Background:
Aberrant activation of STAT3 leads to the overexpression of oncogenes that drive proliferation and metastasis and inhibit apoptosis. The SH2 domain of STAT3 binds to newly phosphorylated tyrosines, followed by the phosphorylation of Y705 of STAT3. Then, two phosphorylated STAT3 monomers dimerize and translocate to the nucleus, where they activate the transcription of many downstream genes. As an activator of the Janus kinase (JAK)-STAT signaling pathway, interlukine-6 (IL-6) can act in both a proinflammatory and anti-inflammatory manner. Suppressor of cytokine signaling 3 (SOCS3), the major negative regulator of IL-6 dependent signaling. Even in the continued presence of SOCS3, STAT3 is rephosphorylated in response to IL-6 after about 4 h through a mechanism that has been obscure until now. The epidermal growth factor receptor (EGFR) dimerize which are activated by EGF to facilitate cross-phosphorylation of several tyrosine residues, including Y1068, the binding site for STAT3 whose intrinsic kinase activity of the receptor without JAKs. In previous study, the authors reported that EGFR activation can mediate both IL-6 production and STAT3 activation. In this study, they continued investigating the role of EGFR in STAT3 activation and IL-6 secretion.

Objective/Hypothesis:
To investigate that initial phosphorylation of STAT3 in response to IL-6 and a second wave of STAT3 activation which leads to ligand-dependent association of IL-6R and EGFR.

Results:
Firstly, the authors examined the second wave of STAT3 phosphorylation in response to IL-6 in two cell lines treated with different substrate which induces the same signal pathway by Western blot. By using the IL-6 inhibitor (Cycloheximide / Brefeldin A) and cytokine array, they showed that IL-6–treated cells secreted higher levels of IL-6 that induced the biphasic pattern. The STAT3 activation in the cells was diminished when treated with EGFR siRNA or specific inhibitor (Erlotinib). Through comparison between different EGFR mutant forms, the authors subsequently pointed out that the phosphorylation of Y1068 of EGFR in the second wave provided a potential docking site for STAT3 even in the presence of SOCS3. The results from CoIP analysis showed that EGFR participated in the second wave of STAT3 activation by their interaction between the EGFR and IL-6 signal pathway. Finally, genes affected by the second wave of STAT3 activation and observed in major physiological effects of prolonged exposure to IL-6 were analyzed by microarray.

Conclusion
The authors figured out an unique model for the two-phase activation of STAT3 in response to IL-6 treatment of cells in which EGFR participates to enhance immune responses and cell proliferation even after the negative regulator SOCS3 exit the feedback loop.