# A closer look into the TSLP cytokine structure

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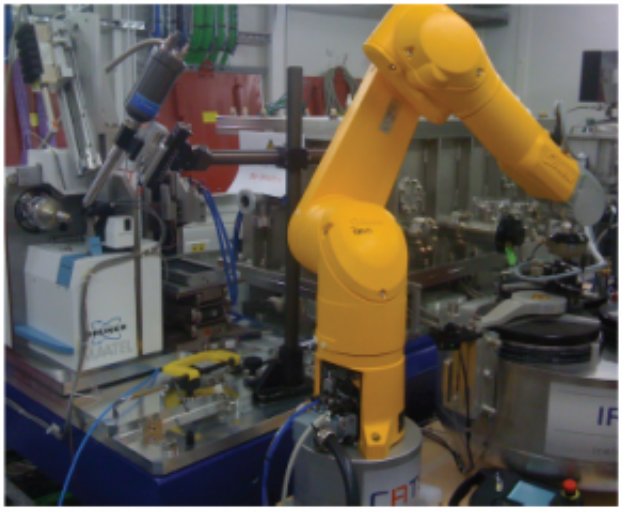


*Photos of crystals (courtesy Dr. A. Haouz, Institute Pasteur), and the experimental station on PROXIMA 2.*

The PROXIMA 2 beamline at Synchrotron SOLEIL recently celebrated its first birthday. It's an occasion to reflect back upon a year of the collaborative work accomplished and its high scientific impact. In particular, a recent experiment performed on PROXIMA 2 at SOLEIL gives a new paradigm in the fight against asthma, which currently affects 235 million persons in the world (WHO estimate). As a laboratory - or "beamline" in synchrotron jargon - PROXIMA 2 can help academics to understand biological macromolecules and the pharmaceutical industry to make new, more potent and tailor-made drugs.

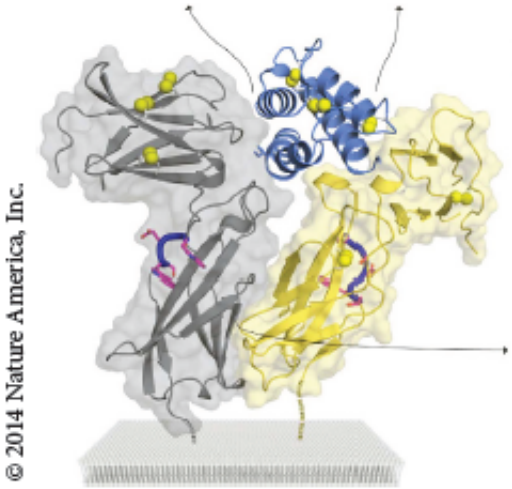
On the 21st of March 2014, PROXIMA 2 celebrated its first year open to external users of the scientific community in France and its neighbouring countries. PROXIMA 2 is at the cutting edge of the characterisation of 3D structures of biological macromolecules at atomic resolution. These include proteins, DNA & RNA, as well as their complexes and assemblies, which make up ribosomes and virus particles. The arrangement of atoms (several thousands) in a biological macromolecule determines its biochemical function. As these molecules are only a few nanometers in size, X-ray crystallography is the most common method used to determine their atomic arrangement. However, one of the biggest challenges faced by the scientist is to grow single crystals of sufficient size and quality to be studied.

Typically, hundreds of crystallization conditions are tested before finding one that will produce crystals and hundreds of crystals are exposed to X-rays before obtaining data suitable to determine a 3D-structure. The micro-focused X-rays on PROXIMA 2 permit the smallest crystals to be tested which for the scientists can save months of work in preparing better crystals.

Furthermore, crystals of bio-molecules are far from single and unique objects. Instead, they are often cracked, deformed and/or clumped together with other crystals. The X-ray data from such "ugly" crystals are difficult to process and fail to yield 3D structures. Fortunately, with the finely focused X-ray beam on PROXIMA 2, the scientists can select out the best zones of these "ugly" crystals. The screening for the best zone of a crystal is currently being automated on PROXIMA 2 with 2D "grid" scans.

Already the structures of a number of important proteins have been determined with the X-rays on PROXIMA 2. These include proteins from viruses, bacteria, and even humans. These proteins have varied functions from catalysis and biosynthesis (enzymes) and cell signaling

(signal transduction) to immunological responses (such as cytokines in asthma).




**Treating asthma, a closer look into the TSLP cytokine structure**

The leading journal *Nature Structural & Molecular Biology* recently published new research results obtained on PROXIMA 2 that open the way for the development of new drugs to improve the treatment of allergic and chronic inflammatory diseases, such as asthma.

Using state-of-the-art synchrotron radiation facilities at SOLEIL in France (PROXIMA 2) and PETRA3 in Germany (P13), researchers from Ghent University have now determined crystal structures of the protein assembly mediated by TSLP cytokine, a protein regulating the action and function of other cells. This protein assembly resides at the surface of epithelial cells and serves to initiate and propagate inflammation. The structures reveal details at high resolution of how

TSLP establishes extensive interfaces with its two co-receptors, TSLPR and interleukin-7 receptor, to organize receptor-receptor contacts poised for intracellular signaling.

A key experimental implementation that led to the structure determination of the complex was the use of micro-focused X-rays at the beamlines at SOLEIL and PETRA3. In addition, the study reports results on a modified form of TSLP that may offer a promising starting point to fight against such allergic diseases.

## What is SOLEIL?

Near Paris, SOLEIL is a source of light endowed with extraordinary and important properties for the scientific community (great brilliance: 10,000 times brighter than sunlight), a wide spectral "white" source range ranging from infrared (1eV) to hard X-rays (50 keV), polarization (linear, circular, etc.), and pulsed light. It provides new perspectives in the study of matter with a resolution down to millionths of meters and sensitivity to all types of materials.

SOLEIL covers fundamental research needs in physics, chemistry, material sciences, life sciences (notably in the crystallography of biological macromolecules), earth sciences, and atmospheric sciences. It offers the use of a wide range of spectroscopic methods from infrared to X-rays, and structural methods in X-diffraction and diffusion.

In applied research, SOLEIL is applied in very different fields such as pharmacy, medicine, chemistry, petrochemistry, environment, nuclear energy, and the automobile industry, as well as nanotechnologies, micromechanics and microelectronics, and more.

**More information:** "Structural basis of the proinflammatory signaling complex mediated by TSLP," Kenneth Verstraete, Loes van Schie,

Laurens Vyncke, Yehudi Bloch, Jan Tavernier, Ewald Pauwels, Frank Peelman, Savvas N Savvides. *Nature Structural & Molecular Biology* (2014) DOI: 10.1038/nsmb.2794

Provided by Synchrotron Soleil