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Global Spotlights

Leveraging non-coding RNAs to fight cardiovascular disease: the EU-CardioRNA network

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Cardiovascular disease (CVD) remains the biggest killer globally, driven in part by the ageing population andlack of recent advances in diagnostic and prognostic tools and effective tailored treatment options. The World Heart Federation has estimated that by 2030, the global financial burden of CVD will exceed 1 trillion USD.[1]

The EU-CardioRNA Cooperation in Science and Technology (COST) Action (www.cardiorna.eu) was launched in October 2018 and included 21 founding members representing 14 European countries. Today, our network stands at 192 members from 32 European countries and 9 international partner countries spanning across all continents.

The goal of the EU-CardioRNA COST Action is to delve into the underlying causes of CVD by understanding transcriptomics changes in the cardiovascular system, to evaluate manipulation of RNA as novel therapeutic strategies and to identify RNA-based biomarkers for CVD.[2] Preparation of technical guidelines and recommendations for RNA-related work to enhance research findings reproducibility, robustness, and translatability is a key endeavour of the Action. EU-CardioRNA is composed of four core working groups, as previously described.[2] Now, more than midway through the project, a number of key outputs, including exchange of scientific staff and expertise and publication of position papers on regulatory RNAs, a state-of-the-art on dissection of the cardiovascular transcriptome and RNA markers, and artificial intelligence to predict cardiovascular outcomes post-COVID-19, have been achieved (*Figure 1*).[3–5]

Several international groups, including EU-CardioRNA members, have supported the understanding that epigenetic, transcriptomics, epi-transcriptomic, and post-transcriptomic changes drive CVD, by dysregulating the expression of both cardioprotective and pathogenic genes. Our community has also contributed to the global effort to reveal cellular sub-types carrying distinct gene expression or chromatin profiles in the healthy and disease CV system. Through the use of single-cell sequencing technologies, we are now starting to understand how cell type-specific molecular remodelling contributes to disease, with strategies such as adeno-associated virus and nanoparticle technology attempting to cell-type selectively manipulate RNAs *in vivo* in preclinical models.

The recent demonstration of the value of studying RNAs to find new CVD drugs has opened the door to a new reservoir of cardiovascular drugs, i.e. non-coding RNAs. Indeed, a synthetic oligonucleotide inhibitor of miR-132, a microRNA promoting pathological hypertrophy, has proven successful and safe in a Phase 1b trial (NCT04045405) to protect against ischaemic heart failure.[6] This is an excellent example of how fundamental understanding of non-coding RNA biology in the CV system, the focus of EU-CardioRNA Working Group 1, can progress within a decade to patient care. Translational research is key and based on partnerships between academia, hospitals, and industry, three arms constituting the foundations of the EU-CardioRNA COST Action.

RNAs produced by the cardiovascular system, or other disease-affected organs, may be released extracellularly and circulate in the bloodstream conjugated to proteins, lipoproteins, or as part of extracellular vesicles, such as exosomes and microvesicles. These carriers prevent RNA degradation, significantly increasing the potential of RNA to be developed into circulating biomarkers. The field of biomarker research to identify highly sensitive and specific indicators of disease presence and severity is ever-expanding with the accessibility to next generation sequencing and screening. One theme emerging in the field is that an RNA or transcriptomic signature or combination of markers along with clinical parameters may prove more effective for diagnosis of CV disease sub-types than the use of individual biomarker. This is exemplified by a collaborative work from EU-CardioRNA members from KU Leuven and Luxembourg Institute of Health, allowing the identification of circulating RNAs *QSOX1* and *PLBD1* as novel independent markers of left ventricular dysfunction following acute myocardial infarction. These candidate new RNA biomarkers were the result of whole blood RNA profiling from an initial discovery cohort of 143 patients with acute myocardial infarction, which were later externally validated in a cohort of 449 patients.[7]

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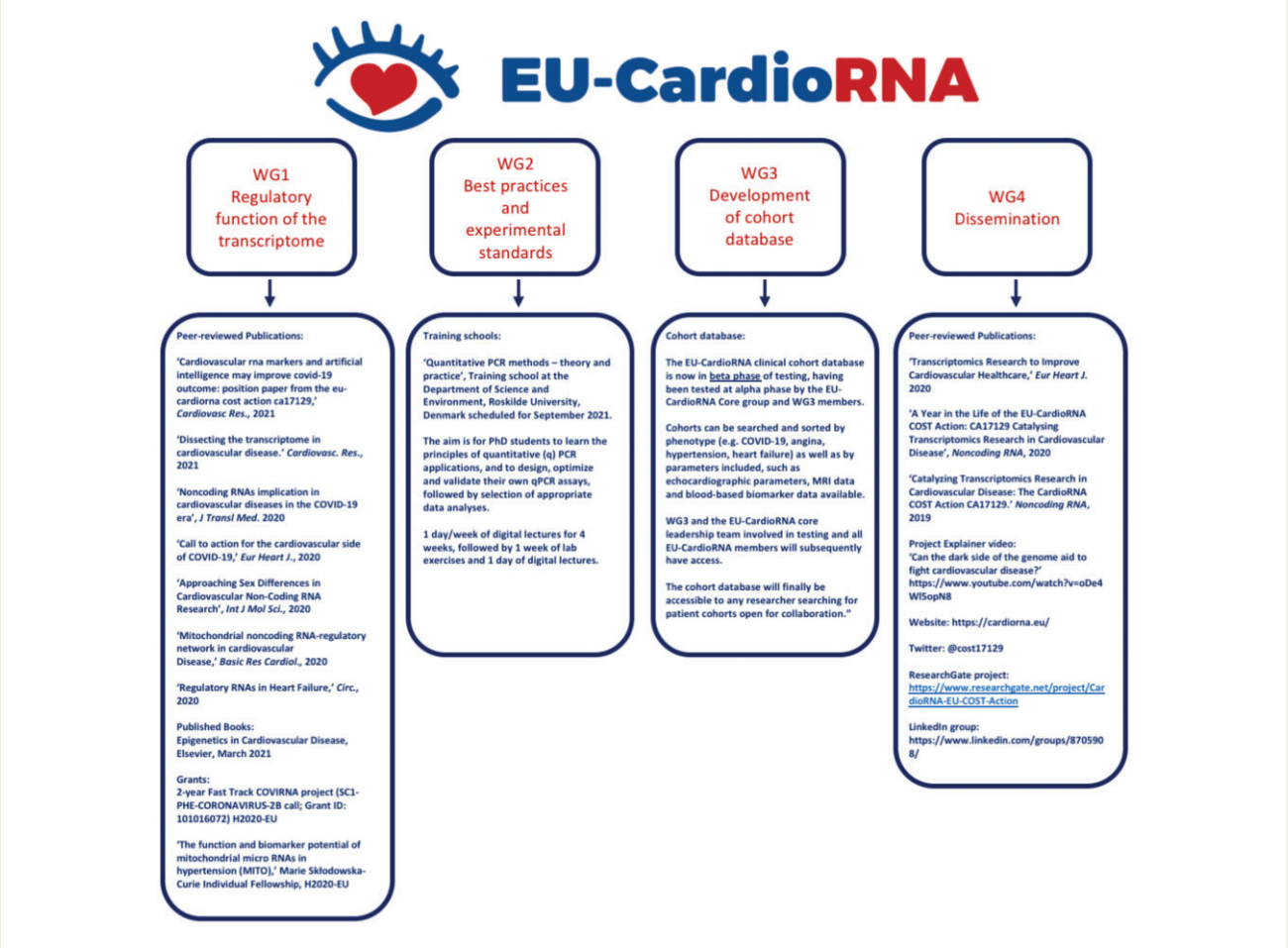

Figure 1 Key outputs and deliverables from the EU-CardioRNA COST Action working groups.

Following its kick-off meeting in Brussels in October 2018, the EU-CardioRNA COST Action has so far played host to three in-person working group meetings in Portugal, Turkey, and the Netherlands. The 4th Working Group meeting held in Maastricht, the Netherlands, played host to 85 speakers and attendees from 33 different countries, including Estonia, Slovakia, Bosnia-Herzegovina, Malta, Russia, and Singapore. Two themes of the meeting were 'Cardiac aging and associated comorbidities' and 'Novel alternative approaches to studying CVD', with scientific sessions as well as roundtable discussions were tailored around these topics.[7]

Outputs from meeting roundtable discussions and collaborations within the EU-CardioRNA COST Action include grant applications, position papers, and special issues in peer-reviewed journals including 'RNAs in Brain and Heart Diseases' in the *International Journal of Molecular Sciences* and 'Genetic and Gene Regulation underlying Sex Differences in Cardiovascular Disease' in *Frontiers in Cardiovascular Medicine*.[8,9]

An important goal of COST Actions is the training and nurturing early career scientists (ECIs, within 8 years of PhD completion or equivalent) in the field. EU-CardioRNA has thus far funded 11 ECIs in short-term scientific missions (STSM) to visit another laboratory within the network for up to 3 months. One EU-CardioRNA STSM award has resulted in a subsequent successful Marie Skłodowska-Curie Individual fellowship with the host laboratory. Furthermore, a hybrid training school is planned for September 2021 at Roskilde University, Denmark (*Figure 1*).

When the COVID-19 pandemic hit Europe in spring 2020, many research laboratories were shut down, or reduced to very essential work only, for several months. Face-to-face meetings and travel were of course cancelled.

Our science communication team (Working Group 4) rapidly launched a CardioRNA group instant messaging for fast and informal interaction between members to share not only latest scientific discoveries, ideas, and technical questions and, especially, to use camaraderie as the instrument of mental health support. This allowed EU-CardioRNA members from all around the world, from Brazil to North America, Europe, Russia, or Singapore, to remain connected and discuss how different laboratories, institutes, and countries were reacting to the pandemic. We held the first EU-CardioRNA live virtual meeting, CardioRNA LIVE! in September 2020, which included 120 speakers and attendees over 4 days of talks and discussion, representing 34 countries including New Zealand, Brazil, South Africa, Armenia, and Russia (*Figure 2*). The sequel virtual meeting, CardioRNA LIVE!Reboot, will be held in July of 2021 (https://cardiorna.eu/news/cardiorna-live-reboot-virtual-meeting-5-7th-july-2021/, date accessed 26 May 2021).

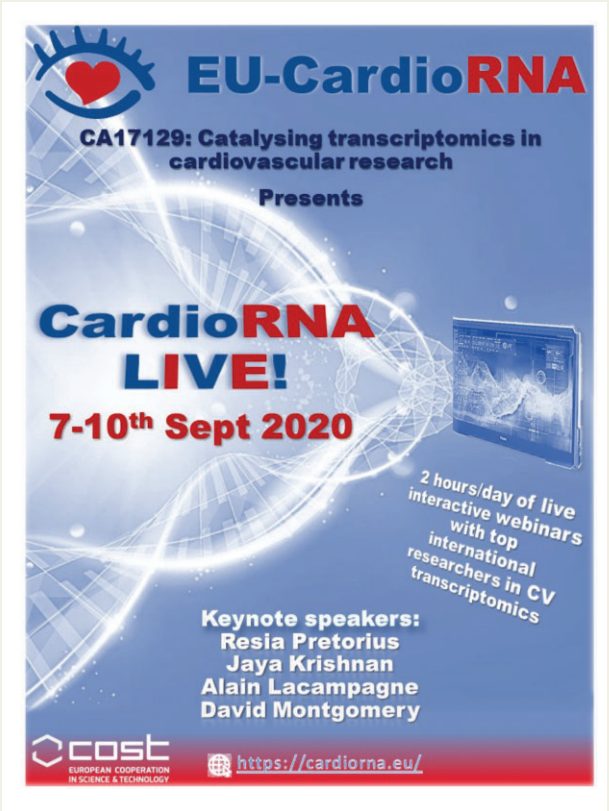

Figure 2 Official flyer advertisement for CardioRNA LIVE! Virtual meeting, 7–10 September 2020.

Moreover, with an interdisciplinary network comprised of clinical and translational researchers as well as experts in artificial intelligence and machinelearning in the cardiovascular field, we were in an optimal position to launch a call to action for the CV side of COVID-19 as well as multicentre and multidisciplinary research projects to understand CV risk of SARS-CoV-2 infection.[10] SARS-CoV-2 CVD as a secondary-consequence of SARS-CoV-2 infection is predicted to escalate the already severe socio-economic burden of CVD throughout the world.

Coordinated from the Luxemburg Institute of Health and lead by EU-CardioRNA Chair Yvan Devaux, a team of researchers, clinicians, experts in artificial intelligence, and industrials from 15 partners institutions from 12 European countries successfully acquired close to 4 million EUROs from the European Commission for the 2-year Fast Track COVIRNA project (SC1-PHE-CORONAVIRUS-2B call; Grant ID: 101016072). In the COVIRNA project (www.covirna.eu, date accessed 26 May 2021), a probe-optimized FiMICs set of 3233 cardiac-enriched lncRNAs detectable in peripheral blood is being examined for its ability to predict cardiovascular outcomes following COVID-19 infection. Moreover, one basic science work package aims to explore the mechanisms underlying COVID-19 cardiometabolic complications, in search for new molecular targets.

More than ever, these recent unprecedented and exceptional times have demonstrated the importance and possibility of connectivity between researchers globally for support, as well as the capacity of large research networks to rapidly join forces to actively tackle very relevant and important gaps in biomedicine. We look forward to further expanding our network, both globally and interdisciplinary, and working together to combat unmet needs in cardiovascular disease.

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YouTube: https://www.youtube.com/watch?v=oDe4Wl5opN8, date accessed 26 May 2021.

Website: https://cardiorna.eu/, date accessed 26 May 2021.

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