Germinating MALT1

By Chris Cain, Senior Writer

AstraZeneca plc has teamed up with the **Flanders Institute for Biotechnology** and the **Centre for Drug Design and Discovery** to make the first disclosed industry play for inhibitors of MALT1. The deal announcement caps five years of progress toward validating MALT1 in B cell lymphoma and autoimmune diseases.

MALT1 (mucosa associated lymphoid tissue lymphoma translocation gene 1) was first identified as a driver of a small subset of B cell lymphomas more than a decade ago. The protein was quickly implicated by **Roche's Genentech Inc.** unit and other groups as a regulator of B and T cell signaling and NF- κ B activity,¹ but its precise molecular function and the potential druggability of the target remained unclear.

That changed in 2008 when two independent teams—one led by the **University of Lausanne**² and one led by Rudi Beyaert at the Flanders Institute for Biotechnology (VIB),³ reported in *Nature Immunology* that MALT1 functions as a protease through a conserved paracaspase domain.

Beyaert is associate department director of the VIB inflammation research center. He was joined on the paper by Thijs Baens, a staff scientist at VIB, and Peter Marynen, a professor of human molecular genetics at the **Catholic University Leuven**. In 2008, the team also filed a patent application describing peptide and small molecule inhibitors of MALT1.

Last week, AstraZeneca licensed a series of small molecule inhibitors from the team and partnered with them to further study MALT1 function.

AstraZeneca will make undisclosed upfront and milestone payments to VIB and the Centre for Drug Design and Discovery (CD3), an organization that performs drug discovery for academic laboratories and small, regional biotechs. The partners also are eligible for royalties.

"The work on building a translation package for this target will be jointly carried out in the labs of VIB/CD3 and AstraZeneca in Moelndal, Sweden. The work on the compounds will be carried out mainly at AstraZeneca in Moelndal," said Stefaan Allemeersch, director of business development at CD3.

Fermenting strength

In the last five years, a series of key studies—most of which were featured in *SciBX*—strengthened the therapeutic rationale of targeting MALT1 in B cell lymphoma and broadened the potential applications of inhibiting MALT1 to autoimmune disease.

For example, a 2009 paper by a University of Lausanne and **National Cancer Institute** team reported that a peptide inhibitor was selectively toxic to activated B cell-like diffuse large B cell lymphoma (ABC-DLBCL) cells.⁴ Separate work published by the **Technical University Munich** and the **German Research Center for Environmental Health** came to a similar conclusion.⁵

In 2011, a **University of Michigan** team published a precise molecular explanation of how a MALT1 fusion oncoprotein drives the T-cell lymphoma subtype by cleaving MAP kinase kinase kinase 14 (MAP3K14; NIK).⁶

In 2012, two teams simultaneously published *in vivo* data showing the potential of small molecule MALT1 inhibitors.

A team led by Ari Melnick, a professor of medicine at **Weill Cornell Medical College**, showed that nanomolar-potent MALT1 inhibitors had efficacy in a mouse model of ABC-DLBCL.⁷ Melnick told *SciBX* last week that the licensing status of his team's series of MALT1 inhibitors is undisclosed.

The other team was led by Daniel Krappmann, head of the research unit for cellular signal integration at the Institute of Molecular Toxicology and Pharmacology at the German Research Center for Environmental Health. His team showed that the antipsychotic compounds mepazine and thioridazine were also nanomolar-potent MALT1 inhibitors with *in vivo* efficacy in ABC-DLBCL.⁸

Krappmann told *SciBX* that his team has since synthesized new inhibitors but also sees potential for thioridazine in the clinic. "We are in the process of working out a clinical repurposing trial with thioridazine because this drug is still available. We are currently still profiling our new MALT1 inhibitors, and they are still available for licensing," he said.

His lab has filed for four patents covering discoveries relating to MALT1.

Most recently, at least two studies have suggested that inhibiting MALT1 could help treat autoimmune disease.

In late 2012, a team from the **University of Toronto** led by Tak Mak showed that *Malt1* knockout prevented mice from developing experimental autoimmune encephalomyelitis (EAE) by suppressing the differentiation of functional T helper type 17 (Th17) cells.⁹ Mak is a professor at the university and director of **The Campbell Family Institute for Breast Cancer**

Research at The Princess Margaret.

In early 2013, a VIB team including Beyaert published similar results.¹⁰ Jérôme Van Biervliet, senior business development manager at VIB, credited recent publications from VIB and other academic teams for functionally validating MALT1 and showing its druggability.

Both Krappmann and Melnick said that some of their next steps include looking at the role of MALT1 in autoimmunity.

Krappmann's MALT1 inhibitors act through an allosteric mechanism.¹¹ AstraZeneca spokesperson Jodi Lewis did not disclose the mechanism of action for the VIB/CD3 compounds licensed by AstraZeneca but added that specificity for the target, often a problem

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AstraZeneca plc

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**—Daniel Krappmann,
German Research Center for
Environmental Health**

from other industry teams.

Lewis said that there has been increasing interest in MALT1, and Krappmann added that his lab has been in contact with undisclosed pharmaceutical companies. “I think the announcement of the MALT1 discovery partnership between AstraZeneca and VIB underscores clearly that MALT1 is a very attractive target for autoimmune diseases and distinct types of cancers,” he said.

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for protease inhibitors, was not a concern.

“MALT1 is the only protease of its kind in the human genome, and the literature confirms that allosteric modes of action may be of particular interest,” she said.

Although Genentech scientists have written at least two recent news pieces for scientific journals highlighting publications about MALT1, they have not published on inhibitors of the target, and no MALT1 inhibitors have been disclosed in patents or publications

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COMPANIES AND INSTITUTIONS MENTIONED

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