

Antibodies to activate our immune system against melanoma

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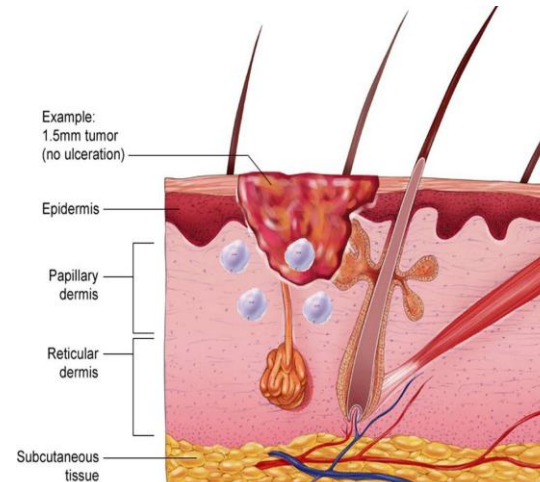
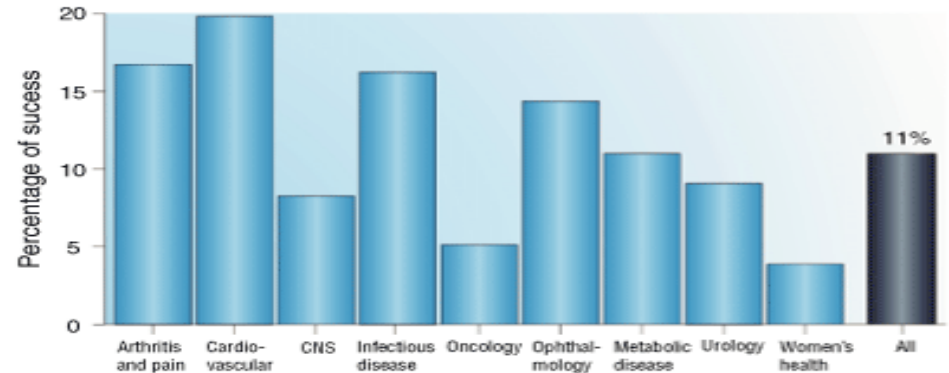
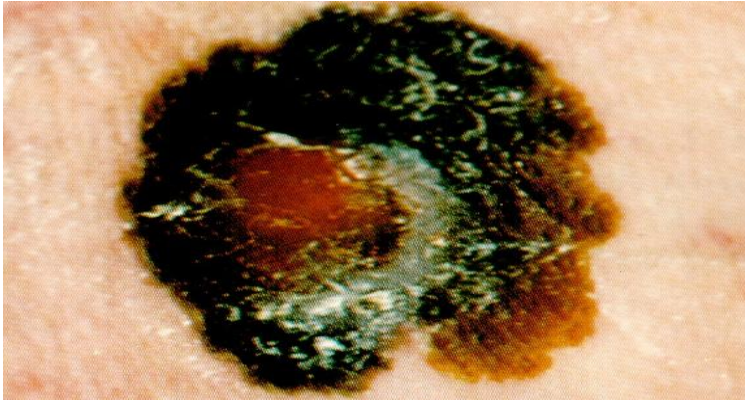


Charter for women in science
Recognising commitment to advancing
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Treating solid tumours: challenges and opportunities



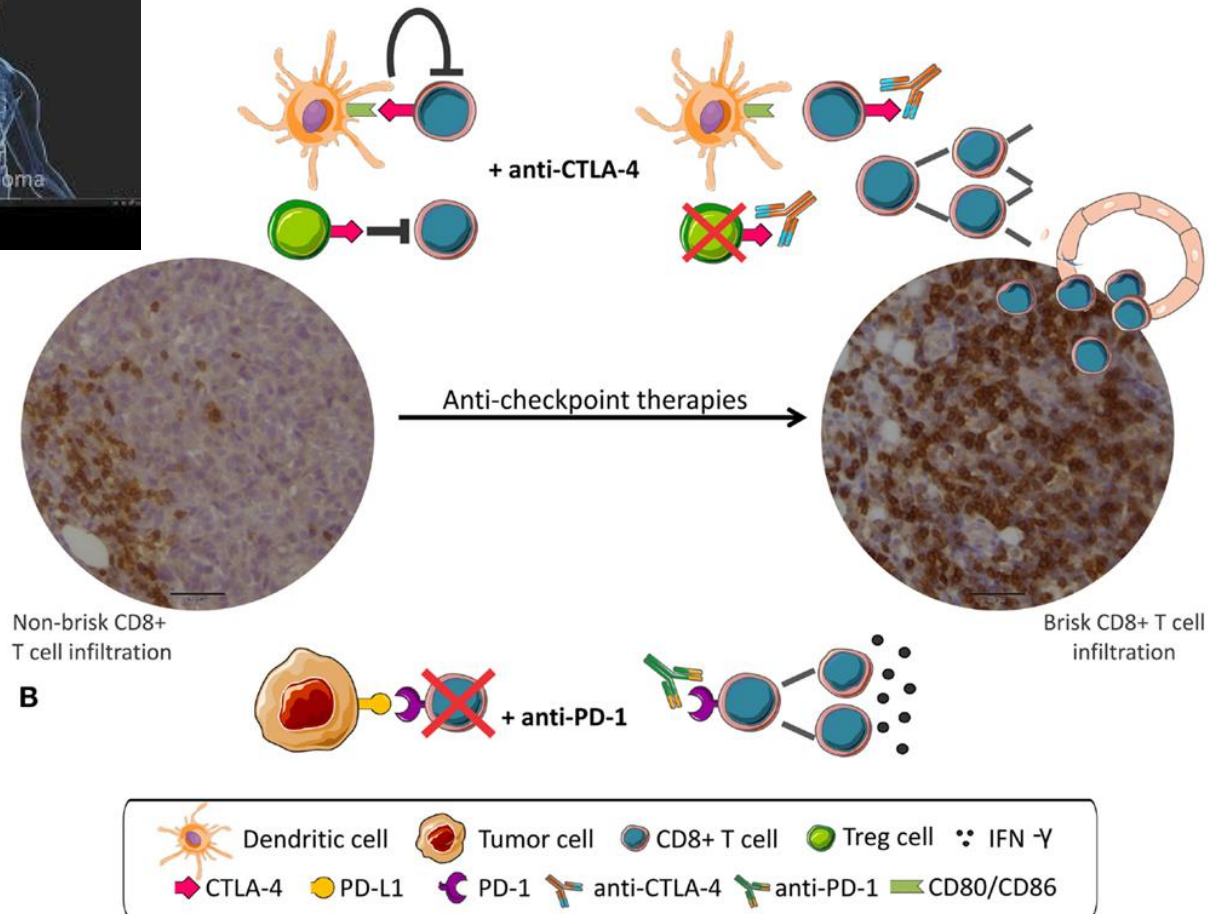
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Adapted from: Cheson B and Leonard J. N Engl J Med 2008;359:613-626

Saul L et al., Scientific Reports, 2016

Antibody immunotherapies are gaining great attention



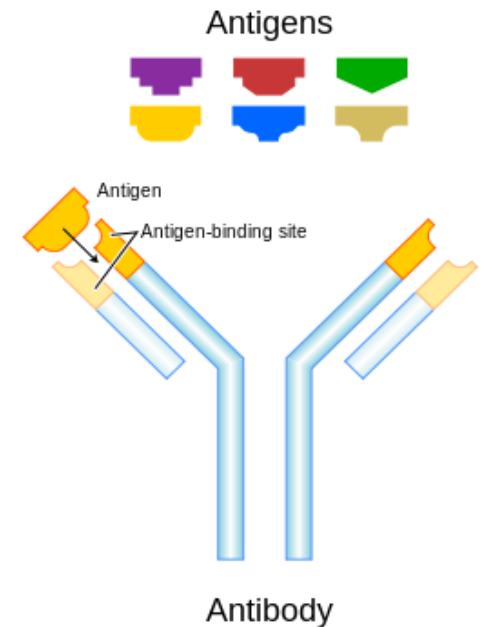
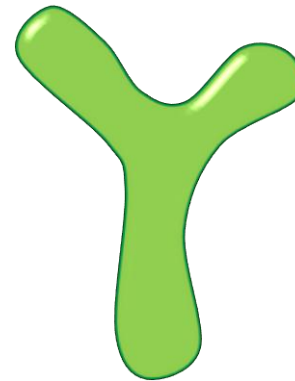
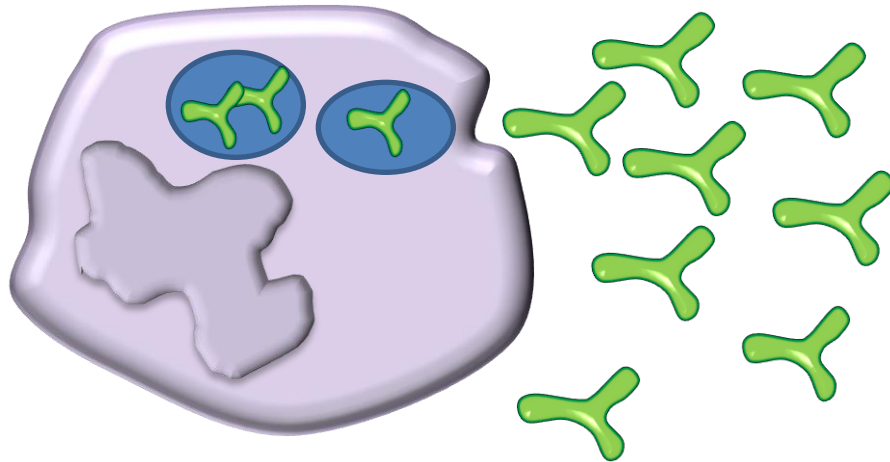
B cells in the human body produce antibodies

The immune system recognises external attack

When our immune system responds B cells produce antibodies

Antibodies can selectively target specific molecules on invading pathogens

B lymphocyte

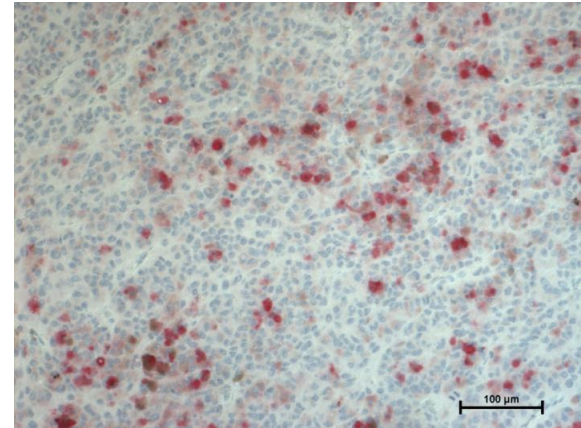


Harnessing the immune response to treat cancers like melanoma?

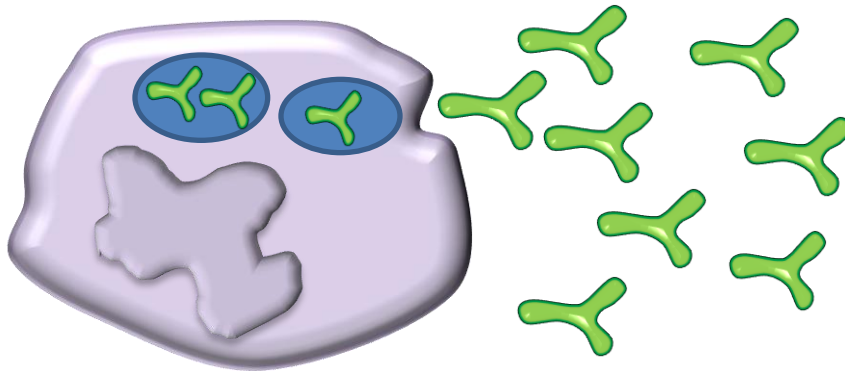
The immune system recognises melanoma cells

When our immune system responds, patients do better!

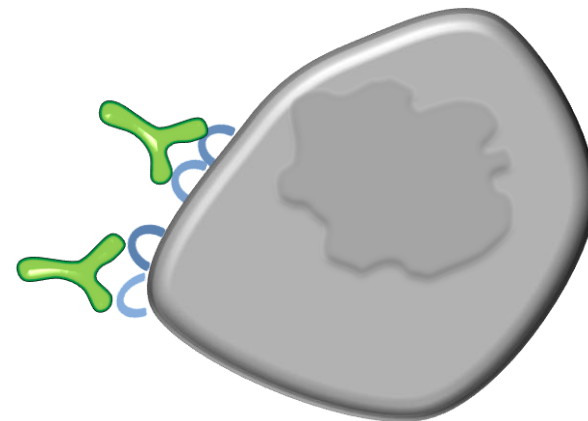
Antibodies can selectively target cancer cells



B lymphocyte

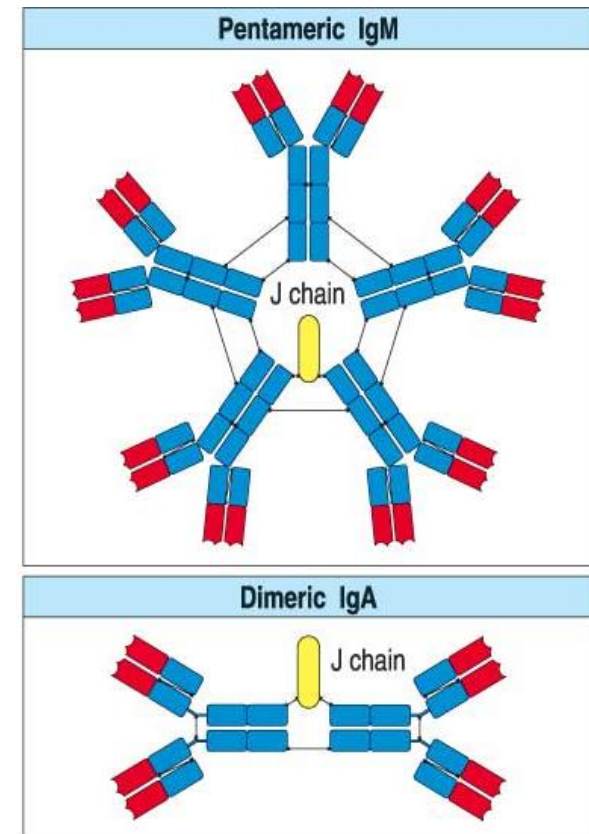
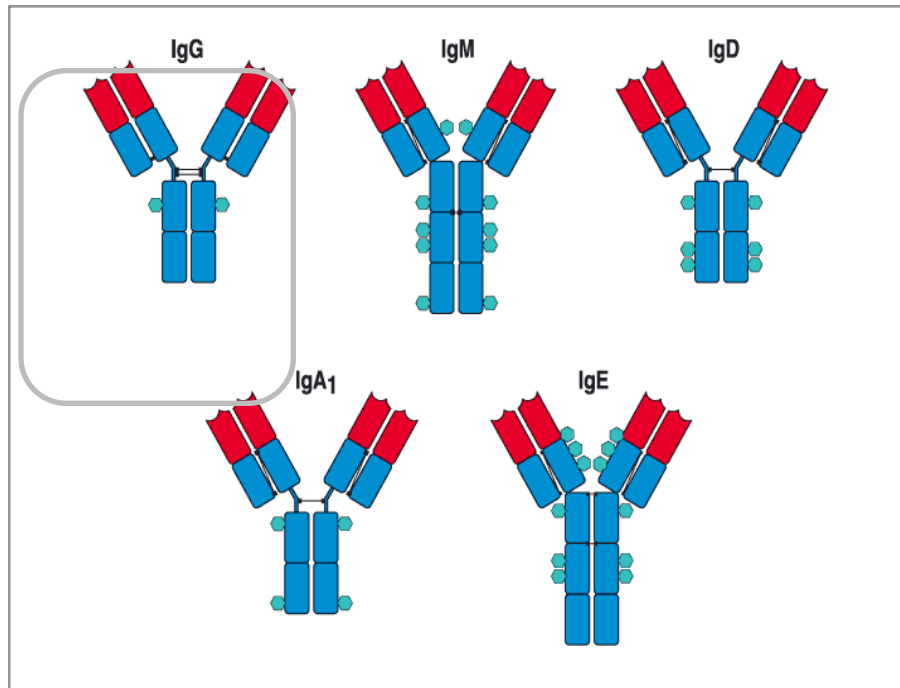


Cancer cell

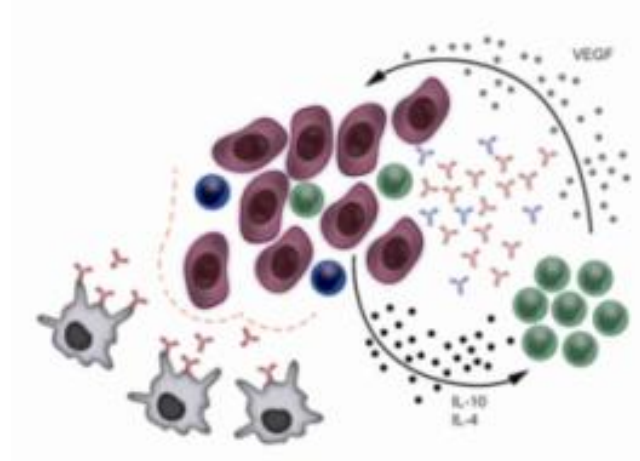
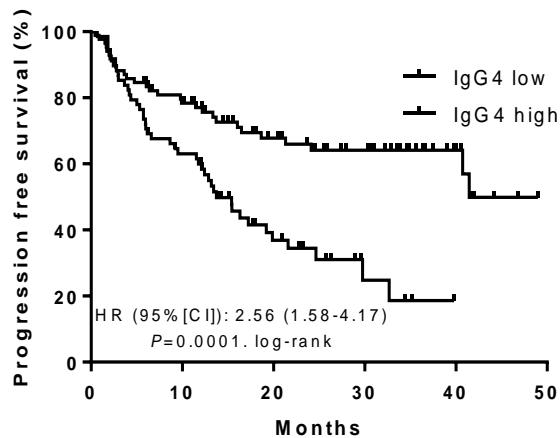
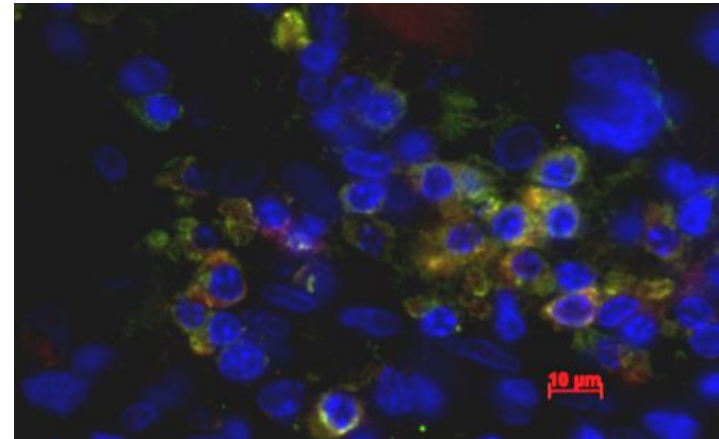
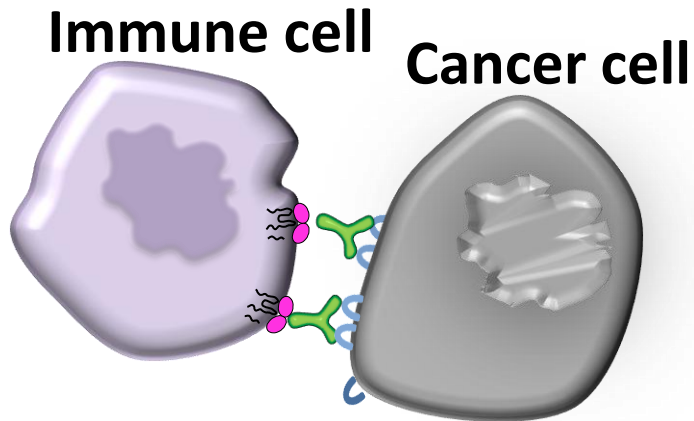


B Lymphocytes Produce Igs of Different Classes

Immunoglobulin classes



Antibodies can activate immune cells to target cancer cells

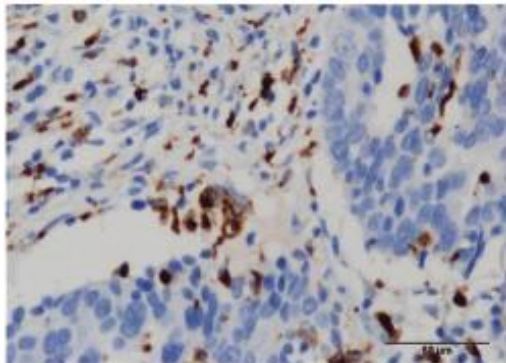
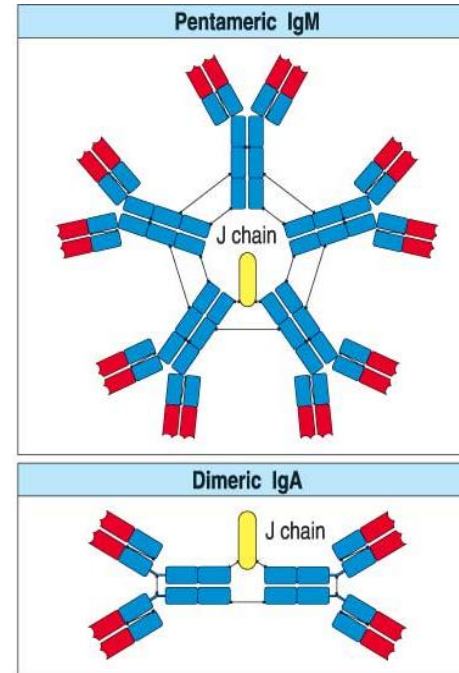
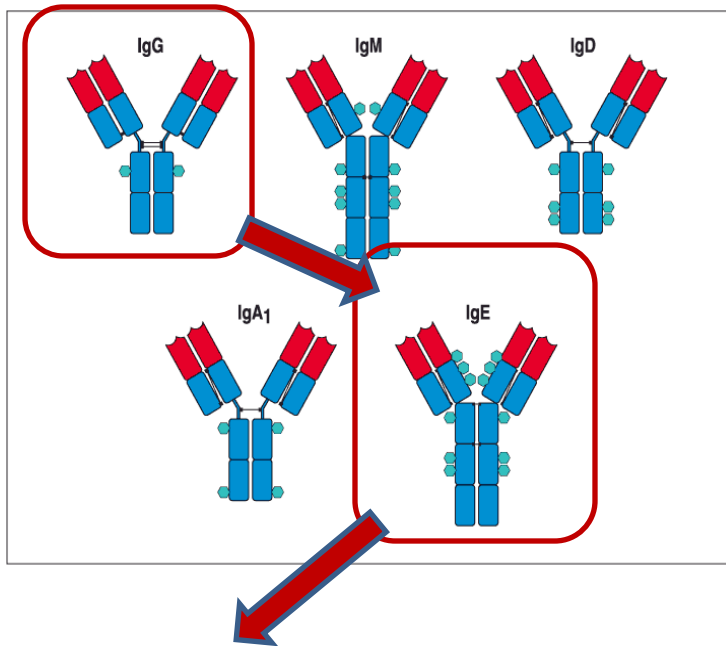


Monoclonal antibody treatments for cancer in the clinic

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

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 in to 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

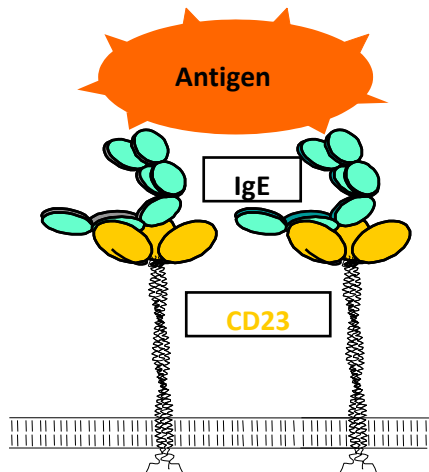
IgE antibodies protect us from parasitic infections

IgE antibodies work best in tissues

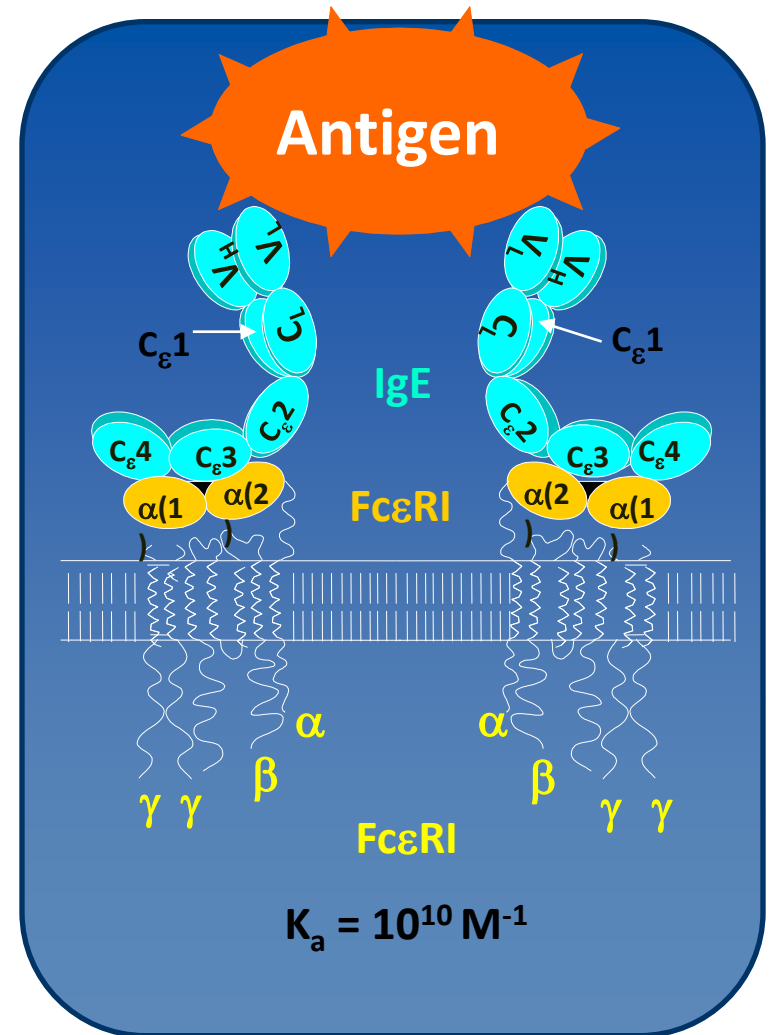
IgE engages powerful Fcε receptors

IgE immune cells in tumours

No blocking Fce receptors



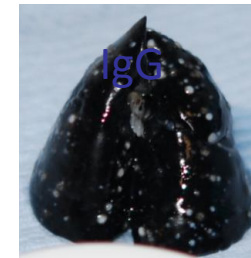
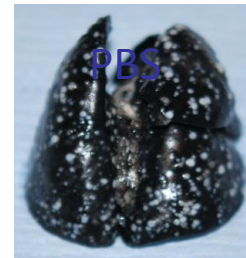
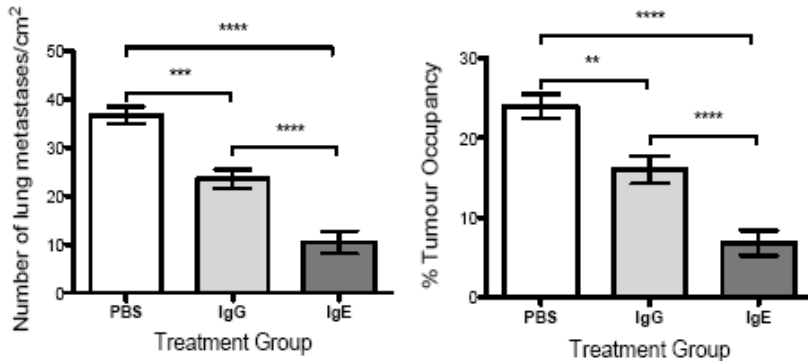
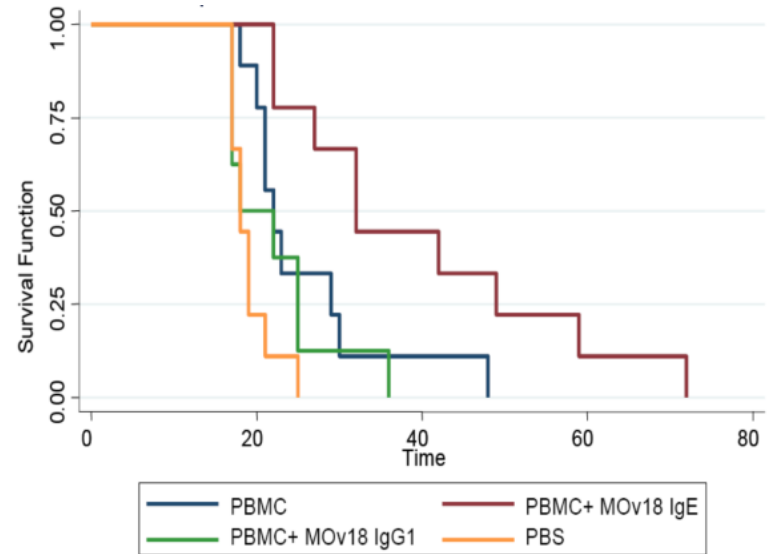
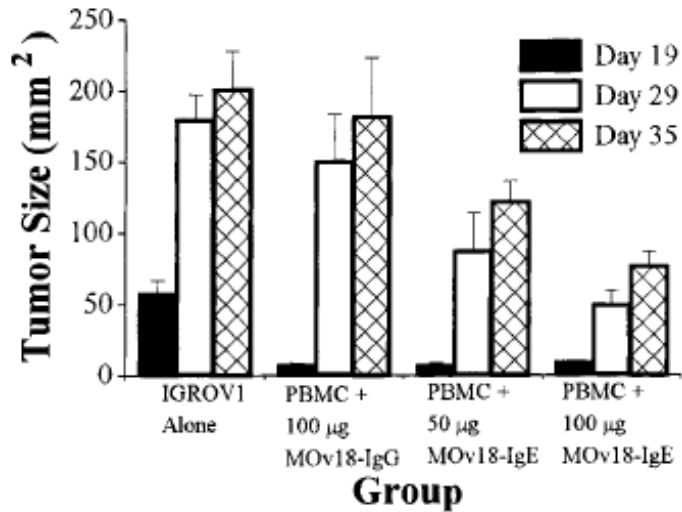
FceRII $K_a = 10^7 - 10^8 \text{ M}^{-1}$



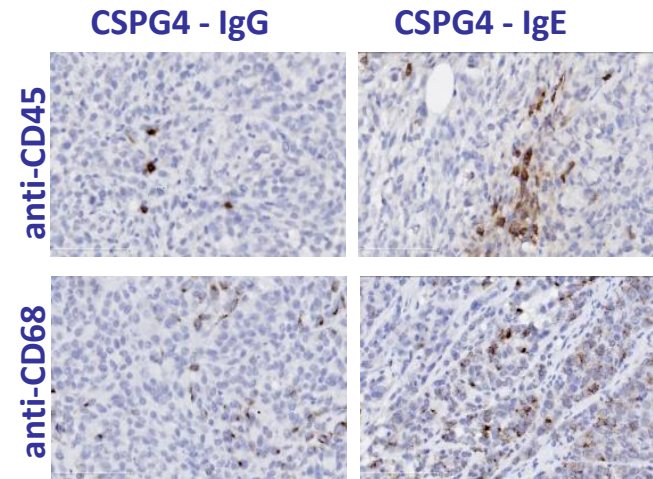
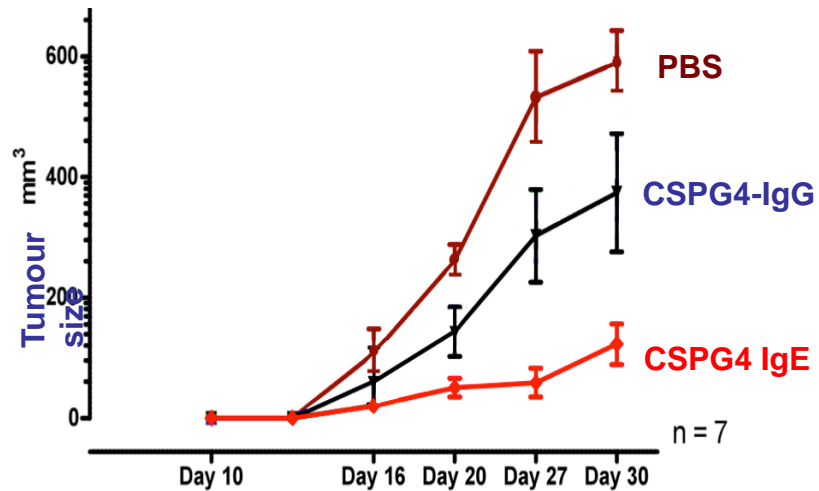
Could we develop a treatment that makes us “allergic” to cancer?

MOv18: First clinical candidate & Proof of concept

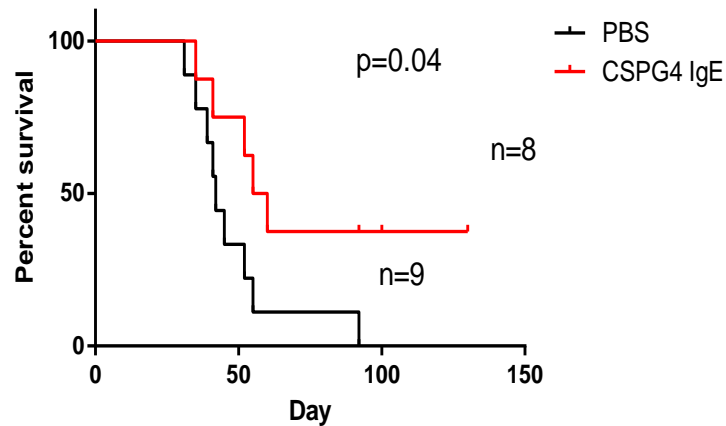
MOv18 IgE was more active than the IgG counterpart in three models of cancer



IgE restricts melanoma growth better than IgG

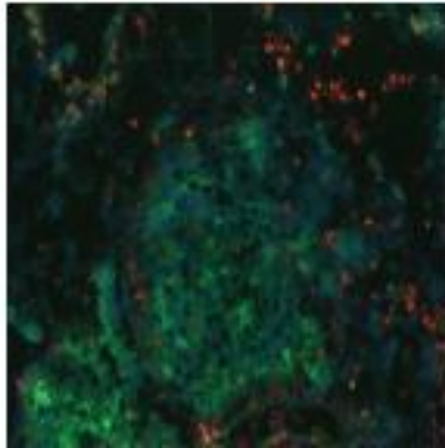


Survival of autologous

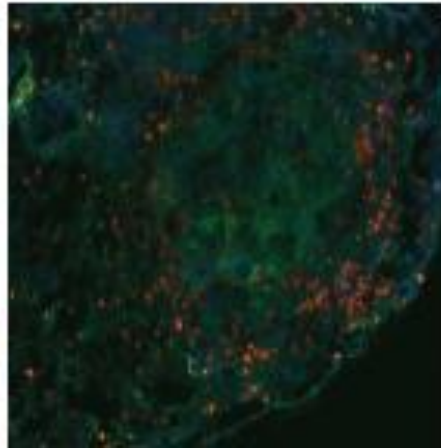


IgE recruits immune cells to destroy cancer cells

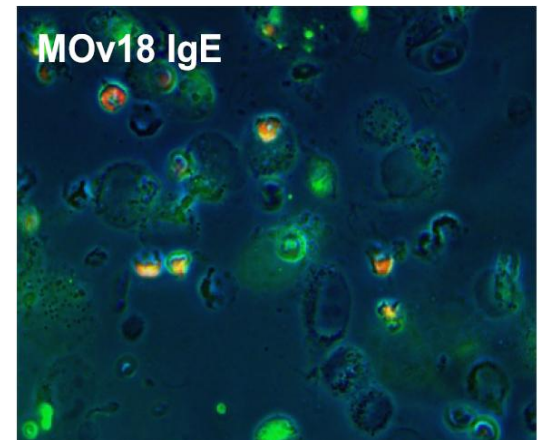
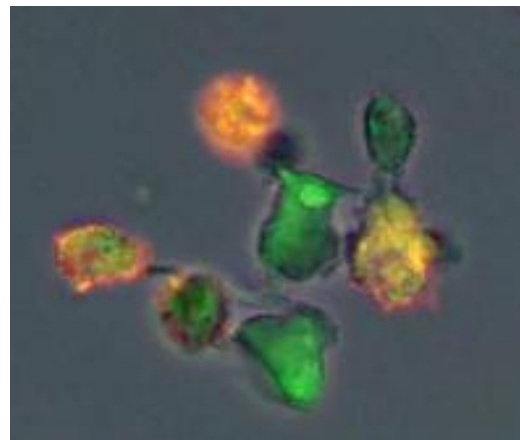
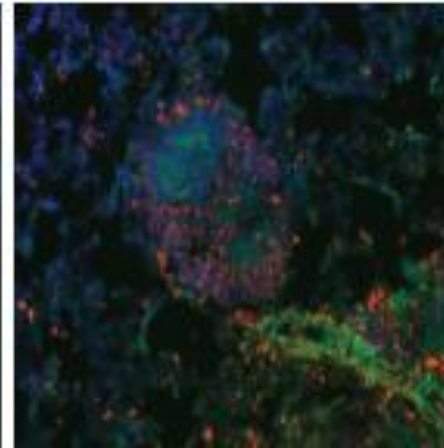
PBS



IgG

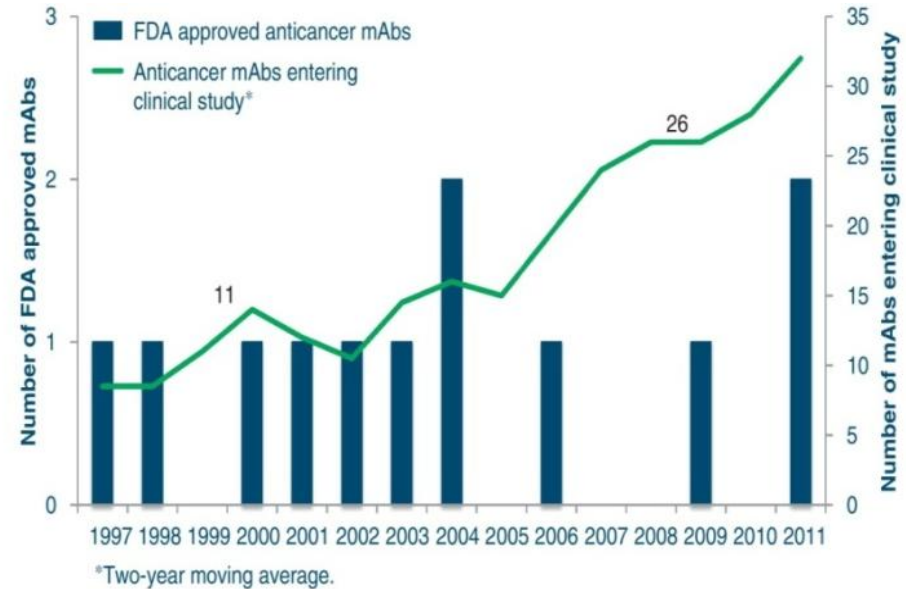
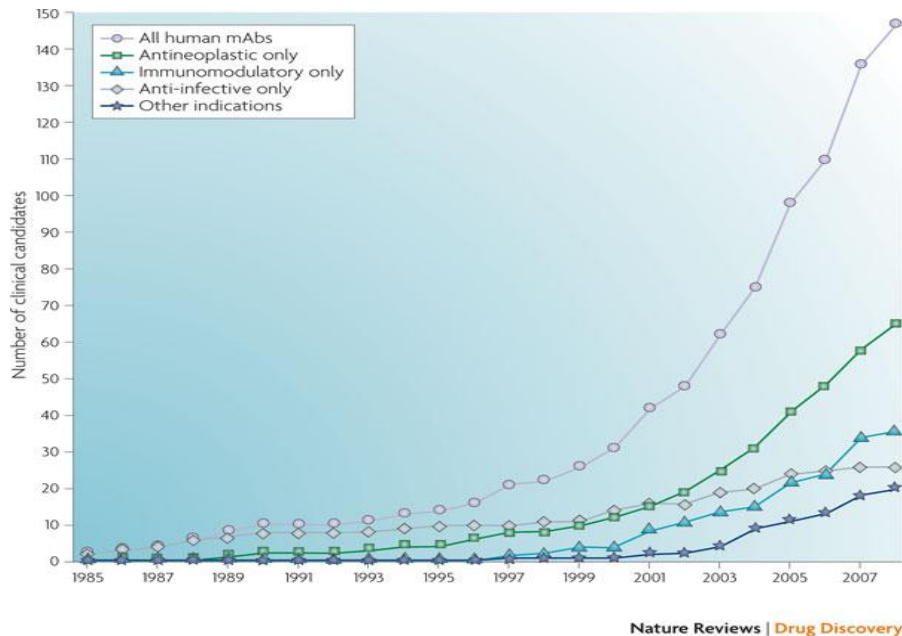


IgE



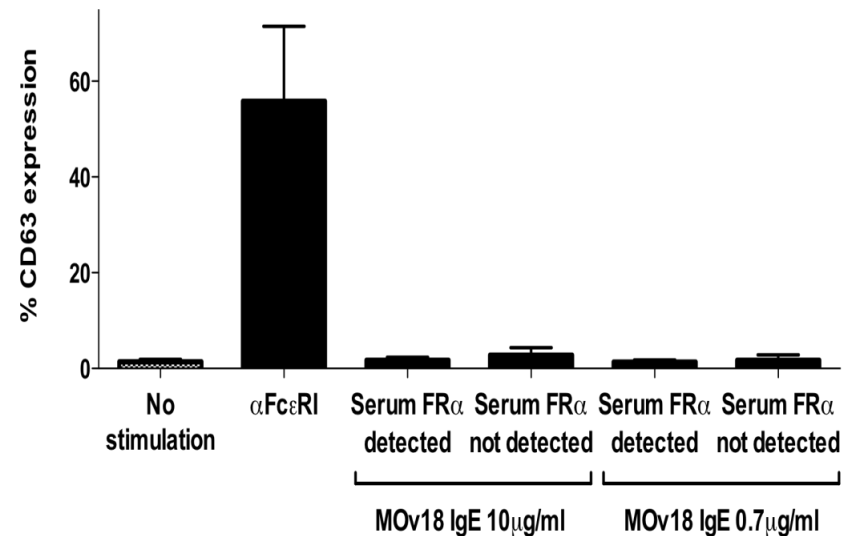
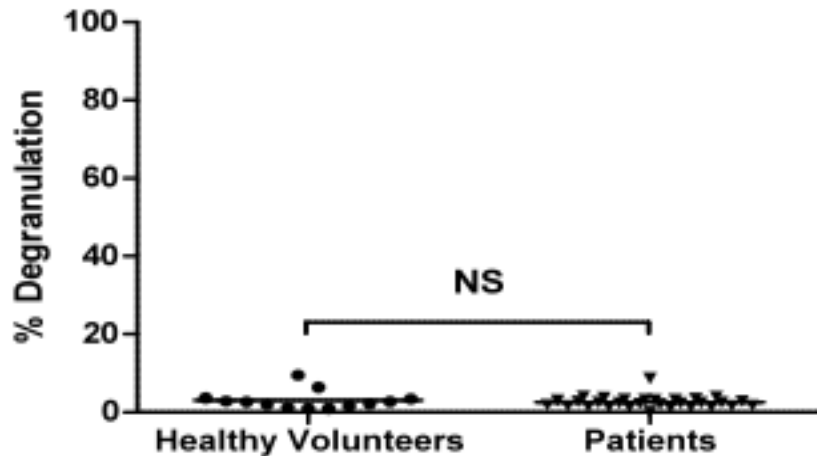
Could we contribute to more effective immunotherapies for cancer?

Could we add IgE antibodies to these charts?



Will IgE immunotherapy be safe in humans?

Two tests that clinicians use to diagnose allergy



doi: 10.1111/j.1365-2222.2011.03770.x

Clinical & Experimental Allergy 41, 1400–1413

ORIGINAL ARTICLE Basic Mechanisms in Allergic Disease

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Harnessing engineered antibodies of the IgE class to combat malignancy: initial assessment of Fc ϵ RI-mediated basophil activation by a tumour-specific IgE antibody to evaluate the risk of type I hypersensitivity

S. M. Rudman^{1,2}, D. H. Josephs^{1,2}, H. Cambrook¹, P. Karagiannis¹, A. E. Gilbert¹, T. Dodev^{3,4}, J. Hunt^{3,4}, A. Koers⁵, A. Montes⁶, L. Taams⁷, S. Canevari⁸, M. Figini⁹, P. J. Blower⁵, A. J. Beavitt^{3,4}, C. F. Nicodemus⁹, C. Corrigan⁴, S. B. Kaye¹⁰, F. O. Nestle¹, H. J. Gould^{3,4}, J. F. Spicer² and S. N. Karagiannis¹

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EDITORIAL

Clinical & Experimental Allergy

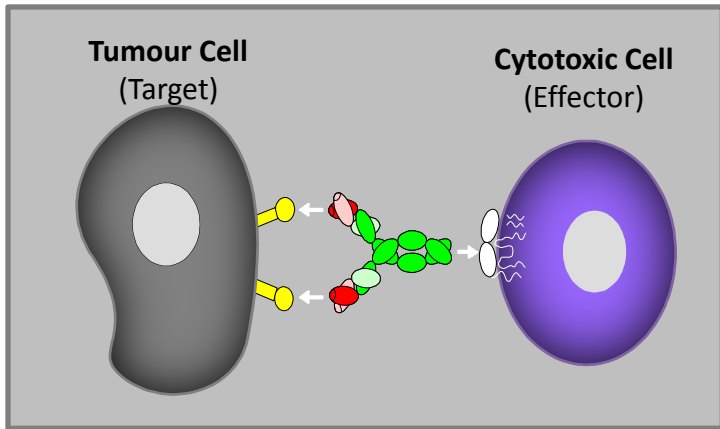
Why could passive Immunoglobulin E antibody therapy be safe in clinical oncology?

This editorial discusses the findings of the paper in this issue by Rudman et al. [35] pp. 1400–1413.

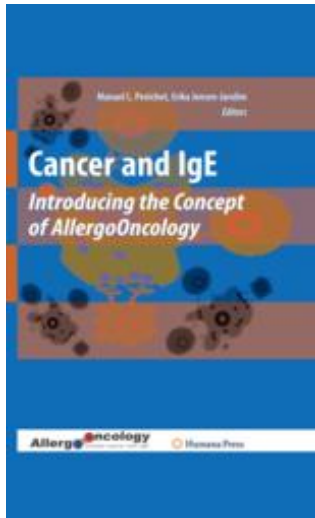
E. Jensen-Jarolim and J. Singer

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A role for IgE in cancer? AllergoOncology



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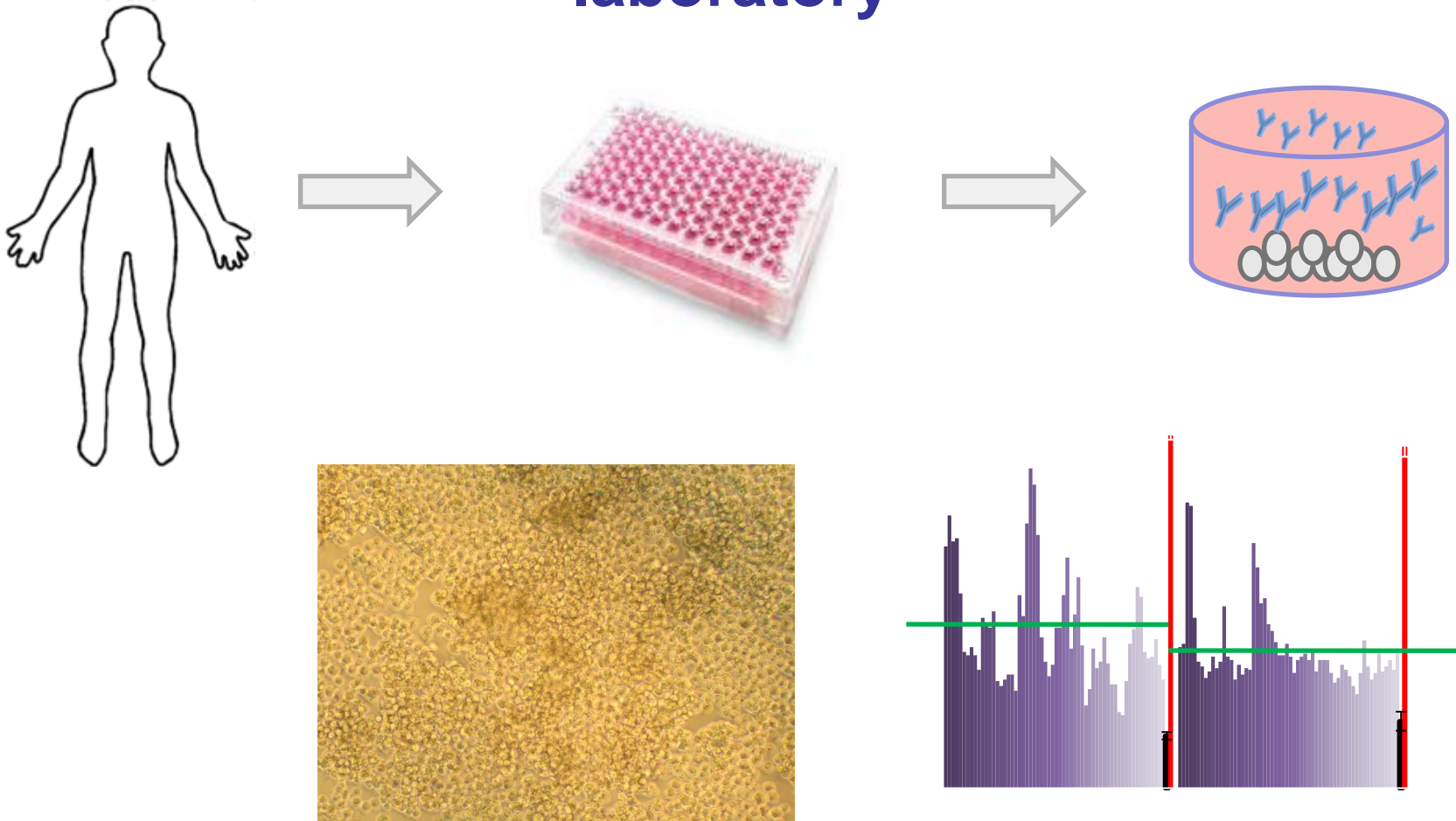
Chapter 8 IgE Interacts with Potent Effector Cells Against Tumors: ADCC and ADCP

Sophia N. Karagiannis, Frank O. Nestle, and Hannah J. Gould

AllergoOncology
Combat cancer with IgE.



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



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Thank you!