TrendsTalk

Advancing cardiovascular translational research

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The recent announcement of the first and only FDA-approved medication (mavacamten) for the treatment of the obstructive form of hypertrophic cardiomyopathy (HCM) is exciting and motivating. Mavacamten is an allosteric and reversible inhibitor selective for cardiac myosin, an important protein in HCM development. Jerry Madukwe, the Editor-in-Chief of Trends in Pharmacological Sciences asked experts in the cardiovascular field to reflect on some of the global challenges and opportunities in translating basic and preclinical research discoveries into new treatments.

Rebecca Ritchie

Suowen Xu

What do you see as the challenges and opportunities in the cardiovascular drug discovery field towards developing efficacious and safer therapeutics?

Rebecca Ritchie (RR): It doesn't matter which part of the world you're from, cardiovascular diseases (CVD) remain the number one cause of death in adults. This is true even with the drugs and diagnostic approaches we have today. It is absolutely vital that the global research community work together, across nations and across all stages of the cardiovascular research pipeline (from molecules and cells through to preclinical, integrative research, and ultimately clinical trials and clinical practice), if we are to develop novel, and effective treatments available to all.

Suowen Xu (SX): CVD are the leading cause of death worldwide. Currently, most of the CVD-related studies are conducted in mouse models. However, no mouse model can fully recapitulate human disease pathology and its multifactorial mechanisms in terms of lipid metabolic traits and inflammation status. This is a major concern and challenge in translating research obtained from mice to humans. Future cardiovascular research in different animal models with various disease comorbidities are warranted. Also, big animal models of CVD, for example, pigs and non-human primates are useful models that can complement translational studies performed in mice.

Serena Zacchigna (SZ): I believe the moment has come to invest in the use of biological drugs in the cardiovascular field. While small molecules can either block or activate a specific target and thus interfere with a unique pathway relevant for disease onset and progression, they will never be able to induce complex biological processes, such as the formation of new blood vessels (therapeutic angiogenesis) or the regeneration of myocardial tissue. Biological drugs, instead, have the potential to induce these processes and therefore they could transform the way we treat CVD.

What are some of the key gaps you think future research should address?

RR: Growing up in rural Australia, 700 km from the nearest major city, I found myself asking 'why' and 'what if' a lot (it drove my parents crazy). I became a scientist because from a young age (high school), I wanted to cure disease; I wanted to make the discoveries that could do this. In recent years, peer-reviewed research funding opportunities in the cardiovascular drug discovery field have focused heavily on 'sure things', supporting ideas where much of the work has already been done, whilst shying away from big, 'blue sky' innovative ideas. Even in 2022, there are some major cardiovascular disorders that

lack effective medicines: diabetes-induced heart failure and heart failure with preserved ejection fraction are two such disorders.

SZ: A major gap is the availability of reliable animal models in which to test new drugs. It is very difficult to reproduce the complexity of human conditions in laboratory animals. Patients are usually old, affected by multiple comorbidities, and heterogeneous in terms of genetic background and exposure to risk factors, etc. By contrast, laboratory animals are generally young and healthy, often genetically identical, and a single insult is induced to mimic a disease, for example, the occlusion of a coronary artery to mimic a myocardial infarction. A solution could be testing new drugs on companion animals, which live in our environment, thus sharing with us the exposure to multiple risk factors, and they become often affected by age-related diseases, including CVD. This would have multiple advantages: (i) it would save money for research, as aging animals in a laboratory is very expensive; (ii) it would offer new therapeutic opportunities to companion animals; and (iii) it would allow testing new therapies in animals that more closely mimic the human condition.

Serena Zacchigna

What do you think are some key requirements within the scientific community or outside of it required to push the field forward?

SZ: I believe we should expose young scientists from the early stages of their careers to all aspect of the drug discovery pipeline. I studied medicine and then a PhD in molecular biology. I have been working on the development of new biotherapeutics for cardiovascular disorders. During my studies I was told my goal was to publish in high-impact journals. However, when I turned 35, I realized I had to patent my results before publishing, if I wished to bring them to the clinic. I had to learn and build skills in intellectual property protection, small business development, attraction of capital at risk, and identification of proper market niches by myself. I believe the education of future generations of scientists should include knowledge on intellectual property and entrepreneurship skills to prepare new professionals to be able to bring the results of academic research to the market and in the clinics.

SX: One of the important factors that can push the field forward is the inclusion of both sexes in cardiovascular research, as most of the cardiovascular research currently is conducted only in male preclinical animal models. In compliance with the National Institutes of Health guideline, future research using both genders of experimental animals should be included in experimental design. Lastly, increases in investment in pharmaceutical companies and funding opportunities for cardiovascular research globally is also important.

RR: It is absolutely imperative that we design and execute our preclinical studies with a mindset similar to clinical trials: randomizing our subjects (e.g., with random number generators), blinding study investigators, predefining primary and secondary endpoints, reporting fate of all study subjects, etc. Moreover, it is absolutely imperative we choose our preclinical models of disease with the clinical question in mind; in the case of diabetes-induced heart failure, ensure you choose a model that replicates as many aspects of the cardiac and systemic functional, structural, and metabolic phenotype as you can and hold off starting your treatment intervention until after this phenotype has become manifest. Patients rarely come to see their cardiologist to treat a heart failure they don't yet have.

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