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Short Takes

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Physician-scientists in neurology: Research contributions of a cohort of neurologists. Bensken WP, Hansen AK, Norato G, et al. Neurology 2018;91:508–514

Flash summary: The objective was to study how physician-scientist publications are quantified using author-level metrics.

Neurology residency alumni were identified from programs with the highest National Institute of Neurology and Stroke funding between the years 2003 to 2005. The publishing history, funding history, and impact factor (h-index) were obtained for each physician. From 15 programs and 252 neurologists, 186 neurologists were identified as being interested in research. The mean h-index, yearly publication rate, and cumulative number of publications were significantly higher for those with RO1 funding compared to two other groups: those with no National Institute of Heart (NIH) RO1 but with other funding and those with no funding. Within the top 50 performers, yearly publication rates were an equal mix between the three groups. Those who were unfunded had 4.9 a publication rate per 1000 research hours, compared to those who were NIH funded (3.2 publications per 1000 research hours) or those who had other funding (3 per thousand hours).

The authors opine that while RO1 grants and early career funding were important components of higher h-index and larger publication numbers, the current definition of physician-scientists was questioned, since those presumed to be without funding were often more prolific than those with funding.

Bottom line: Much of the best clinical science was traditionally done by physician-scientists who were unfunded. In fact, our early papers on mitochondrial disease and MELAS were unfunded. In those days, salaries were not dependent on Relative Value Units. It is my concern that it is becoming harder for unfunded physician-scientists to perform research under current financial constraints.

Some other thoughts about this article: Why were NIH-funded authors potentially less prolific compared with unfunded authors amongst the most productive clinician-scientists? Having served on multiple study sections, I always felt that the granting mechanism was too complicated and often over reviewed to the point of making grants cumbersome and too bureaucratic. Physician-scientists may spend too much time with regulations, writing, and bureaucracy, taking away from research time. Another possibility is that some RO1s become so cumbersome that it is difficult to produce good research. I believe this happens more than people realize. Some of the grants are reviewed in ways that make it more difficult to execute the research. In my experience, this happens not infrequently, especially with the definition of inclusion criteria which sometimes become so specific that the study cannot be done because of poor enrollment. This is a call to develop ways to ensure that clinician-scientists remain engaged, even without funding. The future is problematic in regard to clinical research, and we need to take a lead in improving the research environment.

Age-related changes in the gut microbiota influence systemic inflammation and stroke outcome. Spychala MS, Venna VR, Jandzinski M, et al. Ann Neurol 2018;84:23–36

Flash summary: Chronic systemic inflammation contributes to diseases. Alterations in the gut microbiome may be responsible for age-related inflammation. The authors used stroke as a disease model in mice. The hypothesis was that a youthful microbiota, when established in aged mice, produces positive outcomes in ischemic stroke.

Young or aged mice had either a young or an aged microbiota established by fecal transplant and underwent an experimental stroke. Altering the microbiota of young mice to resemble the gut flora of aged mice increased mortality, morbidity, and cytokine formation after stroke. Conversely, altering the microbiota of aged mice to

Editor's note: Short Takes offers a brief analysis by Steven G. Pavlakis of selected articles that may be of interest to child neurologists. Papers that strike the fancy of the analyst or the editors are selected for inclusion, but we welcome suggestions.

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resemble that of young mice resulted in decreased mortality and improved recovery after experimental stroke.

Bottom line: The authors opine that aged gut biomes increase the levels of systemic proinflammatory cytokines and that the gut microbiota can be modified to positively impact outcomes from age-related diseases.

On reviewing this paper, it seems to me that it has application to pediatric stroke. Young mice that underwent an experimental stroke developed a gut flora similar to aged mice with the implication of increased cytokines and worsening outcomes. It would be rational to consider modifying the gut biome in humans to improve outcome with stroke. This would entail a trial converting the gut flora of stroke victims to be consistent with the young in both adult and pediatric stroke.

I think that there is more and more evidence that inflammation worsens stroke outcome in both the young and aged, The gut flora likely plays a role in this. I suggest that we look at gut flora in humans, young and old, and determine outcomes related to the biome. After this, an attempt at gut flora manipulation could be studied to improve morbidity and mortality in all strokes.

Repurposing of proton pump inhibitors as first identified small molecule inhibitors of endo-beta-acetylglucosaminidase (EnGase) for the treatment of NGLY 1 deficiency, a rare genetic disease. Bi Y, Might M, Vankayalapati H, Kuberan B. Bioorg Med Chem Lett 2017 Jul 1;27 (13):2962–2966

Flash summary: NGLY 1 deficiency is a rare human disease. N-glycanase is an important enzyme involved in deglycosylation of misfolded proteins. NGLY 1 patients produce little or no N-glycanase. The symptoms include global developmental impairment, lack of tears, seizures, and hyperkinesis.

There has been speculation that EnGase inhibitors might be a potential therapeutic intervention for this disease. The authors thus performed structure-based virtual screening utilizing Food and Drug Administration (FDA) approved a drug database on this EnGase target to enable repurposing. The authors found several proton pump inhibitors that seem promising and potent inhibitors of EnGase with one specifically the most efficient inhibitor.

Bottom line: An article in the New York Times entitled “Battle Plan Against Rare Diseases” (Tuesday September 11, 2018 D6), described how researchers screened for drugs already approved by the FDA for potential activity for rare diseases. In this way, one of the study's authors developed a treatment specific for his own son using a proton pump inhibitor. Dr Might, the author whose son has the disease, was driven to find a treatment for his son and concluded that proton pump inhibitors could be repurposed to ameliorate his son's disease.

I have never seen this disease and there are about 50 known cases. Of course, it might be much more common and many of us may have missed the disorder in the past without the aid of gene finding technology. This is a rational approach to treatment of some rare diseases, but it will need to be only one part of the potential treatment of rare diseases. Repurposing currently available medications seems rational and exciting as a first step.