Antibodies to activate our immune system against melanoma

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Treating solid tumours: challenges and opportunities

Saul L et al., Scientific Reports, 2016
Antibody immunotherapies are gaining great attention
B cells in the human body produce antibodies

The immune system recognises external attack

When our immune system responds B cells produce antibodies

Antibodies can selectively target specific molecules on invading pathogens
Harnessing the immune response to treat cancers like melanoma?

The immune system recognises melanoma cells

When our immune system responds, patients do better!

Antibodies can selectively target cancer cells
B Lymphocytes Produce Igs of Different Classes

Immunoglobulin classes

- IgG
- IgM
- IgD
- IgA₁
- IgE
Antibodies can activate immune cells to target cancer cells

![Diagram of Immune Cell and Cancer Cell](image1.png)

**Progression Free Survival (%)**

- **IgG4 low**
- **IgG4 high**

**HR (95% CI):** 2.56 (1.58-4.17)

**P = 0.0001 log-rank**

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## Monoclonal antibody treatments for cancer in the clinic

<table>
<thead>
<tr>
<th>Antibody name</th>
<th>Target</th>
<th>Class/subclass</th>
<th>Format</th>
<th>Indication</th>
<th>Year of FDA Approval</th>
<th>Known mechanisms of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>EGFR</td>
<td>IgG1</td>
<td>Chimeric</td>
<td>Colorectal, breast and lung cancer</td>
<td>2004</td>
<td>Inhibition of EGFR signaling, ADCC</td>
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<tr>
<td>Panitumumab</td>
<td>EGFR</td>
<td>IgG2</td>
<td>Human</td>
<td>Colorectal cancer</td>
<td>2006</td>
<td>Inhibition of EGFR signalling</td>
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<tr>
<td>Nimotuzumab</td>
<td>EGFR</td>
<td>IgG1</td>
<td>Humanized</td>
<td>Head and neck cancer</td>
<td>2004</td>
<td>Inhibition of EGFR signalling, apoptosis, ADCC, CDC, Inhibition of VEGF signaling</td>
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<tr>
<td>Rituximab</td>
<td>CD20</td>
<td>IgG1</td>
<td>Chimeric</td>
<td>Non-Hodgkin lymphoma</td>
<td>1997</td>
<td>ADCC, apoptosis, CDC</td>
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<tr>
<td>Trastuzumab</td>
<td>HER2</td>
<td>IgG1</td>
<td>Humanized</td>
<td>Breast cancer</td>
<td>1998</td>
<td>Inhibition of ERBB2 signaling, ADCC, CDC</td>
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<tr>
<td>Alemtuzumab</td>
<td>CD52</td>
<td>IgG1</td>
<td>Humanized</td>
<td>Chronic lymphocytic leukemia</td>
<td>2001</td>
<td>Apoptosis, CDC</td>
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<tr>
<td>Bevacizumab</td>
<td>VEGFA</td>
<td>IgG1</td>
<td>Humanized</td>
<td>Colorectal and lung cancer</td>
<td>2004</td>
<td>Inhibition of VEGF signaling</td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>CD20</td>
<td>IgG1</td>
<td>Human</td>
<td>Chronic lymphocytic leukemia</td>
<td>2009</td>
<td>ADCC, CDC</td>
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<tr>
<td>Ipilimumab</td>
<td>CTLA-4</td>
<td>IgG1</td>
<td>Human</td>
<td>Metastatic melanoma</td>
<td>2011</td>
<td>CTLA4 signaling block, ADCC</td>
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<tr>
<td>Pertuzumab</td>
<td>HER2</td>
<td>IgG1</td>
<td>Humanized</td>
<td>Breast cancer</td>
<td>2012</td>
<td>Inhibits ligand-dependent HER2 heterodimerization with HER1, HER3, and HER4; ADCC</td>
</tr>
<tr>
<td>Denosumab</td>
<td>RANK Ligand</td>
<td>IgG2</td>
<td>Human</td>
<td>Solid tumor bony metastases</td>
<td>2010</td>
<td>Inhibits this maturation of osteoclasts by binding to and inhibiting RANKL, reducing disease progression</td>
</tr>
<tr>
<td>Brentuximab</td>
<td>CD30</td>
<td>IgG1</td>
<td>Chimeric</td>
<td>Hodgkin's or systemic anaplastic large cell lymphoma</td>
<td>Delivery of toxic payload (ADC)</td>
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<tr>
<td>Gemtuzumab</td>
<td>CD33</td>
<td>IgG4</td>
<td>Humanized</td>
<td>Acute myelogenous leukemia</td>
<td>2000</td>
<td>Apoptosis, CDC</td>
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<tr>
<td>90Y-Ibritumomab tiuxetan</td>
<td>CD20</td>
<td>IgG</td>
<td>Mouse</td>
<td>Low grade or transformed B cell non-Hodgkin's lymphoma</td>
<td>2009</td>
<td>Radiotherapeutic, ADCC, CDC, apoptosis</td>
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<tr>
<td>Tositumomab and 131I-tositumomab</td>
<td>CD20</td>
<td>IgG2a</td>
<td>Mouse</td>
<td>Lymphoma</td>
<td>2003</td>
<td>ADCC and CDC, apoptosis</td>
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</tbody>
</table>
Could we use a different antibody class to treat tissue cancers?

Immunoglobulin classes

All cancer treatments used to date are IgG. This class is good for treating blood cancers but may not be readily directed into tissues such as the skin or internal organs such as the ovaries.
Why design antibodies of the IgE class for cancer therapy

IgE naturally found in our blood and tissues
IgE participates in allergies
IgE antibodies protect us from parasitic infections
IgE antibodies work best in tissues
IgE engages powerful Fce receptors
IgE immune cells in tumours
No blocking Fce receptors

Could we develop a treatment that makes us “allergic” to cancer?
MOv18: First clinical candidate & Proof of concept

MOv18 IgE was more active than the IgG counterpart in three models of cancer
IgE restricts melanoma growth better than IgG

Survival of autologous

Tumour size

CSPG4-IgG  CSPG4-IgE

PBS

Day 10  Day 16  Day 20  Day 27  Day 30

n = 7

Survival of autologous

Percent survival

PBS  CSPG4 IgE

p=0.04

n=8  n=9

Day

0  50  100  150

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NHS Foundation Trust
IgE recruits immune cells to destroy cancer cells
Could we contribute to more effective immunotherapies for cancer?

Could we add IgE antibodies to these charts?
Will IgE immunotherapy be safe in humans?

Two tests that clinicians use to diagnose allergy
A role for IgE in cancer? AllergoOncology

- Karagiannis SN et al., Chapter 8 in Cancer and IgE, ISBN: 978-1-60761-450-0, 2010
- Karagiannis SN et al., *Cancer Immunol Immunother*, 61(9): 1547-64, 2012
- Josephs DH, et al., *mAbs*, 6(1):54-72, 2014

Chapter 8
IgE Interacts with Potent Effector Cells Against Tumors: ADCC and ADCP

Sophia N. Karagiannis, Frank O. Nestle, and Hannah J. Gould
Human B cells can produce antibodies in the laboratory.
From Discovery to Phase I Trials: Therapeutic mAbs for Cancer

New mAbs

Lead mAbs

MOv18 IgE

Discovery

Efficacy/Mechanisms

Development/Mechanisms

Clinical Studies

**Dermatology:**
Katie Lacy
Jenny Geh
Ciaran Healy
Eduardo Calonje

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Andrew Tutt
Mark Harries
Sarah Rudman
Ana Montes

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Thank you!