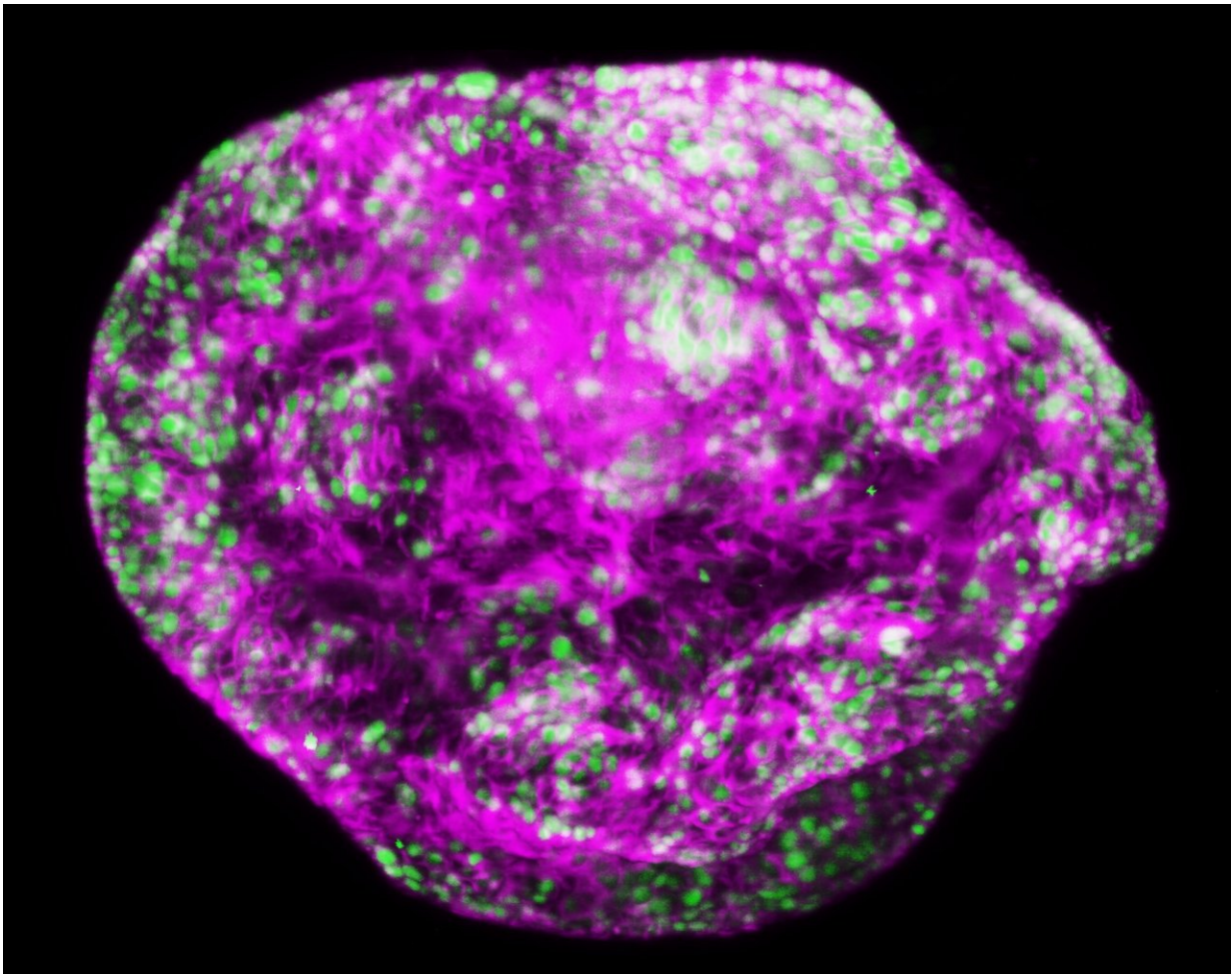


# Odd one out: Protein goes against the family to prevent cancer

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A microscopic image of gastric cancer cells (magenta), with dividing cells shown in green. Credit: Jun Low/Walter and Eliza Hall Institute.

Melbourne researchers have made the surprise discovery that the 'odd one out' in a family of proteins known to drive cancer development is instead critical for preventing stomach cancers.

The research team showed switching off a gene called NF- $\kappa$ B1 caused spontaneous development of stomach cancers, driven by chronic inflammation. The study also revealed that [immunotherapy](#) may prove to be a significant tool for treating stomach cancers that are driven by runaway inflammation, warranting further investigation.

Dr Lorraine O'Reilly, Dr Tracy Putoczki and Professor Andreas Strasser from the Walter and Eliza Hall Institute, with Professor Steve Gerondakis from Monash University, led the research, published in the journal *Immunity*.

Stomach (gastric) cancers are relatively common in Australia, with around 2000 cases diagnosed each year. Twice as many men are affected as women and the disease is often not diagnosed until an advanced stage. Many stomach cancers develop as a result of uncontrolled inflammation over many years.

Dr O'Reilly said the finding was unexpected because previous research had shown that high - not low - levels of activity of other NF- $\kappa$ B family members were drivers of stomach and other cancers.

"Until now, it was thought that abnormally increased activity and levels of any of the members of the NF- $\kappa$ B family was linked to cancer," she said.

"Now, for the first time, we've identified NF- $\kappa$ B1 is the 'odd one out' in the family because abnormally low expression - or 'loss' - of this family member actually causes the development of spontaneous stomach cancers.



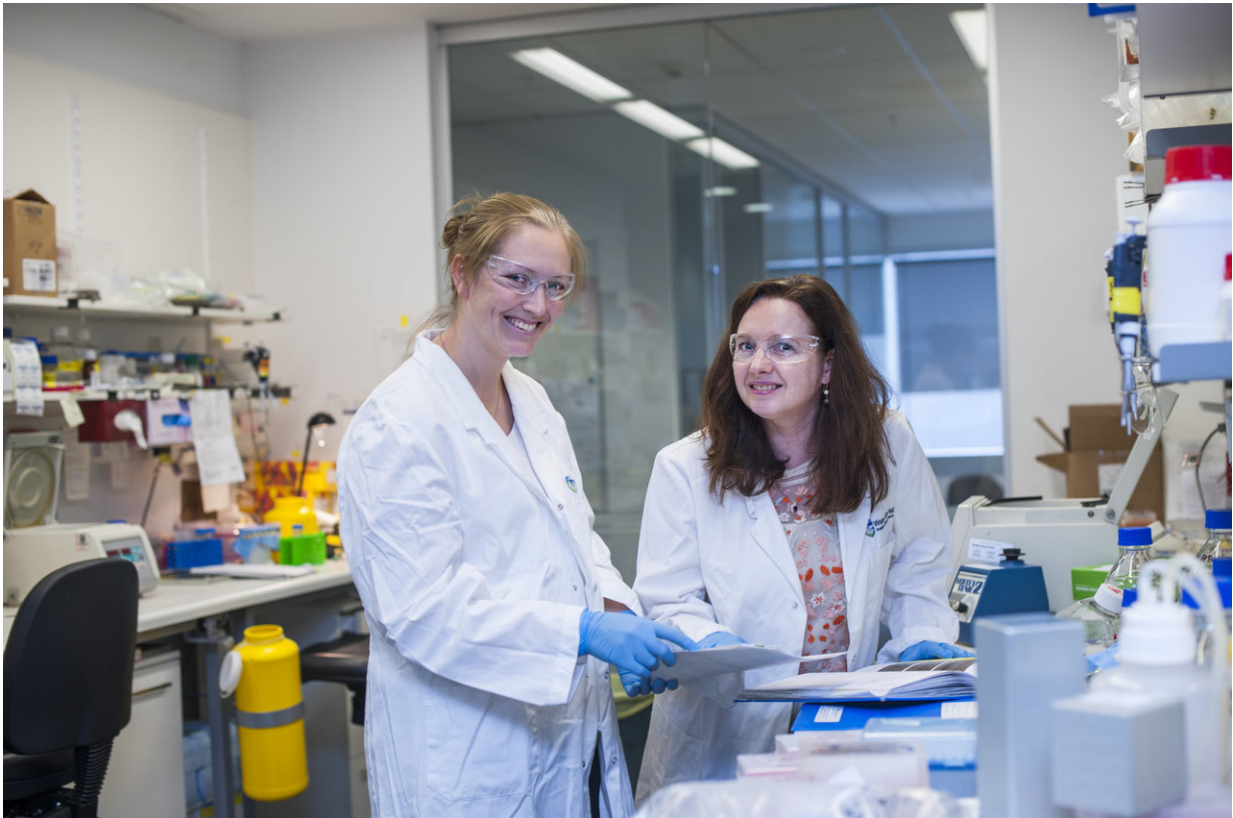
Researchers have made the surprise discovery that the 'odd one out' in a family of proteins known to drive cancer development is instead critical for preventing stomach cancers. The research team from the Walter and Eliza Hall Institute in Melbourne, Australia, showed switching off a gene called NF- $\kappa$ B1 caused spontaneous development of stomach cancers, driven by chronic inflammation. The study also revealed that immunotherapy may prove to be a significant tool for treating stomach cancers that are driven by runaway inflammation, warranting further investigation. Credit: Walter and Eliza Hall Institute

"We found that defects that led to lower than normal levels of NF- $\kappa$ B1 kick-started uncontrolled inflammation in the stomach and, over the long-term, led to invasive stomach cancers."

The findings have ramifications for the understanding and treatment of human cancers.

"It is well established that long-term inflammation can lead to [stomach cancer](#) in humans. The cellular processes that we have identified in this study as being important for the development of stomach cancer provide new targets for therapy that have not been explored before," Dr O'Reilly said.

Dr Putoczki said the preclinical model would be very useful for testing new treatment options, such as immunotherapy.



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spontaneous development of stomach cancers, driven by chronic inflammation. The study also revealed that immunotherapy may prove to be a significant tool for treating stomach cancers that are driven by runaway inflammation, warranting further investigation. Credit: Walter and Eliza Hall Institute

"Stomach cancer is a disease where immunotherapy is still in its infancy. This is the first preclinical model of stomach cancer that repeats the pattern of human stomach cancer development, that involves progression from chronic stomach [inflammation](#) through to fully invasive cancer," Dr Putoczki said.

"We showed that there are markers on these stomach tumour cells that indicate they would be responsive to a type of immunotherapy called immune checkpoint inhibitors, in particular anti-PDL1 immunotherapy, which is already used with great success in the treatment of melanoma and certain other cancers.

"Not only does this research provide compelling evidence for further investigation of immunotherapy for treating [stomach cancer](#), it also provides the first model for preclinical testing of these treatments."

**More information:** Lorraine A. O'Reilly et al, Loss of NF- $\kappa$ B1 Causes Gastric Cancer with Aberrant Inflammation and Expression of Immune Checkpoint Regulators in a STAT-1-Dependent Manner, *Immunity* (2018). [DOI: 10.1016/j.immuni.2018.03.003](https://doi.org/10.1016/j.immuni.2018.03.003)

Provided by Walter and Eliza Hall Institute

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