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Focusing Heart Failure Research on Myocardial Fibrosis to Prioritize Translation

Merry L. Lindsey^{1,2}, Kristine Y. DeLeon-Pennell^{3,4}, Amy D. Bradshaw^{3,4}, R. Amanda C. LaRue^{4,5}, Daniel R. Anderson⁶, Geoffrey M. Thiele^{2,7}, Catalin F. Baicu³, Jeffrey A. Jones^{4,8}, Donald R. Menick^{3,4}, Michael R. Zile^{3,4}, Francis G. Spinale⁹

¹Department of Cellular and Integrative Physiology, University of Nebraska Medical Center, Omaha, NE

²Research Service, Nebraska-Western Iowa Health Care System, Omaha, NE

³Division of Cardiology, Department of Medicine, Medical University of South Carolina, Charleston, SC

⁴Research Service, Ralph H. Johnson Veterans Affairs Medical Center, Charleston, SC

⁵Department of Pathology and Laboratory Medicine, Medical University of South Carolina, Charleston, SC

⁶Division of Cardiovascular Medicine, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE

⁷Division of Rheumatology and Immunology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE

⁸Department of Surgery, Division of Cardiothoracic Surgery, Medical University of South Carolina, Charleston, SC

⁹Cardiovascular Translational Research Center, University of South Carolina School of Medicine, Columbia, SC and William Jennings Bryan Dorn VA Medical Center, Columbia, SC

Abstract

Heart failure (HF) was traditionally been defined by symptoms due to fluid accumulation and poor perfusion, but it is now recognized that specific HF classifications hold prognostic and therapeutic relevance. Specifically, HF with reduced ejection fraction (HFrEF) is characterized by reduced left ventricular (LV) systolic pump function and dilation and HFpEF is defined primarily due to abnormal LV filling (diastolic failure) with relatively preserved LV systolic function. These forms

For Correspondence: Merry L. Lindsey, Ph.D., Department of Cellular and Integrative Physiology, University of Nebraska Medical Center, 985850 Nebraska Medical Center, Omaha, NE 68198-5850, (phone) +1 (402) 836-9274 Merry.Lindsey@unmc.edu.

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of HF are distributed equally amongst patients with HF and will likely require distinctly different strategies to mitigate the morbidity, mortality and medical resource utilization of this disease. In particular, HF is a significant medical issue within the Veteran Administration (VA) hospital system and constitutes a major translational research priority for the VA. Since a common underpinning of both HFrEF and HFpEF appears to be changes in the structure and function of the myocardial extracellular matrix (ECM), a conference was convened sponsored by the VA, entitled, “Targeting Myocardial Fibrosis in Heart Failure” to explore the ECM as a potential therapeutic target and to propose specific research directions. The conference was conceptually framed around the hypothesis that while HFrEF and HFpEF clearly have distinct mechanisms, they may share modifiable pathways and biological mediators in common. Inflammation and ECM were identified as major converging themes. A summary of our discussion on unmet challenges and possible solutions to move the field forward, as well as recommendations for future research opportunities, are provided.

Keywords

heart failure; translational research; research priorities

Introduction

The development and progression of heart failure (HF) is a leading cause of hospitalization, morbidity, and mortality, and HF is predicted to reach epidemic levels.[1, 2] Veterans have an increased risk for cardiovascular disease compared with non-veterans.[3, 4] and HF is a major cause for admission in the Veterans’ Administration (VA) Health Care System.[5] Beginning at age 40, the lifetime risk of developing HF is 20%.[6] Two common pathways that lead to the clinical syndrome of HF are myocardial infarction/ischemia (MI) that yields HF with reduced ejection fraction (HFrEF) and hypertension/pressure overload of the left ventricle (LV) that yields HF with preserved ejection fraction (HFpEF). While the clinical definition of HF is based upon symptoms such as exercise intolerance, fluid accumulation, and respiratory difficulty, the underlying pathophysiology is that of LV dysfunction. The distribution of HF phenotypes into HFrEF or HFpEF is approximately equal, and both combined constitute significant health care challenges within the VA. Despite equal distribution, the risk of HFpEF is higher in women; whereas, men are more likely to develop HFrEF.[7–9]

The standard pharmacotherapy for HF has predominantly involved receptor antagonists such as inhibitors of the renin-angiotensin system. The Prospective Comparison of ARNI With an ACE-Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial identified that in addition to angiotensin II receptor blockade, addition of a neutral endopeptidase inhibitor neprilysin further improved clinical outcomes in HFrEF.[10] The Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF) trial was designed to determine the efficacy and safety of the combination of angiotensin receptor inhibitor valsartan and the neutral endopeptidase inhibitor neprilysin in HFpEF.[11] Baseline NT-proBNP predicted HF events, and combination therapy reduced NT-proBNP consistently in both men and women,

and in patients with lower or higher EF.[12] These trials underscore that activation rather than inhibition of specific receptor pathways could provide favorable cardiovascular effects, opening a new avenue of translational and clinical research for HF. As more recent publications on the PARAGON-HF trial conclude that Sacubitril-valsartan did not lower rates of total hospitalization or death,[13] significant challenges in managing patients with HFpEF remain.

In light of this, the VA has sponsored several focused sessions on HF, with the goal of identifying translationally relevant research objectives. One such collaborative meeting was held in Charleston, SC on July 27–28, 2019. This session was based on recognizing 5 elements relevant to HF research and are shown in Table 1, and these 5 elements formed our initial focus. This is an executive summary report of that meeting, in which fundamental research gaps and opportunities may exist regarding HF and the ECM were identified.

Because the cellular and molecular basis for the development and progression of HF are multifactorial and specific to etiology, therapies are likely to be distinctly different. At the same time, there are common areas of emphasis for future research. In particular, changes in inflammation and within the myocardial interstitial extracellular matrix (ECM) occur in both HF phenotypes (Figure 1). While the canonical thought regarding the ECM is that the response is entirely reflected by an accumulation of fibrillar collagen termed myocardial fibrosis, this is an oversimplification of a highly complex process. Moreover, the ECM is the major reservoir for signaling molecules, such as inflammatory cytokines and growth factors that not only modify the ECM, but the entire structure and physiology of the myocardium. Finally, there is growing recognition that the myocardial fibroblast plays a prominent role in ECM reorganization.

Accordingly, the focus of this meeting was to examine specific aspects of ECM remodeling in both HFrEF and HFpEF, including to identify commonalities and differences in ECM and fibroblast response. The deliverable was to not only identify where improvements in definitions and nomenclature exist, but to also harness important scientific insights from other relevant disease states such as chronic inflammation and cancer, which could be used to guide new directions in HF research. In collaboration with the VA Research Office (Washington DC), a roster of attendees was assembled with synergistic and complementary expertise regarding HF and the intersection of inflammation/ECM (Table 2). It must be recognized that this short meeting by no means encompassed all of the leaders and experts in ECM remodeling, but rather provided recommendations in this specific scientific area that could then be carried forward.

Subject One: Nomenclature and Definitions

The first subject reviewed and discussed was how to improve the definitions and nomenclature to enhance conceptual clarity for HF and ECM research (Table 3). We identified a need for updates in terminology to avoid oversimplification of pathological processes. The six areas of discussion centered around the terms and concepts of HF, remodeling, inflammation, fibrosis, fibroblasts, and plasticity in cell types involved.

Redefining HF and HF phenotyping.

The most up to date definition of HF is when cardiac output is not adequate to meet the oxygen demands of the body while maintaining a normal diastolic filling pressure, either at rest or with exercise.[14] Assessing functional parameters of HF at the time of diagnosis is useful for examining response to therapy but does not inform on the signaling pathways that led to the development of the disease. The opportunity to access patient samples pre-HF would allow longitudinal mechanistic evaluations of the evolution to occur although clear obstacles to obtaining such samples are self-evident. The biggest challenge is that myocardial tissue sampling is not feasible and plasma as a necessary surrogate must adequately reflect the myocardial reaction. This limitation highlights the need for pre-HF animal models that will reliably track progression from the time the injury or stimulus occurs. One such resource is the Hybrid Mouse Diversity Panel (HMDP), a collection of approximately 100 well-characterized inbred strains of mice that can be used to analyze genetic and environmental factors of HF.[15] Using this resource will allow environmental factors to be controlled, provide relevant tissues for global molecular phenotyping, and integrate separate studies because inbred strains are renewable.

Because HF in the VA population is projected to increase 2–3 fold over the next decade, novel and more effective management of HF aimed at decreasing functional disability, morbidity and mortality represents a prime directive. In the cancer field, significant advancements have been made in terms of targeting chemo/immunotherapy to clearly signify phenotype in terms of cellular and molecular pathways invoked.[16] This precision medicine approach has not been well developed in HF therapeutics or even research strategies. Indeed, developing HF phenotyping classifications has been identified as an NIH research priority,[17, 18] and the call for HF phenotyping has resonated through cardiovascular medical societies and expert panel reports. There is a need to identify the specific molecular pathways utilized to improve phenotyping capabilities and develop more strategic management of VA patients with HF.

Denoting remodeling subtypes.

LV remodeling is an all-encompassing term that reflects any changes in size and shape, structure and composition, and physiology of the LV.[14] It is important to note that LV remodeling in response to hypertension is much different than LV remodeling in response to MI. Therefore, defining subtypes of LV remodeling will provide mechanistic insight into how HF develops and progresses under different conditions. A start to this approach will be to designate the cause of remodeling to ensure that the underlying source of HF is clear.

Detailing Inflammation.

Likewise, inflammation generated by pressure overload is different in timing, amplitude, duration, and composition from inflammation generated by MI. The inflammatory environment of the day one MI LV is much different from the inflammatory environment seen one week after MI. Inflammation has been proposed as a fundamental mechanism underlying the development of HF in general and ECM accumulation in particular. However, the term inflammation is broadly defined and encapsulates diverse cellular processes, including immunity, increased leukocytes, and other components. Leukocytes include

lymphocytes, monocytes and macrophages, neutrophils, and other cells. Each of these cells requires precise characterization and definitions of modifications over the progression to HF. The terminology and descriptions for these cells and inflammation in general need both clarification and consensus.

Redefining Fibrosis.

Fibrosis is the generic term for any pathologic ECM accumulation. The term fibrosis encapsulates the general concept of increased ECM, and variations occur across all major organ systems. The term fibrosis is in contrast to normal wound healing, where ECM deposition occurs and is regressed as part of the wounding response. In the heart, excessive ECM accumulation can occur in each chamber of the heart with significant negative consequences leading to increased morbidity and mortality. For example, atrial and ventricular pro-fibrotic pathways can cause significant arrhythmias; an excessive degradation of normal ECM or accumulation of ECM or modified ECM can impair LV physiology and clearly contributes to HF.

The issue with using fibrosis as a general term for ECM accumulation is that scar formation after MI is fibrosis and yet is much different in pathological consequences than ECM accumulation in the remote zone after MI or in the interstitial space in response to pressure overload. The terms reparative and replacement are also unsatisfactory, as both, for example, could be applied to the scar scenario. Measuring net ECM concentration also does not take into consideration differences in the balance between degradation and synthesis pathways, as net amounts can occur under diverse scenarios and through separate mechanisms. Differentiating between total ECM increases and shifts in composition of individual ECM components is also important. Specifying what fibrosis means, what the exact definition is in the individual contexts of HFrEF and HFpEF, will help to define pathways most amenable to therapeutic intervention.

Recognition of the Emergence of Different Fibroblast Populations and Niches.

It had been assumed that the cardiac fibroblast was a generic, fairly static cell type. However, through a number of investigative methods, it has become quite clear that there are a number of subpopulations of cardiac fibroblasts with regional distribution profiles. Moreover, these subpopulations of fibroblasts may react differently to pathological stimuli whereby proliferation of some subpopulations may be accompanied by the disappearance of other subpopulations of fibroblasts.¹⁸ As in cancer or inflammatory disease, fibroblasts are the cellular foundation for the production and homeostasis of ECM. However, methods for identifying shifts in cardiac fibroblast activation and subpopulations remain problematic for several reasons. First, there is no consensus on defining the set of markers that best define fibroblasts, particularly those fibroblast populations undergoing different stages of activation, proliferation and differentiation. Second, histomorphometric or immunocytochemical reagents remain limited, particularly in terms of using these approaches in-situ. Third, the stability of the fibroblast phenotype which is operative in-vivo can be lost when fibroblasts are maintained in culture, particularly after several passages. Thus, in-vitro studies of fibroblast cultures obtained from cardiac disease states must be interpreted with caution.

While neutrophils and macrophages have historically been considered key mediators of necrotic cell removal and indirect regulators of infarct scar formation, more recent evidence indicates these leukocytes also acquire fibroblast-like properties and produce factors that influence ECM composition and structure.[19, 20] Likewise, cardiac fibroblasts at day 1 after MI display a strong pro-inflammatory phenotype with upregulation of several proteases.[21] Therefore, there is cell plasticity among cardiac cell types, creating the need to further define what cell activation and differentiation mean in the context of MI and pressure overload. Notably, fibroblasts have been described in many tissues in binary terms as either quiescent fibroblasts or myofibroblasts. In reality, fibroblasts are never quiescent and there is a continuum of responses in response to stimuli. For example, alpha smooth muscle actin increases linearly with time after MI, indicating that a negative or positive classification is not informative.[21] In the cardiac fibroblast field, the term myofibroblast has been proposed to be redefined as an activated fibroblast to describe the fibroblast responsive population.[22] In addition, sex can influence the way a cell responds to stress or injury through both hormonal and chromosomal mechanisms.[23, 24] With the advent of single cell sequencing, the concept that cardiac fibroblast populations exist in a range of activated phenotypes is emerging.

Thus, an important research recommendation is to develop a consensus on fibroblast identification, nomenclature and standardized histochemical/biochemical approaches that could then be applied to the context of HFrEF and HFpEF.

Subject Two: ECM Evaluation

We identified several gaps in how ECM is currently measured, including; how quantification is performed, which ECM components are assessed, effects of modifications to ECM, and taking advantage of new imaging modalities that can inform us regarding ECM composition and localization.

How regional quantification is performed should be defined, with regions being measured as independent assessments. For example, there are notable differences in ECM accumulation in the infarct scar vs. remote region. Likewise, with pressure overload, both perivascular and interstitial ECM accumulation, and physiological consequences of both, are distinct.

Collagens expressed in the myocardium include types I, III, V, IV and VI, among other less represented family members. Evaluating ECM content by picrosirius red or Masson's trichrome staining only does not provide sufficient details. Of note, whereas picrosirius red staining can be used to visualize collagen fibers under polarized light and thus reflect fibrillar collagen content, Masson's trichrome staining does not provide a sufficient level of detail. Using multi-omics, including both transcriptomics and proteomics strategies, provides the best ways to look more in depth at ECM components. Importantly, the deposition of many ECM components, including collagens, is dependent upon extracellular processing hence transcriptomics might not completely reflect changes in extracellular insoluble ECM incorporation. There is a need to make better attempts to more completely catalogue ECM composition at different stages of HF etiologies. Likewise, ECM is heavily modified, yet few cardiac studies evaluate these differences in post-translational

modifications. Most relevant modifications include glycosylation, cross-linking, and proteolysis by matrix metalloproteinases and other proteases.[25–27]

The ECM is complex, involving a skeletal backbone structure that supports tissue architecture and provides physiological signaling pathways critically important for organ function. These pathways include immune responses, metabolism, and endocrine regulation. Exactly how the ECM is perturbed in HFrEF vs. HFpEF is unclear. Early inflammatory mediators such as transforming growth factor β , which are bound in the ECM in inactive forms and activated during LV remodeling could play distinguishing roles. Pro-inflammatory ECM modifications perpetuate the development and progression of cardiac fibrosis, yet we know very little concerning this complex interplay. ECM post-translational modifications are central to regulation of protein function and aberrant modifications disrupt the regulatory balance. Thus, the impact of inflammation (both local and systemic) have an impact on the tissue fibrosis that amplifies with age. More information is needed on how aging superimposes on HF to alter the pathological response. There is a need to understand the dynamic range of ECM homeostasis that encompasses normal turn-over with age and compare this range to abnormal turn-over seen early after MI or pressure overload to generate excess ECM accumulation that yields a stiffer LV.

Using imaging modalities to qualify and quantify myocardial ECM has been a rapidly evolving technology.[28–30] Imaging should encompass microscopic to macroscopic examination for complete phenotyping, and there is a need to evaluate and incorporate results from across assays, rather than assess in isolation. For example, integrating cardiac physiology with cellular phenotypes and molecular signaling will provide a big data approach that will provide new insight into mechanisms. In vivo, Sahul and coworkers developed a novel MMP-targeted radiotracer in order to monitor serial changes in left ventricular remodeling in a noninvasive manner.[28] This method used SPECT/CT imaging to compare localization of (99m)Technetium-labeled MMP substrate (RP805) with standard (201)Thallium imaging (used to track myocardial tissue perfusion) in a porcine model of MI. Results from their study demonstrated a significant correlation between (99m)Tc-RP805 uptake and *ex vivo* MMP-2 activity in the early post-MI period, and suggested that this novel MMP-tracer may provide unique information about regional myocardial MMP activation and may have utility in predicting late post-MI LV remodeling.

Mass spectrometry coupled with histological sections is a powerful way to image *ex situ*. Matrix-assisted laser desorption/ionization (MALDI) and imaging mass spectrometry (MALDI-IMS) provides multiplexed histological mapping of proteins and protein components inaccessible by antibodies and has been used to generate 2-D maps of ECM.[31, 32] The development of MALDI-IMS technology provides localized access to collagens and elastin sequences that were previously unattainable. Angel and colleagues utilized a MALDI-IMS with matrix metalloproteinase (MMP)-12 to produce informative images that provide elastin localization and quantitation.[32] This approach has been extended to use a MALDI FT-ICR mass spectrometer for *in situ* glycan imaging to reveal N-linked glycan branching and fucosylation that are increased in tumors.[33] Second harmonic generation in confocal microscopy and MRI are other approaches that can target ECM. Likewise, improved *in situ* hybridization protocols provide more refined cell localization. Such

approaches are needed for HF research. For imaging modalities, there is a need to set standards for imaging during the development and progression of HFrEF and HFpEF.

Cardiac magnetic resonance imaging (MRI) has evolved to incorporate a number of measures of myocardial fibrosis. We refer the reader to a recent special issue published by JACC Cardiovascular Imaging on Imaging the Interstitium, published in November 2019 (http://imaging.onlinejacc.org/content/12/11_Part_2). One study in particular found that both focal and diffuse myocardial fibrosis were more prevalent in HFpEF subjects than in control subjects of similar age and sex.[34] The Gd-containing collagen I-specific contrast agent EP-3533 has been used for staging fibrosis and therapy monitoring by 3D molecular MRI in an animal model of liver fibrosis.[35] The collagen-targeted positron emission tomography (PET) probe 68Ga-CBP8 is an analogue of EP-3533 and has been used to evaluate lung fibrosis in the bleomycin mouse model.[35] Whether MRI and PET can distinguish subjects with HFpEF from those with HFrEF remains to be seen.[36]

Subject Three: Harnessing Insights from Other Disease States

There was discussion on how other pre-existing disease states could modify HF; in particular, the focus was on diseases that generate inflammation. Discussion centered on how inflammatory pre-existing conditions could reset the underlying myocardial homeostasis onto which MI or pressure overload changes would be amplified. We also discussed how to borrow concepts from cancer with particular focus on the cancer associated fibroblast and how to use animal models to answer more directed research questions.

Chronic Inflammation.

Diseases with inflammatory components are known to exacerbate HF; in particular, there is a strong connection between rheumatoid arthritis or periodontal disease and HF.[37–41] These disease all share over activation of immune cells, particularly T-cells. Leukocyte subtypes each produce a number of inflammatory mediators, including MMP-9.[42]

Rheumatoid arthritis.—Patients with rheumatoid arthritis suffer disproportionately from cardiovascular disease with a risk of a cardiovascular event equal to 1.48.[43] Rheumatoid arthritis is also prevalent in the Veteran population.[43] Elevated levels of oxidative stress and the generation of reactive oxygen species (ROS) and associated modification of proteins, including ECM proteins, have been proposed to be the principal pro-inflammatory and proatherogenic mechanisms for the increased risk of cardiovascular events in the chronic inflammation of rheumatoid arthritis. Other risk factors for CAD and subsequent MI (e.g. hypertension and diabetes) also exacerbate ROS and tissue inflammation, further accelerating chronic inflammatory diseases. In the National Inpatient Sample database using data from 2005–2014 (unweighted n=774,808), 62.9% of patients with rheumatoid arthritis had hypertension and 26.9% had diabetes.[44]

Compared to individuals without rheumatoid arthritis, patients with rheumatoid arthritis have similar short term outcomes after MI yet experienced poorer long term outcomes such as mortality (hazard ratio= 1.47; 95% confidence interval= 1.04–2.08), recurrent ischemia (hazard ration= 1.51; 95% confidence interval= 1.04–2.18), and development of HFrEF

(hazard ratio: 1.27; 95% confidence interval: 1.07 to 1.51) and HFpEF (hazard ratio= 1.22; 95% confidence interval= 1.04 to 1.43) compared to patients without rheumatoid arthritis. [40, 45] Interestingly, the increased risk of non-ischemic HF occurs early within the first year of rheumatoid arthritis onset and was associated with disease severity.[45] There is also a connection between both RA and HFpEF for prevalence in women over men.

Periodontal disease affects about half of the American adult population and is highly prevalent in the Veteran population.[39, 46] Oral health measurements (number of decayed, missing, or filled teeth, mean probing depth, oral hygiene status, and percentage of bleeding sites) are associated with MI incidence.[47, 48] Co-existing periodontal disease increases MI mortality by seven-fold.[49, 50] Chronic inflammation induced by periodontal disease exacerbates the inflammatory response and induces an imbalance in ECM degradation and deposition resulting in adverse cardiac remodeling.[51, 52] Likewise, periodontal disease is associated with a higher risk of hypertension.[53] Therefore, understanding how underlying inflammation exacerbates HF will provide insight into progression mechanisms. In addition to rheumatoid arthritis and periodontal disease, systemic sclerosis and systemic lupus erythematosus are inflammatory conditions known to alter cardiac responses to injury.

Cancer and cancer-associated fibroblasts (CAFs).

There is pronounced heterogeneity of fibroblasts within the tumor stroma, which have varying phenotypes.[54] One of these cell types is the CAF that influences malignant growth through interaction with immune cells and crosstalk with endothelial cells.[55] CAFs fuel tumor progression by potentiating malignant cell proliferation and regulating immune and fibrotic responses.[56] Specific surface proteins and the secretome of the CAF are important sources of key regulators in tumorigenesis.[57, 58] Borrowing from this literature would provide novel insight into fibroblast subtypes in the HF myocardium. For example, by evaluating whether proteins that demarcate CAFs are also markers for activated cardiac fibroblasts would provide information on how fibroblasts respond across different organ systems.

Animal models.

HFpEF and HFrEF are initiated by different mechanisms and display different pathological progression. Basic science using animal models of disease needs to continue to be informed by clinical medicine, as much as the converse. A clearer understanding of the distinguishing characteristics between MI, ischemia and reperfusion, and pressure overload models in terms of pathological responses of the myocardium and appreciating which model is useful to answer specific questions is essential for those who work and review in the field to understand the complexity of the responses. For example, all 3 models accumulate macrophages in the myocardium, but in different locations, at different times, and with different maximum amplitudes. Macrophage numbers peak at day 3 in MI models, and this is accelerated in the presence of reperfusion and delayed in pressure overload induced by transverse aortic constriction. Guidelines have been developed to define models of myocardial ischemia, including with the use of reperfusion.[59] We identified the need to further use animal models for pre-HF assessment.

Conclusions: developing an actionable collaborative research strategy

Combining the 3 discussion points, Table 4 lists the future directions needed to develop an active actionable collaborative research strategy. Use of existing databases will harness the power of established collections; particularly for human samples. Technologies that include multi-omics approaches will provide big data means to integrate a large amount of data to distill down the most important factors. Proteomics is particularly important, as post-translational changes at the protein level is a key regulation point for ECM. In terms of translation, post-transcriptional and post-translational control of the ECM is a key element, and targeting post-translational events in HF are likely to be fruitful. With these strategies, we can develop a better understanding of the ECM pathways that intersect and those that diverge in HFrEF and HFpEF, leading to new therapeutic targets for HF.

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Figure 1.

An extracellular matrix (ECM) focused roadmap regarding the potential pathways for adverse LV myocardial remodeling in heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). While an oversimplification, a primary initiating stimulus for HFrEF is myocardial ischemia whereas for HFpEF is a prolonged pressure overload. These stimuli are then modified by secondary influences which include age, gender and comorbidities. A key cellular event is the transition and expansion of an activated fibroblast subpopulation leading to changes in ECM structure, and eventually to an adverse myocardial remodeling process. With HFrEF this is commonly manifested by infarct expansion, LV dilation, and systolic dysfunction. Whereas in HFpEF the adverse myocardial remodeling is more global fibrosis, increased LV stiffness, and diastolic dysfunction. Further exploration and targeting of fibroblast activation and ECM synthesis/degradation pathways would form an important avenue of translational research and yield therapeutic strategies for these HF phenotypes.

Table 1.**Focusing Heart Failure (HF) Research on Myocardial Fibrosis to Prioritize Translation: Discussion Points and Key Statements**

1. HF has been canonically defined as a generalized spectrum of symptoms, and approaches to HF therapeutics have been generically applied. Subsequently, a large proportion of patients with HF are refractory to treatment and progression is unabated.
2. Patients presenting with HF requiring hospital admission carry a dismal prognosis-similar to highly malignant forms of cancer. Unlike cancer in which cellular and molecular phenotyping form a critical component of medical management, only recently has it been recognized that phenotyping HF with biological precision may yield improved therapeutic strategies.
3. While phenotype classifications for HF will likely improve in terms of definition and molecular and cellular precision, two distinct HF phenotypes emerge based upon the predominant underlying pathophysiology- HF with a reduced ejection fraction (HFrEF) and HF with a preserved ejection fraction (HFpEF).
4. While HFrEF arises primarily from ischemic heart disease and HFpEF arises primarily from hypertension and aging, structural changes occur within the myocardium of both HF phenotypes. Changes in the structure and physiology of the extracellular matrix (ECM) is a critical flux point contributing to HF progression in both etiologies.
5. A number of intersecting pathways can affect the ECM and converge on a specific cell type- the fibroblast. The regulation of the fibroblast in other disease processes such as cancer metastases and proliferative fibrotic disease may identify potential therapeutic pathways operational in the cardiac fibroblast.

Table 2.**Participant list**

Daniel Anderson, MD PhD [Cardiovascular Medicine, Internal Medicine, University of Nebraska Medical Center (UNMC)]
Catalin Baicu, PhD [Cardiology Division, Medical University of South Carolina (MUSC) and Ralph H. Johnson Veterans Affairs Medical Center (RHJ Charleston VAMC)]
Amy Bradshaw, PhD [Cardiology Division, MUSC and RHJ Charleston VAMC]
Kristine DeLeon-Pennell, PhD [Cardiology Division, MUSC and RHJ Charleston VAMC]
Jeffrey Jones, PhD [Cardiothoracic Surgery Division, MUSC and RHJ Charleston VAMC]
Amanda LaRue, PhD [Pathology and Lab Medicine, MUSC and RHJ Charleston VAMC]
Merry Lindsey, PhD [Cellular and Integrative Physiology, UNMC and Omaha Veterans Affairs Medical Center]
Donald Menick, PhD [Cardiology Division, MUSC and RHJ Charleston VAMC]
Francis Spinale, MD, PhD [Cardiology Division, USC and William Jennings Bryan Dorn VA Medical Center]
Geoffrey Thiele, PhD [Rheumatology Division, Internal Medicine, UNMC and Omaha VAMC]
Michael Zile, MD [Cardiology Division, MUSC and Cardiology Division Director at RHJ Charleston VAMC]

Table 3.**Key definitions**

Heart Failure (HF)	Inadequate cardiac output to meet the demands of the body, both at rest and with exercise, while maintaining a normal diastolic filling pressure; can occur with reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF)
Extracellular Matrix (ECM)	All constituents of the extracellular matrix environment, including cell surface membrane proteins
Fibroblast	Cell type producing ECM and maintaining homeostasis in the normal left ventricle (LV); activated in response to a myriad of stimuli to produce phenotypes ranging from pro-inflammatory to anti-inflammatory to reparative
Fibrosis	Generic term for any pathological accumulation of ECM
Inflammation	Encapsulates cellular immunity, increased leukocytes, and other components that either promote (pro-) or curb (anti-) inflammation
LV remodeling	Any changes in geometry and myocardial structure and composition, which in turn influences LV function

Table 4

An active actionable research collaborative strategy

1. Define distinguishing and overlapping inflammation and ECM phenotypes in HFrEF vs. HFpEF.
2. Define terms and clarify concepts of LV remodeling, inflammation, fibrosis, fibroblasts, and cell plasticity.
3. Develop standard operating procedures for rigorous and reproducible assessment of cardiac ECM, including use of imaging modalities.
4. Evaluate exacerbation of HF development and progression in the setting of underlying inflammatory co-morbidities (e.g., rheumatoid arthritis and periodontal disease) and in the setting of aging.
5. Harness knowledge gathered in the cancer research arena to develop translatable strategies applicable to HFrEF and/or HFpEF.
6. Carefully define animal models of HFrEF and HFpEF for preclinical evaluation for targeted ECM therapeutics.