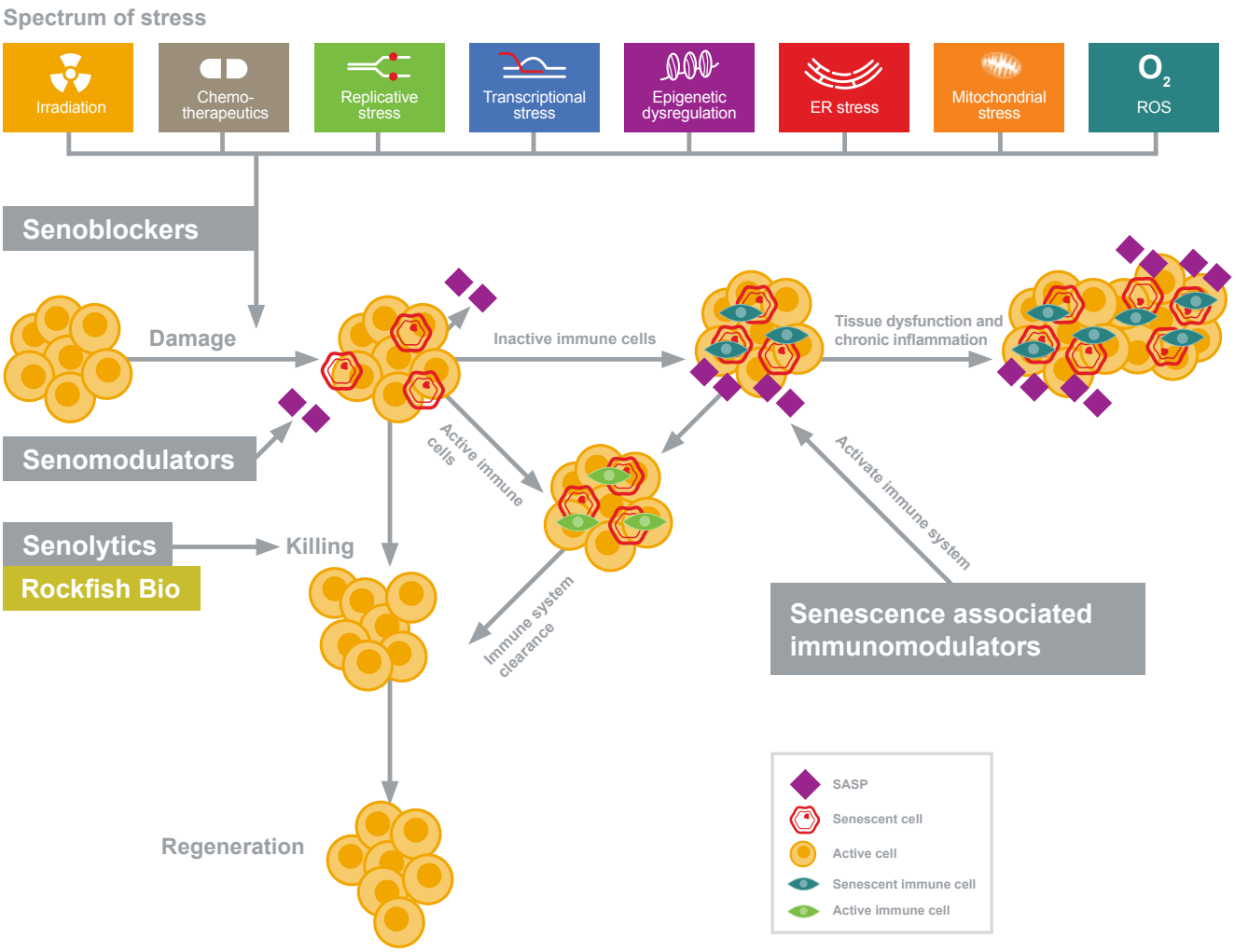
Rockfish Bio





Company profile

Rockfish Bio

Rockfish Bio is the latest member of a series of successful start-ups in the field of cellular senescence and aging emerging from the research groups around Regina and Johannes Grillari. Rockfish Bio is planning to launch in Q2 of 2021 with the mission to develop senolytic therapies. The Rockfish team is convinced that senolytic therapies have an enormous potential for the treatment of age-related diseases and the extension of the human healthspan. Its senolytic compounds are based on a recently discovered druggable pathway that is associated with many age-related diseases and will enable Rockfish Bio to develop senolytics with high efficacy and a favourable safety profile.

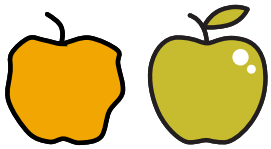
The idea for Rockfish Bio was born in 2019 when co-founders Johannes Grillari, Otto Kanzler and Ingo Lämmermann were inspired by the potential of a newly discovered pathway for the development of senolytics. At that time, the enormous potential of senolytics and the concomitant lack of suitable drugs with high efficacy and good safety profiles became obvious.

“We knew that we were on to something big the moment we saw that the pathway we discovered played a pivotal role in so many age-related diseases, and that existing drugs targeting our pathway were associated with only mild side effects,” says Johannes Grillari.

Rockfish Bio will benefit from synergies formed with its two predecessors Evercyte and TAmiRNA. Evercyte provides know-how on cultivation of human cell lines for *in vitro* screening of senolytic compounds, whereas TAmiRNA is currently developing a blood sample-based method for quantification of the senescent cell load – an essential companion diagnostic, prognostic and treatment monitoring tool for future clinical trials. Additionally, Johannes Grillari is the director of Ludwig Boltzmann Institute for Experimental and Clinical Traumatology which is located at the AUVA Trauma Center, Vienna thereby providing a close connection with clinicians and real-life patients. He is also an associate Professor at the University of Natural Resources and Life Sciences, Vienna (BOKU).

After clarifying the molecular mechanism of its senolytics, identifying renal epithelial cells as a promising therapeutic target (therapeutic index of ~ 700) and successfully testing the first generation of self-designed small molecule senolytics, Rockfish Bio now aims to secure sufficient funding from investors to verify the *in vivo* efficacy of its approach and commence senolytic drug development with chronic kidney disease as its lead indication. Rockfish Bio projects its exit point in six and a half years from now (clinical Phase 2 completion), where it plans to cooperate with, or out-license its asset to, the pharmaceutical industry. It will then switch focus to its next indication.

The senolytic compounds Rockfish Bio uses are based on the elevated formation rate of arachidonic acid (AA) in senescent cells due to increased enzymatic hydrolysis of membrane lipids by phospholipases. By inhibiting the conversion of AA with its compounds, the team at Rockfish Bio can increase the intracellular content of pro-apoptotic AA selectively in senescent cells, thereby inducing a senolytic effect. Downstream metabolites of AA and key enzymes involved in their biogenesis are associated with many age-related diseases including chronic kidney disease. Further, inhibition of AA-converting enzymes by existing drugs, such as NSAIDs, is associated with only mild side effects



especially when only used for a short period. This senolytic pathway is protected by Rockfish Bio with a patent (WO2020084105A2) and it is currently in the process of filing an additional patent for the protection of novel small molecules in collaboration with med chem experts (2nd generation molecules are currently synthesised) targeting this pathway.

Besides chronic kidney disease as the first lead indication, Rockfish Bio plans to develop a medical product for the improvement of kidney transplants during normothermic reperfusion. The quality of transplant organs was shown to be closely correlated to the senescent cell load and recent reports suggest that senolytics can be used to improve their performance (Iske et al., 2020). The team at Rockfish Bio are in contact with leading scientists in the field of normothermic perfusion of kidney transplants who are willing to test its senolytic drugs in human kidney transplants declined by the transplant centres, thereby providing *ex vivo* data of the efficacy of the chosen senolytic drugs and the feasibility of their use to combat the chronic shortage of kidney transplants. In parallel, Rockfish Bio are screening its senolytic compounds in several human cell types to identify additional promising lead indications to pursue, thereby mitigating risk of failure.

Longevity Potential: Senolytic compounds for chronic kidney disease

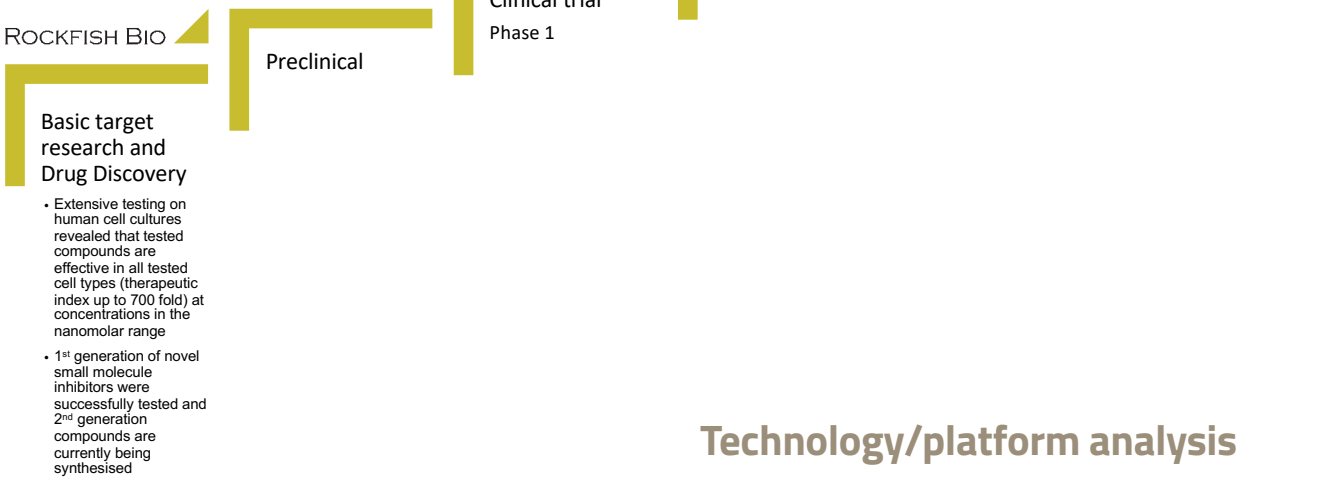
The use of senolytics in mouse models was shown to prevent, delay or attenuate the development and progression of numerous age-related diseases, and disorders, and first clinical trials in humans are ongoing. Yet, most of the investigated senolytics are not effective in all cell types and some are associated with severe side effects. The senolytic compounds discovered by Rockfish Bio proved senolytic capacity in all tested cell types encompassing mesenchymal, endothelial and epithelial cells from skin, lung, kidney, fat and cartilage. In addition, existing drugs inhibiting Rockfish Bio's target enzymes are in daily use and are associated with only mild side effects.

The compounds chosen inhibit the conversion of the pro-apoptotic arachidonic acid (AA). The formation rate of AA is elevated in senescent cells, thereby making them more susceptible to the toxic effect of Rockfish Bio compounds. As the compounds also inhibit the synthesis of downstream metabolites, which are involved in pro-inflammatory signalling pathways, Rockfish Bio also expects a transient senomorphic effect by suppression of the SASP. After verifying its target pathway, with existing inhibitors of AA conversion, the team at Rockfish Bio successfully tested the 1st generation of novel small molecule inhibitors and are currently synthesising 2nd generation molecules. Based on existing drugs, and the molecular structure of its compounds, Rockfish Bio expects a high bioavailability after oral administration. For specific indications, such as osteoarthritis, Rockfish Bio plans to use non-systemic routes of administration (e.g. local injection) to result in a better safety profile.

So far, extensive testing on human cell cultures have been performed indicating that inhibition of the targeted pathway allows for therapeutic windows of up to 700-fold differences in the drug concentrations which are in the nanomolar range. The difference of 700-fold refers to elimination of senescent human cells of non-senescent primary control cells of different tissue origins including kidney, lung, cartilage, skin or vasculature. Pre-clinical studies in rodents are currently planned, using naturally aged c57BL/6 mice. Due to the extensive data on inhibitors of AA-converting enzymes, which are in daily clinical use, Rockfish Bio expects a favourable safety profile of its senolytic compounds in these studies.

The market volume of chronic kidney disease (CKD) and end stage renal disease (ESRD) is enormous with around 10% prevalence worldwide and over US$120 billion spent yearly in the US alone. Progression of the disease through the various stages of CKD not only reduces the quality of life,

Pre-Clinical and Clinical Studies



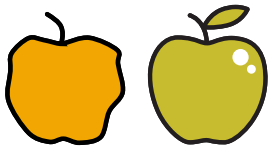
but also increases the cost per patient drastically. The number of ESRD patients undergoing transplantation is relatively low compared with dialysis, although transplantation is associated with the lowest costs and the highest quality of life. This can be explained by the chronic shortage of eligible transplant organs. Rockfish Bio aims to bring in five years a senolytic perfusion solution (approved as a medical device) for the improvement of otherwise discarded kidney transplants to the market. The Phase 2a clinical trial for the use of its senolytic compounds in CKD is envisaged to be completed in six and a half years.

As senolytics are expected to work in several age-related conditions, choosing the right lead indication is a key aspect in starting drug development in the senolytics field. Thus, Rockfish Bio scored around 40 age-related indications in seven categories (medical need, market size, competition, scientific network, senolytic fit, time to market, screening data) using pre-defined objective key point indicators. Chronic kidney disease and kidney transplant failure were the top ranked indications on this list.

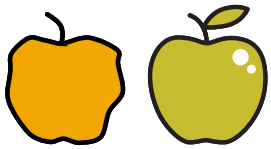
Technology/platform analysis

One key aspect of studied senolytics is their cell type/tissue dependent efficacy which makes comprehensive screening data obtained from cells of different tissue a vital part of the scoring process for identifying the most promising lead indication. Rockfish Bio established a broad *in vitro* screening platform using normal human cells from adult donors. Lead compounds will then additionally undergo an *in vivo* screening in naturally aged mice to verify the target tissue. This will greatly mitigate the risk of choosing an inferior candidate as lead indication.

The quantification of senescent cells before and after treatment is one of the biggest challenges that clinical trials involving senolytics are facing. Methods currently employed are biopsies which are not suitable for most indications and quantification of SASP factors in blood samples which can be greatly influenced by signals derived from the immune system. Therefore, the use of a proprietary (EP17177840.0) and precise (AUC ~ 0.9) quantification via circulating miRNAs with the senomiR system developed by TAmiRNA will be essential for monitoring the efficacy of the senolytic treatment in its clinical trials.



Technology Platform Analysis	Description	Rockfish Biosciences
Class of Senotherapeutic	Senolytic, Senomodulator, SA-immunomodulator, Senoblocker.	Senolytic: Targeting cellular pathways that make senescent cells vulnerable to death.
Target specificity	Features of therapeutic that facilitate targeting of senescent cells without off-target effects; dependent on senescent biomarkers.	As AA converting enzymes already have inhibitors in daily clinical use, Rockfish Bio expects a favourable safety profile by targeting this pathway. Furthermore, due to its relationship with TAmiRNA, effective targeting of senescent cells during treatment can be quantified by assessing circulating miRNAs with the senomiR system developed by TAmiRNA.
Delivery	Approaches (local or systemic), technologies (delivery vehicle), and formulations needed to safely and reliably deliver therapeutic to its target.	Based on existing drugs, and the molecular structure of its compounds, Rockfish Bio expects a high bioavailability after oral administration. For specific indications, such as osteoarthritis, Rockfish Bio plans to use non-system routes of administration (e.g local injection) to result in a battery safety profile.
Adaptability	Foundational technology that can be utilised to systematically improve, or build upon, robustness of therapeutic.	Rockfish Bios senolytic target pathway still offers a huge chemical space free to explore and 1st generation of self-designed small molecule inhibitors were already successfully tested. The team at Rockfish Bio are currently synthesising 2nd generation compounds and are in the process of filling an additional patent for the protection of this compound family.
Regulation	Context specific control over therapeutic action once it has reached its target (spatial, temporal, sensitivity, degradation).	Unknown for Rockfish Bio.
Toxicity	Level of damage that therapeutic can cause to organism; Can include, but not limited to: off-target effects, on-target side effects, immunogenicity, etc.	Target is inhibition on AA converting enzymes, that are already used in daily clinical use with only mild side effects, suggesting favourable safety profiles when tested preclinicallly and clinically *in vivo*.



Safety and Risks

Preclinical trials in rodents are the next steps for Rockfish Bio and, as such, safety is yet to be determined. However, due to the extensive data on inhibitors of AA converting enzymes, which are in daily clinical use, Rockfish Bio expects a favourable safety profile of its senolytic compounds in these studies.

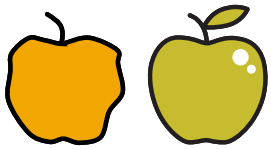
Target Market

Current treatments for CKD slow the progression of the disease, but as it advances the only life-prolonging measurements for end-stage renal disease (ESRD) are dialysis and kidney transplantation, both of which are associated with high costs for the healthcare system and in the case of dialysis with poor quality of life. Thus, stopping or delaying the progression of CKD will drastically reduce patient suffering and costs by lowering the numbers of ESRD patients and keeping the patients in early stages of CKD with a still high quality of life. In addition, expanding the pool of transplantable kidney organs will more than half the patient costs from US$80,000 – 90,000 for dialysis to 35,000 for transplantation and greatly improve the quality of life for these patients. Rockfish Bio hopes its products will address both issues, CKD progression to ESRD and shortage of kidney transplants, thereby creating huge socio-economic benefits for this target market.

Success Factors

Team and Reputation

- CEO of Rockfish Bio, Otto Kanzler, combines extensive experience in the biopharmaceutical industry with proficiency in business development and finance background. Otto is a serial entrepreneur, who has co-founded several successful start-up companies, including Evercyte and TAmiRNA. He also founded Innofly Management GmbH, providing high quality back-office resources to biotech and pharma start-ups. As CEO of Rockfish Bio, this connection will allow Rockfish Bio to benefit from cost savings by these shared services until critical mass within Rockfish Bio is reached. Furthermore, due to his experience in the pharmaceutical industry, Otto has numerous connections to pharma companies and investors that will aid Rockfish Bio in securing the necessary funds for the first growth phase;
- Designated CSO/COO, Dr Ingo Lämmermann, has accumulated more than seven years of experience in aging and senescence research. Dr. Lämmermann discovered the senolytic target pathway that Rockfish Bio has since patented. Another patent of one of Dr Lämmermann's inventions has already been successfully translated into a product;
- Associate Professor Johannes Grillari is the designated head of the strategic advisory board at Rockfish Bio. Professor Grillari has over 25 years of experience in cellular and molecular aging. He has authored and co-authored more than 170 scientific articles, has filed 14 patents, and was invited as a speaker over 100 times at international meetings. This brings vast scientific expertise and networks to Rockfish Bio's strategic board. In addition, Grillari co-founded and holds advisory positions in Evercyte as well as TAmiRNA. Johannes Grillari is Associate Professor at BOKU and director of the Ludwig Boltzmann Institute (LBI) for Traumatology in cooperation with AUVA, Vienna, Austria;
- Rockfish Bio holds strong connections to leading scientists and clinicians in normothermic perfusion of kidney transplants who are willing to test the senolytic in declined kidneys. This is advantageous for Rockfish Bio's strategy to use its senolytic for the improvement of otherwise discarded kidney transplants;
- It also benefits from synergies formed with its two predecessors Evercyte and TAmiRNA. Evercyte provides know-how on cultivation of human cell lines for *in vitro* screening of senolytic compounds, whereas TAmiRNA is currently developing a blood sample-based method for quantification of the senescent cell load – an essential diagnostic tool



for future clinical trials that could be utilised by Rockfish Bio;

- Rockfish Bios main focus is on reliable, high quality data regarding the pre-clinical and clinical results within a short, but realistic timeline. Therefore, the selection process of development partners has been identified as critical for the success of the company's project. The team, including its scientific advisors, has extensive experience in selecting collaboration partners and legal framework for any type of collaborations.

Intellectual Property

- Rockfish Bio has created senolytics based on a completely novel target pathway;
- It currently holds a patent (WO2020084105A2) to protect this druggable pathway, which is based on elevated formation rates of AA in senescent cells;
- The target enzymes in the pathway are AA-converting enzymes that have been extensively studied. Downstream metabolites of AA are associated with many age-related diseases;
- Inhibitors to these enzymes are already in daily clinical use with favourable safety profiles. Rockfish Bio states that these inhibitors showed superior senolytic activities in its *in vitro* screening platform when compared to the well-studied senolytics Navitoclax and the combination of Dasatinib and Quercetin. Furthermore, the inhibitors tested by Rockfish Bio showed senolytic activity in all tested cell types;
- Rockfish Bio is looking to complement its *in vitro* results and demonstrate *in vivo* efficacy by performing an *in vivo* screening in mice and *ex vivo* experiments in human tissues;
- Rockfish Bio's senolytic target pathway still offers a huge chemical space free to explore and 1st generation of self-designed small molecule inhibitors were already successfully tested. The team at Rockfish Bio are currently synthesising 2nd generation compounds and are in the process of filling an additional patent for the protection of this compound family;
- The target for Rockfish Bio's senolytics was chosen by assessing medical need, market size, competition, scientific network, senolytic fit, time to market and screening data in age-related indications. From this assessment it has chosen to target CKD and kidney transplant failure. If effective, Rockfish Bio's treatment could both prevent CKD from becoming ESRD and enhance the pool of kidney transplants for those that do progress;
- Exit points for the medical device (perfusion solution) and for CKD are envisaged to be reached in 5 and 6 and a half years, respectively;
- Depending on available funding and its data from the screening platforms (*in vitro* and *in vivo*) Rockfish Bio is also planning to extend its drug development activities on other high-ranking indications from its scoring system, thereby fuelling company growth and mitigating risk of failure.

Funding

- Rockfish Bio is expecting to close its seed financing round during Q2-Q3/2021 and negotiations are currently ongoing;
- Raised capital from this round will allow further R&D activities, such as *in vivo* screening to support IND applications and validation of its 2nd generation compounds;
- Rockfish Bio plans to seek for series A financing of €6 million in Q1 of 2022. This funding will further support the development of a therapy for CKD;
- Series B financing of €6 million is planned in Q1 of 2023, followed by a series C round of €12 million in Q1 of 2024. Series D of €12 million in Q1 of 2026 will finance development activities until the end of clinical Phase 2a at the end of 2027;
- Rockfish Bio expects to partner with a pharma company for further development (Phase 2b and Phase 3) and market supply in 2028;
- Rockfish Bio believes its approach may be suitable for many different indications. Therefore, we offer the development of additional applications which would lead to extended financial resources.