Evolving Antibody Innovation: New frontiers in cancer R&D

DRUG DISCOVERY Fifty years after the invention of hybridoma technology, biologics have become a cornerstone of oncology drug discovery and development. From the first monoclonal antibody approval in 1995 to today's complex antibody formats and cell-based therapies, biologics are reshaping cancer drug discovery. Yet, despite remarkable progress, the urgent need for novel targets that can exploit recent technological developments remains high.

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One of the striking changes in drug approvals by the US Food and Drug Administration (FDA) is the steadily increasing portion of biologics in the approval portfolio over the past 25 years: In the mid-1990s, only 8% of approved drugs were identified as biologics, a portion that increased ~4-fold to 31% of new approvals in the 2020 to 2024 interval [1]. Most of these biologic drugs are antibodies. While the therapeutic potential of antibodies dates back 100+ years, it was the invention of hybridoma technology 50 years ago that enabled production of monoclonal antibodies as drugs and clinical utility.

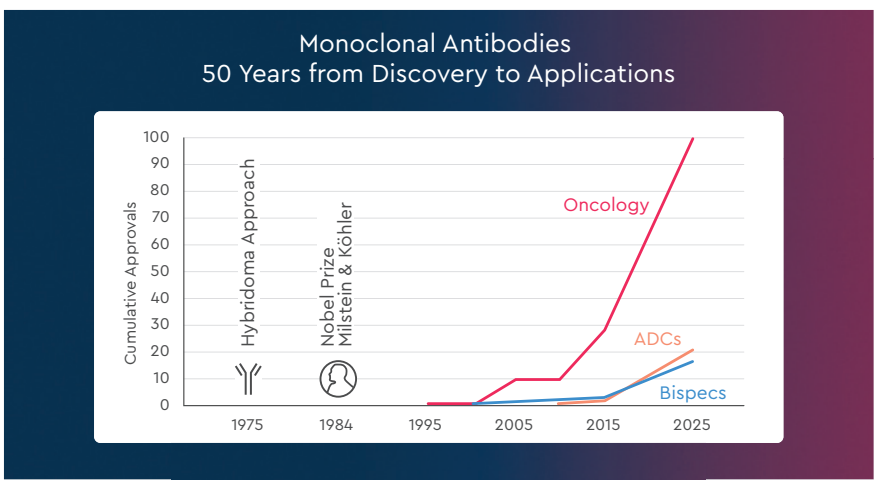
A shift towards antibody-based drugs

In August 1975, Köhler and Milstein published the hybridoma technology and were awarded the Nobel Prize for this work a few years later in 1984. The approach enabled the generation of a single "antibody of predefined specificity" and prompted a revolution in the potential for designing new antibody-based drugs. These biologics can now be generated at any scale with reproducible quality matching chemically defined drugs [2]. This is reflected in their clinical use: The approval of monoclonal antibodies (mAb) for therapy started only 20 years after the initial publication, in 1995 (Figure 1). Today, oncology indications account for about one half (~100) of approved mAb therapeutics worldwide followed closely by autoimmune and infectious disease indications.

Antibodies enter the clinic

The initial generation of antibodies targeted functional pathways similar to a small molecule drug and sought to impact cell function. Some of the biggest successes were the targeting and blockade of growth factor pathways in cancers and the discovery of immune cell activation checkpoints, which can be inhibited by antibodies to activate dormant immune cells. Recent antibody technologies provide a further set of tools to tackle cancers, Antibody Drug Conjugates (ADCs), where a toxic drug is delivered to tumors. This "magic bullet" concept was proposed in the early 1900s by Paul Ehrlich and has been shown to yield significantly improved outcomes over "naked" antibodies in the treatment of cancers, winning approval for ~20 different entities so far.

Another antibody engineering development packs multiple antibody recognition sites into a single antibody molecule. By leveraging two targets, bispecific antibodies can shackle immune cells to cancer cells or hit multiple cancer hallmarks simultaneously and thus increase antibody/tumor selectivity.



Approvals of antibody-based therapies have accelerated sharply since 2000 with oncology dominating the landscape, newer modalities like ADCs and bispecifics gaining momentum [2]

Approval of bispecifics in the last few years is also on the rise due to their treatment efficacy (Figure 1).

Need for novel targets remains

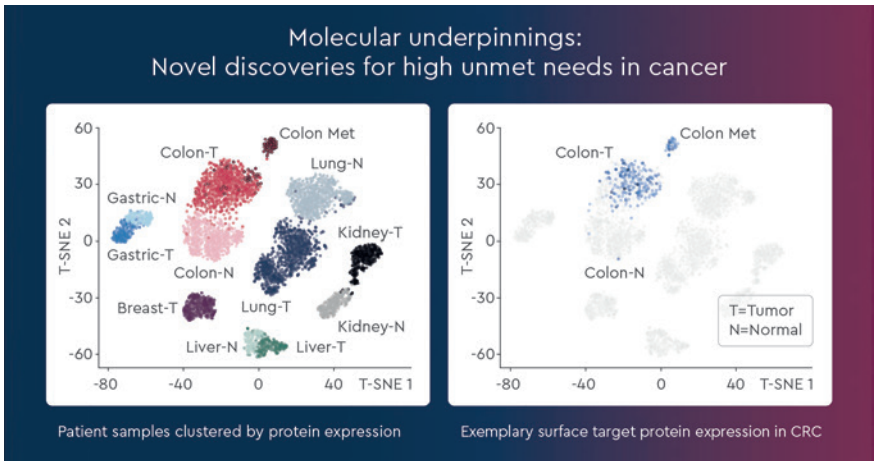
To translate these advances in antibody engineering into breakthrough therapies, the discovery and development of novel targets beyond the usual suspects becomes the key challenge. Luckily, several parallel developments improved our ability to meet these challenges: Molecular analyses of cells and tissues ("omics") became affordable at large scale and the computational power and tools to store and process these complex omics data became ever more refined and cheaper. Thus, it has become feasible to identify those molecules that distinguish cancer from normal cells and adapt antibody targeting to that. Also, rate-limiting growth pathways can be identified and nominated for targeting surface receptors. A technological basis that together with the molecular underpinnings and today's abilities for comprehensive disease understanding will build new frontiers in cancer drug discovery and development.

Patient insights guide discovery

The foundation for an in-depth understanding of the underlying biology of cancer and for novel target discovery lies for Indivumed at the very beginning of their R&D approach. Indivumed built a large repository of well curated tumor and adjacent normal tissues focusing on minimal cold ischemia time. A recent study in nature's Cell Death & Disease [5] has demonstrated that numerous differentially expressed proteins are affected by tissue ischemia time and differential expression of many potential tumor targets disappear after 12 minutes. A unique starting point, that makes a difference in novel discoveries.

Large-scale proteomic profiling of thousands of patient samples revealed clear clustering of tumor and normal tissues with a distinct protein expression across cancers and tissue types, with each dot representing one patient (Figure 2a).

With the overlay of the expression of a single cell surface protein across all samples, the protein is detected in about half



Analysis of Tumor and Normal tissue protein expression (a) paves the way for target discoveries illustrated by the distinct tumor expression of a surface molecule (b)

of the primary and most of the metastatic colorectal cancer (CRC) specimen (Figure 2b). Expression is below detection in other cancers and normal tissues. As a proof-of-principle, this selective expression of the surface protein nominates it as an attractive target for the development of antibody therapeutics such as ADCs.

Furthermore, the patient-based material contains tumor as well as associated stroma and facilitates definition of surface targets as the basis of bispecific immune cell recruiters discussed above. The tissue specimen-based target discovery approach should increase selectivity toward cancer tissues and reduce the risk for adverse events based on low or lacking expression in healthy tissues.

Combinations for lasting success

Cancer treatment has taught us that combinatorial therapies are needed for the best success and least adverse events and will include small and large molecules. Beyond antibody recognition and targeting of cell surface proteins, understanding the molecular underpinning and the contribution of different drivers of malignancy has provided a plethora of opportunities for combinations that target cancer vulnerabilities. A highly successful field of targeted therapeutics has focused on inhibitors of receptor and intracellular kinases that provide potential partners in treatment combinations with antibodies [3]. Such combination partners would also include recently developed inhibitors of a central driver in different lethal cancers, oncogenic RAS that had evaded discovery of an efficacious inhibitor for decades [4].

Establishing a successful combinatorial treatment paradigm companion to augment antibody targeting is a slow and complex process built on in-depth understanding of the molecular networks targeted as well as expected adverse events. Antibodies have become valuable drugs in a relatively short time due to their potential for innovative drug design that takes advantage of the molecular makeup of cancers and minimizes the risk for adverse effects. Uncovering and validating novel targets for antibody-based drugs and integrating them into the patient care is a promising and exciting frontier that Indivumed is driving. ■

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