Newsletter Issue #5
August 2020
Translational quantitative systems toxicology to improve the understanding of the safety of medicines

We are pleased to present the **TransQST-Newsletter** Issue 5

Key Note

Modelling systems toxicology in the time of COVID-19

Since the first reports of a new coronavirus emerged from Wuhan late in 2019 and we began to adapt to a very different world, we can still see that we need to develop safer medicines faster. Researchers in our own Cardiac project are already responding by analysing and assessing safety data on potential COVID-19 therapies. As a team, just as the outbreak was beginning (and it felt like all hell had broken loose), we managed to assemble and formally submit our Annual Report. Our deliverables are on track, and as our work really begins to bear fruit, the number of our publications and presentations are increasing. We held our on-line General Assembly Meeting in April at which, despite not being able to meet, discuss and plan face-to-face, we could still come together as a group, follow the strong scientific progress made by each of the individual work package projects, discuss the basic science, and our ideas for implementation to get the tools and models into Industry practice. Working groups have been formed to develop and harness the energies generated in the project, to ensure that our tools and models are sustained beyond 5 years. The next GAM scheduled for Autumn 2020 will also be in an on-line format. Our Webinars have been re-invigorated and will now run on a monthly basis – ideas for these are welcome, not only tools and models from our own consortium, but perhaps also what is happening externally in our field. We have also been able to fund three new projects. Finally, we are very pleased to welcome a new partner, Vertex, whose formal incorporation will materialize in the upcoming weeks. In the meantime, we wish you all a happy, peaceful and healthy summer and hope that you can take some time with friends and family to relax.

Christopher Goldring, University of Liverpool (Project coordinator)

Project News

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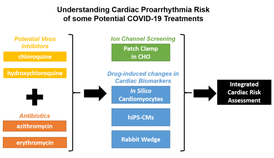
TransQST: Using cardiac QST models to assess the cardiac arrhythmia risk of potential COVID-19 therapies

Apart from new vaccine development, the efficacy of many older drugs against SAR-COV-2 is being tested as a treatment to palliate the effects of COVID-19. Some of the most widely used treatments include the anti-malarial drugs, chloroquine and hydroxychloroquine, with and without the macrolide antibiotics, azithromycin and erythromycin. The TransQST project cardiovascular working group has been developing a cardiac electrophysiology quantitative systems toxicology model which can be combined with physiologically-based pharmacokinetic models to make an assessment of repolarization delay and arrhythmia potential for these drugs on their own or in combination. Manuscripts describing the discoveries of these studies are already under preparation.



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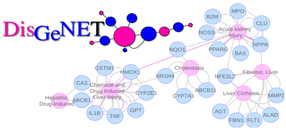
TransQST monthly Webinar series resumed in July with a presentation of the DisGeNET knowledge management platform

The webinar cycle to present tools, models and publications stemming from the project activities, and others of possible interest to the consortium members, restarted on July 6th with the presentation by Hospital del Mar Medical Research Institute (IMIM) researchers of the DisGeNet knowledge management platform for disease genomics. After the summer break, the webinars will continue in September with a presentation by the partner Ocello.



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TransQST GAM4

The fourth TransQST General Assembly meeting took place in Castelldefels (Spain) on September 19th and 20th, 2019.

The 2-day meeting focused on the progress of the models. The discussions were centered around the planning for the mid-term review, initially foreseen for June 2020. A poster session took place at the end of the first day, which supported the main results generated within the project.

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TransQST GAM5

The fifth TransQST General Assembly Meeting was held in a virtual format in two afternoon sessions on April 20th and 21st, 2020.

Due to the worldwide COVID-19 pandemic, the consortium was forced to organize the 5th General Assembly Meeting as a 2-day virtual conference. The sessions were centered around the work carried out within the different Work Packages and preparation for the project Mid-term Review. Discussions were also held involving possible delays and contingency measures regarding the pandemic. The SAB member Chris Evelo (Maastricht University) attended the event and gave his feedback on the project progress and recommendations for next steps during the closing session of the meeting.

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UPCOMING EVENTS

TransQST 6th General Assembly Meeting
5-6 October 2020 | Virtual
Eleventh American Conference on Pharmacometrics (ACoP2020)
4-7 October 2020 | Virtual
19th International Conference on Global Toxicology and Risk Assessment
5-6 November 2020 | Virtual
GRx+Biosims 2020
9-11 November 2020 | Virtual

Publications

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Development, calibration, and validation of a novel human ventricular myocyte model in health, disease, and drug block. Jakub Tomek, Alfonso Bueno-Orovio, Elisa Passini, Xin Zhou, Ana Minchole, Oliver Britton, Chiara Bartolucci, Stefano Severi, Alvin Shrier, Laszlo Virag, Andras Varro, Blanca Rodriguez. *eLife*. 2019; 8: e48890.

Drug-induced shortening of the electromechanical window is an effective biomarker for in silico prediction of clinical risk of arrhythmias. Elisa Passini, Cristian Trovato, Pierre Morissette, Frederick Sannajust, Alfonso Bueno-Orovio, Blanca Rodriguez. *Br J Pharmacol*.2019; 176(19): 3819–3833.

Drug-induced gene expression profile changes in relation to intestinal toxicity: State-of-the-art and new approaches. Daniela Rodrigues, Terezinha Souza, Danyel G.J. Jennen, Lieve Lemmens, Jos C.S. Kleinjans, Theo M. de Kok. *Cancer Treatment Reviews*. 2019; 77: 57-66.

From expression footprints to causal pathways: contextualizing large signaling networks with CARNIVAL. Anika Liu, Panuwat Trairatphisan, Enio Gjerga, Athanasios Didangelos, Jonathan Barratt, Julio Saez-Rodriguez. *NPJ Syst Biol Appl*. 2019; 5: 40.

Quantitative Systems Toxicology Modeling To Address Key Safety Questions in Drug Development: A Focus of the TransQST Consortium. Sofia Ferreira, Ciarán Fisher, Laura I. Furlong, Loic Laplanche, Brian Kevin Park, Carmen Pin, Julio Saez-Rodriguez, Panuwat Trairatphisan. *Chem Res Toxicol*. 2020;33(1):7-9.

Human Purkinje in silico model enables mechanistic investigations into automaticity and pro-arrhythmic abnormalities. Cristian Trovato, Elisa Passini, Norbert Nagy, András Varró, Najah Abi-Gerges, Stefano Severi, Blanca Rodriguez. *Journal of Molecular and Cellular Cardiology*. 2020; 142: 24-38.

PROJECT INFORMATION

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Next issue in December 2020

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