Immunoglobulin E (IgEs): the next generation immunotherapy

By Dr Cristina Oliva, PhD, Chief Medical Officer at Epsilogen

Abstract

Traditionally associated with allergy and anti-parasitic immunity, immunoglobulin E (IgE) has largely been overlooked as a therapeutic antibody class in oncology. However, a growing body of clinical evidence suggests that it may be capable of overcoming some of the limitations of existing antibody-based therapies. Given the cost, limited access and toxicity challenges of some immunotherapy options, the industry is seeking the next wave of innovation, where IgE is emerging as an unexpected candidate.

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Dr Cristina Oliva is Chief Medical Officer at Epsilogen. She is a board certified oncologist with over 20 years' experience in oncology drug development. Her career encompasses senior leadership roles within global pharma, biotech and CROs, successfully advancing oncology compounds from early clinical stages to regulatory approval and global market authorisation. Previous roles include Vice President and Head of the Oncology Center of Excellence at IQVIA, Chief Medical Officer at Nordic Nanovector, and senior clinical development roles at Shionogi, Takeda Pharmaceuticals, GlaxoSmithKline, and Eli Lilly. Most recently, Cristina was CMO at BerGenBio. She obtained her medical degree and oncology board certification from the University of Genoa, and Doctorate in Public Health from Kingston University.

Antibody therapeutics and immunotherapy have transformed oncology over the past decade. Immune checkpoint inhibitors, monoclonal antibodies, cell therapies and more recently, antibody-drug conjugates (ADCs) have all delivered meaningful clinical benefit across multiple tumour types. Yet despite these advances, many cancer patients either fail to respond, develop resistance, or ultimately relapse. As the industry seeks the next wave of innovation in immunotherapy, an unexpected candidate is emerging: immunoglobulin E (IgE).

Traditionally associated with allergy and anti-parasitic immunity, IgE has largely been overlooked as a therapeutic antibody class in oncology. However, a growing body of preclinical and clinical evidence suggests that it may be capable of overcoming some of the limitations of existing antibody-based therapies. First-in-human clinical studies have demonstrated that IgE therapeutics can be administered safely, opening the door to this new class of anti-cancer biologics.

Why are new antibody therapeutics and immunotherapy options needed?

While checkpoint inhibitors and immunoglobulin G (IgG) monoclonal antibodies have become standard components of cancer care, durable responses remain limited to a subset of patients. Tumour immune evasion, suppressive tumour microenvironments, antigen heterogeneity and acquired resistance continue to restrict long-term efficacy.

ADCs are one of the most successful antibody therapeutics in oncology, combining the targeting capability of antibodies with highly potent cytotoxic payloads. However, ADCs can also face significant challenges, including systemic and off-target toxicity, limited tumour penetration, cancer cell drug resistance, and narrow therapeutic window – limiting their widespread use and leading clinicians and researchers to look for potential alternatives or combination therapies.

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Personalised immunotherapies have also been effective for patients, involving treatments tailored to an individual's unique genetic profile and tumour characteristics, in order to stimulate their immune system. These include CAR T-cell therapies where scientists extract a patient's T-cells, genetically engineer them to target the unique proteins on their cancer cells, and multiply them before infusing them back into the body. Neoantigen vaccines are custom-made, mRNA-based vaccines designed from the specific profile of a patient's tumour which teach the immune system to recognise and attack the cancer. Most immune checkpoint inhibitors are also personalised using biomarker testing to predict which patients will respond best to specific drugs.

However, because of the intensive laboratory work and bespoke manufacturing required, these therapies are incredibly expensive and time consuming to produce, meaning that patient access is very limited. Only those with the ability to pay and who can get to the specialist facilities can access these treatments.

So, it is clear that the next generation of cancer immunotherapies must engage multiple components of the immune system, function effectively within the tumour microenvironment and generate a durable anti-tumour effect. The need to provide more accessible and affordable oncology treatments is also compelling. It is these needs which have resulted in renewed interest in harnessing the potential of IgE.

The unique biology of IgE

IgE antibodies evolved specifically to provide immune surveillance in tissue, rather than in circulation like IgG antibodies. This is particularly relevant when looking at treatments for solid tumours, where immune activity occurs mainly within the tumour microenvironment.

IgE is a pro-inflammatory antibody which binds to the high-affinity IgE receptor (FcεRI receptor) of the immune cells within a tumour to activate them and 'warm up' the tumour microenvironment. This releases cytokines and chemokines which in turn activate the T cells inside the tumour, destroying it. This interaction is incredibly strong, resulting in prolonged retention of IgE within cells and a more sustained effect than with other immune mechanisms.

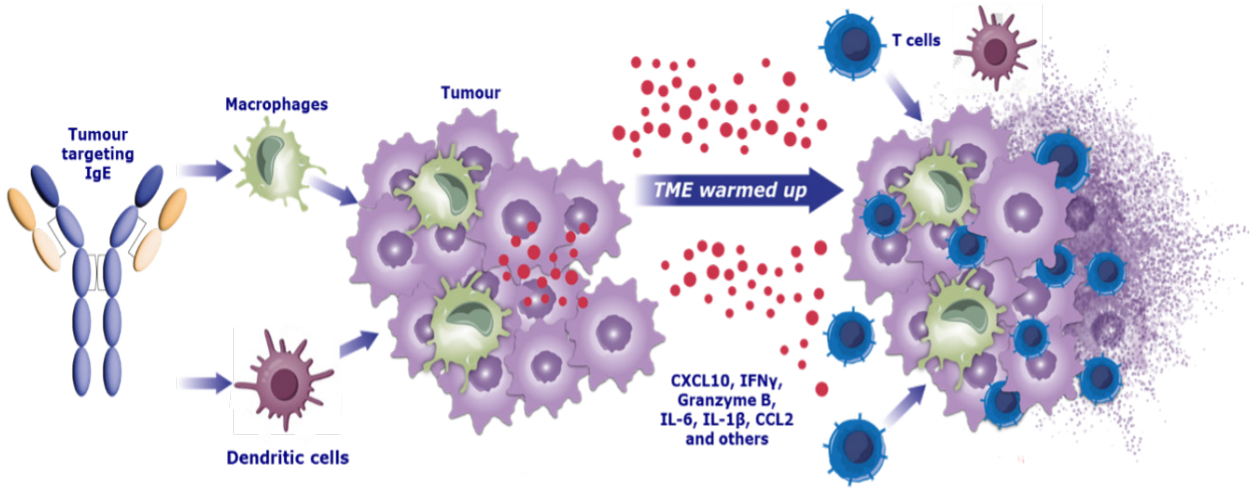
This biology creates several potential advantages for cancer therapy:

1. Recruitment of powerful tissue-resident immune cells
   a. IgE can engage the abundant immune cell populations that already exist within solid tumours, particularly macrophages and monocytes. These cells are increasingly recognised as critical regulators of anti-tumour immunity but are underutilised by conventional antibody therapeutics.
   b. Preclinical studies have demonstrated that tumour-targeting IgE antibodies can activate these cells, lighting the macrophage 'fuse' which then detonates the T cell 'bomb' to destroy the tumour.

2. No inhibitory receptor signalling
   a. A limitation of IgG therapeutics is the clash between the activating and inhibitory receptor pathways as both are triggered when an IgG antibody binds to receptors on immune cells, weakening the level of immune activation. IgE does not engage the inhibitory receptor, potentially enabling stronger immune response.

3. Tissue-based immune surveillance
   a. As IgEs are naturally mostly found within tissue,

Figure 1: IgE Lights the Myeloid Fuse which Detonates the T Cell Bomb



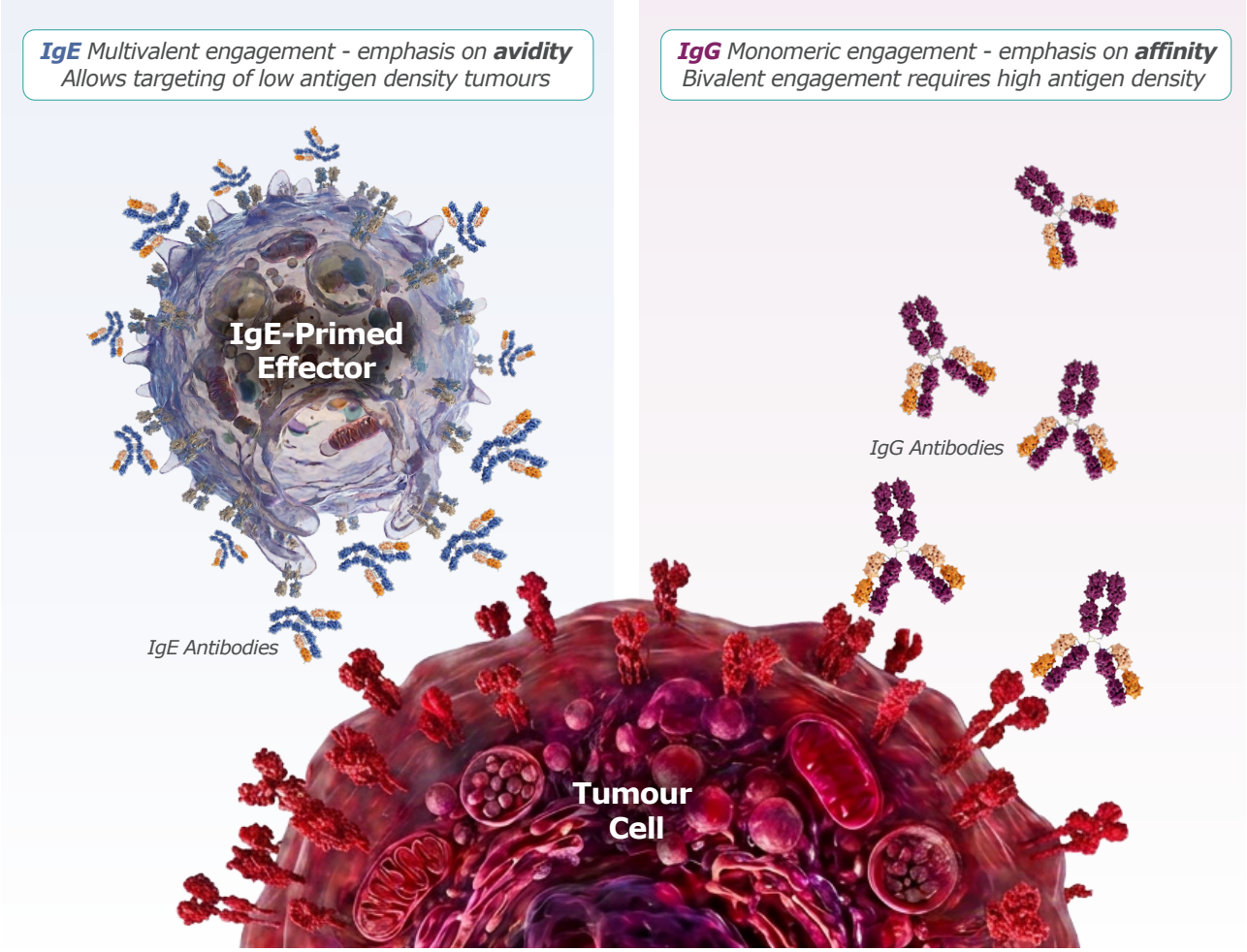


Figure 2: Structure of immunoglobulin G (IgG) Antibodies attack a cancer cell or Virus, 3d illustration

circulating IgE concentrations are naturally low, but studies have shown that FcεRI-bound IgEs can remain associated with immune cells in tissues for extended periods. This may enhance local immune surveillance at tumour sites, remaining in the tissues for longer and potentially resulting in sustained anti-tumour activity.

4. Potential to drive immune memory

a. Emerging evidence suggests that using IgE to activate an immune response to a tumour may also initiate a broader immune response, including enhancing antigen presentation by dendritic cells, activation of antigen specific T cell responses and T cell recruitment to the tumour. Rather than acting solely as a direct tumour-killing agent, IgE may 'warm up' immunologically 'cold' tumours which are not being actively identified by the immune system, into inflamed environments capable of supporting long-term anti-tumour immunity.

How IgEs are different to ADCs

Although ADCs, IgEs and other antibody therapeutics use antibody targeting, their mechanisms of action differ fundamentally.

ADCs function primarily as targeted drug delivery systems. Their efficacy depends on successful tumour binding, internalisation and intracellular release of a cytotoxic payload. The tumour cell itself is the primary target.

IgE antibodies, by contrast, are designed to recruit and activate the patient's own immune system to fight cancer cells.

Importantly, preclinical and clinical data have shown that IgEs have the ability to kill 'cold' tumour cells expressing low levels and even ultra-low levels of antigens – a key differentiator from IgG and traditional ADC therapeutics.

Also, with the benign safety profile of IgEs in the clinic so far, there is also the possibility of using them in combination with a broad spectrum of other agents in oncology treatment including chemotherapeutics, checkpoint inhibitors and ADCs.

Some key distinctions are shown in Table 1.

Because IgE therapies do not rely on intracellular drug release, they can avoid several common ADC resistance

FEATURE	IgE THERAPEUTICS	ADCs	CHECKPOINT INHIBITORS
Primary mechanism	Immune cell activation	Cytotoxic payload delivery	Blockade of inhibitory receptors to reactivate T cells
Dependence on internalisation	Low	High	Low/none
Risk of payload-related toxicity	Absent	Present	Absent
Ability to remodel tumour microenvironment	Potentially significant	Limited	Significant
Immune memory generation	Potentially enhanced	Generally limited	Enhanced

Table 1: Comparison of key features in IgE, ADCs and Checkpoint inhibitors

pathways. Similarly, the absence of a cytotoxic payload eliminates concerns regarding linker instability, off-target payload release and payload-specific toxicities.

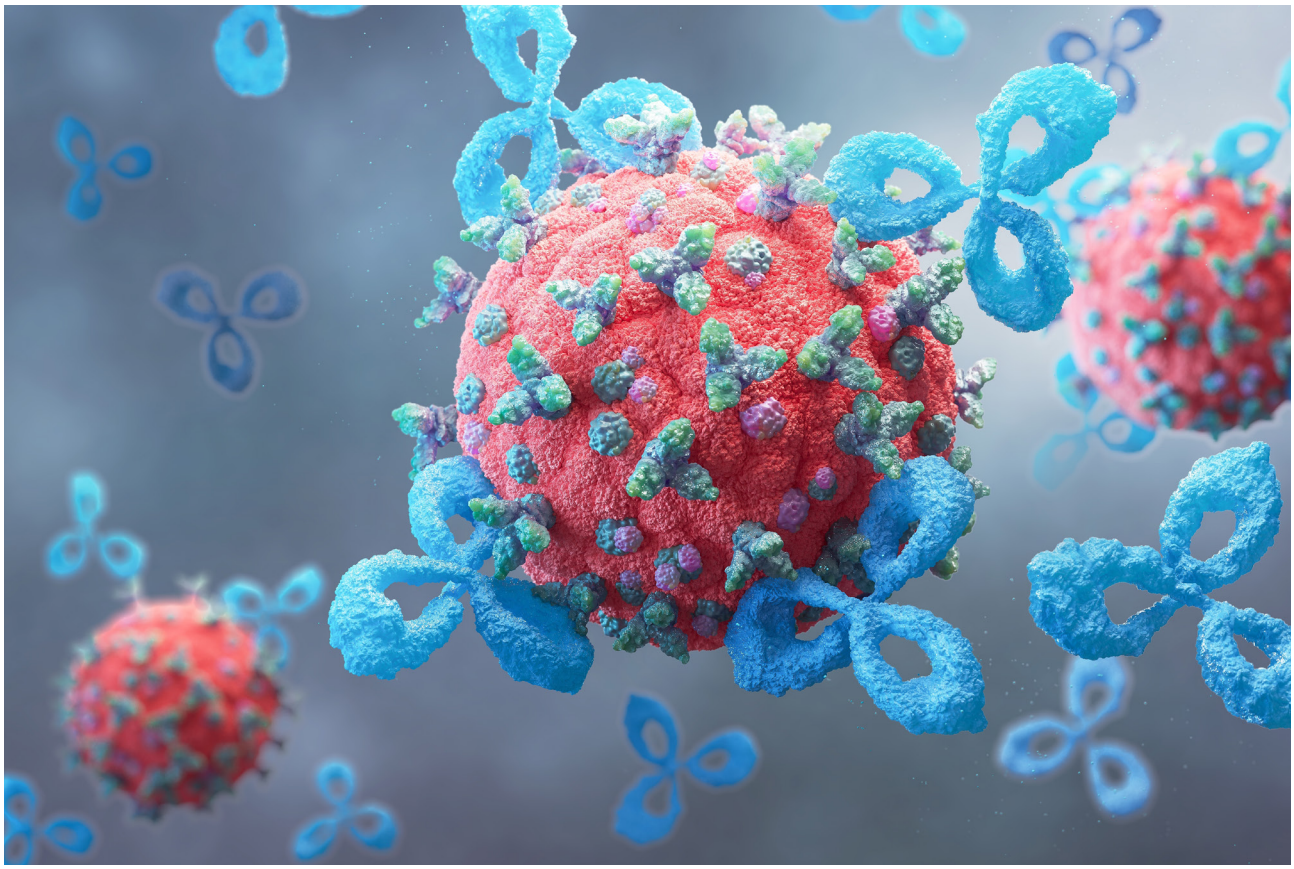
IgE will not replace ADCs – they perform different functions and there is a clinical need for both. However, the two modalities may ultimately prove complementary, with ADCs delivering direct tumour cell killing and IgE antibodies providing deeper immune engagement.

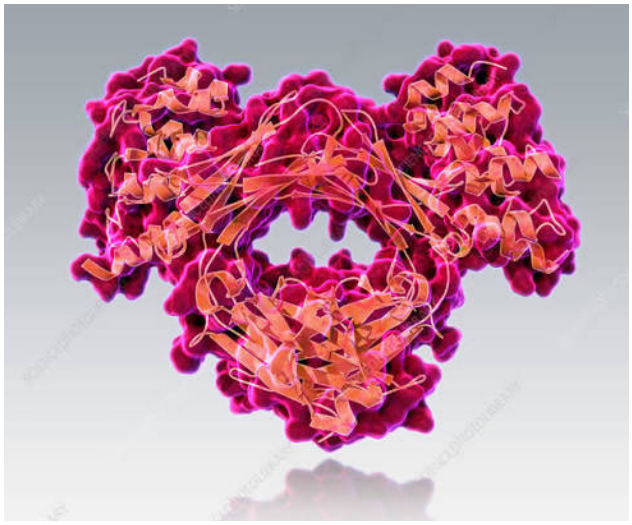
Addressing the safety question

Historically, the greatest concern surrounding the use of IgEs as a therapeutic has been safety. Given IgE's well-established role in producing allergic reactions and anaphylaxis in the body, it was initially questioned whether systemic administration would be clinically feasible.

Epsilogen's MOv18 IgE is the first IgE therapeutic to enter the clinic and has provided important insights for the development of this and future compounds. Having completed a phase 1 trial in cancer patients with advanced solid tumours, the antibody was found to be safe and well tolerated with initial anti-tumour activity

Figure 3: Immunoglobulin antibodies attack a cancer cell or Virus, 3d illustration





also evident.

To mitigate any potential risk of reactions or anaphylaxis in patients, a basophil activation testing strategy was used to identify patients at elevated risk. This approach was effective, with no maximum tolerated dose reached, and efficacy signals seen.

These findings suggest several important safety points for IgE as a therapeutic:

- IgE-related adverse events appear to be predictable and manageable
- Biomarker-based patient selection can effectively mitigate risk
- Severe allergic reactions are not inevitable consequences of therapeutic IgE administration
- The emerging safety profile of IgEs differs fundamentally from the chronic toxicities often associated with cytotoxic payload-based therapies.

As additional clinical programmes enter development, a more comprehensive understanding of safety will emerge. However, the clinical data from an ongoing phase1b study has already substantially reduced concerns that IgE antibodies would be inherently unsuitable for systemic cancer treatment.

Looking ahead

Oncology is entering an era in which success increasingly depends on the ability to engage multiple areas of the immune system and overcome resistance within complex tumour microenvironments. IgE antibodies offer a novel mechanism that differs fundamentally from both conventional IgG therapeutics and ADCs.

Their capacity to recruit tissue-resident immune cells, drive potent Fc receptor signalling and potentially reshape tumour immunity positions IgEs as one of the most intriguing emerging immunotherapy platforms. While clinical development is still relatively early, the first human data demonstrate that IgE therapeutics can be administered safely and generate meaningful anti-tumour activity.

As biopharma searches for new ways to address tumour resistance, improve durability and expand the benefits of immunotherapy to more patients, IgE is rapidly moving from immunological curiosity to serious clinical contender, with the potential to become an exciting new therapeutic class and treatment modality. ●

KEY TAKEAWAYS

- **Immunoglobulin E (IgE) has potential as an innovative antibody therapeutic candidate for the next generation of immunotherapy.**
- **New options are needed for antibody therapeutics as current treatments are limited by systemic and off-target toxicity, limited tumour penetration, cancer cell drug resistance and narrow therapeutic window.**
- **The unique biology of IgE being focused within tissue, rather than circulation means that they are particularly relevant for solid tumour treatments.**
- **Recent first-in-man studies have demonstrated that IgE therapies can be safe and well tolerated, with initial anti-tumour activity seen.**
- **IgE is rapidly moving from immunological curiosity to serious clinical contender, helping address tumour resistance, improve durability and expand the benefits of immunotherapy to more patients.**