An Unexpected Ally in the Fight Against Diabetes: The BCG Vaccine

Dr Denise L Faustman

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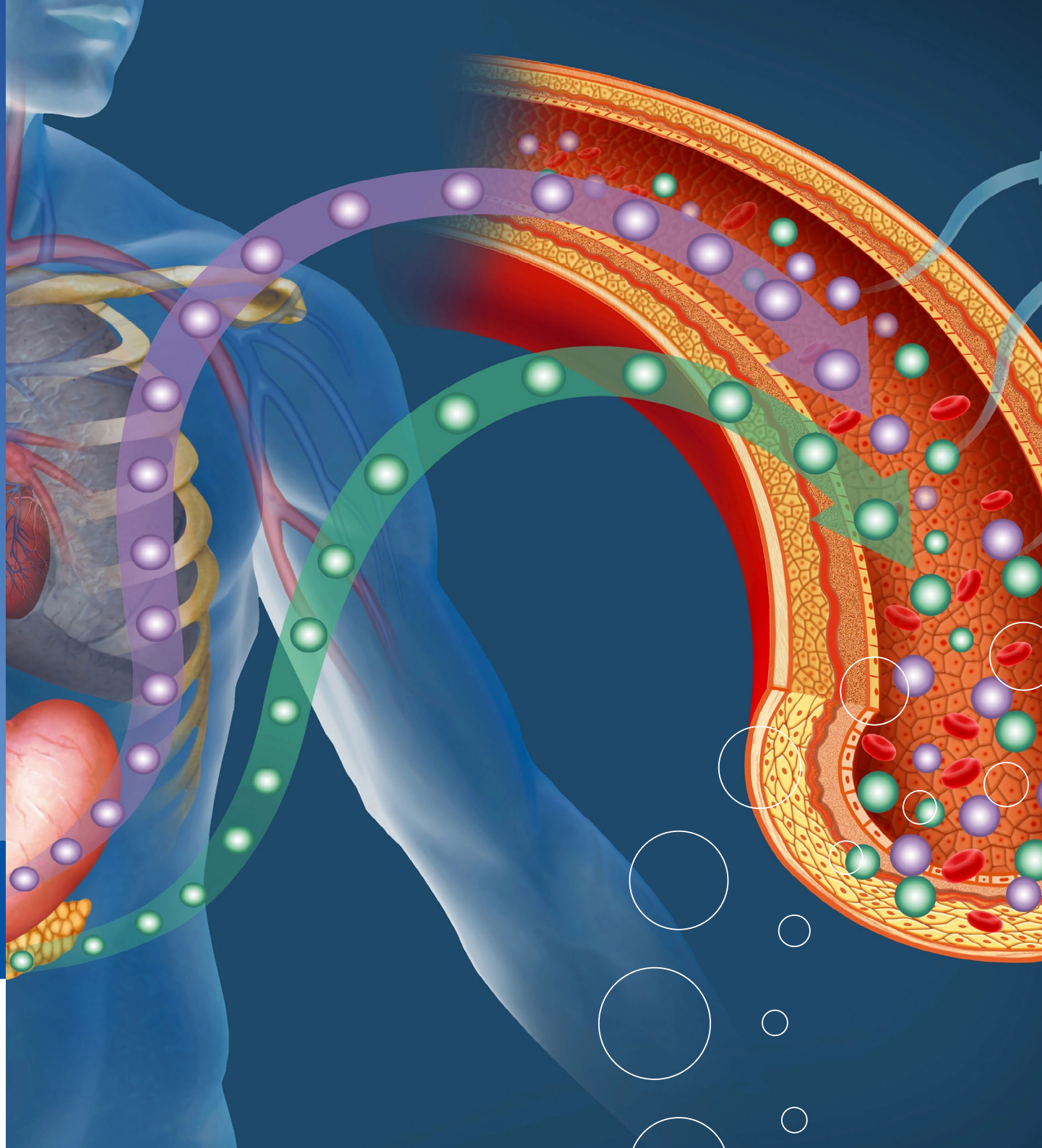
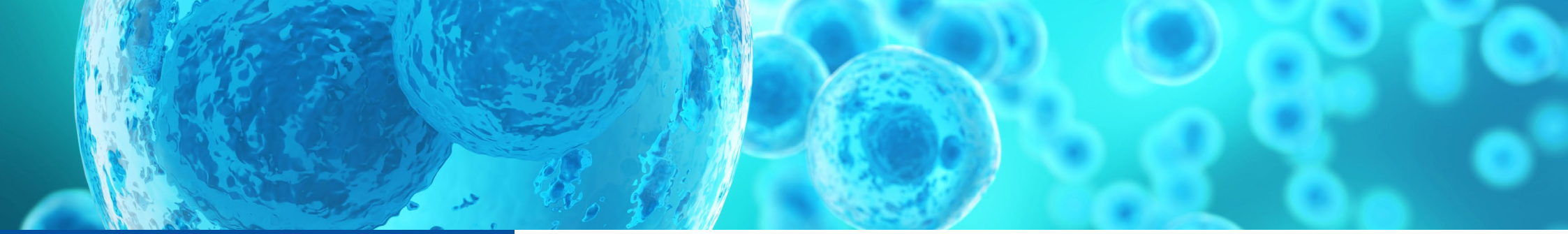




An Unexpected Ally in the Fight Against Diabetes: The BCG Vaccine

Diabetes is a widespread health concern affecting millions worldwide. Recent research suggests an unexpected ally in the fight against this disorder: the Bacille Calmette-Guérin (BCG) vaccine. Originally developed to prevent tuberculosis, BCG is now showing promise in managing and potentially preventing type 1 diabetes. Dr Denise Faustman from Massachusetts General Hospital (MGH) and Harvard Medical School is leading groundbreaking studies that are reshaping our understanding of diabetes treatment and prevention.

A Century-Old Vaccine with Modern Potential

The BCG vaccine, first used in 1921 to combat tuberculosis, has been a cornerstone of global health initiatives for a century. Its strong safety record and widespread use make it one of the most commonly administered vaccines worldwide. However, recent research has uncovered a range of unexpected benefits beyond its original purpose, including potential protective effects against various non-mycobacterial infections and even certain autoimmune conditions.

Dr Denise Faustman and her team at MGH have been at the forefront of investigating BCG's potential in diabetes management and prevention. Their work has revealed intriguing connections between this long-established vaccine and improved blood sugar control in individuals with type 1 diabetes.

Unravelling BCG's Impact on Diabetes

Type 1 diabetes (T1D) is an autoimmune condition where the body's immune system attacks and destroys insulin-producing cells in the pancreas. This leads to a lifelong dependence on insulin therapy. Type 2 diabetes (T2D), on the other hand, is characterised by insulin resistance and, in later stages, insufficient insulin production.

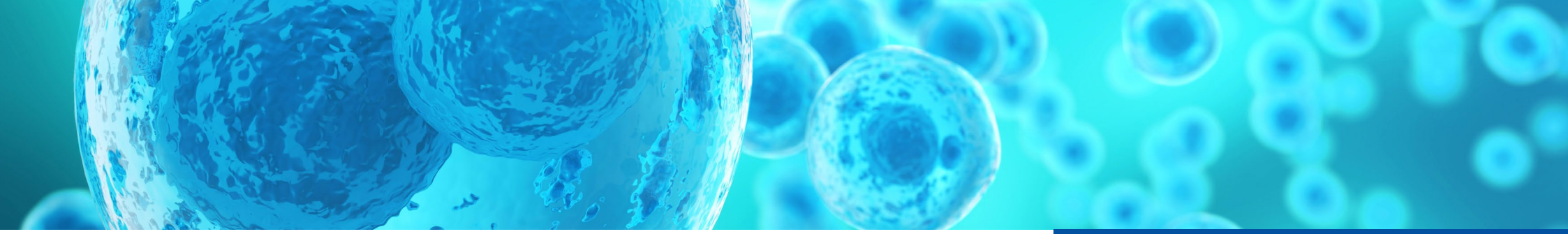
Dr Faustman's research has shown that BCG vaccinations can lead to long-term improvements in blood sugar control for individuals with longstanding T1D. Multiple randomised controlled trials and observational studies in the United States have demonstrated that multi-dose BCG immunotherapy can lower blood sugar levels in individuals with longstanding type 1 diabetes, particularly those with juvenile-onset disease.

The Science Behind the Success

The team's investigations revealed that BCG's beneficial effects on blood sugar levels stem from both immune and metabolic changes. Dr Faustman's research indicates that BCG appears to reset the immune system, increasing levels of regulatory T-cells and reducing the number of autoreactive immune cells that attack pancreatic beta cells.

Perhaps even more intriguingly, BCG treatment was found to induce a systemic shift in glucose metabolism in vivo with participants diagnosed and treated with Type 1 diabetes. Dr Faustman's team discovered that individuals with type 1 diabetes have an underlying defect in their white blood cells' metabolism. Instead of primarily using aerobic glycolysis (which uses sugar for energy), their white blood cells rely more heavily on oxidative phosphorylation (which uses fats for energy).

The BCG vaccine gradually switches glucose metabolism in immune cells from oxidative phosphorylation back to aerobic glycolysis. This metabolic change is driven by increased expression of a protein called Myc, which acts as a master regulator of several glucose metabolism pathways. Dr Faustman's team observed that this shift to aerobic glycolysis represents a state of high glucose utilisation, which may explain the lowering of HbA1c levels seen in treated patients. Remarkably, this effect occurs even in the absence of a functioning pancreas, demonstrating that BCG immunotherapy can systemically lower blood sugar levels through its effects on the immune system.



BCG and Bladder Cancer: An Unexpected Connection

To further explore BCG's potential effects on diabetes, Dr Faustman and her colleagues turned to an unexpected source: bladder cancer treatment data. BCG has been used as a therapy for early-stage bladder cancer since the 1970s, typically administered in high doses directly into the bladder.

The team analysed three large US clinical databases, focusing on individuals with bladder cancer who also had either T1D or T2D. They tracked changes in HbA1c levels following BCG treatment for bladder cancer. Remarkably, they found that T1D patients who received BCG for bladder cancer showed a consistent decrease in HbA1c levels in the years following treatment. This effect was observed across all three databases, with HbA1c reductions of nearly 10% persisting for several years after BCG administration.

A Different Story for Type 2 Diabetes

Interestingly, the team did not observe similar improvements in HbA1c levels for T2D patients treated with BCG for bladder cancer. Dr Faustman suggests this difference may be due to the underlying mechanisms of the two types of diabetes, but also points to a potential confounding factor: the use of metformin. Almost every T2D patient in the US takes metformin, a common diabetes medication. Their research and the research of Dr Mihai Netea indicates that metformin may interfere with the metabolic pathway through which BCG exerts its beneficial effects. More work needs to be done before any conclusions in type 1 can be drawn.

Global Implications: BCG Vaccination and Diabetes Prevention

Beyond its potential as a treatment for existing diabetes, Dr Faustman and her team were also interested in whether BCG might play a role in preventing diabetes onset. To investigate this, they conducted an ecological study examining the relationship between countries' BCG vaccination policies and their diabetes incidence rates.

The researchers analysed data from two international databases, comparing T1D incidence in countries with mandatory neonatal BCG vaccination programmes to those without such policies. The results were striking: countries with BCG vaccination programmes consistently showed lower rates of T1D incidence. In one dataset, the team found an average 65% reduction in T1D incidence for countries with neonatal BCG vaccination policies. Another dataset showed a 47% reduction. While these are observational findings and cannot prove causation, they certainly suggest that BCG may have a protective effect against T1D development. The picture for T2D was less clear. One dataset showed no significant difference in T2D incidence between countries with and without BCG vaccination programmes. However, analysis of a larger dataset did reveal a significant reduction in T2D incidence in countries with BCG vaccination policies, with an average decrease of 28%.

> As research in this field continues to evolve, Dr Faustman and her team remain committed to unravelling the complex interactions between the immune system, metabolism, and chronic diseases like diabetes.

Mechanisms of Action: How BCG Might Prevent Diabetes

Dr Faustman and her colleagues have proposed several mechanisms by which BCG might help prevent diabetes onset. One key factor appears to be BCG's ability to modulate the immune system. The research suggests that BCG promotes a more balanced immune response. It increases regulatory T-cells, which help prevent autoimmune reactions, and it may also reduce the number of autoreactive immune cells that can attack insulin-producing cells in the pancreas.

Additionally, the metabolic changes induced by BCG play a crucial protective role. By promoting a shift towards aerobic glycolysis in immune cells, BCG helps correct the underlying metabolic defect in white blood cells of type 1 diabetics. This shift allows the body to maintain better overall glucose regulation, potentially reducing the risk of both T1D development.

Future Directions and Challenges

While the results of Dr Faustman's research are promising, she emphasises that more work is needed to fully understand BCG's potential in diabetes prevention and management. As research in this field continues to evolve, Dr Faustman and her team remain committed to unravelling the complex interactions between the immune system, metabolism, and chronic diseases like diabetes. Their work not only offers hope for improved diabetes management and prevention but also highlights the importance of looking at established medical interventions in new ways. BCG, from its worldwide use for over 100 years, has an impeccable safety track record.

By thinking outside the box and rigorously investigating unexpected connections, researchers like Dr Faustman are paving the way for innovative approaches to some of our most pressing health challenges. As we continue to learn more about the intricate workings of the human body, vaccines like BCG may prove to be valuable tools in our ongoing efforts to promote health and prevent disease.

MEET THE RESEARCHER

Dr Denise L Faustman
Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Dr Denise Faustman is Director of the Immunobiology Laboratory at Massachusetts General Hospital and an Associate Professor of Medicine at Harvard Medical School. She obtained her MD and PhD from Washington University School of Medicine. Dr Faustman's research focuses on developing new therapeutic approaches for type 1 diabetes and other autoimmune diseases. Her lab made groundbreaking discoveries about the role of the proteasome and NF-⊠B in autoimmunity. She led clinical trials testing BCG vaccination to treat long-standing type 1 diabetes, finding it could restore blood sugar control. Dr Faustman also discovered the TNFR2 receptor as a target for cancer immunotherapy. She has published over 140 papers, holds numerous patents, and her work has been funded by major foundations and the NIH. Dr Faustman's innovative research is advancing the understanding of autoimmunity and diabetes and translating findings into novel therapies.

CONTACT

faustman@helix.mgh.harvard.edu
https://faustmanlab.org/

FURTHER READING

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