Associazione Italiana Sindrome di Shwachman-Diamond (AISS)
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Shwachman-Diamond Syndrome Italian Research Grant

Maximum Amount euro 10.000,00

Firm Deadline for Receipt of Applications: 1st February 2018

Eligibility: Persons applying for these grants if not in a faculty position need to provide a declaration by a supervisor with a position in the department (not a training position) and with authority to hold an independent research grant.

Terms of Support: Support may be provided for one (1) year in an amount not to exceed E 10,000. Indirect costs are permitted and are not to exceed 10% of the total costs.
The AISS will provide preference to those applications in which funds are used for supplies, equipment, technicians and other expenses and not for support of the salary of the PI or co-PIs.

Review: All applications will be reviewed by the AISS Scientific Committee (AISS-SC) or its designees.

Application: The application contains two sections.

Section 1, forms attached. The applicant and co-applicants must also include a current curriculum vitae.
Section 2: Research Plan, divided as indicated below. Parts A through D should not exceed 6 pages, using a font no smaller than 10 point.

Part A. Specific aims
Part B. Significance and background
Part C. Preliminary studies
Part D. Experimental design and methods
Part E. References (not included in the 6 page limit)
Part F. Relevance of the research to Shwachman-Diamond Syndrome
Part G. For junior faculty separate letter from supervisor or department head confirming commitment to project, and to provision of space and facilities
Part K. If human subjects and animals are involved, a statement by the PI or supervisor overseeing human or animal studies is compulsory. If considered as necessary by the AISS-SC, more information about ethical committee study approval may be asked.

Submission by email to the AISS: aiss@shwachman.it

1. Title of Proposal

Effect of Ataluren on cytokine expression in Shwachman-Diamond syndrome

2**. Applicant Information:**

Name: Valentino Bezzerri

Title and Degree(s):
Ph.D. in Cellular and Molecular Biology and Pathology, University of Verona (2014)
Degree in Medical Biotechnology, University Vita-Salute San Raffaele, Milan (2010)
Degree in Pharmaceutical Biotechnology, University of Ferrara (2005)

Work Address:
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3. **Applicant Curriculum Vitae**: beginning on the next page, with 2 page limit. This will form application pages 3 and 4.

Curriculum Vitae

Unique Researcher identifying system: ORCID 0000-0002-6849-4487, Researcher ID K-8132-2016

EDUCATION AND TRAINING

Postdoc fellow, Clinical Research Center, Cystic Fibrosis Center, University Hospital of Verona (August 2014-July 2015)

Postdoc fellow, Laboratory of Molecular Pathology, University Hospital of Verona (May 2014 - July 2014).

PhD in Cellular and Molecular Biology and Pathology, University of Verona (December 2010 - May 2014).
Thesis Dissertation title: Pro-inflammatory signal transduction in epithelial cells: the model of cystic fibrosis lung disease.

Degree in Cellular and Molecular Medical Biotechnology, (Marks 108/110) Vita-Salute San Raffaele University, Milan (October 2008 - March 2010).

Degree in Pharmaceutical Biotechnology (Marks 110/110 summa cum laude), University of Ferrara (October 1999 - December 2005).

EMPLOYMENT AND RESEARCH EXPERIENCE

Group Leader position, Cystic Fibrosis Center (Director Dr. M. Cipolli), Azienda Ospedaliero Universitaria Ospedali Riuniti, Ancona, Italy. Development of novel therapeutic options for Shwachman-Diamond syndrome and Cystic Fibrosis. (April 2018-to date)

Research Associate, University of Verona, Department of Medicine, Unit of General Pathology. Team leader position: study of the molecular mechanisms that underlie acute myeloid leukemia progression in patients affected by SDS. Development of novel cellular model of SDS-related hematological impairment. (August 2015-March 2018).

Postdoctoral Fellow, University Hospital of Verona, Shwachman-Diamond regional Center and Cystic Fibrosis Center, Clinical Research Center (head Dr. Marco Cipolli). Followed several clinical trials, including clinical studies concerning new CFTR corrector molecules. Designed and proposed new preclinical projects aimed to study the molecular mechanisms leading to bone marrow failure and acute myeloid leukemia in Shwachman-Diamond syndrome (September 2014-July 2015).

Postdoctoral Fellow, University Hospital of Verona, Laboratory of Molecular Pathology (head Dr. Giulio Cabrini). Performed in vitro studies to evaluate the efficacy of novel pharmaceutical correctors of Cystic Fibrosis Transmembrane conductance Regulator (CFTR). (May 2014-August 2014).

Ph.D. Student, University of Verona, Department of Pathology and Diagnostics (project reference figure Prof. Marco Antonio Cassatella). Study of pro-inflammatory signal transduction mediated by P.aeruginosa infection in Cystic Fibrosis lung disease. This project has been designed to gain further insights into the molecular mechanisms that underlie cytokine and chemokine gene expression (in particular IL-6 and IL-8) by lung epithelia upon exposure to P.aeruginosa infection. Tested the role of specific miRNA molecules on gene regulation in Cystic Fibrosis lung pathology and in glioma disease progression (December 2010 – May 2014).

Research Fellow, University Hospital of Verona, Laboratory of Molecular Pathology (head Dr. Giulio Cabrini).

Expert of gene transcription and Transcription Factor Decoy (TFD) approach to investigate the molecular mechanisms that activate Interleukin-6 (IL-6) and Interleukin-8 (IL-8) mRNA expression during lung inflammation in Cystic Fibrosis. (December 2005 – December 2010).

SCIENTIFIC PUBLICATIONS (updated: February 2018; Source: Scopus)
34 Publications (h-index 16, total citations 619): 32 full articles in peer-reviewed International Journals, 1 Conference Paper, 1 review.
Complete list of publications available online: 0000-0002-6849-4487 (ORCID)

LEADERSHIP AND TEACHING EXPERIENCE
Invited Scientist, Department of Pediatric Hematology, Oncology & Stem Cell Transplantation, Massey Cancer Center, Virginia Commonwealth University, Richmond, USA (Oct 2017-to date)
Reviewer, Expert Review of Molecular Diagnostics (IF: 3.333)(2016-2017)
Reviewer, Haematologica (IF: 7.702)(2015-2017)
Lead Guest Editor, Mediators of Inflammation Journal (IF: 3.418) (2016)
Reviewer, Evidence-Based Complementary and Alternative Medicine Journal (IF: 1.931)(2015-2016)
Lecturer, PhD Course in Life and Health Sciences, University of Verona (2016-to date)
Lecturer, Degree in Biomedical Laboratory Technician, within the Course in Pathological Anatomy Methods, University of Verona (2013-2016)
Thesis supervisor, Master degree course in Molecular Biology, University of Ferrara (2013-2014)
Invited Speaker, Department of Pediatrics, Yale University, New Haven, USA (2013)

FUNDING
Grant GR-2016-02363570, Italian Ministry of Health - Principal Investigator. "Further insights into the molecular mechanisms underlying the Shwachman-Diamond syndrome: towards new therapeutic approaches" (Euro 368.278,35)
Grant AISS 2017, Italian Shwachman-Diamond Syndrome Foundation - Principal Investigator. "Preclinical evaluation of the effect of Ataluren in restoring the expression of mutated SBDS protein in SDS cells" (Euro 10.000,00)
Grant FFC#8/2014, Italian Cystic Fibrosis Foundation - External Collaborator. “Design and synthesis of improved analogs of trimethylangelicin (TMA) for personalized treatment of cystic fibrosis” (Euro 45.000,00)
Grant FFC#24/2014, Italian Cystic Fibrosis Foundation - External Collaborator. “The role of Glucocerebrosidase GBA2 in cystic fibrosis lung inflammation: from molecular mechanism to therapeutic strategies” (Euro 76.000,00)

LANGUAGES SPOKEN
English (fluent), Italian (native language)

4. **Applicant's Commitment as Investigator of the Project**:

I agree as the applicant to accept responsibility for the scientific management of this project as outlined in this application. I further agree to submit a report at the end of the granting period.

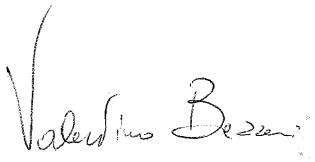
5**. Applicant's Affirmation**:

I certify that the investigations involving human subjects to be carried out in the application will have approval of the applicant's Institutional Ethical Committee

Approvals from the Institutional Ethical Committee must be included with the application.

6**. Research Results**:

Results of research may be made available to the public through appropriate scientific channels. All publications will bear the statement:



Signature of Applicant Date 28/02/2018

7. Applicant's Institution Certification and Commitment:

I certify that the statements herein and the Applicant's Affirmation are true, complete and accurate to the best of my knowledge and I agree to accept responsibility for the fiscal management of this project as outlined in this application. I further agree to commit this institution to comply with the Associazione Italiana Sindrome di Shwachman-Diamond (AISS) terms and conditions if a grant is awarded as a result of this application.

Name of Institution Official: Dr. Marco Cipolli

Title: Director of Cystic Fibrosis Center, AOU Ospedali Riuniti di Ancona

Address: Via Conca 71, Torrette, Ancona, Italy

Phone: +39-071-5962035

Fax: +39-071-34970

E-mail Address: marco.cipolli@ospedaliriuniti.marche.it

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Signature of Institution Official Date 28/02/2018

ABSTRACT OF RESEARCH PLAN

Within the space provided, summarize the long-term objectives, scientific aims and methodology of the proposal.

TITLE: **Effect of Ataluren on cytokine expression in Shwachman-Diamond syndrome**

The overall aim of the project is the development of a personalized therapy based on Ataluren (an orally bioavailable nonsense suppressor molecule), approved by the European Medicines Agency (EMA) for Duchenne muscular dystrophy. We will test Ataluren activity on pro-inflammatory condition in SDS. We recently reported that mTOR/STAT3 pathway is activated by IL6. Furthermore, IL6 plays a key role during activation of STAT3. IL6-dependent STAT3 activation may induce expression of pro-inflammatory cytokines, including IL-6 itself, thus generating a loop which further induces the JAK/STAT3 pathway. Moreover, neutrophils from most SDS patients show altered IL-8 signaling. The role of mTOR/STAT3 in cytokine up-regulation and the effect of Ataluren on this process will be investigated in SDS LCLs and bone marrow stem cells by Luminex technology and ELISA. We will also generate a bio-bank for SDS bone marrow CD34+ progenitors and plasma samples. Cryopreserved cells might be de-frozen and studied worldwide. To date no therapies have been developed for SDS. This study could be an innovative approach to SDS pediatric cancer research, representing a key step for a first clinical trial of SDS based on drug repurposing of Ataluren.

BUDGET

List below a budget by categories for the support. The review committee will carefully consider the appropriateness of your budget. It must be well defined, justified, and realistic to complete the work proposed. The first column defines the total expenses that are expected to be necessary to realistically complete the project. The second column indicates the expenses requested from the AISS. Applicants **will not** be penalized in funding considerations for requiring additional funds beyond what is requested from the Foundation(AISS); however, the true costs of the project must be acknowledged.[This and the section on page 1 re: Other Funding need to be consistent]

EURO Amount Requested for:

	TOTAL COSTS REQUIRED TO COMPLETE PROJECT:	**COSTS REQUESTED FROM AISS**:(not to exceed E 10,000)
Personnel (including fringe benefits): PI: Name: Valentino Bezzerri	31000 euro	0 euro

Co-I Name: Marco Cipolli Additional personnel (identify role): Name:	0 euro	0 euro
Equipment:	0	0
Supplies:	25000	5000
Other Expenses:	10000	5000
Indirect Costs (not to exceed 10% of total)	0	0
TOTAL COSTS:	66000	10000

Justification: Define and justify expenses in each category. Explain the role of each of the individuals named in the Personnel section. The justification must include an explanation of what each category contributes to the project. Also explain any marked differences between the first- and second-year expenses in a particular category. The AISS will provide preference to those applications in which funds are used for supplies, equipment, technicians and other expenses and not for support of the salary of the PI or co-PIs. The AISS-SC may ask for further expense details.

Personnel: Salary of Dr. Valentino Bezzerri will be full paid by the AOU Ospedali Riuniti di Ancona. Dr. Bezzerri will design and carry out most of the experiments. Dr. Marco Cipolli will coordinate patient recruitment and clinical sample withdrawals.

Supplies: Kit ELISA for IL6, IL8 and other cytokines involved in SDS; Kit Luminex for cytokine expression analysis, Culture media for both stem cells and SDS cell lines; recombinant human IL6 (major STAT3 activator); consumables (tubes, flasks, pipettes etc.).

Other: Cell models (EBV-mediated immortalization of B cells); costs for cell storage (bio-banking), costs for ethical committees (statistical analysis, fees etc.), conferences and scientific meetings (registration to conferences, flights, accommodations), IT service (PC updating, specific software).

Other Support for this Project:
Applicants are allowed to receive funding from other sources for parts of the project not funded by the AISS. Please, list all other funding sources.

Grant GR-2016-02363570, Italian Ministry of Health - PI Valentino Bezzerri. "Further insights into the

molecular mechanisms underlying the Shwachman-Diamond syndrome: towards new therapeutic approaches" (Euro 368.278,35)

Research Plan

Part A. Specific aims

1. Analysis of cytokine expression in SDS. We will investigate the expression of several cytokines and chemokines including IL6, IL8, IL10, IL12 and IL13 in terms of mRNA and in terms of protein release in plasma samples of SDS patients as well as in cell models such as LCLs, PBMCs, bone marrow MSCs and CD34+ stem cells.
2. Analysis of Ataluren activity on pro-inflammatory condition in SDS. We recently reported that mTOR/STAT3 pathway is activated by IL6. Enhanced IL6 expression might further take place in SDS. The role of mTOR/STAT3 in cytokine up-regulation and the effect of Ataluren on this process will be investigated in SDS LCLs and bone marrow stem cells.
3. Development of a cellular Bio-bank for SDS bone marrow CD34+ hematopoietic progenitors and plasma samples. Cryopreserved cells might be de-frozen and studied worldwide.

Part B. Significance and background

Shwachman-Diamond syndrome is mainly caused by *SBDS* gene mutations [Boocock et al. 2003], although other genes have been recently associated with SDS-like phenotype, including *DNAJC21*, *EFL1* and *SRP54* genes [Boocock et al. 2003; Dhanraj et al. 2017; Stepensky et al. 2017; Carapito et al 2017; Cipolli 2001]. SDS is a multiple-organ disease which leads to haematological disorders, bone malformation, pancreas insufficiency and cognitive impairment [Cipolli 2001]. SDS patients can develop bone marrow failure, the major cause of morbidity and mortality, causing severe neutropenia and myelodysplasic syndrome, (MDS), with increased risk to AML progression. The current therapy mainly consists in pancreatic enzyme supplementation, bone surgery and bone marrow transplantation. However, any treatment for bone marrow failure or neutropenia has been proposed so far. The nonsense suppressor molecule Ataluren, which is already approved for the treatment of Duchenne muscular dystrophy, is directed against the most common *SBDS* mutation, namely 183-184TA→TC [Boocock et al. 2003; Bezzerri et al. 2017]. We recently reported that Ataluren is able to rescue full length SBDS protein expression in vitro, improving myeloid differentiation in bone marrow hematopoietic progenitors, restoring the normal apoptotic rate and reducing the excessive mTOR phosphorylation in SDS cells [Bezzerri et at, 2016; Bezzerri et at, 2017]. IL6 has been reported to activate mTOR pathways in hematopoietic stem cells both in human cells and in mice [Chen et al., 2010]. Previous studies show that IL6 expression and release is induced in mesenchymal stromal cells of SDS patients [Andrè et al., 2012]. IL6 is the most common cytokine known to activate STAT3 through JAK1 and JAK2 triggering, with a variety of hematological consequences [O'Shea et al., 2013]. IL6-dependent STAT3 activation may induce expression of pro-inflammatory cytokines, including IL-6 itself, thus generating a loop which further induces the JAK/STAT3 pathway [Wake et al., 2015]. We recently reported that SDS leukocytes present hyper-phosphorylation of both mTOR (S2448) and STAT3 (Y705 and S727), which is further enhanced upon IL6 stimulation [Bezzerri et al., 2016]. Moreover, neutrophils from most SDS patients show altered IL-8 signaling [Kuijpers et al., 2005]. IL-8 is a chemokine which plays a key role in neutrophil chemotaxis, which in turn is impaired in SDS [Dror et al, 2001]. This study might represent a key step for a first clinical trial of SDS based on drug repurposing of Ataluren. Moreover, this study might open new therapeutic perspectives also for other genetic bone marrow failure syndromes caused by nonsense mutations.

Part C. Preliminary studies

Our preliminary results show that plasma levels of IL6, IL8, IL10 and IL13 are increased in SDS patients (Figure 1A). Consistently with this finding, IL6 and IL8 releasing is up-regulated also in LCLs obtained from SDS patients (Figure 1B). Thus, our hypothesis is that the hematological disorder in SDS might be sustained by a loop of activation IL6-mTOR-STAT3-IL6.

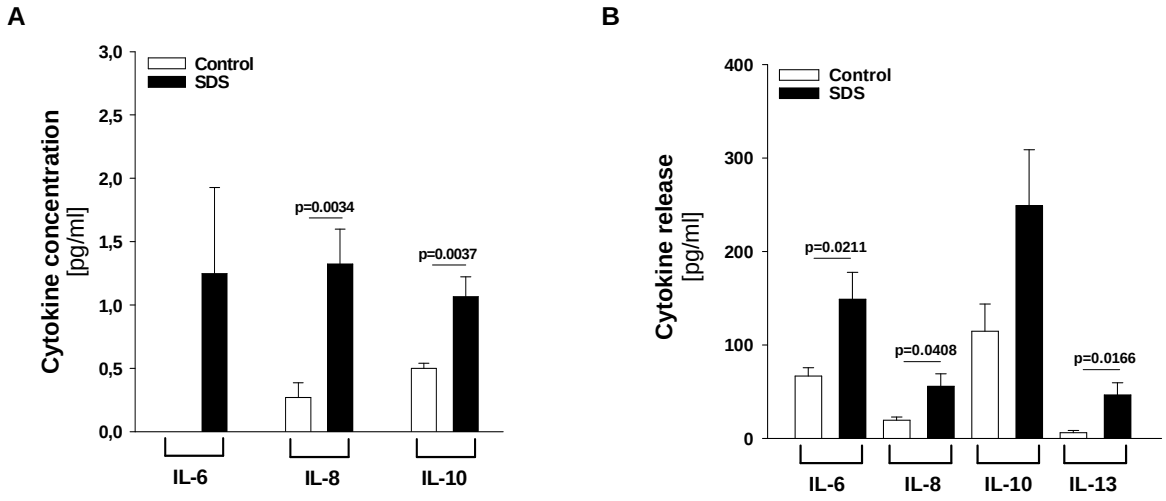

Figure 1. Cytokine expression is up-regulated in SDS patients. (A) Peripheral blood samples were collected in citrate-containing tubes and plasma samples were separated by centrifugation and analyzed by Bioplex assay. Data are mean ± SEM of 10 plasma samples obtained from 10 SDS patients carrying the 183-184TA→TC mutation performed in duplicate. (B) LCLs were incubated in the presence of 0.5% FBS for 16 hours in order to synchronize cell cycle. Subsequently, cells were incubated in complete RPMI-1640 medium supplemented with10% FBS for 24 hours. Culture supernatants were collected and analyzed by Bioplex assay. Data are mean ± SEM of 10 independent experiments performed in duplicate. Statistical analysis (p value) has been performed using Student's t test.

Part D. Experimental design and methods

Task 1. Patient recruitment.

SDS patients known to carry a nonsense mutation will be recruited during a programmed outpatient visit at the Cystic Fibrosis Center, Azienda Ospedaliero Universitaria Ospedali Riuniti, Ancona, Italy and Verona Hospital, Italy. Blood will be obtained during a routine outpatient visit as usually performed in the centre for routine blood chemistry, one additional sample (6 ml) will be obtained for the purpose of the present study. Samples and data will be obtained and used for analysis only after that informed consent will be signed according to the guidelines already approved by the local hospital IRB. A bone marrow sample (5 ml) will be obtained during programmed hospitalization. Bone marrow samples (5 ml) from healthy donors undergoing bone marrow harvest as donors for a related matched human-leukocyte-antigen transplant, will be used as healthy controls. Informed consent will be obtained according to the guidelines of the local hospital IRB.

Task 2. Analysis of SBDS protein after Ataluren treatment in SDS.

We reported that Ataluren restored SBDS protein expression in bone marrow mononuclear stem cells (MNCs) obtained from single patients carrying nonsense mutation. We need to verify these very interesting preliminary results evaluating the effect of Ataluren on SBDS expression in other bone marrow stem cell populations, including purified

CD34+ cells. Thus, we will check the expression of SBDS full-length protein in lymphoblastoid cells, bone marrow MNCs , mesenchymal stromal cells as well as in CD34+ stem cells obtained from SDS patients, using increasing doses of Ataluren for 24, 48 and 72 hours. Western blot analysis and immunofluorescence will be performed to detect SBDS expression. In all the cases the SBDS mRNA will be quantifies by droplet digital PCR (ddPCR) in order to possibly identify and stratify SDS patients exhibiting different starting SBDS levels and differentially respond to Ataluren treatment with respect to this parameter.

Task 3. Analysis of Ataluren activity on pro-inflammatory condition in SDS.
We recently reported that mTOR/STAT3 pathway is activated by IL6. Nevertheless, IL6 itself is known to be regulated by STAT3 [Wake et al., 2015]. STAT3 has been investigated in the last decade as a gene significantly associated to leukemia and lymphoma progression [O'Shea et al., 2013]. Since our hypothesis is that an autocrine loop enhancing IL6 expression might take place in SDS, we will investigate the role of mTOR/STAT3 in cytokine expression up-regulation and the effect of Ataluren on this process. Moreover, neutrophils from most SDS patients show altered IL-8 signaling [Kuijpers et al., 2005]. Thus, we will also investigate the effect of Ataluren in restoring IL-8 signaling. In order to address these issues, we will check the expression of several pro-inflammatory cytokine genes, such as IL6, IL8, IL10 and IL13 in terms of mRNA by qRT-PCR, and in terms of protein release, by ELISA and/or Luminex assays (Bio-Rad Laboratories, Hercules, CA), in bone marrow stem cells incubated in the presence or in the absence of 2.5-5 μM Ataluren for 24, 48 or 72 hours. In order to check whether Ataluren can reduce the STAT3 nuclear translocation and binding to the cytokine gene promoter region, the occupancy by STAT3 of cytokine gene promoter region will be assessed by chromatin immunoprecipitation (ChIP) Assay Kit (Upstate Biotechnology) in SDS cells incubated in the presence or in the absence of 2.5-5 μM Ataluren and confirmed by PCR analysis.

Task 3. Development of Bio-bank for SDS bone marrow CD34+ progenitors and plasma samples. No SDS CD34+ stem cellular bio-bank is currently available. The Bio-bank will be established from SDS bone marrow samples using CD34 MicroBead Kit, human (MACS Miltenyi) [Schreiber et al., 2009].

Part E. References

1. Bezzerri, V. et al. Ataluren-driven Restoration of Shwachman-Bodian-Diamond Syndrome Protein Function in Shwachman-Diamond Syndrome Bone Marrow Cells. Am. J. Hematol. (2017)
2. Bezzerri, V.et al. New insights into the Shwachman-Diamond Syndrome-related haematological disorder: hyper-activation of mTOR and STAT3 in leukocytes. Sci. Rep.6:33165 (2016)
3. Boocock, G.R. et al.Mutations in SBDS are associated with Shwachman-Diamond syndrome. Nat. Genet.33, 97-101 (2003)
4. Carapito, R.et al.Mutations in signal recognition particle SRP54 cause syndromic neutropenia with Shwachman-Diamond-like features. J.Clin. Invest.127, 4090-4103 (2017)
5. Chen, C., Liu, Y., Zheng, P. Mammalian target of rapamycin activation underlies HSC defects in autoimmune disease and inflammation in mice. J.Clin. Invest.120, 4091-4101 (2010)
6. Cipolli, M. Shwachman-Diamond syndrome: clinical phenotypes. Pancreatology1, 543-548, (2010)
7. Dhanraj, S.et al. Biallelic mutations in DNAJC21 cause Shwachman-Diamond syndrome. Blood.doi: 10.1182/blood-2016-08-735431 (2017).
8. Dror, Y., Freedman, M.H. Shwachman-Diamond syndrome: An inherited preleukemic bone marrow failure disorder with aberrant hematopoietic progenitors and faulty marrow microenvironment. Blood94, 3048-3054 (1999)
9. Dror, Y., Freedman, M.H. Shwachman-Diamond syndrome marrow cells show abnormally increased apoptosis mediated through the Fas pathway. Blood97, 3011-3016 (2001)
10. Dror, Y. et al. Immune function in patients with Shwachman-Diamond syndrome. Br. J.Haematol.114, 712-717 (2001)
11. Fabbri, E. et al. Modulation of the biological activity of microRNA-210 with peptide nucleic acids (PNAs).

ChemMedChem6, 2192-2202 (2011)
12. Hoshii, T., Matsuda, S., Hirao, A. Pleiotropic roles of mTOR complexes in haemato-lymphopoiesis and leukemogenesis. J.Biochem.156, 73-83 (2014)
13. Kuijpers, T.W. et al. 2005. Hematologic abnormalities in Shwachman Diamond syndrome: lack of genotype-phenotype relationship. Blood 106, 356-361 (2005).
14. McElroy, S.P.et al. A lack of premature termination codon read-through efficacy of PTC124 (Ataluren) in a diverse array of reporter assays.PLoSBiol.11:e1001593 (2013)
15. Mercuri, A. et al. Immunophenotypic analysis of hematopoiesis in patients suffering from Shwachman-Bodian-Diamond Syndrome. Eur.J.Haematol.95, 308-315 (2015).
16. Moosajee, M.et al. Functional rescue of REP1 following treatment with PTC124 and novel derivative PTC-414 in human choroideremia fibroblasts and the nonsense-mediated zebrafish model. Hum. Mol. Genet.25, 3416-3431 (2016)
17. O'Shea JJ, Holland SM, Staudt LM. JAKs and STATs in immunity, immunodeficiency, and cancer. N Engl J Med. 368, 161-70 (2013)
18. Peltz, S.W.et al. Ataluren as an agent for therapeutic nonsense suppression. Annu. Rev. Med. 64, 407-425 (2013)
19. Ryan NJ. Ataluren: first global approval. Drugs. 74, 709-14 (2014)
20. Schreiber TD, Steinl C, Essl M, Abele H, Geiger K, Müller CA, Aicher WK, Klein G. The integrin alpha9beta1 on hematopoietic stem and progenitor cells: involvement in cell adhesion, proliferation and differentiation. Haematologica. 94, 1493-501 (2009)
21. Wake MS, Watson CJ. STAT3 the oncogene - still eluding therapy? FEBS J. 282, 2600-11. (2015)

Part F. Relevance of the research to Shwachman-Diamond Syndrome

Ataluren is an orally bioavailable nonsense suppressor molecule which has been already approved by the European Medicines Agency (EMA) for Duchenne muscular dystrophy. The development of a personalized therapy based on Ataluren and directed against the most common SBDS mutation represents an example of drug repurposing and a novel therapeutic strategy for SDS patients.