The Institute for Experimental Cardiovascular Medicine in Freiburg

Julia Verheyen¹ · Peter Kohl^{1,2} · Rémi Peyronnet^{1,2}

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The ‘Institut für Experimentelle Kardiovaskuläre Medizin’ (IEKM, <http://www.iek.m.herzzentrum.de>), directed by Prof. Peter Kohl, MD, PhD, was inaugurated in 2016. The festive opening fittingly coincided with the 7th International Workshop on Cardiac Mechano-Electric Coupling and Arrhythmias (<http://cardiac-mec.org/cardiac-mec/past-workshops/2016.html>), hosted by IEKM and highlighting the importance attributed to mechano-biology at the institute (Rog-Zielinska and Peyronnet 2017).

The IEKM is embedded in the University Hospital Freiburg, as part of the University Heart Centre (Universitäts-Herzzentrum, UHZ). The UHZ was founded in 2012 by merger of three cardiovascular departments of the University Hospital Freiburg (cardiovascular surgery, cardiology and angiology, congenital heart defects and paediatric cardiology) with the then charitable trust-run rehabilitation centre for cardiovascular patients at Bad Krozingen. With 1500 staff, the heart centre is one of the largest of its kind in Europe. The vision for its translational research centre, the IEKM, is to build bridges between basic and clinical research and to drive the advancement of knowledge on cardiovascular disease and therapy.

The English-language-operated IEKM (50 staff and students from 12 countries) is housed in a new tailor-made research building (Fig. 1). It has a flat hierarchy, with six highly interactive sections (Fig. 2) that are led by internationally recruited investigators with educational backgrounds in bio-

physics, biology, engineering, computing, physiology, and medicine. IEKM sections are structured by expertise area, rather than a disease or a structural component of the cardiovascular system. They are dedicated to: instrumentation (with strong focus on novel or improved functional imaging techniques), biophysics (cell and tissue electro-mechanics), optogenetics (developing optogenetic reporters and actuators, and applying them to cardiovascular science), 4D imaging (dynamic structure-function imaging from electron tomography to whole heart), computational modelling (to integrate the above data across spatial scales and between species), and translational medicine (with co-appointments of clinicians at the UHZ). This structure allows the IEKM to respond flexibly to new research ideas and targets. It branches out beyond the IEKM to provide know-how, training, and hands-on expertise in quantitative cardiovascular medicine, supporting and expanding interdisciplinary science in cardiovascular research at Freiburg.

Instrumentation, headed by Callum Zgierski-Johnston, PhD, develops specialized equipment for cardiovascular research. This is required as our questions often cannot be addressed with off-the-shelf solutions. To this end, IEKM offers facilities for prototyping of mechanical and electrical components, and expertise in sensors, imaging, signal processing, control systems, and user-interfacing (Johnston et al. 2017).

Biophysics, directed by Rémi Peyronnet, PhD, studies the adaptation of cells to their mechanical environment and focuses on early steps of mechano-sensing by characterizing the identities and roles of mechano-receptors in cardiac cells. Understanding their role in medium- to long-term responses is one of the major aims of this team (Peyronnet et al. 2016).

Optogenetics, led by Emmy-Noether-Fellow Franziska Schneider-Warme, PhD, develops genetically encoded, light-activated tools to study the biophysics of cardiac processes, from single cell–signalling to whole-heart electro-mechanic activity (Sierra et al. 2018).

✉ Rémi Peyronnet
remi.peyronnet@universitaets-herzzentrum.de

¹ Institute for Experimental Cardiovascular Medicine, University Heart Center Freiburg · Bad Krozingen, and Faculty of Medicine, University of Freiburg, Freiburg, Germany

² Signalling Research Centres BIOS and CIBS, University of Freiburg, Freiburg, Germany

Fig. 1 The IEKM is based in a new research building with state-of-the-art laboratories and offices. A teaching block with 32 seminar and lecture rooms is next door. Clinical Cardiology, Cardiac Surgery, Pathology, Centre for Translational Cell Research, and the Engineering Campus are all within easy walking distance

4D imaging, headed by Emmy-Noether-Fellow Eva Rog-Zielinska, PhD, combines experimental and computational research into cardiac structure (3D) and function (3D + time). The spatial domains studied can be split roughly into nano-to-micro and micro-to-macro levels, while the temporal domain requires resolution from milliseconds (to resolve a cardiac contraction cycle) to months (for disease-related remodelling Toomer et al. 2019).

Computational modelling, led by Gunnar Seemann, Dr-Ing, is working on the quantitative numerical description of cardiac histo-anatomy, and its interrelation with electrical and mechanical functions of the heart. Modelling ranges from the description of ion channel protein function to realistic simulations of the electrocardiogram. Data from experimental studies at IEKM or other partners are integrated with the models, both for input and for validation, to drive hypothesis generation and prediction (Hulsmans et al. 2017).

Translational research, directed by Prof Katja Odening, MD, links basic research and clinical application, using biological systems ranging from transgenic rabbit models of

inherited arrhythmogenic diseases (such as long-QT and short-QT syndromes) to large animal research involving clinical equipment and procedures (Odening et al. 2019).

IEKM trainees are normally associated with at least two of the sections, to cross traditional boundaries between fields (e.g. engineering, biophysics, biology, computing) and levels (i.e. from ion channel to whole organ and patient) of investigation. The IEKM enjoys close interactions and co-supervises student projects from BSc to MSc and PhD with other university departments within and outside the medical school, including biology, physics, and engineering, as well as at the Freiburg Max-Planck-Institute for Immunology and Epigenetics. Research and education activities are supported by strong intramural and externally raised funding from the European Research Council and the German Research Foundation (DFG), as well as from industry partners such as Amgen and Medtronic.

IEKM—together with the University of Auckland—is currently establishing a structured graduate programme, consisting of a 1-year fast-track MSc + 3-year PhD, with focus on *Cardiovascular Mechano-Biology*. Students recruited from any discipline relevant to modern biomedical research will be provided with broad-based subject-related insight, conceptual understanding, and technical ability (MSc) needed for successful in-depth original research (PhD). As such, the programme aims to take up the integrative, interdisciplinary, and international IEKM research concept to train medically aware translational scientists. Graduates will be equipped with a hands-on understanding of interdisciplinary research, familiarity with ‘wet’ and ‘dry’ research methodology, ability to use engineering-inspired approaches to data analysis and interpretation, and combining knowledge of concepts from different research domains with the ability to communicate across subject boundaries. The following are three examples of mechano-biology-inspired projects at IEKM.

One of our major aims is to explore dynamic changes in cardiomyocyte nanostructure, on a beat-by-beat basis. Transverse tubules (T-tub)—surface membrane invaginations that convey electrical signals throughout the entire volume of cardiac muscle cells—serve as signalling hubs that support homogeneous electro-mechanical activity of atrial and ventricular myocytes (Brandenburg et al. 2016). Thus far, little is known about T-tub behaviour during cell contractions. As it turns out, T-tub cross section changes during cell stretch and contraction. This alters T-tub surface-to-volume ratio. Since lipid bilayers are non-extensible, this should give rise to advection-assisted fluid exchange between T-tub lumen and free extracellular space. This hypothesis is currently being investigated, using a combination of contraction cycle synchronized high-pressure freezing for electron microscopic tomography reconstructions of nanostructural dynamics, and fluorescence recovery studies after photo-bleaching to quantify microscale functional behaviour. To cut a long story short: yes—cardiac contractions aid ‘pumping’, not only at the level

Fig. 2 The five expertise-based sections underlying translational research at IEKM

of the whole organ, but also at the level of subcellular T-tubule conduits.

Another target is to better understand the pump action of the heart, which relies both on forces produced by the myocytes and on their integration across the structural organization of cardiac tissue. Forces generated by cardiomyocytes in 3D remain poorly characterized until now. Using the carbon fibre technique to control the mechanical loading of single cells axially, and atomic force microscopy to explore radial mechanics simultaneously, we are in the process of addressing this gap in our knowledge. Such 3D insight into myocyte force production will be instrumental for a better understanding of cardiac wall motion. This takes into account active forces and passive mechanics, from native tissue level to the nucleus (Karoutas et al. 2019).

Thirdly, we are trying to better understand drivers and modulators of fibrosis, a common feature of all cardiac pathologies. The bi-directional interplay between passive viscoelastic tissue properties and fibrosis is ill investigated, in part for a lack of suitable experimental model systems. We use novel hydrogels, developed at the Freiburg Biological Signalling Centre (Hörner et al. 2019), whose stiffness can be tuned reversibly and with high spatial and temporal resolution by exposure to visible light of different wavelengths. This allows one to mimic changes in extracellular stiffness, such as occurs during cardiac lesion development, to explore how this alters cellular functions, such as differentiation, proliferation, and extracellular matrix production, and to test possible pharmacological interventions. In short, we aim to dissect the bi-directional cross talk of mechanics and structure in cardiac myocytes and non-myocytes, to support targeted functional research.

These are but a few examples of biomechanics-inspired research. As we are investigating a ‘pulsating’ organ system, mechano-biology is always a key component of our conceptual, experimental, and computational models, and a key

determinant of mechano-electric cross talk with relevance for normal steady state and for the origin and termination of arrhythmias (Kohl et al. 2011).

If you are interested in cardiac mechano-biology and would like to see more—come and visit!

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