BMPR Ⅱ or Novel Combination Therapy, What Should Our Priority be?

▲Yi Qun, from West China Hospital of Sichuan University

As Prof. Sheila G Haworth (London, UK), the chairman, said, "A very strong man" (Nick Morrell of Cambridge, UK) and the "Two same strong women "(Lucy Clapp, London, UK; Mandy MacLean, Glasgow, UK) brought the attendees an interesting debate on translational science about what should our priority be, directly targeting the BMPR Ⅱ or novel combination therapy.

Bone morphogenetic protein receptor type II or BMPR Ⅱ is a serine/threonine receptor kinase. It binds Bone morphogenetic proteins, members of the TGF beta superfamily of ligands, involving in paracrine signaling. BMPs are involved in a host of cellular functions including osteogenesis, cell growth and cell differentiation. BMPR Ⅱ mutations was found to be the most common cause of familial pulmonary hypertension (FPAH), some research also found which is the etiological basis to part of idiopathic PAH as well as some pulmonary hypertension patients of congenital heart disease. So far, we have found more than 140 different BMPR Ⅱ mutations in about 75% FPAHs and 20% IPAHs. Thus, what should our priority be, directly targeting the BMPR Ⅱ or novel combination therapy, becomes to the focus of research and debate.

In the debate, Nick held the opinion that we should consider treatment targeting the BMPR-II because available therapies for PAH failed to reverse the underlying disease process, and survival in PAH patients remained poor despite existing therapies. He introduced BMP signaling pathway, molecular analysis of BMPR Ⅱ , and potential mechanisms under consequence of BMPR Ⅱ in details. He also enumerated many evidences of targeting genetic therapies such as phospholipase A2 inhibitor, cAMP elevating agents and FK506. Restoration of BMPR Ⅱ expression provides a novel therapeutic target in PAH. There are many potential therapeutic approaches to restore BMPR Ⅱ function and BMP9 offers a selective approach to enhancing endothelial BMPR2/

ALK1 activation in PAH. BMP9 induces endothelial BMPR2 expression via a Smad-dependent pathway and reverses pulmonary hypertension in BMPR2 R899X mice. In response to the question from the opponent that whether mouse genetic experiments help us clarify the role of BMPRII, he quoted a sentence saying that “genetically modified mice present opportunities to further identify environmental and genetic factors that influence PAH pathogenesis in terms of frequency, time of onset, and severity”.

However, in opinions of Lucy and Mandy, restoration of BMPRII function in PAH could not improve hemodynamics, slow or reverse vascular remodeling and improve survival.

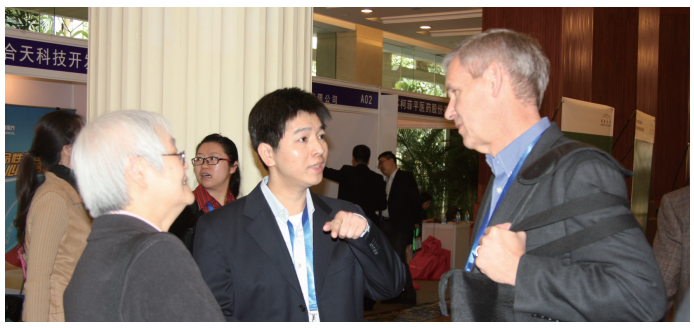
They thought that only combination therapies superior on all fronts. Moreover, evidences from multiple research revealed low prevalence of BMPR Ⅱ mutations in both adults and children with familial PAH, idiopathic PAH and pediatric IPAH including in congenital heart disease. Only 20% of persons with mutations go onto develop PAH (FPAH) and mutations found in other proteins were much rarer. Research showed that patients with BMPR Ⅱ and ALK-1 mutations respond to epoprostenol therapy. Mechanisms of prostacyclins and PPARγ ligands in treatment of PAH were also illustrated in their debate.

In the end, debaters asked again the same question, though there were more people in favor of novel combination therapy, they didn’t reach an agreement on this issue.

Fascinating debate ended, exactly directly targeting the BMPR Ⅱ or novel combination therapy, which should our priority be is not ended. (By Yi Qun)

Introduction of Physically Re-engineering the Cardio-pulmonary Circulation

Compliance, cardiac output and ventriculo-vascular coupling should be the target of choice in Pulmonary Arterial Hypertension (PAH) treatment, the report from Prof. Harm Boogard, the netherlands, showed. It is concluded that, firstly, for PAH patients, quality of life had been deternined by right ventricle compliance during diastolic and systolic phase; secondly, right ventricle function, independent of load, could be reflected by ventriculo-vascular coupling mostly; thirdly, however, the prediction value towards prognosis from compliance and ventriculo-vascular coupling was limited and the detective method was also complicated. He suggested that improvement of pulmonary circulation was critical for PAH patients life. Otherwaise, Prof. Marc Pritzker from America introduced their study about how to use mechanical devices to add compliance to the pulmonary circulation. He futher showed the technology using sensitive pressure receptor and multiplier to mimic pulmonary vascular compliance and regulated the compliance .



When and how to perform intra-cardiac shunting technology? Prof. Julio Sandoval from Mexico gave his answer through summarizing related international animal and clinical studies. It was reported that atrial septostomy was still a supplementary therapy for PAH patients with severe right heart failure (right ventricular dysfunction). The operation/therapy played an effective role in improving clinical symptoms and hemodynamic parameters related to patients survival and decreasing the mortality. “cardiac intervention therapy and surgery can be applied to some PAH patients to improve their quality of life and prolong survival.”Prof. Sandoval said, “however, the choice of the best time to perform it still needs further studies.”

Re-synchronizing right ventricle for PAH patients was introduced by Prof. Thenappan Thenappan, America. PAH patients would always be associated with cardiac load increasing, raising β-MHC and fibrous degeneration, and increasing aerobic oxidation of sugar. All those factors could contribute to electrophysiological remodeling of right ventricular. Professor Thenappan suggested that cardiac resynchronous therapy would make re-synchronizing the right ventricle happen.

Prof. Shahin Moledina coming from Britain recommended the intra-cardiac shunting to the conference, which used Potts operation methods to benefit patients.

In the end, Prof. Shaoliang Chen from Nanjing, China, presented how to treat PAH by pulmonary artery denervation (PADN). New techonology created by Professor Chen’s team could improve hemodynamic parameters and survival quality, which has been proved in 66 patients with PAH.