QUESTIONS

1. How many transferrin bands are typically seen in CSF?
2. What might cause the absence of $\beta_1$-transferrin in a biological fluid?

The answers are below.

ANSWERS

Serum contains $\beta_1$-transferrin, and CSF contains $\beta_1$ and $\beta_2$ transferrins. The $\beta_2$-transferrin in CSF is desialylated because of the presence of neuraminidase in the central nervous system. Hence, $\beta_2$-transferrin is used as a marker of CSF leakage (1).

Because $\beta_1$-transferrin was present in serum but absent in drainage fluid, additional neuraminidase activity was suspected. This suspicion was supported by the culture of *Staphylococcus aureus* from the fluid.

Most *S. aureus* strains have neuraminidase activity (2), and sepsis is associated with decreased sialylation of circulating transferrin (3).

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References


News & Views

Personalized Therapeutics and Companion Diagnostics: A New Paradigm in Testing and Treatment

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The emerging field of personalized medicine has been touted as the next big revolution in medicine, promising customized therapies for a variety of notoriously hard-to-treat diseases. The realization of these benefits is largely dependent on advances in pharmacogenomic, proteomic, and biomarker testing technologies, which can be used to identify individuals most likely to benefit from a particular drug therapy, or to evaluate their course of treatment. A recent article in *Nature Biotechnology* entitled “Maximizing the Commercial Value of Personalized Therapeutics and Companion Diagnostics,” by Zhang et al. (1), discusses...
several key concepts that need to be addressed to successfully develop drugs and diagnostics synergistically. As pharmaceutical companies continue to realize the potential profits of drugs targeted to population sub-sets, the number of drug–diagnostic pairs seeking Food and Drug Administration (FDA)\(^2\) approval is sure to grow in the future.

Zhang et al. advocate for a codevelopment strategy between pharmaceutical and diagnostic firms, consistent with the model proposed by the FDA in 2011. In this approach, both entities collaborate on the research, development, preclinical/clinical validation, and ultimately the patent filing of a drug and its companion diagnostic methods. As therapeutics and their companion diagnostics may be produced by separate entities with differing timetables and biomarker-related intellectual property (IP) interests, establishing a cogent codevelopment scheme early in the research and development phase is sound advice. A cautionary tale is exemplified with the pharmaceutical company ChemGeneX and its drug omacetaxine for T315I mutant chronic myelogenous leukemia. Because no diagnostic test was available to identify the patients for whom omacetaxine would be indicated, the FDA did not grant approval in 2010. As such, considering the utility of a companion diagnostic at the outset of drug discovery is advantageous.

Another important aspect in drug–diagnostic pair development concerns securing patent protection. The 2012 US Supreme Court Mayo v Prometheus ruling dictated that certain “natural principles” are not patentable: namely, measuring drug metabolite concentrations for the purpose of adjusting dosage. To address this potential hurdle in drug–diagnostic patent attainment, Zhang et al. recommend crafting patents as unique “methods of treatment,” whereby the diagnostic procedure is incorporated into the drug labeling. As generic drugs typically require the same labeling as market-branded pharmaceuticals, patenting a joint drug–diagnostic therapy may both prevent encroachment from generics and protect diagnostic-related IP. Additionally, such patents are eligible for term extensions, which help to further preserve market exclusivity.

From a clinical laboratory perspective, implementing companion diagnostic testing will require careful consideration. To assess overall demand, it is necessary to consider how the test will be used: to screen all eligible candidates for a drug (1 test/patient), or for monitoring therapy (multiple tests/patient). When selecting a vendor for a new test, clinical laboratories may have some flexibility. Logistically, sticking with instruments and methodologies already in use is often the most straightforward approach. Some laboratories may even elect to create a laboratory-developed test, which can translate into sizeable per test cost savings. However, for companion diagnostics for which a specific branded test is indicated, as with “method of treatment” patents, there may be considerable upfront expenses in the form of capital equipment purchases and essential technical staff. Even for the largest laboratories, such hurdles may prove a challenge to overcome and may warrant sending the test out to a reference laboratory.

In the end, the overall commercial success of drug–diagnostic pairs will rest upon evidence that the diagnostic, prognostic, or predictive information provided by the companion test is directly correlated with patient outcomes. There continues to be a general lack of agreement among insurance companies regarding reimbursement for companion diagnostic tests (\(^2\)). To ensure that laboratories and patients are not left with the bill, the onus will ultimately lie with manufacturers to emphasize the clinical utility of their drug–diagnostic pair to the payers.

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References
