Basic Science and Clinical Trials: Accelerating the Future

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The Scientific Sessions at the 2018 Pulmonary Hypertension Association International Conference began with presentations on the theme of “Basic Science and Clinical Trials: Accelerating the Future.” These presentations, by leading pulmonary hypertension researchers, focused on recent breakthroughs in understanding the pathobiology of the disease, preclinical models of new treatments, early-phase clinical trials, and future directions for the treatment of pulmonary arterial hypertension.

NOVEL THERAPIES TARGETING THE RIGHT VENTRICLE

Harm J. Bogaard, MD, PhD of Vrije Universiteit Medical Center, Amsterdam, The Netherlands, began the session with his presentation on clinical trials and preclinical studies of novel therapies targeting the right ventricle in pulmonary arterial hypertension (PAH).

Dr Bogaard began by explaining that despite recent advances in the treatment of PAH, survival is still poor, and significant room for improvement remains.1 Much of the mortality in PAH is explained by right ventricular (RV) response to pressure overload, and 2 PAH patients with otherwise similar characteristics may have very different functional capacity and prognosis on the basis of RV function.2 Furthermore, the response of the RV to current PAH treatment is poorly correlated with improvement in RV function; the response of the RV to current PAH treatment is poorly correlated with change in pulmonary vascular resistance (PVR). Patients with persistently low RV ejection fraction (RVEF) have poor outcomes, even if their PVR decreases after vasodilator therapy.3 The presentation focused on recent findings related to mechanisms of RV failure in PAH and potential targets for intervention, in particular chronic sympathetic neurohormonal activation.4 Chronic activation of the sympathetic nervous system in PAH has been known for decades.4 However, there has been controversy around trials with beta-blockers because cardiac output in PAH patients is dependent on heart rate, given known reduction in RV stroke volume.5 Historically, physicians have feared that slowing heart rate with beta-blockers would worsen exercise capacity in PAH patients. This concern, along with case reports of syncope associated with beta-blocker use in PAH patients has led to the widespread recommendation to avoid beta-blockers.6,7

Challenging this long-held belief, Dr Bogaard explained that in SUGEN/hypoxia rat models of PAH, carvedilol (a nonselective alpha- and beta-blocker with some antioxidant properties) was shown to improve RV function, which led to a small clinical trial.8,9 A 6-patient proof-of-concept trial of carvedilol in PAH patients showed improvement in RVEF and less RV dilatation on cardiac MRI.9 A second study by his group in the Netherlands using bisoprolol, a selective beta-1-receptor blocker, did not show an improvement in RVEF; however, in a subgroup analysis, they reported that patients with poor RVEF prior to treatment may have improvement in RVEF with treatment, whereas patients with preserved RVEF and exercise capacity did not.10

Another trial of carvedilol in patients with PAH showed a decrease in heart rate and RV glycolysis, and proved to be safe in PAH patients, but did not show an increase in cardiac output or 6-minute walk distance (6MWD).11 In light of the present data Dr Bogaard emphasized that he does not advocate use of beta-blockers in PAH patients, and that further clinical trials are needed with careful patient selection to identify patients who are most likely to respond to therapy. An alternative for targeting chronically activated sympathetic neurohormonal signaling in PAH may be to increase parasympathetic tone. A recent paper by their research group showed that in the SUGEN/hypoxia rat model, blocking acetylcholinesterase improved survival and RV remodeling, and this may be a safer option than beta-blockers, which they hope to pursue in clinical trials.12,13

A more controversial potential mechanism for RV failure in PAH is impaired microcirculation and ischemia. This is especially important because of ongoing trials using anti-angioproliferative agents targeting endothelial cell proliferation.14 Previous autopsy studies have shown preserved capillaries and microcirculation in PAH patients with...
RV hypertrophy and preserved RVEF, and loss of capillaries in PAH patients with decompensated RV failure and dilatation.\(^\text{16}\) If impaired microcirculation is causative in RV failure, then targeting this would make for a promising PAH treatment. This is supported by a recent study using an miRNA 126 mimic in experimental PAH that showed improved capillarization of the RV, which correlated with improved RV function.\(^\text{17}\)

Another novel therapy targeting the right ventricle in PAH is nintedanib, an antifibrotic drug currently approved for the treatment of idiopathic pulmonary fibrosis. A recent experiment in rats showed that nintedanib reduced fibrosis and improved RV function, despite having no significant effects on the pulmonary vasculature.\(^\text{18}\)

Lastly, for advanced PAH, novel interventional techniques such as RV assist devices, devices to improve pulmonary arterial compliance, and advances in balloon septostomy are being explored as options for bridging to transplantation.

**FINDING NEW THERAPIES FOR PULMONARY HYPERTENSION: HARNESSENG NEW KNOWLEDGE IN BIOLOGY, BIOINFORMATICS, AND BIOENGINEERING**

Marlene Rabinovitch, MD, of Stanford University gave the second presentation of the Scientific Sessions. Like Dr Bogaard, she began by discussing the shortcomings of current PAH therapy, and specifically that none of the currently approved treatments address the underlying pathologic or genetic causes of PAH. PAH is characterized by progressive loss of the distal pulmonary vasculature, endothelial cell apoptosis, occlusive proliferation of smooth muscle cells, and inflammation, none of which are currently targeted by the vasodilators in clinical use.\(^\text{19,20}\) Genetic studies have also led to the discovery of the key role of bone morphogenetic protein receptor II (BMPR2) signaling in PAH pathogenesis, with BMPR2 mutations found in approximately 70% of familial PAH patients, and 20% of "sporadic" idiopathic PAH patients.\(^\text{21-23}\) Furthermore, mutations in other genes that affect BMPR2 signaling such as ALK1, CAV1, and SMAD9 have also been associated with PAH, although their exact prevalence is unclear.\(^\text{24}\)

BMPR2 mutations have been shown to underlie endothelial cell dysfunction, impaired regeneration of small vessels and enhanced smooth muscle cell proliferation in response to injury, impaired assembly of elastic fibers causing vascular stiffness, and enhanced recruitment of inflammatory cells to injured pulmonary arteries.\(^\text{25-28}\) Given the centrality of BMPR2 to PAH pathogenesis, there are now several agents on the horizon aiming to improve the function of this receptor and signaling pathway in PAH (Figure 1). Elafin is an endogenous elastase inhibitor that enhances BMPR2 signaling by promoting interaction with CAV1, and has been shown in vitro to induce neointimal apoptosis and improve endothelial cell function.\(^\text{29}\) FK506 is an immune suppressor that has been shown to improve BMPR2 receptor activity.
These cells have the advantage of shar-
tional clinical trials planned.\textsuperscript{31,32} Sotater-
may lead to improved clinical outcomes
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endothelial or smooth muscle cells.\textsuperscript{39}
cell types, such as pulmonary vascular
treated again to differentiate into various
terminated stem cells.\textsuperscript{36-38}
from a PA catheter, and induced plurip-
organ culture of intact pulmonary arter-
approaches for disease models, including
this, several groups are exploring novel
treatment instead of stage disease rather than
PAH. Because of this, several groups are exploring novel
clinical trials to improve patient outcomes.
Dr Rabinovitch also discussed emerging therapies for PAH that are not
directly related to the \textit{BMPR2} pathway but target other pathways in the patho-
genesis of PAH. These include dichloro-
acetate (DCA) for treatment of mito-
chondrial metabolic disorders, histone
deacetylase (HDAC) inhibitors to target
the epigenetic changes that occur in
PAH, and poly ADP ribose polymerase
(PARP) inhibitors to halt abnormally
proliferating pulmonary artery (PA)
smooth muscle cells.

In developing novel treatment mo-
dalities for PAH, Dr Rabinovitch noted
that a major challenge has been that
animal models of PAH do not recap-
itate human disease. Furthermore,
the cell cultures of PA endothelial cells,
smooth muscle cells, and fibroblasts that
are used for in vitro studies are obtained from
PAH patients at the time of lung transplant, and therefore may repre-
ent only end-stage disease rather than the full spectrum of PAH. Because of
this, several groups are exploring novel
approaches for disease models, including
organ culture of intact pulmonary arter-
ies, culture of endothelial cells obtained from a PA catheter, and induced plurip-
ton stem cells.\textsuperscript{36-38}

Induced pluripotent stem cells are dif-
ferentiated cells, typically obtained from the
dermis or epidermis, that are treated
to induce pluripotency, and can then be
reprogrammed again to differentiate into various
cell types, such as pulmonary vascular
endothelial or smooth muscle cells.\textsuperscript{39}
There are several relatively new study
design approaches being used in other
fields of medicine, such as “enrichment”
designs, where patients undergo some
type of diagnostic screening and are then
randomized on the basis of positive re-
results.\textsuperscript{42} “Adaptive enrichment designs” use
early results from an interim analysis of a
trial to guide later recruitment targeting a
long-term outcome, such as survival.\textsuperscript{42}
“Umbrella” or “basket” designs are often
biomarker-based and require fairly large
numbers of patients. Unfortunately, none of
these design approaches are easily
applicable to future PAH trials because of
the generally low number of eligible par-
ticipants, and lack of reliable diagnostics
to identify potential “responders.”

In future PAH trials, rather than
adopting one of these designs, it will be
important to assess the underlying risk
for a patient to have an event (eg, death, clinical worsening) and therefore select
patients most likely to have detectable
treatment benefit. Dr Kawut illustrated
this point using meta-analyses of previ-
ous PAH trials. In a logistic regression
model predicting clinical worsening
based on pre-enrollment variables, he
showed that in 11 clinical trials the pa-
tients with the lowest risk had very few
events and did not derive benefit from
treatment, whereas the patients with the
highest risk had many events and de-
ferred significant benefit from therapy.\textsuperscript{13}
By narrowing enrollment in trials to
higher-risk patients that are more likely
to have an event, sample sizes could be
reduced, decreasing the time and cost
of clinical trials, without affecting the
power of these trials to detect treatment
effect. This would be a valuable applica-
tion of the various risk prediction mod-
els recently published (REVEAL, ESC,
French).\textsuperscript{1,7,44} He also showed preliminary
data that machine learning algorithms
may be able to identify “clusters” of
patients more likely to have events and
respond to therapies in general.

Other trial designs have been used
with some success in PAH trials, such as
crossover studies, in which each patient
enrolled is treated with multiple interven-
tions (eg, active drug vs placebo, or 2 or
more drugs) at different time points. This
has the advantage of allowing for smaller
sample sizes and reducing confounding,
with each patient serving as their own
control, but also has several limitations.
With the lack of validated surrogate endpoints, an alternative suggested by Dr Kawut is the use of intermediate endpoints. These are true clinical endpoints with direct benefit to the patient, such as improved quality of life, activity levels, or prevention of hospitalization, but are not the ultimate endpoint of survival. Such novel intermediate endpoints in current use are actigraphy and patient-reported outcomes/questionnaires. Use of these intermediate endpoints could make both phase 2 and 3 studies more feasible while also improving the validity of the results.

Lastly, composite endpoints offer the ability to increase power to detect differences between treatments by incorporating several clinically meaningful endpoints. However, they are also limited by mixing definitive endpoints (eg, death) with "softer" endpoints (eg, change in 6MWD) that risk diluting the overall impact of the findings.

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High Points:

• Right ventricular function is a major determinant of functional capacity and survival in PAH. While there are currently no medications approved for PAH directly targeting the right ventricle, several new and repurposed drugs are in development.

• Current PAH therapies do not address the underlying pathology or genetics of PAH, but treatments targeting the BMPR2 pathway, altered cellular metabolism, and epigenetic changes are in development and clinical trials.

• Induced pluripotent stem cells offer potential for accelerating research in PAH drug development and treatment of PAH.

• Novel study designs incorporating modern PAH risk prediction scores, and the use of intermediate clinical endpoints offers a way to modernize and improve PAH clinical trials.

• Patient-Specific Induced Pluripotent Stem Cells Offer Potential for Accelerating Research in PAH Drug Development and Treatment of PAH.

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