GBS and CIDP – a potpourri of interesting stuff

Gareth Parry

GBS/CIDP

- New potential viral triggers for GBS:
  - Zika
  - Dengue
  - [West Nile, Japanese encephalitis, chikungunya]
- GBS treatment:
  - IVIg vs therapeutic plasmapheresis exchange (TPE)
- CIDP treatment:
  - Steroids vs IVIg vs TPE
  - Rituximab
  - Role of antibody testing in choice of treatment
- Ongaonga update

GBS triggers

- 70%-80% of GBS cases have an identifiable illness that occurs 10-20 days prior to onset of weakness and is thought to trigger the immunological attack on the nerves.
- In NZ and other western countries the commonest antecedent illness is an upper respiratory illness; the specific infecting organism is seldom identified.
- Gastroenteritis is the next most common GBS trigger and is usually due to Campylobacter jejuni, a common contaminant of chicken and sometimes other meat.
- There has been a recent upsurge in interest in new potential viral triggers, two of which (Zika, dengue) are relevant to NZ

Viral GBS triggers

- Dengue and Zika virus infections are common in the Pacific Basin.
- Both are transmitted via the female Aedes mosquito which is found widely throughout the Pacific Islands.
- This family of mosquitoes has not established itself in NZ but with global warming and the recently shown cold adaptation of the mosquito it may well do so in the near future.

Viral GBS triggers

- NZ'ers visiting the Pacific Islands are at risk of contracting one of these illness which may be asymptomatic or not manifest itself until after returning home.
- Because there is a 10-20 day gap between infection and GBS, even if the viral illness itself does manifest in the Islands the GBS may not occur until the patient has returned home.

Dengue and GBS

ÅA few isolated cases of GBS have occurred following dengue but the population of the Pacific Islands is so small it is impossible say with certainty whether dengue has triggered the GBS or is just a coincidental association.

Dengue and GBS

- Dengue is also common in South India (and other south and SE Asian countries), occurring mainly during the monsoon season (June-August).
- GBS in South India is a seasonal disease that peaks shortly after the dengue season, suggesting that dengue may be a trigger for GBS.
- Because the population of that region is so vast it may be possible to establish whether dengue is an important GBS trigger.
- An international study has been launched to identify all GBS cases in 9 countries where viral fevers are common to determine whether they constitute an important GBS trigger.
- This may drive programs to develop effective vaccines against dengue.

Zika and GBS

- Zika virus was first identified in Uganda in the 1950's.
- Like dengue it is transmitted by the Aedes mosquito.
- Quickly spread through Africa, the Middle East and India, reaching South India within about 10 years.
- Typically Zika usually causes fever and rash and recovers spontaneously.
- About 80% of patients in epidemics have no symptoms of the infection.
- No cases of GBS had been reported during the march of the virus through its early territory:
  - The original virus did not trigger GBS.
  - The symptoms of Zika are so nonspecific that it was not identified as a trigger.

Zika and GBS

- During the early 2000's Zika spread south and east through SE Asia, Australia and the Pacific, eventually reaching South America.
- Subsequent northward spread got the attention of the world because the US was threatened.
- The virus mutated during this south-east march and it developed neurotrophism – an attraction for nervous tissues:
  - Many cases of microcephaly, a failure of the brain to develop, if pregnant women were infected.
  - A 10-20 times increase in GBS

Zika and GBS

- Because the virus has established a foothold in the Pacific it potentially threatens NZ:
  - Individuals may contract the virus while living, working or vacationing in the Pacific.
  - Infected individuals may develop GBS while in the Pacific or when they return to NZ (at least 2 such cases have been identified).
  - The disease is unlikely to gain a foothold here because the mosquito vector is not endemic here.
  - Sexual transmission and transmission via blood products can occur and remain a small risk for NZ-ers.
  - Like dengue, there is a risk of establishing the vector here because of climate change or because the mosquito becomes cold-adapted.

GBS treatment

- By far the most important aspect of GBS treatment is medical support and physical/occupational therapy.
- Specific immunological therapy if administered early (within 2 weeks) hastens recovery but impact on the ultimate degree of recovery is small.
- Intravenous immunoglobulin (IVIg) and therapeutic plasma exchange (TPE or PLEX) are probably equally effective.

GBS treatment

- IVIg is perceived as being easier to administer and safer:
  - Ease of administration perception is based on 1980's technology
  - Head-to-head studies have failed to confirm greater safety.
- TPE is 25%-40% less expensive than IVIg in most healthcare delivery systems.
- IVIg constitutes a major cost to DHB's but peculiarities of the NZ Blood Service funding model provide no incentive for them to provide easy access to TPE as 1st line treatment for GBS patients.
- IVIg costs are escalating and periodic shortages have occurred.
- We calculated that switching all GBS patients to TPE would save the DHB's ~$350,000 p.a.

Eculizumab and GBS treatment

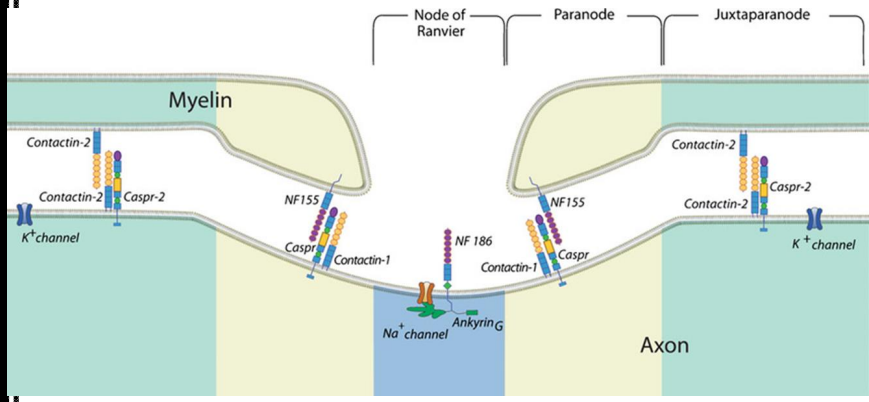
- The immune attack on nerves in GBS requires the participation of a chemical called *complement*.
- Inhibition of complement in experimental models of GBS prevents the development of the disease.
- Eculizumab is a complement inhibitor that is highly effective in other complement-mediated diseases.
- International studies are currently underway in GBS.
- Current cost of eculizumab is ~$500,000/yr for chronic diseases, down from ~$1M 2 years ago.

CIDP treatment update

- CIDP is a treatable disease.
- Rapidly evolving forms (2-6 months) tend to be more severe but also respond best to treatment.
- If treatment is not started within 2 years of onset of symptoms response to treatment is more likely to be slow and incomplete.
- Steroids (e.g., prednisone), IVIg and TPE have all been shown to be effective:
  - Treatment roughly equally divided between IVIg and steroids in NZ
  - Almost all patients treated with IVIg in the US
  - TPE is rarely used because of the inconvenience associated with a chronic disease.

CIDP treatment update

- None of the proven effective treatments is ideal and individual patients respond to different treatments differently.
  - IVIg and TPE control the disease but do not induce remission
  - Steroids may induce remission which is why I prefer them as 1st line treatment
  - Pulsed steroid regimens are just as effective as daily dosing and carry fewer risks.
- Treatment usually needs to be continued for years although long-term remission may occur, allowing withdrawal of treatment.
- Treatment may be withdrawn if the disease becomes inactive, even if residual effects of the nerve damage persist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Paranode
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Myelin
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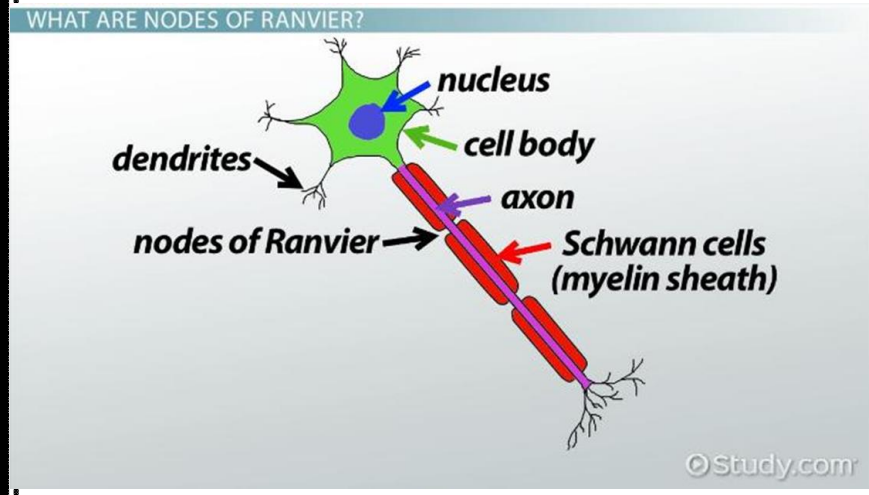
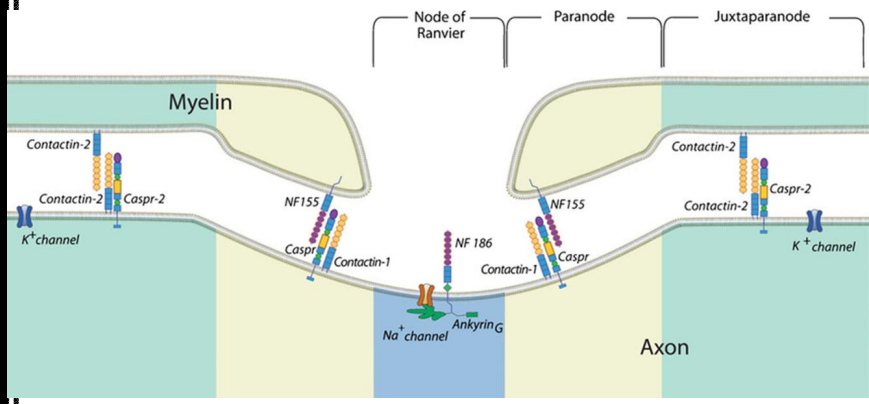

WHAT ARE NODES OF RANVIER?
nucleus
cell body
dendrites
axon
nodes of Ranvier
Schwann cells
(myelin sheath)
Study.com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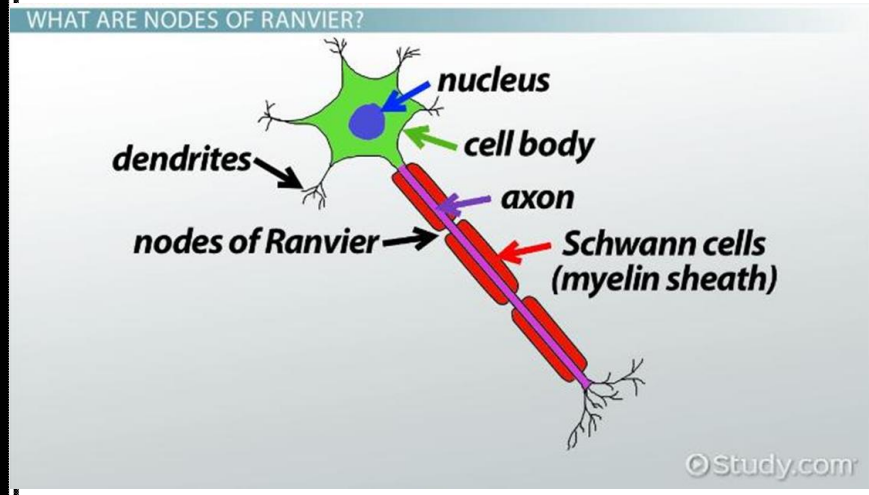
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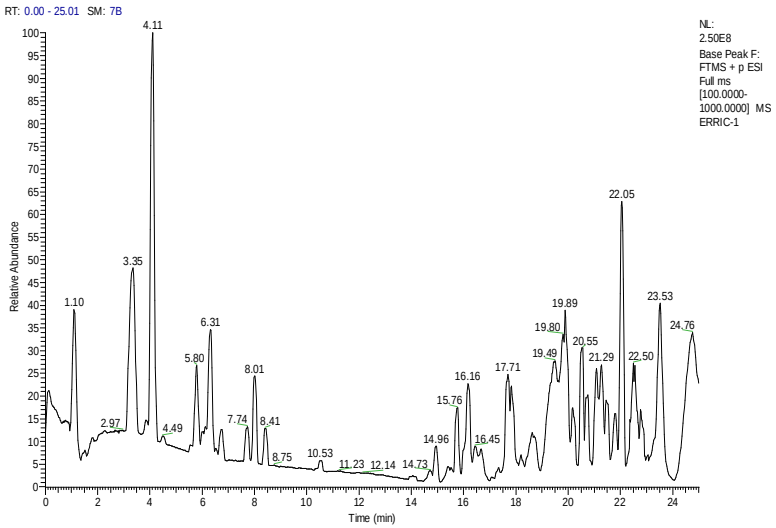
2019 progress on Ongaonga research project



Ongaonga research update

- Neuropathic pain is a common residual effect of GBS and also occurs in about 40% of patients with CIDP.
- Currently available treatments are only partly effective and their usefulness is limited by adverse effect.
- We have been investigating the therapeutic potential of the native NZ nettle, ongaonga (Urtica ferox) for the treatment of neuropathic pain.
- The GBS Support Group Trust, NZ, has provided generous funding to help defray the costs of the research.

Only the trichomes contain the neurotoxin(s); exposure results in evanescent pain with subsequent sustained numbness

Neurotoxicity of ongaonga – an exercise in inadvertent self-experimentation

- While harvesting trichomes a single spine penetrated the glove over D2 and another over D3.
- Estimated volume of toxin in one trichome - ~0.5-1 microliter
- Immediate burning pain (intensity ~7/10) which began to improve in ~5 minutes and had largely resolved by 30 mins.
- Intense tingling after ~5 minutes which was constant for ~18 hours and then continued intermittently for ~48 hours, particularly exacerbated by cold.
- Numbness after ~15 minutes lasting ~3 days. Light touch and cold thermal sensation were lost.
- Symptoms not just at penetration site but involved an area about 1 cm diam.

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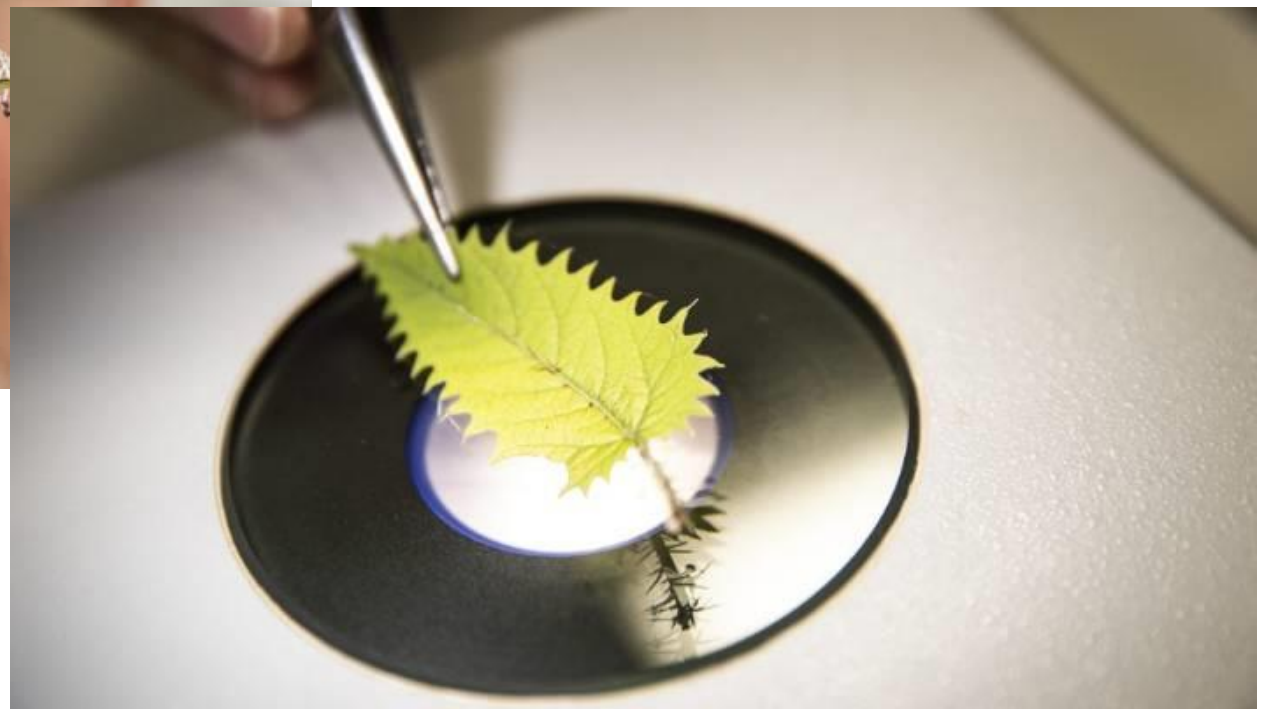


ñTheir stinging efforts were published in the prestigious Christmas edition of the *British Medical Journal…*”

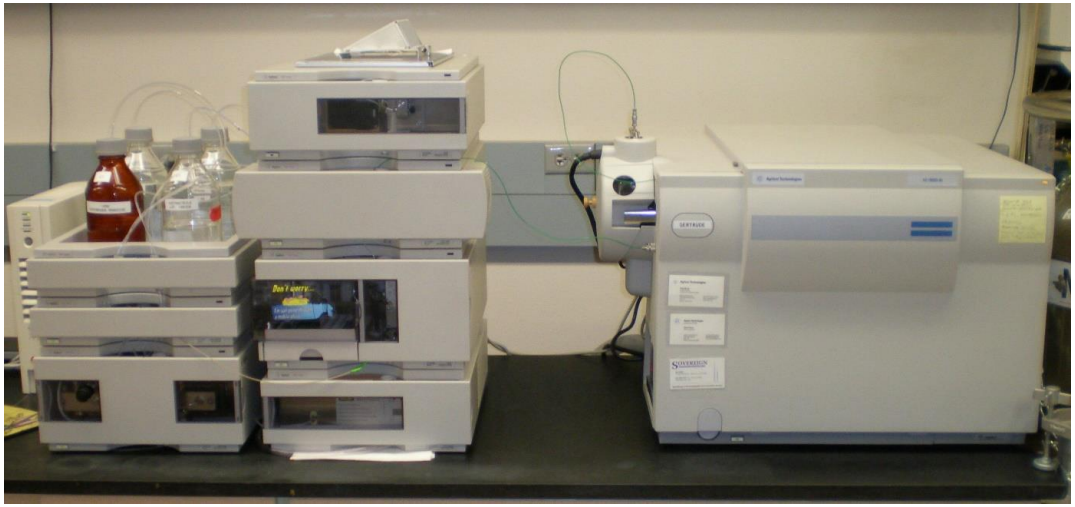
thebmj

Feats of self experimentation

Gareth Parry and **Eric Buenz** explore the storied history of scientists using themselves as guinea pigs

A significantly-improved extraction method

Additional funding from the Royal Society of New Zealand to support collaboration with Chinese Academy of Sciences



CATALYST FUND
LEADERS

For distribution via Research Office
Professor Buenz
eric.buenz@nmit.ac.nz

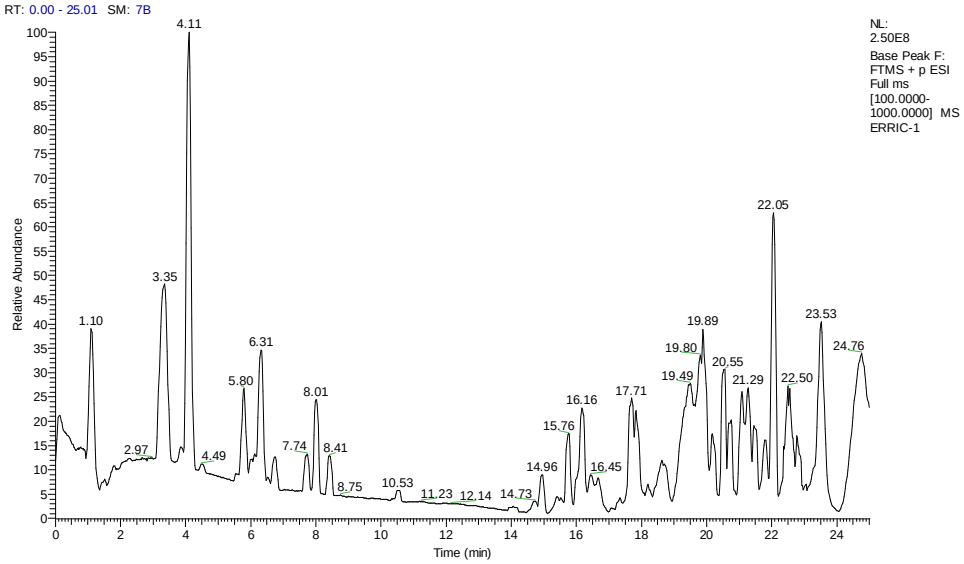
5 June 2018

RE: Application to January 2018 Catalyst: Leaders New Zealand-China Scientist Exchange Programme

Reference Number: 18-NMI-001-CHN
Project Title: A novel natural product compound for treating diabetic neuropathy

Dear Professor Buenz,

It gives me great pleasure to advise you that your application for a Catalyst: Leaders New Zealand-China Scientist Exchange Programme grant in the January 2018 funding round has been successful.



Monday we start enrolment for a new trial examining the comparison to 4% lidocaine

Self-experimentation suggests that the active component of ongaonga lasts >20xs longer than lidocaine