Abstract

Pulmonary hypertension (PH) platform for deep phenotyping in Korean subjects (PHOENIKS) cohort and discovery Korean specific biomarkers for PH

Kim Minsu, Moon Eunkyung, You Mi Ju, Jang Albert Youngwoo, Ahn Kyung Jin, Hyun Gyeong-Lim, Oh Seyeon, Byun Kyunghee, Chung Wook-Jin
Gachon Cardiovascular Research Institute and Division of Cardiovascular Disease, Department of Internal Medicine Gachon University Gil Hospital, Medical Center
Kim Seungwoo, Hong Jung Yeon, Lee Seung Hee, Kim Won-Ho
Division of Cardiovascular Disease Research, Department of Chronic Disease Convergence Research, Korea National Institute of Health, KDCA

Pulmonary arterial hypertension (PAH) is a rare and fatal disease resulting from several causes including heterogeneous genetic defects. Despite the development of various treatments, it is still impossible to cure, and the average survival rate is 7.4 years. Although the lethality for PAH is very high, in Korea, only the prevalence rate, survival rate within 3 years and the relationship between the prevalence of *BMPR2* gene mutants and Korean Idiopathic PAH (IPAH) have been identified through PAH registration project. With increasing interest in personalized medicine, the "biomarker" market for PAH is growing rapidly. In this situation, in order to enhance international competitiveness, we should induce the diversification of therapeutic target candidates by discovering new biomarkers, and produce basic data necessary for new drug development. For these reasons, not only clinical data on deep phenotyping but also biological specimens in patients with PAH are required.

In the field of translational research in PAH, where there is no research using biological specimens to date, the long-term cohort research platform for Korean PAH (PHOENIKS) ordered by The Korea National Institute of Health, Korea Disease Control and Prevention Agency (KDCA) was designed to collect human samples for deep phenotyping in patients with PAH and to build a database of patients with PAH in Korea. In this project, we obtained basic data and human samples of 102 patients with primary and secondary PAH for about 3 years from 2018 to 2020. Throughout this research, we collected the clinical data of not only patients with inherited pulmonary arterial hypertension but also of patients with connective tissue disease, congenital heart disease, and portopulmonary hypertension, which belong to the accompanying diseases and secured an efficient follow-up observation system through a multi-center research network. From these processes, we discovered the therapeutic targets by investigating causes and pathophysiology of PAH and produced basic data necessary for the development of effective new drugs.
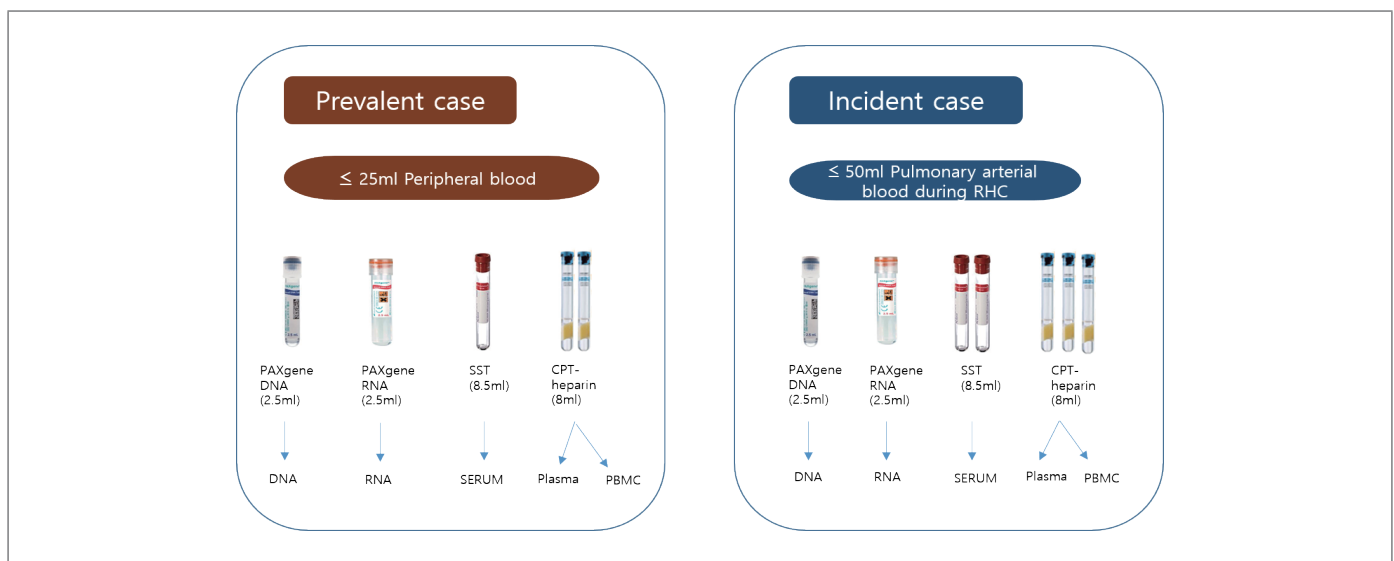
In the second project (from 2021 to 2023) of a follow-up study, we are planning to research an additional deep phenotyping study of group 2 pulmonary hypertension patients and have already begun analyzing genomes and proteomics to discover Korean-specific diagnostic biomarkers and new therapeutic targets.

Keywords: Pulmonary hypertension, Deep phenotyping, Blood bank, Registries, Precision medicine

Table 1. Clinical data entries of the pulmonary arterial hypertension (PAH) platform for deep phenotyping in Korean subjects (PHOENIKS) cohort

Parameter	Specific categories
WHO functional class at diagnosis	Class Ⅰ, Ⅱ, Ⅲ, Ⅳ
6-minute walk test	Distance (meters), blood pressure (before & after), pulse rate, O_2 saturation
Blood chemistry and hemodynamics	NT-proBNP, troponin I, blood count, blood coagulation test, Cr, electrolyte, liver/renal function test, thyroid function test, uric acid, serum iron, blood gas analysis
Cardiopulmonary exercise test	Right ventricular hypertrophy
Chest X-ray	pulmonary artery dilatation, cardiomegaly
Echocardiography	Left ventricle ejection fraction, TAPSE, RV FAC, TASV, Right ventricle size, systolic arterial pressure, right ventricular outflow acceleration time, pulmonary artery diameter, IVC size & respiratory fluctuation, pericardial effusion
Cardiopulmonary exercise test (option)	pCO_2, VE/VCO_2, VO_2/HR, peak VO_2
Cardiac MRI (option)	Right ventricle size, left ventricle size, heart rate, cardiac output, left ventricle ejection fraction, right ventricle ejection fraction, pulmonary artery diameter
Right heart categorization	Pulmonary arterial pressure (systolic/diastolic/mean), pulmonary wedge pressure, right heart pressure, central vein, SvO_2%, pulmonary vascular resistance

* NT-proBNP: N-terminal prohormone of brain natriuretic peptide; Cr: creatinine; TAPSE: tricuspid annular plane systolic excursion; FAC: fractional area change; TASV: tricuspid annular systolic velocity; IVC: inferior Vena Cava

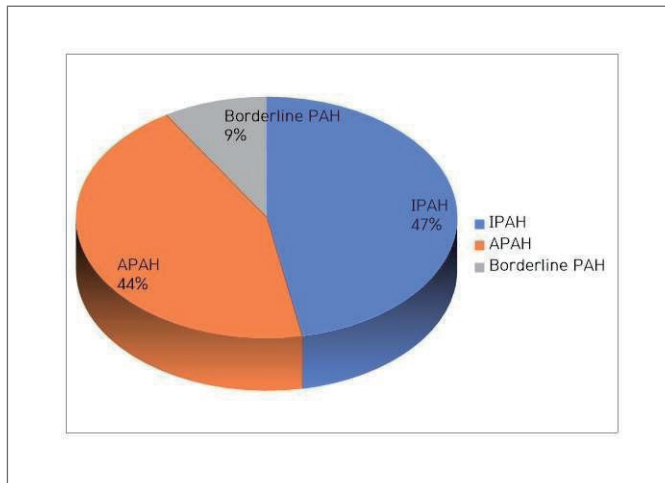**Figure 1.** Laboratory methods for biological specimen collection

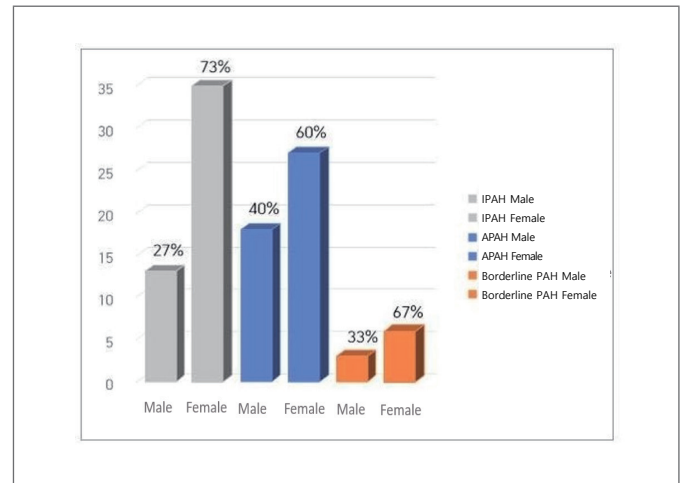**Figure 2.** Classification of underlying causes

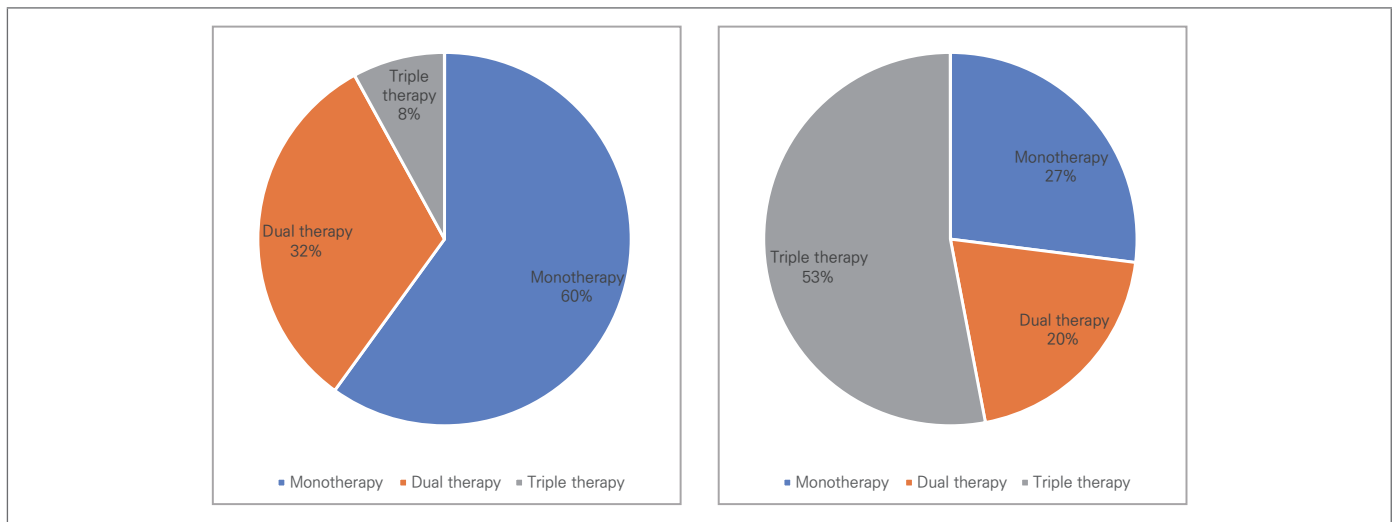**Figure 3.** Sex distribution of underlying causes

Figure 4. Initial PAH-specific theraphy (Left) and change in the use of a PAH-specific medications after one year (Right), in idiopathic PAH patients
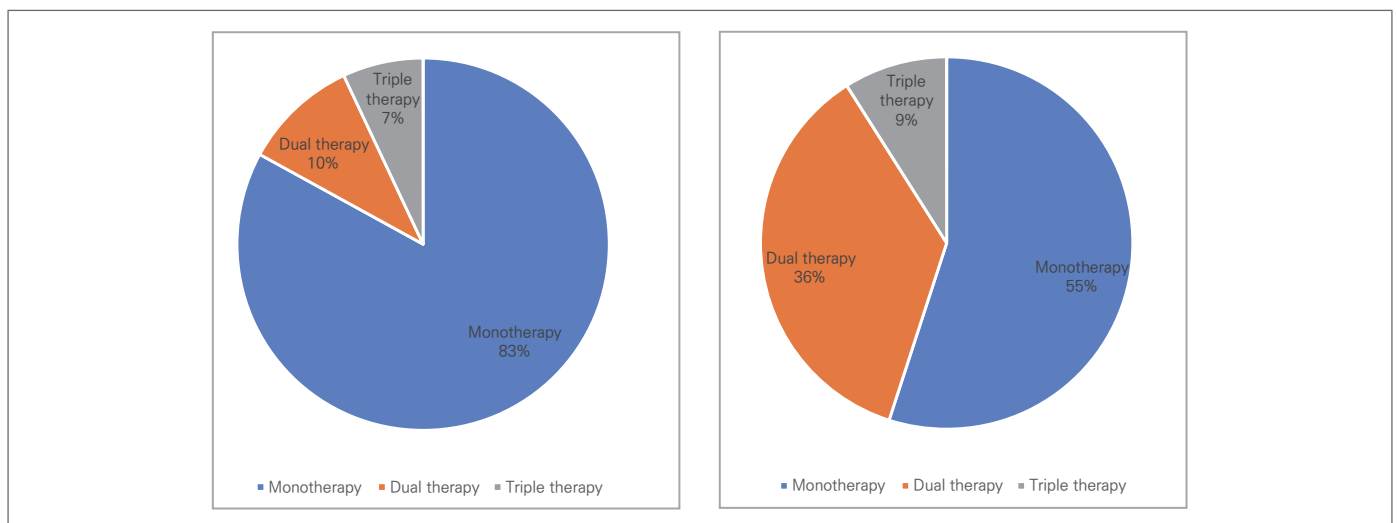

Figure 5. Initial PAH-specific theraphy (Left) and change in the use of a PAH-specific medications after one year (Right), in secondary PAH patients
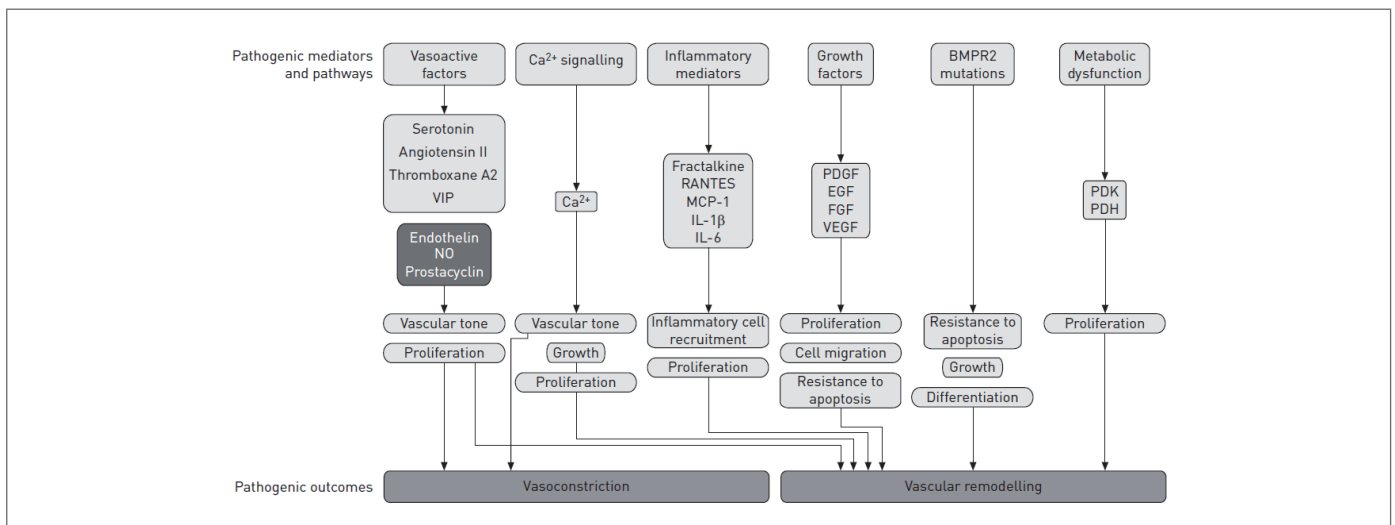
Figure 6. Factors associated with pulmonary arterial hypertension (PAH) and summary of molecular mechanisms
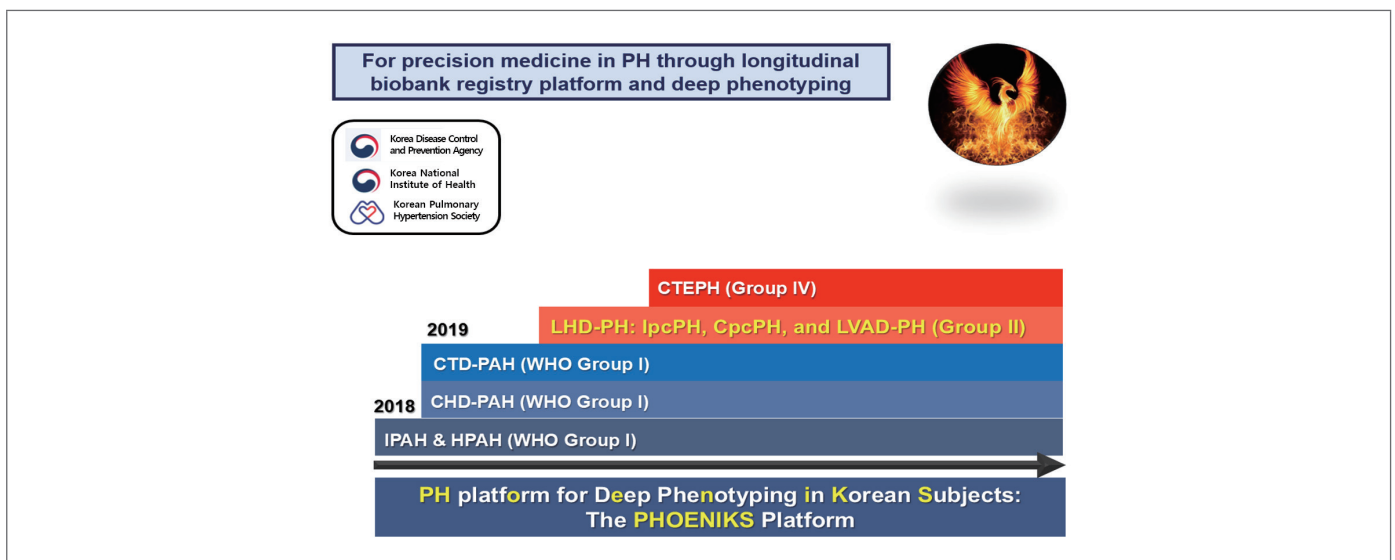

Figure 7. Pulmonary hypertension (PH) platform for deep phenotyping in Korean subjects, PHOENIKS long term plan