

## Denali lets Rip with biggest funding round



[Madeleine Armstrong](#)

The biggest biopharma fundraiser of the year so far, Denali Therapeutics, is a surprise on several levels: first, it is in the high-risk CNS space; second, its lead project has not yet entered the clinic; and third, it already raised a \$217m series A round last year.

But there is obviously still an appetite for novel drugs for neurodegenerative diseases, and Denali is one of only a handful of players targeting the receptor-interacting protein (Rip) kinase family, according to *EvaluatePharma* (see table below).

One of the others is GlaxoSmithKline – but its most advanced contender, GSK2982772, is in phase II for psoriasis and rheumatoid arthritis. The fact that Rip inhibitors are being developed in a range of disorders is likely down to the fact that their targets are [known to play a role in inflammation](#) – which is also seen in Alzheimer's, along with the characteristic plaques and tangles.

**Selected Rip kinase targeting drugs in development**

Project	Company	Mechanism	Indication	Status
GSK2982772	GlaxoSmithKline	RIP1 kinase inhibitor	Psoriasis/rheumatoid arthritis	Phase II
Unnamed	GlaxoSmithKline	RIP1 & 2 kinase inhibitor	Inflammatory disease	Preclinical
Unnamed	Denali Therapeutics	RIP1 kinase inhibitor	Alzheimer's/ALS	Preclinical
Unnamed	Oncodesign	RIP2 kinase inhibitor	Inflammatory disorders	Preclinical

Denali's project could therefore complement drugs targeting amyloid or tau – or provide an alternative avenue for Alzheimer's should these approaches continue to fall short. Some researchers even believe that inflammation is the trigger for Alzheimer's.

But the company's as-yet-unnamed lead compound is still a long way from the market. Denali has applied to start a European phase I study in healthy volunteers and eventually hopes to progress the Rip1 inhibitor into trials in Alzheimer's and amyotrophic lateral sclerosis.

Meanwhile, Denali has other irons in the fire through a series of deals funded by its recent windfall. It has acquired Incro Pharmaceuticals to get access to its Rip1 inhibitor program, and has signed an agreement with Roche's Genentech division that will see it develop LRRK2 inhibitors, which are in preclinical trials in Parkinson's disease.

Roche previously flagged up cases of lung toxicity in primate studies of the drugs, but the Michael J Fox Foundation continued research and seems to have assuaged these fears; nevertheless, the project remains a risky bet for Denali.

Several other companies are developing LRRK2 inhibitors, but these are also all at the preclinical stage, according to *EvaluatePharma*.

### Crossing the blood-brain barrier

Two more deals – with F-Star and Blaze Bioscience – focus on technology that can cross the blood-brain barrier, a common stumbling block for CNS drugs. The agreement with F-Star, worth \$6m up front, covers bispecific antibodies and gives Denali the option to acquire F-Star Gamma, the group's latest vehicle.

Finally, Denali is taking another approach in Alzheimer's, licensing ApoE-targeting antibodies from the Washington University School of Medicine in St Louis. Certain ApoE gene mutations increase the risk of Alzheimer's.

### Top-five biopharma funding rounds in 2016\*

Company	Amount (\$m)	Sector	Country	Round
Denali	130	CNS	US	Series B
DalCor Pharmaceuticals	100	Cardiovascular	Canada	Series B
Zai Lab	100	Oncology/respiratory	China	Series B
Mission Therapeutics	86.4	Oncology/CNS	UK	Undisclosed
Forty Seven	75	Oncology	US	Series A

\*As of August 26.

With this slew of deals, the question is probably not why Denali needed to raise more cash, but how long the latest injection of funds will last. It might not have hit the heights of Moderna's record-breaking \$450m round last year, but with long development paths for CNS drugs – particularly those for Alzheimer's – it seems likely that Denali will need to go back to its investors in the not too distant future.

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