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Monoclonal Antibodies in Cancer Therapy: Mechanisms of Action and Resistance

Despina Karagiannis¹●, Elisabeth Moser²●, Darragh Fitzgerald³●

¹Scientist, Department of Transfusion Medicine, Epirus Institute of Biomedical Sciences, Ioannina, Greece.

²Scientist, Department of Transfusion Medicine, Salzkammergut Institute of Immunology, Gmunden, Austria.

³Associate Professor, Department of Transfusion Medicine, Shannon Estuary Institute of Nursing and Health Sciences, Ennis, Ireland.

Email: ¹d.karagiannis@eibs.gr, ²e.moser@sii-g.at, ³d.fitzgerald@seinhs.ie

ORCID: ¹0000-0001-3396-7208, ²0000-0001-4096-5112, ³0000-0001-1859-2321

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ABSTRACT

Therapeutic monoclonal antibodies are now part of routine care for several cancers, yet the reasons they work in one patient and fail in another remain only partly understood. This mini review summarises, from published literature, how antibodies act on tumours and how tumours escape them. Four broad mechanisms are described: blockade of growth-factor receptor signalling, engagement of immune effector cells and complement through the Fc region, release of immune checkpoints, and interference with tumour blood supply, with a fifth route, delivery of a toxic payload, noted briefly. Resistance is then considered at three levels: the tumour cell, where antigen loss, downstream mutation and bypass signalling blunt the effect; the immune compartment, where host genetics and effector exhaustion matter; and the vasculature, where alternative pro-angiogenic routes take over. The best-documented example is the loss of benefit from EGFR-directed antibodies in colorectal tumours carrying KRAS mutations. The review is narrative, reports no new data, and does not claim a systematic search. Its main conclusion is that mechanism and resistance cannot be separated: each way an antibody works is also a way it can be bypassed, and combination design should follow from that logic. Predictive markers remain scarce, and most laboratory findings still need confirmation in patients.

Keywords: Monoclonal antibodies; Cancer therapy; Mechanism of action; Drug resistance; Antibody-dependent cellular cytotoxicity; HER2; EGFR; Narrative review

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Article Class: Mini Review

1. Introduction

When Köhler and Milstein showed that fused cells could secrete antibody of a single, predefined specificity, the practical consequence was not obvious (1). It took

decades of engineering to turn mouse antibodies, which the human immune system promptly rejected, into chimeric, humanised and fully human molecules that could be given repeatedly (2, 3). Today



several of these agents sit inside routine oncology, and the field has grown into one of the most commercially and clinically significant parts of cancer drug development (4, 5).

Antibodies differ from small-molecule drugs. They recognise targets on the outside of the cell, they persist in the circulation for a long time, and the Fc region of the molecule can recruit the immune system. One antibody can therefore act in several ways at once, and the relative weight of each way is rarely known for an individual patient. Benefit is real but uneven. Many tumours never respond, and many that do later progress: primary and acquired resistance (6). A clinician reading a trial wants to know why a drug helped some patients and not others.

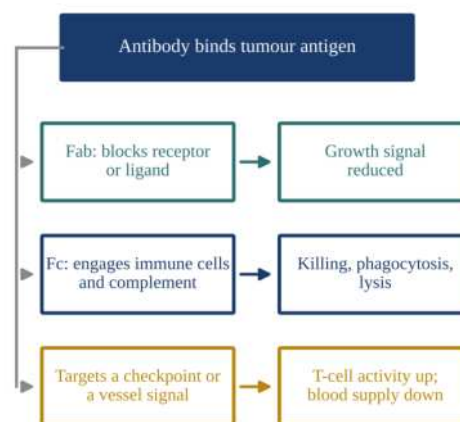
This mini review sets out how antibodies are thought to act on tumours and how tumours escape them, with a focus on rituximab, trastuzumab, cetuximab, bevacizumab and ipilimumab. It reports no new patient data. Its argument is simple: every mechanism of action depends on a condition that the tumour or the host can remove. The aim is a fair account of what is established and what is still assumed.

2. Literature Review

2.1 Structure and Engineering

An immunoglobulin G molecule has two jobs. The antigen-binding Fab arms select the target, while the Fc region binds Fc-gamma receptors on immune cells and the first component of complement. Naming conventions record how far an antibody is humanised but say little about function (2, 7). Removing fucose from the Fc glycan improves binding to the activating receptor on natural killer cells and raises cell killing in the laboratory (8), and amino-acid changes in the Fc region can do the same (9). A conjugate that attaches a cytotoxic drug to trastuzumab

uses the target mainly as a doorway (10). Figure 1 sketches the principal routes from binding to effect.



Schematic, not data

Figure 1. From antibody to anti-tumour effect: principal routes (schematic, not data).

2.2 Blocking Growth Signals

Several antibodies act first as receptor antagonists. Crystal structures show trastuzumab binding the extracellular region of HER2 near its membrane-proximal end (11), whereas pertuzumab binds elsewhere on the same receptor and interferes with its pairing partner (12). Cetuximab occupies the ligand-binding region of EGFR and holds the receptor in an inactive conformation, so that growth factor cannot switch it on (13). HER2 has no known ligand and signals mainly through partnership with other receptors of its family, particularly HER3 (14). Blocking a receptor helps only if the tumour still depends on it. In patients, trastuzumab probably combines signalling blockade with immune engagement (15). This is one reason why the same antibody can look decisive in one disease and ordinary in another.

2.3 Recruiting Immune Effectors

The immune route has the best experimental support. In mouse models, antibodies lost much of their activity when



activating Fc receptors were absent, and gained activity when the inhibitory receptor was removed, showing that the Fc region is part of the drug (16). Human data point the same way, though less cleanly. Patients with follicular lymphoma who carry the higher-affinity variants of Fc-gamma receptor IIIa appeared to respond better to rituximab (17, 18), although not every later analysis agreed and the association should not be taken as a validated test. Rituximab also activates complement (19). Table 2 sets out what each mechanism depends on. Effector function is therefore a variable to measure, not to assume.

Table 2. Mechanisms of antibody action and what each depends on.

Mechanism	What happens	Depends on
Signalling blockade	Receptor held inactive or removed (11, 12)	Pathway driven by the target
ADCC and phagocytosis	Immune cells kill or engulf coated cells (16)	Fc receptors, effector cells
Complement	Target cells lysed (19)	Antigen density, complement supply
Checkpoint release	T-cell inhibition lifted (20, 21)	Pre-existing T-cell response
Vessel signal	Ligand or receptor neutralised (22)	Dependence on that vessel signal
Payload delivery	Toxin carried into the cell (10)	Internalisation of the antibody

Note: The final column lists conditions that, when absent, make the mechanism fail; it is the usual entry point for resistance.

Two further approaches act on the immune system rather than on the tumour. Antibodies against CTLA-4 lift a brake on T cells, a strategy first shown to enhance anti-tumour immunity in mice (20) and later associated with improved survival in metastatic melanoma (23). Tumour cells can also express a PD-1 ligand and deliver an inhibitory signal to T cells (21). Both

need a pre-existing T-cell response (24). Seen this way, resistance is less an accident than a predictable consequence of the biology.

2.4 Starving the Tumour

Bevacizumab neutralises vascular endothelial growth factor A and was developed to cut off the blood supply on which growing tumours rely (25). The simple picture of starvation has since given way to a subtler one. In preclinical work, moderate anti-angiogenic treatment prunes the most abnormal vessels and for a time makes the remaining ones more efficient, which may improve the delivery of chemotherapy (22). It has mostly been given alongside cytotoxic drugs (26).

3. Materials and Methods

3.1 Scope and Question

The review asks two linked questions. By what main mechanisms do therapeutic monoclonal antibodies act on solid and haematological tumours, and at what points do those mechanisms fail? Small-molecule inhibitors appear only where they inform resistance biology. These scope limits shape what a reader can conclude.

3.2 Literature Assembly

This is a narrative synthesis. We drew on landmark trials, structural studies, mechanistic experiments and reviews published up to 2011. We did not run a formal systematic search and we do not claim one, so the selection reflects judgement and could be challenged.

3.3 Appraisal Framework

Each mechanism was read against three questions. What must be true for the mechanism to work? What evidence shows that it operates in patients rather than only in cell lines or mice? And how might the tumour or host alter the requirement? Animal and cell studies were used to frame



hypotheses, not to support claims of clinical effect. Table 1 lists the principal agents and the modes of action discussed.

Table 1. Representative therapeutic antibodies and their principal modes of action.

Antibody	Target	Principal mechanism
Rituximab	CD20	Fc-mediated killing, complement, some direct signalling (19, 27)
Trastuzumab	HER2	Receptor signalling blockade plus Fc-mediated killing (15, 28)
Cetuximab	EGFR	Blocks ligand binding, receptor internalisation (13, 29)
Panitumumab	EGFR	Blocks ligand binding (30)
Bevacizumab	VEGF-A	Neutralises the ligand, vascular effects (25, 26)
Ipilimumab	CTLA-4	Releases a T-cell checkpoint (20, 23)

Note: Qualitative summary of agents discussed in this review; indications are not listed.

4. Results

4.1 Where Benefit Has Been Shown

Antibodies entered standard treatment when they were added to chemotherapy. Rituximab, first tested alone in relapsed low-grade lymphoma (27), later improved outcomes in combination with CHOP chemotherapy in elderly patients with diffuse large B-cell lymphoma (31). Adding trastuzumab to chemotherapy did the same for HER2-overexpressing metastatic breast cancer (28), a result that made HER2 testing part of routine care. Cetuximab showed activity in irinotecan-refractory colorectal cancer (29). The antibody rarely replaces cytotoxic treatment; it extends what that treatment can do. Figure 2 shows, in qualitative terms, which routes each agent is mainly credited with. Such differences are subtle individually, yet they add up across a treatment course.

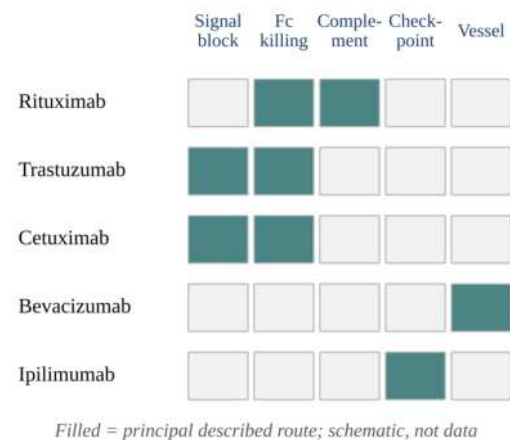


Figure 2. Qualitative matrix of mechanisms by antibody (schematic, not data).

4.2 Resistance Within the Tumour Cell

The simplest route to resistance is losing the target. Anti-CD20 antibodies of the type that includes rituximab can be taken into the cell together with their target, which removes the antibody from the surface before effector cells can use it (32). Rituximab has also been reported to sensitise lymphoma cells to chemotherapy through survival signalling (33). In breast cancer, a truncated form of HER2 lacking the antibody-binding region has been linked to poorer response to trastuzumab (34).

Resistance can also arise below the receptor. Loss of the tumour suppressor PTEN, which leaves the PI3K pathway unrestrained, was associated with trastuzumab resistance in patients and cell models (35), and a genetic screen reached a similar conclusion (36). The clearest clinical example comes from colorectal cancer. Tumours with mutant KRAS, which switches on signalling downstream of EGFR, gained little from cetuximab or panitumumab (30, 37, 38). Blocking the receptor is pointless when the pathway no longer needs it. Alternative receptors can take over: in lung cancer cells treated with an EGFR inhibitor, MET amplification reactivated survival signalling through



ERBB3 (39), and bypass is a recognised concern for HER2 therapy (40). Table 3 groups the levels at which these changes arise. The point is not that the antibody fails, only that its effect is conditional.

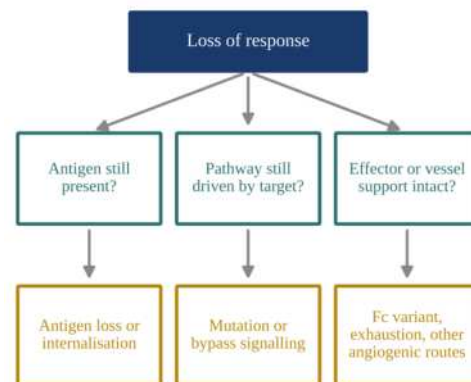
Table 3. Levels at which resistance to antibody therapy arises.

Level	Example	Direction explored
Target antigen	Loss or internalisation of the antigen (32)	Antibodies against other epitopes
Downstream pathway	PTEN loss, PI3K activation (35, 36)	Add a pathway inhibitor
Mutation below the receptor	KRAS mutation with EGFR antibodies (37, 38)	Select patients by genotype
Bypass signalling	Parallel receptors take over (39, 40)	Combine receptor-directed agents
Immune effector	Fc receptor variants (17, 18)	Engineered Fc regions (9)
Vasculature	Alternative pro-angiogenic factors (41, 42)	Multi-target or sequential use

Note: Examples are those cited in the text; the third column indicates directions under study, not established practice.

4.3 Resistance Beyond the Tumour Cell

Anti-angiogenic therapy offers its own resistance stories. In a mouse model of pancreatic islet cancer, tumours that escaped blockade of VEGF signalling switched on other pro-angiogenic factors (41), a mechanism reviewed in detail elsewhere (42). Experiments with inhibitors of VEGF signalling suggested that, in some models, treatment could make tumours more invasive or speed metastasis (43, 44). These are findings from animals and are not shown to hold in patients, but they illustrate how a single-target intervention can reshape the disease it treats. Figure 3 offers a way of sorting a loss of response by level. A mechanism proved in a dish is a hypothesis about a patient, not a finding about one.



A "no" at each question points to the box below it

Schematic, not data

Figure 3. How a resistance question can be sorted by level (schematic, not data).

5. Discussion

5.1 Interpretation

The main finding is a conditional one. Each mechanism of action carries a precondition, and each precondition is a place where resistance can start. Signalling blockade needs a driver pathway, Fc-mediated killing needs antigen and effector cells, checkpoint release needs a T-cell response, and anti-angiogenic therapy needs a tumour that depends on the vessel signal. Nothing in this argues against antibody therapy; it argues for measuring what happens after it.

This framing has a practical consequence for combination design. Adding an agent aimed at a different precondition, such as a pathway inhibitor for a downstream mutation, is more coherent than adding one that fails in the same way. The KRAS finding is so far the clearest case of a marker used to withhold an antibody, and it came from asking a mechanistic question of clinical samples. That is a modest claim, and it is the one the literature can currently carry.

5.2 Limitations

This is a narrative review and shares the weaknesses of that form. The selection of



sources was not systematic and may under-represent negative studies. Several key claims rest on animal or cell experiments, and the associations with Fc receptor genotype and with PTEN loss are not uniformly replicated. Reviews of this kind are most useful when they say where the evidence stops.

5.3 Future Work

Three needs stand out. First, studies that measure several preconditions in the same patients, antigen level, pathway status and effector function, so that their separate contributions can be weighed. Second, prospective trials that test resistance hypotheses, with tissue taken at progression. Third, systematic reviews to test how consistent these associations are. It is a habit worth keeping even when the expected answer seems obvious.

6. Conclusion

Monoclonal antibodies work through a handful of mechanisms, each tied to a condition that the tumour or the patient can remove. Resistance should therefore be expected and studied as part of the mechanism, not as an afterthought. The most useful advances will probably come from matching antibodies to the biology of the tumour, from combining agents that fail for different reasons, and from honest accounting of what laboratory findings have and have not been confirmed in patients. These cautions apply to any targeted agent, not only to antibodies.

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9. Conflict of Interest

The authors declare no conflict of interest.

10. Author Contributions

D.K. conceived the review and wrote the sections on mechanisms of action. E.M. wrote the sections on resistance and immune effectors. D.F. wrote the sections on methods and discussion. All authors revised the manuscript and approved the final version.

11. Ethics Statement

This is a review of published literature. No patients or animals were involved and no ethical approval was required.

12. Data Availability

No new data were generated. All sources are cited in the reference list.

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