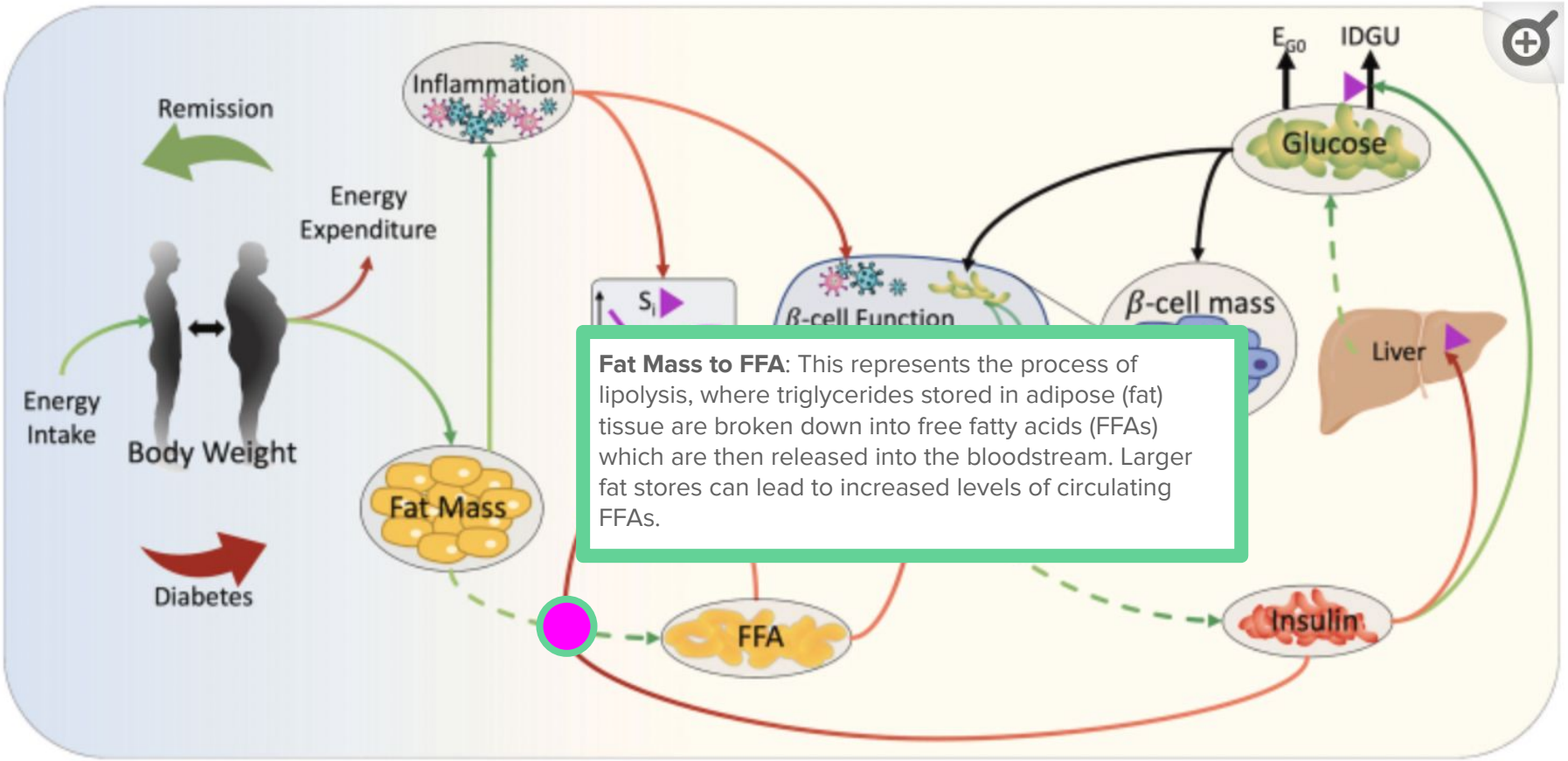
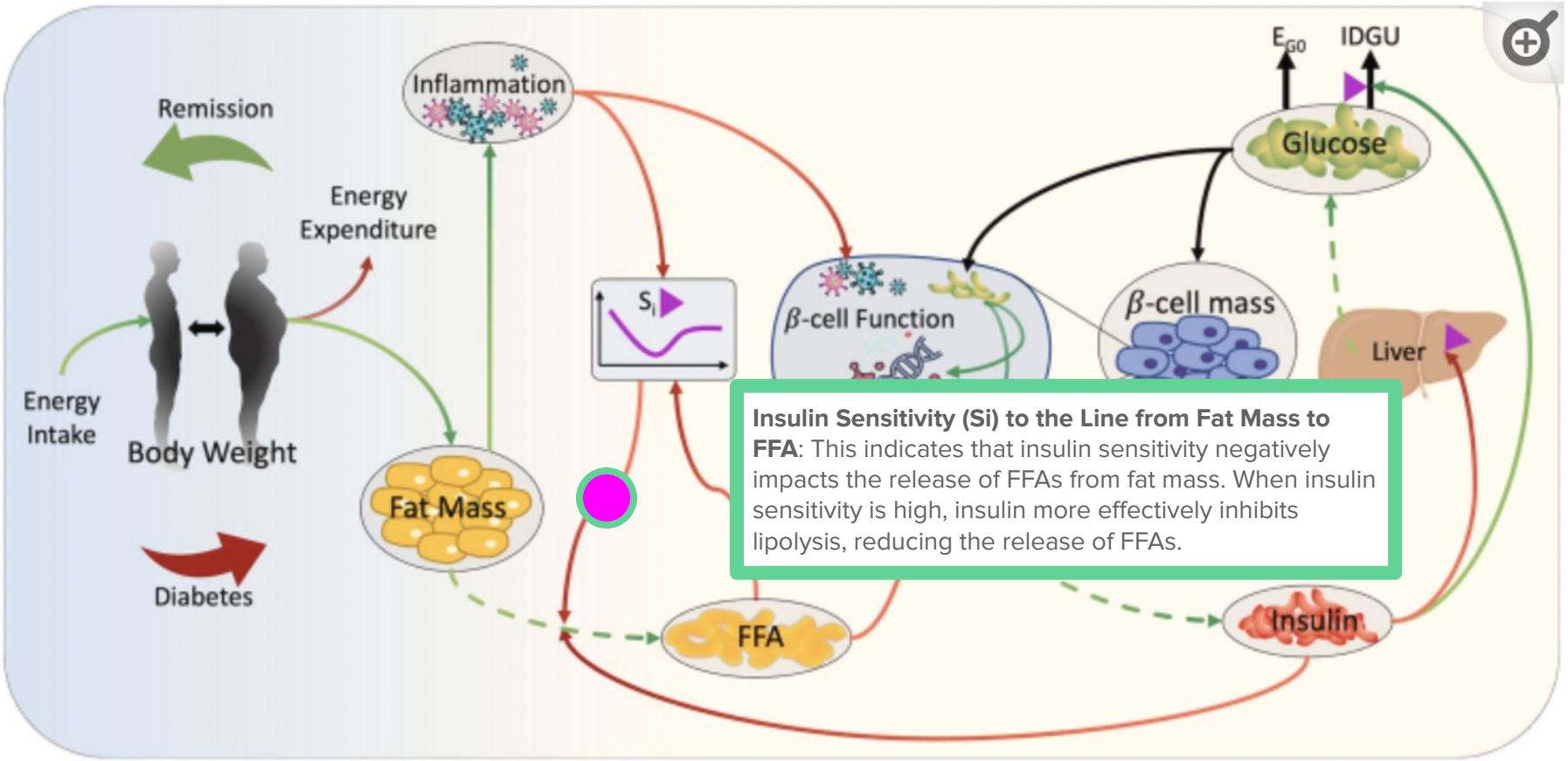
FFA to Insulin Sensitivity (Si): High levels of circulating FFAs can cause insulin resistance in peripheral tissues, making them less responsive to insulin. This is a central feature of type 2 diabetes, where the body's normal response to insulin is impaired, necessitating higher levels of insulin to achieve the same effect on glucose uptake and metabolism



Fat Mass to FFA: This represents the process of lipolysis, where triglycerides stored in adipose (fat) tissue are broken down into free fatty acids (FFAs) which are then released into the bloodstream. Larger fat stores can lead to increased levels of circulating FFAs.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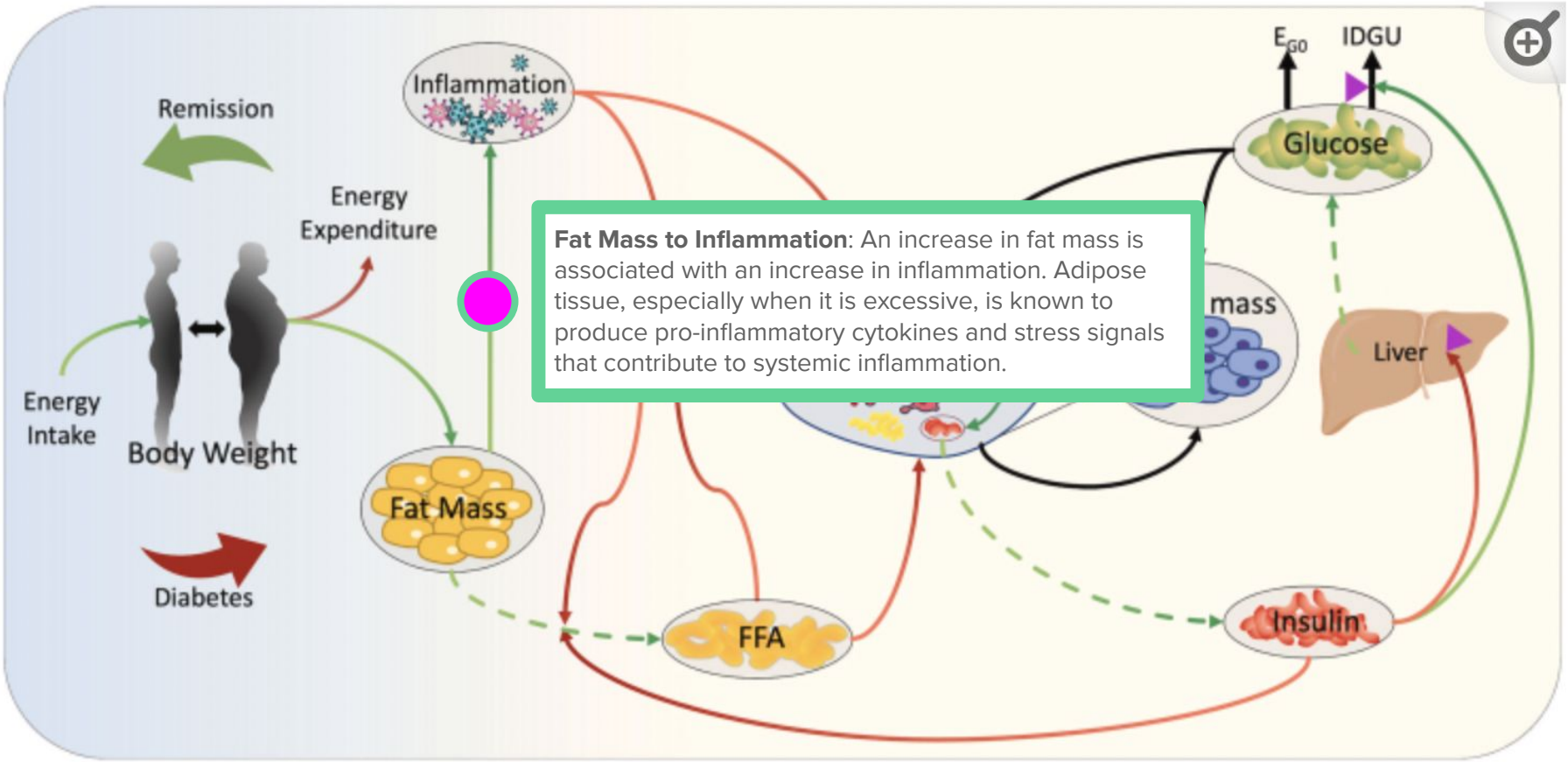
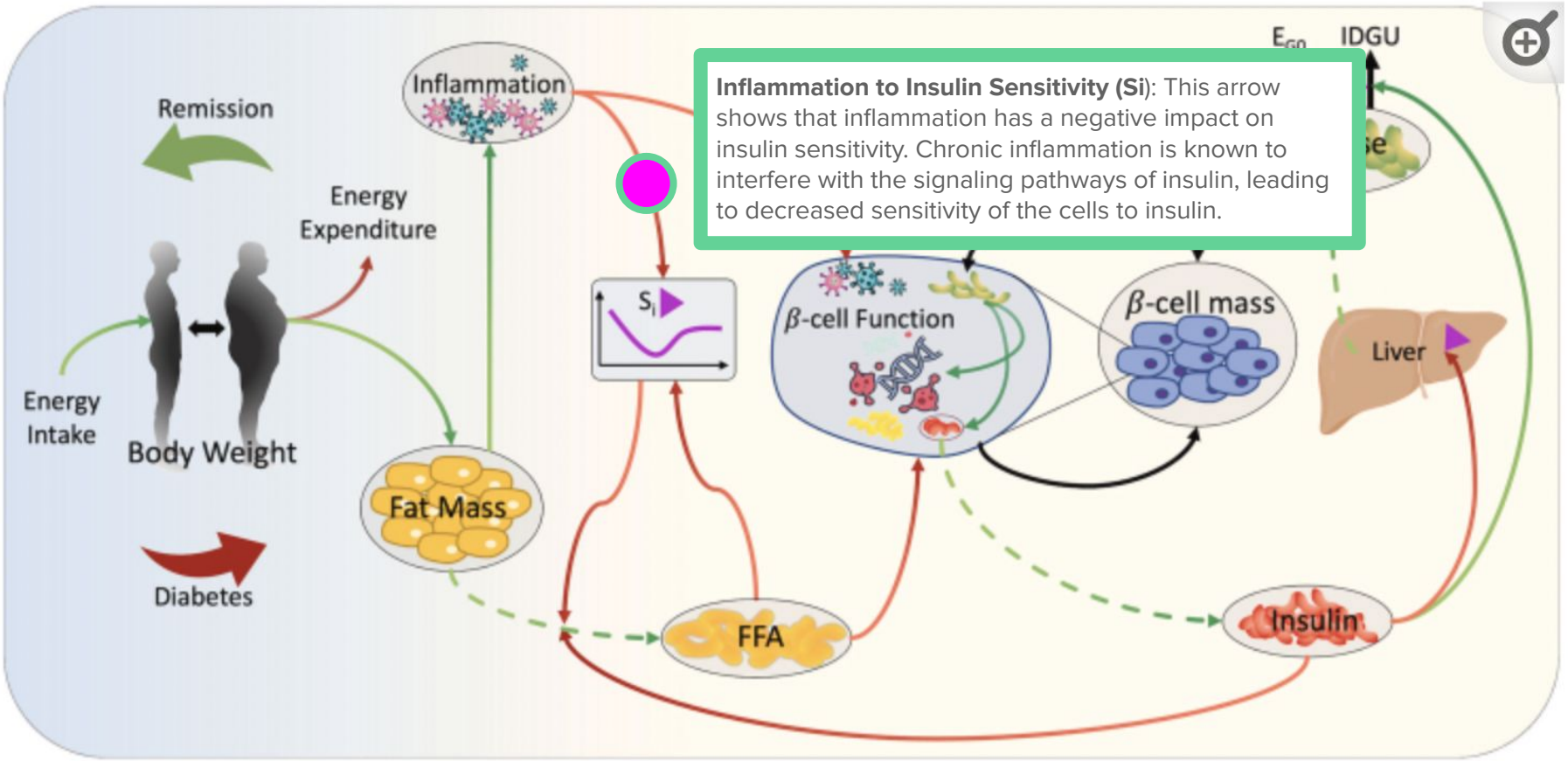
Insulin Sensitivity (Si) to the Line from Fat Mass to FFA: This indicates that insulin sensitivity negatively impacts the release of FFAs from fat mass. When insulin sensitivity is high, insulin more effectively inhibits lipolysis, reducing the release of FFAs.



Fat Mass to Inflammation: An increase in fat mass is associated with an increase in inflammation. Adipose tissue, especially when it is excessive, is known to produce pro-inflammatory cytokines and stress signals that contribute to systemic inflammation.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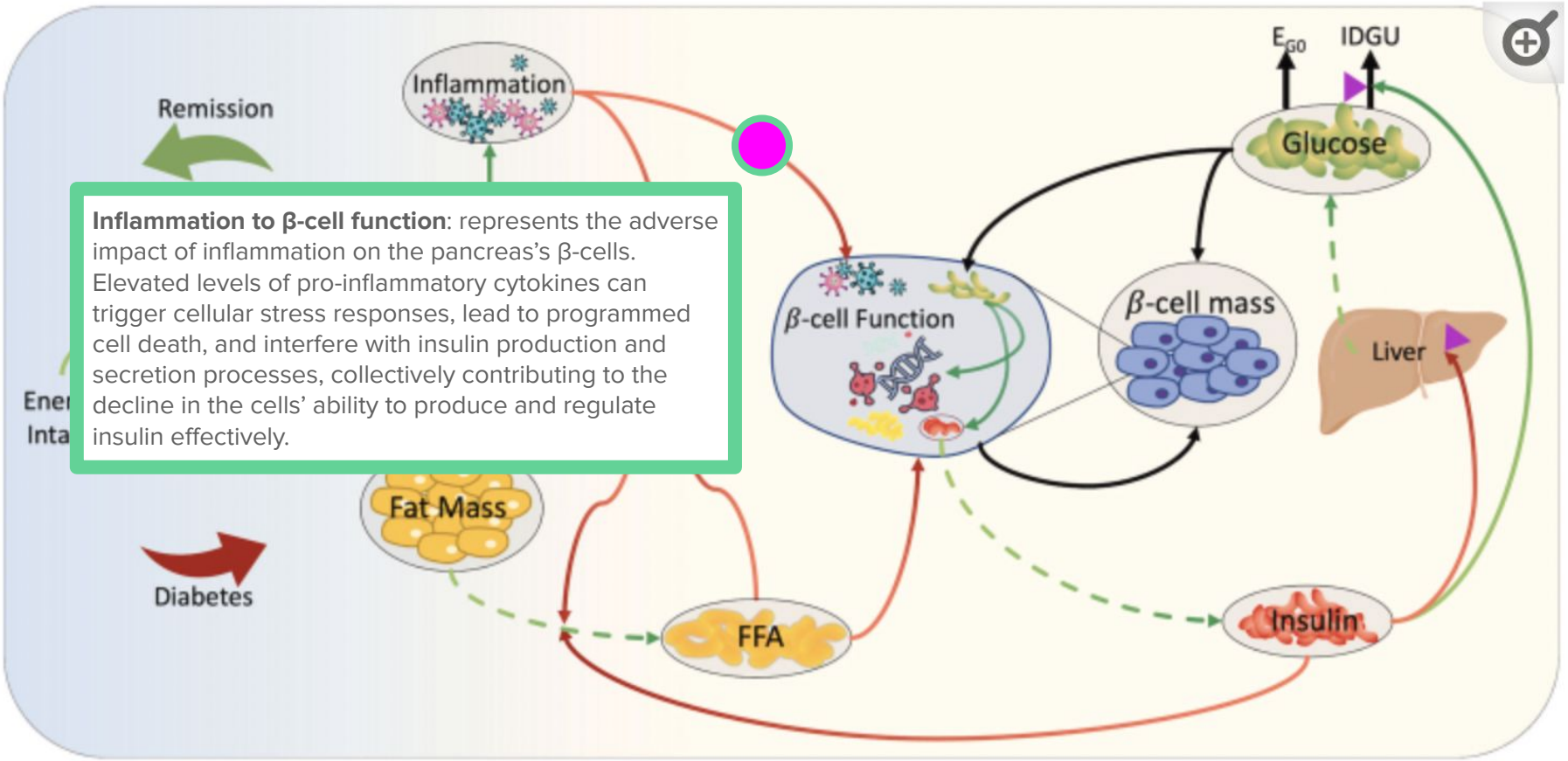
Inflammation to Insulin Sensitivity (Si): This arrow shows that inflammation has a negative impact on insulin sensitivity. Chronic inflammation is known to interfere with the signaling pathways of insulin, leading to decreased sensitivity of the cells to insulin.



Inflammation to β-cell function: represents the adverse impact of inflammation on the pancreas's β-cells. Elevated levels of pro-inflammatory cytokines can trigger cellular stress responses, lead to programmed cell death, and interfere with insulin production and secretion processes, collectively contributing to the decline in the cells' ability to produce and regulate insulin effectively.

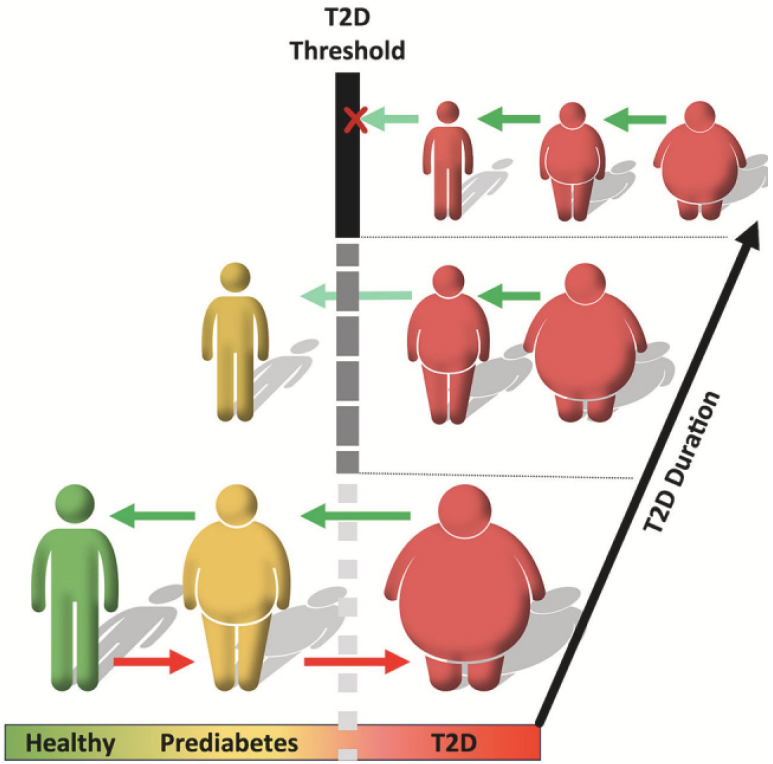
Is this model accurate?

Why they think their model is accurate

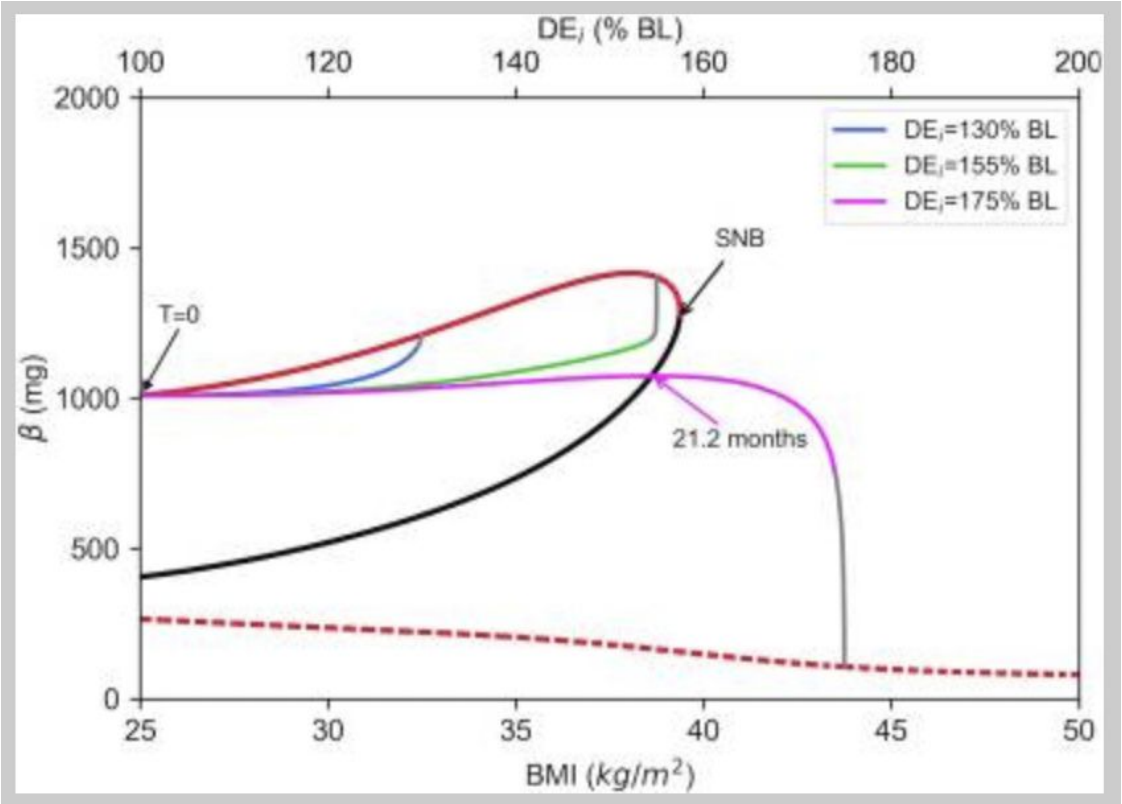
- It incorporates what we know of as the most important processes in the formation of diabetes and T2D
- It reproduces experimental findings from the DIRECT study which compared weight intervention vs. diabetes treatment only. It reproduced:
  - Longer T2D duration for non-responders compared with responders
  - β-cell function increases in both groups but β-cell mass only increases in responders
  - Higher pancreas volume in non-diabetic controls
  - Greater increase in pancreas volumes of the responders vs non-responders

How did the paper use this model?

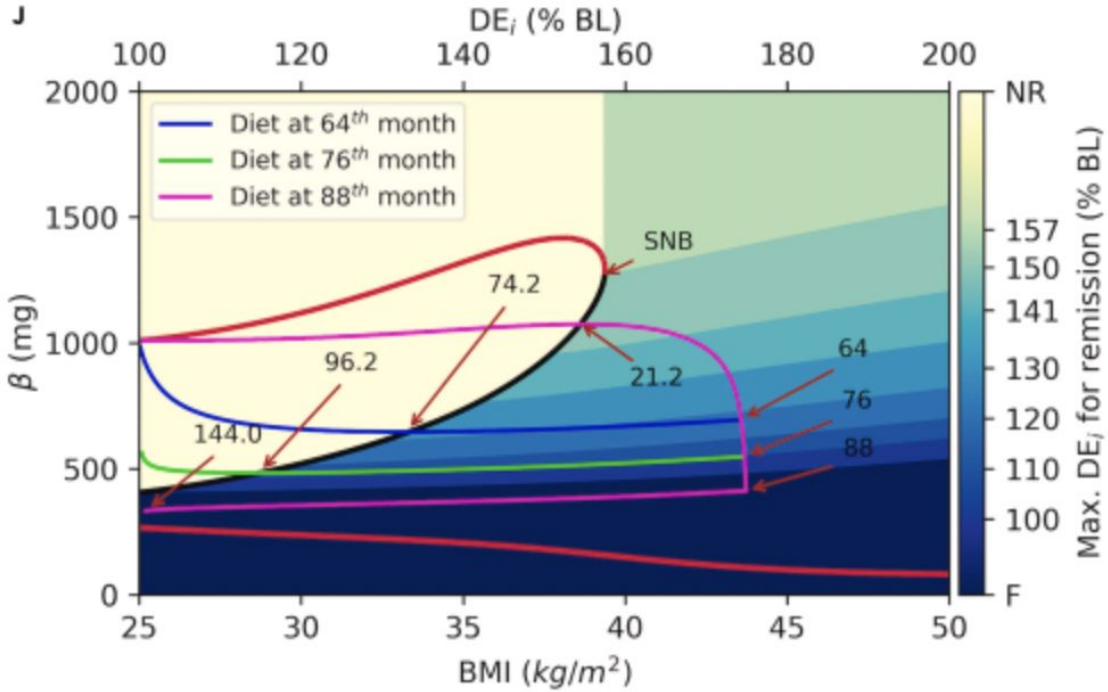
Importance of Treatment Timelines



Bifurcation Analysis



Treatment efficacy based on BMI and beta cell mass

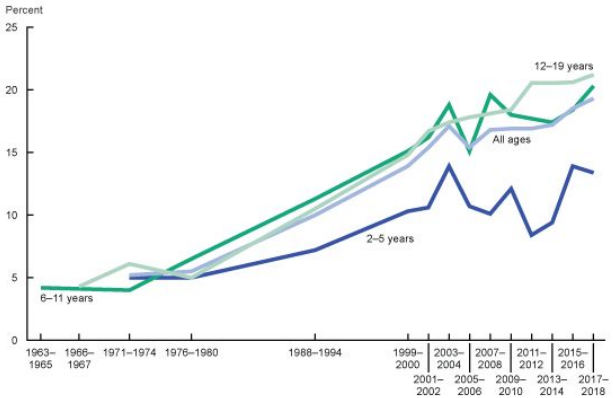


My contribution

Trends I think are relevant

1. Introduction of **GLP-1 agonist drugs like Semaglutide and Tirzepatide**. They have multiple effects that act potently on diabetes **and** obesity.

2. **Rises in rates of childhood obesity**. This means that by the time people are eligible for treatment with these GLP-1 agonists, **their window for effective treatment is already partly closed**



My research plan:

1. Get the model fully running on my computer using their provided python and xpp code posted on github.

2. Format trial data as necessary from the GLP-1 agonist drug trials - most importantly weight information of participants

3. Model different treatment timelines for ages at which to start treatment with the different drugs and their efficacy rates

Any Questions?