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An Answerable Challenge

Exploring low-dose and new combinations of drugs, including repurposed ones, could be the fresh perspective needed to drive treatment of neurodegenerative diseases

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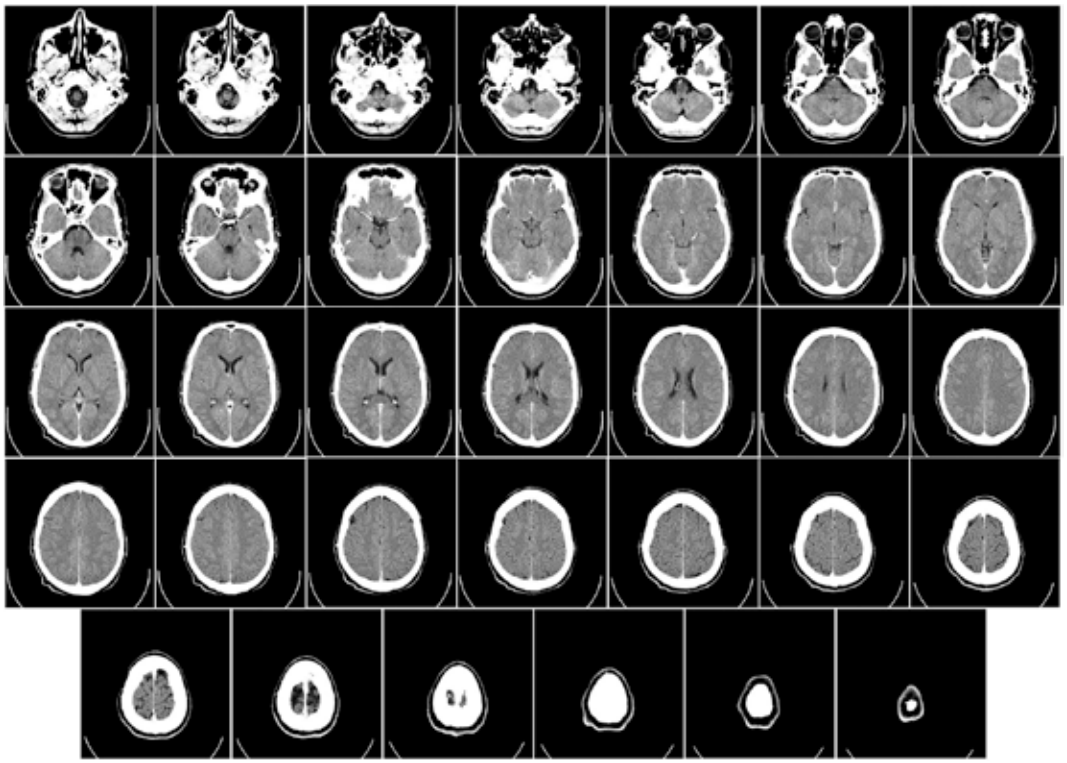

While cancer and cardiovascular diseases continue to hold the top ranks of the causes of mortality in Europe and North America, we have become accustomed to the burden of disease from neurodegenerative conditions increasing, mostly as a consequence of population ageing. If one were to cast the net wider (not only focusing on conditions that have neurodegeneration as a cause, but all neurological disorders), one would see that these were the leading cause of disability-adjusted life years – which refer to the sum of lost life years and years lived with disability – worldwide in 2016. While infectious causes have decreased over the past 25 years, stroke and dementia continue to loom large across the globe (1). In high-income countries, these two conditions rank second and third respectively in terms of crude death rate.

The Neurodegeneration Universe

Looking at neurodegenerative diseases only, different conditions have many causes and facets. For some, we have a very good mechanistic understanding, even if we cannot do very much about them. This class includes conditions with evident vascular and metabolic causes, such as stroke, vascular dementia, and diabetic neuropathy. For idiopathic epilepsy, multiple sclerosis, and some motor neurone diseases, we have solid, evidence-based working hypotheses, and, while we have no cures for these conditions either, their disease course can be modified to a degree.

However, Alzheimer's disease (along with other primary degenerative dementias) and Parkinson's disease defy us on

every level because we do not understand their ultimate causes, of which there might be several. On the other hand, these conditions share so many features that it seems justified viewing them as different manifestations of a protein aggregation/associated disease spectrum (2). Whether this aggregation of proteins (α-synuclein into Lewy bodies in Parkinson's disease and Lewy body dementia, misprocessed amyloid into plaques, and hyperphosphorylated tau into tangles in Alzheimer's disease) is causative, protective, or just an epiphenomenon is still being debated.

What we have in terms of drug therapies for these diseases is quite limited. For Alzheimer's disease, three cholinesterase inhibitors and one open-channel N-methyl-D-aspartate receptor blocker can offset the cognitive deterioration for a few months. For Parkinson's disease, levodopa and dopamine receptor agonists can ameliorate the motor symptoms for a while. None of these drugs ultimately modify the disease course, no new drugs have been approved for almost two decades, and the development pipelines may be empty because all candidates have failed, reflecting the general situation in neuropsychiatry in a more pronounced fashion.

Nodes in a Net of Pathways

Those who are familiar with network pharmacology and systems medicine have long realised that this is a situation where any breakthrough requires a new way of looking at disease: a perspective that appreciates that any curative treatment must act at the common root cause, which, in itself, might not even be clinically manifest (in this case, aggregation of certain proteins). Even further upstream from this common node, there may be any number of causes, or only one, but even if we remain agnostic of these ultimate causes, we could act at the node on which the pathways converge before they separate again. The concept of targeting multiple points in the deleterious pathways downstream of the aggregation event – for example, the overactivation of microglia that causes neurodegeneration through sterile inflammation – represents another strategy that needs exploration and exploitation.

> **"Patents discuss not so much what is scientifically attractive, but rather what the applicants believe can be developed into a commercial product"**

The Agents at the Ready

Do new targets need to be discovered and new drugs developed for these targets? Certainly, but, in many cases, new molecules may not be necessary at all. There is a large pool of marketed drugs, and a much larger one of discontinued drug candidates, that have all conceivable sorts of activities, including some that have never been appreciated. How so? This is because the intricate, time-honoured interplay between regulatory authorities and corporate marketers favour the 'one drug, one target'

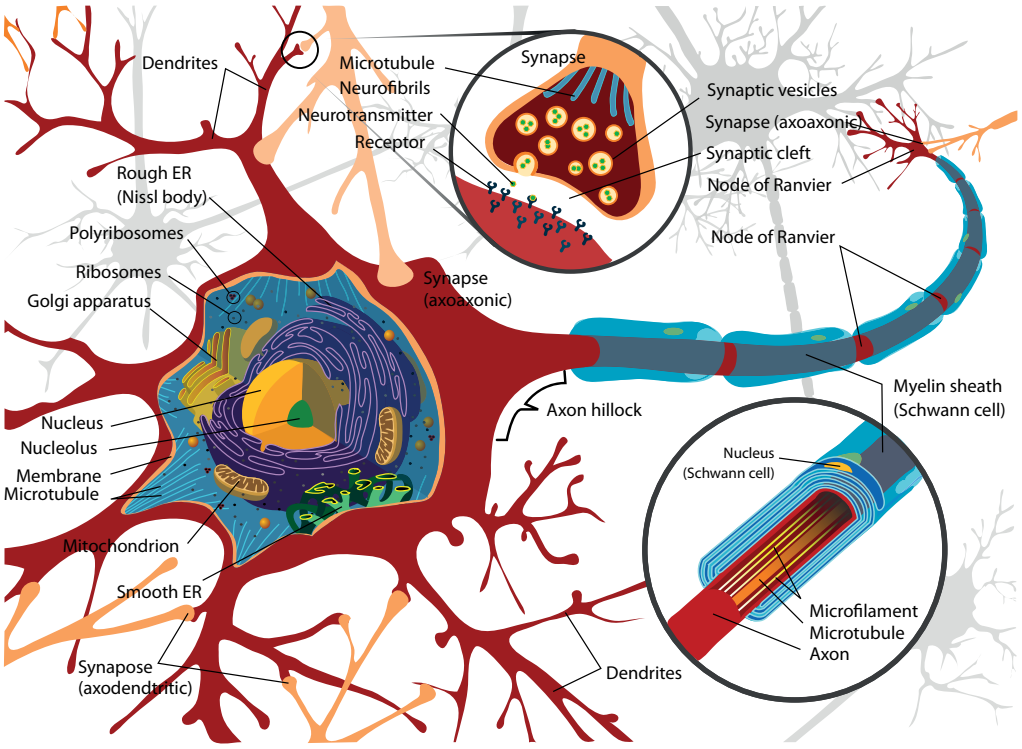

Figure 1: Schematic of a typical myelinated motor neuron. The myelin sheath and the dendrites are major targets in neurodegeneration

principle. In reality, few pharmacologically active compounds are limited to a single target at relevant concentrations.

We may not even have to look very far: even generically available off-patent agents could offer interesting possibilities. Cromolyn, a mast cell stabiliser that has been used for the treatment of asthma, allergic rhinitis, and allergic conjunctivitis since the 1970s, not only inhibits the formation of β-amyloid aggregates, it also decreases the amount of soluble β-amyloid in the brains of transgenic mouse models of Alzheimer's disease by 50% after only one week of treatment (3). Any drug that enhances central serotonergic signalling should have similar effects (4). Doxycycline, an antibiotic that has been in use for over half a century and which is on the WHO List of Essential Medicines, prevents the aggregation of α-synuclein oligomers at subantibiotic doses; other tetracyclines seem to share such neuroprotective capacities (5-6). Plenty of downstream opportunities are available as well. Several antipsychotics, mood stabilisers, and antidepressants have been shown to reduce microglial overactivation in models considered relevant for Alzheimer's disease and Parkinson disease (7).

Patient cooperation treaty disclosure	Active ingredient(s)	Original use	Repurposed use
WO/2019/031425	Src kinase inhibitors (saracatinib, dasatinib)	Cancer	Motor neurone disease
WO/2019/010146	Statin drugs	Dyslipidemia	Synucleinopathies (augmentation of pramipexole)
WO/2018/206465	Arsenic trioxide	Leukaemia	Multiple sclerosis
WO/2018/203751	Guanabenz	Hypertension	Vanishing white matter (a severe leukodystrophy)
WO/2018/140965	Senicapoc	Sickle cell disease, asthma	Ischemic stroke
WO/2018/082814	Luminol*	Chemoluminescent tag for redox reactions	Multiple sclerosis
WO/2018/071548	Apilimod	Inflammatory bowel diseases, rheumatoid arthritis, psoriasis	Alzheimer's disease
WO/2018/023036	Glibenclamide (glyburide)	Type 2 diabetes	Alzheimer's disease
WO/2017/186934	Gliptins	Type 2 diabetes	Retinal neurodegeneration
WO/2017/118857	Tacrolimus	Immunosuppression	Amyotrophic lateral sclerosis Frontotemporal dementia
WO/2016/147146	Citalopram, escitaloram	Major depression	Spinocerebellar ataxia type 3
WO/2016/067265	Stavudine and other reverse transcriptase inhibitors	HIV infection	Neurodegenerative diseases
WO/2015/049608	Propylparaben*	Antifungal preservative	Neuroprotection in status epilepticus
WO/2015/042286	Fenofibrate	Dyslipidemia	Neurodegenerative diseases
WO/2015/028659	Torasemide and baclofen	Edema and muscle spasm, respiratory	Neurodegenerative diseases
WO/2014/210544	Beta blockers	Cardiac arrythmia	Neurodegenerative diseases

*Originally not a drug or drug candidate

Table 1: Selected international patent disclosures for drug repurposing towards neuroprotection

Drug Repurposing for Neurodegeneration is a Reality

The following are just a few examples from a steadily growing spectrum of drug repurposing opportunities in this field. Some opportunities have already been exploited to considerable commercial success. Tacrine, the first drug to secure approval for the symptomatic treatment of Alzheimer's disease, had been synthesised at the University of Sydney, Australia, in the early 1940s in a war-driven effort to develop antibiotics and antimalarials, but proved inactive in both respects. Dimethylfumarate was used as a mould inhibitor for leather furniture in long-term storage before it was repurposed for multiple sclerosis and is now selling for more than US $4 billion per year.

Attacking Multiple Targets in a Single Stroke Pathway

Even with ischemic stroke, where the root cause (a blood clot cutting off the blood supply to a brain area) is abundantly clear, nothing has been developed beyond thrombolytics, which can dissolve the clot but have no neuroprotective effect against the reperfusion injury, which is often much more damaging than the ischemia. Today,

stroke congresses concern themselves with diagnosis, clinical management, prognosis, and rehabilitation, but almost never with neuroprotective drug candidates: too many have failed in the clinical trials of the 1980s and 1990s. No single compound seems to be powerful enough to protect at least those brain areas that still get perfusion through collateral vessels, are compromised by cortical spreading depolarisation, or are at risk of reperfusion injury.

Two closely related EU projects that receive funding from the Horizon 2020 research and innovation program currently attempt to tackle this problem. Repurposed drugs and drug candidates are used to synergistically target three sites in a stroke-relevant signalling pathway involving free radical formation and nitric oxide. SAVEBRAIN, one of the projects, attempts to validate the principle, as well as the suitability of the selected drugs, in animal experiments. In the next step, REPO-STROKE – the other project – will conduct a clinical pilot trial using an adaptive design. This is part of the larger REPO-TRIAL project, which aims to improving efficacy and precision of drug repurposing trials in a broader range on cerebro-cardiovascular phenotypes that share communalities from the systems medicine perspective (8).

Repurposing Patents Indicate Development Considerations

To fully appreciate the extent of drug repurposing activities towards neurodegeneration, examining the patent space is essential. Intellectual property documents and the data disclosed therein offer information that is, to an extent, orthogonal to what peer review papers report. Patents discuss not so much what is scientifically attractive, but rather what the applicants believe can be developed into a commercial product. Table 1 gives examples of recently published intellectual property documents that claim drug repurposing for applications in neurodegenerative diseases.

Big Data Analysis as a Driver for Neuroprotection

No single button can be pressed to prevent neurodegeneration. Just as many mechanisms can be utilised to combat cancer, brain tissue can be preserved in many different ways. As a result, many potential solutions are possible, some of them quite unlikely at first sight. Looking at the disclosures in the table, one sees widely disparate approaches: the revival of arsenic trioxide for neuroinflammation in multiple sclerosis (this time with routes of administration that avoid the gastrointestinal side effects), the highly innovative use of anti-HIV reverse transcriptase inhibitors to block the induction of long interspersed nuclear elements in Parkinson's disease, or the use of beta blockers to prevent synuclein aggregation.

So far, drug repurposing for neurodegenerative diseases has mostly been done through the ingenuity of pharmacologists. However, the amount of data that may hold potentially useful information is much larger than can be handled by unassisted humans, and, in addition, the information is widely dispersed. Focused efforts to develop expert systems (nowadays erroneously labelled as 'artificial intelligence') dedicated to drug repurposing and interactively trained by pharmacologists and neurologists should soon open up a much broader range of opportunities. However, in the end, it will always need human oversight to design a realistic repurposing program, draw up a patent strategy, and guide the entire project through vicissitudes of scientific and regulatory affairs.

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About the author

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