Calcium Ion (Ca++) Homeostasis for Epilepsy and Migraines

Overview: This repurposing opportunity is based on the newly identified pathogenesis underlying epilepsy (seizures) and migraines, and as disclosed in our US Patent 8,197,858.

Prior Art Versus Us: Prior art has focused on the direct impact of known migraine and seizure triggers on nerve cells, which could not consistently explain the underlying etiology. In contrast, we found that all of these known triggers result in the release of calcium ions (Ca++) from bone, which in turn affects nerve and muscle in a way that explains the underlying etiology and resulting pathogenesis, without contradiction. This opens the door to using bone homeostasis drugs (that inhibit release of Ca++ from bone) for full spectrum inhibition of the underlying etiology.

The Pathogenesis: The known triggers all have disclosed pathways that cause the release of Ca++ from bone. The detailed pathways are presented in our US Patent 8,197,858.

Compound	Effect
decrease estrogen	increases extracellular Ca++
decrease testosterone	increases extracellular Ca++
increase prostaglandins	increases extracellular Ca++
increase Vitamin D (1,25D)	increases extracellular Ca++
decrease growth hormones (GH, IGF, BMP)	increases extracellular Ca++
increase parathyroid hormone (PTH)	increases extracellular Ca++
decrease calcitonin	increases extracellular Ca++
increase Vitamin A / Retinoids	increases extracellular Ca++
increase Lithium	increases extracellular Ca++

In turn, the known effects of elevated Ca++ levels on nerves and muscles are as follows:

Hypersensitization of nerves by:

1) depolarization of nerve membranes per the Nernst Equation
   - 1 mM to 2 mM rise in Ca++ levels drops the stimulus voltage required by 40%

2) enhanced Ca++ channel mediated neurotransmitter release
   - 1 mM to 2 mM rise in Ca++ levels doubles the amount of Ca++ for inrush through the channels
   - also boosts the concentration gradient differential (driving force for the inrush) by 63%

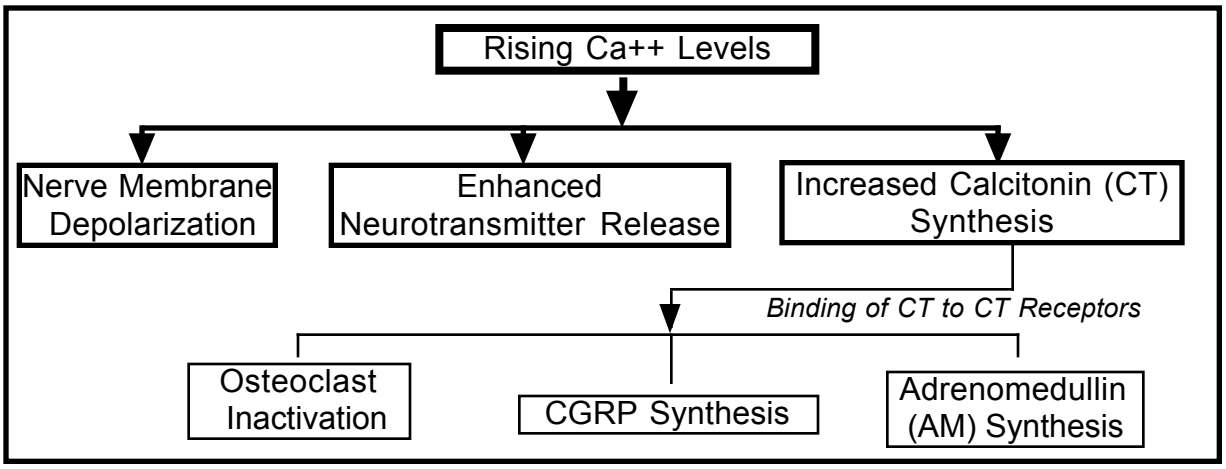
Hypersensitization of muscles by:

1) enhanced neurotransmitter release at the neuromuscular junction, per the above
2) enhanced muscle contractility via SRCaRC and removal of tropomyosin block between actin and myosin

Synthesis of Calcitonin Gene Related Peptide (CGRP) by:

- Rising Ca++ levels trigger synthesis and release of calcitonin (CT)
- CT binding with calcitonin receptors (CTR) results in synthesis of CGRP
- Conversely, it is known that CGRP antagonists provide therapeutic benefit to migraine sufferers

A simplified flowchart of the downstream nerve effects is shown below:



As disclosed in our patent, drugs that could be repurposed to inhibit Ca++ release from bone and hence inhibit the the underlying etiology from occurring in the first place, include:

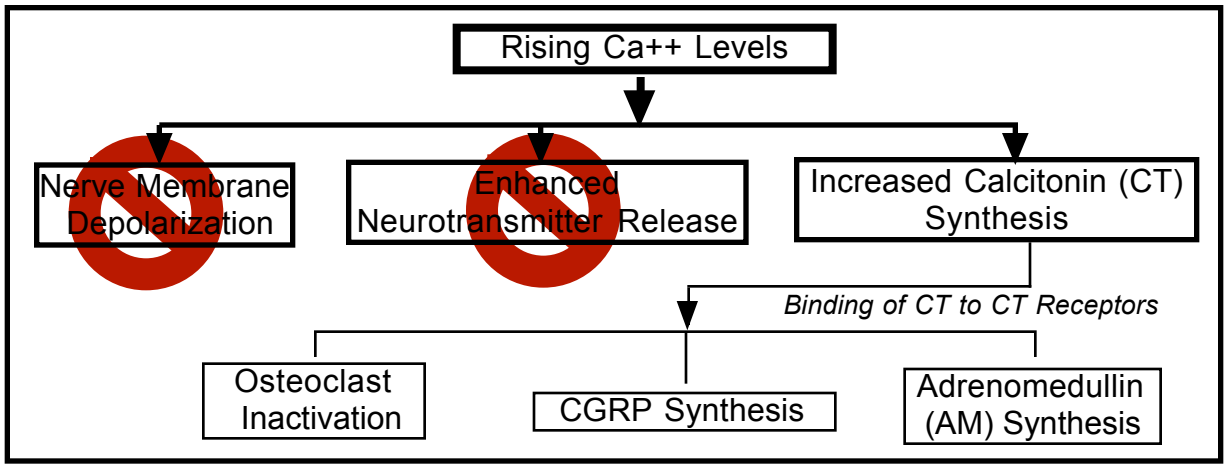
- SERMs or SARMs (e.g. raloxifene)
- RANKL inhibitors (e.g. denosumab)
- Calcimimetics (e.g. cinacalcet)
- Bisphosphonates (e.g. risedronate, pamidronate, clodronate, zoledronate, etc...)
- Vitamin D Inhibitors (e.g. ketoconazole, chloroquine)
- Endocrines that inhibit bone resorption (e.g. testosterone, estrogen, GH/IGF-1, etc...)

Epilepsy Market Opportunity: Epilepsy is a $ 3 Billion market dominated by drugs that inhibit nerve function and have bad side effects (e.g. zombie-like mental state).

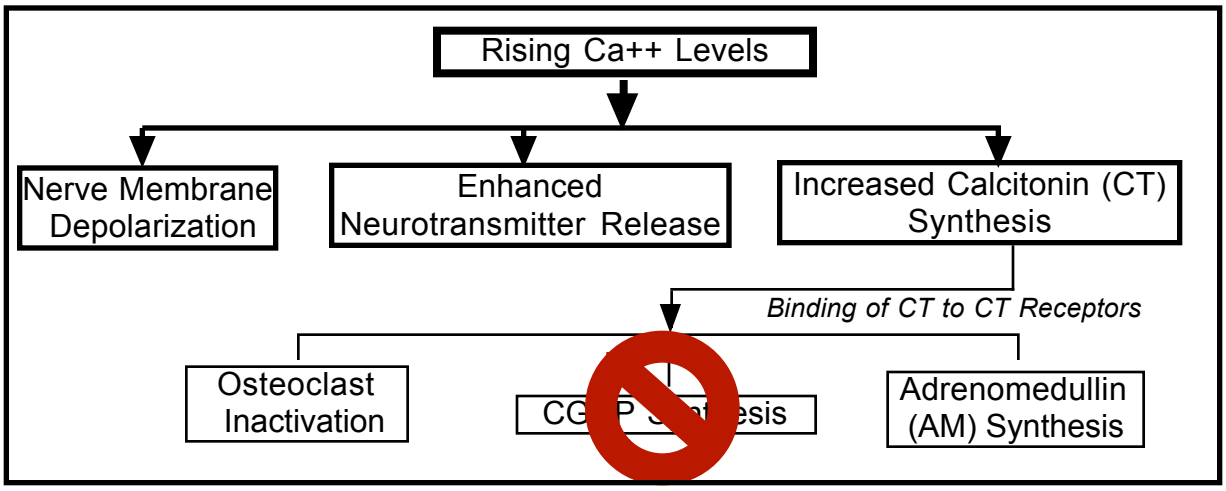
Our value proposition is a new etiology / full pathogenesis inhibition based treatment approach that works by a different MOA (mechanism of action) than any other existing drug and should provide much greater potency.

Furthermore, because the MOA is unlike anything is use today, it can be used in combination with other drugs currently available. Combination use with nerve inhibitors could be used to lower the doses of nerve inhibitors used, and hence reduce the bad side effects associated with nerve inhibiting drugs.

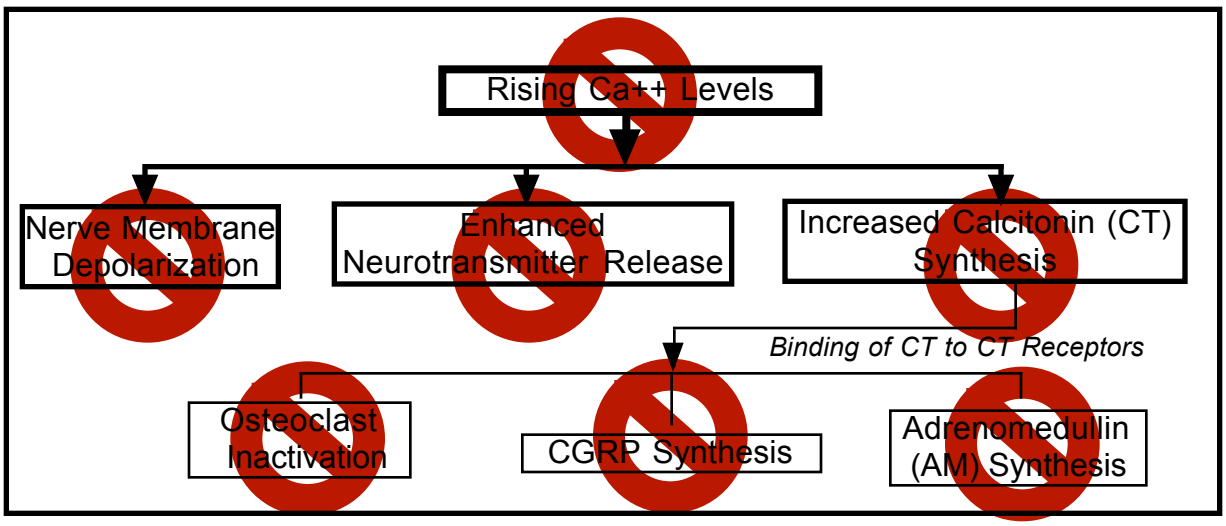
Competitors 1: Nerve Inhibitors only counteract the downstream nerve hypersensitization.



Competitors 2: CGRP antagonists target the downstream activity of CGRP



We inhibit the initial etiology and hence everything downstream in the pathogenesis.



The mechanistic advantage should be unsurpassed efficacy.

Epilepsy / Seizures Intellectual Property:

We were awarded US Patent 8,197,858 for the treatment of epilepsy / seizures using the bone homeostasis drug raloxifene.

While raloxifene is currently off patent, our patent 8,197,858 would provide patent protection for the use of raloxifene in treating epilepsy / seizures until 2030.

Current USPTO practice greatly narrows the scope of examination of an application to a single drug in a single indication. In a requirement to narrow the claim to a single drug, we chose Raloxifene , out of the long list of functionally equivalent drugs we presented, because of raloxifene's superior potency (triple action) in preventing release of Ca++ from bone.

Patent office practice now also requires direct proof of efficacy data, and we lucked out in that our filing date beat out a publication showing that a similar bone homeostasis drug (tamoxifen) showed promise in seizures. This was accepted by the examiner as adequate proof of efficacy data.

While the newer, narrower claim restrictions to a single drug imposed by the USPTO effectively eliminate the principle of functional equivalence, they effectively also turn a patent such as 8,197,858 into a "scorched earth" patent, against the use of the other bone homeostasis drugs.

The Issued Claim (as rewritten by the Examiner)

1. A method of treating seizures consisting of administrating, to a patient in need thereof, a therapeutically effective amount of raloxifene in a dosage form to inhibit release of calcium from bone.

Contact Info: **Mark Zamoyski,** e-mail: zamoyski@metricmail.com