Axcella Health Inc.
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Axcella antes up in key liver diseases with EMM (endogenous metabolic modulator) compositions

Using systems biology and machine learning to design multi-targeted EMM compositions for complex multifactorial diseases

Axcella (Nasdaq: AXLA) is a clinical-stage biotechnology company leveraging systems biology and machine learning to develop novel, multi-targeted combinations of EMMs (endogenous metabolic modulators) to treat complex diseases and restore health. One such disease, nonalcoholic steatohepatitis (NASH), is characterized by dysregulated metabolism, inflammation and fibrosis. According to Axcella's Chief Medical Officer and Executive Vice President of Clinical Development, Manu Chakravarthy, "In NASH, patients may benefit from approaches that coordinately modulate multiple pathways to safely restore normal health processes." Axcella's next steps in developing its pipeline of product candidates include a phase 2b trial of AXA1125, which is an EMM composition that targets multiple biological pathways associated with NASH.

EMMs include amino acids (AAs), among other metabolically active molecules. While sometimes thought of solely as protein building blocks, AAs are master regulators acting at the intersection of diverse pathways. EMMs also have well-validated therapeutic precedence, e.g. omega-3 fatty acids in lipid lowering, inflammation, and reducing cardiovascular risk. AXA1125 combines six AAs in a proprietary composition in specific ratios in order to target each of the three core drivers of NASH: metabolism, inflammation and fibrosis. In prior non-IND clinical studies in subjects with presumed NASH, AXA1125 has been safe and well tolerated while also generating clinically relevant reductions in markers of liver fat, inflammation and fibrosis (Fig. 1). Given these attributes, AXA1125 has the potential to become a first-line therapy for patients with NASH, while also being well positioned for combination with other drugs. Axcella's product candidates are packaged in dry-powdered sachets mixed with four to six ounces of water and administered orally. The company has expertise in formulating compositions with pleasant taste and texture.

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>
> Manu Chakravarthy, CMO and EVP of Clinical Development, Axcella

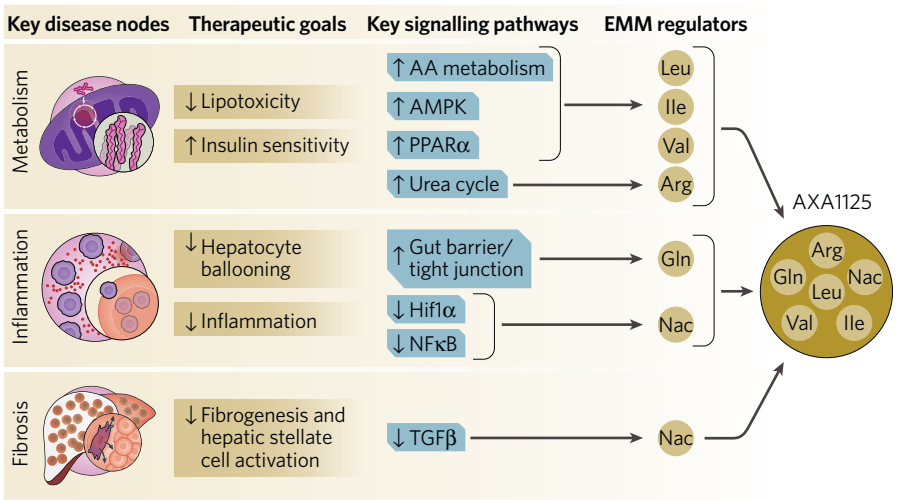

Fig. 1 | AXA1125 targets multiple pathways to reduce NASH-associated metabolic, inflammatory and fibrotic pathological processes. AA, amino acids; AMPK, AMP-activated protein kinase; Hif1, hypoxia-inducible factor (HIF)-1; NFκB, nuclear factor-κB; PPAR, peroxisome proliferator-activated receptor; TGF-β, transforming growth factor beta 1.

AXA1125 for NASH

In NASH, which affects an estimated 16.5 million people in the USA alone, the liver is not only fatty but also inflamed and fibrotic. If left unchecked, the disease can progress to cirrhosis, hepatocellular carcinoma, and for some, end-stage liver disease. Despite the large and rapidly expanding prevalence of this population, there are no approved therapies in the USA.

Because NASH is a chronic and often asymptomatic disease, it is critical that therapies offer a compelling benefit-to-risk profile to achieve regulatory approval and commercial success. Comorbidities in NASH patients further complicate the picture. Obesity and type 2 diabetes are both risk factors for NASH, suggesting that metabolic dysregulation is the underlying driver of liver inflammation and fibrosis. In fact, up to 80% of people with type 2 diabetes are believed to have fatty liver disease. Because of these overlapping comorbidities, many patients with NASH are already taking many medications. Ideally, a NASH treatment should minimize the polypharmacy burden that these patients already experience. AXA1125 has the potential to achieve this aim by benefiting multiple pathways simultaneously with a highly favorable safety and tolerability profile. And because the EMMs that are utilized in AXA1125 are intrinsic to the body, this modality may also present less risk of toxicity or drug-drug interactions.

In a 16-week, multi-center, randomized, placebo-controlled, proof-of-concept study in 102 adults with presumed NASH, with or without type 2 diabetes, AXA1125 was active and well tolerated. This candidate also demonstrated reductions from baseline in clinically relevant biomarkers, including those measuring liver fat (MRI-PDFF) and insulin resistance (HOMA-IR), inflammation (ALT, cT1) and fibrosis (ProC3, Fib4). Higher proportions of subjects receiving AXA1125 achieved clinically relevant reductions in key markers: 39% achieved ≥30% reduction in MRI-PDFF, 39% achieved ≥17U/L drop in ALT, and 35% had >80 mSec reduction in corrected T1 (cT1). Changes of this magnitude have been correlated with improvements in liver histology. Notably, consistently greater reductions in these same markers were observed in the subgroup of subjects with type 2 diabetes. In 2021, Axcella plans to begin enrolling a 48-week serial liver biopsy phase 2b clinical trial under an IND with primary endpoints based on liver histology. In addition to this adult trial, Axcella is also exploring the investigation of AXA1125 in pediatric NASH, which is a rapidly expanding population for which there is very little clinical development activity today.

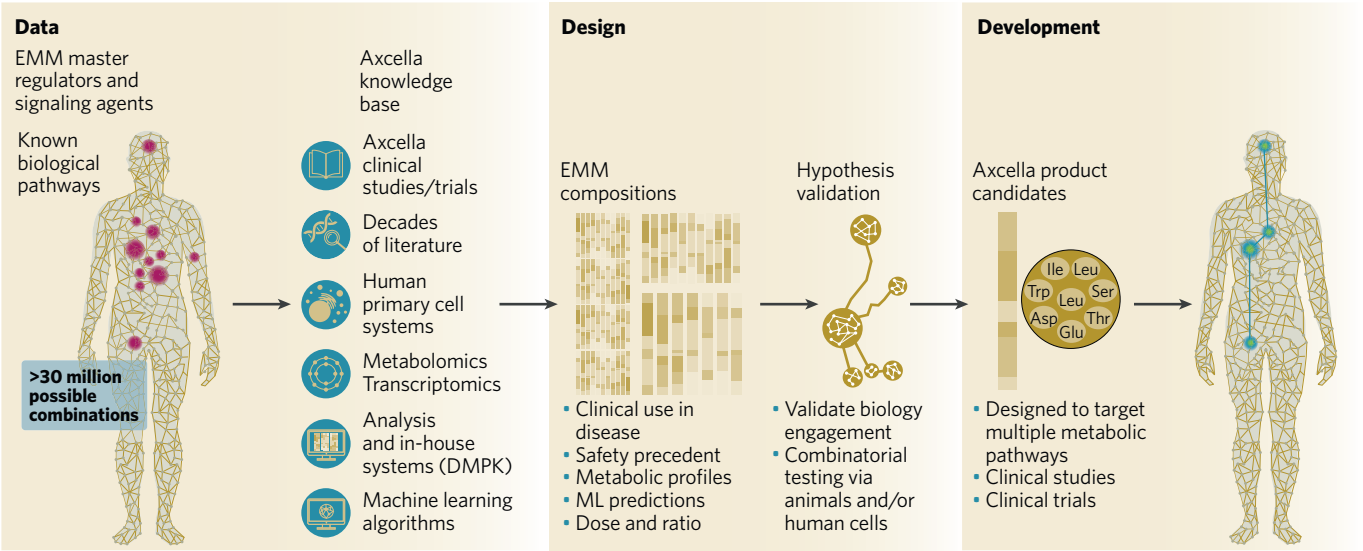

Fig. 2 | Axcella platform EMM design and development process. DMPK, drug metabolism and pharmacokinetic; EMM, endogenous metabolic modulator; ML, machine learning.

> **The platform allows Axcella scientists to screen more than 30 million possible EMM combinations to identify candidates that have the potential to effect multiple targeted pathways**

Pipeline

Axcella's pipeline extends beyond NASH, with another lead candidate in cirrhosis also planned to enter a phase 2 trial in 2021. This study will evaluate the efficacy and safety of AXA1665 in patients with overt hepatic encephalopathy (OHE). AXA1665 has previously demonstrated clinically relevant biological effects on nitrogen/ammonia metabolism, as well as physical and cognitive function in subjects with mild and moderate hepatic insufficiency.

HE is a common complication of cirrhosis, which affects more than 650,000 patients in the USA. Similar to NASH, HE also is complex, with a pathogenesis involving excess circulating ammonia that ultimately results in cognitive impairment. High circulating ammonia levels result from the reduced capacity of the cirrhotic liver to convert excess nitrogen into urea for excretion. In addition to excess ammonia, cirrhosis also leads to imbalances in circulating AA levels and muscle wasting (sarcopenia). Muscle wasting, due in part to reduced muscle protein synthesis, eventually affects almost all cirrhotic patients over the course of their disease.

Unlike today's standards of care in HE, which focus exclusively on ammonia reduction, AXA1665 has the potential to serve as a new foundational therapy by coordinately impacting the amino acid imbalance, dysregulated nitrogen/ammonia and muscle metabolism that underlie the multifactorial pathogenesis of HE. In a 12-week proof-of-concept non-IND clinical study in subjects with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic insufficiency, AXA1665 had positive effects on markers of nitrogen metabolism, muscle, and neurocognitive function. These data support the continued clinical testing of AXA1665 in phase 2.

Platform and preclinical models

Axcella's technology platform (Fig. 2) integrates systems biology and metabolic network analyses with a proprietary knowledge base containing data from Axcella's clinical and non-clinical studies as well as more than 1,100 EMM clinical trials that have been conducted over the past decade. The platform allows Axcella scientists to screen more than 30 million possible EMM combinations to identify candidates that have the potential to effect multiple targeted pathways. Using such analyses, Axcella identified the central role that AAs play in a wide array of diseases, revealing the effects of these powerful bioactive molecules on dozens of unique cellular pathways[1]. This finding underscores the important role that EMMs play as master regulators and signaling nodes for integration of metabolism and transcriptional regulation in normal physiology and disease.

Using insights generated from the knowledge base and machine learning platform, Axcella can rapidly generate and screen potential EMM compositions in proprietary cell-based models of disease. In-house cell and animal models can then be applied to refine EMM compositions in specific ratios for clinical testing.

Axcella has built an extensive EMM intellectual property portfolio consisting of multiple composition-of-matter and methods-of-use patents on its lead product candidates with approximately 190 patents pending and various trade secrets.

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1. Hamill, M. J. *iScience* **23**, 101628 (2020). https://doi.org/10.1016/j.isci.2020.101628