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Connexin-43 is a promising target for pulmonary hypertension due to hypoxaemic lung disease

Claire Bouvard[1,2], Nafiisha Genet[1,2], Carole Phan[3,4], Baptiste Rode[1,2], Raphaël Thuillet[3,4], Ly Tu[3,4], Paul Robillard[1,2], Marilyne Campagnac[1,2], Raffaella Soleti[5], Eric Dumas De La Roque[1,6], Frédéric Delcambre[6], Laurent Cronier[7], Thibaud Parpaite[1,2], Elise Maurat[1,2], Patrick Berger[1,2,6], Jean-Pierre Savineau[1,2], Roger Marthan[1,2,6], Christophe Guignabert[3,4], Véronique Freund-Michel[1,2] and Christelle Guibert[1,2]

Affiliations: [1]INSERM, Centre de Recherche Cardio-Thoracique de Bordeaux, U1045, Pessac, France. [2]Univ-Bordeaux, Centre de Recherche Cardio-Thoracique de Bordeaux, U1045, Bordeaux, France. [3]INSERM UMR_S 999, Hôpital Marie Lannelongue, Le Plessis-Robinson, France. [4]Université Paris-Saclay, Faculté de Médecine, Le Kremlin-Bicêtre, France. [5]SOPAM, U1063, INSERM, Univ Angers, SFR ICAT, Angers, France. [6]CHU de Bordeaux, Pessac, France. [7]Laboratoire Signalisation et Transports Ioniques Membranaires, CNRS ERL 7003, Université de Poitiers, Poitiers, France.

Correspondence: Christelle Guibert, Centre de Recherche Cardio-Thoracique de Bordeaux, INSERM U1045, Plateforme Technologique d'Innovation Biomédicale (PTIB), Hôpital Xavier Arnozan, Avenue du Haut Lévêque, 33604 Pessac Cedex, France. E-mail: christelle.guibert@u-bordeaux.fr

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Connexin (Cx)-43, part of intercellular channels, is increased in patients with chronic hypoxia-induced pulmonary hypertension (CH-PH). It is crucial in lung inflammation and pulmonary artery remodelling in mice with CH-PH, suggesting Cx43 as a therapeutic option http://bit.ly/35zNkGm

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ABSTRACT The mechanisms underlying pulmonary hypertension (PH) are complex and multifactorial, and involve different cell types that are interconnected through gap junctional channels. Although connexin (Cx)-43 is the most abundant gap junction protein in the heart and lungs, and critically governs intercellular signalling communication, its contribution to PH remains unknown. The focus of the present study is thus to evaluate Cx43 as a potential new target in PH.

Expressions of Cx37, Cx40 and Cx43 were studied in lung specimens from patients with idiopathic pulmonary arterial hypertension (IPAH) or PH associated with chronic hypoxaemic lung diseases (chronic hypoxia-induced pulmonary hypertension (CH-PH)). Heterozygous Cx43 knockdown CD1 ($Cx43^{+/-}$) and wild-type littermate ($Cx43^{+/+}$) mice at 12 weeks of age were randomly divided into two groups, one of which was maintained in room air and the other exposed to hypoxia (10% oxygen) for 3 weeks. We evaluated pulmonary haemodynamics, remodelling processes in cardiac tissues and pulmonary arteries (PAs), lung inflammation and PA vasoreactivity.

Cx43 levels were increased in PAs from CH-PH patients and decreased in PAs from IPAH patients; however, no difference in Cx37 or Cx40 levels was noted. Upon hypoxia treatment, the $Cx43^{+/-}$ mice were partially protected against CH-PH when compared to $Cx43^{+/+}$ mice, with reduced pulmonary arterial muscularisation and inflammatory infiltration. Interestingly, the adaptive changes in cardiac remodelling

in $Cx43^{+/-}$ mice were not affected. PA contraction due to endothelin-1 (ET-1) was increased in $Cx43^{+/-}$ mice under normoxic and hypoxic conditions.

Taken together, these results indicate that targeting Cx43 may have beneficial therapeutic effects in PH without affecting compensatory cardiac hypertrophy.