EFIC fellowship
pain clinic

Diagnostic and Therapeutic Workout for Chemotherapeutic Induced Neuropathy (CIPN) (current Evidence)

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Chair Esmo Designated Center

Chair Comprehensive Center of Excellence in Pain Practice, EPP – WIP (2014)

Radboud University Nijmegen Medical Center, The Netherlands

Future Developments in Cancer Pain

Special focus topic

Radboudumc

Disclosures of K. Vissers

MOTIVATORS

- Fulltime chair- and professorship at the Radboudumc University Nijmegen Medical Center, the Netherlands
- Member of national taskforces for chronic pain and palliative care of the ministry of health
- Past President of WIP / past chair of the Board of Examination of WIP, currently director education and certification WIP
- Past President of Pain Alliance in the Netherlands (IASP Chapter)
- Ambassador of the Dutch Cancer Pain Foundation

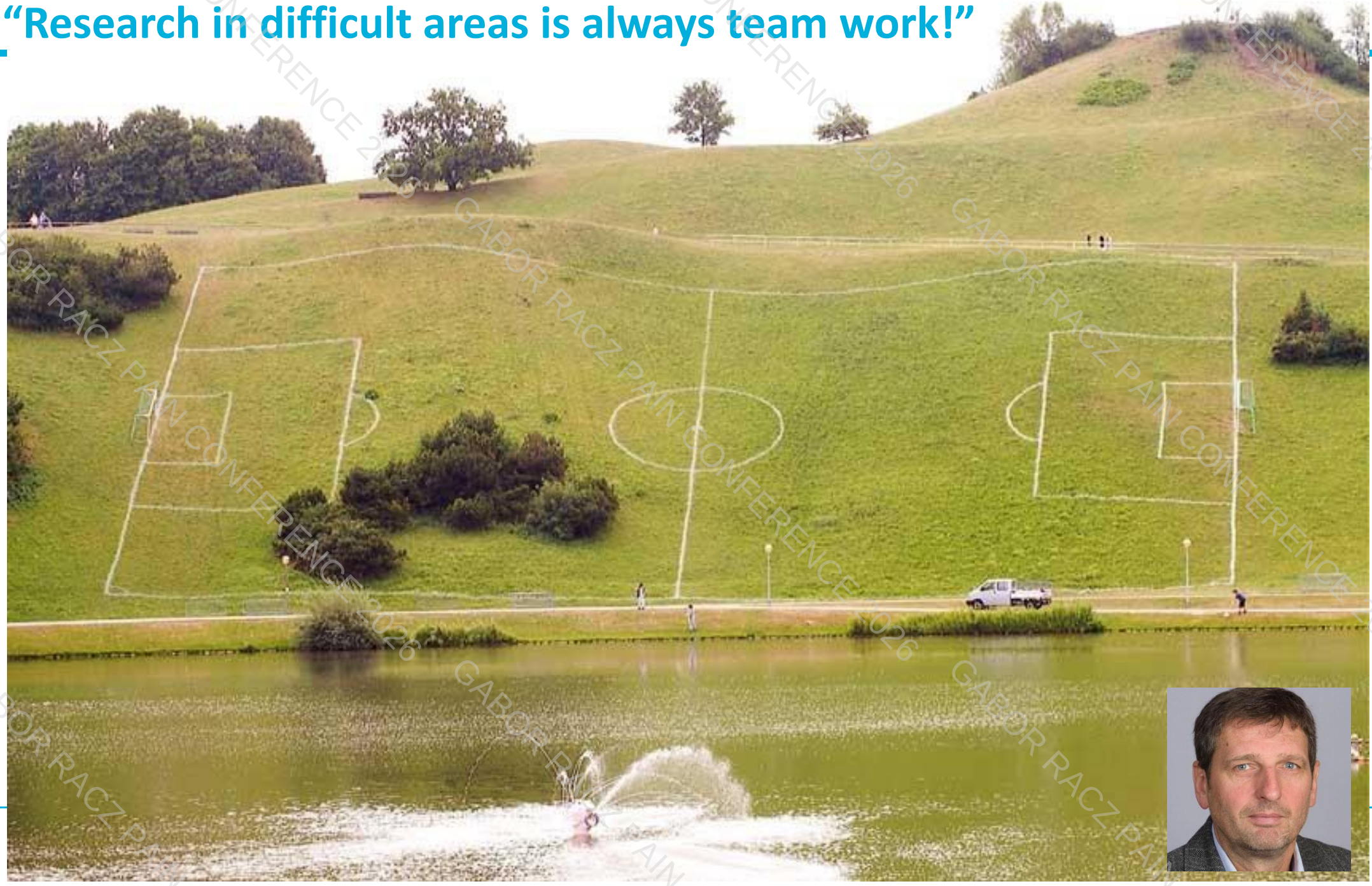
DISCLOSURES

- No disclores related to this lecture

In Memory of Dr. Gabor B. Racz

1937–2025

“Research in difficult areas is always team work!”



Program & learning objectives for : CIPN

1. The problem of pain in oncology
2. Pain is an important symptom in oncology but often neglected!
3. Open invitation of important oncological societies
4. Drug induced peripheral neuropathy (DIPN): diagnosis & epidemiology
5. Chemotherapeutic-induced peripheral neuropathy (CIPN)
6. CIPN Pathophysiology
7. CIPN diagnosis & assessment
8. CIPN evidence of prevention & treatment
9. Important pilot studies
10. Conclusion and take home messages

Promotion Commission & team:

Drs. Frank van Haren, MD, FIPP,
PhD candidate

dr. Sandra van den Heuvel,
MD, FIPP, CIPS, copromotor

Prof.dr. M. Steegers
promotor

prof.dr. Nens van Alfen
promotor

prof.dr. K. Vissers
promotor

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CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY (CIPN)
Determinants in the diagnosis and treatment of persistent pain

July, 2026

1. The problem of Cancer Pain

Number of cancer survivors USA 1977 - 2022

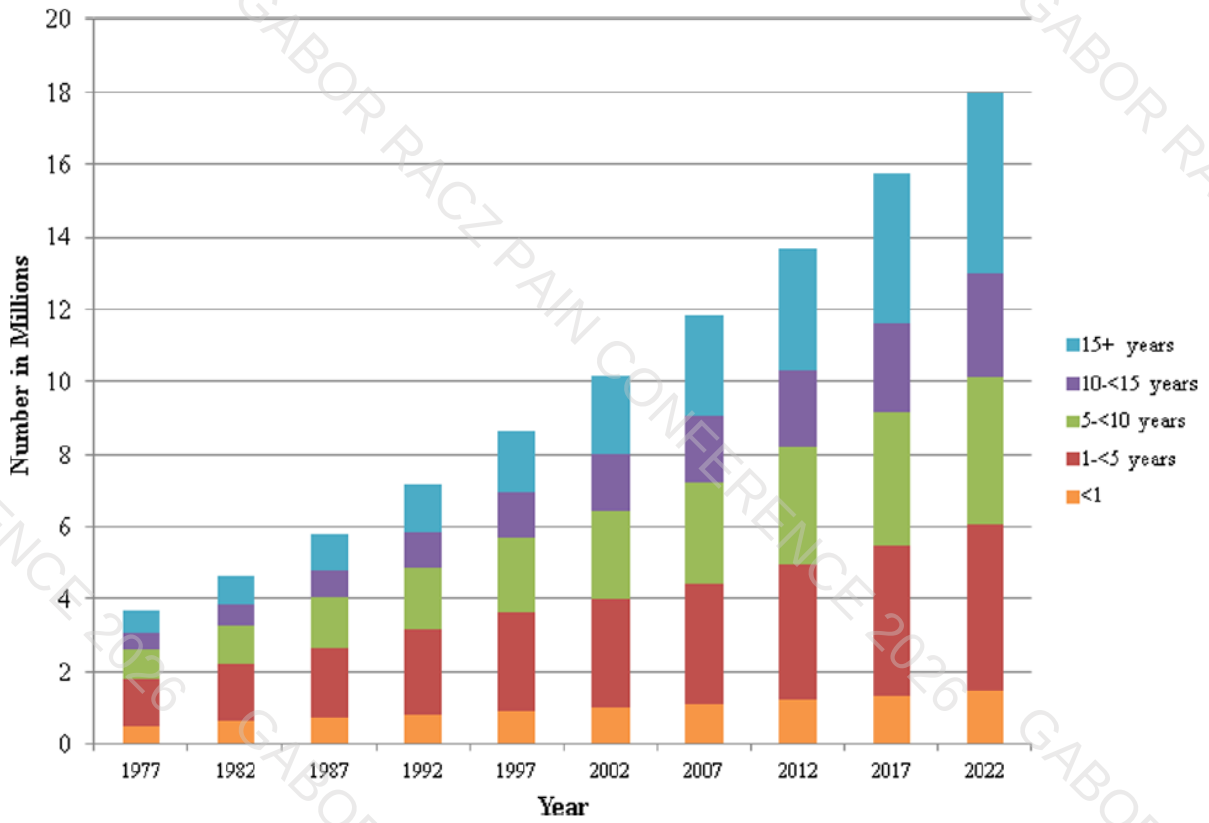

Figure 1.
Estimated and projected number of cancer survivors in the United States from 1977–2022 by years since diagnosis.

High Investment programs

Focus on life prolongation!

De Moor J, Cancer epidemio biomarkers Prev, 2023

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Is pain equally important as the cancer battle? Misconceptions!

- Pain is seen as unrelated as a consequence of toxicity
- Pain is not part of the inflammatory – immune cycle observation
- Pain is not considered having any impact on life prolonging strategies
- Pain is not seen as a part of patients overall quality of life determinants
- Consequently Pain & quality of life issues
  - Are not part of the research protocol of oncological research protocols
  - Is absent in the clinical checklist for safety and outcome
  - Is not considered as part of the human body as a whole!

2. Pain is an important symptom in oncological states

Pain: important symptom in oncological states

- Pain is most prominent symptom in oncological states
- Present in / due to
  - 30 – 40 % of cases on diagnosis:
  - 40 – 70 % of cases during treatment:
  - 70 – 90 % of cases in terminal (supportive) care:
  - Also present in survivors!

All cancer patients suffer from cancer pain!

Tumor related Cancer Pain

Treatment related Cancer Pain

Inflammation related Cancer Pain

Syndromal >< mechanistic construct

www.oncoline.nl, 2008 – 2015

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

NCCN National Comprehensive Cancer Network®

3. Open invitation of important scientific organisations!

WORLD INSTITUTE OF PAIN® WIP 1993 2023 30 YEARS

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

NCCN National Comprehensive Cancer Network®

Both ESMO and NCCN (national comprehensive cancer network) guidelines support the use of interventional treatment for severe cancer-related pain, although the timing of intervention is still debatable.

- Previous studies suggest that **an early application of interventions**
  - could improve pain control,
  - decrease risks for adverse effects,
  - reduce the consumption of opioids and opioid-associated side effects,
  - increase survival time in cancer patients

Open invitation from international oncological societies!

- Advanced technology has expanded the interventional options and made them safer and less invasive, thus reducing the rate of complications overall.

It is reasonable to consider interventional treatment before strong opioids are initiated at the **early stage of cancer-related pain management**

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Current Oncology Reports (2022) 24:223–226
https://doi.org/10.1007/s11912-021-01166-z

ANESTHESIOLOGY AND CRITICAL CARE (JP CATA, SECTION EDITOR)

Cancer Pain Management—New Therapies

Haijun Zhang[1]

- Despite the rapid advance in anti-cancer treatment in recent years, the treatment to cancer-related pain remains largely unchanged.
- the management of cancer-related pain is considered far more complex than the simplifed 3-tiered “analgesic ladder”
- Incorporating interventional techniques such as PNS properly can optimize the current treatment strategy and improve outcomes.

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What is the validity of our pain diagnosis and assessment compared to cancer diagnosis and assessment? Are we serious medical partners for the oncologist?

4. Drug Induced Peripheral Neuropathy (DIPN)

Drug Induced Peripheral Neuropathy (DIPN)

- Iatrogenic development of Drug Induced Peripheral Neuropathy (DIPN)

- Can include
  - chemotherapeutic agents
  - antimicrobials,
  - cardiovascular drugs,
  - psychotropic, anticonvulsants
- Check for concommittant risk factors

Vinca alkaloids	all grade 96 % / severe 37 %
Platinum	40 %
Thalidomide	23 -70 % , severe 13 %
Taxanes	30 % in monotherapy, 70 % combi
Statines	odds ratio 1,3 – 4,6
Amiodarone	2 / 1000
Antibiotics	between 2 – 85 % (metronidazole)
NRTIs	30-100 %
Levodopa	20-55 %

Beware with the following clinical symptoms:

Pain, paresthesia or weakness or preexisting neuropathy, diabetes or genetically predisposing diseases

2020, Jones M, Current Clin Pharmalogy

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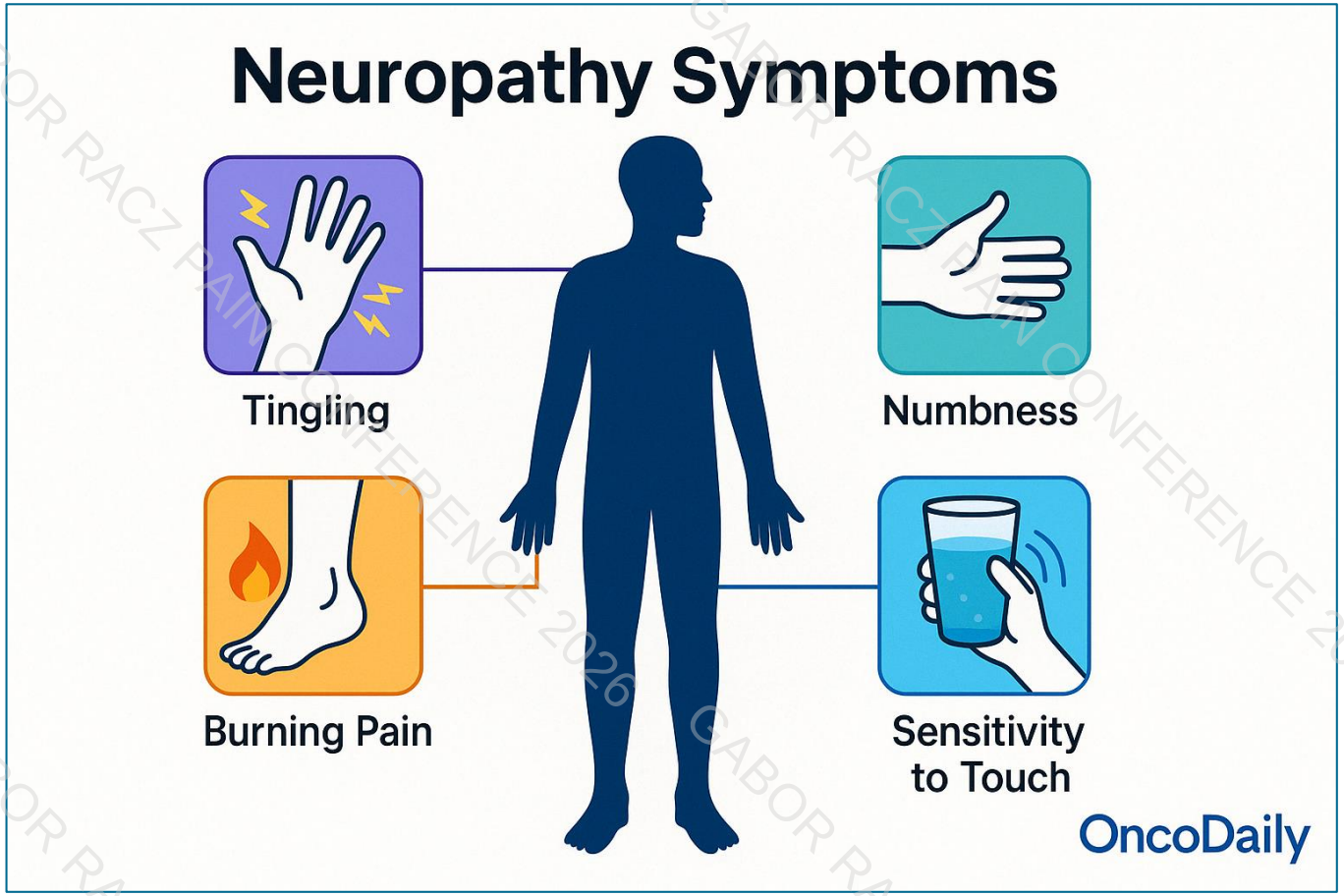
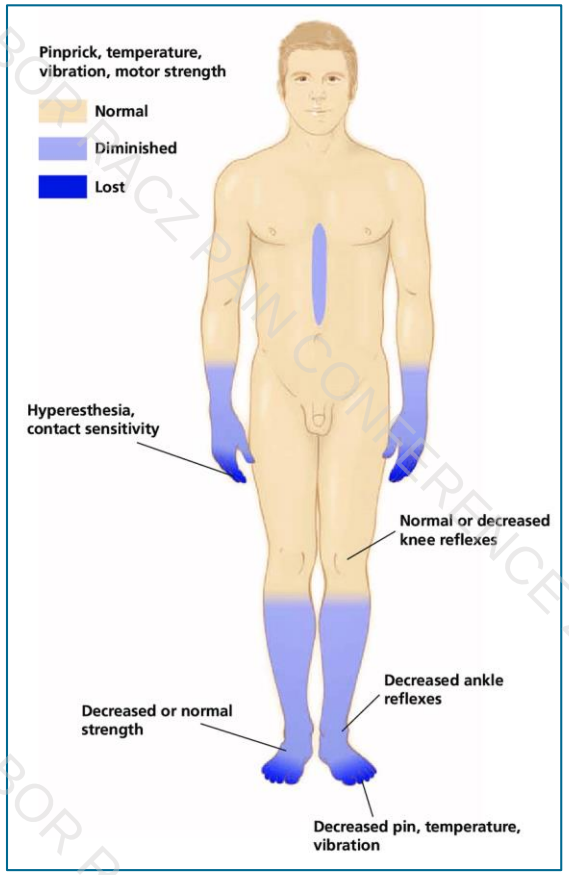
5. Chemotherapy - Induced Peripheral Neuropathy (CIPN)



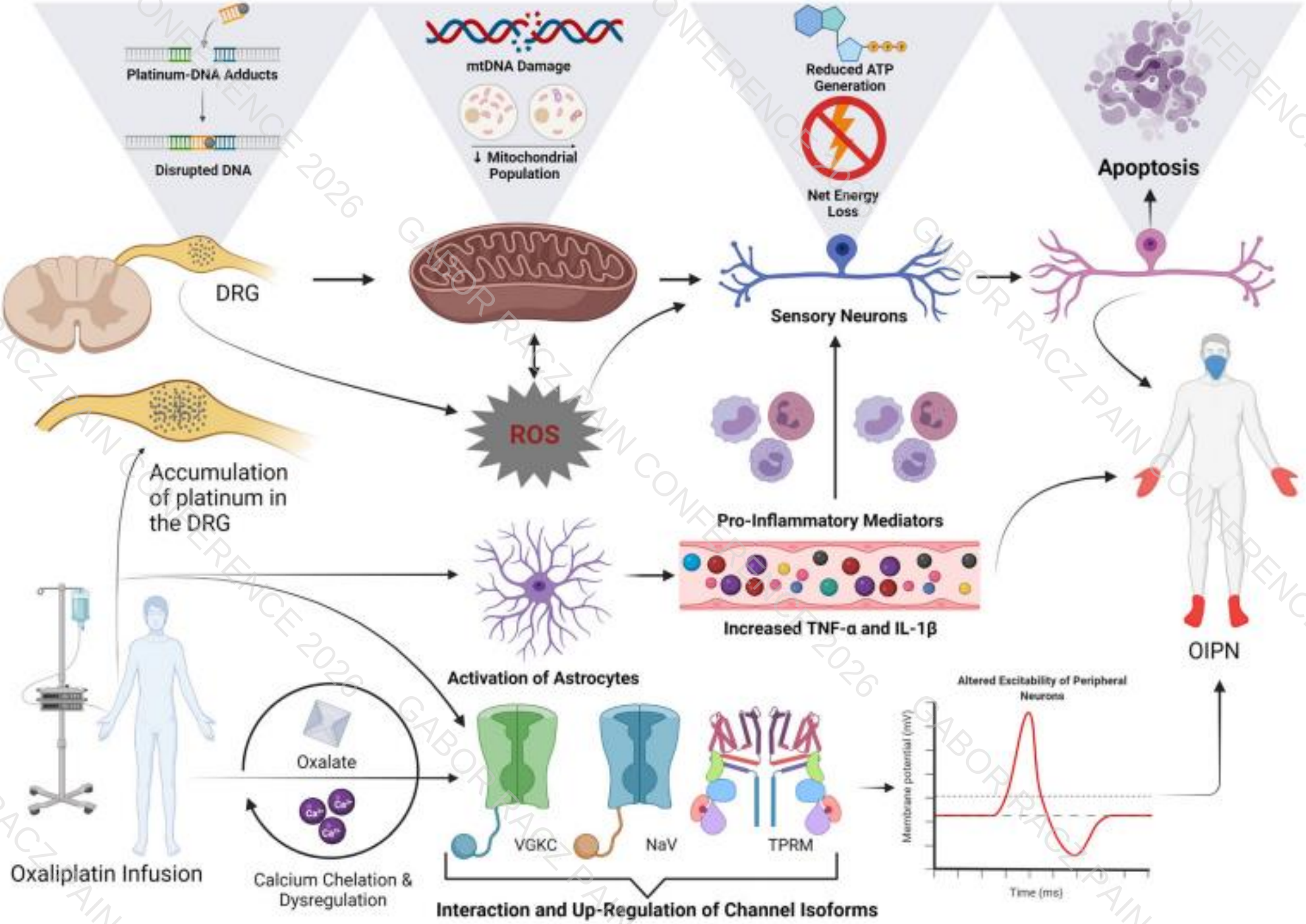


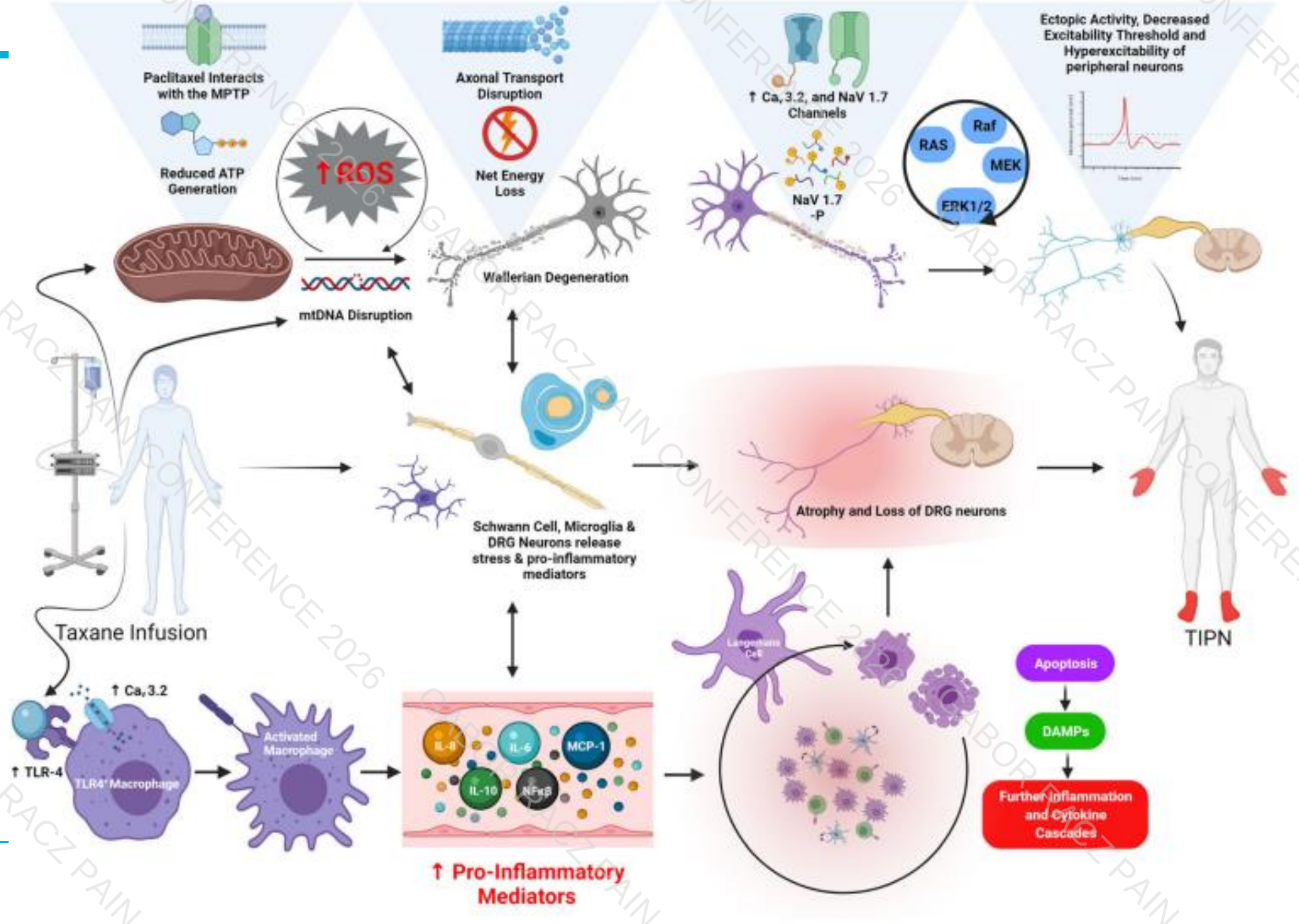
CIPN

- CIPN is a **common adverse event** which affects the sensory, motor and autonomic nerves
- The diagnosis of chemotherapy-induced peripheral neuropathy lacks a gold standard
- There are currently no proven strategies or interventions to prevent or limit the development of CIPN
- A mechanistic approach is needed to address strategies for prevention and treatment of CIPN
- High impact on quality of life of individuals
- Painfull CIPN incur a significant economic burden (analgesics, hospitalisations, emergencies, OPD)

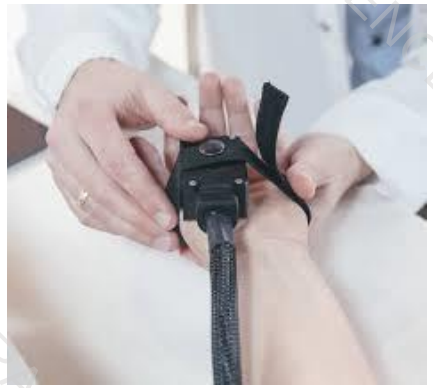
2021, Burgess J, Oncol Ther 9

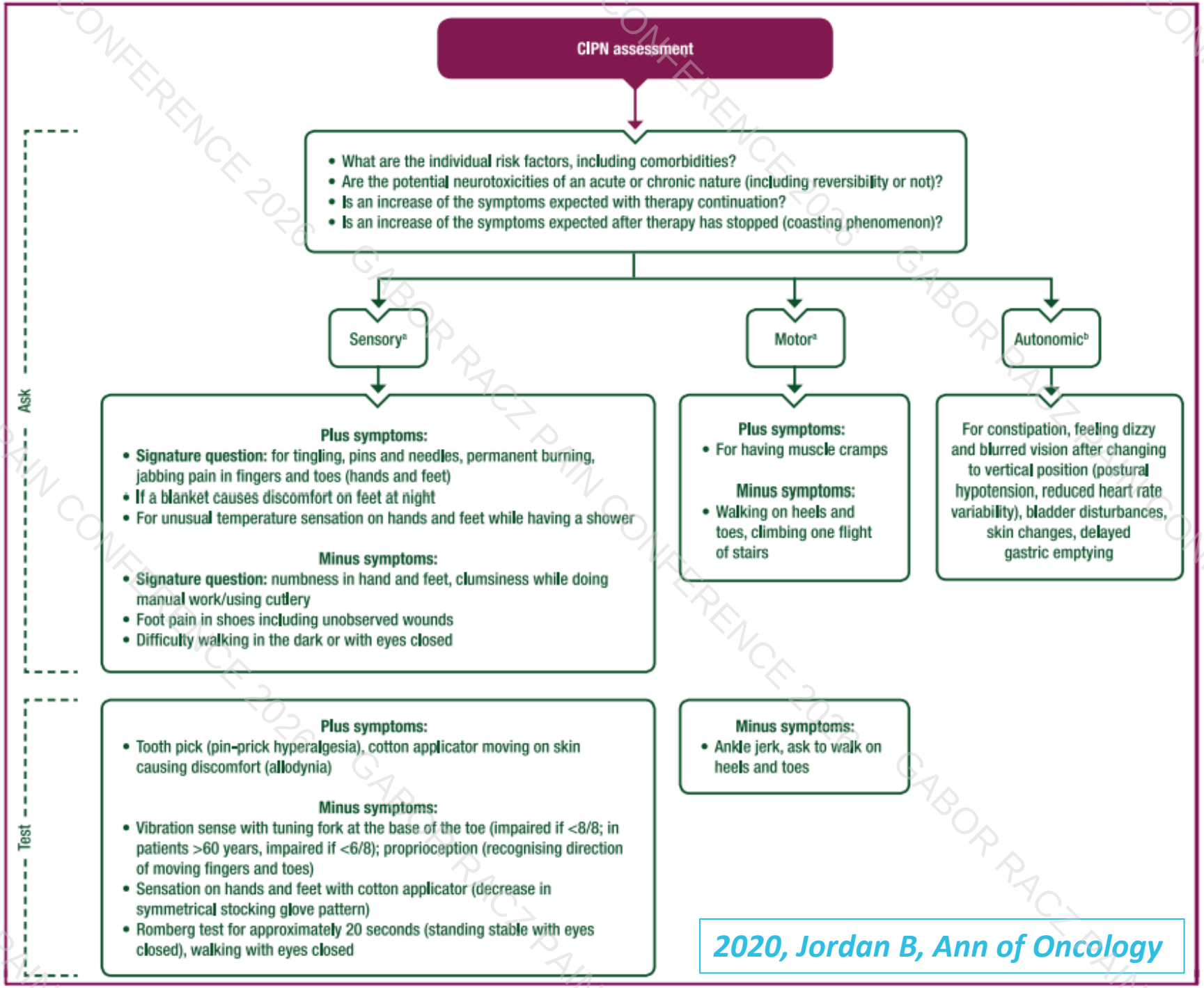
6. CIPN -Pathophysiology


Platinum-DNA Adducts
Disrupted DNA
mtDNA Damage
↓ Mitochondrial Population
Reduced ATP Generation
Net Energy Loss
Apoptosis
DRG
Sensory Neurons
ROS
Accumulation of platinum in the DRG
Pro-Inflammatory Mediators
Increased TNF-α and IL-1β
OIPN
Activation of Astrocytes
Oxalate
Calcium Chelation & Dysregulation
Oxaliplatin Infusion
VGKC
NaV
TPRM
Interaction and Up-Regulation of Channel Isoforms
Altered Excitability of Peripheral Neurons
Membrane potential (mV)
Time (ms)


Paclitaxel Interacts with the MPTP
Reduced ATP Generation
↑ROS
Axonal Transport Disruption
Net Energy Loss
↑ Ca, 3.2, and NaV 1.7 Channels
NaV 1.7 -P
RAS
Raf
MEK
ERK1/2
Ectopic Activity, Decreased Excitability Threshold and Hyperexcitability of peripheral neurons
mtDNA Disruption
Wallerian Degeneration
Taxane Infusion
Schwann Cell, Microglia & DRG Neurons release stress & pro-inflammatory mediators
Atrophy and Loss of DRG neurons
TIPN
↑ Ca, 3.2
↑ TLR-4
TLR4+ Macrophage
Activated Macrophage
IL-8
IL-6
MCP-1
IL-10
NFκB
Langerhans Cell
Apoptosis
DAMPs
Further Inflammation and Cytokine Cascades
↑ Pro-Inflammatory Mediators

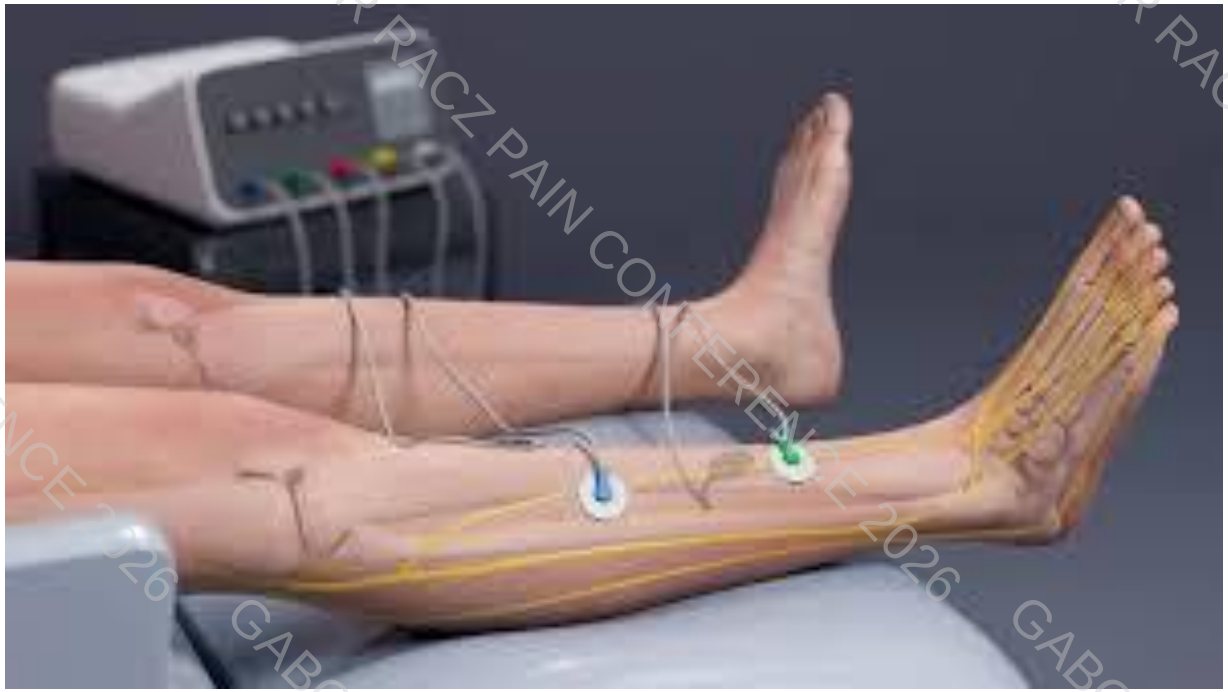
7. Diagnosis & Assessment



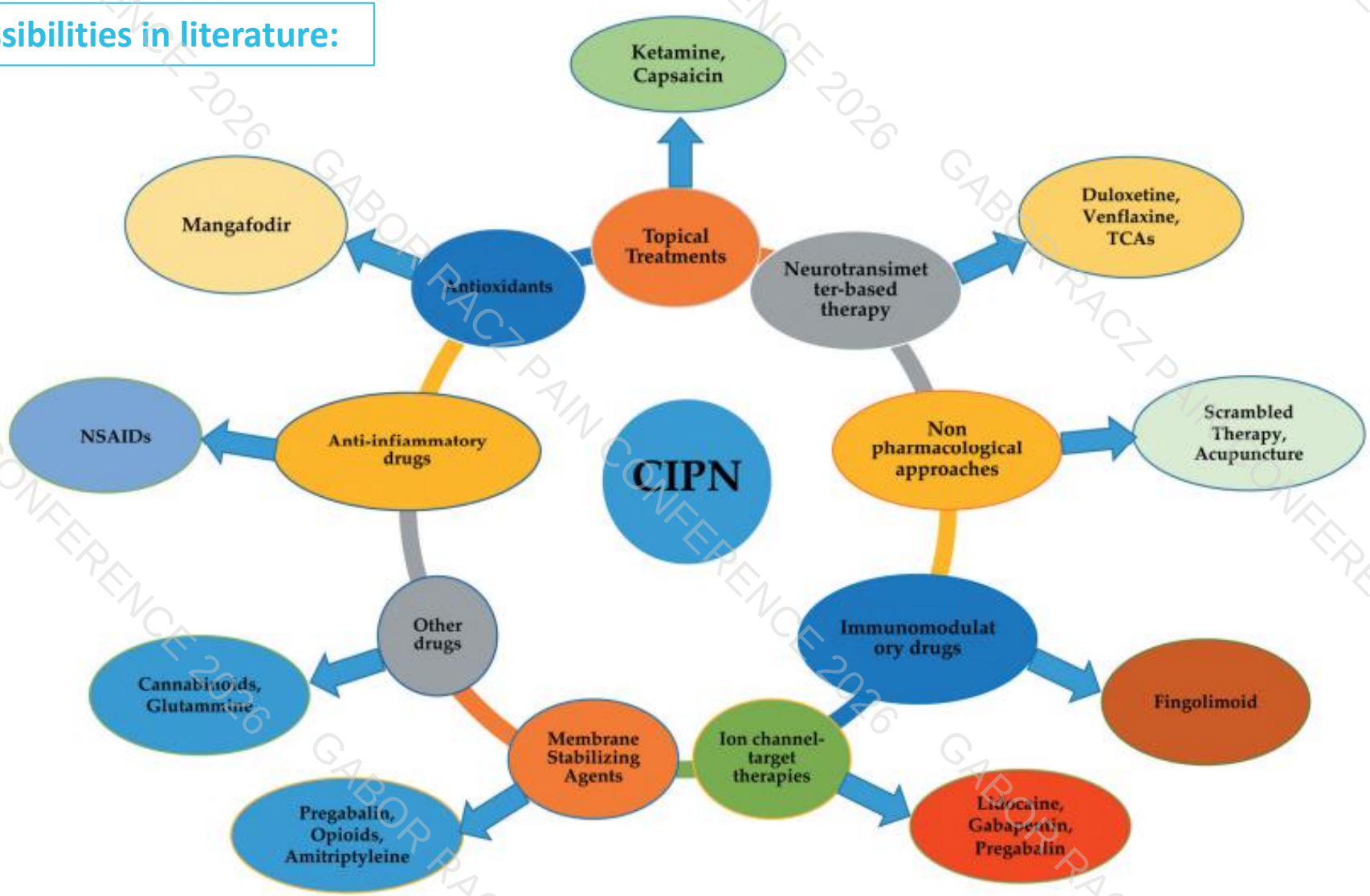


2020, Jordan B, Ann of Oncology

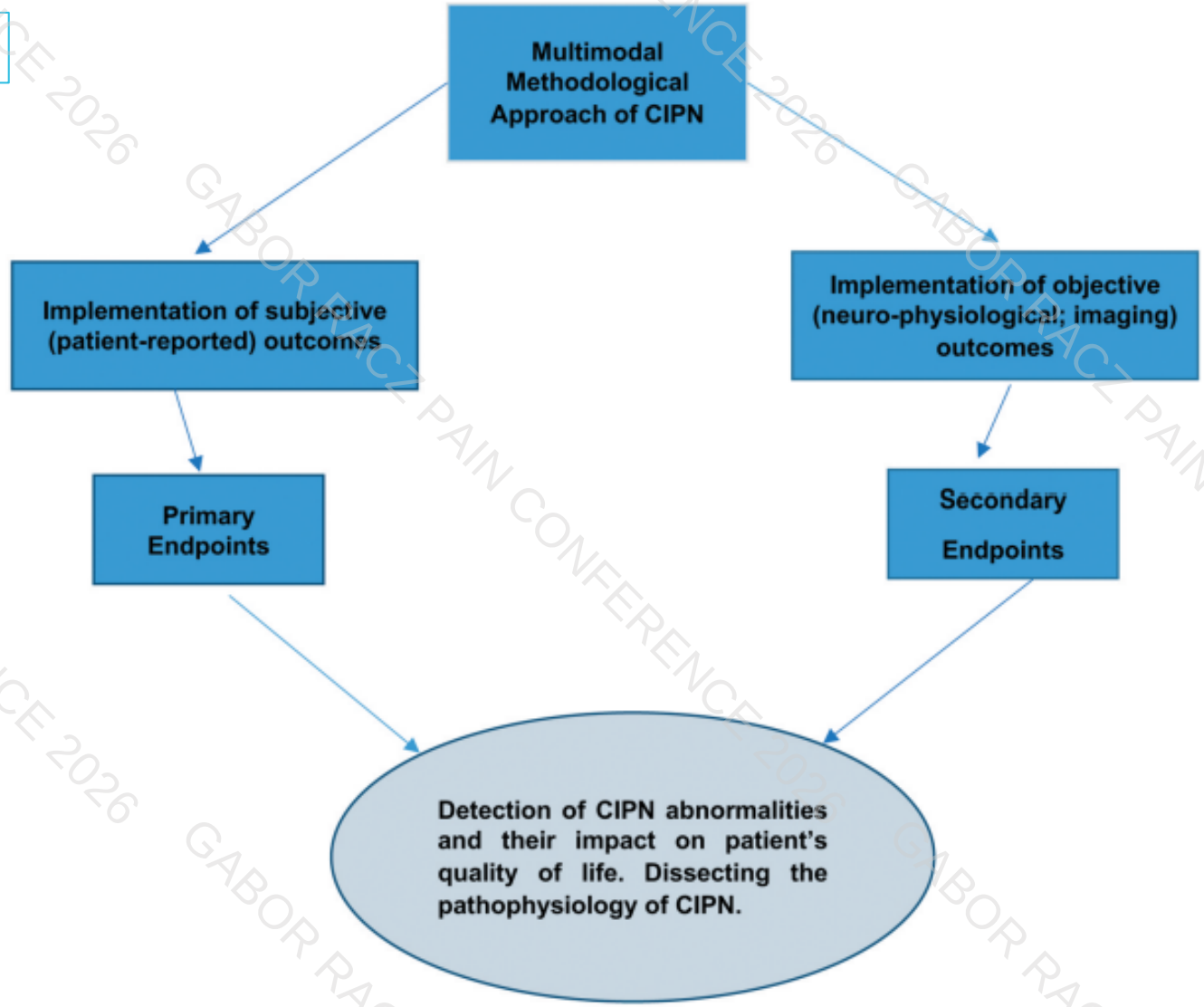
8. Evidence of prevention & treatment



CIPN treatments possibilities in literature:



Multimodal Approach of CIPN



Chemotherapy-Induced Peripheral Neuropathy (CIPN)

ASCO EBM guidelines 2020:

- Oxaliplatin and paclitaxel cause **acute neuropathy**:
  - Symptoms: cold sensitivity, throat discomfort, discomfort swallowing cold liquids and muscle cramps
  - during infusion and increases 2-3 days later with each dose
  - With each cycles symptoms double!
- More prolonged often **refractory chronic neuropathy**:
  - Primarily sensory, only later motor or autonomic neuropathy
  - Numbness, tingling and pain
  - Stocking-glove distribution fingers and toes
- Diagnosis: history, neurological examination, electromyography (EMG), (QST), (Skin Biopsy),

2020, Loprinzi C.L., J Clin Oncol 38

Chemotherapy-Induced Peripheral Neuropathy (CIPN)

ASCO EBM guidelines 2020:

- Prevention and treatment:
  - No agents are recommended for the prevention of CIPN
  - The use of acetyl-L-Carnitine should be discouraged
  - When intolerable painful symptoms of functional impairment arise discuss appropriateness of **dose delaying, dose reduction, substitutions or stopping chemotherapy**
  - Duloxitine is the only agent that has appropriate evidence to support its use in CIPN

ESMO guidelines 2020: evidence and recommendations of therapy:

- Regular assessment of CIPN should be done as it enables the health care professionals to discover potential symptoms early, before the neuropathy becomes irreversible [IV, A].
- No effective drug exists to prevent CIPN [II, DeI, E].
- Cryotherapy with, for example, frozen socks and gloves can be considered (most evidence is available for taxane therapy) [II, C]
- **SCS has been reported to be successful in several cases; however, no RCT is available in patients with CIPN**. It may be discussed for selected patients, with truly refractory neuropathic pain and for whom conservative approaches failed [V, C]

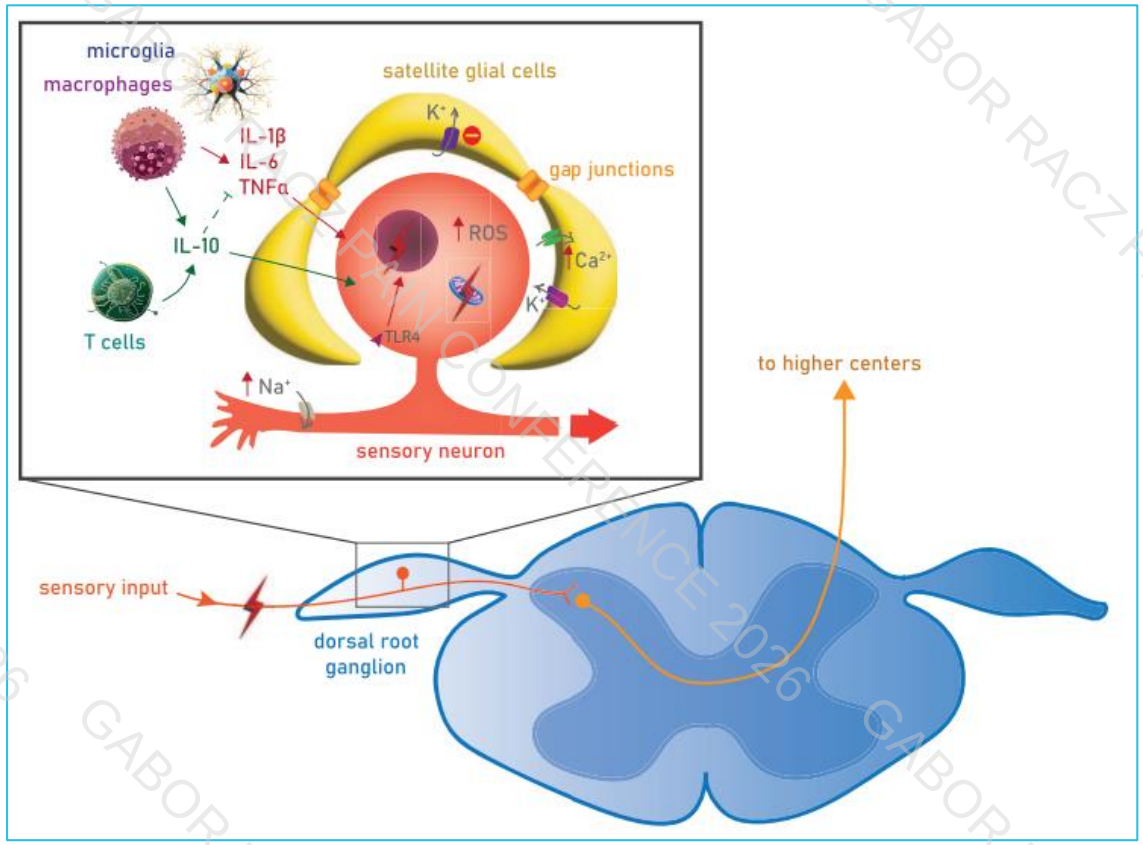
Evidence of interventional treatments for CIPN

- IDDS –Intrathecal Drug delivery is not well studied and no evidence:
  - Therefore, **future studies are warranted** to investigate the potential role in CIPN
- Scrambler therapy: modest improvement, low evidence
- Neuromodulation:
  - Spinal cord stimulation: only limited data, very low quality, only case reports, series
  - Peripheral nerve stimulation:
  - Percutaneous auricular nerve stimulation
    - Future studies are needed to investigate the role of SCS/DRG-S (no level of evidence, degree I) and PNS in CIPN (level II-2, degree C)

2023, D'Souza R & Abd-Elsayed, Current Pain and Headache Reports, 27:99 - 116

9. Important pilot studies and mission for WIP!

Further exploration and need for RCTs from mechanistic approach:



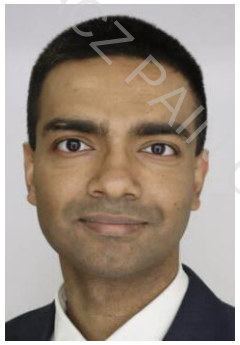
- **Targeting dorsal root ganglia from bench to bedside:**
- If patients with CIPN do not respond to conventional therapies:
- DRG-S deserve more rigorous evaluation in longterm survivors with CIPN!
- Alternatively: Rhizotomy and RF ablation of the DRG
- RCTs are needed (none reported in trial.gov!)

Important pilot studies

Case Reports > Pain Med. 2019 Apr 1;20(4):857-859. doi: 10.1093/pm/pny209.

Chemotherapy-Induced Peripheral Neuropathy Treated with Dorsal Root Ganglion Stimulation

Pauline S Groenen [1 2], Noud van Helmond [1], Kenneth B Chapman [1 3 4]



biomedicines MDPI

Systematic Review

Neuromodulation Therapy for Chemotherapy-Induced Peripheral Neuropathy: A Systematic Review

Ryan S. D'Souza [1], Yeng F. Her [1], Max Y. Jin [2], Mahmoud Morsi [3] and Alaa Abd-Elsayed [2,*]

> Pain Pract. 2023 Sep;23(7):793-799. doi: 10.1111/papr.13259. Epub 2023 Jun 1.

Dorsal root ganglion stimulation for chemotherapy-induced peripheral neuropathy

Eliana Ege [1], Daniel Briggi [1], Steven Mach [2], Billy K Huh [2], Saba Javed [2]

Conclusion and take home messages

CIPN: Conclusions and take home messages

- CIPN
  - Is a complex iatrogenous effect of oncological agents
  - Needs better diagnosis and assessment tools
  - Presents as acute neuropathy with increasing symptoms per cycle
  - Prolonged chronic neuropathy in the majority of the patients / survivors
  - Needs a high skilled standardized evaluation methodology to identify risk factors
  - Needs better treatment opportunities
  - Points out that dorsal root ganglia are strongly involved in the pathophysiology

  - Therefore, more DRG focused research is needed by:
    - RCTs in DRG-S and PNS


Nijmegen, Valkhof, 2017
Chapel from anno 1159 PC