platform technology “RaPPIDS”. Since IRAK-M is a pseudokinase which lacks kinase activity, it is considered 'undruggable’, i.e. it could not be targeted pharmacologically by conventional small molecules. FIMECS developed heterobifunctional degrader molecules comprising an IRAK-M-binding moiety linked to proprietary E3 binders to eliminate the IRAK-M protein. When examined in mouse models, IRAK-M degrader showed significant anti-tumor activity in several syngeneic models at tolerated doses and schedules. Advanced profiling of the drug candidate is ongoing in IND-enabling studies.

HC-X022 is a project of Hinova Pharmaceuticals for the discovery of an androgen receptor (AR) “destructor” (PROTAC) by using small molecules to target AR for degradation. It is believed that drug-induced AR mutations, either point mutations or the C-terminus lacking splice variants such as the predominant form of AR-v7 contribute to the formation of drug resistance. Hinova’s ultimate goal is to find a small molecule that targets both the full-length AR and the splice variants for degradation. This PROTAC project is close to the preclinical candidate (PCC) stage. HC-X022 targets the splice variant 7 (V7) of androgen receptor (AR).

Drug discovery efforts are ongoing to find a proteolysis targeting chimeric (PROTAC) small molecule to degrade the androgen receptor (**HC-X025**).

Kronos is advancing two preclinical programs built upon hits identified from its small molecule microarrays (SMM) platform. The lead program in preclinical development targets cyclin-dependent kinase 9 (**CDK9**). The second program in the discovery stage addresses transcription factors and oncoproteins (multiple).

Signal transducer and activator of transcription 3 (STAT3) is a transcription factor and an attractive therapeutic target for cancer. Targeting STAT3 has been very challenging. Oncopia reported the structure-based discovery of potent small-molecule STAT3 degraders based upon the proteolysis targeting chimera (PROTAC) concept. They first designed SI-109 as a potent, small-molecule inhibitor of the STAT3 SH2 domain. Employing ligands for cereblon/cullin 4A E3 ligase and SI-109, they obtained a series of potent PROTAC STAT3 degraders, exemplified by SD-36. **SD-36** induced rapid STAT3 degradation at low nanomolar concentrations in cells and failed to degrade other STAT proteins. SD-36 achieved complete and long-lasting tumor regression in multiple xenograft mouse models at well-tolerated dose schedules. Degradation of STAT3 protein, therefore, is a promising cancer therapeutic strategy. Co-founder Wang and his

collaboration. In addition, Vertex will pay tiered royalties on future net sales on any products that may result from this collaboration.

Pegasus Technology of Targeted Protein Degradation

Targeted protein degradation redirects the body's innate protein degradation and recycling machinery, the ubiquitin proteasome system, to degrade disease-causing proteins not fully addressed by other modalities. Kymera's Pegasus platform was designed to improve upon current approaches to targeted protein degradation and accelerate drug discovery and development with an unmatched ability to identify, target and degrade dysregulated proteins.

The Pegasus platform consists of informatics-driven target identification, novel E3 ligases and ligands, proprietary ternary complex predictive modeling capabilities and degradation tools, including novel linkers and protein-binding ligands, as well as whole-cell proteomics capabilities.

According to the company's CSO, "E3 ligase discovery is part of Kymera's larger strategy to expand the current E3 ligase toolbox, advance the chemistry and the biology of E3 ligases and provide a next-generation solution to developing protein degrading therapeutics".

Using a small molecule-mediated knockdown strategy, Kymera rationally designs and develops heterobifunctional molecules that recruit disease-causing proteins to E3 ubiquitin ligases, resulting in the target protein's ubiquitination and degradation, and the ultimate resolution of cellular dysregulation.

The Pegasus technology is described in more detail in the Technology Profiles section of this report.

Pipeline

The company has selected two clinical development candidates in oncology targeting IRAK4 and STAT3, respectively. With its recently completed series C financing round, Kymera expects to advance up to three programs to the clinic by 2021 (Press Release Mar 12, 2020).

KYM-001

Kymera's lead candidate addresses IRAK4, a key component of a signaling pathway implicated in the pathophysiology of multiple diseases, including cancer, autoimmune, and inflammatory disorders. Kinase inhibitors have been developed to address this target, but with limited efficacy.

Den Besten from Amgen described two ligase ligands and showed how target degradation coupled with modulation of ligase biology leads to increased cellular efficacy (source).

5.3 AstraZeneca

One of the new, emerging drug modalities AstraZeneca research is working on apart from bicyclic peptides and therapeutic proteins are proteolysis targeting chimera (PROTAC). PROTACs are heterobifunctional molecules containing two small molecule-binding ligands joined together by a linker.

AstraZeneca is undertaking internal efforts to build state-of-the-art assay cascades towards understanding the molecular mechanism underlying this biology, the build of a proteomics platform to define the binding and degradation selectivity of protein degraders and the hit finding for novel E3 ligase ligands. AstraZeneca is identifying novel degraders against two **oncogenic targets** and their utility as target validation tools and as potential therapeutics for many solid and haematological malignancies (source). Beyond oncology, AstraZeneca is exploring protein degradation in cardiovascular, renal and metabolic and respiratory disease.

PROTAC assisted protein degradation is affected by several cellular factors (concentration of target and E3, native turnover rate of target) as well as PROTAC dependent parameters (affinity to target, ligase, ternary complex formation and the rate of ubiquitin transfer). To that purpose, AstraZeneca is developing high throughput assays for studying PROTAC-mediated protein degradation. AstraZeneca scientists are exploring novel in vitro assays for understanding the mechanism of PROTAC-mediated protein degradation (source).

Liu et al. (2019) reported about the development of high throughput assays measuring PROTAC-driven ternary complex formation and subsequent protein degradation for both VHL and CRBN E3 ligases. Novel reliable and quantitative high-throughput protein degradation related assays are required to deliver AstraZeneca's rapidly expanding PROTAC project portfolio. They demonstrated that HiBiT-technology based assays could be developed to study PROTAC-driven BRD4 protein degradation as well as the preceding recruitment of the E3 ligase (VHL or CRBN) to the binary target-PROTAC complex, resulting in the ternary complex. The HiBiT-BRD4

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