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Commentary

The coming era of nudge drugs for cancer

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We propose an emerging strategy for advanced cancer treatment based on progressive, stepwise remodeling of tumor microenvironments (TMEs). TMEs are variable but show conserved archetypes across patients and tissue origins. Deep learning over single-cell atlases collected from perturbed tumors can uncover gene and cellular networks shifting between archetypes. This allows for designing "nudge" or "state-shifting" drugs whose sequential application achieves stepwise transformation of a TME from an adverse to a more favorable state, dismantling deleterious tumor-host interactions to achieve patient remission.

Introduction

The development of cancer therapeutics has historically been driven by the ultimate objective of improving patient survival. Evaluating this critical endpoint requires rigorous clinical trials, which are inherently time intensive and costly. The quest to eliminate cancer is often framed as finding therapies with substantial single-agent efficacy. To date, nearly all approved cancer treatments have demonstrated success by providing a measurable survival benefit as monotherapies, regardless of the magnitude of their effect.

Beyond measuring the duration of patient survival, additional quantitative criteria have been introduced, such as Response Evaluation Criteria in Solid Tumors (RECIST), which uses imaging methods to evaluate tumor size at early time points and has helped advanced drugs that may only be partially effective move into further development. Conversely, drugs that effectively hit their molecular target but fail to independently induce tumor shrinkage or achieve remission are often considered failures.

It is typically only after approval that we have been able to pursue combinatorial trial campaigns in which new drugs are partnered with existing ones to seek possible synergies. As a recent example of this, the dramatic success of checkpoint blockade drugs as single agents was followed by pairing them with chemotherapy, radiotherapy, and other agents to seek improved outcomes. Many clinical trials are grounded in preclinical evidence and mechanistic intuition, aiming to test combinations in which two drugs are given simultaneously with the expectation of additive effects or synergism based on their mechanisms of action.[1] In some cases, for chemotherapeutics, focus has been placed on devising second drugs that prevent resistance to the first.[2] Combinations arrived at through such mechanistic intuition have often failed due to toxicity or lack of efficacy, and even some that provide benefit, for example, ipilimumab plus nivolumab, induce severe adverse events and toxicity that result in nearly 40% of patients discontinuing treatment.[3] Crystallizing these failures, a recent study concluded that most approved combination therapies for cancer barely have additive effects.[4]

In this commentary, we step back to first consider classifications of tumors and their tumor microenvironments (TMEs). In thinking about the varieties of networks of cells in TMEs that cooperate with mutation-bearing cancer cells to permit unfettered growth, immune evasion, and metastatic spread, there are opportunities to perform precision discovery of drugs for each class of TME that may never be identified as single agents. In contrast to considering screens for new drugs based largely on modifying the tumor or the immune system in isolation, we consider the merits of searching for pathways that sequentially reconfigure their collaborations, through a series of intermediate states, to promote disease resolution. The strategy we suggest is motivated and enabled by the leaps made in single-cell genomics and deep representation learning.[5]

High-resolution methods identify TME archetypes

The concept that host cells collaborate with tumor cells to promote cancer progression is well established. As with many chronic disease states, tumors exist and grow through a semi-stable cooperation of the tumor together with immune and stromal cells and their pathways. However, TMEs vary significantly in both the quantity of immune infiltrates and the composition and density of non-immune stromal cells, such as fibroblasts. Different TMEs are expected to thus respond variably to different drugs, and the absence of this knowledge may in some cases obscure the efficacy of drugs under trial. This motivates the question: can the sheer diversity of individual tumors be classified and organized into definable classes of tumors sharing common biological features and connections between cell types?

Over the past 20 years, a series of studies have profiled tumors

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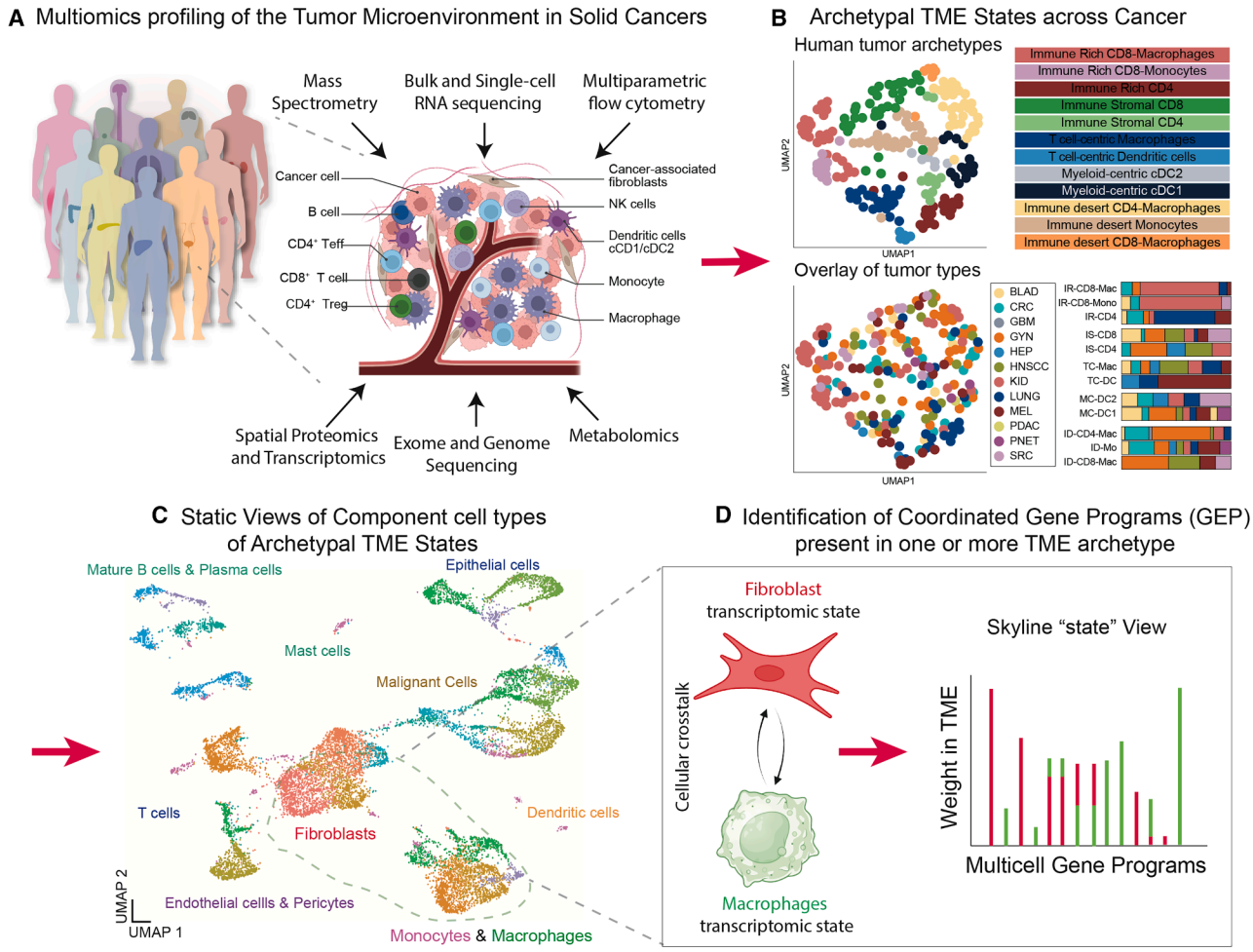

Figure 1. Technologies and clustering approaches for identifying archetypal cancer states

(A) Overview of high-dimensional assays used to characterize the tumor microenvironment (TME), focusing on compositional, proteomic, transcriptomic, and spatial features. (B) uniform manifold approximation and projection (UMAP) visualization of tumor immune archetypes from the UCSF Immunoprofiler cohort.[8] Top: Louvain graph-based clustering on a 10-feature input was used to classify patients into recurring tumor immune archetypes. Each dot represents one patient, colored by archetype. Bottom: the same UMAP, color-coded by tumor type, is shown. A stacked bar plot shows the tumor type distribution within each archetype. (C) Illustration of dimensionality reduction applied to a TME snapshot, highlighting distinct clusters that represent different cell types and cell states. (D) Inset on tumor-associated macrophages and fibroblasts, showing the coordination of transcriptomic programs between the two cell types. Left: gene expression programs (GEPs) capture coordinated activity. Right: "skyline plot": bar plot indicates gene program distribution. Columns represent GEPs with colors representing different cell types in which the GEP occurs.

independently of—and usually prior to—treatment. Chief among them is The Cancer Genome Atlas (TCGA), which has cataloged >20,000 tumor tissues by bulk RNA-seq and whole-genome sequencing (Figure 1A). More recently, enabled by the advent of single-cell omics technologies, individual tumors can now be analyzed at the resolution of tens of thousands of cell transcriptomes via single-cell RNA sequencing (scRNA-seq) (Figure 1A).

The recent advent of spatial omics (Figure 1A) has further elaborated the cellular collaborations in TMEs, including the identification of "neighborhoods" or "hubs"[6] in which key cell types are arrayed together in a subregion of the tumor. In addition, when larger tumor regions are studied at the level of composition or bulk RNA expression, more holistic "ecotypes"[7] or "archetypes"[8] spanning the tissue of origin of the tumor emerge (Figure 1B). These recurring patterns—in the frequency and composition of cell types recruited to the TME, the gene expression programs (GEP) of those cell types, and the corresponding gene expression programs of tumor cells themselves—are strongly associated to one another and to disease outcomes. One of the most interesting features of TME archetypes is how they canbe conserved across tumors originating in different tissues and at the same time how a single tumor indication can ultimately display a great variety of archetypes (Figure 1B). For instance, about half of melanomas possess a T cell- and macrophage-rich TME, while many others are classified as various forms of immune deserts.

Uncovering existing multicellular gene expression networks in a TME

Most of the existing data on shared TME subtypes lack an understanding of how drugs would differentially impact these conserved TME archetypes. To obtain

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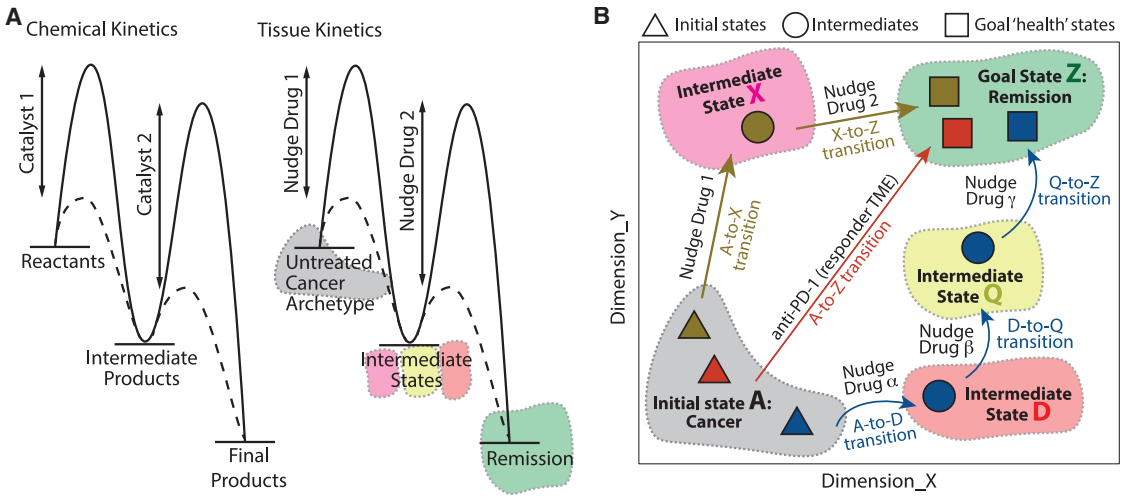

Figure 2. Conceptualization of drugs akin to chemical catalysts that promote sequential transitions in tissues

(A) A theoretical energetics diagram illustrating the initial reactant chemicals and the role of a catalyst in lowering the activation energy required for the reaction to proceed to an intermediate state. A similar conceptual transition is proposed for TME archetypes, where the application of a drug facilitates shifts between states. (B) A schematic of sequential perturbations ("nudges") in cancer treatment. The untreated TME belongs to an archetype A, which is characterized by a set of GEPs. A successful therapy shifts the original TME state A to a remission state Z. Single agents may not be able to achieve this (represented here as a direct A→Z transition). Instead, a drug agent may nudge the tumor into an intermediate state, where new GEPs (and drug targets) emerge. The new intermediate state may be susceptible to the application of a second drug agent, nudging the TME into a new state, and so forth. Ultimately, a chain of sequential treatments nudges the TME step-by-step to the end goal of tumor elimination and patient remission (represented here as A→X→Z or A→D→Q→Z transitions).

such an understanding, it may be critical not only to rely on studies of diverse TMEs from a compositional perspective but also to achieve a complete mapping of all cellular and transcriptional networks within a TME or TME archetype. We propose that this should involve both accounting for the contained cell populations (cell-specific transcriptomic programs) and understanding the transcriptional similarities among these populations (cross-cellular transcriptomic programs), both in their unperturbed state and upon drug administration. This can be achieved through matrix factorization[9] of the single-cell gene expression profiles, whereby collections of genes that tend to be up- or down-regulated in synchrony (here called gene expression programs [GEPs]) are identified, and single cells are assigned weights quantifying their usage of each GEP (Figure 1C). Mathematically, the factorization procedure discovers a set of concise, yet informative, latent dimensions (GEPs) and summarizes single-cell profiles along these dimensions. Typically, the result is a low-dimensional representation of the dataset, which is then further reduced to two dimensions by non-factorization methods (e.g., t-SNE and UMAP) for visualization purposes.

We suggest that representation learning of GEPs is particularly suited to capture TME archetypes and drug-induced TME state transitions. Previous studies have found that GEPs expressed in one cell type can be well correlated with other GEPs expressed in their neighboring cells in a variety of tissues,[10] indicative of broad biological programs linked across cell types. Furthermore, the use of GEPs enhances our ability to highlight and understand the nature of cell-cell interactions *in situ* at any given time. In this way, an archetypal state of any tissue, tumor or otherwise, can be described as a series of linked gene expression profiles acting within its component cells (Figure 1D).

When thinking about how to use such information to find new drugs, it is notable that considerable and successful effort has already gone into learning how to use high-throughput genomic screens to perturb model cells as a process for identifying novel targets or drugs that can fundamentally change a cell's behavior. In particular, Perturb-seq methods[11] allow the introduction of multiple mutations to cell lines or cell populations, followed by scRNA-seq analyses to understand the breadth of whole-cell transcriptional changes that result from each perturbation. However, studying drug or gene reactions in cells out of context and in separation from both their native archetypal partners and specific tissue organization is very likely to miss the biological feedback loops that make a chronic disease so stable. Hence, a separate strategy needs to be based around the entire network as a starting point from which to consider the useful transitions.

An emerging strategy is becoming apparent, one that integrates drug-perturbation studies, single-cell genomics, and machine learning to identify the gene and cellular networks that shift TME archetypes. We postulate that developing these methods—and the insights they yield—will be critical for answering the following questions. How might we reconceive the entire archetypal network and access hard-coded major perturbations that change the TME network? How do we leverage TME perturbation studies to understand the multi-step processes of tumor development and immune system accommodation, which likely occur differently in each archetype? And, finally, how can we learn to reverse these processes and push the entire system toward archetypes that are sensitive to tumor elimination?

A framework for steering tissues along a therapeutic trajectory

Figure 2A outlines the theoretical energetics diagram for a series of initial reactant chemicals and the effect that a

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catalyst can have in lowering the activation energy needed for them to react and reach a new state (here, the "intermediate state"). Application of a second catalyst (or the addition of another reactant) can then create a low-energy path for that collection of chemicals to react and form a final state of products. Notably, the second catalyst may have no effect, or have a different and possibly undesirable effect, if the reaction driven by the first has not occurred or is incomplete.

A tumor and its TME are effectively a nearly stable state, and we conceive it as being similar to a collection of chemical reactants in an equilibrium. Effective drugs can then be considered as lowering the energy to reach a new state. That may occur by changing the transcriptional state within a given cell (or cells) as well as by changing the relative positioning of cells within the tissue, the proliferation or viability of some cells, or recruitment from distal locations such as a draining lymph node in the case of a solid tumor. Some of those changes may reversibly occur even in the absence of an initiating drug. However, following the application of this initial drug, a new TME state is stabilized and may be able to respond to a second drug catalyst. This could occur, for example, if the receptor for that drug was only expressed following a first perturbation or if its target now has increased capacity to lead to a transition—e.g., due to reconfiguration of its ligands or binding partners. Some of these intermediate states may be reached following prolonged exposure to the initial drug.

If cancers do indeed share dominant archetypal states before drug treatment, then finding a drug combination that leads to tumor clearance and protective immunity may not be possible with the same immune-modulating drugs across all patients. However, it may be achievable for patients whose tumors initially started from the same dominant archetype. A strategy emerges in which the empirical learnings of resolution processes and perturbations for a given TME archetype can help to predict sequences of transitions that can be achieved via sequential application of multiple drugs, two or more, in a timed series (here "in sequence" is distinguished from "in combination"—which typically means two drugs at the same time). Instead of hoping to get a single drug or two drugs to move a tumor from A to Z, this approach could first find a drug that takes a tissue through the A-to-D transition, empowering administration of a second drug that takes the tissue from state D to Q and a third that carries the system from state Q to Z. In this framework, we anticipate the second and third drugs to have no effect unless the TME is brought to "receptive" states D and Q, respectively (Figure 2B).

A critical distinction between this approach and conventional combination therapy is the offset timing of drug administration. Biological systems can take time to realign following exposure to a first drug, and we postulate that a second drug may be most effective only in the tumor milieu created in the wake of the first drug's administration. As a theoretical example, the targeted depletion of one cell type in the TME may initially lead to heightened inflammation, one that restricts a measured T cell response. However, following the resolution of that phase, if a modestly stable and modified TME remains, we can hypothesize that it may more favorably license a T cell-directed therapeutic. In line with this concept, one recent study showed that CAR T therapy worked best when delivered 3 days after targeted removal of folate receptor-β-expressing macrophages but not when given simultaneously.[12] The authors of this work suggested that changes in the immune composition of the TME, established over the 3-day gap, were necessary for the improved CAR response. Other studies investigated the benefits of staggered timing of chemo- or radiotherapies and immune-modulating drugs. Our perspective offers a comprehensive framework that departs from optimizing the timing of drug administration after drug discovery and instead reorients the drug discovery pipeline toward finding promising therapies that would be missed if not considered as part of sequential administration.

In this setting, one does not presume to fully destroy tumors and activate immunity all at once, but rather to nudge the system into a receptive state from which a second drug can take you further. A model for the variety of sequences of this type, some built around checkpoint drugs, others accessing different modalities, is depicted in Figure 2B. A further benefit of these sequential nudges is the potential to reduce harmful side effects by avoiding dose-limiting escalation of single agents and therefore the compounded toxicities of co-administered drugs at high dose.

Computational methods for establishing milestones in disease resolution

The key to this approach will be to learn many real-world multicellular GEP transitions, as a community, such that we can rationally find the paths (Figure 2B) for transitioning a given dominant TME archetype to another one and eventually for reaching a tumor-eliminating archetype.

The origin of the ground truth data for this will be a direct probing of collections of tumors of different archetypes. While treating patients with large collections of existing or new drugs is infeasible, the treatment of tumor slices[13] or small fragments of cancer tissues[14] has been validated as accurately representing biological activity and responses to real-world perturbations (e.g., drugs). These studies are amenable to being performed in multiple cancer types, and, since they are amenable to scRNA-seq, they will be able to capture the real-world consequences of treating a multicellular collection of cells with many drugs across all tumor archetypes. In this way, we can learn the changes that take place in multicellular GEPs for each archetype and for each drug (Figure 3A).

Computationally, the next building block for nudge drug prediction and application is *in silico* mapping of tissue state transition that occurs following a given perturbation. A collection of GEPs describing relevant TME properties is derived through a combination of knowledge-driven and data-driven methods and is then refined to ensure their recurrence across multiple patients, conditions, etc. The GEPs serve as a coordinate system—individual tumors are represented as vectors of GEP scores, each coordinate reflecting the activity of a given GEP in the tumor. Next, drug effects are quantified as shifts in the same GEP coordinate system (shown as "skyline plots" in Figure 3B). A sequence of drugs can then be appropriated (or designed) to achieve a *stepwise* effect such that a drug-susceptible GEP is treated with the corresponding drug only after the susceptible GEP has been established (via an earlier administered drug; Figure 3C).

More generally, this is a question of *representation learning*, namely,

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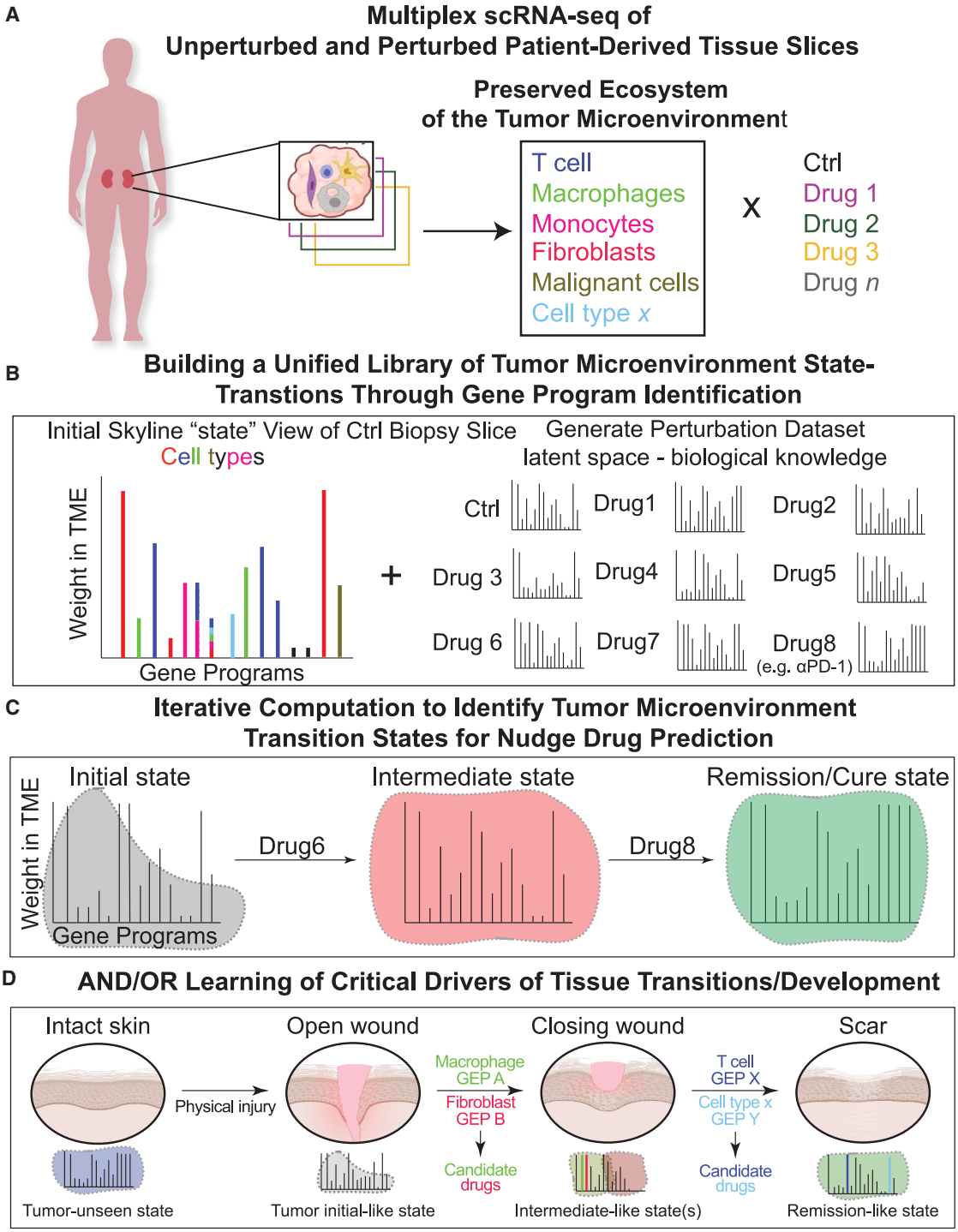

Figure 3. Real-world perturbation platforms to learn and test sequential nudge drug combinations

(A) Proposed experimental layout utilizing patient-derived tissue slice models combined with multiplex scRNA-seq to study the real-world effects of drug perturbations on a preserved TME or TME archetype. (B) Computational framework for identifying GEPs and their distribution across different cell types within the TME. "Skyline" bar plot illustrates GEP weights, with colors representing specific cell types, enabling insights into how drugs affect distinct cellular populations in the TME. (C) Iterative computational approach leveraging machine learning to identify TME transition states and predict nudge drug combinations for driving therapeutic outcomes. (D) Conceptual schematic illustrating how studying other biological processes, such as wound healing, using the same experimental and computational framework can uncover shared GEPs with the TME. This approach offers an additional avenue for identifying candidate drugs to shift TME archetypes toward improved outcomes, including long-term remission.

transforming the high-dimensional omics profiles of single cells into low-dimensional representations capturing meaningful biological patterns. The creation of perturbation atlases (Figure 3B) motivated learning representations of cell states by deep generative models that can then be used to predict the outcomes of perturbations,[15] including unseen and combination perturbations. Generative models can already predict perturbation responses through latent-space arithmetic. Newer work applies single-cell foundation models—self-supervised neural networks pre-trained on vast datasets and subsequently adapted to perform desired downstream tasks—to predict perturbation response. Building such foundation models for tumor archetypes should enable *in silico* predictions for unseen perturbations.

Another avenue for discovering "nudge drugs" will come from time-resolved analysis of other biological processes, notably those that result in resolution, such as healing of wounds, or from studies of the development of tissues or organs. In the framework of tissue biology, nature already encodes some of the fastest low-energy transitions. In such time-resolved studies, cell states can be observed as they evolve and co-evolve in tissues undergoing transformation[10] (Figure 3D). Furthermore, this type of study has been able to discover component gene products of a GEP that can induce the next set of GEPs.[10] Such studies illuminate how the new drugs needed for these types of strategies may be specifically defined from time-resolved studies. We can track nature's trajectories for resolution and evolution of tissue states, and we can then test drugs that target or are the key drivers of those transitions. In this sense, cancer treatments may be learned by studying other biological transitions. Application and validation of the nudge sequences will likely take place not only in on-slice/on-fragment perturbations (Figure 3A) but also in basket clinical trials or in some cases via well-validated mouse models.

The path ahead

Throughout the history of cancer research and therapeutic development, patient outcomes have remained the gold standard for evaluating drug efficacy. However, the inability to precisely characterize the impact of each therapeutic agent—particularly when it does not achieve remission as a monotherapy—has biased drug discovery toward single-agent approaches. This limitation has likely resulted in the premature dismissal of clinical trial data without fully understanding the biological effects of a given drug.

In reality, effective cancer treatments must operate within highly complex biological systems, where a single agent may not independently induce durable responses. However, this does not imply a pure lack of therapeutic activity. Every drug influences a trajectory of tumor evolution, and without subsequent interventions—potentially ineffective on their own but critical in a sequential strategy—the system may ultimately revert to its original state or reach ineffective semi-stable states (such as senescence). To address this challenge, the integration of high-dimensional data and advanced computational tools is essential. By leveraging insights from perturbation-based studies, we can better identify transitional states that render tumors more susceptible to follow-up therapies. This approach has significant clinical implications, as it could enable a paradigm shift in drug development—moving beyond a rigid focus on single-agent efficacy toward a more nuanced understanding of therapeutic synergies. Such a framework is urgently needed to overcome the limitations of current drug discovery strategies and to optimize treatment sequencing for improved patient outcomes.

The challenge lying ahead is generalizing the methods we describe above by combining two research directions. Namely, the field will benefit from the combination of (1) high-dimensional data collection of the organization of cell networks and their responses to existing and new real-world perturbations (i.e., drugs) and (2) the development of computational models that accurately define both states and their available transitions. Clinical trials may increasingly need to collect initial high-dimensional molecular profiling/archetyping data about a TME to facilitate application of these principles. Data sharing and the generation of complex datasets from intact or nearly-intact tissues subject to perturbation will be critical. So too will be the coordinated generation of high-dimensional molecular data in clinical trials that will provide ground-truth datasets as this approach is put into practice and, ultimately, refined.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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