Cancer Cell

CellPress

Commentary

Charting the tumor antigen maps drawn by single-cell genomics

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https://doi.org/10.1016/j.ccell.2021.11.005

The remarkable specificity of antibodies has enabled precision cancer immunotherapies, including chimeric antigen receptor T cells and antibody-drug conjugates. In parallel, single-cell genomics technologies present the possibility of a comprehensive annotation of antigen expression throughout tissues of the human body and on cancer cells. We reflect on the rationale for antigen targets currently used in immunotherapies, their adverse effects revealed in the clinic, and the opportunity to utilize large genomics datasets to de-risk potential targets and nominate optimal antigens for therapy.

Over a century ago, the German chemist and Nobel Laureate Paul Ehrlich reasoned that if we could design a compound that selectively targeted a disease-causing agent, we should be able to kill a pathogen without harming the host (Strebhardt and Ullrich, 2008). Since then, the concept of Ehrlich's *zauberkugel* or "magic bullet" has captured the imaginations of researchers who seek a viable therapy that effectively and specifically treats disease. Despite many remarkable accomplishments that emerged from his laboratory, Ehrlich struggled to identify an effective and selective treatment for cancer. He had dozens of failed experiments using aniline dyes and alkylating agents as chemotherapy. Eventually, Ehrlich mounted a sign outside his cancer research laboratory reading, "Give up all hope oh ye who enter." Though enticing, the concept of precision oncology—therapies that target cancer without affecting the rest of the body—appeared to be more imagination than reality.

In the decades that followed Ehrlich's conceptualization, emerging therapeutic modalities have reinvigorated the possibility of magic bullets against cancer. With rare exceptions, the development of chemotherapeutic drugs or other targeted small-molecule therapies against cancer-specific targets has been challenging (with imatinib for chronic myelocytic leukemia as one of a few notable exceptions). Specifically, these drugs tend to modulate targets that are expressed in multiple tissues throughout the body, and the drugs often lack the requisite therapeutic index needed to kill cancer without causing serious adverse effects in other tissues (Chang et al., 2021). However, immunotherapies that capitalize on the exceptional specificity of mammalian antibodies have unlocked new possibilities, making therapies possible by honing of cytotoxic agents to cancer cells (Carter and Lazar, 2018). In particular, three specific modalities, antibody-drug conjugates (ADCs), bispecific T cell engagers (BiTEs), and chimeric antigen receptor T cells (CAR T cells), each couple a specific antibody binder to a different cytotoxic partner—either a chemotherapeutic drug, an engaged native T cell, or an engineered T cell, respectively. Ultimately, these methods provide a rationale for selectively killing cancer cells without harming other cells in the host.

In recent years, clinical data have demonstrated that these precision therapies are not only conceptually plausible but also have delivered exceptional outcomes over the previous standard of care. In particular, CD19-directed CAR T cell therapies have yielded durable clinical benefits for B cell malignancies whereby approximately 43%–71% of patients with certain lymphomas achieved complete remission in recent trials (Schuster et al., 2017). However, nearly 40% of patients treated with these CD19 CAR T therapies experienced neurotoxicity, and similar neurological adverse events have been observed in patients who received CD19/CD3-BiTE therapies (Klinger et al., 2020). Noting the quantitative and qualitative difference in the incidence and presentation of neurotoxicity in CD19-directed therapies compared to those directed at CD20/CD22 (all B cell antigens), we recently hypothesized that "on-target, off-tumor" effects driven by other cell types that express CD19 may contribute to this common adverse neurological effect (Parker et al., 2020). Indeed, we utilized large-scale single-cell genomics analyses to characterize a rare population of mural cells that line the blood-brain barrier and that express CD19 (but not CD20 or CD22). Our analyses indicated that these mural cells may be targeted by BiTEs and CAR T cells, producing a potential mechanism for the neurotoxicity that could be explained by the target antigen (Parker et al., 2020). Importantly, because mural cells are extremely rare and B cells can infiltrate tissues, such a determination was not possible through the use of older-generation technologies (e.g., bulk RNA-seq, microarrays, or proteomic methods) that do not quantify antigen expression at the single-cell resolution. More generally, our approach showcased the use of single-cell genomics as a tool not only to assess potential off-target toxicities and to de-risk candidate antigens, but also to nominate optimal targets in a data-driven manner.

Conceptually, we propose that the ideal targets for ADCs, BiTEs, CAR Ts, and other forms of antigen-directed therapies can and should be identified in a fully data-driven manner (Figure 1). For example, in

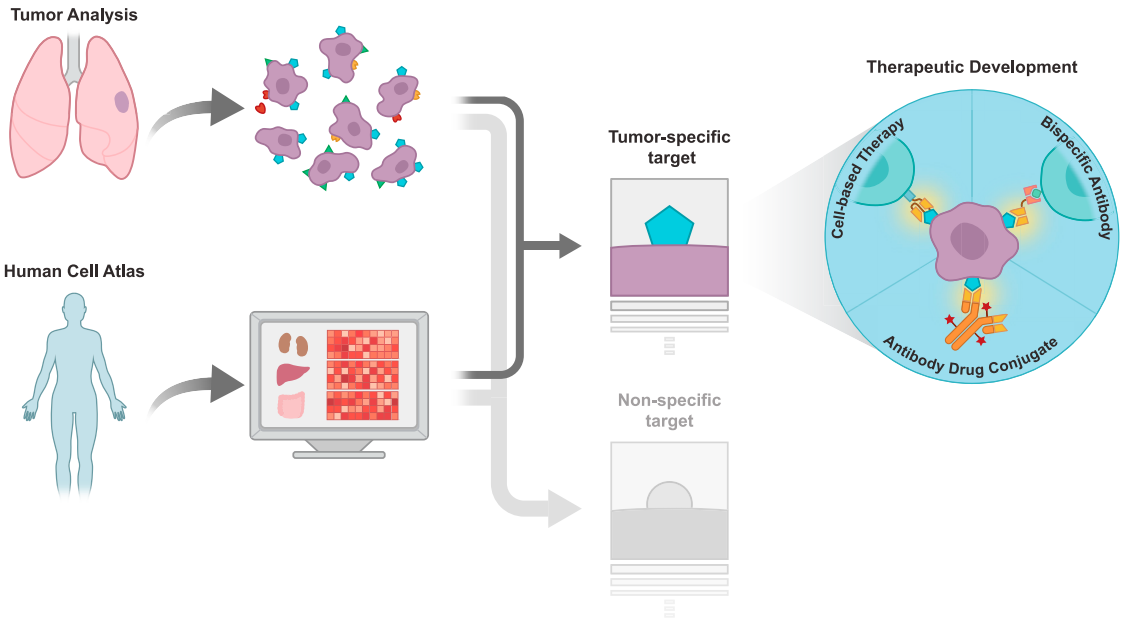

Figure 1. Discovery of optimal antigens for precision therapies via single-cell genomics
Shown is a schematic of potential antigen targets that may be identified via large-scale, single-cell atlases and prioritized via on-tumor attributes. The intersection of large-scale single-cell genomics datasets may be used to identify optimal cancer-specific antigen targets and de-prioritize non-specific targets found on indispensable cell types. For optimal targets nominated via single-cell atlases, several antibody-based therapies may be utilized (right), including antibody-drug conjugates, bispecific antibodies, or cell-based therapies.

the case of leukemias and lymphomas, the inference of true B cell-specific targets, both individual and combinatorial, could eliminate off-target honing to important cell types, such as mural cells, or minimally provide an indication of potential adverse effects to be closely monitored during treatment. To achieve this vision, we would require a full understanding of antigen expression across all cell types of the human body. Fortunately, recent advances in single-cell genomics technologies have made it possible to create massive reference maps of gene expression across a breadth of human tissues as well as their alterations in disease. The strength of genomics is the ease and affordability of making comprehensive measurements in a large number of cells with relatively standardized library preparation protocols. Therefore, the possibility of optimal targeted therapies may be realized via large-scale single-cell maps. Here, we reflect on antigens that are currently targeted in precision oncology, their shortcomings, and the challenges that limit the discovery of ideal targets for cancer therapy.

Current targets

In reflecting on the current landscape of tumor antigens for immunotherapies, an obvious question emerges: *How did we choose the current targets used in the clinic*? In a workflow similar to that shown in the paper by Jing et al. (2021), we aggregated the most common antigens for targeted therapy in an effort to understand the rationale for how cancer antigen targets were identified. We have identified three rationales that have been used to nominate existing targets: (1) genes known as cell lineage markers with shared expression on both healthy and malignant cells of that lineage; (2) genes identified as being overexpressed in tumors relative to corresponding tissue; and (3) true cancer-specific targets that are not appreciably expressed in any normal adult somatic tissue.

The most common targets belong to the first class, and these include markers such as CD19, CD20, CD22, and BCMA, each of which have been targeted in B cell malignancies. All of these were identified during the 1980s and 1990s through the use of low-resolution molecular techniques such as subtractive hybridization and cDNA library screening. Importantly, these surface proteins represent the lineage-defining markers that occur not just on tumor cells but also on healthy B cells. Fortunately, because B cells are not necessary for human survival in homeostasis, these relatively crude targets remain viable, and this evokes an important consideration for the identification of new targets: even if an antigen is expressed on other healthy cells, such targets may make for effective therapies if the on-target, off-tumor cell types are dispensable.

Beyond these lineage-defining markers, the characteristic cellular dysregulation during oncogenesis often coincides with a global reprogramming of gene expression within cancer cells. This leads to a second class of targets: antigens that are overexpressed in cancer relative to healthy cells. For example, HER2 and mesothelin were identified in the 1980s and are expressed in homeostatic cell types. However, both are vastly upregulated in cancer through copy number alterations or altered gene regulatory circuits. In contrast to the aforementioned B cell targets (which are not significantly overexpressed in cancer cells relative to healthy cells), the overall antigen abundance of targets in this second class generally enables a more proficient killing of cancer cells via a specific antibody binder. Ultimately, these targets indicate that the overall antigen abundance and its interaction with specific binders must be properly tuned in order to maximize on-target, on-tumor killing (Majzner et al., 2020). Thus, though

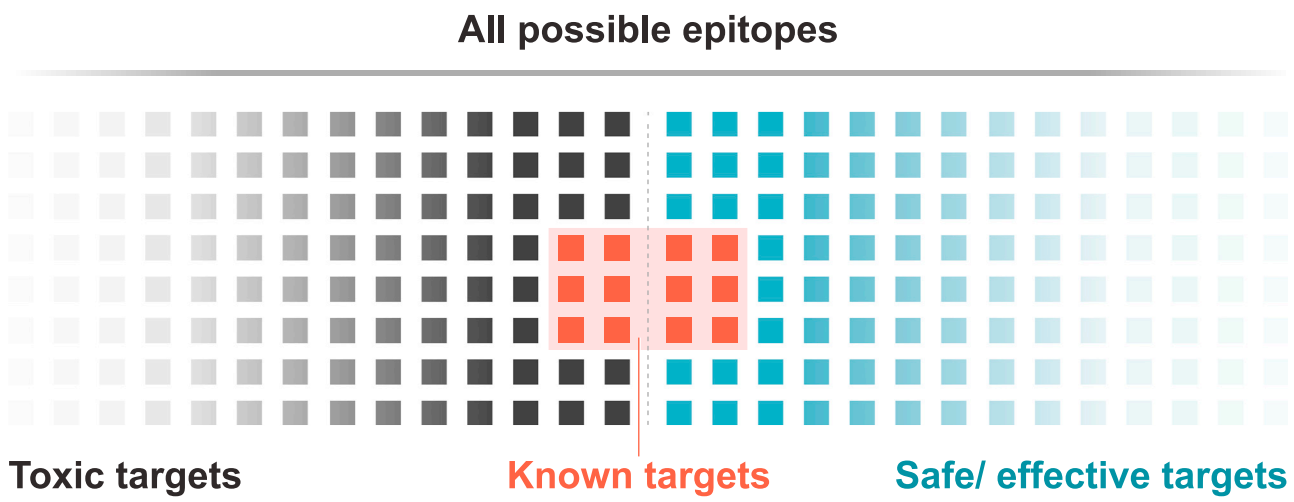

Figure 2. Landscape of known and unknown epitope targets in cancer
Shown in red is a schematic of known targets which are currently used in the clinic and that possess undesirable attributes, including targeting indispensable cell types such as mural cells. Conversely, additional epitope targets for precision therapies (blue) have yet to be discovered. Integrative analyses of single-cell genomics datasets facilitate the discrimination of these antigen classes and the ability to identify additional safe and effective targets depicted in blue. Note: the true sizes of these classes may not be represented by the relative size in this figure.

imperfect, the extreme overexpression of genetic targets may indeed provide useful targets for cancer antigens.

Lastly, antigens such as NY-ESO-1 represent ideal targets strictly in the context of specificity. NY-ESO-1 (CTAG1) was identified in 1997 through the screening of cDNA libraries derived from tumors (Chen et al., 1997). Through a series of RT-PCR and Northern blot analysis of five tissues, the expression of NY-ESO-1 was determined to be restricted to cancer. Our current understanding of NY-ESO-1 is that its expression is restricted to immune-privileged tissues, including the testes and placenta. Although large-scale genomics datasets have corroborated the restricted expression of NY-ESO-1, we note that at its discovery, the validity of the tumor-restricted claim was insufficiently supported by low-throughput experimental techniques.

Altogether, after surveying the landscape of existing targets, we conclude that high-dimensional genomics technologies have not yet been fully leveraged as a means for identifying or de-risking potential therapeutic targets. We suggest that this shortcoming presents a unique opportunity to capitalize on the vast amounts of high-dimensional data to expand the reach of clinically targeted antigens to additional targets that may be safe and efficacious with current immunotherapies (Figure 2) and to improve on many already existing and promising antigen targets that have been identified through less robust methods and techniques.

On-target, off-tumor toxicity

Noting that high-dimensional data have not been routinely utilized in the pre-clinical study of targeted therapies, we emphasize that most of our understanding of toxicity has been derived through clinical observations from early-stage clinical trials. However, prospective data-driven de-risking of targets could dramatically change the speed and safety of new targets brought into the clinic.

In addition to the widespread neurotoxicity phenotype that is associated with CD19 BiTES and CAR T cells, several other toxicity phenotypes have been observed. In one study, use of an ADC against a hypothesized cancer-specific isoform of CD44 resulted in the development of toxic epidermal necrolysis and death of a patient (Tijink et al., 2007). Additional analyses ultimately revealed that keratinocytes also expressed the targeted isoform, resulting in a lethal on-target, off-tumor side effect. Similarly, trials that utilized carboxyanhydrase-IX (CAIX)-specific CAR T cells resulted in patients developing cholestasis due to expression of CAIX on the healthy bile duct epithelium (Lamers et al., 2013). More recently, clinical trials assessing FLT3-targeting BiTEs and PSMA-directed CAR T cells have been suspended. Furthermore, a recent report suggests that BCMA-directed CAR T therapy may be responsible for features of parkinsonism, including neurocognitive and hypokinetic movement disorders observed in patients from a recent trial (Van Oekelen et al., 2021). Although further analyses of patient side effects are ongoing, a cursory examination of single-cell transcriptomic data confirmed the presence of these antigens expressed in cells that comprise healthy tissues throughout the body. For example, the expression of BCMA was reported to be present on neurons and astrocytes (specifically in the basal ganglia), which was explicitly confirmed utilizing cells from the patient experiencing features of parkinsonism (Van Oekelen et al., 2021). This collection of clinical evidence indicates that on-target, off-tumor toxicity is currently a pressing problem that will continue to impact early-stage trials unless it is systematically addressed. In this sense, comprehensive analyses should utilize multi-tissue cell atlases, such as those shown in (Jing et al., 2021), that can identify and eliminate potentially risky genes in targeted therapy.

We further note that the expression of the antigen may vary under a range of physiological conditions. As an example, there is a profound induction of CD38 and CD123 (potential antigen targets in acute myeloid leukemia) in human endothelial cells upon stimulation with IFNγ

and TNFα (cytokines that are often upregulated in the presence of CAR T cells or other immunotherapies) (Richards et al., 2021). Because the characterization of antigen expression in a variety of physiological conditions represents an added complication, we suggest that multiple cell atlasing efforts will be required to chart antigen expression in homeostasis as well as in disease states.

Single-cell measurements

Our identification of rare (approximately 1 in 1,000) $CD19^+$ mural cells lining the blood-brain barrier motivates the routine use of single-cell data to robustly identify on-target, off-tumor effects (Parker et al., 2020). Here, the ease and accessibility of single-cell transcriptomic sequencing, driven by innovations in droplet-based library preparations and next-generation sequencing, have opened the possibility of a complete antigen expression atlas that could both de-risk antigens and accelerate the nomination of improved targets. However, added layers of biological regulation can cause the recognition of specific antigens to deviate from their underlying gene expression value.

As a specific example, $CD4^+$ T cells express low levels of the CD4 transcript but very high levels of CD4 protein (Stoeckius et al., 2017). This inequality of readily measured transcriptomic abundance to the actionable protein abundance has motivated the development of sequencing-based technologies for protein detection, including the cellular indexing of transcripts and epitopes by sequencing (CITE-seq) that utilizes oligonucleotide-conjugated antibodies (Stoeckius et al., 2017). Notably, successful applications of CITE-seq have demonstrated simultaneous protein detection of nearly 300 antigen targets with the theoretical capacity to scale to thousands of epitopes. For the purposes of current targeted therapies, single-cell proteomic quantifications undoubtedly represent a more accurate measurement of potential off-target expression. In this example, potentially indispensable cell types may be expressing the CD4 epitope without a meaningful abundance of the CD4 transcript, thus confounding interpretations about off-target expression. Therefore, although initial versions of large, single-cell atlases will focus on transcriptomic measurements, we anticipate that multiomic measures will be required in order to fully identify and de-risk antigen targets. In this sense, multiple iterations of the Human Cell Atlas will be necessary, akin to the now refined human genome reference nearly 20 years after its initial draft. Therefore, we anticipate that all antigens for targeted therapies, whether approved, in clinical trials, or in development, must be regularly interrogated against up-to-date antigen maps charted by consortia and smaller-scale efforts led by individual groups.

What are the challenges ahead?

Although current targets have been nominated through less comprehensive means, key lessons have been learned through their clinical monitoring but have relied on anecdotes thus far. For a proper, data-driven optimization of cancer targets, these anecdotes must be generalized into rules that govern the selection of actionable targets. To establish clear guidelines for advancing new targeted therapies, we identify key questions that must be addressed.

First, what are the cell types that are dispensable or targetable in the body, and how might these change as a function of age, sex, or related attributes? As the clearest example of this, anti-CD19 therapies target healthy B cells in addition to malignant cells. Thus, the clinical success of CD19-directed therapies is due to the fact that patients can survive without healthy B cells. We anticipate that the targeting of other cell types may be tolerated or clinically manageable in patients and that genes normally selectively expressed in these cells may represent a promising and untapped reservoir of cancer targets.

Second, what is the difference in expression between cells in a patient's tumor and the next-highest healthy cell type that makes a given gene "targetable"? In effect, how should we conceptualize and predict the therapeutic index of a potential target antigen, given expression on cancer and healthy cell types? As with targeted small molecules, different targets may have distinct therapeutic indices that could dictate overall success or toxicity depending on range of exposure, thus separating an efficacious dose from a toxic dose (Chang et al., 2021), which may be distinct for the different modes of precision therapy. In the case of antigens that are normally expressed in healthy cell types, such as HER2 and Mesothelin, the higher abundance of the antigen on malignant cells relative to healthy cells makes therapeutic targeting possible. With these targets in mind, this leads to an obvious question: can we identify a binder with an appropriate affinity to target cancer cells without significant cytotoxicity to healthy tissues?

Finally, what are the physiological factors that underlie antigen expression? By immunohistochemical staining, we previously observed marked variability in CD19 expression in blood vessels, and this may be due to differences in abundance within the mural cell population or due to inter-patient differences in mural cell frequency (Parker et al., 2020). In turn, this observed variability in target antigen expression may underlie patient-to-patient variation in adverse effects, such as the CD19-associated neurotoxicity. To address this challenge, we recommend comprehensive efforts such as the Human Cell Atlas to map antigen expression across a diverse group of donors in order to account for age-related variation as well as expression differences linked to genetic ancestry. In particular, we emphasize that current large-scale genomics datasets on tumors have resulted in atlases in which donors of European ancestry are vastly overrepresented, ranging from 73.3%–91.1% of all genomic libraries (Guerrero et al., 2018). However, profiling tissues from ancestrally diverse donors is required to ensure equitable benefits for these promising new therapies, including minimizing risk to all populations that may receive these therapies. Importantly, antigen levels may be highly dynamic in the context of inflammation or other conditions induced by a given treatment.

Ultimately, once discovered, the expression of the targets in these therapies must be screened regularly in a clinical setting. Thus, a new lexicon of tumor diagnoses should be established in order to characterize the molecular features that can be targeted by approved therapies. We note that refinement of tumor classifications has already occurred with advances in new and emerging technologies, including the identification of specific mutations driving oncogenic programs. Our proposed lexicon would define tumors based on patterns of antigen expression that could be directly linked to actionable, targeted

immunotherapies. In this framework, a complete assessment of antigen expression, including a potential target's level of expression per malignant cell, overall heterogeneity on cancer cells, and co-occurrence with other markers for combinatorial targets, would be required features for an effective molecular characterization and classification. In other words, current conventions that note whether a tumor is "positive" for a single marker are inadequate to supply sufficient information for clinical decision making. Rather, a quantitative characterization within tumors relative to a healthy reference may dictate a more appropriate antigen binder for efficacious therapy.

In total, these challenges span a range of basic and clinical sciences—from the molecular biology of antigen-binder interactions to how patients' tumors are identified and diagnosed. Although the prospectof highly specialized therapies that target tumor-specific antigens are attractive, the challenges noted here will require decades of integrative research and clinical collaboration to attain actionable stratification of tumors based on antigen expression.

Outlook

The advent of precision therapies like ADCs, BiTEs, and CAR T cells have crafted the mold for a magic bullet for many cancers—a far cry from the foreboding testament advertised outside Ehrlich's laboratory. Although we share in the excitement about the unique opportunity of directing the targeted therapies to the right cells, we emphasize the breadth of complications and challenges that must be overcome to reach this goal. Specifically, a comprehensive resource that decomposes variation in antigen expression across cell types, patient age, ancestry, sex, and physiological exposures may be required in order to properly de-risk antigen targets before *in vivo* human testing. In the absence of such a comprehensive map, the inefficient and often fatal inference of new "on-target, off-tumor" toxicities will be discovered only after early-stage clinical trials.

In conclusion, we posit that the significance of antigen presence and abundance on cancer cells elicits a key dimension for tumor classification beyond histological grade or oncogenic somatic mutations. We anticipate that as more targeted therapies are discovered and de-risked by large-scale single-cell atlases, characteristics of targetable antigens on tumors may emerge as a feature that is highly predictive of clinical outcomes for patients. As such, we envision a comprehensive characterization of potential cancer-specific antigens that is driven by innovations in single-cell genomics and proteomics. After these antigens have been mapped and vetted against a complete Human Cell Atlas, we suggest that routine assessment of surface antigens for individual tumors may identify personalized and optimal strategies for precision therapies. If this vision is realized in the coming decades, Ehrlich's conception of a magic bullet—a therapy that kills cancer without any other side-effects—may indeed be speeding toward its elusive target.

ACKNOWLEDGMENTS

We are grateful to members of the Satpathy Lab for helpful discussions and to SciStories for assistance with the figures. C.A.L. is funded by a Stanford Science Fellowship. C.A.L. and A.T.S. are supported by research awards from the Parker Institute for Cancer Immunotherapy. A.T.S. is supported by a Technology Impact Award from the Cancer Research Institute, a Burroughs Wellcome Fund Career Award for Medical Scientists, and a Pew-Stewart Scholars for Cancer Research Award.

DECLARATION OF INTERESTS

C.A.L. is a consultant for Immunai and Cartography Biosciences. K.R.P. is a founder of Cartography Biosciences. A.T.S. is a founder of Immunai and Cartography Biosciences. A.T.S. receives research funding from Arsenal Biosciences, Allogene Therapeutics, and 10x Genomics.

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