

Is Exercise an Immunotherapy, and Can It Enhance Tumour-Immune Regulation?

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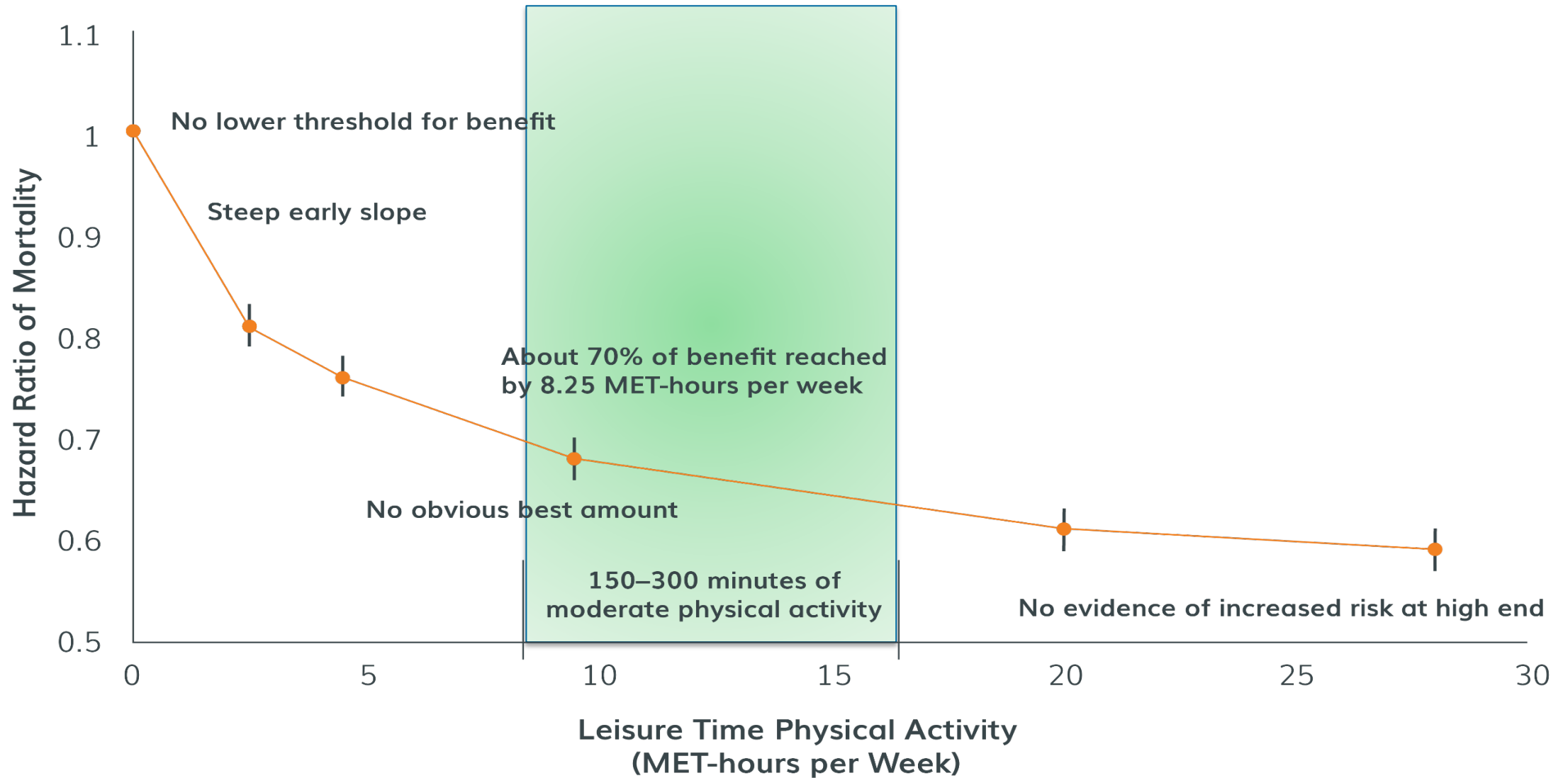
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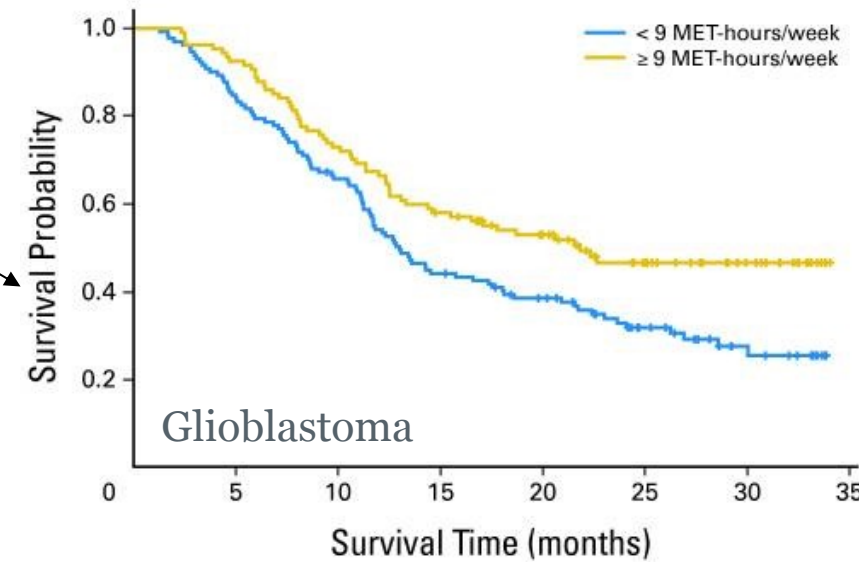
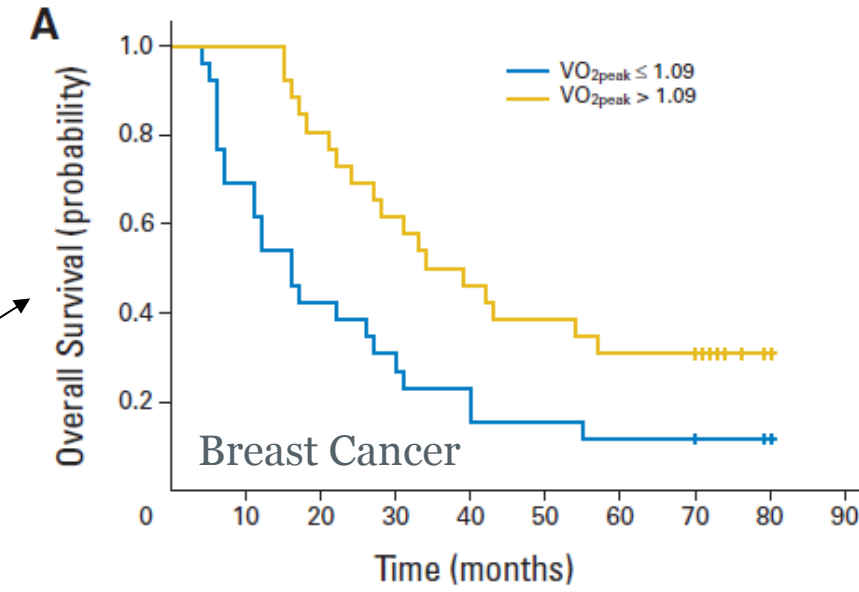
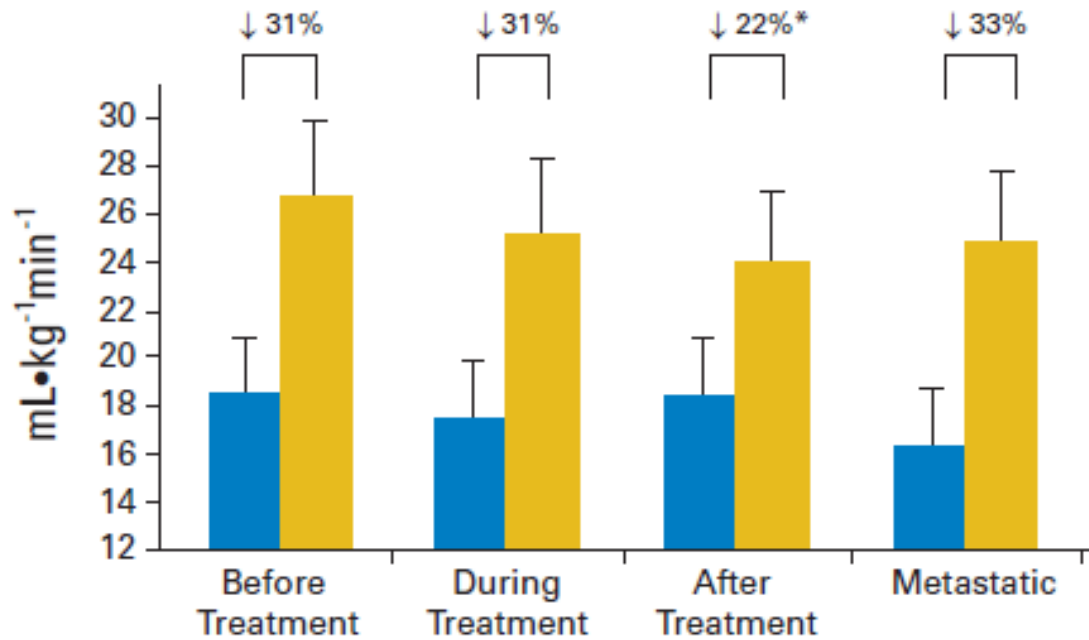


Being Physically Active Lowers Your Risk of Premature Mortality from Several Cancers



High Physical Fitness (VO_{2peak}) Before & During Cancer Improves Survival

Patients with cancer (blue bars) are less fit than age-matched controls (yellow bars)!



Exercise is Recommended for Cancer Prevention, Treatment and Survivorship

Exercise For Cancer Prevention and Treatment



colon cancer



breast cancer

For all adults, exercise is important for cancer prevention and specifically lowers risk of **seven common types of cancer:**



stomach cancer



endometrial cancer



esophageal cancer



bladder cancer



kidney cancer

Exercising during and after cancer treatment:

- decreases fatigue, anxiety and depression
- improves physical function and quality of life
- does **NOT** exacerbate lymphedema



For cancer survivors, incorporate exercise to improve survival after a diagnosis of breast, colon and prostate cancer

Cancer guidelines are similar to the general population

150 – 300 mins/week of **Moderate** Intensity

Or

75 – 150 mins/week of **Vigorous** Intensity

+

2 sessions/week of strength

Most benefits are quality of life related

No consensus (yet!) on how to use exercise as an immune enhancer

MOVING THROUGH CANCER:

Exercise for people living with and beyond cancer

TO GET STARTED

Avoid inactivity; moving more and sitting less benefits nearly everyone

FOR OVERALL HEALTH

Aim to meet the current exercise guidelines for adults¹



Moderate Aerobic Exercise
At least 150–300 mins per week
(or a combination of moderate/vigorous aerobic exercise)

OR

Vigorous Aerobic Exercise
At least 75–150 mins per week



+



Resistance Exercise
2x per week

FOR PEOPLE DURING & FOLLOWING CANCER TREATMENT

Research shows lower amounts of exercise can still help with the following cancer treatment-related symptoms:



Cancer-related fatigue



Health-related quality of life



Physical function



Anxiety



Depression



Sleep



Lymphedema²



Bone health³

To improve these symptoms, choose an exercise plan below:



OR



OR



Aerobic Exercise
3x per week
30–60 mins

Helps to manage the following symptoms:

Resistance Exercise
2x per week
2 sets/8–15 reps

Helps to manage the following symptoms:

Aerobic Exercise
2–3x per week
20–40 mins

Resistance Exercise
2x per week
2 sets/8–15 reps

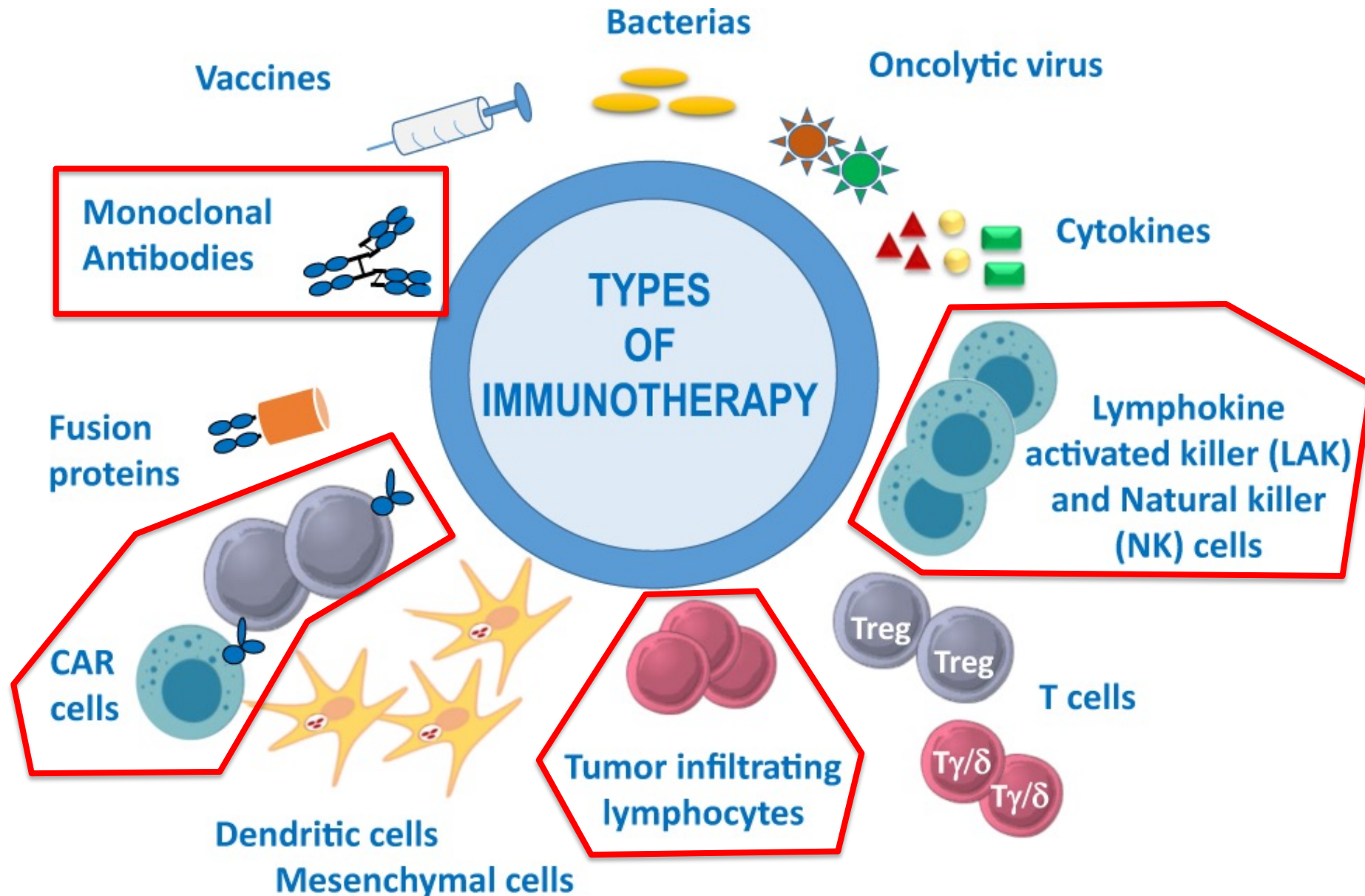
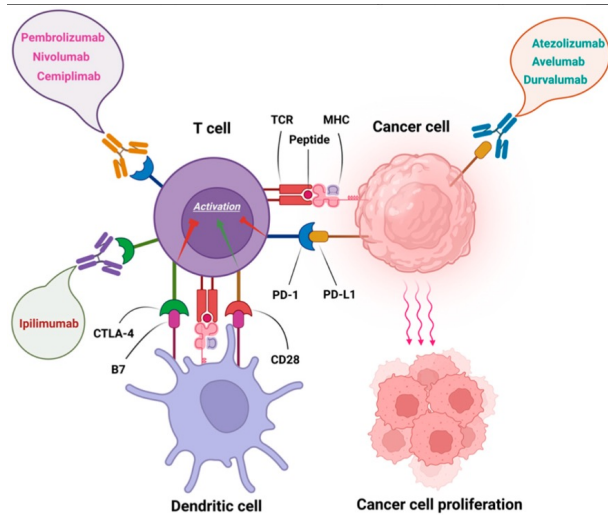
Helps to manage the following symptoms:

¹ Physical Activity Guidelines for Americans, 2018

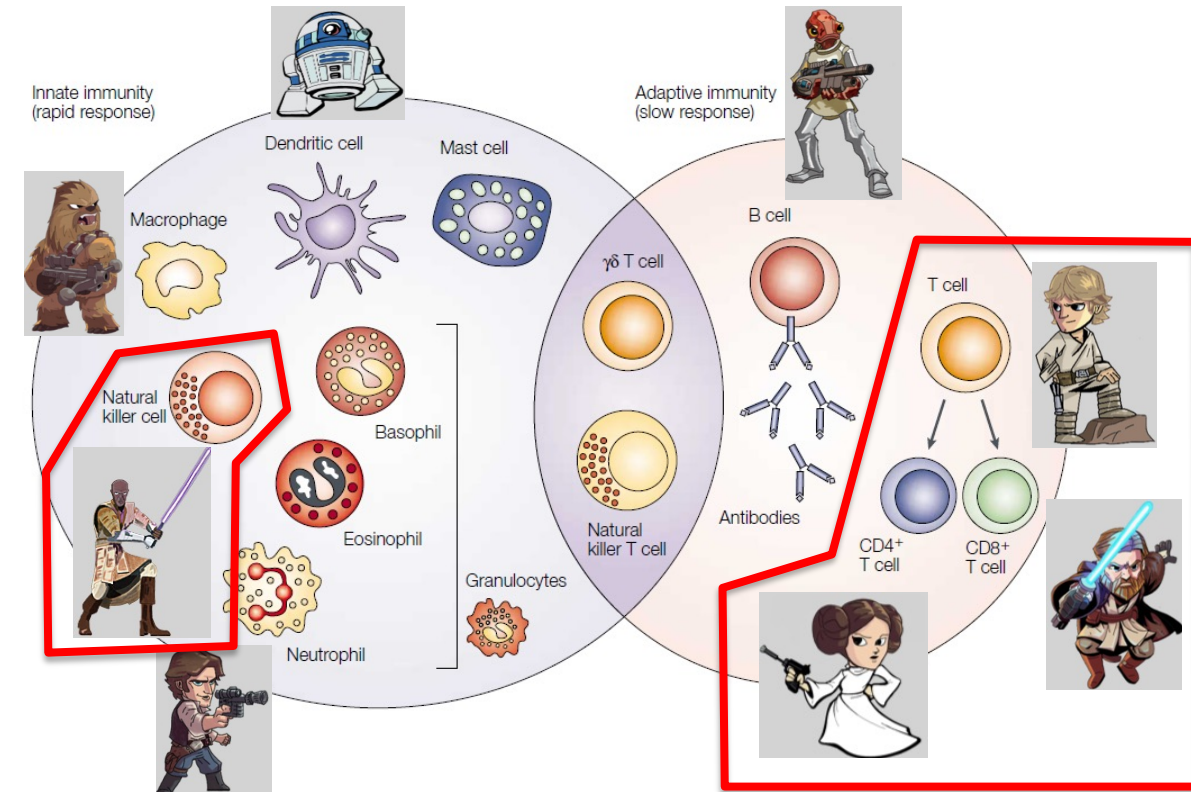
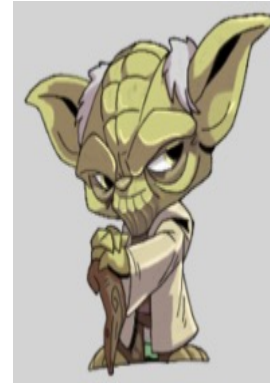
² Progressive supervised resistance training does not exacerbate lymphedema

³ At least 12-months of resistance training plus high impact training needed

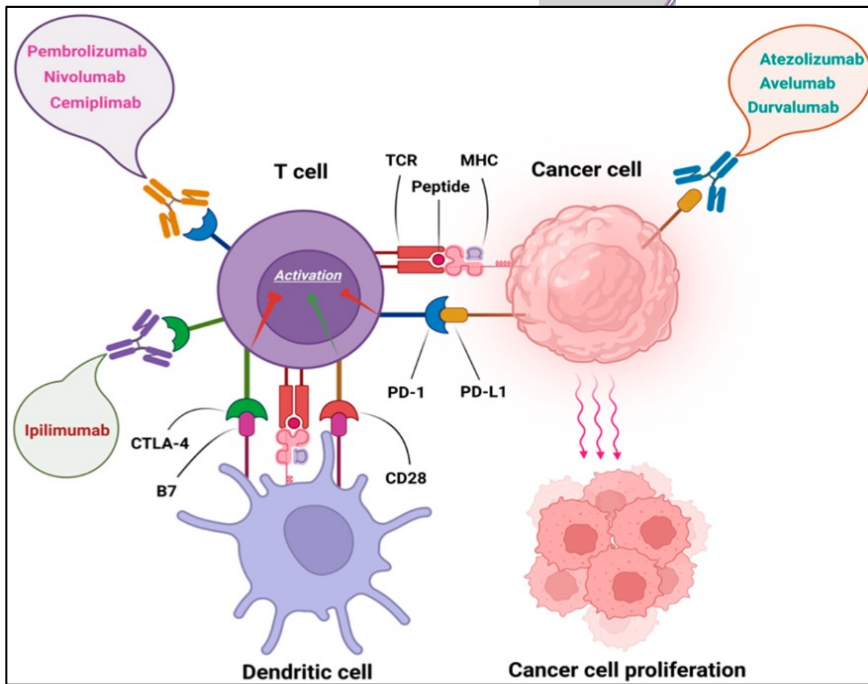
Is Exercise an Immunotherapy?



The Immune System and Cancer – The Light and Dark Side of the Force



Every Bout of Exercise is Effective at Killing Tumours



Every single bout of exercise preferentially moves effector CD8+ T cells and NK-cells into the peripheral blood

In patients with cancer, this effect is severely impaired

Before Exercise

Low PD-1
Low sPDL1

Low Killing of Cancer Cells

This panel shows a low density of NK cells (represented as brown figures with 'NK' on their heads) and a large, dense cluster of cancer cells. A T-shaped bar is positioned above the cancer cells, indicating a low level of killing.

During Exercise

High PD-1
High sPDL1

High Killing of Cancer Cells

This panel shows a high density of NK cells and a smaller, less dense cluster of cancer cells. A T-shaped bar is positioned above the cancer cells, indicating a high level of killing.

After Exercise

Low PD-1
Low sPDL1

Efficient Killing of Cancer Cells

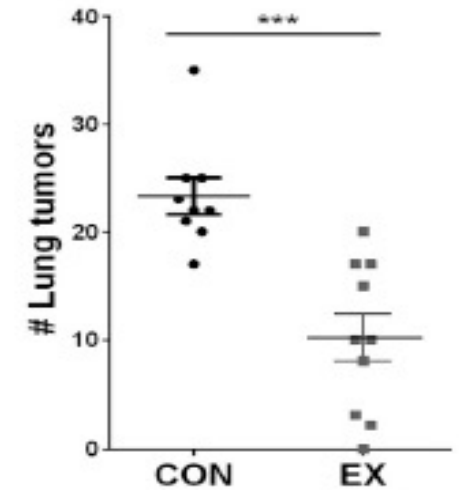
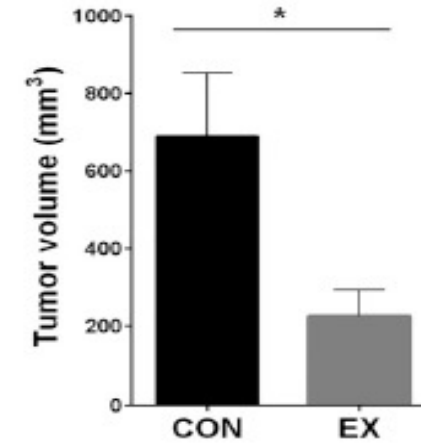
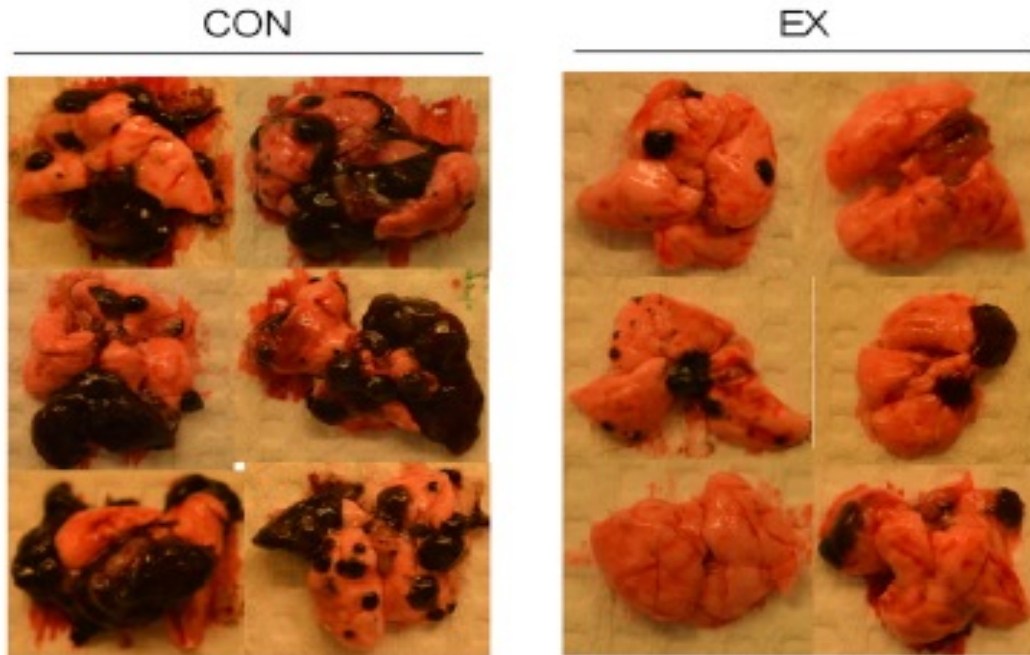
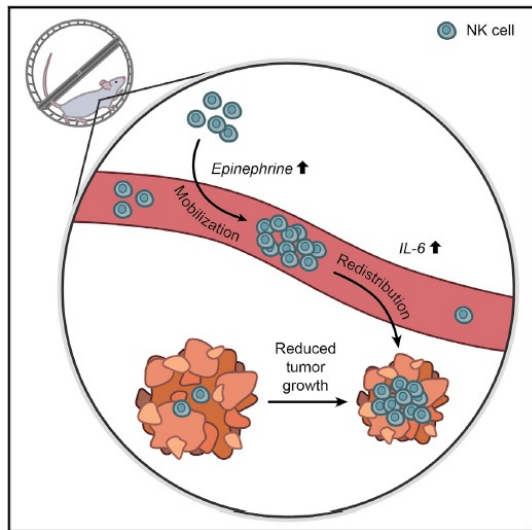
This panel shows a low density of NK cells and a very small, sparse cluster of cancer cells. A T-shaped bar is positioned above the cancer cells, indicating efficient killing.

Exercise Promotes Immune-Mediated Tumour Suppression & Tumour Infiltration by Lymphocytes

Cell Metabolism

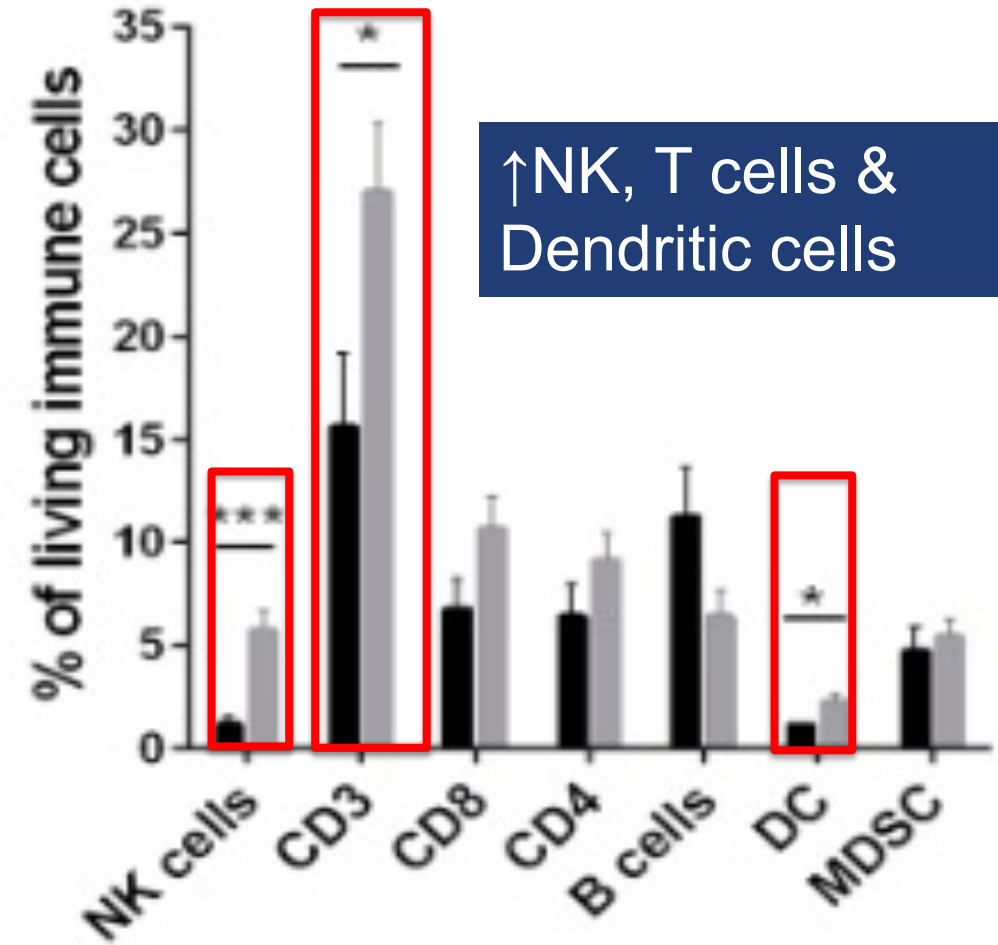
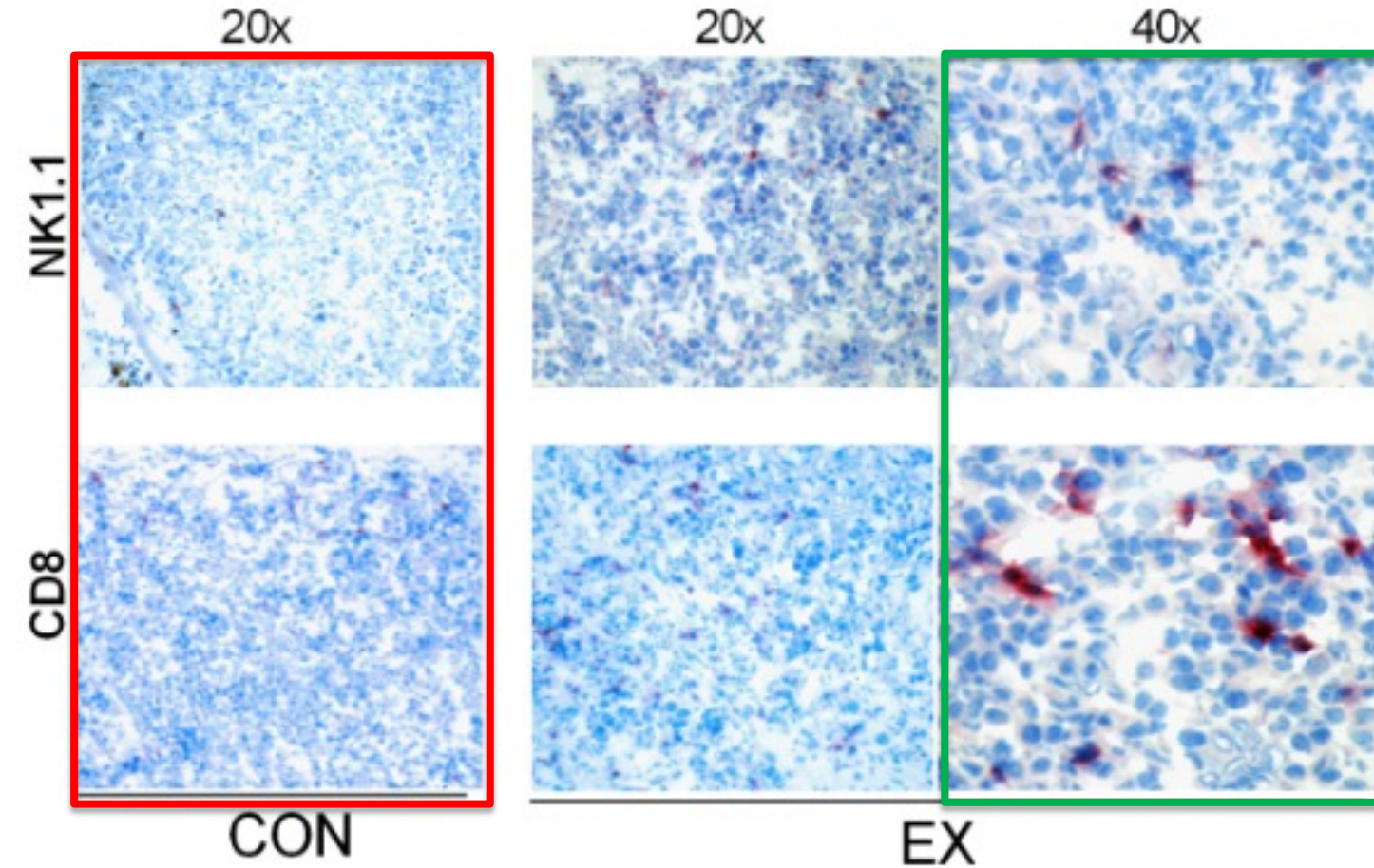
Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution

Graphical Abstract



Four weeks of exercise training reduces tumour incidence and growth by ~60% in lung (localised and metastatic), skin (localised and metastatic) and localised liver cancer.

Exercise Training Controls Tumour Growth Through NK and T Cell Tumour Infiltration – In Mice



What evidence do we have that this works in humans?

12-months of Exercise Training Increases Mucosal Tissue Lymphocytes In High-Risk for Colon Cancer

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

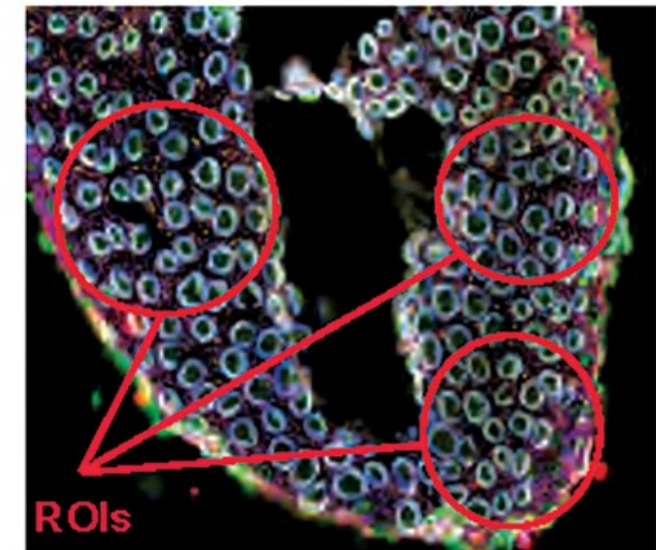
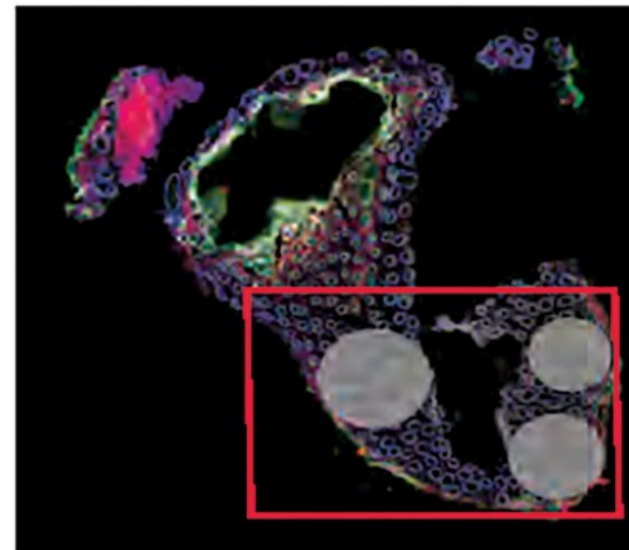
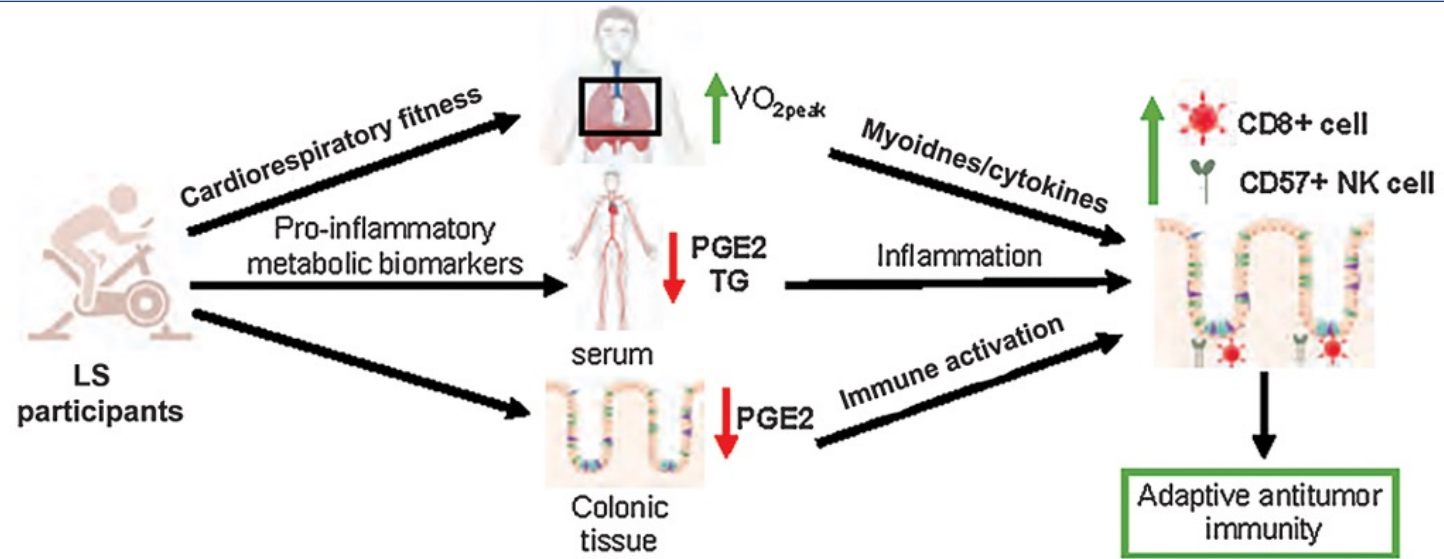
Exercise Training Reduces the Inflammatory Response and Promotes Intestinal Mucosa-Associated Immunity in Lynch Syndrome

Nan Deng¹, Laura Reyes-Urbe¹, Johannes F. Fahrman¹, Whitney S. Thoman¹, Mark F. Munsell², Jennifer B. Dennison¹, Eunice Murage¹, Ranran Wu¹, Ernest T. Hawk¹, Selvi Thirumurthi^{3,4}, Patrick M. Lynch^{3,4}, Christina M. Dieli-Conwright^{5,6}, Alexander J. Lazar^{7,8}, Sonali Jindal⁹, Khoi Chu⁹, Manoj Chelvanambi¹⁰, Karen Basen-Engquist¹¹, Yisheng Li², Jennifer A. Wargo^{8,10}, Florencia McAllister^{1,4,12,13}, James P. Allison^{9,12}, Padmanee Sharma^{9,12,14}, Krishna M. Sinha¹, Samir Hanash¹, Susan C. Gilchrist^{1,15}, and Eduardo Vilar^{1,4,13}



Exercise training reduces the inflammatory burden associated with CRC and promotes increased CD8+ and NK cell infiltrates in tissues commonly associated with malignancy.

What if your patient has cancer? Twelve months is a long time to exercise.



■ PanCK ■ CD8⁺ ■ CD45 ■ DNA

Prehabilitation Exercise During Neoadjuvant Chemotherapy for Oesophageal Cancer Promotes Increase Tumour Infiltrating Lymphocytes



Ann Surg Oncol (2022) 29:1839–1850
<https://doi.org/10.1245/s10434-021-11002-0>

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

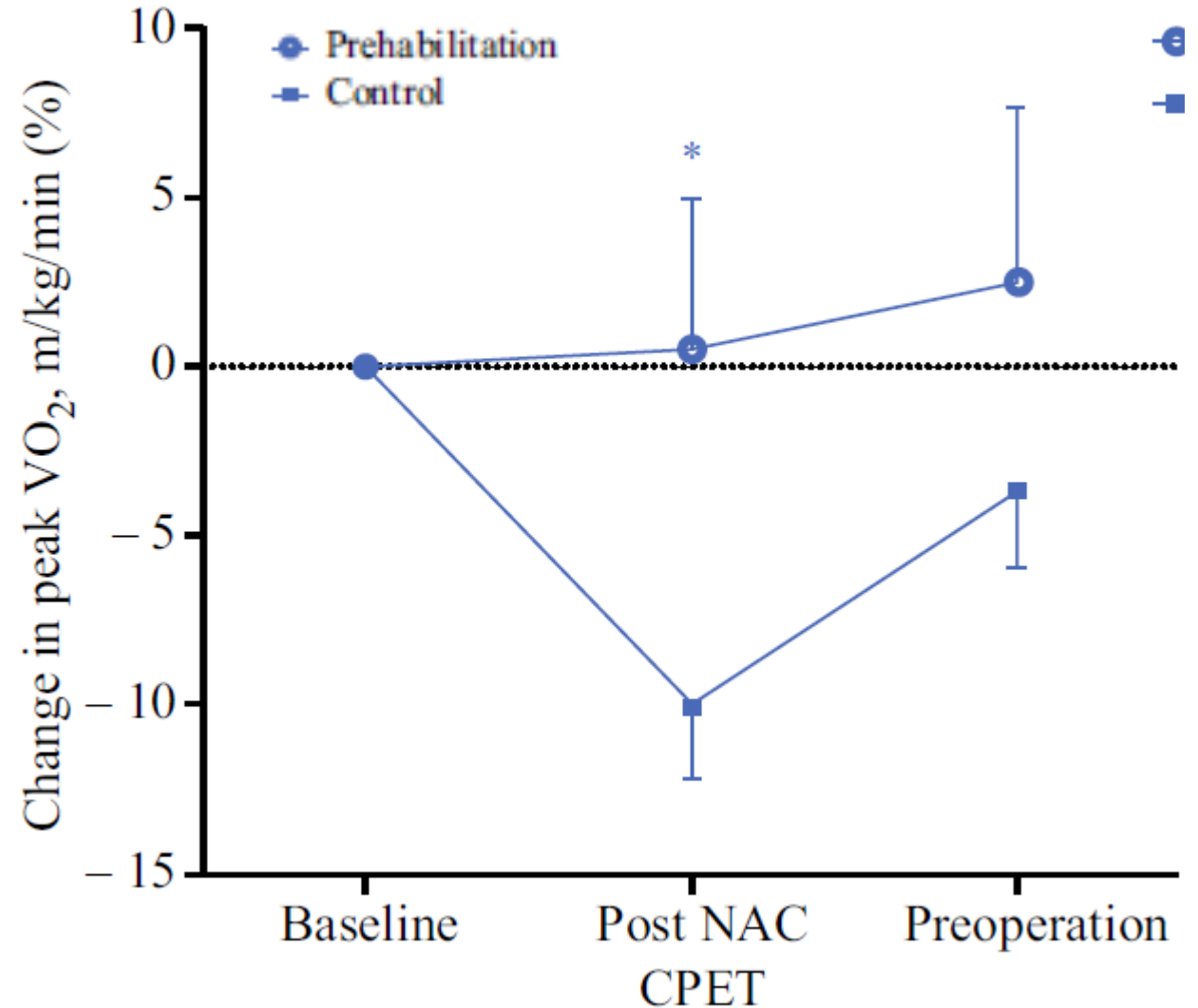


ORIGINAL ARTICLE – THORACIC ONCOLOGY

Multimodal Prehabilitation During Neoadjuvant Therapy Prior to Esophagogastric Cancer Resection: Effect on Cardiopulmonary Exercise Test Performance, Muscle Mass and Quality of Life—A Pilot Randomized Clinical Trial

Chemotherapy reduces patient aerobic fitness and capacity for exercise

Prehabilitation exercise training prevents the loss in aerobic fitness



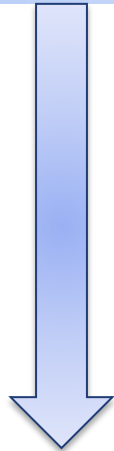
Exercise training was associated with more tumour-infiltrating lymphocytes

Exercise =

More CD8+ Lymphocytes in Tumours

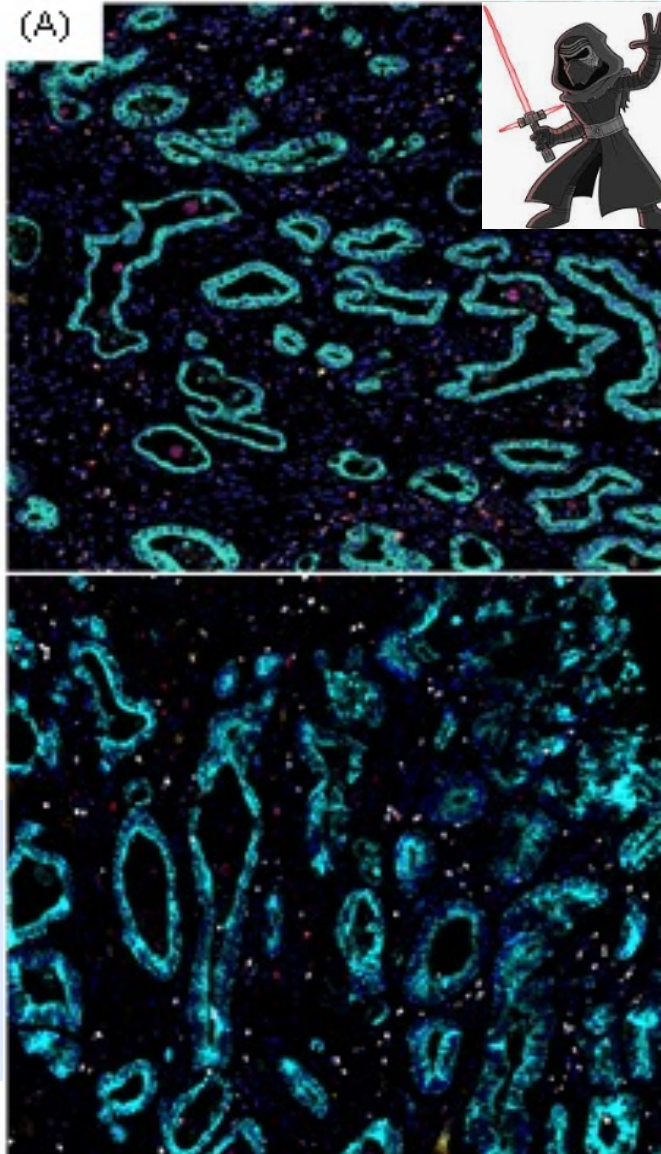
More NK cells in Tumours

More Mature Tertiary Lymphoid Structures



In essence, exercise has allowed T cells and NK cells to act similarly to anti-PD1 checkpoint inhibitors such as nivolumab or pembrolizumab!

Control

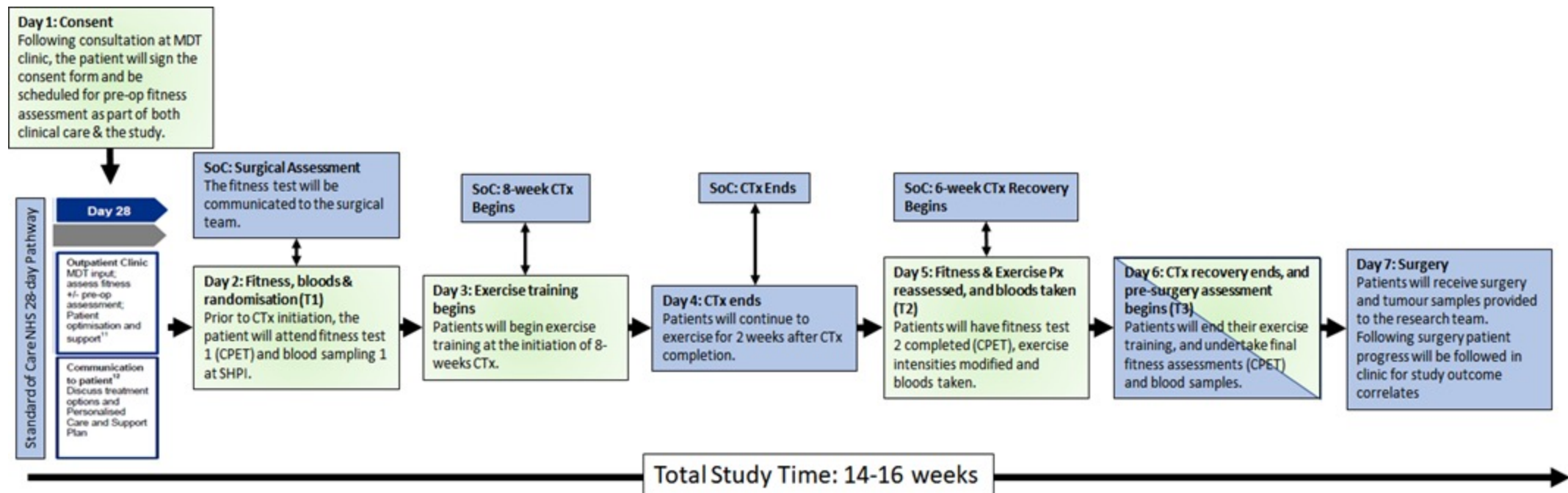


In April, we will open our next trial to determine if there is a dose-response effect of exercise on TILs

Tumour Immunology: Nicola Annels

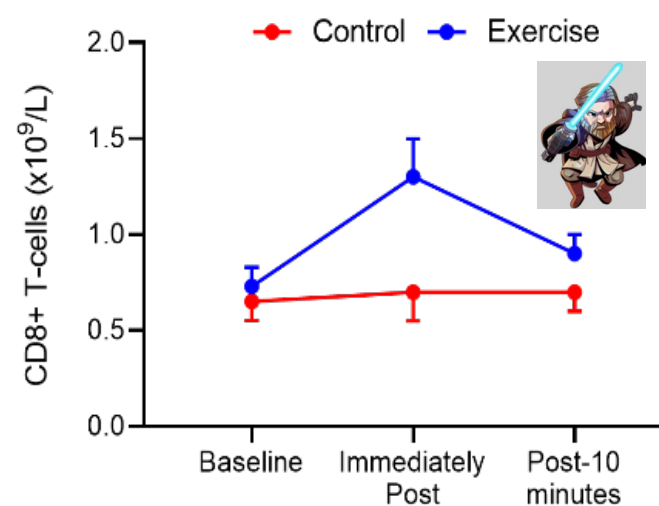
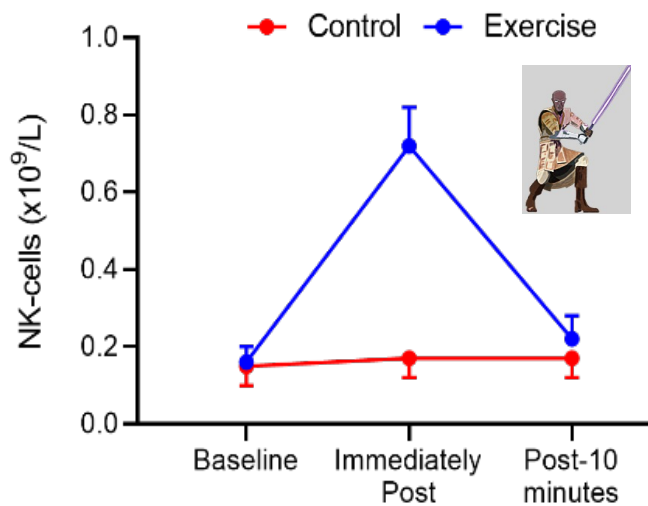
Clinical: Adam Frampton, Charles Rayner, Nima Abbassi-Ghadi

Exercise Immunology: David Bartlett



Exercise During the Infusion of a Checkpoint Inhibitor?

- Does acute exercise mobilise immune cells into the blood while patients receive their immunotherapy infusions?
- Are the mobilised immune cells able to better identify and destroy cancer cell lines?



	N=12
Sex	5F/7M
Age (yrs.)	57 (8)
BSA (m ²)	2.1 (0.3)
BMI (kg/m ²)	30 (6.2)
Cancer (N)	
Bladder	2
Prostate	1
Renal Cell Carcinoma	8
Urethral-SCC	1
Treatment (N)	
Nivolumab	6
Sipuleucel-T	1
Pembrolizumab	6
Resting HR (bpm)	58 (7)
Predicted max HR (bpm)	168 (6)
60% HRR (bpm)	124 (5)
Average Step counts/day	6532 (3836)

Exercise During the Infusion of a Checkpoint Inhibitor?

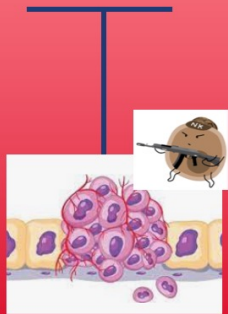
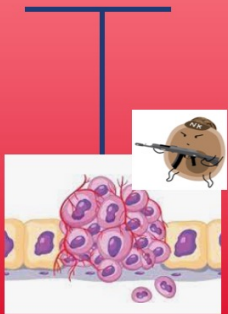
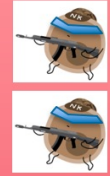
No Exercise + Immunotherapy

No Exercise + Immunotherapy

During infusional therapy, immune cells don't kill tumour cells any better than if they didn't have the therapy

Adding exercise to infusions increased the killing of tumour cells

If acute bouts of exercise can promote *in vitro* tumour killing, perhaps all patients undergoing infusional immunotherapy should engage in exercise during infusions



Low Killing of Cancer Cells

Low Killing of Cancer Cells

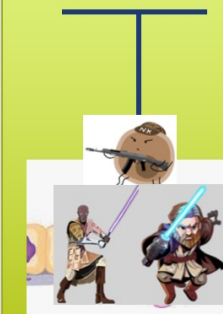
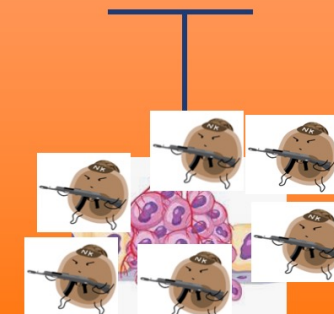
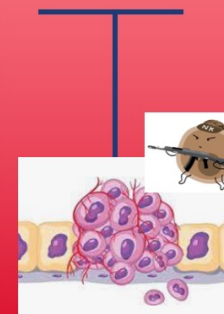
Before infusion starts

End of infusion (30mins)

Before Exercise + Immunotherapy

During Exercise + Immunotherapy

After Exercise + Immunotherapy



Low Killing of Cancer Cells

High Killing of Cancer Cells

Efficient Killing of Cancer Cells

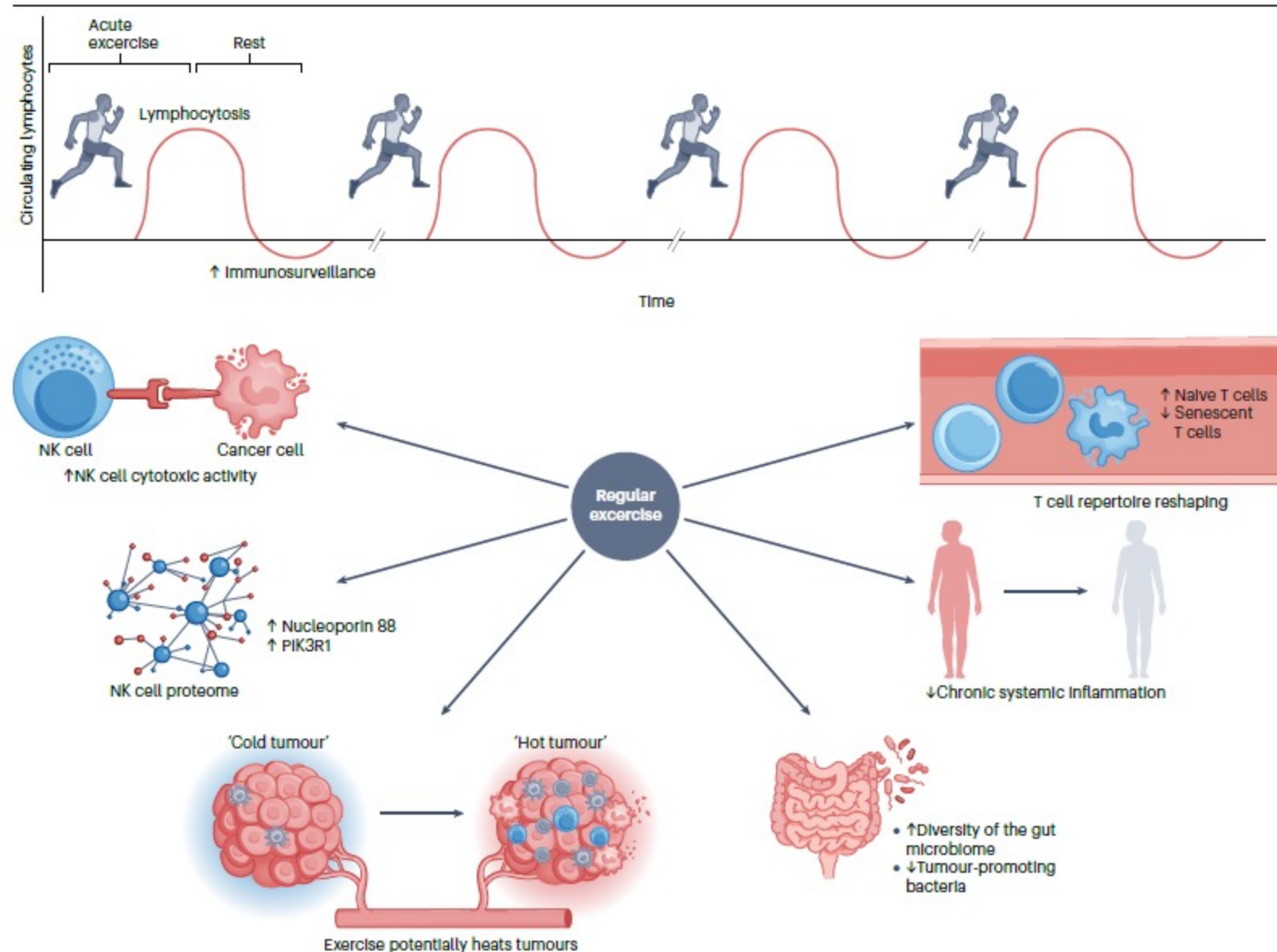
Before infusion starts

End of infusion (30 mins)

15 mins after end of infusion

Summary – Exercise is Medicine and Impacts Cancer Through an Immune-Mediated Pathway

1. Acute Exercise mobilises effector immune cells into the blood.
2. Regular exercise promotes improved immune surveillance and increased thymic output
3. Working muscle releases immune-priming cytokines (e.g., IL-7, IL-6, IL-15)
4. Primed immune cells then efficiently traffic to tumours or high-risk sites for tumour development
5. Trafficking of immune cells is enhanced likely through exercise-induced perturbations to the tumour including metabolic requirements and oxygen availability



Thank You & Happy to Take Questions

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Adjunct Assistant Professor of Medicine

