Peritoneal Surface Oncology Group International

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A quarterly newsletter with the latest news, views and announcements

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Section 1: Progress in Clinical or Laboratory Research

From Bench to Belly: Intraperitoneal Adoptive Cell Therapies

By Ian S. Goldlust, MD PhD and Steven A. Rosenberg MD, PhD

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Hyperthermic intraperitoneal chemotherapy (HIPEC) has been a standard adjunct after cytoreductive surgery for peritoneal metastases since the late 1990s. Its appeal is intuitive. A one-time bath of heated cisplatin or mitomycin can penetrate millimeter scale nodules that evade the surgeon's scalpel. Yet even in the best designed ovarian cancer trial HIPEC prolonged median overall survival by only a year, from 34 to 46 months, and required two extra hours in the operating room with no clear quality-of-life dividend (*NEJM 2018;378(3):230-240*). The incremental nature of that benefit has fueled a search for more potent regional treatment strategies. As a result, attention has shifted to living drugs—tumor-educated immune cells delivered directly into the peritoneal cavity.

The peritoneal cavity is uniquely suited to cellular immunotherapy. It is an anatomically closed compartment with a slow lymphatic outflow, allowing exceptionally high local effector-to-target ratios while limiting systemic exposure and cytokine release risk. Because most cancer implants lie on serosal surfaces, infused lymphocytes, natural killer cells, macrophages, or dendritic cell vaccines do not need to traverse the dense stroma that complicates intravenous approaches. Moreover, ascites can be serially drained and replaced with fresh cell products, providing a built-in mechanism for repeat dosing and pharmacodynamic sampling.

Early clinical experience with intraperitoneal tumor infiltrating lymphocytes (TIL) laid the conceptual groundwork. In the 1990s investigators harvested autologous TILs from platinum refractory ovarian carcinoma patients, expanded them *ex vivo*, and reintroduced them into the postoperative cavities with low-dose interleukin-2 (*J Immunother 1994;16(3):198-210*). The regimen was safe and occasionally produced CA-125 declines, but clinical responses were limited due to the polyclonal TIL containing a minority of tumor specific clones. Today, high throughput neoantigen screening and single cell T-cell receptor (TCR) sequencing have revitalized TIL therapy by enabling selection of the most reactive subclones, shortening manufacture time and allowing a truly personalized product.

Studies using intraperitoneal chimeric antigen receptor T cells

Parallel advances in synthetic biology have opened the door to engineered receptors. Chimeric antigen receptor (CAR) T cells targeting MUC16 (CA-125) (*Oncoimmunology 2015;4(3):e994446*), mesothelin (*Int J Biol Sci 2021;17(14):3850-3861*), carcinoembryonic antigen (CEA) (*Cytotherapy 2024;26(2):113-125*), folate receptor α (*J*

Immunother Cancer 2023;11(5):e006509), and Claudin-6 (*Int J Biol Sci 2024;20(5):1578-1601*) have all demonstrated superior activity when delivered intraperitoneally rather than systemically in mouse models. The MUC16 program offered the first human data. In a single center phase I dose escalation study, 18 women with heavily pretreated, recurrent high grade serous ovarian cancer were treated using autologous CAR-T cells that both targeted the retained ectodomain of MUC16 and secreted IL-12 (*Gynecol Oncol 2020;159:42*). Each cohort received half the dose intravenously and, 24–48 hours later, the remainder intraperitoneally through an implanted port. Doses ranged from 3×10^5 to 1×10^7 CAR-T cells kg^{-1}. No dose limiting toxicities emerged during the chemotherapy free escalation, and cytokine release syndrome was limited to grade 1–2. However, when lymphodepletion was added in a small expansion cohort, two of three patients experienced a macrophage activation like syndrome. Although no objective responses were observed, the best outcome was stable disease, and serial sampling demonstrated CAR-T persistence in ascites and peripheral blood for up to eight weeks.

Building on these early findings, subsequent trials have continued to explore the clinical potential of intraperitoneal CAR-T cell therapy. In an open label phase I study of "hypoxia responsive" CEA CAR-T cells (NCT05396300), 40 patients with CEA positive, chemotherapy refractory solid tumors were randomized to receive either intraperitoneal (IP; n = 16) or intravenous (IV; n = 24) infusion (*J Clin Oncol 2024:42,16_suppl*). The IP arm yielded a 25% objective response rate and an 88% disease control rate, substantially outperforming the IV arm (8% ORR, 67% DCR) despite comparable in vivo CAR-T expansion. Treatment-related toxicity was manageable. Cytokine release syndrome was limited to grade 1–2, no cases of immune effector cell-associated neurotoxicity (ICANS) were observed, and grade 3 immune-mediated diarrhea/colitis occurred in 17.5% of patients, alongside universal grade 3–4 cytopenias.

In parallel, IP delivery of mesothelin directed CAR-T cells is being evaluated in a phase I trial enrolling patients with mesothelin positive esophagogastric carcinoma and peritoneal carcinomatosis. This trial will administer escalating doses (1×10^6 – 3×10^7 CAR-T cells kg^{-1}) via peritoneal catheter following fludarabine and cyclophosphamide lymphodepletion. The primary endpoints are safety, dose determination, and correlative immune analyses (*J Clin Oncol 2025;43,4_suppl*) February 2025.

Myeloid cell therapy

While T cell platforms have led the charge in intraperitoneal immunotherapy, emerging studies are now investigating whether other immune cell types can be similarly harnessed—either through genetic engineering or *ex-vivo* activation—to achieve comparable therapeutic benefit.

In a 2023 phase I trial at the NCI, platinum-resistant ovarian cancer patients received autologous monocytes, incubated with IFN-α and IFN-γ, and then infused intraperitoneally every four weeks (*Clin Cancer Res*

2023;29(2):349-363). The interferons drove TRAIL dependent, caspase-8 mediated apoptosis of tumor cells in-vitro, and two of nine evaluable patients achieved a radiographic partial response while a third met CA-125 response criteria, with only one grade 3 toxicity (anemia). Long-term responders exhibited distinct baseline innate immune signatures, hinting at biomarkers that could guide future trials. While the response rate is modest, these data demonstrate that myeloid cell therapy can be manufactured quickly, delivered safely, and induce measurable regression.

Strategies to overcome intraperitoneal immunosuppression

Multiple strategies are being tried to overcome the immunosuppressive ascitic milieu, whose high concentrations of TGF-β, IL-10 and prostaglandin E_2 can exhaust effector cells. "Armored" CAR-T cells that secrete IL-12 (*Oncoimmunology 2015;4(3):e994446*) or IL-15 (*Nat Commun 2023;14(1):6942*), or that carry dominant negative TGF-β receptors (*Cancer Immunol Immunother 2023;72(4):917-928*), have shown improved cytokine production and tumor control in preclinical peritoneal carcinomatosis models. A complementary strategy is to redirect natural killer (NK) cells or macrophages, which resist many checkpoint pathways that blunt T-cell activity. Allogeneic NK-cell platforms have the advantage of faster manufacturing and, when equipped with CARs or high affinity CD16 variants, have cleared micro metastases in murine ovarian- and gastric cancer models with negligible cytokine release. Early phase human trials of intraperitoneal NKG2D-CAR NK cells are enrolling in Asia, banking on greater allogeneic scalability if efficacy signals emerge (*Mol Ther 2025 May 27:S1525-0016(25)00396-X*).

Hurdles in front of success with intraperitoneal immunotherapy

Nevertheless, the chasm between compelling biology and clinical utility remains wide. Antigen heterogeneity within peritoneal metastases means a single target CAR-T is unlikely to eradicate every clone of cancer. Multiplexed approaches, either dual CAR-T constructs or mixtures of CAR-T, CAR-NK and TIL or TCR products, will probably be required, but each component adds regulatory and manufacturing complexity. Persistence is another hurdle, as the peritoneal cavity provides few homeostatic cytokines, and repeated cell infusions can provoke adhesions that sequester or physically trap lymphocytes.

Cost is a final, inescapable consideration. The cost of autologous CAR-T cell treatment approaches USD 400,000. That is before the cost of managing adverse events and perioperative logistics of catheter placement. Allogeneic and point-of-care manufacturing pipelines along with outpatient administration promise decrease the cost but cannot eliminate it. How, then, should clinicians integrate cell therapy into current practice? A pragmatic path for incorporating cell therapy is a dual modality strategy. First, maximal cytoreduction—primary debulking followed by systemic chemotherapy—eliminates visible disease and yields fresh tumor tissue for isolating, testing, or engineering neoantigen specific lymphocytes. The cells can then be expanded or gene edited *ex-vivo* while the

patient completes adjuvant chemotherapy and once manufactured, delivered via intraperitoneal infusion into a compartment where their high effector-to-target ratio and immunologic memory can eradicate chemo resistant deposits and maintain long term surveillance. The sequencing dovetails with the natural timeline of front-line therapy and, crucially, does not depend on perfect cytoreduction.

Enthusiasm must remain tempered, however, until randomized evidence accrues. The CEA CAR-T cell program illustrates the risk of premature extrapolation. In a sophisticated colorectal cancer xenograft model, a single intraperitoneal dose of CEA CAR-T cells achieved complete responses in 80 per cent of mice and established memory capable of rejecting rechallenge, but the first human case report of off trial CEA CAR-T infusion documented severe colitis and fatal sepsis, mimicking our own experience with CAR T cells against CEA (*Cytotherapy 2024;26(2):113-125*), (*Ther Adv Med Oncol 2024;16:17588359241309825*), (*Mol Ther 2011;19(3):620-626*). A reminder that local delivery does not eliminate off-target risk when cognate antigen is expressed on normal mucosa. Rigorous dose escalation and long-term surveillance will therefore be essential, especially for antigens such as CEA and EpCAM with low level expression on healthy epithelium.

HIPEC took nearly 30 years to progress from rationale to level-I evidence, and even now its impact is measured in months, not years. The first phase III trials of peritoneal CAR- or T-cell therapy are unlikely to read out before 2030, so today's surgeons and oncologists must navigate an evidence gap. At present, the most responsible stance is measured optimism, continue offering HIPEC where guidelines support it, encourage eligible patients to enroll in intraperitoneal cell therapy trials, and develop institutional pathways that facilitate rapid tissue acquisition and cell manufacture during the peri-operative window.

If those studies confirm early signals, intraperitoneal adoptive cell therapy could support a sustained, precision immune patrol leading to durable responses in epithelial malignancies. Whether or not that promise materializes will depend on solving antigen heterogeneity, manufacturing scale, and cost. But the conceptual leap has already occurred. The peritoneal cavity is no longer viewed merely as a receptacle for heated drugs but as a dynamic immunologic arena where engineered cells can be deployed, reinforced, and recalled. In that light, cell therapy is the next logical evolution of regional treatment—a living, adaptable therapy. For now, surgeons should not retire their heat exchangers, but they might keep a seat at the tumor board for the cellular engineers who aim to redefine intraperitoneal oncology.

Section 2: Exposition of progress and productivity of an established PSM Center of Excellence

Intra-Peritoneal Immunotherapy: Past, Present and Future Opportunities

By Patrick L. Wagner and David L. Bartlett

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Introduction

Immunotherapy for gastrointestinal cancers has revolutionized the management of these diseases over recent years. Although this wave has passed through systemic treatment with dynamic changes in the outcome of once incurable conditions, it has not yet made its way into the peritoneal microenvironment in patients with carcinomatosis (PC). We believe that the unique immunologic milieu within the peritoneal cavity can be leveraged using regional delivery of immunotherapy to optimize treatment while sparing patients the systemic morbidity of immunomodulatory agents.

While the available treatment modalities have improved over time, the concept of regional immunotherapy is far from novel. Edwards et al., at the University of Pittsburgh, published their experience with intra-peritoneal (IP) recombinant IL-2 therapy for patients with platinum-resistant ovarian cancer in a study completed between 1995-1999 (*J Clin Oncol. 1997,15(11):3399-407; Cancer Immunol Immunother. 2010, 59(2):293-301*). Even earlier pilot studies explored the use of IP cellular therapy in ovarian cancer patients using tumor-infiltrating lymphocytes (TIL) or natural killer (NK) cells (*J Immunother Emphasis Tumor Immunol. 1994,16(3):198-210; Cancer Res. 1990, 50(19):6302-10*). These pioneering studies foreshadow modern strategies in combining cellular therapies with IP immune-conditioning regimens, although they were hampered by a relatively primitive understanding of tumor immunology and a lack of both modern translational research and technical resources (e.g. for cellular therapy manufacturing) and availability of systemic immune regimens, such as immune checkpoint inhibition (ICI).

The 2000s and 2010s brought massive changes to the landscape of immunotherapy, with the development and approval both of systemic ICI therapy for melanoma, and subsequently other solid tumors; as well as the profoundly successful experience of chimeric antigen receptor (CAR)-T cell therapy for B-cell malignancies. With subsequent FDA approval of an oncolytic viral therapy (T-VEC) for melanoma, a dendritic cell vaccine (sipuleucel-T) for prostate cancer, and a tumor-infiltrating lymphocyte (TIL) therapy (lifileucel) for melanoma, the stage is set for adaptation of these strategies into regional delivery concepts for PC.

During the 2010s, a number of pivotal proof-of-concept steps were achieved, related to the task of IP delivery of immunotherapy. Our laboratory developed tumor-selective oncolytic vaccinia virus vectors to induce an immune response in the peritoneal cavity. Immune-activating cytokines and chemokines expressed by vaccinia can induce a robust anti-tumor cellular immune response that can eliminate carcinomatosis in animal models. We also demonstrated in animal models that the T-cells induced by the viral infection in the peritoneal cavity can be harvested, expanded, and given back to the host to treat metastatic cancer (*Front Immunol 2021 Feb 18:12:610042*). Others have explored intraperitoneal CAR-T cells, autologous vaccines, and bispecific antibodies to treat PC. Katz et al. had success delivering anti-CEA CAR-T cells into mice to treat PC, demonstrating that intraperitoneal CAR-T were superior to intravenous CAR-T (*Cancer Gene Ther. 2016, 23, 142–148*). At UPMC, we performed an autologous dendritic cell vaccine trial in patients with PC (*Ann Surg Oncol 2021 Aug;28(8):4637-4646*). Tumor nodules excised at the time of cytoreductive surgery (CRS) were used to pulse autologous dendritic cells which were then polarized (alpha-type-1 polarized) and injected back into the patient's lymph nodes along with systemic immune stimulatory agents. Some unexpected long-term survival resulted, but the numbers were too small to determine overall efficacy. Another IP immunotherapy that has been studied in humans is the use of bispecific antibodies combining binding sites for epithelial markers (EpCAM) and T cells (CD3). Catumaxomab is the brand name for this clinical product and demonstrated success as a treatment for ascites. A randomized study from Germany (*Br J Cancer. 2018 Aug;119(3):296-302*) demonstrated promise for Catumaxomab as a treatment for gastric cancer PC.

Unfortunately, most of the aforementioned studies of IP immunotherapy were either terminated early, did not meet efficacy targets, or remain unfinished and unpublished. However, we believe that these unsatisfactory early results should not dissuade investigators from pursuing IP immunotherapy as a potentially game-changing strategy for patients with PC, particularly in light of the ever-changing landscape of immunologic knowledge regarding the peritoneal tumor microenvironment and the breadth of emerging immunotherapy agents across a wide range of mechanisms beyond immune checkpoint blockade.

At Allegheny Health Network, we have developed a state-of-the-art immunotherapy program to supplement our busy referral practice in peritoneal surface malignancy. We believe that the peritoneal and pleural tumor environments have unique characteristics that not only distinguish them from the systemic immunity but also provide niche therapeutic targets that can be manipulated with regional treatment strategies that minimize systemic immune toxicity, similar to the therapeutic advantages seen with IP chemotherapy. Our program has developed a sequential train of early phase clinical trials, dubbed the RIOT series (Regional Immuno-Oncology Trials), aimed at delivery and manipulation strategies for peritoneal immuno-oncology.

RIOT-1 (NCT05751837) was a phase I study in which a single dose of a toll-like receptor 4 agonist (lipopolysaccharide from Escherichia coli 0113) was delivered via IP intra-tumoral injection during diagnostic

laparoscopy. Twelve patients were treated on protocol without injection-related toxicity. All patients underwent subsequent definitive or palliative CRS fourteen days post-injection, at which time the LPS-injected and control (saline-injected) tumors were harvested for translational biomarker analysis, which remains underway. Early indications of a defined immunologic response to the injection have been presented in abstract form from this study, which we believe establishes the important principle of using pre-operative laparoscopy as a vital surgical window-of-opportunity to prospectively test immunotherapy agents for use in PC (*Pleura Peritoneum. 2025; 9(Suppl1):P0 76*). In particular, we feel that intra-tumoral injections could maximize the yield of TIL harvest at the time of CRS, which could be stored for future use in a given patient to develop a cell therapy product at the time of subsequent disease progression.

RIOT-2 (NCT06016179) is a phase I study testing the safety and tolerability, along with biomarkers of immunologic efficacy, of tocilizumab, which is an interleukin-6 receptor antagonist commonly used for autoimmune diseases and cytokine release syndrome. In RIOT-2, tocilizumab is administered via IP or intra-pleural catheters or injection in a dose-escalation model, to patients with malignant ascites or effusions. The rationale for this study involves a wealth of literature documenting highly elevated levels of IL-6 and its cognate soluble receptor subunit (IL-6Ra) in malignant ascites and effusions. We hypothesize that antagonism of the IL-6 pathway, as a broad anti-inflammatory strategy, could both reduce the inflammatory influx of fluid into the affected compartments, as well as modulate the immune microenvironment within these spaces toward a more adaptive immune response with anti-tumor effects. The study has accrued eight patients to date, with an expected total enrollment of 24 patients and a wealth of translational studies planned for the pre- and post-treatment fluid samples.

The RIOT-3 study (NCT07001592) examines the safety and immunologic efficacy of intra-tumoral injection of an oncolytic vaccinia virus, vvDD-hIL-2-RG-1, which encodes a rigid peptide membrane-bound IL-2 designed to promote T-cell activation within the tumor microenvironment. Patients with metastatic gastrointestinal cancer, including those with accessible/injectable peritoneal tumors, will be enrolled at 3 different dose escalation levels. The primary study objective is to determine the safety and maximum tolerated and feasible doses. Secondary objectives are to profile the replication, pharmacokinetics and immune response to vvDD-hIL-2-RG-1 injection via blood draws, oral swabs, urinalysis and tissue biopsies from participants. This study was opened to accrual in May 2025, and has accrued its first patient, who suffers from colorectal PC, with an abdominal wall lesion that was amenable to intra-tumoral injection.

RIOT-4 (NCT pending) is currently in late development and will serve as a pivotal study investigating the utility of pleural effusion-derived T cells as a cell therapy product. Because malignant effusions (MPE) are rich in T cells, and are drained to relieve symptoms, this body fluid has rich potential to yield an autologous cell therapy (ACT) following short-term activation and expansion of fluid-derived TIL. The manufacturing procedure closely mirrors the procedure that we developed for in-house CAR-T manufacture and leverages our existing instrumentation and

experience. Patients with MPE will be enrolled, and the primary objectives are to demonstrate the safety of intrapleural administration of the locally manufactured ACT product plus IL-2 to study patients. Secondary objectives include indicators of clinical response to therapy, as well as translational biomarkers of therapeutic efficacy, including changes in the immune cell population and a secretome of pleural fluid. A subsequent study mirroring this approach in malignant ascites-derived T cells for PC patients (RIOT-5) is expected to follow closely behind.

In summary, we believe that the field of peritoneal surface malignancy has likely squeezed as much mileage as possible out of surgical technical refinement and IP dosing of conventional cytotoxic chemotherapy agents. Further success in this field will rely on the development of entirely novel treatment concepts that exploit the unique immunologic milieu of the peritoneal microenvironment via regional interventions. By developing a systemic, sequential approach to early phase clinical trials at Allegheny Health Network in this area, we hope to make meaningful progress over the coming years toward our ultimate goal of providing durable relief from peritoneal surface malignancy by harnessing patients' inherent immunologic surveillance mechanisms to combat their disease.

Section 3: Listing of upcoming events

The 15th PSOGI International Congress on Peritoneal Surface Malignancies: PSOGI-Barcelona-2025. A Ten-Point Guide to the Congress.

By Aditi Bhatt

Shalby Cancer and Research Institute, Ahmedabad, India

The 15th PSOGI international congress on peritoneal surface malignancies will be held from the 29th-31st October, 2025, in one of Europe's trendiest cities, Barcelona, Spain. The congress theme, '***From Small Beginnings to Global Force***' aptly captures the journey of the biennial PSOGI congresses which started with a mere 20 participants, mainly surgeons in the year 2000 increasing to over 1000 participants in 2024 including surgeons, medical oncologists, radiologists, pathologists, molecular oncologists, nurses, patients and patient support groups.

The program is crafted with great precision and planning to interest both newcomers and seasoned experts in peritoneal oncology. https://psogicongress2025.com/programme-psogi2025/

1. ***For beginners and young surgeons, radiologists and pathologists***

The congress is preceded by a **pre-conference video workshop and live demonstration of cytoreductive surgery** to be held at CHU Moises Broggi in Barcelona. This course offers a complete package of the techniques of peritonectomy procedures and of visceral resections in which participants will have the opportunity to interact with some of the most experienced peritoneal malignancy surgeons learning about all the nuances of the procedure.

The congress will see the return of the '**meet the professor' breakfast sessions** which will cover topics related to surgery, radiology and pathology.

Day 1 has a **session dedicated to young surgeons** which will include presentation of new trial ideas by young surgeons.

A **mini-competition on 'pitch your trial idea'** is currently open for participation.

More information can be sought at https://psogicongress2025.com/pitch-your-trial-idea/

Other sessions of interest for this group are the one on **advanced surgical techniques in cytoreductive surgery, the role of hyperthermia, preoperative CT/MRI for peritoneal disease**.

2. ***Patient advocacy and release of a 'patient manifesto'***

Patient voices have been a feature of previous PSOGI meetings. The 15th Annual meeting will take a step further in the clinician-patient partnership by releasing a **patient manifesto** during the congress on Thursday October 30, 2025 at 17:00 CEST in Barcelona, Spain. That session will not only include the Manifesto but some additional original contents for patients and also of interest to clinicians.

3. ***Why do we do what we do and how do we evolve?***

To advance any field, clinicians and researchers need to revisit the principles of treatment of the disease in light of recent advances and see if they retain their validity. The **session on the plasma peritoneal barrier**, revisits the age-old basis of administering drugs into the peritoneal cavity.

Two keynote lectures will discuss the current role of **HIPEC** and the emerging role of **intraperitoneal CAR-T cells**.

Another session is dedicated to **alternatives to HIPEC** covering the current role of **intraperitoneal hydrogels**, **oncolytic viruses** and **nanomedicine** in the management of peritoneal malignancies.

4. Common principles for managing peritoneal malignancies

Is there a possibility to have a uniform approach to management of peritoneal malignancies irrespective of the site of origin? Two sessions will cover this subject- **neoadjuvant therapy** in peritoneal malignancies and the **PSOGI-ESGO-ISSPP consensus** on peritoneal malignancies.

5. Clinical trials and research on peritoneal malignancy

There are two sessions on clinical trials - one that will have presentation of the results of **trials that have been completed** and updates on those that are nearing completion.

There is another session on **trials that are still in the stage of planning** or in an **early phase of recruitment** and require international collaboration. This is an opportunity to interact with the principal investigators of these trials and to consider participating in those open to multicenter international participation.

A dedicated session on **challenges in research** in peritoneal malignancies will cover challenges in both translational and clinical research and what can be learned from the experiences with other rare tumors and diseases. The ISSPP session on day one will cover **translational research and the emerging role of artificial intelligence**.

6. Partnership with other global societies

The International Society for Study of the Pleura and Peritoneum **(ISSPP)**, European Society of Coloproctology **(ESCP)** and European Society of Gynecologic Oncology **(ESGO)** are collaborating with PSOGI in this congress. Each society will have its own session (s) which will cover the latest updates on common areas of interest - **colorectal malignancy** (ESCP), **gynecological malignancy** (ESGO) and **perioperative management**, **management of elderly patients** with peritoneal malignancy and **translational research** in PSM (ISSPP).

7. Pro-con sessions

Controversy is a powerful catalyst for progress and positive change. In the era of personalized medicine, there are two sides to every controversial treatment or treatment principle. Two pro-con sessions will elucidate the **current role of PIPAC** in the management of unresectable peritoneal metastases and the role of surgical treatment of **peritoneal metastases secondary to pancreatic adenocarcinoma**.

8. History and PSOGI consensuses

One tradition in all the PSOGI meeting has been to **honor a surgeon who has made a humongous contribution** to the advancement of peritoneal malignancies. This session is a source of inspiration to many highlighting why in-person meetings are still needed.

The congress will feature presentation of **previous PSOGI consensuses** and how they are applicable to current practice. The results of two ongoing consensuses will be presented at the congress- the **Barcelona consensus on minimally-invasive cytoreductive surgery** and the **PSOGI-ESGO-ISSPP consensus on cytoreductive surgery-PART-2**.

9. Opportunities to get involved in the congress

The best way to participate in any meeting is to contribute to the scientific program by sharing one's own research. The **abstract submission is still open**. Nearly 30 abstracts will be selected for oral presentation and many others for poster presentation.

Abstract submission guidelines: https://psogicongress2025.com/abstracts/

Tumor board sessions offer the opportunity to discuss complex and controversial clinical scenarios.

10. Enjoy the weekend in Barcelona

The congress ends on a Friday afternoon. It is the perfect time to spend a weekend in the city that offers a perfect blend of modernity and history with its vibrant art and culture. At that time of the year (end of October), one can expect pleasant weather and smaller crowds.

Avail yourself of the early bird registration till 31st July, 2025: https://psogicongress2025.com/registration/

Special rates for low- and low-middle income countries will be available soon.

Section 4: Alternatives to traditional HIPEC

CAR T-cell Treatment for Peritoneal Metastases

By Else Marit Inderberg, Sébastien Wälchli, and Kjersti Flatmark

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The treatment for resectable peritoneal surface malignancies (PSM) is typically cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC). CRS-HIPEC is shown to be safe and to improve survival for patients with PSM. However, higher quality evidence of efficacy is required to reach a consensus on treatment strategies in cases of extensive peritoneal disease. PSM often has a dismal prognosis and upon peritoneal recurrence, repeat CRS-HIPEC treatment is only feasible in highly selected patient groups with a limited extent of peritoneal disease. Other therapeutic options remain very limited.

Immunotherapy

Immunotherapy has been very successful in the treatment of numerous different cancer types, in particular immune checkpoint inhibitors (ICI) blocking the PD-1/PD-L1 pathway. These are also efficient in melanoma and in microsatellite instable (MSI-H) cancers with a high tumor mutational burden (TMB) such as gastrointestinal and endometrial cancers. However, they have otherwise limited efficacy in PC due to a very immunosuppressive tumor microenvironment (TME).

Chimeric antigen receptors (CAR)

Another type of immunotherapy that has been very successful in treatment-refractory hematological malignancies is chimeric antigen receptor (CAR)-based T-cell therapy. CARs are synthetic receptors which are composed of an extracellular part which binds a biomarker onto the surface of cancer cells and an intracellular part that provides a stimulatory signal to the expressing T cell. When CARs bind to a target, the molecules aggregate on the T-cell surface creating a favorable intracellular environment for signal transduction. The binding domain is most often derived from an antibody in the form of single chain fragment variable (scFv), which is a smaller entity mimicking the antibody recognition domain (Fig. 1). Thus, CAR T cells are T lymphocytes that have been genetically modified to express a CAR that recognizes a specific surface antigen on the cancer cells. As CARs were first designed to redirect T cells against a target, both the signaling domains and other parts of the construct (hinge and transmembrane domains) were originally derived from receptors involved in the T-cell receptor signaling but have also been adapted to other cell types. CAR T cells can potentially be more effective than the antibodies they are derived from against tumors with lower antigen levels and can infiltrate and eliminate tumors not accessible to antibody-based therapy.

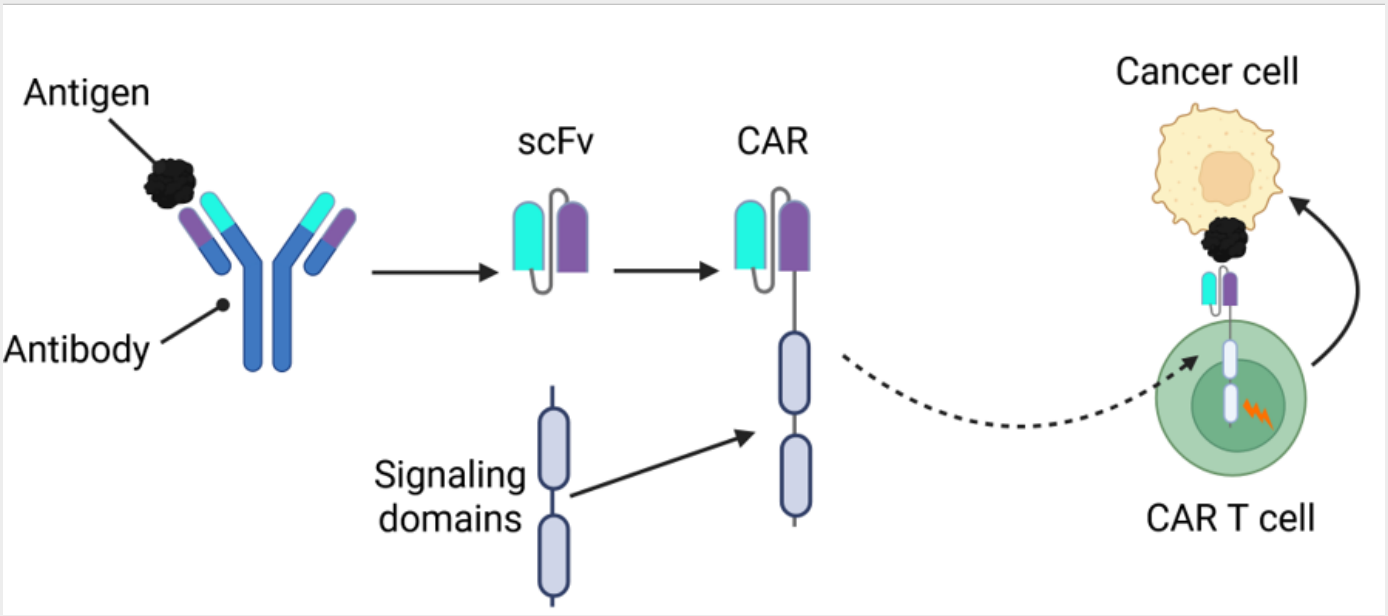

Figure 1. *CAR design: scFv are derived from antibody binding domain. Sequences are identified and assembled with a molecular linker. CAR is composed of a scFv connected through a transmembrane domain to intracellular signaling domains. CAR expressed in T cells provide them with the ability to detect cancer cells and kill them.*

CAR T-cell therapy

CAR T-cell products are generally based on the patients' own T cells. To produce CAR T cells, lymphocytes are harvested from the patients through leukapheresis (Fig. 2). The T cells are then modified genetically mainly by using viral vectors to express the CAR construct of interest, before going through an *ex-vivo* expansion to have sufficient cell numbers for infusion. Seven CAR-T products have currently been FDA-approved for therapeutic use in B-cell malignancies. The treatment of solid cancer types has so far been less successful, due to factors such as a limited availability of cancer-specific surface antigens and the risk of toxicity, as well as the immunosuppressive TME.

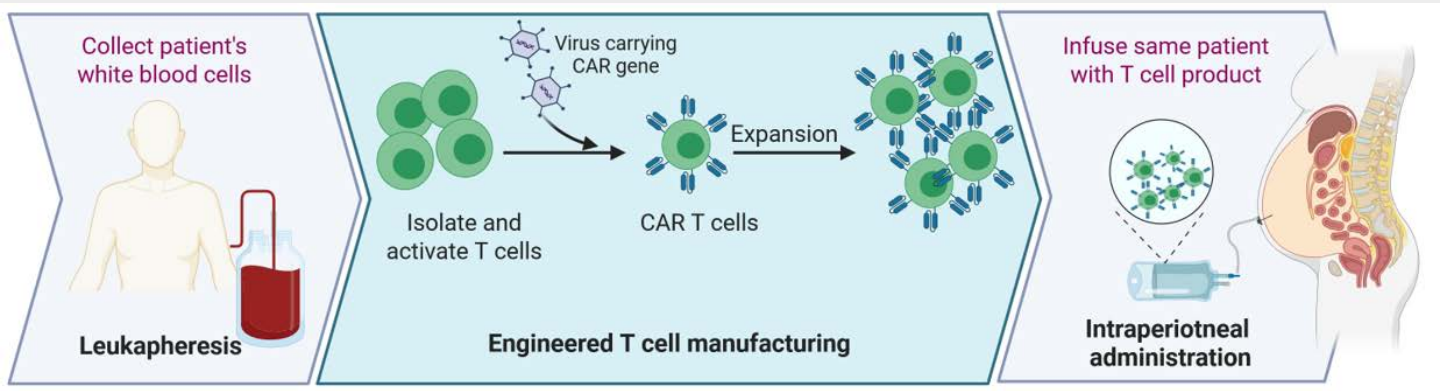

Figure 2. *CAR T cells in the clinic. White blood cells are isolated from patient blood by leukapheresis. T cells are isolated, genetically modified by viral transfection and expanded before injection into the same patient by the intraperitoneal route.*

Routes of administration

Currently approved CAR-T products are infused intravenously to treat B-cell malignancies, but there are examples of locoregional administration of CAR T cells. The treatment has been administered either intratumorally for several cancers or intraventricularly for glioblastoma (*Papa, Adami et al. 2023, J Immunother Cancer 11(6); Brown, Hibbard et al. 2024, Nat Med 30(4):1001-1012*), intrapleurally for mesothelioma, or intraperitoneal delivery for gastric cancer (Li, Guo et al. 2023). Preclinical studies suggest that intraperitoneal administration of CAR T-cells is superior to intravenous infusion for the treatment of metastatic colorectal cancer (*Qian, Chen et al. 2024, Cytotherapy 26(2):113-125*). Locoregional treatment alternatives are likely more suited for treating PSM and intraperitoneal infusion is a robust delivery route for effective treatment.

It has been shown that CAR T-cell therapy is more successful with lower tumor burdens in the treatment of hematological malignancies (*Schultz, Baggott et al. 2022, J Clin Oncol 40(9):945-955*). CAR T cells are not likely to be highly effective in patients with extensive unresectable PSM but could be used as adjuvant therapy in tumors that cannot be completely excised or early in recurrence where repeat CRS-HIPEC is not an option. These CAR T cells could be delivered intraperitoneally either alone, or in combination with ICI or other drugs expected to act synergistically within the TME. In the case of incomplete resection, there are numerous ongoing efforts to design hydrogels that can act as scaffolds and support for CAR T cells in the peritoneum. These hydrogels are based on different active ingredients including gelatin, alginates, hyaluronan that should improve CAR T-cell viability and persistence, as well as preserving their cytotoxic activity. Evidence of their efficacy in clinical trials is still required, but they have great potential.

Limiting adverse events

Intraperitoneal delivery of CAR T cells will limit the risk of systemic toxicity. Toxicity can occur due to off-target effects if there is cross-reactivity of the CAR molecule, and it recognizes similar structures or antigens on normal tissues. The major concern in solid tumors has been on-target/off-tumor toxicity if the antigen expression is not strictly restricted to tumor tissue. An example of this is the use of CAR targeting carcinoembryonic antigen (CEA) in colorectal cancer and other CEA-expressing adenocarcinomas where patients experienced pulmonary CAR T-cell infiltration and respiratory toxicity (*Thistlethwaite, Gilham et al. 2017, Cancer Immunol Immunother 66(11):1425-1436*). Another way to mitigate CAR T-cell toxicity is to use CARs with lower affinity for their target antigen. This has been nicely exemplified in the case of CARs targeting the Human epidermal growth factor receptor 2 (HER2) antigen, a well-established therapeutic target in breast cancer and gastric cancers that is also expressed at low levels in normal cells. The first report of clinical use of HER2 CAR T-cells was of HER2-expressing colon cancer where a patient died due to CAR T-cell recognition of HER2 in lung epithelium resulting in inflammatory cytokine release causing pulmonary toxicity and multi-organ failure *(Morgan, Yang et al. 2010, Mol Ther 18(4):843-851*). However, using low-affinity and/or lower CAR T dosage, HER2 CARs could lead to safe and efficacious therapy (*Shabaneh, Stevens et al. 2024, J Immunother Cancer 12(2)*).

New targets

As mentioned, most cell surface antigens are not cancer-restricted, however, their post-translational modifications such as glycosylation often are. Indeed, aberrant carbohydrate structures are recognized as a cancer-specific pattern and these can be detected by antibodies. Interestingly, the first CAR that was tested in the clinic, TAG-72 CAR, was directed against a glycan modification not exposed on the cell surface of normal cells (*Hege, Bergsland et al. 2017, J Immunother Cancer 5: 22*). The trials were performed in the 1990s in the early days of CAR T-cell therapy and although the therapy was found to be safe, no clinical response was observed. The main reason for this lack of effect was attributed to the intracellular design of the molecule where a so-called first-generation CAR design was used, now accepted to be unfit to trigger sustained stimulation of the expressing T cells. CAR molecules have since been improved, and TAG-72 CAR T-cells are presently being tested in the clinic in a more adapted format (NCT05225363). Aberrant glycosylations have since received renewed interest as targets for CAR therapy. We have recently isolated an antibody highly specific for an aberrant glycosylation which was subsequently used to design a CAR that we tested preclinically. The CAR T cells, which were administered intraperitoneally, were shown to be efficacious in several *in vivo* peritoneal carcinoma models. Importantly, they also demonstrated efficacy in a patient-derived xenograft (PDX) model of mucinous colorectal cancer, which supports further investigations in clinical trials (Abrantes, Forcados *et al*., in revision). We will in the future use the same animal model to test the combination of surgery and local CAR T cell administration using hydrogels (Fig. 3). If this technique proves efficient, it will open novel possibilities for post-surgical immune surveillance to prevent cancer recurrence.

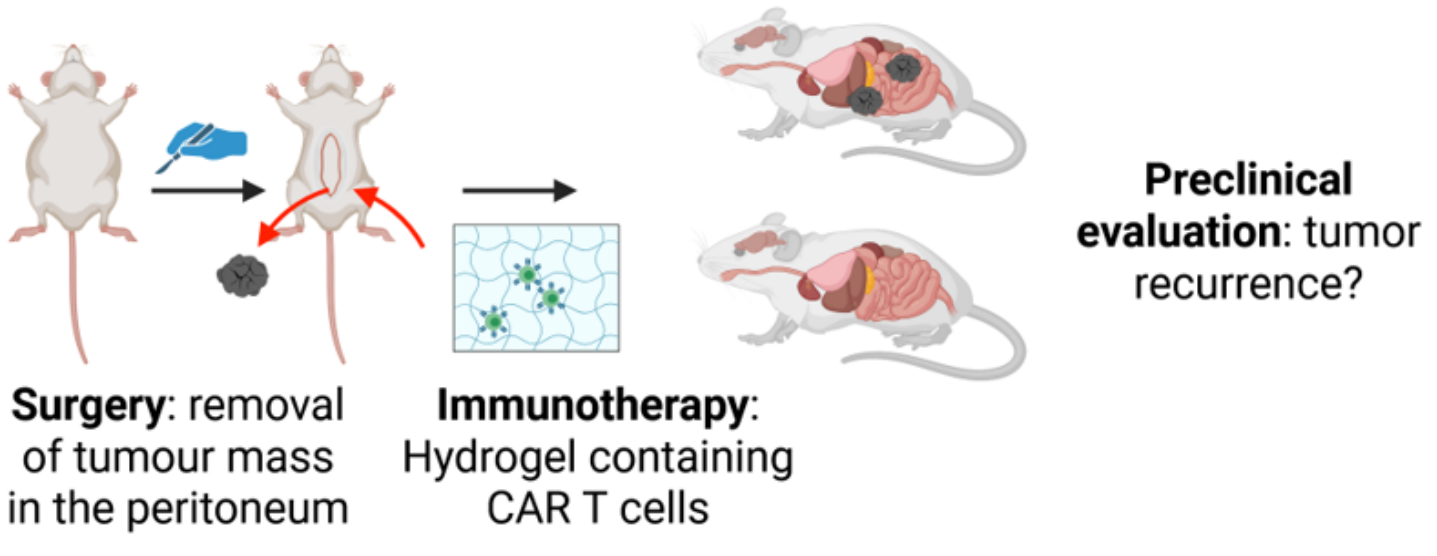

Figure 3. *Experimental design of the combination of surgery and locoregional CAR therapy. Animal models of PSM are used to test a 2-step strategy in which the tumor mass is removed and a hydrogel containing CAR T cells is placed into the peritoneum before closing. CAR T cells are expected to detect and kill residual cancer cells, thus avoid recurrence. This figure was created using Biorender.com.*

Conclusion

CAR T-cell therapy is still in early stages for most solid cancer and CAR T cells face several challenges in PSM. It is likely that the identification of more tumor-restricted targets, innovative solutions for CAR T-cell delivery, combination treatments to tackle the TME, and pinpointing disease characteristics that can identify patients more likely to clinically benefit from this treatment can lead to promising outcomes. These are all areas of intense research and development, which should yield more efficacious treatment for PSM patients in coming years.

Section 5: Pioneers of Progress in Peritoneal Surface Malignancy

Intraperitoneal Immune Modulation with Toll-like Receptor Agonists to Prevent Postoperative Recurrence after Surgical Treatment of Peritoneal Metastases

By Wim Ceelen, MSc, MD, PhD

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Current management of peritoneal metastasis (PM) is based on a combination of systemic and locoregional therapies. However, current treatment strategies are deficient in that clinical studies have shown that 80% of colorectal and ovarian cancer patients will develop peritoneal recurrent disease after initial treatment. Recurrent PM causes significant symptoms and complications, including ascites, bowel obstruction, and urinary tract obstruction. The major cause of recurrent PM after surgical or multimodal treatment is the presence of minimal residual disease (MRD). This small extent of cancer exists within an immune-suppressed, hostile postoperative peritoneal environment.

Studies from our laboratory show that regrowth of minimal residual disease may be prevented by intraperitoneal immune modulation. A promising method to achieve this is to activate the toll-like receptor (TLR) mediated pathways. Toll-like receptors are type I transmembrane pattern recognition receptors (PRRs) expressed by nearly all immune cells, as well as by some non-immune cells such as epithelial cells and adipocytes. Of the 10 TLRs expressed in humans, six are found on cell surfaces (TLR1, 2, 4, 5, 6, and 10), and four are localized to endosomes (3, 7, 8, and 9). The potential immune enhancing efficacy of TLRs depends on their ability to stimulate immature antigen presenting cells (APC) such as dendritic cells, macrophages, and B cells into mature professional APCs presenting antigens to T cells through MHC I/II - T cell receptor binding, in the presence of CD80 and CD86. In addition, TLRs are expressed on the T cells themselves, where they act as costimulatory receptors to enhance proliferation and cytokine production. Also, TLR stimulation can reverse the immune suppressive properties of Tregs (T regulatory cells) and reprogram immune suppressive M2-like macrophages into anti-tumorigenic M1-like, pro-inflammatory macrophages. As a consequence, immune modulation using TLR agonists, either alone or in combination with immune checkpoint inhibitors, holds significant promise to reverse the immune suppressive postoperative peritoneal ecosystem. The observation that clinical

studies using systemic (IV) administration of TLR agonists in cancer patients often failed due to off-target toxicities, further supports the rationale for intraperitoneal (IP) delivery. Most TLR agonists in clinical development for the treatment of solid tumors target intracellularly expressed receptors (7, 8, or 9).

Most TLR agonists are relatively small: resiquimod, for instance, has a molecular weight of 314 g/mol. As a consequence, intraperitoneally delivered TLR agonists are expected to be cleared quite rapidly from the peritoneal cavity. Efforts are therefore directed towards pharmaceutical formulations that prolong the peritoneal residence time (so called 'prolonged release' formulations). Numerous approaches have been tested in preclinical models, including micro- and nano-sized drug carriers, hydrogels, nanotextiles, and drug impregnated meshes. Biocompatible hydrogels hold particular promise, since in the postoperative setting they may not only release therapeutic cargo, but also act as an anti-adhesive agent. The physical and biological properties of hydrogels such as drug release rate, resorption time, pore size, and gelation dynamics can be controlled by chemical synthesis. In our lab, we are focusing on a pH sensitive supramolecular hydrogel, which forms a biocompatible gel when injected intraperitoneally due to a pH change (Fig.1). The hydrogel is loaded with TLR agonists; we are currently focusing on agonists of TLR7, 8, and 9.

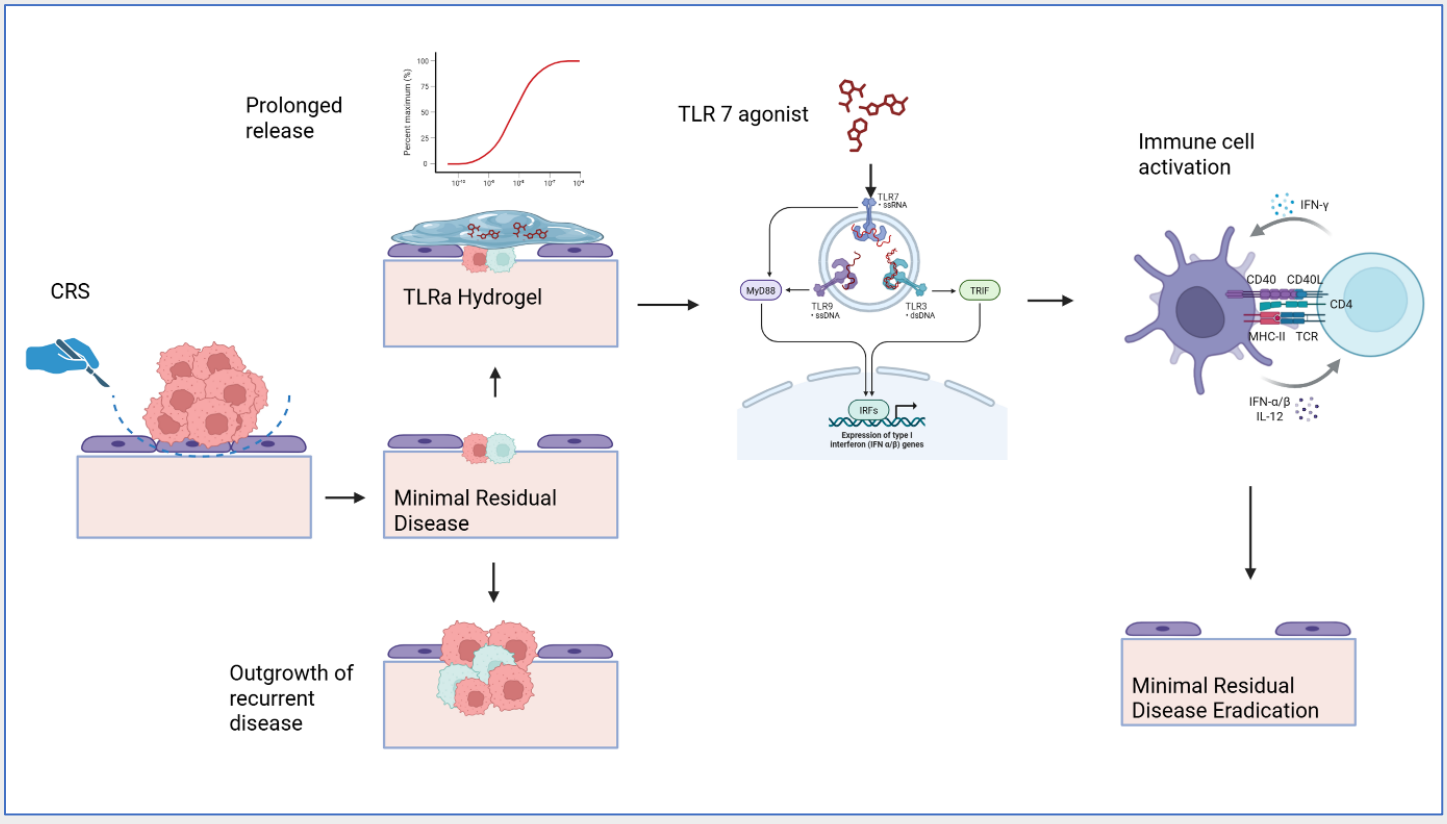

Figure 1. *Rationale for intraperitoneal delivery of a drug loaded hydrogel in the postoperative setting. After cytoreductive surgery for peritoneal metastases, recurrent disease is common, due to the outgrowth of minimal residual disease, facilitated by the postoperative immune suppressive peritoneal ecosystem. Intraperitoneal delivery of a toll-like receptor 7/8/9 agonist as a pH sensitive prolonged release hydrogel activates the peritoneal immune system and may prevent or eradicate minimal residual disease, thus preventing recurrent peritoneal metastasis. At the same time, the hydrogel may prevent postoperative adhesion related complications.*

Toll-like receptors 7 and 8 recognize single stranded RNA, and administration of agonists results in dendritic cell (DC) activation, leading to expansion of antigen specific CD8+ T cells and enhanced anticancer activity. Unmethylated cytidine phosphate guanosine (CpG) and oligodeoxynucleotides (CpG ODNs) in double stranded DNA are the main ligands for TLR9 receptors. Based on their different molecular backbones and sequence motifs, three different classes of CpG ODNs are recognized by TLR9 receptors. Type A CpG preferentially activate plasmacytoid plasmacytoid DC and natural killer (NK) cells and induce significant IFN-α production by pDCs. Type B CpG preferentially activate B cells and less so NK cells with no effect on DCs, while type C CpG have features of both classes A and B with strong direct B cell stimulation, IFN-α production by pDC, APC activation and maturation, and indirect natural killer cell activation.

Despite their potential to engineer the tumor immune microenvironment, TLR agonists alone are likely insufficient to generate an effective antitumor immune response in mismatch repair proficient cancers such as the large majority of colorectal cancers. For that reason, we explore combination therapies, using TLR agonists in conjunction with IP Oxaliplatin (unformulated, or as a nanoparticle) and immune checkpoint inhibitors. The aim of adding a cytotoxic compound such as Oxaliplatin is to cause cancer cell death and thus release epitopes to be recognized by the immune system. In addition, Oxaliplatin is recognized as a potent inducer of immunogenic cell death (ICD).

In preliminary experiments, we have established colorectal peritoneal metastases (CT26 cell line, regarded as having a mismatch repair proficient phenotype) in mice, and treated them IP with unformulated TLR 7/8 agonists. To verify the clinical relevance of the treatment, we compared the observed cytokine and chemokine expression as well as gene expression (bulk RNA sequencing) with patient derived tumor fragments (‘cuboids’). Using an automated tissue chopper, 0,125 mm^3 cubes were cut from freshly resected clinical PM specimens. Comparison of murine with human data shows adequate correspondence (Fig. 2).

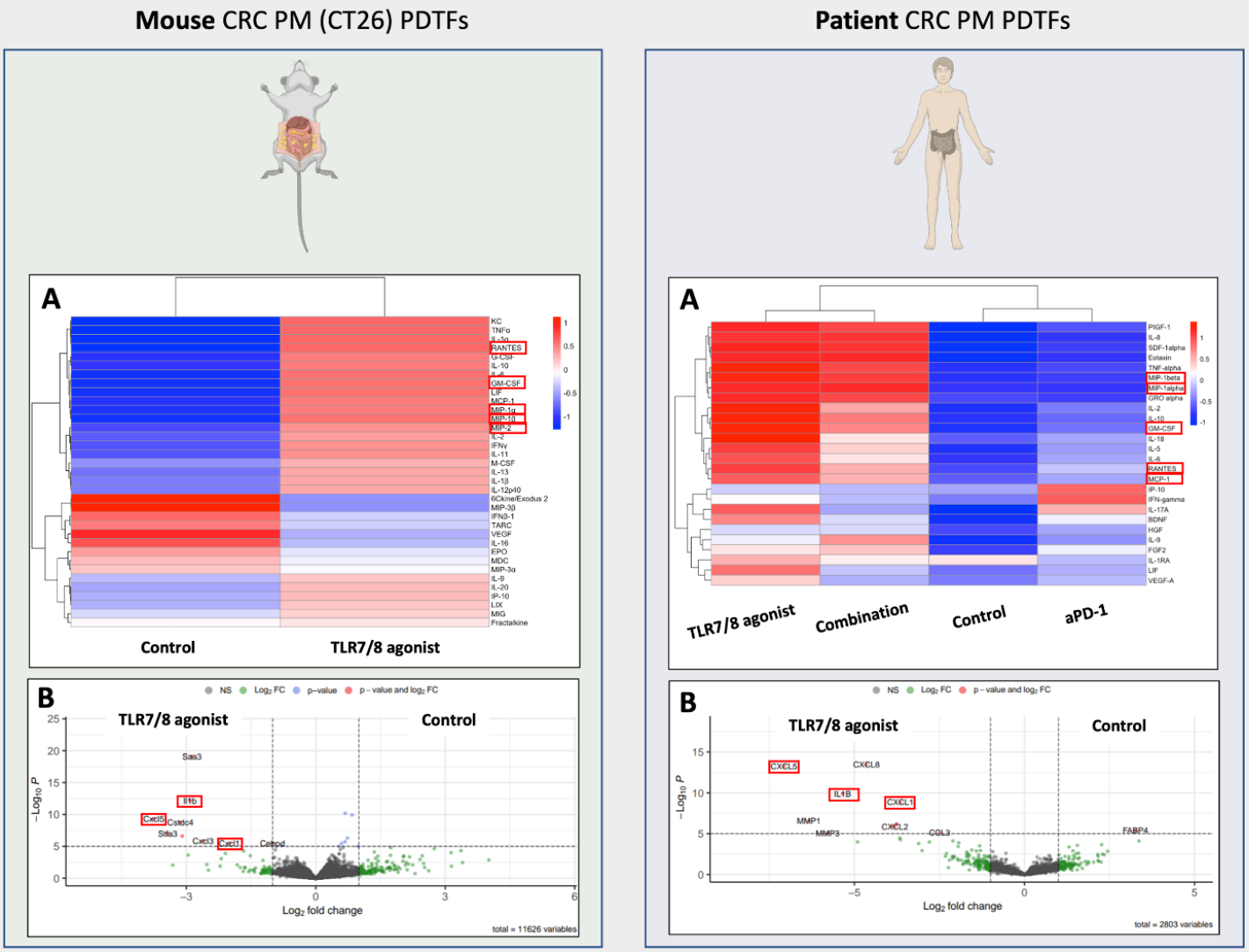

Figure 2. *PDTFs from patients treated with a TLR7/8 agonist mimic the response of murine PDTFs treated with a TLR7/8 agonist. A-B. Murine and patient PDTFs were treated for 48 hours with a TLR7/8 agonist (1 µg/ml) and, in the case of patient PDTFs, an immune checkpoint inhibitor (aPD-1) (10 µg/ml). A. Luminex analysis shows increased secretion of biologically relevant cytokines and chemokines. RANTES, GM-CSF, MIP-1α, MIP-1β and MIP-2 are highlighted in red and are detected in both murine and patient PDTFs. B. RNA sequencing of PDTFs treated with a TLR7/8 agonist confirms the significant upregulation of biologically relevant cytokines and chemokines. IL-1β, CXCL5 and CXCL1 are highlighted in red and are found in both murine and patient PDTF. Abbreviations: PDTF, patient-derived tumor fragment. Courtesy of Sam Ernst MSc, PhD student.*

Ongoing experiments focus on survival effects, immune effects, and PKPD of the hydrogel loaded with TLR 7/8/9 agonists with or without Oxaliplatin and immune checkpoint inhibitors. We aim to test toxicity and pharmacokinetics in a large animal model within two years, as the final step before a first in human study. When successful, this approach could contribute to improved outcomes after cytoreductive surgery for peritoneal metastases, which remain a formidable challenge.

Section 6: Focus on Active PSM Protocols

Target Radiotherapy for Peritoneal Surface Malignancies: Radioimmunotherapy and Radioligand therapy

By Shigeki Kusamura

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Radioimmunotherapy (RIT) and radioligand therapy (RLT) represent two targeted radiopharmaceutical approaches that can be exploited for the treatment of peritoneal surface malignancies (PSM). PSMs are often confined to the peritoneal cavity and difficult to eradicate with systemic chemotherapy due to low peritoneal bioavailability of drugs. Both RIT and RLT aim to selectively deliver radiation to tumors while minimizing exposure to healthy tissues. They differ, however, in the molecular vehicles they employ, the cellular or stromal targets they recognize, and their pharmacokinetic, safety, and logistical profiles.

Radionuclides used in targeted therapies are broadly categorized by the type of radiation they emit. Alpha emitters (e.g., ^{211}At, ^{225}Ac, ^{212}Pb) release high-energy, short-range particles capable of inducing lethal double-strand DNA breaks, making them ideal for eliminating microscopic disease with minimal collateral damage. Beta emitters (e.g., ^{90}Y, ^{177}Lu, ^{131}I) emit lower-energy, longer-range particles, which are more suited to treating bulkier or confluent lesions. Auger electron emitters (e.g., ^{111}In) produce very short-range, high-linear energy transfer (LET) emissions that require nuclear localization for effectiveness. The choice of radionuclide significantly affects tissue penetration, required dosimetry, and toxicity profiles.

RIT uses monoclonal antibodies (mAbs) that selectively bind to tumor-associated antigens (TAAs) expressed on the surface of malignant cells. These antibodies are conjugated to therapeutic radionuclides and administered systemically or intraperitoneally. The IP route is particularly attractive in PSM due to the pharmacokinetic advantage conferred by peritoneal compartmentalization, allowing high locoregional concentrations and slower systemic absorption. Antibodies used in RIT typically target markers such as HER2, CEA, and EpCAM, which are variably expressed in gastrointestinal and gynecologic malignancies.

Current clinical evidence on RIT for peritoneal surface malignancies remains limited but encouraging. Modak et al. (2020) reported the feasibility of intraperitoneal ^{131}I-omburtamab in patients with desmoplastic small round cell tumor, demonstrating favorable biodistribution and tolerability. Andersson et al. (2009) administered ^{211}At-MX35 F(ab')$_2$ fragments intraperitoneally in women with ovarian cancer in clinical remission after savage therapy, observing high peritoneal-to-blood ratios and negligible hematologic toxicity. Despite promising safety and pharmacokinetics, therapeutic efficacy remains modest, primarily due to dose limitations related to organ-specific radiation exposure and challenges in achieving uniform tumor targeting. These early-phase studies highlight the

biological rationale of RIT but also underline the need for improved delivery platforms and more consistent antigen expression to enhance clinical outcomes in PSM.

The pharmacokinetic properties of full-length antibodies pose key limitations for RIT. Their large size results in slow tumor diffusion and prolonged circulation time, increasing exposure to sensitive organs such as the bone marrow and kidneys. This reduces the therapeutic index and complicates repeat dosing. Moreover, the reliance on TAAs is problematic in advanced tumors, where antigen expression is often heterogeneous or downregulated under treatment pressure of advanced disease stage. These biological and technical challenges, along with the need for complex manufacturing and radiolabeling infrastructure, constrain the scalability and cost-effectiveness of RIT.

Radioligand therapy (RLT) offers an alternative strategy that addresses many of RIT's shortcomings. Instead of antibodies, RLT uses small-molecule ligands—often enzyme inhibitors or peptides—labeled with radionuclides to target specific proteins in the tumor or its microenvironment. A leading target is fibroblast activation protein (FAP), expressed abundantly by cancer-associated fibroblasts (CAFs) in the tumor stroma. CAFs play a critical role in several solid tumor progression by remodeling the extracellular matrix, facilitating immune evasion, angiogenesis, and promoting resistance to anticancer therapy. Because FAP expression is more uniform and stable than many TAAs, FAPI (FAP inhibitor)-based agents offer a broader therapeutic window in a tumor agnostic fashion.

In recent review by Luo et al. (2025) the authors detail the development of multiple FAPI compounds, highlighting their rapid tumor uptake, favorable tumor-to-background ratios, and excellent safety profiles. Initial diagnostic agents such as FAPI-02 and FAPI-04 provided excellent PET imaging quality but had limited tumor retention. Subsequent generations like FAPI-46, and more recently FAP-2286, incorporated albumin-binding domains and cyclic structures to enhance circulation time and tumor residence. In early-phase studies, FAPI tracers showed high uptake in peritoneal metastases from gastric, colorectal, and ovarian origins, with minimal uptake in normal tissues, with very promising results. Therapeutic applications using ^{177}Lu-FAP-2286 resulted in symptomatic improvement and disease stabilization in patients with advanced disease, although larger efficacy trials are still underway.

Pharmacokinetically, FAPI ligands clear quickly from circulation and exhibit fast tumor penetration, making them particularly well-suited to alpha- and beta-emitting therapies that benefit from short exposure durations. Their small size and non-immunogenic nature also reduce the risk of systemic toxicity, do not require IP administration to widen the therapeutic index, and allow for repeated administration. In contrast to RIT, FAPI-based RLT is easier to synthesize, radiolabel, and distribute, requiring less specialized infrastructure and potentially enabling broader clinical adoption at lower cost.

Safety profiles further distinguish these modalities. While RIT may cause hematologic and renal toxicity—especially with prolonged systemic antibody exposure—FAPI RLT has demonstrated minimal toxicity to date. That said, renal

uptake has been observed with some constructs and remains an area for careful monitoring and molecular optimization. From a cost and logistical perspective, RLT benefits from simplified production pipelines and faster turnaround times, allowing integration into outpatient clinical workflows.

In conclusion, RIT and RLT are mechanistically distinct targeted radiotherapy strategies with enormous potential for PSMs. RIT provides tumor-cell specificity through antibody targeting of surface antigens, but is limited by pharmacokinetics, antigen heterogeneity, and complex logistics. RLT, particularly FAPI-based radiotherapy, leverages the stromal stability of FAP expression across several tumor types, to deliver radiation efficiently with favorable safety and pharmacologic properties. While RIT has a longer clinical track record, RLT shows strong translational potential and may offer broader applicability across histologies.

Peritoneal metastases when optimally treated can be cured; in selected patients peritoneal metastases can be prevented. The ultimate goal is to eliminate local-regional recurrence and peritoneal metastases from the natural history of gastrointestinal and gynecologic malignancy.