MARIE CURIE ITN Celleurope

Developing a future of entrepreneurial researchers

Our Newsletter is launched!

Issue 1, January 2015

Welcome to the first edition of our project newsletter

Firstly, we would like to wish you a Happy New Year for 2015! We hope you had a wonderful holiday season and send our best wishes for the year ahead.

This newsletter is intended to keep you up to date about our project activities and focus on current research in the field.

In this issue, we will highlight 3 of our research projects in summarising current scientific literature, we will put one of our Marie Curie Fellows in the spotlight and hear about an exciting secondment experience in Paris.

We hope you enjoy!

News...

CONGRATULATIONS to Monica Reis (ESR9 Newcastle) for securing BioLegend's Travel Award. Monica will use this money to attend the ISCT conference, taking place 27th to 30th May 2015. Monica is currently preparing her ISCT abstract for submission.

Some of our fellows have submitted abstracts for EBMT 2015 which will take place in Istanbul in March 2015. This is an exciting time for CELLEUROPE, potentially the results from the past 2 years of the project will be published for the first time.

We wish all the fellows the best of luck with their submissions!

The group is looking forward to meeting up in Munich this month for the next consortium meeting.

We have been busy revising some of the content on our website and introducing Twitter to the project.

The project also now has a research blog that the fellows have been populating.

Happy Reading!

Next Workshop

Risk Factors in HSCT

Where

EBMT Venue, Istanbul

When

Saturday 21st March 2015

Issue 2 of the newsletter will be released May 2015. In the meantime remember to stay connected and keep track of the project activities!

Adoptive T cell therapy on the cusp…

Michael Lutteropp ER3, Miltenyi Biotech

Anti-cancer therapy with adoptively transferred T cells is becoming a clinical reality. However, multifaceted challenges have to be overcome before more than small numbers of patients with specific diseases can benefit.

One very promising T cell therapy approach involves the equipment of T cells with a chimeric antigen receptor (CAR) enabling recognition of virtually any cell surface structure. Clinical studies with CARs directed towards CD19, a surface antigen present on various lymphoid leukaemias, have shown exceptional anti-tumour responses [1-3]. Such CARs, now considered a breakthrough therapy by the US food and drug administration (FDA), have recently left behind the academic research environment and are being driven to market by the pharmaceutical industry.

Although clinical outcomes for CD19 CARs have been remarkable, application of CAR T cell therapy to other leukaemias or even solid tumours is complex. CARs have to be optimised for every new target, with function depending on multiple parameters such as affinity and design of the CAR or structure and expression level of the antigen. The biggest challenge, however, remains the identification of targets present exclusively on tumour tissue. This is highlighted by reports describing lethal off-tumour toxicity due to unexpected target expression in other body tissues [4-6].

Therefore our research not only focuses on the search for novel target antigens but includes the development of alternative CAR T cell therapy approaches. One important aspect is the utilization of safety mechanisms allowing the switch-off or depletion of CAR T cells in the event of CAR related toxicity [7, 8].Equally exciting are strategies that combine activating and inhibitory CARs to direct killing towards cells with particular antigen expression signatures. Replacement of haematopoietic cells after depletion of CAR T cells might also be a feasible option in some circumstances [9].

Finally, to transform CAR T cell therapy into a standard treatment option a whole new infrastructure has to be created. Current CAR T cell production is performed at few sites, high costs and requires highly skilled personal, restricting it to small scale clinical trials within a research setting. Large scale application requires automated cell manufacturing processes, that can be operated by technical personal at multiple centres and at reduced costs. Last but not least such processes must create final products that meet quality standards approved by the relevant authorities.

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GvL effects of NK cells against leukaemia cell lines

Shuang Li ESR6, Charles University Prague

After allogeneic hematopoietic stem cell transplantation (HSCT) natural killer (NK) cells mediate graft versus leukemia (GVL) effects by the production of inflammatory cytokines and by direct target lysis. The receptors of NK cells rely on recognition of major histocompatibility complex class I or class-I-related molecules. So NK cells may have the potential to initiate the GvL effect.

NK cells express both activatory and inhibitory receptors and the access of stimulatory signals triggers NK cell-mediated elimination of leukemia cells. The affinity of inhibitory receptors is stronger than activatory receptors. Leukemia cells often have a reduced expression or loss of HLA class I alleles and become susceptible to NK cell lysis.(Figure 1)[1] In haploidentical HSCT the donors take advantage of anti-leukemic activity of NK cells. NK cells are inhibited by cross-reactive groups of self-HLA-antigens via an inhibitory killer immunoglobulin-like receptor.[2] In the case of the patients' cells expressing antigens of a different group from the donor, the transplanted NK cells are not inhibited and exert strong GvL effect. Although the interaction of inhibitory NK cell receptors with HLA class I molecules controls the NK cell activation, the activating signal is also needed. Some studies indicate that acute and chronic leukemia cells could modulate NK cell activity by secreting soluble and exosomal ligands for NK cell receptors.[3] So the up-regulation of NK activatory receptors can induce NK cell mediated elimination of leukemia cells. It is generally accepted that IL-2 induces the expression of the activatory NKp44 receptor on NK cells.[4] IL-2, IL-15 and IL-18 have been shown to increase the expression of activatory NKG2D receptor.[5,6] But IL-15 can also stimulate the inhibitory CD94/NKG2A and KIR2DL2/3 receptors.[6] So cytokines can also increase the inhibitory signals that counterbalance NK cell activation.

Previous studies showed that the addition of cytokines has the capacity to increase NK cell proliferation and cytotoxicity. IL-15 plays an important role in the survival of NK cells, and it can increase the number of NK cells and contributes to the faster immune reconstitution after transplantation.[7] IL-2 and IL-18 induce IFN-gama production in NK cells.[8] Finally, it has been shown that combinations of low dose cytokines are associated with a synergistic anti-tumor effect and lower toxicity and hence could be used as an immuno therapy for treatment of leukemia.

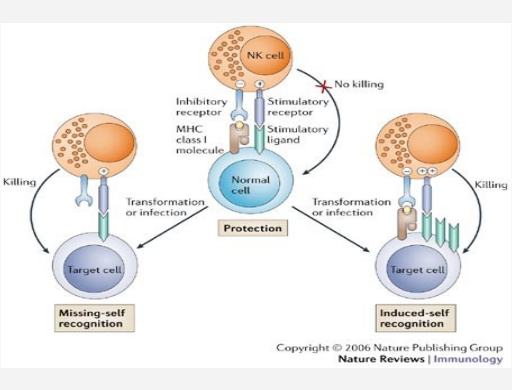

Figure 1

Normal target cells are protected from killing by natural killer (NK) cells when signals delivered by stimulatory ligands are balanced by inhibitory signals delivered by self MHC class I molecules. If, however, a target cell loses expression of self MHC class I molecules (as a result of transformation or infection), then the stimulatory signals delivered by the target cell are unopposed, resulting in NK-cell activation and target-cell lysis (known as missing-self recognition). Transformation or infection might also induce expression of stimulatory ligands such that constitutive inhibition delivered by inhibitory receptors is overcome (known as induced-self recognition). In many contexts, it is probable that both missing-self and induced-self recognition operate simultaneously to provide NK cells with the maximal ability to discriminate between normal cells and transformed or infected target cells.(David H Raulet , Russell E Vance. Self-tolerance of natural killer cells.)

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Fellow in the spotlight!

In this issue, we are talking to Rihab Gam from Newcastle University to learn a little more about her….

About me:
I am 26 years old, from Monastir Tunisia.

Where I live:
I live in Fenham close to the University with fellow Celleurope ESR Monica Reis and an IT professional who works for British Airways. We all get on very well.

Start date and current position with Newcastle:
I started at Newcastle on 9th September 2013 as an Early Stage Researcher.

What I like best about working and living in Newcastle:
What I like best about working in Newcastle, is the fact that Newcastle University really encourages engagement with their students. There are so many workshops and courses to attend constantly, and I feel like I am up to date with not only what is going on in my Institute, but the Medical Faculty and the University as a whole too.

About living in the city, I love the product returns policy here in the UK and in Newcastle! I have for the first time in my life, the freedom to 'try and buy' in the knowledge that I can return for a full refund. The only problem is everything seems to close at 5pm, I wish they would stay open longer!

Best job:
This is my first proper job and the first time actually away from home. One of the best training experiences I had in Monastir Hospital was in the Pathology department. I really enjoyed the patient slide analysis assessing for disease (cytology). I found it an emotional experience at first, especially if a slide was positively graded, but it was good nonetheless.

Rihab Gam in the Haematological Sciences Laboratory —October 2014

Worst job:
The worst training experience I have encountered was in the same hospital, for cytology of parasites. The microscopy was very interesting but the smell was horrible and like nothing I want to experience again!

What would you like the project members to know about you?
I am a really keen social networker and really see the value of spreading your research online. I am eager to connect with you ALL! And others in the field, other scientists, members of the public who want to learn more!

Motto or Personal Mantra:
Dream It. Build It. Live It. It was after I heard a Professor in a Toxicology lesson at my University back in 2010 talking about making your dreams big that I had the idea to go and study abroad. Now I am here and have the Professor to thank for this.

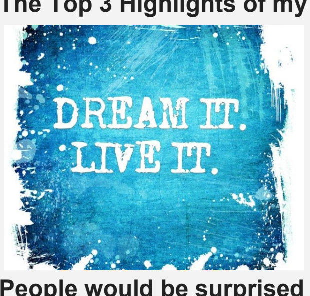
I'm happiest when:
I have significant p values when doing my stats!! And when I am shopping for my family to take home gifts!

What I fear most:
The dark. I even sleep with the lights on and I don't know why I am so scared of it.

I'm proudest of:
Making my parents proud of me.

Favorite sports or pastimes:
I love swimming, I swim all the time in Tunisia. I also love social networking, particularly updating my Facebook Biotechnology page 'Ryhab Biotech" where I showcase the latest news in science and make it accessible for all audiences.

The Top 3 Highlights of my Life:



Getting my driving license, being accepted for the Marie Curie position and it's not a highlight as such, but I learnt a lot from the passing of my grandparents.

People would be surprised to know:
..that I am a runner! I am trying to run anyway because I have always hated it and the competitor in me is trying to overcome this dislike for running. I also want to be healthy so I am running 12KM a week, as a challenge to myself.

Before I die, I would like to:
..win a Noble Prize and live in Japan for a while.

Most interesting/ surprising thing you have done since beginning the project
The secondment to Regensburg has been the most interesting and rewarding time so far, because it was such a great opportunity to learn and meet lots of new, interesting people. The most surprising thing has been handling so much Blood on a daily basis!! I guess it is to be expected within Academic Haematology but I naively thought that as my project is Genetics/DNA and molecular biology I would be more shielded from it, as I don't really like blood!

If I could do it all over again, I would:.
..not change anything, because life is not for regrets.

In our next issue we are talking to the director of a spin out business. How did they find success? Don't miss it!

Current controversies in virus specific T cell allo-reactivity...

Marsela Qesari ER2, Alcyomics Ltd

Adoptive virus specific T cells have been used to treat human leukocyte antigen (HLA) matched and mismatched transplantation recipients to reconstitute cellular immunity and reduce the severity of viral disease with an apparent lack of graft versus host disease (GvHD)[1, 2, 3]. The transfer of virus-specific T cells directly after isolation has been demonstrated to restore antiviral immunoreactivity by further in vivo expansion and by persisting in the recipient for a long period[4]. Controversially, in vitro investigations have demonstrated that HLA-mismatched virus- specific T cells cross-react against non self HLA molecules suggesting a potential risk of GvHD and solid organ rejection[5, 6]. Amir et al demonstrated in vitro that virus (EBV, CMV, VTZ and influenza virus) specific T cells (both CD4+ and CD8+) were cross-reactive against allo-HLA-molecules. From a large panel of virus specific T cells tested, this study showed that 80% of virus specific T cell lines and 45% of T cell clones exerted allo-HLA-reactivity. This was determined by IFN-ϒ secretion after co-incubation with a panel of HLA-typed target cells. Similar results have been demonstrated by another study where infused EBV-specific T cell lines were tested for potential allo-reactivity. However, the in vitro data did not support the in vivo outcome since the recipients of the tested T cell lines lacked clinical evidence of GvHD suggesting the absence of correlation between in vitro alloreactivity and the risk of developing GvHD[7]. Moreover the evaluation of in vitro alloreactivity has highlighted tissue specificity or rather the capacity of virus specific T cells to cross-react with other cell types expressing relevant allogeneic HLA alleles, such as endothelial cells[5, 8], CD40L activated B cells, phytohemagglutinin blasts or dendritic cells[6]. The cross-reactive capacity of virus specific T cells has been further supported by evidence that virus reactivation is correlated with a reduced donor chimerism after allogeneic stem cell transplantation[9] and the promotion of solid organ rejection[10].

In conclusion, virus specific T cell therapy remains an alternative approach to control virus reactivation in transplant patients refractory to conventional anti-viral drugs. Despite the promising results in small clinical trials, the safety of virus specific T cells has not yet been elucidated.

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A French scientific adventure!

Monica Reis ESR9, Newcastle University

In August 2014, I had the opportunity to work as an intern at Thery's laboratory at INSERM, Institut Curie in Paris. The goal of this internship was to learn how to isolate and characterize extracellular vesicles (ECV) isolated from cell culture.

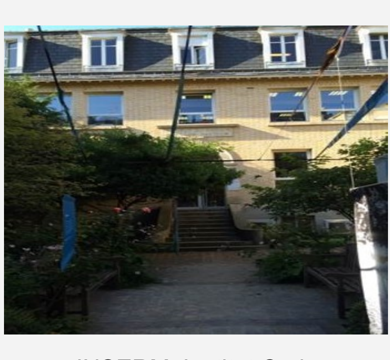
"This opportunity was made possible by a fellowship sponsored by Newcastle University's Institutional Strategic Support Fund (ISSF), funded by the Welcome trust."

My main research goal in my PhD project is to test the immunomodulatory capacity of mesenchymal stromal cells for future application in cellular therapy for the treatment of graft-versus-host-disease. While researching the literature I came across studies describing the immunomodulatory properties of MSC-derived exosomes and decided to explore this new field in my project. However, given this field's novelty, I was faced with many challenges when planning my experiments. It didn't take long until I realized that most exosome isolation protocols were based on the protocol published in 2006 by Clotilde Thery's group whose main focus is the study of ECVs secreted by tumour and immune cells and their role in immune responses relevant to potential clinical applications. Driven by the motivation to learn these techniques, I contacted Dr. Thery in Paris requesting an opportunity to learn in her laboratory.

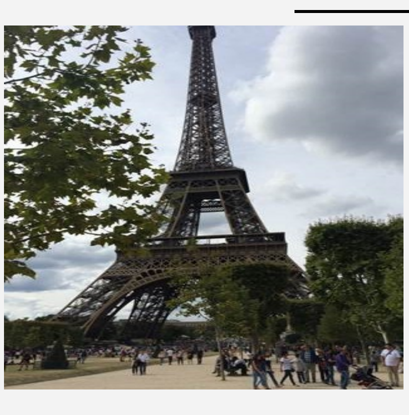
"I was welcomed by a multicultural group of people, comprised of PhD and Post-docs."

During my time at Thery's laboratory, I was able to learn in detail the protocol for ECV isolation and characterization which allowed me to set up a detailed experimental plan for my project at Newcastle University. Institut Curie is a leading medical, biological and biophysical research centre, located at the facilities given by the University of Paris to Marie Curie. Situated in central of Paris, the Campus is composed of picturesque buildings surrounded by trees and flowers. While the underlying research conduct stayed constant, the people, culture and atmosphere changed. I found myself in a very connected lab, that took the time to eat lunch together every day and provided support for each other as friends and scientists.

Life outside the lab was equally enjoyable. Paris is a cosmopolitan city which possesses a great number of historical touristic attractions that captivate people from all over the world. It was very rewarding to be a tourist in Paris and experience attractions such as, The Louvre and the Eiffel Tour. I also took the time to experience the Parisian lifestyle by walking by the Seine and through the narrow Parisian streets, and sitting at Cafés leisurely reading a book and eating amazing French delicacies. Life in Paris is indeed a "Cliché" that I was able to experience while also improving my research skills.



INSERM, Institut Curie



Eiffel Tower in Summer

A visit to Sacre Coeur!

I am looking forward to my next CELLEUROPE secondment experience in Germany, with Associate Partner Miltenyi Biotech!