Serendipity leads to lifesaving discovery

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About two years ago, Dr. Philippe Gros, a McGill University professor in the Department of Biochemistry and a Principal Investigator in thd McGill Life Sciences Complex, described a mouse mutant that was immunodeficient and hypersensitive to the Bacille Calmette-Guérin (BCG) vaccine and to tuberculosis (TB). In this model, Gros's team had found that the immunodeficiency was caused by a mutation in a regulatory protein of the immune system named IRF8.

A year later, a physician in Newcastle who had heard about Gros's work, contacted him about a three-month-old patient who was gravely ill and dying. The infant was suffering from an infection following a perinatal BCG vaccination. She had been treated aggressively with antibiotics but relapsed with additional infections. In addition, she showed a complete absence of circulating monocytes and dendritic cells in her blood – two critically important types of immune cells. She was admitted into an ICU and it seemed nothing could be done to save her.

The clinical aspects of the infant's immuno-deficiency were so strikingly similar to those of Gros's earlier mouse model findings, that his research team investigated the human IRF8 gene for the presence of mutations in this infant. Dr. Gros group also examined IRF8 in a number of additional clinical cases of disseminated BCG infection following

vaccination.

What they found were two distinct disease-causing mutations – one that causes the severe reaction seen in the infant (autosomal recessive) and requires stem cell transplantation, and the other that causes a milder form of disease (autosomal dominant).

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According to Gros, the best part of this story is that the infant received the much needed stem cell transplant that ultimately cured her. Based on the team's research, her doctors were going to transplant her with one of the parents' cells as they were found to be a perfect match. However, when the team learned that the father was carrying one copy of the dysfunctional gene, and knowing that such a situation is deleterious in mice, the physicians opted instead to graft her with an unrelated donor.

"I think this is a great example of the 'discovery pipeline' we have tried to set up at the Complex Traits Group lab," said Gros. "This began as basic research. It evolved from genetic discoveries in mouse models through to validation in humans and knowledge translation to a positive clinical outcome."

"This is archetypal translational research," said Dr. Richard I. Levin, Vice-Principal of Health Affairs and Dean of Medicine at McGill. "When results from lab work conducted in the Life Sciences Complex can be shared across the ocean in context and in time to save a child's life, we know our objectives are being fulfilled."