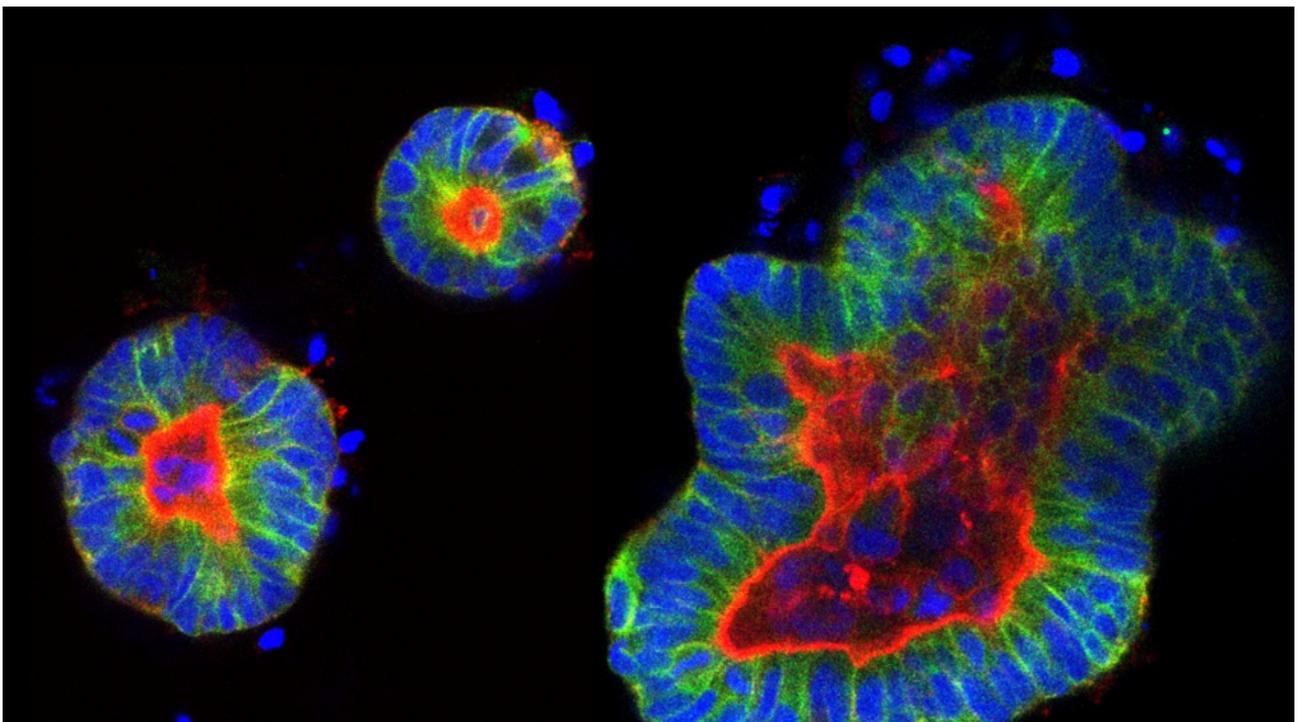


Inside the tumor: a journey into cellular diversity to defeat colorectal cancer

by **Sabrina Fletcher, Alberto Puliafito**

Cancer research and treatment have evolved over time, with novel scientific discoveries emerging in each era, marking a shift in focus toward specific tumor characteristics. Recently, researchers have turned their attention to the diversity of cells that coexist within a single tumor. This cell diversity, known as heterogeneity, could be leveraged to improve cancer treatments if better understood. Our project “POPYNA” focuses on colorectal cancer, exploring tumor heterogeneity to gain insights into tumor progression and resistance to therapy.



The fight against cancer is a long one, with several victories accomplished throughout history. Still, much remains to be deciphered about this cellular disease. Cancer is a complex disease in which cells in our body begin to grow uncontrollably, forming masses called tumors. There are two major categories of tumors: solid tumors and blood cancers (such as leukemia). Solid tumors, which are the focus of our study, are those that form compact masses of cells in organs and tissues, such as the lungs, breast, prostate, and colon. One main characteristic of solid tumors is the presence of cells with different traits within the same tumor, a phenomenon known as intra-tumor heterogeneity.

But what does this mean exactly? Imagine a tumor as a powerful gang made up of several large and influential families. All members work together to expand their control over surrounding territories, constantly finding ways to evade the city's surveillance system—that is, the immune system. When a chemotherapy drug is administered, it might be effective in exposing the Montecchi family's operations, but it could be completely useless in revealing the illicit activities of the Capuleti family. The result? While one faction is eliminated, the others remain in the shadows, ready to take over and continue expanding.

Thus, the study of this tumor diversity could help us in understanding treatment resistance as well as recurrences. It is possible that a specific cancer drug efficiently kills a subpopulation of cells within the tumor, while another subpopulation remains unaffected. This could potentially lead to re-emergence of cancer after treatment. It is thought that these different cells, which constitute diverse subpopulations, could have different roles in tumor progression, some being more “relevant” than others.

With our project “POPYNA”, which earned me an MSCA postdoctoral fellowship, we focus on colorectal cancer, one of the most diagnosed cancers worldwide. This type of cancer develops in the large intestine or rectum and often begins with small clusters of abnormal cells called polyps, which can sometimes gradually transform into malignant tumors over time. Currently, there are different treatment approaches available to treat this malignancy, including [surgery](#), chemotherapy, radiotherapy, targeted therapy and immunotherapy. Surgery is often the first step, physically removing the visible tumor. However, since some cancer cells may remain in the body and spread elsewhere, additional treatments like chemotherapy or targeted therapies are used to reduce the risk of recurrence and metastasis. However, almost a million people still die from this disease each year worldwide.

This multidisciplinary project relies on cutting-edge techniques to unravel the basic features of intra-tumor heterogeneity and subpopulation dynamics. We aim to identify distinct subpopulations within tumor samples using colorectal cancer organoids, which are 3-dimensional cell cultures that mimic tumors *in vitro*. Imagine these organoids as tiny “tumors in a dish,” allowing us to observe cancer cell behavior in a controlled environment without studying them directly in patients.



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We will analyse these tumor cultures at the single-cell level with the goal to identify groups of cells with similar characteristics. Some of these subpopulations have already been identified by the scientific community, others are still unknown. We aim to discover and characterise previously unknown subpopulations and to understand their role during tumor progression and response to treatment. . We also aim to understand whether it is possible for one subpopulation to “transform” into another subpopulation, a process known as cell plasticity.

This project is expected to provide the scientific community with a deeper understanding of intra-tumor heterogeneity and subpopulation dynamics in colorectal cancer. Potentially, we could identify new therapeutic targets, such as specific subpopulations, that could lead to the development of more precise and personalized treatment strategies. Instead of using a one-size-fits-all approach, future therapies could be designed to selectively target the most aggressive or treatment-resistant cancer cells, making them more effective.

This is an exciting era in cancer research. Recent technologies have allowed us to look deeper and closer into tumors as never before, giving us the possibility to finally decipher key aspects of malignancies. The path is still long, but science continues to make great strides forward.

ERC CLASSIFICATION

LS2_8 Transcriptomics

LS3_1 Morphology and functional imaging of cells and tissues

LS3_8 Cell differentiation, physiology and dynamics

LS4_6 Fundamental mechanisms underlying cancer

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