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09 Aug 2023 | **News**

Astex Bags Another Cancer Deal With MSD, This Time For 'Undruggable' p53 Target

Gets $35m Upfront

by Ayisha Sharma

The UK-based biotech will license its Pyramid platform to MSD to develop anticancer compounds targeting p53, a key transcription factor dubbed the 'guardian of the genome' that has proven highly complex and challenging to drug.

Astex Pharmaceuticals, Inc. has clinched its third oncology partnership with *MSD* with a focus on the notoriously difficult p53 transcription factor target for $35m upfront after two prior deals successfully yielded lead compounds.

Under the terms of the deal, the pharma major will get access to Astex's proprietary fragment-based drug discovery platform, Pyramid, to develop compounds targeting several forms of the p53 protein. Astex will be eligible for up to $500m in milestones per program as well as tiered royalties on product sales while MSD will be responsible for all future research, development and commercialization.

Key Takeaways:

- Astex could get up to $500m in milestones per program as well as tiered royalties on sales.
- The p53 transcription factor is difficult to target because of its structure and specificity.
- Astex believes its fragment-based approach could unlock understanding of mutated p53.

"Fragment-based drug discovery is an approach which ... requires the screening of very small

chemical fragments against the target protein, rather than larger compounds which you often find in high-throughput screening campaigns in a big pharma," Astex CEO Harren Jhoti told *Scrip*. Its benefits include reduced attrition and delivery of low molecular-weight compounds.

In recent years, the UK firm has worked to integrate Cryo-electron microscopy (Cryo-EM) as well as AI and machine learning computational methods into its platform to keep its approach cutting edge.

The MSD partnership follows on from a prior deal between Astex, *Taiho Pharmaceutical Co. Ltd.* – both wholly owned subsidiaries of *Otsuka Pharmaceutical Co. Ltd.* – and the pharma major inked back in 2020. That deal saw the two biotech firms share $50m upfront and the promise of up to $2.5bn in milestones to help MSD develop small-molecule KRAS inhibitors. (Also see "*Merck Joins KRAS Stampede In Deal With Otsuka Affiliates*" - Scrip, 6 Jan, 2020.)

In 2021, Astex and Taiho jointly out-licensed the rights to their small-molecule drug discovery program targeting SHP2 to MSD for an undisclosed fee. SHP2 is a KRAS-related oncology target that offers potential for combination use. Jhoti revealed both partnerships have since successfully produced lead compounds that have entered clinical development, with the small-molecule KRAS inhibitor named MK1084. (Also see "*Merck & Co Takes Up Astex/Taiho SHP2 Program*" - Scrip, 13 Jan, 2021.)

However, the latest partnership struck between Astex and MSD is noteworthy due to the traditionally challenging nature of drugging the target involved. "p53 is a protein that binds to DNA and it's function is to protect the cell from becoming cancerous … but when you get a mutation, it causes instability in the protein which stops it from performing that function," Jhoti explained.

The gene that encodes for the protein, *TP53*, was discovered several decades ago and has been dubbed the 'guardian of the genome' due to its crucial role in regulating the cell cycle, apoptosis and genomic stability. It is mutated or deleted in half of all cancers while its signalling pathway is disrupted in the remaining half, according to a 2021 article in *Pharmacology & Therapeutics*.

p53 was long considered undruggable due to its specificity, its smooth surface that lacks an ideal drug-binding site and a poor understanding of its biology. Past attempts by industry have ended in failure, with 14 anticancer drug candidates targeting the protein having been discontinued, according to the Citeline database Pharmaprojects (see table below).

"Using our structural knowledge of p53, which we developed from using our X-ray crystallography and Cryo-EM techniques, we are beginning to understand why the protein becomes unstable when mutated," Jhoti said.

“We are thus developing an understanding of what kind of small molecules we may need to design to stop that instability from developing … and the goal here is to recapitulate the normal function of a mutated p53 protein.”

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Notably, other big pharma companies are also dipping their toes in the p53 space. Last year, *AstraZeneca PLC* acquired oncology cell therapy specialist *Neogene Therapeutics, Inc.* for $200m upfront plus $120m in potential milestones, getting hold of NT-175, an autologous TP53 R175H-targeting T-cell receptor therapy candidate, which recently entered Phase I development for the treatment of solid tumors. (Also see "*AstraZeneca Takes Personalized Approach To Cell Therapy With Neogene Buy*" - Scrip, 29 Nov, 2022.)