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

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NIH National Institutes of Health

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

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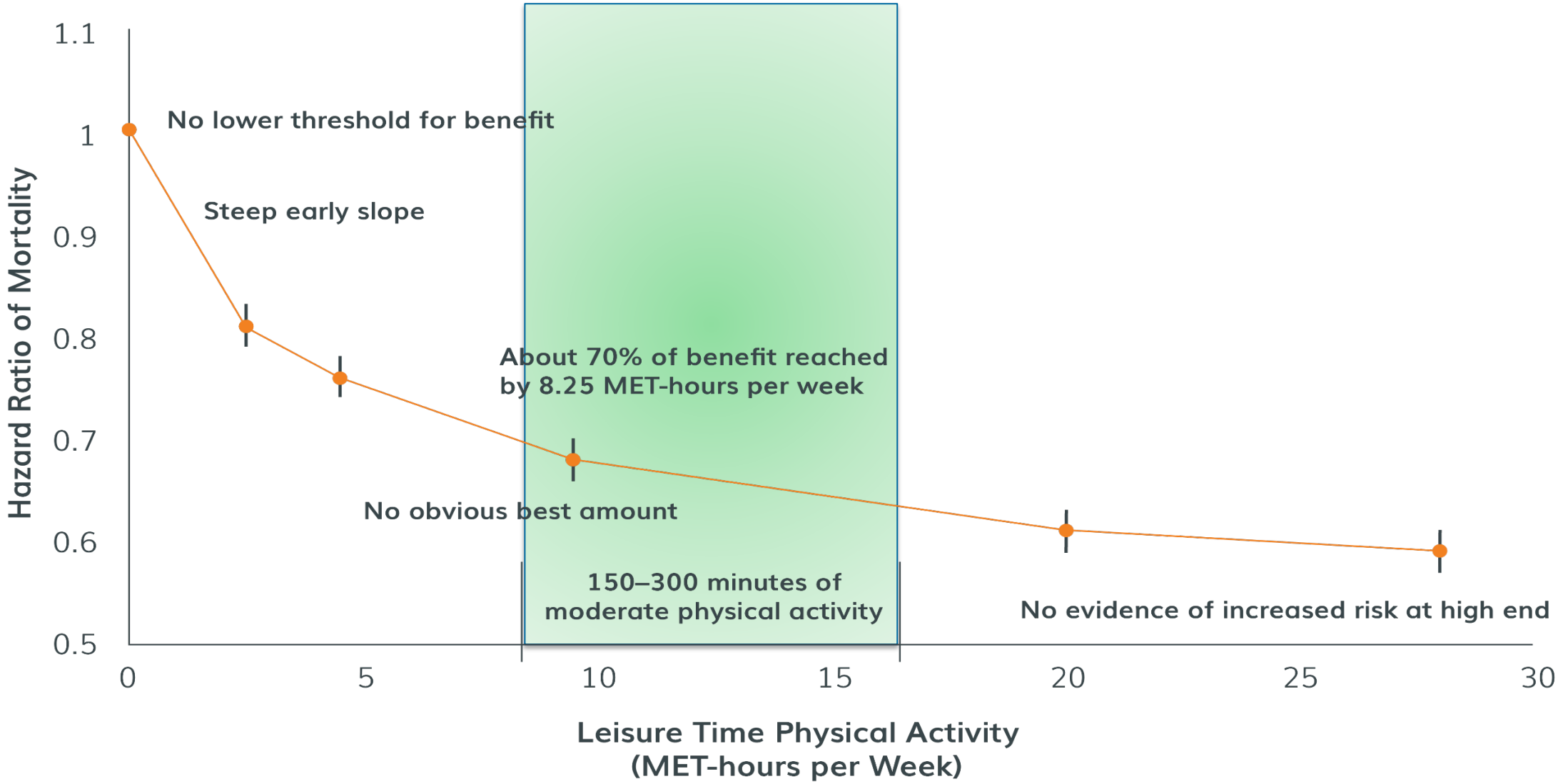


Adapted from Moore et al. 2012 PLoS Med

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

Duke Cancer Institute

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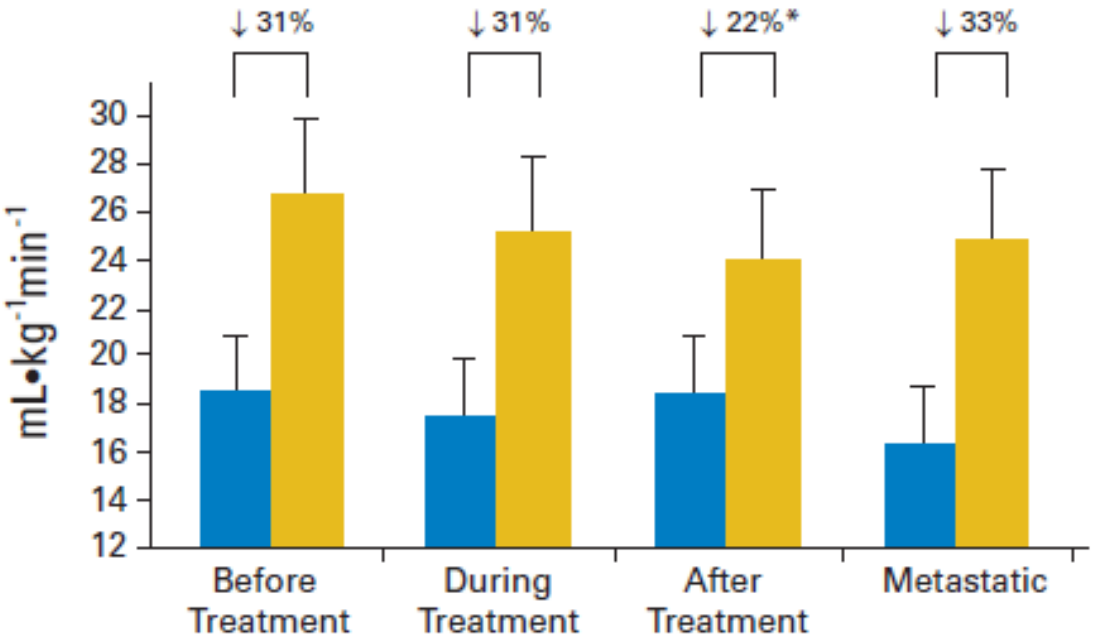
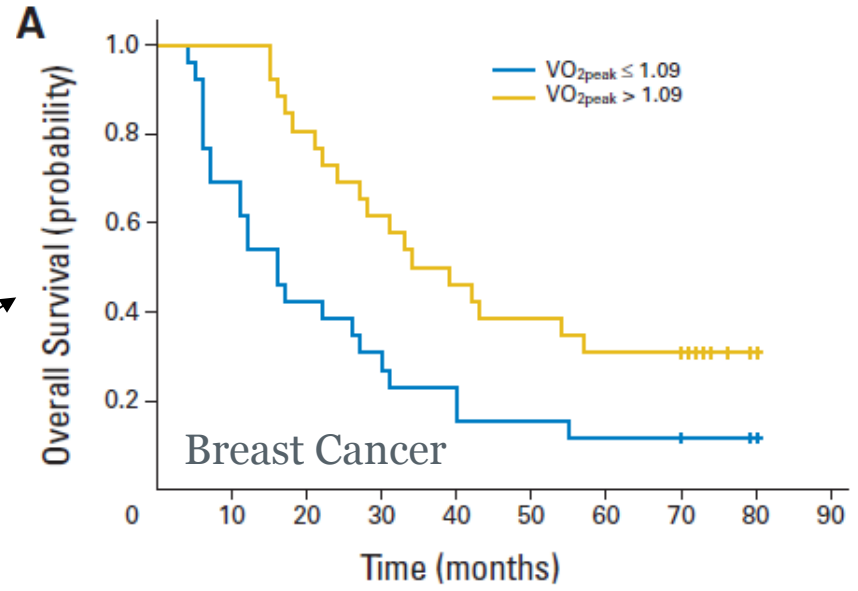
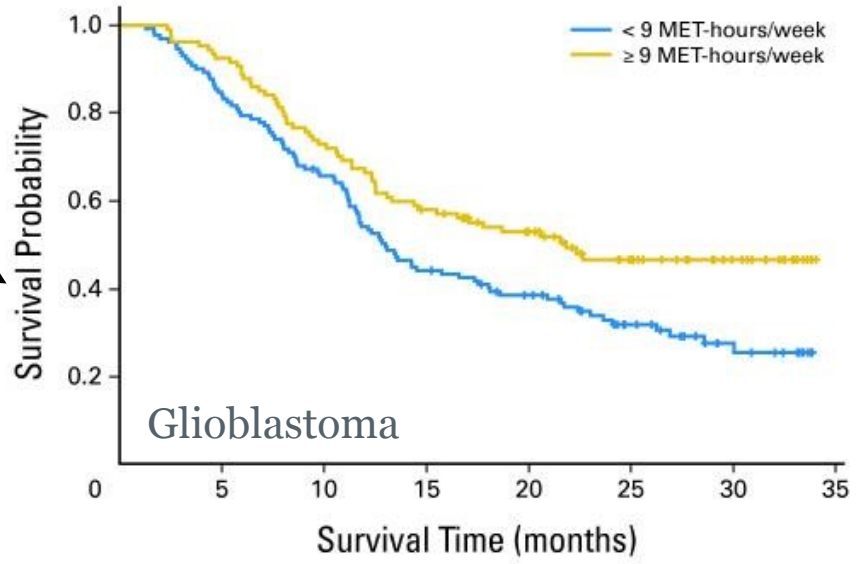
**Patients with cancer (blue bars) are less fit than age-matched controls (yellow bars)!**




Jones *et al*. 2012 J Clin Onc & Ruden *et al*. 2011 J Clin Onc

# Exercise is Recommended for Cancer Prevention, Treatment and Survivorship

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Cancer guidelines are similar to the general population

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

Or

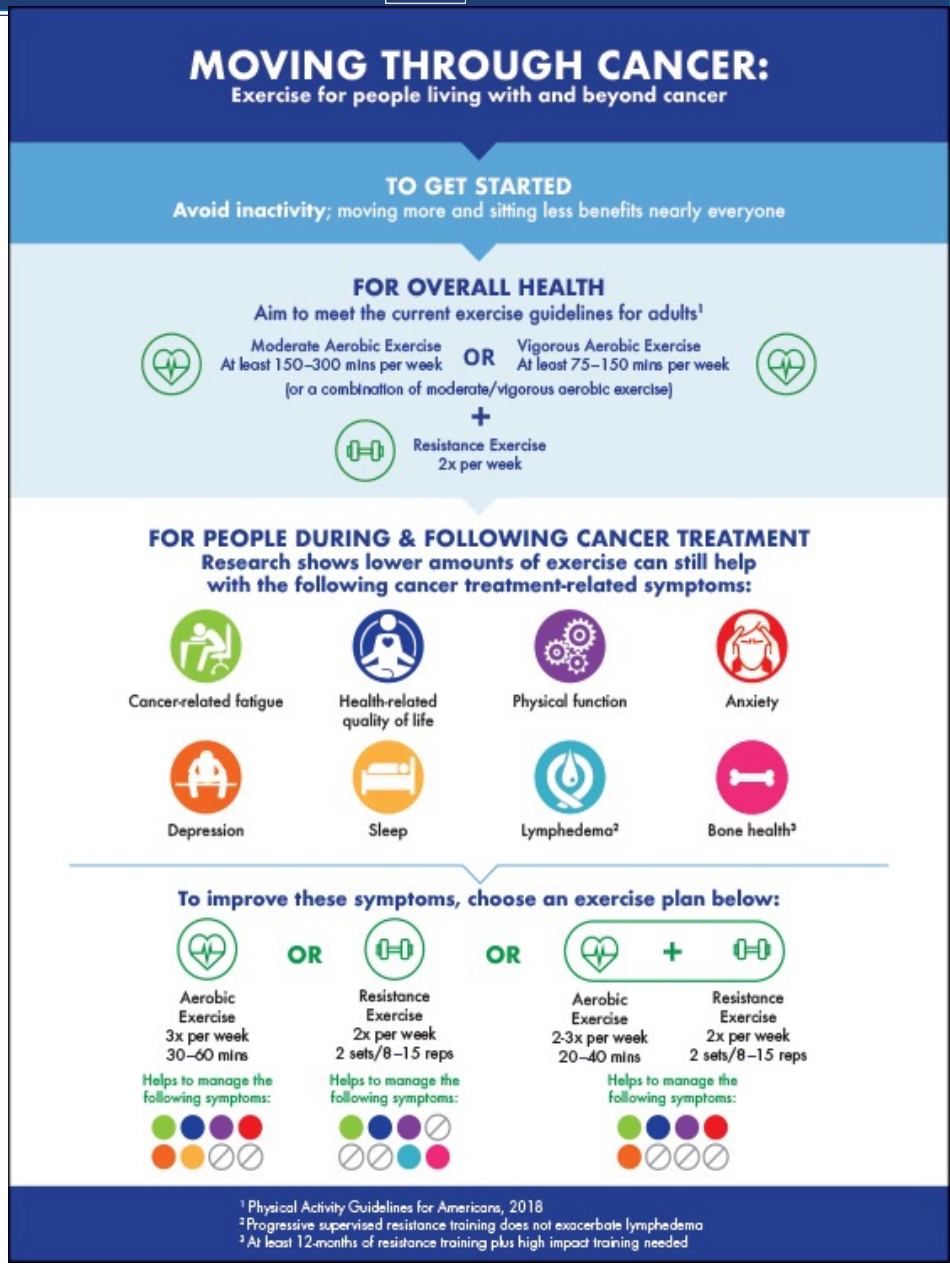
75 – 150 mins/week of **Vigorous** Intensity

+

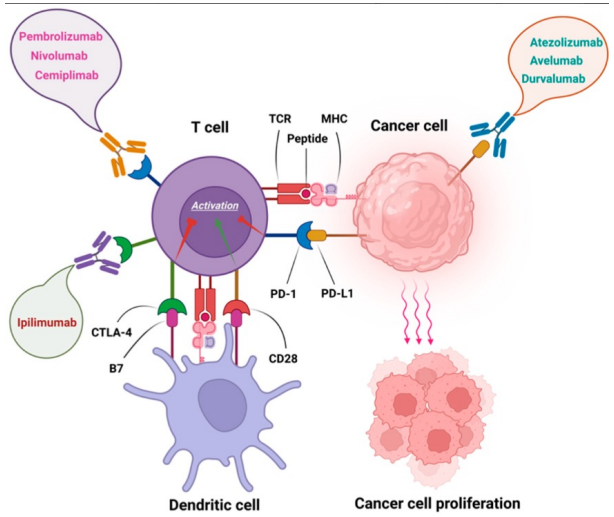
2 sessions/week of strength

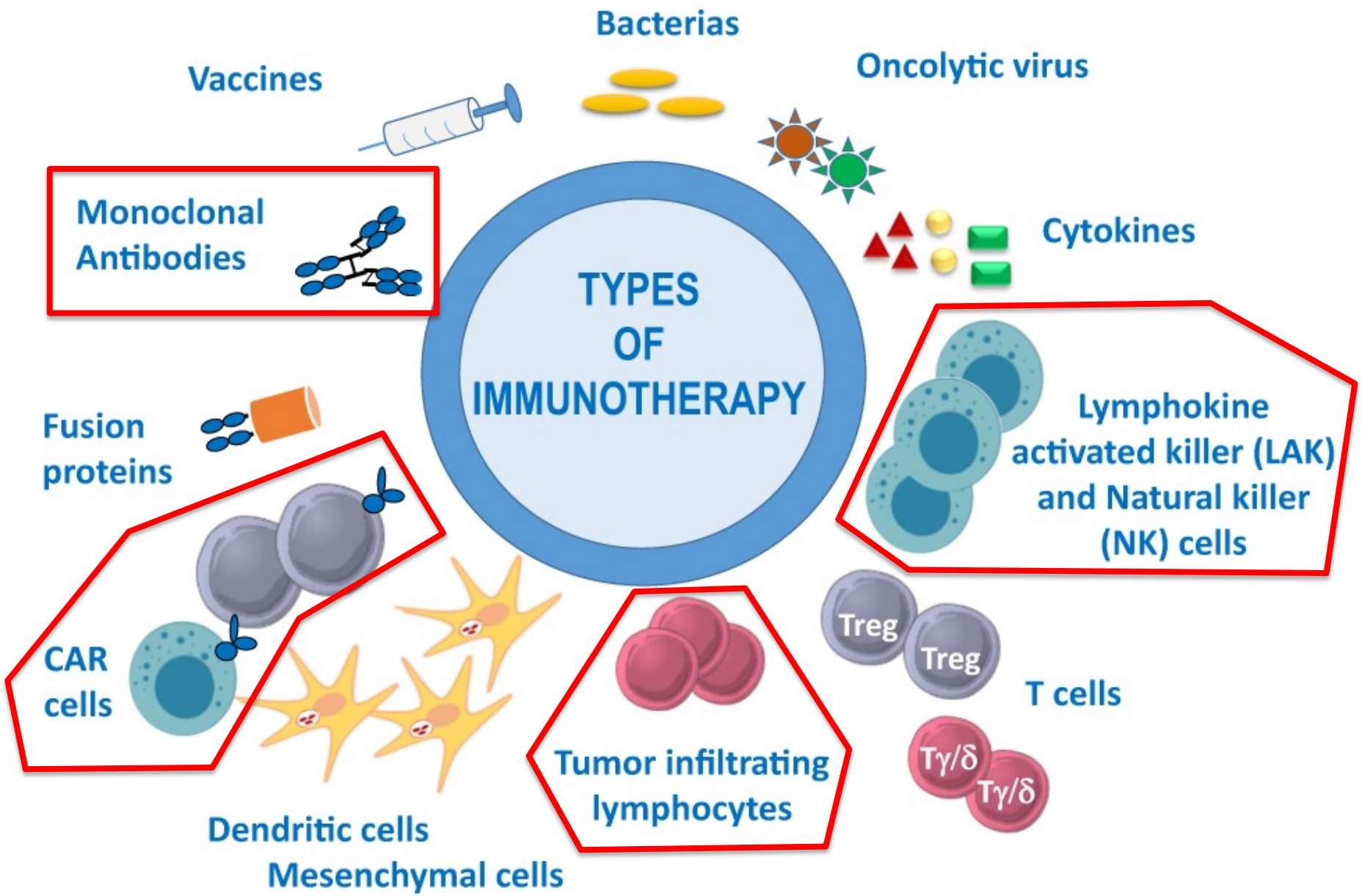
Most benefits are quality of life related

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



# Is Exercise an Immunotherapy?



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

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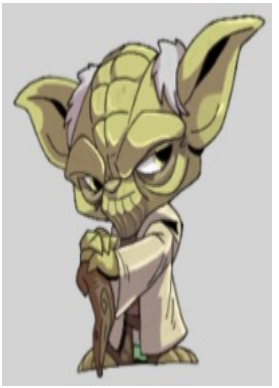
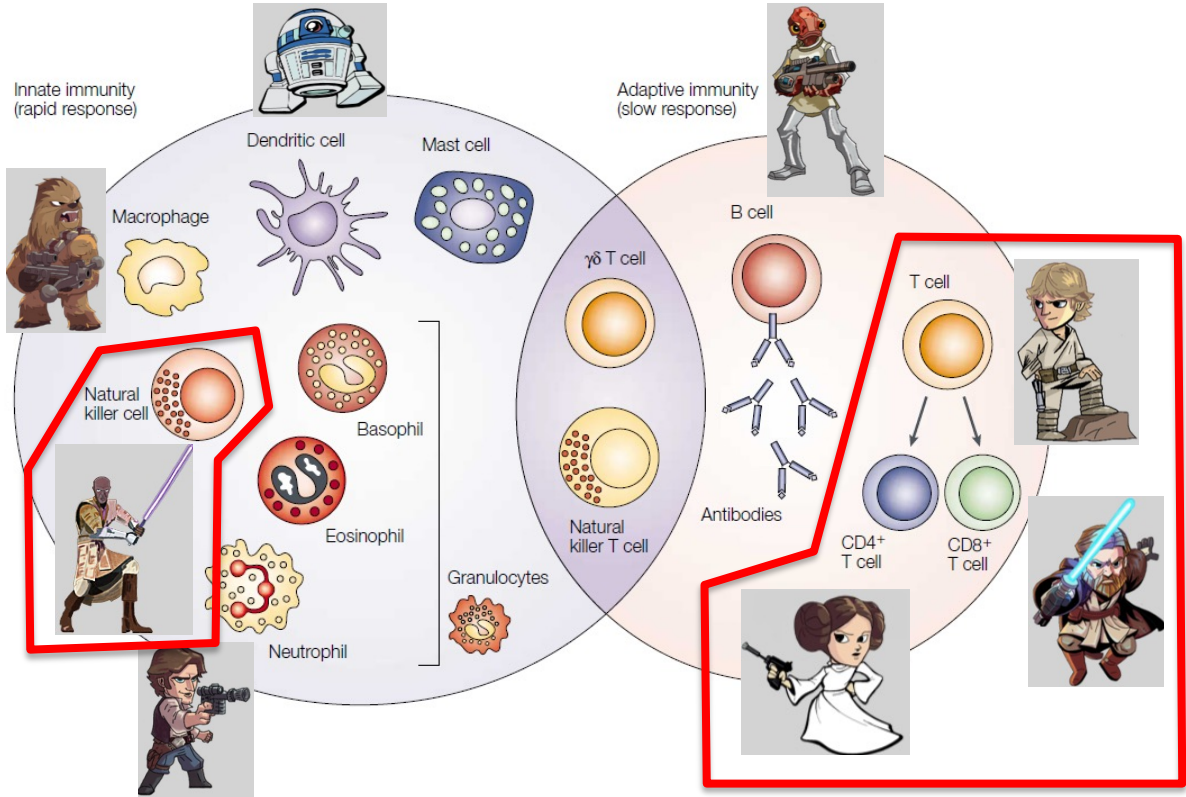
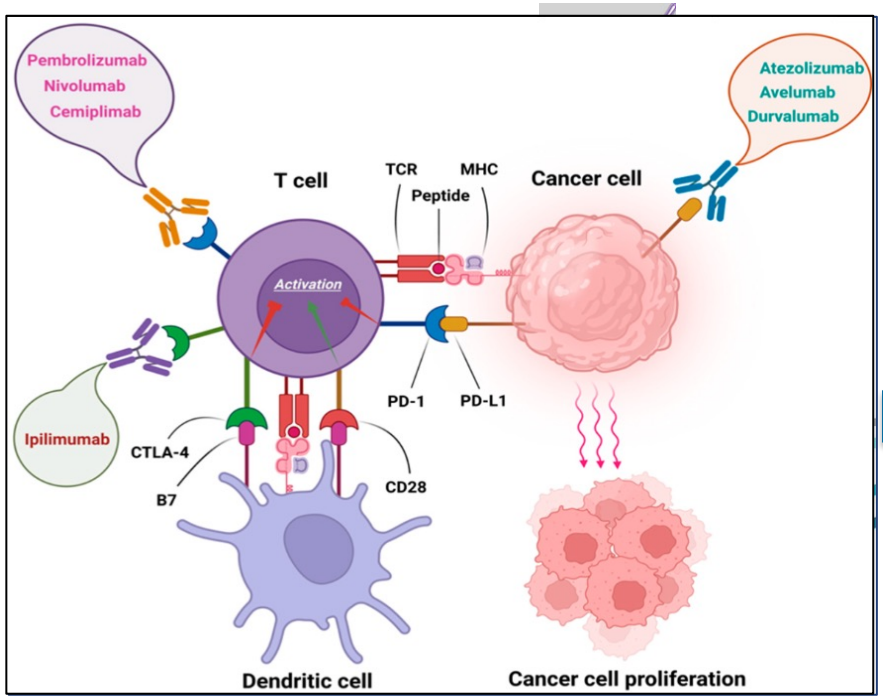


# Every Bout of Exercise is Effective at Killing Tumours

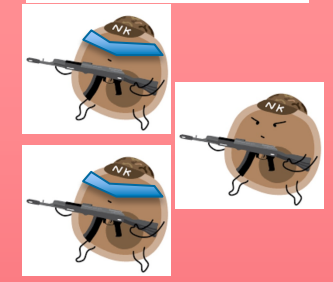



Every single bout of exercise preferentially moves effector CD8+ T cells and NK-cells into the peripheral blood

In patients with cancer, this effect is severely impaired

## Before Exercise

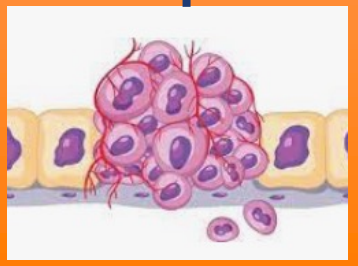
Low PD-1
Low sPDL1



Low Killing of Cancer Cells

## During Exercise

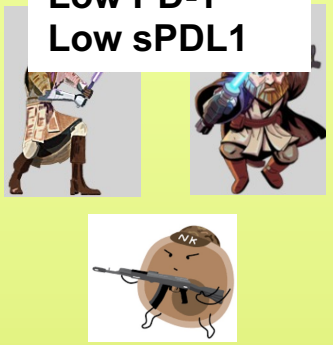
High PD-1
High sPDL1

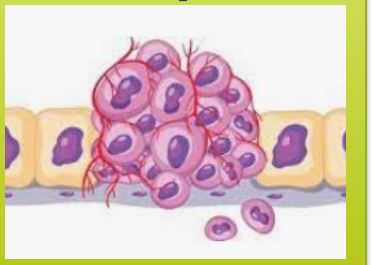


High Killing of Cancer Cells

## After Exercise

Low PD-1
Low sPDL1





Efficient Killing of Cancer Cells

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

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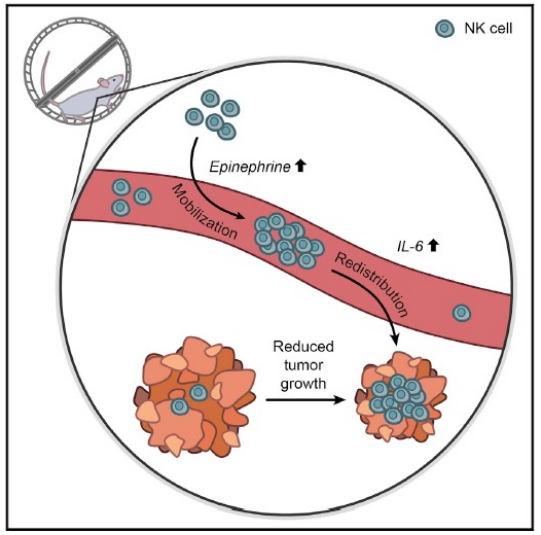
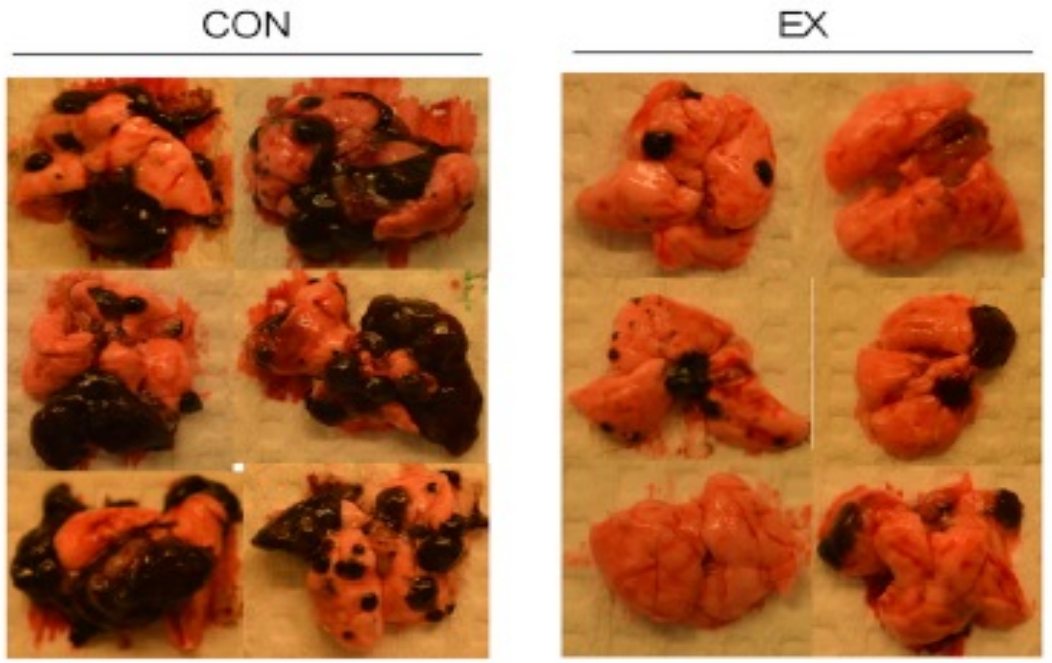
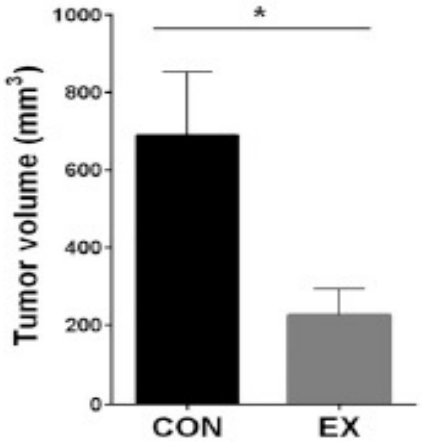
**Cell Metabolism**

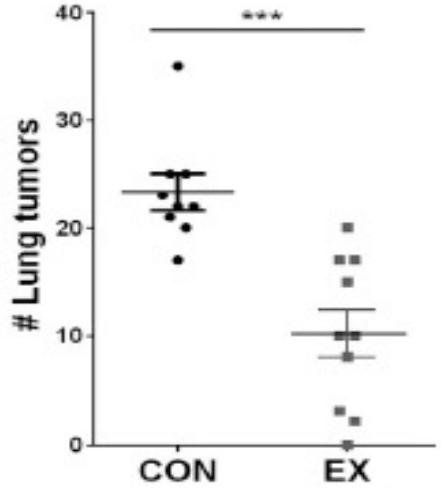
**Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution**

Graphical Abstract



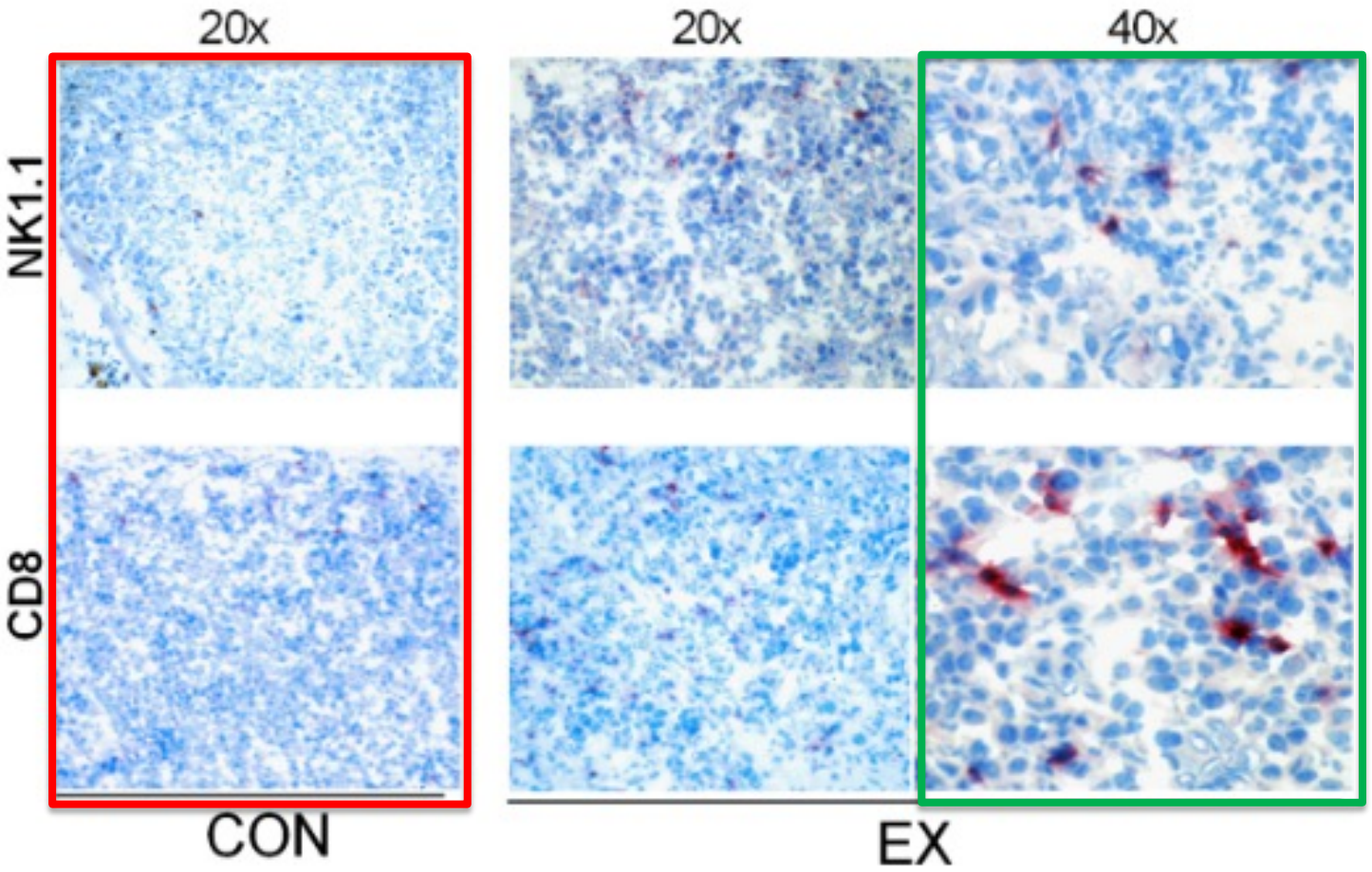



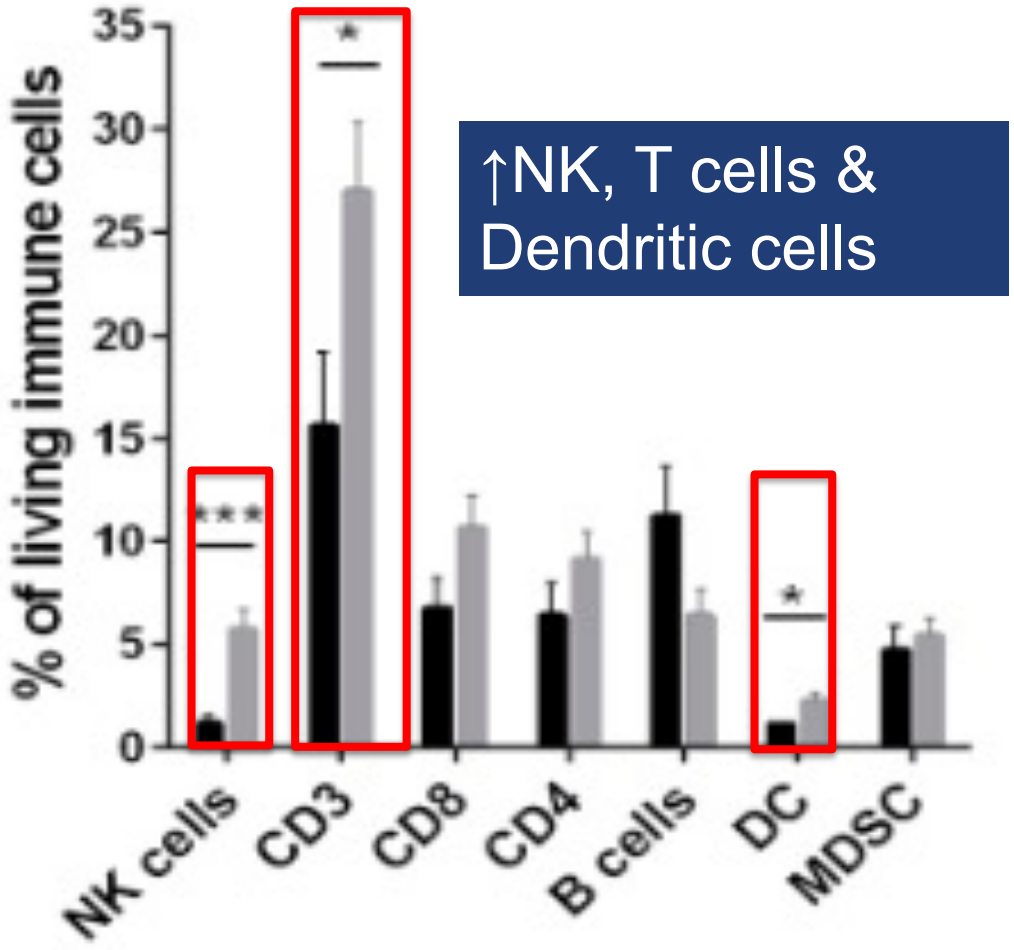




Four weeks of exercise training reduces tumour incidence and growth by ~60% in lung (localised and metastatic), skin (localised and metastatic) and localised liver cancer.

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




↑NK, T cells & Dendritic cells

What evidence do we have that this works in humans?

Pedersen *et al*. 2016 Cell Metabolism

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

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Duke Cancer Institute

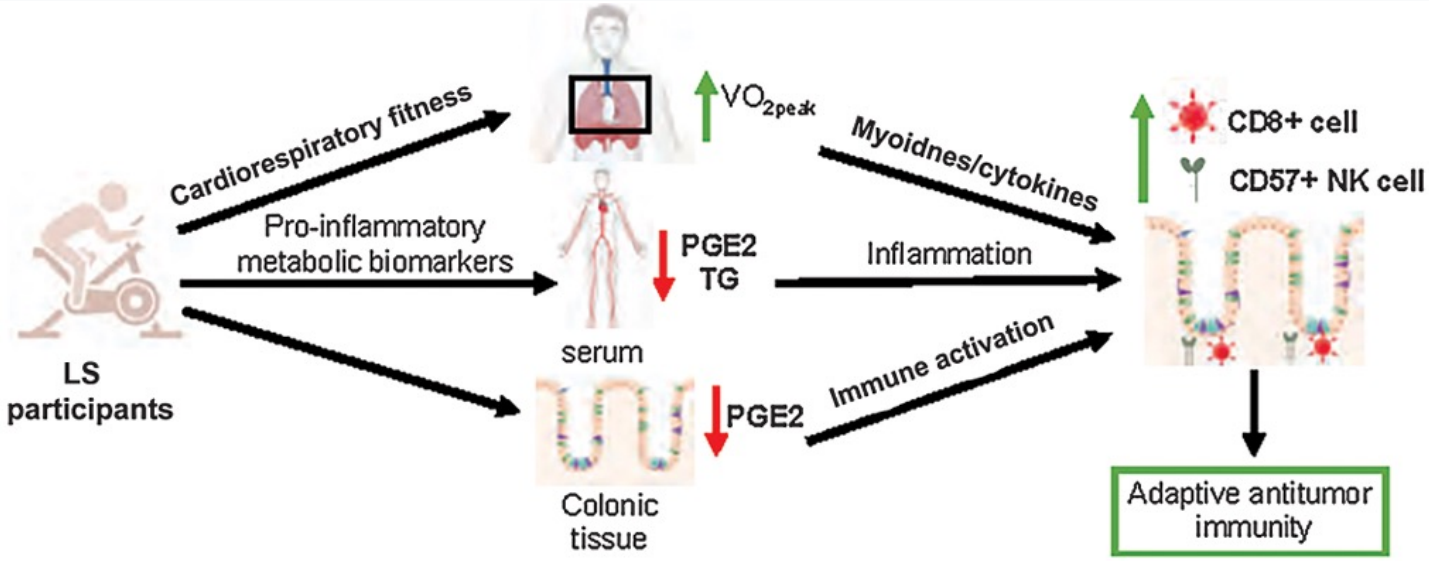
CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

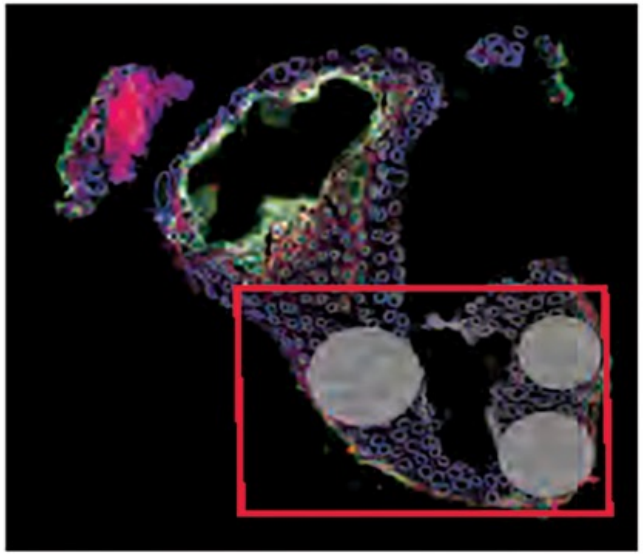
**Exercise Training Reduces the Inflammatory Response and Promotes Intestinal Mucosa-Associated Immunity in Lynch Syndrome**

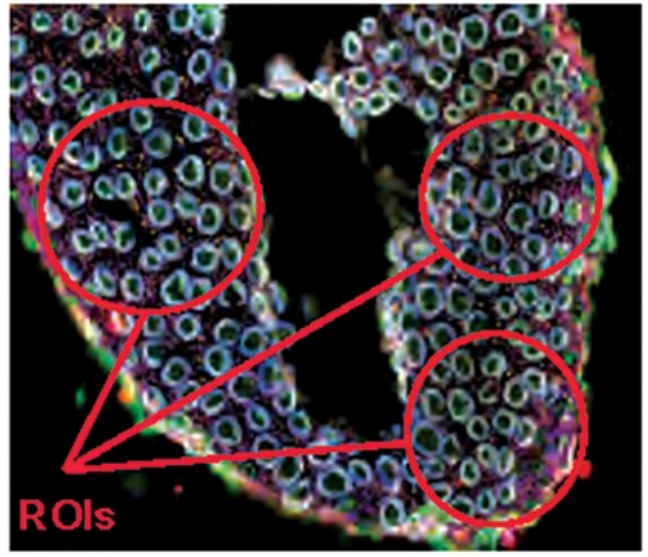
Nan Deng[1], Laura Reyes-Uribe[1], Johannes F. Fahrmann[1], Whittney S. Thoman[1], Mark F. Munsell[2], Jennifer B. Dennison[1], Eunice Murage[1], Ranran Wu[1], Ernest T. Hawk[1], Selvi Thirumurthi[3,4], Patrick M. Lynch[3,4], Christina M. Dieli-Conwright[5,6], Alexander J. Lazar[7,8], Sonali Jindal[9], Khoi Chu[9], Manoj Chelvanambi[10], Karen Basen-Engquist[11], Yisheng Li[2], Jennifer A. Wargo[8,10], Florencia McAllister[1,4,12,13], James P. Allison[9,12], Padmanee Sharma[9,12,14], Krishna M. Sinha[1], Samir Hanash[1], 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

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

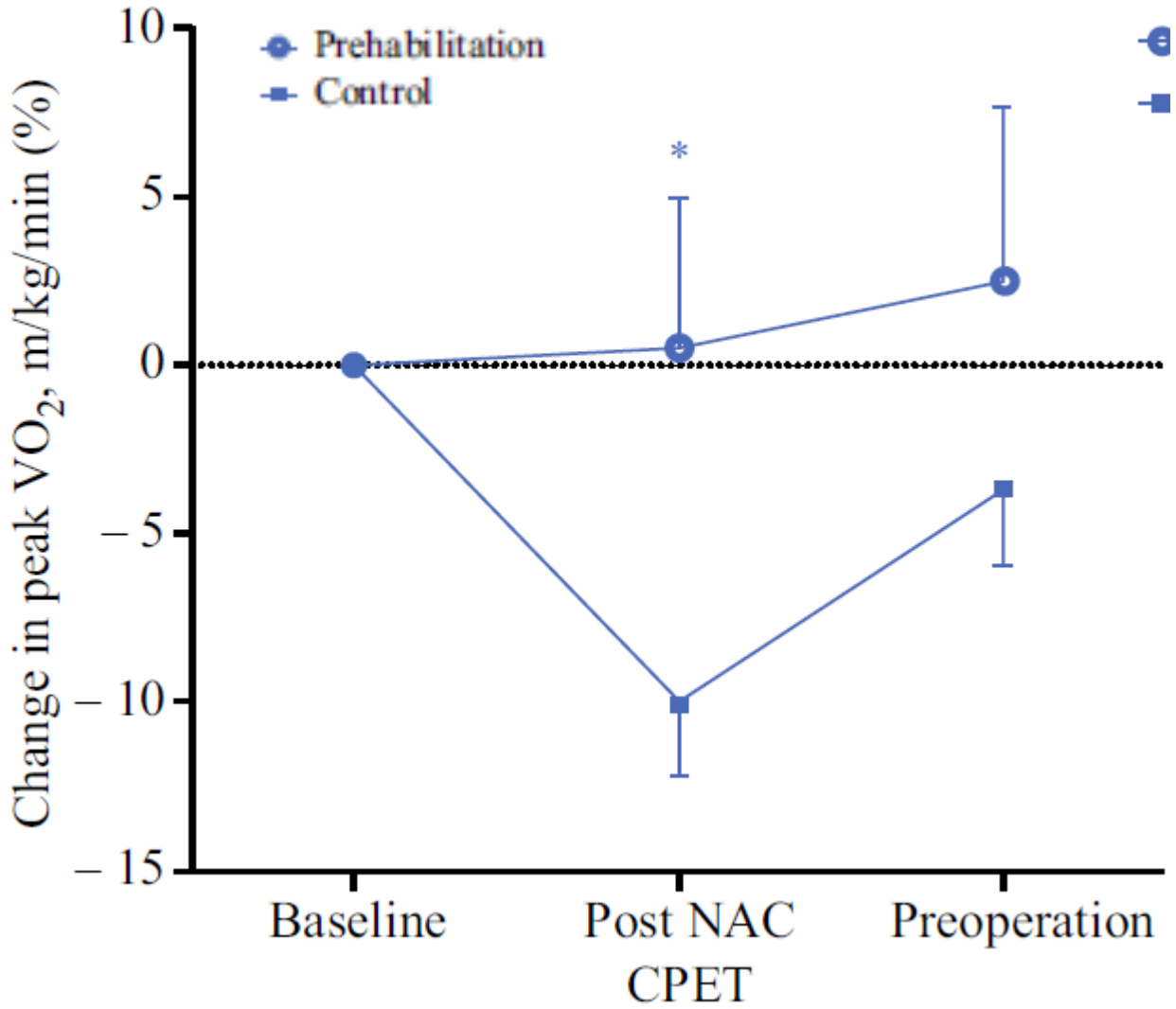
Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

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




Allen *et al*. 2022 *Ann of Surg Oncol*

# Exercise training was associated with more tumour-infiltrating lymphocytes

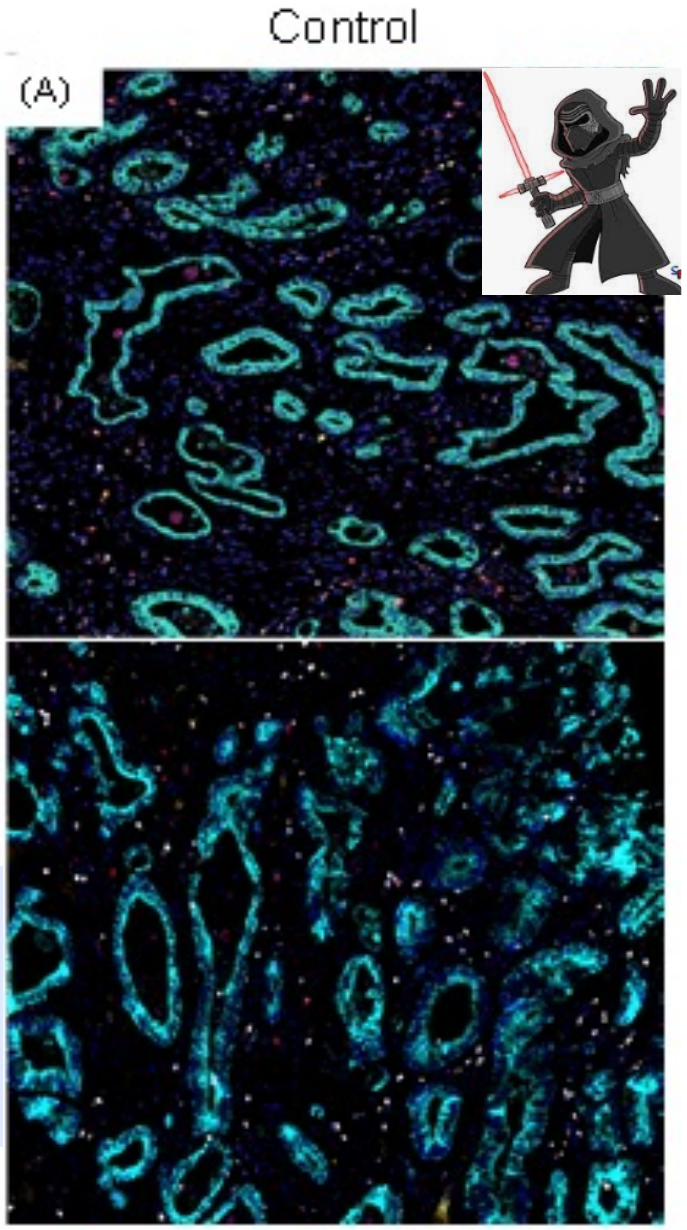
Exercise =

**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!**




Rayner *et al*. Under review Clinical Cancer Research

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

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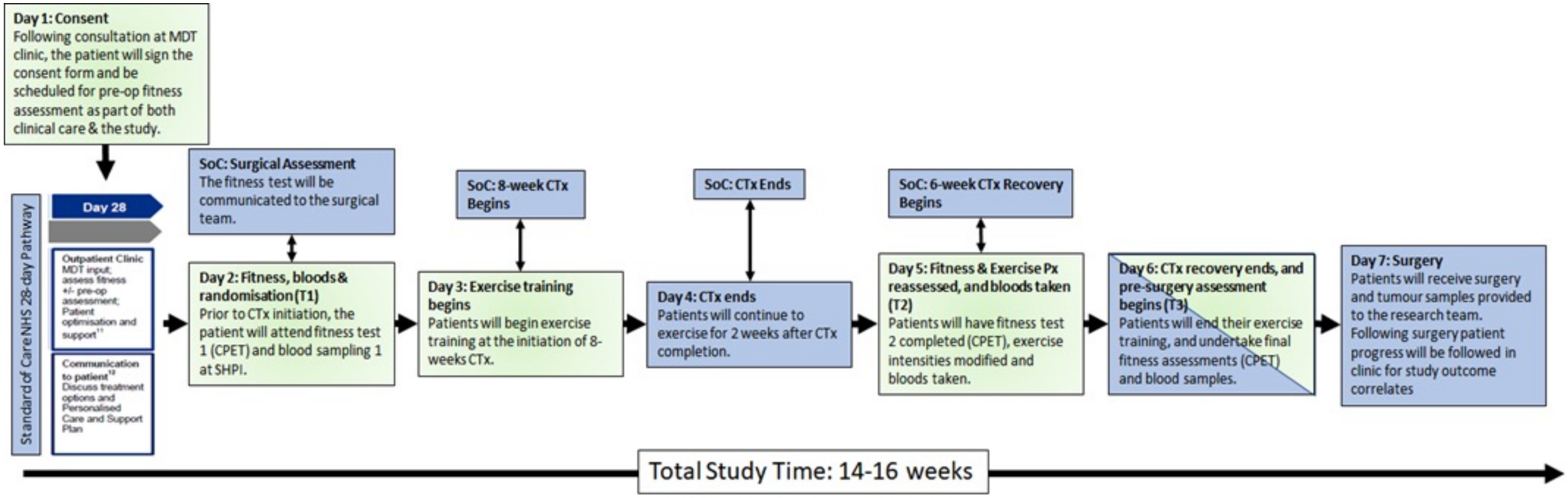
In April, we will open our next trial to determine if there is a dose-response effect of exercise on TILs

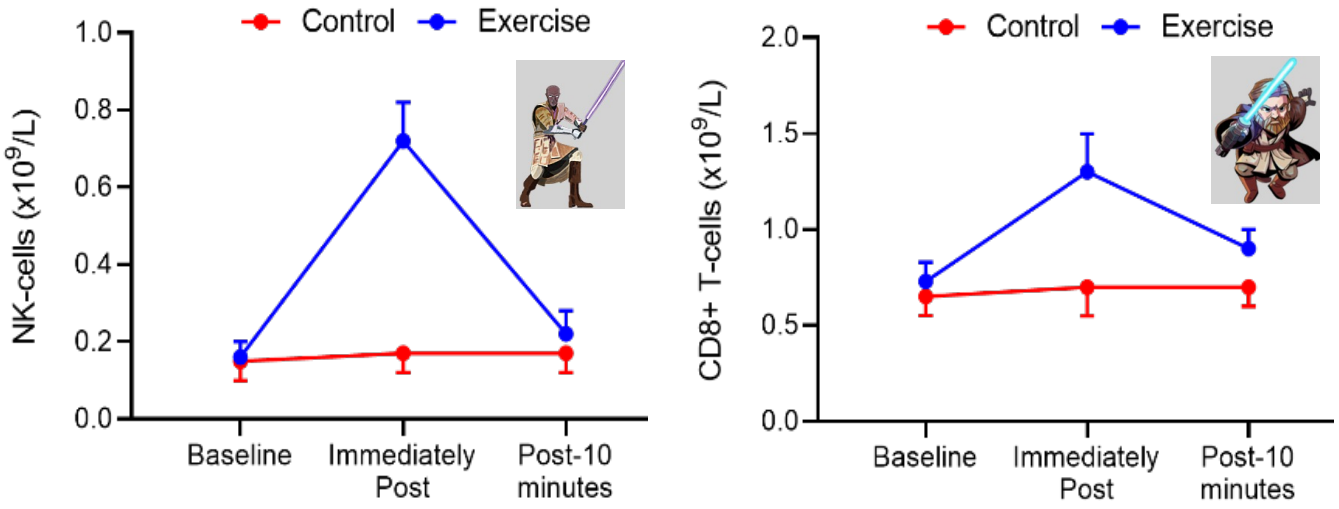
Tumour Immunology: Nicola Annels
Clinical: Adam Frampton, Charles Rayner, Nima Abbassi-Ghadi
Exercise Immunology: David Bartlett



# Exercise During the Infusion of a Checkpoint Inhibitor?

- Does acute exercise mobilise immune cells into the blood while patients receive their immunotherapy infusions?

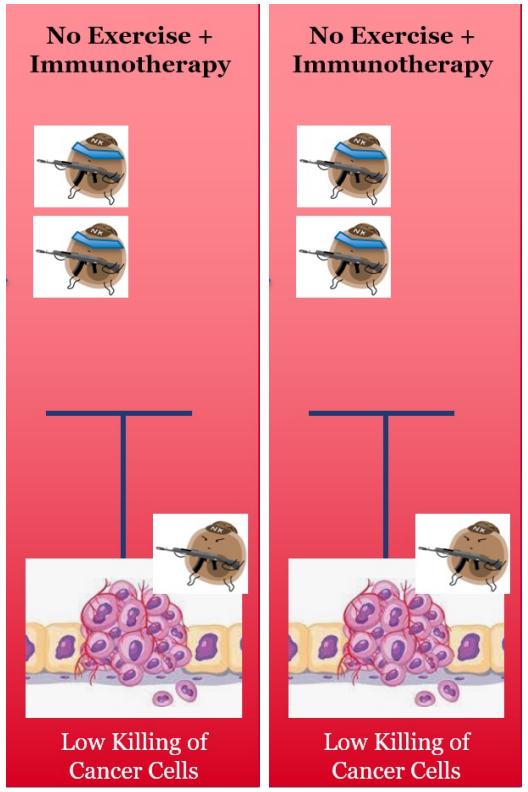
- Are the mobilised immune cells able to better identify and destroy cancer cell lines?




| | 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) |

Bartlett *et al*. In Submission

# Exercise During the Infusion of a Checkpoint Inhibitor?




Before infusion starts

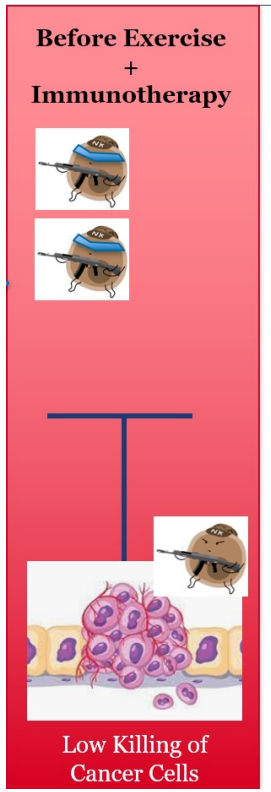



End of infusion (30mins)

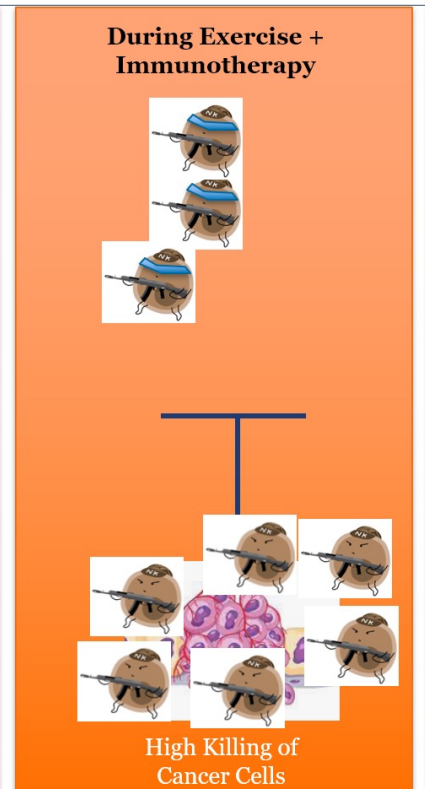
During infusional therapy, immune cells don't kill tumour cells any better than if they didn't have the therapy

Adding exercise to infusions increased the killing of tumour cells

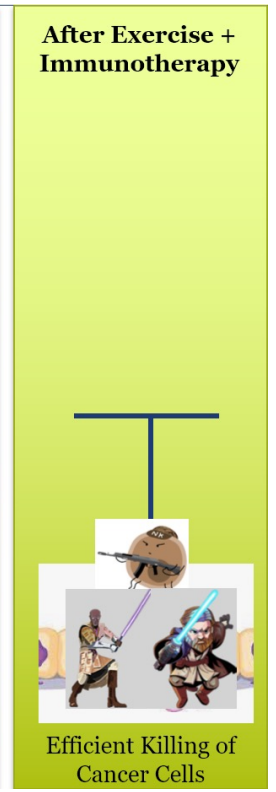
If acute bouts of exercise can promote *in vitro* tumour killing, perhaps all patients undergoing infusional immunotherapy should engage in exercise during infusions




Before infusion starts




End of infusion (30 mins)




15 mins after end of infusion

Bartlett *et al*. In Submission

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

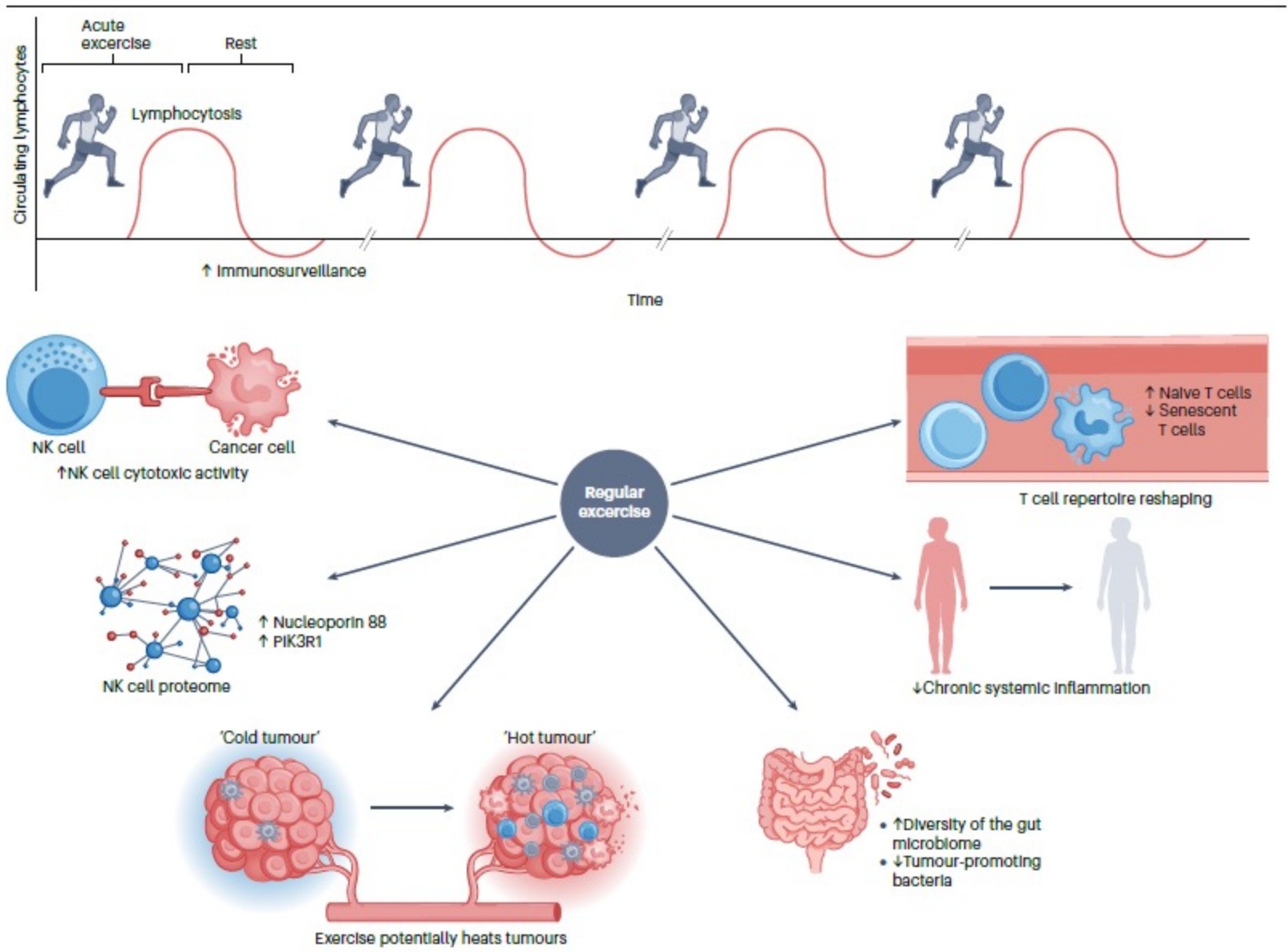
1. Acute Exercise mobilises effector immune cells into the blood.

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