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Reply to MS #ALN-D-16-00130

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We appreciate the opportunity to respond to Dr. Laudanski's critical commentary. The key result of our study suggests that signaling activity of the Toll-like receptor 4 (TLR4) in a pre-surgical whole blood sample predicts the speed at which patients regain function of their operated hip.[1] We agree with Dr. Laudanski that NFkB is ubiquitous. However, our findings are related to specific signaling events downstream of TLR4, including MAPKAPK2, CREB, and rpS6, that occurred in a precisely phenotyped subset of monocytes.[1,2] The detected signaling patterns were highly specific with respect to pathway and cell type, which diverges from Dr. Laudanski's view that "activation of the immune system is often non-specific". Our findings further highlight the sentinel role of TLR4 in detecting tissue damage and mediating sterile inflammation, and extend previous work by linking TLR4 activation patterns to patients' functional recovery.[3,4] Functional recovery is at the very core of current ERAS (enhanced recovery after surgery) protocols, and delays of weeks, as reported by us and others, matter greatly to patients and health care providers.[2,5,6] A blood test identifying patients at risk for delayed functional recovery is an important step toward providing individualized, effective, cost-conscious, and high-value care in the context of the perioperative surgical home.[7] While we agree that the blood test used an external or "artificial" TLR4 ligand (LPS) that may not recapitulate biology as it unfolds during surgery, the use of LPS to activate a specific signaling pathway does not negate the predictive value of the test.

The scientific endeavor never stops and interesting results will always trigger the next set of important questions. While our strong correlative findings provide a link to relevant biology, we agree that they do not prove cause and effect - and we never in our report suggested such a relationship. This is the next obvious question that we need to address. The prospect of validating TLR4 as a therapeutic target is exciting in light of preclinical studies suggesting that preemptive dampening of TLR4 with a non-toxic agonist attenuated pro-inflammatory

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Competing interests

Dr. Nolan has a personal financial interest in Fluidigm (South San Francisco, California), the manufacturer of the mass cytometer used in this article. The other authors declare no competing interests.

events and enhanced host resistance to infection and survival in models of burn injury and systemic infection.[8,9]

There is certainly important work ahead of us and room to improve on all fronts. However, our bets have been placed and we see a clear light at the end of the tunnel.

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