

LEAF4Life, Inc.

Category:

Best Startup

Company Name:

LEAF4Life, Inc.

Turnover and/or Funding:

\$0 Turnover

\$140 million Funding

Sub-Category:

Biotechnology

Corporate history (creation, key milestones, main funding,...)Information on Condition / Disease and need for solution / product (prevalence, existing treatments / solutions):

Founded in 2018, LEAF4Life, Inc. ("L4L") is a pioneering pharmaceutical company developing the breakthrough therapeutic LEAF-4L6715. The company's management and advisory team have a track record, having developed multiple blockbuster drugs including ALIMTA®, GEMZAR®, EVISTA®, ONIVYDE®, and DOXIL®. Our team has leaders in drug discovery, development and commercialization, including:

- Clet Niyikiza, PhD-Inventor and developer of LEAF-4L6715 drug. Founder, Chairman, CEO and seed investor of LEAF4Life, Inc. Former EVP at Merrimack (Onivyde®), VP at GSK (Tykerb®/Tyverb®). Lilly Research Fellow (ALIMTA®, GEMZAR® and EVISTA®) and sole inventor of Patent No. 7,772,209 that commercialized ALIMTA® (over 34 Billion USD in sales).
- Dr. Daniel Von Hoff, MD, FACP (Genomics), Physician in Chief, Distinguished Translational Research Division at Translational Genomics Research Institute (TGen) in Phoenix, Arizona, USA.
- Prof. Xavier Pivot, MD, PhD (Professor of Oncology), General Director of Strasbourg Institute of Cancer (ICANS), Strasbourg, France and Former Chairman of the Oncology Department at the University Hospital of Besançon, France.
- Dr. Victor Moyo, MD (Hematology & Oncology), Co-Inventor of LEAF-4L6715, Former EVP, CMO and Head of R&D for both LEAF4Life and L.E.A.F. Pharmaceuticals; Former VP of Clinical Investigations, Merrimack - Developed Onivyde ®. Former Medical Director at

JNJ for DOXIL®.

L4L has completed FDA-indicated non-clinical studies, secured EMA Phase I/II clinical proof-of-concept trials, and is currently conducting three Phase III clinical trials targeting glioblastoma, sarcoma, and ARDS. LEAF-4L6715 has received compassionate use approval in France for ARDS across all causes. To date, the company has raised \$26 million in equity funding and secured \$112 million in grant support. Manufacturing is contracted to Piramal in Kentucky, with significant production capabilities. Strategic partners include Polaris Technology Solutions (a Disabled Veteran-Owned company), Prevail InfoWorks, Inc. (a leading CRO), and Piramal (CMO).

The Unmet Need

Hypoxia or oxygen deprivation in tissues, is a leading cause of over 30 million deaths annually worldwide. It results from various conditions such as respiratory and cardiovascular diseases, trauma, infections, toxins, and radiation-induced tissue damage. Evidence indicates hypoxia exacerbates multiple pathologies, leading to inflammation, organ failure, and death. Addressing hypoxia offers a universal therapeutic opportunity to mitigate life-threatening tissue and organ damage across diverse causes, including infectious, chemical, biological, radiological, and nuclear (CBRN) threats. Hypoxia plays a pivotal role in solid and hematological malignancies, ARDS, cardiovascular, and respiratory diseases-conditions with no effective current medicinal treatments.

Solution

LEAF-4L6715 enhances oxygen and nutrient delivery at the microcirculatory level, promoting repair of damaged microvasculature and organ rescue. In ICU patients with ARDS on mechanical ventilation, LEAF-4L6715 achieved a 92% survival rate at 60 and 90 days at therapeutic doses, compared to a historical 50% with standard care. The treatment demonstrated rapid improvements across respiratory, neurological, and cardiovascular systems. The company holds extensive IP rights, with 28 patents pending or granted.

Market Opportunity

- Primary Indication (ARDS): Total Addressable Market (TAM): ~600,000 cases/year in the US and EU (~\$31.5 billion). Orphan Indications: Glioblastoma and Sarcoma: ~31,380 cases in EU (~\$1.7 billion).

Revenue Projections

Projected revenue of \$2.4 billion by 2030, based on 38,585 patients.

History of the development of the solution/product (Intellectual

Property, preclinical and clinical datas, development collaborations):

Candidate Therapeutic

LEAF-4L6715 is a novel liposomal formulation of transcrocetin (TC), a small molecule that enhances oxygen diffusion. Due to TC's short half-life and poor bioavailability, it has been encapsulated in liposomes, resulting in a sixfold increase in half-life and a twelvefold increase in exposure levels. This IV formulation can be administered rapidly alongside standard treatments using fixed dosing.

Preclinical Data

Multiple studies demonstrate the drug's potential. In a murine sepsis model, mice treated with 5 mg/kg LEAF-4L6715 plus imipenem showed 80% survival at five days, versus 30% in controls ($P=0.0281$) (FigureX).

[For Figure X See the Development & Clinical or Preclinical Evidence Section of the Attached Document titled LEAF4Life-START UP+SUBMISSION-FINAL - 2025.06.28]

Clinical Data

A Phase I/II trial involving 37 ICU patients with COVID-19-induced ARDS on mechanical ventilation showed significant improvements in PaO₂/FiO₂ ratios (Figure Y) and rapid multi-organ recovery.

[For Figure Y See the Development & Clinical or Preclinical Evidence Section of the Attached Document titled LEAF4Life-START UP+SUBMISSION-FINAL - 2025.06.28]

Importantly there was a 92% survival rate at 60 and 90 days at therapeutical relevant doses used in 67% of patients (Figure Z), which was, substantially higher than the 50% historical control. The company received FDA guidance in 2019 and 2022, with an IND submission anticipated in H2, 2025. A Phase III trial enrolling 300 patients across Europe is underway, with topline results expected in H1 2026.

[For Figure Z See the Development & Clinical or Preclinical Evidence Section of the Attached Document titled LEAF4Life-START UP+SUBMISSION-FINAL - 2025.06.28]

Intellectual Property and Data Rights

L4L holds exclusive worldwide rights to LEAF-4L6715, including over 28 patents pending or granted, covering manufacturing, use, and administration. All clinical and non-clinical data are owned by L4L, with licensing options available under fair terms.

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

LEAF-4L6715 is a groundbreaking therapeutic targeting hypoxia—a fundamental driver of numerous diseases and the focus of the 2019 Nobel Prize in Medicine. The Nobel laureates William G. Kaelin Jr., Sir Peter J. Ratcliffe, and Gregg L. Semenza uncovered cellular mechanisms sensing oxygen levels, laying the foundation for innovative treatments.

Currently, there are no approved medicines directly addressing hypoxia. LEAF-4L6715's approach—delivering oxygen at the microvascular level—aims to prevent multi-organ failure across a wide spectrum of conditions, including ARDS, cancer, and aging-related diseases. The drug's design leverages advanced liposomal technology to improve stability, pharmacokinetics, and bioavailability, inspired by insights into cellular adaptation to oxygen deprivation.

Beyond immediate medical applications, hypoxia influences many aging hallmarks—such as endothelial and immune cell senescence, mitochondrial dysfunction, and epigenetic alterations. LEAF-4L6715 could potentially slow aging processes by mitigating these effects, representing a paradigm shift in both disease treatment and age-related health span extension.

The innovation lies in translating Nobel-winning insights into a practical, scalable therapeutic, with broad implications for future research, disease management, and improving human health.

Summary of Benefits of the Technology

Addresses a Critical Unmet Need: No current approved treatments directly target hypoxia, a key driver of multiple life-threatening conditions, including ARDS, cancers, and organ failure.

Improves Survival Rates: In ICU patients with ARDS, LEAF-4L6715 has demonstrated a 92% survival rate at 60 and 90 days, significantly higher than historical controls.

Enhances Organ Function: Rapidly improves respiratory, neurological, and cardiovascular functions, facilitating organ rescue.

Novel Mechanism of Action: Increases oxygen and nutrient delivery at the microvascular level, promoting repair of damaged tissues and preventing multi-organ failure.

Broad Therapeutic Potential: Applicable across multiple conditions related to hypoxia, including ARDS, solid and hematological cancers, cardiovascular diseases, and possibly slowing aging processes.

Strong Intellectual Property: Extensive patent portfolio supports proprietary use and development.

Market and Revenue Potential: Large addressable markets with projected revenues of \$2.4 billion by 2030, and profitability anticipated as early as 2026.

Innovative Technology: Utilizes a novel liposomal formulation of transcrocetin, with enhanced stability (4 years at 2-8°C), pharmacokinetics, and bioavailability, enabling rapid administration and potential for oral delivery.

Foundation in Nobel-Winning Science: Based on groundbreaking discoveries about how cells sense and adapt to oxygen levels, with implications for future research and therapies.

Potential to Slow Aging: By mitigating hallmarks of aging related to hypoxia, LEAF-4L6715 could contribute to healthier aging and improved human healthspan.

Please provide appropriate references (PubMed, Abstract, Website):

REFERENCES

1. Gainer JL1, Stennett AK, Murray RJ. The effect of trans sodium crocetinate (TSC) in a rat oleic acid model of acute lung injury. *Pulm Pharmacol Ther.* 2005;18(3):213-6. Epub 2005 Jan 22.
2. Yang et al. Suppression of NF-κB pathway by crocetin contributes to attenuation of lipopolysaccharide-induced acute lung injury in mice. *European Journal of Pharmacology* 674 (2012) 391-396
3. Roy et al, *Shock*, 10, 215 - 217, 1998
4. Giassi, Poynter and Gainer *SHOCK*, Vol 18, No. 6, p 585-588, 2002 Data Adapted from Giassi et al. *J Trauma.* 2001; 51: 932-938
5. Manabe, H. et al., *J. Neurosurgery*, 113, 802-9, 2010. Lapchak, P, *Brain Res.*, 1309, 136-75, 2010
6. Song, L, et al. Crocetin Inhibits Lipopolysaccharide-Induced Inflammatory Response in Human Umbilical Vein Endothelial Cells. *Cell Physiol Biochem* 2016;40:443-452
7. Zhang, D, et al. Crocin alleviates lipopolysaccharide induced acute respiratory distress syndrome by protecting against glycocalyx damage and suppressing inflammatory signaling pathways. *Inflammation Research* (2020) 69:267-278.
8. Yang J, Luo K, Guo Z, Wang R, Qian Q, Ma S, Li M, Gao Y. Evaluation of Crocetin as a Protective Agent in High Altitude Hypoxia-Induced Organ Damage. *Pharmaceuticals*. 2024; 17(8):985
9. J. L. Gainer, "Trans-sodium crocetinate for treating hypoxia/ischemia," *Expert Opin Investig Drugs*, vol. 17, no. 6, pp. 917-924, Jun. 2008, doi: 10.1517/13543784.17.6.917.
10. A. K. Stennett, G. L. Dempsey, and J. L. Gainer, "trans-Sodium crocetinate and diffusion enhancement," *J Phys Chem B*, vol. 110, no. 37, pp. 18078-18080, Sep. 2006, doi: 10.1021/jp064308+.
11. Gainer JL1, Stennett AK, Murray RJ. The effect of trans sodium crocetinate (TSC) in

a rat oleic acid model of acute lung injury. *Pulm Pharmacol Ther.* 2005;18(3):213-6. Epub 2005 Jan 22

12. Mertes PM, Collange O, Coliat P et al. Liposomal encapsulation of trans-crocetin enhances oxygenation in patients with COVID-19-related ARDS receiving mechanical ventilation. *Journal of Controlled Release.* 336: 2021; 252-261 and supplement ,<https://doi.org/10.1016/j.jconrel.2021.06.033>

13. Adaptation from Hypoxia white paper_www.novusbio.com/whitepapers/hypoxia_accessed January 21, 2021.....Value shown at sea level unless stated otherwise

14. C Karagiannidis, C Mostert, C Hentschker, T Voshaar, J Malzahn, G Schillinger, J Klauber, U Janssens, G Marx, S Weber-Carstens, S Kluge, M Pfeifer, L Grabenhenrich, T Welte, and R Busse, 2020, Case Characteristics, Resource Use, and Outcomes of 10021 Patients with COVID-19 Admitted to 920 German Hospitals: an Observational Study, *Lancet Respir Med*, 8(9):853-862.

15. Manabe, H. et al., *J. Neurosurgery*, 113, 802-9, 2010.

16. Diringer MC, Coliat P, Mathieu C, Laurent N, Mura C, Banerjee M, Zhu C, Grabowska A, Ritchie A, Clarke P, Bernard A, Vit C, Burckel H, Noel G, Harvey P, Pivot X, Detappe A. Clinically Translatable Transcrocetin Delivery Platform for Correction of Tumor Hypoxia and Enhancement of Radiation Therapy Effects. *Small.* 2023 Mar;19(12):e2205961. doi: 10.1002/sml.202205961. Epub 2023 Jan 1. PMID: 36587987..

17. Lopez-Otin C., et al. The hallmarks of aging. *Cell.* 2013;153:1194-1217. doi: 10.1016/j.cell.2013.05.039 Ting KK, Coleman P, Zhao Y, Vadas MA, Gamble JR. The aging endothelium. *Vasc Biol.* 2021 Jan 12;3(1):R35-R47. doi: 10.1530/VB-20-0013. PMID: 33880430; PMCID: PMC8052565. Hazeldine J and Lord JM (2020) Immunesenescence: A Predisposing Risk Factor for the Development of COVID-19? *Front. Immunol.* 11:573662. doi: 10.3389/fimmu.2020.573662

References File Document upload:

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