Mesothelioma Immunotherapy

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Cancer immunotherapy

- How does it work?
  - Therapy triggers anti-tumour immune responses
  - Patients own immune cells eliminate tumour cells
- What are the pros?
  - Non-toxic
  - Long lasting memory (c.v. virus vaccines)
  - Kills the cancer cells everywhere in the body
- What are the contras?
  - Autoimmunity can be a side-effect

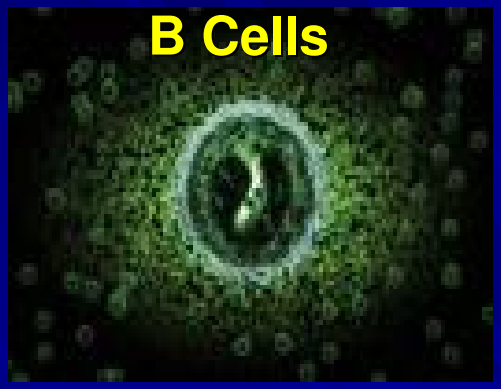
Immune cells (white blood cells)

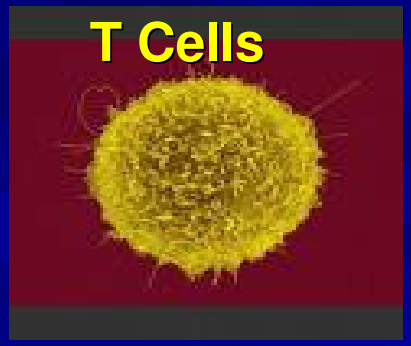
In: Blood

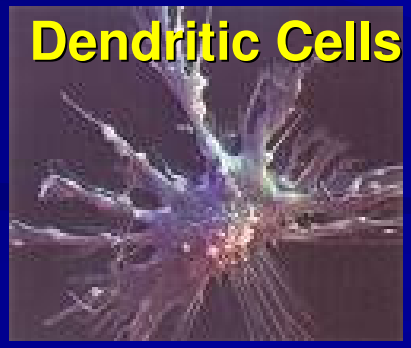
Lymph nodes

Lymphatic vessels

Thymus, bone marrow, spleen







The aim of immunotherapy

To eliminate tumour cells by the patients' own immune cells.

There are several types of cancer vaccines – common feature: **activation of killer T cells**

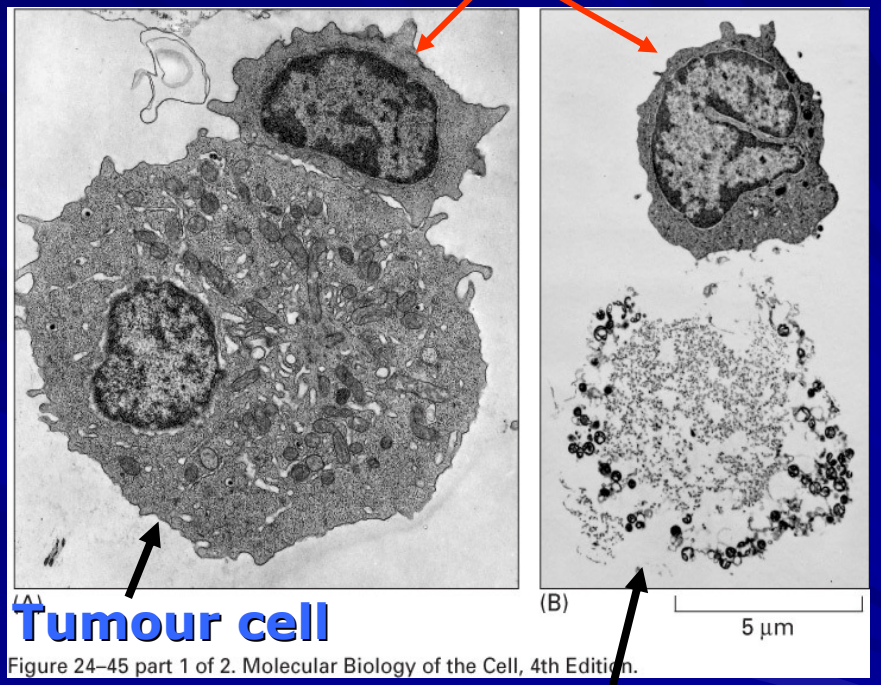
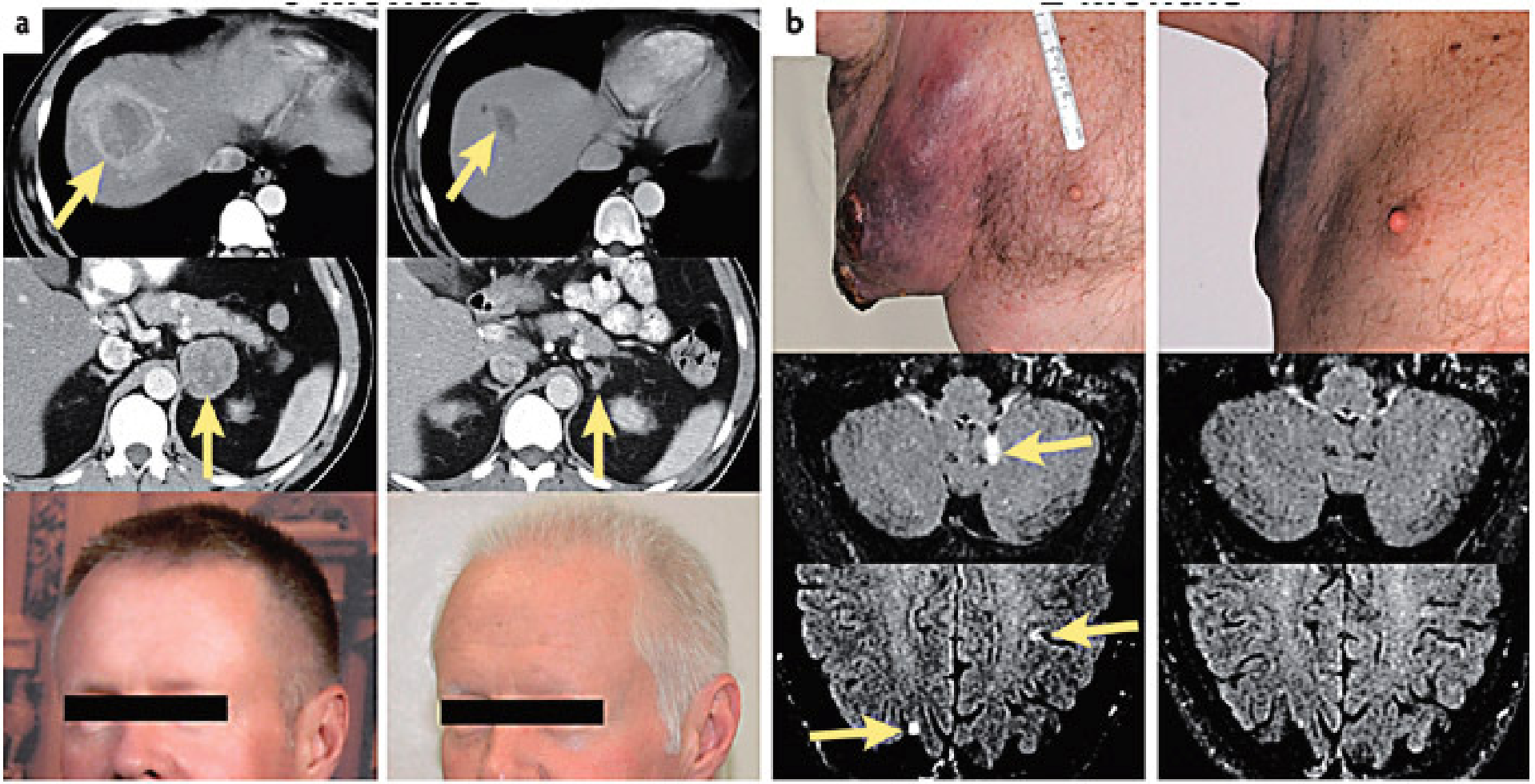


Figure 24–45 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

Metastatic melanoma treatment with T cell therapy

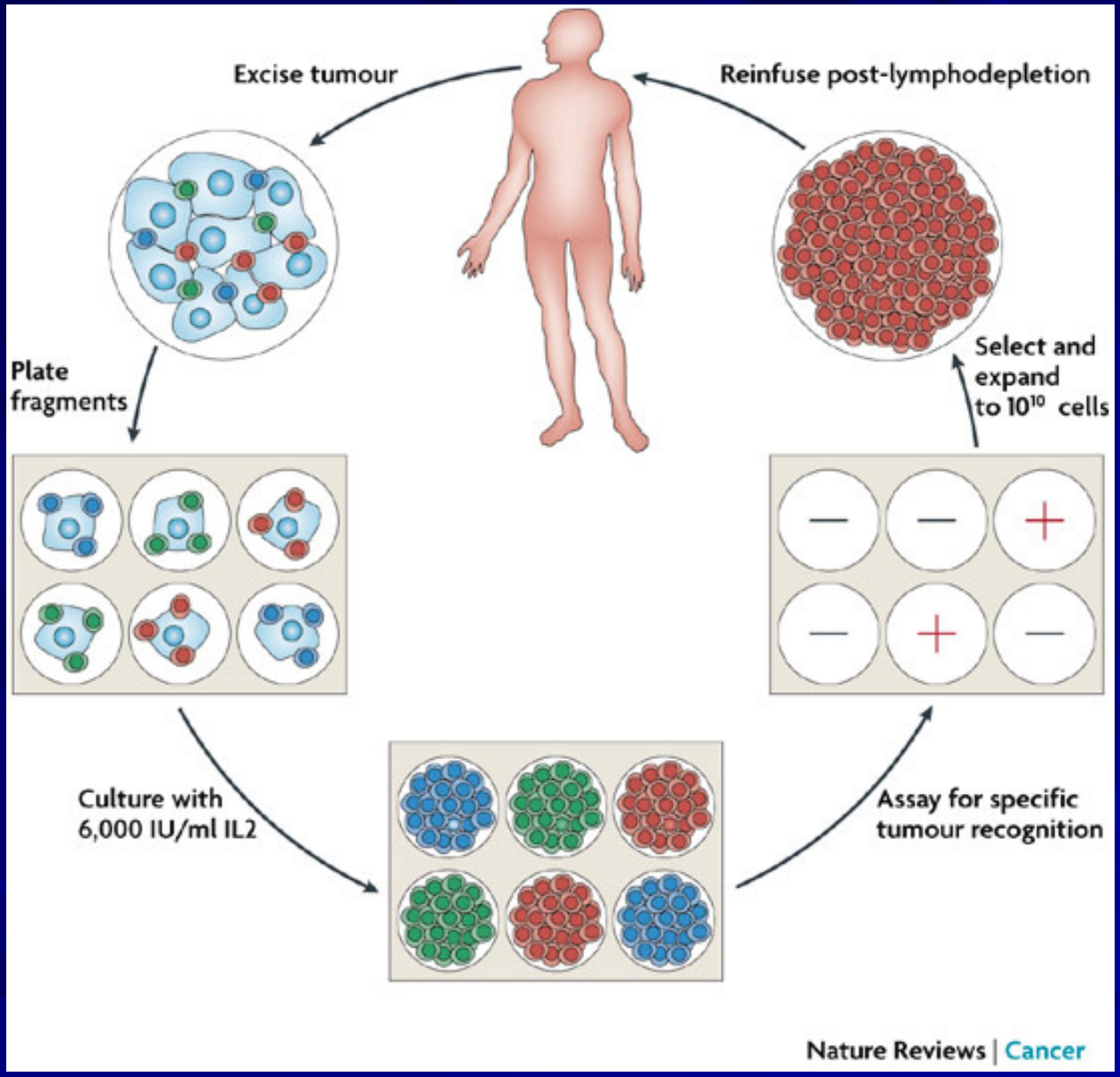
National Cancer Institute, Bethesda, Maryland, USA

Metastatic melanoma treatment with T cell therapy



Nature Reviews | Cancer

National Cancer Institute, Bethesda, Maryland, USA



Some of these melanoma patients are alive and well after 7 years (Klebanoff, PIVAC 10, Cambridge UK, 2010)

National Cancer Institute, Bethesda, Maryland, USA

Can the immune system work against mesothelioma?

Indirect evidence:

- Activated immune cells in pleural fluid correlate with better prognosis
- Inhibitors of immune responses have been found in pleural fluid
- Mesothelioma cells are capable of activating an immune response
- Spontaneous tumour regression in a patient was associated with improved immune responses

Current mesothelioma immunotherapy
I. The Pennsylvania approach (Daniel Sterman):

Gene therapy: genetically modified virus vector which makes interferon (immune stimulatory molecule)

The vector is injected into the pleural cavity and produces interferon.

1st trial: 6 MPM patients: 2 stable disease and 4 partial responses

2nd trial: 10 MPM patients - 2 doses of the virus.

3 partial response, 4 stable disease

2 doses were not better than 1 dose. Reason: antibody responses developed against interferon.

Current trial: Combination with chemotherapy, patients with high levels of anti-interferon responses excluded.

Current mesothelioma immunotherapy
II. Trial with dendritic cells.

American FDA approved a dendritic cell based vaccine for the treatment of advanced prostate cancer – first ever cancer vaccine approved!

In mesothelioma: Hegman et al., Rotterdam.

10 patients.

Dendritic cells are loaded with tumour cell lysate (dead tumour cells) and injected into patients. Immune responses develop against all the abnormal molecules present in the tumour cells.

The treatment was non-toxic. 3 partial responses and one stable disease were observed.

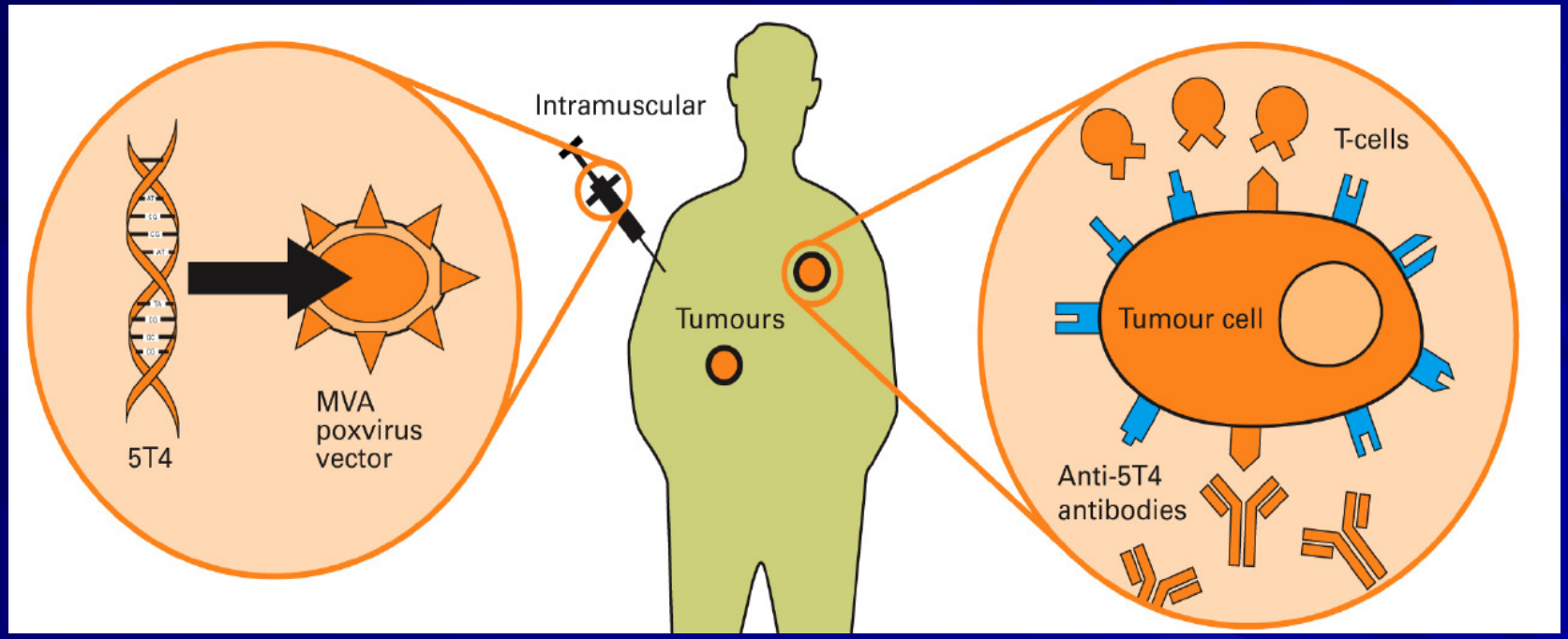
What are we studying?

- By learning more about anti-mesothelioma immunity we can reveal what trigger is needed to turn the immune system “on”
- Discovering new antigens (immune targets) on mesothelioma cells – cancer vaccine development
- Studying why immune cells in the pleural fluid can not reject the tumour
- Designing a clinical trial using a “cancer vaccine”

Vaccine against mesothelioma
Clinical trial, Cardiff

- The vaccine against 5T4 is called TroVax.
- It is a vaccinia virus which is modified to make 5T4 when infecting cells.
- The virus only multiplies once, then dies.
- The immune system reacts with the virus and with 5T4.
- 5T4 reactive immune cells circulate in the body and attack all cells (i.e. cancer cells) which have 5T4 on the cell surface.

TroVax
Product Composition & Concept



- Vaccine is donated free by Oxford BioMedica

Tumour Specificity (1)

5T4 is present on most solid tumours

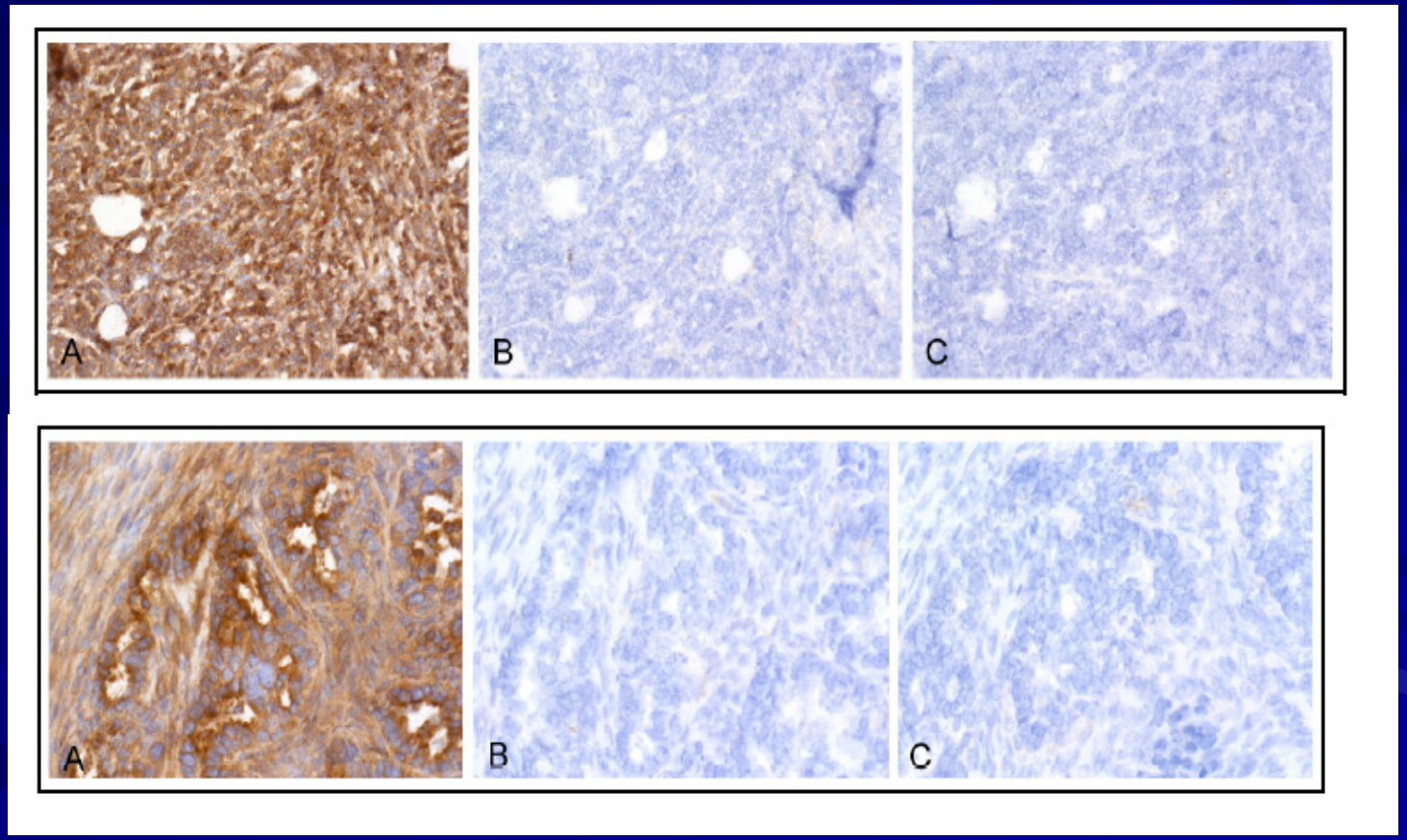
5T4 Expression on Human Tumours

Tumour Type	5T4 Frequency (%)	Number of Samples
Colorectal[1]	85	72
Renal[2]	95	20
Breast[3]	88	42
Ovarian[4]	71	58
Gastric[5]	74	86
Lung[6]	100	30
Prostate[6]	78	27

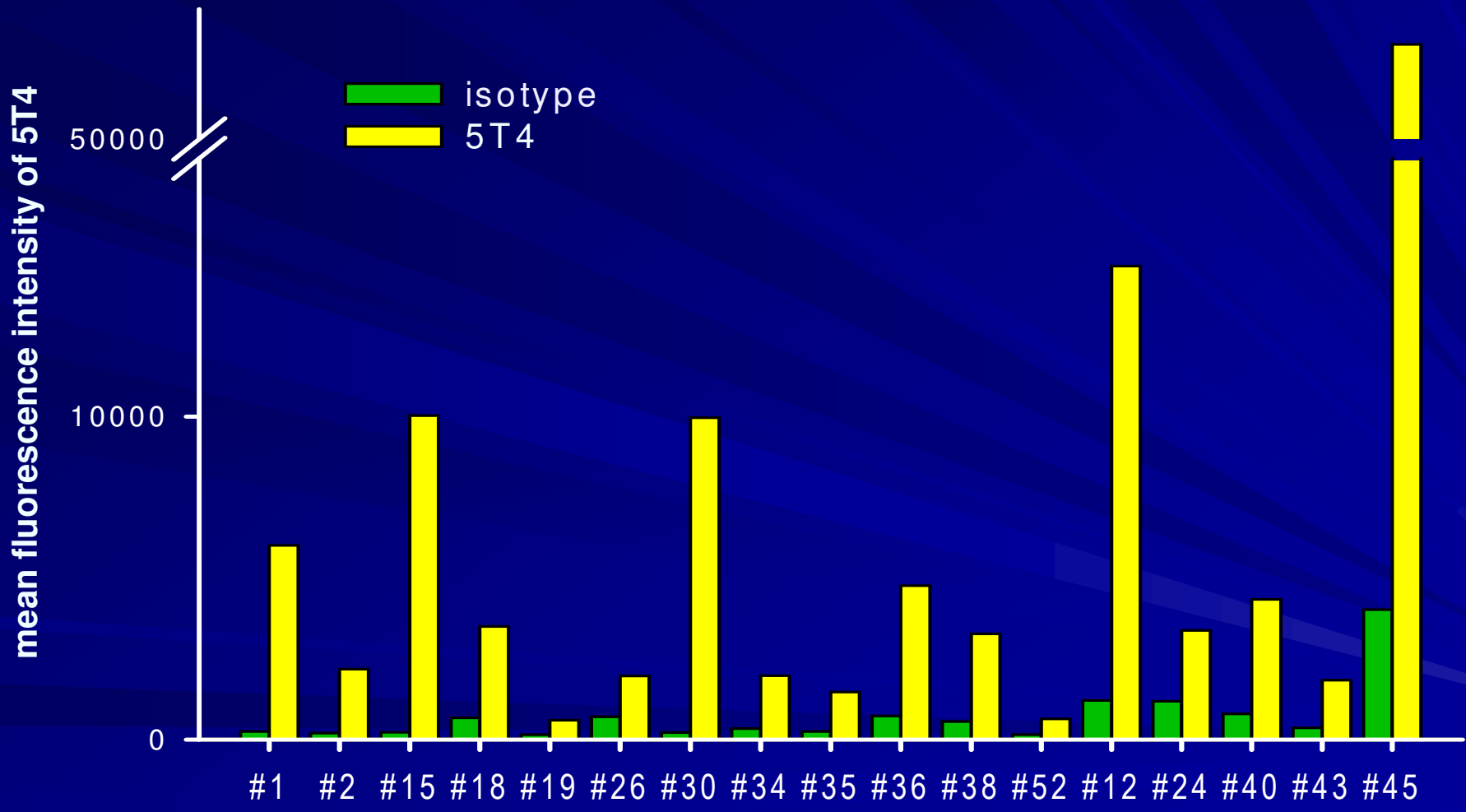
[1]Starzynska et al., 1992; [2]Griffiths et al, 2005; [3]Braybrooke et al., 2005 and Unpublished
[4] Wrigley et al., 1995; [5]Starzynska et al., 1998; [6]Unpublished

Tumour Specificity (2)

5T4 is present on most solid tumours



5T4 expression in mesothelioma cell lines

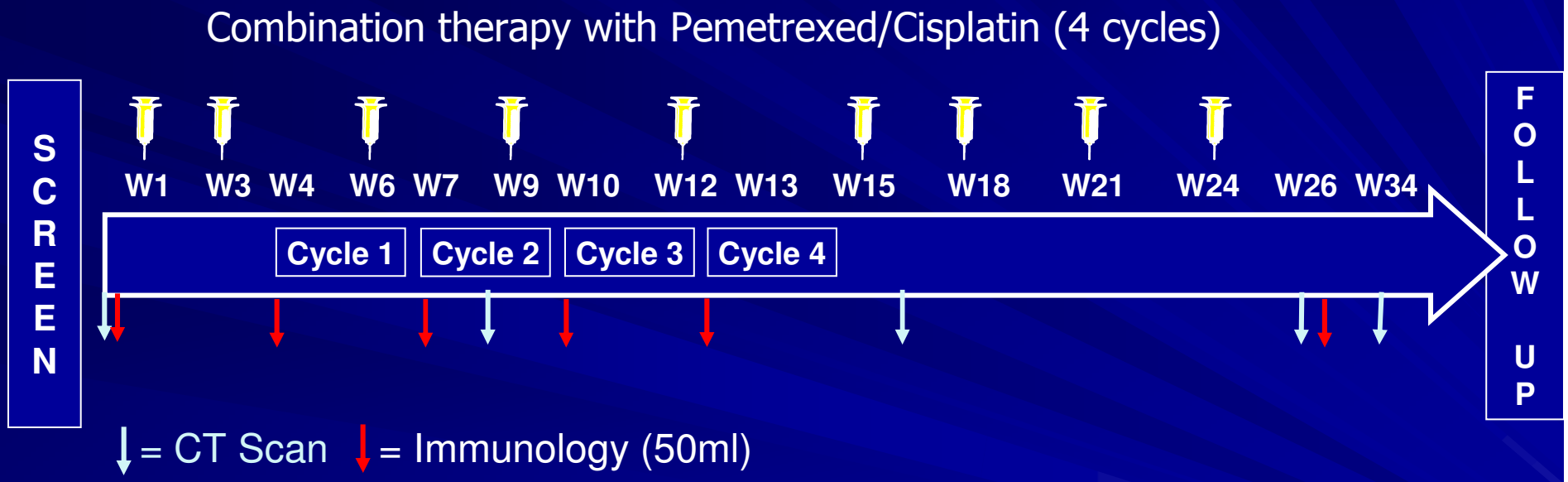


5T4 expression in mesothelioma

- All mesothelioma cell lines (17/17)
- All pleural fluid tumour cells (12/12)
- All tumour biopsies (12/12) were positive for 5T4
- Immune responses are present (at low levels) in patients

5T4 is a valid target for the therapy of mesothelioma

Phase II clinical trial with TroVax®
Vaccination and monitoring scheme in MPM



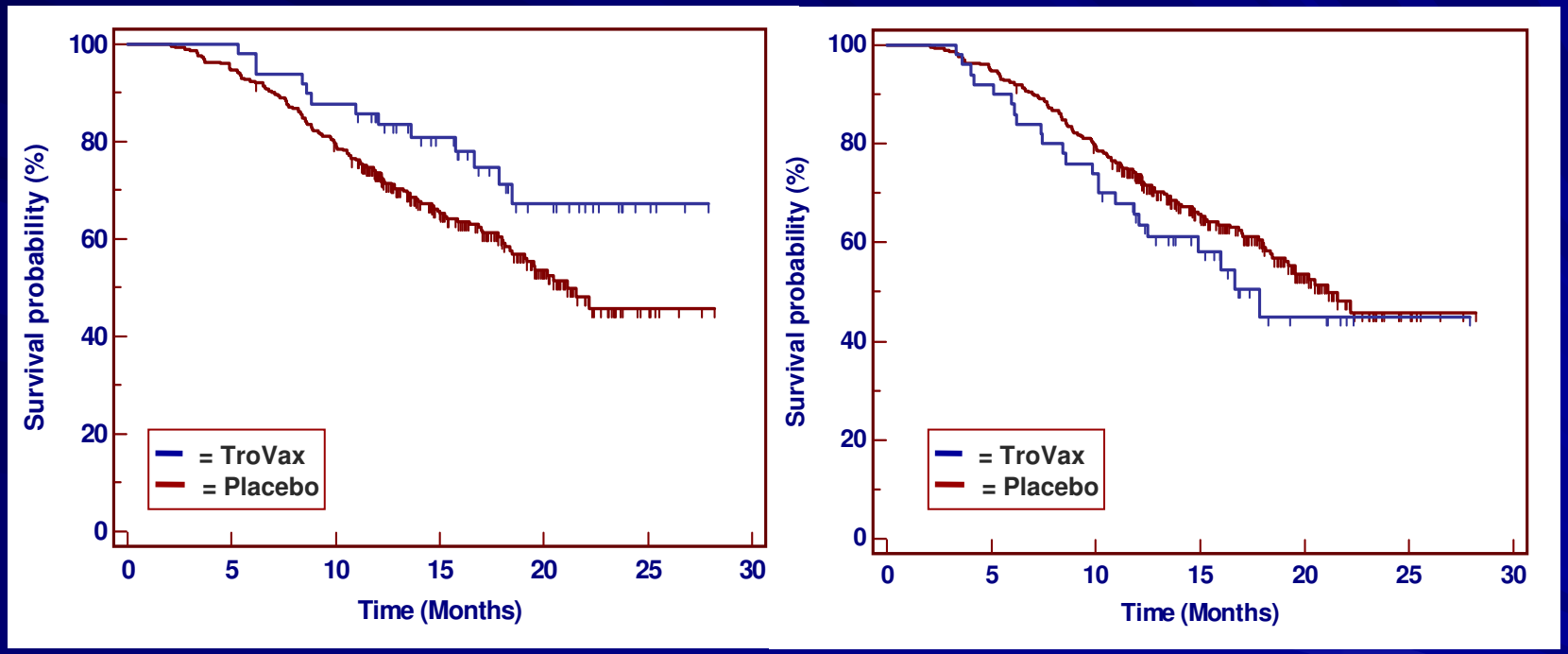
Single Arm study, 26 patients

1º Endpoints: Immune Response, Safety

2º Endpoint: clinical effect

5T4 Antibody Responses are Associated with Patient Survival – Renal Cell Cancer

High 5T4 Antibody Responders (n=50) **High MVA Antibody Responders (n=50)**



HR = 0.55 (95% CI: 0.39 - 0.97)
P=0.04

HR = 1.30 (95% CI: 0.82 - 2.12)
P=0.25

Magnitude of 5T4-specific (but not MVA) antibody response associated with increased survival

(Amato et al. Clin. Cancer Res. 2010)

SUMMARY

- The immunotherapy of cancer is in an experimental phase.
- There are some promising results indicating that if we find the most efficient ways to stimulate the patients' immune system, even big, bulky and multi-resistant tumours can be successfully treated by immunotherapy.

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