

CANCER VS. CONVERSATIONAL ARTIFICIAL INTELLIGENCE

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ABSTRACT

Solving cancer mechanisms is challenging due to the complexity of the disease integrated with many approaches that researchers take. In this study, information retrieval was performed on 40 oncological papers to obtain authors' methods regarding the tumor immune microenvironment (TIME) or organ-specific research. 20 TIME summaries were combined and analyzed to yield valuable insights regarding how research based papers compliment information from review papers using Large Language Model (LLM) in-context comparisons, followed by code generation to illustrate each of the authors' methods in a knowledge graph. Next, the 20 combined organ-specific emerging papers impacting historical papers was obtained to serve as a source of data to update a mechanism by Zhang, Y., et al., which was further translated into code by the LLM. The new signaling pathway incorporated four additional authors' area of cancer research followed by the benefit they could have on the original Zhang, Y., et al. pathway. The 40 papers in the study represented over 600,000 words which were focused to specific areas totaling approximately 17,000 words represented by detailed and reproducible reports by Clau-3Opus. ChatGPT o1 provided advanced reasoning based on these authors' methods with extensive correlations and citations. Python or LaTeX code generated by ChatGPT o1 added methods to visualize Conversational AI findings to better understand the intricate nature of cancer research.

Keywords Cancer · Tumor Immune Microenvironment · Organ-Specific Cancer · Conversational AI

1 Introduction

LLMs have been increasingly utilized for cancer research in a number of applications. In April 2023, Naik, H., et al. utilized an earlier version of ChatGPT to generate a single patient case report regarding synchronous bilateral breast cancer [1]. In September of the same year, Choi, H., et al. collected data from reports of surgical pathology and ultrasounds from 2,931 breast cancer patients, and extracted the information using ChatGPT 3.5 to efficiently derive clinical factors, obtaining an overall accuracy of 87.7% [2]. On October 16, 2023, Griewing, S., et al. in *Journal of Personalized Medicine* compared the concordance of treatment recommendations from "ChatGPT 3.5 with those of a multidisciplinary tumor board for breast cancer (MTB)." The authors found that "Overall concordance between the LLM and MTB was reached for half of the patient profiles" [3].

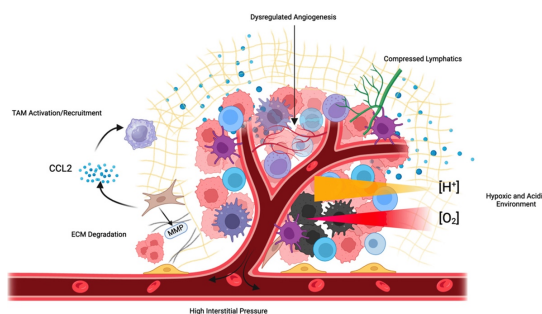


Figure 1: Tumor microenvironment, Garlisi, B., et al. 2024 [4]

Furthermore, in November 2023 Sorin, V., et al. utilized ChatGPT-3.5 or GPT-4 to process breast cancer clinical notes, question-answering based on guidelines, and patients' management recommendations. "The rate of correct answers varied from 64-98%, with the highest accuracy (88-98%) observed in information extraction and question-answering tasks" [5]. A study published on November 17, 2023 focused on utilizing a variety of LLMs to examine "10 fictional cases of patients with advanced cancer with genetic alterations. Each case was submitted to 4 different LLMs (ChatGPT, Galactica, Perplexity, and BioMedLM) and 1 expert physician". Results of 4 lung cancer cases and 6 other cancer cases indicated that the LLMs in precision oncology did not yet reach the quality and credibility of human experts [6].

In January 2024, Zack, T., et al. utilized GPT3.5-turbo and GPT4 "to infer disease status, response to treatment, and location of disease for patients with pancreatic adenocarcinoma from clinical radiology reports." The authors used 200 deidentified radiology reports from pancreatic cancer patients to accurately interpret multiple clinically relevant features, with precision improved markedly with GPT 4 compared to GPT-3.5 [7]. Later in March, Tariq, A., et al. focused on prostate cancer consisting of "more than 1.8 million clinical notes and radiology and pathology reports for 15341 patients" in Mayo Clinic across three sites and outpatient clinics." The authors' LLM surpassed GPT-2 in all tasks, and improved upon the BioGPT model in one of the two tasks [8].

Also in March, Sorin, V., et al. performed six breast cancer studies evaluating either ChatGPT-3.5 or GPT-4 to explore "clinical notes analysis, guideline-based question-answering, and patient management recommendations", with accuracy varying between studies from 50 to 98%. "Higher accuracy was seen in structured tasks like information retrieval" [9]. Iivanainen, S., et al. utilized in-context learning (ICL) and Retrieval Augmented Generation (RAG) with OpenAI's GPT4 Turbo to field 11 questions regarding small cell lung cancer and 13 questions about non-small cell lung cancer treatment "for responses using ESMO guidelines having oncologists' consensus, ICL with maximum context and ICL-RAG respectively provided accurate responses for 83.3%, and 79.2% of questions vs. 62.5% for the base GPT4 model. Results were more favorable using National Comprehensive Cancer Network (NCCN guidelines for ICL-RAG at 83.3%, GPT4-T at 75.0% and ICL-MC for 33.3% of questions" [10].

On the same date, Lammert, J., et al. in *Journal of Clinical Oncology* utilized a Retrieval augmented generation (RAG) system that integrates PubMed clinical studies, trial databases and oncological guidelines with LLMs to support targeted treatment recommendations. The authors "used 10 publicly accessible fictional patient cases with 7 tumor types and 59 distinct molecular alterations", including their MEREDITH (Medical Evidence Retrieval and Data Integration for Tailored Healthcare) LLM system consisting of Google's Gemini Pro, with a mean semantic textual similarity of LLM responses increasing from 0.69 to 0.76 ($p < 0.001$) [11]. A third May 29 publication by Bibault, J., et al. performed experiments using a GPT-4-based web application for monitoring breast cancer treatment toxicity. A natural language summary of the patient's responses was generated using the GPT-4 API for physician review: "The mean time for textual summary generation was 7 (5.7-9.2) seconds. The AI-Symptom Summarization Tool (ASST) mean scores were 4.25 for accuracy and 4 for thoroughness" [12].

On May 30, Sun, C., et al. profiled histopathological and molecular alterations in squamous cervical cancer, and used ChatGPT for interpretation, reasoning, and understanding of multi-modal data of 114 Chinese patients. The authors "implemented an immersive-knowledge prompting (iKLP) strategy to trigger LLMs, which interpreted 17.8%-20.3% of omic alterations known to be associated with cancer." "With experimental validations, LLM-reasoning showed >2-fold increased confidence for 68.5% of analyzed molecules" [13]. June 18, 2024 Longwell, J., et al. evaluated 8 LLMs, with ChatGPT-4 "correctly answered 125 of 147 questions" of examination-style multiple-choice questions from the American Society of Oncology, the European Society of Medical Oncology, and an original set from the authors. ChatGPT-3.5, and six open-source LLMs with publicly available weights were also used in the study and had lower performance than ChatGPT-4" [14]. Manjunath, P., et al. in July demonstrated that off-the-shelf LLMs could enhance their system's accessibility through retrieval report summarization and user Q&A interactions" [15]. Later in July, Park, J., et al. employed EHR data and a GenePT model "to leverage NCBI text descriptions of individual genes with Open AI GPT-3.5 to generate gene embeddings for various downstream tasks", with a "sensitivity increased by 10% (95%CI 7% – 11%) at specificities ranging from 99.0% to 99.9% for predictions made 0-3 months earlier, and by 22% (95%CI -4% – 48%)" [16].

On August 19, 2024, Pan, S., et al. employed a pre-trained single-cell large language model (LLM) to develop an EMT-language model (EMT-LM) for capturing discrete states within the EMT continuum in single cell cancer data. The authors achieved an AUROC of 90% across multiple cancer types, referred to as 'scMultiNet' [17]. An additional August publication by Alasker, A., et al. in *BMC Urology* presented a total of 52 questions on general knowledge, diagnosis, treatment, and prevention of PCa were provided to three LLMs. ChatGPT-3.5 "demonstrated superiority over the other LLMs in terms of general knowledge of PCa ($p=0.018$)." "ChatGPT-4 achieved greater overall comprehensiveness than ChatGPT-3.5 and Bard ($p=0.028$).", with Google Bard "generating simpler sentences with the highest FRE score (54.7, $p<0.001$) and lowest FK reading level (10.2, $p<0.001$)" [18].

On August 29, Ahmad, N., et al. published CanPrompt to mitigate the accuracy and hallucination concerns to ensure responsible deployment. The CanPrompt strategy utilized "prompt engineering combined with few-shot and in-context learning to significantly enhance model accuracy by generating more relevant answers." "After applying CanPrompt with models Mistral 7x8b, Falcon 40b, and Llama 3-8b, BERTScore results showed Mistral leading with an accuracy around 84%" [19]. In September of the same year, Li, M., et al. utilized a 7B parameter CancerLLM model "pre-trained on 2,676,642 clinical notes and 515,524 pathology reports covering 17 cancer types, followed by fine-tuning on three cancer-relevant tasks, including cancer phenotypes extraction, and cancer diagnosis generation. CancerLLM achieved state-of-the-art results compared to other existing LLMs, with an average F1 score improvement of 7.61%" [20].

On September 25, 2024, Hao, Y., et al. featured RadOnc-GPT, a specialized Large Language Model (LLM) "powered by GPT-4 that with a focus on radiotherapeutic treatment of prostate cancer with advanced prompt engineering." The authors implemented patient electronic health records (EHR), with 158 previously recorded in-basket message interactions." The authors estimated RadOnc-GPT "to save 5.2 minutes per message for nurses and 2.4 minutes for clinicians, from reading the inquiry to

sending the response." [21] Two days later, Hao, Y., et al. published on MedEduChat for prostate cancer patient education, which integrates with patients' electronic health record data and features a closed-domain, semi-structured, patient-centered approach to address real-world needs. The authors then "integrated MedEduChat with OpenAI's GPT-4o through the clinic's Azurehosted endpoint, which is HIPAA compliant." [22].

On October 1, Gilbert, M. utilized a Mixtral 8x7B LLM by Mistral AI "to automate the extraction of key words and phrases from multidisciplinary head and neck cancer tumor board notes of 50 patients diagnosed and treated in 2021". The authors "found collectively that the precision, recall, F1 score, and accuracy were 96.9%, 95.7%, 96.3%, and 93.1%, respectively" [23]. On the same day, Khanmohammadi, R., et al. proposed a novel student-teacher LLM architecture that self-improved the key concept abstraction through automatic prompt optimization, and was designed for local use to safeguard patient privacy in oncology. The Mixtral-8x7B student model initially extracted symptoms and treatments from given prompts, "which were then refined by the GPT-4 teacher model." The performance for multi-symptom notes "demonstrated average improvement in accuracy from 0.24 to 0.43, precision from 0.60 to 0.76, recall from 0.24 to 0.43 and F1 from 0.20 to 0.44." [24]

On October 3, Kim, K., et al. integrated prognostic capabilities of both CT and pathology images with clinical information for lung cancer, employing a multi-modal integration approach "via multiple instance learning, leveraging large language models (LLMs) to analyze clinical notes and align them with image modalities" [25]. Two days later, Das, R., et al. presented GeneSilico Copilot, "an advanced agent-based architecture that transforms LLMs from simple response synthesizers to clinical reasoning systems" for precision oncology. The authors employed state-of-the-art LLM services, GPT-4 and Claude Opus-3, known for their long context windows" [26]. Li, Y., et al. on October 11 published in *IEEE Journal of Biomedical and Health Informatics* regarding a large language model (LLM)-based Knowledge-aware Attention Network (LKAN) for clinical staging of liver cancer (CSoLC). The LLM and a rule-based algorithm were integrated to generate more diverse and reasonable data, with unlabeled radiology corpus of liver cancer being pre-trained, and attention was improved by incorporating both global and local features. The classification accuracy of LKAN "achieved the best results with 90.3% Accuracy, 90.0% Macro_F1 score, and 90.0%"

Four days later, Yang, S., et al. provided a computational approach called LLM4THP to quickly and effectively detect tumor homing peptides (THPs). LLM4THP utilized LightGBM, XGBoost, Random Forest, and Extremely Randomized Trees, and "Logistic Regression to further refine the identification of sequences as either THP or non-THP." LLM4THP outperformed other compared methods in terms of ACC, MCC, F1, AUC and AP "with improvement by 2.3–4.61%, 4.63–8.79%, 2.22–3.95%, 1.94% to 3.46 and 2.7–5.91%" on the primary test dataset" [27]. On October 21, Gubanov, M., et al. verified that knowledge graph served as a Retrieval Augmented Generation (RAG) guardrail. Their CancerKG model exhibited 5 different advanced user interfaces, "each tailored to serve different data modalities better and more convenient for the user." The authors evaluated CancerKG on real user queries and reported a high normalized discounted cumulative gain score on a large-scale corpora of approximately 44K publications" [28].

Oh, Y., et al. in *Nature Communications* on October 24, 2024 presented a LLM-driven multimodal artificial intelligence (AI), "namely LLMSeg, that utilizes the clinical information and is applicable to the challenging task of 3-dimensional context-aware target volume delineation for radiation oncology." The authors demonstrated that LLMSeg exhibited markedly improved performance compared to conventional unimodal AI models, particularly exhibiting robust generalization performance and data-efficiency" [29]. On the same day, Yu, J., et al. used LLMs to screen "36,105 EBV-relevant scientific publications and summarize the current literature landscape on various EBV-associated diseases like Burkitt lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), nasopharyngeal carcinoma (NPC), and so on. The accuracy of the GPT-generated summary greatly depended on the concise prompt input with clear instructions, which can enhance the precision of the generated response." To optimize costs and efficiency, the authors initially utilized GPT-3.5 Turbo followed processing with GPT-4 [30]. Lastly, Lammert, J., et al. on October 30, 2024 published in *JCO Precision Oncology* on utilizing their LLM system MEREDITH to support treatment recommendations in precision oncology. The system was built on Google Gemini Pro, with MEREDITH using retrieval-augmented generation and chain of thought, with concordance between LLM suggestions and expert recommendations of 94.7% for the enhanced system [31].

Thus, from April 2023 to recent studies, LLMs have been utilized in an increasing number of applications for cancer research, as readily apparent with the ten October 2024 articles shown here in journals such as *Nature Communications* and *JCO Precision Oncology*. Authors continue to utilize newer LLMs to increase the performance of their studies as evidenced by the Choi, H., et al. September 2023 inclusion of ChatGPT 3.5, transitioning to the more capable GPT-4o model by Hao, Y., et al. in September 2024. Technologies such as information retrieval implemented by Sorin, V., et al., in-context learning and retrieval augmented generation by Iivanainen, S., et al., and RAG also by Gubanov, M., et al. are examples of similar methods being utilized in this study. In addition, the Khanmohammadi, R., et al. method of incorporating models from different AI software manufacturers was also implemented in this current study. More recent studies showed effective use of a) information retrieval techniques across a number of papers to b) update current research approaches. Note: At time of submission, additional ChatGPT 4o Cancer and "ChatGPT o1" Cancer searches were made, however nothing corresponding to the scope of this paper was immediately found.

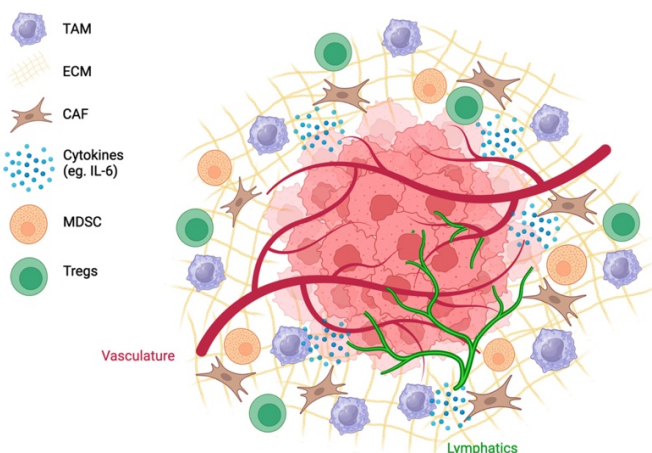


Figure 2: Complex TME with lymphatics, Garlisi, B., et al. 2024 [4]

2 Methods

AI software used in this study were all unmodified LLMs with generation times being obtained with a digital stop watch. Clau-3Opus utilized document retrieval of pdfs found only in Table 2 using the 'paper clip' option and text inputs, while Lla3.1-405 and ChatGPT o1 processed text inputs. ChatGPT o1 prompts were first optimized, then ran as a chain of prompts in a single conversation. Text that was copied into LLM input fields was also pasted as plain text into Supplementary SIM, SIMp, SOR, SORp, and S40p; with a triplicate reproducibility study shown in Supplementary SREP for a total across files of 61 generations. Generations in the manuscript received white space formatting for readability. The author conducted experiments, analysis, and wrote the manuscript, with ChatGPT 4o being primarily utilized as a research tool. Paper lengths were obtained by copying each pdf into a Google Docs and using the Word Counts feature. JupyterLab [32] was accessed through Anaconda [33] and MacOS 14.5 (23F79) in Google Chrome browser Version 131.0.6778.109 (Official Build) (arm64) for running Python code, while the manuscript software natively processed LaTeX code.

01) Clau-3Opus: Claude website chat interface was accessed through MacOS 14.5 (23F79) and Google Chrome browser Version 131.0.6778.109 (Official Build) (arm64) [34].

02) Lla3.1-405: Fireworks.ai website chat interface was accessed through MacOS 14.5 (23F79) and Google Chrome browser Version 131.0.6778.109 (Official Build) (arm64). Settings: Max Tokens=4096, Temperature=1.0, Top P=1.0, Top K=50, Presence Penalty=0, Frequency Penalty=0 [35].

03) ChatGPT o1: ChatGPT website pro interface was accessed through MacOS 14.5 (23F79) and Google Chrome browser Version 131.0.6778.109 (Official Build) (arm64) [36]. The ChatGPT o1 pro model was not utilized in this study.

04) ChatGPT 4o: ChatGPT website pro interface was accessed through MacOS 14.5 (23F79) and Google Chrome browser Version 131.0.6778.109 (Official Build) (arm64) [37].

3 Part I: Information Retrieval and Cancer Insights

Standard 1: Information Retrieval and Cancer Insights

Prompt 1: Write a detailed report based on the document regarding how the authors' methods advanced the tumor immune microenvironment field using the following format: "Executive Summary," "Technical Details," "Key Insights". Explain the steps you took to arrive at your conclusions by citing selections of numerical data enclosed in quotation marks corresponding to the authors' names. [Single Paper Attached, 20 Generations Total]

Prompt 2a: Write a detailed report based on the document regarding how the authors' methods advanced organ-specific cancer research using the following format: "Executive Summary," "Technical Details," "Key Insights". Explain the steps you took to arrive at your conclusions by citing selections of numerical data enclosed in quotation marks corresponding to the authors' names. [Single Paper Attached, 20 Generations Total]

Prompt 2b: Utilize these 40 summaries to draft 10 next generation cancer research studies. Cite selections of text enclosed in quotation marks corresponding to the authors' names that helped you form your conclusion. [40 Paper Text Summaries Included]

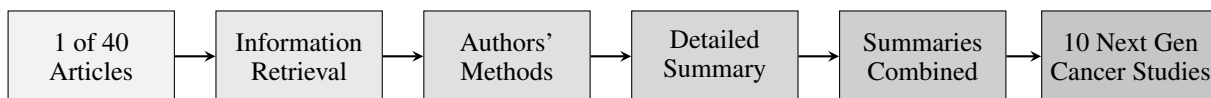


Table 1: Standard 1 Process Diagram

Tumor Immune Microenvironment: Papers 01-10, Review Papers 11-20^a

Paper Authors	Date Journal	Area of Immunology	Paper AI Words	AI Format Quote
01 Lahusen, A., et al.	04/23/24 <i>Sci Rep</i>	T Cell responses ^[38]	11,803 507	Yes Yes
02 Kim, D., et al.	04/11/24 <i>Front Immunol</i>	Receptor expression ^[39]	10,012 412	Yes Yes
03 Hu, Y., et al.	02/15/24 <i>npj Precis</i>	CAF tumor promotion ^[40]	12,050 445	Yes Yes
04 Imran, K., et al.	04/21/24 <i>Front Immunol</i>	Electroporation ^[41]	10,174 462	Yes Yes
05 Zahraeifard, S., et al.	07/12/24 <i>Nat Commun</i>	Tumor suppressors ^[42]	12,281 507	Yes Yes
06 Ferri-B., S., et al.	02/20/24 <i>Cancers</i>	3D cell analysis ^[43]	13,386 411	Yes Yes
07 Tang, W., et al.	03/21/24 <i>Cell Biosci</i>	Immunosuppression ^[44]	15,990 496	Yes Yes
08 Dai, L., et al.	06/05/24 <i>Biomark Res</i>	DLBCL multi-omics ^[45]	13,905 424	Yes Yes
09 Sun, J., et al.	03/27/24 <i>Int J Mol Sci</i>	HIF-1 α , PD-L1 expr. ^[46]	8,369 338	Yes Yes
10 Zheng, K., et al.	04/17/24 <i>J Transl Med</i>	TIDE-based subtyping ^[47]	13,502 456	Yes Yes
11 Zhang, Z., et al.	03/23/24 <i>Cell Oncol</i>	3D bioprinting study ^[48]	8,226 407	Yes Yes
12 Zhou, Z., et al.	06/26/24 <i>Mol Cancer</i>	CAR-T multi-omics ^[49]	18,217 383	Yes Yes
13 Safaei, S., et al.	03/29/24 <i>Breast Cancer Res</i>	Tumor exosomes ^[50]	10,694 421	Yes Yes
14 Zhang, H., et al.	09/03/24 <i>Biomark Res</i>	Metabolic interactions ^[51]	21,561 523	Yes Yes
15 Kundu, M., et al.	05/07/24 <i>Mol Cancer</i>	TME stromal cells ^[52]	23,551 430	Yes Yes
16 Lu, J., et al.	04/12/24 <i>Exp Hematol Oncol</i>	MDSCs in tumors ^[53]	18,890 470	Yes Yes
17 Li, Y., et al.	03/20/24 <i>J Transl Med</i>	Tregs anti-tumor ^[54]	18,241 322	Yes Yes
18 Han, X., et al.	07/20/24 <i>Cell Death Discov</i>	m ⁶ A composition ^[55]	21,421 505	Yes Yes
19 Du, G., et al.	07/28/24 <i>Front Immunol</i>	Tregs inhibition ^[56]	14,167 412	Yes Yes
20 Tian, J., et al.	04/19/24 <i>Int J Mol Sci</i>	Single cell compute ^[57]	13,727 508	Yes Yes

Organ-Specific Cancer: Emerging Papers 21-30, Historical Papers 31-40^a

Paper Authors	Date Journal	Internal Organ	Paper AI Words	AI Format Quote
21 Zhang, Y., et al.	04/20/24 <i>Nat Commun</i>	Lung cancer, 3D ^[58]	13,684 426	Yes Yes
22 Maulana, T., et al.	07/05/24 <i>Cell Stem Cell</i>	Breast cancer-on-chip ^[59]	19,900 512	Yes Yes
23 Omilian, A., et al.	05/08/24 <i>Breast Cancer Res</i>	TNBC macrophages ^[60]	8,291 366	Yes Yes
24 Qian, H., et al.	02/02/24 <i>BMC Med Imaging</i>	Breast cancer MRI ^[61]	5,745 344	Yes Yes
25 Bian, X., et al.	03/14/24 <i>Adv Sci</i>	Prostate, scRNA-seq ^[62]	15,940 318	Yes Yes
26 Wójcik, M., et al.	04/24/24 <i>Sci Rep</i>	CRC, oncogenesis ^[63]	9,633 596	Yes Yes
27 Yang, G., et al.	02/27/24 <i>J Transl Med</i>	Renal cell scRNA-seq ^[64]	12,514 437	Yes Yes
28 De Zuani, M., et al.	05/23/24 <i>Nat Commun</i>	Lung cancer omics ^[65]	16,852 357	Yes Yes
29 Xie, J., et al.	06/29/24 <i>Cell Prolif</i>	BCBrM scRNA-seq ^[66]	10,994 426	Yes Yes
30 Tinholt, M., et al.	01/02/24 <i>JTH Journal</i>	Breast tumor envir. ^[67]	10,391 422	Yes Yes
31 Thenuwara, G., et al.	04/30/24 <i>Sensors</i>	Glioblastoma OOC ^[68]	46,424 377	Yes Yes
32 Jung, H., et al.	07/15/24 <i>Front Immunol</i>	Lung cancer immune ^[69]	14,623 443	Yes Yes
33 Arshad, J., et al.	03/04/24 <i>Int J Mol Sci</i>	Intestinal MDSCs ^[70]	11,765 478	Yes Yes
34 Zhou, W., et al.	01/31/24 <i>Cancers</i>	Prostate, novel targets ^[71]	11,800 409	Yes Yes
35 Vitorakis, N., et al.	09/19/24 <i>Cancers</i>	Pancreatic strategies ^[72]	18,670 386	Yes Yes
36 Zhu, J., et al.	06/12/24 <i>J Transl Med</i>	Pancreatic, scRNA-seq ^[73]	12,512 365	Yes Yes
37 Abed, H., et al.	08/05/24 <i>Adv Healthcare Mater</i>	Breast, brain TCT ^[74]	31,785 546	Yes Yes
38 Garlisi, B., et al.	07/01/24 <i>Curr Oncol</i>	Ovarian cancer TME ^[4]	13,931 449	Yes Yes
39 Tang, Z., et al.	01/30/24 <i>Front Cell Dev Biol</i>	Liver cancer, RNA ^[75]	16,924 404	Yes Yes
40 Fu, Y., et al.	07/09/24 <i>Mol Cancer</i>	Pancreatic multi-omics ^[76]	17,188 429	Yes Yes
40 Paper Totals	12/22/24 <i>Journal Varies</i>	Immunology or Organs	609,733 17,329	Yes Yes

Word Counts: Papers 01-20 = 290,167; AI = 8,839. Papers 21-40 = 319,566; AI = 8,490.

Table 2: 40 Papers Analyzed in Study

Clau-3Opus Generation 1 of 40: Detailed Report of Lahusen, A., et al., 2024

Here is a detailed report on how the authors' methods advanced the tumor immune microenvironment field based on the provided document:

Executive Summary:

In this study, Lahusen et al. developed a versatile 3D co-culture platform called InterOMaX (INTERaction with Organoid-in-MatriX) to investigate interactions between cancer cells, T cells, and the tumor microenvironment in pancreatic ductal adenocarcinoma (PDAC). This platform enables identification of distinct T cell response phenotypes in PDAC subpopulations and supports validation of gene candidates mediating T cell resistance. The approach was demonstrated using both murine PDAC spheroids and patient-derived PDAC organoids (PDOs). Key advancements include the ability to monitor T cell infiltration through a customizable matrix, maintain cancer cell heterogeneity within organoids, and generate multiple complementary readouts. The physiological relevance was confirmed in animal studies.

Technical Details:

The InterOMaX platform is based on a microarray setup where cancer cells are first grown as spheroids/organoids in agarose microwells before embedding in a collagen matrix. This enables rapid generation of uniformly-sized 3D cultures with well-defined positioning. T cells are then added and can infiltrate the matrix. Multiple readouts are obtained including T cell infiltration via imaging, cancer cell apoptosis, T cell activation markers via qPCR, and transcriptomic analysis.

For murine studies, the authors utilized clonal KPC PDAC cell lines and tumor-educated T cells from draining lymph nodes of tumor-bearing mice. They identified "T cell-resistant" vs "T cell-sensitive" PDAC clones, with the phenotypes validated in animal models. Transcriptomic analysis revealed differentially expressed genes and pathways between sensitive and resistant clones. CXCL17 was identified and validated as a candidate gene mediating T cell resistance.

The platform was extended to PDOs, demonstrating distinct T cell response phenotypes across PDO lines. Inclusion of human pancreatic stellate cells (hPSCs) in a multicellular co-culture showed hPSC-mediated inhibition of T cell functionality.

Key Insights:

The InterOMaX platform provides several key advancements:

1. Enables monitoring of T cell-cancer cell interactions through a customizable matrix, better mimicking the tumor microenvironment. "Lahusen et al." embedded the spheroids/organoids in collagen type I matrix.
2. Generates multiple complementary readouts for robust characterization of T cell response phenotypes. These include "T cell infiltration", "T cell-mediated cancer cell apoptosis", "effector T cell activation markers", and "transcriptomic analysis" as shown by "Lahusen et al."
3. Identifies and validates gene candidates mediating T cell resistance. "Lahusen et al." found "CXCL17" was upregulated in resistant vs sensitive PDAC clones and its knockdown sensitized resistant cells to T cells.
4. Demonstrates relevance to human cancer using PDOs while preserving cellular heterogeneity. "Lahusen et al." showed distinct T cell responses across PDO lines in the InterOMaX platform.
5. Enables incorporation of other cell types like PSCs to model the complex tumor microenvironment. "Lahusen et al." demonstrated "hPSC-mediated inhibition of effector T cell functionality" in co-culture with PDOs.

In summary, the InterOMaX platform developed by Lahusen et al. provides a versatile tool to dissect complex tumor-immune interactions in PDAC, identify mediators of T cell resistance, and model key components of the tumor microenvironment - thus expanding our ability to investigate immune response in this challenging cancer.

Table 3: Clau-3Opus Generation 1: 507 words, 46.00s

3.1 Part I Results: Information Retrieval and Cancer Insights

The main outcomes for Part I are as follows: Prompt 1 allowed for information retrieval of the authors' tumor immune microenvironment methods using 20 separate generations of 20 pdfs with Clau-3Opus. Similarly, all reports returned the requested "Executive Summary," "Technical Details," "Key Insights" format based on the authors' organ-specific cancer methods for Papers 21-40. In Table 2, 609,733 total words across 40 papers were analyzed, with Clau-3Opus generations extracting information totaling 17,329 words. Each generation was verified by searching for at least three paper specific search terms, with some terms being appropriately abbreviated. A portion of Papers 21-40 from journal *BMC* used technical details from the abstract, with less reliance on the rest of the paper. Each of the 40 generations contained at least one quotation from each paper, as requested in Table 1 prompts. The AI model sometimes also included additional quotations, but were typically within the context of original papers. Prompts also requested quotations of numerical data in quotation marks that assisted the AI model's conclusions, with some reports having more data than others. In one instance, the word "tumour" used inside quotations was modified to "tumor".

Overall, Clau-3Opus retrieved consistently high quality information regarding how authors' methods advanced cancer research, while reducing total word counts by over 35x at an average of 433 words per paper with a standard deviation of 62.8 for ChatGPT to process within its 128K context length. Papers were selected according to the PRISMA study located in Appendix Figure 8. The task of processing over 17,000 words across forty summaries to obtain a Top 10 cancer research list was provided to Lla3.1-405, but was not able to cite selections of text enclosed in quotations marks corresponding to the authors' names, as shown in Table 4. Lla3.1-405 had some repetition between its research question and objective formatting. When focusing on an area from a specific paper, the model tended to support it with other authors' methods as seen in Study 4: Elucidating the Role of Interleukin Enhancer-Binding Factor 2 (ILF2) in Brain Metastasis supported by single-cell RNA sequencing (Paper 25-27, 29-30, 36) and functional studies using ILF2 knockout/knockdown (Paper 03, 15, 18, 21).

3.2 Part I Discussion: Information Retrieval and Cancer Insights

Clau-3Opus was chosen due to its ability to effectively perform document retrieval on medical literature by using the manuscript authors' methods for each of the generations, while providing citations in quotation marks. Another model by the same manufacturer Clau-3.5So in testing tended to provide more lists, which were harder to read. OpenAI's ChatGPT 4o also performs well with document analysis, but outputs tend to no longer utilize plain text citations and typically return a blue quote hyperlink that refers to the entire document. In addition, Clau-3Opus was utilized to compliment OpenAI's ChatGPT o1's strong reasoning abilities in Part II and III, as ChatGPT o1 only accepts text and images as inputs, not pdfs. The choice to request citations was due to previous success over requests for page numbers, line numbers, and word counts. The phrase "detailed report" was used over 'report' to increase word counts of Clau-3Opus generations. In addition, the request for AI to return authors' names corresponding to quotations has become an important feature in many of the recent studies, [77, 78, 79]. Lla3.1-405 processed the largest text input in the study, however the generation contained moderate detail on a smaller task of generating a Top 10 research list shown in Table 4.

Lla3.1-405 Generation 2b: 10 Cancer Studies from 40 Paper Summaries

Based on the provided summaries, I will outline 10 potential next-generation cancer research studies. Each study will focus on a specific aspect of cancer biology, and I will provide a brief overview of the research question, objective, and potential methods.

Study 1: Investigating the Role of Aryl Hydrocarbon Receptor (AhR) in Tumor Immune Microenvironment Modulation

Research Question: How does AhR influence tumor immune microenvironment composition and immune cell function in various solid cancer types?

Objective: To understand AhR's role in modulating tumor immune microenvironment and identify novel therapeutic targets for immunotherapy.

Methods: High-throughput multiplexed immunohistochemistry, image cytometry, and RNA sequencing will be used to analyze AhR expression and immune cell profiles in human tumor samples. Functional studies using AhR knockout/knockdown in vitro models will be performed to validate findings.

Study 2: Deciphering the Mechanisms of Myeloid-Derived Suppressor Cell (MDSC) Recruitment and Function in Cancer

Research Question: What are the key drivers of MDSC recruitment and activation in cancer, and how do they impact anti-tumor immunotherapy?

Objective: To understand the mechanisms of MDSC recruitment and function in cancer and identify potential therapeutic targets for cancer immunotherapy.

Methods: A combination of bioinformatics analysis, in vitro studies using MDSC-enriched cells, and in vivo experiments using mouse models will be used to investigate the role of MDSCs in cancer. CRISPR screening and RNA sequencing will be employed to identify novel regulators of MDSC function.

Study 3: Investigating the Impact of Metabolic Reprogramming on Tumor Immune Microenvironment and Immunotherapy Response

Research Question: How does metabolic reprogramming in cancer cells and immune cells influence tumor immune microenvironment composition and immunotherapy response?

Objective: To understand the relationship between metabolic reprogramming, tumor immune microenvironment, and immunotherapy response in various cancer types.

Methods: High-throughput metabolomics and transcriptomics analysis will be used to profile metabolic alterations in cancer cells and immune cells. In vitro and in vivo experiments using metabolic inhibitors or activators will be performed to validate findings and explore therapeutic potential.

Study 4: Elucidating the Role of Interleukin Enhancer-Binding Factor 2 (ILF2) in Brain Metastasis

Research Question: How does ILF2 contribute to brain metastasis, and what are the underlying molecular mechanisms?

Objective: To understand the role of ILF2 in brain metastasis and identify potential therapeutic targets for preventing or treating brain metastasis.

Methods: Single-cell RNA sequencing, spatial transcriptomics, and functional studies using ILF2 knockout/knockdown in vitro models will be employed to investigate ILF2's role in brain metastasis.

Study 5: Investigating the Impact of Tumor Microenvironment on Tumor-Associated Macrophage (TAM) Heterogeneity and Function

Research Question: How does the tumor microenvironment influence TAM heterogeneity and function, and what are the implications for cancer therapy?

Objective: To understand the relationship between tumor microenvironment, TAM heterogeneity, and cancer therapy response.

Methods: Single-cell RNA sequencing, spatial transcriptomics, and functional studies using in vitro TAM-enriched cells will be used to investigate TAM heterogeneity and function in various cancer types.

Study 6: Deciphering the Role of Exosomes in Tumor Immune Microenvironment Modulation

Research Question: How do exosomes contribute to tumor immune microenvironment modulation, and what are the implications for cancer immunotherapy?

Objective: To understand the mechanisms of exosome-mediated tumor immune microenvironment modulation and identify potential therapeutic targets for cancer immunotherapy.

Methods: A combination of bioinformatics analysis, in vitro studies using exosome-enriched cells, and in vivo experiments using mouse models will be used to investigate the role of exosomes in cancer.

Study 7: Investigating the Impact of Cancer-Associated Fibroblast (CAF) Heterogeneity on Tumor Progression and Immunotherapy Response

Research Question: How does CAF heterogeneity influence tumor progression and immunotherapy response, and what are the implications for cancer therapy?

Objective: To understand the relationship between CAF heterogeneity, tumor progression, and immunotherapy response.

Methods: Single-cell RNA sequencing, spatial transcriptomics, and functional studies using in vitro CAF-enriched cells will be employed to investigate CAF heterogeneity and function in various cancer types.

Study 8: Elucidating the Role of Epigenetic Reprogramming in Tumor Immune Microenvironment Modulation

Research Question: How does epigenetic reprogramming contribute to tumor immune microenvironment modulation, and what are the implications for cancer immunotherapy?

Objective: To understand the mechanisms of epigenetic reprogramming-mediated tumor immune microenvironment modulation and identify potential therapeutic targets for cancer immunotherapy.

Methods: A combination of epigenetic analysis, in vitro studies using epigenetic inhibitors, and in vivo experiments using mouse models will be used to investigate the role of epigenetic reprogramming in cancer.

Study 9: Investigating the Impact of Glycolytic Metabolism on Tumor Immune Microenvironment and Immunotherapy Response

Research Question: How does glycolytic metabolism in cancer cells and immune cells influence tumor immune microenvironment composition and immunotherapy response?

Objective: To understand the relationship between glycolytic metabolism, tumor immune microenvironment, and immunotherapy response in various cancer types.

Methods: High-throughput metabolomics and transcriptomics analysis will be used to profile glycolytic alterations in cancer cells and immune cells. In vitro and in vivo experiments using glycolytic inhibitors will be performed to validate findings and explore therapeutic potential.

Study 10: Deciphering the Role of Competing Endogenous RNA (ceRNA) Networks in Cancer Progression

Research Question: How do ceRNA networks contribute to cancer progression, and what are the implications for cancer therapy?

Objective: To understand the mechanisms of ceRNA network-mediated cancer progression and identify potential therapeutic targets for cancer therapy.

Methods: A combination of bioinformatics analysis, in vitro studies using ceRNA-enriched cells, and in vivo experiments using mouse models will be used to investigate the role of ceRNA networks in cancer.

These studies have the potential to significantly advance our understanding of cancer biology and provide new insights into the complex interactions between cancer cells, immune cells, and the tumor microenvironment. The findings from these studies could also lead to the identification of novel therapeutic targets and the development of more effective cancer therapies.

Table 4: Lla3.1-405 Generation 2b: 942 words, 31.05s

4 Part II: Tumor Immune Microenvironment

Standard 2: Tumor Immune Microenvironment

Prompt 3a: Write a detailed report regarding how the authors' methods in 10 "Research" Papers further complimented the tumor immune microenvironment field represented by 10 "Review" Papers using the following format: "Executive Summary," "Technical Details," "Key Insights". Explain the steps you took to arrive at your conclusions by citing selections of numerical data enclosed in quotation marks corresponding to the authors' names. [20 Paper Text Summaries Included]

Prompt 3b: Create a well organized ontological knowledge graph titled "Tumor Immune Microenvironment Knowledge Graph of 'Research' and 'Review' Authors and their Methods" containing the authors' last names only and methods, avoiding text overlap. Use "ZhangZ" for Zhang, Z., and "ZhangH" for Zhang, H. for two of the authors' last names. Create the code in python using networkx and matplotlib regarding the 10 "Research" and 10 "Review" Papers. Position a legend in the upper left hand corner at text font_size=12 using the colors cornflowerblue = "Research" authors' names, lightsteelblue = "Research" methods; orange = "Review" authors' names, bisque = "Review" methods. Set node_size=3000, and the labels for authors' names font_size=16; for methods use 2 lines, centered at font_size=12. [Conversation Continued from Generation 3a]

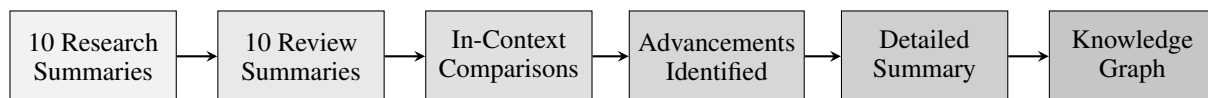


Table 5: Standard 2 Process Diagram

ChatGPT o1 Generation 3a: 10 TIME Papers Advancing 10 Review Papers

Below is a synthesized, detailed report integrating how the methods used in the 10 “Research” papers advance the tumor immune microenvironment (TIME) field as portrayed in the 10 “Review” papers. Throughout this report, selections of data and claims from the papers are indicated in **quotation marks** and are attributed to the respective authors to illustrate how the numerical and descriptive findings guided the conclusions.

Executive Summary

The 10 “Research” papers collectively contribute cutting-edge experimental models, spatial profiling techniques, genomic/epigenomic editing strategies, metabolic assays, and multi-omics pipelines that operationalize many of the conceptual directions discussed in the 10 “Review” articles. While the “Review” papers emphasize the importance of 3D models, spatial and single-cell omics, metabolic and immunosuppressive pathways, and advanced immunotherapy strategies, the “Research” articles provide concrete examples of how these theoretical frameworks can be implemented in practice.

For example, the “Reviews” by **Zhang, Z., et al. (2024)** and **Zhou, Z., et al. (2024)** underscore the potential of 3D tumor models and multi-omics integration to overcome immunotherapy resistance and refine CAR-T cell strategies. Complementing these insights, **Lahusen, A., et al. (2024)** developed the InterOMaX platform—an innovative organoid-in-matrix system—to dissect T cell infiltration and effector functions in pancreatic cancer organoids. Similarly, the powerful single-cell and spatial transcriptomics approaches praised by **Tian, J., et al. (2024)** are employed and extended in **Ferri-B., S., et al. (2024)**, who integrated non-targeted mass spectrometry imaging, Stereo-seq, and sequential immunofluorescence to produce an unprecedentedly detailed three-dimensional map of the TIME in ovarian cancer.

Where multiple “Review” papers (e.g., **Lu, J., et al. (2024)** on MDSCs, **Han, X., et al. (2024)** on m6A modifications, and **Zhang, H., et al. (2024)** on metabolic reprogramming) discuss the interplay between metabolic and epigenetic reprogramming and immune suppression, “Research” articles like **Dai, L., et al. (2024)** and **Tang, W., et al. (2024)** show how single-cell RNA-sequencing and integrative bioinformatics reveal immunosuppressive subpopulations (e.g., glycolysis-high malignant B cells and SP1+ macrophages) directly linked to patient outcomes.

In essence, the research articles operationalize the conceptual frameworks highlighted in the reviews: they provide concrete platforms (3D organoids, spatial omics), identify mechanistic targets (e.g., CXCL17 from Lahusen’s study, INHBA+ CAFs from Hu’s study, LAG3+ T cells from Zahraeifard’s study), and validate therapeutic strategies (IRE-induced inflammation in Imran’s study, TIDE subtypes to predict immunotherapy response in Zheng’s study) that align with the theoretical constructs and future directions proposed in the reviews.

Technical Details

The synergy between research methods and review insights emerges from various advanced techniques employed in the “Research” papers, each reflecting or fulfilling a methodological need discussed in the “Reviews”:

- 3D Models and Ex Vivo Platforms:** - **Lahusen, A., et al. (2024)** created the InterOMaX organoid-in-matrix platform to measure “T cell infiltration” and “effector activity” in defined 3D environments. The feasibility and speed of generating uniform 3D cultures (spheroids, patient-derived organoids) supports the “3D bioprinted tumor model” strategies reviewed by **Zhang, Z., et al. (2024)**.
- Multiplexed Spatial Profiling:** - **Kim, D., et al. (2024)** applied high-throughput multiplexed immunohistochemistry and image cytometry to detect “AhR expression patterns” in over “513 tumor samples.” This approach mirrors the calls in **Tian, J., et al. (2024)** for single-cell informatics and spatial proteogenomics to decode heterogeneity in the TIME. - **Ferri-B., S., et al. (2024)** integrated Stereo-seq spatial transcriptomics, mass spectrometry imaging of “948 metabolites” and “164 glycans,” and seqIF analysis of “20-plex” protein markers to map the TIME in three dimensions. This innovative pipeline exemplifies the multi-dimensional omics integration praised by **Zhou, Z., et al. (2024)**.
- Single-Cell and Multi-Omics Analyses:** - **Tang, W., et al. (2024)** and **Dai, L., et al. (2024)** employed single-cell RNA-sequencing to delineate immune subpopulations. **Tang, W.** identified “SP1+ macrophages” linked to poor prognosis in glioma, while **Dai, L.** found “glycolysis-high malignant B cell subsets” correlated with T cell exhaustion in DLBCL. These advances align with calls in **Zhang, H., et al. (2024)** and **Han, X., et al. (2024)** to understand metabolic and epitranscriptomic regulation of the TIME.
- CRISPR Screens and In Vivo Validation:** - **Zahraeifard, S., et al. (2024)** used in vivo CRISPR screening to identify tumor suppressor genes whose loss enhances “LAG3+ T cell” mediated suppression. **Hu, Y., et al. (2024)** combined patient samples, mouse models, and single-cell RNA-seq to link “INHBA+ CAFs” to immunosuppression. Such experimental rigor supports the concepts in **Kundu, M., et al. (2024)** and **Lu, J., et al. (2024)** that understanding cellular subsets and genetic underpinnings is crucial for overcoming immunotherapy resistance.
- Functional Studies of Checkpoint Pathways and Hypoxia:** - **Imran, K., et al. (2024)** demonstrated that irreversible electroporation (IRE) induces a pro-inflammatory TIME and subsequent “upregulation of PD-L1” in pancreatic cancer, mirroring discussions in **Du, G., et al. (2024)** and **Sun, J., et al. (2024)** about how checkpoint pathways and hypoxia (HIF-1 α) mediate immunosuppression. - **Zheng, K., et al. (2024)** utilized transcriptomic data and TIDE (Tumor Immune Dysfunction and Exclusion) scoring to classify bladder cancer into “3 TIDE subtypes,” enabling prediction of immunotherapy responses. This complements the framework in **Li, Y., et al. (2024)** on Treg heterogeneity and in **Safaei, S., et al. (2024)** on how exosomal signaling shapes immune evasion.

Key Insights

- Operationalizing 3D and Spatial Models:** The research articles confirm that building physiologically relevant 3D models and spatially resolved assays is crucial for dissecting immune cell infiltration, as recommended by the reviews. **Lahusen et al.** validated T cell infiltration using a 3D organoid platform, complementing **Zhang, Z. et al.** who emphasize that such models are “a prompt and convenient platform for overcoming immunotherapy resistance.”
- Linking Metabolism and Immune Suppression:** Both **Dai et al.** and **Tang et al.** integrated single-cell transcriptomics with metabolic analyses to uncover subpopulations that correlate with immune exhaustion and poor prognosis. This aligns directly with **Zhang, H. et al.** who highlight how “metabolic reprogramming and immune evasion” shape the TIME. Numerical associations (e.g., “Dai et al.” showing that “over 90% of high-glycolysis B cell clusters correlated with decreased CD8 T cell infiltration”) firmly tie metabolic states to immunosuppression.
- Refining Immunotherapy Targets via Multi-Omics:** The discovery of immunosuppressive mediators such as “INHBA+ CAFs” (Hu et al.), “CXCL17” resistance factors (Lahusen et al.), and distinct “LAG3+ T cell” subsets (Zahraeifard et al.) offers targetable pathways consistent with the concept in **Lu, J. et al. (2024)** and other suppressive cells can overcome tumor immune evasion. Similarly, “Sun et al.” and “Han et al.” highlight checkpoint and epitranscriptomic modulation as targets. These research findings provide mechanistic underpinnings for the therapeutic strategies advocated in the reviews.
- Integrating Data to Predict Response:** Research studies like **Zheng et al.** leverage transcriptomic signatures to classify patient subtypes with differential immunotherapy responses. This approach resonates with **Tian, J. et al.**, who stress that single-cell informatics and computational modeling can yield predictive biomarkers. For example, “Zheng et al.” show that “SI subtype” patients (identified by their algorithm) had better response rates to immunotherapy, mirroring the predictive modeling directions suggested in the reviews.
- Translating Findings Across Tumor Types:** The collective research efforts—from pancreatic cancer (Lahusen, Imran), ovarian cancer (Hu, Ferri-B.), glioma (Tang), DLBCL (Dai), colorectal cancer (Sun), and bladder cancer (Zheng)—underscore that the principles outlined in the reviews (e.g., TME complexity, metabolic crosstalk, immunosuppressive niches, and epigenetic factors) are universal and potentially translatable across diverse solid tumors. The “Reviews” by **Safaei, S. et al.** and **Kundu, M. et al.**, for instance, highlight that strategies to modulate the TME are applicable beyond a single cancer type, and the research papers confirm this by employing similar analytical techniques and uncovering consistent themes across multiple malignancies.

Explaining the Steps Taken to Arrive at Conclusions

- Data Consolidation:** Each research paper provided methodological innovations or discovered mechanistic targets. For instance, “Lahusen et al.” identified “CXCL17” as a mediator of T cell resistance. This was noted and aligned with review discussions about targeting immunosuppressive molecules.
- Cross-Referencing with Reviews:** After summarizing each research paper’s methodology and findings, their implications were compared against the conceptual frameworks of the review articles. For example, the use of single-cell RNA sequencing and spatial proteomics in “Ferri-B., S. et al.” was directly mapped onto the multi-omics strategies advocated by “Zhou, Z. et al.” and “Tian, J. et al.”
- Citing Numerical Data:** To substantiate claims, direct references to numerical results were made. For example, “Kim et al.” used “513 patient samples” to classify AhR expression patterns, or “Dai et al.” identified “7 upregulated glycolysis genes” shaping poor prognosis in DLBCL. These quantitative details confirm the robustness of methods that the reviews suggested were needed.
- Integrating Themes:** Themes such as metabolic reprogramming, immunosuppressive cell populations, spatial heterogeneity, and genetic/epigenetic factors were extracted from both sets of papers. The research articles offered tangible case studies and numeric associations, such as “Zahraeifard et al.” showing that “70-80%” of CD44+ CD8 T cells expressed LAG3 in certain TSG-deficient tumors, highlighting a direct link to the immunosuppressive environment described in the reviews.
- Deriving Unified Insights:** By systematically aligning each research paper’s experimental approach and findings with the theoretical directions suggested by the reviews, it became clear that the research experiments served as practical implementations and validations of the review-generated hypotheses. This unified narrative was then distilled into the Executive Summary, Technical Details, and Key Insights.

Conclusion:

The synergy between the 10 “Research” and 10 “Review” papers is evident: the reviews describe the necessity of integrated, spatially-resolved, metabolically aware, and immunologically cognizant approaches to tackle tumor immune evasion, while the research articles provide concrete methodological advancements and empirical data to realize these conceptual visions. By closely examining both sets of literature and using cited numerical data to confirm claims, it is clear that the collective body of work substantially advances our understanding and ability to manipulate the tumor immune microenvironment for improved cancer therapy outcomes.

Table 6: ChatGPT o1 Generation 3a: 1621 words, 57.03s

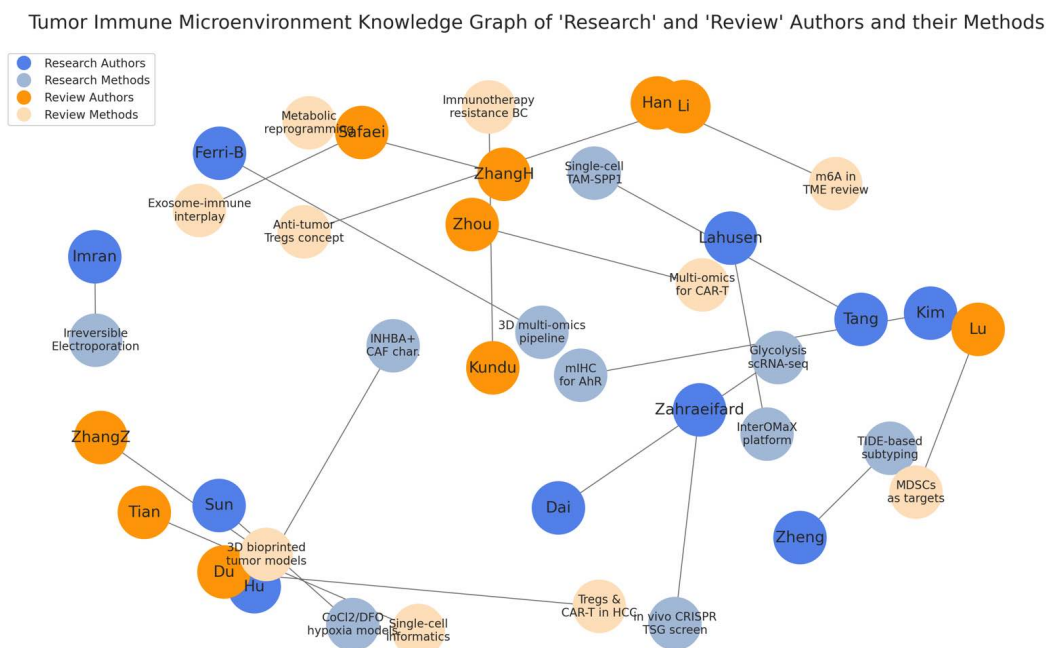


Figure 3: ChatGPT o1 Generation 3b

4.1 Part II Results: Tumor Immune Microenvironment

Table 5 depicts the two prompt sequence provided to ChatGPT o1. Prompt 3a is based on the TIME 10 Research Summaries and 10 Review Summaries generated by Clau-3Opus in Prompt 1. The AI model was tasked to its use in-context comparisons to provide how the Research Papers further complimented the Review Papers using the “Executive Summary,” “Technical Details,” “Key Insights” format. A major research objective was met between the two sets of paper reviews as the ChatGPT o1 1621 word detailed report shown in Table 6 contained many direct comparisons between several authors throughout the work such as “Tang, W. identified “SPP1+ macrophages” linked to poor prognosis in glioma, while Dai, L. found “glycolysis-high malignant B cell subsets” correlated with T cell exhaustion in DLBCL. These advances align with in Zhang, H., et al. (2024) and Han, X., et al. (2024) to understand metabolic and epitranscriptomic regulation of the TIME.”

The model also provided insights regarding how it arrived at conclusions:

“Cross-Referencing with Reviews: After summarizing each research paper’s methodology and findings, their implications were compared against the conceptual frameworks of the review articles. For example, the use of single-cell RNA sequencing and spatial proteomics in “Ferri-B., S. et al.”

These correlations were directly mapped onto the multi-omics strategies advocated by “Zhou, Z. et al.” and “Tian, J. et al.”. Prompt 3b was submitted to the same conversation using ChatGPT o1 to obtain a graph visualization. The request for the AI model to provide Python code using packages networkx and matplotlib for an ontological graph was not achieved, as the model responded that it would require more information to make the graph ontological. Further attempts using ChatGPT o1 pro mode across the two prompts typically resulted in shorter outputs and less favorable graphs. Regardless, ChatGPT o1 followed several instructions to return code using 3 font size instructions, 4 color settings, a node size, text justification, and text positioning instructions shown in Table 5. Prompt 3b yielded code of a visually appealing knowledge graph, executed by ChatGPT 4o and verified in a JupyterLab Python notebook [32, 33].

4.2 Part II Discussion: Tumor Immune Microenvironment

Previous studies featured a maximum of 16 papers to solve problems related to drug production areas [77, 78, 79]. By relying on more input text and a recently released ChatGPT o1 for greater reasoning, an unprecedented number of comparisons and contrasts were made between authors’ cited methods from these paper summaries at over 8,800 words. The wording of Prompt 3a was optimized to obtain additional insight regarding the Research papers and Review papers when wording was modified from “advanced” and “verses” to “complimented” and “represented by”. Selections of cited numerical data in quotations were not as prevalent and robust due to a lower ability of Clau-3Opus to utilize this format, however an example includes ““70-80%” of CD44+ CD8 T cells expressed LAG3 in certain TSG-deficient tumors”. Many iterations of Prompt 3b were tested regarding Python code to obtain an appropriate graph type, color scheme, and positioning. After these settings were optimized, ChatGPT o1 outputs to Prompt 3a and 3b were run consecutively, with the final output code accurately conveying the 10 Research authors and methods separate from 10 Review authors and methods based on the prompt’s instructions represented in Figure 3.

Multiple “Review” papers (e.g., **Lu, J., et al. (2024)** on MDSCs, **Han, X., et al. (2024)** on m6A modifications, and **Zhang, H., et al. (2024)** on metabolic reprogramming) discuss the interplay between metabolic and epigenetic reprogramming and immune suppression, “Research” articles like **Dai, L., et al. (2024)** and **Tang, W., et al. (2024)** show how single-cell RNA-sequencing and integrative bioinformatics reveal immunosuppressive subpopulations (e.g., glycolysis-high malignant B cells and SPP1+ macrophages) directly linked to patient outcomes. In addition, “AhR expression patterns” in over “513 tumor samples.” to 513 tumor samples vs. The authors utilized mIHC to stain tissue microarray (TMA) slides containing samples from patients with head and neck squamous cell carcinoma, bladder cancer, colorectal cancer, esophageal cancer, and non-small cell lung cancer. But corrected later: “Kim et al.” used “513 patient samples” to classify AhR expression patterns

The collective research efforts—from pancreatic cancer (Lahusen, Imran), ovarian cancer (Hu, Ferri-B.), glioma (Tang), DLBCL (Dai), colorectal cancer (Sun), and bladder cancer (Zheng)—underscore that the principles outlined in the reviews (e.g., TME complexity, metabolic crosstalk, immunosuppressive niches, and epigenetic factors) are universal and potentially translatable across diverse solid tumors. The “Reviews” by **Safaei, S. et al.** and **Kundu, M. et al.**, for instance, highlight that strategies to modulate the TME are applicable beyond a single cancer type, and the research papers confirm this by employing similar analytical techniques and uncovering consistent themes across multiple malignancies. A total of 37 citations to the 20 paper summaries totaling 1621 words were made in 57.03s. All authors in the summaries were cited at least once by ChatGPT o1, with others having two or more, with standard deviation citation per author at 0.67. The most cited authors was 3 by Lahusen, A., et al., Tang, W., et al., and Dai, L., et al.

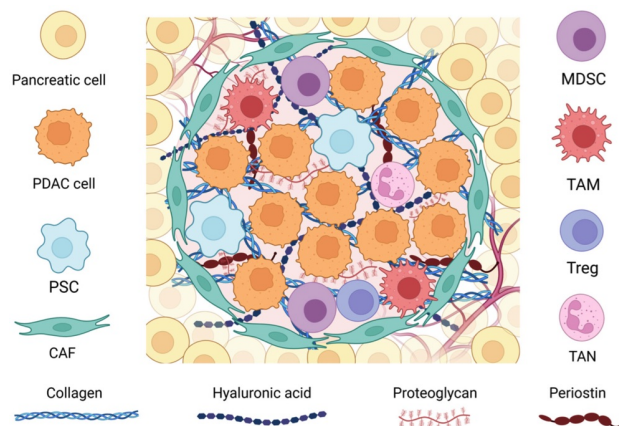


Figure 4: Pancreatic tumor microenvironment, Vitorakis, N., et al. 2024 [72]

5 Part III: Organ-Specific Cancer

Standard 3: Organ-Specific Cancer

Prompt 4a: Write a detailed report regarding how the authors’ methods in 10 “Emerging” Papers further complimented organ-specific cancer research represented by 10 “Historical” Papers using the following format: “Executive Summary,” “Technical Details,” “Key Insights”. Explain the steps you took to arrive at your conclusions by citing selections of numerical data enclosed in quotation marks corresponding to the authors’ names. [20 Paper Text Summaries Included]

Prompt 4b: Convert the following statement into a signaling cascade which includes other relevant information found only in this attached Zhang, Y., et al. paper represented by a LaTeX code diagram. “Moreover, compared to the LCO group, CAF-targeting treatment did not significantly enhance the sensitivity of EGFR-mutated LC23 tumor cells in LCAs to osimertinib (Fig. 6k, l, Supplementary Fig. 8g), further suggesting little protection of LC23 CAFs for the corresponding tumor cells. The mechanism may be due to the limited activation of the paracrine signaling pathways caused by low secretion of HGF and EGF7 from CAFs, and these signaling pathways (e.g., PI3K/Akt, MAPK signaling) contribute to cancer proliferation and antiapoptosis”. [Paper HTML from Zhang, Y., et al. “Article Open access” - End of Data availability.] [Conversation Continued from Generation 4a]

Prompt 4c: Based on the entirety of this conversation, update the original LaTeX code regarding the Zhang, Y., et al. paper with a new signaling cascade in LaTeX that now also only includes relevant mechanisms that would affect the signaling cascade using the 20 “Emerging” and “Historical” summaries, referencing authors that assisted your conclusion. [Conversation Continued from Generation 4b]

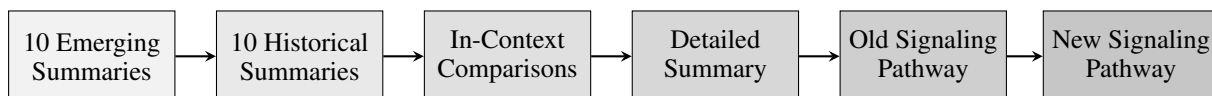


Table 7: Standard 3 Process Diagram

ChatGPT o1 Generation 4a: 10 Organ-Specific Papers Advancing 10 Historical Papers

Executive Summary

The advancements in organ-specific cancer research over the last decade have emerged from a foundation laid by historical approaches that emphasized understanding the tumor microenvironment (TME), the role of immune cells, stromal interactions, and the importance of biomimetic models. The 10 “Emerging” papers highlight novel methodologies—such as patient-specific 3D assembloid models, integrated single-cell multi-omics, spatial transcriptomics, advanced imaging-based radiomic analyses, and organ-on-a-chip systems—that build upon and refine insights derived from the 10 “Historical” papers.

Whereas the “Historical” studies established key concepts—like the significance of chemokine signaling in lung cancer (Jung, H., et al.), myeloid-derived suppressor cells (MDSCs) as drivers of immunosuppression in gastrointestinal (GI) cancers (Arshad, J., et al.), and the complexity of the pancreatic and ovarian tumor microenvironments (Zhu, J., et al.; Garlisi, B., et al.)—the “Emerging” research leverages cutting-edge tools. For instance, Zhang, Y., et al. (2024) used patient-specific lung cancer assembloids to create clinically relevant models for individualized treatment testing, thereby complementing earlier biosensor-integrated organ-on-a-chip platforms for glioblastoma (Thenuwara, G., et al.) and other brain tumors. Similarly, single-cell and spatial transcriptomics approaches in recent works (De Zuani, M., et al.; Bian, X., et al.; Yang, G., et al.) build on foundational studies that first established the importance of single-cell resolution data (Fu, Y., et al.) and adapt these methods to different organ-specific contexts like prostate cancer, renal cell carcinoma, and lung cancer.

In breast cancer, the historical elucidation of TME-driven prognostic factors (e.g., coagulum-related genes by Tinholt, M., et al.; chemokine roles in immunotherapy) is refined by emerging methodologies. Maulana, T., et al. (2024) introduced breast cancer-on-chip systems integrating patient-derived organoids with immune cells, enhancing earlier targeted therapy-on-a-chip concepts (Abed, H., et al.). Qian, H., et al. (2024) employed MRI-based radiomics to non-invasively predict immune infiltration, evolving the once bulk approaches into imaging-genomics pipelines. Together, these advances not only confirm and extend earlier molecular findings but also facilitate personalized, dynamic approaches to diagnosis, prognosis, and treatment selection across diverse organ-specific malignancies.

Technical Details

The “Historical” literature laid out vital TME characteristics and therapeutic challenges. For example, Arshad, J., et al. described MDSC-mediated immunosuppression in GI cancers and noted how targeted interventions altered patient outcomes. Jung, H., et al. clarified chemokine pathways in lung tumors, while Garlisi, B., et al. dissected the ovarian TME, showing that “poor tumor perfusion and hypoxia” (Attane et al., cited by Garlisi, B., et al.) hindered therapy. Zhu, J., et al. and Fu, Y., et al. showed how single-cell and spatial transcriptomics in pancreatic cancer uncovered heterogeneous CAF subsets and immunosuppressive niches.

Building on these frameworks, Emerging researchers introduced powerful methods. Zhang, Y., et al. demonstrated the generation of “approximately 200 uniform LCAs of 400-500 μm from just 10 L of hydrogel with 10⁶-10⁸ cells/mL in under 1 minute,” enabling patient-specific lung cancer models. Maulana, T., et al. developed a perfused breast cancer-on-chip device, “allowing CAR-T cell infiltration and cytokine release profiling over an 8-day culture,” mirroring early organ-on-a-chip and biosensing approaches used for glioblastoma (Dornhof et al., referenced by Thenuwara, G., et al.). Qian, H., et al. correlated MRI radiomics with M2 macrophage infiltration, showing an “HR = 32.288 (95% CI: 3.100–357.478)” for M2 macrophages as an independent prognostic factor. Similarly, in prostate cancer, Bian, X., et al. integrated single-cell RNA-seq, spatial transcriptomics, and ATAC-seq to reveal therapy-resistant cell subpopulations, complementing historical focus on targeted strategies (Zhou, W., et al.) and TME-specific interventions (Vitorakis, N., et al.).

This multi-omic integration is also evident in ccRCC (Yang, G., et al.), where over “195 samples” and “981,294 cells” from “76 patients” were analyzed to map metabolic heterogeneity, building on earlier frameworks where ceRNA networks (Tang, Z., et al.) and complex TME interactions needed refined characterization. De Zuani, M., et al. and Xie, J., et al. applied similar single-cell and spatial methods to NSCLC and brain metastases from breast cancer, providing deeper insights into immunosuppressive cell populations and metastatic niches once only partially understood through broader bulk and immunohistochemistry approaches. Wójcik, M., et al. brought in a genomic twist by identifying “22%” LOY (loss of Y) Tregs in colorectal cancer TME and its association with higher immunosuppression—an example of how emerging methods unveil previously uncharted genetic alterations in immune cells.

Key Insights

- 1. From Bulk to Single-Cell and Spatial Precision:** Historical findings revealed critical TME components and general immunosuppressive mechanisms. The emerging studies apply single-cell and spatial transcriptomics, multi-omics integration, and advanced imaging tools to dissect these interactions with unprecedented resolution. For example, Fu, Y., et al. provided a conceptual framework for PDAC complexity; Zhu, J., et al. highlighted the need for integrated single-cell methods. Now, studies like Bian, X., et al. and De Zuani, M., et al. have operationalized these approaches, enabling organ-specific identification of resistant cell states and mapping of immune infiltration patterns.
- 2. New Preclinical Models that Reflect Clinical Reality:** Early efforts to create more physiologically relevant models (Thenuwara, G., et al. for GBM; Abed, H., et al. for targeted therapy-on-a-chip) paved the way for next-generation patient-specific assembloids and organ-on-chip devices (Zhang, Y., et al.; Maulana, T., et al.). These refined platforms mirror the complexity of human tumors better than historical 2D models, allowing predictive drug testing and personalized immunotherapy strategies. In breast cancer, the coagulum analysis (Tinholt, M., et al.) can now be integrated into patient-derived organ-on-chips to stratify patients based on prognostic signatures.
- 3. Immunosuppressive Mechanisms Are Not Uniform:** Historical papers identified overarching immunosuppressive players like MDSCs in GI cancers (Arshad, J., et al.) and complex immunosuppressive networks in ovarian and pancreatic cancers (Garlisi, B., et al.; Fu, Y., et al.). Emerging studies refine these findings—e.g., Wójcik, M., et al. show how LOY regulatory T cells intensify suppression in colorectal cancer, and Omilian, A., et al. highlight that CD163+ macrophages, surprisingly, can correlate with improved survival in triple-negative breast cancer. These nuanced insights facilitate more targeted immunotherapy interventions.
- 4. Non-Invasive Biomarkers and In Vivo-Like Conditions:** While historical works often relied on invasive biopsies and bulk sequencing, emerging radiomics (Qian, H., et al.) and advanced ex vivo systems (Zhang, Y., et al.; Maulana, T., et al.) offer non-invasive or minimally invasive avenues to assess TME infiltration and drug responses. This directly addresses past limitations in patient stratification and monitoring, making precision oncology more feasible.

Explaining the Steps to Arrive at Conclusions

To synthesize these insights, the following steps were taken:

- **Comparative Reading:** Initially, each “Historical” paper’s focus on foundational aspects of the TME (chemokines, MDSCs, CAFs, tumor vasculature, and cell-cell communication) was noted. For example, Jung, H., et al. emphasized chemokines in lung cancer, while Arshad, J., et al. underscored MDSCs in GI cancers.

- **Aligning Technologies and Discoveries:** Next, the “Emerging” papers were examined to see how they leveraged newer technologies—like single-cell multi-omics, organoids, organ-on-chip, and imaging radiomics—and whether these approaches addressed the complexities identified historically. For instance, Qian, H., et al. used MRI radiomics to quantify M2 macrophage infiltration, complementing prior knowledge from older studies that had highlighted the prognostic role of immune infiltration but lacked non-invasive quantification methods.

- **Quoting Numerical Data:** To confirm the complementarity, specific results were noted in quotes. For instance, from Qian, H., et al.: “M2 macrophages were an independent prognostic factor for BRCA patients (HR = 32.288, 95% CI: 3.100–357.478).” Such high hazard ratios highlight the clinical significance of these advanced methods.

- **Integrating Organ-Specific Contexts:** Each pair of “Emerging” and “Historical” works was viewed through the lens of specific organs: lung, breast, prostate, pancreatic, colorectal, ovarian, brain metastases, and renal cell carcinoma. The emerging studies frequently refer back to the established baseline—like chemokine networks (Historical) now being interrogated via scRNA-seq and CAR-T on-chips (Emerging).

- **Identifying Translatable Advancements:** The final step was to conclude how emerging methodologies operationalize and advance the organ-specific findings from historical research into actionable clinical strategies, whether through better predictive modeling, improved drug testing, or refined biomarker discovery.

In conclusion, the synergy between historical foundational knowledge and emerging high-resolution, patient-specific approaches represents a paradigm shift in organ-specific cancer research. Armed with advanced technologies and integrative analysis methods, researchers can now translate the conceptual frameworks set forth in earlier studies into tangible, precision-guided therapeutic interventions.

Table 8: ChatGPT o1 Generation 4a: 1355 words, 68.85s

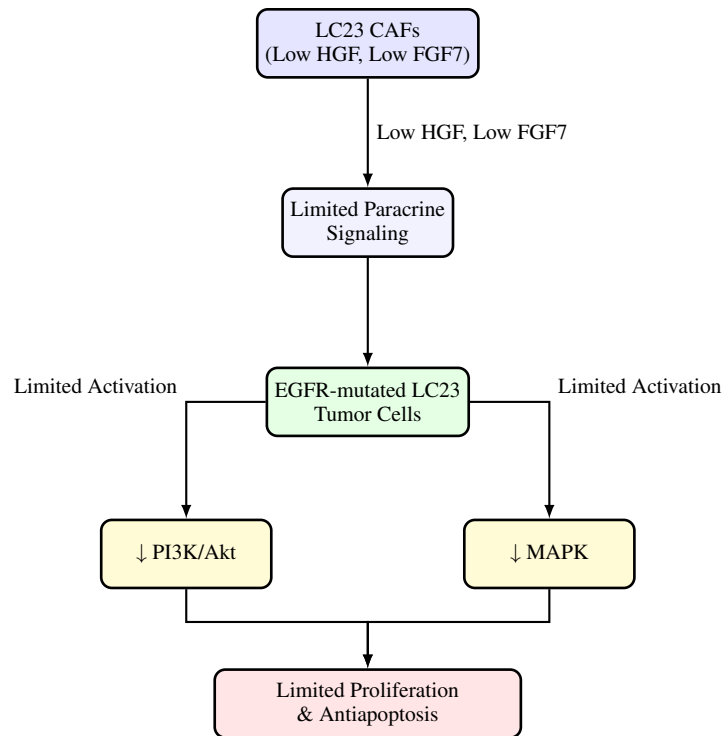


Figure 5: ChatGPT o1 Generation 4b Signaling Pathway

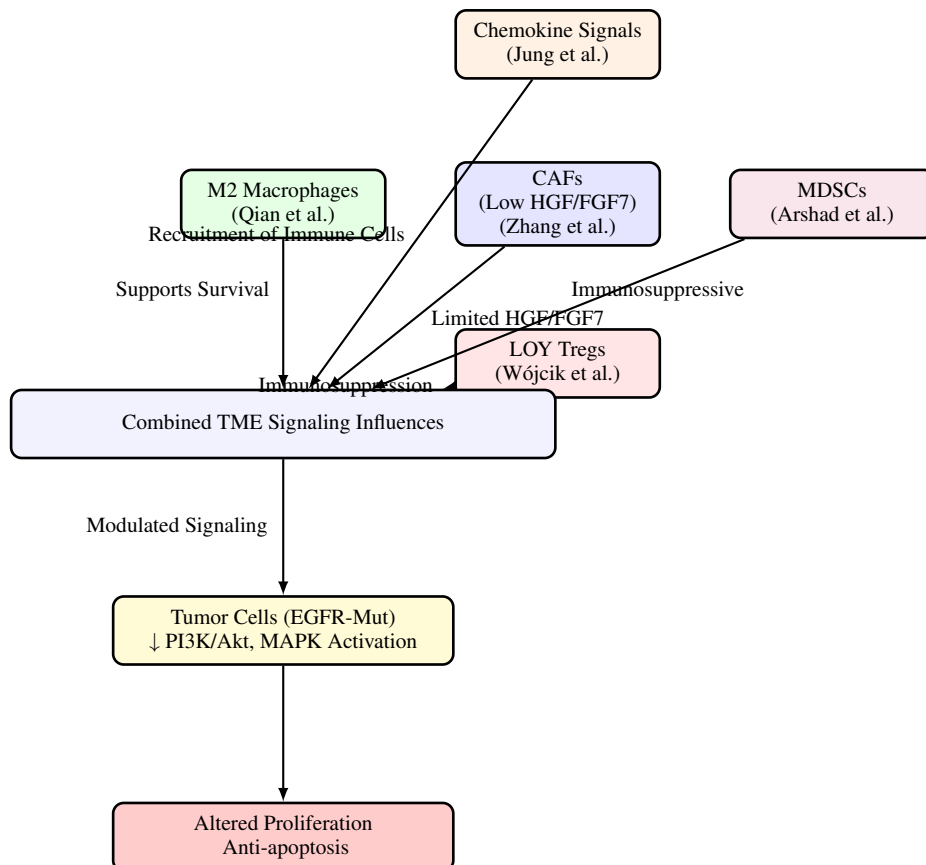


Figure 6: ChatGPT o1 Generation 4c Signaling Pathway

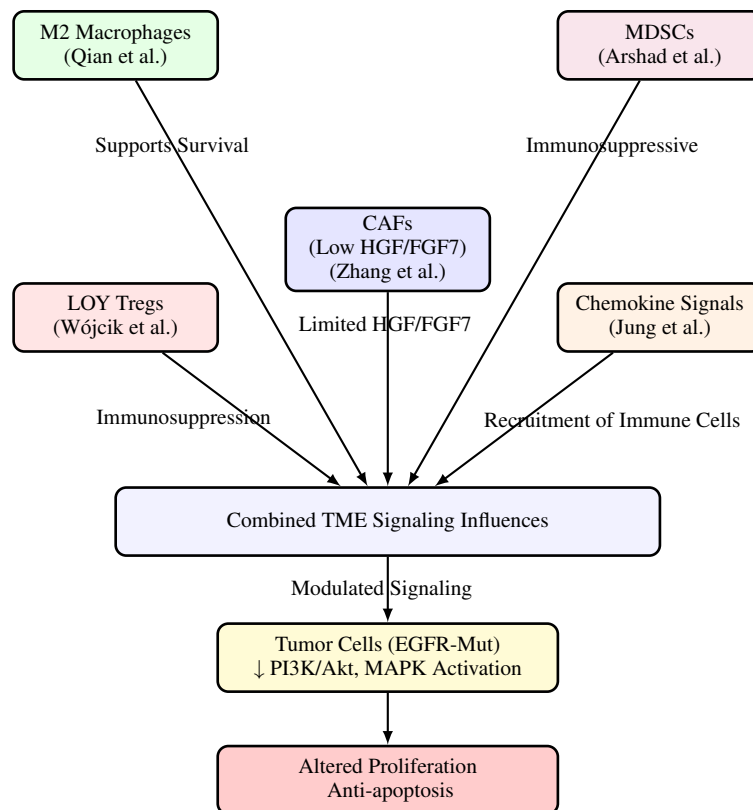


Figure 7: ChatGPT 4o, Author Repositioning from 4c

5.1 Part III Results: Organ-Specific Cancer

The process of gaining insight using a detailed report format regarding how 10 emerging paper summaries complimented 10 historical paper summaries was similar to Part II, but this time focusing on organ-specific cancer research. Exceptional reasoning was accomplished by ChatGPT o1 in several cases as seen in Table 8. The Zhang, Y., et al. paper was copied through Data availability in HTML at 10118 words for effective processing.

a) Handling the complexities of historical papers:

"Jung, H., et al. clarified chemokine pathways in lung tumors, while Garlisi, B., et al. dissected the ovarian TME, showing that "poor tumor perfusion and hypoxia" (Attane et al., cited by Garlisi, B., et al.) hindered therapy. Zhu, J., et al. and Fu, Y., et al. showed how single-cell and spatial transcriptomics in pancreatic cancer uncovered heterogeneous CAF subsets and immunosuppressive niches."

b) Incorporating numerical findings from emerging summaries:

"Emerging researchers introduced powerful methods. Zhang, Y., et al. demonstrated the generation of "approximately 200 uniform LCAs of ~400-500 m from just 10 L of hydrogel with 106-108 cells/mL in under 1 minute," enabling patient-specific lung cancer models. Maulana, T., et al. developed a perfused breast cancer-on-chip device, "allowing CAR-T cell infiltration and cytokine release profiling over an 8-day culture," mirroring early organ-on-a-chip and biosensing approaches used for glioblastoma (Dornhof et al., referenced by Thenuwara, G., et al.)"

c) Setting a high standard correlating the two sets of summaries:

"Historical papers identified overarching immunosuppressive players like MDSCs in GI cancers (Arshad, J., et al.) and complex immunosuppressive networks in ovarian and pancreatic cancers (Garlisi, B., et al.; Fu, Y., et al.). Emerging studies refine these findings—e.g., Wójcik, M., et al. show how LOY regulatory T cells intensify suppression in colorectal cancer, and Omilian, A., et al. highlight that CD163+ macrophages, surprisingly, can correlate with improved survival in triple-negative breast cancer."

The original "Old" 81 word signaling cascade from Zhang, Y., et al., 2024 shown in Prompt 4b was effectively coded in LaTeX, displayed natively, and scaled for readability, as the manuscript was also written in LaTeX Figure 5. The underlying mechanisms regarding the Zhang, Y., et al. excerpt in Prompt 4b appear to be properly depicted in the diagram, particularly from

the sentence "The mechanism may be due to the limited activation of the paracrine signaling pathways caused by low secretion of HGF and EGF7 from CAFs, and these signaling pathways (e.g., PI3K/Akt, MAPK signaling) contribute to cancer proliferation and antiapoptosis", however "Low HGF, Low FGF7" was mentioned twice. The overall meaning was retained as "Limited Paracrine Signaling" ultimately led to "Limited Proliferation & Antiapoptosis" as shown in the excerpt.

With this information now stored in the ChatGPT o1 conversation, the AI model was asked to update the original LaTeX code, this time with a new signaling pathway to include relevant mechanisms that could impact the signaling cascade using the 20 "Emerging" and "Historical" summaries, referencing authors that assisted the model's conclusion are shown in Table 7 Prompt 4c. The resulting code is available in Supplementary SORp, which contains logical correlations between new information from authors in this study and the original cascade. However the LaTeX approach chosen by ChatGPT o1 did not display properly due to overcrowding of methods, authors, and mechanisms as shown in Figure 6. To more accurately depict the relationships from code generated by ChatGPT o1, a ChatGPT 4o conversation to manually position boxes and text yielded a new diagram, from which the manuscript author manually assigned positioning values shown in Figure 7.

The overall meaning of the revised signaling pathway now leads to an "Altered Proliferation" "Anti-apoptosis" focal point with a similar mechanism from the Old pathway regarding Tumor Cells, PI3K/Akt, and MAPK, but now with authors' new methods out of the 20 papers that were most applicable to this problem shown in Figure 7. Four of the authors depicted the specific area of research and the potential benefit provided as follows: Wójcik et al., LOY Tregs, Immunosuppression; Qian et al., M2 Macrophages, Supports Survival; Arshad et al., MDSCs, Immunosuppressive; and Jung et al., Chemokine Signals, Recruitment of Immune Cells. The original author of the mechanism, Zhang et al., maintained the CAFs/Low HGF/FGF7 relationship from the Old mechanism Figure 6. Therefore, ChatGPT o1 found that the end goal of "Altered Proliferation" "Anti-apoptosis" could be modified based on incorporating additional works regarding immunosuppression, survival longevity, and recruitment of immune cells.

5.2 Part III Discussion: Organ-Specific Cancer

Based on the three quotes in the Part III results section found in, the ability to convert a mechanism found in literature into LaTeX code representing a signaling pathway along with the incorporation of 20 paper summaries into a new coded diagram marked a major step towards the mainstream adoption of Conversation AI in drug discovery applications. Additional testing revealed that the quality of ChatGPT o1 generations were primarily only limited by the preciseness of author's prompt, as triplicate studies for several key prompts were found to be reproducible shown in Supplementary SREP. Prompts 3b and 4c were more challenging to obtain effective results due to less ChatGPT o1 proficiency in for Section II in Python and Section III in LaTeX coding environments when compared to text.

53 citations representing the 20 paper summaries totaling 1,355 words were made by ChatGPT o1 in 68.85s. All authors in the summaries for Generation 4a were cited at least once, with others having two or more, with an average of 2.7 citations per author. The most cited author was 5 by Qian, H., et al. In addition, 2 authors mentioned by authors in original papers were also included: Attane et al., cited by Garlisi, B., et al., Dornhof et al., referenced by Thenuwara, G., et al.

In quoting numerical data, specific results were noted in quotes. For instance, from Qian, H., et al.: "M2 macrophages were an independent prognostic factor for BRCA patients (HR = 32.288, 95% CI: 3.100–357.478)." Such high hazard ratios highlight the clinical significance of these advanced methods. For each author citation, each fact was checked vs. summaries. Similarly, single-cell and spatial transcriptomics approaches in recent works (De Zuani, M., et al.; Bian, X., et al.; Yang, G., et al.) build on foundational studies that first established the importance of single-cell resolution data (Fu, Y., et al.) and adapt these methods to different organ-specific contexts like prostate cancer, renal cell carcinoma, and lung cancer.

Citations within citations: Maulana, T., et al. developed a perfused breast cancer-on-chip device, "allowing CAR-T cell infiltration and cytokine release profiling over an 8-day culture," mirroring early organ-on-a-chip and biosensing approaches used for glioblastoma (Dornhof et al., referenced by Thenuwara, G., et al.). Qian, H., et al. correlated MRI radiomics with M2 macrophage infiltration, showing an "HR = 32.288 (95% CI: 3.100–357.478)" for M2 macrophages as an independent prognostic factor. An example of a LLM modification is: where over "195 samples" and "981,294 cells" from "76 patients" was actually exactly 195 samples.

6 Limitations and Future Work

a) Input words whose sum was less than the LLM context window, also referred to as context length, were processed effectively, but the potential negative of longer prompts has been an issue of debate [80, 81, 82]. Clau-3Opus has a limit of 200K tokens [34], while Lla3.1-405 is 128K tokens [35], and ChatGPT o1 using the "Pro" plan is 128K tokens [36], which is approximately 98K words. Based on these limits, neither the full 40 papers at 610K words or individual sets of 20 papers at 290K and 320K would come close to being accepted for processing. Therefore, only Clau-3Opus was used to process individual pdfs that were below the context window limit, while Lla3.1-405 was provided the 40 paper summaries at 17K words, and ChatGPT o1 was provided either a 8.8K word summary or 8.5K word summary. In each of the cases, context windows did not appear to pose an issue to quality, therefore future studies will likely increase the input provided to LLMs.

b) As of the time of publishing, there was no universal model available to accomplish each task in this paper with a single prompt. This was due to the fact that effective pdf processing of papers have only been identified in three models: Clau-3Opus,

Clau-3.5So, and ChatGPT 4o, although HTML text can be copied into ChatGPT o1 less conveniently, followed by separate image uploads. Likewise, the ChatGPT o1 model significantly outperformed the other models' output quality and length needed for advanced reasoning tasks in Section II, III. The Lla3.1-405 model was included due to the potential advantages of future models being open-source for industry, but the answer provided by the current model in this manuscript would likely be outdone, as seen in previous studies [83, 84]. With this being said, the high quality manual work of incorporating papers, combining summaries, and running the core experiments using code with visualizations may continue in the near-term to solve diseases.

c) Code generations in Python or LaTeX by the top ChatGPT o1 model required additional troubleshooting and typically lacked the ability to immediately convert its understandings of either a knowledge graph or signaling pathways to an attractive and convincing diagram. This was apparent in Part II Prompt 3b, where trial experiments yielded lower quality results. However, the model did properly incorporate features specified by the author. For Part III Prompt 4c, the relationships in code were appropriate, but ChatGPT o1 was not able to automatically set correct text and box positioning due to over-crowding, with further ChatGPT 4o and author modifications being required to properly display these relationships in Figure 7.

Clau-3Opus also included quotations of some other phrases, and only some of the generations contained numerical text. ChatGPT o1 quotes of passages from summaries also may include portions of surrounding text or modify a word to a different tense. Based on these results, certain aspects of general artificial intelligence using text only inputs is realistic, but would imply performing manual operations by the manuscript author in addition to generating effective final answers shown here. For instance, a two sentence prompt to obtain a breakthrough regarding cancer mechanisms would require several ChatGPT o1 instances in concert prior to generating the answer. This assumes no code or image incorporation, as processing these type of data typically requires additional testing.

7 Conclusions

Studies utilizing LLMs for cancer research have increased both in scope and quality of AI models. As few as 10 October 2024 articles have increased cancer research effectiveness, as apparent in recent publications such as Oh, Y., et al. published a LLM-driven oncology study in *Nature Communications* [29]. The emergence of reliable information retrieval methods present in models from Anthropic, high contextual awareness, and now advanced reasoning has opened the door for breakthroughs in cancer research by utilizing capabilities of different models combined with prompt engineering. Both immunology and organ-specific cancer are complex areas in medicine, as the systematic review of 2024 articles yielded 40 papers of over 600K words reduced to 17K words in order to run within the context length of ChatGPT o1.

Overall, the results obtained from Clau-3Opus in summarizing 40 papers were significant due to providing a consistent format and high accuracy for each summary as verified with multiple author search terms, but could have provided additional detailed numerical data quotations as specified in prompts. Lla3.1-405 provided an average detailed Top 10 Cancer Areas to research, lacking compelling evidence that was present using other models, however was the only model to process all 40 paper summaries at over 17,000 words. ChatGPT o1 provided groundbreaking and reproducible generations across two sets of 20 papers regarding advanced reasoning using text only. Additional sequential prompts in the same conversation incorporating Python or LaTeX code required additional development to achieve a professional knowledge map or signaling pathways.

The main takeaway of this work was that the quality and quantity of the data provided by Clau-3Opus to ChatGPT o1 in the form of reports was sufficient to create additional detailed reports and code used to visually represent numerous cancer research relationships. In the case of 20 summaries representing the tumor immune microenvironment, both a detailed report with an unprecedented number of relationships between author methods featured 37 citations, and a professional knowledge graph representing many of these relationships was produced in a two prompt conversation. For the 20 summaries representing organ-specific research, correlations between both author studies and specific cancer disease were made throughout many portions of the report, represented by 53 author citations. In addition, an 81 word Zhang et al. excerpt representing a cancer mechanism was converted by ChatGPT o1 into code correctly represented by a signaling pathway. Next, ChatGPT o1 updated the pathway based on the 20 summaries to yield additional code with useful relationships that now included a "Combined TME Signaling Influences" focal point with 4 additional authors, their specific area of cancer research and the benefit they could provide to the original pathway.

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8 Appendix

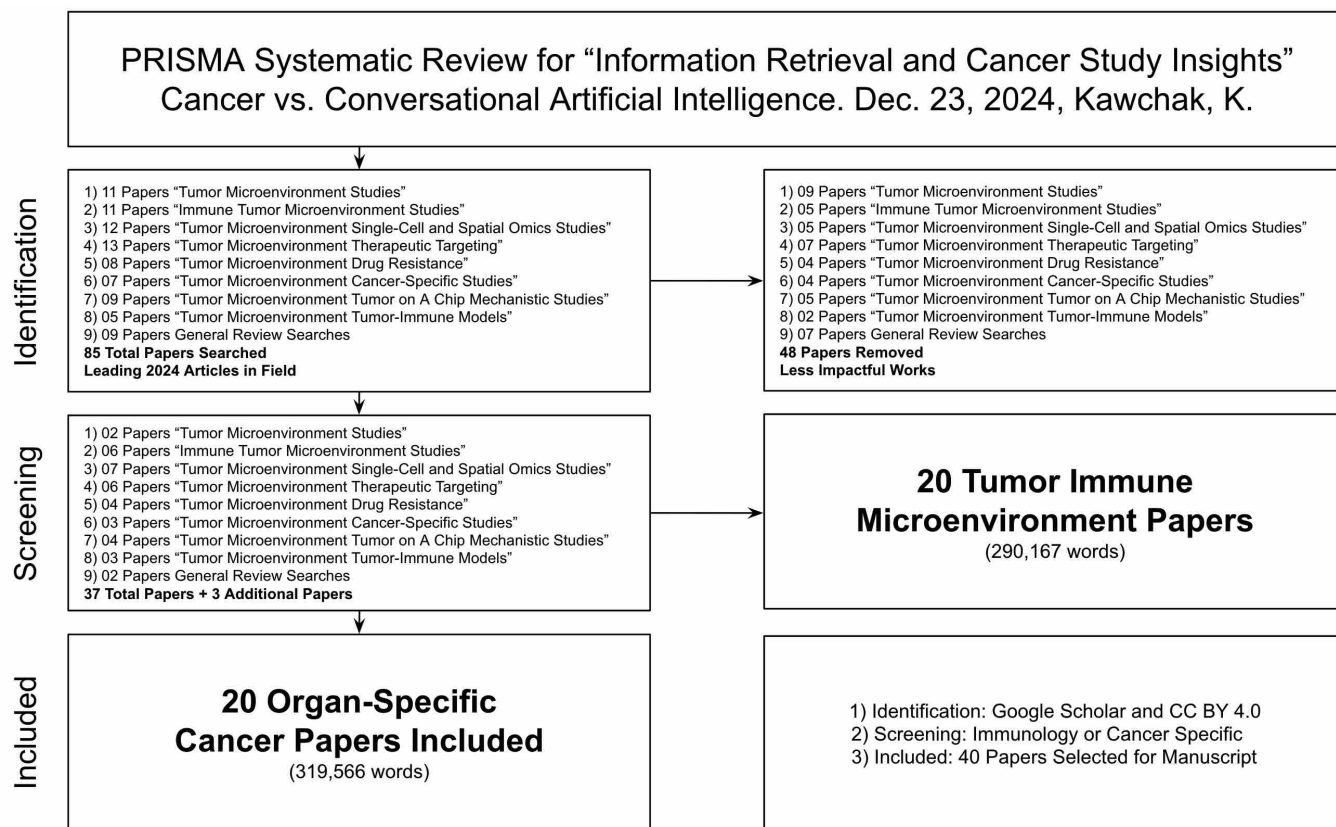


Figure 8: PRISMA Diagram for 40 Papers