FROM DIVESITE
TO BENCH
TO BEDSIDE

PHYPODE Project
Physiopathology of decompression

HOW DIVING MEDICINE CAN HELP CANCER PATIENTS

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SBMHS / BVOOG
13th November 2013
Brussels

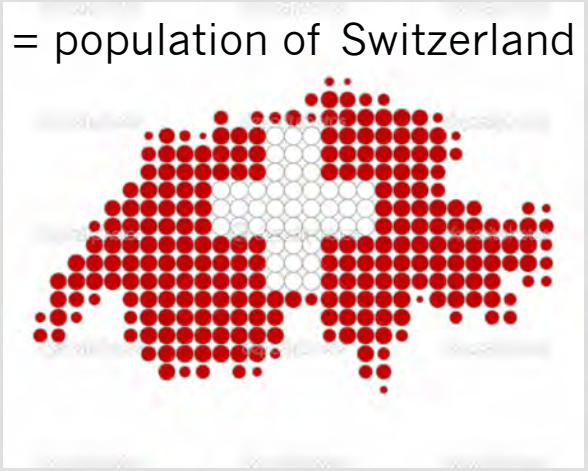
WHY ARE WE INTERESTED IN CANCER?

- Cancer is the **leading cause of death** worldwide (2nd in the US)

- Most common cancers *diagnosed* in Men:
  1. Lung
  2. Prostate
  3. Colon
- Most common cancers *diagnosed* in Women:
  1. Breast
  2. Colon
  3. Cervix

- Cancer **deaths per year**: 7.6 Million →

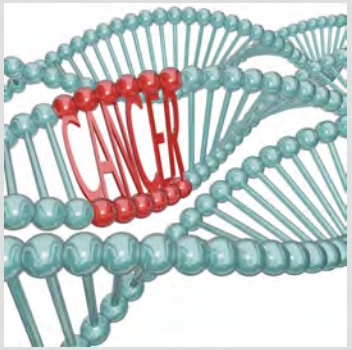
- Cancer **survivors** worldwide: 28 Million

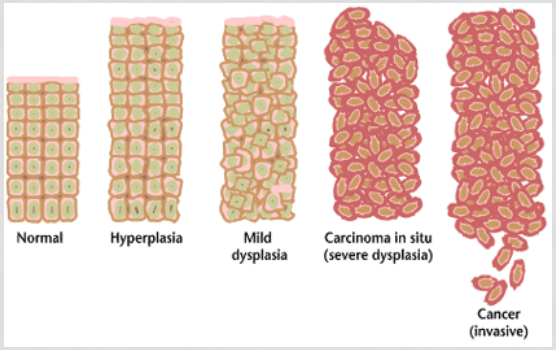


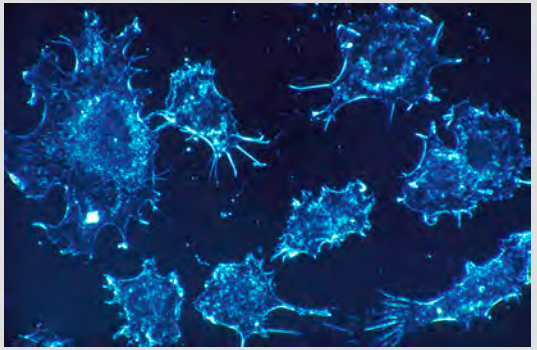
http://www.wcrf.org

WHAT IS CANCER?

- abnormal and unregulated replication, growth and activity
- Alterations in DNA or environmental factors (disrupting DNA and cellular function)
- Resistance to apoptosis (programmed cell death)







→results in tissue masses (tumors)

PREVENT–DIAGNOSE–TREAT–PREVENT

- Regular Health Maintenance:
  - Colonoscopy
  - Mammography
  - Cervical Cytology
- When in doubt:
  - microscopic evaluation of biopsied tissue
  - cytology
  - computerized tomography (CT)
  - positron emission tomography (PET)
  - magnetic resonance imaging (MRI)
  - surgical exploration

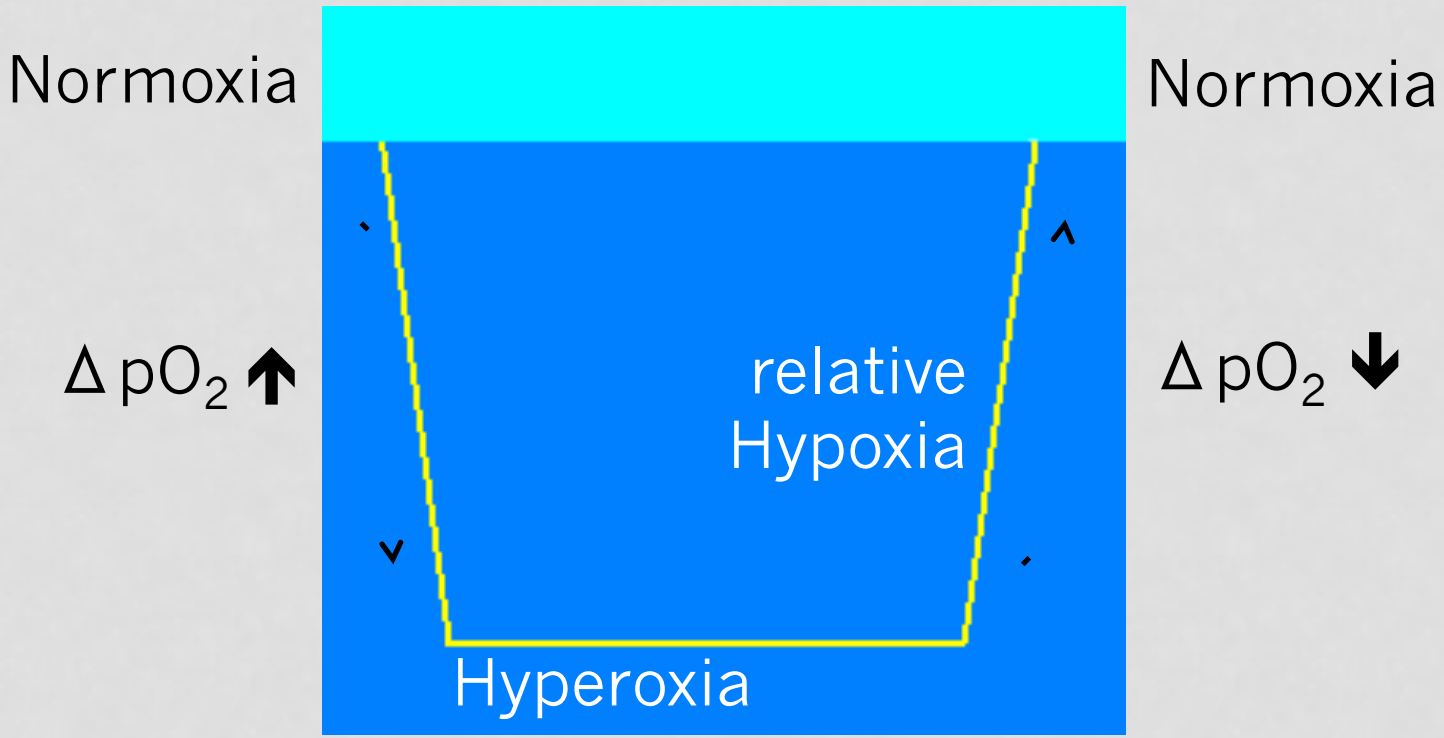
PREVENT–DIAGNOSE–TREAT–PREVENT

- Treatment(s):
  - Surgery
  - Chemotherapy
  - Radiation
  - Bone marrow transplantation
- Depending on: size, grade/stage, location, tumor genetics (tumor type/sensitivity to treatment), likelihood of treatment success, risk of treatment, probability of recurrence

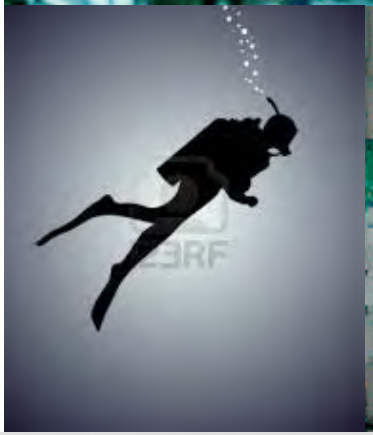
- Decreasing Risk of Reoccurrence:
  - LIFESTYLE CHANGES

TRANSIENT NORMOBARIC HYPEROXIA

Oxygen partial pressure changes



TRANSIENT NORMOBARIC HYPEROXIA

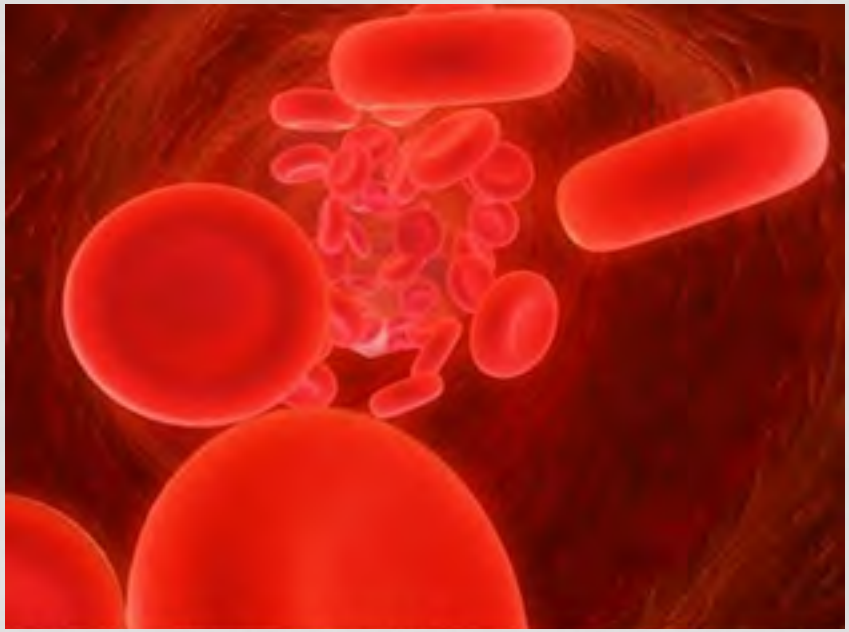


WHAT CAN NORMOBARIC OXYGEN DO?

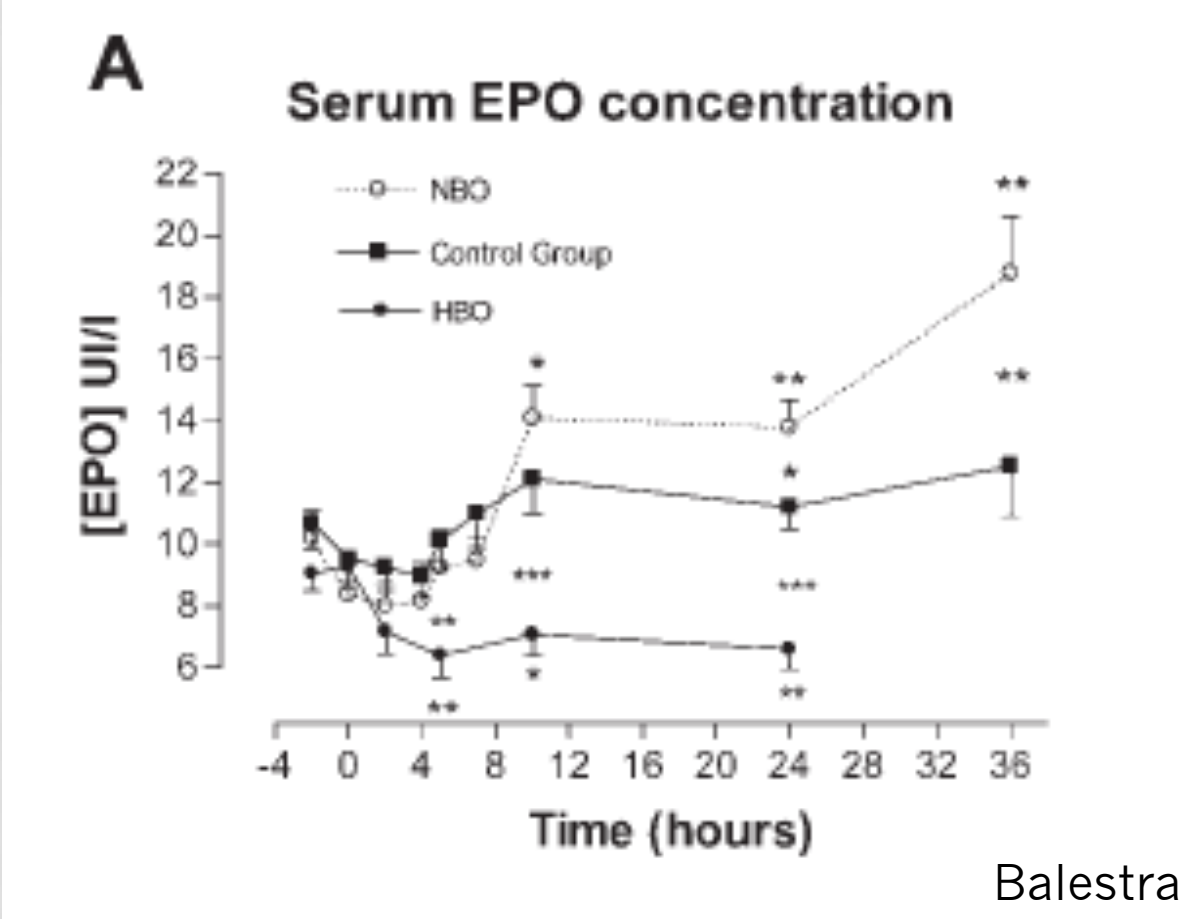
ERYTHROPOIETIN (EPO)

- Glycoprotein hormone
- Red blood cell production
- Cytokine (Signalling Molecule)

- Performance enhancing drug



SERUM EPO-CONCENTRATION AFTER 2H OF 100% O_2

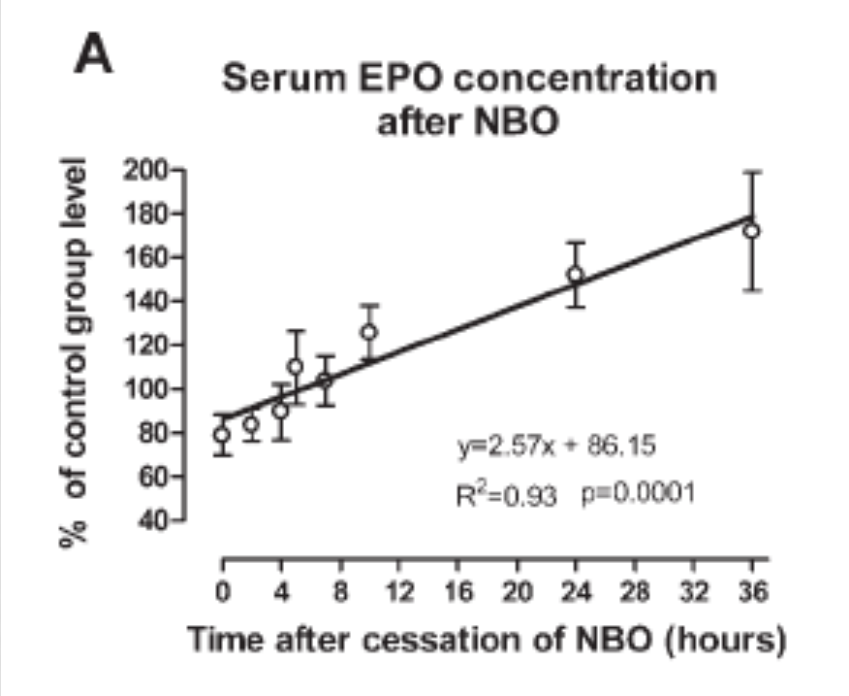


Balestra et al. 2004

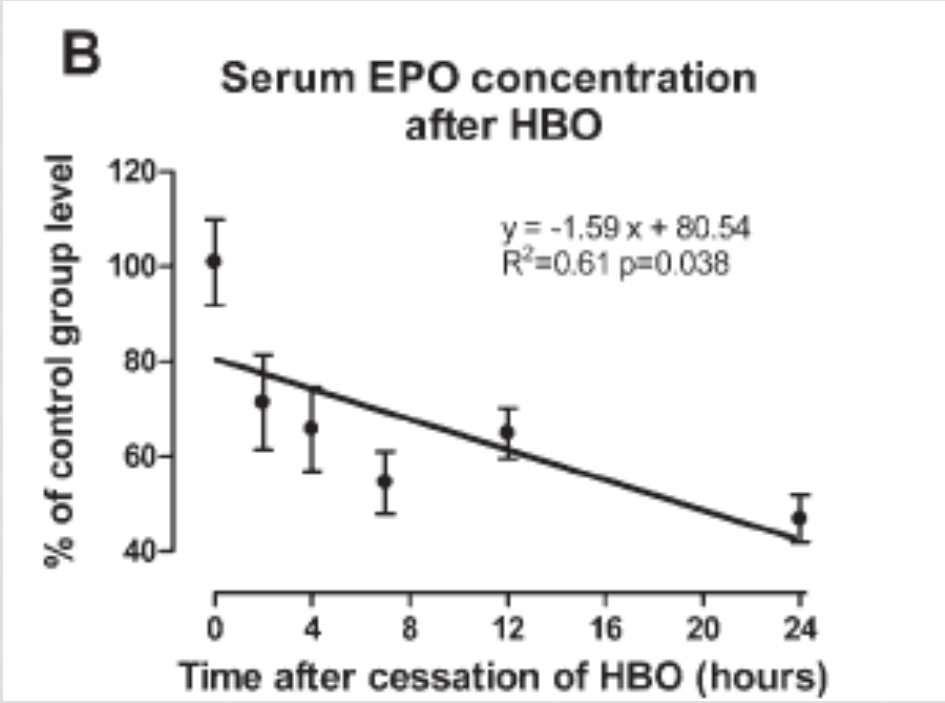
Healthy volunteers, 2h Oxygen 100%, each volunteer functioned as his own control

SERUM EPO CONCENTRATION

Normobaric Oxygenation



Hyperbaric Oxygenation



Balestra et al. 2006

DOES IT WORK ON HEMOGLOBIN?
A CASE STUDY

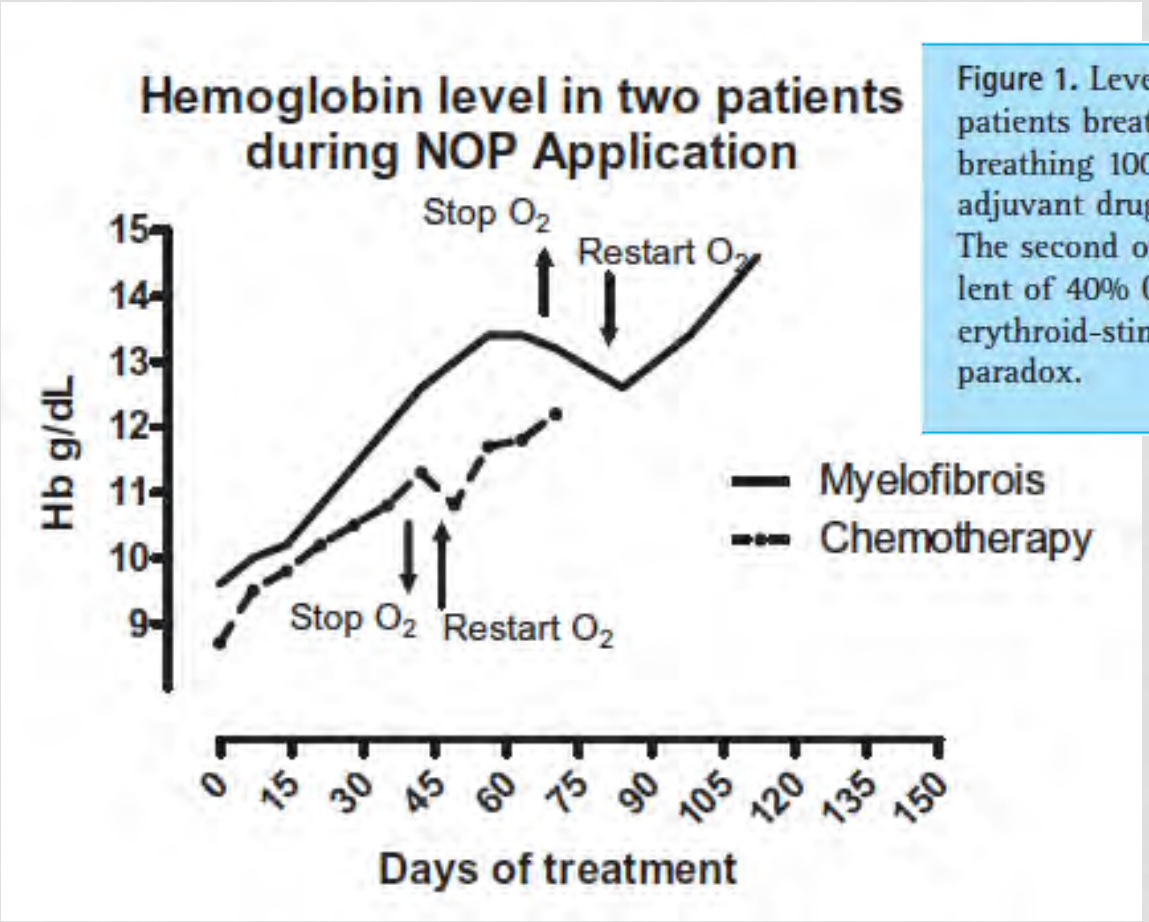
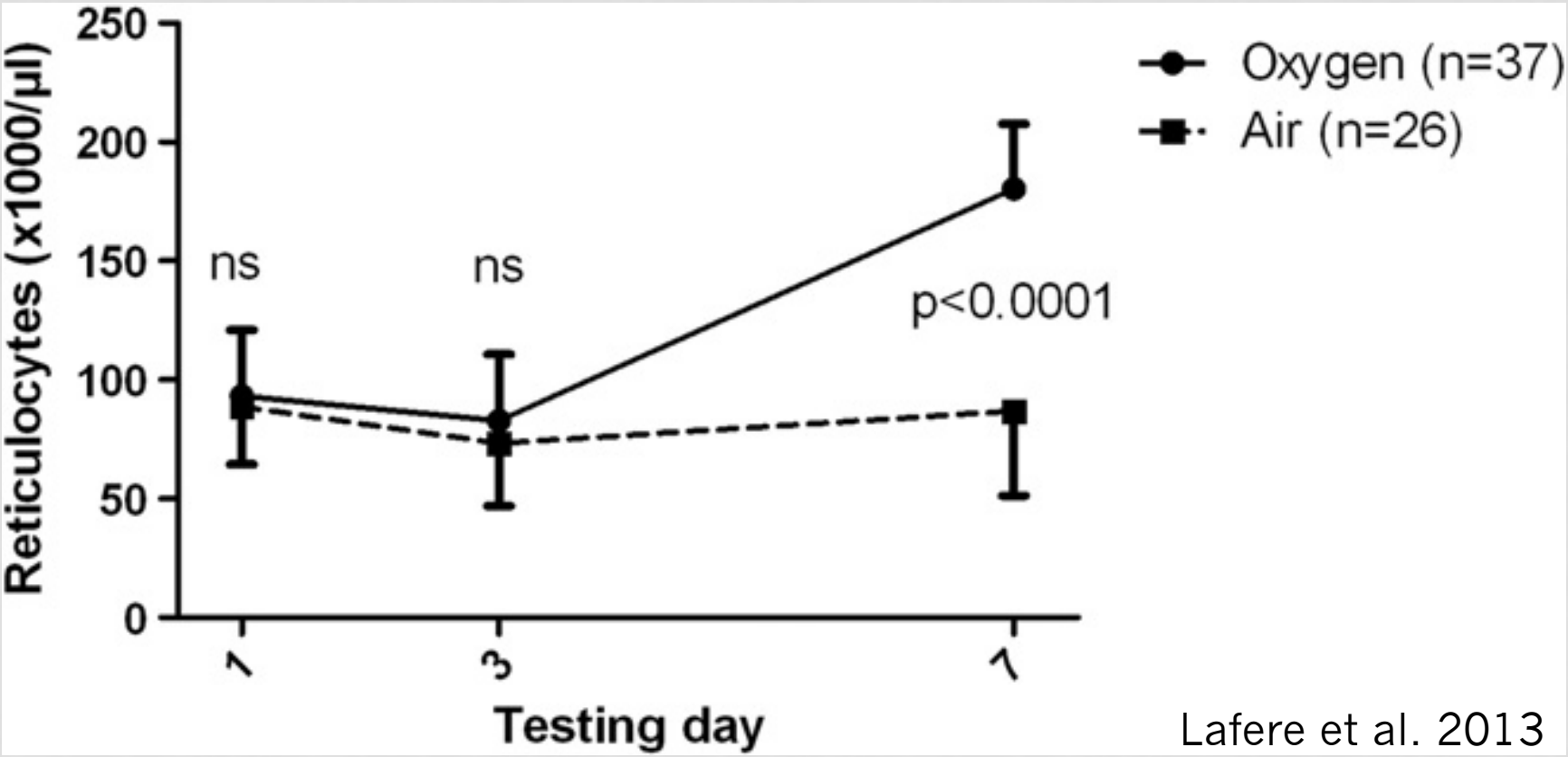


Figure 1. Levels of hemoglobin (Hb) (g/dL) in two patients breathing oxygen. The first one (Myelofibrosis) breathing 100% O_2 every other day with concomitant adjuvant drug therapy (darbepoetin alpha + IV iron). The second one (Chemotherapy) breathing the equivalent of 40% O_2 three times per week with no other erythroid-stimulating agents. NOP, normobaric oxygen paradox.

Balestra et al. 2010

AND WHAT ABOUT RED BLOOD CELLS?

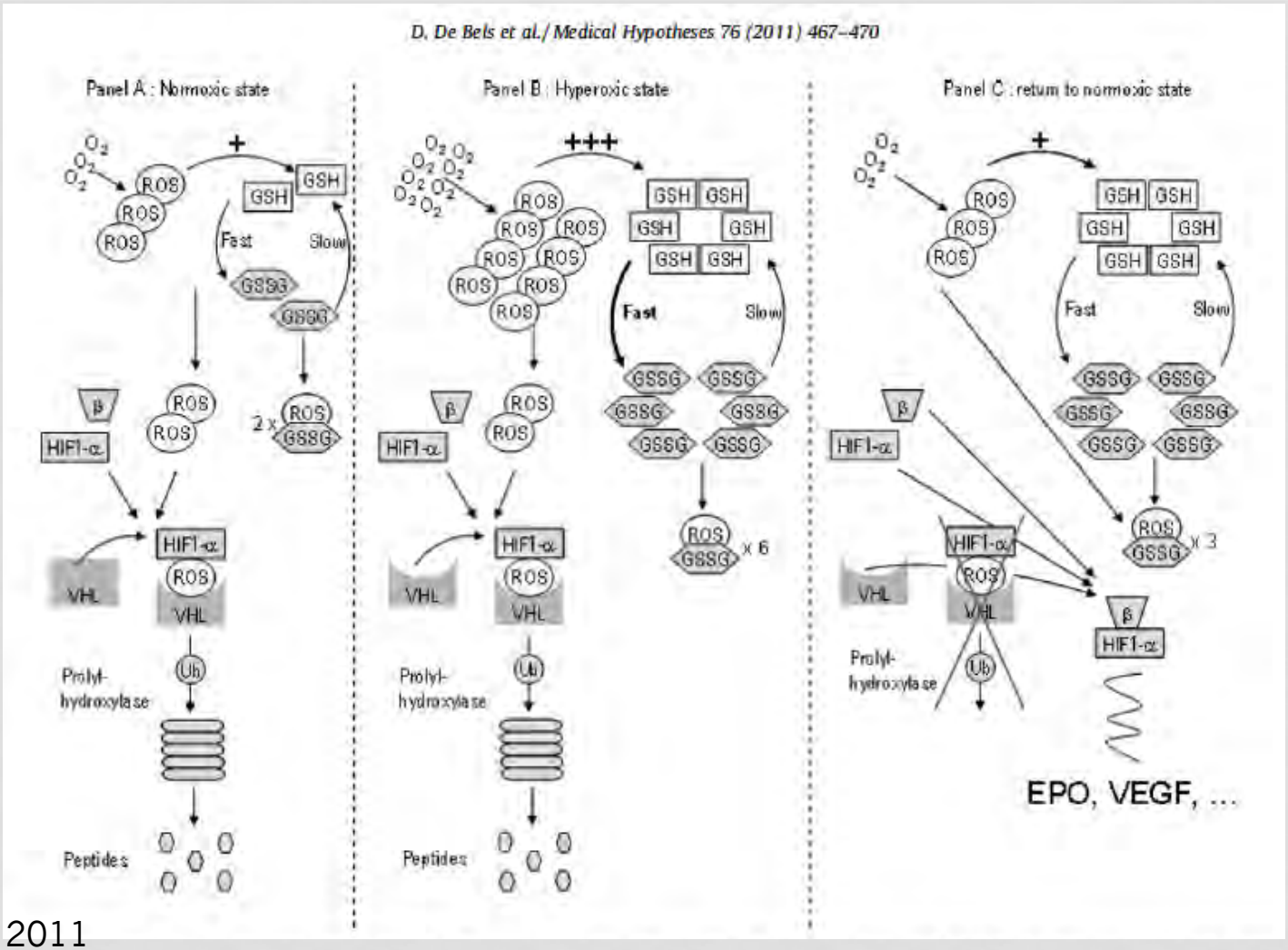


Lafere et al. 2013

reticulocyte count in non-tranfused patients after hip surgery. ns = not significant. ***P b 0.001 for between-group comparison. 30 min. O_2 every postoperative day. (no hematocrit or hemoglobin changes until day 7.)

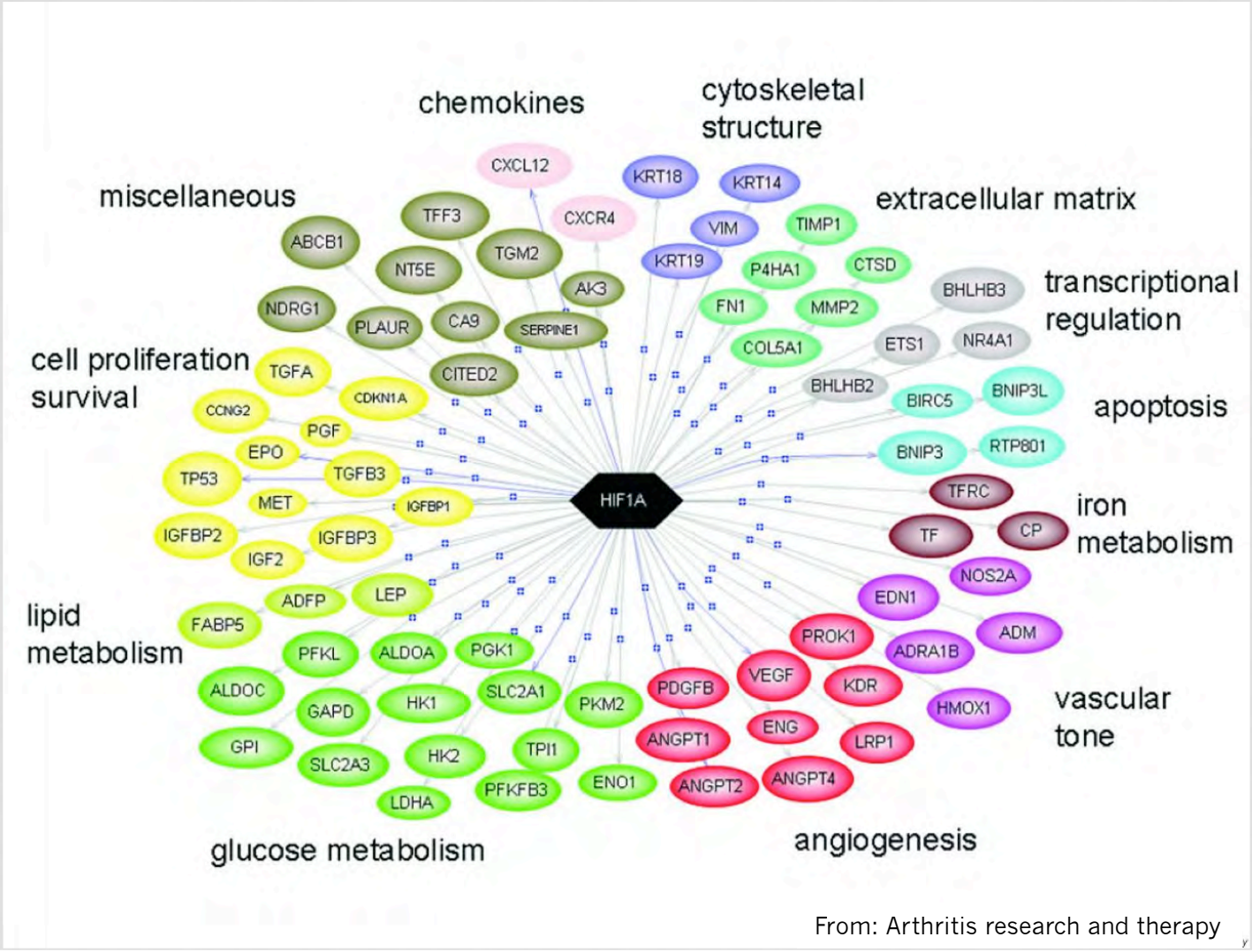
HOW TO EXPLAIN THIS?

THE NORMOBARIC OXYGEN PARADOX PART I – THE HEALTHY CELL



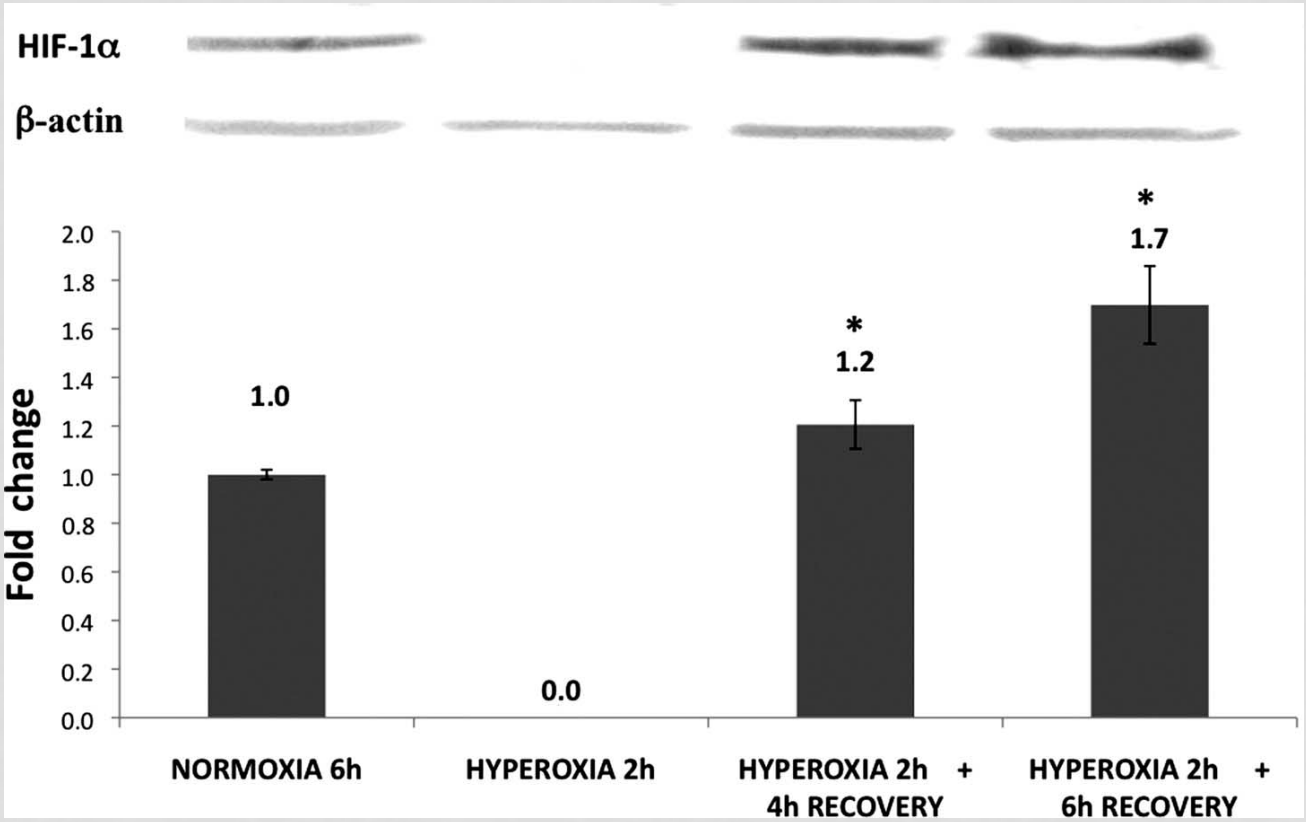
DeBels et al. 2011
Med. Hypotheses

HIF1-ALPHA



From: Arthritis research and therapy

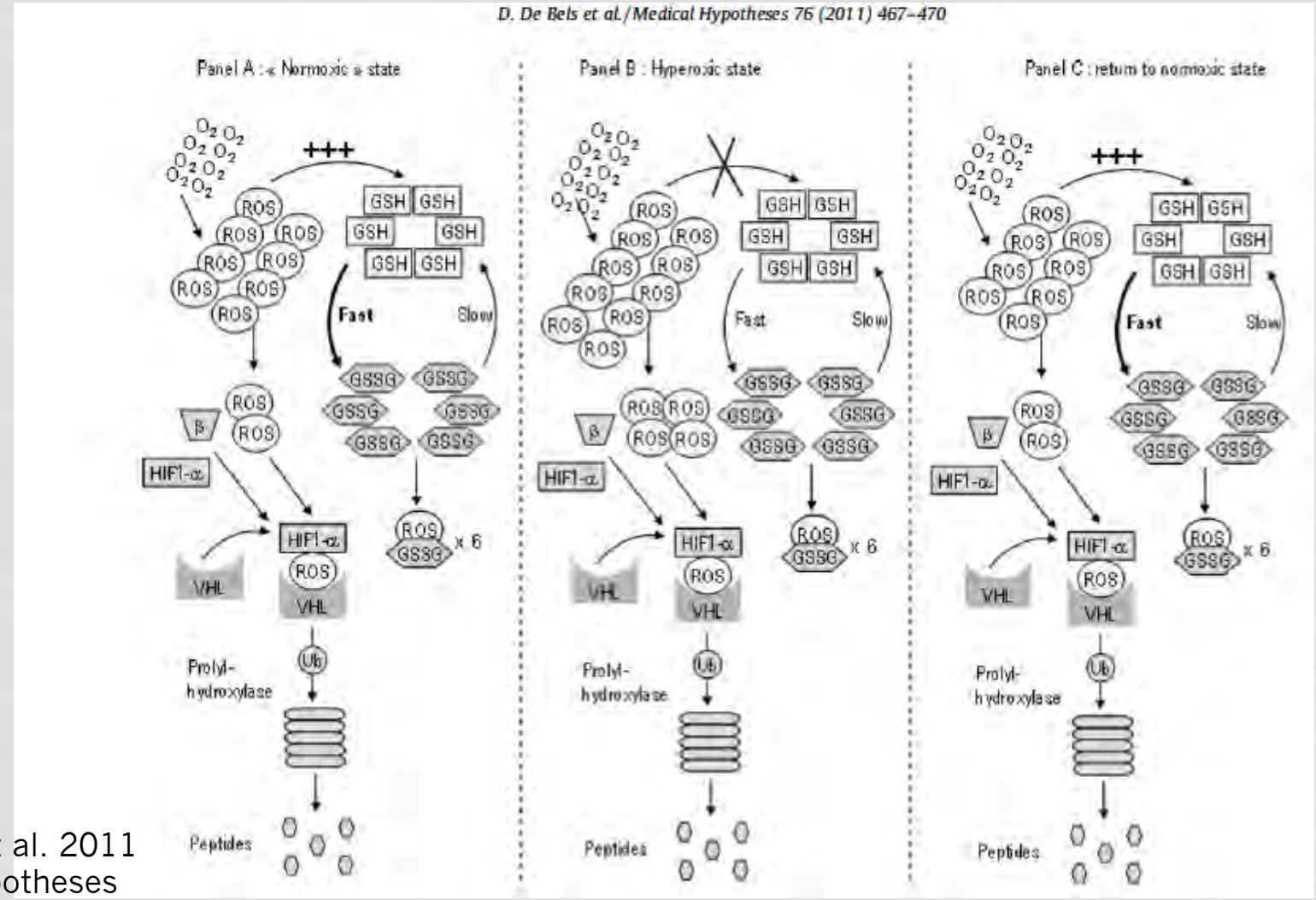
EXPRESSION OF HIF1-alpha
AFTER 2H NORMOBARIC HYPEROXIC EXPOSURE



Modulation of HIF1-a in human umbilical vein endothelial cells (HUVEC) exposed to hyperoxia (32% O2) for 2 h and then recovered to normoxia for following 6 h.

Cimino et al. 2012

THE NORMOBARIC OXYGEN PARADOX PART II – THE CANCER CELL



DeBels et al. 2011
Med. Hypotheses

HAS THIS BEEN TRIED?

CANCER AND OXYGEN
(CLINICAL TRIALS FROM THE LITERATURE)

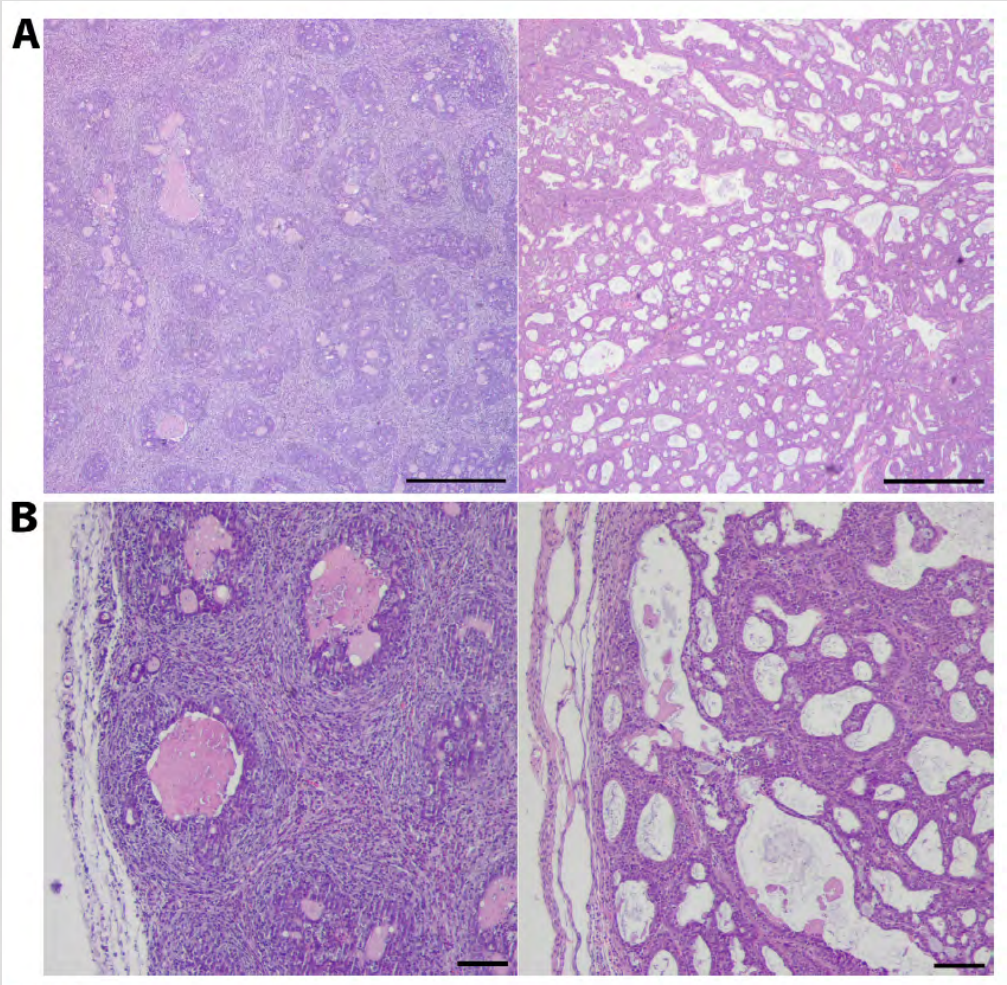
HBO

- Hyperbaric oxygenation results in a significant increased oxygen concentration within solid tumors (2002, Becker)
- Consensus that HBO does not have cancer-promoting or accelerating properties (Review 1993, Feldmeier)

NBO

- Breast cancer: improved outcome for patient after chemotherapy with NBO (2007, Burk)
- Breast cancer reduction in tumour size after 2h O_2 every 3rd day (Raa, 2007)

BREAST CANCER BEFORE AND AFTER NORMOBARIC HYPEROXIA



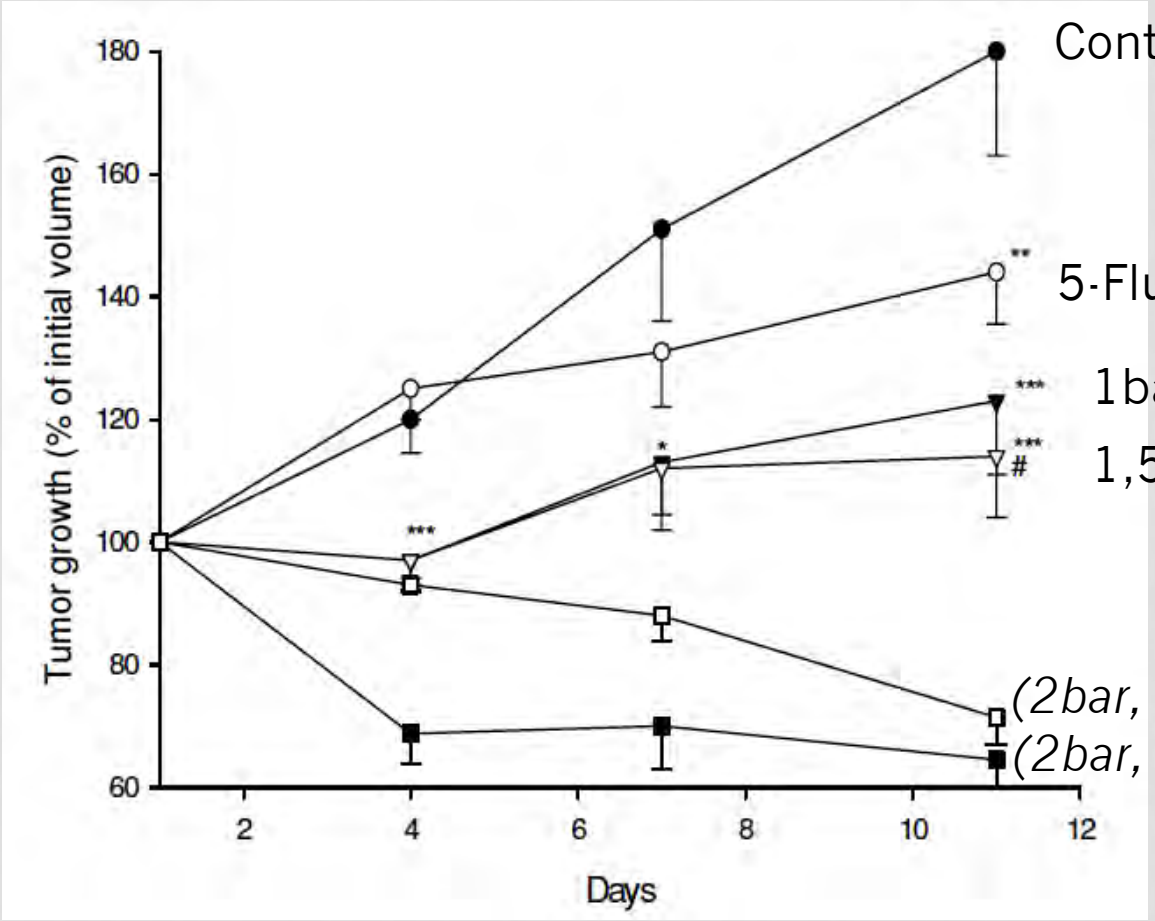
Central Tissue

Peripheral Tissue

Raa et al. 2007

TUMOR GROWTH AFTER NORMOBARIC AND HYPEROXIC OXYGENATION

The effect of normoxic and hyperoxic treatment on tumor growth compared to controls and 5-FU treated. Treatments were given on day 1, 4, 7 and 10. Values represent means ± SE.



Control, 21% O_2

5-Fluorouracil (FU)

1bar, 100% O_2

1,5bar, 100% O_2

(2bar, 100% O_2 + 5-FU)

(2bar, 100% O_2)

Raa et al. 2007

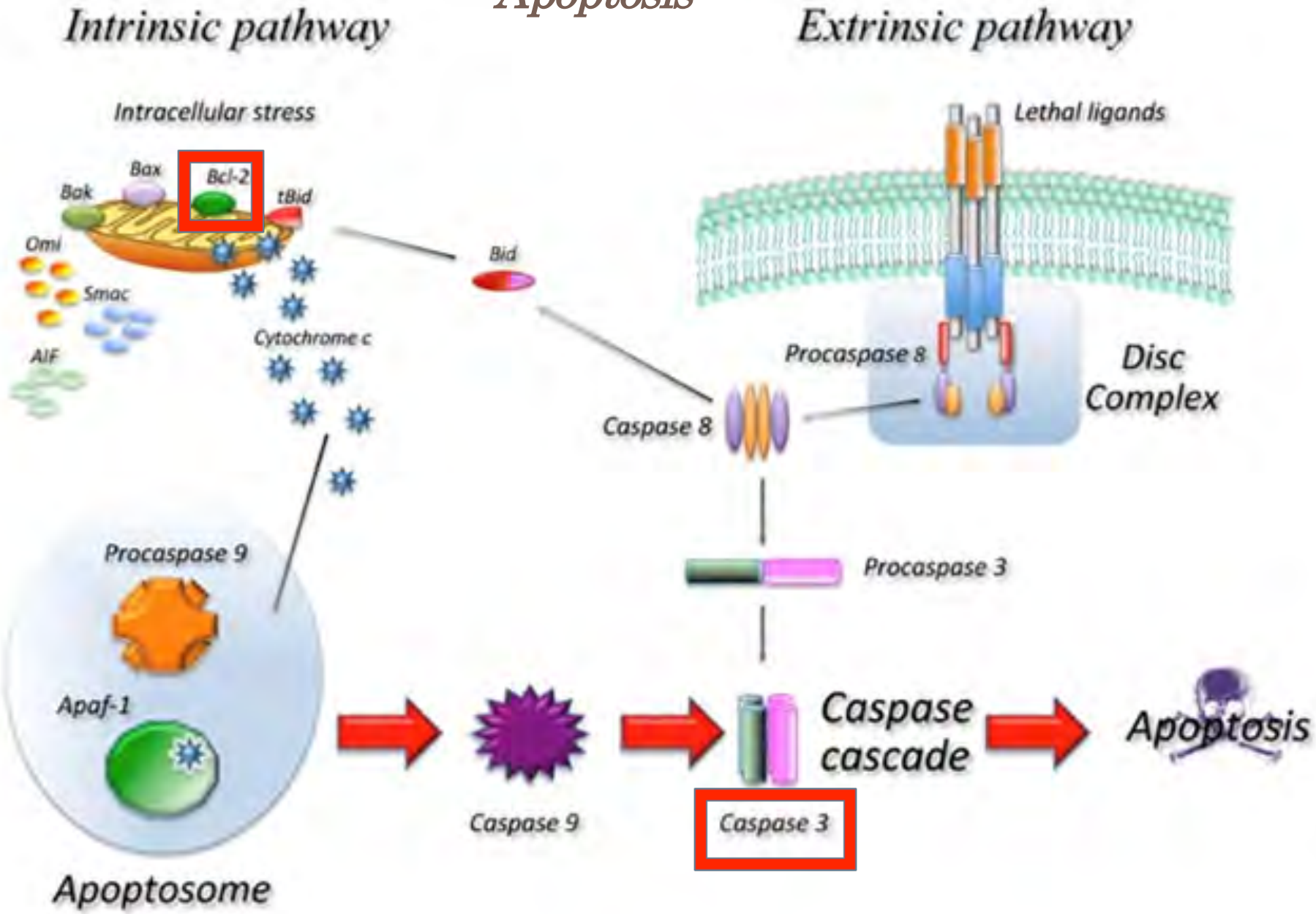
Note: the 2bar – Exposure was from external experiment, so no statistics available.

OXYGEN PLAYS A KEY ROLE IN CANCER AND IN DIVING

PATHWAYS INVOLVED IN DIVING AND CANCER

- Immune Response
  - Inflammation and release of ROS
  - Cytokine regulation
  - Increase in white blood cells
- Apoptosis and Anti-Apoptosis
- Mitochondrial Reaction to Oxygen Exposure and Energy Demands

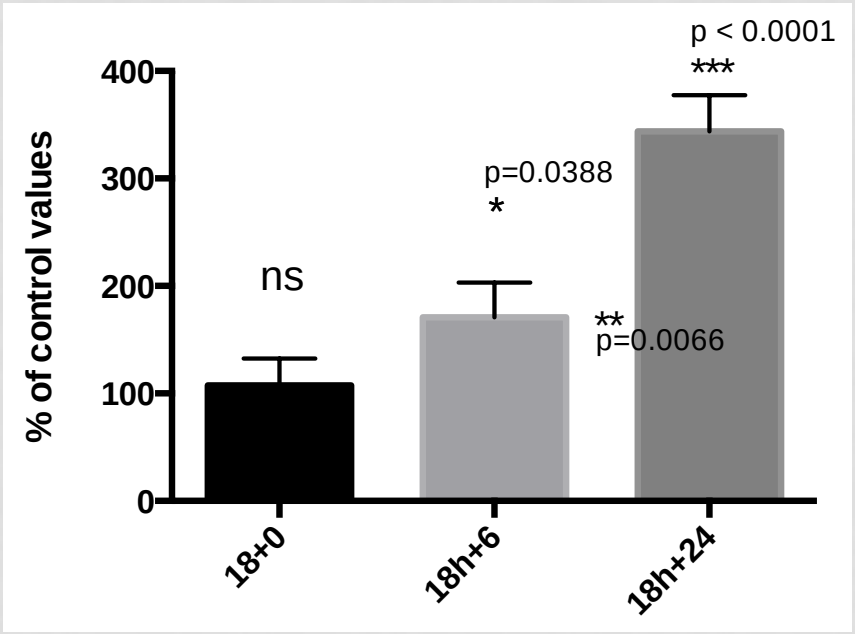
Apoptosis


Intrinsic pathway
Extrinsic pathway
Intracellular stress
Bax
Bcl-2
Bak
tBid
Omi
Smac
AIF
Cytochrome c
Bid
Lethal ligands
Procaspase 8
Disc Complex
Caspase 8
Procaspase 3
Procaspase 9
Apaf-1
Apoptosome
Caspase 9
Caspase 3
Caspase cascade
Apoptosis

LEUKEMIC T-CELLS
65% OXYGEN FOR 18H

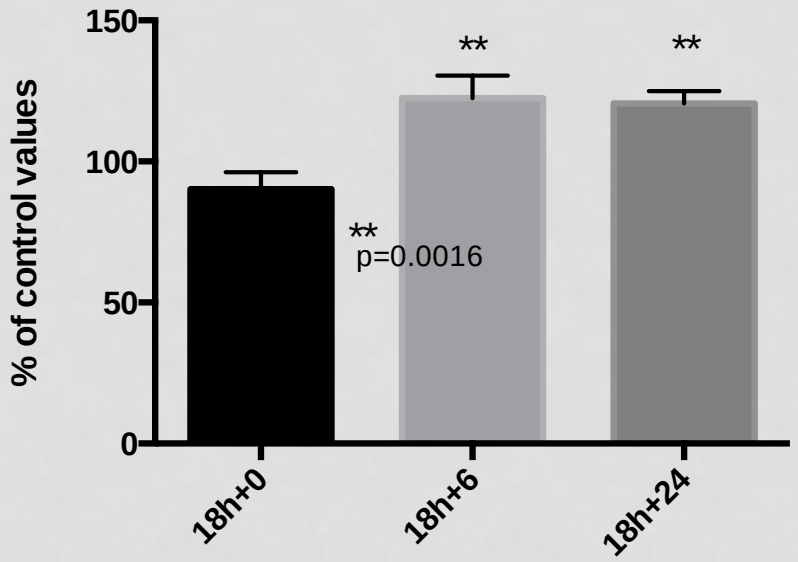
Cleaved Caspase-3

Apoptosis marker in leukemic T-cells (Jurkat)



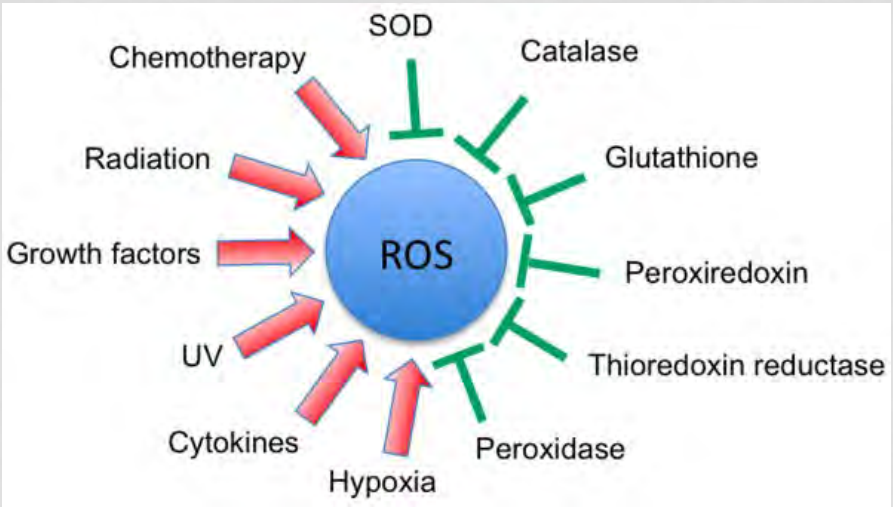
Bcl-xL

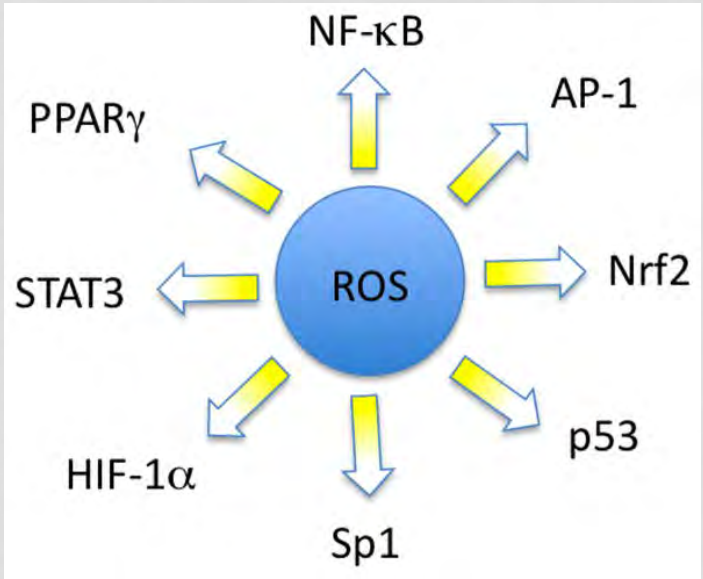
Anti-Apoptosis marker in leukemic T-cells (Jurkat)



CANCER AND OXIDATIVE STRESS

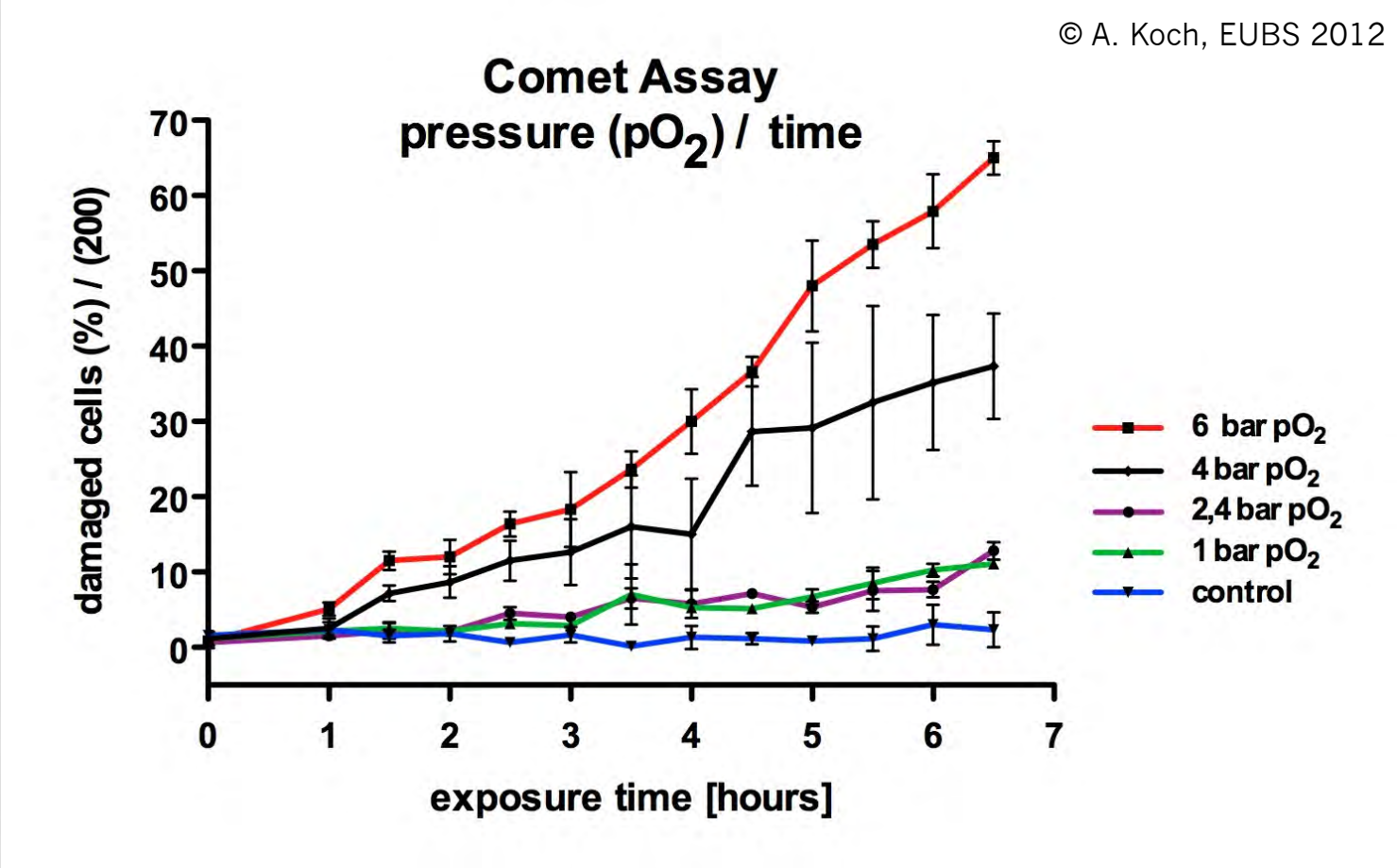
- Chemo- and Radiotherapy influence ROS modulation
- PRO-oxidant therapies to recover apoptotic capacity of the cell
- Antioxidant overexpression results in increased tumor size and thus to a decrease in apoptosis
- → We need ROS as signalling molecules, transcription factors, …





Further Reading: Davis W (2001)

DNA DAMAGE IN DIVING



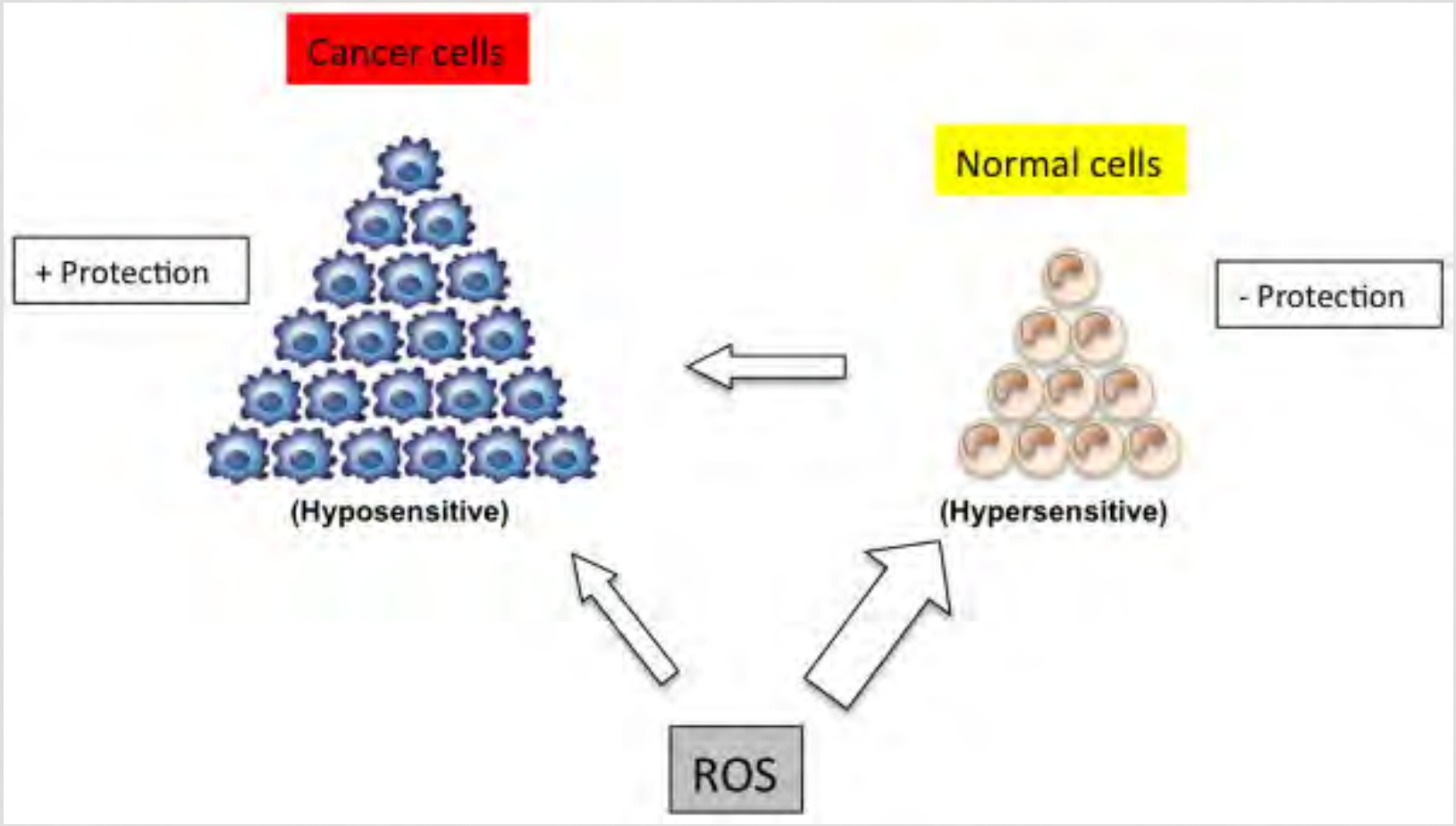
Extracted Lymphocytes from healthy volunteers exposed to oxygen over several hours. % of cells with DNA-damage were calculated.

WHO IS RESPONSIBLE FOR ALL THE FREE RADICALS?

MITOCHONDRIA AND CANCER

- 1924: Warberg effect / Pasteur effect
- 1950s: Weinhouse: mitochondrial function in cancer cells remains normal
- 1972, Eakin: mitochondrial dysfunctions exist in some tumors but this is not a hallmark of cancer.
- 1979, Reizer: cancer cells derive 96% of their ATP from oxidative phosphorylation using glutamine as energy substrate
- 2004, Carew: increased mtDNA content is reported in chronic lymphocytic leukemias

CANCER CELLS ARE MORE STRESSED

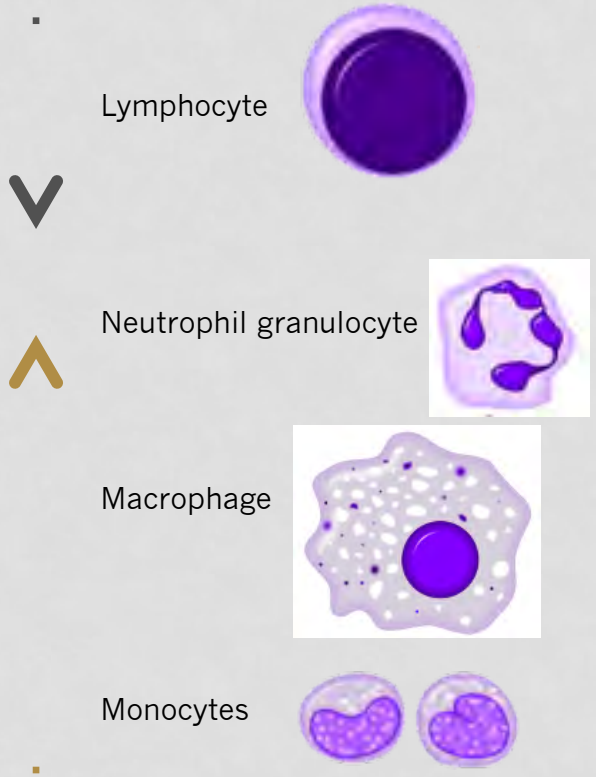


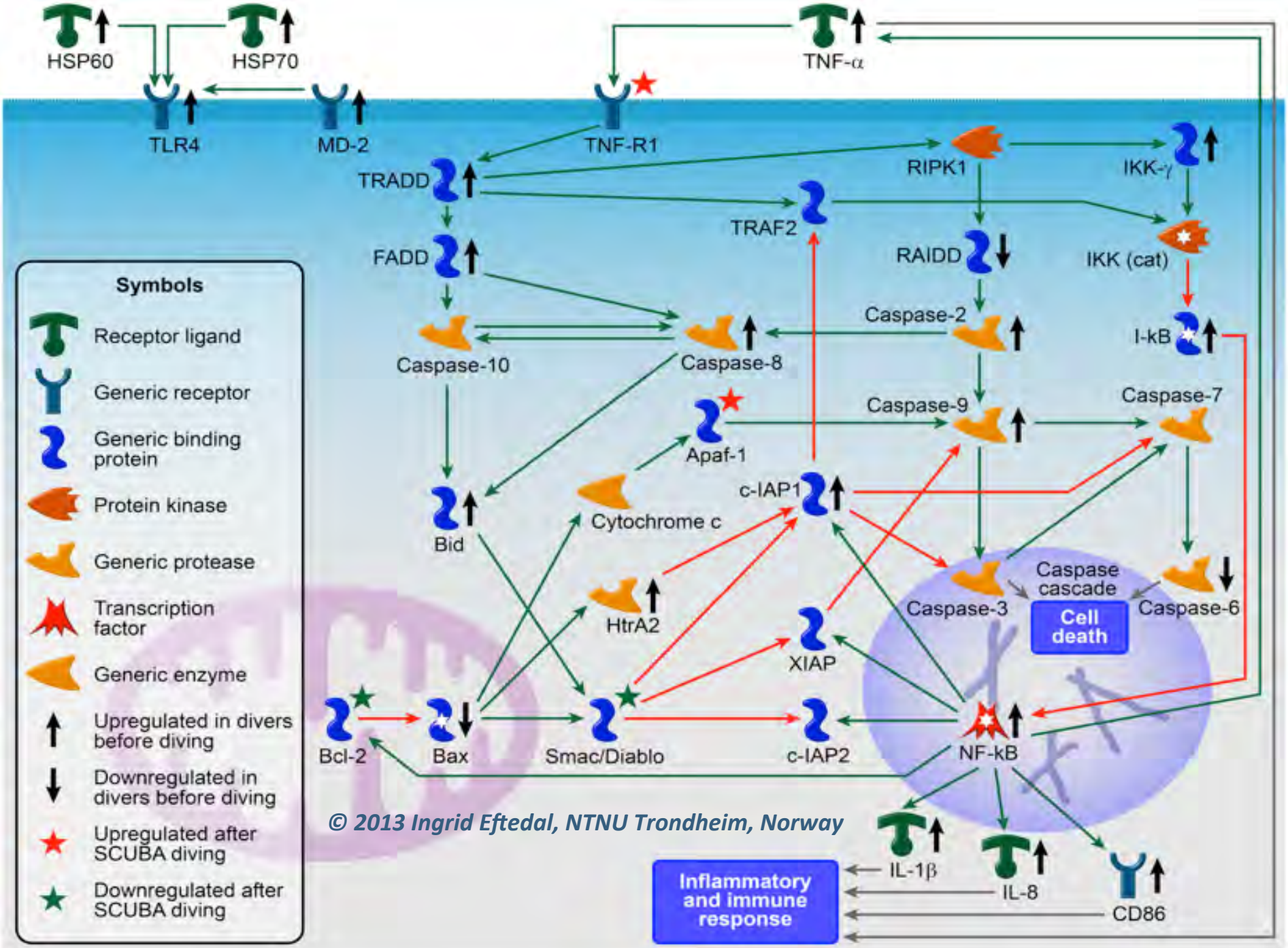
ROS ACTIVATE THE IMMUNE SYSTEM

ACUTE LEUKOCYTE RESPONSES TO SCUBA DIVING

Table 2. *Selected blood cell associations for genes that were down- and upregulated after scuba diving*

Cell Types	Genes (*n*) in Data	Genes (*n*) in Reference	*P* Value
Downregulation			
Activated T cells, CD8+ CD45.1+	65	387	3.514e-18
NK cells, NK1.1+ TCRb− Ly49H+	61	370	1.747e-16
NK cells, NK1.1+ CD3− Ly49C/I+	62	385	2.913e-16
Upregulation			
Neutrophils, CD11b+ Ly6-G+	54	418	5.072e-20
Macrophages, CD45+ F4/80+ CD11b+	38	402	6.142e-9
Classical monocytes HMCII−, CD115+ B220− CD43+ Ly6C+	36	408	1.737e-7




HSP60
HSP70
TNF-α
TLR4
MD-2
TNF-R1
TRADD
RIPK1
IKK-γ
TRAF2
FADD
RAIDD
IKK (cat)
Caspase-2
I-kB
Caspase-10
Caspase-8
Caspase-9
Caspase-7
Apaf-1
c-IAP1
Bid
Cytochrome c
HtrA2
XIAP
Caspase-3
Caspase cascade
Cell death
Caspase-6
Bcl-2
Bax
Smac/Diablo
c-IAP2
NF-kB
IL-1β
IL-8
CD86
Inflammatory and immune response
Symbols
Receptor ligand
Generic receptor
Generic binding protein
Protein kinase
Generic protease
Transcription factor
Generic enzyme
Upregulated in divers before diving
Downregulated in divers before diving
Upregulated after SCUBA diving
Downregulated after SCUBA diving
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BACK TO REACTIVE OXYGEN

DO WE NEED PROTECTION?

N-ACETYL-CYSTEINE
(AN UNDER-UTILIZED FRIEND)

- Anti-Oxidant Nutrition Supplement
- Protects healthy cells from chemo- and radiation (DNA protection)
- Used in many diseases (COPD, Diabetes,…) and as cancer preventive medicine

TAKE HOME MESSAGE

- Can hyperbaric oxygen help your patients?
  - There is controverse scientific evidence that cancer patients profit from HBO, but it is overall agreed that it does not do harm.
- Can normobaric oxygen help your patients?
  - Very good results in Breast Cancer and first promising Leukemia trials, but further research to investigate the *underlying mechanisms* is needed.
  - Every 2-3 days seems to be more promising than every day.
- All cancers are equal, but some cancers are more equal than others

TAKE HOME MESSAGES

- Overlapping Research in Diving and Cancer
  - Immune system activation
  - Increased ROS production
  - Apoptotic pathway induction, inhibition and protection
  - (reversible) DNA disruption
- Understanding the underlying mechanisms is the key to introducing new treatments
- Divers are very good guinea-pigs!

PHYPODE Project
Physiopathology of decompression

TEAM BRUSSELS

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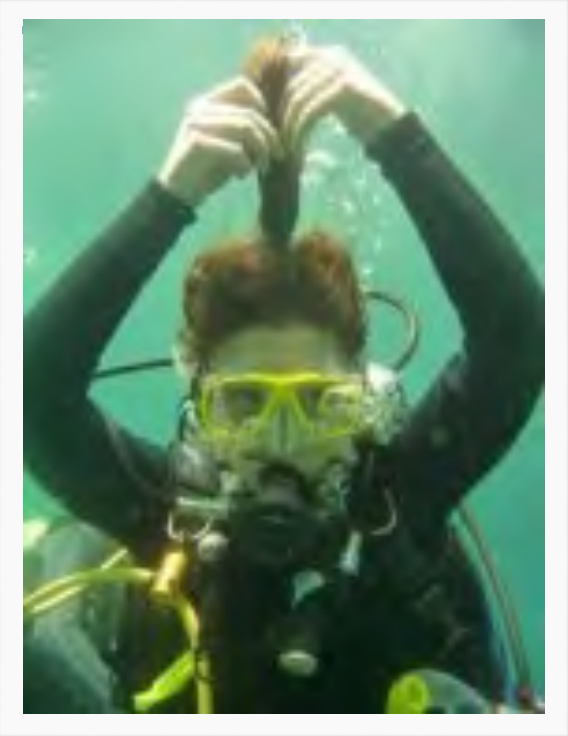
PHYPODE Project
Physiopathology of decompression

Research Focus in Brussels:

- Diving Physiology
  - DCI, Inert Gas Narcosis, Apnea,...
- Exercise Physiology
- Anatomy
- Altitude Physiology
- Free Radicals (Oxidative and Nitrosative Stress)
- Cellular Function and Dysfunction

ISEK

THANK YOU



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PICTURE SOURCES

- Slide 1: depositphotos, www.PHYPODE.org
- Slide 2: depositphotos
- Slide 3: avonro.info, thepresidentpost.com, en.wikipedia.org
- Slide 7: notfall-symposium.de, dan-europe.org, news4jax.com, 123rf.com, writerscafe.org, kernunited.blogspot.com,
- Slide 9: interactive-biology.org
- Slide 16: Arthritis research and therapy
- Slide 25: anti-agingfirewalls.com
- Slide 27&31: sfrbm.org
- Slide 30: photo-dictionary.com
- Slide 36: drugstore.com

- If you are interested in any full text publications cited in this presentation, E-Mail me and I will happily provide them for you.

SIDE NOTE FOR THE DIVING PHYSICIANS:

IS YOUR PATIENT "FIT TO DIVE"?

CONSIDER...

- Patient diagnosed and currently treated:
  - potential to affect critical organ systems (**brain**, **lungs**, colon, kidney) → NOT ftd
  - fatigue, immunosuppression, bleeding or the potential need for urgent medical support? → NOT ftd
- Patient recovering from treatment
  - Surgery: Follow conservative postsurgical guidelines
  - Radiation and Chemo: return to "normal" stamina/fitness levels
- If you are not an oncologist, get in touch with one!