Novel Approaches for Treating Advanced Abdominal Cancers

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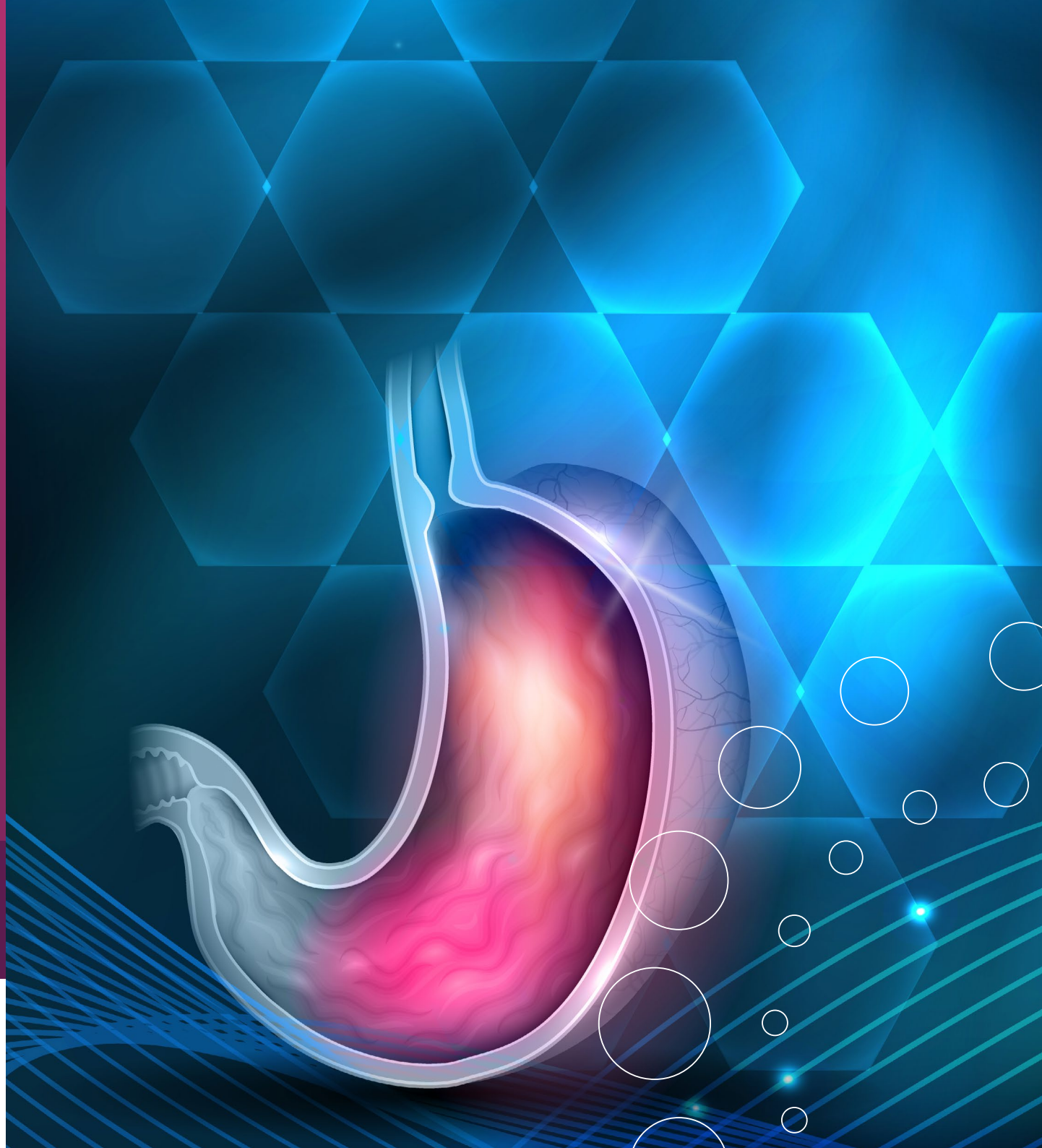

Novel Approaches for Treating Advanced Abdominal Cancers

Metastatic abdominal cancers pose a unique set of challenges for clinicians. Dr Patrick Wagner from the Allegheny Health Network Cancer Institute is exploring important new ways to tackle these malignancies. With the help of his team, he carries out groundbreaking research into utilising the patient's own immune system as well as exploring methods of drug delivery to fight these extremely challenging forms of cancer effectively.

Challenging Carcinomatosis

According to the World Health Organization, cancer accounted for almost one in every six deaths globally in 2020. Although many types of cancers are curable with effective treatment and early detection, some unfortunately spread (metastasise) and can become incurable. Cancers of the gastrointestinal system, such as colon, rectum, and pancreas, as well as gynaecological malignancies such as ovarian cancer, can sometimes advance, resulting in carcinomatosis, a distinct pattern of metastatic cancer in which cancer spreads into the space around the organs within the body's abdomen and chest cavities.

Dr Patrick Wagner carries out his vital research at the Allegheny Health Network Cancer Institute in Pittsburgh. He explains that carcinomatosis poses challenges for treatment and currently has limited therapeutic options. Many modern cancer treatments consist of immunotherapy, which involves careful manipulation of the patient's own immune system to help tackle the cancer, often allowing more individualised treatments. He adds that understanding the functions of the immune system cells in the abdominal cavity is vital to developing effective immunotherapy treatments for these types of advanced cancers.

A Closer Look at Peritoneal Fluid

The membranes lining the abdominal cavity are called the peritoneum, and often, malignancies which start in the abdominal organs can spread to the surfaces of these membranes, resulting in carcinomatosis. The space between the layers of the peritoneum is called the peritoneal cavity, and it contains a special fluid which helps to lubricate and, in turn, minimise friction between the organs.

Dr Wagner explains gaining a better understanding of the immune cells at work in the peritoneal fluid is crucial for the development of effective immunotherapy treatments for carcinomatosis.

Dr Wagner and his team carried out a study to characterise the immune environment in the peritoneal fluid of patients both with and without carcinomatosis with the aim of identifying targets for new treatment strategies. They extracted and analysed serum and peritoneal fluid samples from 39 surgical patients, as well as gathering information about patient characteristics and the sites of the tumours. Levels of soluble immune mediators were measured and compared. The immune mediators are molecules used by the immune system cells to communicate and organise themselves in order to destroy unwanted substances in the body, such as pathogens and cancer cells.

Immune Mediators Identified

Dr Wagner found significant differences in soluble immune mediator levels between the peritoneal fluid and serum, with the peritoneal fluid having far lower concentrations. Carcinomatosis was linked with high levels of proinflammatory markers (linked with inflammation), whilst other immune markers were found to be low in the peritoneal fluid. The immune microenvironment of the peritoneal fluid presents a challenging environment for an effective response against malignancy as it favours innate immunity, a non-specific line of defence. However, the high levels of proinflammatory mediators could be a potential target.

The findings provided valuable insights for possible new immunotherapy strategies.

Dr Wagner highlights that one of the soluble immune mediators identified in higher concentrations in peritoneal fluid was interleukin-6 (IL-6). For his next piece of research, he focused on the role of IL-6 and its receptor, sIL-6-Rα, in the peritoneal cavity of patients with carcinomatosis.

A Promising Lead: Interleukin-6

Dr Wagner stresses that currently, there are limited treatment options and often a poor prognosis for patients with peritoneal carcinomatosis. However, there are fresh hopes when it comes to potential treatment targets. Exploring the current understanding of IL-6 and its role in the development and progression of carcinomatosis is vital to outline the next steps for treatment development. There are various mechanisms and cascades of reactions that involve IL-6, which may contribute to the spreading of the tumour cells and their adhesion, invasion, and proliferation onto the peritoneal surfaces.

The team reported that targeting IL-6 and the various signalling pathways, the chain reaction of events that occur when it acts on its receptor when combined with other treatment regimes has demonstrated promise in clinical studies for various cancers which can cause carcinomatosis. There are also ongoing studies investigating the blocking actions of IL-6. Dr Wagner notes that it may not all be smooth sailing as IL-6 has complex and diverse functions, and could potentially have both pro and anti-tumour effects. Also, targeting IL-6 could result in immunosuppressive effects, putting the patient at risk of serious infections. However, this effect could, in theory be minimised by administering the treatment directly into where it is needed – into the peritoneal cavity. This approach is exactly what the team plans to try next.

Hitting the Target with Tocilizumab

In the Regional Immuno-Oncology Trial (RIOT)-2 Study, Dr Wagner and his team will test an IL-6 blocker using administration into the intra-pleural and intra-peritoneal routes, which deliver the dose directly to the site of the tumours and avoid any harmful systemic side effects. He explains that common symptoms of cancers in this region are malignant pleural effusions (MPE) and malignant ascites (MA), which are results of carcinomatosis into the thorax (MPE) or abdomen (MA) cavities. These build-ups of fluid around the lungs and abdominal cavity can cause debilitating symptoms and have limited treatment options. Dr Wagner highlights that there is an abundance of data suggesting that IL-6 signalling might play a central role in the development of MPE and MA, so being able to block this pathway could offer new therapeutic and also palliative options for patients with advanced disease.

In the RIOT-2 study, the IL-6 receptor antagonist called tocilizumab will be delivered straight into the body cavity. It works by blocking the IL-6 receptors, preventing IL-6 from having an effect. They will give doses of tocilizumab each week via a catheter placed into the body cavity, which is also used to drain away the excess fluid to help relieve symptoms. Dr Wagner says eligible patients will be those with MPE or MA with metastatic cancer who are scheduled to undergo drainage with a catheter. The team will monitor immunological and pharmacokinetic parameters, how the immune system reacts and how the drug is processed by the body, and check for any side effects. They aim to assess the safety of intra-cavitary tocilizumab therapy, and hope their findings could pave the way for future research into clinical applications of immunotherapy administered using this more direct route.

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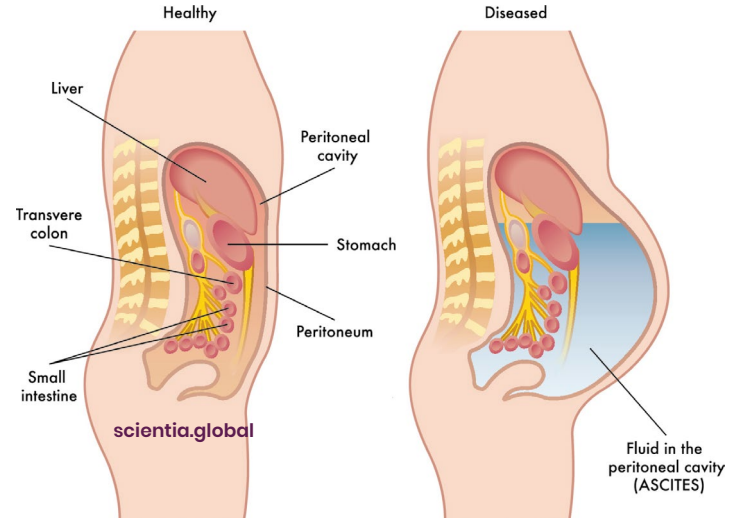


Using Bacteria

Dr Wagner and his team have further investigations planned. In previous work, they have explored lipopolysaccharide (LPS), which is a molecule found in the outer membrane of certain types of bacteria. LPS has long been known to stimulate the immune system to respond to infections, as a signal of the presence of bacteria within the body. Dr Wagner says that LPS can also cause the immune system to recognise tumours, by engaging with receptors on human immune cells called toll-like receptors, stimulating an immune response to the markers on the tumour cells so they are targeted and destroyed.

There is a drawback when it comes to LPS in that it can be quite toxic if given intravenously, so other routes of administration need to be explored. Intra-dermal (under-the-skin) administration and intra-tumoural (directly into the tumour) routes have been used successfully in animal models. Dr Wagner adds that to their knowledge, intra-tumoral injection of LPS as an immunotherapy agent has not yet been studied in humans.

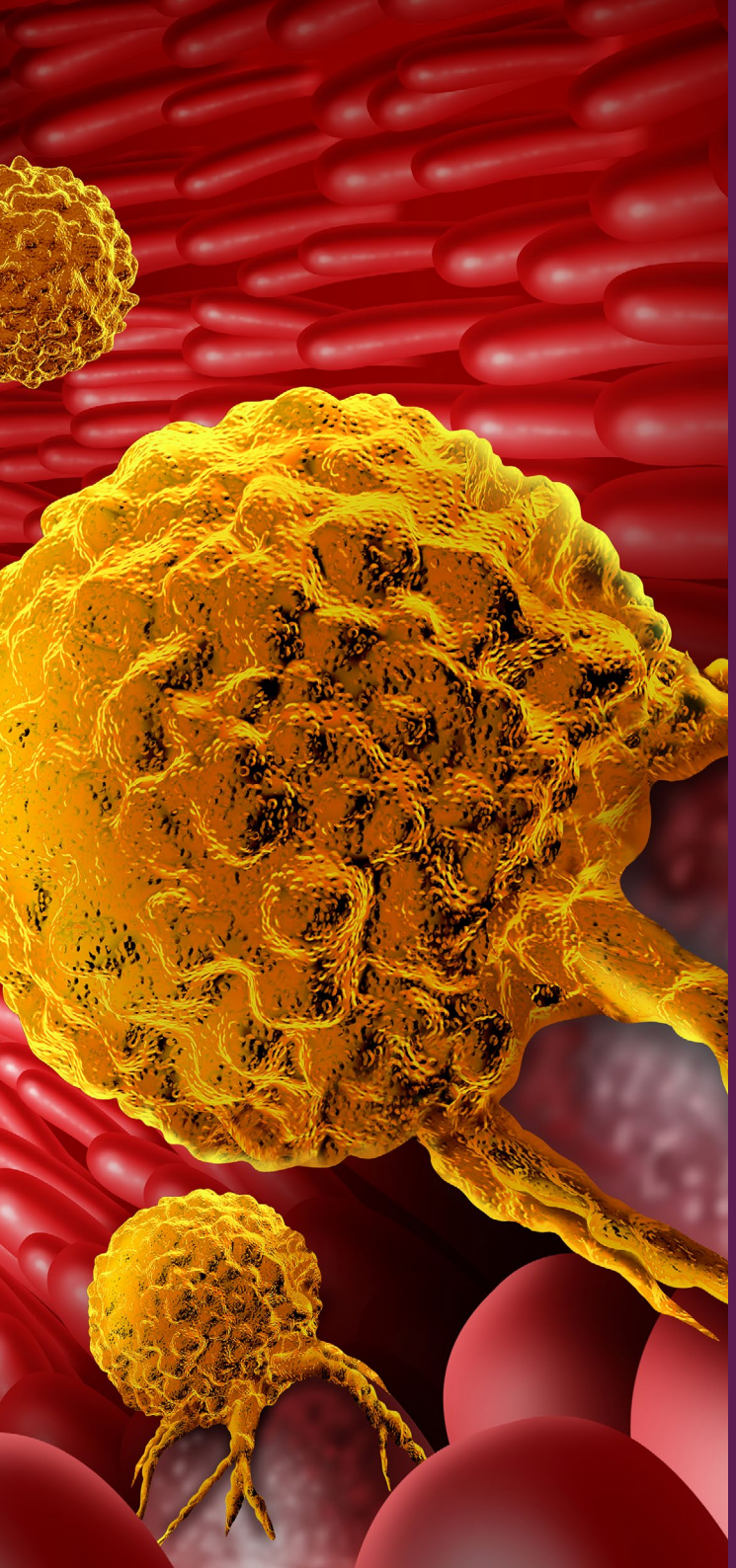
RIOT-1

Dr Wagner highlights that intra-tumoral immunotherapy has shown great potential in treating advanced cancers. However, being able to deliver a dose when the tumours are inside the abdomen of a patient is a challenge, so there has been limited exploration of this treatment to date.

The Regional Immuno-Oncology Trial-1 (RIOT-1) set out to change this. Dr Wagner explains that in this study, the safety of injecting intra-abdominal tumours with LPS was established. They used LPS from a particular bacteria, Escherichia coli 0113, which has shown great promise as an agent to enhance the anti-tumour effects of the immune system. They recruited adult patients with peritoneal tumours, which spread from a primary gastrointestinal cancer, who had at least two suitable tumours for injection. LPS doses were given to the patients when undergoing a diagnostic laparoscopy, a small surgery to examine the internal organs using a scope. To be eligible, they also needed to have a subsequent laparotomy planned, a more significant operation where the abdomen is opened up. At the time of the second surgery, the injected tumours were removed for in-depth analysis of the results, which remains ongoing.

Next Steps for Treating Metastatic Abdominal Cancers

Dr Wagner highlights that for RIOT-1, they reported no adverse events (complications) related to the LPS injection, indicating that this treatment is safe and well-tolerated by patients. They will continue to analyse the tumours to collect data about cellular and molecular markers of the immune response. He adds that this type of treatment might be an option for future patients undergoing treatment for peritoneal carcinomatosis. Dr Wagner and his team are certainly paving the way for the development of new immunotherapy cancer treatments, bringing fresh hopes to those with advanced abdominal cancers. From identifying novel targets to exploring alternative drug delivery methods, they are making significant progress for these highly challenging cancers with only limited treatment options. Building on these early studies, Dr. Wagner's team plans to expand into trials of oncolytic (cancer-killing) virus therapy and immune cellular therapy (patient-derived lymphocytes) over the next 12-18 months. The goal of these trials is to provide new and innovative options for patients with metastatic cancer based on immunotherapy.



MEET THE RESEARCHER

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Dr Patrick Wagner obtained his MD from Harvard Medical School in 2002. He underwent post-graduate training at the Hospital of the University of Pennsylvania, the New York Presbyterian Hospital, Weill Cornell Medical Centre, Memorial Sloan Kettering Cancer Center and the Uinversity of Pittsburgh Medical Center. He currently holds the position of Division Director for Complex General Surgical Oncology at Allegheny Health Network Cancer Institute. Throughout his well-published career, he has received funding from the Pittsburgh Foundation, the Glimmer of Hope Foundation, and the Appendix Cancer and Pseudomyxoma Peritonei Foundation.

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FURTHER READING

C Lewisa, N Dadgarb, M Najafic, *et al.*, Intra-tumoral immunomodulatory therapy for advanced abdominal cancers using lipopolysaccharide: The Regional Immuno-Oncology Trial-1 (RIOT-1) protocol (NCT05751837), *Surgical Oncology Insight*, 2024, 100042. DOI: https://doi.org/10.1016/j.soi.2024.100042

H Parka, C Lewisa, N Dadgarb, *et al.*, Intra-pleural and intra-peritoneal tocilizumab therapy for managing malignant pleural effusions and ascites: The Regional Immuno-Oncology Trial (RIOT)-2 study protocol, *Surgical Oncology Insight*, 2024, 100045. DOI: https://doi.org/10.1016/j.soi.2024.100045

N Dadgar, C Sherry, J Zimmerman, *et al.*, Targeting interleukin-6 as a treatment approach for peritoneal carcinomatosis, *Journal of Translational Medicine*, 2024, 22, 402, DOI: https://doi.org/10.1186/s12967-024-05205-8

PL Wagner, CM Knotts, VS Donneberg, *et al.*, Characterizing the Immune Environment in Peritoneal Carcinomatosis: Insights for Novel Immunotherapy Strategies, *Annals of Surgical Oncology*, 2024, 31, 2069–2077. DOI: https://doi.org/10.1245/s10434-023-14553-6