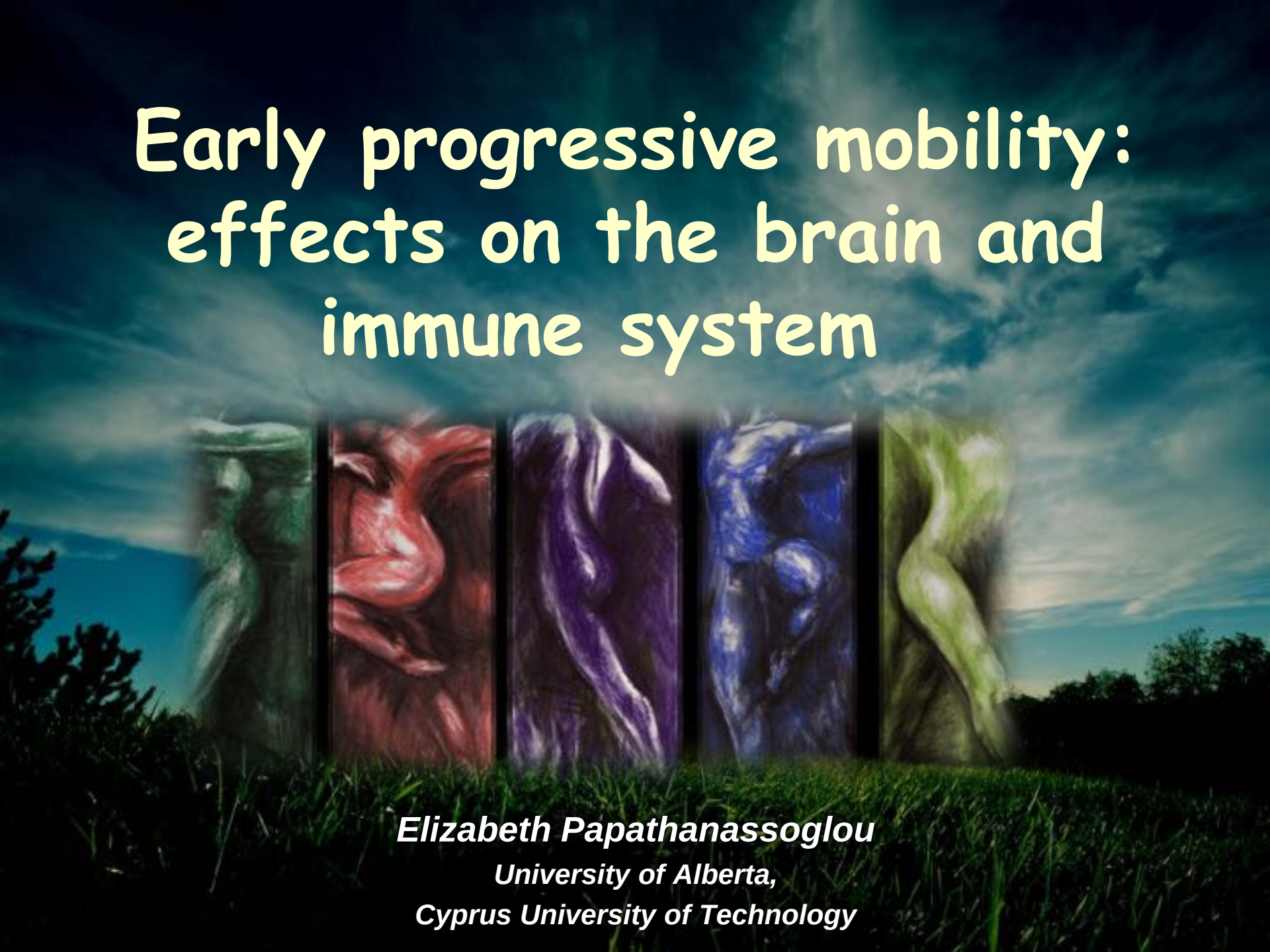
Early progressive mobility: effects on the brain and immune system



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Aim

i. *To review evidence on the anti-inflammatory effects of physical activity and EPM in critical care, especially in relation to the role of BDNF*
   - *a) immunity and inflammation*

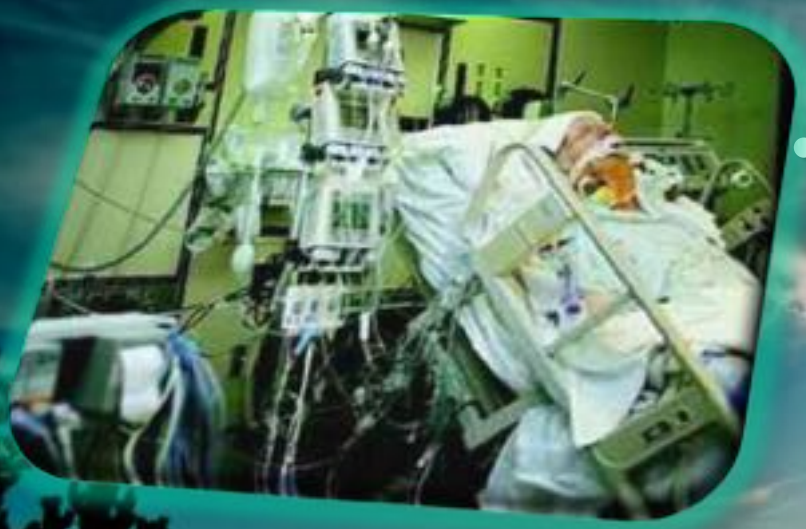
ii. *implications for future research in EPM.*

Early Progressive Mobility (EPM)

- ***Stepwise implementation of activities throughout hospital stay:***
  - ***turning, passive ROM, HOB elevation***
  - ***chair position in bed***
  - ***dangling at the bedside***
  - ***transferring to chair***
  - ***ambulation in the room and hallway,***
  - ***stair climbing***
  - ***treadmill and sedentary biking***
  - ***arm and leg strengthening exercises and physical therapy***

(Freeman & Maley, 2013).

EPM: Improved patients' outcomes



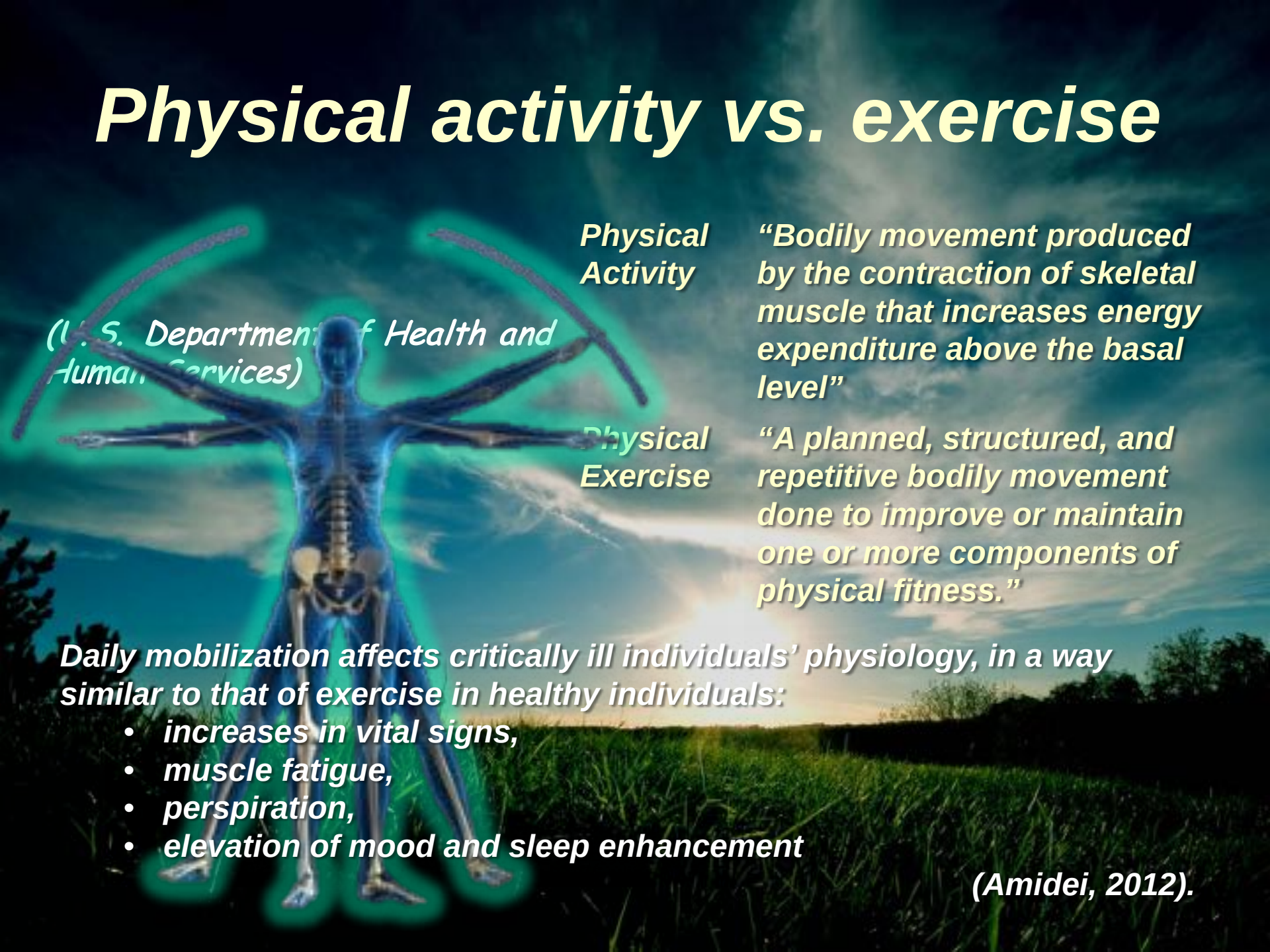
- ***EPM is implemented to prevent loss of muscle mass and weakness***
- ***it has been associated with improved intensive care unit (ICU) patient outcomes***

Li, Liang, Xie, et al, 2013)

- ***Improves muscle strength, ventilator weaning rates, LOS***

(Adler & Malone, 2012; Li et al., 2013),

Physical activity vs. exercise



(U. S. Department of Health and Human Services)

Physical Activity	"Bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above the basal level"
Physical Exercise	"A planned, structured, and repetitive bodily movement done to improve or maintain one or more components of physical fitness."

Daily mobilization affects critically ill individuals' physiology, in a way similar to that of exercise in healthy individuals:

- increases in vital signs,
- muscle fatigue,
- perspiration,
- elevation of mood and sleep enhancement

(Amidei, 2012).

Physical Activity & Inflammation

- ***Physical activity is involved in regulation of inflammation***

  (Lavie, Church, Milani,& Earnest, 2011).

- ***Attenuation of inflammation is a key event for survival in critical illness.***
- ***Exaggerated systemic inflammation & intense neuro-endocrine stimulation trigger the onset of sepsis and multiple organ dysfunction (MODS).***

  (Cobb, Suffredini,& Danner, 2008).

Can physical activity attenuate inflammation?

- *Physical activity enhances parasympathetic tone*

  (Buch, Coote,&Townend, 2002)

- *Cholinergic anti-inflammatory pathway: CNS regulates systemic inflammation, via efferent vagus nerve signals.*
  - **↑ α7-nAChR signaling**
- *Parasympathetic activity, release of acetylcholine (ACh) suppresses production of pro-inflammatory cytokines.*

Tracey, 2007; Oke & Tracey, 2008

Mobilization & Immunity?

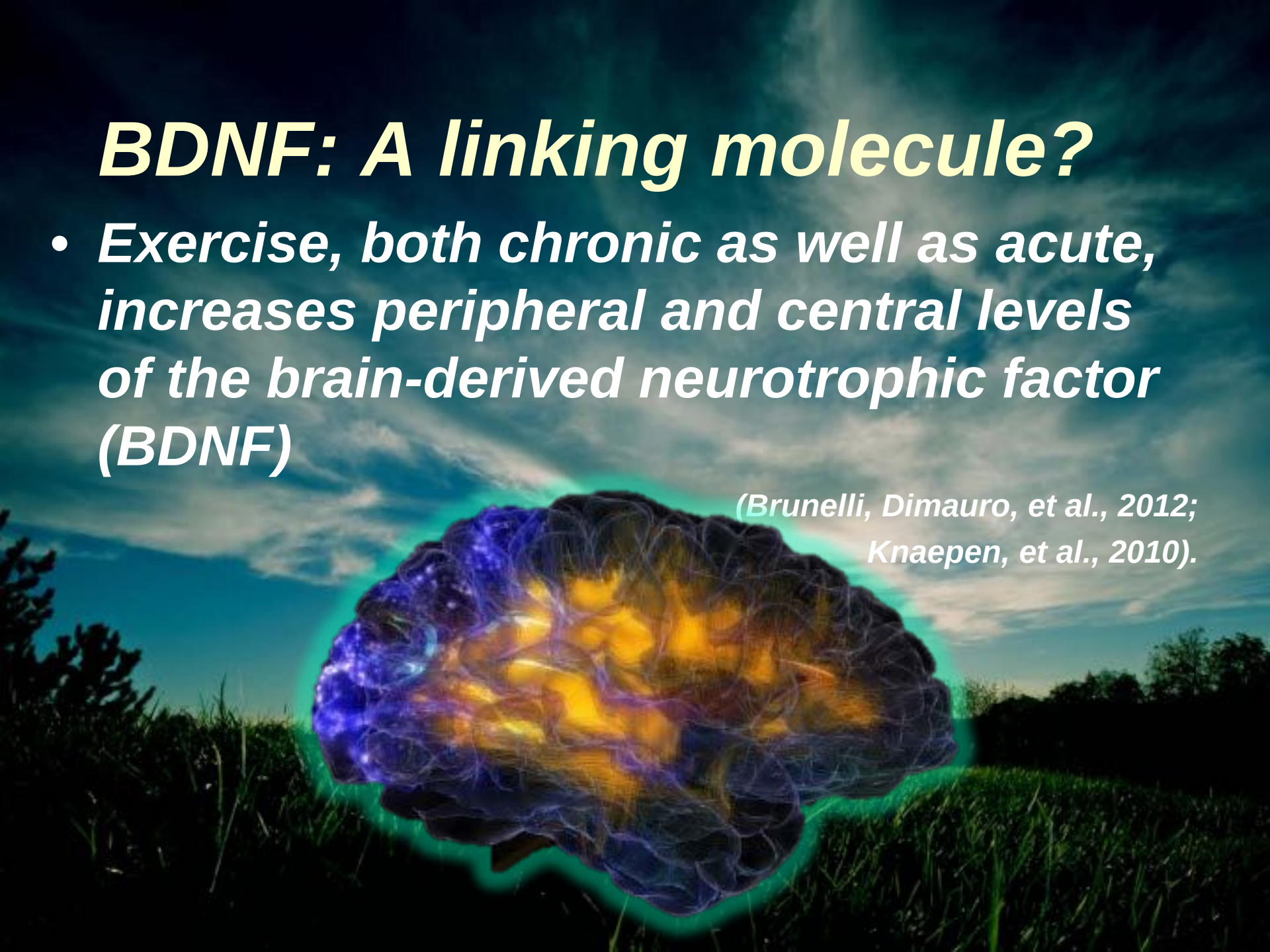
- ***Can physical activity and early mobilization during the course of critical illness contribute to the prevention of inflammatory sequlae?***
- ***Physical activity may exert anti-inflammatory effects by activating the cholinergic anti-inflammatory pathway***

  (Lujan &DiCarlo, 2013).
- ***Effects of EPM on immunity and inflammation have not been addressed.***

BDNF: A linking molecule?

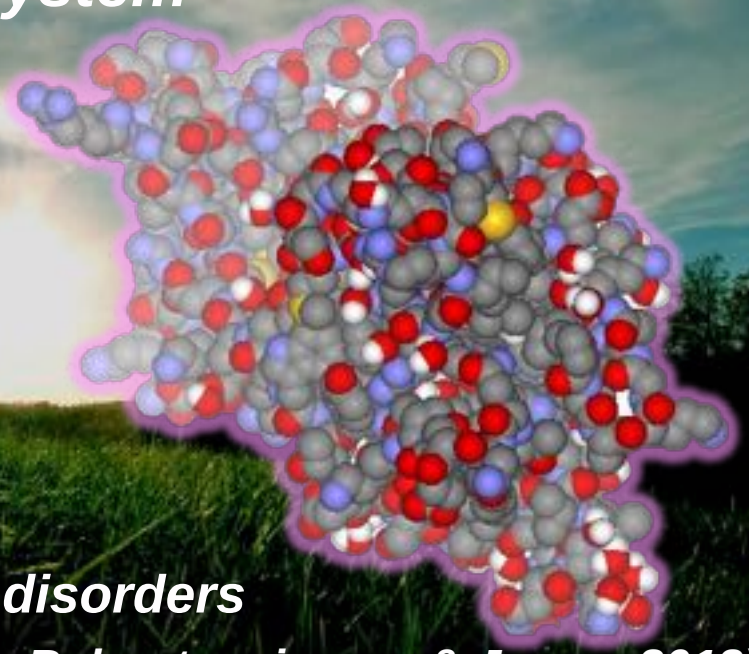
- ***Exercise, both chronic as well as acute, increases peripheral and central levels of the brain-derived neurotrophic factor (BDNF)***

(Brunelli, Dimauro, et al., 2012; Knaepen, et al., 2010).



Brain Derived Neurotrophic Factor (BDNF): a very pleiotropic molecule

- *Expressed in the brain and the periphery*
  - *(hippocampus, cortex, basal forebrain, cerebellum, striatum, amygdala)*
- *Neurotrophic role*
- *Maturation of Parasympathetic system*
- *Involved in:*
  - *Inflammation,*
  - *Nociception,*
  - *Regulation of mood, memory,*
  - *Learning, higher thinking,*
  - *Stress response,*
  - *Metabolism and food intake*
  - *Exercise physiology*
  - *Neurodegenerative and psychiatric disorders*



(Zoladz & Pilc, 2010; Balaratnasingam & Janca, 2012)

Brain Derived Neurotrophic Factor

- ***BDNF appears to modulate immunity and inflammation via its central and peripheral receptors***
  - **TrkB, $p75^{NTR}$**

(Laste, et al., 2013; Xin, Mesnard, et al., 2012).

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Brunelli et al., 2012	PBMCs produce & secrete BDNF isoforms as part of the **physiological stress response** induced by acute exercise

BDNF & Inflammation

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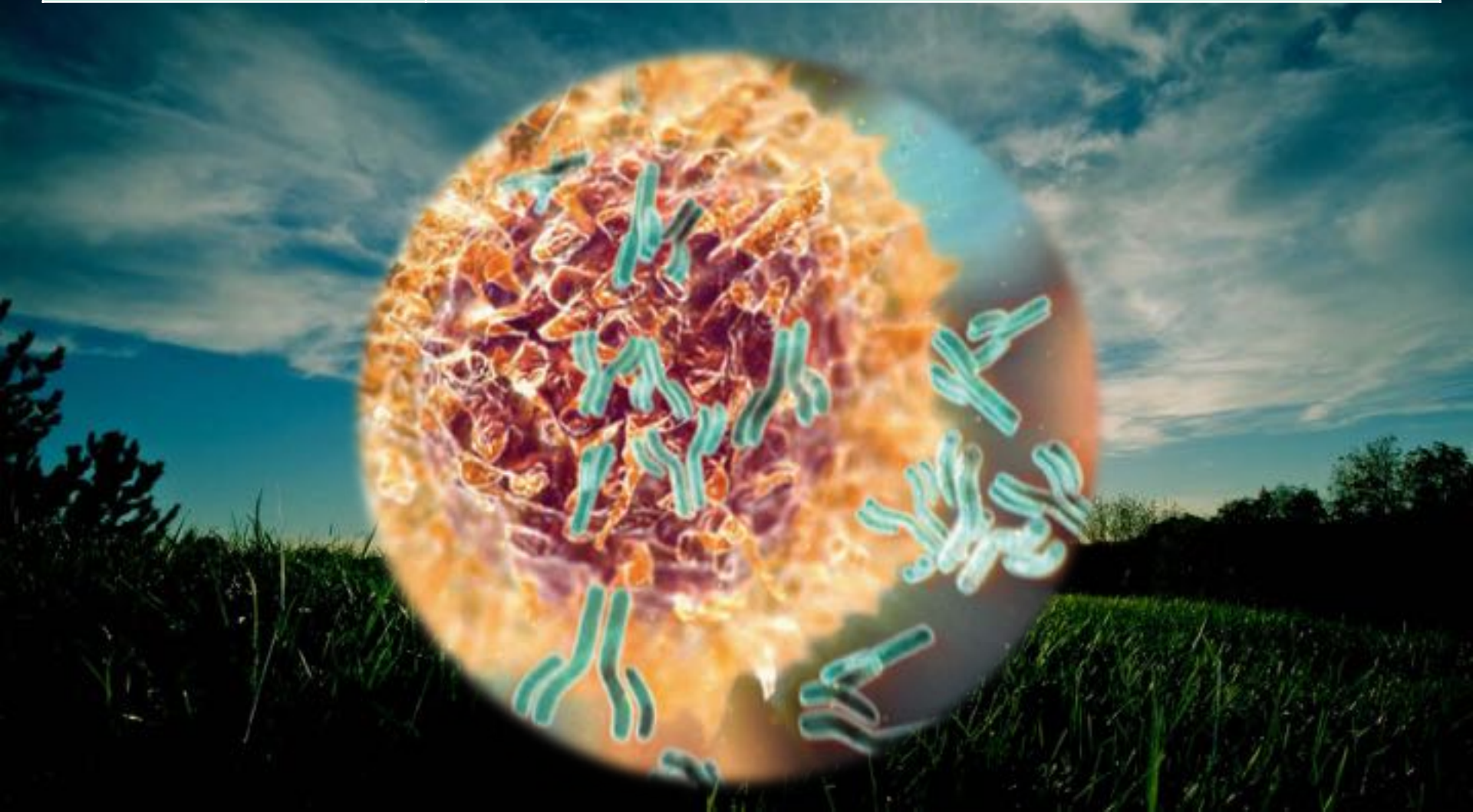

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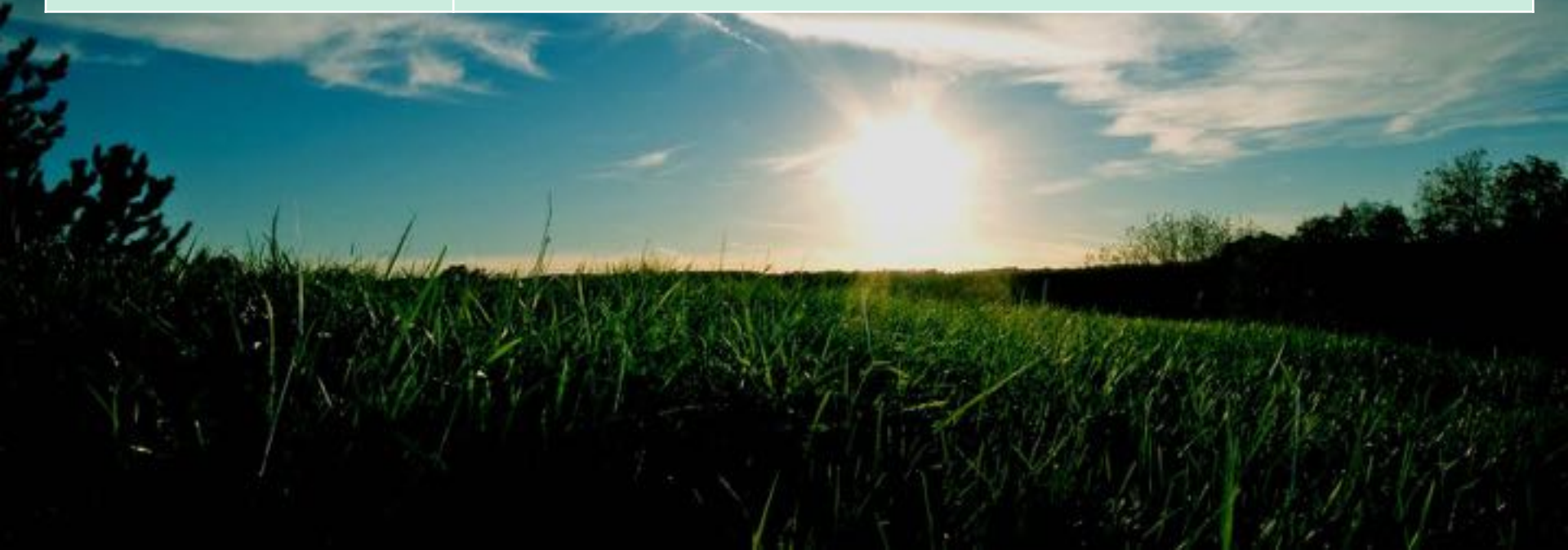

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Jiang et al., 2011	Rat ischemic stroke model. Intranasal BDNF: BDNF: **less apoptotic neurons** ↓**TNF-α ,↑ IL-10** ,↑ NF-κB activity
Joosten & Houweling 2004	Dorsal spinal cord transaction: BDNF resulted in **anti-inflammatory & anti-oxidant effects**.
Wu et al., 2010	**Neuroinflammation**: Exercise prevented loss of DA neurons & the LPS-induced ↓ of BDNF in the Striatum nucleus. Administration of BDNF: counteracted the LPS-induced neuron loss.

BDNF and PNS system

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BDNF in critical illness

Study	Evidence
Ritter et al., 2012 	**In ICU patients:** • Plasma levels of BDNF were higher in ICU patients when compared with healthy volunteers. • **↓BDNF 48h after enrollment in non-survivors.** • BDNF levels in patients (mechanical ventilation & sepsis) were associated with mortality.

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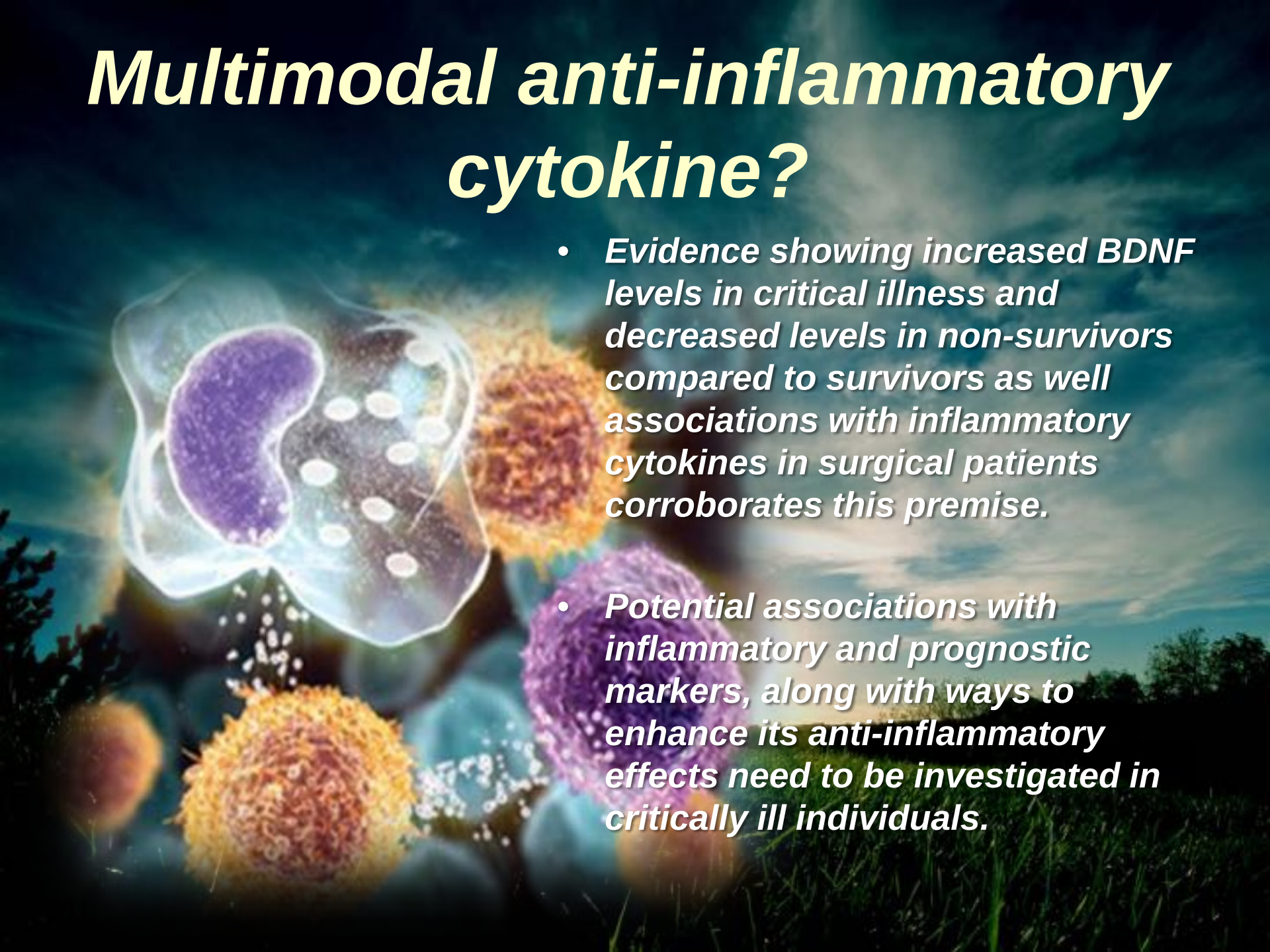
Grandi, et al., 2011	**In ICU patients:** • Serum BDNF levels at admission were **significantly higher in patients who developed delirium.** • BDNF levels already elevated on admission in susceptible patients- may reflect neuronal damage before or soon after ICU admission.

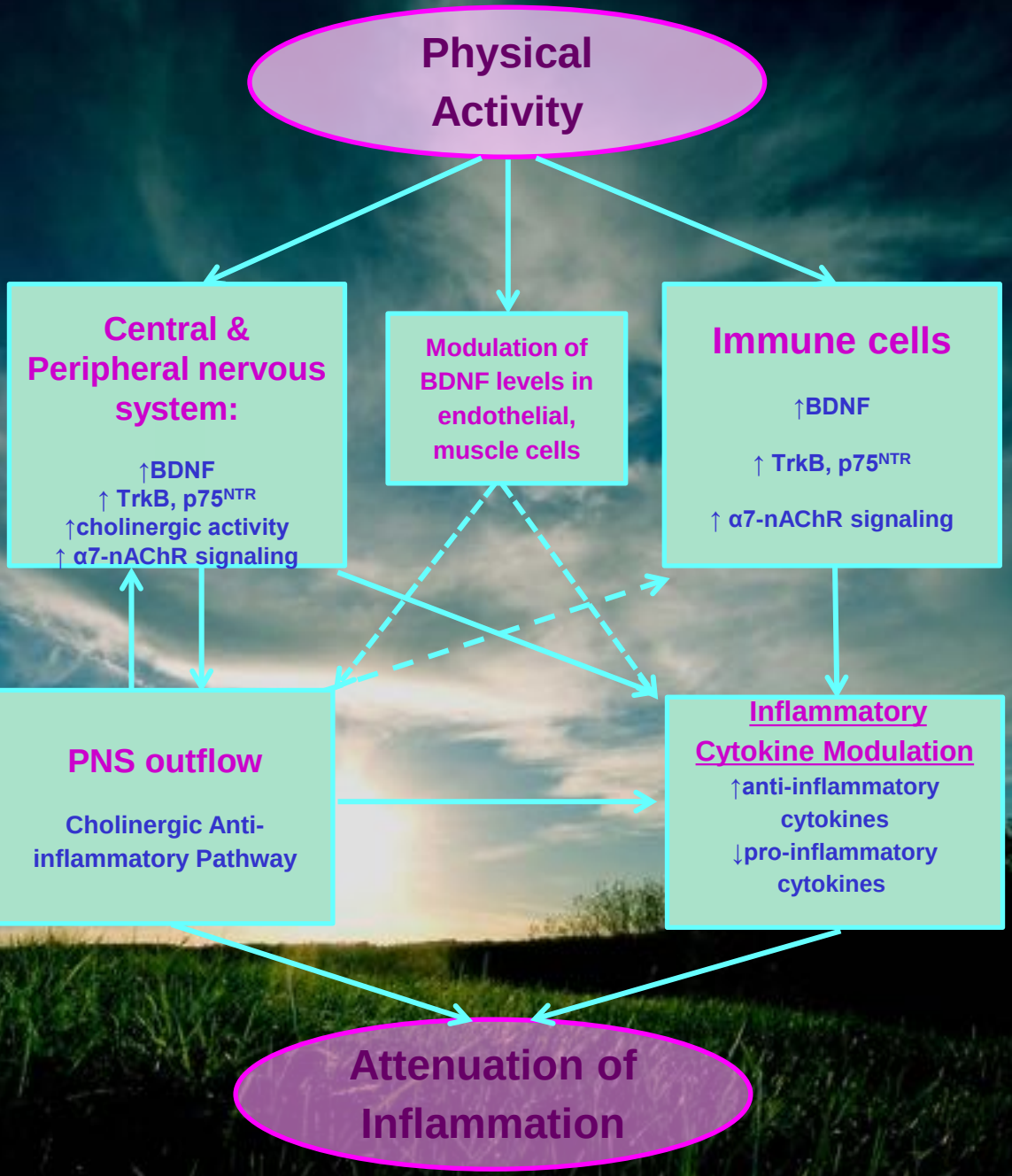
Multimodal anti-inflammatory cytokine?



- *Evidence showing increased BDNF levels in critical illness and decreased levels in non-survivors compared to survivors as well associations with inflammatory cytokines in surgical patients corroborates this premise.*

- *Potential associations with inflammatory and prognostic markers, along with ways to enhance its anti-inflammatory effects need to be investigated in critically ill individuals.*

Framework: Activity, BDNF & attenuation of inflammation



Can we modulate BDNF by EPM?

- ***Inflammatory markers have not been addressed in relation to mobilization activities in critically ill individuals***

  (Amidei, 2012).

- ***The capacity of EPM to modulate BDNF levels and inflammation in the critically ill is presumptive.***

Conclusions

- ***EPM (and BDNF) need to be investigated as potential modulators/ mediators of the inflammatory response in critical illness.***


Movement is survival
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