HEART RESEARCH

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ISSN 2377-164X Open Journal http://dx.doi.org/10.17140/HROJ-2-112

Review

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Volume 2 : Issue 2
Article Ref. #: 1000HROJ2112

Article History
Received: April 14th, 2015
Accepted: May 27th, 2015
Published: May 28th, 2015

Citation
Fiedler LR. Cardiovascular research: past, present and future. *Heart Res Open J*. 2015; 2(2): 70-81. doi: 10.17140/HROJ-2-112

Cardiovascular Research: Past, Present and Future

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ABSTRACT

Cardiovascular disease remains a leading cause of death and significant burden on healthcare systems worldwide. While interventional and preventative medicine has considerably changed the face of clinical practice, at the molecular level, treatment has not altered in recent decades and is still directed towards alleviating symptoms or mitigating the underlying cause rather than regenerating damaged heart muscle. This is surprising, given the explosion of research in this area in the 1970's, and the fact that research output has continued to increase exponentially. With the incidence of heart failure on the rise, a trend predicted to continue, it is imperative that treatment strategies are improved. The development and adoption of molecular interventions might therefore present the most fruitful avenue in providing the greatest impact on mortality rates. This commentary aims to reflect on the earliest documented studies of human cardiovascular physiology, to surgical interventions in the 12th, to the first molecular studies in the 20th, to current pharmacological treatments. With this knowledge in mind, the future of molecular approaches in treating heart failure and cardiovascular conditions will be considered.

KEYWORDS: Cardiovascular disease; Heart failure; Cell biology; Drug discovery; Therapeutics; Clinical translation.

ABBREVIATIONS: CAESAR: Consortium for preclinicAl assESsment of cARdioprotective therapies; LVADs: Left Ventricular Assist Devices; CAP: The Cardiac Atlas Project; AMD: Anatomical Models Database; VIP: Virtual Imaging Platform; MRI: Magnetic Resonance Imaging; OSF: Open Science Framework; CVRG: Cardio Vascular Research Grid; ICDs: Implanted Cardioverter Defibrillators; ACE: Angiotensin-converting enzyme; S-ICDs: Subcutaneous ICDs.

INTRODUCTION

Heart disease is a leading cause of morbidity and mortality worldwide. In order to maintain its ability to meet the metabolic needs of the whole body, the heart has an innate capacity to remodel in response to injury or stress. However, loss of cardiomyocytes is particularly detrimental since these do not proliferate and are not replaced. Subsequent reparative processes such as fibrosis maintain structural integrity but cannot restore lost pump function and in a background of systemic conditions, structural defects or genetic mutations, cardiomyocyte loss is greatly exacerbated and indeed, is a defining feature of heart failure. Ultimately, the heart is unable to preserve its pump function, with death resulting from this or from lethal arrhythmias.[1,2]

Rather worryingly, the worldwide incidence of cardiovascular disease is predicted to rise from 17.1 million in 2004 to 23.4 million by 2030, and heart failure itself by 23%.[3] This is at least partly due to more prevalent risk factors including obesity and age in an increasingly industrialised world.[4] Thus heart research remains a very active and integral part of the study of disease pathology.

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This commentary aims to document a (very brief) history of cardiovascular research from the 8th Century BC to the 20th Century AD and consider how this has shaped where we are today. A summary of the impact of this history on current clinical practice is presented, with an appraisal of existing obstacles to advancing our understanding of the pathophysiology of the cardiovascular system and therapeutic interventions at the physical and molecular level. Finally, these reflections are used to consider what is yet to come. Confucius said, 'study the past if you would define the future'. By reviewing the history of cardiovascular research, we can hope to gain insight into what the future holds to predict and pre-empt emerging and future challenges that will be faced on this journey.

THE PAST

8th Century BC to 2nd Century AD

The earliest record of the heart comes from Homer, who compiled anatomical descriptions of exposed organs on the Trojan battlefield in 8th Century BC, in *The Iliad*.[5] Since the weapon of choice was frequently the spear, penetrating wounds giving visual access to the chest cavity were common.[6] *The Iliad* demonstrates that the vital organs were known and named, and that soldiers knew that a blow to the heart could be fatal.[7] An extract states (translated by Lattimore):[8]

"*...while fighting Idomeneus stabbed at the middle of his chest with the spear, and broke the bronze armour about him which in time before had guarded his body from destruction. He cried out then, a great cry, broken, the spear in him, and fell, thunderously, and the spear in his heart was struck fast but the heart was panting still and beating to shake the butt end of the spear. Then and there Ares the huge took his life away from him...*"

The Iliad also demonstrates an early knowledge of physiology and medicine. One such description states that an arrow was removed, blood drawn from the wound to prevent the poison from entering the body, and therapeutic herbs applied.[6,7] Another shows that herbs with pain relief and possibly antithrombotic properties were known and used in the battlefield:

"*Patroclus laid him down, cut the sharp point of the arrow out of his thigh with a knife, and washed away the dark blood from the wound with warm water. Then he teased out the root of a bitter herb in his hands and applied it to the place. It was a sedative, which banished all his pain. The wound began to dry and the blood ceased to flow.*"

Of course, *The Iliad* is not a medical text, but gives insight into the medical knowledge of the time. Of note, an editorial comment suggests that fibrinous pericarditis is actually recorded here; Homer describes "*the hairy hearts of hoary heroes*". Pericarditis would have been common at the time due to prevalent tuberculosis and typically, results in a hairy appearance of the heart (Dr. J. Roelandt, Professor of Cardiology, Thorax centre Erasmus MC Rotterdam).[7]

More generally, medical texts are frequently the oldest preserved manuscripts, suggested to be due to healing interventions, many of which were incantations, being too long to remember.[7] Authentic medical texts were chronicled by Greek philosophers in the form of case studies. These philosophers were particularly interested in respiration; they recognised that it was necessary for supporting life and consequently the breath was known as the vital power or innate heat. However the heart was thought to control the breath by transmitting innate heat to the lungs to drive expansion, while other organs existed only to cool the heart (Empedocles (490-430 BC) and Aristotle (384-322 BC)).[5,9] Perhaps the earliest form of research however, can be said to be anatomical dissection. Herophilos (335-280 BC) was the first to (legally) dissect human cadavers, work that extended to live dissection permitted on criminals (an effective deterrent strategy no doubt) and led him to postulate that the brain, not the heart, as Aristotle had thought, was the 'seat of intelligence'.[9,10]

Some years later, Galen (129-216 AD) was especially influential in preserving previous knowledge and in substantially advancing heart research. In fact, his works replaced many entrenched and inaccurate theories by, for example, showing that arteries contain blood not air (an idea based on studies of dead animals, where blood vessels appeared to be empty). However, many inaccuracies still existed; Galen asserted that blood moves from the heart in an ebb-and-flow motion rather than by circulation[9,10] and believed that blood passed from the right to the left ventricle of the heart through invisible holes in the septum.[11]

2nd to 17th Century AD

A more thorough anatomical and physiological understanding of the human body led to development of surgical interventions as early as the 12th Century. By performing surgery on goats, Abu-Marwan Abdel-Malik Ibn Zuhr (Avenzoar, 1093-1162 AD) demonstrated the feasibility of safe operations in humans, while Muhadhdhab Al-Deen Al-Baghdadi (1117-1213 AD), developed clinical practice in a way that is still recognisable today, stressing the need for thorough history taking, physical examination, diagnosis and prognosis.[12] However, it wasn't until Leonardo da Vinci studied physiology (1452-1519) that the first accurate drawings of the internal working of the heart were recorded, specifically in his *Quaderni di Anatomia*, vol 2; folio 3v (Figure 1). He also asserted that the heart is a muscle and that the atria are chambers, and was the first to document atherosclerotic coronary arteries.[11]

Galen's ideas continued unchallenged for a curiously long time, from the 2nd Century until the 16th. One explanation for this stagnation might be the long period (500-1400 AD) in which research activities were controlled by religion. The Church did not advocate acquiring new knowledge, though importantly was

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committed to preservation and re-examination of previous work if only to reconcile science with theology.[13-15] This no doubt played a part in propagating Galen's theories, since his findings were considered to be aligned with Christian doctrine. His work therefore gained a significant theological standing and new findings or anomalies were forced to fit his theories.[11]

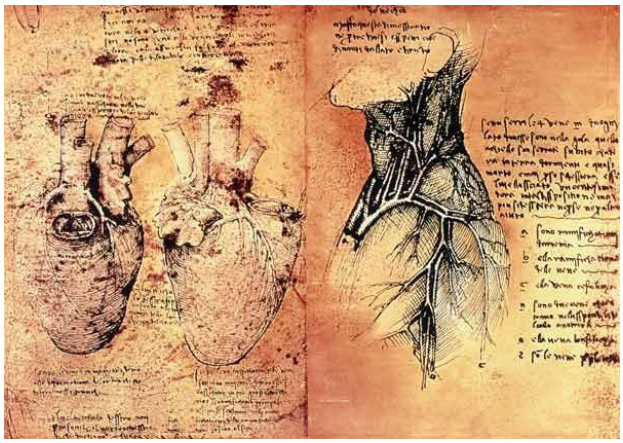

Figure 1: Anatomical drawings of the heart and major blood vessels, Leonardo da Vinci, *Quaderni di Anatomia*, vol 2; folio 3v. Attribution: Leonardo da Vinci [Public domain], *via* Wikimedia Commons.

Finally, in 1628, inspired by the work of Andreas Vesalius (1514-1564) and Heronymus Fabricius (1537-1619), William Harvey published his crucial research, *On the Motion of the Heart and Blood in Animals*. This work accurately described systemic circulation and the mechanical function of the heart for the first time.[10,11] Harvey was also a forefather of modern research practices, asserting that formulation of a hypothesis is essential and that this must be tested by observable, repetitive and rationally designed experiments. He was also careful to distinguish between fact and speculation and, crucially, was able to use his social standing and medical and royal connections to promote his new theory. However, not surprisingly, given the status given to Galen's work, it was not widely accepted until after his death.[11]

The recent past - 18th and 19th century

The study of anatomy flourished in the 18th and 19th centuries, and more widespread use of the printing press following its introduction in the 16th Century facilitated publication and exchange of ideas. Science was becoming more accessible, and the foundations of previous ages more open to all. Crucially, in 1832, the Anatomy Act was passed by parliament in the UK, legalising use of studies on unclaimed or donated human cadavers. As a result of this, the still authoritative text Gray's Anatomy, came into existence[10] (Figure 2).

The immense contribution that animal research has made to progress in heart research should also be emphasised, and the responsibility of this was realised by the first animal protection laws in 1822, followed by the Cruelty to Animals Act in 1876. The latter was strongly promoted by Darwin, who clearly found *in vivo* work distasteful though necessary, and in 1871, writes:

"*You ask about my opinion on vivisection. I quite agree that it is justifiable for real investigations on physiology; but not for mere damnable and detestable curiosity. It is a subject which makes me sick with horror, so I will not say another word about it, else I shall not sleep to-night*".[16]

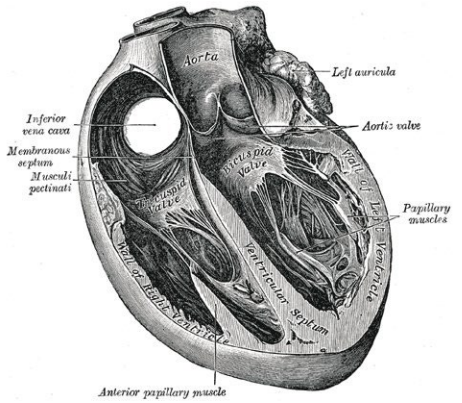

Figure 2: The human heart from Gray's Anatomy depicting the four chambers and the ventricular septum. Henry Gray (1825-1861). *Anatomy of the Human Body. 1918.* Attribution: [Public domain], *via* Bartleby, 20th Edition.

In 1986, the Animals (Scientific Procedures) Act was introduced to regulate the use of animals used for research in the UK, and is continually revised to this day.

The 20th century

The era of physiological, interventional and preventative cardiology

Although physiological intervention i.e. surgery, has its origins in the 12th Century, it was not until the 1900's that this became standard practice. Significant progress in detailed physiological knowledge combined with the development of diagnostic and interventional technologies allowed this to become a reality in clinical practice. A key example of such technologies is electrocardiography,[17] introduced in 1903 by the Dutch physiologist Willem Einthoven who was awarded a Nobel prize for his work '*discovery of the mechanism of the electrocardiogram*'.[18,19] His work was also instrumental in the development of mechanical devices that aim to restore normal electrophysiological properties of the heart such as pacemakers and Implanted Cardioverter Defibrillators (ICDs).[17]

By the 1970's these approaches were more fully established, and the term 'interventional cardiology' came into play. Andreas Gruentzig has been credited with strongly influencing this concept by changing the use of the catheter from that of a diagnostic to a therapeutic tool, when he developed percutaneous coronary angioplasty (widening of narrowed or blocked arteries); indeed the introduction of catheterisation itself, in addition to coronary angiography were also significant advances.[17]

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Cardiovascular prevention was also conceptualised in the mid 1900's; in 1944, Paul Dudley White pioneered this idea,[20] from which the famous Framingham Heart Study emerged.[21] This identified hypertension, smoking, and left ventricular hypertrophy (evidenced from electrocardiography) as key coronary risk factors, and suggested that recommendations regarding lifestyle changes or pharmacological interventions would dramatically improve survival.[21] In fact, in the last half of the 20th Century, death as a result of coronary artery disease had declined by 70%, and preventative measures such as these have been suggested to contribute to at least half of this statistic.[17]

The era of molecular heart research

While much of the early 20th Century was concerned with physiological and interventional cardiology, a small number of seminal studies delved into the biology of the cardiovascular system at a cellular level. In 1921, Otto Loewi demonstrated that neuronal communication occurred *via* chemical not electrical means, an idea that came from a dream and ended in him being awarded a Nobel Prize in 1936 along with Sir Henry Dale, for his work on chemical transmission of nerve impulses.[22] Loewi stimulated the vagus nerve of a beating frog heart in a perfusion chamber to decrease the heart rate and showed that application of the perfusate from this heart to a second, denervated, heart similarly decreased heart rate. Thus he demonstrated a chemically based mechanism of cell-cell communication, *via* an 'inhibitory factor', today known as acetylcholine.[22] Another important study described the authors' own measurements of the relationship between heart and body weight, which were combined with data collated from previously published work.[23] It notes that the heart to body weight ratio (hypertrophy) can be affected by factors altering body weight, such as growth, inactivity, obesity and weight loss, and by those affecting the heart, including exercise and pathological conditions. Therefore it had been realised that the heart undergoes compensatory remodelling in response to pathological and non-pathological stimulation.[23]

However, it wasn't really until the 1970's that dissection of the heart reached a truly molecular level, and in 1980 an accurate and practical approach for generating transgenic mice was described,[24] providing the basis for techniques used today.[25] Generation of the first knock-out mouse in 1989 resulted in its creator being awarded a Nobel Prize in 2007 (awarded jointly to Mario R. Capecchi, Sir Martin J. Evans and Oliver Smithies *'for their discoveries of principles for introducing specific gene modifications in mice by the use of embryonic stem cells').*

On the back of an understanding of the heart at a cellular and molecular level, came pharmacological interventions. Drugs that are still in widespread use today were introduced into the clinic, most notably beta-blockers, Angiotensin-converting enzyme (ACE) inhibitors and statins.[26] The 20th Century therefore also saw the establishment of the commercial pharmaceutical sector, which now represents a multi-million pound industry integral to drug development today.

Simultaneously, the advent of non-invasive imaging technology such as Magnetic Resonance Imaging (MRI) and echocardiography enabled researchers to study heart function and the cardiovascular system *in situ*, in the living organism. MRI has its origins in a study from 1973[27] but was not fully realised until the 80's and 90's where rapid advances in hardware, acquisition and image processing permitted the study of heart function at a global and regional level.[28] For the first time, essential phenotypic knowledge regarding the effect of a particular gene or genes on cardiac function could be gained. In addition, this provided a non-invasive means of assessing cardiovascular dysfunction to direct diagnosis and treatment. Thus the 70's brought about an explosion of research exploring the basic biology of the heart and the cell biology of its disease.

THE PRESENT

The 20th Century presented an immense and impressive leap in basic research and medical practice, and gave birth to sub-specialties in electrophysiology, imaging, interventional, pharmaceutical and preventative medicine. These advances changed the face of cardiovascular treatment from being crude and ineffective, to sophisticated and highly successful. Together, these tenets of modern medicine have saved, and improved the quality of life of millions of people.

Clinical Impact

Physiological and interventional cardiology

The importance of approaches such as electrocardiography, catheterization and coronary angiography in cardiac care is evidenced by the continued use, development and evolution of these approaches in the clinic. The work of Andreas Gruentzig for example, paved the way for further applications of catheterization such as balloon angioplasty and stenting (a permanent means of widening blood vessels). Stents have evolved past simply structural units to those capable of regenerating or mitigating damage to blood vessels, and many now incorporate biodegradable materials and locally released pharmacological agents.[29,30]

Implanted cardiac cardioversion and defibrillation devices are also still in wide use. In fact survival of end-stage heart failure patients is heavily dependent on mechanical devices in general. In management of heart failure (aside from pharmacological treatments, see www.nice.org.uk/ guidance for current guidelines on these), surgical, catheter-based, intracorporeal (Left Ventricular Assist Devices; LVADs) and extracorporeal (pumps) devices as well as mechanical hearts, are in widespread use and are continuously being refined.[31,32]

Molecular interventions

At present, heart failure treatment in general largely relieves symptoms, treats the underlying cause, or aims to improve pump function (see The National Institute for Health and Care

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Excellence (NICE)) for specific guidelines on recommended treatments (www.nice.org.uk/guidance)). Molecular interventions can lessen the workload placed on the heart by controlling blood pressure e.g. beta-blockers or improving blood flow e.g. ACE inhibitors; these drugs also contribute directly to preserving or improving contractile function of the myocardium at a molecular level.[33]

However, these treatments in addition to those described above do not address the underlying issue of existing cardiac damage and/or loss of cardiomyocytes. Without this, treatment must be continued long-term to prevent further deterioration and maintain existing myocardium. While some regeneration has been observed in the case of LVAD placement for example, this is minimal at best; unsurprising given that the regenerative capacity of the heart is meagre. Four general approaches to regenerate non-viable or damaged myocardium to restore normal heart physiology and function have emerged, namely stimulation of endogenous stem or progenitor cells; exogenous stem or progenitor cells; inhibition of cardiac cell death (to limit loss of cardiomyocytes in the first place); and stimulation of cardiomyocyte proliferation.[34] These approaches are the subject of intense study, though have yet to provide real clinical impact (Figure 3). The current and future challenges of cell-based therapy are important topics of scrutiny, and the reader is directed to a comprehensive review on this subject.[35]

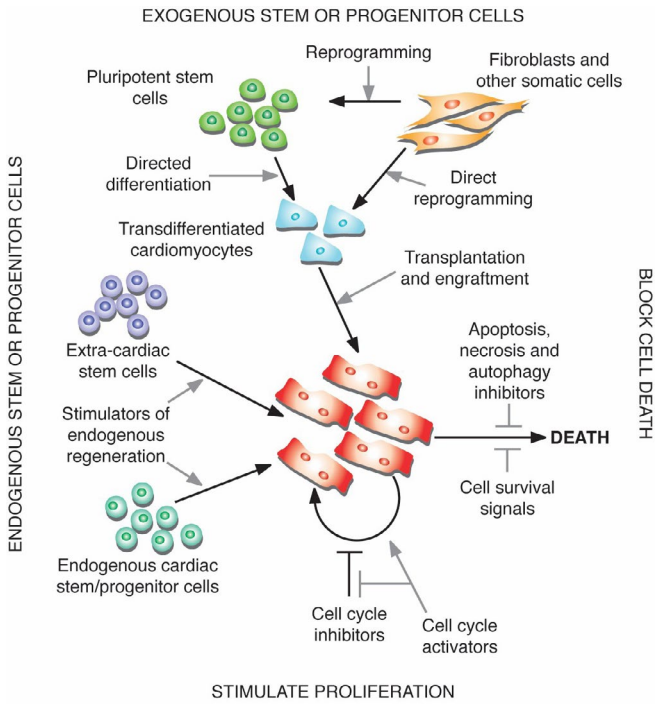

Figure 3: Strategies to increase cardiac muscle cell number as a therapeutic target. In principle, the limited ability of the heart to replace cardiomyocytes can be improved by reactivating cell division of pre-existing cardiomyocytes and/or inhibiting cell death or augmenting survival. Alternatively, new myocytes can be produced from multipotent stem or progenitors that reside within niches in the myocardium, circulating stem cells with cardiac potency, or *ex vivo* cells transplanted into the injured heart. Challenges to regeneration include an endogenous restorative capacity that appears limited by an insufficient number of available stem or progenitor cells, and the need to develop efficient means to produce or deliver exogenous cells. Developmental signals are being investigated for use in enhancing therapeutic regeneration from endogenous and exogenous sources. *Reproduced from Mercola, Ruiz-Losano & Schneider, 2011.*[34]

Multidisciplinary approaches

Many approaches now combine knowhow from multiple disciplines. For example, development of stents that are used currently is a product of close collaboration between clinicians and basic scientists with expertise in disciplines ranging from pharmacology, biomaterials and bioengineering to cell biology. These advances have significantly improved the quality of life and survival of many patients, and would not have been possible without effective communication between clinical and basic scientific researchers.

In the case of preventative cardiology, this is no longer based simply on the Framingham study, where historical factors such as age, obesity, hypertension status etc. are used to calculate a risk score. A wide variety of additional or alternative scoring systems are now available as a result of molecular information that was not available at the time. As a consequence, risk reclassification and group-specific risks are receiving notable attention.[36] Biomarkers are fast become a key component of this, with C-reactive protein for example, shown to be a suitable predictive marker for women but not men, and being most effective in those designated as being medium risk.[36] In addition, it has been shown that individual markers rarely make a big impact, and specific groups of markers are emerging as being more useful. Imaging technologies combined with metabolomics profiling (in itself receiving considerable attention of late) is fast becoming an area of interest and significant potential in this context.[37] These studies demonstrate the very real impact and importance of combining disciplines such as biological, statistical and epidemiological research.

Current challenges

Translation of molecular approaches into the clinic

Given the volume of research dedicated to the identification and study of specific molecular targets, it might be expected that therapeutic interventions at this level would have made a substantial impact on clinical practice. Disappointingly, however, many have simply not yet made an impression.[38,39] Further, molecular treatment regimens in particular have not substantially changed since they were first introduced into standard clinical practice in the 1980's.[26,33] Due to frequent failure at the stage of human clinical trials, investment is considered by the pharmaceutical industry to be high risk, undermining support from this quarter. This is of concern since the incidence of heart disease and failure is rising and predicted to increase further due to more prevalent risk factors such as obesity and old age.[3,4] However, there are some promising trials in which pharmacological agents have been used to target pro-survival kinase signalling pathways (ANP and exenatide) or to protect against oxidative stress induced cell death (Cyclosporin A).[38,40-42] Another approach is gene therapy, which is fast becoming a more viable approach than previously thought,[43] and which has

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been used successfully in clinical trials to stimulate activity of the calcium ion transporter SERCA2a, improving both mechanical function and cell survival.[44,45] For a complete list of further clinical trials worldwide the reader is directed to https://clinicaltrials.gov/.

Since some of the most promising clinical trials utilise approaches that activate pro-survival kinases, perhaps an alternative or complementary approach would be the direct inhibition of pro-death kinases. Such interventions are relatively unexplored and only a small number of studies use this strategy.[46] Though early, these encouraging observations in general indicate targeting cardiomyocyte cell death to be a productive approach.

It has been suggested that an underlying issue with failure in translation from 'bench to bedside' lies with use of murine models in pre-clinical testing. Indeed, the usefulness of animals in research is still an intense and passionate area of debate, and poor experimental design and interpretation have been suggested to be key factors.[47,48]

Another reason for poor translation from small to large mammal is variable anaesthesia effects. A detailed comparison of the cellular, organ and global compositions and function of mouse and man has been described,[28] in which the relevance of anaesthesia protocols is high-lighted and optimal conditions suggested. Overall, under physiological conditions, this study suggests that bioenergetically, hemodynamically and mechanically, the mouse scales linearly with larger mammals and humans.[28] However, the authors caution that differences between mouse and man might be unmasked in pathological conditions or under stress.

Prevalent comorbidities and risk factors (including hypertension, hyperlipidaemia, diabetes, psychological disorders), age, gender and existing drug regimens (cardioprotective and otherwise) have also rarely been considered in murine models. Without mirroring these in pre-clinical trials the interactions and outcomes in humans cannot be accurately predicted.

Collaborative approaches

The need for a more unified, collaborative approach in research has been recognised, leading to the establishment of a US based organization for more systematic, preclinical *in vivo* assessment of cardioprotective therapies: CAESAR (Consortium for preclinicAl assESsment of cARdioprotective therapies (http://www.nihcaesar.org). This consortium uses multicentre randomized controlled studies to perform pre-clinical testing in three species across three centres.[49] The European Society of Cardiology Working Group Cellular Biology of the Heart has also recently made recommendations for a similar Europe based consortium, and provided key recommendations for improving preclinical assessment and the design and efficacy of human clinical trials.[50]

THE FUTURE

In the absence of a crystal ball or any psychic ability on my part, the future is purely speculative. However, the patterns of the past together with current trends can be used to envisage patterns of the future.

Refinement of existing approaches has always been, and might be predicted to be, a significant focus of future efforts. One very prominent current example of this is that of ICDs. These have been critically important in treating patients at risk of sudden cardiac death. However, drawbacks include invasive procedures for placement, battery replacement or repair. Just recently, Subcutaneous ICDs (S-ICDs) have been introduced, placement or maintenance of which is a relatively minor procedure. Clinical trials have thus far yielded encouraging results[51-53] although more extensive favourable evidence would be required before adoption into clinical practice. This does however illustrate an exciting example of increasingly sophisticated and lower risk approaches that can emerge following continued investment and evolution of specific technologies.

In keeping pace with modern cardiology and all its complexities in diagnosis and treatments, in addition to emerging new technologies such as S-ICDs, a high level of expertise and subspecialisation is undoubtedly required in specific areas. However this can fragment patient care and therefore presents a major challenge for the future.[17] There is a need for integration of not just various aspects of cardiac care (from diagnosis to hospital treatment to that following discharge) but in taking account of increasingly prevalent co-morbidities or factors such as diabetes, obesity and old age. In the future, maintaining a clear perspective of the patient as a whole and preserving continuity from the perspective of the patient will present a very real challenge. Like many future obstacles to progress, the answer to this may lie in close interdisciplinary collaboration, open communication and effective dissemination of progress to allow the physician to utilise all the available information to its fullest. Indeed, interdisciplinary research has become a 'buzzword' of the 21st Century, and is reflected in particular, in the pharmaceutical industry. Drug development is no longer limited to this sector, and is an increasingly active component of academic establishments. Drugs that are most successful in mitigating heart disease or failure in the clinic are those that have the backing of significant collaboration between academic and commercial sectors, underscoring the importance of crossing bridges between these disciplines.

Ultimately, the basic challenge at the core of all of these efforts; that of healing the cardiovascular patient, will only be met by viewing the patient from all angles and dimensions and bringing this massive wealth of information together. However, this in itself highlights an increasing problem. How can we effectively communicate and assimilate such a wealth of knowledge?

ISSN 2377-164X Open Journal http://dx.doi.org/10.17140/HROJ-2-112

The information technology era has provided an answer to this, with the vast majority of publications now available on the internet, the existence of databases to permit researchers to examine this information and increasingly open and free access for all. Computational approaches and virtual modelling systems are becoming more widely available, although the predictive power of many of these is unclear. As more scientists engage with this technology, both in depositing data and in utilising it, its predictive power will no doubt improve and drive both basic mechanistic understanding and translational potential. Combinations of models, *in vivo*, *ex vivo* and *in vitro*, should ideally be used to drive a more quantitative, integrative, systems biology approach.[54] Indeed, for a complex condition such as heart failure (with diverse environmental and genetic causes and interactions) a network-based approach might prove particularly fruitful in identifying key signalling convergence points or in better predicting the outcome of therapeutic interventions.

The Information Technology Era

Computational tools

The Cardiac Atlas Project (CAP), established in 2010, is a worldwide consortium and one of the foremost data sharing repositories in the cardiovascular field.[55] It combines imaging data with diagnostic, clinical and biomarker information on an unprecedented scale, offering the potential for significant advances in treatment of cardiovascular disease. The Anatomical Models Database (AMDB, formerly euHeart) is a web based resource that allows researchers to computationally model cardiac electrophysiology and mechanics using information from geometriccardiac models. It allows the user to generate a geometric heart model based on binary images of the heart and cardiac parameters[56] while the Virtual Imaging Platform (VIP) focuses on multi-modality medical image simulation.[57]

Other resources include iDASH (integrated Data analysis, anonymization and sharing), designed to share and access medical data in general,[58] PhysioNet holds ECG and biomedical data from healthy subjects and cardiac patients[59] and the Cardio Vascular Research Grid (CVRG) aims to provide a more complex resource for sharing genomic, proteomic, imaging and clinical data from cardiovascular research.[60] The Open Science Framework (OSF, https://osf.io) aims to provide support in project planning and development by linking online services and facilitating collaborations by providing an accessible platform for date sharing and storage.

The rise of big data

'Big Data' is a term used to describe vast amounts of data that cannot be analysed by standard means. Such a large volume of data might be expected to provide a complete and accurate understanding of the subject of interest. This in turn will drive translation of therapies directed against molecular targets from basic science to the clinic, by enhancing the power of preclinical models. From the point of view of the pharmaceutical sector, improved predictive power of success in the clinic equals reduced risk and therefore increased investment. However, sharing, analysing and disseminating information on this scale introduces numerous challenges in data collection, organisation, storage, analysis and accessibility to name but a few. In particular, computational and statistical approaches must be sufficiently accurate to limit erroneous statistical inferences and scientific conclusions based on these. Some of these immediate issues are outlined by Fan, et al.[61]

It would probably not be disputed that data sharing and open resources are important for advancing cardiac research and therapeutic approaches however, and recent progress in 'big data' in the cardiovascular field has recently been summarised.[56] Perhaps the future holds a virtual network of physiological, molecular, computational and bioinformatics scientists, statisticians and clinicians willingly working together to drive the utility of computational approaches to a unprecedented level, though this will no doubt be tempered by intellectual property and patenting issues.

Improving translation from bench to bedside

A unified workflow for assessing therapeutic approaches that is agreed and adhered to worldwide would provide a much improved pathway from target identification to the patient. Such a workflow will rapidly evolve as more data becomes available to substantially increase predictive power of the models used. Early studies in target validation might benefit from utilising multiscale models from cell to tissue to whole body, to provide a more complete picture. Studies in these settings should systematically probe the general molecular mechanisms involved and may provide the advantage of uncovering key convergence points common to cardiomyopathy from diverse etiologies.

Once an appropriate target has been identified and a firm biological basis established, therapeutic strategies can be explored. A multifactorial approach should be taken to provide a more reliable basis for further development. For instance it might be advantageous to assess efficacy of pharmacological (or other) intervention in both genetic and microsurgical models of heart failure that where possible, incorporate factors such as age and obesity. Cost is certainly a limiting factor in testing such approaches in aged mice for example, however genetically aged mice (Terc-null mice) have recently been described and could provide a workable alternative.[62] Furthermore, many models of obese or diabetic mice currently exist that could also be utilized. In addition, use of a carefully selected panel of genetically engineered mouse models that exhibit explicit, instructive features of heart failure itself might provide a particularly suitable test-bed to predict clinical success.[46]

The use of imaging technologies

Imaging is becoming ever more sophisticated. Echocar-

ISSN 2377-164X Open Journal http://dx.doi.org/10.17140/HROJ-2-112

diography, pulse wave and tissue Doppler has developed from a 2-Dimensional (2D), to 3D and now a 4D tool, capable of revealing cardiovascular dysfunction with remarkable accuracy. Disease diagnosis, informed treatment decision making and monitoring can now be conducted to a level that would have been previously unimaginable. For more expert reviews on this subject and its future applications the reader is directed to other publications.[63,64]

The other main imaging technology used in the clinic, MRI, is now capable of exploring the cardiovascular system at a cellular and molecular level. Perhaps some of the most disappointing results in clinical trials to date lie in stem cell based regenerative therapies. This might simply reflect a lack of understanding at the cellular level, of stem or progenitor cell fate, localisation and engraftment. Adequate methods for monitoring these aspects have recently been described; it was shown recently that iron-oxide labelled cells can be visualized by MRI thereby allowing migration and engraftment to be directly monitored in the heart.[65] In addition, hybrid imaging systems (two or more imaging modalities) are emerging,[66-69] paving the way for simultaneously monitoring the heart at a global, regional and molecular level under the conditions of interest. Based on these trends, the future of imaging seems to be in multi-scale approaches; from global to regional to imaging at the molecular level, in a multimodality based manner. This kind of information can allow us to better assess old, current, and new stem cell based therapies to aid in the utility and application of this approach in regenerating the damaged myocardium.

Mouse or man/woman?

A mouse (or indeed any other animal) cannot fully replicate human physiology. Though animal research undoubtedly has paved the way for scientific discovery, it is widely accepted to be an obstacle to effective clinical translation. Since there are some obvious difficulties in persuading human subjects (especially healthy ones) to part with pieces of their heart or to try untested drugs, animal research is still an essential component of cardiovascular research. Increasingly important and alternative resources are human model systems, which are becoming more accessible and suitable for use in research. Many models are now at our disposal that were not in previous decades and there is an emerging need and trend for utilisation of these models in the preclinical pipeline. Importantly, this is particularly lacking in cardiac drug discovery, and since most drugs fail in the clinic due to cardiotoxicity, testing for toxicity in human cardiac cell systems would seem particularly prudent.

Another avenue of increasing interest that directly addresses the problem of a mouse not being able to fully replicate human physiology or signalling responses is the use of human pluripotent stem cell-derived cardiomyocytes.[70,71] Patient-specific induced pluripotent stem cells[72] carrying disease-causing genetic mutations provide a useful and direct means of dissecting signalling pathways relevant to congenital heart disease and heart failure, as well as providing a relevant test bed for more tailored therapeutic interventions. In short, a target that is validated both in mouse models (providing information from the adult, intact heart) and human cardiomyocytes (providing information from a human platform, even if stem cell-derived) could be considered to carry a lower risk for investment, and provide better-posed targets with significantly improved translational potential, than programs based on either criterion alone.

Personalised medicine

Landmark genetic studies such as the human genome project have created an era in which personalised medicine can form a significant component of preventative measures and treatment plans. So called ‘pharmacogenomics’ can be used to identify patients most likely to exhibit adverse or positive effects to specific drugs. Genetic variants strongly associated with a particular response can be screened for, allowing treatment to be tailored on an individual level.[17,36] This has already led to the advent of gene-informed treatment, or ‘smart’ therapy.[17] Gene informed preventative measures can also be applied; risk scoring models could be replaced by individual risk-based prevention strategies though this would require significant resource. Perhaps a combination of these, first to identify populations at risk (risk scoring) then to apply individual testing, might prove to be the most efficient system. Indeed, this kind of approach is already emerging as a component of clinical care.[36]

CONCLUDING REMARKS

With cardiovascular disease on the rise, development of new therapies is a dynamic and essential area of research. However, the mistakes of the past should not be ignored on this quest, and we can only learn from these if we frankly admit and understand them. The advent of stem cell based therapies for example, elicited great excitement but has not yielded the anticipated revolution in clinical treatments. Perhaps many trials were doomed to failure by being undertaken at too early a stage, without the support of a strong foundation of pre-clinical and mechanistic studies. Further, technical limitations have not yet been overcome, with cell retention still being sub-optimal. It is worth noting that the most promising (non-stem cell) trials to date are those that have been the most extensively understood prior to clinical trials. The timeline for initial target discovery to pre-clinical testing in this approach might be rather longer, but lead to greater success. More substantial target validation and mechanistic information in multiple model systems will increase investment potential and inevitably benefit endeavours for research to impact on clinical practice. However, these approaches will rely heavily on the willingness of scientists to collaborate and coordinate their efforts and expertise in a more logical and efficient manner. Efficient dissemination of results and communication across disciplines is an increasingly pressing necessity, as is a more rational, regulated approach to pre-clinical target discovery and validation.

ISSN 2377-164X Open Journal http://dx.doi.org/10.17140/HROJ-2-112

Let us not forget where we came from: philosophy, discussion and debate always have been, and should be at the heart of research. Modern-day conferences could be said to echo the philosophical debates of the past, and the practice of summarising or collecting publications in one volume (similar to modern day reviews or focus issues) has been around for some time. A particularly famous example is the Hippocratic Collection (*Corpus Hippocraticum*) that incorporates Ancient Greek medical texts from the 4th to 6th Century BC. One particular excerpt documents an interesting idea of the time (from 'On the Heart', unknown author, but originating from the age of Aristotle, 'Hippocrates of Cos – Heart,' volume LCL 509 (Loeb Classical Library, Harvard University Press):

"*The heart, in its shape, is like a pyramid, in colour, deep red. It is enclosed in a smooth tunic which contains a little urine-like liquid, so that you might imagine that the heart dwells in a bladder. This is so arranged in order that it may beat vigorously in safety, having a quantity of moisture just sufficient to protect it against being ignited. This liquid the heart passes through like urine after lapping up drink from the lung.*"

Though different from current views, it should be remembered that publications such as this provided the foundation for where we are today and highlight that progress relies on documenting, discussing and building on previous research. Of note, strongly opposing points of view are also aired in this collection, with many texts containing direct challenges and (sometimes heated) retorts to other scholars of the time;[73] discussion of this nature is a driving force in the pursuit of knowledge and continues to this day.

By reviewing the history of cardiovascular research, we can not only predict future challenges such as data assimilation and dissemination, but also potential successes. It wasn't until the 1970's that molecular studies really emerged so it is not surprising that this technology has not yet translated fully into the clinic. Indeed, early electrophysiology studies in the 1920's only translated into current treatments some 60 years later, and surgical methods originated as far back as the 12th Century. Thus cellular and molecular studies are in their relative infancy, and the future no doubt holds momentous progress in this area. Based on the lag between early electrophysiology and its established use today, perhaps we can surmise that molecular therapies will reach a practical level around 2030. In fact, promising clinical trials using molecular interventions already exist, and provide hope that clinical practice will undergo a real change in molecular medicine in the near future.

So what does the future hold? We now have the perspective, technical capabilities and resources at our disposal to truly understand the cell biology of the heart at an unprecedented level, and discern highly translatable molecular targets that will provide the best candidates for drug discovery. At the core of this however, lies open communication and collaboration across boundaries and disciplines, and critical appraisal and development of models and workflows. Together, we can considerably diminish the impact of cardiovascular disease, one of the biggest killers of the 21st Century.

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