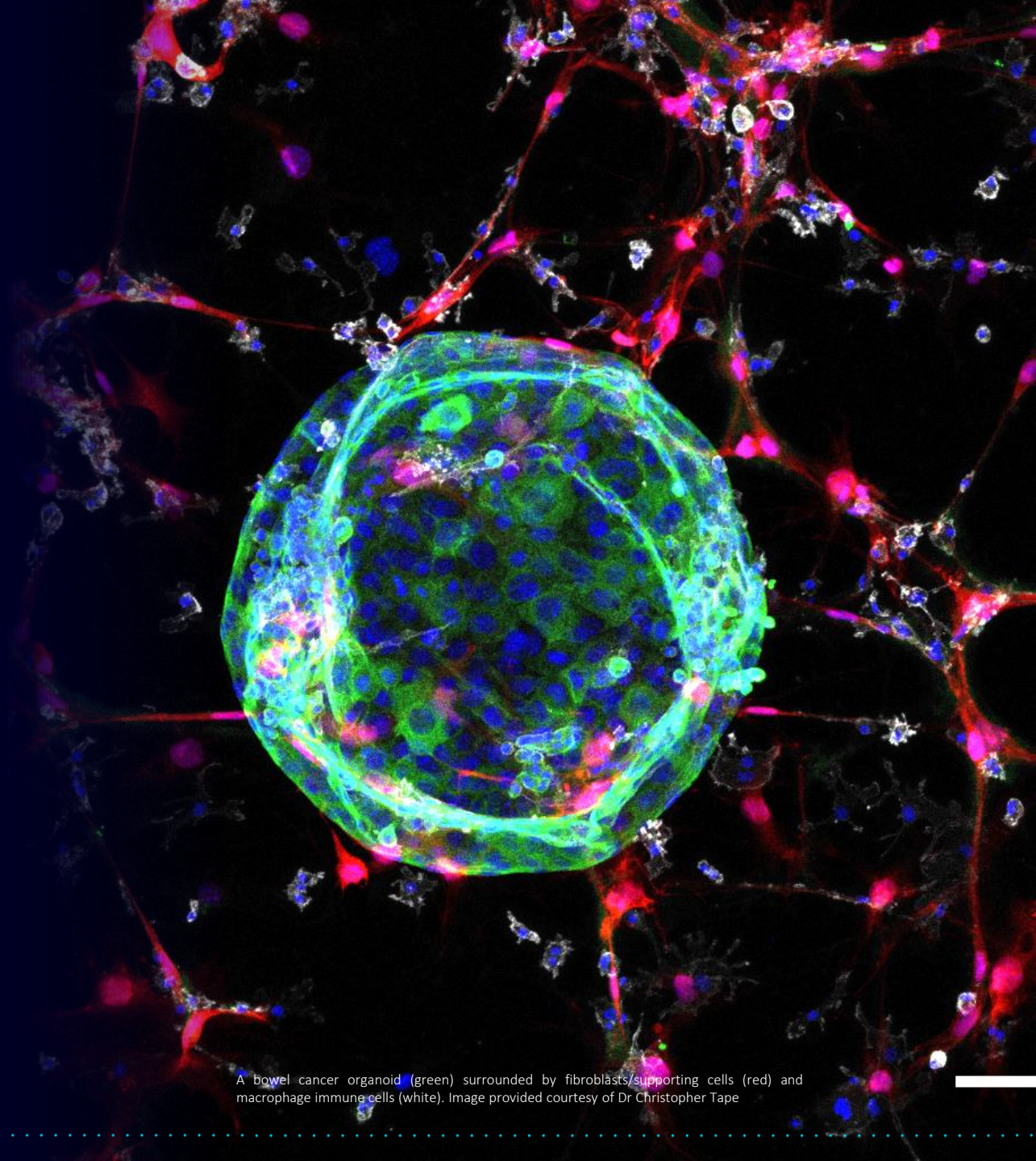
CANCER RESEARCH HORIZONS

FURTHER FASTER TOGETHER

LICENSING OPPORTUNITY:

FCγR-INDEPENDENT "SUPER-AGONISTIC" 4-IBB ANTIBODIES

April 2022



A bowel cancer organoid (green) surrounded by fibroblasts/supporting cells (red) and macrophage immune cells (white). Image provided courtesy of Dr Christopher Tape

OPPORTUNITY OVERVIEW

LICENSING OPPORTUNITY

- IP and materials around a series of novel human and murine antibodies specific for 4-1BB antigens, covering multiple different complementarity-determining region (CDR) sequences.
- Also included are methods for their use in stimulation of anti-tumour T cell immunity as a monotherapy or in combination with other therapeutic moieties.
- These antibodies utilise a proprietary technology that enables generation of hinge-engineered FcγR independent agonistic antibodies with added therapeutic benefit over that of other anti-4-1BB antibodies in development.
- Strong potential for clinical benefit. The mechanistic insights gained into the effector mechanisms by the development team provide a robust foundation for their translation and downstream commercialisation.
- Patent family WO2017/077085 protecting antibodies generated towards 4-1BB and their therapeutic application.

Diagram: Complex structure of human 4-1BB and 4-1BBL with Utomilumab bound. Retrievable here

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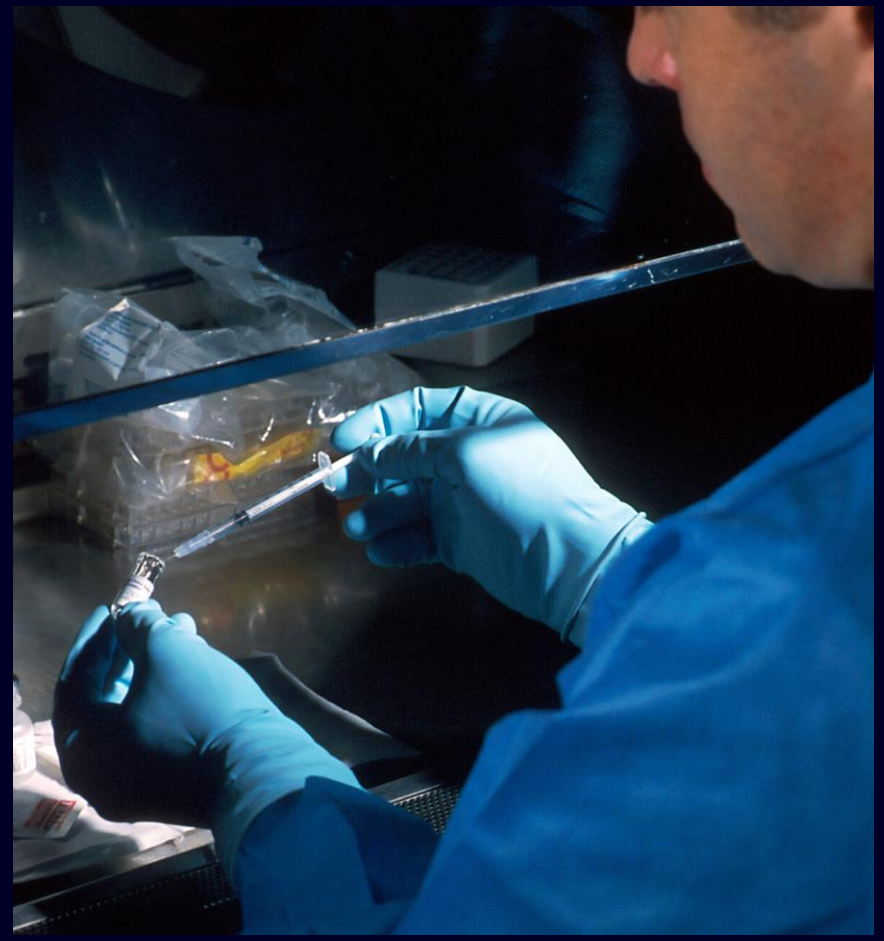
DEVELOPMENT & BACKGROUND



4-1BB – A VALIDATED CANCER TARGET

4-1BB is a member of the TNFR superfamily and a promising target for cancer immunotherapy. 4-1BB is expressed following activation of CD4+ and CD8+ T cells.

- Antibodies targeting 4-1BB enhance the proliferation and survival of antigen-stimulated T cells in vitro and promote CD8 T cell-dependent anti-tumour immunity via
    1. Induction of effector molecules released from CD8+ T cells,
    2. Increase proliferation and decrease apoptosis of CD8+ T cells,

However, a deeper understanding of the mechanisms reveal that:

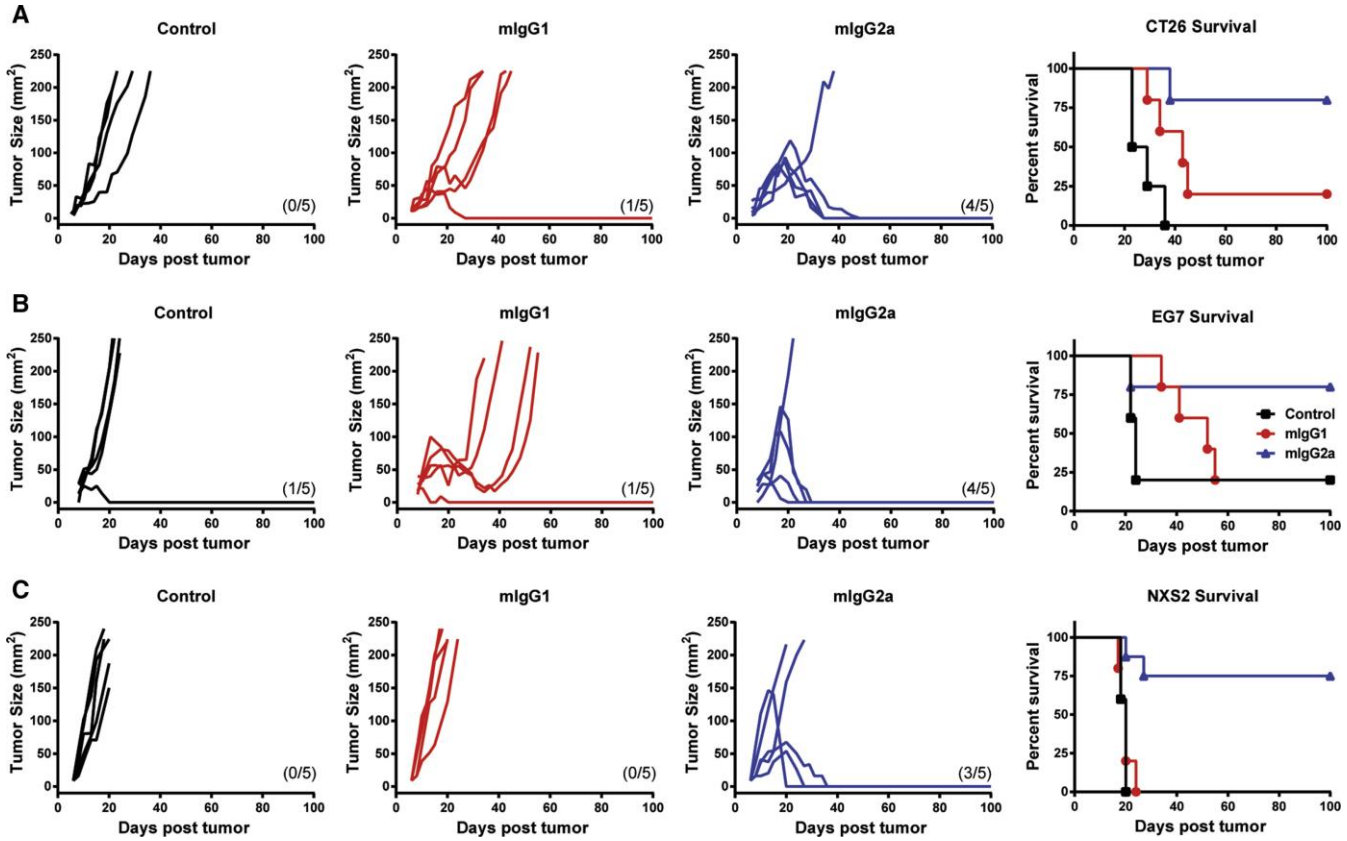
- Antibodies targeting 4-1BB may act in part through the depletion of Treg cells, in a context dependent on its FcγR engagement.

Fc–FcγR INTERACTION CONTEXT

Indeed, whether anti-4-1BB is a depleting or a stimulating antibody is depends on its FcγR engagement.

The optimal isotype for therapeutic anti-4-1BB mAbs in tumours:

- a mIgG1 isotype mAb exerted superior **agonistic** activity and direct immune stimulation of CD8+ T cells, in established solid tumour settings, **however**:
- the mIgG2a mAb provided optimal therapeutic activity due to intratumoural Treg cell **depletion**.



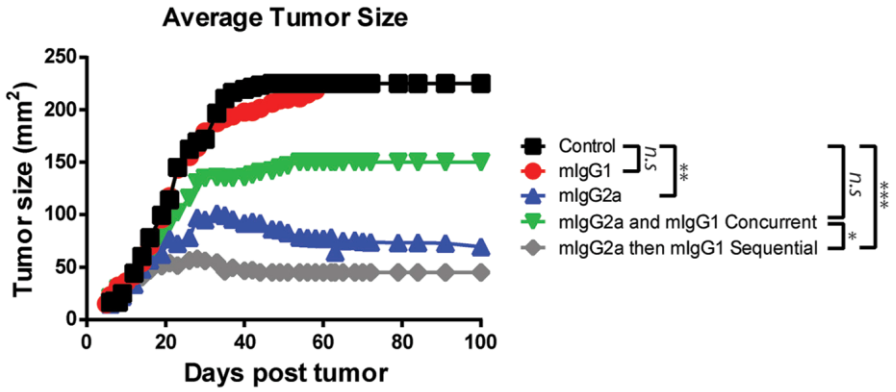
Therapeutic potential of mouse anti-4-1BB mAbs in three different established solid tumour models: CT26 colon carcinoma, EG7 thymoma, and NXS2 neuroblastoma. The high A:I mIgG2a mAb gave considerable therapeutic benefit (80% long-term survival in all three models) while the low A:I mIgG1 version delayed growth of CT26 and EG7 but failed to confer significant long-term benefit (0%–20% survival).

Buchan et al (2018): Retrievable here

DEPLETION & AGONSIM - COMPETING MECHANISMS

Since depletion of Treg cells (mIgG2a) and delivery of co-stimulation (mIgG1) both rely on engagement of FcγRs, combined use leads to reduced efficacy.

- This blunting of activity could be overcome through **sequential** rather than concurrent administration of Treg cell depleting and then immunostimulatory isotypes.

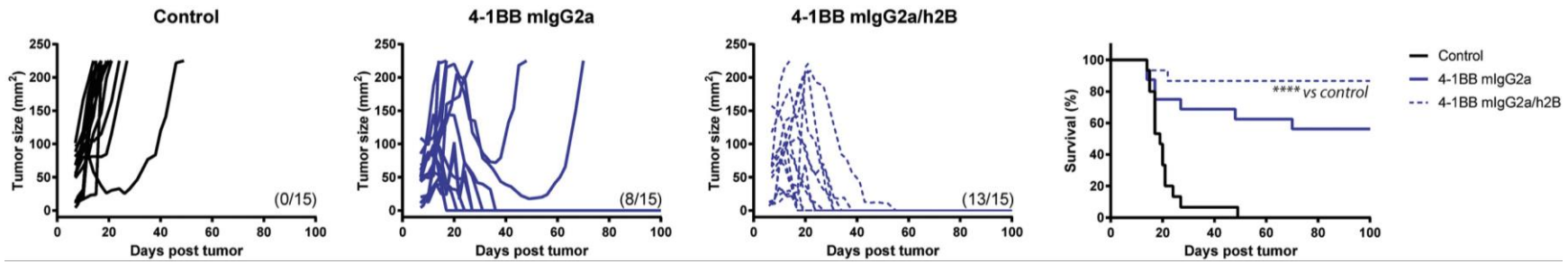


Concurrent administration of mIgG2a and mIgG1 anti-4-1BB mAbs resulted in reduced therapeutic efficacy as indicated by increased tumour size compared to mIgG2a single-agent treatment

DEPLETION & AGONSIM - DUAL ACTIVITY

Alternatively the use of IgG-hinge engineering produces a dual-activity anti-4-1BB mAb (anti-4-1BB mIgG2a/h2B) possessing optimal FcγR-depleting capacity together with FcγR-independent agonism.

- This dual-activity mAb also demonstrated greater therapeutic potential, curing 86% of mice compared to 53% with the standard mIgG2a.
- These data demonstrate that a single mAb can be engineered to optimally mediate depletion and agonism, and through this enhanced dual activity deliver better therapy.



Groups of age- and sex-matched C57BL/6 mice were challenged with 5x10^5 EG7 s.c. on day 0. On days 3, 5, and 7, mice received 200 mg mAb or PBS control i.p. as indicated. Tumor growth was monitored and mice culled when mean tumour area exceeded 225 mm2 . Data represent examples of at least 2 independent experiments where n = 5 mice per group

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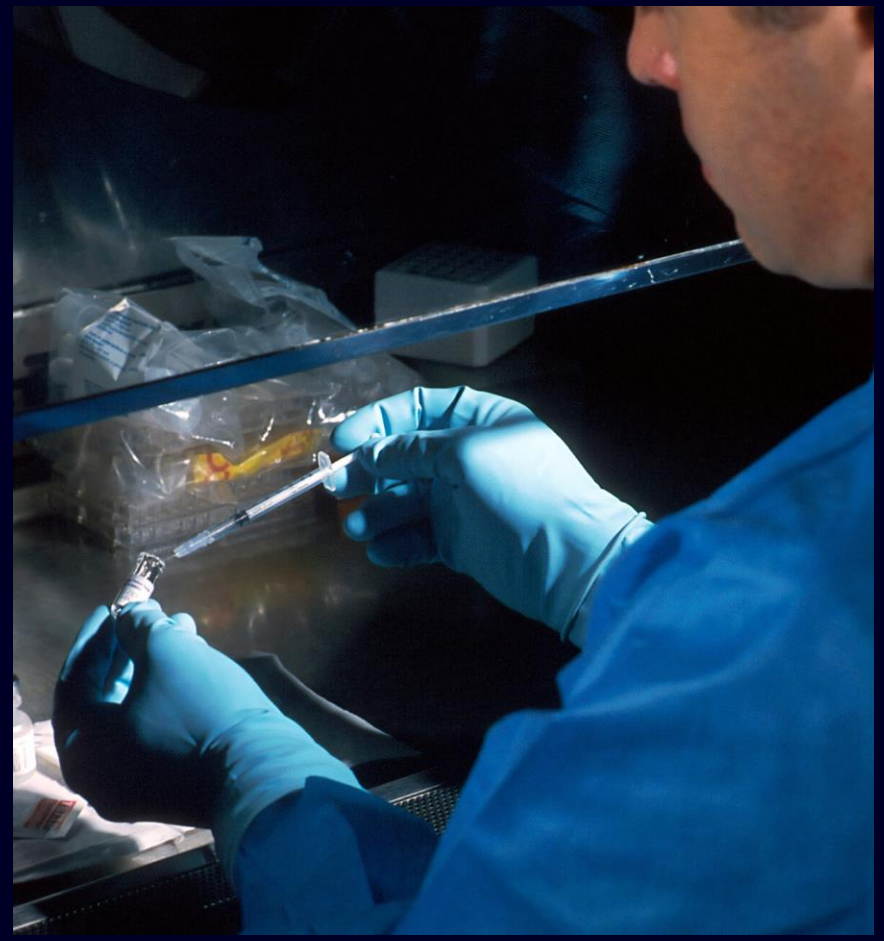
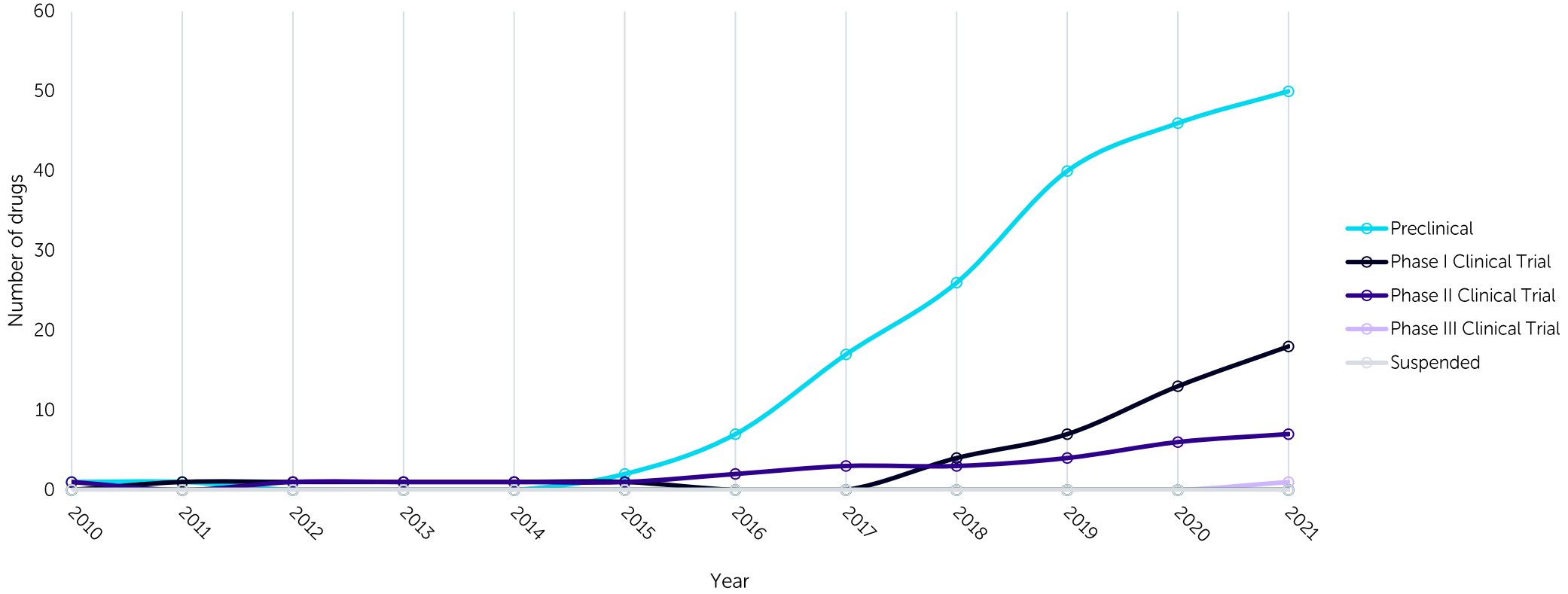
COMMERCIAL DEVELOPMENT



DIFFERENTIATION

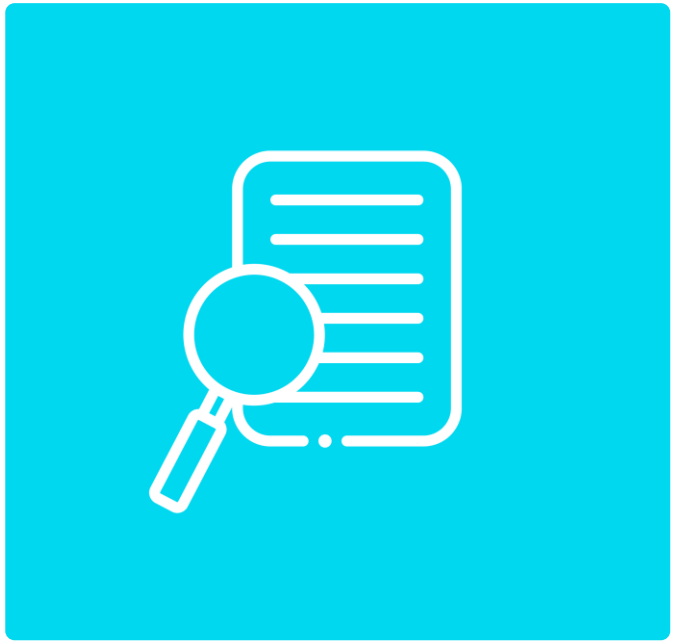
These are key observations with important implications for the development of the new immunostimulatory mAb, and in the light of these some of the mAbs used in the clinic to date (anti-4-1BB, BMS-663513 human IgG4, anti-OX40, 9B12, mouse IgG1) which may not be optimal and so may underestimate potential clinical activity of this class of reagent.



Drug trends by development stage – Drug Target = TNF receptor superfamily member 9

INTELLECTUAL PROPERTY

- IP and materials around a series of novel human and murine antibodies specific for 4-1BB antigens, covering multiple different complementarity-determining region (CDR) sequences.
- Methods for their use in stimulation of anti-tumour T cell immunity as a monotherapy or in combination with other therapeutic moieties.
- WO/2017/077085 The invention relates to antibodies specific for 4-1BB and OX40, as well as to methods for using such antibodies and therapeutic uses thereof.



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THANK YOU

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