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Who dares, wins

It's time for a bolder approach to developing drugs for progressive multiple sclerosis, says Bibi Bielekova.

The economic and human cost of central nervous system (CNS) disorders is enormous[1], and neurodegenerative diseases, such as progressive multiple sclerosis (MS) represent the fastest-growing portion of this cost. But drug development for these diseases has so far been slow, expensive and mostly unsuccessful[2]. It's time for a re-think.

Current disease-modifying treatments for MS, all of which target the immune system, have convincingly demonstrated that processes other than the formation of new lesions underlie much of the disability that develops as MS progresses. Many potentially pathogenic cellular processes have been implicated, but we still do not know which, if any, are actually involved.

It is unlikely that such a complex disease can be stopped by targeting a single process, so treating progressive MS will probably require a combination of carefully targeted therapies. But making such personalized combination treatments a reality will require a major overhaul of approaches to drug development and clinical trials, including new ways of measuring their success.

Evidence that this is feasible comes from cardiovascular diseases, where this kind of individualized ‘polypharmacy’ is already a mainstream approach. Using biomarkers to identify multiple pathogenic processes, such as hypertension, hypercoagulability or hyperlipidaemia, allows physicians to provide the optimal combination of drugs.

Compare that with MS care, where someone with an MS diagnosis is offered one of many available treatments based on side-effect profile and perceived efficacy, but not on the mechanisms responsible for that person’s disease. When follow-up examinations reveal the development of a new CNS lesion, the old medicine is withdrawn and a new one is provided, equally blindly. Obviously, such a strategy is suboptimal: if there are multiple pathogenic processes, they need to be targeted simultaneously by several drugs.

Unfortunately, this need is at odds with our current mode of drug development, which strives to demonstrate the clinical efficacy of each candidate drug individually. If multiple pathogenic processes contribute to the destruction of CNS tissue, then targeting any single one of them, even with a highly effective therapy, will have only a small effect on the clinical outcome that is impossible to measure reliably in small, proof-of-principle phase II trials.

Despite our lack of knowledge about the molecular mechanisms that underlie MS progression, we continue to use only insensitive clinical or imaging outcomes that require the study of hundreds of patients for at least two years to screen one drug at a time. This expensive and slow strategy has had some partial successes: systemically administered

immunomodulatory agents have shown some efficacy when treating progressive MS. When given early enough, generally before the age of 50, such treatments may reduce the accumulation of disability by up to 25%. But how do we target the remaining 75%?

Whenever a research goal seems beyond our reach, it is time to examine whether the path we have taken assures the highest probability of success. At some point, the prohibitive cost of screening MS drugs in de facto phase III trials will force us to adopt other, more creative solutions.

Sampling cerebrospinal fluid (CSF) could provide comprehensive molecular information about processes in the CNS, but current clinical practice avoids it because lumbar puncture is considered to be an invasive procedure. Some argue that adding lumbar puncture to clinical trials would severely limit patient participation. But in my extensive experience of running MS clinical trials in which lumbar punctures are as frequent as every 3–6 months, fewer than 10% of patients decline to participate because of the procedure. My team has been able to measure with sufficient statistical power the varied pharmacodynamic effects of drugs being tested in as few as 15 patients treated for as little as 3 months[3,4]. This greatly outperforms the most sensitive clinical or structural-imaging MS outcomes[5] and is analogous to using biomarkers such as blood pressure or lipid levels to screen drugs for their potential efficacy in cardiovascular diseases.

The major drawback of using CSF biomarkers for drug development is not the invasiveness of a lumbar puncture, but the uncertainty about the predictive power of the biomarkers themselves. This gap in the knowledge can be filled only through clinical trials in which any early effects on biomarkers can be linked to later clinical outcomes. Adding biomarkers to the early stages of clinical trials can rapidly eliminate any treatments that have limited effects on the targeted process[4], and can provide solid data for the optimization of doses and the number of participants required for phase III trials of promising agents. And finally, broad measurements of biomarkers in clinical trials would eventually improve the knowledge base sufficiently to allow the assembly of effective drug combinations during the drug-development process and later in clinical practice.

If we are to successfully tackle the burden of neurological diseases before their costs overwhelm us, it is time for neurology to become a more daring clinical discipline.

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