



# Promise, Progress, and Pitfalls in the Search for Central Nervous System Biomarkers in Neuroimmunological Diseases: A Role for Cerebrospinal Fluid Immunophenotyping

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**Biomarkers are central to the translational medicine strategic focus, though strict criteria need to be applied to their designation and utility. They are one of the most promising areas of medical research, but the “biomarker life-cycle” must be understood to avoid false-positive and false-negative results. Molecular biomarkers will revolutionize the treatment of neurological diseases, but the rate of progress depends on a bold, visionary stance by neurologists, as well as scientists, biotech and pharmaceutical industries, funding agencies, and regulators. One important tool in studying cell-specific biomarkers is multiparameter flow cytometry. Cerebrospinal fluid immunophenotyping, or immune phenotypic subsets, captures the biology of intrathecal inflammatory processes, and has the potential to guide personalized immunotherapeutic selection and monitor treatment efficacy. Though data exist for some disorders, they are surprisingly lacking in many others, identifying a serious deficit to be overcome. Flow cytometric immunophenotyping provides a valuable, available, and feasible “window” into both adaptive and innate components of neuroinflammation that is currently underutilized. Semin Pediatr Neurol 24:229-239 Published by Elsevier Inc.**

## Introduction

Biomarker has been defined as a “characteristic that is objectively measured and evaluated as an indication of normal biologic processes, pathogenic processes, or pharmacological responses to a therapeutic intervention”.<sup>1</sup>

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Use of the term dates back to 1980.<sup>2</sup> In an era called the “biomarker revolution,” medical biomarker studies are extremely timely and widely recognized as important.<sup>3</sup> Now there is a multiplicity of biomarker types and applications (Table 1).<sup>4,5</sup> From a US regulatory perspective, integration of biomarkers in drug development would help alleviate stagnation and foster innovation in the development of new medical products, leading to more translational and personalized medicine.<sup>6</sup> Biomarker-guided decision making would have a competitive clinical advantage over the existing empirical approach.<sup>7</sup>

The first part of this article discusses the unique need for biomarkers in neurological diseases, the importance of cerebrospinal fluid (CSF) as the best source, and the life cycle of the biomarker. It vets the biomarker process and provides tangible steps needed to improve the interpretability of biomarker data for neurological disorders. In the second part, putative CSF cellular immune markers, as revealed by flow cytometric *immunophenotyping*, are evaluated as candidate biomarkers of neuroinflammation.<sup>8</sup> Recent advances in flow cytometry have presented greater capacity to identify and refine immune cell

**Table 1** Multiplicity of Biomarker Types and Applications

Type	Definition/Application
Combinatorial	Panel- or pattern-based
Diagnostic	Disease specific
Differentiation	Efficacy or safety of drugs within same class
Efficacy	Reflects positive outcome of a treatment
Exploratory	Delimited, may be driven by discovery, not hypothesis
Pharmacodynamic	Contrasting pharmacodynamic patterns may offer utility for treatment (optimal dose?)
Prognostic	Predicts course of disease
Predictive	Provides information on obtaining response to treatment (optimal drug?)
Qualified	The data support its use for stated purpose
Risk	Can be used for risk stratification
Toxicity	Avoid/monitor potential toxic effects
Screening	Early disease detection
Staging	Differentiates different stages, activity, and subtypes of disease
Stand-alone	A single biomarker sufficient for purpose by itself
Stratification	Select best treatment for given patient
Surrogate	Intended as substitute for clinical endpoint
Translational	Can be used in preclinical and clinical studies

phenotypes.<sup>9</sup> Although most immunophenotyping studies have been of peripheral blood, only CSF studies are reviewed here.

## Biomarkers

### Why Are Molecular Biomarkers Uniquely Needed for Neurological Diseases?

*Biomarker-guided personalized medicine* is not a novel concept, but one applied in most areas of clinical medicine, including some neurological disorders, for years. For example, stroke specialists will investigate and treat all cardiovascular risks factors they can identify, such as hypercoagulable state, sources of embolism, hyperlipidemia, diabetes, and hypertension. Consequently, a patient having a stroke will receive personalized, rational combination of drugs that target simultaneously all risk factors that contribute to a phenotypical expression of their disease. Furthermore, treating physicians will not wait for the second stroke to make necessary therapeutic adjustments; rather they will use normalization of biomarker measurements as a guiding principle. Of course, this strategy required clinical trials that have proven surrogacy of these biomarkers to the clinically relevant outcomes, such as mortality from cardiovascular diseases.

Indeed, molecular biomarkers (ie, clinical laboratory tests) have been assessing functions of different cellular components of the endocrine, hematological, gastrointestinal and immune systems, or cardiomyocytes and renal epithelium for decades. In stark contrast, neurologists lack molecular biomarkers that measure physiological functions (or dysfunctions) of the cellular components of the central nervous system (CNS).

Instead, neurology practice and drug development rely on imaging modalities, especially magnetic resonance imaging (MRI), which provides structural information about CNS tissue. The undisputable utility of MRI in neurology practice

makes us often forget that structural imaging does not provide molecular or even cellular information. For example, although brain atrophy reflects loss of CNS tissue, it may be masked for a long time by replacement of one cellular component (eg, neurons) by another (eg, microglia, astroglia, or immune cells) or by alternative processes such as edema or expansion of extracellular matrix. Furthermore, even in the instances when pathologic correlations showed links between certain cellular processes and MRI features, such as perivascular inflammation underlying contrast-enhancing lesions (CELs) in multiple sclerosis (MS), assumptions can be misleading. Assuming that *all CELs are inflammatory* causes misdiagnosis of ischemic and malignant lesions,<sup>10</sup> while assuming that *CELs capture all inflammatory activity* underestimates the amount of inflammation, for example, in progressive MS.<sup>11</sup> It is rather common radiology practice to call T2 – FLAIR white matter lesions of a certain size and location “*demyelinating*,” even though this MRI contrast captures differences in the relaxations of hydrogen protons and therefore cannot possibly differentiate one type of tissue integrity change (ie, edema) from another (eg, demyelination or astrogliosis).<sup>12</sup>

On the contrary, although clinical deficit correctly reflects loss of cellular functions, it provides limited insight about its reversibility or causes. Additionally, clinical deficit lacks sensitivity, that is, it becomes obvious only after substantial damage to the underlying CNS tissue has accumulated; this is true for virtually any neurological conditions where clinicopathologic correlations exists, including Parkinson disease, primary progressive MS or mild cognitive impairment.

It is reasonable to conclude that this lack of molecular information about CNS tissue is one of the main reasons for the slow therapeutic progress in neurology. Inability to detect earliest stages of CNS diseases prevents initiating treatments at the time when their efficacy is highest. On the contrary, once the clinical defects become apparent, the physiological compensatory processes are exhausted and pathologic processes are well-established and wide-spread. To stop the disease

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