Rapport Annuel

Annual Report

2020

BLACKSWAN®
FOUNDATION

SWISS FOUNDATION FOR RESEARCH ON ORPHAN DISEASE S
SCHWEIZERISCHE STIFTUNG FÜR DIE FORSCHUNG SE LTENER KRANKHEITEN
FONDATION SUISSE POUR LA RECHERCHE SUR LES MALADIES ORPHELINE S
FONDAZIONE SVIZZERA PER LA RICERCA SULLE MALA TTIE ORFANE

TABLE DES MATIÈRE
TABLE OF CONTENTS

WE AMPLIFY COLLECTIVE ACTION FOR RESEARCH ON RARE DISEASES

SWISS FOUNDATION FOR RESEARCH ON ORPHAN DISEASES
SCHWEIZERISCHE STIFTUNG FÜR DIE FORSCHUNG SELTENER KRANKHEITEN
FONDATION SUISSE POUR LA RECHERCHE SUR LES MALADIES ORPHELINES
FONDAZIONE SVIZZERA PER LA RICERCA SULLE MALATTIE ORFANE

MESSAGE DU PRÉSIDENT

L'année 2020 marque les 10 ans d'activité de la Fondation. Malheureusement, une pandémie qui paralyse toutes activités ne nous permet pas de le célébrer comme nous l'aurions voulu. Mais ce n'est, je l'espère, que partie remise. L'année 2020 est aussi profondément marqué par l'absence de toute activité de levées de fonds, ce qui personnellement me fait douter de la possibilité de financer des projets de recherche en 2021.
Cependant, l'année 2020 est une année très importante pour la Fondation car des changements profonds se sont effectués au sein du conseil de Fondation. Les départs de Vincenzo Piantedosi et Massimo Riccardi, que je remercie du fond du cœur pour leur implication pendant ces 10 années, font place aux arrivées de nouveaux membres que je laisse se présenter ci-dessous. Leur motivation pour trouver des solutions alternatives en période de pandémie afin d'obtenir des financements et ne pas interrompre notre activité de soutien à la recherche me rassure quant au futur.
Pour ma part, je souhaite un bon 10ème anniversaire. Ce fut un privilège de voir et de participer au développement de notre Fondation. Je suis sûr que le meilleur est à venir.

Dr. Olivier Menzel
Président et fondateur

"Nous travaillons dur pour tirer le meilleur parti de chaque centime investi dans la recherche!"

MESSAGE FROM THE PRESIDENT

The year 2020 marks 10 years of activity of the Foundation. Unfortunately, a pandemic that paralyzes all actions does not allow us to celebrate as we would have liked. But I hope it will be a postponement. The year 2020 is also deeply marked by the absence of any fundraising activity, which personally makes me doubt the possibility of funding research projects in 2021.
However, 2020 is a very important year for the Foundation as there have been profound changes in the Foundation Board. The departures of Vincenzo Piantedosi and Massimo Riccardi, whom I thank from the bottom of my heart for their involvement during these 10 years, make way for the arrival of new members whom I will introduce below. Their motivation to find alternative solutions in times of pandemic to obtain funding and not interrupt our research support activity reassures me about the future.
For my part, I wish you a happy 10th anniversary. It has been a privilege to see and participate in the development of our Foundation. I am sure that the best is yet to come.

Dr. Olivier Menzel
Chairman and Founder

"We are working hard to make the most of every cent invested in research!"

CONSEIL DE FONDATION
BOARD OF DIRECTORS

STEFANO BERTI

La Fondation BLACKSWAN a une mission vitale et inspirante, qui consiste à donner de l'espoir aux personnes touchées par les maladies les plus rares et donc les plus méconnues. Ne laisser personne de côté (« Leaving No One Behind ») est un principe fondamental dans mon travail, et c'est exactement ce que fait la Fondation BLACKSWAN, en sensibilisant et en trouvant des solutions pour les personnes oubliées. Après de nombreuses années de travail dans le domaine du développement, de l'humanitaire et de la consolidation de la paix dans des pays fragiles et touchés par des conflits, je trouve très stimulant de relever ce nouveau défi avec un conseil de Fondation composé de professionnels compétents et très motivés.
Avec les autres membres du conseil, je ferai de mon mieux pour explorer et ouvrir de nouvelles opportunités afin de soutenir et renforcer le travail de la Fondation BLACKSWAN. Bien que le nouveau conseil de Fondation ait eu un début difficile pendant le Covid-19, je suis étonné de voir combien d'idées nouvelles et inspirantes nous avons pu amener. Certaines ont déjà abouti et sont sur la bonne voie, d'autres doivent être affinées, mais dans l'ensemble, tous les ingrédients sont réunis pour que la Fondation continue à se développer et à remplir son mandat essentiel.

The BLACKSWAN Foundation has a vital and inspirational mission, giving hope to those affected by the rarest, thus disregarded, diseases. Leaving No One Behind is a fundamental principle in my line of work, and the BLACKSWAN Foundation is doing exactly that, raising awareness and finding solutions for the forgotten ones. After many years working on development, humanitarian, and peacebuilding in fragile and conflict-affected countries, I find it very stimulating to take on this new challenge with a board of skilled and highly motivated professionals.
Together with the other board members, I will do my best to explore and open new opportunities to support and strengthen the work of the BLACKSWAN Foundation. While the new Board had a challenging start during Covid-19, I am amazed at how many new and inspiring ideas we could bring to the table. Some have already landed and are on track, some others need further refinement, but all in all, the ingredients are all there for the Foundation to continue growing and delivering its essential mandate.

CONSEIL DE FONDATION
BOARD OF DIRECTORS

CHIARA CIRIMINNA SWAN

Il y a presque dix ans, j'ai croisé pour la première fois le chemin de la Fondation BLACKSWAN et j'ai découvert le monde des maladies rares qui m'était presque inconnu auparavant. Ce qui m'a immédiatement surpris, c'est le manque d'informations publiques sur un problème de santé qui causait la mort et la souffrance de millions de patients, en particulier des enfants. J'ai ressenti un sentiment d'urgence à m'attaquer aux nombreuses problématiques des maladies rares et en 2012, j'ai eu le privilège de rejoindre la Fondation en tant que coordinatrice de projet.

Au cours des 6 années suivantes, j'ai été témoin et j'ai contribué aux efforts de la Fondation pour mettre en relation des centaines de chercheurs travaillant sur les maladies rares et combiner leurs connaissances et leurs ressources pour faire progresser la compréhension de ces maladies et découvrir de nouvelles thérapies. J'ai compris le rôle crucial et le courage des patients, très souvent les seuls et principaux «experts» de leur maladie rare ou ultra-rare et l'importance de leur implication pour le développement de traitements.

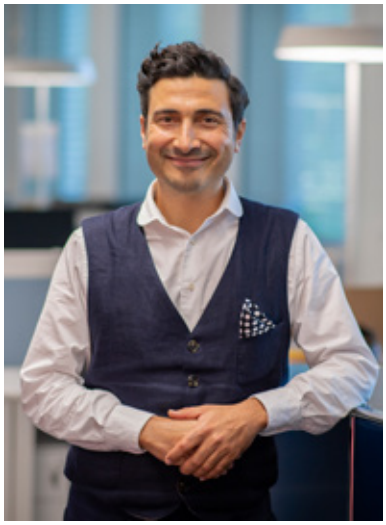
Être membre du conseil de Fondation aujourd'hui est un grand honneur et j'espère contribuer à une meilleure sensibilisation au niveau national et international et faciliter le financement de la recherche scientifique. Je suis impatiente de travailler avec les autres membres du conseil pour mettre nos différentes compétences et expériences au service de la communauté des maladies rares.

Almost ten years ago, I crossed for the first time the path of the BLACKSWAN Foundation, and I discovered the world of rare diseases that were practically unknown to me before. What surprised me immediately was the lack of public information on a health issue that was causing death and suffering to millions of patients, especially children. I felt a sense of urgency to tackle the many problems of rare diseases, and in 2012 I had the privilege to join the Foundation as Project Coordinator.

Over the following six years, I witnessed and contributed to the efforts of the Foundation in connecting hundreds of researchers working on rare diseases and combining their knowledge and resources to advance the understanding of these diseases and discover new therapies. I understood the crucial role and the courage of patients, often the only and main "experts" of their rare or ultra-rare disease, and the importance of their involvement in the development of treatments.

Being a member of the Board of the BLACKSWAN Foundation today is a great honor, and I hope to contribute to increasing awareness at the national and international level and facilitate funding for scientific research. I am excited to work with the other board members to bring together our different skills and experience at the service of the rare disease community.

CONSEIL DE FONDATION
BOARD OF DIRECTORS



SKANDER NAJAR

Dans tout type de performance requise, l'objectif est un facteur de motivation essentiel. Cela est également vrai pour les objectifs individuels et collectifs. La Fondation BLACKSWAN est un exemple pur d'un projet ambitieux, significatif et dynamique avec un but profondément humaniste.

En tant que membre du conseil de Fondation, je suis honoré de collaborer avec un groupe unique de professionnels sélectionnés. En même temps, je ressens la grande responsabilité d'apporter la meilleure expertise possible des secteurs de la communication et de l'innovation, où je suis actif la plupart du temps.

Je suis sûr qu'avec l'aide de nos partenaires, le nouveau comité honorera les efforts de nos prédécesseurs et continuera à construire au profit des personnes atteintes de maladies rares, de leurs familles et de la communauté tout entière.

The purpose is a key motivational factor in any type of required performance. This is equally true for individual and collective objectives. The BLACKSWAN Foundation is a pure example of an ambitious, meaningful, and dynamic project with a deep humanistic purpose.

As a foundation board member, I am honored to collaborate with a unique panel of selected professionals. At the same time, I feel the great responsibility of bringing the best possible expertise from the communication and innovation industries, where I am active most of the time.

I am sure that with the help of our partners, the new committee will honor the efforts of our predecessors and will continue to build for the benefit of people affected by rare diseases, their families, and the entire community.

CONSEIL DE FONDATION
BOARD OF DIRECTORS

KARIMA SOUDANI

Après avoir travaillé pendant plus de 20 ans dans l'industrie pharmaceutique, c'est un grand honneur et un privilège pour moi de pouvoir faire partie du conseil d'une fondation dont l'objectif est aussi important que celui de la Fondation BLACKSWAN.
En étroite collaboration avec les autres membres du conseil de Fondation, j'espère sincèrement contribuer à sensibiliser davantage la société aux maladies rares, en renforçant la communication autour des nombreux projets et activités en cours, et en veillant à ce que de nouveaux projets soient lancés.
J'espère également sensibiliser certaines des principales parties prenantes du monde pharmaceutique à la création de partenariats et/ou au soutien nécessaire à certaines recherches scientifiques en vue d'une collaboration étroite avec le RE(ACT) Discovery Institute nouvellement créé, dans le but final de développer de nouvelles thérapies ciblées pour traiter certaines maladies rares spécifiques qui touchent de nombreuses personnes dans le monde.
Je suis ravie de collaborer avec les autres membres du conseil de Fondation et de mettre nos diverses expériences au service de la Fondation BLACKSWAN pour servir au mieux sa mission.

After more than 20 years working in the pharmaceutical industry, having the possibility to be part of the Board to serve a Foundation with a fundamental purpose as the BLACKSWAN Foundation has, is a great honor and privilege for me.
In close collaboration with the other Board members, I sincerely hope to contribute to raising more awareness around the rare diseases within the society by strengthening the communication around the many great activities and projects that are running and ensuring new ones are rising. I also hope to create awareness among some of the key stakeholders in the pharmaceutical world to create partnerships and/or required support for some scientific research to closely collaborate with the newly created RE(ACT) Discovery Institute, with the final goal to develop new targeted therapies to treat some specific rare conditions, which affect many humans across the world.
I am thrilled to collaborate with the others board members and combine our diverse experiences at the service of the BLACKSWAN Foundation to serve its mission best.

CONSEIL DE FONDATION
BOARD OF DIRECTORS

DAVIDE STAEDLER

J'ai rejoint le Conseil de fondation en 2020 avec beaucoup de curiosité et d'enthousiasme. Les attentes n'ont pas été déçues : le nouveau Conseil a apporté des idées passionnantes et de nouveaux projets. Il était clair dès le début qu'il était essentiel de poursuivre et en même temps d'innover la stratégie de collecte de fonds. Dans ce contexte, l'année 2020, caractérisée par l'urgence covid-19, était particulièrement critique. L'année 2020 est aussi, et surtout, l'année du démarrage officiel du projet RE(ACT) Discovery Institute, le bras thérapeutique de la Fondation. Ce projet m'enthousiasme beaucoup, à la fois en tant qu'entrepreneur et en tant que scientifique. Les défis à relever pour le mettre en œuvre sont multiples, mais il représente une opportunité précieuse pour la Fondation et, plus généralement, pour donner une impulsion concrète au développement de traitements pour les maladies rares. La conduite de ce projet, partagée avec mes collègues du Conseil de Fondation et en particulier avec le Président, est un défi à plusieurs niveaux. En ce qui me concerne, par rapport à mon expérience professionnelle, il s'agit presque d'un changement de paradigme : collecter des fonds pour produire des résultats et non l'inverse. Dans cette optique, les années à venir seront riches en stimuli et en nouveautés au sein de la Fondation BLACKSWAN.

I joined the Council of Foundation in 2020 with curiosity and enthusiasm. The expectations were not disappointed: the new Board brought exciting ideas and new projects. It was clear from the beginning that it was essential to continue and at the same time innovate the fundraising strategy. In this context, it is clear that the year 2020, characterized by the covid-19 emergency, was particularly critical. The year 2020 is also, and above all, the year of the official start of the RE(ACT) Discovery Institute project, the therapeutic arm of the Foundation. This project has me very excited, both as an entrepreneur and scientist. The challenges to implementing it are manifold, but it represents a valuable opportunity for the Foundation and, more generally, to provide a concrete stimulus to developing treatments for rare diseases. Leading this project, shared with my colleagues on the Foundation Board and in particular with the President, is a challenge on many levels. As far as I am concerned, compared to my professional experience, it is almost a paradigm shift: raising funds to produce results instead of the other way around. With this in mind, the coming years will be full of stimuli and novelties within the BLACKSWAN Foundation.

QU'EST-CE QU'UNE MALADIE RARE OU ORPHELINE

En Suisse et dans l'Union européenne, une maladie est dite rare lorsque moins d'une personne sur 2'000 est atteinte, que la maladie est chronique et incapacitante et qu'un effort particulier doit être fourni pour développer un traitement. L'on retient aussi que les maladies rares réduisent souvent l'espérance de vie de qui en souffre.

Au niveau international, il n'y a pas de consensus autour du seuil d'incidence retenu pour définir la rareté. Aux États-Unis par exemple, il s'agit de toute pathologie ou condition de santé affectant moins d'une personne sur 1'500 (soit 200'000 personnes sur le territoire). L'on désigne par ailleurs une maladie comme orpheline lorsqu'il n'existe aucun traitement pour en venir à bout. Les médecins ne connaissent pas l'affection, la recherche et le diagnostic sont inexistants et les victimes, totalement délaissées du système sanitaire, souffrent d'un manque de reconnaissance quasi total.

Os de verre, syndrome du cri du chat, syndrome de Lowe… Les maladies rares et orphelines recouvrent une réalité très diversifiée. Elles peuvent empêcher de bouger (myopathies), de voir (rétinites), de comprendre (X fragile), de respirer (mucoviscidose), de résister aux infections (déficits immunitaires) etc. On en dénombre à ce jour au moins 8'000 dont le 80% au moins a une origine génétique. Il s'agit de pathologies infectieuses ou auto-immunes dans le 20% restant

UN PARCOURS DU COMBATTANT

Les enfants sont particulièrement concernés : trois malades sur quatre ont moins de dix-huit ans, et les maladies rares sont spécialement mortelles et incapacitantes dans leur cas. Ce alors que le corps médical peine souvent à établir un diagnostic de par le faible nombre de personnes touchées.
Outre la difficulté à se faire reconnaître et une espérance de vie réduite, les malades souffrent de handicaps à l'origine de discrimination et d'isolement. Il existe heureusement des associations pour leur venir en aide ainsi qu'à leurs proches.

WHAT IS A RARE OR ORPHAN DISEASE ?

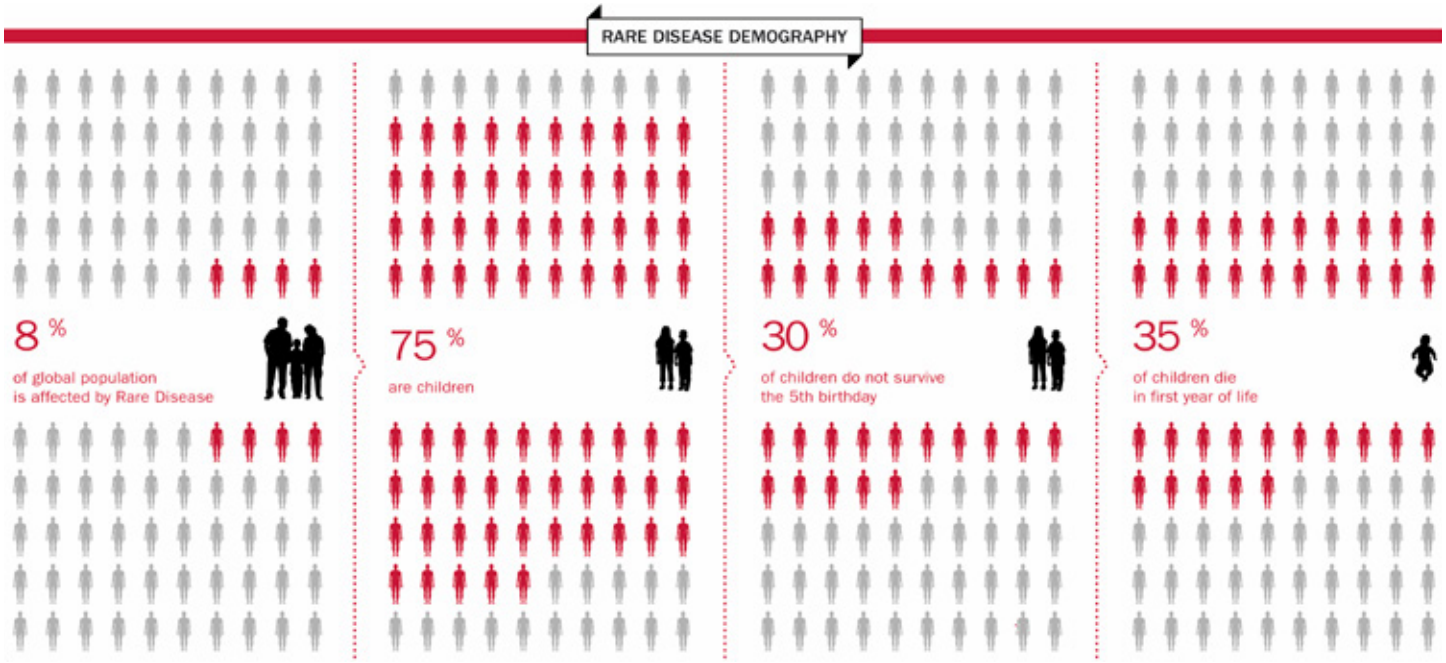
A disease or disorder is defined as rare in Europe and Switzerland when it affects not more than 1 in every 2,000 persons. These conditions are generally chronic, progressive, debilitating, and often life-threatening. In addition, these rare diseases present specific challenges for the development of new treatments.

There is no internationally accepted definition of rare diseases. For example, in the United States, a condition is rare when it affects 1 in every 1,500 persons (or less than 200,000 citizens). Furthermore, it is considered orphan any rare disease for which no treatment has been developed. Practitioners do not know the condition, research is not ongoing, and it is extremely difficult to receive a diagnosis for lack of scientific knowledge. For these reasons, patients feel abandoned by the health system and suffer from an almost total lack of care.

Osteogenesis imperfecta, Lowe syndrome, cri-du-chat syndrome…rare, and orphan diseases are a very diverse reality. These may affect one's ability to move (myopathies), to comprehend the world around us (fragile X syndrome), to breathe (cystic fibrosis), or to combat infection (immune deficiencies). It is estimated that there are at least 8,000 orphan diseases today, 80% of them are genetic in origin. The remaining 20% are autoimmune and infectious disorders.

A REAL STRUGGLE

Children are particularly concerned by rare diseases: three out of four patients are under the age of eighteen. In their case, rare diseases are particularly life-threatening and disabling, and medical professionals struggle to make a diagnosis because of the small number of people affected.
In addition to the difficulty in obtaining recognition and to a reduced life expectancy, patients suffer from disabilities that lead to discrimination and isolation. Fortunately, some associations help them, their families, and loved ones.



LA RECHERCHE SUR LES MALADIES RARES SE HEURTE À PLUSIEURS DIFFICULTÉS MAJEURES

> Des obstacles d'ordre scientifique: le faible nombre de malades recensés ne permet souvent pas de valider scientifiquement les résultats du travail de recherche, ce qui empêche la publication d'articles qui pourraient mobiliser l'attention et l'intérêt de la communauté des chercheurs;

> Des obstacles d'ordre financier: les agences nationales de financement public ne sont pas proactives dans le soutien de la recherche à cause du manque d'expertise des commissions internationales d'évaluation des projets et du nombre restreint de publications scientifiques de la part des chercheurs demandant un financement.

> Des obstacles d'ordre commercial: ces pathologies touchant un nombre très restreint de personnes, les grandes firmes pharmaceutiques négligent d'investir des moyens dans le développement de médicaments.

La recherche sur les maladies rares et orphelines présente pourtant un intérêt majeur, car elles peuvent servir de modèles pour des affections plus communes et aider à développer des médicaments efficaces à plus large échelle.

On l'a vu dans le cas de la leucémie, maladie qui est devenue chronique plutôt que mortelle grâce au développement par une grande firme pharmaceutique d'un médicament conçu à la base pour soigner une forme de leucémie rare des enfants, réfractaire aux médicaments à l'époque sur le marché. Par ailleurs, certaines start-ups ou entreprises se sont spécialisées dans la vente de médicaments pour les maladies rares et leur business model, bien que marginal, a prouvé qu'il fonctionnait.

Pour relever le défi de la recherche, il est cependant nécessaire que les spécialistes puissent échanger autour de compétences pluridisciplinaires et de bonnes pratiques, et que le plus grand nombre de patients participent à la recherche. Il s'agit aussi de renforcer les liens entre le monde académique et l'industrie pour que celle-ci puisse concrétiser les résultats obtenus en nouveaux outils diagnostiques et thérapeutiques.

RESEARCH ON RARE DISEASES FACES SEVERAL MAJOR CHALLENGES

> Scientific obstacles: the small number of patients often does not allow to scientifically validate the results of the research work, which prevents the publication of articles that could mobilize the attention and interest of the research community;

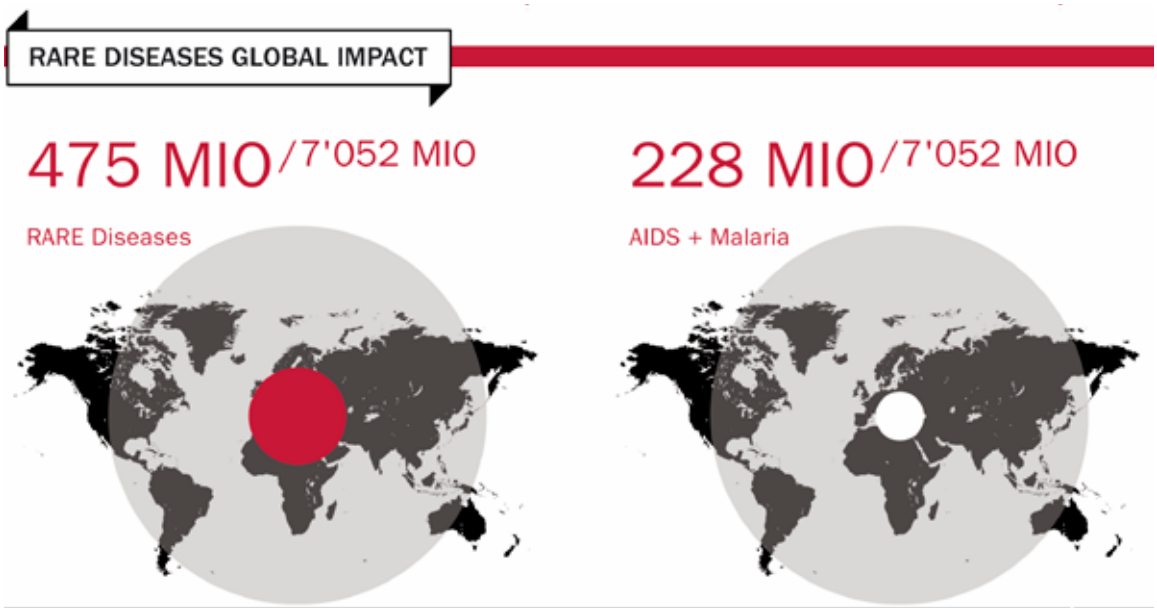
> Financial barriers: National public funding agencies are not proactive in supporting research because of the lack of expertise of international project assessment boards and of the limited number of scientific publications by researchers requesting funding.

> Commercial obstacles: these diseases are affecting a minimal amount of people are often neglected by large pharmaceutical companies that are reticent to invest resources in the development of medicines. Research on rare and orphan diseases is of considerable importance as it can serve as a model for more common diseases and help develop effective drugs on a larger scale.

For example, in the case of leukemia: when a large pharmaceutical company developed a drug designed at the base to cure a rare pediatric form of leukemia that was resistant to the drugs available at the time on the market. This drug then revealed to be effective at fighting off all types of leukemia.

In recent years, some start-ups and companies specialized in the development of drugs for rare diseases, and their business model proved to be effective.

To meet the challenge of research, however, it is necessary for specialists to exchange best practices and use collaborative models and that the most significant number of patients participate in research. There is a need to strengthen partnerships between the academic world and the industry to obtain new diagnostic and therapeutic tools.



LA FONDATION

LA FONDATION EN BREF

Les maladies rares affectent 6 à 8% de la population mondiale et quelque 500'000 personnes en Suisse. Lorsqu'il s'agit d'enfants – dans trois cas sur quatre – l'issue est très souvent fatale. La quête de médicaments adaptés est donc une priorité, d'autant que leur efficacité a été démontrée dans le traitement de pathologies plus fréquentes.

La Fondation BLACKSWAN a été créée en Suisse en 2010 pour aider partout dans le monde celles et ceux qui sont impliqués dans ce combat. Elle soutient la recherche sur tout type de maladie rare ou orpheline, ce qui la rend unique au monde.

Outre son travail dans la quête de fonds, elle organise chaque deux ans un congrès appelé RE(ACT) Congress, devenu une référence internationale. En cinq éditions, plus de 1500 scientifiques ont pu mettre en place une cinquantaine de collaborations. Enfin, la Fondation mène depuis 2015 une campagne appelée #RAREvolution afin que les maladies rares deviennent une priorité de la recherche et de la santé publique.

THE FOUNDATION

THE FOUNDATION IN BRIEF

Rare diseases affect 6% to 8% of the world population and approximately 500,000 people in Switzerland. The majority of these conditions affect children, and in three out of four cases, have a fatal outcome. The quest for specific drugs is a priority, especially as the effectiveness of certain rare disease drugs has been demonstrated in the treatment of most common diseases.

The BLACKSWAN Foundation was established in Switzerland in 2010 to contribute to the development of research on rare and orphan diseases worldwide. The Foundation supports research on all different types of rare and orphan diseases, making its vision unique and finding new solutions that can assist a large variety of projects.

Besides its funding research mission, the Foundation organizes the RE(ACT) Congress every two years, which became an international reference point for rare disease experts. In five editions, more than 1,500 scientists were able to establish approximately fifty collaborations. Since 2015, BLACKSWAN Foundation has also started an international advocacy and awareness campaign called #RAREvolution to ensure rare diseases are recognized as a global public health and research priority.

1 338 612 968 CHINA POPULATION

1 156 897 766 INDIA POPULATION

475 304 355 RARE DISEASE POPULATION

302 074 000 USA POPULATION

2020 ACTIVITIES
SUPPORT FOR SCIENTIFIC RESEARCH

in english only

1. **De Vivo disease / GLUT1 deficiency: The syndrome can cause infantile seizures refractory to anticonvulsive drugs, developmental delay, acquired microcephaly and neurologic manifestations including spasticity, hypotonia, and ataxia.**

The development of a therapeutic solution for De Vivo disease proposed is in line with research carried out for several years in Prof. Magistretti's laboratory at the EPFL. These years of research have allowed us to discover and describe the essential role of astrocytes in regulating brain metabolism. In particular, aerobic glycolysis is triggered in astrocytes during glutamatergic transmission, leading to lactate production. After lactate transfer from astrocytes to neurons, lactate is metabolized to enter the neuronal Krebs cycle (Maeschler et al., 2016). Studies have highlighted the critical role of lactate production mediated by astrocytic lactate production for memory formation (Suzuki et al., 2011) and transcription of genes for plasticity (Margieanu et al., 2018). Importantly, lactate also has neuroprotective effects (Jourdain et al., 2018) and is currently the subject of prospective clinical trials on traumatic brain injury (Careteron et al., 2018).
The strategy developed by Professor Magistretti and his collaborators promotes lactate production by astrocytes, which can then supply it to neurons. Professor Magistretti and his collaborators have identified and developed several molecules to increase the output of astrocytic lactate. Various preliminary experiments have indicated that the lactate induced by these newly identified molecules significantly increases neuroprotection and memory in different preclinical mouse models. New iterations of the most effective molecule were synthesized following these promising results to increase their efficacy.

The goal of the project is to cover the testing of these promising new molecules in vitro (cell cultures), in vivo (mice), and as well in a transgenic mouse model of the disease and De Vivo (mutation of the glucose transporter GLUT1).

PI: Professor Pierre Magistretti, GliaPharm SA, Geneva

Budget: CHF 48'500

Results:

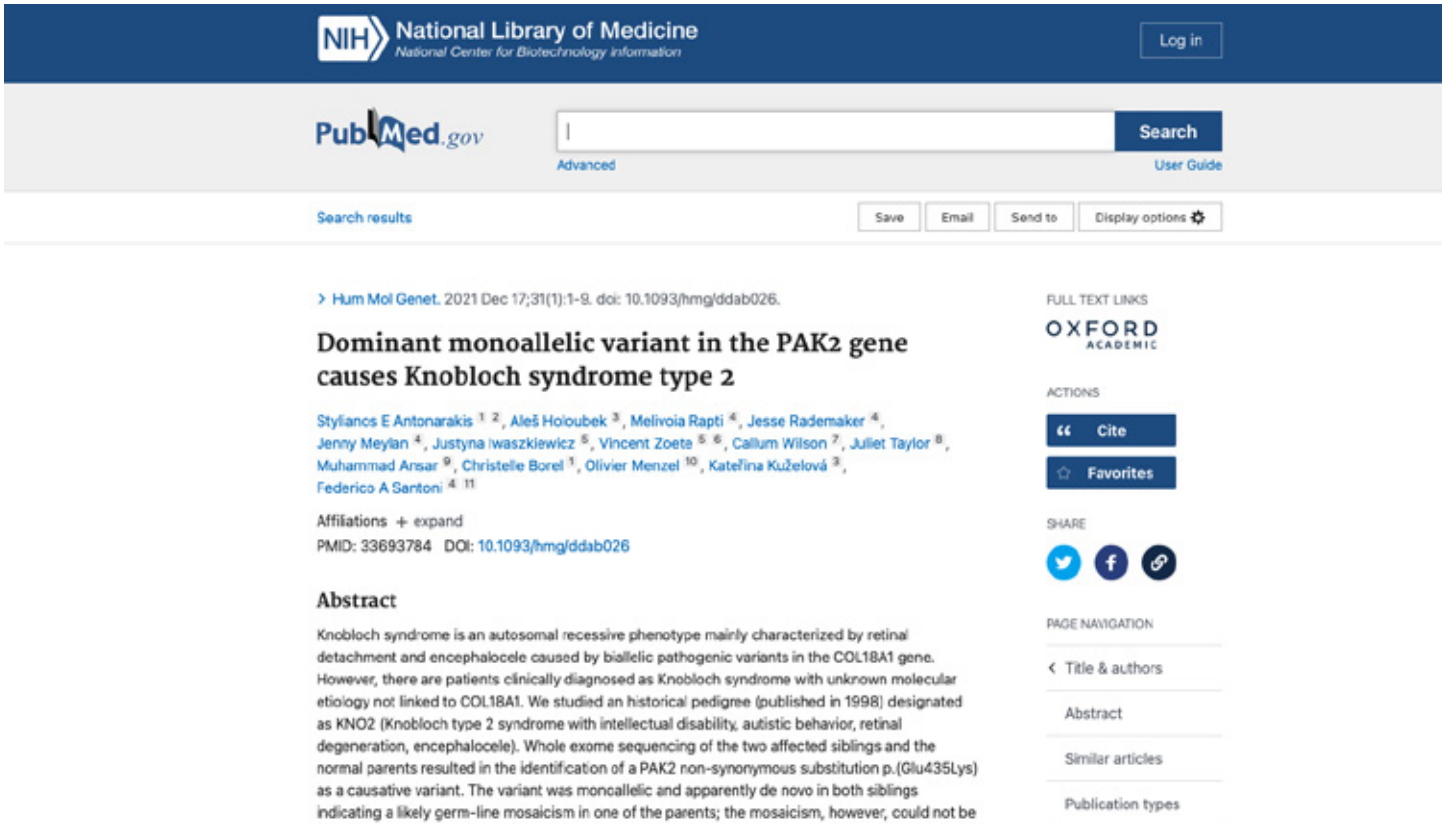
- The compound enhances glycolysis in mouse and human astrocytes in a cell-specific manner at therapeutic concentrations.
- Oral administration of the compound enhances glucose and lactate levels in the brain of mice and has therapeutic effect on motor symptoms of GLUT1-DS mice.
- Drug development program of the compound series has led to the selection of a lead optimized preclinical candidate.
- Patent of compounds series molecule and its impact on GLUT1-DS has been filed on 29 of December, 2020 (European Patent Office- Patent PCT/EP2020/087950).

2. **De Knobloch syndrome: identification of the molecular etiology of a family not linked to COL18A1**

Knobloch syndrome is an autosomal recessive phenotype mainly characterized by retinal detachment and encephalocele caused by biallelic pathogenic variants in the COL18A1 gene. However, there are patients clinically diagnosed as Knobloch syndrome with unknown molecular etiology not linked to COL18A1. We studied an historical pedigree (published in 1998) designated as KNO2 (Knobloch type 2 syndrome with intellectual disability, autistic behavior, retinal degeneration, encephalocele). Whole exome sequencing of the two affected siblings and the normal parents resulted in the identification of a PAK2 non-synonymous substitution p.(Glu435Lys) as a causative variant. The variant was monoallelic and apparently de novo in both siblings indicating a likely germ-line mosaicism in one of the parents; the mosaicism, however, could not be observed after deep sequencing of blood parental DNA. PAK2 encodes a member of a small group of serine/threonine kinases; these P21-activating kinases (PAKs) are essential in signal transduction and cellular regulation (cytoskeletal dynamics, cell motility, death and survival signaling and cell cycle progression). Structural analysis of the PAK2 p.(Glu435Lys) variant that is located in the kinase domain of the protein predicts a possible compromise in the kinase activity. Functional analysis of the p.(Glu435Lys) PAK2 variant in transfected HEK293T cells results in a partial loss of the kinase activity. PAK2 has been previously suggested as an autism-related gene. Our results show that PAK2-induced phenotypic spectrum is broad and not fully understood. We conclude that the KNO2 syndrome in the studied family is dominant and caused by a deleterious variant in the PAK2 gene.

PI: Dr Federico Santoni, Faculty of Biology and Medicine, University of Lausanne, Lausanne 1011, Switzerland.

Results: Scientifc publication



2020 ACTIVITIES
SUPPORT FOR SCIENTIFIC RESEARCH

THE RE(ACT) CONGRESS & IRDIRC CONFERENCE 2020 – INTERNATIONAL CONGRESS OF RESEARCH ON RARE AND ORPHAN DISEASES

In February 2020, the development of the COVID-19 outbreak and the uncertainty of its outcome opened a list of questions regarding the potential restrictions that would be adopted by the health ministries and the international authorities. Following the uncertainty, we decided to postpone our international event, the RE(ACT) Congress & IRDiRC Conference 2020, in 2021. collective efforts and voice in rare diseases research.

2020 ACTIVITIES
INITIATIVES TO INCREASE AWARENESS AND COLLECT FUNDS

Due to the COVID-19 outbreak, we could not organize any event to increase awareness and collect funds.

FINANCIAL REPORT 2020

ALBA

Lugano, 7th July 2021

To the
General meeting of the
Blackswan Foundation
For research on orphan diseases
Via Cantonale 26
6948 Porza

REPORT OF THE STATUTORY AUDITORS
YEAR 2020

As statutory auditor, we have audited the accounting records and the financial statements (balance sheet, income statement and notes) of **Blackswan Foundation for research on orphan diseases** for the year ending 31 December 2020.

These financial statements are responsibility of the board of directors. Our responsibility is to express an opinion on these financial statements based on our audit. We confirm that we meet the legal requirement concerning professional qualification and independence.

Our audit was conducted in accordance with Swiss Auditing Standards, which require that an audit be planned and performed to obtain reasonable assurance about whether the financial statements are free from material misstatement. We have examined on a test basis evidence supporting the amounts and disclosures in the financial statements. We have also assessed the accounting principles used, significant estimates made and the overall financial statement presentation. We believe that our audit provides a reasonable basis for our opinion.

The Foundation closed the accounting year 2020 with a deficit balance of Chf 144'302.50. The net asset of the Foundation, after capitalizing the annual result turn into an asset balance of the amont Chf. 114'394.35.

In our opinion, the accounting records and financial statements comply with Swiss law and the Foundation's articles.

We recommend that the financial statements submitted to you be approved.

Alba Advisors SA
Dir. Memmo Favre

Enclosures

Alba Advisors SA
Via Curti 5 - CP 5117 - 6901 Lugano (CH) - Tel. +41/91.912.56.10 - Fax +41/91.912.56.17
info@albadvisors.ch - www.albadvisors.ch - No. IVA: CHE-108.642.160

FINANCIAL REPORT
2020 BALANCE

BLACKSWAN FONDAZIONE
Via Cantonale 26
6948 Porza

Stampato il 16.06.2021/10:39:18
Contabilità 2020 dal 1.1.2020 al 31.12.2020

BILANCIO patrimoniale al 31.12.2020

Conto	Descrizione	Dare (CHF)	Avere (CHF)	(2019 al 31.12.2019) Saldo prec (CHF)	Variazione	
	ATTIVI					
10	**Sostanza circolante**					
100	***Mezzi liquidi***					
1020	Banca EFG - 007 (Ex AA)	7'811.45		76'313.20 D	-68'501.75	*-89.8*
1021	Banca EFG - 015 (Ex AB)	11'319.71		1'259.67 D	10'060.04	*798.6*
1022	Banca EFG - 031 (Ex MA)	76'605.60		86'573.89 D	-9'968.29	*-11.5*
1023	Banca EFG - 023 (Ex LA)	0.00		49'406.91 D	-49'406.91	*-100.0*
1024	Banca EFG - 058 USD	14'621.09		14'621.09 D	0.00	*0.0*
	Totale Mezzi liquidi	***110'357.85***	***0.00***	***228'174.76*** D	*-117'816.91*	*-51.6*
109	***Transitori***					
1090	Transitori attivi	7'900.00		8'172.77 D	-272.77	*-3.3*
1093	Transitorio Carta di credito		595.15	70.58 A	524.57	*-743.2*
	Totale Transitori	***7'900.00***	***595.15***	***8'102.19*** D	*-797.34*	*-9.8*
	Totale Sostanza circolante	**118'257.85**	**595.15**	**236'276.95** D	-118'614.25	*-50.2*
11	**Sostanza fissa**					
1105	Mobilio e macchine ufficio	510.00		670.00 D	-160.00	*-23.9*
1106	Hardware e Software	1'910.00		3'180.00 D	-1'270.00	*-39.9*
1200	Attivazione Progetto RARevolution (2016-2019)	0.00		26'630.00 D	-26'630.00	*-100.0*
	Totale Sostanza fissa	**2'420.00**	**0.00**	**30'480.00** D	-28'060.00	*-92.1*
	Totale ATTIVI	**120'677.85**	**595.15**	**266'756.95** D	-146'674.25	*-55.0*
	PASSIVI					
20	**Capitale di terzi**					
200	***Debiti a breve termine***					
2006	Creditore AVS		1'025.30	0.00 A	1'025.30	*100.0*
2007	Creditore LPP		14.60	0.00 A	14.60	*100.0*
	Totale Debiti a breve termine	***0.00***	***1'039.90***	***0.00*** A	*1'039.90*	*100.0*
209	***Transitori***					
2090	Transitori passivi		3'500.00	6'500.00 A	-3'000.00	*-46.2*
2093	Transitorio stipendi		1'148.45	1'560.10 A	-411.65	*26.4*
	Totale Transitori	***0.00***	***4'648.45***	***8'060.10*** A	*-3'411.65*	*-42.3*
	Totale Capitale di terzi	**0.00**	**5'688.35**	**8'060.10** A	-2'371.75	*-29.4*
21	**Capitale proprio**					
2150	Risultati riportati		258'696.85	218'378.23 A	40'318.62	*18.5*
2170	Risultato d'esercizio	144'302.50		40'318.62 A	-184'621.12	*-457.9*
	Totale Capitale proprio	**144'302.50**	**258'696.85**	**258'696.85** A	-144'302.50	*-55.8*
	Totale PASSIVI	**144'302.50**	**264'385.20**	**266'756.95** A	-146'674.25	*-55.0*
	Totale a pareggio	**264'980.35**	**264'980.35**			

FINANCIAL REPORT
2020 INCOME STATEMENT

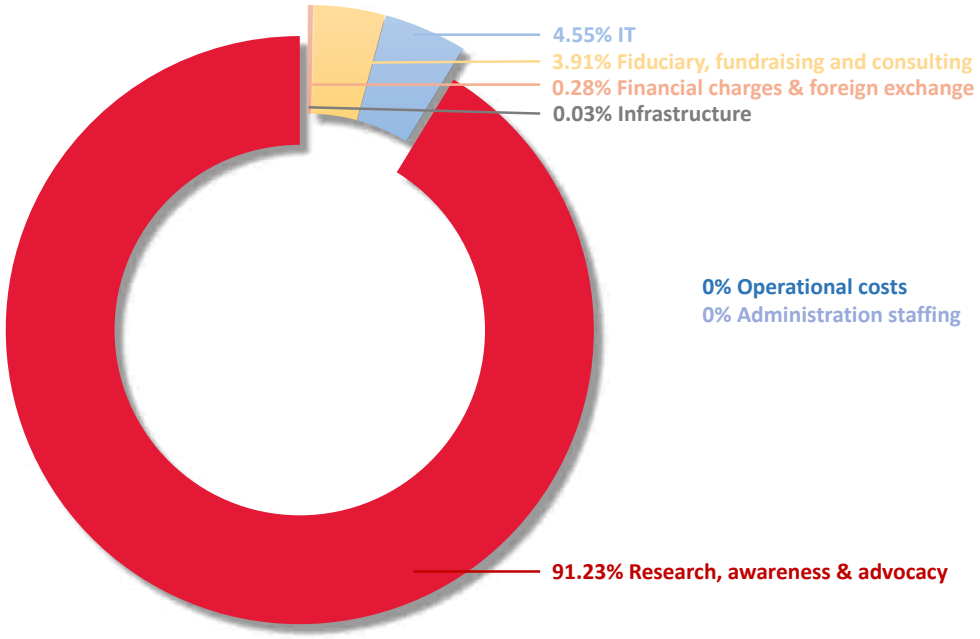
BLACKSWAN FONDAZIONE
Via Cantonale 26
6948 Porza

Stampato il 21.06.2021/08:54:16
Contabilità 2020 dal 1.1.2020 al 31.12.2020

CONTO economico dal 1.1.2020 al 31.12.2020

Conto	Descrizione	Dare (CHF)	Avere (CHF)	(2019 dal 1.1.2019 al 31.12.2019) Saldo prec (CHF)		Variazione
	RICAVI D'ESERCIZIO					
60	**Ricavi da vendite**					
600	***Ricavi da vendite***					
6001	Registrazioni RE(ACT) congress		6'029.67	21'047.11 A	-15'017.44	*-71.4*
6006	Donazioni PayPal		205.00	683.00 A	-478.00	*-70.0*
6008	Donazioni varie		13'269.50	128'915.78 A	-115'646.28	*-89.7*
6010	Donazioni progetto RAREvolution		28'537.49	134'381.34 A	-105'843.85	*-78.8*
6013	Sponsoring RE (ACT) Congress		0.00	134'104.51 A	-134'104.51	*-100.0*
6014	Rimborsi		0.00	144.30 A	-144.30	*-100.0*
	Totale Ricavi da vendite	***0.00***	***48'041.66***	***419'276.04*** A	*-371'234.38*	*-88.5*
	Totale Ricavi da vendite	**0.00**	**48'041.66**	**419'276.04** A	-371'234.38	*-88.5*
	Totale RICAVI D'ESERCIZIO	**0.00**	**48'041.66**	**419'276.04** A	-371'234.38	*-88.5*
	Risultato d'esercizio		***144'302.50***	***40'318.62*** D	-184'621.12	*-457.9*
	Totale a pareggio	**192'344.16**	**192'344.16**			

FINANCIAL REPORT
2020 EXPENSES OVERVIEW



NOTES TO FINANCIAL STATEMENTS FOR THE YEAR ENDED 31 DECEMBER 2020

1. ORGANIZATION

The BLACKSWAN Foundation (BSF) is a Swiss Foundation, established as a not-for-profit legal entity registered in Porza under statutes dated 15th April 2010 and in accordance with article 80 and those that follow of the Swiss Civil Code. It is managed by a foundation board. BSF contributes to the development of research on rare and orphan diseases worldwide. The Foundation supports research on all different types of rare and orphan disease, which makes its vision unique and helps in finding new solutions that can assist a large variety of projects. As with all Swiss foundations recognized for international public good, BSF is monitored by the Swiss Federal Supervisory Board for Foundations.

The capital fund is fully subscribed at CHF 50,000 as stipulated under the original legal statutes of BLACKSWAN Foundation.

2. GOVERNANCE

The Foundation Board is the Foundation's supreme body. It takes all decisions necessary or effective for the achievement of the Foundation's aims. It has general responsibility for the affairs of the Foundation and supervises all activities carried out under its authority by the Foundation's other bodies to which power and authority have been delegated.

Members of the Board act on voluntary basis and may not claim any financial compensation other than expenses incurred such as travel and accommodation. For activities over and above the normal requirements of the position, each Member may receive appropriate reimbursement and compensation. Payment of any such reimbursement or compensation is only permissible where it corresponds to a service carried out of for the benefit of the Foundation.

3. RECOGNITION OF DONATIONS

Contribution from donors (public, private and philanthropic sources) are recognised in the financial statement on an accrual basis when they have been received or confirmed in writing pledges. Contributions which are subject to donor-imposed stipulation for a specific purpose or use in future years may be deferred or attributed to a restricted reserve according to the particular nature of the specific conditions.

FINANCIAL REPORT
2020 INCOME STATEMENT

BLACKSWAN FONDAZIONE
Via Cantonale 26
6948 Porza

Stampato il 21.06.2021/08:54:16
Contabilità 2020 dal 1.1.2020 al 31.12.2020

CONTO economico dal 1.1.2020 al 31.12.2020

Conto	Descrizione	Dare (CHF)	Avere (CHF)	(2019 dal 1.1.2019 al 31.12.2019) Saldo prec (CHF)	Variazione	
	COSTI PER MATERIALE E MERCI					
	Totale COSTI PER MATERIALE E MERCI	**0.00**	**0.00**	**0.00** D	0.00	*100.0*
	COSTI D'ESERCIZIO					
41	**ALTRI COSTI D'ESERCIZIO**					
4210	Interessi e spese diverse	0.00		24.99 D	-24.99	*-100.0*
4220	Spese bancarie	544.09		494.84 D	49.25	*10.0*
4250	Differenze di cambio	0.00		750.91 D	-750.91	*-100.0*
4400	Ammortamenti	1’430.00		2’340.00 D	-910.00	*-38.9*
4401	Ammortamento progetti	26’630.00		8’870.00 D	17’760.00	*200.2*
4700	Materiale ufficio e stampati	49.65		644.30 D	-594.65	*-92.3*
4701	Promozione - stampati	1’572.33		320.00 D	1’252.33	*391.4*
4706	Spese brand, web domains	0.00		700.00 D	-700.00	*-100.0*
4760	Spese di rappresentanza	1’240.88		5’273.24 D	-4’032.36	*-76.5*
4771	Tasse, Fiduciaria, membership	3’339.96		3’267.07 D	72.89	*2.2*
4775	Salari, Spese Sociali	0.00		78.90 A	-78.90	*100.0*
4780	Spese legali e notarili	4’122.70		0.00 D	4’122.70	*100.0*
4802	Sito web e webmaster	8’684.64		5’402.76 D	3’281.88	*60.7*
4830	RE(ACT) congress	41’137.08		113’060.07 D	-71’922.99	*-63.6*
4831	RE(ACT) Community	0.00		6’948.96 D	-6’948.96	*-100.0*
4832	RDI (Rare Disease International)	52’506.61		90’265.48 D	-37’758.87	*-41.8*
4891	Mix (carta di credito)	0.00		192.60 D	-192.60	*-100.0*
5000	Grants	51’086.22		140’481.10 D	-89’394.88	*-63.6*
	Totale Altri costi d'esercizio	**192’344.16**	**0.00**	**378’957.42** D	-186’613.26	*-49.2*
	Totale COSTI D'ESERCIZIO	**192’344.16**	**0.00**	**378’957.42** D	-186’613.26	*-49.2*

BLACKSWAN FOUNDATION AFFILIATIONS & PARTNERS

- ProRaris - Swiss rare disease alliance - www.proraris.ch
- EURORDIS - European alliance of patient organizations - www.eurordis.org
- E-RARE - European consortium of national funding bodies for research on rare diseases - www.erare.eu
- European Joint Programme on Rare Diseases - www.ejprarediseases.org
- RDI - Rare Disease International - The the global alliance of people living with a rare disease of all nationalities across all rare diseases - www.rarediseasesinternational.org

MEMBERS OF THE FOUNDATION

BOARD OF DIRECTORS

CHAIRMAN AND FOUNDER

Dr OLIVIER MENZEL, PhD, MBA;
Vuarrens, Switzerland

MEMBERS

STEFANO BERTI
Swiss Agency for Development and Coopertion
CHIARA CIRIMINNA SWAN
Swiss Federal Institute of Technology (EPFL)
SKANDER NAJAR
NASK (Network for Advanced Strategy and Knowledge)
KARIMA SOUDANI
HealthCare Consultant
PD DR DAVIDE STAEDLER
Entrepreneur, CEO, Consultant in BioTech

ADVISORY BOARD

DEMIAN CONRAD, Branding & Communication;
Lausanne

SCIENTIFIC COMMITTEE

PRESIDENT

Prof. BARBARA WILDHABER MD, PD;
Children's Hospital, Geneva, Switzerland

MEMBERS

Prof. STYLIANOS E. ANTONARAKIS MD, PhD;
Head of the Dept. of Medical Genetics
and Development, Geneva, Switzerland
Prof. JACQUES S. BECKMANN, PhD;
Professor emeritus at the University of Lausanne,
Lausanne, Switzerland
Dr. JACQUES BIRRAUX MD;
Children's Hospital, Geneva, Switzerland
Prof. BRUNO DALLAPICCOLA MD;
Scientific Director of Pediatric Hospital
Bambino Gesù, Rome, Italy
Dr. CELIA DELOZIER-BLANCHET PhD;
Director of Clinical Services,
University of California, USA
Dr. MARISA JACONI PhD, MER;
University of Geneva, Switzerland
Prof. STANISLAS LYONNET MD, PhD;
Professor of Genetics, University of Paris,
Hospital Necker, France
Prof. MARTIN MEULI MD;
Head of Department of Pediatric Surgery
University Hospital of Zurich, Switzerland
Dr. MICHAEL NICOLAS PhD;
University of Lausanne, Switzerland
Prof. ALEXANDRE REYMOND PhD;
University of Lausanne, Switzerland
Dr. PATRICK SALMON Pharm., PhD;
University of Geneva, Switzerland
Prof. HAMISH S. SCOTT PhD;
University of Adelaide, Australia
Prof. ETIENNE SOKAL MD;
Head of the Pediatric Gastroenterology-Hepatology
Unit, Catholic University of Leuven, Belgium

DONATIONS

ONLINE
www.blackswanfoundation.ch
(secured payment by credit card or PayPal)

BY BANK TRANSFER
Banca Raiffeisen del Cassarate
Piazza Motta, 6950 Tesserete
Switzerland

Donation in CHF:
IBAN: CH74 8080 8008 1468 1323 8

Donation in Euro:
IBAN: CH12 8080 8009 4017 8357 3

Donation in USD:
IBAN: CH41 8080 8001 0905 5135 4

SWIFT: RAIFCH22XXX

CONTACT

BLACKSWAN Foundation
Chemin de la Riaz 11
1418 Vuarrens - Switzerland
Infoline: +41 21 887 64 34
contact@blackswanfoundation.ch

www.blackswanfoundation.ch
www.react-congress.org

FACEBOOK
www.facebook.com/Blackswan.Foundation
www.facebook.com/REACT.community.official

TWITTER
twitter.com/blackswanfound
twitter.com/react_community

LINKEDIN
www.linkedin.com/company/blackswan-foundation
www.linkedin.com/grp/home?gid=3830895

INSTAGRAM
instagram.com/blackswan_foundation/

BLACKSWAN®
FOUNDATION

SWISS FOUNDATION FOR RESEARCH ON ORPHAN DISEASE S
SCHWEIZERISCHE STIFTUNG FÜR DIE FORSCHUNG SE LTENER KRANKHEITEN
FONDATION SUISSE POUR LA RECHERCHE SUR LES MALADIES ORPHELINE S
FONDAZIONE SVIZZERA PER LA RICERCA SULLE MALA TTIE ORFANE