GMP Newsletter

Groupe de Métabolisme et Pharmacocinétique

Group of Metabolism and Pharmacokinetics

GMP is an organization gathering together scientists from the industry or the university involved in the practice of bioanalytic, pharmacokinetic and metabolism studies, whatever the areas of application (pharmacy, agro-chemistry, agro-veterinary, environment).

January 2021

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NUMERO 5

EDITORIAL

Dear colleagues, dear members of the GMP,

Despite the constraints of Covid-19, we were able to keep our congress on the original dates. Even in a digital format, it has been a real satisfaction to interact with you. Many of you attended the 5 scientific sessions (from 50 to 150 attendees per session) and the Question/Answer sessions after each conference were rich and opportunities for fruitful exchanges.

Your presence during these virtual sessions reflects your interest in our association and the quality of the scientific program offered. We particularly attribute this success to Jérôme Henri (President of the Scientific Committee) and Florence Gattacceca (President of the Board), to whom we extend our warmest thanks. We also thank Simulations Plus and Elsevier for their support in the organization of two of the scientific sessions.

The new team of the CA was introduced to you during our General Assembly. Jérôme Henri (President of the SC) and Florence Gattacceca (President of the Board) were reaching the end of their fourth and last year at the GMP. The GMP has benefited from their commitment and dynamism during these 4 years: a thousand thanks! Florence has kindly accepted to act as logistics advisor for the GMP in 2021 to give us the benefit of her experience in the implementation of the 2021 Congress.

The GMP Board had the pleasure to welcome two new members, **Yannick Parmentier and Madani Rachid**, who already bring us their commitment and motivation.
We have formed our scientific committee (CS) and decided to integrate this year a student who, associated with members of CS and CA, will have a dedicated role in the interactions between the GMP and the students. In addition, "GMP Student Grants/Aid" to facilitate access to the GMP 2021 congress will be offered to a few students who are particularly active and promising in our fields of activities.

We have already started to work on the GMP 2021 congress which will take place at the Institute Pasteur (Paris) and to set up actions to offer you the best possible format that will include, for example, satellite sessions. The team is also currently working on the preparation of a recurrent European DMPK congress in collaboration with other scientific associations, for the coming year(s).

You will find in this letter an analysis of your comments following our 2020 sessions. We very much appreciated your support in 2020. It is crucial because the vitality of our association is built on our exchanges and interactions and remains the basis of our commitment within the GMP Board and the SC. Your comments on the new actions that will be implemented are therefore welcome and expected by our teams.

Two scientific articles are presented in this letter. The first, written by Pr Olivier Fardel, discusses the relationship between inflammation, anti-inflammatory therapeutic proteins and the risk of DDI related with CYP450 metabolism. The second, written by Dr Antoine Coquerel (member of the Board), talks about Covid-19 vaccination and the emergence of RNA vaccines. Thank you both for your essential scientific contribution to this Newsletter.

You will also find in this letter pictures of your CS and CA teams. But first of all, we wish you on behalf of the GMP team a very very good year 2021 full of health, happiness and success for you and all your loved ones.
Yann Courbebaisse, President of GMP

GMP 2021 SYMPOSIUM

The GMP 2021 Symposium will be held at the **Institute Pasteur (Paris) from 20 to 21 October 2021.** Save the date.


We look forward to you joining us in Paris!

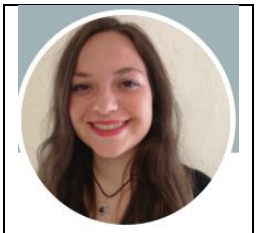
2021 SCIENTIFIC COMMITTEE

The scientific committee has been set up early January. This scientific committee is composed of **8 scientists from various backgrounds** (pharmaceutical and Biotech companies, CROs, scientific software and service providers and also academic institutes), all this combined expertise will offer you an exciting program including innovative topics. **The Scientific Committee President Quyen Nguyen (Ipsen) and its Vice-president Antoine Coquerel (Caen Hospital)** have been very happy to welcome, in addition to the GMP board members!

			
Etienne Chatelut (Oncopole Toulouse)	Nicolas Grégoire (Poitiers University),	Olivier Nicolas (Sanofi)	Vassilios Aslanis (Ipsen)

			
Vincent Duval (Certara)	Rola Barcham (Oroxcell)	Olivier Barberan (Elsevier)	Christine Bain (Active Biomarkers)

For the first time, we are very pleased to welcome Carla Troisi, a PhD. Student, winner of the GMP poster blitz edition in 2020, as a satellite member of the scientific committee, with specifically a role focused on the activities linked to the students and the GMP Association.


Carla Troisi (student)

We warmly thank all the scientific committee members for their time and enthusiasm!

COMING EVENTS 2021

We are currently working on several projects to be organized in 2021. You can directly contact the members in charge of a specific project to make some suggestions or to submit new ideas:

- A **scientific webinar** will be organized in Q2 2021. Work in progress for the selection of topic and the date (contact: Fabrice : Fabrice.Hurbin@sanofi.com).
- Similarly to the GMP Symposium 2019 in Lyon, we are planning to have a **Workshop pre-Symposium 2021**. The selected subject(s) will be focused on innovation and/or a hot topic (contact : Madani, Quyen, Yann : m.rachid@genosciencepharma.com, quyen.nguyen@ipsen.com, y.courbebaisse@adocia.com)

EUROPEAN SYMPOSIUM PROJECT

Breaking news: the GMP Board is currently working on a recurrent (every 4 years) European symposium project) in collaboration with other scientific European associations. More to come in the next future: of course, we will keep you updated.

SURVEY RESULTS

In total, 22 attendees completed the survey on the GMP Symposium 2020.
This first virtual Symposium has been globally appreciated. The quality of the different sessions has been found good or excellent by most of the participants. Warm thank you to the speakers and organizers.
Responses indicated your preference to have the following topics more developed in 2021: innovative therapies, Drug-drug interactions, in-vitro testing and drug development in pediatrics.
Some proposals have been made for the future scientific events such as DMPK of ADC (antibody drug conjugate) and oligonucleotides, cellular therapies, bioequivalence studies and biowaivers, drug development in rare diseases, special population and precision medicine.

We will do our best to integrate those topics in the program of our 2021 Symposium or in a scientific webinar.

It has been also suggested new scientific interaction ways such as round-table, papers presenting subject matter expert (SME) opinions and proposals of GMP. It is also accepted that scientific webinar could be organized during lunch time or early in the morning.
The ¾ of you are in favor of no hardcopy brochure and OK using an application for the 2021 Symposium (more ecology friendly☺).

We greatly appreciate your feed-back and support. We will do our best to meet your expectations. We will consider your suggestions in 2021 to propose an exciting program for the next Symposium.

STUDENTS CORNER

STUDENT RATE: 10 €

It has been decided to have a very **reduced yearly rate: 10 €** for all students.

We hope that many of you will take advantage of this offer and will join us. Please share the offer!

STUDENT PRESENTATION BLITZ AWARDS GMP 2020

A newly format has been adopted in 2020 for the Student Presentation Blitz. Participants have posted a video describing their work on the GMP Channel YouTube: thank you so much to all of them!

Congratulations to the winners of the Student Presentation Blitz Awards GMP 2020: **Carla Troisi, Anna Chan-Kwong and Nina Choublier**

STUDENTS AND GMP

The GMP Board is working on several projects involving students. We are therefore recruiting volunteers' students to contribute to those projects in 2021. Carla Troisi (satellite member of the scientific committee) will be in charge of the coordination between GMP and the students for those activities:

- A webinar specifically dedicated to students in 2021 (date to be confirmed) (contact: Carla, Max, Yann, Quyen: carla.troisi2@unibo.it, Massimiliano.Fonsi@crl.com, quyen.nguyen@ipsen.com, y.courbebaisse@adocia.com)
- Conditions for students sponsoring during the Symposium GMP 2021 (contact: Carla, Florence, Fabrice, Madani: Fabrice.Hurbin@sanofi.com, m.rachid@genosciencepharma.com, florence.gattacceca@univ-amu.fr)
- Organization of student's posters session during the Symposium GMP 2021 (contact: Carla, Yannick: carla.troisi2@unibo.it, yannick.parmentier@servier.com)

CALL FOR SPONSORS

A call for sponsors (bronze, silver, gold or platinum) is available on our website. Please do not hesitate to distribute it, to allow us to offer you an exceptional symposium with high quality. Please do not hesitate to contact Fabrice Hurbin (Fabrice.Hurbin@sanofi.com) and Massimiliano Fonsi (Massimiliano.Fonsi@crl.com) for any question or clarification.

We are counting on each of you.

SCIENTIFIC TOPIC: **Inflammation-related regulation of drug detoxifying proteins as a source of potential drug-drug interactions: Time to evaluate according to a regulatory point of view? (**by Olivier Fardel, Institut de Recherche en Santé, Environnement et Travail (IRSET/INSERM U 1085), Université de Rennes 1, France (olivier.fardel@univ-rennes1.fr))

Inflammation is well-known to repress expression of cytochromes P-450 (CYP) and drug transporters, notably at the hepatic level. This reduces the clearance of drugs substrates for these detoxifying proteins and increases their exposure levels. Such an impairment of pharmacokinetics usually occurs in patients suffering from acute or chronic inflammatory diseases, including viral infections, cancers or autoimmune diseases. It can be the source of drug-drug interactions (DDIs), notably for therapeutic proteins (TPs). Indeed, TPs, that are proinflammatory cytokines by themselves (such as peginterferon) or that increase proinflammatory cytokine levels, can theoretically enhance levels of exposure to co-administrated drugs, through decreasing their metabolism and membrane transport. Conversely, TPs that reduce proinflammatory cytokine levels and/or effects, such as monoclonal antibodies directed against cytokines or cytokine receptors, can relieve CYP and transporter down-regulation caused by inflammatory diseases, thereby enhancing clearance of co-administrated drugs and reducing exposure to these compounds. Such a DDI mechanism has been clinically described for the TP anti-interleukin (IL)-6 receptor tocilizumab, as a perpetrator, and simvastatin, as a victim, in patients suffering from rheumatoid arthritis, with an AUCR=0.43, reflecting induction of simvastatin metabolism/clearance through the relieve of IL-6 repressing effects. These potential TPs-mediated DDIs have now to be considered according to the US FDA guidance "Drug-Drug Interaction Assessment for Therapeutic Proteins" (released as a draft on August 10, 2020), through a systematic risk-based approach. For TPs acting as a pro-inflammatory cytokines, the sponsor should perform DDI potential evaluation. For TPs increasing proinflammatory cytokine levels, the sponsor should first characterize the time course and the extent of the increase in cytokine levels, in order to determine the need for a DDI study, its design and an appropriate mitigation strategy, if necessary; any low risk of DDIs should be justified. For TPs repressing proinflammatory cytokines, the nature and severity of the targeted diseases exhibiting increased proinflammatory cytokine levels are important to take into account and it may be challenging to design a DDI study that can be extrapolated beyond the study population. In this context, the sponsor has the possibility of including labelling language indicating potential for CYP/transporter-mediated DDI and no further action is then required. Alternatively, the sponsor can provide justification for no interaction potential or can conduct DDI evaluation, with labeling describing study results and any clinical actions. When performing DDI studies, sponsors have to primarily consider the putative mechanisms of the TP-related DDIs. The types of DDI assessments are (1) in vitro and animal studies, (2) clinical studies, (3) population pharmacokinetics modeling (nested DDI studies) and/or (4) physiologically-based pharmacokinetics modeling. FDA nevertheless indicates that the translocation of in vitro data or animal data to humans remains yet limited and further validation of relevant in vitro and animal models is required. Like TPs, cells-based therapies, including the use of chimeric antigen receptor T-cells (CAR T cells), can deeply modify the inflammatory status of patients; they have therefore to be additionally considered for potential DDIs according to the FDA. Besides TPs and other biological products, some small molecules drugs can also drastically impair activity of proinflammatory cytokines. This is notably the case for Janus kinase (JAK) inhibitors like ruxolitinib or tofacitinib, which potently blocks the signaling pathways of cytokines like IL-6 and type I interferons. Like TPs, these JAK inhibitors are thus expected to prevent cytokine-mediated

repression of CYPs and transporters, which may deserve dedicated studies, especially in targeted populations, even if there is currently no recommendation for this from drug agencies. Overall, inflammation-related regulation of CYPs and transporters appears now as a potential source of DDIs for TPs, cell-based therapies and small molecules. This has likely to be considered during the pharmaceutical development of TPs and other biological products according to a regulatory point of view, even if the exact clinical relevance of the incriminated DDIs remains to be fully characterized.

SCIENTIFIC TOPIC: Vaccination against COVID19 : emergence of RNA vaccines (by Dr Antoine Coquerel, CHU Rouen, France)

History of vaccination and its developments

Since Jenner's initial work, who used bovine vaccinia scabs to immunize individuals at risk for human smallpox by scarification, different approaches have been developed to induce a protective immune response against bacterial or viral infection. This strategy is useful as an alternative to antibiotics or antivirals and becomes essential when not available, especially in the event of a highly contagious pandemic. Conventionally, we vaccinate with attenuated (therefore "live") or inactivated (not capable of reproduction) viruses or more recently harmless viruses genetically modified to express one or more proteins of the infectious agent. From the 1980s it was possible to administer purified proteins of viral origin or obtained by biotechnology. Finally, nucleic acids can be used which, when administered into human cells, will produce viral proteins. All of these strategies are applicable to the SARS-CoV-2 coronavirus, responsible for the COVID-19 pandemic.

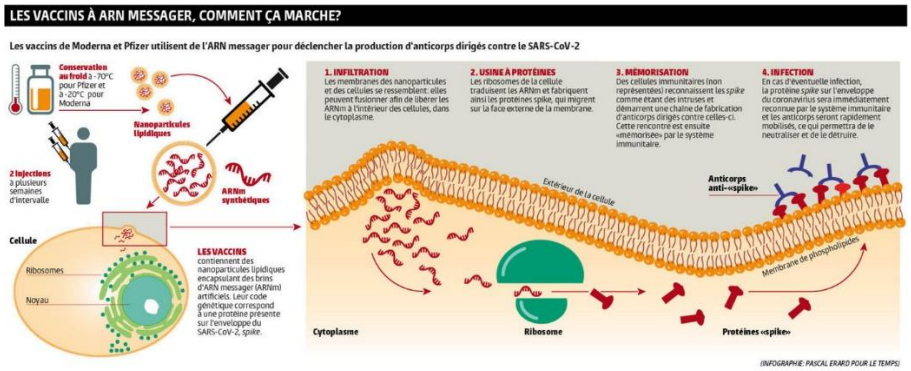
Vaccination to get out of the pandemic

The COVID-19 pandemic has already killed 2 million people since December 2019. Vaccination has become a global priority, especially since no antiviral drug has proven to be truly effective ... We have therefore seen a real race for vaccines [1]: According to the WHO, at the start of 2021 there were more than 60 vaccines in the clinical study phase, and nearly 200 candidates in preclinical research. Following the pioneering work of Katalin Kariko in the 1990s, mRNA vaccines were created, which have been used for nearly 10 years in farm animals. Their advantage is the rapidity of their obtaining: from the genome of the virus one can select the coding sequence of a protein of interest [2] which produced by the inoculated tissue will very quickly induce immunization against this protein (fig. 1); when this pattern is confirmed, specific antibodies are obtained (type B immunization) but also cellular immunization by T4 and T8 lymphocytes and memory lymphocytes. However, to master this technology it will have been necessary to make many developments, in particular on 3 points (1) choice of the target sequence. For the 2 large Western laboratories which have just obtained MAs, the choice has been made on the key 'Spike' protein of the immune response because it recognizes the ACE2 receptor on which viruses attach themselves before penetrate [3, 4]; (2) protecting mRNA and facilitating its transport to the site of inoculation; this involves mastering nanoparticles made from complex lipids such as C16 fatty acid esters, phosphocholine, etc. but also PEG, sucrose and buffered salts. An important logistical constraint persists here: these encapsulated mRNAs must be stored and transported frozen. (3) monitor efficacy and safety from animal models (luckily many rodents and small mammals are sensitive to SARS-Cov-2). Once these steps have been taken, we enter the classic clinical phases: in phase I, here atypical, we assess tolerance but also the production of "Spike" and then the transformation of immunocompetent cells. Phases I and II went very well, we quickly ended up with phase III against a control group. All the necessary steps for an MA have been respected and if the time taken to obtain it has never been shorter, it is also thanks to an intensification of the work of agencies such as the FDA and the EMA.

We must vaccinate but also respond to fears!

Trials of BioNTech-Pfizer and Moderna vaccines are made public by their publications in leading medical journals [5, 6]. In addition to efficacy (decrease in the number of serious cases, hospitalized), which is 90-95%, there are tolerance studies with a follow-up of more than 2 months without serious adverse events (SAEs) except for very rare allergic reactions, compensable. The 2 vaccines covered populations >> 10,000 people vaccinated and monitored. As with any vaccine, and even any drug, there can be no guarantee that there will never be an SAE when millions of people have to be immunized. The idiosyncratic accidents observed with modern vaccines are nevertheless very rare and, from a collective point of view, out of proportion to the risks incurred by the diseases from which these vaccines protect us. In the case of COVID, if the general mortality seems less than 0.5%, it reaches 15-20% in populations at risk, that is to say elderly and / or with comorbid factors. On the other hand, we must rule out aberrant anxieties about the risks of integration into the human genome or even into the germinal lines, which is nonsense since mRNA is a fleeting and fragile polymer, pure slave of its function of translation into proteins! As for the choice of the IM route and the deltoid muscle, these are the most rational to date.

Figure 1: Schematic of the mechanism of action of anti-COVID-19 mRNA vaccines ('Le temps' [CH] 12-2020). NB the final part is simplified and incomplete because the 'Spike' protein is exported outside the cells which then allows the phagocytosis immune cascade, antigen presentation and then the maturation of B and T lymphocyte responses (Callaway[1]). https://assets.letemps.ch/sites/default/files/styles/original/public/media/2020/11/30/file7dffwt35qmsy6gtc6nc.jpg?itok=raJCDzuF



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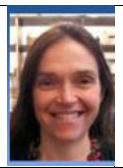
2021 GMP BOARD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