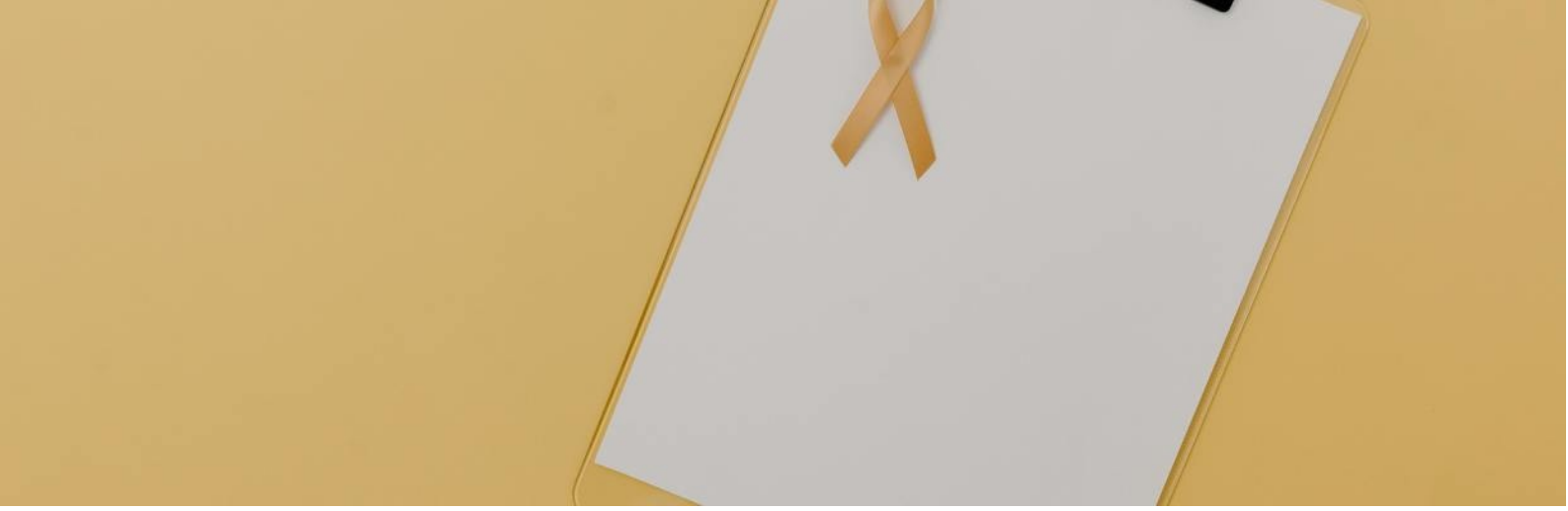

Spotlight on Scientific Discovery & Engineering: Cancer Complexity and Cellular Innovation

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Abstract:

This JOSHA Spotlight curates five advances that illuminate cancer as a problem of both cellular engineering and clinical decision-making. Mechanistic work in colorectal cancer shows how loss of ATRX disrupts colonic identity, unleashing multilineage plasticity and highly metastatic behaviour. A microfluidic–machine learning platform in breast cancer quantifies how metronomic drug schedules can outperform conventional combinations. A landmark trial in node-positive breast cancer refines care by safely omitting regional nodal irradiation after excellent chemotherapy response. In pancreatic cancer, paired articles reveal “cryptic” antigens from noncoding regions as shared, tumour-restricted targets that can be recognised and attacked by engineered T cells, yet remain constrained by an immunosuppressive

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Abstract

This JOSHA Spotlight curates five advances that illuminate cancer as a problem of both cellular engineering and clinical decision-making. Mechanistic work in colorectal cancer shows how loss of ATRX disrupts colonic identity, unleashing multilineage plasticity and highly metastatic behaviour. A microfluidic–machine learning platform in breast cancer quantifies how metronomic drug schedules can outperform conventional combinations. A landmark trial in node-positive breast cancer refines care by safely omitting regional nodal irradiation after excellent chemotherapy response. In pancreatic cancer, paired articles reveal “cryptic” antigens from noncoding regions as shared, tumour-restricted targets that can be recognised and attacked by engineered T cells, yet remain constrained by an immunosuppressive microenvironment. Together, these curated contributions spanning cellular identity in colorectal cancer, dosing logic in breast cancer, and immune recognition in pancreatic cancer showcase how tightly linked molecular identity, dosing logic, and immune recognition are reshaping the future of precision oncology and patient care.

Keywords: Multilineage Plasticity; Metronomic Chemotherapy; Radiotherapy De-escalation; Cryptic Tumor Antigens; Non-coding Cancer Antigens.

1. Loss of colonic fidelity enables multilineage plasticity and metastasis

By Patrizia Cammareri, Michela Raponi, Yourae Hong *et al*

A recent study identifies the chromatin-remodeling enzyme ATRX as a crucial guardian of colonic cellular identity, whose loss triggers a cascade of events leading to highly aggressive and metastatic colorectal cancer. Using mouse models and human patient data, researchers found that when ATRX is lost, colon cancer cells lose their defining characteristics and enter a state of extreme plasticity, acquiring features of other cell lineages, including mesenchymal and, notably, squamous-like cells. This "identity crisis" is driven by epigenetic changes that impair the function of HNF4A, a key transcription factor responsible for maintaining colonic cell fate. Critically, the resulting squamous-like gene signature was identified in human patient samples, where it correlates with the most aggressive cancer subtypes and predicts poor patient prognosis. The research fundamentally reframes metastasis not just as a journey of a cell, but as a loss of its original identity, opening up new avenues for targeting epigenetic drivers of cancer progression.

This article was previously published in *Nature* on June 4, 2025.

Read the full article here

2. Metronomic doses and drug schematic combination response tested within chambered coverslips for the treatment of breast cancer cells (JIMT-1)

By Gustavo Rosero, Gisela Pattarone, Ana Peñaherera *et al*

This study presents a novel, interdisciplinary approach to evaluating chemotherapy schedules for aggressive breast cancer. Using the JIMT-1 cell line (a model for triple-negative breast cancer), researchers combined microfluidic chambered coverslips with a machine learning image-analysis algorithm to assess treatment efficacy. They compared a standard doxorubicin-paclitaxel combination against a low-dose metronomic (LDM) regimen of paclitaxel administered over five days. The analysis of 7,500 images revealed that while the conventional combination had a limited effect, the LDM schedule was markedly more potent. It significantly reduced the population of live cells and was most effective at triggering programmed cell

death (apoptosis). The work establishes a powerful new method for rapidly and reproducibly quantifying how cancer cells respond to different drug treatment patterns.

This article was previously published in *PLOS ONE* on September 29, 2022.

Read the full article here

3. Omitting regional nodal irradiation after response to neoadjuvant chemotherapy

By Eleftherios P. Mamounas, Hanna Bandos, Julia R. White *et al*

A pivotal clinical trial has found that breast cancer patients who present with cancerous lymph nodes, but whose nodes are cleared of cancer (ypN0 status) by chemotherapy given before surgery (neoadjuvant chemotherapy), can safely omit further radiation therapy to the lymph node region. In the study, over 1,600 patients who achieved ypN0 status were randomly assigned to receive either regional nodal irradiation or no further radiation. After five years of follow-up, the data showed no significant benefit from adding the radiation. There was no difference in the cancer's return, its spread to distant organs, or the overall survival rate between the two groups. The findings support a new treatment standard, allowing many patients to avoid the side effects and burden of extensive radiation without increasing their risk of recurrence.

This article was previously published in *The New England Journal of Medicine* on June 5, 2025.

Read the full article here

4. Pancreatic cancer–restricted cryptic antigens are targets for T cell recognition

By Zackery A. Ely, Zachary J. Kulstad, Gurcan Gunaydin *et al*

Researchers have discovered that pancreatic cancer cells produce unique "cryptic" antigens, protein fragments generated by the erroneous translation of noncoding genomic regions, which are then presented on the cell surface by HLA-I molecules. Profiling patient tumors and organoids revealed that nearly a third of these cryptic

peptides are "cancer-restricted," being largely absent from a wide range of healthy tissues, thus making them ideal, tumor-specific targets. Critically, these peptides proved highly immunogenic, and the study successfully isolated specific T cell receptors (TCRs) that recognize them. When engineered into T cells (TCR-T therapy), these cells demonstrated a powerful ability to recognize and kill patient-derived pancreatic tumor cells both in lab dishes and in animal models, unveiling a promising new class of targets for immunotherapy in a cancer notoriously resistant to existing treatments.

This article was previously published in *Science* on May 8, 2025.

Read the full article here

5. The hunt for common tumor antigens

By David A. Tuevson

This perspective article highlights a pivotal study that uncovers a new class of "cryptic" tumor antigens in pancreatic cancer, which originate from the erroneous translation of noncoding genomic regions. These noncoding cancer antigens (nc-CAs) are not only specific to the tumor cells but are also shared among multiple patients who carry a specific MHC-I haplotype, making them potential "common" targets for therapy. The research demonstrated that T cells engineered to recognize these antigens could effectively attack pancreatic tumors in mice. While this discovery opens a promising new avenue for developing "off-the-shelf" immunotherapies or vaccines, the author notes a significant challenge: pancreatic tumors are notorious for creating a highly immunosuppressive microenvironment—a hostile fortress of dense tissue, suppressive cells, and deactivating signals—that could still neutralize this potent T-cell response, and overcoming this barrier will be crucial for clinical success.

This article was previously published in *Science* on May 8, 2025.

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