Translational research in pulmonary hypertension: challenge and opportunity

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The literature is filled with individual conclusions, and not many theories to tie them together.
– Agus and Gell-Mann [1]

The first World Health Organization conference on pulmonary hypertension, held in 1971 in Geneva, Switzerland [2], had been convened to investigate the first drug-induced epidemic of so-called "primary" pulmonary hypertension. The clinicians had noted an unusual increase in the number of patients with often fatal pre-capillary pulmonary hypertension and, by connecting the dots, they identified the drug menocil (aminorex fumarate) as the cause of the outbreak. This first epidemic of anorexigen drug-induced pulmonary hypertension moved the "lesser or small circulation" [3] into the visual field of cardiologists and pulmonologists. From the perspective of today's knowledge base a contemporary statement from Kenneth Moser is of historical interest: "The key historical event was the labeling of this vascular bed as the lesser circulation. Presumably, this description was not used in the pejorative sense; but it seems to have operated in that way, intentionally or not. Who would deign to study the lesser circulation when one could attack questions about the "greater circulation"? Furthermore, was not the lesser circulation simply a passive system of pipes leading from right ventricle to left atrium, where the really important events would occur? Of course, along the way, the blood perfusing these passive conduits did participate in gas exchange, but that was a "pulmonary" not a "hemodynamic" event. Which brings us to the political problems experienced by the pulmonary vascular bed; namely, under which aegis does concern with this bed properly fall?" [3].

Since the time of this writing, the universe of pulmonary hypertension has expanded, some say the field has exploded. Perhaps the "big bang" event was the success of the first treatment for primary pulmonary hypertension (now classified as idiopathic pulmonary arterial hypertension (PAH)), intravenous continuous prostacyclin therapy [4, 5]. In addition, we want to point out that more than a decade had passed between the first report of the single case treatment and the publication of the first prospective clinical trial. Since then, the initially very small group of pulmonary hypertension investigators has grown substantially around the globe and a large number of specialised pulmonary hypertension centres now exist. Dozens of randomised controlled clinical trials have been reported to date and many more trials are underway. In parallel, experimental and mechanistic animal and cell studies are now published every week. The article in this issue of the *European Respiratory Journal* by Paulin *et al.* [6] on the inhibition of the focal adhesion kinase (FAK) in a rat model of pulmonary hypertension merits attention and comment.

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An explosion produces pieces and fragments, in the case of pulmonary hypertension research new cells, genes and proteins that are associated in a variety of arrangements with the disease or diseased tissues. Increasingly there is a need for synthesis and synopsis and for pattern recognition. This need is recognised at a time when the limitations of the widely used vasodilator drugs are being assessed with little understanding of why some patients respond to drug treatment, but other patients do not. With complete awareness of the many problems and potentially false conclusions drawn from *post hoc* analysis of trial data we propose the following plan for the establishment of ''responder profiles''. We suggest analysing the data after a rigorous *a priori* definition of ''responder'' has been arrived at by consensus and before the study begins. For example, patients may (or may not) respond to a given drug because they are younger, in functional class II, have a relatively preserved right ventricular ejection fraction and are already being treated with a prostacyclin. If a responder profile emerges, it certainly needs to be validated by further prospective studies.

We propose that the way forward for pulmonary hypertension research is to invest in the full spectrum of translational research.

''Translational research is a paradigm for research alternative to the dichotomy of basic research and applied research. It is allied in practice with the approaches of participative sciences and participatory action research'' [7]. Translational research has the potential to drive the advancement of applied science due to its focus on removing barriers [7]. The word ''bridge'' or ''bridging'' is frequently used when describing the essence of translational research. This implies that building bridges is part of the job description of the translational researcher. Translational research builds bridges between basic and clinical sciences, preclinical studies and clinical trials. The traffic across the bridge flows in both directions. This bridge image of translational research conveys the concept of spanning a gap and perhaps also that there are barriers to effective exchange of information submerged in the water. A practical definition of translational research in our opinion is: ''translational research is the necessary work that is not done by the basic scientist (for example by a crystallographer) and also not by the clinical trialist''. We do not wish to forget that the translation of findings from clinical trials to everyday practice remains another important function of translational research. ''Translational research can be applied more generally where researchers try to shorten the time-frame and conflate the basic applied (research) continuum, to translate fundamental research results into practice applications'' [7].

We propose that the way forward to improved patient outcome is for the basic scientist to learn from the clinician observing the patient at the bedside, and for the clinician involved in drug testing to listen to the basic scientists. A common, effective information exchange and dialogue will probably connect more dots, patterns will emerge that will generate novel hypotheses, which can then, more quickly than before, be subjected to preclinical and clinical testing. As every language translator knows: translation is first and most importantly about effective communication. The way forward is not only based on large cohort multicentre clinical trials but is equally based on multi-investigator groups (for example, cell biologists plus molecular biologists plus immunologists, plus cancer researchers) that share models, reagents and data. This will lead to a more rapid identification of blind alleys and testing of the hypotheses. At present the gap between hypothesis formulation and verification is too big; both in relation to the time and effort spent and in relation to the intended clinical application.

We have briefly mentioned the need for effective communication, and we urge the building of bridges between investigator groups. Another building activity of translational research is the creation of disease models. As new drug development is an unmet need, so is the development of pertinent disease models. A handful of publications have begun by critically evaluating the existing pulmonary hypertension models [8–10]. Our collective knowledge of the cellular components of complex vascular lesions has increased and is now more secure. Cells of the immune system and precursor cells are unlikely to be identified as mere bystanders and without animal models will not be able to close the gap between observation and causality.

While the explosive production of data by a critical mass of investigators provides an interpretive challenge, the opportunities for investigators to interact productively have increased and the mechanisms for effective communications are in place. There are now more meetings around the world where the topic of pulmonary vascular diseases is being discussed more than ever before. Figure 1 illustrates the main important elements of the translational research process.

It is obvious that the central and critical element of the translational research process is the formulation of the hypotheses. The physician in charge of the patient's care and who has access to the primary data or information stored in databases is often overwhelmed by the phenomena. Databases are only as valuable as the specific data that have been collected, and there are few hypothesis-driven databases. The diagram suggests a linear top to bottom flow of activities, while in reality there are multiple feedback loops. Given that severe PAH [8] is associated with such a wide spectrum of disorders and conditions, from congenital

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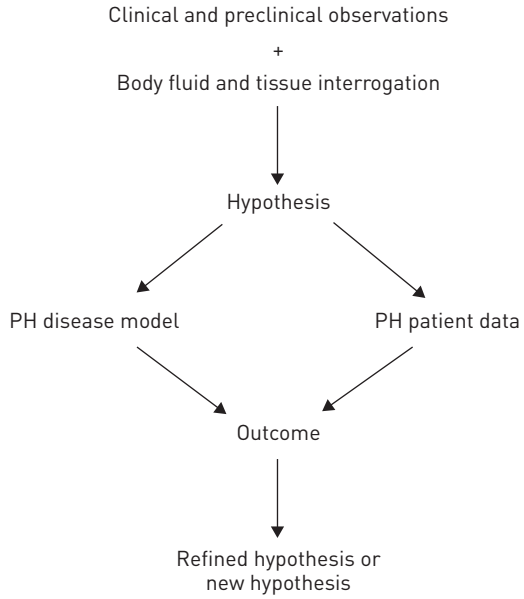

FIGURE 1 Translational research: from clinical observation to the formulation of hypotheses, and examination of the hypotheses. PH: pulmonary hypertension.

cardiac malformations to drug exposure and viral infections [11–13], this group of pulmonary vascular disorders is ready for "personalised medicine" or individualised treatment based on the aetiology of PAH and the functional status of the patient. Because many of the clinical PAH drug trials have been conducted for the purpose of drug approval and not for the purpose of phenotyping responders and non-responders, an enormous amount of information is buried and could be excavated.

The marching orders of translational research are to improve the understanding of the critically important mechanisms of pathobiology. Which of the mechanisms examined by the pulmonary hypertension investigators are of critical importance? Is it inflammation, autoimmunity, angio-obliteration, a sick lung circulation or right heart axis [14–16]? The answer is possibly all of the above.

The article by PAULIN *et al.* [6] focuses on FAK, a broadly expressed non-receptor kinase, which is a key participant in a range of cell functions, including cell adhesion, migration, proliferation and survival [17], contributing to angiogenesis, wound healing, cardiac hypertrophy and tissue fibrosis [18]. The current model for FAK signalling shows that FAK activation is triggered by integrin-dependent cell adhesion, by growth factor receptor activation or activation of G protein-coupled receptors [17]. Whereas UMAR *et al.* [19] previously reported activation of FAK in the right ventricle of monocrotaline-induced pulmonary hypertensive rats [19], PAULIN *et al.* [6] concentrated on pulmonary vascular remodelling and on a proof-of-concept inhibition of FAK. Postulating that FAK may function as a signalling hub, they treated rats with established monocrotaline-induced pulmonary hypertension either with a single inhalation of FAK-small interfering RNA or oral treatment with a FAK inhibitor. Making use of this particular pulmonary hypertension model, the authors proved their concept: both interventions improved the haemodynamics, and reduced the pulmonary arteriolar media thickness and the degree of right ventricle hypertrophy. Although frequently used by many investigators, the monocrotaline rat model is not without problems. One of these problems is that too many treatment strategies "work", *i.e.* reverse the disease that is induced by this alkaloid [20]. Using immunofluorescence histochemistry in pulmonary arteries from patients with PAH, the authors found an increased fluorescence signal representing phosphorylated (activated) FAK.

It will be important to assess the translational potential of this elegant work. FAK inhibitors are being investigated in early cancer trials [21, 22]. The intended target of FAK inhibition in severe PAH appears to be the angiogenic remodelling of obliterated vessels [23]. Indeed FAK function is of vital importance for endothelial cell survival during development [24]. An additional concern is that activation of FAK during cardiomyocyte stress may protect the heart from injury [25]. The risks and benefits of anti-angiogenic drugs in the treatment of PAH will have to be carefully weighed [26]. Lumen obliterated vessels may perhaps be reopened, but the dysfunctional right ventricle may not be able to tolerate such treatment [14].

In our opinion we now have plenty of concepts and some hypotheses that can guide us. A new era has begun. What we need is to start moving together as a globally interacting pulmonary hypertension

community. It was the ''singing cowboy'' Will Roger who famously quipped: ''Even if you are on the right track, you'll get run over if you just sit there!''

As we move we also must acknowledge that clinical trials are driven by the quest for positive end-points which require large patient groups and sponsorship from companies that can afford to underwrite large clinical trials. Any novel treatment strategy for PAH will have to be tested in a phase II study and in a phase III pilot study before larger trials as a basis for drug registration can be designed or sponsored. The introduction of drugs like FAK inhibitors into clinical application is no exception. We advocate conducting small pilot studies, following evaluation of the drug's safety and assessment of its risk/benefit profile. The pulmonary hypertension community is encouraged to develop procedures and mechanisms which facilitate this transition from preclinical proof of principle investigations to exploratory clinical pilot studies.

References

1 Agus DB, Gell-Mann M. Perspective: meeting of minds. *Nature* 2012; 491: S61.
2 Hatano S, Strasser T, eds. Primary Pulmonary Hypertension: Report on a WHO meeting. Geneva, World Health Organization, 1975.
3 Moser KM. Preface. *In:* Moser KM, ed. Pulmonary Vascular Diseases. Lung Biology in Health and Disease. New York, Marcel Dekker, 1975; pp. vii–viii.
4 Higenbottam T, Wheeldon D, Wells F, *et al.* Long-term treatment of primary pulmonary hypertension with continuous intravenous epoprostenol (prostacyclin). *Lancet* 1984; 1: 1046–1047.
5 Barst RJ, Rubin LJ, Long WA, *et al.* A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med* 1996; 334: 296–302.
6 Paulin R, Meloche J, Courboulin A, *et al.* Targeting cell motility in pulmonary arterial hypertension. *Eur Respir J* 2014; 43; 531–544.
7 Wikipedia. Translational research. http://en.wikipedia.org/wiki/Translational_research Date last accessed: November 20, 2013. Date last updated: October 29, 2013.
8 Voelkel NF, Tuder RM. Hypoxia-induced pulmonary vascular remodeling: a model for what human disease? *J Clin Invest* 2000; 106: 733–738.
9 Ryan J, Bloch K, Archer SL. Rodent models of pulmonary hypertension: harmonisation with the world health organisation's categorisation of human PH. *Int J Clin Pract Suppl* 2011; 172: 15–34.
10 Stenmark KR, Meyrick B, Galie N, *et al.* Animal models of pulmonary arterial hypertension: the hope for etiological discovery and pharmacological cure. *Am J Physiol Lung Cell Mol Physiol* 2009; 297: L1013–L1032.
11 Galie N, Hoeper MM, Humbert M, *et al.* Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009; 30: 2493–2537.
12 Montani D, Bergot E, Günther S, *et al.* Pulmonary arterial hypertension in patients treated by dasatinib. *Circulation* 2012; 125: 2123–2137.
13 Savale L, Chaumais MC, Cottin V, *et al.* Pulmonary hypertension associated with benfluorex exposure. *Eur Respir J* 2012; 40: 1164–1172.
14 Erzurum S, Rounds SI, Stevnes T, *et al.* Strategic plan for lung vascular research: an NHLBI-ORDR workshop report. *Am J Respir Crit Care Med* 2010; 182: 1554–1562.
15 Voelkel NF, Gomez-Arroyo J, Abbate A, *et al.* Pathobiology of pulmonary arterial hypertension and right ventricular failure. *Eur Respir J* 2012; 40: 1555–1565.
16 Dib H, Tamby MC, Bussone G, *et al.* Targets of anti-endothelial cell antibodies in pulmonary hypertension and scleroderma. *Eur Respir J* 2012; 39: 1405–1414.
17 Santos AM, Schechtman D, Cardoso AC, *et al.* FERM domain interaction with myosin negatively regulates FAK in cardiomyocyte hypertrophy. *Nat Chem Biol* 2012; 8: 102–110.
18 Peng X, Wu X, Druso JE, *et al.* Cardiac developmental defects and eccentric right ventricular hypertrophy in cardiomyocyte focal adhesion kinase (FAK) conditional knockout mice. *Proc Natl Acad Sci USA* 2008; 105: 6638–6643.
19 Umar S, Hessel M, Steendijk P, *et al.* Activation of signaling molecules and matrix metalloproteinases in right ventricular myocardium of rats with pulmonary hypertension. *Pathol Res Pract* 2007; 203: 863–872.
20 Gomez-Arroyo JG, Farkas L, Alhussaini AA, *et al.* The monocrotaline model of pulmonary hypertension in perspective. *Am J Physiol Lung Cell Mol Physiol* 2012; 302: L363–L369.
21 Schultze A, Fiedler W. Therapeutic potential and limitations of new FAK inhibitors in the treatment of cancer. *Expert Opin Investig Drugs* 2010; 19: 777–788.
22 Infante JR, Camridge DR, Milesjkin LR, *et al.* Safety, pharmacokinetic, and pharmacodynamic phase I dose-escalation trial of PF-00562271, an inhibitor of focal adhesion kinase, in advanced solid tumors. *J Clin Oncol* 2012; 30: 1527–1533.
23 Dasari VR, Kaur K, Velpula KK, *et al.* Downregulation of focal adhesion kinase (FAK) by cord blood stem cells inhibits angiogenesis in glioblastoma. *Aging (Albany NY)* 2010; 2: 791–803.
24 Zhao X, Peng X, Sun S, *et al.* Role of kinase-independent and -dependent functions of FAK in endothelial cell survival and barrier function during embryonic development. *J Cell Biol* 2010; 189: 955–965.
25 Cheng Z, DiMichele LA, Hakim ZS, *et al.* Targeted focal adhesion kinase activation in cardiomyocytes protects the heart from ischemia/reperfusion injury. *Arterioscler Thromb Vasc Biol* 2012; 32: 924–933.
26 Force T. Double-edged sword of the new cancer therapeutics. *Circulation* 2012; 125: 2057–2058.

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