EraCal Therapeutics Ltd.
www.eracal.ch

How to fight obesity and other metabolic disorders—swimmingly

EraCal Therapeutics is developing a novel oral-active anti-obesity drug, Era-379, identified using the company's state-of-the-art, zebrafish-based platform technology. EraCal is raising a series A to generate human proof-of-concept data for Era-379 and expanding its portfolio through co-development partnerships.

Swiss startup EraCal Therapeutics is a preclinical-stage company focused on the development of novel treatments for metabolic syndromes, primarily obesity. Using a unique, zebrafish-based phenotypic screening platform developed by EraCal's founders at Harvard University and the University of Zürich, the company is advancing a portfolio of translationally relevant assets identified through phenotypic screening using multi-behavioral profiling and whole-organism safety assessments.

EraCal's lead asset, Era-379, is an orally active, small-molecule appetite suppressor. Once-daily oral Era-379 monotherapy reduced body weight in obese mice by more than 20% within 2 weeks. Era-379's target is an undisclosed novel protein that drives peripheral liver–brain signaling and acts in concert with glucagon-like peptide-1 (GLP-1)-targeting agents in vivo. Era-379 is expected to enter proof-of-concept studies in non-human primates next year. Other assets include Era-107, an injectable appetite suppressor that targets two novel molecular targets distinct from Era-379's target, and additional small-molecule programs addressing the control of energy expenditure, appetite induction, and circadian cycles.

"At EraCal, we want to identify signaling pathways that could be targeted to improve metabolic health," said Josua Jordi, founder and CEO of EraCal. "With 98% of human drug targets identified to date have orthologues in zebrafish, this versatile eukaryote model gives us a new handle on characterizing the regulatory circuits that control behavior and on identifying drug candidates that could improve the treatment of chronic and undertreated human diseases such as obesity."

EraCal continues to expand its pipeline through internal as well as external programs seeking to maximize the potential of its state-of-the-art phenotypic screening platform. EraCal recently signed a collaboration with pharmaceutical company Novo Nordisk to identify novel peptides to improve food intake regulation and other disease-associated metabolic phenotypes.

Of zebrafish and men

Over the past decade, phenotype-based drug discovery has experienced a revival as an integral part of drug discovery alongside target-based approaches. Using whole organisms can greatly accelerate the identification of hits and the selection of promising leads for complex conditions for which a complete mechanistic picture is lacking. High-throughput screening (HTS) is a key driver of phenotype-based drug discovery, but developing disease-relevant and scalable biological systems to power phenotypic HTS platforms remains a challenge.

EraCal has developed a unique platform for evaluating compounds in a whole-organism context that harnesses the multi-organ complexity of zebrafish physiology and behavior, and is readily translatable to humans. By determining drug-induced changes at a whole-organism level, EraCal captures a comprehensive and unbiased readout of a drug's effect across the whole mechanistic target space, while also obtaining an initial absorption, distribution, metabolism and excretion (ADME) and safety assessment. Such functional readouts are key for selecting hits with the highest a priori probabilities of becoming viable drug leads. In addition, the high predictive validity of zebrafish for human physiology considerably shortens the chain of translatability by paving a direct path to proof-of-concept studies in humans (Fig. 1).

"By quantifying the impact of small molecules on a broad array of behavioral markers, EraCal can identify novel compounds such as Era-379 that are highly potent and highly selective for appetite suppression, that is, without affecting the animal's overall physiological or neuronal function," said Jordi. "This is a key selectivity metric in a field in which many drugs have failed due to unforeseen and often serious side effects."

EraCal's unique *in vivo* drug discovery system

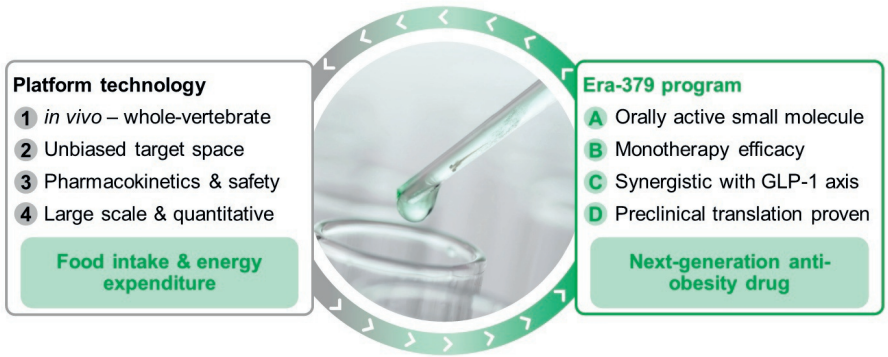

Fig. 1 | EraCal pioneers zebrafish-based drug discovery targeting metabolic diseases. Driven by its zebrafish-based phenotypic screening platform (left) EraCal has developed a pipeline of candidates with preclinical translational demonstrated efficacy, including its lead candidate Era-379 (right).

Tackling obesity without side effects

Obesity remains one of the most under-treated chronic diseases worldwide, and its incidence is rising at an alarming pace. With bariatric surgery as the only permanent, if not always perfect or accessible, solution for patients today, developing anti-obesity medications that target body weight loss and improve chronic comorbidities remains a challenge.

Era-379 is an oral treatment to suppress food intake that could help modulate body weight in obese individuals with a body mass index (BMI) ≥30 kg m^{-2} and potentially provide a viable alternative to bariatric surgery. Importantly, Era-379 does not bind known anti-obesity drug targets such as serotonin 5HT2C or GLP-1 receptors, or classic neurotransmitter targets such as dopamine or the cannabinoid system, indicating that the serious side effects observed with many of the current anti-obesity treatments could be greatly reduced.

As summarized by Jordi: "EraCal is pioneering a new approach to address one of the highest unmet needs of our time, the regulation of body weight and its consequences, whether it is in the context of obesity, anorexia, sleep or healthy aging."

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