EUROPEAN COMMISSION

7th Framework Programme for
Research, technological
Development and Demonstration

Table of contents

EUROPEAN COMMISSION

7th Framework Programme for
Research, technological
Development and Demonstration

A1: General information on the proposal

Proposal Number	620220	Proposal Acronym	Psoriasis-Treat
Project Type	PoC		

General Information

Proposal Title	Directed Evolution of Soluble IL-17A Receptor for Psoriasis Therapeutics		
Duration in months	12	Call Identifier	ERC-2013-PoC
Related ERC project ID number	201177		

Abstract (min. 100 chars, max. 2000 chars)

Protein therapeutics has increased dramatically over the last two decades and currently includes more than 130 therapeutic proteins in almost all fields of medicine. However, many proteins are not suitable for therapeutic application due to the lack of sufficient in vivo stability and biological efficacy. Thus, engineering of existing proteins for improved affinity and stability will significantly increase their potential for therapeutic applications. In recent years, the cytokine interleukin 17A (IL-17A) was identified as an important pro-inflammatory protein that plays an essential role in the progression of several autoimmune diseases including psoriasis, rheumatoid arthritis and inflammatory bowel disease. Thus, IL-17A is a promising drug target, and blocking its interactions with the endogenous IL-17RA receptor may constitute an important strategy for the treatment of common autoimmune diseases. We have recently applied protein engineering to generate decoy IL-17RA mutants with improved binding affinity and stability relative to the native soluble receptor. These variants showed promising results in inhibiting psoriasis plaque formation in a human psoriasis mouse model. Here, I propose to further develop the engineered IL-17RA for future pre-clinical and clinical development and pave the way for its commercialization. I propose to perform final lead optimization of the engineered IL-17RA variants by reducing the number of mutations while maintaining the improved characteristics of the engineered receptor. In parallel, I intend to perform detailed intellectual property (IP) and market analysis for identifying the ideal partner to promote the commercialization of the engineered IL-17RA. Further development of engineered IL-17RA and its commercialization will increase our chances for obtaining a highly efficient and a more affordable therapeutic approach for psoriasis and potentially for other common autoimmune diseases.

In order to best review your application, do you agree that the above non-confidential proposal title and abstract can be used, without disclosing your identity, when contacting potential reviewers? (●) Yes ( ) No

EUROPEAN COMMISSION

7th Framework Programme for Research, technological Development and Demonstration

The Principal Investigator - Mandatory

The following information of the Principal Investigator is used to personalise the communications to applicants and the evaluation reports. Please make sure that your personal information is accurate and please inform the ERC in case your e-mail address changes.

Family Name	Aharoni	Family Name at Birth	
First Name(s)	Amir	Gender	(•) Male ( ) Female
Title	Prof.	Country of residence	IL
Nationality	IL	Country of Birth	US
Date of Birth (DD/MM/YYYY)	19/08/1968	Town of Birth	Rochester, NY

Contact address

Current organisation name (if applicable)	Ben-Gurion University of the Negev		
Current Department/Faculty/Institute/ Laboratory name (if applicable)	Life Sciences		
Street name	Ben-Gurion Blv	Number	1
Postal Code/Cedex	84105	Town	Beer Sheva
Country	IL	Fax	+
Phone 1	+ 972 86472645	Phone 2	+
E-Mail 1	aaharoni@bgu.ac.il	E-Mail 2	

This proposal submission is in compliance with the eligibility criteria (please consult the ad-hoc Work Programme and Guide for Applicants for further details).	(•) Yes ( ) No

EUROPEAN COMMISSION

7th Framework Programme for
Research, technological
Development and Demonstration

Do you allow the ERC to disclose the evaluation results together with your name, non-confidential proposal title and abstract, proposal acronym, host institution and your contact details to the relevant national funding agency in case your proposal is recommended for funding at the end of the evaluation process (for example if requested by national funding agencies interested in funding your proposal)? In addition, for purposes related to monitoring, study and evaluation foreseen by the Ideas Work programmes, the ERCEA may need that submitted proposals be processed by third parties (Contractors and/or beneficiaries of Coordination and Support Actions. The subject and required data of the processing are identified in the Ideas Work Programmes.) in compliance with the requirements of Regulation (EC) No 45/2001 of the European Parliament and of the Council (For details, please refer to the Specific Privacy Statement on Grants published on the ERC website). Do you give your consent that the content of your proposal, including your personal data, be processed by such third parties? This consent is not requested on a compulsory base and it is only provided on a voluntary base. Refusal to give the individual consent does not affect the evaluation process.	◉ Yes ○ No
Ethical Issues Does the proposal raise any ethical issues, as specified in the Ethical Issues table at the end of Part B2?	○ Yes ◉ No

EUROPEAN COMMISSION

7th Framework Programme for Research, technological Development and Demonstration

The Authorized Legal Representative of the Host Institution

The person who can commit the Host Institution according to the requirements of the applicable ERC Model Grant Agreement (C(2007)1625, 16/04/2007).

Family Name	Rittberg
First Name(s)	Sharona
Title	Mrs
Gender	○ Male ◉ Female
Position in the Host Institution	Director, Research and Development Authority

Contact address of the Host Institution and contact person for the ERC

Organisation legal name	BEN-GURION UNIVERSITY OF THE NEGEV		
Office/Section/Department/ Faculty	Research and Development Authority		
Family Name (contact person)	Tripto	First Name (contact person)	Daphna
Street name	P.O.BOX	Number	972
Postal Code/Cedex	84105	Town	Beer-Sheva
Country	IL	Fax	+ 972 86472930
Phone1	+ 972 86472425	Phone2	+ 972 86472425
E-Mail 1	resco@bgu.ac.ill	E-Mail 2	dtripto@bgu.ac.il

EUROPEAN COMMISSION

7th Framework Programme for
Research, technological
Development and Demonstration

A2.1 Host Institution #1

BGU

Participant Identification Code	***999846222***
Legal Name	***BEN-GURION UNIVERSITY OF THE NEGEV***
Organisation short name	***BGU***

Organisation Town	BEER SHEVA	Organisation Country	IL
Department/Faculty/ Institute/Lab name	Research and Development Authority		
Department/Faculty/ Institute/Lab town	Beer-Sheva	Department/Faculty/ Institute/Lab country	IL
Internet homepage	www.bgu.ac.il		

• For further questions about the Host Institution please consult the Guide for Applicants for the Consolidator Grant 2013 call on the Participant Portal website and the Grant Agreement documentation on the ERC website.

• Please ensure that the information given for each organisation corresponds precisely to the information provided in the A1 form and the research proposal. In case of discrepancy, the data contained in this A2 form will prevail.

EUROPEAN COMMISSION

7th Framework Programme for
Research, technological
Development and Demonstration

A3. Budgets

Participant Number in this proposal	Organisation short name	Organisation country	Personnel costs (in €)	Other direct costs (excluding subcontracting) (in €)	Indirect costs (in €)	Subcontracting (in €)	Total eligible costs (in €)	Requested grant (in €)
1	BGU	IL	54800,00 €	73000,00 €	8946,00 €	13000,00 €	149746,00 €	149746,00 €
Total			54800,00 €	73000,00 €	8946,00 €	13000,00 €	149746,00 €	149746,00 €

- *Please ensure that the amount given in this form corresponds precisely to the information provided in the research proposal text (Part B section 2 c., resources section). In case of discrepancy, the data contained in this A3 form will prevail.*
- *Please ensure that all costs are given in whole Euros (integer), not thousands of Euros. All costs must be given exclusive of value added tax (VAT).*
- *Please ensure that the total requested grant does not exceed the total eligible costs.*
- *For further questions about the budget please consult the FAQs on the ERC website.*

Directed Evolution of a Soluble IL-17A Receptor for Psoriasis Therapeutics

Section 1: *The idea*

The idea to be taken to proof of concept*:** Protein therapeutics have increased dramatically over the past two decades and currently include more than 130 therapeutic proteins in almost all fields of medicine (1). Protein therapeutics offer several advantages over small-molecule drugs due to their high specificity and complex function, which cannot be mimicked by simple chemical compounds (1). However, many proteins are not suitable for therapeutic applications due to a lack of sufficient *in vivo* stability and biological efficacy. Thus, engineering existing proteins for improved affinity and stability will significantly increase their potential for therapeutic applications. In the past decade, protein engineering using directed evolution has emerged as a central approach for the generation of proteins with improved properties. By exerting a defined selection pressure on a known protein to change and to adopt a new function, directed evolution not only provides meaningful insights into enzyme substrate specificity and protein-protein interactions but also endows proteins with broad utility. Here, I propose to apply the directed evolution approach developed in my ERC SULTENG project to generate and promote the commercialization of therapeutic proteins with improved binding affinity and stability. These proteins will serve as superior drug candidates – relative to their parent wild-type (WT) proteins – and allow us to obtain more efficient and affordable therapeutic agents. Currently, the most common therapeutic proteins are antibodies that block the ligand-receptor interaction that promotes different disease states. An alternative prominent approach is to use a soluble "decoy" receptor that competes with the endogenous cell surface receptors and thereby blocks ligand-receptor interaction (2). The advantage of the latter approach is the perfect recognition between the soluble receptor and the target ligand, which can efficiently inhibit their physiological interaction (2). In the proposed project, my team will focus on the development and promotion of the commercialization of engineered soluble receptors for blocking the binding of a pro-inflammatory cytokine to its endogenous cell surface receptor. A promising target for such intervention is the binding inhibition of the pro-inflammatory cytokine interleukin 17A (IL-17A) to its endogenous IL-17 cell surface receptor (IL-17RA). In recent years, IL-17A has been identified as an important pro-inflammatory protein that plays an essential role in the progression of several autoimmune diseases, including psoriasis, rheumatoid arthritis and inflammatory bowel disease (3,4). These studies suggest that IL-17A is a promising drug target and that blocking its interaction with the endogenous IL-17RA cell surface receptor may constitute an important strategy for the therapy of a variety of autoimmune diseases. Recently, we have used directed evolution for the generation of improved decoy IL-17RA that can efficiently block IL-17A binding to its endogenous cell surface receptor (5). *Specifically, we generated improved soluble IL-17RA with* ***higher stability, IL-17A binding affinity *and* ***biological activity*** *relative to the WT receptor. The engineered IL-17RA mutants were shown to be highly efficient in inhibiting the in vivo IL-17A induced secretion of pro-inflammatory cytokines in an acute mouse model and successfully inhibited the progression of human psoriatic plaque formation in another mouse model (5). The aim of this proposal is to further develop and promote the commercialization of the engineered soluble IL-17RA for therapeutic applications. We propose to perform final lead optimization of the engineered IL-17RA towards its preparation for pre-clinical trials. In parallel, we will carry out the in-depth market and IP analyses needed for the commercialization of the engineered protein for therapeutic applications. The engineered IL-17RA can open a new avenue for obtaining an efficient and affordable therapeutic approach for treating the large number of people suffering from psoriasis and other autoimmune diseases.*

***The relationship between the idea and the related ERC-funded project*:** The underlying ERC Starting Grant – SULTENG – proposed several approaches for engineering proteins with improved functions with the aims to study basic biological processes (e.g. DNA replication) and to acquire an understanding of the fundamental principles of the broad specificity of hub proteins and enzymes. During the course of the SULTENG project, we developed directed evolution methodologies, including methods for library generation and high-throughput screening, that are currently used for basic research [e.g., to study structure-function relationships in broad-specificity proteins, including sulfotransferases and proliferating cell nuclear antigen (6-9)]. Thus, the SULTENG project facilitated the development of directed evolution methodologies that enabled the generation of a new drug candidate, the engineered IL-17RA, for the treatment of psoriasis. Interaction with BGN Technologies (BGN), the technology transfer office of Ben-Gurion University of the Negev (BGU), has highlighted the commercial potential of this approach for the development of new protein therapeutics. The proof-of-concept (PoC) project described here – paving the way for the commercialization of the engineered IL-17RA for the treatment of psoriasis – is clearly distinct from the basic research performed in SULTENG, yet is the next natural step following it.

Section 2: *Early stage innovation strategy*

(a) Description of the innovation potential: As described in the previous section, IL-17A binding to IL-17RA plays an essential role in the progression of autoimmune diseases, including psoriasis (3,4). Using directed evolution approaches, we have generated an engineered decoy IL-17RA with improved properties that can efficiently block the interaction of IL-17A with its cognate surface receptor both *in vitro* and *in vivo* (5). Our demonstration of the ability of the soluble IL-17RA receptor to inhibit the progression of psoriatic plaque formation in a human psoriasis mouse model has highlighted its potential as an effective therapeutic agent for psoriasis. The innovation potential of the engineered IL-17RA stems from its higher affinity, stability and biological activity relative to the native IL-17RA. These superior properties can lead to a significant reduction in the dose of the engineered IL-17RA that must be administered to patients, relative to the native soluble receptor, in order to achieve the desirable therapeutic effect. In addition it can lead to a reduction in the frequency of administration due to its high stability in the serum (5). Thus, we believe that the engineered soluble IL-17RA has high potential for further development through pre-clinical and clinical trials for obtaining an effective and affordable therapeutic agent for psoriasis.

***(b) Economic and/or social benefits*:** Psoriasis is one of the most prevalent autoimmune diseases; the International Psoriasis Foundation estimates that 125 million people worldwide have psoriasis, with 1.5% and 2% of the population in the UK and the USA suffering from the condition (10,11). The most common form of psoriasis, plaque psoriasis, is commonly seen as red and white scaly patches on the top layer of the epidermis. The disease is categorized into three severity levels: mild, moderate, and severe. About 30% of all patients have the moderate to severe forms of the disease. Although, in most cases, psoriasis is not a life-threatening disease, it complicates patients' lives. In the USA in 2008, nearly 60% of patients reported the disease to impose a large burden on their daily lives, with patients with moderate to severe psoriasis experiencing a larger adverse impact on their quality of life (12). Moreover, between 10-30% of the patients suffering from psoriasis also develop psoriatic arthritis, which puts an additional levy on their daily routine (13). Treatment of psoriasis ranges from local topical agents, through ultraviolet light treatment, up to systemic drugs and biologics. Patients with unresponsive moderate and/or severe psoriasis are treated with systemic drugs, which may not be effective and carry the risks of side effects. In the USA in 2008 the total direct and indirect health care costs of psoriasis were calculated at $8.6 billion annually, with work loss accounting for 40% of the cost burden (14). Approximately 60% of psoriasis patients missed an average of 26 days of work a year due to their illness.

(c) Commercialization process: The PoC project will allow us to pave the way for commercialization of the novel engineered IL-17A soluble receptor, generated in our laboratory, as a drug candidate for the treatment of psoriasis. We initially started a collaboration with Teva Pharmaceutical Industries Ltd., which led to a patent application (see below). However, due to changes in its strategic and business plan, Teva is currently transferring its rights (IPR), including development and commercialization, back to BGU. We therefore need to find alternative paths that will allow us to reach the market. Thus, the PoC project will provide us with the opportunity to perform all the essential activities that are needed for future commercialization of our invention. These activities will allow us to obtain a detailed understanding of the psoriasis market and to find partners for further development of the engineered IL-17RA through preclinical and clinical trials. Specifically, we plan to perform a detailed market analysis for understanding the market potential, for identifying the competitive advantages of our engineered IL-17RA relative to currently available treatments for psoriasis and for identifying ideal potential partners (see further details in *Plan of Activities*, section 3). When looking ahead at the ways to reach the market, we have to consider both the options of licensing to an existing company or of establishing a new company (spin-off) and their pros and cons. In the first case, we aim to license our invention and IPR to a pharma/biotech company that will further test the therapeutic effects of the engineered IL-17RA in animal models and initiate preclinical and clinical trials. For example, we recently initiated a primary contact with one of the most promising Israeli companies, Protalix Biotherapeutics Ltd., which has expressed interest in the engineered IL-17RA (see further examples in section f *Contact with industry*). However, one of the main aims of this proposal is to diversify our contacts with the industry and deepen our understanding of the market. Alternatively, should we reach the conclusion that the establishment of a start-up company is the best option to attain our goal, we are interested in identifying and contacting venture capital (VC) firms. Raising funds will be essential for the establishment of a start-up company that will develop the IL-17RA drug candidate. Such a company will also seek to apply the directed evolution approach for the development of other therapeutic proteins with improved properties. Currently, we are in contact with the Arkin Holdings VC fund for further financing the project (see letter of collaboration attached to the application). All commercialization activity will be performed in close collaboration with BGN, the technology transfer company of BGU. BGN is exclusively in charge of the

protection, management and commercial exploitation of the IP and know-how of BGU. BGN works together with BGU researchers and inventors and, when needed, with external technical and business consultants. Specifically, BGN had identified the commercialization potential of the engineered IL-17RA and is committed to managing the commercialization of this protein and assist with identifying potential partners.

(d.1) Proposed plans for technical testing (see details in section 3 *Plan of activities*)**:** We aim to test the performance of the engineered IL-17RA following lead optimization of the improved mutants for reducing the risk of eliciting an immune response following administration. Throughout the final development of the engineered IL-17A receptor as a drug candidate, we will compare the engineered mutants to the WT IL-17RA and to current drugs available on the market in different mouse models.

(d.2) Market research**:** In 2009 the global market for psoriasis therapies was valued at US$3.5 billion, with systemic therapies accounting for 74%, or $2.6 billion, of the total market (15). Biologics comprise the large majority of the systemic psoriasis therapeutics; the biologics for psoriasis market is growing and is expected to reach $6.8 billion by 2019. Currently, the biologics market is dominated by IL-12/IL23 ustekinumab (Stelara) and TNF-α antagonists, including etanercept (Enbrel), infliximab (Remicade) and adalimumab (Humira). Currently, three antibodies that target the IL-17 pathway are in clinical trials and are showing promising results; two of the antibodies, ixekisumab and secukinumab, target the IL-17A ligand, whereas one antibody, brodalumab, targets the IL-17A receptor (16). The engineered IL-17RA proposed in this project yielded very promising results in a human psoriasis mouse model (5); thus, we are confident that this protein can serve as an alternative or complementary treatment to the IL-17A antibodies and other biological treatments. We believe there is a great need for the IL-17 decoy receptor therapeutic approach due to the large number and diversity of patients that can respond differently to diverse therapeutic agents. This situation is similar to the case of the TNF-α blockers in which some of the patients respond better to the soluble TNF-α receptor, Enbrel, while others respond better to the anti-TNF-α antibodies, Remicade and Humira (17).

(d.3) IPR position and strategy**:** A worldwide PCT patent application regarding our invention entitled: "NOVEL IL-17R-ECD MUTANTS" (Publication No. WO2013/011368) was filed on 18/7/2013 claiming priority on US provisional application No. 61/509,236. The application has been filed by Teva and is currently being transferred to BGU. The application's main claims include novel compositions of mutant IL-17RA extracellular domain (ECD) peptides, isolated nucleic acid molecules encoding such mutants, as well as their use in the treatment and/or the prevention of inflammatory disorders. The application includes engineered soluble IL-17RA receptors with high affinity to IL-17A that inhibit downstream IL-17A-induced signaling events in cells. Also provided are methods of inhibiting IL-17A-induced secretion of CXCL1 and/or IL-6 in cells as well as methods for treating inflammation and/or inflammatory disorders. Regarding the patent status, no feedback from the examiner (such as a Search Report) has so far been received. However, we have conducted a preliminary search in scientific publications, in issued patents, and in published patent applications. We did not find any prior-art publication mentioning IL-17RA mutants with superior characters to the native IL-17RA having an anti-inflammatory effect or an anti-autoimmune diseases effect. We believe that we will be entitled to a patent due to our novel compositions, their non-obviousness, and their superiority over the native IL-17RA.

(d.4) Contacts with industry**:** We have established initial contacts with several pharmaceutical companies, including GlaxoSmithKline (GSK), BiolineRX and Protalix Biotherapeutics for the commercialization and further development of the IL-17RA. In addition, we formed initial contact with Arkin Holdings VC fund, which is interested in investing in the development of IL-17RA receptor and may provide financial and business support for further developing our project in the framework of establishing a spin-off company (see letter of collaboration). One of the main aims of this proposal is to expand our contacts with industry for finding the ideal partner for the development of the engineered IL-17RA toward therapeutic application and for the future application of our technology for the generation of new potent and affordable therapeutic proteins. We will start our work of contacting additional companies as soon as the market research will allow us to identify the major players in the field. The contact with companies, which will be carried out with the help of BGN, will provide the essential information needed to take a decision whether to pursue licensing or to establish a spin-off. In principle, we prefer the first option, but the feed-back from the industrial world will be crucial for the decision as to which option will be chosen.

Section 3: *The proof of concept plan*

(a) Plan of activities: Based on our successful application of directed evolution for the development of engineered IL-17RA mutants that exhibit *in vivo* activity in an acute and human psoriasis mouse model (**Fig. 1,** (5)), we will proceed with final lead optimization for the preparation of our IL-17RA drug candidate for pre-clinical and clinical trials. In parallel, we will perform detailed market and IPR analysis to identify pharmaceutical companies suitable for forming fruitful collaboration for the development of the engineered IL-17RA as therapeutic agent for psoriasis. The partnership with pharmaceutical companies or with the spin-off will allow further applications of the directed evolution approaches, developed during the ERC Starting Grant project, for the generation of other therapeutic proteins with improved functions as promising drug candidates.

***(a.1) Final lead optimization steps for IL-17RA*:** The engineered IL-17RA mutants exhibiting high binding affinity, stability and biological activity contained various mutations that led to these improved properties. In order to minimize the risk of an immune response upon administration of these proteins, we dissected the contribution of each individual mutation to the binding affinity and stability of the IL-17RA variants (5). This analysis showed that, for example, out of the 6 mutations originally found in the improved IL-17RA V3 mutant, three individual mutations do not significantly contribute to the V3 improved properties and can potentially be eliminated from this variant. In this PoC project, we will generate IL-17RA variants, based on IL-17RA V3 and V10 (5), with a smaller number of mutations. These variants will first be tested *in vitro* using the enzyme-linked immunosorbent assay (ELISA) and a cell-based assay. In addition, selected variants will be tested *in vivo* in an acute mouse model (**Fig. 1A**) and later in a psoriasis mouse model (**Fig. 1B**) in order to identify variants containing a minimal number of mutations that still maintain the characteristics of IL-17RA with improved properties. This final lead optimization step will minimize the risk of eliciting an immune response upon administration of the engineered IL-17RA, allowing us to focus on one or two variants for initiating preclinical trials. In the future, following the formation of a collaboration with a pharmaceutical company or with the new established spin-off, these variants will be produced on a large scale in accordance with the guidelines of Good Laboratory Practice (GLP) for performing safety studies as part of the preclinical development of the engineered IL-17RA.

Resources: 6 person months (Dr. Marianna Zaretsky, Dr. Itay Levine and Sivan Frilich), € 45,000 for reagents and IL-17RA mutant production in HEK293F cells, € 10,000 for testing the proteins in the acute mouse model.

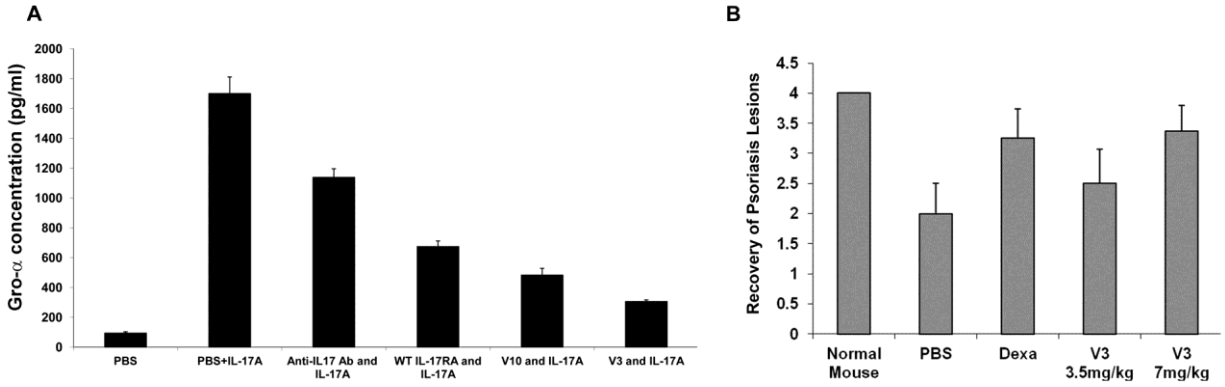

Fig. 1: *In vivo* activity of the engineered IL-17RA in inhibiting IL-17A induced cytokine secretion and promoting the recovery of psoriasis lesions in mouse model (A) The engineered IL-17RA variants V3 and V10 better inhibit IL-17A induced Gro-α secretion in mice, relative to the WT. Injection of IL-17A into groups of mice (five per group) led to a significant increase in Gro-α secretion. Pre-incubation of IL-17A with antibody against IL-17A, WT IL-17RA, V3 or V10 led to inhibition of Gro-α secretion. The antibody against IL-17A was used as a positive control for IL-17A-induced Gro-α secretion *in-vivo*. (B) The recovery of psoriasis lesions following administration of V3 IL17R variant at two concentrations. Doses were administered via subcutaneous injection twice a week for 4 weeks in the psoriasis model at concentrations of 3.5 and 7 mg/kg. The data represents the average of eight independent measurements (eight mice per group). Dexamethasone (Dexa) was used as a positive control in this experiment. For details regarding experimental conditions see (5).

(*a.2*) *Marketing study*: Market research will help to identify potential partners for further development of IL-17RA through preclinical and clinical stages. Since future investments in drug development are extremely large, this process is essential for future commercialization of our invention and enabling its development

toward clinical applications. The market analysis will allow us to map all current drugs that are used for the treatment of psoriasis and drug candidates that are in different stages of clinical development. We will then examine the advantages and weaknesses of the engineered IL-17RA relative to other drugs for psoriasis and focus on identifying the competitive advantages of our engineered receptor over other drugs. We will carefully map all companies that are active in the development of biological drugs for autoimmune diseases and identify companies that invest considerable effort in developing drugs for psoriasis. Finally, we will analyse the market size of psoriasis drugs and perform market segmentation between the companies that act in this field. Careful examination of all market analysis data will allow us to identify potential partners that we will contact for establishing collaboration for the development of the engineered IL-17RA for clinical application. The PoC project will allow us to determine the best marketing strategy more systematically. We will first do ground work in-house together with BGN to perform detailed market analysis and will then engage a consultant or a market research company to refine the analysis of the market and search for the best partner for developing the IL-17RA. The whole market research process, including in-house work, identifying the suitable consultant, defining the agreement, up to the delivery of the final market research report may take up to 6 months.

Resources: 2 person months (Specialized in business development with strong background in Life Sciences, to be determined), € 10000 for travel (to potential partners and fairs/conferences in the US and Europe for principal investigator and coworkers), and € 8000 for external consultancy.

***(a.3) Clarifying intellectual property rights*:** The initial prior art and patent landscape search conducted by BGN will be supplemented by further research to review the freedom to operate issues. Starting with an in-house analysis, we will consider engaging an external patent attorney to carry out a more detailed analysis of the patent landscape that may influence the commercialization strategy. Analysis of the IP landscape by an external consultant would help to identify any freedom to operate concerns, which would influence future claims to ensure a strong IP position. Filing of any new intellectual property, during the lead optimization step on engineered IL-17RA (e.g. with smaller number of mutations, see *plan of activities* section a.1), will be monitored and managed together with the existing IP, and would be licensed as a package to an appropriate third party.

Resources: € 5000 for external consultancy.

***(b) Project management plan*:** The management plan for the project includes a well-defined timetable based on specific milestones, which are: (i) Final IL-17RA lead optimization (months 1-5 followed by an additional 2 months of experimental analysis spread over the rest of the year for testing the receptor as part of a collaboration with pharm/biotec company), (ii) Market analysis (as described above, months 1-6), and (iii) Contact with potential partners and negotiations (months 7-12), As part of a contingency plan, in event of difficulties in the establishment a collaboration with pharma/biotech company, we will initiate collaboration with VC funds for assessing the possibility of establishing a spin-off company.

***(c) Description of the team*:** Aharoni, the PI, is a Professor at the Department of Life Sciences of BGU. The research lines of his group include protein engineering, biochemistry and molecular biology. Prof. Aharoni has so far published ~40 papers, with a large number of papers in the field of protein engineering using directed evolution.

Specifically involved in the present project will be the following individuals:

• Dr. Marianna Zaretzky has gained extensive knowledge and experience in the field of directed evolution, ELISA, mammalian expression and the establishment of cell based assays (5). She will perform the majority of experiments for the lead optimization of the IL-17RA.

• Dr. Itay Levine has an extensive background in microbiology, molecular biology and biochemistry. In particular, he has experience in large-scale expression and purification of proteins in mammalian cells and various binding assays. He will be responsible for the large-scale production and purification of the IL-17RA lead proteins following expression in mammalian cells.

• Ms. Sivan Frilich provides technical assistance with molecular biology manipulation and transfection of the IL-17RA containing plasmids to mammalian cells.

• Mr. Yuval Kupitz will perform the initial IP and market analysis. He has a MBA degree in Business Management and Industrial Chemistry and an M.Sc. in Biochemistry. He serves as Director of Applied Biotechnology at the National Institute for Biotechnology in the Negev Ltd. (NIBN), a subsidiary of BGU, and in close collaboration with BGN is responsible for the business development of applied projects. Prior to his current position, Mr. Kupitz served for 11 years as VP of Business Development Pharmaceuticals and Diagnostics IP at Hadasit Ltd., the technology transfer company of Hadassah Medical Organization.

(Section 4) The budget

a. Resources (incl. project costs)

	Cost Category	Management[1]	Other Activities	Total (in €)
Direct eligible Costs:	***Personnel:***			
	PI (25%)	4,000	22,000	26,000
	Post-Doc		10,800	10,800
	Technician		18,000	18,000
	Total Personnel:	4,000	50,800	54,800
	Other Direct Costs:			
	Equipment			0
	Consumables		55,000	55,000
	Travel		10,000	10,000
	Other		8,000	8,000
	Total Other Direct Costs:		73,000	73,000
	Total Direct Costs:	4,000	123,800	127,800
Indirect eligible Costs (overheads):	Max 7% of Direct Costs	280	8,666	8,946
Subcontracting Costs:	(No overheads)		13,000	13,000
Total eligible Costs of project:		4,280	145,466	149,746
Requested Grant:		4,280	145,466	149,746

b. Justification (description of the budget)

Personnel cost: To fund part of the salary of the PI (Dr. Amir Aharoni) who will be involved in all stages of the proposed project, of the technicians (Dr. Marianna Zaretsky and Sivan Frilich, part time) and one post-doc (Dr. Itay Levine, 30% of his time) who will perform all the experimental work that is needed for the IL-17RA lead optimization.
Management: The project management performed by Amir Aharoni, will include all parts of the PoC project including contacts with industrial partners and negotiations, detailed market analysis and IP analysis carried out by experts and meetings with potential partners.
Consumables: To purchase chemicals, biochemicals, and enzymes for use in molecular biology in order to generate and examine novel IL-17RA mutants for lead optimization. In addition, reagents are needed at a relatively large scale to facilitate the production and purification of IL-17RA in mammalian cells. Finally consumables are needed for the *in vivo* mice experiments.
Travel: To fund travel to key international conferences on the subject of autoimmune inflammatory diseases and for visiting potential partners.
Other: To fund the use of in house peptide and oligonucleotide synthesis and sequencing facilities.
Subcontracting cost: To fund market analysis and IP research activities by external consultancy.

(Section 5) Ethical and security issues

a. Ethical issues table

All FP7 funded action shall comply with the relevant national, EU and international ethics-related rules and professional codes of conduct. Where necessary, the beneficiary(ies) shall provide the responsible Commission services with a written confirmation that it has received (a) favourable opinion(s) of the relevant ethics committee(s) and, if applicable, the regulatory approval(s) of the competent national or local authority(ies) in the country in which the research is to be carried out, before beginning any Commission approved research requiring such opinions or approvals. The copy of the official approval from the relevant national or local ethics committees must also be provided to the responsible Commission services.

	Work on Human Embryo/ Foetus	**YES**	**Page**
	Does the proposed work involve human Embryos?		
	Does the proposed work involve human Foetal Tissues/ Cells?		
	Does the proposed work involve human Embryonic Stem Cells (hESCs)?		
	Does the proposed work on human Embryonic Stem Cells involve cells in culture?		
	Does the proposed work on Human Embryonic Stem Cells involve the derivation of cells from Embryos?		
	I CONFIRM THAT NONE OF THE ABOVE ISSUES APPLY TO MY PROPOSAL	X	

	Work on Humans	**YES**	**Page**
	Does the proposed work involve children?		
	Does the proposed work involve patients?		
	Does the proposed work involve persons not able to give consent?		
	Does the proposed work involve adult healthy volunteers?		

	Does the proposed work involve Human genetic material?		
	Does the proposed work involve Human biological samples?		
	Does the proposed work involve Human data collection?		
	I CONFIRM THAT NONE OF THE ABOVE ISSUES APPLY TO MY PROPOSAL	X	

	Privacy	**YES**	**Page**
	Does the proposed work involve processing of genetic information or personal data (e.g. health, sexual lifestyle, ethnicity, political opinion, religious or philosophical conviction)?		
	Does the proposed work involve tracking the location or observation of people?		
	I CONFIRM THAT NONE OF THE ABOVE ISSUES APPLY TO MY PROPOSAL	X	

	Work on Animals[1]	**YES**	**Page**
	Does the proposed proposal involve work on animals?		
	Are those animals transgenic small laboratory animals?		
	Are those animals transgenic farm animals?		
	Are those animals non-human primates?		
	Are those animals cloned farm animals?		

[1] The type of animals involved in the research that fall under the scope of the Commission's Ethical Scrutiny procedures are defined in the Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes Official Journal L 358 , 18/12/1986 p. 0001 - 0028

	I CONFIRM THAT NONE OF THE ABOVE ISSUES APPLY TO MY PROPOSAL	X	

	Work Involving non-EU Countries (ICPC Countries[2]) [3]	**YES**	**Page**
	Is the proposed work (or parts of it) going to take place in one or more of the ICPC Countries?		
	Is any material used in the work (e.g. personal data, animal and/or human tissue samples, genetic material, live animals, etc) : a) Collected in any of the ICPC countries?		
	b) Exported to any other country (including ICPC and EU Member States)?		
	I CONFIRM THAT NONE OF THE ABOVE ISSUES APPLY TO MY PROPOSAL	X	

	Dual Use	**YES**	**Page**
	Work having direct military use		
	Work having the potential for terrorist abuse		
	I CONFIRM THAT NONE OF THE ABOVE ISSUES APPLY TO MY PROPOSAL	X	

[2] In accordance with Article 12(1) of the Rules for Participation in FP7, 'International Cooperation Partner Country (ICPC) means a third country which the Commission classifies as a low-income (L), lower-middle-income (LM) or upper-middle-income (UM) country. Countries associated to the Seventh EC Framework Programme do not qualify as ICP Countries and therefore do not appear in this list.

[3] A guidance note on how to deal with ethical issues arising out of the involvement of non-EU countries is available at: ftp://ftp.cordis.europa.eu/pub/fp7/docs/developing-countries_en.pdf

References

1. Leader, B., Baca, Q. J., and Golan, D. E. (2008) *Nat Rev Drug Discov* **7**, 21-39
2. Huang, C. (2009) *Curr Opin Biotechnol* **20**, 692-699
3. Iwakura, Y., and Ishigame, H. (2006) *J Clin Invest* **116**, 1218-1222
4. Kolls, J. K., and Lindhn, A. (2004) *Immunity* **21**, 467-476
5. Zaretsky, M. et al. (2013) *Chemistry & biology* **20**, 202-211
6. Amar, D., et al. (2012) *J Mol Biol* **416**, 21-32
7. Berger, I., et al. (2011). *PLoS One* **6**, e26794
8. Fridman, Y., et al. (2010) *PLoS Biol* **8**, e1000507
9. Zamir, L., et al. (2012) et al. *Proc Natl Acad Sci U S A* **109**, E406-414
10. Gelfand, J. M., et al. (2005) *Archives of dermatology* **141**, 1537-1541
11. Schon, M. P., and Boehncke, W. H. (2005) Psoriasis. *The New England journal of medicine* **352**, 1899-1912
12. Gelfand, J. M., et al. (2004) Determinants of quality of life in patients with psoriasis: a study from the US population. *Journal of the American Academy of Dermatology* **51**, 704-708
13. Gelfand, J. M., et al. (2005) *Journal of the American Academy of Dermatology* **53**, 573
14. Horn, E. J., et al.. (2007) *Journal of the American Academy of Dermatology* **57**, 963-971
15. Reich, K., Yasothan, U., and Kirkpatrick, P. (2009) *Nat Rev Drug Discov* **8**, 355-356
16. Crow, J. M. (2012) *Nature* **492**, S58-59
17. Wiens, A., et al. (2010) *Pharmacotherapy* **30**, 339-353

ARKIN HOLDINGS

Dear Dr. Amir Aharoni

I'm writing to support your application to the ERC proof-of-concept grant and to emphasize my enthusiasm for the potential of using protein engineering for the generation of improved therapeutic proteins. Arkin Holdings fund is a family office type organization offering a distinctive combination of practical pharmaceutical knowledge, wide acquaintance with the market along with significant & proven financial capabilities.

The extensive usage and success of therapeutic proteins in the last several years highlight the large potential in further development of proteins as therapeutic agents. Directed evolution is a highly important approach for the improvement of existing proteins for better therapeutic application. Specifically, as proposed by Dr. Aharoni, the generation of soluble receptors with higher affinity and stability relative to their wild type progenitors is highly promising. The proven success of Dr. Aharoni in the development of IL-17 receptor as drug candidate for the treatment of various autoimmune diseases provides an excellent indication for the feasibility of this approach and its high potential.

We are therefore very excited about the potential of directed evolution for the generation of improved soluble receptor to block the interaction of ligands with their endogenous cell surface receptors. Therefore, we would be happy to consider significant investment and fruitful partnership on engineered soluble receptor as drug candidates for the development of novel therapeutic. The proof-of-concept studies proposed in this application will allow the generation of an early drug candidates providing new valuable IP and can pave the way for future collaboration for the development of these drug candidates as therapeutic proteins.

Best Regards,

Pini Orbach, Ph.D

Head of Pharma, Arkin Holdings Ltd.

Life Plaza, 6 Ha'choshlim St. Herzliya 46724 Israel | Tel: 972.9.788.3333 | Fax: 972.9.957.9165

Annex 1: Commitment of the host institution

Commitment of the host institution

The **Ben Gurion University of the Negev,** which is the ***applicant legal entity***, confirms its intention to engage **Prof. Amir AHARONI**, throughout the duration of the grant, should the proposal entitled **Psoriasis-Treat : Directed Evolution of Soluble IL-17A Receptor for Psoriasis Therapeutics,** be retained.

Performance obligations of the applicant legal entity that will become the beneficiary of the grant agreement, should the proposal be retained and the preparation of the grant agreement be successfully concluded:

The *applicant legal entity* commits itself to:

a) Ensure that the work will be performed under the guidance of the *principal Investigator*.

b) Carry out the work to be performed, as it will be identified in Annex I of the ERC Grant Agreement, taking into consideration the specific role of the *principal Investigator*.

For the institution:

Ben Gurion University of the Negev

Mrs. Sharona Rittberg, Director

Research and Development Authority

Email: resco@bgu.ac.il

Date: April 22, 2013

Research & Development Authority
Ben-Gurion University of the Negev

Stamp of institution (applicant legal entity)

This electronic receipt is a digitally signed version of the document submitted by your organisation. Both the content of the document and a set of metadata have been digitally sealed.

This digital signature mechanism, using a public-private key pair mechanism, uniquely binds this eReceipt to the modules of the Participant Portal of the European Commission, to the transaction for which it was generated and ensures its full integrity. Therefore a complete digitally signed trail of the transaction is available both for your organisation and for the issuer of the eReceipt.

Any attempt to modify the content will lead to a break of the integrity of the electronic signature, which can be verified at any time by clicking on the eReceipt validation symbol.

More info about eReceipts can be found in the FAQ page of the Participant Portal. (http://ec.europa.eu/research/participants/portal/page/faq)