Category

Best Startup

Product/Solution Name

FX909 - Flare Therapeutics

Date of Approval

2021-05-13

Indications

We do not have an approved product yet. Out lead asset, FX909, has received 'Safe to Proceed' communication from the FDA for our phase 1 trial. Our phase 1 clinical trial will be enrolling patients in the August/September 2023 timeframe. ('Date of approval' submitted in this application is the date we announced our founding Series A financing.)

Therapeutic Categories

Our company is focused on precision oncology approaches to drugging transcription factors, Our lead indication for the FX909 program is muscle-invasive urothelial cancer, a disease which continues to have a high unmet medical need.

Attached Files:

- FlareTxLogoOverLightBG.png

Background information and need for solution/product

We are taking on one of the most formidable challenges in drug discovery – broadly drugging transcription factors, which have long been viewed as prime therapeutic targets playing a key role in a broad range of diseases, particularly cancers, where they represent one-third of all oncogenes. While targeting transcription factors has the potential for incredible impact, their complex structure makes them notoriously difficult to drug, requiring a new approach and new thinking.

Flare Therapeutics is the only company exclusively focused on drugging transcription factors. Our differentiated and comprehensive approach to uncovering, targeting and systematically drugging switch sites, which dictate transcription factor conformation and function, holds tremendous therapeutic potential.

Additionally, the team is comprised of world-renowned, cross-disciplinary thinkers that not only think creatively about how to design the platform, but also how to apply translational insights to ensure efficient drug development at scale.
,Flare Therapeutics is the only biotechnology company exclusively focused on drugging transcription factors to discover precision medicines for cancer and other diseases. The complex structure of transcription factors makes them notoriously difficult to drug, requiring a new approach and new thinking. Flare was incubated by Third Rock Ventures in 2020 and launched with a Series A round in 2021 followed by a $123M Series B round in Feb 2023.

Flare's differentiated and comprehensive approach to uncovering, targeting and systematically drugging switch sites – druggable pockets that dictate conformation and function – on transcription factors holds tremendous therapeutic potential for this class of targets in oncology and in other indications. We have made impressive strides quickly, all enabled by our powerful platform, which to date has successfully identified more than 170 switch sites across multiple families of transcription factors, providing opportunities to treat a broad range of diseases. Our platform is based on a broad and comprehensive approach that layers chemoproteomics, functional biochemistry, covalent chemistry and genetic insights. This allows us to gain a deeper understanding of the structural underpinnings driving transcription factor function and a proprietary library of compounds designed to modulate transcription factor behavior.

Transcription factors are master regulators of gene expression and are considered the guardians of cell fate. Proper transcription factor tuning drives healthy cell growth, differentiation and division, while dysfunction can drive diseases such as cancer. Transcription factors function through direct binding of DNA sequences, typically upstream of the target genes, to turn gene transcription on or off. A single transcription factor can regulate a small handful or up to thousands of genes within the cell depending on the specific details.

This may result in increased or decreased gene transcription, protein synthesis, and subsequent altered cellular function.

There has been success targeting nuclear receptors, a specialized sub-family of transcription factors that have been hugely impactful for patients – think steroids or hormone therapies. Unfortunately, nuclear receptors are a small fraction of the broader transcription factor family, and these successes have not been broadly transferrable. Efforts to drug transcription factors more broadly were fundamentally limited stemming from an incomplete understanding of the relationship between structure and function and historical technology roadblocks. As a result, modification of natural ligands and/or purely empirical approaches have dominated transcription factor discovery efforts for over 50 years.

Transcription factors support essential processes for cell growth, differentiation and division. When their activity becomes aberrant, transcription factors can drive cancer initiation, progression, metastasis and resistance to treatment.

Transcription factors have long been viewed as prime therapeutic targets playing a key role in a broad range of diseases, particularly cancers, where they represent one-third of all oncogenes. While targeting transcription factors has the potential for incredible impact, their complex structure makes them notoriously difficult to drug, requiring a new approach and new thinking.

Flare’s novel approach is based on our unique understanding of switch sites – druggable targets that dictate conformation and function – on transcription factors and exerts the ability to control gene expression.

,We are the only company exclusively focused on drugging transcription factors. Flare’s differentiated and comprehensive approach to uncovering, targeting and systematically drugging switch sites on transcription factors may unlock the therapeutic potential of this class of targets in oncology and in

other indications.

Our lead indication is in advanced urothelial cancer, and we are developing FX-909, a small molecule inhibitor targeting the PPARG transcription factor – slated to enter the clinic in mid-2023. Treatments for advanced urothelial cancer still remian a high unmet medical need.

Targeting cell lineage has been a backbone therapy in breast and prostate cancer for decades, through the successful inhibition of the ER and AR transcription factors. Similar to ER and AR, PPARG drives luminal cell identity, but in urothelial cancers, as opposed to breast and prostate cancer. More recently, PPARG was found to be over-expressed and genetically altered in the luminal subtype of urothelial cancer, highlighting its potential as a therapeutic target. Prior to Flare, no small molecules had been discovered that effectively inhibit PPARG.

We are vying to build a pipeline of potentially first-in-class therapies against genetically validated transcription factor targets for cancer. FX-909 has the potential to become a backbone therapy in advanced urothelial cancer, much like to anti-AR in prostate cancer and anti-ER in ER+ breast cancer. FX909 shows robust activity in preclinical animal models and displays excellent PK/PD correlation and anti-tumor activity in vivo in mouse models of urothelial cancer (PPARG-amp and RXRA-mut). FX-909 furthermore demonstrates durable efficacy in vivo at very low oral doses, with a favorable toxicity profile.

We are also expanding our pipeline of novel transcription factor targets in oncology, including identifying at least one additional development candidate from Flare's research pipeline in 2024.

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History of the development of the solution/product

Flare Therapeutics was ideated at Third Rock Ventures in 2020 and then launched with a Series A financing round in 2021 by a team of global scientific leaders in the biology and drug discovery of transcription factors whose goal was to rationally design transcription factor targeting therapies that have the potential to treat multiple cancers driven by transcription factor dysregulation.

We have made impressive strides quickly, all enabled by our platform, which to date has successfully identified more than 170 switch sites across multiple families of transcription factors, providing opportunities to treat a broad range of diseases. Our continued investor support since launch is testament to our rapid progress. This will be a pivotal year for Flare as we progress our first precision oncology program, FX-909, into the clinic, continue to expand our collection of druggable transcription factor targets, and build a pipeline of first-in-class therapies against genetically validated transcription factor targets for cancer. This includes our goal of identifying at least one additional development candidate from Flare's research pipeline in 2024 with line of sight to a third clinical candidate in 2025.

Why this solution/product is innovative, the broad implications for future research, and/or how it will improve the human condition

There is a high unmet need for new therapies for patients with urothelial carcinoma (UC), which accounts for 90% of bladder cancers and 10 to 15% of kidney cancers. In 2022, 81,000 people in the USA are expected to be diagnosed with bladder cancer. UC, also described as bladder cancer, is the 10th most common cancer type worldwide, with the most important risk factor being tobacco smoking, which accounts for ~50% of cases. Approximately 25% are diagnosed with muscle-invasive disease. Five-year survival for patients with locally advanced muscle-invasive disease is < 40% in the USA and falls to 8% with distant metastasis. Platinum-doublet chemotherapy, PD(L)1 checkpoint inhibition, and antibody-drug conjugate therapy (enfortumab-vedotin and sacituzumab-govitecan) are the standard of care for most patients with advanced disease, but the median overall survival of front-line patients treated with the latest regimens is only 2 years. To date, erdafitinib is the only targeted therapy that has been approved in urothelial carcinoma, for use in patients whose tumors carry genetic alterations in fibroblast growth factor receptor (FGFR)2/3. However, the limited reach of erdafitinib (only 5-20% of advanced urothelial carcinoma patients carry actionable mutations), and modest clinical activity (an ORR of 32%) suggest that there are opportunities to improve outcomes in urothelial carcinoma.

PPARG is a transcription factor that is one member of the PPAR subfamily of type II nuclear hormone receptors. Research has revealed that PPARG drives the initiation and development of urothelial carcinomas with a luminal phenotype and is the top selective dependency factor for urothelial carcinoma cell lines in genome-wide screens. Moreover, genetic profiling of urothelial carcinomas has identified recurrent oncogenic alterations in the PPARG transcriptional complex, including focal amplification, missense mutation, and fusions, and missense mutations in the heterdimeric partner of PPARG, the retinoid X receptor alpha (RXRA). Together these results highlight the potential for an inhibitor of PPARG to treat urothelial carcinomas.
We are vying to build a pipeline of potentially first-in-class therapies against genetically validated transcription factor targets for cancer. FX-909 has the potential to become a backbone therapy in advanced urothelial cancer, much like to anti-AR in prostate cancer and anti-ER in ER+ breast cancer. FX909 shows robust activity in preclinical animal models and displays excellent PK/PD correlation and anti-tumor activity in vivo in mouse models of urothelial cancer (PPARG-amp and RXRA-mut). FX-909

furthermore demonstrates durable efficacy in vivo at very low oral doses, with a favorable toxicity profile. FX909 is currently in clinical development with a phase 1 study to assess safety and pharmacokinetic parameters in individuals with UC with exploratory endpoints assessing efficacy.

Please provide appropriate references (ie Pubmed links)

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