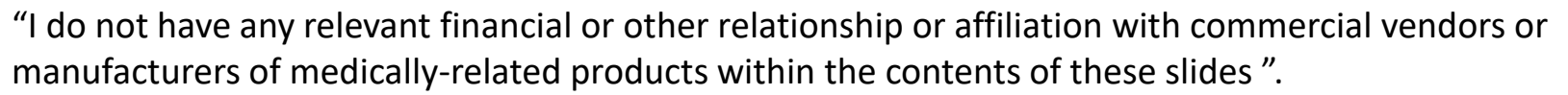


# HBOT2017 New Orleans 11<sup>th</sup> Annual International Symposium for Hyperbaric Medicine

## Hyperbaric Oxygen Therapy – Elite Sports Recovery & Performance

Malcolm R. Hooper  
Clinical Director  
OXYMED Australia ©

















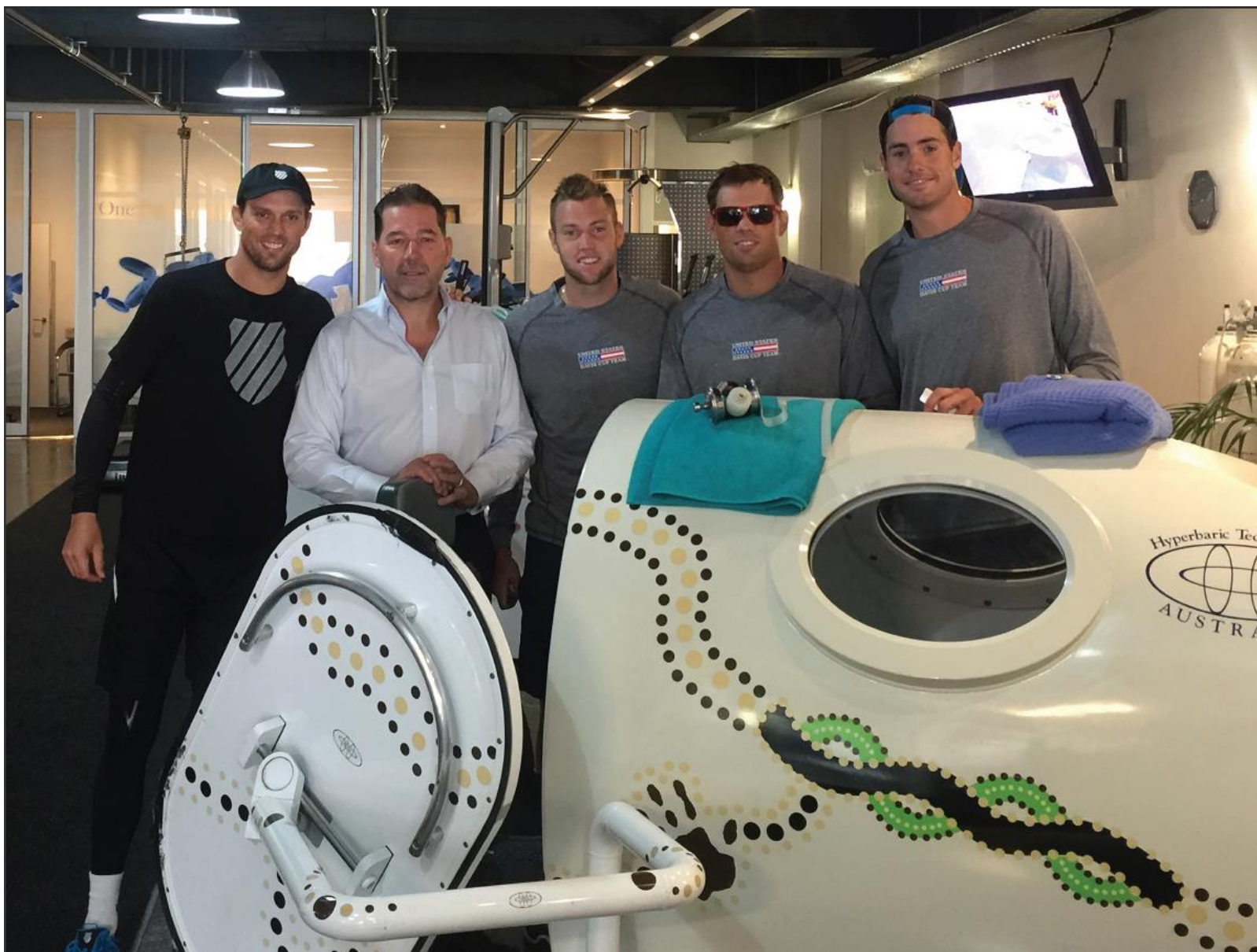




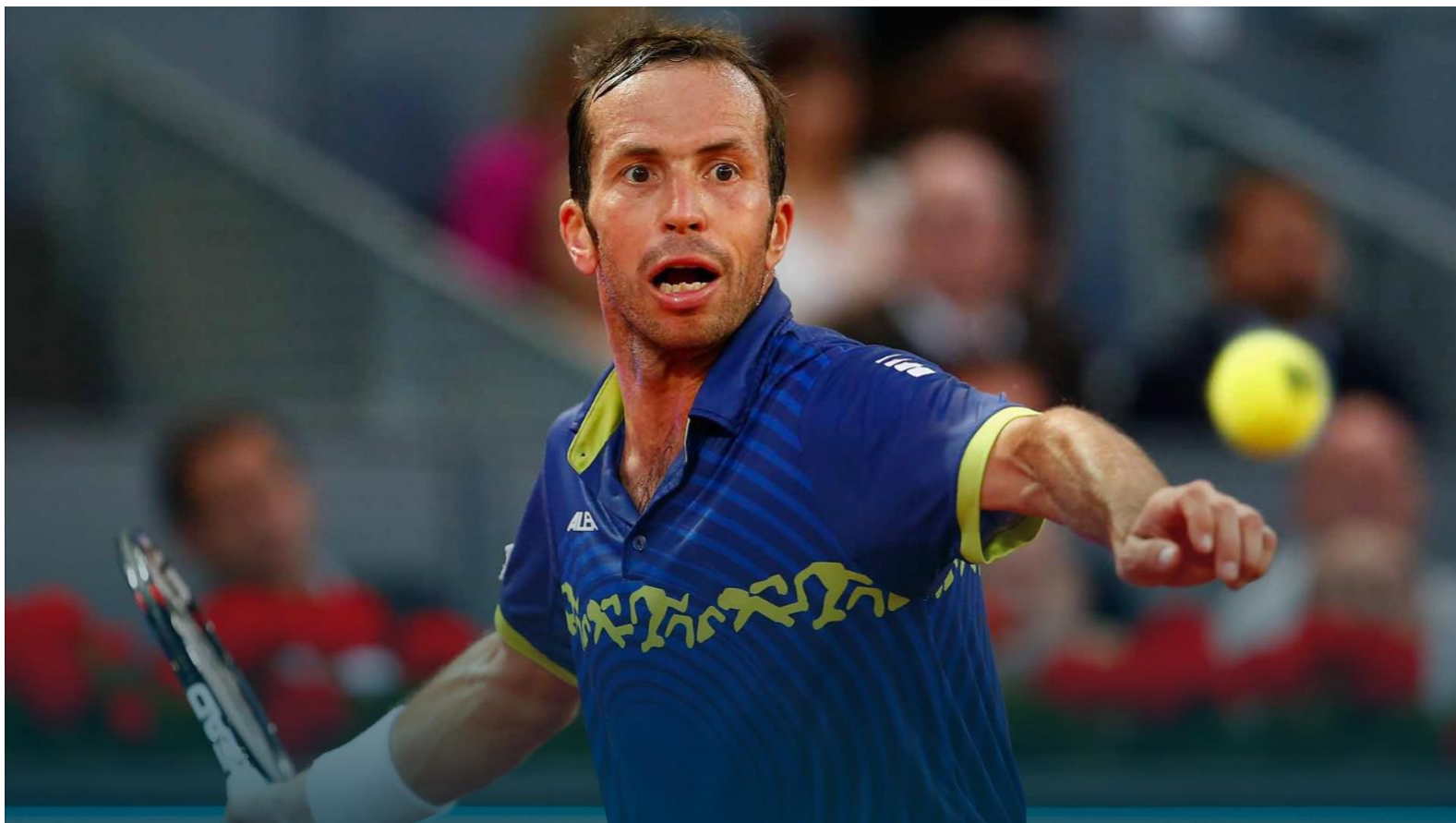
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## Intermittent Vacuum Therapy (IVT)

- Medical product class 11a used for the treatment of **peripheral arterial occlusive diseases, diabetic foot syndrome, chronic wounds, post-thrombotic syndrome, lymph oedemas, passive vascular and walking distance training.**
- Variable intervals of negative and normal pressure phases producing **rhythmic dilation and compression** of the vessels and capillaries.
- Physically this increases the circulation, the venous reflux and the disposal of lymph and lymph-dependent waste products.



## Acute effects of partial-body cryotherapy on isometric strength: maximum handgrip strength evaluation.

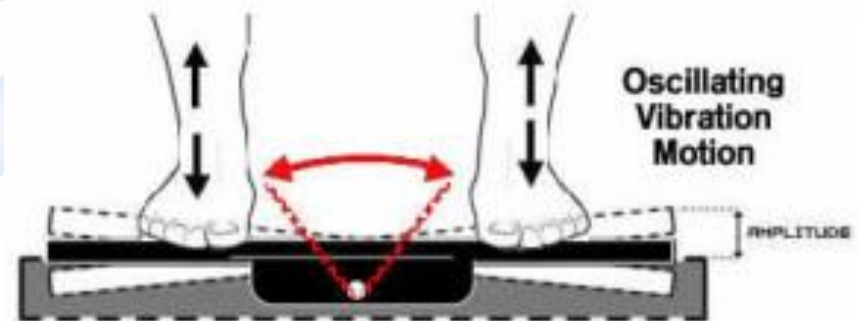
- The results of the study implies that partial body cryotherapy **increased hand isometric strength** and could be performed before a training session or a sport competition.



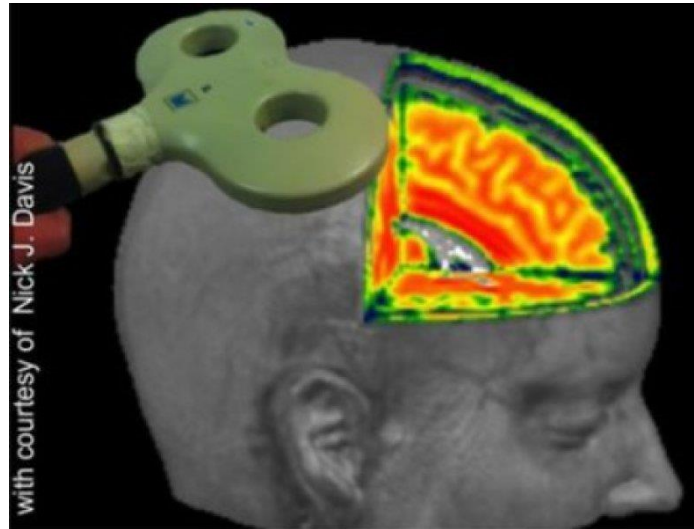


## Efficacy of Whole-Body Vibration Board Training on Strength in Athletes After Anterior Cruciate Ligament Reconstruction: A Randomized Controlled Study.

- Increase in knee muscle **isokinetic strength** values was statistically significant in the WBV group and an effective additional treatment option in the rehabilitation of athletes after **ACL arthroscopic reconstruction**.



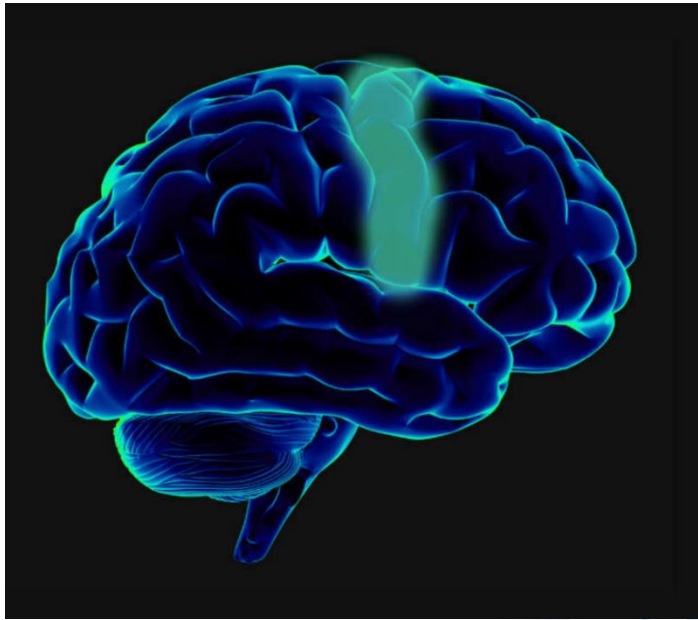
## Transcranial Magnetic Stimulation - TMS





## Transcranial Direct Current Stimulation - TDCS





Neuropriming is the process of using electrical stimulation during movement-based training to build stronger, more optimized connections between your brain and muscles.

This process induces a temporary state of hyper-learning or "hyperplasticity" in the brain, which refines the brain's ability to learn and adapt to training. This allows you to see better results, faster.





# A Real-World Investigation into the Benefits of Transcranial Direct Current Stimulation to the Primary Motor Cortex on Muscular Performance in Elite Athletes

Halo Neuroscience


February 10, 2016

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**ABSTRACT:** As interest in non-invasive brain stimulation grows, many potential users are seeking applications for the heightened learning state associated with this technology. One possible application is in sports, where stimulation has shown promising results in the form of increased training efficiency, improving both motor skills and raw power. In this study, athletes training for strength- and power-intensive sports received neurostimulation treatment in the form of transcranial direct current stimulation (tDCS) from the Halo Neurostimulation System during their normal training routine. Athletes who received stimulation showed significantly greater improvement in their jumping ability compared to non-stimulation athletes. The current study demonstrates the ability of non-invasive brain stimulation to improve athletic performance; however, further testing with larger populations and sham controls is needed in the future.

---

- **Athletes training for strength and power intensive sports** received neurostimulation via TCDS - **showing significantly greater improvement in performance measures.**
- [Transcranial direct current stimulation and sports performance](#) Frontiers in Human Neuroscience 2017
- [Cooperation not competition: bihemispheric tDCS and fMRI show role for ipsilateral hemisphere in motor learning](#) Journal of Neuroscience 2017
- [Basic and functional effects of transcranial electrical stimulation: An introduction](#) Neuroscience & Biobehavioral Reviews 2017



# Tim O'Donnell won Ironman Boulder by 21 minutes

**Neuropriming maximizes improvement in biomechanical efficiency and power output**

[WATCH HIS STORY](#)

**Timothy O'Donnell**  
Ironman Champion





## **Professional and Olympic athletes improve performance above a control group after training with Halo Sport**



**BarwisMethods®**



**INVICTUS**  
ATHLETE

**Halo helps Olympic ski jumpers produce more power and precision**

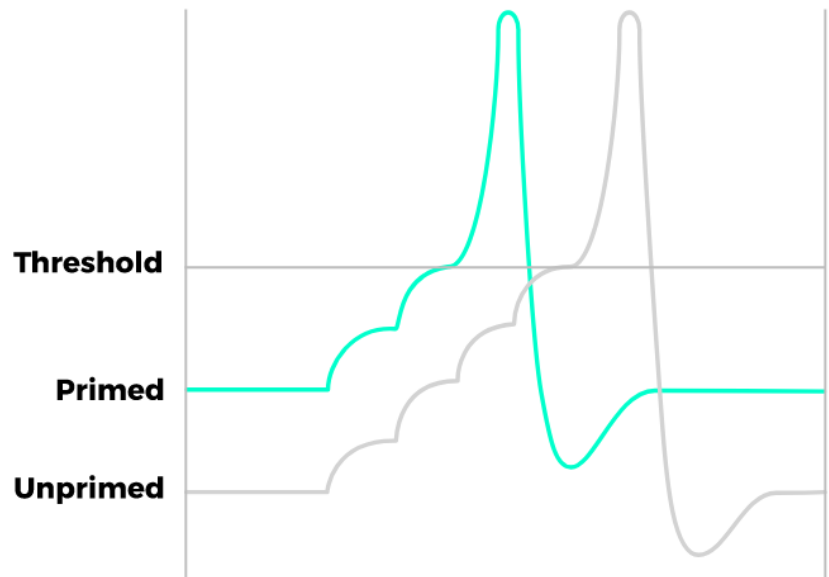
[Play Video](#)

**13% gain in propulsion force and 11% gain in jump smoothness over control in 4 weeks**



## Hyperplasticity – Neural Priming

- A mild electric field to the motor cortex - induces a state of **hyperplasticity**.
- When you train in a hyperplastic state, the brain's normal fine-tuning process occurs more rapidly — **meaning better results from each practice rep.**
- The grey line is a **non-primed neuron**.
- The green line represents a **neuron primed** with an **elevated starting point**.
- The difference is that it now **takes less input to trigger the neuron to send a signal**. This means that **more signals will be sent** for a constant amount of input and **nearby neurons will be more likely to fire together.**
- **Preconditioned hyperplasticity** — **primed, responsive fine-tuning of the athlete's neuronal connections.**









## Australian Football League (AFL) - Essendon Football Club (EFC) 2012

- EFC approached HyperMED in 2012 to assist recovery for the ‘**mounting list of soft tissue injuries**’.
- During the “**period in question**” challenged by the AFL, ASADA and WADA - the EFC win loss was **9 wins out of 11 consecutive games** whilst players were attending HyperMED. One of the 2- games the Essendon team lost was to the Sydney Swans team, however **Essendon kicked 9-goals and 1-point in the final quarter to lose the game by only 1-point.**
- There were ‘**no reported soft tissues injuries**’ during the “period in question”.
- The use of peptides were established in 2011 prior to attending HyperMED.
- So why were the **players 30% up on their AFL Dream team scores** during the “period in question”?
- **What was the real reason for the improved performance?**
- **Why isn't any Australian media outlet prepared to discuss the role of Hyperbaric Oxygen Therapy in recovery and performance?**
- Why did the Australian Broadcasting Commission (ABC) **4 Corners program** censor my Corporate Counsel's interview which negated the WADA decision that there was : ***“no other evidence to challenge their circumstantial evidence that it must have been peptides causing the early season out performance”.***



## SPORTS

# Tennis Players Get an Oxygen Fix

To aid recovery, tennis pros in Melbourne rent hyperbaric chambers

BY TOM PERROTTA

Melbourne, Australia  
**AFTER HE WON** a four-hour, 32-minute match at the Australian Open on Sunday, Novak Djokovic, the world's best tennis player, showered, spoke to the media, and then hustled over to a quiet late-night spot that's popular among several players: A small clinic two miles from the tournament that has four hyperbaric oxygen pods for rent.

The machines look like deep-sea diving submarines with glass windows and hatches in the back. Inside, players slip on a plastic breathing mask attached to a long tube. Once the hatch seals they're off, compressor and regulator whirring and pressure building until they're basically 40-feet under water and breathing 100% oxygen through the mask (outside air contains just 21% oxygen).

Players have their own masks and tubes and don't share them (that's bad hygiene). They wear blue hospital booties over their socks and must leave behind their phones, watches or anything with a battery that could spark a fire. Outside each pod's front window is a television equipped with Netflix. American Bethanie Mattek-Sands binged on episodes of "Making a Murderer" before leaving Melbourne on Thursday after losing in mixed doubles. Djokovic spent an hour in the pod after his five-setter against Gilles Simon on Sunday, from around 10 p.m. to 11 p.m. He'll use it before matches too, as he did for an hour Tuesday afternoon before playing Kei Nishikori later that evening. Djokovic watched M. Night Shyamalan's "The Last Airbender."

"I either like comedy or, somebody calls it science fiction," he said. "I call it the world we still didn't explore."

The pods are located at HyperMED, a ground-floor clinic nestled between a hair salon and a bakery about a 10-minute drive from the Open. A few hotels popular among players are nearby. Djokovic, known as the most meticulous player on the tour, has used the pods here for several years with the hope of aiding recovery and preventing injury. Mattek-Sands started last year. This



Left, Novak Djokovic uses hyperbaric oxygen therapy to help with recovery. Above, a pod at the HyperMED clinic in Melbourne, Australia.

morning, whatever the requirements are," he said.

Top athletes around the world, including football, basketball and soccer stars, use hyperbaric oxygen therapy. Djokovic said he only uses hyperbaric pods in the U.S. and Australia, because access and regulations are challenging in Europe. He said there is still a stigma about oxygen therapy, that it gives athletes who use it an unfair advantage.

"It's very sensitive, especially in the European part of the world," he said. "I wish I can have this all over the place, I wish."

Mattek-Sands said she would be thrilled if the sport's major tournaments provided pods on site. "It's just kind of the new wave for the future," she said.

Hyperbaric therapy doesn't suit everyone. Andy Murray has tried it and decided it isn't for him, according to a representative. Some question its merits. A paper published last year in *PeerJ*, a peer-reviewed journal, found lower lung cancer incidence among people living at high elevations, which suggests oxygen could be a driver of cancer. Kamen Simeonov, an MD-PhD trainee at the University of Pennsylvania and co-author of the paper, wrote via email, "Basically, it's exposing yourself to risks with no logical reward."

Hooper, who is an affiliate member of the International Hyperbaric Medical Association, said he has seen gains in his patients, and that research suggests hyperbaric treatment can help many ailments. "Ev-

ery athlete has a growing list of injuries that may benefit," he wrote in an email.

Hooper's chiropractic license was suspended for two years in 2013 after a dispute with a former cerebral palsy patient in part over the effectiveness of treatment, though the Chiropractic Board of Australia viewed Hooper's "conduct as an error of judgment rather than a defect in character," and that he was a "true believer in the treatment that was being given." (He said he hasn't practiced as a chiropractor for 20 years and no longer has a need for the license.)

Hooper also was treating Aussie Rules football players in 2013 when they separately came under investigation for the possible use of banned substances. A Court of Arbitration for Sport panel that imposed a two-year ban on 34 players earlier this month made no mention of Hooper in its findings and didn't assign him any fault. Hooper says he tells all his clients about his history. Justin Sands, the husband of Mattek-Sands, said Hooper has been open since they first met.

"He's been nothing but an upstanding, good guy," Sands said.

Sands, who played college football in the U.S., said he used hyperbaric therapy in his playing days. He says he's surprised so few tennis players use it, given the grueling demands of the game. It might even be useful, he said, for the tour's traveling husbands and wives, though for other reasons. "It's great for a hangover," he said.

year, doubles star Mike Bryan became a pod regular. His twin brother, Bob, tried it too, though just once.

"It's great," Djokovic said. "It should get out there more, not just for athletes."

Mike Bryan said: "It just helps recovery. I felt a little better doing it."

Bryan also likes the VacuSport, a long tube with a skirt that seals a player's legs in a vacuum and flushes lactic acid. There is also a cryotherapy chamber, which cools to minus 150 degrees Fahrenheit for a few minutes. HyperMED's website has a picture of Milos Raonic, the Canadian star, standing in its chamber.

Oxygen sessions last anywhere from an hour to two hours and cost 150 Australian dollars (US\$105).

Mattek-Sands said the benefits are subtle but valuable. "It's not like you walk out of there feeling like Superman or anything," she said. "You sleep pretty good that night, I'll say that. You crash and you dream pretty heavy."

The facility is run by Malcolm Hooper, a former chiropractor, who sat in Djokovic's box in Rod Laver Arena Thursday evening as the world No. 1 beat Roger Federer and earned a spot in Sunday's Australian Open final, the sixth of his career. Hooper's clients include people with cerebral palsy, traumatic brain injuries and disabilities, as well as other athletes. During the Open, he opens his clinic day and night depending on players' needs. "Two, three in the

WILLIAM WEST/ALBION IMAGE PRESS/GETTY IMAGES

TOM PERROTTA FOR THE WALL STREET JOURNAL



**November 2016 – “After 4-years of Media Spin”**

**"Neither ASADA nor WADA alleges that any player was given a banned substance at the South Yarra clinic".**

**<http://www.theaustralian.com.au/sport/afl/the-one-question-that-brought-down-jobe-watson/news-story/f13971f9ae1a695f73c1677c52a6785>**

Watson provided further evidence about being given a Thymosin injection when he and other players were receiving hyperbaric treatment at a South Yarra clinic in preparation for the Anzac Day match. The injection he describes was intramuscular, rather than subcutaneous, and was almost certainly Cerebrolysin, a peptide permitted in sport. Neither ASADA nor WADA alleges that any player was given a banned substance at the South Yarra clinic.





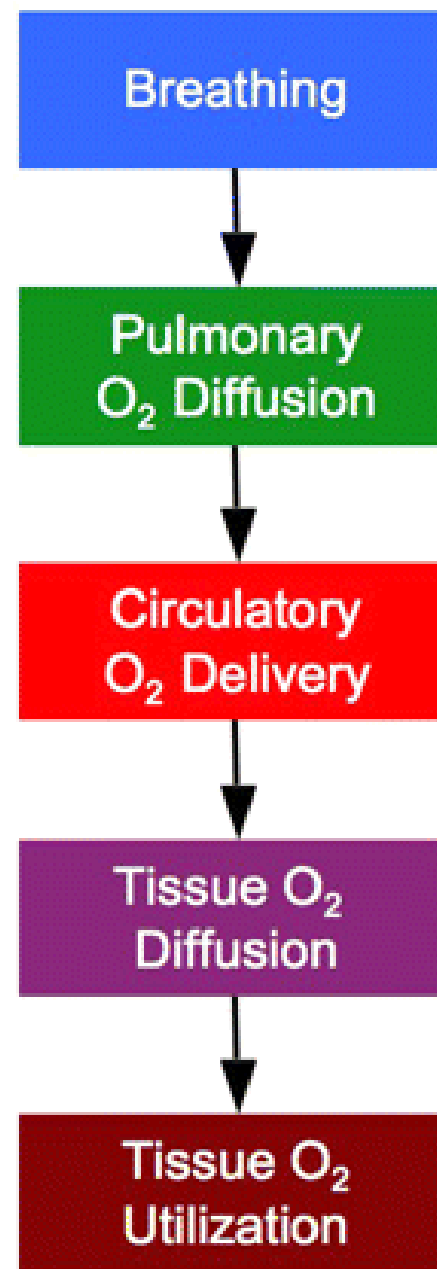
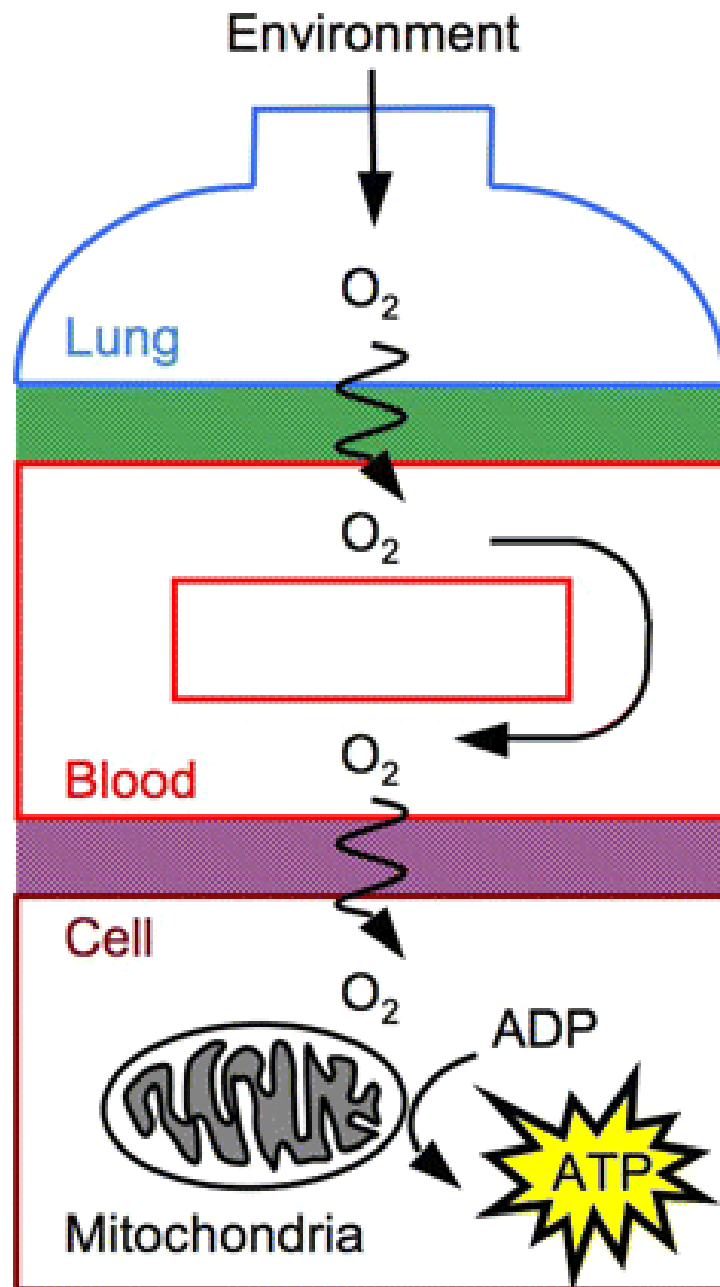
## Commonly 'Advertised' Benefits of HBOT

Source: [www.ihmf.org](http://www.ihmf.org) ....

- Preconditioning against injury
  - Shortens recovery time after extreme exercise, injury or surgery
  - Revitalizes by improving blood flow and oxygen to all organs
  - Regenerates small blood vessels (capillaries), nerves and bones
  - Improved performance
  - Increased strength
  - Enhanced endurance
  - Energy boost preventing exhaustion
  - Reducing inflammation, swelling, pain
  - Reducing fatigue and recovery time
  - Speeding up healing of muscles, ligaments and fractured bones
  - Rejuvenates by releasing stem cells from bone marrow for tissue repair
  - Reducing and preventing infection
  - Reducing scar tissue formation
  - Cleansing blood from toxins and toxic substances
  - Maintaining general health
- 
- **Why do many athletes feel flat or even come down with 'flu like' symptoms after HBOT?**







## The common denominator – ‘Burn Out’

The majority of Elite Athletes are in a constant burn-out and with a **‘growing injury list’**

- High end athletes are confronted with a range of metabolic issues due to fatigue, lactic acid overload, and ... **constant international travel.**
- **Preparation, performance, recovery, travel - preparation, performance, recovery, travel ... an endless loop ...**
- As tissue Oxygenation diminishes the **range of injuries increases dramatically.**
- Tissues exposed to **excessive lactic acid & inflammation** rapidly become **‘energy poor’** – that acts like as **mitochondrial handbrake** - **Your done!**
- It requires more than **replacing your coach** or getting another **mind therapist.** It is more than simply **training harder** or taking another **supplement.**





## Sydney Morning Herald - March 8, 2006 "Lay Down Sally"

Sally Robbins, the Australian rower who dramatically **downed oars in the women's eight at the Athens Olympics**. "There was a lot of contributing factors," said Robbins who had spent 18-months out of the sport. Robbins said **she considered quitting the sport during her hiatus**.





# Athlete Burnout

- A multidimensional, cognitive-affective syndrome characterized by emotional and physical exhaustion, reduced sense of accomplishment, and sport devaluation
- Negative impacts include:
  - Performance decrements,
  - Decreased motivation
  - Potential dropout
  - Troubled social relations that negatively impact team climate
  - Mental (anxiety, depression, eating disorders) and physical (illness susceptibility, substance abuse) health
- Approximately 1% to 10% of athletes suffer from it
- With no consistent diagnostic criteria, that number may be skewed

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- **Multidimensional Cognitive Affective Syndrome** – emotional, physical exhaustion, reduced sense of accomplishment and sport devaluation.
- **Burn-out affects 1-10% of all athletes** (figure probably much higher).
- Negative impact – **social relationship breakdowns; mental anxiety, eating disorders, self abuse, PTSD etc.**



## What happens when you 'Burn-Out' – Cytokine Storm

'Burn-out' is typically an **'over-expression of inflammatory Cytokines'**

### What are Cytokines?

- Cytokines 'orchestrate' & modulate immune response & gene expression.
- Cytokines are **gene signalling proteins and glycoproteins** that 'orchestrate' immunity, inflammation and hematopoiesis.
- Cytokine modulate cell growth and differentiation, cell death (apoptosis), angiogenesis, normal development and neuromodulations.
- They are known as either **pro-inflammatory or anti-inflammatory**.
- Cytokines **"Cross Talk"** - **Cells 'Talk' to other cells** – mediated by pro-inflammatory Cytokines and other glycoproteins including **HIF** other factors including **NFkB, TGFb**



## Symptoms associated with **Cytokine Storm**

- Brain Fog, Fatigue, Fibromyalgia, Weakness, Aches, Muscle Cramps, Unusual Pain, Headache, Light Sensitivity, Red Eyes, Blurred Vision, Recurrent Sinus Problems, Non productive Cough, Shortness of Breath, Abdominal Pain, Diarrhea, Joint Pain, Morning Stiffness, Memory Issues, Focus & Concentration Issues, Word Recollection Issues, Decreased Learning of New Knowledge, Confusion, Disorientation, Skin Sensitivity, Mood Swings, Appetite Swings, Night Sweats, Temperature Dysregulation, Excessive Thirst, Increased Urination, Numbness, Tingling, Vertigo, Metallic Taste, Tremors.





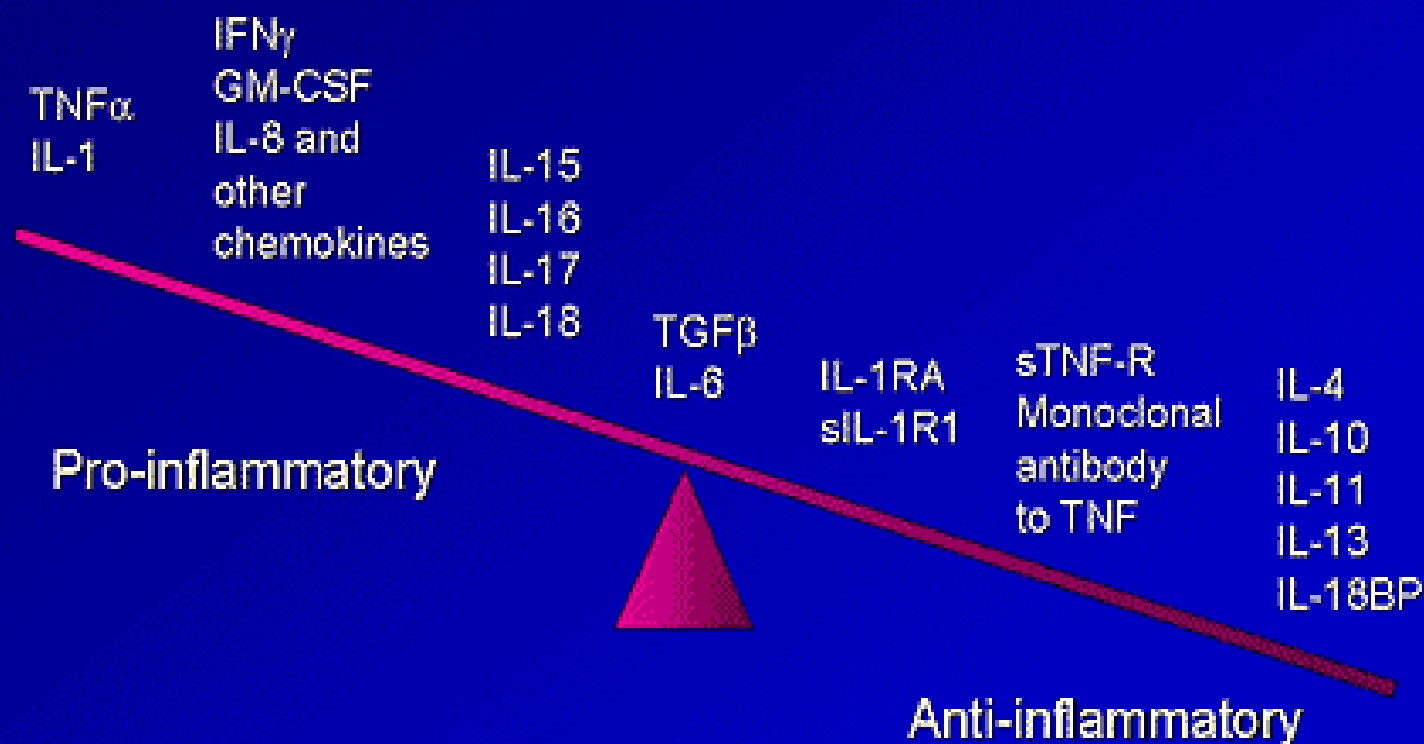








# Role of Cytokines and Cytokine Inhibitors in Chronic Inflammation



*Arend. Arthritis Rheum 2001.*

## But Cytokine Storm Masks the Injury Site

Cytokine Storm makes the entire body looks inflamed, injured and infected



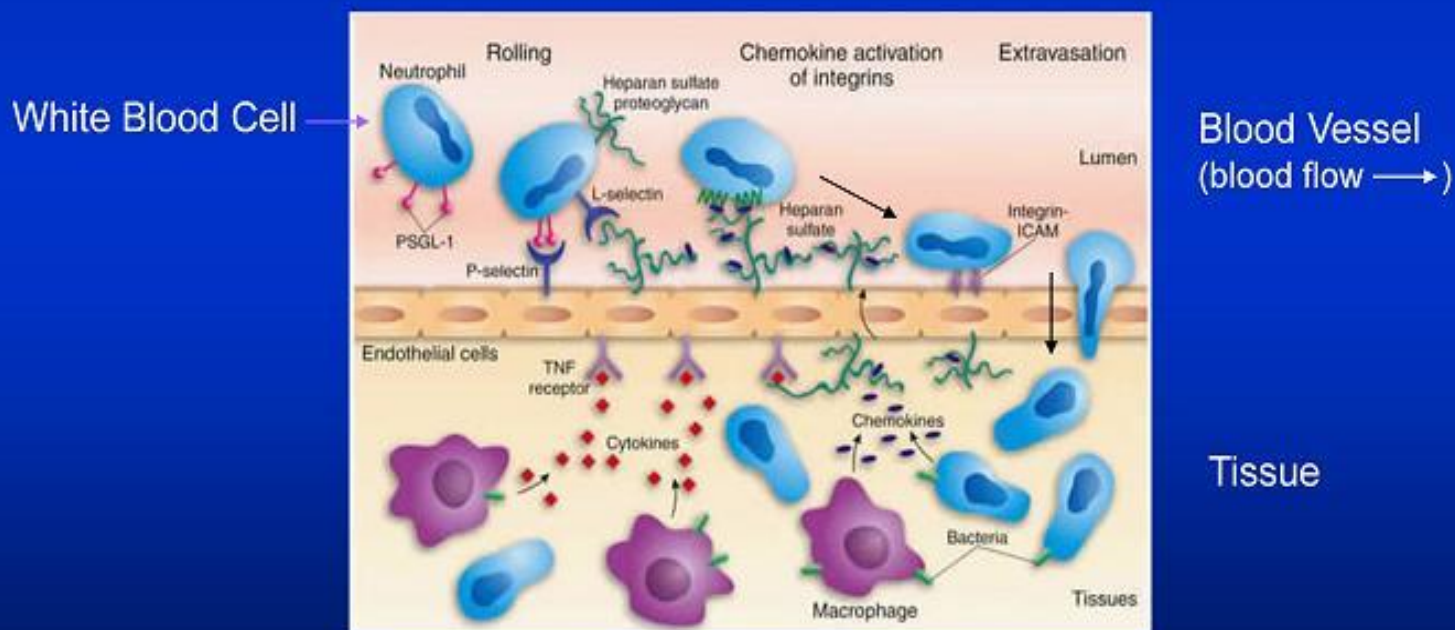
Cytokine  
Storm

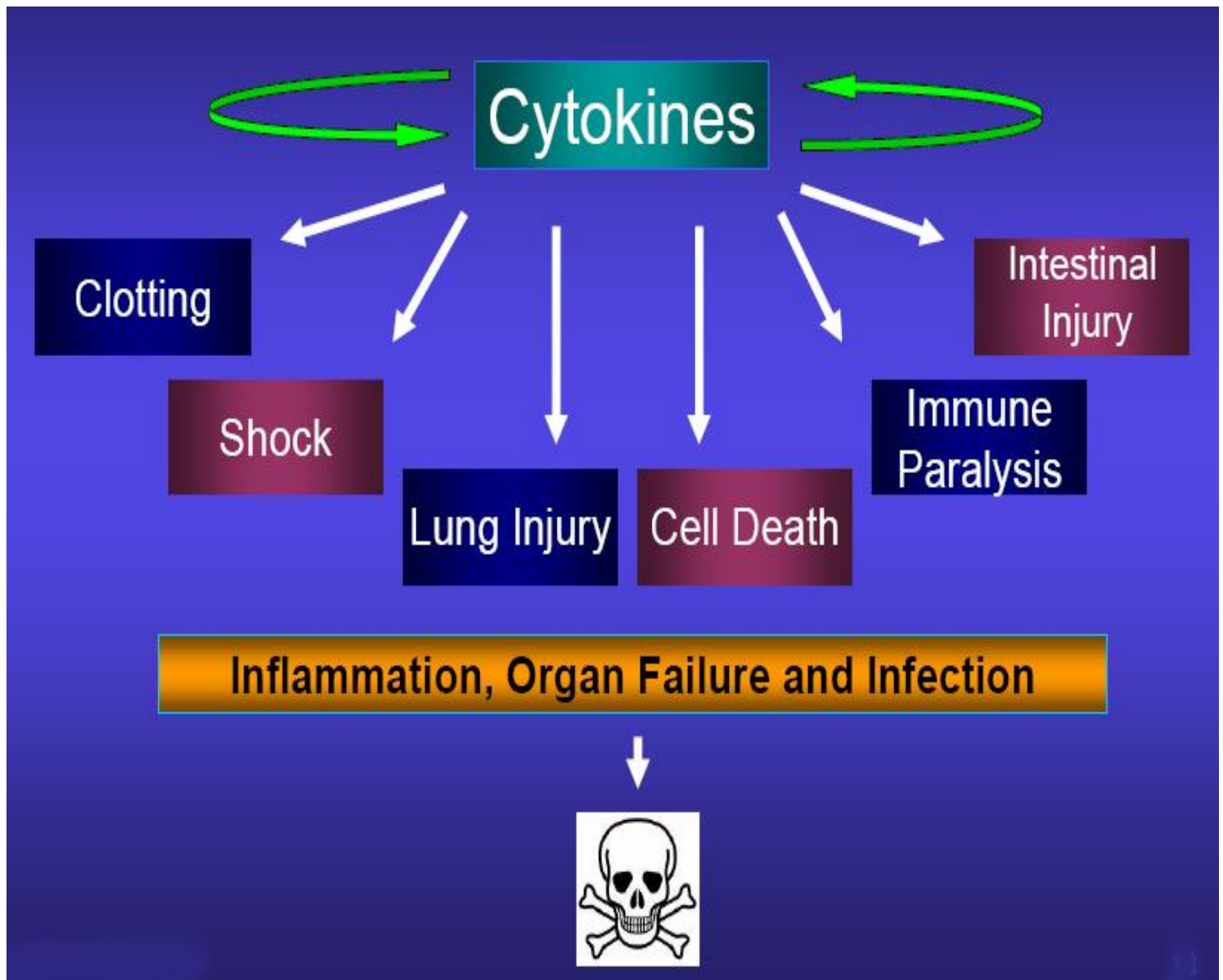




# Cytokine Storm Also Causes “Immune Confusion”

An injury or infection usually leads to the local production of cytokines. Normally, these cytokines allow white blood cells to home in on the infection and migrate from the blood stream into the affected area.







P: 1300 688 522  
E: info@nutripath.com.au  
A: PO Box 442 Ashburton VIC 3142

Date of Birth : 29-Apr-1978  
Sex : M  
Collected : 20-Jan-2016  
C/O HYPERMED 643 CHAPEL STREET  
SOUTH YARRA VIC 3141  
Lab id: **3413608** UR#:

HYPERMED  
643 CHAPEL STREET  
SOUTH YARRA VIC 3141

## INTEGRATIVE MEDICINE

### BLOOD - SERUM

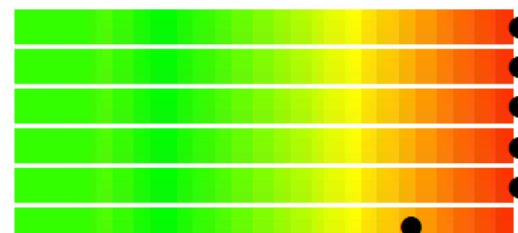
Hyperbaric Oxygen Therapy (HBO)

Result Range Units  
0.0 Hours

### CYTOKINES, Extensive Panel

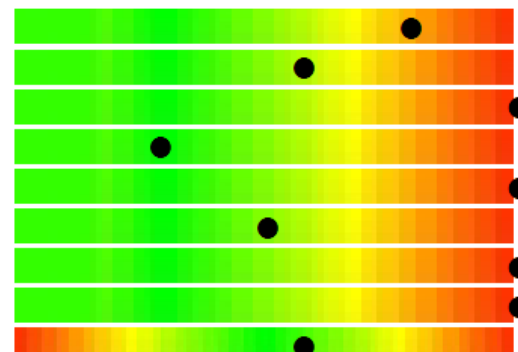
#### ProInflammatory Cytokines (TH1)

Cytokine	Result	Range	Units
Interleukin 1	161.0 *H	0.0 - 2.8	pg/mL
Interleukin 6	35.0 *H	0.0 - 11.0	pg/mL
Interleukin 7	23.3 *H	0.0 - 16.0	pg/mL
Interleukin 8	>2500.0 *H	0.0 - 28.0	pg/mL
TNFa	39.10 *H	0.00 - 13.00	pg/mL
TNFb	149.0	0.0 - 156.0	pg/mL



#### AntiInflammatory Cytokines (TH2)

Cytokine	Result	Range	Units
GM-CSF	77.7	0.0 - 80.0	pg/mL
Interleukin 2	6.8	0.0 - 10.0	pg/mL
Interleukin 4	26.2 *H	0.0 - 19.0	pg/mL
Interleukin 5	1.6	0.0 - 13.0	pg/mL
Interleukin 10	10.1 *H	0.0 - 7.0	pg/mL
Interleukin 12	7.5	0.0 - 14.0	pg/mL
Interleukin 13	13.2 *H	0.0 - 6.0	pg/mL
INFg	75.2 *H	0.0 - 28.0	pg/mL
TGFb	50.6	28.0 - 64.0	pg/mL







P: 1300 688 522  
E: info@nutripath.com.au  
A: PO Box 442 Ashburton VIC 3142

Date of Birth : 29-Apr-1978  
Sex : M  
Collected : 24-Jan-2017  
C/O HYPERMED 643 CHAPEL STREET  
SOUTH YARRA VIC 3141  
Lab id: **3463764** UR#:

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643 CHAPEL STREET  
SOUTH YARRA VIC 3141

## INTEGRATIVE MEDICINE

### BLOOD - SERUM

Hyperbaric Oxygen Therapy (HBO)

CYTOKINES, Extensive Panel

ProInflammatory Cytokines (TH1)

Interleukin 1

**82.2 \*H** 0.0 - 2.8 pg/mL

Interleukin 6

**137.6 \*H** 0.0 - 11.0 pg/mL

Interleukin 7

8.9 0.0 - 16.0 pg/mL

Interleukin 8

<0.6 0.0 - 28.0 pg/mL

Interleukin 17

6.9 < 13.0 pg/mL

TNFa

**46.50 \*H** 0.00 - 13.00 pg/mL

TNFb

91.0 0.0 - 156.0 pg/mL

AntiInflammatory Cytokines (TH2)

GM-CSF

**298.2 \*H** 0.0 - 80.0 pg/mL

Interleukin 2

2.7 0.0 - 10.0 pg/mL

Interleukin 3

**88.4 \*H** < 5.0 pg/mL

Interleukin 4

<3.7 0.0 - 19.0 pg/mL

Interleukin 5

1.8 0.0 - 13.0 pg/mL

Interleukin 10

<3.0 0.0 - 7.0 pg/mL

Interleukin 12

3.1 0.0 - 14.0 pg/mL

Interleukin 13

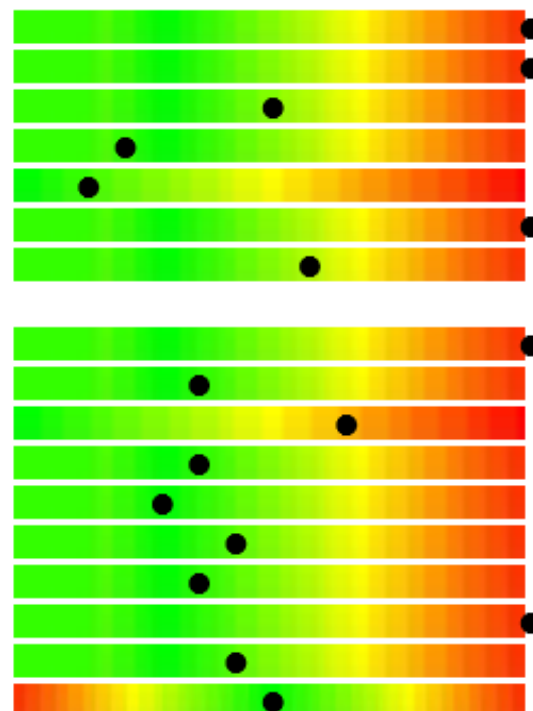
**10.9 \*H** 0.0 - 6.0 pg/mL

INFg

9.2 0.0 - 28.0 pg/mL

TGFb

44.0 28.0 - 64.0 pg/mL





P: 1300 688 522  
E: info@nutripath.com.au  
A: PO Box 442 Ashburton VIC 3142

Date of Birth :  
Sex : M  
Collected : 16-Jan-2017  
643 CHAPEL STREET  
SOUTH YARRA VIC 3141  
Lab id: **3462703** UR#:








OXYMED  
643 CHAPEL STREET  
SOUTH YARRA VIC 3141

## INTEGRATIVE MEDICINE











### BLOOD - SERUM

#### CYTOKINES, Extensive Panel

##### ProInflammatory Cytokines (TH1)

	Result	Range	Units	
Interleukin 1	<b>5.6 *H</b>	0.0 - 2.8	pg/mL	
Interleukin 6	<b>8.9</b>	0.0 - 11.0	pg/mL	
Interleukin 7	<b>21.7 *H</b>	0.0 - 16.0	pg/mL	
Interleukin 8	<b>1701.6 *H</b>	0.0 - 28.0	pg/mL	
Interleukin 17	<b>4.1</b>	< 13.0	pg/mL	
TNFa	<b>10.00</b>	0.00 - 13.00	pg/mL	
TNFb	<b>112.0</b>	0.0 - 156.0	pg/mL	

##### AntiInflammatory Cytokines (TH2)

GM-CSF	<b>101.8 *H</b>	0.0 - 80.0	pg/mL	
Interleukin 2	<b>5.6</b>	0.0 - 10.0	pg/mL	
Interleukin 3	<b>&lt;3.2</b>	< 5.0	pg/mL	
Interleukin 4	<b>4.0</b>	0.0 - 19.0	pg/mL	
Interleukin 5	<b>2.8</b>	0.0 - 13.0	pg/mL	
Interleukin 10	<b>18.5 *H</b>	0.0 - 7.0	pg/mL	
Interleukin 12	<b>4.9</b>	0.0 - 14.0	pg/mL	
Interleukin 13	<b>13.2 *H</b>	0.0 - 6.0	pg/mL	
INFg	<b>15.3</b>	0.0 - 28.0	pg/mL	
TGFb	<b>38.6</b>	28.0 - 64.0	pg/mL	



P: 1300 688 522  
E: info@nutripath.com.au  
A: PO Box 442 Ashburton VIC 3142

Date of Birth :  
Sex : M  
Collected : 11-Jan-2017  
32 ST EDWARDS ROAD  
SOUTH YARRA VIC 3141  
Lab id: **3462097** UR#:

OXYMED  
643 CHAPEL STREET  
SOUTH YARRA VIC 3141

## INTEGRATIVE MEDICINE

### BLOOD - SERUM

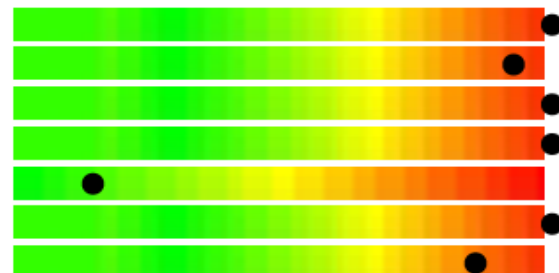
#### Hyperbaric Oxygen Therapy (HBO)

Result **0.0** Range Units  
Hours

#### CYTOKINES, Extensive Panel

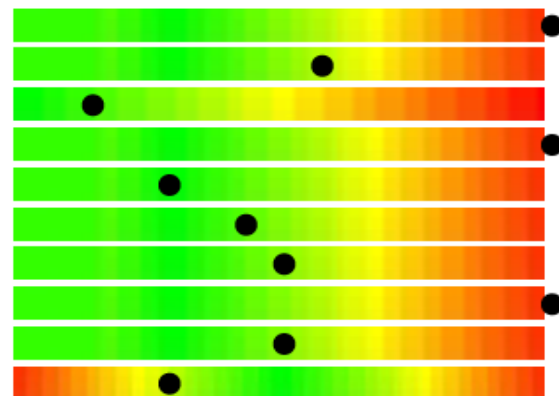
##### Proinflammatory Cytokines (TH1)

Interleukin 1	<b>9.0 *H</b>	0.0 - 2.8	pg/mL
Interleukin 6	<b>13.4 *H</b>	0.0 - 11.0	pg/mL
Interleukin 7	<b>21.1 *H</b>	0.0 - 16.0	pg/mL
Interleukin 8	<b>2177.7 *H</b>	0.0 - 28.0	pg/mL
Interleukin 17	<b>5.6</b>	< 13.0	pg/mL
TNFa	<b>21.00 *H</b>	0.00 - 13.00	pg/mL
TNFb	<b>166.0 *H</b>	0.0 - 156.0	pg/mL



##### Antinflammatory Cytokines (TH2)

GM-CSF	<b>146.3 *H</b>	0.0 - 80.0	pg/mL
Interleukin 2	<b>6.4</b>	0.0 - 10.0	pg/mL
Interleukin 3	<b>&lt;3.2</b>	< 5.0	pg/mL
Interleukin 4	<b>67.0 *H</b>	0.0 - 19.0	pg/mL
Interleukin 5	<b>&lt;1.0</b>	0.0 - 13.0	pg/mL
Interleukin 10	<b>&lt;3.0</b>	0.0 - 7.0	pg/mL
Interleukin 12	<b>6.5</b>	0.0 - 14.0	pg/mL
Interleukin 13	<b>12.8 *H</b>	0.0 - 6.0	pg/mL
INFg	<b>14.6</b>	0.0 - 28.0	pg/mL
TGFb	<b>32.9</b>	28.0 - 64.0	pg/mL





## Salivary IL-8, IL-6 and TNF- $\alpha$ as Potential Diagnostic Biomarkers for Oral Cancer.

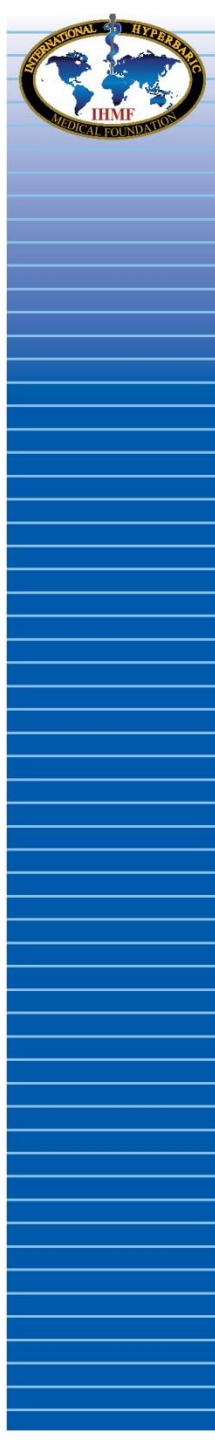
Sahibzada HA<sup>1</sup>, Khurshid Z<sup>2</sup>, Khan RS<sup>3</sup>, Naseem M<sup>4</sup>, Siddique KM<sup>5</sup>, Mali M<sup>6</sup>, Zafar MS<sup>7,8</sup>.

### Abstract

Saliva has been useful as a liquid biopsy for the diagnosis of various oral or systemic diseases, and oral squamous cell carcinoma (OSCC) is no exception.

- **Salivary cytokines expression**, specifically **Interleukin-8 (IL-8), Interleukin-6 (IL-6) and Tumor necrosis factor (TNF- $\alpha$ )**, contribute to the pathogenesis of cancer and these cytokines serve as **potential biomarkers**.
- Their excessive production plays a role in cancer progression and establishment of angiogenesis. However, other inflammatory or immunological conditions may affect the levels of cytokines in saliva.

Apart from serum, the **saliva-based test can be a cost-effective tool** in the follow-up and diagnosis of OSCC. Moreover, large-scale investigations are still needed for the validation of salivary cytokines.

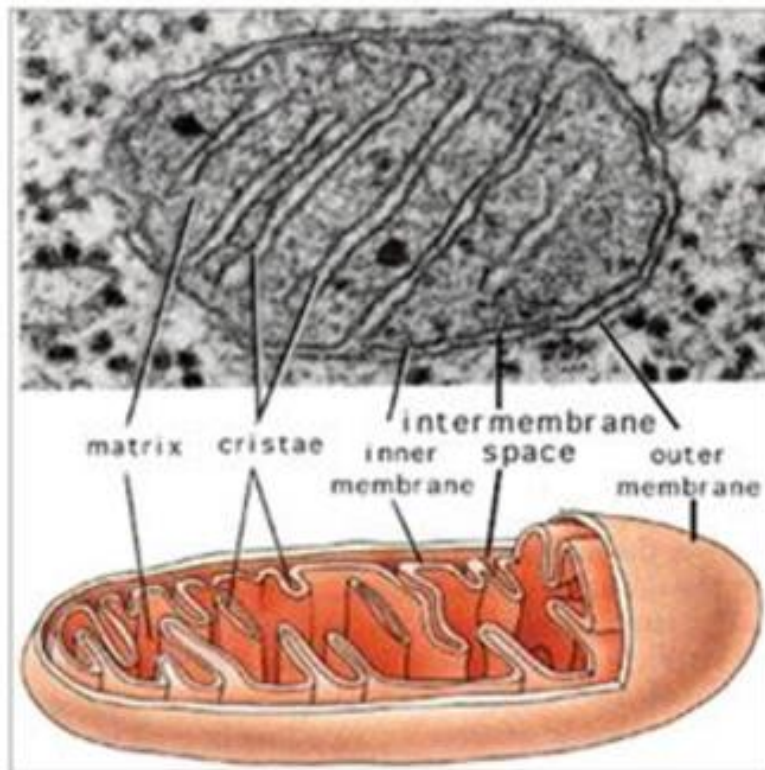


# Cancer as a metabolic disease: implications for novel therapeutics

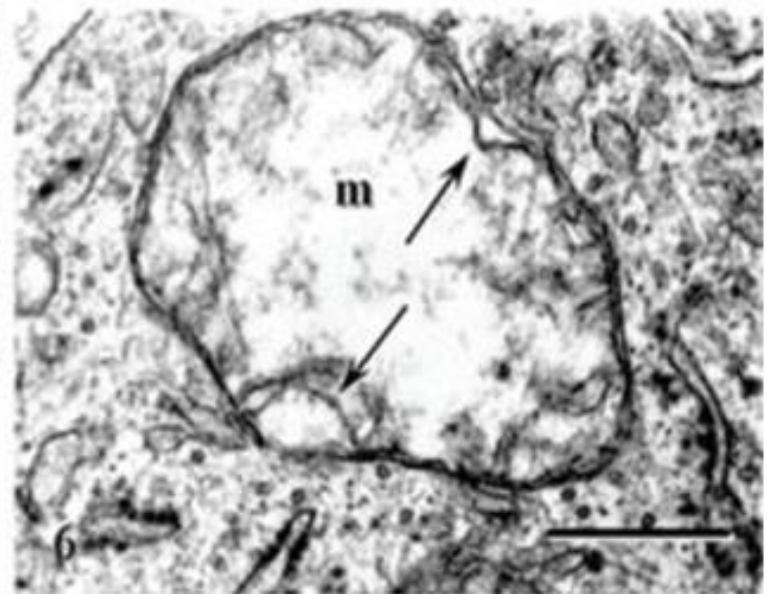
Thomas N. Seyfried , Roberto E. Flores, Angela M. Poff, Dominic P. D'Agostino

*Carcinogenesis*, Volume 35, Issue 3, 1 March 2014, Pages 515–527,

**Normal Mitochondria**



**GBM Mitochondria**







# Mimicking oxygen delivery and waste removal functions of blood.

Zhang H<sup>1</sup>, Barralet JE<sup>2</sup>.

## Oxygen In - Garbage Out - 'Wash-out' (Herxheimer's Effect)

### Abstract

**Blood delivers oxygen to cells and tissues and removes metabolic wastes.**

Oxygen is crucial for the long-term survival of tissues and cells in vertebrates.

- **Metabolic waste accumulation** is another issue in biological systems when blood flow is insufficient. **Metabolic wastes change the microenvironment of cells and tissues, influence the metabolic activities of cells, and ultimately cause cell death.**
- This review examines advances in blood mimicking systems in the field of biomedical engineering in terms of **oxygen delivery and metabolic waste removal.**

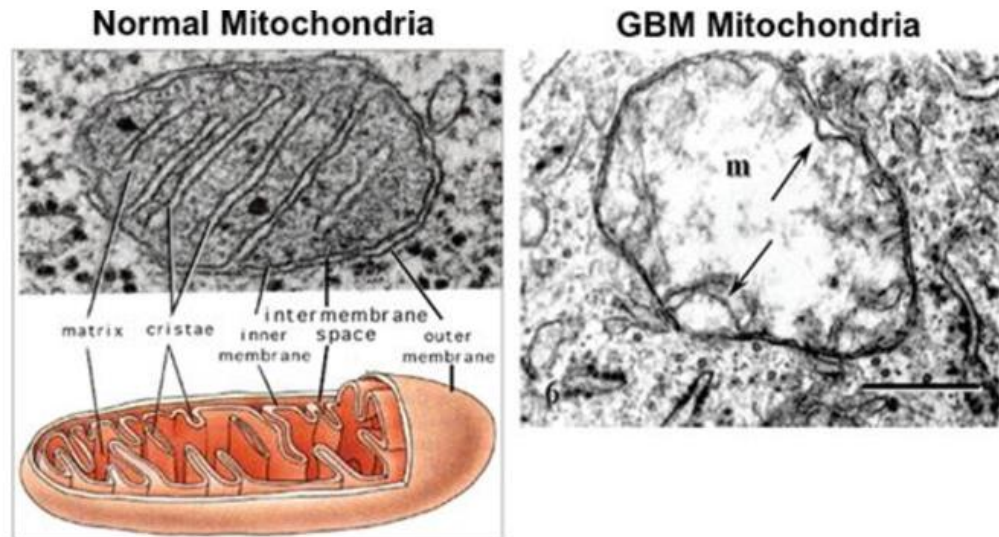
## 'Oxygen In – Garbage Out'

- The cytokine landscape appears to change dramatically with progressive HBOT.
- Depending on the complexity and chronicity, **bio-markers alter significantly and at different stages** of the HBOT modulation.

## Why?

- Does all mitochondrial function respond at the same time?
- Is there a 'progressive unveiling' of metabolic respiratory disturbances?
- How does the mitochondrial correct mutated bioenergetics and dysfunction?
- What is the process of washout of **intra and extra cellular matrix apoptosis** with improved cell respiration?
- Are mitochondria critol restored with **changing & challenging oxygen tension**?

## • HBOT Cyclic Protocols



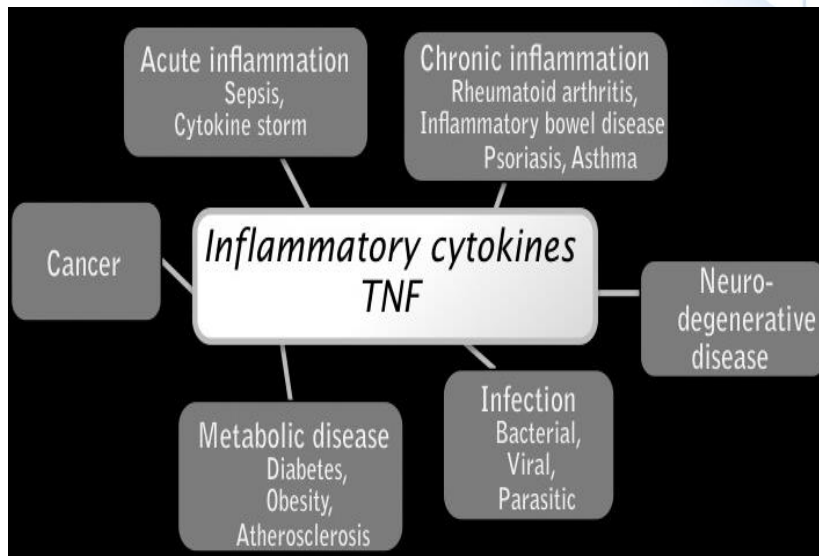






## Tumor Necrosis Factor Alpha

- TNF $\alpha$  is a cytokine produced by white blood cells, released during the **acute inflammatory response**. It plays a pivotal role in **systemic inflammation** as it induces the **synthesis of C-reactive protein**, vasodilatation, and vascular permeability.
- **Master regulator of the human inflammatory response.**
- Linked with autoimmune disorders including **chronic pain, arthritis, tendinitis**.
- **Elevated TNF $\alpha$  in the brain hippocampus results in atrophy** and associated with **traumatic brain injuries, post traumatic stress disorders, concussion syndrome** and conditions **depression, psychosis, addiction and dementia**.
- Reason for many '**retired**' athletes combating depression and other progressive mental health issues.

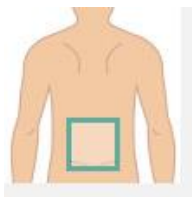
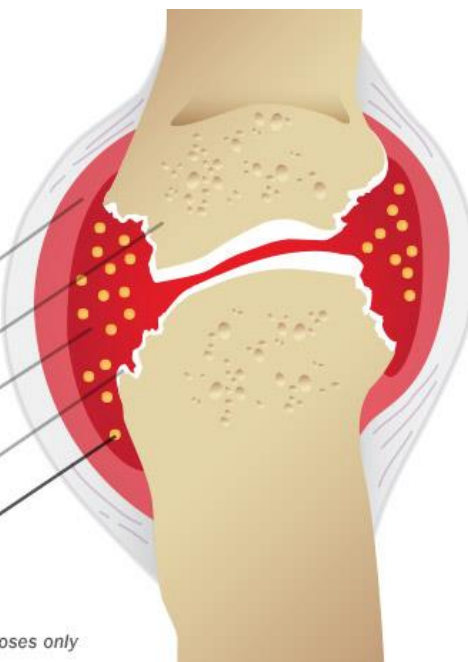






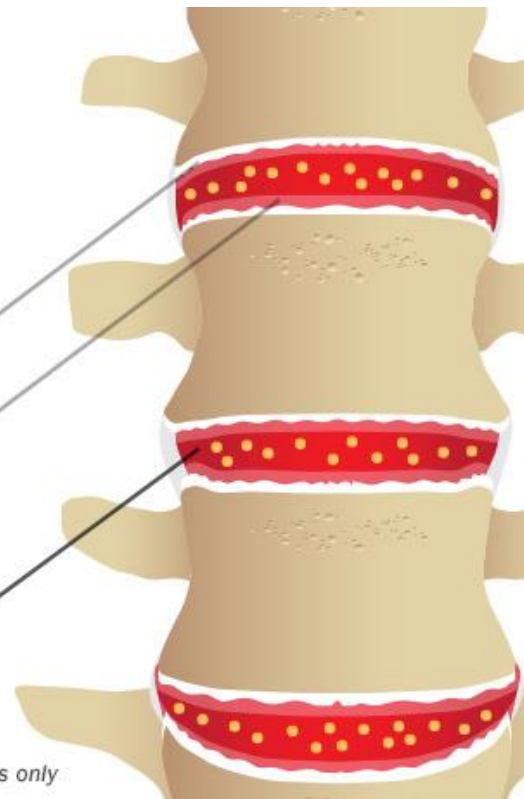
Swollen joint lining  
Bone damage  
Inflamed joint fluid  
Damaged cartilage  
Too much TNF

*For illustrative purposes only*

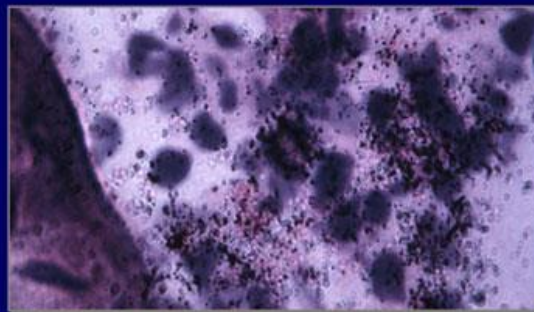


Damaged cartilage  
Inflammation  
Too much TNF

*For illustrative purposes only*



## TNF-alpha mRNA in a Sacroiliac Biopsy





## Autoimmune diseases



Ankylosing spondylitis

Multiple sclerosis

Eczema

Hidradenitis suppurativa



Inflammatory bowel disease

Atopic dermatitis

Rheumatoid arthritis



Psoriasis

Sarcoidosis

Scleroderma

Systemic lupus erythematosus

## Cardiovascular diseases



Atherosclerosis

Myocardial infarction



## Neurologic diseases

Alzheimer's disease

Epilepsy

Bipolar disorder

Parkinson's disease

Depression



## Osteoporosis



## Cancer

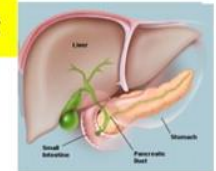


## Non-alcoholic fatty liver disease

## Metabolic diseases

Obesity

Diabetes, type 2

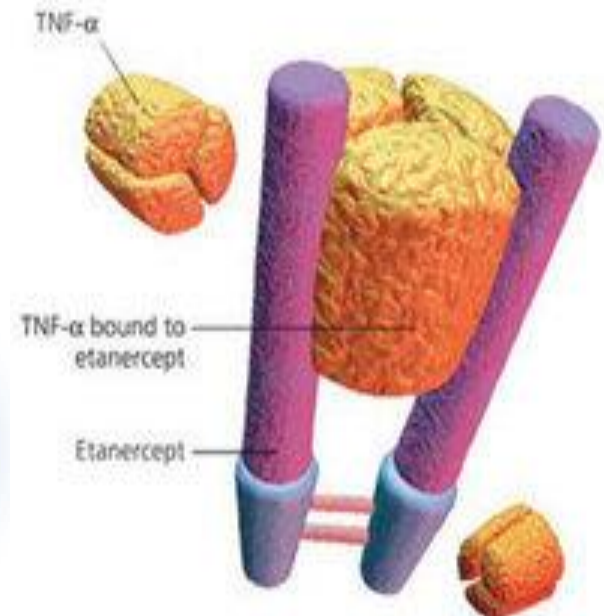
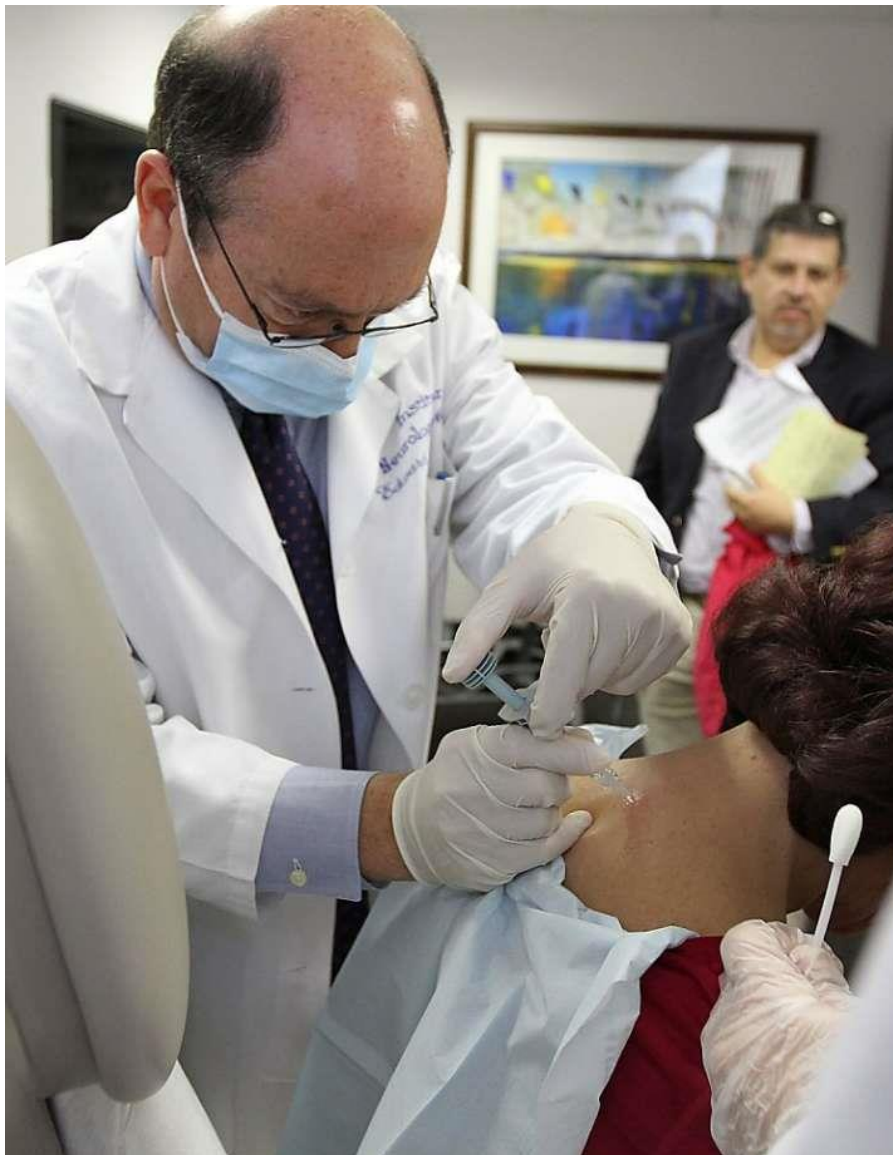


## Pulmonary diseases

Asthma

Chronic obstructive pulmonary disease







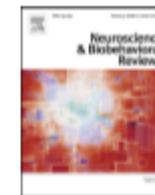


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# Neuroscience and Biobehavioral Reviews

journal homepage: [www.elsevier.com/locate/neubiorev](http://www.elsevier.com/locate/neubiorev)



## Review

## The hippocampus and TNF: Common links between chronic pain and depression



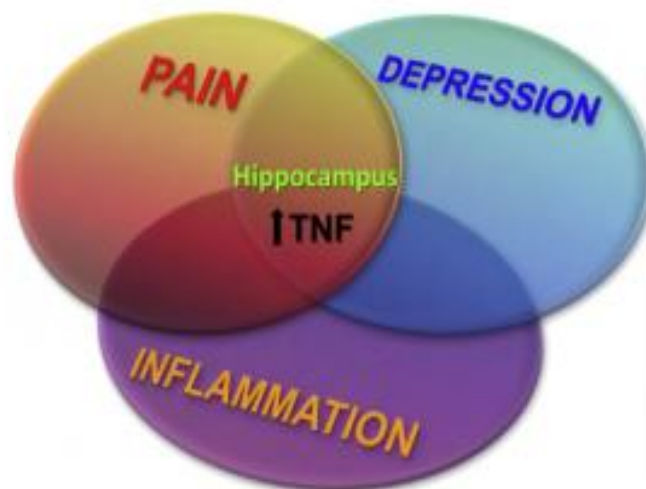
Victoria Fasick<sup>a</sup>, Robert N. Spengler<sup>b</sup>, Shabnam Samankan<sup>a</sup>, Nader D. Nader<sup>a,c</sup>, Tracey A. Ignatowski<sup>a,b,d,\*</sup>

<sup>a</sup> Department of Pathology and Anatomical Sciences, School of Medicine and Biomedical Sciences, University at Buffalo, The State University of New York, Buffalo, NY 14214, United States

<sup>b</sup> NanoAxis, LLC, Clarence, NY 14031, United States

<sup>c</sup> Department of Anesthesiology, School of Medicine and Biomedical Sciences, University at Buffalo, The State University of New York, Buffalo, NY 14214, United States

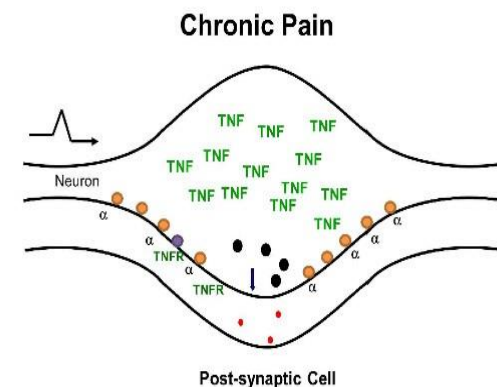
<sup>d</sup> Program for Neuroscience, School of Medicine and Biomedical Science, University at Buffalo, The State University of New York, Buffalo, NY 14214, United States





## Abstract

- This review discusses the interaction between **depression and chronic pain**, emphasizing the fundamental **role of the hippocampus** in the development and maintenance of both disorders. Reduced CBF to the hippocampus results in TNF $\alpha$  overexpression coupled with other proinflammatory chemokines.
- **Hippocampus expressed TNF $\alpha$**  serves as a therapeutic target for management of chronic pain and major depressive disorder.
- A novel method of reducing TNF - **increasing BDNF levels**
- In animal subjected to **chronic stress and pain** demonstrated **elevated TNF $\alpha$  associated with decreased BDNF expression in the hippocampus.**
- Administration **BDNF synthesis exerts antidepressant and analgesic effects on chronic pain** via induction of BDNF in the brain.
- Increasing BDNF may be a novel treatment strategy for **chronic pain associated with depression.**
- HBOT down regulates TNF and upregulates BDNF.

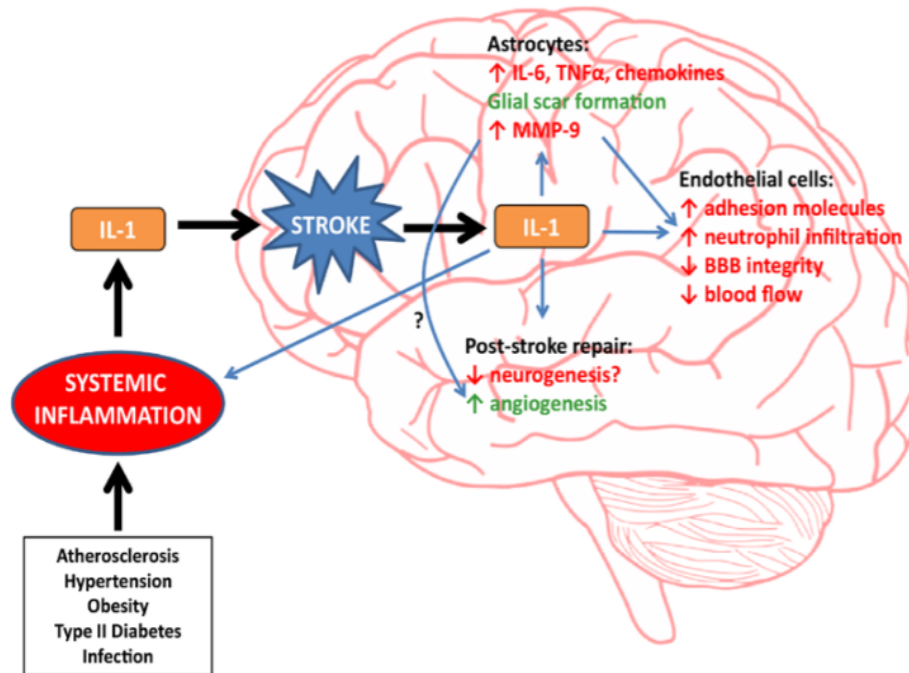


## Inflammatory mechanisms in ischemic stroke: therapeutic approaches

### Interleukin 1

- IL1 elevation is linked with **reduction in cerebral blood flow** and increase in **infarct volume**.
- **Blockade of endothelin-1 receptors** reversed this **hypoperfusion, reduced tissue damage, and improved functional outcome**.
- IL1 linked with **systemic inflammation including the gut and brain**.
- Increasing number of athletes suffering **chronic irritable bowel syndrome (IBS)** corresponding with **IL1 overexpression**.
- Increased in **synovial joint fluids** detected in **rheumatoid arthritis**.
- Increased in plasma and CSF levels of patients with **schizophrenia**.
- Significantly elevated **bladder cancer**.
- Induced by other cytokines, endotoxins, and viruses, and antigens.
- Elevated serum or blood levels of IL-1 $\alpha$  have been found in of several carcinomas such as **head and neck cancer, pancreatic cancer and thyroid cancer**, in experimental acute pyelonephritis, in acute viral hepatitis and in septic shock.
- **Acts anti-proliferatively on many tumor cell types, increases the tumor cytotoxicity of macrophages and induces tumor regression**.

## Inflammatory mechanisms in ischemic stroke: therapeutic approaches



**Figure.** Mechanisms of interleukin-1 (IL-1) action in stroke. Stroke-related comorbidities and risk factors are associated with a raised systemic inflammatory profile, mediated in part by IL-1. Post-stroke increases in IL-1 in the brain mediate detrimental (indicated in red) inflammatory processes in the acute phase that contribute to worse outcome. In the subacute and chronic phase after stroke, certain actions of IL-1 may be beneficial (indicated in green). Figure provided and used with permission courtesy of Christopher Hoyle, University of Manchester, United Kingdom. MMP indicates matrix metalloproteinases; and TNF, tumor necrosis factor.

Downloaded from <http://stroke.ahajournals.org/> at University of Manchester (man) / England on June 16, 2016

- Post Stroke IL1 mediates inflammatory effects (in red) – negative cascade - including increased adhesion molecules, neutrophil infiltration, reduced BBB integrity, decreased blood flow.
- Elevated IL1 on astrocytes reveal increased IL6, TNFα and other chemokines.
- Elevated IL1 inhibits stroke repair – reduced neurogenesis.



## INTERLEUKIN 6 MEDIATES NEUROINFLAMMATION AND MOTOR COORDINATION DEFICITS AFTER MILD TRAUMATIC BRAIN INJURY AND BRIEF HYPOXIA IN MICE

Published online 2014 Oct 13. doi: [10.1016/j.ygeno.2014.10.003](https://doi.org/10.1016/j.ygeno.2014.10.003)

### Whole Blood Gene Expression and Interleukin-6 Levels

- IL6 increase up to a **1,000-fold during trauma and infection.**
- Associated with the **progression of atherosclerosis.**
- Elevated IL6 in midlife **predicts cognitive decline.**
- **Disc herniation and chronic lumbar radicular pain** - IL6 and IL8.
- IL6 is a **growth and survival factor** in **human glioblastoma cells** and plays an important **role in malignant progression.**
- Increased levels associated with **elevated cancer risk.**
- Increased levels in **coronary heart disease, insulin resistant patients, advance stage cancer patients, atopy/asthma** and in patients with blood circulating **micrometastasis.**

# Interleukin-7: from bench to clinic

Terry J. Fry and Crystal L. Mackall

Blood 2002 99:3892-3904; doi: <https://doi.org/10.1182/blood.V99.11.3892>

## Interleukin-7 (IL-7) and IL-7 receptor (IL-7R) signalling complex in human solid tumours

M.A.A. Al-Rawi, R.E. Mansel and W.G. Jiang

Metastasis Research Group, University Department of Surgery, University of Wales College of Medicine, Heath Park, Cardiff, UK

### Interleukin 7

- **Hematopoietic growth factor** secreted by red marrow and thymus.
- Stimulates the differentiation of **multipotent (pluripotent) hematopoietic stem cells**.
- Elevated levels detected in the plasma of **HIV-infected patients**.
- Elevated IL7 **promotes tumour development and progression**.
- Linked with **malignancies** (acute lymphoblastic leukemia).
- **Proliferative and trophic cytokine** that induces the development and proliferation of **haematopoietic cells and malignancies**.
- The production of IL7 linked in the **process of tumourgenesis upregulated in several solid tumours including breast, lung, prostate, renal, ovarian, melanomas as well as head and neck tumours**.



## Chemokine Interleukin-8 (IL-8) in Alzheimer's and Other Neurodegenerative Diseases

- IL8 linked with neuroinflammation associated with **activated microglia** resulting in neurotoxicity in the inflamed brain.
- IL8 are significantly elevated in **neurodegenerative disease**.
- Activated microglia increased levels of IL8 which contribute to a **positive feedback process amplifying and sustaining inflammatory reactivity in Alzheimer's Disease brain**.
- **Chronic microglial activation** is associated with sustained cellular production of a **milieu of inflammatory mediators** including pro-inflammatory cytokines including IL8, reactive oxygen species and matrix metalloproteinases which cause **abnormalities to blood vessels and neurotoxicity**.



# Interleukin 8 and cardiovascular disease

Stavros Apostolakis, Konstantina Vogiatzi, Virginia Amanatidou,  
[Demetrios A. Spandidos](#) 

*Cardiovascular Research*, Volume 84, Issue 3, 1 December 2009, Pages 353–360,

- IL8 was first characterized in 1987.
- Identified with **systemic inflammation of the blood** and involved in **cerebrovascular disorders and cardiovascular disease**.
- IL8 and other chemokines are produced in several tissues upon infection, inflammation, ischemia, trauma etc - main cause of local **neutrophil accumulation**.
- **Gross overproduction of IL8 from Endothelial cells** in presence of **hypoxia**.
- Chronic systemic inflammation including: **Progressive vascular disease, atherosclerosis lesions, main source for atherosclerosis plagues, predictive biomarker for ischemia induced oxidative stress**.
- Pathogenesis of **hypertension**.
- Progression of **ischemic induced necrosis**.
- IL8 reported in **ventricular fibrillation** complicating myocardial infarction.
- IL8 is a **powerful independent predictive factor for cardiovascular and overall mortality** in patients with end stage renal disease.
- Biomarker of outcome following **cardiopulmonary arrest**.

# Hyperbaric Oxygen: Does it promote growth or recurrence of malignancy?

J. FELDMEIER<sup>1</sup>, U. CARL<sup>2</sup>, K. HARTMANN<sup>3</sup>, P. SMINIA<sup>4</sup>.

<sup>1</sup>Radiation Oncology Department, Medical College of Ohio, Toledo, OH, USA; <sup>2</sup>Department of Radiation Oncology and Nuclear Medicine, Diakoniekrankenhaus Rotenberg, Germany; <sup>3</sup>Department of Radiation Oncology, Heinrich Heine University, Duesseldorf, Germany; <sup>4</sup>Department of Radiation Oncology, VU University Medical Center, The Netherlands

iii. Interleukin-8 release is increased by hypoxia<sup>68</sup> This has been demonstrated in human glioblastoma cells in culture. IL-8 has been shown to have angiogenic properties in this model. The work of Shi and associates<sup>69</sup> confirms an increase in IL-8 by hypoxia and acidosis and suggest this contributes significantly to the aggressive biology of pancreatic cancer.

- **Hypoxia, IL8 and acidity contributes significantly to the aggressive biology of pancreatic cancer growth (UHMS 2003)**

Vaccines (Basel). 2016 Jun 24;4(3). pii: E22. doi: 10.3390/vaccines4030022.

## The IL-8/IL-8R Axis: A Double Agent in Tumor Immune Resistance.

David JM<sup>1</sup>, Dominguez C<sup>2</sup>, Hamilton DH<sup>3</sup>, Palena C<sup>4</sup>.

- **Tumorigenesis analysis further proved that tumor tissues from patients with higher serum IL-8 levels grew faster than those with lower IL-8 levels.**

## The interleukin-8 pathway in cancer.

Waugh DJ<sup>1</sup>, Wilson C.

- IL8 is a **signalling factor** produced by **Endothelial cells** and **macrophages**.
- IL8 elevated in **tumor cells** - often induced in response to **chemotherapeutic interventions or environmental stresses such as hypoxia**.
- IL8 signalling **increases proliferation and survival** of endothelial and cancer cells, and **potentiates the migration of cancer cells, endothelial cells, and infiltrating neutrophils at the tumor site**.
- Overexpression in **hypoxic cells** suppresses **mitochondrial metabolism**.
- **Hypoxia induced IL8** causes **HIF-1 $\alpha$ , HIF-2 $\alpha$  overexpression** induces pro-metastatic cells generation of involved mitochondria leading **formation of highly metastatic cells**.
- Accordingly, IL8 expression correlates with the **angiogenesis, tumorigenicity, and metastasis of tumors** in numerous clinical models.



## IL17A interleukin 17A [ *Homo sapiens* (human) ]

Gene ID: 3605, updated on 13-Aug-2017

- The protein encoded by this gene is a **proinflammatory cytokine** produced by activated T cells. This cytokine can **stimulate the expression of IL6 and cyclooxygenase-2** (PTGS2/COX-2), as well as enhance the production of **nitric oxide** (NO).
- High levels of this cytokine are associated with **several chronic inflammatory diseases** including **rheumatoid arthritis, psoriasis and multiple sclerosis**.
- IL17 is an inflammatory infiltrate in **early tendinopathy** and increased levels of IL17 coupled with proinflammatory cytokines **TNF- $\alpha$ , IL-6** in **torn supraspinatus**.

SCIENTIFIC REPORTS

OPEN

IL-17A mediates inflammatory and tissue remodelling events in early human tendinopathy

## Autophagy suppresses host adaptive immune responses toward *Borrelia burgdorferi*.

Buffen K<sup>1</sup>, Oosting M<sup>1</sup>, Li Y<sup>2</sup>, Kanneganti TD<sup>3</sup>, Netea MG<sup>1</sup>, Joosten LA<sup>4</sup>.

- Mice that were **intra-articular injected** with **Borrelia spirochetes** displayed **increased joint swelling, cell influx, and enhanced IL1, IL6 and IL17 production by inflamed synovial tissue.**
- High levels of IL17 have been found in patients with **confirmed, severe, chronic borreliosis.** We propose that the modulation of IL17 may be a **potential target for anti-inflammatory therapy** in patients with persistent Lyme disease.



*Curr Rheumatol Rep.* 2016 Jun;18(6):33. doi: 10.1007/s11926-016-0585-9.

## **The Bench-to-Bedside Story of IL-17 and the Therapeutic Efficacy of its Targeting in Spondyloarthritis.**

*J Neuroimmunol.* 2015 Aug 15;285:125-8. doi: 10.1016/j.jneuroim.2015.05.022. Epub 2015 Jun 12.

### **Effect of high dose vitamin D intake on interleukin-17 levels in multiple sclerosis: a randomized, double-blind, placebo-controlled clinical trial.**

- Vitamin D has immunomodulatory effects in multiple sclerosis (MS).
- **Interleukin-17 (IL17) is a critical interleukin in inflammatory response in MS.**
- This study assessed the effect of **oral high dose vitamin D intake on IL17** levels in MS patients in a double blind randomized clinical trial.
- 94 patients with a diagnosis of **relapsing remitting multiple sclerosis (RRMS)** were randomized to two groups.
- One group received **50,000 IU vitamin D3** every five days for 12 weeks. The other group was given placebo. **Serum levels of IL-17 were measured at the beginning of the study and after 12weeks.**
- IL17 levels showed **significant reduction change in RRMS** patients after receiving **high dose vitamin D3 for 12weeks.**



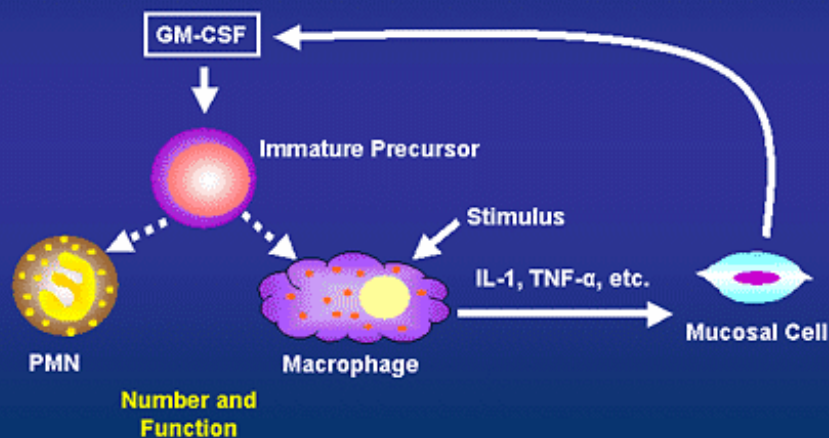


## Anti-Inflammatory Cytokines

### Granulocyte Macrophage Colony Stimulating Factor (GM-CSF)

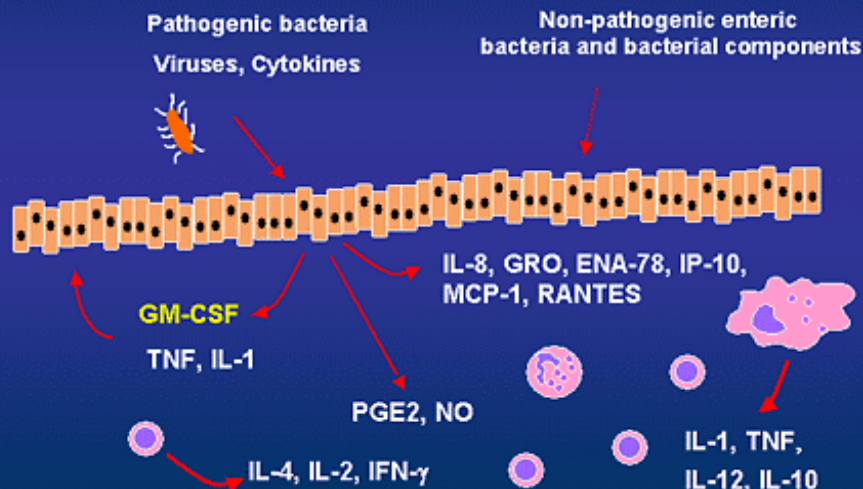
- Glycoprotein **growth factors**.
- **Stimulates blood stem cells** to produce more **white blood cells** (neutrophils, eosinophils, basophils, and monocytes) to **reduce the risk of infection** notably after **types of cancer treatment**.
- GM-CSF stimulates **bone marrow** and make **stem cells move from the bone marrow into the blood**.
- GM-CSF also stimulates **“regulatory T (Treg) cells”**
- Regulatory T (Treg) cells **maintain order in the immune system**. T-cells are a type of white blood cell that circulate around our bodies, **scanning for cellular abnormalities and infections**.
- Treg cells are particularly important for **calming down effector T cells** (or T-eff cells). **If there are too many T-eff cells, there is increased chances of autoimmunity** – or the **immune system attacking healthy cells**.
- During the proinflammatory destructive phase of activated microglia - **GM-CSF induction of Treg cells modulates the activated microglia** calming them down, **returning them to a resting state** and the healthy surrounding neurons survive intact.

## GM-CSF Is a Central Regulator of Innate Immunity



Hamilton J. *Trends in Immunology* 2002;23:403-408.

## GM-CSF Is a Central Regulator of Innate Immunity



Siegmund B, Zeitz M *Annales Academiae Medicae Bialostocensis* 2004;49:22-30.





## Therapeutic strategy of BMC transplantation and GM-CSF.

Stem Cells 2007;25:2066 –2073

- GMCSF (Sargramostim -SGS) stimulates and mobilizes the **bone marrow stem cells**.
- GMCSF (SGS) can have intrinsic spinal cord repair mechanisms including **neuroprotection from apoptosis, endogenous stem cell activation, inhibition of glial scar formation, and microglial cell activation**.
- GMCSF (SGS) **decreased neuronal apoptosis and improved the functional outcome** in SCI animal models.
- GMCSF (SGS) stimulates microglial cells to **increase brain-derived neurotrophic factor** (BDNF) synthesis.
- The total number of recruited white blood cells in the peripheral blood was elevated after GMCSF (SGS) administration.
- The number of white blood cells in patients showing **improved neurologic function was significantly higher** than that in the patients without neurologic improvement.
- Following GMCSF (SGS) - Spinal MRI Findings - **42.9% of patients in the GMCSF treated group showed an increase in the diameter of the spinal cord** at the cell transplantation site. **Six patients (28.6%) showed evidence of spinal cord enhancement**.



# Granulocyte colony stimulating factor attenuates inflammation in a mouse model of amyotrophic lateral sclerosis

Eveliina Pollari, Ekaterina Savchenko, Merja Jaronen, Katja Kanninen, Tarja Malm, Sara Wojciechowski, Toni Ahtoniemi, Gundars Goldsteins, Raisa Giniatullina, Rashid Giniatullin, Jari Koistinaho and Johanna Magga ✉

*Journal of Neuroinflammation* 2011 8:74 | <https://doi.org/10.1186/1742-2094-8-74>

- GM-CSF reduced pro-inflammatory cytokines, **reduced inflammation in the CNS** in mouse **ALS model** and **delayed progression of MND**.
- Increased **neutrophil and stem cell counts** in the peripheral blood.
- Decreased induced TNFa release in **primary microglia cells**.
- Decreased TNFa in **bone marrow** monocytes.
- **Bone Marrow and Spleen Nitrous Oxide** release increased.
- Increase **hematopoietic cell populations**.
- Increased the number of total **splenocytes**.
- Reduces CNS inflammation with **enhanced neuronal function**.
- TNFa increases **30-fold in spinal cord injury** associated with **astro and microgliosis** indicating significant inflammation. GM-CSF **reduces TNFa production** accompanied by modest elevation of NO.
- Induced BM stem cells capacity to '**home and migrate**' to sites of **hypoxic inflammation** ie **spinal cord, damaged cardiac cells, peripheral nerves/muscles** reducing the inflammatory cascade and promoting regenerative responses.

REVIEW ARTICLE

**Interleukin-4: A Prototypic Immunoregulatory Lymphokine**

## Interleukin 3

- IL3 is a Th2 anti-inflammatory cytokine - multiple hematopoietic growth factor, which **enhances stem cell expansion and hematopoiesis regeneration.**

## Interleukin 4

- IL4 is an Th2 anti-inflammatory cytokine, **acting synergistic with IL10 and IL13** responsible for cell **growth factor that stimulates the growth** and survivability of certain B cells and T cells.
- IL4 **inhibits the production of pro-inflammatory cytokines** including **TNF, IL1, and IL6.**
- IL4 is an **immune-stimulating** molecule. As such it is one of the more recent targets being studied for new **asthma** treatments.
- IL4 has striking **antitumor activities** - may have **potent biologic agents to enhance immune elimination of certain tumor cells.**
- Ameliorates **non-resolving neuro-inflammation** that causes **neuropathic pain** after nerve injury (crush injury).

## Interleukin-10 Therapy—Review of a New Approach

- Potent anti-inflammatory TH2 cytokine that has a critical role in **limiting the immune response to pathogens** to prevent host damage.
- Strong inhibitor of inflammation.
- Elevated levels in **parasitic infection**, high expression levels of IL10 are also found in **retroviral infections inducing immunodeficiency**.
- The **immunosuppressive properties of IL10** suggest a possible clinical use in suppressing rejections of grafts after **organ transplantations**.
- Patients with **Crohn's disease** react favourably to treatment with bacteria producing recombinant IL10.
- Pre conditioning elevation of IL10 induces a **resistance of the brain cells to ischemia-evoked damages**.
- This protective effect in cultured hippocampal cells is developed rapidly after application of IL10, capable to exert the **rapid neuroprotective effects** through transcription-independent modulation of ischemia-induced intracellular  $\text{Ca}^{2+}$  responses in the brain cells.
- IL10 upregulates **BDNF production**.



## Interleukin 13

- IL13 is a cytokine found to **powerfully inhibits proinflammatory cytokines**.
- Elevated IL13 levels in the CSF are reported to have **neuroprotective effects in** multiple **neurodegenerative disorders** including **Multiple Sclerosis**.
- IL13 enhances **neuronal integrity and synaptic function** in patients neurodegenerative disorders including MS.
- IL13 specifically **induces physiological changes in parasitized organs** that are required to **expel the offending organisms or their products**. For example, **expulsion from the gut** of a variety of mouse helminths requires IL13.
- IL-13 induces several changes in the gut that **create an environment hostile to the parasite**, including enhanced contractions and glycoprotein hypersecretion from gut epithelial cells, that ultimately lead to **detachment of the organism from the gut wall and their removal**.

### Reoxygenation of Hypoxic Glioblastoma Multiforme Cells Potentiates the Killing Effect of an Interleukin-13-Based Cytotoxin

Tie Fu Liu,<sup>1,2</sup> Jiaozhong Cai,<sup>2</sup> Denise M. Gilbo,<sup>1</sup> and Waldemar Debinski<sup>1</sup>

- IL13 has **anti-tumour effects** and when **combined with HBO** enhances the killing effects of **Glioblastoma and other cancers**.
- **Interleukin-13 receptor-targeted cytotoxin (IL13-PE38)** is highly cytotoxic to **human glioblastoma (GBM)** cells.



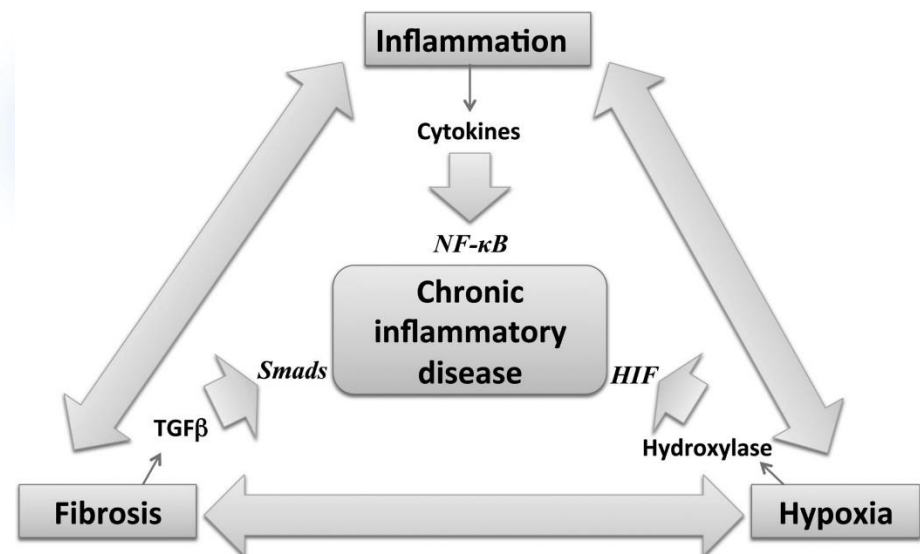
## Inflammatory bowel disease, colorectal cancer and type 2 diabetes mellitus: The links

Abdo Jurjus <sup>a,b</sup>, Assad Eid <sup>a</sup>, Sahar Al Kattar <sup>a</sup>, Marie Noel Zeenny <sup>a</sup>, Alice Gerges-Geagea <sup>b</sup>, Hanine Haydar <sup>a</sup>, Anis Hilal <sup>a</sup>, Doreid Oueidat <sup>a</sup>, Michel Matar <sup>b</sup>, Jihane Tawilah <sup>b</sup>, Inaya Hajj Hussein <sup>c</sup>,

Pierre Schembri-Wismayer <sup>d</sup>, Francesco Cappello <sup>e</sup>, Giovanni Tomasello <sup>e</sup>, Angelo Leone <sup>e</sup>, Rosalyn A. Jurjus <sup>f,?</sup>

<sup>a</sup>Department of Anatomy Cell Biology and Physiology, Faculty of Medicine, American University of Beirut, 1107-2020 Beirut, Lebanon <sup>b</sup>Lebanese Health Society, Beirut, Lebanon

<sup>c</sup>Oakland University William Beaumont School of Medicine, Rochester, MI, USA <sup>d</sup>Department of Anatomy, Faculty of Medicine and Surgery, University of Malta, Msida MSD06, Malta <sup>e</sup>Department of Experimental and Clinical Neurosciences, University of Palermo, 90133, Italy <sup>f</sup>Department of Anatomy and Regenerative Biology, Georges Washington University, Washington, DC 20037, USA



## Hypoxic Cross-Talk

- **Hypoxia drives molecular crosstalk** of multiple pro-inflammatory loops.
- **NFkB** is also another key regulator in the crosstalk among the pathways leading to the three disease entities: **inflammatory bowel disease (IBD), colorectal cancer (CRC) and type 2 diabetes mellitus (T2DM), along with systemic inflammation.**
- **NFKB** is a matchmaker between inflammation, IBD, cancer and diabetes.
- In addition, **TNF $\alpha$  plays a pivotal role in systemic inflammation.**
- **TNF $\alpha$  is increased in the mucosa of IBD patients** and has a central role in its pathogenesis. It also **activates other signaling pathways like NFKB and MAPK leading to CRC.**
- **TNF $\alpha$  is also overexpressed in the adipose tissues of obese patients thus linking it to T2DM, chronic inflammation and consequently CRC.**
- **‘Hypoxic Cross Talk’** plays a major role in **linking inflammation to cancer development** through its ability to **up regulate** inflammatory **tumor promoting** cytokines including **IL6, IL1 $\alpha$  and TNF $\alpha$**  and genes like BCL2 and BCLXL.
- Chronic ‘over-expression’ and ‘cross-talk’ of **HIF, TGF $\beta$ , NFKB, TNF $\alpha$ , IL1, IL6, IL8** could be considered as the **matchmaker between inflammation, IBD, cancer and diabetes.**



## Pro-Inflammatory

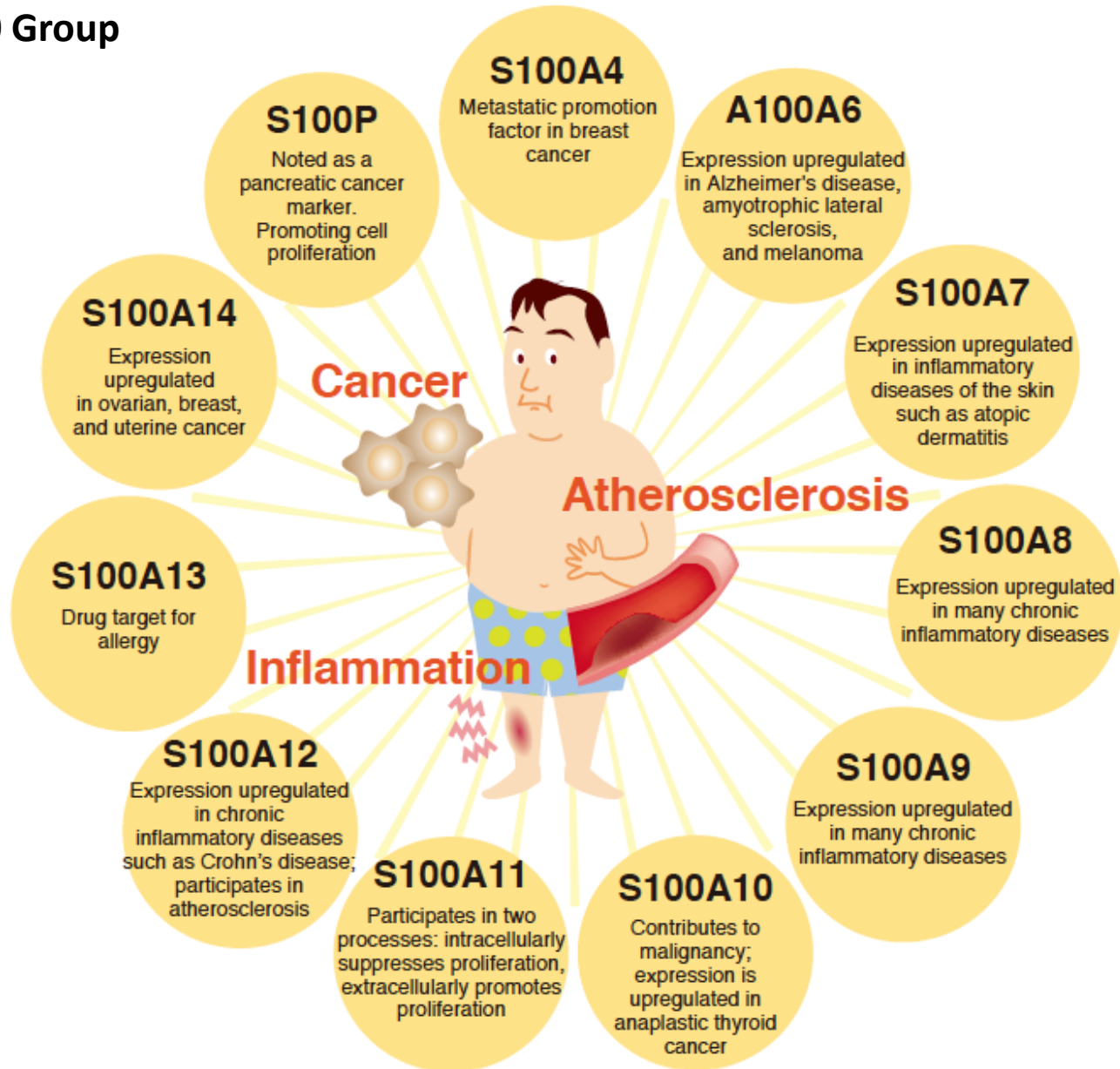
### S100B - Astrocyte Neurotrophic Cytokine

- S100B is a useful **neurobiochemical marker of brain damage** and used as a measure of **BBB dysfunction**
- S100B is a marker for **circulatory arrest, stroke and traumatic brain injury.**
- S100B is also associated with **neurodegenerative diseases** like **Alzheimer's disease or other chronic neurological diseases.**





## S100 Group





## Identifying S100B as a Biomarker and a Therapeutic Target For Brain Injury and Multiple Diseases.

*Chong ZZ<sup>1</sup>, Changyaleket B, Xu H, Dull RO, Schwartz DE.*

### Abstract

The calcium binding protein **S100B** has attracted great attention as a biomarker for a variety of diseases.

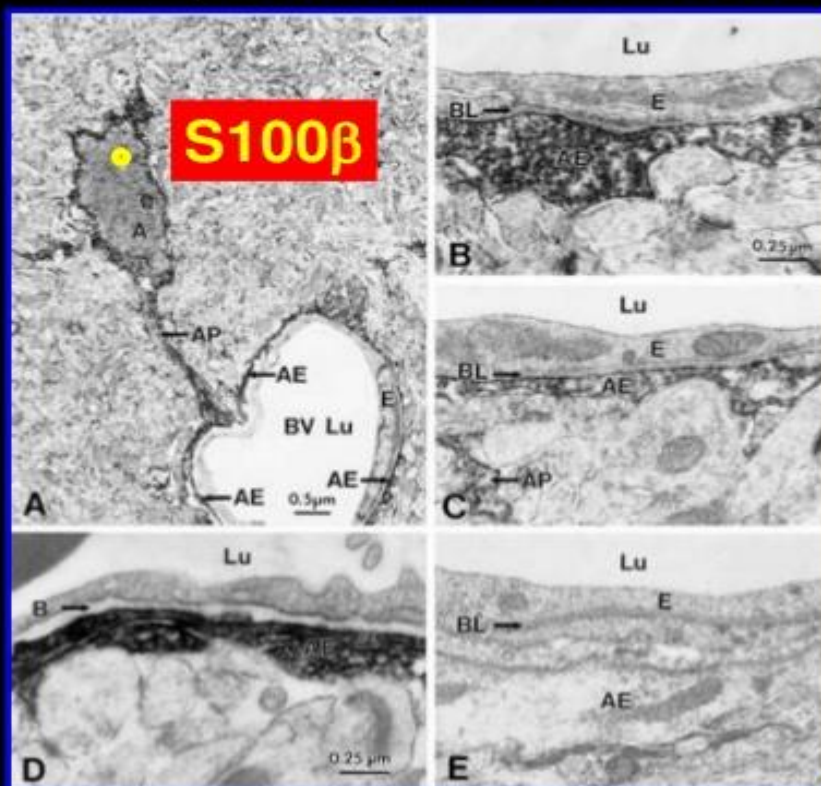
- S100B is mainly expressed in **glial cells**.
- The levels of S100B in the blood may function to predict the progress or the prognosis of many kinds of diseases, such as **cerebrovascular diseases, neurodegenerative diseases, motor neuron diseases, traumatic brain injury, schizophrenia, depression, diabetes mellitus, myocardial infarction, cancer, and infectious diseases**.
- Given that the activity of S100B has been implicated in the pathological process of these diseases, **S100B should not be simply regarded as a biomarker**, it may also function as **therapeutic target for these diseases**.
- Further elucidation of the roles of S100B may formulate innovative therapeutic strategies for multiple diseases.

## Re-exposure to the hypobaric hypoxic brain injury of high altitude: plasma S100B levels and the possible effect of acclimatisation on blood-brain barrier dysfunction.

Winter CD<sup>1,2</sup>, Whyte T<sup>3</sup>, Cardinal J<sup>4,5</sup>, Kenny R<sup>6</sup>, Ballard E<sup>7</sup>.

- Hypobaric hypoxic brain injury results in **elevated peripheral S100B** levels which may relate to **blood-brain barrier (BBB) dysfunction**.

### S100 $\beta$ as marker of BBB function



0.25  $\mu$ m

Emmi and Janigro  
J. Neuroscience, 2000

## **Intermittent hypoxia training as non-pharmacologic therapy for cardiovascular diseases: Practical analysis on methods and equipment.**

Serebrovskaya TV<sup>1</sup>, Xi L<sup>2</sup>.

### **Intermittent Hypoxia Training:**

**“short-term daily sessions consisting 3-4 bouts of 5-7 min exposures to 12-10% O<sub>2</sub> then, alternating with normoxic durations for 2-3 weeks”**

‘can result in remarkable beneficial effects in treatment of cardiovascular diseases such as hypertension, coronary heart disease, and heart failure’.



## The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy.

Muz B<sup>1</sup>, de la Puente P<sup>1</sup>, Azab F<sup>1</sup>, Azab AK<sup>1</sup>.

- **Tumor oxygenation** is a critical factor of cancer progression - **overexpression of HIF- $\alpha$**  subunits is associated with the aggressiveness of the majority of human cancers and correlates with **poor overall survival**.
- **Hypoxic cells are more aggressive, invasive and metastasize.**
- For instance, **multiple myeloma cancer cells cultured in hypoxic conditions and injected into mice were able to spread to the new bone marrow faster than the cells cultured in normoxic conditions.**
- Exposing an mouse model of cervical carcinoma to a **dozen cycles of 10 minutes 7% O<sub>2</sub>, followed by 10 minutes of air exposure daily, increased the number of lymph node metastases.**
- Similar observations in mice bearing sarcoma tumors - **exposure to acute hypoxia augmented the lung metastases.**
- **HIF-1 $\alpha$  expressed in 90% of human gastric cancer** biopsies at the front edge.
- **HIF inhibition** - significantly reduced the metastasis of gastric cancer cells.

- **HIF- $\alpha$  in all steps of metastasis.**
- Hypoxia is one of the main features of solid tumors becoming **resistant to chemo- and radiotherapy.**
- Hypoxia causes **slow-proliferating stem-cell-like phenotype of cells, creates chaotic and malfunctioning blood vessels, and augments metastasis,** which all together further induces **therapy resistance.**
- Assessment of **tumor oxygenation and HIF expression pattern** helps determine tumor chemo- and radio-sensitivity.
- Head-and-neck cancer with **high expression of HIF-1 $\alpha$  and HIF-2 $\alpha$**  were more **resistant to chemotherapy** (carboplatin) compared to biopsies with **low HIF- $\alpha$  expression which were chemo-sensitive.**
- Oropharyngeal cancer demonstrating high expression of HIF-1 $\alpha$  had a **lower chance to achieve complete remission after irradiation.**
- In addition, **irradiation was shown to induce HIF-1 activity,** leading to **production of angiogenic molecules such as VEGF which protects cancer cells from irradiation-induced apoptosis.**
- Therefore **HIF-1 represents a valid predictive marker and therapeutic target** for manipulation, in combination with chemotherapeutics and radiotherapy, in order to sensitize the cells to treatments.

## Efrati - Hypoxic Altitude Training - Risks Associated

Crit Care. 2015 Sep 1;19(1):307. doi: 10.1186/s13054-015-1034-2.

### Oxygen - a limiting factor for brain recovery & performance

Hadanny A<sup>1,2</sup>, Efrati S<sup>3,4,5,6</sup>.

<sup>1</sup>Sagol Center for Hyperbaric Medicine and Research, Assaf Harofeh Medical Center, Zerifin, 70300, Israel.

#### Abstract Summary

Effective brain metabolism is highly dependent on a narrow therapeutic window of oxygen.

- Slight decrease in oxygen supply, as occurs in a **hypobaric environment at high altitude**, has devastating effects on the injured and performing brain tissue.
- Conversely, **increasing brain oxygenation, by the use of hyperbaric oxygen therapy**, can **improve brain metabolism and its dependent regenerative & recovery processes**.



# Flight Hypoxia (Long Haul Flights) Induces Inflammatory Cytokines In IBS

Dig Dis. 2016;34(1-2):78-83. Epub 2016 Mar 16.

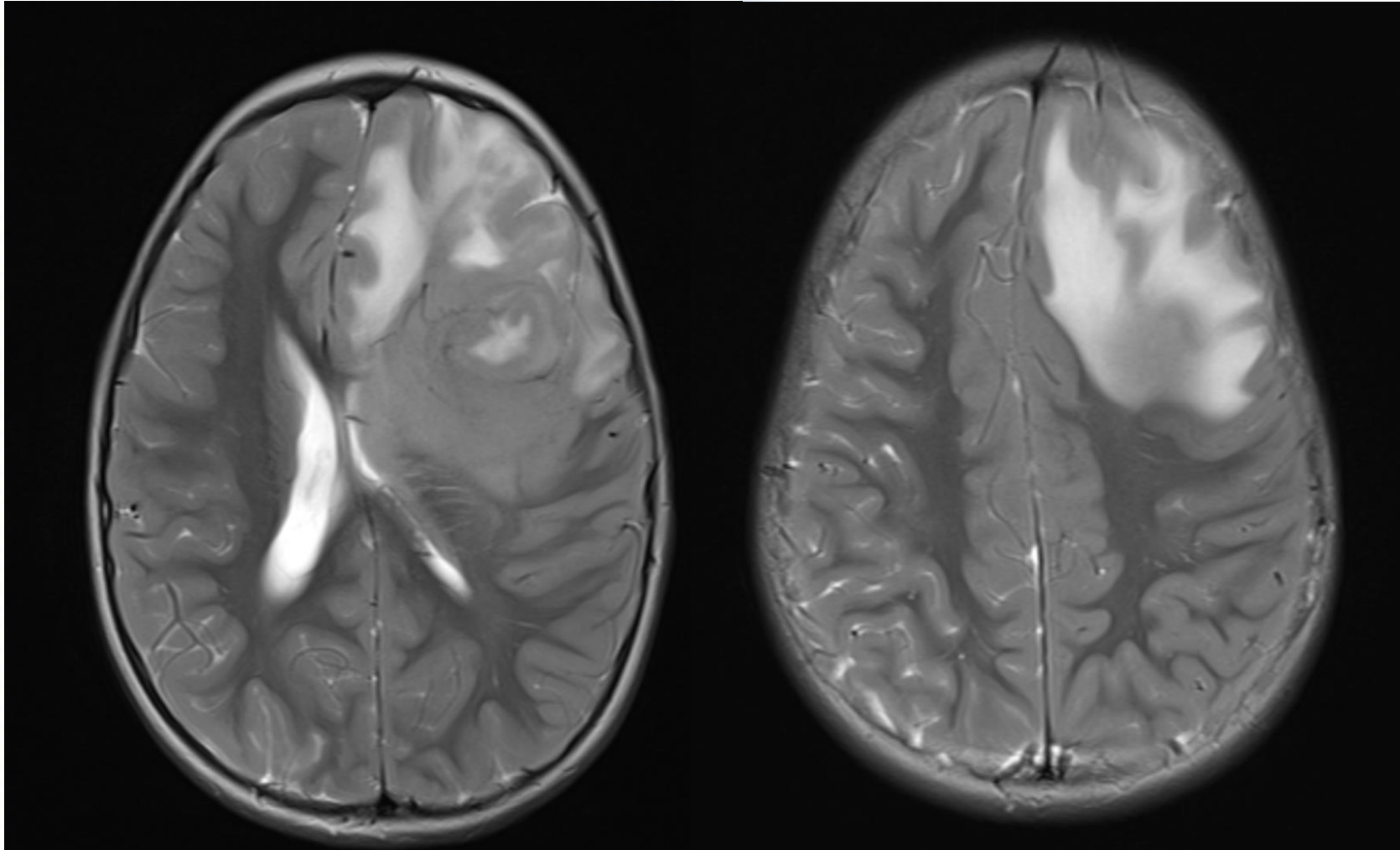
Vavricka SR<sup>1</sup>, Rogler G, Biedermann L.

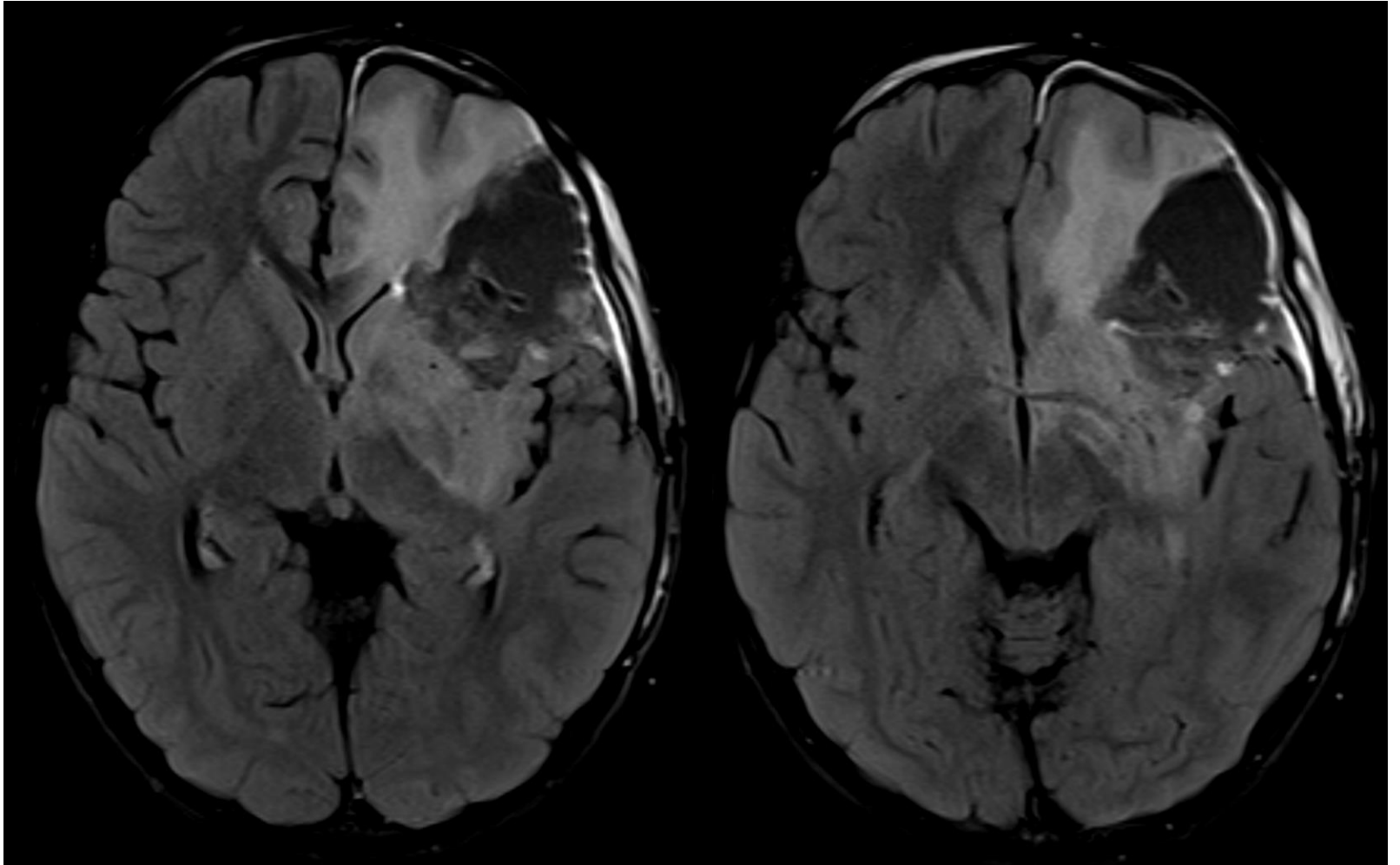
<sup>1</sup>Division of Gastroenterology and Hepatology, Triemli Hospital, Zurich.

## Abstract

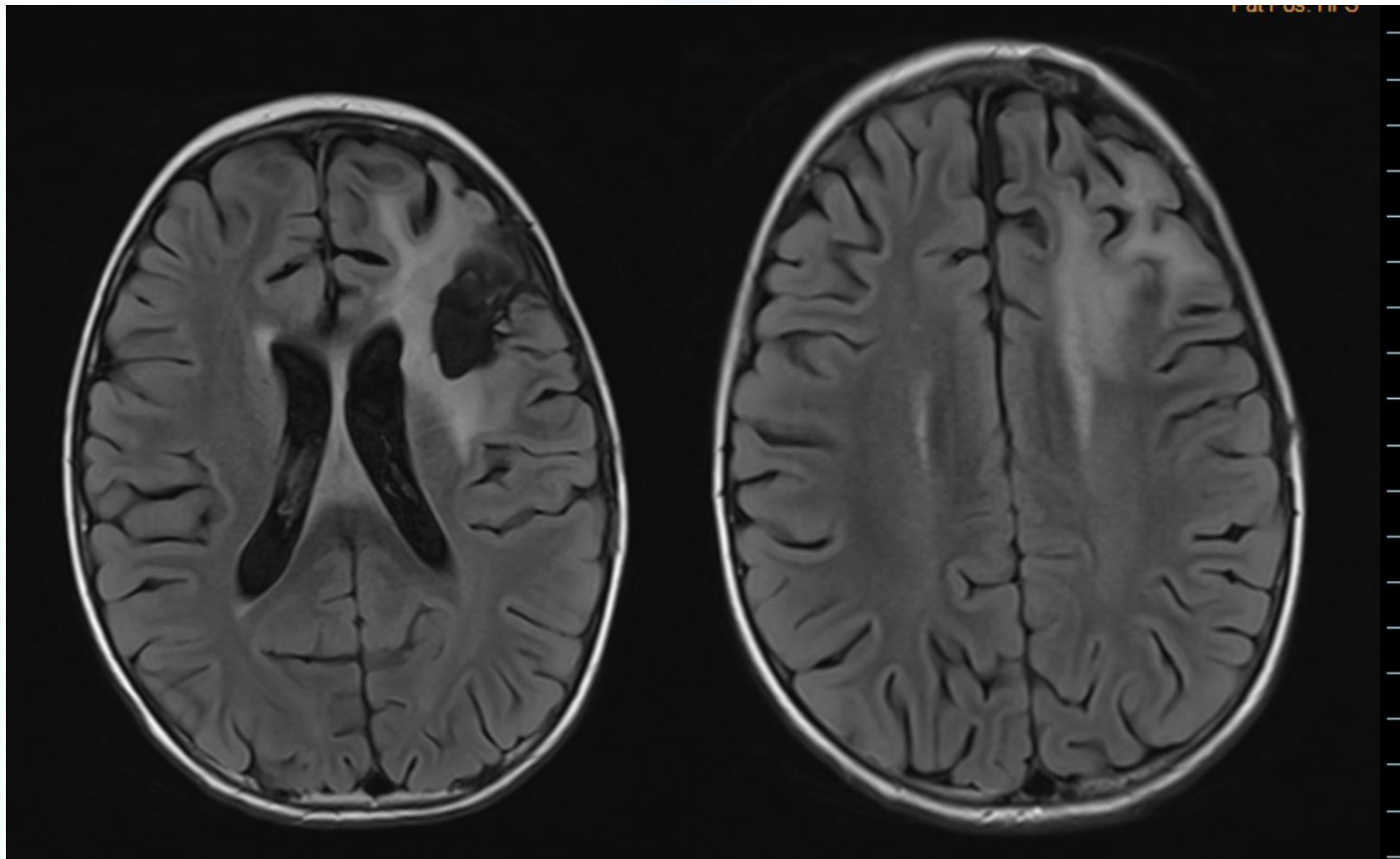
- **Inflammatory bowel disease (IBD) - prevalence and incidence of IBD are on the rise** especially in non-western countries.
- One of those factors is believed to be **hypoxia**. The role of hypoxia as a modifying or even causative factor in the genesis and maintenance of inflammation has been increasingly elucidated in recent years.
- **Hypoxia is believed to be a main inducing factor of inflammation.**
- **Animals exposed to short-term hypoxia accumulated inflammatory cells in multiple organs and showed elevated cytokines in the blood.**
- The study participants underwent a **3-hour exposure to hypoxic conditions simulating an altitude of 4,000 m above sea level.**
- According to these findings, we concluded that aircraft flights and stays at high altitudes are a risk factor for **increased disease activity in IBD.**
- **The average Airbus flights are at an altitude of 35-39,000 feet or 11,887 m.**
- International Long Haul Flights elevates the occurrence of **Hypoxic Induced Cascade, pro-inflammatory expressions and cell cross-talk.**

## OXYMED Case Study 7 year old - Glioblastoma Multiforme (GB4) Pre HBOT





HBO 87 hours





- MALCOLM HOOPER



Date of Birth : 21-Oct-2009  
Sex : M  
Collected : 01-Mar-2017

OXYMED  
643 CHAPEL STREET  
SOUTH YARRA VIC 3141

P: 1300 688 522

E: info@nutripath.com.au

A: PO Box 442 Ashburton VIC 3142

Lab id: **3469531** UR#:

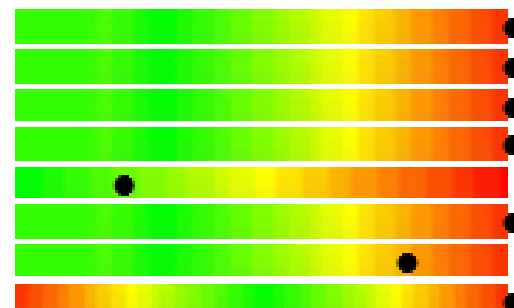
## INTEGRATIVE MEDICINE

BLOOD - SERUM

CYTOKINES, Extensive Panel

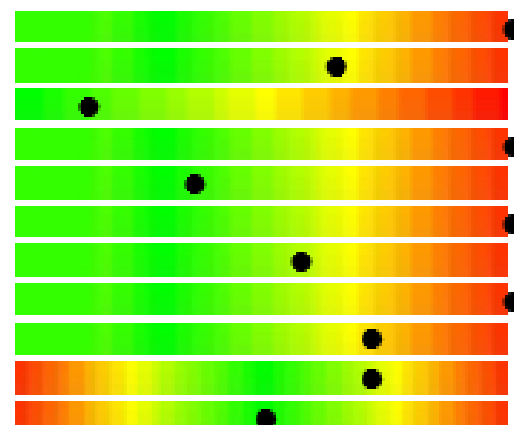
ProInflammatory Cytokines (TH1)

Interleukin 1	<b>3463.0 *H</b>	0.0 - 2.8	pg/mL
Interleukin 6	<b>1252.0 *H</b>	0.0 - 11.0	pg/mL
Interleukin 7	<b>67.8 *H</b>	0.0 - 16.0	pg/mL
Interleukin 8	<b>&gt;2500.0 *H</b>	0.0 - 28.0	pg/mL
Interleukin 17	10.4	< 13.0	pg/mL
TNFa	<b>816.00 *H</b>	0.00 - 13.00	pg/mL
TNFb	<b>164.0 *H</b>	0.0 - 158.0	pg/mL
S100B	<b>151.8 *H</b>	80.0 - 100.0	pg/mL



AntiInflammatory Cytokines (TH2)

GM-CSF	<b>1620.0 *H</b>	0.0 - 80.0	pg/mL
Interleukin 2	7.4	0.0 - 10.0	pg/mL
Interleukin 3	<3.2	< 5.0	pg/mL
Interleukin 4	<b>127.2 *H</b>	0.0 - 19.0	pg/mL
Interleukin 5	3.8	0.0 - 13.0	pg/mL
Interleukin 10	<b>99.7 *H</b>	0.0 - 7.0	pg/mL
Interleukin 12	7.9	0.0 - 14.0	pg/mL
Interleukin 13	<b>21.7 *H</b>	0.0 - 6.0	pg/mL
INFg	25.8	0.0 - 28.0	pg/mL
TGFb	57.7	28.0 - 64.0	pg/mL
Brain Derived Neurotrophic Factor BDNF	33.2	20.0 - 50.0	ng/mL





P: 1300 688 522

E: info@nutripath.com.au

A: PO Box 442 Ashburton VIC 3142

Date of Birth : 21-Oct-2009

Sex : M

Collected : 02-May-2017

T

4

Lab id: **3478581** UR#:

- MALCOLM HOOPER

OXYMED, 643 CHAPEL STREET  
SOUTH YARRA VIC 3141

## INTEGRATIVE MEDICINE

### BLOOD - SERUM

Hyperbaric Oxygen Therapy (HBO)

CYTOKINES, Extensive Panel

ProInflammatory Cytokines (TH1)

Interleukin 1

1.9 0.0 - 2.8

pg/mL

Interleukin 6

4.9 0.0 - 11.0

pg/mL

Interleukin 7

**24.8 \*H** 0.0 - 16.0

pg/mL

Interleukin 8

**48.4 \*H** 0.0 - 28.0

pg/mL

Interleukin 17

7.8 < 13.0

pg/mL

TNFa

10.80 0.00 - 13.00

pg/mL

TNFb

144.0 0.0 - 158.0

pg/mL

S100B

**13.6 \*L** 80.0 - 100.0

pg/mL

AntiInflammatory Cytokines (TH2)

GM-CSF

**1510.3 \*H** 0.0 - 80.0

pg/mL

Interleukin 2

3.6 0.0 - 10.0

pg/mL

Interleukin 3

<3.0 < 5.0

pg/mL

Interleukin 4

**44.4 \*H** 0.0 - 19.0

pg/mL

Interleukin 5

1.8 0.0 - 13.0

pg/mL

Interleukin 10

**14.8 \*H** 0.0 - 7.0

pg/mL

Interleukin 12

2.4 0.0 - 14.0

pg/mL

Interleukin 13

**7.1 \*H** 0.0 - 6.0

pg/mL

INFg

17.7 0.0 - 28.0

pg/mL

TGFb

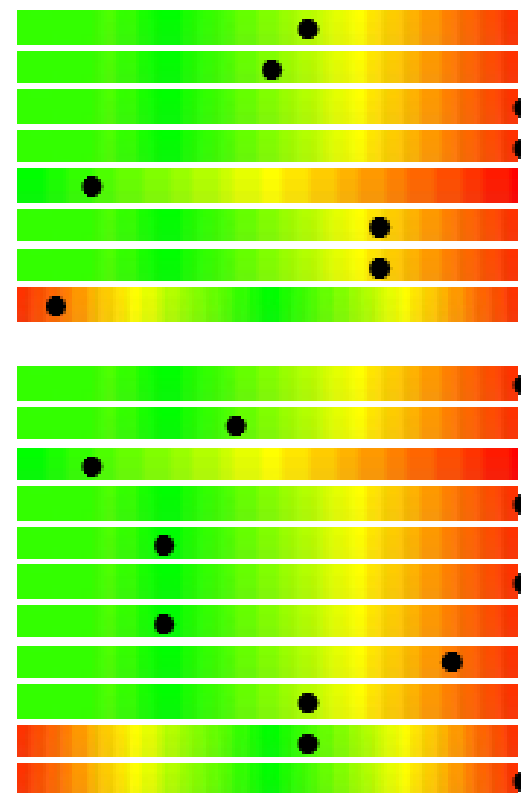
50.2 28.0 - 64.0

pg/mL

Brain Derived Neurotrophic Factor BDNF

**382.0 \*H** 20.0 - 50.0

ng/mL



## The Typical Hyperbaric Patient – ‘the last hope’



*"Nurse, get on the internet, go to SURGERY.COM, scroll down and click on the 'Are you totally lost?' icon."*