UCL GOS ICH TRAVEL AWARD

REPORT FORM

Student's name:	Gaetano Naso
PhD Project title:	CRISPR/Cas9 genome editing of Recessive Dystrophic Epidermolysis Bullosa mutation hotspot
Primary Supervisor:	Waseem Qasim

Conference Title:

Cold Spring Harbor meeting: Genome Engineering Frontiers of CRISPR/Cas

Dates of Travel:

10-13/10/2019

Venue/Location:

Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, USA

For most PhD research students, presenting a poster is an excellent way to showcase your original work at conferences and meetings. It is not just a self-estimation of your research but a priceless opportunity to engage in valuable discussions with current and future international leaders in the field which might help to advance your project further. Unlike oral presentations, the audience is not static and questions could be very specific thus, having a 360 degree knowledge of your project is essential. The specific importance of attending this meeting was to foster creative ideas and have fruitful discussions with other researchers interested in applying state-of-the-art genome engineering tools in human cells.

The aim of my research project as well as my poster is to investigate the potential of developing a robust and precise CRISPR/Cas9 mediated gene editing platform for a rare skin disease called dystrophic epidermolysis bullosa (DEB). Due to the aggressive systemic nature of the disease, the use of patient skin cells are limited. However, DEB induced pluripotent stem (iPSCs) cells can be generated and CRISPR/Cas9-mediated genome correction can be applied to "edit and correct" or to change a single DNA base in a targeted way. Genome-edited patient-derived iPSCs can be differentiated into keratinocytes providing the opportunity to develop novel personalized treatment options.

Epidermolysis bullosa (EB) is a group of rare debilitating genetic disorders which primarily affects the skin. Painful blisters and erosions can develop on any part of the body, even after simple rubbing or friction of the skin. Dystopic EB (DEB) is one of the most life-threatening forms of EB and is caused by mutations within the *COL7A1* gene. DEB children have a very high risk of developing aggressive life-threatening skin cancers by young adulthood. No effective cure is currently available and treatment is restricted to wound care and pain management.

CRISPR/Cas9 (Clustered Regularly Interspaced Palindromic Repeats) is a molecular tool able to tweak the genome by removing, adding or altering sections of the DNA sequence. The technique can be compared to the "find and replace" function in Microsoft Word (ctrl-F) alongside its ability to cut (Ctrl-C) and edit (Ctrl-V) the target DNA sequence, thus re-write the genetic code.

Induced pluripotent stem cells are adult cells that, upon treatment with specific transcription factors, revert back to their de-differentiated stem cell state. As embryonic stem cells, iPSCs have the intrinsic potential to propagate indefinitely (self-renewal) as well as the ability to differentiate *in vitro* into relevant cell types providing the opportunity to develop personalized treatment or to be used for disease modelling when patient's cells are not available. Nowadays, a combination of CRISPR/Cas gene editing and iPSCs helps researchers to identify the specific genes that contribute to a particular biological function or revert a disease mutation back to the wild type.

Genome editing has the potential to treat and cure intractable and rare disorders, providing a precise and personalized therapy for all patients. In the last decade, gene editing mediated therapies, using molecular tools that are able to knockout and/or replace mutated genes with functional versions, have been described and developed for pre-clinical and clinical applications. A pioneering example of one such breakthrough has been reported at Great Ormond Street Hospital (GOSH), in collaboration with the Institute of Child Health, for the treatment of childhood leukaemia. Despite their incredible potential, a full clinical application of these gene-editing tools is still challenging. In particular, efforts must be made in order to make these molecular editors as precise as possible thus minimizing the chance of off-target effects in the human genome.

I have over 6 years of experience working within gene editing with my first traineeship at the University of Modena, Italy, where I worked on the development of gene editing strategies for corneal and skin diseases. Throughout my years of working within gene editing, my passion in this field has not changed and has continued to grow. In fact, countless ground-breaking gene editing–based applications have emerged over the past 10 years making genome engineering a novel milestone in cell and gene therapy settings. What excites me most about genome editing is its tangible potential to develop safe and precise gene editing platforms to treat life-threating diseases. Moreover, advances in CRISPR/Cas9 gene editing approaches to “edit and correct” or to change a single DNA base in a targeted way have shown promising broad applications in human health spanning from diagnostic to clinical applications.

In this direction, I would like to purse my career in the development and application of novel gene editing tools and make my contribution to find a cure for those diseases with unmet clinical need.