India's first-in-class MALT1 blocker deal

AbbVie has gained exclusive global rights to develop a portfolio of small-molecule inhibitors of mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) to treat hematological cancers from Mumbai-based Lupin. Lupin, long known as a maker of generic drugs, was developing the MALT1 program out of its Novel Drug Discovery and Development Division (NDDD).

The MALT1 protein, also known as paracaspase, acts in the 'signalosome' involved in NF- κ B signaling and T-cell and B-cell lymphocyte activation. Aberrant NF- κ B activation and exaggerated MALT1 activity are hallmarks of human lymphomas, and hence MALT1 inhibitors are a promising new class of antitumoral drugs.

Tom Hudson, vice president of discovery at AbbVie, commented in a press release issued on December 24, "Lupin's MALT1 program is exploring a new and innovative approach in difficult-to-treat cancers. [...] We look forward to partnering our expertise in hematological oncology with Lupin's discovery program to offer new hope to patients."

Lupin will receive an up-front payment of \$30 million and up to \$947 million on the successful completion of regulatory, development and commercial milestones; a double-digit royalty on the sales of any developed therapies; and commercial rights to the MALT1 program in India.

Lupin's NDDD program dates to 2010 and aims to build a pipeline of innovative new chemical entities in the therapeutic areas of oncology, immunology and metabolic disorders. Raj Kamboj, the program president, says, "This is a first-in-class drug discovery program delivered exclusively by Lupin right from concept generation through the various stages of drug discovery and development."

Published online: 4 February 2019
<https://doi.org/10.1038/s41587-019-0026-1>

Table 1 | Small molecule RIPK1 inhibitors in development

Company	Small molecule	Indications	Stage
GlaxoSmithKline	GSK2982772	Psoriasis, ulcerative colitis, rheumatoid arthritis	Phase 2
GlaxoSmithKline	GSK3145095	Pancreatic cancer	Phase 1/2
Sanofi, Denali Therapeutics	DNL747	Alzheimer's disease, amyotrophic lateral sclerosis, multiple sclerosis	Phase 1
Sanofi, Denali Therapeutics	DNL758	Systemic inflammatory disease	Preclinical

Sources: ClinicalTrials.gov; company websites

also from recent genetic findings that point towards a role in intractable conditions, such as Alzheimer's disease and amyotrophic lateral sclerosis (ALS). In ALS, for example, loss-of-function mutations in the optineurin gene, which normally suppresses RIPK1, are associated with both familial and sporadic forms of the disease. If the optineurin protein—involved in protein trafficking, autophagy and signaling—is absent, RIPK1 signaling increases and activates RIPK3 and its substrate MLKL, which results in axon degeneration, a hallmark of ALS.

Also linked to ALS are mutations in the Tank-binding kinase 1 (*TBK1*) gene, according to a recent human genetics study from Yuan's group. Heterozygous mutations in *TBK1* are a major risk factor for patients with either ALS or frontotemporal dementia. *TBK1*, which is involved in antiviral innate immunity, is an endogenous inhibitor of RIPK1, and its partial loss may be exacerbated by reductions in another RIPK1 inhibitor, transforming growth factor- β -activated kinase 1 (TAK1), the production of which declines with age.

In Alzheimer's disease, the first report of a link with RIPK1 expression came from Salvatore Oddo's lab at Arizona State University. His group observed evidence of necroptosis, as well as elevated levels of RIPK1 and MLKL, in the brains of patients with Alzheimer's disease. These correlated positively with levels of neurofibrillary tangles and negatively with cognitive function and brain weight. They also reported that RIPK1 levels predict dysregulation of expression of multiple genes already known to be associated with Alzheimer's. In an Alzheimer's mouse model, Yuan's lab showed that RIPK1 suppression reduces amyloid burden and cytokine expression while improving cognition.

So far, Denali and its partner Sanofi are the only companies in the clinic exploring RIPK1 inhibition in neurodegeneration. The French pharma licensed rights to DNL747 for ALS and multiple sclerosis and has an option on the molecule for

Alzheimer's. But the alliance is not limited to these conditions. "It's potentially broader than the three indications we have spoken about publicly," says Rita Balice-Gordon, global head of Sanofi's rare and neurologic diseases therapeutic area. The drug has successfully completed a phase 1 safety study in healthy volunteers, and data from initial studies in patients are expected later this year. In the meantime, Denali is also closing in on potential biomarkers that will guide clinical development, in the absence of suitable clinical endpoints for early-stage trials. "If we can identify RIPK1-sensitive biomarkers, we're on the right track," says Yuan. In Alzheimer's, Denali has identified four novel but undisclosed biomarker candidates from a single, undisclosed pathway by conducting mass spectrometry of cerebrospinal fluid of phase 1 subjects. For ALS and multiple sclerosis, cytokine profiling is one of several avenues the company is exploring. Denali is also studying neurofilament light-chain protein, a general marker of neuronal injury, which increases as neurodegeneration progresses. The collaboration in inflammatory peripheral disease is at an earlier stage of development; the companies have not yet selected a lead indication. This will be guided by phase 1 data, Balice-Gordon says.

In neurodegenerative disease, much of the focus of RIPK1 research is on microglia, which are widely implicated in neuroinflammation. For studies in cancer, the attention is on tumor-associated macrophages. George Miller, a professor of surgery and cell biology at New York University's school of medicine, in collaboration with GSK, recently reported that RIPK1 is highly expressed in tumor-associated macrophages in pancreatic cancer, which results in an immunosuppressive phenotype in a mouse model of that condition (*Cancer Cell* **34**, 757–774, 2018). Interest in RIPK1 inhibition in cancer has flourished since a group headed by Nicholas Haining at the Dana Farber Cancer Institute in Boston used loss-of-function CRISPR screens in B16