

UNDERSTANDING IMMUNE CELLS AND INFLAMMATION: OPENING NEW TREATMENT AVENUES FOR RHEUMATOID ARTHRITIS AND OTHER CONDITIONS

Most of the 1.5 million adults in the United States who have rheumatoid arthritis (RA) take medications to control their pain and slow the damage that is occurring in their joints. RA causes inflammation and pain in the hands, wrists, knees, or other joints and, over time, leads to permanent damage. Like other autoimmune diseases, RA occurs when the immune system attacks a person's body instead of defending it against invading organisms.

Some RA drugs protect joints by blocking interactions between inflammatory molecules and the healthy tissues that they are erroneously targeting. Others destroy the cells that produce the damaging molecules. While these disease-modifying antirheumatic drugs (DMARDs) help many people, some patients do not respond or cannot

NIH-funded investigators played a large role in discovering and characterizing the molecular interactions that tofacitinib acts on and in predicting the usefulness of this and related pathways as drug targets. Some of that research is described here to illustrate how knowledge about cell behavior at the molecular level can be used to improve health.

tolerate the side effects. In 2012, FDA approved another option for people with moderate to severe RA who are not helped by other treatments. This new drug, tofacitinib, fights inflammation from inside immune cells. Because it works differently than many RA drugs, it can be taken as a pill, rather than an injection.

IMMUNE CELLS AND INFLAMMATION: THEN AND NOW



THEN

Since the late 1990s, drugs that prevent inflammatory molecules called cytokines from interacting with healthy tissue have helped hundreds of thousands of people who have autoimmune diseases such as rheumatoid arthritis, but these drugs did not work for everyone.

**Many of
the medications
need to be
injected instead
of swallowed.**



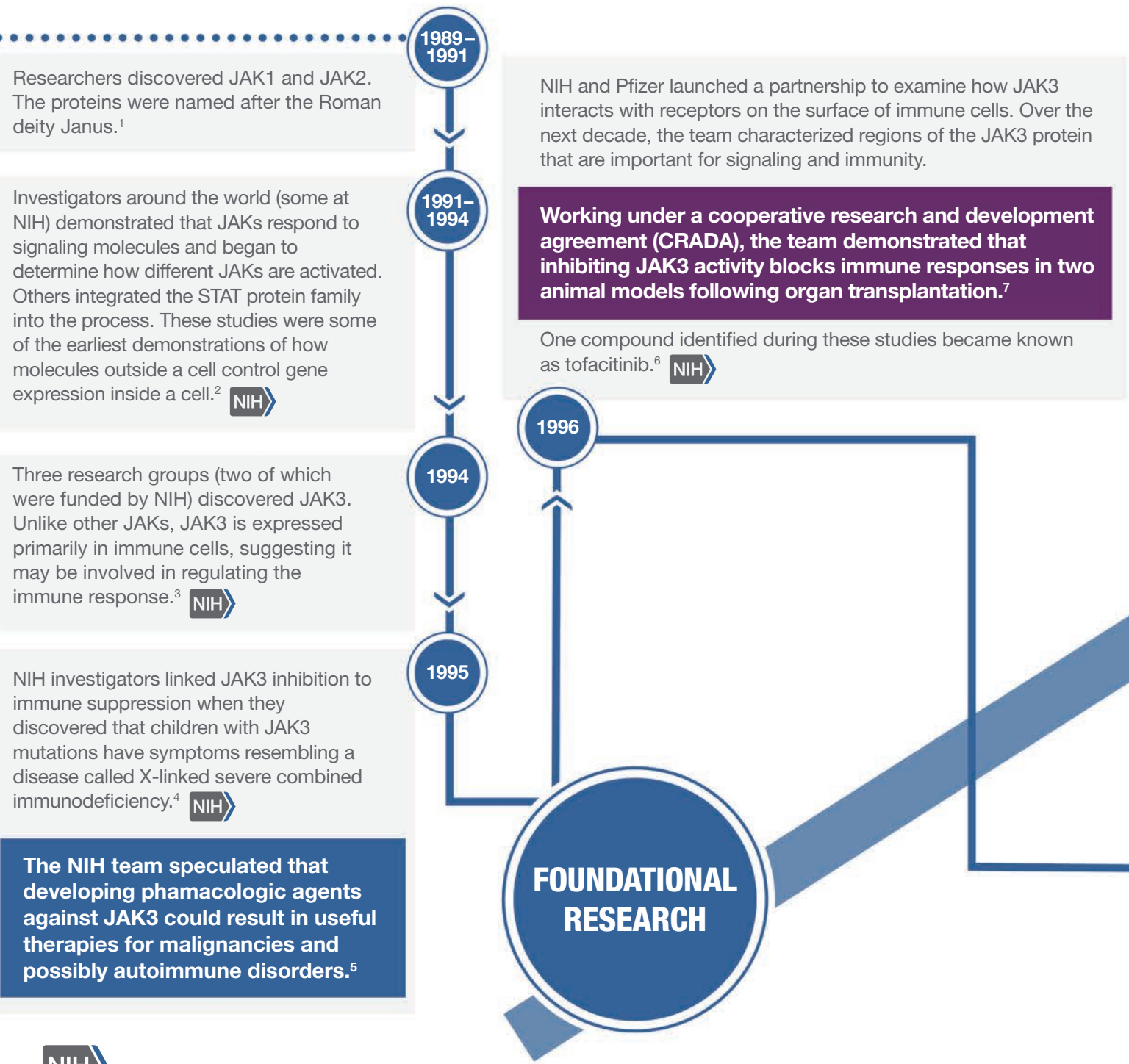
NOW

A drug that targets a signaling pathway inside immune cells has been approved for people who have moderate to severe rheumatoid arthritis if they do not benefit from one of the older treatments.

**The new drug is
taken as a pill.
Versions that can
be absorbed
through the skin
are being
developed to treat
other diseases.**

SELECTED RESEARCH-TO-PRACTICE MILESTONES IN THE DEVELOPMENT OF TOFACITINIB

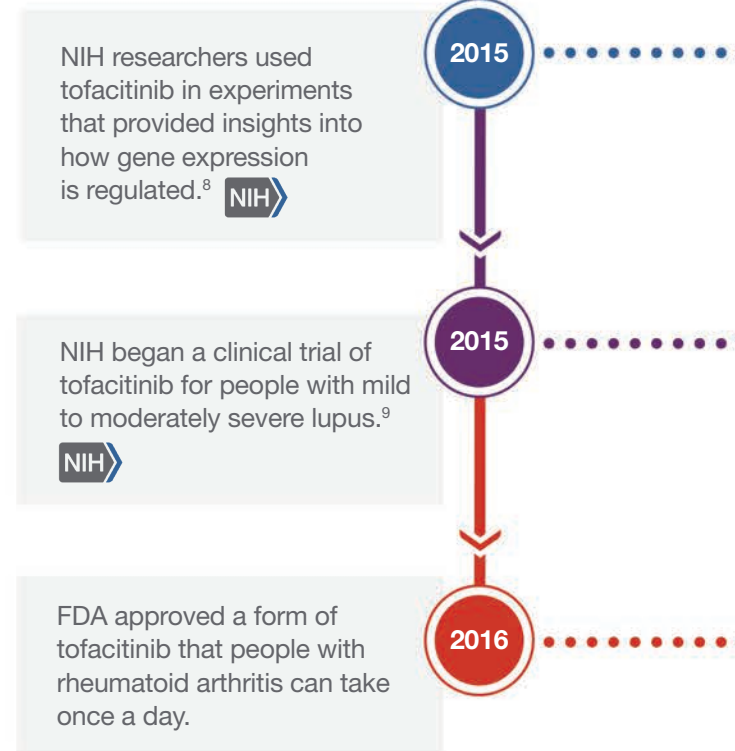
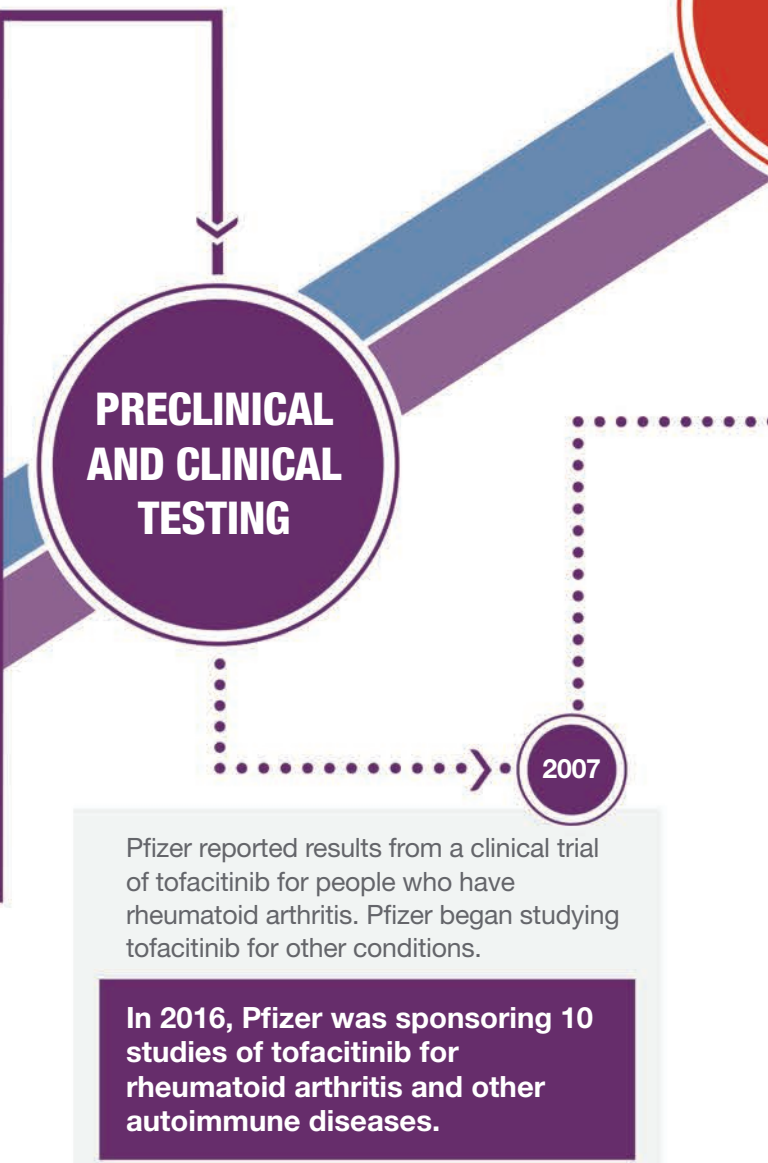
For more information on the supporting evidence and research sponsors for these milestones, see the Web appendix.



FDA approved tofacitinib for the treatment of people with moderate and severe rheumatoid arthritis who had not done well on an older drug (methotrexate). Patients take tofacitinib as a pill twice daily.

Depiction of tofacitinib's target, the Jak3 kinase domain.

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IMPACT OF STUDYING THE JAK-STAT SIGNALING PATHWAY

KNOWLEDGE

Discovery and characterization of the JAK-STAT pathway was one of the earliest demonstrations of how molecules outside a cell control gene expression inside a cell.



Researchers know that signals transmitted through the four JAK family members and seven STAT family members affect tens of thousands of sites in the human genome, regulating the production of thousands of proteins and other molecules.¹⁰

HEALTH

The finding that alterations in the JAK-STAT pathway are associated with diseases of the immune system and human cancers has led to the development of a new class of drugs, called Jakinibs.



Jakinibs that act on JAK1 or JAK2 are FDA-approved for dogs with allergic dermatitis or for people with certain blood cancers.

People who do not respond to at least one older RA treatment have a new option in the form of tofacitinib, which acts on JAK3. This is the first new oral drug approved for RA in a decade.

SOCIETY

At the beginning of 2016, a dozen compounds that inhibit JAK1, JAK2, or JAK3 signaling (alone or in combination) were in clinical trials for autoimmune diseases, including psoriasis, RA, ulcerative colitis, spondyloarthritis, juvenile idiopathic arthritis, Crohn's disease, and lupus.¹¹



JAK-STAT SIGNALS CONTROL CELL BEHAVIORS, INCLUDING THE IMMUNE RESPONSE

Discovery of the JAK-STAT molecular pathway in the early 1990s was a landmark advance explaining how cells sense and respond to their immediate environment. Research teams from around the globe quickly capitalized on this finding and began exploring different aspects of the complicated signaling mechanisms. They found that when certain receptors on a cell's surface encounter signaling molecules called cytokines, at least one of the four types of JAK (Janus kinase) proteins inside the cell is activated.

The specific combination of cytokines, receptors, and JAKs dictate which member of another family of proteins, called STATs (signal transducers and activators of transcription) is mobilized. Activated STATs migrate to the nucleus, where they interact with DNA and other molecules to precisely control gene expression. Researchers have learned that changes in this process can cause disease. For example, too much JAK3 activity is associated with autoimmune diseases such as RA; too little puts people at high risk of infections.

Twenty-five years later, researchers are conducting clinical trials of molecules that alter the activity of the JAK-STAT pathway to treat autoimmune diseases and other conditions that are caused by dysregulated cell signaling. In addition to tofacitinib, two JAK inhibitors (or Jakinibs) have received FDA approval: ruxolitinib for people who have bone marrow diseases and oclacitinib for atopic dermatitis in dogs.

For references, supplementary information, and more on the impact of NIH, please visit <http://www.nih.gov/impact>.