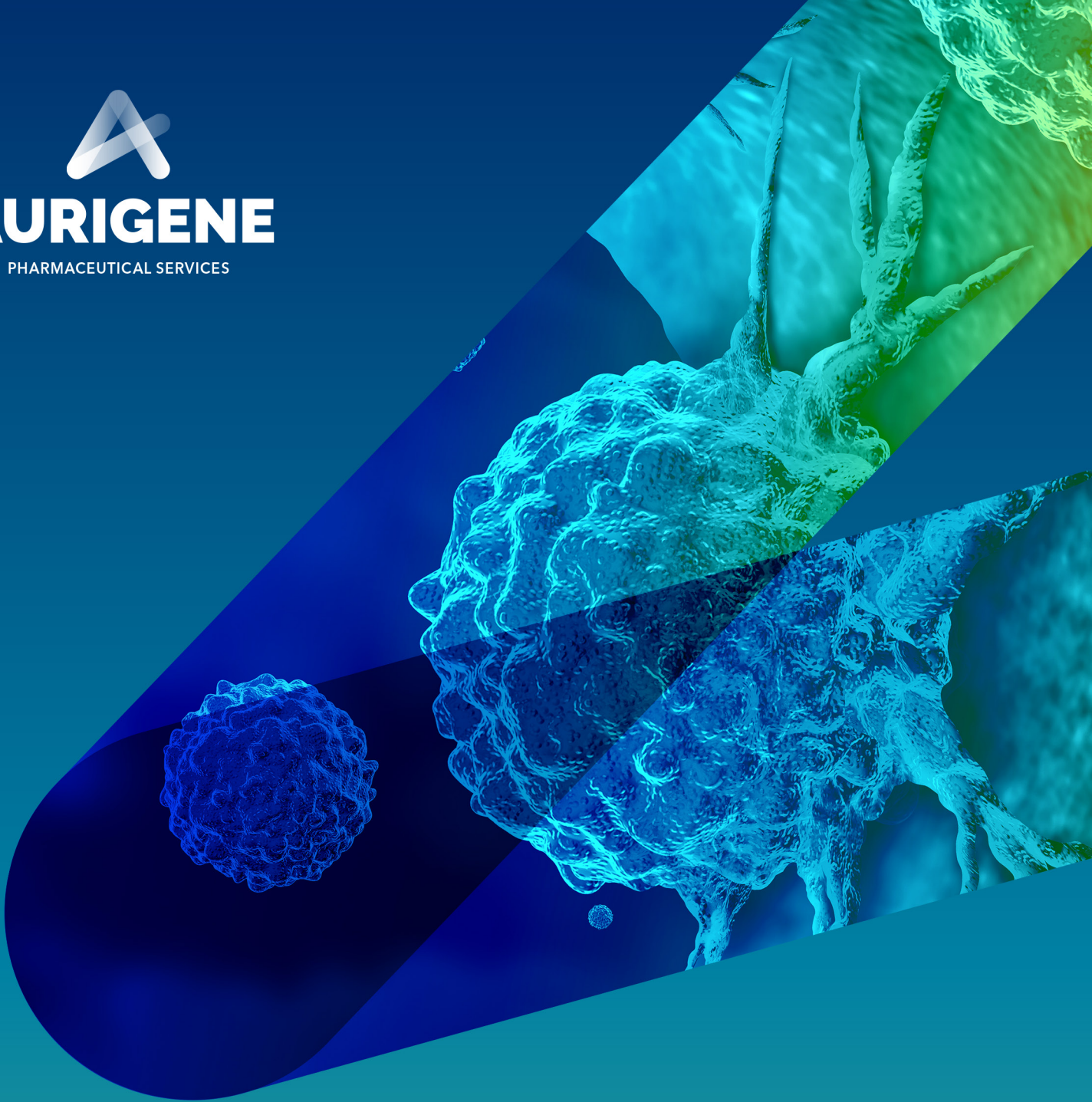




Immuno-Oncology:

Therapies and challenges



Introduction

With more than 200 distinct cancer types recognized and steady increase in cancer incidence rates, the fight with cancer takes a new shape with each emerging decade. First was surgery, followed by radiotherapy and chemotherapy. The fourth one was targeted cancer therapeutics, also known as precision therapies. Precision therapies were established with the discovery of imatinib by Glivec Novartis in late 1990s and relied on modern structural biology methods to produce small molecules, proteins and antibodies to target the unique biomarkers of cancer on tumor cells. Currently all these four strategies are used in various combinations to treat cancer and while mortality rates have shown a considerable decline, survival is improving mostly owing to earlier diagnosis. The reasons include low target selectivity, drug resistance, inability to effectively address metastasis and severe side effects.

In the past decade, Immune-oncology (IO) has emerged as an important approach to fight cancer. IO is defined as the study and

development of treatments that uses body's own immune system to fight cancer. This field is rapidly evolving with many accelerated approvals from US Food and Drug Association and European Medicines Agency leading to the emergence of several therapeutic classes. Combining IO agents with conventional therapy have significantly improved the patient outcomes. As immunotherapies are demonstrating prolonged survival of patients with rapidly fatal cancers, the number of patients eligible for immune based cancer treatments have sky rocketed. Concurrently, rapid advances in IO with novel treatment combinations and newly identified druggable targets expand the role of immunotherapy in the treatment of cancers in decades to come. The global immune oncology market is expected to experience significant growth in the next decade, reaching the value of more than \$150 billion by 2030 with a compound annual growth rate (CAGR) of approximately 20%.

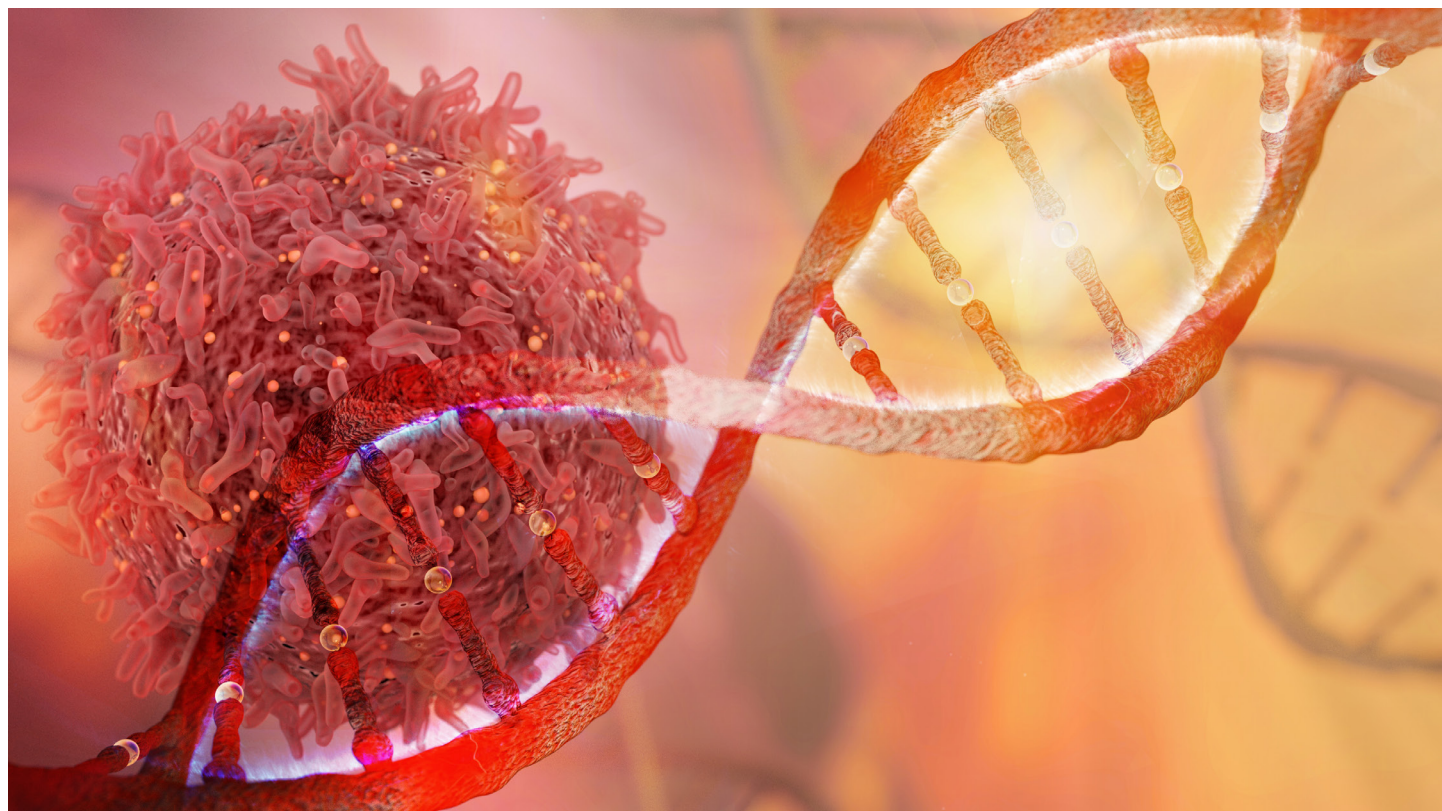
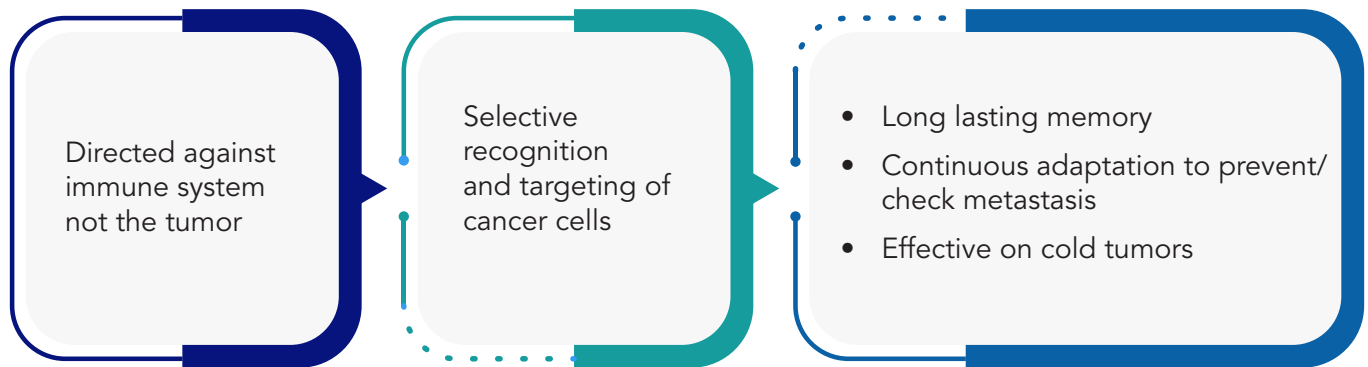


Table 1: What is Immuno-Oncology



Immuno-Oncology landscape

Immune system, comprising of specialized organs and cells, differentiates foreign antigens from self and mounts an immune response to protect the body against infections. Since cancer cells are different from normal cells in the body, immune system attacks them and this process of harnessing body's own immune defense against cancer cells is called immune therapy. However, cancer cells often evade detection by immune system. The evasion is either by restricting antigen expression, inhibiting immune response by modifying tumor micro-environment and inducing T cell exhaustion. IO deals with educating the immune system to defer this evasion and effectively eradicate hard to detect tumor cells before or after metastasis.

Tumor micro-environment (TME) is made of a diverse set of cells which include immune cells, non-immune cells and extra cellular matrix. Most tumors are often recognized and cleared by NK cells and T-cells but a complex cellular crosstalk in TME leads to the emergence of immune suppressive network. This network involves Adipocytes, regulatory T cells (Treg),

myeloid derived suppressor cells (MDSCs) and fibroblasts along with a network of cytokines, growth factors that hinders the action of immune systems and promote tumor growth. All these components of tumors, TME and their mediators of inter cellular communication are potential targets of immune therapy. Consequently, T cell checkpoint inhibitors specifically PD-1 and CTLA-4 revolutionized immuno therapy and are considered as first generation immuno therapy modalities. Keeping these checkpoint inhibitors as backbone, second generation immunotherapies involving synergistic combination are being developed and tested in labs and clinic.

The field of immunotherapy has come a long way to add diverse modalities which include tyrosine kinase inhibitors, co-stimulatory mAbs, bifunctional agents, epigenetic modulators, vaccines, Adoptive-T-cell therapy, nanoparticles, oncolytic viruses and synthetic gene circuits. APSL team is experienced in providing services in the sphere of adoptive T cell (ATC) transfer and bispecific antibodies related therapies.

Bispecific antibodies

Bispecific antibodies (bsAb), as name suggests have dual specificity thus binding to two antigens simultaneously. Blinatumomab, the first FDA approved bsAb binds T-cell CD3 and CD19-expressing B-cell acute lymphoblastic leukemia (B-ALL) bringing the two cells closer, whereby T-cells then unleash cytotoxic response unto them leading to their clearance. BsAbs rely on the engagement of endogenous T-cells to trigger the immune response against tumor cells. This circumvents the need to expand the T-cells ex-vivo and re-introduce them to the patients. With more than 30 mature commercial technology platforms to create and develop BsAbs, three different kinds of BsAbs have received market approval and more than 110 BsAbs are under various stages of clinical trials. BsAbs can be used for diagnosis as well as

therapy. Since they bind to specific antigen and specific detection site simultaneously, the design is flexible, sensitive and convenient. Half-life of BsAbs that usually depends on their molecular size can be optimized by modifications to the Fc portion or adding nanobodies. Similarly, altered outcomes can be achieved by varying the strength and affinity of two receptors. For example, BsAb with low affinity for CD3 and high affinity for Tumor associated antigen (TAA) gives best results in terms of killing capacity, safety and tolerability by the tissues.

APSL runs collaborative projects helping run multiple BsAb related projects providing services starting from hybridoma generation till functional activity assessment.

Immune checkpoint inhibitors and Combination therapies

Immune checkpoints are part of body's natural defense against hyper active immune response. These checkpoints work engage proteins on immune cells and their partner proteins on target cells. Once the pairing is done, 'off' signals are sent to the immune system and it has a dampening effect on total immune response. Immune checkpoint inhibitors actively prevent this pairing thus allowing T cells to mount an immune response against tumor. Two such drugs against PD1 and CTLA4 have changed the landscape of immunotherapy and won Nobel prize for the contribution. Although these immune therapies demonstrate promise

in reducing cancer, considerable immune related adverse events related to them limit their efficiency. Here, synergistic combination therapies hold greater promise by simultaneously targeting more than one components of cancer and significantly increasing the efficacy and response rate owing to improvement of T-cell mediated immune response. Efforts are ongoing to combine co-stimulatory receptor mAbs with checkpoint blockade antibodies, 4-1BB, TIGIT being the most advanced one to be developed. This is appealing since it targets T-cells as well as APCs thus boosting T cell effector function, expansion and survival.

Cancer vaccines

Discovery of TAA (tissue associated antigens) have opened the doors for cancer vaccines, either prophylactic or therapeutic. However, since TAA are often recognized as 'self' by the immune system, challenges to develop effective cancer vaccines are large. Nonetheless, Sipuleucel-T is one of the FDA approved vaccine in many more to come. To circumvent the silencing of immune system due to 'self/non self' struggle, cancer vaccines are being developed in combination with checkpoint inhibitors. Anti-PD1 and anti-CTLA-4 therapy when combined with various cancer vaccines have yielded promising results in lab and are numerous autologous tumor vaccines are in phase II and phase III trials.

Future perspective and role of APSL

In 'difficult to treat' tumors, IO based therapies have better effect size in clinical trials as compared to traditional chemotherapeutic agents. IO has emerged as a powerful tool with lot of untapped potential. The ability to identify neoantigens through next-generation sequencing of tumor samples from patients has opened avenues for improvement of specific as well as supra-physiological therapies including ATC and cancer vaccines. With strong molecular biology and CADD team, APSL offers solutions to identify tumor based-peptides that can be suitable TAA or tumor neoantigen. APSL also offers several strategies to formulate therapies using synthetic peptides and mRNA.

Although immune therapies come with lot of benefits, removing the naturally established checkpoints or activating immune system artificially leads to many adverse effects as well. Thus, Immuno-oncologists tread a very fine line while educating the immune system so as to maximize anti-tumor efficacy while minimizing triggering autoimmunity. APSL understands these complexities of working with immune-oncology related modalities and ensures to provide every possible help to our collaborators during planning as well as execution of the projects.

The immune oncology market is segmented on the basis of therapy type in the table given below for representing the ongoing clinical trials(Reference: ASCGT data)

S.No.	IO Modality/therapy	Phase I	Phase II	Phase III
1	Antibodies • Monoclonal Ab • Bispecific Ab	97	94	13
2	Cell therapy • CAR-T • T-cell therapy	639	221	33
3	Others • Hormonal therapy • Vaccine therapy • Stem cell therapy	155	156	28

Note: Clinical trial numbers above includes trials which are open, Active not recruiting, not yet recruiting trials across the world

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Author's bio

Shalini Tanwar is an accomplished cellular immunologist specializing in cellular crosstalk during inflammation, autoimmunity, and immuno-oncology. With over 12 years of experience, she excels in designing and executing complex immune assays.

Shalini's impressive achievements include validating experiments for immune cell redirection, expanding GD-T-cell populations by 300-fold, and uncovering the crosstalk between Treg cells and MDSCs. Currently serving as team lead - *In Vitro* Biology (NBE-Oncology) at APSL, her expertise, and leadership in the field make her an invaluable asset in advancing research and development in the exciting and rapidly evolving field of immuno-oncology.



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