Multidimensional Molecular Biomarkers In Advanced Heart Failure – Reviewing the MyLeukoMAP™ Hypothesis Rationale

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ABSTRACT

This review develops the hypothesis that in patients with advanced heart failure (AdHF) accurate longitudinal clinical phenotype assessment and leukocyte transcriptome/phenome modeling allows the development of a multidimensional molecular biomarker (MMB)-predictor of “progression/death on optimal medical management (OMM) in heart failure with reduced ejection fraction (HFrEF)” termed MyLeukoMAP™ which provides a better comparative survival benefit prediction of AdHF treatment options than by clinical predictors alone.

Key Words: heart failure, mechanical circulatory support device, multiorgan dysfunction, whole blood, peripheral blood mononuclear cells, gene expression profiling

Funding: Funding for the MyLeukoMAP™ pilot study phase was obtained by Columbia University NIH SCCOR Grant (PI Rose, Co-PI Deng), UCLA NIH R21 (PI Deng), UCLA R01 (PI Weiss, Joint PI Deng), UCLA R01 (PI Ping, Co-I Deng), UCLA DOM and Columbia University (Geier, Milo, Tocco) and UCLA patient philanthropy (Mulder).

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THE GROWING EPIDEMIC OF HEART FAILURE

In the United States, heart failure (HF) affects 6 million persons (Yancy 2013). HF with reduced ejection fraction (HFrEF) affects 3 million people. The lifetime risk of developing HF is 1 in 5 for men and women older than 40 years of age. The death rate remains unacceptably high at approximately 50% within 5 years from the time of index diagnosis. In the US, an annually estimated 300,000 persons are diagnosed with Stage D heart failure, also classified as AdHF (Hunt 2009). Patients with this etiology may benefit from therapies such as long-term, lifetime or destination therapy such as mechanical circulatory support (MCS, approx. 30,000) or heart transplantation (HTx, approx. 3,000) in lieu of optimal medical management (OMM) or palliative/hospice care (PC). HF is a major public health concern due to its tremendous societal and economic burden, with an estimated direct and indirect costs in the U.S. of $37.2 billion in 2009, which is expected to increase to $97 billion by 2030 (Roger 2012). While 25% of all spending occurs during the last year of life (Orszag 2008, Zhang 2009), in patients hospitalized with HF, more resource spending is associated with lower mortality rates (Ong 2009). A key question is: Which of these therapies does a healthcare provider recommend to the individual AdHF-patient in order to tailor personal benefits in the most cost-effective way?

PREDICTION OF DISEASE PROGRESSION IN ADHF

While in Stage C HF guideline-based medical therapy is well established, the comparative benefit of OMM, MCS, HTx or PC in Stage D HF is not as well defined. This ambiguity suggests unpredictability of clinical trajectories, even with current clinical prediction tools tailored to the progressive clinical trajectory of HF severity and HF-related organ dysfunction (OD). Such models include Brain Natriuretic Peptide (BNP) measurements (Troughton 2000, Gardner 2003, Doust 2003), the Heart Failure Survival Score (HFSS) (Aaronson 1997), Seattle Heart Failure Model (Levy 2006, Ketchum 2010), MAGGIC score (Sartipy 2014), Frailty Scores (Martinez-Selles 2009, Flint 2012), INTERMACS Score (Smits 2013, Kirklin 2014), UCLA score (Chyu 2014), Sequential Organ Failure Assessment (SOFA) Score (Vincent 1996), HeartMate II risk score (Cowger 2013), Model of End-stage Liver Disease (Matthews 2010), Model of End-stage Liver Disease Except INR (MELD-XI) Score (Abe 2014) and right ventricular failure score (Kormos 2010). However, most validated prediction tools have the tendency to underestimate risk among the most severely ill patients. (Sartipy 2014). Due to the uncertainty of predicting Stage D HF progression, what is the impact of this lack of accuracy on individual patients’ health and healthcare costs? Can adding leukocyte biomarkers to clinical predictors alone achieve an improved prediction of risk associated with each treatment option and ultimately an improved prediction of risk reduction when choosing one treatment option over another treatment option, i.e. an improved prediction of comparative survival benefit from
interventions in AdHF-patients suffering from HFrEF?

THE LINK BETWEEN THE DISEASED HEART MUSCLE IN ADHF, NEURO-ENDOCRINE ACTIVATION, AND INFLAMMATORY LEUKOCYTE BIOLOGY

For more than 25 years, the associations between diseased heart muscle, neuro-endocrine activation, and inflammatory leukocyte biology have been well-established (Levine 1990, Deng 1996, Deng 1997, Caruso 2010, Kaur 2009, Soejima). For example, higher levels of the proinflammatory and cachectogenic cytokine tumor necrosis factor (TNF) correlate with more severe AdHF, as indicated by extreme weight loss and cachexia. Since TNF is produced by leukocytes called monocytes which mediate innate immunity, this suggests involvement of innate immunity in the pathophysiology of HF (Levine 1990). A more pronounced inflammatory response after HF-related surgery is linked to worse outcomes in HF (Mann 2002, Braunwald 2012) and other heart disease conditions (Deng 1996, Caruso 2010, Deng 1995). Additionally, more pronounced degrees of OD mediate the severity of such disease (Caruso 2010). In critical illness and injury situations, immunological activation is characterized by virtually global leukocyte transcriptome changes and aberrant leukocyte activation or suppression (Rittirsch 2008).

THE ROLE OF SERIAL PERIPHERAL BLOOD MONONUCLEAR CELL GENE EXPRESSION PROFILING IN ADHF

Circulating peripheral blood leukocyte populations continuously survey tissues and blood (Matzinger 2007) and thus sense the functional state of the heart under various conditions of HF (Yndestad 2002, Cappuzzello 2009, Sinha 2010, Bondar 2014), coronary artery disease with in-stent restenosis (Ganesh 2011), hypertensive heart disease (Gerling 2013) and other organs in a coordinated manner. Blood leukocytes can be easily monitored to assess the state of various tissues and can provide diagnostic information. Gene expression profiling (GEP) of peripheral blood mononuclear cells (PBMC) has been used to understand the underlying physiology and improve diagnostic tools (Deng 2014, Deng 2014). PBMC GEP has been helpful to characterize the systemic inflammatory response syndrome (SIRS) following intravenous endotoxin administration in healthy individuals. Since this experiment is not replicable on animals or human cell lines, it had to be conducted in human subjects. In one study, healthy individuals injected with endotoxin showed significant gene expression changes as opposed to healthy control subjects injected with placebo. Over half of injected subjects’ gene transcripts were immediately down-regulated, while a smaller number of genes showed a delayed response. All these genes returned to baseline after 24 hours (Calvano 2005).
Inflammation is also prevalent in many other diseases such as AdHF, heart transplant rejection, and in MOD following trauma (Laudanski 2006). The factors that are involved in the establishment and regulation of the PBMC phenotype in critical illness are complex and regulation of gene expression occurs at multiple levels, including transcriptome, proteome, and metabolome (Ping 2009, Singer 2007).

The Deng UCLA research lab has a longstanding interest, in the context of the expanding global epidemic of heart failure, in translational systems biology, systems medicine, health systems development, and Personalized Medicine and is positioned at the intersection of the immune and cardiovascular systems. The MyLeukoMAP™ project focuses on a translational research question: How can one better understand the mechanisms of HF while incorporating current scientific knowledge and interpretive abilities to predict the best treatment option for a given heart failure patient at a particular timepoint (Figure 1) Over the last 20 years, from past contributions at Stanford University, Muenster University and Columbia University, the Deng Lab has co-developed the conceptual translational framework and first diagnostic and prognostic leukocyte (PBMC-GEP) biomarker test in transplantation medicine. This test gained US-FDA-regulatory clearance and international evidence-based medicine guideline acceptance to rule out rejection without invasive biopsies (Deng 1995, Deng 1995, Deng 1998, Deng 2006, Pham 2010, Deng 2014).
COMPARATIVE SURVIVAL BENEFIT
RATIONALE FOR MyLeukoMAP™
TEST DEVELOPMENT

Based on this success, the NIH-
United States Critical Illness and Injury
Trials (USCIIT) Group invited the Deng lab
in 2008 to expand this work to develop a
similar PBMC-GEP biomarker test to better
understand HF-related frailty and OD,
diagnose and predict outcomes, and treat
HF-related OD which was named MyLeukoMAP™. This test is expected to
predict more precisely comparative survival
benefit (Deng 2000) of HTx/MCS over
OMM than current clinical tests alone.

As a long-term vision, this new
genomic blood test will assist the HF-
specialist in recommending the best
treatment option (OMM vs. HTx/MCS) to
an individual patient for the best outcome.
Following the path of the successful
AlloMap™ heart transplant rejection rule-
out test, it is expected that MyLeukoMAP™
addresses two test goals of clinical utility
(Figure 2).

Goal 1: Is OMM for a patient at a
particular timepoint best recommended
because of a low likelihood of
progression/death on OMM? To assist in the
clinical decision-making, a rule-out test with
a high negative predictive value would be
helpful to achieve this goal. If
MyLeukoMAP™ confirms the clinical
impression of a low likelihood of
progression/death on OMM, and, therefore,
no expected survival benefit from
HTx/MCS, then OMM continues until the
next encounter and the test is repeated.

Goal 2: If either the clinical data or
MyLeukoMAP™ suggest an elevated
likelihood of progression/death on OMM,
more aggressive therapies such as
HTx/MCS are considered over PC. Next, the
following question must be answered: Is HTx/MCS for a patient at a particular timepoint best recommended because of a low likelihood of progression/death on HTx/MCS? To assist in the clinical decision-making, a rule-out test with a high negative predictive value would again be helpful. **If the test confirms a low likelihood of progression/death on HTx/MCS in contrast to OMM, HTx/MCS is recommended.** However, if either the clinical data or test suggests a high likelihood of progression/death on HTx/MCS and no sign of risk reduction under OMM (no survival benefit expected), PC is recommended.

**MyLeukoMAP™ TRANSCRIPTOMIC BIOMARKER DEVELOPMENT PHASES**

A multiphase MyLeukoMAP™ development program (Pilot Phase, Phases 1-3) (**Figure 3**) achieves this long-term goal. The MyLeukoMAP™ Pilot study, completed in 2014, tested the hypothesis that PBMC GEP is feasible in AdHF patients (**Sinha 2010, Bondar 2014**). MyLeukoMAP™ phase 1 that is currently testing the hypothesis that PBMC GEP correlates with AdHF phenotypes is expected to conclude in 2017. MyLeukoMAP™ phase 2 that will be testing the hypothesis that PBMC GEP is improving outcome prediction precision over clinical predictors alone in AdHF patients suffering from HFrEF is currently being organized. MyLeukoMAP™ phase 3, based on the multidimensional molecular biomarkers (MMB) generated in phase 2, will be testing the hypothesis that PBMC GEP is improving survival comparative benefit prediction over clinical predictors alone in AdHF patients suffering from HFrEF.
**MYLEUKOMAP™ PILOT STUDY**

**PHASE HYPOTHESIS: PBMC-GEP IN AdHF IS FEASIBLE**

The MyLeukoMAP™ Pilot study, completed in 2014, tested the hypothesis that PBMC GEP is feasible in AdHF patients. In preparation to develop the MyLeukoMAP™ test based on the overall project hypothesis that the interaction between altered leukocyte and endothelial cell biology in hypoperfused organs and tissues has the potential to worsen organ dysfunction and further activate the immune system, leading to uncontrolled systemic inflammatory response, MOD and death, it has been demonstrated that this approach of multiparametric immune monitoring to elucidate this conundrum is feasible (Deng 1995, Deng 1996, Deng 1999, Plenz 2001, Li 2006, Cadeiras 2011).

Implementation of genome-wide molecular diagnostics was made possible by microarray technologies. Integrative genomics and systems biological methodologies provided the basis for the development of a new generation of molecular tools as reliable biomarkers. Flow cytometry is a robust methodology that allows for the characterization of many subsets of cells in a complex mixture such as blood by identifying cell-surface proteins, intracellular phosphoproteins and cytokines, as well as other functional readouts. Research has demonstrated the feasibility of PBMC GEP in AdHF patients undergoing longterm/destination MCS surgery and identified patterns of inflammatory response after MCS assessed by PBMC gene expression that are directly and specifically related to increasing degrees of OD (Shahzad 2008, Shahzad 2009, Sinha 2010). The MyLeukoMAP™ pilot phase (Figure 3) has also demonstrated the feasibility of using the clinically-translationally more applicable whole-blood approach by PAX tubes instead of CPT tubes in AdHF patients (Bondar 2014).

**MYLEUKOMAP™ PHASE 1 HYPOTHESIS: PBMC GEP CORRELATES WITH ADHF PHENOTYPES**

Phase 1 of the MyLeukoMAP™ project currently tests the hypothesis that MMB correlate with AdHF phenotypes (Figures 1, 3). MMBs incorporate genome-wide transcriptome analysis using RNA Sequencing and multi-parameter immune cell flow cytometry analysis of PBMC, evaluated in a time-dependent design, using systems-based computational analysis. To test the hypothesis, the study is conducting a prospective time-dependent study designed to characterize (1) temporal patterns of PBMC gene expression and PBMC immune phenotypes in AdHF to (2) reconstruct the temporal PBMC gene expression and immunophenotype program in AdHF.

PBMC GEP is correlated with early manifestations of frailty and organ dysfunction in HF-patients at the time of HTx/MCS-evaluation. The study plans to complete an analysis with 100 AdHF patients on OMM (Heart Failure Controls, HFC), after HTx and after MCS as well as 10 healthy volunteers (HV). Preliminary data shows that the organ dysfunction effects are mediated by PBMC mitochondrial energy metabolism changes (Chang 2014) and that the mathematical
modeling of these high dimensional datasets faces optimization challenges (Wisniewski 2015).

**MYLEUKOMAP™ PHASE 2 HYPOTHESIS: PBMC GEP IMPROVES OUTCOME PREDICTION IN ADHF**

Phase 2 (Figure 3), aims to develop an MMB test that improves risk prediction of “progression/death on OMM in heart failure with reduced ejection fraction (HFrEF)” over current clinical predictors alone and has the potential, by conducting phase 3, to increase the precision of prediction of comparative survival benefit in patients with HFrEF. The MyLeukoMAP™ phase 2 that will be testing the hypothesis that PBMC GEP is improving outcome prediction in ADHF patients suffering from HFrEF over current clinical predictors alone is currently being organized.

The study will enroll 300 HFrEF patients (150 UCLA, 150 UC San Diego/UC Irvine/UC Davis/VA WEST-Los Angeles, hereafter called Consortium) over three years and follow them ≥ 1.5 years. All consecutive adult HF patients with reduced EF (HFrEF) undergoing formal evaluation for HTx/MCS surgery providing consent will be included. Patients with preserved EF (HFrEF), patients with complex congenital HF will not be included because of their heterogeneous clinical phenotype. Based on the UCLA experience, up to the end of the follow-up period (estimated median follow-up: 3.0 years), 170 patients are expected to continue OMM or PC (expected deaths 20), 30 patients are expected undergo MCS, and 100 patients are expected to be listed United Network for Organ Sharing (UNOS) status 1 for HTx. In summary, a total of 150 patients are expected to have reached the primary endpoint of “progression/death on OMM in HFrEF” (HTx Status 1, MCS, death on OMM) by the end of the follow-up period. 26/130 (20%) patients reach the secondary endpoint of “progression/death on HTx/MCS” by this time. For the primary analysis, the study will use the baseline samples of all co-acquired 300 patients (300 samples). A second sample will be analyzed in the 100 patients who are expected to experience “progression/death on OMM in HFrEF” (100 samples) in the MMB development cohort of 200 patients. For the 20 patients in this cohort expected to die on OMM/PC, the sample closest to death will be analyzed. The study will use a stratified randomization based on outcome to ensure that the model building (training) (200) and validation (testing) (100) cohorts have the same proportion of progressors and have similar distributions of patient level characteristics.

The study is interested in predicting the likelihood of HF-progression and comparative survival benefit from HTx/MCS over OMM. The time point of initiation of evaluation for HTx/MCS represents a milestone in the patient trajectory because it is based on a consensus clinical impression of progression of HF-severity between patient and cardiologist. As a clinically meaningful, measurable and temporally well-defined primary outcome measure of HF-progression on OMM (Hicks 2015), the study uses either of three first events after initial evaluation including
death from any cause while on OMM or PC, MCS implantation, or listing for HTx in the UNOS status 1 category. These events can be combined to a composite endpoint of “progression/death on OMM in HFrEF”. Since the decision about the cardiologist’s recommendation of MCS-implantation or listing for HTx in the UNOS status 1 category requires the patient to make the ultimate decision, the proposed study includes modeling under different primary endpoint assumptions. A secondary outcome measure is “progression/death on HTx/MCS” to identify patients with too high risk for MCS or HTx. Primary and secondary outcome measures combine to “progression/death in HFrEF”.

Decision-making in HF is shared between patient and physician (Allen 2012). Various primary endpoint scenarios will be modeled since preferences of patients and, therefore, the number of accrued primary endpoint events may differ from recommendations made by the treating cardiologists. This will consist of the construction of an alternate study outcome based on the clinician recommendation rather than the observed study outcome. The subjects in which there will be a difference between the observed study outcome and this alternate outcome will be cases when the cardiologist recommends that the subjects undergo MCS or UNOS 1 listing, but the subject chooses against this recommendation. The various clinical models will be applied in the 200 subjects in the model building cohort. The study will compare the model-based predictions with the observed progression endpoint the cardiologist recommendation-based progression endpoint. A comparison of the area under the curve (AUC) for the model predictions versus the two endpoints will also be made to evaluate if the models better predict observed vs recommended endpoints. This alternate endpoint will also be evaluated in the model building and validation. The complexity of AdHF patients requires a highly individualized shared decision-making. If the iterative 3-monthly data review suggests that higher granularity of understanding of the shared decision-making information is required for the endpoint analyses, all recruited patients will be offered participation in the ongoing UCLA Encounter Research Project. This research model that has been published (Raia 2014) proceeds iteratively in three stages of data collection and analysis. The study is interested in predicting progression at the time of AdHF-evaluation, utilizing the combined information from the PBMC eigengene network, immune-phenotyping, and clinical phenotyping. The study will use the network based strategy previously discussed to assign gene significance scores based on network connectivity, pathway connectivity, and log p-value from the corresponding univariate predictive model. Next, researchers will create a predictive model using 200 HFrEF-etiology-stratified (non-ischemic versus ischemic dilated cardiomyopathy) and outcome-stratified patient samples randomly selected from the total sample pool of 300 of the Consortium population. The model structure will be multivariable Cox model that will be built on the baseline data. We will use Least Absolute Shrinkage and Selection Operator (LASSO) penalization
and k-fold cross-validation to perform variable selection and model building. Selection of the optimal model without overfitting occurs by using the results of k-fold cross-validation to minimize the mean squared prediction error while minimizing the number of predictor variables. As in the process of the Allomap™-development (G6b-B expression in PBMC during acute cellular cardiac allograft rejection) (Li 2007), it is planned that equivalent validation studies during the MMB development in this MyLeukoMAP™ phase 2 are tailored to the reproducibility of those biomarkers incorporated into the MMB classifier.

After completion of model development using the 200 samples, researchers will be able to determine the improvement of prediction precision of progression adding the MMB-model on top of the clinically established prediction models. After the GEP MMB model is built using a co-acrued 200 randomly selected patient samples (expected HF progression event rate 100), the MMB model is fixed and applied to the validation subjects (100), at the same time as predictions from key clinical prediction tools are calculated, including HFSS (Aaronson 1997), Seattle HF (Levy 2006), UCLA (Chyu 2014), and MELD-XI (Abe 2014) scores as stand-alone models. Each model alone, the standard model and the new combined model provides a score for an individual patient from the validation cohort. This study will use AUC (area under the ROC curve) to obtain a measure of performance. Next, models will be compared using the change in AUC (delta AUC) and Net Reclassification Improvement (NRI) (Pencina 2008) algorithms to measure the increase in performance precision predicting progression/death on OMM in HFrEF.

MYLEUKOMAP™ PHASE 3 HYPOTHESIS: PBMC GEP IMPROVES SURVIVAL BENEFIT PREDICTION IN ADHF

The MyLeukoMAP™ phase 3, based on the MMB generated in phase 2, will be testing the hypothesis that PBMC GEP is improving survival benefit prediction over current clinical predictors alone in AdHF. Phase 3 (Figure 3) plans to evaluate the predictive utility of the MMB predictors on comparative survival benefit. The phase 3 multicenter study will test the following hypothesis: If the MMB developed in the proposed project will allow better prediction of HF-progression than current clinical prediction models alone, AdHF-therapies guided by incorporation of this MMB on top of the clinical prediction tools into the decision-making process will yield a better comparative survival benefit prediction than by clinical predictors alone. For example, an AdHF-patient whose likelihood of HF-progression is low, would benefit from continuation of OMM and deferral of HTx or MCS. In contrast, an AdHF-patient whose likelihood of HF-progression is high, would benefit from more urgent HTx-listing or more urgent DT-MCS-surgery before HF-related OD ensues and before PC is indicated. The optimal study design for phase 3 is an appropriately powered randomized clinical trial in which one arm is allowing the MMB to be incorporated into the clinical-decision-making process.
PERSONALIZED PRECISION MEDICINE RESEARCH INFRASTRUCTURE

The study is innovative because it proposes the integration of a multi-system-level approach into a single predictive test towards the goal of Personalized Precision Medicine (Dzau 2015, Mensah 2015, Collins 2015). There is currently no molecular classifier of AdHF that incorporates a multidimensional pattern into its prediction algorithm. It will follow strict methodologies and robust information platforms characteristic of the new era of “Big Data” (Committee 2012). This information is captured at a high-dimensional multi-omic level, embedded in a comprehensive distilled set of clinical characteristics facilitated by the UCLA electronic medical record (CareConnect) and a Big Data infrastructure developed by the investigators with the UCLA Clinical-Translational Science Institute (CTSI), UCLA-Research Theme “Immunity, Infection, Inflammation & Transplantation” (I3T) and University of California Biomedical Research Acceleration, Innovation and Development (UC-BRAID). We will use the UC-BRAID mechanism (http://www.ucbraid.org) to optimize patient population identification, representing a population of 12 million Californians, patient recruitment & IRB-consent, shared sampling logistics & repository, shared data analysis & publication, and integrated product development & regulatory approval.

SUMMARY

Based on the hypothesis for the MyLeukoMAP™ project reviewed here, it is anticipated that discoveries made by the MyLeukoMAP™ project will lead to novel molecular biomarkers for the improved evaluation of complex phenotypes, risk prediction and ultimately survival benefit prediction in AdHF patients. The discoveries will improve the understanding of mechanisms, detection, prediction and treatment of AdHF across the disease spectrum. The clinical decision-making challenge at the time of evaluation may culminate in the differential recommendation between “all that high-tech modern medicine has to offer” to “compassionate care at the end of life”. The clinical situations leading up to this ultimate – medically, ethically and economically challenging - scenario requires a humanistically sound practice of high-tech modern medicine (which is termed “Relational Medicine™”) and deserves the best evidence-based decision-making support that post-genomic bioscientific translational research has to offer to enable a practice that lives up to the highest humanistic expectations that society has entrusted us with.
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