Review

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Unravelling the Barriers: Current Limitations in Cancer Biology Research and How to Overcome Them

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Simple Summary: Cancer research faces significant biological, technological, and systemic limitations that hinder the development of effective therapies and improved patient outcomes. Traditional preclinical models, often fail to accurately replicate the complex architecture, microenvironment, and immune interactions present in human tumors. This disconnects results in promising laboratory findings not translating effectively into clinical success. A core obstacle is tumor heterogeneity, characterized by genetic, epigenetic, and phenotypic variations within tumors, complicating treatment strategies and contributing to therapeutic resistance. The biological processes driving metastasis are only partially understood, limiting therapeutic advances. Beyond biological barriers, systemic challenges include limited funding, regulatory complexities, and disparities in care access across different populations. Overcoming these obstacles requires multidisciplinary collaborations, advanced modeling techniques that better emulate human cancer, and innovative technologies for early detection and targeted therapy. While the cancer complexity and systemic challenges are formidable, ongoing scientific progress and collaborative efforts inspire hope for breakthroughs that can transform cancer diagnosis, treatment, and survival outcomes worldwide.

Abstract: Cancer research faces significant biological, technological, and systemic limitations that hinder the development of effective therapies and improved patient outcomes. Traditional preclinical models such as 2D and 3D cell cultures, murine xenografts, and organoids, often fail to reflect the complexity of human tumor architecture, microenvironment, and immune interactions. This disconnects results in promising laboratory findings, not always translating effectively into clinical success. A core obstacle is tumor heterogeneity, characterized by diverse genetic, epigenetic, and phenotypic variations within tumors, which complicates treatment strategies and contributes to therapeutic resistance. Current early detection technologies lack sufficient sensitivity and specificity, impeding timely diagnosis. The tumor microenvironment, with its intricate interactions and resistance-promoting factors, further promotes treatment failure. Additionally, we only partially understand the biological processes driving metastasis, limiting therapeutic advances. Overcoming these barriers involves not only the use of new methodological approaches and advanced technologies, but also requires a cultural effort by researchers. Many cancer studies are still essentially observational. While acknowledging their significance, it is crucial to recognize the shift from deterministic to indeterministic paradigms in biomedicine over the past two to three decades, a transition facilitated by systems biology. It has opened the doors of deep metabolism where the functional processes that control and regulate cancer progression operate. Beyond biological barriers, systemic challenges include limited funding, regulatory complexities, and disparities in cancer care access across different populations. These socio-economic factors exacerbate research stagnation and hinder the translation of scientific innovations into clinical practice. Overcoming these obstacles requires multidisciplinary collaborations, advanced modeling techniques that better emulate human cancer, and innovative technologies for early detection and targeted therapy. Strategic policy initiatives must address systemic barriers, promoting health equity and sustainable research funding. While the complexity of cancer biology and systemic challenges are formidable, ongoing scientific

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progress and collaborative efforts inspire hope for breakthroughs that can transform cancer diagnosis, treatment, and survival outcomes worldwide.

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1. Introduction

Cancer remains one of the most formidable challenges in modern medicine, affecting millions globally and posing a significant threat to human health. While decades of dedicated research have yielded remarkable progress in understanding, diagnosing, and treating various forms of this disease, several fundamental limitations continue to impede our ability to win. This review aims to provide a comprehensive overview of the most significant current limitations in cancer research and our biological understanding, drawing upon recent scientific findings and expert perspectives. These limitations span the entire spectrum of cancer research, from the initial stages of preclinical modeling to the complexities of clinical translation, the intricacies of tumor heterogeneity, the quest for early detection, the influence of the tumor microenvironment, the challenges of selective targeting, the pervasive issue of drug resistance, and the elusive nature of metastasis [1]. Addressing these multifaceted barriers is crucial for accelerating progress and ultimately improving outcomes for individuals affected by cancer.

In cancer research, accurately modeling the disease in the laboratory setting is one of the major hurdles. Traditional preclinical models, such as two-dimensional (2D) and three-dimensional (3D) cell cultures and murine xenograft models, have long served as the cornerstone of initial drug testing and biological investigation [2]. However, these systems often cannot capture the intricate complexity of human cancers, leading to a significant disconnect between promising preclinical findings and disappointing results in clinical trials [1]. For instance, 2D cell cultures lack the complex three-dimensional architecture, the crucial cell-cell and cell-matrix interactions, and the diverse cellular composition that characterize tumors within the human body [3]. While 3D cell cultures offer some improvements in structural organization, they often still lack vital components such as a functional vascular network, a comprehensive tumor microenvironment, and a competent human immune response [4]. Murine xenograft models, which involve implanting human cancer cells into immunocompromised mice, also present substantial limitations [5]. The absence or impairment of a fully functional immune system in these mice cannot account for the critical role the immune system plays in both cancer development and the response to immunotherapies. Cancer cell lines may not metastasize or might exhibit altered responses when grown in a murine microenvironment, which differs significantly from the human milieu [6]. Even patient-derived xenografts (PDXs), while better at maintaining the original tumor's histology and genomic characteristics, often lose human stromal components like fibroblasts, which are replaced by murine counterparts, further distorting the tumor microenvironment [7]. The exceptionally high failure rate of new cancer drugs in clinical trials—approximately 95% never reaches the market despite promising lab results, stems, experts believe, from these fundamental inadequacies in traditional preclinical models. Difference of opinion highlights a critical need for more sophisticated and physiologically relevant preclinical systems that can better predict how potential therapies will behave in human patients.

2. Genetically Engineered Models

Recognizing the limitations of traditional models, researchers are actively pursuing more advanced preclinical systems to better mimic human cancer biology. Scientists engraft human cells, tissues, or even a human immune system into immunodeficient mice to create humanized mice [8]. These models offer potential advantages, such as the ability to test therapies that are not yet approved

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for human use and a more relevant immune context for evaluating immunotherapies. However, even humanized mice have limitations, including the incomplete reconstitution of the human immune system, the considerable cost and technical complexity involved in their generation and maintenance, and that their underlying murine physiology still differs from that of humans [8]. Patient-derived xenografts (PDXs) represent another step towards improved modeling; in this process, researchers implant tumor tissue directly from a patient into immunodeficient mice [9]. While PDXs can preserve the original tumor's histological and genomic features, they suffer from the lack of a fully intact human tumor microenvironment, as murine ones often replaced human stromal components [2,9]. The expense and difficulty of generating PDXs, along with their limited applicability for large-scale drug screens, restrict their widespread use. Organoids, three-dimensional in vitro cultures derived from patient tumor tissues or stem cells, have emerged as a promising avenue for preclinical research [10]. These models can recapitulate some aspects of tissue architecture and cellular heterogeneity, offering a better representation of human cancer compared to traditional cell lines [10,11]. However, current organoid systems often lack a fully developed vascular system, a complete tumor microenvironment with all its cellular and acellular components, and standardized culture protocols, which are needed to ensure reproducibility across different labs. Genetically engineered mouse models (GEMMs), in which researchers genetically modify mice to develop cancer, are valuable for studying cancer development driven by specific genetic mutations [11,12]. However, they may not always accurately predict drug responses in humans because of species-specific differences in pharmacology and safety, and their generation and maintenance can be time-consuming and expensive [13–15]. The ongoing evolution of preclinical models, from simple cell lines to sophisticated organoid systems and humanized animals, reflects a growing understanding of the need to capture the complexity of human cancer more accurately. However, that each model system still presents its own set of limitations underscores the significant scientific challenge of perfectly mimicking the intricate biology of this disease in a controlled laboratory setting. This causes a careful consideration of the strengths and weaknesses of each model in relation to the specific research question and often requires a multi-model approach for a more comprehensive understanding.

3. Tumor Heterogeneity

A major limitation that pervades all aspects of cancer research and treatment is the inherent heterogeneity of tumors. Cancer is not a monolithic disease but a complex collection of diverse cell populations that exhibit significant variations at the genetic, epigenetic, and phenotypic levels [16]. Genetic heterogeneity refers to the variations in the DNA sequence among different cancer cells within the same tumor (intratumoral heterogeneity) or between tumors from different patients with the same cancer type (intertumoral heterogeneity) [16,17]. This genetic diversity arises from the accumulation of mutations, genomic instability (such as increased mutation rates and chromosomal abnormalities), and exposure to environmental mutagens [16,17]. Epigenetic heterogeneity describes the differences in gene expression patterns that occur with no changes to the underlying DNA sequence. These variations in gene expression can be driven by factors such as DNA methylation and histone modifications, leading to different cellular phenotypes even among genetically identical cells. Phenotypic heterogeneity refers to the resulting variations in observable characteristics and functional behaviors of cancer cells, including differences in morphology, proliferation rate, metabolism, drug sensitivity, and metastatic potential [18]. This heterogeneity is not a static feature but a dynamic process, with different subclones of cancer cells constantly evolving and adapting over time and in response to various selective pressures, including anticancer treatments [19]. The multi-layered and dynamic nature of tumor heterogeneity represents a profound challenge to our understanding and treatment of cancer.

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4. Effectiveness of Cancer Therapies

The existence of this intricate cellular diversity within and between tumors has significant implications for the effectiveness of cancer therapies, particularly targeted therapies and immunotherapy [19]. Intratumoral heterogeneity is a major driver of both intrinsic and acquired resistance to targeted therapies. If a targeted therapy focuses on a specific mutation or pathway present in only a subset of cancer cells, those cells lacking the target will be inherently resistant and can eventually proliferate to repopulate the tumor [20]. The selective pressure exerted by the therapy can lead to the outgrowth of minor, resistant subclones that were present from the beginning or arise during treatment because of ongoing genetic and epigenetic evolution [19]. Tumor heterogeneity also poses considerable challenges for the effectiveness of immunotherapy [21]. Immunotherapies often rely on the immune system, recognizing specific tumor-associated antigens. However, heterogeneous tumors may contain subpopulations of cells that express these antigens at different levels or even lack them entirely, leading to immune evasion [21].

Different subclones within a tumor may display varying immunogenicity and express immune-suppressing molecules, thus creating an immunosuppressive microenvironment that impairs the ability of immune cells to target and eliminate cancer [22]. Tumor heterogeneity also complicated the diagnostic process. A single biopsy, often used to guide treatment decisions, may not capture the full spectrum of genetic and molecular alterations present throughout the entire tumor or in distant metastatic sites, potentially leading to inaccurate treatment selection [23,24]. Overcoming the challenges posed by tumor heterogeneity causes the development of novel therapeutic strategies that can simultaneously target multiple vulnerabilities across different cell populations within a tumor. This may involve the use of combination therapies, adaptive treatment approaches guided by real-time monitoring of tumor evolution, and the exploration of therapies that target the underlying mechanisms driving heterogeneity itself [24]. Single-cell sequencing and spatial genomics technologies offer unprecedented opportunities to characterize and understand tumor heterogeneity at an unprecedented level of detail, paving the way for more personalized and effective treatment strategies [24]. Table 1 shows some aspects of tumor heterogeneity on cancer therapy.

Table 1. Impact of Tumor Heterogeneity on Cancer Therapy.

Level of heterogeneity	**Mechanisms Contributing to Heterogeneity**	**Implications for Targeted Therapy**	**Implications for Immunotherapy**
Genetic	Mutations, genomic instability, exposure to mutagens	Resistance because of lack of target in subclones; outgrowth of resistant subclones with different mutations.	Variable antigen expression leading to immune evasion in some subclones.
Epigenetic	DNA methylation, histone modifications	Resistance through altered expression of drug targets or resistance-conferring genes.	Variable expression of immune-related molecules.
Phenotypic	Genetic and epigenetic variations, TME	Differential drug sensitivity	Varying levels of immunogenicity; different

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	interactions	across subclones selection of drug-tolerant or resistant phenotypes.	interactions with immune cells; creation of immunosuppressive microenvironment by some subclones.

5. Early Cancer Detection

Experts widely recognize early cancer detection as critical for significantly improving patient survival rates and treatment outcomes because early-stage cancers are more localized and amenable to curative therapies [25,26]. However, currently available cancer screening methods for various cancer types face significant limitations. Imaging techniques such as mammography, CT scans, and MRI, while valuable for detecting morphological changes, often lack the sensitivity to detect slight, early-stage tumors and may not always be inherently cancer-specific, leading to false positives [27,28]. Their accessibility and cost can be limiting factors for widespread screening [27,28]. Many established tumor markers, such as PSA and CA-125, have showed poor accuracy and efficacy, particularly for screening prevalent cancers. These markers exhibit low sensitivity and specificity, leading to both false positives and false negatives. Non-cancerous conditions may also elevate their levels.

Invasive procedures like colonoscopy and biopsy, while crucial for definitive diagnosis, can be uncomfortable, carry inherent risks, and may not be suitable for widespread screening of asymptomatic individuals [29–31]. The challenge of overdiagnosis, where screening detects cancers that would never have progressed to cause symptoms or death, leading to unnecessary anxiety and treatment, also remains a concern [29–31]. Factors like lead-time bias and length bias can complicate the evaluation of screening effectiveness, where earlier diagnosis through screening may not translate to improved overall survival [32]. Significant disparities in cancer screening rates and outcomes persist across different population groups, often linked to socioeconomic factors, access to healthcare, cultural beliefs, and mistrust of the healthcare system [33]. These limitations highlight the ongoing need for more accurate, less invasive, and more accessible early detection strategies that can benefit all populations equally. The development of multi-cancer early detection (MCED) tests, which aim to detect multiple cancer types through a single blood test, represents a promising but still investigational approach to overcome some of these limitations [34]. However, widespread implementation requires rigorous validation in large clinical trials to show their effectiveness in reducing cancer mortality and carefully assess the risks of false positives and overdiagnosis. Table 2 shows limitations and challenges in early cancer detection.

Table 2. Limitations and Challenges in Early Cancer Detection.

Screening/Detection Method	Key Limitations	Associated Challenges
Imaging (Mammography, CT, MRI)	Limited sensitivity for small tumors; not always cancer-specific; false positives; accessibility and cost.	Improving resolution and specificity; reducing false positives; increasing accessibility.
Tumor Markers (PSA, CA-125)	Poor accuracy and efficacy for many cancers; low sensitivity and specificity; false positives and negatives; Non-cancerous conditions may raise	Identifying more specific and sensitive markers; improving positive predictive value.

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	levels.	
Multi-Omics	Ethical considerations on standardization of data interpretation and integration (data privacy).	Developing robust computational tools for data analysis and integration; establishing ethical guidelines.
Nanotechnology	Translation from lab to clinic, ensuring safety and efficacy in vivo.	Overcoming biological barriers for targeted delivery; long-term safety assessment.
AI and Machine Learning	Data quality and security; algorithm reliability and transparency; integration with existing systems; implementation costs; ethical and regulatory considerations.	Ensure explainability and fairness of algorithms; validate performance in diverse populations; establish regulatory frameworks.
Liquid Biopsies (ctDNA, etc.)	Low analyte concentration in early stages; need for highly sensitive and specific detection methods.	Improving detection sensitivity and specificity; distinguishing cancer-derived signals from background noise.

6. Emerging Technologies

Emerging technologies hold considerable potential for overcoming the limitations of current early detection methods. Multi-omics approaches, integrating data from genomics, transcriptomics, proteomics, and metabolomics, may provide a more comprehensive and sensitive way to detect early cancer signals [35]. However, challenges in data integration, interpretation, and standardization, as well as ethical considerations regarding data privacy, need to be addressed [35]. Nanotechnology offers the potential to develop novel molecular contrast agents for imaging and highly sensitive in vitro assays for detecting circulating tumor cells (CTCs) and other early cancer biomarkers [36,37]. However, translating these technologies from the laboratory to clinical practice and ensuring their safety and efficacy remain key challenges [36,37]. Artificial intelligence (AI) and machine learning can analyze medical images and other data to detect subtle signs of early cancer that the human eye may miss, and to integrate various data types to improve diagnostic accuracy [38,39]. Challenges aim to ensure data quality and security, verify algorithm reliability and transparency, integrate AI into existing healthcare systems, manage implementation costs, and address ethical and regulatory considerations [40–42]. Liquid biopsies, which involve analyzing blood or other bodily fluids for cancer-derived molecules, offer a less invasive approach to early detection and monitoring [43]. However, the low concentration of these analytes in early-stage cancers and the need for highly sensitive and specific detection methods remain significant hurdles [43,44]. While these emerging technologies offer exciting possibilities for improving early cancer detection, their successful translation into clinical practice requires overcoming significant technical hurdles, ensuring clinical validity and utility, and pondering ethical and regulatory implications. A collaborative effort involving researchers, clinicians, technology developers, regulatory agencies, and patient advocates is essential to navigate these challenges and realize the full potential of these innovations to affect cancer outcomes. Table 3 summarizes some discussion's key aspects.

Table 3. Limitations of Traditional Preclinical Cancer Models and Emerging Alternatives.

Model Type	Key Advantages	Key Limitations

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2D Cell Culture	Simple, inexpensive, high-throughput screening	Lacks 3D architecture, cell-cell/matrix interactions, complex microenvironment, immune component; limited clinical relevance.
3D Cell Culture	Improved structure over 2D; some cell-cell interactions	Often lacks vasculature, complex microenvironment, immune component; variability in protocols.
Murine Xenografts	Allows in vivo drug testing	Immunocompromised mice lack human immune system; murine microenvironment differs from human; limited metastasis in some models; physiological differences.
Humanized Mice	More relevant immune context for immunotherapy testing; can test unapproved drugs	Incomplete human immune system reconstitution; murine physiology still differs; expensive and technically complex.
PDXs	Preserves original tumor histology and genomics	Lacks fully intact human microenvironment (murine fibroblasts); expensive and difficult to generate; limited scalability.
Organoids	Better representation of human cancer heterogeneity; higher success rate than cell lines	Often lacks vasculature, complete microenvironment (stromal and immune components); need for standardized protocols.
GEMMs	Useful for studying cancer development driven by specific genetic alterations	Species-specific pharmacological and safety responses; time-consuming and expensive to generate and maintain.

7. Tumor Microenvironment

The tumor microenvironment (TME), the complex ecosystem surrounding cancer cells, plays a critical role in all stages of cancer development and treatment response [45]. This dynamic environment comprises various non-cancerous cells, including stromal cells (like fibroblasts), endothelial cells forming blood vessels, and immune cells, as well as the extracellular matrix (ECM), soluble factors (like growth factors and cytokines), and the local physical conditions (such as oxygen and nutrient levels) [45,46]. The TME can provide essential growth signals, nutrients, and physical support that promote cancer cell proliferation and survival [47,48]. It is also crucial for angiogenesis, the formation of new blood vessels that supply tumors with oxygen and nutrients [49]. Interactions with the TME can facilitate cancer cell invasion into surrounding tissues and metastasis to distant organs, with the ECM often being remodelled to create pathways for cancer cell migration. The TME can contain immune cells that are suppressed or reprogrammed by cancer cells to promote tumor growth rather than attack it, and cancer cells can express molecules that directly inhibit immune cell activity [50]. Notably, the TME can significantly contribute to resistance against various cancer therapies, including chemotherapy, radiation therapy, targeted therapy, and immunotherapy, by providing a protective niche, secreting factors that shield cancer cells from drugs, hindering drug penetration, and creating hypoxic regions that reduce the efficacy of certain treatments [50,51]. The inherent heterogeneity within the TME itself, with different spatial regions exhibiting variations in cellular composition, oxygen tension, nutrient availability, and signaling molecule concentrations, further complicates treatment responses [52]. The tumor microenvironment is not a passive spectator but an active participant in cancer development and treatment response [53], making the understanding of its intricate interactions with cancer cells crucial for developing more effective therapies.

The growing recognition of the TME's critical role has led to the exploration of therapeutic strategies that target its various components. Immunotherapies aim to modulate the immune cells

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within the TME, such as T cells, to enhance their anti-tumor activity and overcome immune suppression [54]. Targeting stromal cells, particularly cancer-associated fibroblasts (CAFs), which are a major component of the TME in many cancers and contribute to ECM remodelling and therapy resistance, is also being investigated [55]. Anti-angiogenic therapies aim to inhibit the formation of new blood vessels within the TME, starving tumors of oxygen and nutrients [56]. Emerging research also suggests that the gut microbiota can influence the response to certain cancer therapies, particularly immunotherapies, leading to the investigation of strategies to modulate the gut microbiome to enhance treatment efficacy [57]. While targeting the TME offers a diverse range of therapeutic opportunities that complement traditional approaches focused on cancer cells themselves, the complexity and heterogeneity of the TME cause a deeper understanding of its specific roles in different cancer types and stages to develop effective and safe interventions. Advances in spatial multiomics technologies are providing new ways to map and understand the heterogeneity of the TME at a cellular and molecular level [58,59], offering invaluable information for identifying novel therapeutic targets and developing more precise strategies for modulating the TME in cancer treatment.

8. Treatments Selectively Targeting Cancer Cells

A central goal in cancer therapy is to develop treatments that can selectively target cancer cells while minimizing harm to healthy tissues [60], reducing treatment-related toxicities and improving patient quality of life [61]. However, achieving this selectivity is inherently challenging because cancer cells arise from normal cells and share many of their fundamental molecular characteristics and pathways. This makes it difficult to identify therapeutic targets that are only present in or essential for cancer cells. The concept of "undruggable" targets further complicates this issue [62,63]. These are proteins that play critical roles in cancer development and progression but lack suitable binding sites for traditional small-molecule drugs or antibodies, making them inaccessible to therapeutic intervention [64,65]. Even targeted therapies, while designed to focus on specific molecular alterations, can still have off-target effects because of the presence of the target in some normal cells or the involvement of the targeted pathway in normal cellular processes [66]. Traditional cytotoxic chemotherapies, which lack specific targeting mechanisms, often cause significant side effects by damaging rapidly dividing normal cells besides cancer cells [67,68]. The pursuit of highly selective cancer therapies is therefore a continuous endeavour that requires innovative approaches to overcome the inherent similarities between cancer and normal cells and to expand the repertoire of druggable targets.

Researchers are constantly exploring novel approaches to enhance the specificity of cancer therapies. Targeted therapies continue to be refined to focus on more specific molecular alterations that are uniquely or predominantly found in cancer cells, including the development of more potent and selective inhibitors of known oncogenic drivers [63,64,69,70]. Immunotherapy has emerged as a transformative approach that leverages the patient's own immune system to recognize and selectively destroy cancer cells based on their unique antigens [71]. Advances in understanding tumor immunology have led to the development of various immunotherapeutic strategies, such as immune checkpoint inhibitors and CAR T-cell therapy [72,73]. Antibody-drug conjugates (ADCs) represent another strategy to enhance specificity by combining the targeting ability of antibodies that recognize cancer-specific surface antigens with the potent cytotoxic effects of chemotherapy drugs, allowing for targeted delivery directly to cancer cells and reducing systemic toxicity [74,75]. Strategies for protein degradation, such as PROTACs and molecular glues, offer a completely new way to target previously "undruggable" proteins [76]. These strategies use the cell's own protein degradation machinery for the selective breakdown of these proteins [77]. While these more targeted approaches represent significant advancements, they are not universally effective, and resistance can still develop, underscoring the need for continued research to identify new targets and refine these approaches to improve their efficacy and reduce side effects. Integrating advanced diagnostics, such as genomic profiling and liquid biopsies, is becoming increasingly important for

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identifying patients who are most likely to benefit from specific targeted therapies and for monitoring treatment response and resistance mechanisms [78,79].

9. Drug Resistance

The development of drug resistance, where cancer cells become less responsive or unresponsive to treatment, is a major obstacle to successful long-term cancer therapy and a primary reason many cancers recur and progress [80]. Cancer cells can acquire resistance through a variety of complex mechanisms, including genetic mutations in the drug target or downstream signaling pathways, epigenetic modifications that alter gene expression, activation of alternative survival pathways, increased expression of drug efflux pumps that remove the drug from the cell, changes in drug metabolism that inactivate the drug, and interactions with the tumor microenvironment that provide protection [81–83]. Notably, intratumoral heterogeneity plays a critical role in the development of drug resistance. The presence of diverse subclones within a tumor increases the likelihood that some cells will possess or acquire resistance mechanisms. The selective pressure of the drug then eliminates the sensitive cells, allowing the resistant clones to expand and dominate [84,85]. Researchers believe that cancer stem cells (CSCs), a subpopulation of cancer cells with self-renewal and differentiation capabilities, also contribute to drug resistance and tumor recurrence [86]. The ability of cancer cells to develop and adapt under the selective pressure of therapy is a fundamental limitation in oncology.

To overcome the challenge of drug resistance, researchers are exploring various strategies. Combination therapies that target multiple pathways simultaneously with different drugs can reduce the likelihood of resistance development by making it harder for cancer cells to adapt [87]. Developing drugs that specifically inhibit known resistance mechanisms can restore the sensitivity of cancer cells to the primary therapy [88,89]. Epigenetic therapies, which modify gene expression patterns, have the potential to reverse drug resistance by altering the expression of resistance-conferring genes [90]. Adaptive therapy, which involves adjusting the dose or type of therapy based on the tumor's response, aims to maintain a balance between drug-sensitive and drug-resistant clones, potentially prolonging the effectiveness of treatment [91]. Liquid biopsies can monitor the emergence of resistance-conferring mutations in real-time, allowing for early detection of resistance and timely switching to alternative therapies [43,44,78,79]. Ultimately, overcoming drug resistance will probably require a multifaceted approach that combines different therapeutic modalities, targets both cancer cells and their microenvironment, and uses sophisticated monitoring strategies to adapt treatment in real-time. International collaborations and data sharing are crucial for accelerating the discovery and development of new therapies and strategies to combat drug resistance in cancer [92].

10. Metastasis and Molecular Mechanisms

Metastasis, the spread of cancer cells from the primary tumor to distant sites in the body, is the leading cause of the vast majority of cancer-related deaths [93]. This complex, multi-step process involves a local invasion of surrounding tissues, intravasation into the bloodstream or lymphatic vessels, survival in circulation, extravasation at a distant site, and colonization to form a secondary tumor [93,94]. Despite significant research efforts, there are still considerable gaps in our understanding of the specific molecular mechanisms that govern each step of this metastatic cascade. For instance, we do not fully understand what makes some cancer cells gain the ability to metastasize while others do not, what determines the specific organs to which a particular cancer type will metastasize (metastatic tropism), how metastatic cells survive and thrive in the microenvironments of distant organs, and what early events start the formation of a pre-metastatic niche in distant organs, preparing them for cancer cells. Modelling the metastatic process accurately in preclinical animal models remains a significant challenge because many models, particularly those using cell lines, fail to spontaneously metastasize or to metastasize to the same organs as in humans [95,96]. The complexity of metastasis, coupled with our incomplete understanding of its underlying mechanisms, represents a major barrier to improving cancer survival rates.

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Researchers are focusing on identifying and targeting key molecules and pathways involved in metastasis. This includes targeting cell migration and invasion by inhibiting molecules that promote cancer cell motility and their ability to degrade the ECM [97,98]. Preventing the formation of new blood vessels (angiogenesis) at metastatic sites, which is necessary for the growth of secondary tumors, is another important strategy [99]. Understanding how cancer cells adapt to the microenvironment of distant organs and developing therapies that interfere with this process are crucial for preventing the formation of secondary tumors. Researchers are also investigating the signals that prepare distant organs for cancer cells and developing therapies that can disrupt the formation of these pre-metastatic niches [100]. Leveraging the immune system to detect and eliminate metastatic cancer cells through immunotherapeutic approaches is another promising avenue [101]. Preventing and treating metastasis requires a multi-pronged approach that targets various stages of the metastatic cascade and involves a combination of therapies aimed at both the cancer cells and their interactions with the microenvironment at both primary and secondary sites [102]. The development of more sophisticated preclinical models that accurately mimic human metastasis and allow for real-time tracking of metastatic spread, along with the identification of early biomarkers of metastatic potential, is crucial for accelerating progress in this critical area of cancer research [103].

11. The Transition from Determinism to Indeterminism in the Biomedicine

Much of cancer research is based on observational studies that correlate macroscopic aspects [104], such as symptoms or molecular markers, to cancer and its progression. This simplistic perspective has evolved into probabilistic and indeterministic biological Systems Biology view of the present-days [105–107], where the interactions between biomolecular populations determine functionality. However, even today, many reductionist approaches [108,109] are quite common [110]. It is a cultural problem that has deep roots in the methodologies of the last century.

Cellular metabolism operates through interactions between proteins, in networks of deep and highly regulated molecular processes that interact functionally with each other [111–113]. Regarding the protein interactions, very often proteins interact briefly, by transient interactions with other proteins within a functional module, or they may interact over a longer duration to integrate into a protein complex by a permanent interaction (e.g., ribosomes) or it may interact with a protein for transportation. All this means that without knowing where, how and when the protein interacts, it is impossible to define its real biological role. The concept of coordinated interaction between genes and/or proteins is fundamental [114–116]. Therefore, we can identify entire regulatory networks, in which genes and proteins work together in a coordinated manner to promote tumor growth and survival. Some of them are crucial nodes that modulate multiple cellular pathways, even simultaneously, and therefore may represent interesting therapeutic targets, but it is unlikely that a single gene suffices to block disease progression [117–119]. For example, in pancreatic cancer, recent studies have gone beyond identifying single mutations. They analyzed gene expression patterns and epigenetic modifications to understand how the cellular environment influences tumor malignancy [120–122]. This approach helps to develop combination therapies that target entire molecular circuits, rather than relying on a single target, reducing the risk of drug resistance. Biomolecules, in actuality, communicate via interactions and functional relationships [123]. Biological functions have a very complex informational origin [124]. They can arise from the interaction of single molecules that exchange information from the outside, which is then communicated to the set or group of molecules to which they belong and with which they develop common activities [125]. A typical example used for information transfer in cells is the well-known physical and functional interaction between proteins. Therefore, it is a group of biomolecules, not a single biomolecule, that performs any biological function [126,127]. By interacting with each other, they exchange data/information (elementary information event) that is then mediated by the entire group or relational system (subgraph or functional module) [130–132]. The common relational activity leads to the emergence of a functional property, characteristic of that subgraph/functional module [133,134]. These biological events are informational because the function is the element that derives from the joint processing of

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elementary events of physical interaction (or even sequences of elementary acts (or bits) of analog communication), whether long-lasting (e.g., in complexes) or momentary, transmitted through a very complex interactive network (digital communication) that processes them producing a biological function (the meaning of the processing) [135,136]. Therefore, inter-cellular and intra-cellular metabolic relationships are tightly connected to implement specific and common functional purposes for a tissue (or organ) (implementation of informed decisions) by nonlinear dynamics [137,138]. We can consider their behavior similar to that of an internet network, with nodes and hubs and a modular organization of subgraphs with organizing centers often organized according to hub-spoke patterns [139–141]. The organization of the organism's circadian homeostasis critically depends on this complex informational network [142,143]. Homeostasis expresses the robustness in responding to internal metabolic variations to maintain metabolism in its fundamental state, but also to respond quickly and effectively to external perturbations, be they metabolic or environmental. The organizational model with Hub-Spoke centers guarantees both robustness and the adaptations, where the HUB center concentrates and regulates, through its network of nodes (spoke centers), many functional "services" [144–146]. This pattern is common to very different sectors of human activity, such as urban planning, flight control or social systems [140]. For rapid response and information security in such a complex system, specific paths (e.g., signaling pathways) direct information flow [147,148]. Sequential interaction between component nodes (proteins), exchanging elementary bits of information to aggregate and form complex data, defines the physical support for signaling pathways [149,150]. The Hub and Bottleneck nodes (proteins) represent the regulatory components of the flows and the crossing points between different flows that can be calculated from the topological parameters of the network [150]. As in IT, the bit is the standard unit for measuring information, defining the quantity of biological information as entropy (Shannon entropy) [151–154]. These flows define deep molecular processes or mechanisms, and they are the ones that represent the cause of what happens at the macroscopic observational level. At these levels, within the realm of biomolecules, governing processes are subject to indeterministic physical laws, which are not linearly correlated with the macroscopic world's classical cause-and-effect principles [155–157]. This also means that, when we identify a tumor marker, we must also characterize it, demonstrating to which specific deep functional sub-network it actually belongs. The lack of this characterization renders all statements and their opposites statistically equivalent, which accounts for the lack of efficacy or presence of side effects in some anti-cancer drug molecules despite successful target binding.

12. Importance of Deep Molecular Mechanisms in the Study of Cancer

The study of the deep molecular mechanisms of cancer is fundamental to understand its onset, progression, and resistance to treatments [158,159]. In recent years, research has made progress in identifying genetic mutations and metabolic alterations that influence tumor growth. Where metabolic alterations focus on the metabolic plasticity of tumor cells, i.e., their ability to adapt to environmental conditions and develop drug resistance. For example, the EU-funded CANCER METASTASIS project (ADAPTMET) aims to address metastasis from four key scientific angles (cell fate, environment, latency and expansion) in order to identify key genes involved in cancer metastasis. It is a multidisciplinary approach whose results could lead to the development of new targeted treatments to counteract the spread of tumors.

However, as we have noted, no gene acts in isolation [160,161]. Each gene is part of complex molecular networks that interact dynamically during cancer progression. The concept of "key gene", which is often used to simplify scientific communication, can be misleading if not correctly contextualized. We often read that "cancer arises from a mutated gene". We also use this phrase to describe the cause of the disease. Despite its general usage, this phrase might lead to a flawed understanding of genetics. It expresses a reductive, deterministic view, which equates an individual's entire genetic code with a single individual trait, as if we could also have another single gene that makes us immune to cancer. The growing use of a single gene as a tool for understanding causal aspects of a disease supports a deterministic thinking that suggests an immutable genetic makeup

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operating through single disease-causing genes. After all, even the native protein, the one decoded by the gene, does not exist in metabolic reality.

Almost always, the protein passes through the Golgi/ER system after expression. This system chemically modifies and tailors it to a specific cellular location where it interacts with other biomolecules to create a function [162]. Thus, although the gene always expresses the same native protein, the different covalent modifications generate many and various proteoforms [163], each of which is adapted to specific molecular relationships in nonidentical cellular locations. Each type of proteoform is a chemically distinct entity from the others, with its own highly specific chemical-physical characteristics. This requires researchers to identify the entire regulatory network in which the specific proteoform works in coordination with other proteins to promote tumor growth and survival [164,165]. Although the theoretically calculable number of proteoforms is astronomical (>1027), a limit to this complexity is the copy number present in cells, which is rather limited, as well as the number of genes simultaneously expressed in cell [163]. However, the question of how many proteoforms exist is very difficult if not impossible to answer [163]. It does not escape the reader that in this context the characterization of the proteoform is also crucial to understanding what its specific molecular properties are. Some nodes are crucial because they intersect and modulate multiple cellular pathways, and therefore become interesting therapeutic targets, but a single gene is rarely enough to block disease progression [166,167]. For example, analyzing gene expression patterns helps to prepare therapies that target molecular pathways that often intersect through a common component. This means hitting at multiple points the ability of tumor cells to adapt their metabolism in response to environmental conditions. As mentioned above, this approach closely relates to cancer progression and treatment resistance.

In addition, cancer cells must face hostile, hypoxic, nutrient-poor environments [168]. To survive, they modify their metabolism in different ways by regulating a series of deep molecular mechanisms that involve the reprogramming of cellular metabolism and the interaction with the tumor microenvironment [169,170]. For example, alterations in AMPK and mTOR signaling, increased expression of glucose transporters (GLUT1, GLUT3) and increased activity of aerobic glycolysis that with the strong production of lactate favors tumor growth [171,172] or even the use of glutamine for the synthesis of nucleotides and the production of NADPH, essential for resistance to oxidative stress [173,174], are part of this picture. Metabolic plasticity is, therefore, also a key element in cancer biology and may represent a target for new therapies. However, epigenetic modifications, such as DNA methylation and histone modification, influence it and regulate the expression of genes involved in metabolism; we also cannot exclude its interaction with the tumor microenvironment [175–177]. Tumor cells also communicate with fibroblasts and immune cells to modulate local metabolism [178]. For example, they can induce tumor-associated fibroblasts (CAF) to produce lactate, which is then used by tumor cells as an energy source. The overall picture that emerges is that the combination of these mechanisms makes tumor metabolism extremely adaptable, contributing to treatment resistance and disease progression.

However, we note that cancer molecular mechanisms influence the human mechanisms, i.e., the specific human phenotype that acts as a filter in that specific context [179,180]. The result depends on the filtering capacity of the phenotype, i.e., the molecular mechanisms of contrast that it will use against cancerous ones. This means that, where a specific cancer always produces the same molecular activity to attack, the phenotype counteracts and modifies it. Cancer is not a static disease, but an evolutionary phenomenon that interacts with the host phenotype, creating a complex dynamic between tumor molecular mechanisms and the body's defense mechanisms [180,181]. Although there are common oncogenic pathways, such as activation of oncogenes (e.g., RAS, MYC) and dysfunction of tumor suppressor genes (e.g., TP53, RB1), cancer develops continuously through somatic mutations, metabolic plasticity, and interactions with the tumor microenvironment [183], as mentioned above. But this means that even if a tumor starts with a series of initial alterations, its progression can vary based on the biological context in which it develops. In order to evolve, cancer must overcome phenotypic filtering [184,185]. The immune system and the patient's cellular repair

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mechanisms act as evolutionary barriers, forcing the tumor to develop new strategies to survive [186], for example, by selecting helpful mutations, or by creating a highly adaptable population within the same tumor, as cell clones with different mutations can coexist within the cancerous tissue.

This means that we cannot consider cancer a single entity, but a series of diseases adapting to the host's phenotype [187–189]. This also explains why the same type of tumor can have different responses to treatments in different patients. Its evolution is driven by selective pressures, just as occurs in natural evolutionary processes [190].

Lung cancer's genetic heterogeneity is well known. This leads to clonal selection, where the most drug-resistant cells proliferate, making the tumor more aggressive. Or, in breast cancer, some tumor cells develop resistance to hormone therapy through mutations in oestrogen receptors. This phenomenon is an example of evolutionary adaptation, in which the tumor changes its biology to survive therapies. Melanoma is a highly adaptable tumor. Cancer cells can change their gene expression profile, moving from a proliferative to an invasive state, allowing them to metastasize more easily. This type of plasticity is an obvious example of tumor evolution. These examples show that cancer is not a static disease, but a biological system that is constantly developing to promote invasion [191,192]. Appendix A explains the biological meaning of macroscopic and microscopic levels.

13. Advanced Approaches to Study Cancer Progression

To follow the progression of cancer and its interaction with human molecular mechanisms, we need dynamic techniques to analyze changes in real time. Some innovative approaches that provide crucial information on its deep mechanisms are:

13.1. Cancer Genomics

DNA Sequencing (Next-Generation Sequencing - NGS) [193]: It allows to read the entire DNA sequence of the tumor genome. It allows to identify point mutations, insertions/deletions, structural rearrangements and copy number alterations (gene amplifications or deletions) that are at the basis of cancer development. Technologies such as whole genome sequencing (WGS), whole exome sequencing (WES) or panels of specific genes (panel sequencing) are fundamental to identify driver genetic alterations.

Single nucleotide sequencing (SNP array) [194]: Useful to identify large-scale copy number variations and loss of heterozygosity.

13.2. Transcriptomics

RNA sequencing (RNA-Seq) [195]: Measures the expression of all genes in a sample (tumor or normal). It allows to identify genes over- or under-expressed in cancer, gene fusions at the RNA level, alternative splicing and the expression of non-coding RNAs. It provides crucial information on altered transcriptional programs in tumor cells.

Gene expression microarray [196]: An older technology but still used to measure the expression levels of thousands of genes simultaneously.

13.3. Proteomics

Mass spectrometry (MS) [197]: Allows the identification and quantification of proteins present in a sample. Comparative proteomics of tumor and normal tissues identify proteins with altered expression or post-translational modification in cancer. It is a fundamental approach to study the actual quantity and functional state of the molecules that carry out most cellular processes. It also includes an analysis of post-translational modifications (such as phosphorylation), which are crucial for regulating protein activity.

Protein arrays [198]: Similar to DNA microarrays, they allow analysis of the expression or activity of many proteins at once.

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13.4. Epigenomics

Bisulphite DNA sequencing (BS-Seq) and derivatives [199]: Studies DNA methylation patterns, an epigenetic modification that can alter gene expression without changing the DNA sequence. Cancer profoundly alters methylation patterns.

CHiP sequencing (CHiP-Seq) [200]: Identifies protein binding sites on DNA, such as transcription factors or histone modifications. Alterations in chromatin structure and protein binding to DNA are common in cancer and affect gene expression.

ATAC-Seq [201]: Measures chromatin accessibility, showing regions of the genome that are actively transcribed or regulated.

13.5. Single-Cell Technologies

Single-Cell DNA/RNA Sequencing [202,203]: Allows to analyze the genomic or transcriptomic profile of single cells within a heterogeneous population. This is crucial in cancer in understanding tumor heterogeneity, identify subpopulations of cells with unique characteristics and study their evolution and interaction.

13.6. Advanced Imaging

Super-resolution microscopy and live imaging [204]: Allows to visualize molecules and their interactions within cells in unprecedented detail and to study dynamic processes in real time.

Mass Spectrometry Imaging [205]: Allows to determine the spatial distribution of molecules (proteins, lipids, metabolites) within a tissue sample.

13.7. Bioinformatics and Computational Biology

These are not "wet" experimental technologies, but they are essential to analyze, interpret and integrate the massive amount of data generated by the above technologies. Computational models and algorithms are used to identify patterns, build molecular networks (such as interactomes), predict gene function, simulate cellular behavior and identify potential therapeutic targets [206].

13.8. Mathematical Modeling and Stochastic Control

Random and unpredictable factors influence the evolution of cancer. For this reason, scientists are developing stochastic mathematical models that simulate tumor growth and response to treatments, improving the ability to predict the evolution of the disease [207].

13.9. Artificial Intelligence and Big Data

Using AI and machine learning can revolutionize oncology research. Advanced algorithms analyze huge amounts of genetic, epigenetic, and metabolic data to identify cancer evolutionary patterns and can suggest personalized therapeutic strategies [208–210].

Each of these approaches provides a piece of the puzzle to understand the complex molecular mechanisms of cancer. Scientists believe that integrating data from different platforms (a "multi-omics approach") is the most effective strategy to gain a comprehensive and in-depth view of the disease. Interactomics plays a key role in this integration, providing the "wiring" that connects the different molecular components and allows us to understand how alterations at one level (e.g., gene mutation) translate into changes at the protein and pathway levels, ultimately influencing cellular behavior and tumor progression [211,212].

These and other approaches are transforming the understanding of cancer and opening new avenues for more effective therapies. But almost these advanced approaches require "cognitive" interventions on biomedical big data banks. Current data banks are years old and contain heterogeneous data, making it impossible to distinguish reliable from unreliable data [213–215]. Under these conditions, no advanced technique will give reliable results. These problems of

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heterogeneity, obsolescence, and data quality can significantly affect the reliability of analyses based on advanced techniques.

For example, many databases contain information collected years ago, which may not reflect the current genetic and epigenetic landscape of tumors. The data comes from studies with different methodologies, different analytical tools, and heterogeneous populations, making consistent integration difficult. Almost always, the patient cohorts analyzed are not representative of all human phenotypes, limiting the generalizability of the results [216].

The results are only as good as the data they're based on. If these improve, advanced tools will also be more effective. The creation of new dynamic databases with continuous updates through advanced sequencing tools and real-time data collection [217], new AI models for filtering heterogeneous data, which distinguish between reliable and noisy information, and multi-omics integration techniques, which combine genomic, epigenetic, metabolic and transcriptomic data, will give a more complete view of tumor plasticity. Without forgetting the standardization of protocols, to avoid inconsistencies in data from different laboratories [218], the use of AI to filter noisy data, to extract only reliable information [219] and, above all, activate international collaborations, to create homogeneous datasets on different populations.

However, to transcend current limitations rooted in heterogeneous data, integrating quantitative, multi-modal datasets has emerged as a pivotal strategy in advancing cancer research. By combining genomics, transcriptomics, proteomics, metabolomics, and advanced imaging within a unified analytical framework, researchers can develop comprehensive models that capture tumor heterogeneity, evolutionary dynamics, and treatment responses more accurately [220]. Computational approaches, including machine learning and mathematical modeling, enable the synthesis of these complex datasets into predictive tools that can guide personalized therapy decisions [221]. Such integrative efforts not only enhance our biological understanding but also facilitate the development of more precise diagnostic and prognostic strategies, ultimately addressing the systemic and biological barriers that currently limit translation into clinical benefit.

14. Barriers Hindering Progress in Cancer Research

Beyond the specific biological and technological limitations, several overarching barriers hinder progress in cancer research. The substantial financial investment required for cancer research, spanning basic science to clinical trials, presents a significant challenge [222]. Securing adequate and sustained funding from both public and private sectors, particularly for high-risk, high-reward research and the translational phase, remains a major hurdle [223]. The often-skewed distribution of research funding can also hinder the progress of young and emerging researchers with novel ideas [224]. The complex regulatory landscape governing cancer research, especially clinical trials, can be time-consuming and challenging. Stringent ethical considerations must always be paramount in research involving human participants [225]. Variability in regulatory processes across different countries can also complicate international collaborations [226]. Finally, the persistent and unacceptable disparities in cancer incidence, mortality, survival rates, and access to care across various population groups represent a major ethical and public health challenge [227]. Addressing these disparities requires a comprehensive understanding of the contributing factors and targeted interventions to promote health equity in cancer prevention, screening, treatment, and research.

15. Conclusion and Socio-Economic Aspects

All the above considerations show that cancer research and our biological understanding of this multifaceted disease are currently facing a complex web of interconnected limitations. These include the inadequacies of preclinical models in fully recapitulating human cancer, the profound challenges posed by tumor heterogeneity at genetic, epigenetic, and phenotypic levels, the limitations in sensitivity, specificity, and accessibility of current early detection technologies, the intricate and often resistance-promoting influence of the tumor microenvironment, the ongoing quest for therapies that

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can selectively target cancer cells without harming healthy tissues, the pervasive problem of cancer cells developing resistance to treatment, and the significant gaps in our knowledge of the metastatic process.

Overarching these biological and technological hurdles are systemic barriers related to funding and resource allocation, regulatory and ethical considerations in research, and the persistent disparities in cancer research and care across different populations. Overcoming these limitations will require sustained and collaborative efforts from researchers across diverse disciplines, policymakers, funding agencies, and patient advocates. Continued innovation in preclinical modeling, advanced technologies for characterizing tumor heterogeneity and the microenvironment, the development of more precise and less invasive early detection methods, the discovery of novel therapeutic targets and strategies to enhance specificity and overcome drug resistance, and a deeper understanding of the mechanisms driving metastasis are all crucial for making significant strides against cancer. Addressing the systemic barriers through strategic funding initiatives, streamlined regulatory processes, and focused efforts to achieve health equity in cancer research and care is equally essential. While the challenges are substantial, the ongoing progress, and the promising directions for future research offer hope we can continue to unravel the complexities of cancer and ultimately improve outcomes for patients worldwide. In conclusion, there is only one real barrier: the human capacity to interact with these issues [228,231]. The problem is not only technological, but socio-political, because the ability to manage, interpret and integrate biomedical data is an organizational aspect, still rather limited today compared to the complexity of tumor diseases.

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Appendix A

This appendix tries to explain why scientific projects and discussions about cancer must be based on reliable, certain, true, and experimentally validated data, deliberating the specific context we investigate. Corning and Kline in a paper [152] discussing the role of thermodynamics and information theory defined control information in living systems as “the capacity (know-how) to control the acquisition, disposition, and utilization of matter/energy in purposive (teleonomic) processes”. I think this is an important, albeit collateral, point of discussion to justify how the flow of information existing in living systems is connected to thermodynamic processes and what can be some practical consequences. Without going into the heated discussions on the functional meaning of certain thermodynamic quantities in living beings, we can simply say that living systems are, in thermodynamic terms, open dissipative structures, far from equilibrium, which continuously need energy and matter. This requires that living organisms, as open systems and, despite entropy being a continuously growing quantity, in determining the complex functional organizational processes necessary for life, inevitably also involve local decreases in entropy.

Self-organizing functional processes require energy, but each complex function needs a highly specific pattern of relationships and interactions between its constituent parts to achieve functional emergence; without this crucial element, the system fails, and the function does not emerge. The cellular environment, where a functional module of interacting and cooperating biomolecules operates, must allow biomolecules and energy to flow freely to get locally an optimal control of the biomolecules (mass)/energy ratio, necessary for the precise control of information flows to develop a precise functional work [152]. From this arises the concomitant need to operate a quality control of these relationships, so that they are true, effective and reliable. Shannon, with the term entropy, referred to the statistical uncertainty (noise) in the transmission in a context, while "information" referred to the ability to reduce such statistical uncertainty [153,154]. Using the binary bit as a basic

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unit of measurement, we can empirically define the degree of information uncertainty (entropy) as a function of the number of bits needed to eliminate it. From an informational standpoint, noise minimization is essential. However, physically and interactively, noise reduction is contingent upon the certainty and validity of biomolecular interactions. We can achieve this only by experimentally validating protein interactions. Any interaction identified using indirect methods requires experimental validation to ensure high certainty. We could briefly summarize by saying that, if a complex living system needs energy to self-organize, it also needs a set of highly specific relational processes between the parts that operate together in context and not randomly. All this to determine the emergence of the function. It is self-evident that these principles are fundamental to any scientific planning.

We will now undertake an analysis of the aforementioned sentence, considering both its general implications and its specific relevance to cancer. That phrase describes a top level of control and understanding associated with a complex and sophisticated system, such as an organism. For simplicity and clarity, let's break the sentence down into its components:

- "The ability (know-how)": This emphasizes that it is not just about having the tools, but possessing the knowledge, skill, and practical understanding to do something. It implies expertise.
- "to control": This is the core action. It means to direct, regulate, and influence the behavior or properties of something.
- "the acquisition, disposition, and use of matter/energy,": This is the "what" is being controlled.
    - Acquisition: The ability to get or gather matter (physical substance) and energy (the capacity to do work). This could involve sourcing raw materials, absorbing nutrients, capturing sunlight, etc.
    - Disposition: The ability to get rid of, arrange, or distribute matter and energy. This could involve waste removal, storage, or the structured organization of components.
    - Use: The ability to apply or use matter and energy for specific purposes. This is about converting them into work, structure, or information.
- "in a targeted (teleonomic) process": This is the "how" and "why."
    - Targeted: Implies a specific goal, aim, or desired outcome. The control is not random but directed towards achieving something.
    - Teleonomic: This is a more formal term. It refers to processes that appear goal-directed because of the operation of a program or a pre-existing design. It's often used in biology to describe how living organisms seem to strive towards certain ends (like survival or reproduction) even though there isn't conscious intent in every cellular process. It differentiates from "teleological," which implies conscious, purposeful design, by focusing on the appearance of purposefulness because of underlying mechanisms.

The "phrase" describes the capacity of a system (whether it is a living organism, a complex machine, or even an organization) to skillfully and purposefully manage its physical resources and power to achieve specific goals. If we apply these considerations to a living organism, we have that a plant controls the acquisition of sunlight and nutrients, disposes of waste, and uses energy to grow and reproduce in a teleonomic process towards its survival. We can also do it to an advanced AI system (in a theoretical sense): If an AI could independently manage its energy consumption, acquire new data, and dispose of outdated information to achieve a specific learning or problem-solving goal, it would fit this description. But also, to a highly automated factory: It controls the acquisition of raw materials, the disposition of finished products and waste, and the use of energy to manufacture goods in a targeted process for profit.

As we can see, it is a very broad and powerful definition of intelligent and effective operation. We can also include cancer in the definition. Cancer effectively exemplifies the ability to control the acquisition, disposition, and use of matter and energy in a targeted, teleonomic process.

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- Targeted (Teleonomic) Process: The "target" for cancer cells is their own unchecked survival and proliferation, often at the expense of the host organism. Although they don't have a conscious "purpose", genetic and epigenetic alterations influence their actions, giving them a competitive advantage and making them constantly grow and spread. This appears teleonomic because the cell's entire machinery rewrites itself to achieve this singular, self-serving goal.
- Control over Acquisition of Matter/Energy:
    - Nutrients: Cancer cells often reprogram their metabolism to gain and use nutrients efficiently. For instance, many cancer cells exhibit the "Warburg effect," preferentially using glycolysis (fermentation) even in the presence of oxygen, allowing them to generate ATP and building blocks for proliferation, even if it's less efficient than oxidative phosphorylation. They "acquire" glucose at a much higher rate than normal cells.
    - Growth factors: They can overexpress receptors for growth factors, or even produce their own, thus effectively gaining the signals needed for continuous division.
    - Blood Supply (Angiogenesis): A critical aspect of cancer progression is its ability to induce the formation of new blood vessels (angiogenesis). Tumor cells release signaling molecules (like VEGF) that instruct nearby normal cells to build a fresh blood supply, ensuring a constant "acquisition" of oxygen and nutrients.
- Control over Disposition of Matter/Energy:
    - Waste Products: While cancer cells are metabolically inefficient, they dispose of their waste products (like lactate from glycolysis) into the surrounding microenvironment. This can even alter the local pH, creating a more favorable environment for their own growth and inhibiting immune cells.
    - Metastatic Spread: We also see the disposition of matter in metastasis. Cancer cells must detach from the primary tumor, break through the basement membrane, enter blood or lymphatic vessels, survive in circulation, exit the vessels, and then establish a new colony in a distant organ. This involves a highly coordinated "disposition" of their own cellular structure and movement through the body.
    - Immune Evasion: Cancer cells "dispose" of signals that would normally trigger an immune response. They can express proteins that turn off immune cells or shed antigens that would identify them as foreign.
- Control over Use of Matter/Energy:
    - Proliferation: The vast majority of the gained matter and energy is directly "used" for rapid cell division, synthesizing new DNA, proteins, and organelles to create more cancer cells.
    - Invasion: Cancer cells use energy to express enzymes that degrade the extracellular matrix, allowing them to "use" the surrounding tissue as a pathway for invasion.
    - Survival in Hostile Environments: They can adapt their metabolism and gene expression to "use" limited resources or survive in hypoxic (low oxygen) environments, which would be lethal to normal cells.
    - Drug Resistance: Cancer cells can develop mechanisms to "use" drugs ineffectively or even pump them out, demonstrating a targeted ability to evade therapeutic interventions.

In summary, cancer's progression is a powerful illustration of that "phrase". The disease, driven by a series of accumulated cellular aberrations, demonstrates a remarkable, albeit destructive, "know-how" in manipulating matter and energy to fulfill its self-serving, teleonomic drive for survival and propagation. But to study cancer, we need to consider the fundamental principles that guide a targeted teleonomic process, having reliable, high-quality information. Understanding the sentence as a broad description of cellular control and its disruption in cancer places it within the general context of cancer knowledge; however, the complex concepts expressed connect different levels of scientific understanding of cancer. There is an inherent challenge in bridging these different levels of scientific inquiry. We can indeed use the sentence "the capacity (know-how) to control the acquisition, disposition, and utilization of matter/energy in purposive (teleonomic) processes" for

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both macroscopic and microscopic levels in cancer, but we must interpret it with an awareness of the different physical laws and emergent properties at play. Therefore, we need to adapt the sentence to a multilevel framework:

1. The Macroscopic Deterministic Observational Level:

At this level, we observe the emergent properties and collective behavior of millions or billions of cells, forming tissues and organs. Here, the "know-how" of the organism is about maintaining homeostasis, regulating growth, and responding to external stimuli. At this level, we observe cancer as:

Uncontrolled macroscopic growth: Tumors are visible masses, showing a failure to control the "acquisition, disposition, and utilization of matter/energy" at a tissue or organ level. Uncontrolled growth overcomes the organism's deterministic processes for regulating organ size and function.

Metastasis: The spread of cancer cells to distant sites, demonstrating a breakdown of the organism's "know-how" to restrict cell movement and maintain tissue boundaries.

Systemic effects: Cachexia (wasting), immune dysfunction, and organ failure, which are deterministic consequences of the cancer's uncontrolled "utilization of matter/energy" for its own benefit, at the expense of the host.

Predictable patterns: While individual cases vary, there are often statistically predictable patterns of tumor growth, response to treatment, and disease progression at the macroscopic level, allowing for a deterministic view of clinical management.

Here, we largely operate under classical physics and deterministic biological models, where cause and effect are relatively clear (e.g., a tumor grows, it puts pressure on an organ, leading to dysfunction). We see this "know-how" reflected in the observable, predictable physiological processes of a healthy body.

2. The Microscopic and Deep Indeterministic Level:

This level delves into the world of individual cells, molecules, and even quantum phenomena. Here, the "know-how" becomes much more nuanced and involves:

Genetic and Epigenetic Control: Epigenetic mechanisms and DNA encode and regulate the "know-how" for cellular function at the deepest level. Mutations (random events at the molecular level) can disrupt this code, leading to a loss of the "know-how." While the mutation itself might be indeterministic (a random error during DNA replication, or damage from an environmental factor), its downstream consequences on cellular behavior can be quite deterministic at the cellular level.

Stochastic Processes in Cell Biology: Many cellular processes, like gene expression, protein folding, and even cell division timing, have a stochastic (probabilistic) component. This means that while there's an underlying "know-how" (the cell's machinery), the precise outcome of individual events can have a degree of randomness. For example, minor, random fluctuations in molecular concentrations might influence whether a specific cell undergoes apoptosis or continues to divide.

Quantum Indeterminacy: The sheer number of molecules usually averages out direct quantum effects at the cellular level, but the underlying reality of quantum mechanics remains inherently probabilistic. Some theories explore how quantum phenomena might play a role in mutations or protein interactions, adding a layer of indeterminacy at the most fundamental level.

At this microscopic level, the "know-how" refers to the intricate molecular machinery and regulatory networks that guide cellular processes. Losing this "know-how" in cancer can stem from:

Random mutations: Indeterministic events at the DNA level that disrupt the genetic "blueprint" for normal cell behavior.

Stochastic failures: The accumulation of random errors in cellular processes that, over time, can push a cell towards a cancerous state.

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Emergent properties of chaotic systems: Even with deterministic rules at the molecular level, complex biological systems can exhibit chaotic behavior, where small, unmeasurable variations lead to drastically different outcomes (e.g., whether or not a cell transforms).

How the Sentence Fits Both Levels (and Bridges the Gap):

The key to applying the sentence across these levels is to view "capacity (know-how) to control" as a hierarchical concept with emergent properties:

From Microscopic Indeterminacy to Macroscopic Determinism:

Individual molecular events might be indeterministic, but the collective behavior of many molecules within a cell, and many cells within a tissue, leads to more deterministic, predictable outcomes at higher levels.

Think of it like gas in a container: the movement of individual gas molecules is chaotic and indeterministic, but the pressure and temperature of the gas are deterministic and predictable.

Similarly, while a single mutation might be random, the selection and proliferation of cells with helpful mutations (in the cancer context) are more deterministic processes driven by evolutionary pressures within the body.

"Teleonomic" as a Guiding Principle Across Scales:

The term "teleonomic" (purposive) is crucial. At the macroscopic level, the purpose is the survival and function of the organism. At the microscopic level, the purpose of a healthy cell is to perform its specific role within the tissue, replicate appropriately, and maintain its integrity.

In cancer, the "purpose" shifts: the cancer cell's teleonomy becomes its own unchecked proliferation and survival, regardless of the organism's well-being. This re-direction of "purpose" (from organismal to cellular) is clear at both scales.

No Need for Modification, But Context is Key:

While the sentence remains unaltered, its interpretation causes contextualization based on the observer’s perspective. It serves as a powerful, unifying concept:

At the macroscopic level, it describes the observed breakdown of ordered physiological processes.

At the microscopic level, it describes the underlying molecular and cellular failures (often started by indeterministic events) that lead to this breakdown.

The "know-how" of a healthy system is robust enough to manage a certain degree of microscopic indeterminacy. When this robustness fails, cancer arises; the organism’s beneficial “know-how” then yields to the cancer cell’s selfish “know-how,” which the cell uses to gain, use, and dispose of resources for its own uncontrolled growth. This bridging of scales is a fundamental challenge and a key area of research in cancer biology.

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