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Editorial

The manifold works of Prof. Michal Novak

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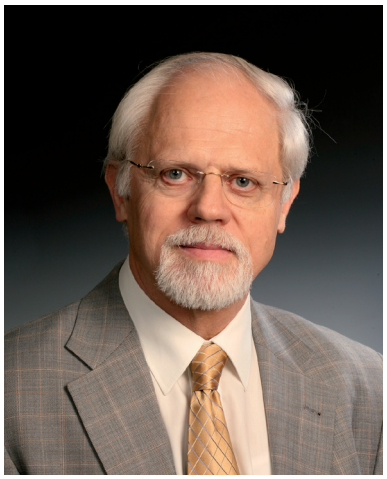

It is not common that a veterinary doctor with a passion for training and rehabilitating horses would go on to become a leading researcher into human dementias. But then it is not the common tales that stand out, but rather the exceptional ones that capture our attention and resonate within. While the numerous insights into equine health and psychology prof. Michal Novak made during his early career at the Veterinary College in Kosice have gone largely unpublished, his track record in research of human neurodegeneration is well known.

Prof Novak´s first international acclaim came in 1987 for his research into the pathogenesis of cystic fibrosis, in particular for his monoclonal antibody work (Dorin et al. 1987). Despite the shackles of the Iron Curtain, this work led to Michal Novak being invited to the MRC Laboratory of Molecular Biology in Cambridge, England, to apply his talents with antibodies in the field of Alzheimer's research. This gave Michal Novak the opportunity to work with giants in the field, such as the remarkably polyhistoric professor of psychiatry, sir Martin Roth, who began to build upon Alzheimer's original findings on neurofibrillary pathology, sir Aaron Klug, who received his Nobel Prize for work on crystallographic electron microscopy, and sir Cesar Milstein, honoured for the creation of hybridoma technology. It is most fitting then, that Michal Novak's approach towards immunological diagnostics and treatment of Alzheimer's disease (AD) and non-Alzheimer tauopathies would rely heavily on these technologies.

The research at MRC bore fruit soon – where Inge Grundke-Iqbal, Khalid Iqbal and Henryk M. Wisniewski identified tau protein as a component of neurofibrillary tangles in AD (Grundke-Iqbal et al. 1986), the Cambridge team showed this protein to be their principal constituent, and thus at the very core of a lesion that is central to AD (Wischik et al. 1988a, 1988b). From this moment onwards, prof. Novak's work was focused on the understanding of this complex protein, and how its dysfunction leads to neurodegeneration. The stay in the MRC Cambridge brought further understanding on this topic, especially the notion that tau in disease is post-translationally modified, and thus a distinct molecular and immunological entity from physiological tau (Jakes et al. 1991; Novak et al. 1991, 1993). Presently, it is increasingly becoming apparent that aberrant post-translational modification of CNS proteins is a common denominator of numerous neurodegenerative disorders.

Following his return to Slovakia in 1994, he pursued this line of research further. As the magnitude of the problem posed by dementing disorders became increasingly apparent (Ott et al. 2006), he saw a need to create an institution dedicated to their study – the **Institute of Neuroimmunology** of the Slovak Academy of Sciences. Founded in 1996 amidst massive layoffs at the academy, its creation was seen by some as audacious – but then, in the words of Theodore Roosevelt, "nothing in the world is worth having or worth doing unless it means effort, pain, difficulty". The new institute proved its mettle in due time, and was designated Centre of Excellence for AD and related disorders in 2004.

Observing that some research endeavours were best handled by an independent company, prof. Novak founded Axon Neuroscience in Vienna, Austria, in 1999. Over the

following 20 years, it would deliver numerous pioneering discoveries. In 2006, his team conclusively proved that non-mutant truncated tau, exactly as seen in the paired helical filament core in AD, is fully capable and sufficient to cause progressive lethal neurodegeneration, establishing the first rat model of tau pathology that develops mature tangles without using mutant tau (Zilka et al. 2006). The relevance of this discovery becomes apparent when one considers that mutations in tau protein cause tauopathies other than AD, yet a majority of tau-targeted compounds for the treatment of AD are being developed utilising rodent models with tau mutations – thus, this novel line of rat models replicates AD tau pathology more faithfully than most.

With the world single-mindedly focused on the other main feature of Alzheimer's disease, amyloid-β, and most of the world's AD researchers firmly seated on the amyloid bandwagon (Blennov et al. 2006), Prof. Novak has adhered to his research into tau pathology as the lesion that is proximal to cognitive loss and disease progression. His persistence was vindicated by other groups that showed neurofibrillary pathology to be a condition *sine qua non*, and the most direct correlate and predictor of cognitive loss and brain atrophy in AD (Nelson et al. 2012; Murray et al. 2015; La Joie et al. 2020). In plain words, one's brain can be clogged with amyloid-β without pronounced effect on cognition, but truly rare is the person with a brain full of tau lesions whose faculties are even somewhat intact.

A major milestone was the initiation of the world-first immunotherapy trial aimed at tau pathology in AD in 2013. This forerunner vaccine, AADvac1, is designed to induce antibodies that are specific to pathological tau protein *via* displaying a conformational tau epitope that is found in AD in the domain of tau that is necessary for aggregation and propagation of tau pathology. The aim is to prevent tau aggregation and propagation of tau pathology, and to label pathological tau moieties for removal by microglia (Kontsekova et al. 2014a, 2014b; Novak et al. 2018a). The *in vitro* and animal findings confirmed the expectations. While willing to take up tau on their own, with the aid of antibodies, microglia display a far greater appetite for the pathological protein, while neurons are shielded from tau uptake; treated transgenic animals develop less neurofibrillary lesions, and deposit far lower amounts of insoluble tau in their brains (Kontsekova et al. 2014b; Weisova et al. 2019; Zilkova et al. 2020). In humans, treatment with AADvac1 was remarkably safe; despite the immune senescence that is common in the elderly, almost all AD patients treated with AADvac1 developed the desired IgG1-dominated antibody response (Novak et al. 2017). Considering the number of tau-targeted immunotherapies that entered clinical development following the initiation of the AADvac1 program, it is evident that the encouraging early safety findings of AADvac1 gave other groups the courage to move ahead with their own compounds.

Similarly, the long-term safety and immunogenicity results were encouraging; this is vital, as AD patients can be expected to require treatment for years or decades. Similarly encouraging were results suggesting that patients with higher levels of AADvac1-induced antibodies display slower disease progression and less brain atrophy (Novak et al. 2018b). Last but not least, it became apparent that the antibody response induced by the vaccine could target tau not only in AD, but non-AD tauopathies as well, thus opening an avenue to aid patients suffering from these rare 'orphan' diseases as well (Novak et al. 2018b).

Based on these positive findings, AADvac1 was advanced into phase 2 development. The results of this study aligned with the hypothesis – the vaccine was safe and immunogenic; in comparison to patients on placebo, the AADvac1-treated patients displayed lower levels of pathological tau and phospho-tau in the cerebrospinal fluid, and lower levels of neurofilament light chain protein (a neurodegeneration marker) in the blood, and less white matter degeneration in vital tracts such as the fornix. In patients who were most likely to have bona fide AD, treatment slowed clinical decline (Novak et al. 2021). Further longitudinal studies on a sizable AD patient cohort are necessary to provide unequivocal evidence of clinical benefit – then, we shall know the outcome of this pioneering journey.

In addition to his personal effort towards finding a cure for AD, prof. Michal Novak understood that this is an endeavour greater than any one human can bring to fruition. Every step along the way, he has fostered cooperation and created structures that would help researchers, clinicians, caregivers, and patients, to coordinate their efforts to combat AD. Especially worthy of a mention are the founding of the Slovak Alzheimer's Society in 1998, and the founding of the MEMORY Centre in Bratislava in 2002 – a facility specialised in care, prevention, diagnostics and education for people with memory disorders and AD and their caregivers. The centre is a self-sustaining pilot project that aims to serve as a template for other such facilities in Slovakia. In line with his emphasis on cooperation, Prof. Novak has consistently been a clarion voice for cooperation and unity within the Academy, to make it more than the sum of its parts and a force to be reckoned with. Remarkable also, are his efforts to create a national Alzheimer plan for Slovakia starting in 2016.

The list of lectures he has been invited to speak at, the many awards, and similar would exceed the scope of this article – suffice to say, his work drew abundant international acclaim, including invitations to speak at the WHO forum, and receiving His Highness Sheikh Sabah Al-Ahmad Al-Jaber Al-Sabah's Prize for Research in Health Care for the Elderly and in Health Promotion.

In this year, Prof. Novak received the prestigious award – Khalid Iqbal Lifetime Achievement Award of the Alzheimer's Association USA – for his crucial role in the discovery of tau as the constituent of neurofibrillary tangles and the protein's major role in Alzheimer's disease.

The teachings of Prof. Novak's work are perhaps best studied in detail within a more expansive text; thus, we will conclude with a quote from Richard P. Feynman, that best summarises Michal Novak's approach based on intellectual humility, scientific rigor, and a strict natural selection process applied to every hypothesis – "It doesn't make any difference how beautiful your guess is, it doesn't matter how smart you are who made the guess, or what his name is… If it disagrees with experiment, it's wrong. That's all there is to it."

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