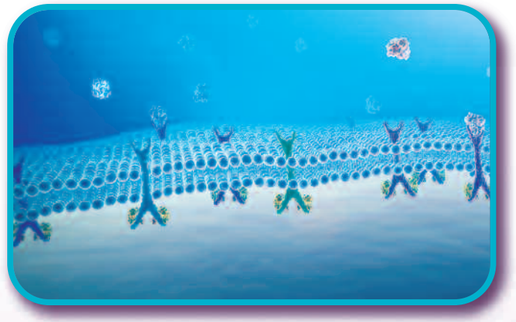
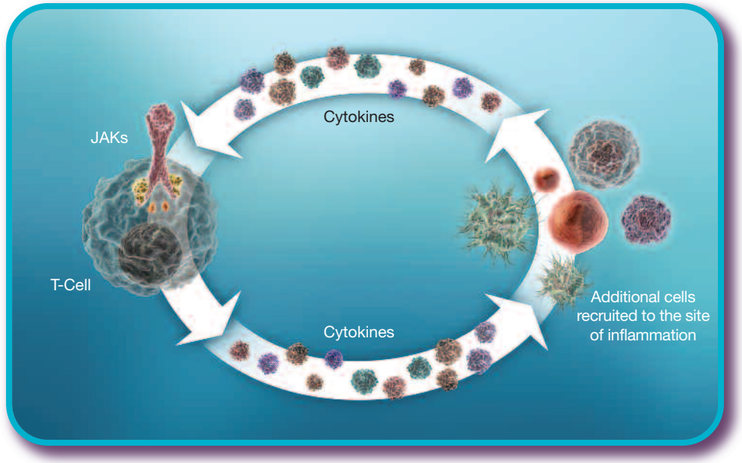
DISCOVERING THE JAK PATHWAY

- The Janus Kinases (JAKs) are a family of non-receptor tyrosine kinases that were discovered in 1988[12]
- The discovery was so compelling that the National Institutes of Health continued researching the family of JAK pathways[13]

THE SIGNIFICANCE OF THE JAK PATHWAY

- Certain intracellular Janus Kinases (JAKs) mediate the effects of many pro-inflammatory cytokines involved in several human diseases, including RA[14-16]
- Activation of many cytokine receptors known to be involved in RA promote pro-inflammatory gene expression by signaling through JAK pathways[14-16]

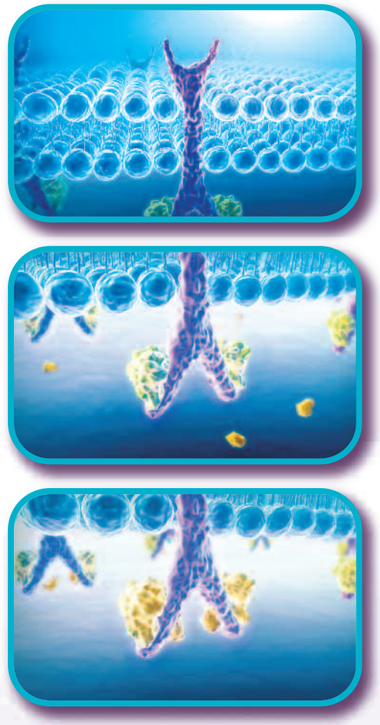




JAK-related intracellular signaling participates in a feedback loop that accelerates and sustains cytokine-mediated recruitment and activation of T-cells and other cells that promote joint inflammation and destruction.[17,18]

THE JAK SIGNALING CASCADE

- Multiple pro-inflammatory cytokines utilize JAK signaling to modify gene expression associated with the chronic inflammation of RA[14]
- Step 1: Cytokines signal cells by binding to specific cell surface receptors[19]
  - A specific cytokine receptor exists for each cytokine
  - There are multiple receptors, such as the IL-1 receptor, the IL-15 receptor and the IL-6 receptor
- Step 2: For many cytokines, regardless of receptor type, binding by the cytokine results in activation of 2 intracellular JAKs attached to the cytoplasmic portion of the receptor[14,16,19]
- Step 3: These activated JAKs in turn activate proteins called STATs, which are also associated with the receptor[14]
- Step 4: Activated STATs regulate gene expression in the nucleus[14,15]



EXPLORING NEW PATHWAYS IN RA