Emerging Targets and Pathways in Cancer-Related Cognitive Impairment (CRCI)

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Overview

• A Clinical Conundrum: CRCI

• Review on Known Mechanisms

• Emerging Pathways and Targets
Cancer-Related Cognitive Impairment (CRCI)

• Commonly known as ‘chemobrain’ or ‘chemofog’
  • Memory, concentration, execution function, psychomotor speed, verbal ability are most likely to be affected

• Incidence varies, depending on the cognitive assessments used

• Distinct and heterogeneous trajectories

Ng T., Chan A. Psychooncology 2018;27(4): 1185-92
CRCI: Unmet Needs

Systematic review of pharmacologic and non-pharmacologic interventions to manage cognitive alterations after chemotherapy for breast cancer

*Conclusion:* Current evidence does not favour the pharmacologic management of cognitive alterations associated with breast cancer treatment. Cognitive training and physical activity interventions appear promising, but additional studies are required to establish their efficacy.

Currently ‘Known’ Mechanisms

- Inflammation
- Direct neurotoxicity to the brain
  - Mitochondria damage
  - Glucose metabolism
  - Apoptosis
  - Necrosis
- Hypothalamic-Pituitary-Adrenal Axis
- Genetic Polymorphisms

# Current Ongoing Trials

<table>
<thead>
<tr>
<th></th>
<th>Mechanism of Action of Potential Targets</th>
<th>Clinical Trial Registry Number</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-dementia agents</strong></td>
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<td></td>
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<tr>
<td>Donepezil</td>
<td>Protecting the forebrain cholinergic system</td>
<td>NCT02822573</td>
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<tr>
<td>Memantine</td>
<td>Encouraging glutamatergic neurotransmission</td>
<td>NCT02360215 NCT03342443</td>
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<tr>
<td><strong>CNS Stimulants</strong></td>
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<tr>
<td>Methylphenidate</td>
<td>Activating the frontostriatal network</td>
<td>NCT02970500</td>
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<tr>
<td><strong>Neuroprotective Agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Protecting cell division in hippocampus</td>
<td>NCT01615055</td>
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<tr>
<td>Docosahexaenoic acid</td>
<td>Reducing microglia infiltration</td>
<td>NCT02517502</td>
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<tr>
<td>Ibuprofen</td>
<td>Protecting against neuronal injury</td>
<td>NCT03186638</td>
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<tr>
<td>Nicotine</td>
<td>Encouraging glutamatergic neurotransmission</td>
<td>NCT02312934</td>
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</tbody>
</table>

Emerging Pathways and Targets in CRCI
Astaxanthin Ameliorates Doxorubicin-Induced Cognitive Impairment (Chemobrain) in Experimental Rat Model: Impact on Oxidative, Inflammatory, and Apoptotic Machineries

Sara Emad El-Agamy¹ · Amal Kamal Abdel-Aziz¹ · Sara Wahdan¹ · Ahmed Esmat¹ · Samar S. Azab¹

- A carotenoid (phytochemical) widely found in marine organisms
- Potent antioxidant capacity– currently used as a dietary supplement
- Exhibits anti-inflammatory and anti-apoptotic activities

PAN-811 prevents chemotherapy-induced cognitive impairment and preserves neurogenesis in the hippocampus of adult rats

Zhi-Gang Jiang¹, Gordon Winocur²,³,⁴, J. Martin Wojtowicz⁵, Olga Shevtsova⁵, Steven Fuller¹, Hossein A. Ghanbari¹

- A ribonucleotide reductase inhibitor, originally designed for cancer therapy.
- Scavenging free radicals and to inhibit H₂O₂-induced neurotoxicity.


Fewer Errors
Less Memory Problems
KU-32 Prevents 5-Fluorouracil Induced Cognitive Impairment

Michael J. Sofis, David P. Jarmolowicz, Sam V. Kaplan, Rachel C. Gehringer, Shea M. Lemley, Brian S. Blagg, and Michael A. Johnson
University of Kansas

- KU-32 repairs mitochondrial dysfunction to prevent myelin degradation and protects the cells from damages by cytotoxic drugs

How does Methotrexate (MTX) induce CRI?

Figure 1. Frontal Lobe White Matter Depletion of Oligodendrocyte Lineage Cells following Chemotherapy
(A) Representative photomicrographs of Olig2+ (brown) cells in frontal lobe white matter of a 3-year-old child exposed to chemotherapy and a non-chemotherapy exposed, age-matched control subject.
(B) Chemotherapy exposure selectively depletes Olig2+ cells in frontal lobe white matter (p = 0.0211; n = 4), but not in gray matter (p = 0.0913; n = 4).
(C) Frontal lobe Olig2+ cells throughout early life and young adulthood following chemotherapy treatment, compared to age-matched controls.

Methotrexate-Induced Oligodendrocyte Damage

• Microglial activation is necessary for the persistent dysregulation of oligodendrocyte lineage cells, myelin and astrocytes, causing CRCI after MTX exposure.

Microglia in the CNS

- Innate immune cells of the CNS

- Microglia serve as resident phagocytes that dynamically survey the CNS
  
  ✓ Protect against Alzheimer's Disease

  ✓ However, activated microglia can also secrete inflammatory factors that injure neurons directly or via activation of neurotoxic astrocytes
Colony-stimulating factor-1 receptor (CSF-1R)

- PLX5622, a CSF1R inhibitor
  - May inhibit the activity of microglia and restore astrocyte reactivity in the CNS

Elimination of microglia improves cognitive function following cranial irradiation

Munjal M. Acharya, Kim N. Green, Barrett D. Allen, Allison R. Najah, Amber Harutyun Minasyan, Mi T. Le, Takumi Kawashita, Erich Giedzinski, Vipan K. Brian L. West, Janet E. Baulch & Charles L. Limoli

Targeting macrophage and microglia activation with colony stimulating factor 1 receptor inhibitor is an effective strategy to treat injury-triggered neuropathic pain

SeungHwan Lee, Xiang Qun Shi, Anni Fan, Brian West and Ji Zhang
Minocycline prevents microglia activation

Minocycline, a putative neuroprotectant, co-administered with doxorubicin-cyclophosphamide chemotherapy in a xenograft model of triple-negative breast cancer

Lauren E. Himmel\textsuperscript{a,b}, Maryam B. Lustberg\textsuperscript{c}, A. Courtney DeVries\textsuperscript{d}, Ming Po\textsuperscript{e}, Ching-Shih Chen\textsuperscript{b,f}, Samuel K. Kulp\textsuperscript{b,*}

\textsuperscript{a} Department of Veterinary Biosciences, College of Veterinary Medicine, The Ohio State University, Columbus, OH 43210, USA
\textsuperscript{b} Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, Columbus, OH 43210, USA
\textsuperscript{c} Department of Internal Medicine, College of Medicine, The Ohio State University, Columbus, OH 43210, USA
\textsuperscript{d} Department of Neuroscience, College of Medicine, The Ohio State University, Columbus, OH 43210, USA
\textsuperscript{e} Envisage of Pharmacy Practice and Science, College of Pharmacy, The Ohio State University, Columbus, OH 43210, USA
\textsuperscript{f} Institute of Biological Chemistry, Academia Sinica, Taipei, Taiwan

Representative partial sections of mice hippocampus and dentate gyrus are shown for H&E, Iba1, and GFAP stains from the AC treatment group

\textit{In vivo} studies

No detection of activated microglia and astroglial scars

Himmel LE, Lustberg MB, et al. Experimental and Toxicologic Pathology 2016; 505–515
Protein gene may protect from ‘chemobrain’: Study

WHAT IS CHEMOBRAIN?
• Cognitive impairment, such as memory loss and difficulty in decision-making and multitasking, after chemotherapy.

WHAT CAUSES IT?
• The exact cause of chemobrain remains unknown, but studies have identified numerous biological, chemical and demographic factors that may contribute to it, such as age, anxiety, baseline intelligence and depression.
• The types and dose intensity of chemotherapy regimens may also contribute to cognitive changes.

MORE STUDIES NEEDED
• While chemobrain has been observed in patients with other types of cancer besides breast cancer, more studies are needed to confirm if the findings can be extrapolated to other cancer types.

A patient receives chemotherapy treatment. Researchers have linked some side effects to the BDNF gene. (Photo: Reuters)

30% of breast cancer patients in one study reported cognitive impairment after chemotherapy.

The study, conducted from December 2011 to April 2014, followed an earlier study co-led by Assoc Prof Chan, which found that almost one-third (29.3 per cent) of 99 breast cancer patients reported cognitive impairment after chemotherapy.

Breast cancer is currently the top-ranked cancer among females in Singapore, representing 29.2 per cent of all cancer diagnosed among females between 2006 and 2014.

More than 90 per cent of patients with stage 1-4 breast cancer will undergo chemotherapy, said Dr Raymond Ng, a senior consultant medical oncologist at the NCSS, who was involved in the study.

Mr Forence Ng, who was the study’s lead investigator, said the exact cause of chemobrain remains unknown, but studies have identified numerous biological, clinical and demographic factors that may contribute to it, such as age, anxiety, baseline intelligence and depression.

The types and dose intensity of chemotherapy regimens may also contribute to cognitive changes, he added.

There’s still some way to go before the study findings can result in treatments for cognitive impairment.

The team is now collecting additional patient samples for further studies to validate their findings. More studies on the impact of the gene variation among breast cancer patients are needed.

While chemobrain has been observed in patients with other types of cancer, including colorectal cancer and prostate cancer, more studies are needed to confirm if the findings can be extrapolated to other cancer types.
Brain-derived neurotrophic factor (BDNF)

TrkB = tropomyosin related kinase B receptors

Furin

BDNF gene

ProBDNF

mBDNF

Secretory vesicle

Pre-synaptic terminal

Post-synaptic terminal

Neuronal survival, Neuronal growth, Synaptic plasticity, Long term potentiation

Long term depression, Neuronal apoptosis

Ng T,.., Chan A. BMC Cancer 2017; 17:867
BDNF Val66Met polymorphism and CRCI

Brain-derived neurotrophic factor genetic polymorphism (rs6265) is protective against chemotherapy-associated cognitive impairment in patients with early-stage breast cancer

Terence Ng, Shu Mei Teo, Hui Ling Yeo, Maung Shwe, Yan Xiang Gan, Yin Ting Cheung, Koon Mian Foo, Mooi Tai Cham, Jung Ah Lee, Yee Pin Tan, Gilbert Fan, Wei Sean Yong, Madhukumar Preetha, Wei-Jen Kiley Loh, Si-Lin Koo, Amit Jain, Guek Eng Lee, Mabel Wong, Rebecca Dent, Yoon Sim Yap, Raymond Ng, Chiea Chuen Khor, Han Kiat Ho, and Alexandre Chan

Ng T,.., Chan A. Neuro Oncol 2016; 18(2):244-51
Carriers of at least one Met allele were associated with lower odds to develop impairment in the multi-tasking and verbal fluency domains.

Ng T,..., Chan A. *Neuro Oncol* 2016; 18(2):244-51
**BDNF Val66Met polymorphism and CRCI**

### Table 6: Pooled odds ratios of CRCI among patients carrying BDNF Met allele (Val/Met or Met/Met) compared to Val/Val genotype

<table>
<thead>
<tr>
<th>Domain</th>
<th>Cohort</th>
<th>OR (95% CI)</th>
<th>Weight</th>
<th>Pooled OR (95% CI)</th>
<th>p value</th>
<th>I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Summation</td>
<td>Previous</td>
<td>0.40 (0.16–1.04)</td>
<td>39.1</td>
<td>0.52 (0.29–0.94)</td>
<td>0.03*</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>0.62 (0.29–1.30)</td>
<td>60.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory</td>
<td>Previous</td>
<td>0.53 (0.19–1.53)</td>
<td>45.7</td>
<td>0.34 (0.17–0.70)</td>
<td>0.003*</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>0.24 (0.09–0.61)</td>
<td>54.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multitasking</td>
<td>Previous</td>
<td>0.37 (0.15–0.91)</td>
<td>43.0</td>
<td>0.33 (0.18–0.59)</td>
<td>&lt;0.001*</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>0.30 (0.14–0.67)</td>
<td>57.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal ability</td>
<td>Previous</td>
<td>0.34 (0.12–0.90)</td>
<td>43.0</td>
<td>0.46 (0.24–0.88)</td>
<td>0.02*</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>0.57 (0.24–1.38)</td>
<td>57.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentration</td>
<td>Previous</td>
<td>0.61 (0.23–1.59)</td>
<td>40.9</td>
<td>0.75 (0.40–1.39)</td>
<td>0.36</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>0.86 (0.38–1.90)</td>
<td>59.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental acuity</td>
<td>Previous</td>
<td>1.03 (0.37–2.86)</td>
<td>36.5</td>
<td>0.62 (0.33–1.15)</td>
<td>0.13</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>0.46 (0.21–0.99)</td>
<td>63.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional interference</td>
<td>Previous</td>
<td>0.38 (0.13–1.14)</td>
<td>42.6</td>
<td>0.54 (0.26–1.09)</td>
<td>0.08</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>0.69 (0.27–1.75)</td>
<td>57.4</td>
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</tbody>
</table>

*p < 0.05

Evaluation of plasma brain-derived neurotrophic factor levels and self-perceived cognitive impairment post-chemotherapy: a longitudinal study

Terence Ng¹,²†, Ying Yun Lee¹†, Jung-woo Chae¹,², Angie Hui Ling Yeo³, Maung Shwe¹, Yan Xiang Gan², Raymond C. H. Ng³,⁴, Pat Pak Yan Chu⁵, Chiea Chuen Khor⁶, Han Kiat Ho³ and Alexandre Chan¹,²,³*

Ng T.,... Chan A. BMC Cancer 2017; 17:867
Efficacy of Acupuncture Therapy for Chemotherapy-Related Cognitive Impairment in Breast Cancer Patients

Table 2. Summary of neuropsychologic assessment.

<table>
<thead>
<tr>
<th>Metabolites</th>
<th>Treatment (n=39)</th>
<th>Control (n=36)</th>
<th>Repeated measures ANOVA</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>T1 Mean ±SD</td>
<td>T2 Mean ±SD</td>
<td>T value</td>
</tr>
<tr>
<td>FACT-COG</td>
<td>98.75±12.94</td>
<td>102.38±13.78</td>
<td>4.840**</td>
</tr>
<tr>
<td>PCI</td>
<td>55.42±10.95</td>
<td>56.29±11.49</td>
<td>3.494**</td>
</tr>
<tr>
<td>QOL</td>
<td>11.33±3.42</td>
<td>11.75±3.38</td>
<td>2.632*</td>
</tr>
<tr>
<td>OTH</td>
<td>11.63±2.89</td>
<td>12.5±3.31</td>
<td>2.991**</td>
</tr>
<tr>
<td>PCA</td>
<td>20.38±4.19</td>
<td>21.79±4.40</td>
<td>2.298*</td>
</tr>
<tr>
<td>AVLT1</td>
<td>9.13±1.48</td>
<td>9.17±1.55</td>
<td>0.440</td>
</tr>
<tr>
<td>AVLT2</td>
<td>9.42±1.61</td>
<td>9.63±1.50</td>
<td>2.005</td>
</tr>
<tr>
<td>AVLT3</td>
<td>10.92±1.44</td>
<td>11.42±1.18</td>
<td>2.202*</td>
</tr>
<tr>
<td>VFT</td>
<td>17.88±3.33</td>
<td>18.21±3.74</td>
<td>1.163</td>
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<tr>
<td>SDMT</td>
<td>34.75±5.15</td>
<td>35.71±5.54</td>
<td>1.558</td>
</tr>
<tr>
<td>CDT</td>
<td>8.08±1.50</td>
<td>8.54±1.14</td>
<td>2.696*</td>
</tr>
<tr>
<td>TMT-B</td>
<td>95.58±26.67</td>
<td>95.46±26.80</td>
<td>0.901</td>
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</tbody>
</table>

Figure 2. Levels of BDNF in s

Dehydroepiandrosterone (DHEA)

- **PRE-SYNAPTIC TERMINAL**
  - DHEA
  - DHEA-S

- **POST-SYNAPTIC TERMINAL**
  - DHEA
  - DHEA-S

- Inhibitory effect at GABA receptor
- Agonistic effect at NMDA receptor
- Simulates neurite growth

- DHEA(S) exert neuroprotective effects that help to regulate brain function and behaviour.
Prechemotherapy Levels of Plasma Dehydroepiandrosterone and Its Sulfated Form as Predictors of Cancer-Related Cognitive Impairment in Patients with Breast Cancer Receiving Chemotherapy

Yi Long Toh,1, 2Juliana Shariq Mujtaba,1 Sumit Bansal,1 Angie Yeo,1 Maung Shwe,1,2 Aik Jiang Lau,1,3 and Alexandre Chan1,2,4,*

1Department of Pharmacy, Faculty of Science, National University of Singapore, Singapore; 2Department of Pharmacy, National Cancer Centre Singapore, Singapore; 3Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; 4Oncology Academic Clinical Program, Duke-National University of Singapore Medical School, Singapore

Figure 2. Box plots of mean ± SD baseline plasma dehydroepiandrosterone sulfate (DHEAS) levels for the non–cognitively impaired and cognitively impaired groups defined by the verbal fluency domain.

Toh YL,,, Chan A. Pharmacotherapy 2019;39(5):553-563

More details on June 22nd (Saturday) 3:50pm @ Station 3!
Take home messages

- CRCI is a debilitating adverse effect of cancer and cancer therapy, yet effective management strategies are still lacking.

- Emerging targets and pathways, such as anti-inflammation, anti-oxidant, microglia activation, BDNF and DHEA, are being investigated for their roles in CRCI.

- Increase understanding of basic mechanisms is vital for the development of therapeutics that will mitigate this debilitating side effect of chemotherapy.
THANK YOU