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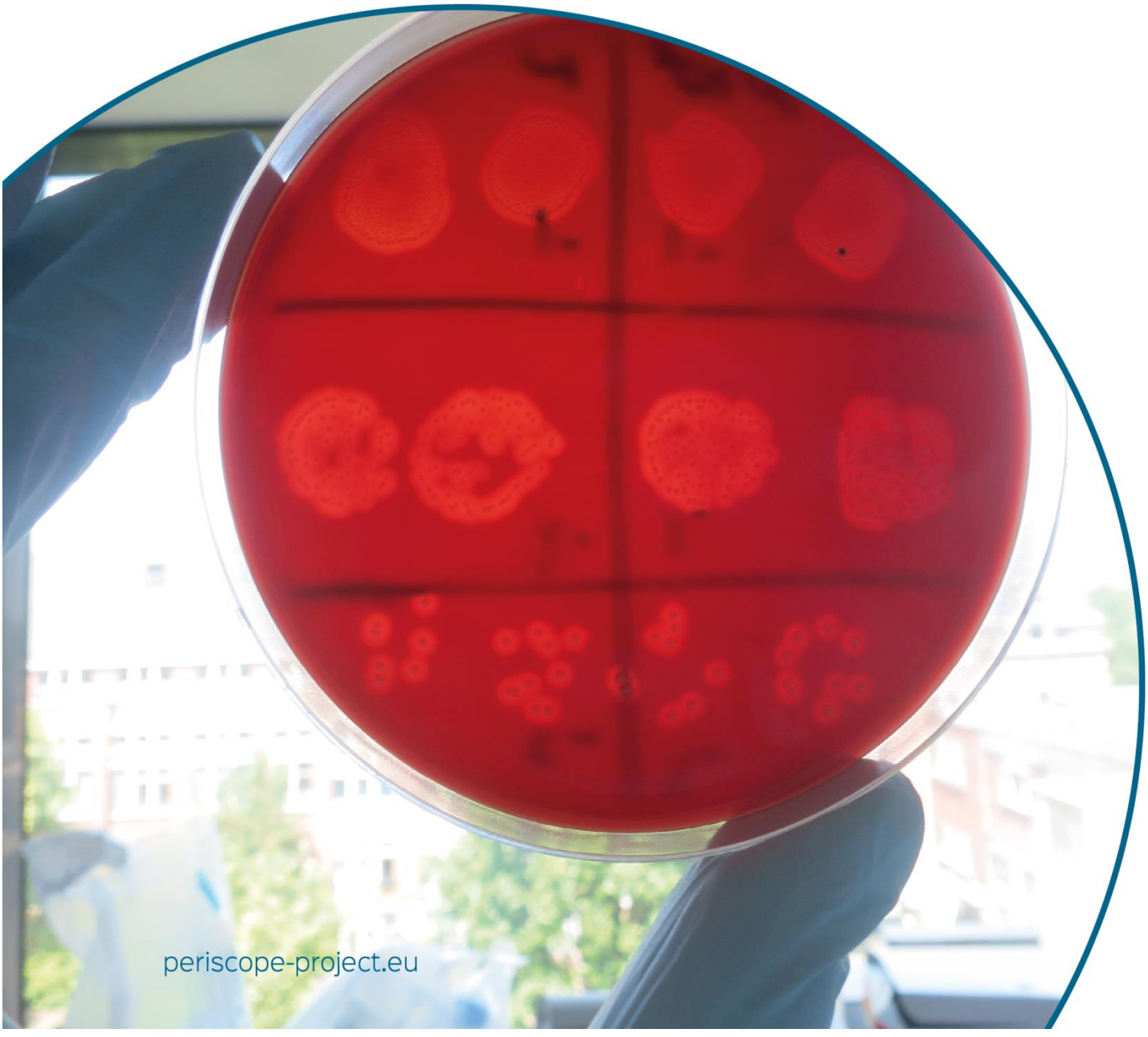
Newsletter Issue 8 - June 2020



periscope-project.eu

Editorial

Dear colleagues and followers of the PERISCOPE Newsletters,

Whilst Europe is slowly easing the COVID-19 lockdown, its impact on PERISCOPE is becoming clearer. Many of the partners in PERISCOPE have been at the forefront of the fight against COVID-19 and both public and EFPIA partners have taken up the challenge to develop vaccines against COVID-19. During the past months, national public health institutes have made a huge effort to bring the coronavirus outbreak under control. Due to their essential role in patient care, academic hospitals have had to stop regular PERISCOPE research activities and put enrolment for clinical studies on hold. It is highly motivating and humbling to see the PERISCOPE partners take up their social responsibility with regards to COVID-19.

This has truly been a challenging time for all partners. Significant efforts were made to mitigate the impact of COVID-19 on PERISCOPE, with activities being redirected towards data analysis as much as possible. Now that the first wave is receding, most partners are preparing to resume PERISCOPE research activities. Some of the partners' laboratories have re-opened and clinical study investigators are preparing to continue enrolment or have even already resumed enrolment.

With PERISCOPE activities now slowly resuming, the true impact of COVID-19 remains to be determined. Nonetheless, I feel confident that PERISCOPE is very well-positioned for these challenges and that we will successfully deliver on our overall objective: to have an impact on pertussis.

Dimitri Diavatopoulos, Radboudumc (NL),
Work Package Leader

Facts

The PERISCOPE consortium unites internationally renowned experts in the largest public-private partnership in Pertussis Vaccine Research in Europe. It was launched in March 2016 receiving support from the Innovative Medicines Initiative (IMI), a joint undertaking of the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA). Additionally, PERISCOPE is the first IMI project to receive funding from the Bill & Melinda Gates Foundation (BMGF). The participating experts combine many years of experience in *Bordetella pertussis* (Bp) research, clinical trials, bioinformatics, immunology and public health.

Acronym:	PERISCOPE
Full title:	PERtussIS COrrelates of Protection Europe
Call Topic:	IMI2-2015-03-05 - Vaccines
Contract N°:	115910
Duration:	60 months (01/03/2016 -28/02/2021)
Funding:	28.000.000 €
Partners:	22
Website:	www.periscope-project.eu.

PERISCOPE has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115910.
This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA and BMGF.

PERISCOPE featured as success story by IMI !

PERISCOPE has received a special mention from IMI and stood out among 101 ongoing IMI projects.

A short overview of the project was published under the title *New tools and trials combat the resurgence of whooping cough*. https://www.imi.europa.eu/projects-results/success-stories-projects

Bravo PERISCOPE – Way to go!

Objectives of the PERISCOPE project

The PERISCOPE consortium seeks to create an environment conducive to the development of a new generation of pertussis vaccines by facilitating collaboration between Pertussis stakeholders, particularly from vaccines manufacturing and the academic and public research communities in Europe.

The key objective of the project is to gain a better understanding of the immune mechanisms needed to ensure long lasting immunity to Pertussis in humans. This will be achieved by investigating of the immune response generated by infection and colonization of *Bordetella pertussis* and comparing the immune response to whole-cell and acellular Pertussis vaccines in humans and preclinical models. To achieve this goal, the consortium aims to develop an extensive toolbox of bioassays to apply in vaccination studies in Europe and the Gambia. It is expected that the data generated will ultimately allow the vaccine-R&D community to define an ideal immunological profile or signature that vaccines need to generate to ensure durable protection against Pertussis infection and disease in humans.

What opportunities does PERISCOPE offer young scientists ?

Education of young scientists in vaccinology, especially targeting pertussis, and in the use of state-of-the-art technological tools to discover biomarkers of protection is an important priority for the PERISCOPE consortium. Many training courses (e.g. workshops on specific assays, EuroFlow training courses) have been and continue to be organized by PERISCOPE members

We asked Joshua Gillard, a junior scientist involved in the project from the beginning, what opportunities the PERISCOPE consortium offered him to develop his expertize and network.

“I relocated from Montreal to the Netherlands in late 2016 and joined PERISCOPE as a PhD student at the Radboud University Medical Center under the direct supervision of Dimitri Diavatopoulos. The framework established by PERISCOPE has provided a truly awesome combination of research questions, clinical study designs, and technology platforms for studying pertussis and pertussis vaccines. The high degree of collaboration, which spans academia and industry, and the multidisciplinary nature of the consortium, have altogether created an exciting and

unique training experience. As a young researcher, I am grateful for the opportunities that this training has opened, enabling me to conduct systems-level immunology research for deconvoluting human innate immune responses.

Embedded within an international team of researchers, I have been able to draw upon the expertise and resources of our collaborators to focus experimental and computational methods on the immune response to pertussis booster vaccination. I helped establish the EUROFLOW experimental workflows outlined within PERISCOPE, which enabled single-cell sorting for transcriptomics analysis. I was able to use the cells to establish a computational pipeline for single-cell RNA sequencing (scRNA-seq) and ultimately highlight a vaccine-associated transcriptional signature in monocytes and dendritic cells. Mass cytometry (CyTOF) enables a data-driven, functional analysis of immune cells and within PERISCOPE this capacity was provided by our collaborators at the CHUV in Lausanne. My trips to Lausanne, including a work visit, have been essential for learning and implementing a standard computational pipeline for exploring CyTOF data. Together, we identified a common pattern of cytokine secretion in monocytes and dendritic cells that is line with our scRNA-seq analysis.

I believe that controlled human infection trials represent the frontier for studying processes of infection and immunity. In collaboration with the University Hospital of Southampton and the CMBI at the Radboudumc, I have had the opportunity to study the immune response to the first-ever experimental human infection with pertussis. Integration of multiple data types (cytokine production, RNA sequencing, antibody responses, etc.) poses a real data analysis challenge, for which it was essential that I build expertise in applied statistics.

The ambitious goals of PERISCOPE have presented me with many challenges that are shaping my development into a broadly knowledgeable scientist. My exposure to the diversity of research interests within pertussis research has also been enriching and have contributed to a more holistic view on the disease and its complexity. Taken together, I believe that these opportunities are paving the way toward a promising future career."

Highlights from some recent publications from the PERISCOPE consortium


frontiers in Microbiology

METHODS
published: 23 April 2020
doi: 10.3389/fmicb.2020.00777

Development and Standardization of a High-Throughput *Bordetella pertussis* Growth-Inhibition Assay

Anaïs Thiriard, Dominique Raze and Camille Locht*

One mechanism that may be important for the control pertussis is the induction of antibodies that are able to kill *B. pertussis* or to prevent its growth. The team of Camille Locht at the Institut Pasteur de Lille, France, has established here a *Bordetella* growth inhibition assay (BGIA) that is able to measure the potential of compounds or antibodies to prevent growth in the presence or absence of complement. This assay is based on the measurement of ATP produced by live bacteria, using a luminescence-based read-out. The BGIA is scalable, rapid and adaptable for high-throughput studies on essentially any *B. pertussis* strain. A strong correlation between luminescence and colony-forming units was found and the BGIA showed high sensitivity and reproducibility. The BGIA can thus effectively be implemented for large-scale serum studies to further investigate anti-

B. pertussis immune responses at a functional level.

Link to the publication: https://www.frontiersin.org/articles/10.3389/fmicb.2020.00777/full

PLOS ONE

RESEARCH ARTICLE

A qPCR assay for *Bordetella pertussis* cells that enumerates both live and dead bacteria

Stacy Ramkissoon[1,2], Iain MacArthur[1,2], Muktar Ibrahim[3,4,5,6], Hans de Graaf[3,4,5,6], Robert C. Read[3,4,5,6], Andrew Preston[1,2]*

In some studies such as the human challenge model developed within PERISCOPE it is very useful to not only confirm that the volunteers have *B. pertussis* in their respiratory tract following infection, but the relative numbers of the bacteria that are alive and dead, to follow the dynamics of bacterial growth and the effectiveness of immune responses in killing the bacteria.

To reach this objective, Andrew Preston and his colleagues from the University of Bath, UK, modified the standard PCR diagnostic assay for *B. pertussis*, to enable it to distinguish it between live and dead bacteria. They use a chemical that is able to enter only dead cells and modify the bacterial DNA such that it is not detected by PCR. They split samples into two portions and modify one portion in this way. Running this sample using PCR detects only the live bacteria, whereas the untreated sample allows detection of both live and dead. Comparing the results of the two samples allows calculation of the relative proportions of live and dead.

They apply this approach to the monitoring of colonisation volunteers, the growth of bacteria within their respiratory tracts and the gradual clearance of bacteria as the immune response develops.

Link to the publication: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0232334

vaccines MDPI

Article

Uncovering Distinct Primary Vaccination-Dependent Profiles in Human *Bordetella pertussis* Specific CD4+ T-Cell Responses Using a Novel Whole Blood Assay

Eleonora E. Lambert [1], Véronique Corbière [2], Jacqueline A. M. van Gaans-van den Brink [1], Maxime Duijst [1], Prashanna Balaji Venkatasubramanian [3], Elles Simonetti [4], Martijn Huynen [3], Dimitri D. Diavatopoulos [4], Pauline Versteegen [1], Guy A. M. Berbers [1], Françoise Mascart [2] and Cécile A. C. M. van Els [1,*]

The team led by Cecile van Els, RIVM, The Netherlands, has developed together with PERISCOPE partners (ULB and Radboudumc) a whole blood assay to evaluate *B. pertussis* specific CD4+ T-cell responses. This assay is based on cytokine detection inside cells and in secreted form, which allows the analysis of CD4+ T-cell differentiation. In this study, they used the assay in the BERT-NL study, a large clinical booster study run in the Netherlands as part of the PERISCOPE project (for more information: http://periscope-project.eu/patients/study-2-bert/).

Participants with different vaccination backgrounds received an acellular booster vaccination and blood was sampled longitudinally. The results of this study show that for the first time, Th1, Th2 and Th17 lineages can be identified simultaneously. In addition, they confirmed that the acellular pertussis vaccine-primed cohort was hallmarked by a stronger Th2 response in blood.

Link to the publication: https://www.mdpi.com/2076-393X/8/2/225

frontiers in Immunology
ORIGINAL RESEARCH
published: 27 February 2020
doi: 10.3389/fimmu.2020.00166

Age Distribution of Multiple Functionally Relevant Subsets of CD4+ T Cells in Human Blood Using a Standardized and Validated 14-Color EuroFlow Immune Monitoring Tube

Vitor Botafogo [1,2,3,4], Martín Pérez-Andres [1,2,3], María Jara-Acevedo [1,3,5], Paloma Bárcena [1,2,3], Georgiana Grigore [6], Alejandro Hernández-Delgado [1,2,3,6], Daniela Damasceno [1,2,3], Suzanne Comans [7], Elena Blanco [1,2,3], Alfonso Romero [8], Sonia Arriba-Méndez [9], Irene Gastaca-Abasolo [10], Carlos Eduardo Pedreira [11], Jacqueline A. M. van Gaans-van den Brink [12], Véronique Corbiere [13], Françoise Mascart [13,14], Cécile A. C. M. van Els [12], Alex-Mikael Barkoff [15], Andrea Mayado [1,2,3], Jacques J. M. van Dongen [7], Julia Almeida [1,2,3†] and Alberto Orfao [1,2,3†] on behalf of the EuroFlow and PERISCOPE consortia*

In recent years, important advances have been made in the identification of a myriad of functionally distinct subsets of innate and antigen-specific immune cells. Such functional complexity has emerged particularly among T CD4+ cells which comprise multiple functionally distinct T helper (Th) and regulatory (Treg) cell populations. PERISCOPE in collaboration with EuroFlow have reported on the design and validation of a single 14-color antibody combination and database for sensitive and reproducible flow cytometry monitoring of CD4+ T-cell populations in human blood. In this publication, PERISCOPE also established normal age-related reference values from cord blood to donors aged >80y and demonstrated the presence of distinctly altered TCD4 profiles in three disease models-monoclonal B-cell lymphocytosis, systemic mastocytosis (SM), and common variable immunodeficiency (CVID). The 14-color tube can identify ≥89 different CD4+ T-cell populations in 200 microliters of blood, with high multicenter reproducibility achieved via several EuroFlow-PERISCOPE educational workshops, particularly when software-guided automated gating of TCD4 cell populations was used. Age-related reference values showed different kinetics for distinct subsets: progressive increase of naïve T cells, Th1, Th17, follicular helper T (TFH) cells and Tregs from birth until 2 years, followed by a decrease of naïve T cells, Th2, and Tregs in older children and a subsequent increase in multiple Th-cell subsets toward late adulthood. Similar approaches have been designed and validated for Innate, Tcytotoxic/NK and B-cells/plasma cells, setting the basis for in-depth immune cell monitoring in the ongoing PERISCOPE vaccination studies.

Link to the publication: https://www.frontiersin.org/articles/10.3389/fimmu.2020.00166/full

Portrait

In each newsletter we portray one or several of our PERISCOPE members. In this eighth issue, the senior PERISCOPE scientist Debora Dominici introduces herself and presents her views on the project.

Debora Dominici, GSK, Rixensart, Belgium

Why do we need PERISCOPE?

"Despite the availability of effective prophylactic vaccines against whooping cough, this disease remains a major public health concern worldwide. Not only does it affect vulnerable infants, with devastating consequences to families in developing countries, but its incidence is increasing in adolescents and adults of industrialized

countries, reaching epidemic proportions in Europe, US and Australia during the last decade. A new generation of improved pertussis vaccines is therefore needed. However, to be able to develop this we need to gain a better understanding of the complex immune mechanisms underlying protection against *B. pertussis.* PERISCOPE brings together the best experts in the pertussis field, including vaccinologists, immunologists, clinicians, microbiologists and statisticians. It also brings together Industry and Academia. I believe this is its great strength as it is only by joining together and coordinating our efforts that we will be able to identify new and effective solutions."

What is your expertise and role in the consortium?

"I have been trained as an immunologist with a specific focus on autoimmune diseases. After completing my PhD at Imperial College London, I decided to go back to Belgium and join the Vaccines Industry. This is when I started my career at GSK. In 2015, I joined the department of External R&D where I have been working ever since. My role focuses on the management of externally funded collaborations, specifically within the European ecosystem. Within PERISCOPE, I act as a representative of GSK in the Consortium's Management Team, helping with the overall coordination of the project activities, including communication, planning and budget exercises. For example I have been involved in the coordination of GSK vaccines supply for the different clinical trials of PERISCOPE, in the planning and organization of annual meetings and in the preparation of the IMI mid-term review."

What aspect will you enjoy most working with this consortium?

"I feel extremely privileged to be part of the PERISCOPE consortium. First of all because I am learning so much. The multidisciplinary nature of PERISCOPE means that its members are exposed to the pertussis field from a plethora of different angles. It also brings together researchers from all over Europe, with different backgrounds, and coming from either Academia or Industry. This is extremely exciting and also very enlightening. Finally the people in the consortium are passionate and committed, which is very inspiring and stimulating."

PERISCOPE Stakeholder meeting 2021 in Ghent, Belgium

Due to the Covid-19 pandemic, we had to postpone the next stakeholder meeting to spring 2021 in Ghent, Belgium. We will announce the precise date in the next newsletter.

The topic of the 2021 stakeholder meeting will be: ***"New models for development of next generation pertussis vaccines: potential impact on regulatory pathway".***

More information coming soon.

About PERISCOPE- *Progress beyond the state of the art*

Beyond the public health objectives of PERISCOPE, the project will revitalize and connect the Pertussis research community in Europe and beyond. It is expected that this network of stakeholders will continue to contribute to the development of novel

vaccines and immunization methodologies beyond the life of the project. A variety of discussion forums and meetings have been held throughout this third year of the program in order to plan the operational aspects of the PERISCOPE program. Through these discussions, areas for future work were identified, new interfaces created among partners and long-standing collaborative links strengthened. This has already had a positive impact on the Pertussis community in Europe and beyond.

Bringing together industrial and academic partners with different approaches and working practices means that both learn from each other, not only about what they do, but also how they do it.

Partners and experts in PERISCOPE

The PERISCOPE consortium brings together internationally renowned scientists with many years of experience in *Bordetella pertussis* (Bp) research, clinical trials, bioinformatics, immunology and public health.