(injurious and beneficial) and possible management strategies. Modifiable factors such as ventilator settings (3), respiratory drive (4), level of consciousness, and prescribed sedatives and opiates may predispose differentially to reverse triggering depending on the mechanism. Regarding clinical significance, some degree of permissive dyssynchrony is probably benign or even beneficial for patients at low risk of lung or diaphragm injury. For patients at highest risk, including those with moderate and severe ARDS, clinical consequences of reverse triggering likely depend on the subtype, duration of exposure, and tradeoffs of interventions such as neuromuscular blockade.

Despite the uncertainties surrounding reverse triggering, the following is clear: a rapidly expanding literature indicates reverse triggering occurs often in mechanically ventilated patients at risk of injury and might be underrecognized at the bedside. What, if anything, should be done clinically remains to be determined. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Irene Telias, M.D.
Interdepartmental Division of Critical Care Medicine
University of Toronto
Toronto, Ontario, Canada
Li Ka Shing Knowledge Institute
St. Michael's Hospital
Toronto, Ontario, Canada
and
Department of Medicine
University Health Network and Sinai Health System
Toronto, Ontario, Canada

Jeremy R. Beitler, M.D., M.P.H.
Division of Pulmonary, Allergy, and Critical Care Medicine
Columbia University
New York, New York
and
Center for Acute Respiratory Failure
New York-Presbyterian Hospital
New York, New York

ORCID ID: 0000-0003-0797-2374 (J.R.B.).

References

1. Pham T, Telias I, Piraino T, Yoshida T, Brochard LJ. Asynchrony consequences and management. *Crit Care Clin* 2018;34:325–341.
2. Akoumianaki E, Lyazidi A, Rey N, Matamis D, Perez-Martinez N, Giraud R, *et al*. Mechanical ventilation-induced reverse-triggered breaths: a frequently unrecognized form of neuromechanical coupling. *Chest* 2013;143:927–938.
3. Baedorf Kassis E, Su HK, Graham AR, Novack V, Loring SH, Talmor DS. Reverse trigger phenotypes in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2021;203:67–77.
4. Beitler JR, Sands SA, Loring SH, Owens RL, Malhotra A, Spragg RG, *et al*. Quantifying unintended exposure to high tidal volumes from breath stacking dyssynchrony in ARDS: the BREATHE criteria. *Intensive Care Med* 2016;42:1427–1436.
5. Yoshida T, Nakamura MAM, Morais CCA, Amato MBP, Kavanagh BP. Reverse triggering causes an injurious inflation pattern during mechanical ventilation. *Am J Respir Crit Care Med* 2018;198: 1096–1099.
6. Simon PM, Zurob AS, Wies WM, Leiter JC, Hubmayr RD, *et al*. Entrainment of respiration in humans by periodic lung inflations: effect of state and CO(2). *Am J Respir Crit Care Med* 1999;160:950–960.
7. Graves C, Glass L, Laporta D, Meloche R, Grassino A. Respiratory phase locking during mechanical ventilation in anesthetized human subjects. *Am J Physiol* 1986;250:R902–R909.
8. Petrillo GA, Glass L, Trippenbach T. Phase locking of the respiratory rhythm in cats to a mechanical ventilator. *Can J Physiol Pharmacol* 1983;61:599–607.
9. Simon PM, Habel AM, Daubenspeck JA, Leiter JC. Vagal feedback in the entrainment of respiration to mechanical ventilation in sleeping humans. *J Appl Physiol (1985)* 2000;89:760–769.
10. Remmers JE, Marttila I. Action of intercostal muscle afferents on the respiratory rhythm of anesthetized cats. *Respir Physiol* 1975;24: 31–41.
11. Delisle S, Charbonney E, Albert M, Ouellet P, Marsolais P, Rigollot M, *et al*. Patient-ventilator asynchrony due to reverse triggering occurring in brain-dead patients: clinical implications and physiological meaning. *Am J Respir Crit Care Med* 2016;194:1166–1168.
12. Reinoso MA, Sieck GC, Hubmayr RD. Respiratory muscle coordination in acute spinal dogs. *Respir Physiol* 1996;104:29–37.
13. Decima EE, von Euler C. Intercostal and cerebellar influences on efferent phrenic activity in the decerebrate cat. *Acta Physiol Scand* 1969;76:148–158.
14. Chen BY, Vasilakos K, Boisteanu D, Garma L, Derenne JPH, Whitelaw WA. Linkage of hiccup with heartbeat. *J Appl Physiol (1985)* 2000;88: 2159–2165.

Molecular Imaging of Pulmonary Fibrosis: Another Step Forward

Molecular imaging enables *in vivo* visualization of molecular processes within a tissue or organ of interest using targeted molecular probes. Because of advancements in molecular imaging in fields ranging from neurology to oncology, there are now multiple U.S. Food and Drug Administration–approved molecular probes for use in clinical care. Within the field of fibrotic diseases, the application of molecular imaging in the preclinical arena and early-phase clinical trials is growing (1, 2). Over the past year, the results of the first in-human studies using the αvβ6 integrin–targeted positron emission technology (PET) probes [^{18}F]FB-A20FMDV2 and [^{18}F]FP-R$_0$1-MG-F2 and the type 1 collagen–targeted PET probe ^{68}Ga-CBP8 demonstrated increased PET signal in patients with pulmonary fibrosis consistent with increased αvβ6 integrin expression and type 1 collagen, respectively (3–5). In addition, ^{18}F-fluorodeoxyglucose

Supported by grants from the Francis Family Foundation, the Scleroderma Foundation, and the NIH (K23HL150331) (S.B.M.).

Originally Published in Press as DOI: 10.1164/rccm.202007-2897ED on August 13, 2020

PET/computed tomography (CT) was used in a phase I study of the PI3K/mTOR inhibitor omipalisib in idiopathic pulmonary fibrosis (IPF) to confirm target engagement (6). With ongoing development, molecular imaging is poised to advance the field of pulmonary fibrosis in several notable and important ways.

First, molecular imaging can provide information as to fibrosis pathobiology that is not otherwise available (7). Most of the knowledge as to aberrant molecular pathways driving lung fibrosis has come from studies using the bleomycin mouse model. Validating these findings in patients with pulmonary fibrosis is difficult. Although the ability to obtain tissue for molecular phenotyping has revolutionized the field of oncology, obtaining lung tissue carries considerable risks for patients with pulmonary fibrosis, and this precludes its use for investigational purposes. Thus, molecular imaging emerges as a noninvasive alternative to invasive tissue sampling. It can enable the degree of activation of a molecular process of interest to be quantified and, at the same time, reveal the anatomic distribution where the process of interest is occurring. Second, and perhaps most notably, molecular imaging could be incorporated into clinical trials for the assessment of target engagement and expression, cohort enrichment, or the detection of treatment response (1), and in doing so, it could address several unmet needs that have hampered the development of IPF therapies. Molecular imaging could be used to stratify patients based on the degree of abnormality in the pathway of interest and enable clinical trials to be enriched with subjects with active disease. A molecular probe that targets a molecule or process along the pathway of fibrogenesis could serve as a much-needed early marker of treatment response overall, improving trial feasibility and accelerating the identification of effective therapies.

In this issue of the *Journal*, Brody and colleagues (pp. 78–89) add to the expanding field of molecular imaging by applying the CCR2 (chemokine receptor 2)-targeted PET probe ^{64}Cu-DOTA-ECL1i to detect C-C motif CCR2-positive macrophages and monocytes in pulmonary fibrosis (8). Studies have demonstrated an important role for CCR2 signaling in pulmonary fibrosis pathogenesis (9). This peptide-based probe binds the extracellular loop 1 of the CCR2 and has been used to assess inflammation in mouse models and explanted human tissue of other pulmonary diseases (10, 11). Multiple macrophage/monocyte-targeting probes have been developed; however, this probe is unique in that it recognizes CCR2$^+$ immune cells. Other macrophage-targeting probes applied to pulmonary fibrosis have targeted the folate receptor-β or cysteine cathepsin as markers of activated macrophages (12, 13). It should be noted that these probes detect inflammation in the context of fibrosis and are not specific for fibrosis.

This study has several important findings. First, in mice injured with bleomycin, ^{64}Cu-DOTA-ECL1i uptake in the lung was increased at Day 14 and 28 in a pattern similar to the degree of elevation of CCR2$^+$ cells. Increased probe uptake was also seen in explanted human fibrotic lungs with good correlation between probe accumulation determined by autoradiography and CCR2 intensity. Second, ^{64}Cu-DOTA-ECL1i uptake decreased in response to both an IL-1β antibody and pirfenidone in the bleomycin model. It is important to note that other probes have detected response to fibrosis-targeting treatment (14–16), and although ^{18}F- fluorodeoxyglucose detected a response to pirfenidone in mice, it was unable to do so in patients with IPF (16). Third, dosimetry studies demonstrated that ^{64}Cu-DOTA-ECL1i is primarily renally cleared, with minimal background uptake in healthy lungs, an important feature for detecting pulmonary pathology. The persistent high signal in the liver adds complexity to quantifying signal uptake in the surrounding lower lung. Lastly, performing ^{64}Cu-DOTA-ECL1i PET-CT in subjects with IPF was feasible. Areas of increased lung PET signal were seen visually in the four subjects with IPF compared with one healthy volunteer. Within the patients with IPF, areas of increased signal appeared to correspond with areas of fibrosis on CT. Although promising, these findings should be considered preliminary, as the number of subjects with IPF imaged ($n = 4$) was small, the results were presented in comparison with only one healthy volunteer, and no statistical analyses were performed.

Several important issues remain to be addressed regarding the potential for the clinical translation of this probe. Larger studies are needed to validate the ability of this probe to detect increased PET signal in patients with IPF even when adjusting for potential confounders given the presence of monocytes and macrophages in other pulmonary diseases. Although increased PET signal was detected within areas of fibrosis on corresponding CT, whether or not the degree of signal will provide additive information to CT and pulmonary function tests and inform as to the risk of disease progression, thus serving as a viable disease activity measure, remains to be determined. Performing test-retest studies over a small time interval will be essential to determine the ability of this probe to detect small changes that may occur with IPF therapy. Lastly, should this probe detect a decrease in PET signal in the setting of IPF treatment(s), ongoing research would be needed to determine whether a reduction in CCR2$^+$ cells corresponds with therapeutic efficacy.

The application of CCR2-targeted PET imaging to pulmonary fibrosis represents another step forward in the emerging field of molecular imaging of fibrosis. Given the overlapping molecular processes across both subtypes of pulmonary fibrosis and fibrotic diseases in general, advancements in molecular imaging of IPF may prove beneficial to patients with other forms of pulmonary fibrosis and other fibrotic diseases. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Sydney B. Montesi, M.D.
Division of Pulmonary and Critical Care Medicine
Massachusetts General Hospital
Boston, Massachusetts

References

1. Montesi SB, Désogère P, Fuchs BC, Caravan P. Molecular imaging of fibrosis: recent advances and future directions. *J Clin Invest* 2019;129: 24–33.
2. Désogère P, Montesi SB, Caravan P. Molecular probes for imaging fibrosis and fibrogenesis. *Chemistry* 2019;25:1128–1141.
3. Lukey PT, Coello C, Gunn R, Parker C, Wilson FJ, Saleem A, *et al*. Clinical quantification of the integrin αvβ6 by [^{18}F]FB-A20FMDV2 positron emission tomography in healthy and fibrotic human lung (PETAL Study). *Eur J Nucl Med Mol Imaging* 2020;47:967–979.

4. Kimura RH, Wang L, Shen B, Huo L, Tummers W, Filipp FV, *et al*. Evaluation of integrin $\alpha v\beta_6$ cystine knot PET tracers to detect cancer and idiopathic pulmonary fibrosis. *Nat Commun* 2019;10:4673.
5. Montesi SB, Izquierdo-Garcia D, Désogère P, Abston E, Liang LL, Digumarthy S, *et al*. Type I collagen-targeted positron emission tomography imaging in idiopathic pulmonary fibrosis: first-in-human studies. *Am J Respir Crit Care Med* 2019;200:258–261.
6. Lukey PT, Harrison SA, Yang S, Man Y, Holman BF, Rashidnasab A, *et al*. A randomised, placebo-controlled study of omipalisib (PI3K/mTOR) in idiopathic pulmonary fibrosis. *Eur Respir J* 2019;53: 1801992.
7. Montesi SB, Rao R, Liang LL, Goulart HE, Sharma A, Digumarthy SR, *et al*. Gadofosveset-enhanced lung magnetic resonance imaging to detect ongoing vascular leak in pulmonary fibrosis. *Eur Respir J* 2018; 51:1800171.
8. Brody SL, Gunsten SP, Luehmann HP, Sultan DH, Hoelscher M, Heo GS, *et al*. Chemokine receptor 2–targeted molecular imaging in pulmonary fibrosis: a clinical trial. *Am J Respir Crit Care Med* 2021;203:78–89.
9. Moore BB, Paine R III, Christensen PJ, Moore TA, Sitterding S, Ngan R, *et al*. Protection from pulmonary fibrosis in the absence of CCR2 signaling. *J Immunol* 2001;167:4368–4377.
10. Liu Y, Li W, Luehmann HP, Zhao Y, Detering L, Sultan DH, *et al*. Noninvasive imaging of $CCR2^+$ cells in ischemia-reperfusion injury after lung transplantation. *Am J Transplant* 2016;16: 3016–3023.
11. Liu Y, Gunsten SP, Sultan DH, Luehmann HP, Zhao Y, Blackwell TS, *et al*. PET-based imaging of chemokine receptor 2 in experimental and disease-related lung inflammation. *Radiology* 2017;283: 758–768.
12. Schniering J, Benešová M, Brunner M, Haller S, Cohrs S, Frauenfelder T, *et al*. ^{18}F-AzaFol for detection of folate receptor-β positive macrophages in experimental interstitial lung disease-a proof-of-concept study. *Front Immunol* 2019;10:2724.
13. Withana NP, Ma X, McGuire HM, Verdoes M, van der Linden WA, Ofori LO, *et al*. Non-invasive imaging of idiopathic pulmonary fibrosis using cathepsin protease probes. *Sci Rep* 2016;6:19755.
14. John AE, Luckett JC, Tatler AL, Awais RO, Desai A, Habgood A, *et al*. Preclinical SPECT/CT imaging of αvβ6 integrins for molecular stratification of idiopathic pulmonary fibrosis. *J Nucl Med* 2013;54: 2146–2152.
15. Désogère P, Tapias LF, Hariri LP, Rotile NJ, Rietz TA, Probst CK, *et al*. Type I collagen-targeted PET probe for pulmonary fibrosis detection and staging in preclinical models. *Sci Transl Med* 2017;9: eaaf4696.
16. Bondue B, Castiaux A, Van Simaeys G, Mathey C, Sherer F, Egrise D, *et al*. Absence of early metabolic response assessed by 18F-FDG PET/CT after initiation of antifibrotic drugs in IPF patients. *Respir Res* 2019;20:10.

Therapeutic Interception of Early Lung Adenocarcinoma Progression: Not Just How, but When?

In this issue of the *Journal*, Treekitkarnmongkol and colleagues (pp. 90–101) present data on a pathway of early adenocarcinogenesis of the lung, demonstrating the effect of lipocalin-2 on the development of KRAS-mutated lung adenocarcinoma (KM-LUAD) and suggesting that airways damaged by chronic obstructive pulmonary disease (COPD) show the effect of a high–lipocalin-2 microenvironment (1). Their experiments were based on an observed elevation of *Lcn2* in the nonneoplastic airways of mice with knockout of *Gprc5a* (2) followed by studies examining lipocalin-2 in these mice exposed to tobacco carcinogen, increased tumor development in $Lcn2^{-/-}$ mice, and translation into human tissues with COPD and LUAD.

The review of the literature of the relationship of LCN2 to human cancer would identify it as having a protumoral function (3–6), by mechanisms that include survival advantage through iron scavenging and enhancement of migration. In some tumor types, it is proposed as a target for therapy or, at a minimum, a biomarker for diagnosis or of aggressive behavior (7).

Although LUAD showed an increase in lipocalin-2, the authors show through their mouse model that loss of lipocalin-2 reduced antitumoral immune responses and enhanced a protumoral immune environment, such that the loss of *Lcn2* enhanced tumor formation. The induction of LCN2 was not seen in squamous carcinoma, occurring in KM-LUAD preferentially and by immunohistochemistry in tumor cells. An inverse relationship between NKX2-1 (TTF1) reactivity and LCN2 reactivity suggested differentiation away from club cell and type 2 pneumocyte, toward a gastric-type cell differentiation. In addition, the upregulation of *LCN2* was seen in COPD airways when compared with smokers without COPD but importantly included elevation in KM-LUAD from patients with COPD.

At first glance, there is a paradox—LCN2 is protumoral in several tumor types in prior reports yet here antitumoral. Also, LCN2 levels are high in LUAD, especially KM-LUAD. There are potential explanations for this type of paradox, which can include cell type or differentiation, differences in tumor microenvironment, and/or temporal switches in the stepwise progression toward neoplasia. Even among T1 adenocarcinomas, the antitumoral effect seems already lost; it is possible that the role of LCN2 in tumor initiation is different than a later role in cell migration. Additionally, it remains possible that non–tumor cell LCN2 becomes a factor in different phases of the disease. When we observe a tumor mass lesion, we are seeing the outcome of numerous potentially antagonistic tumor–host events that have occurred over time, which eventually fail to control tumor growth and spread. Such an explanation allows for an antitumoral effect for LCN2 that creates a balance between preneoplasia and cell death, a balance that accounts for a period of latency to adenocarcinoma development in COPD not seen for squamous or small cell carcinoma.

This could allow for risk stratification for the development of KM-LUAD that are smoking-associated LUAD among patients

Originally Published in Press as DOI: 10.1164/rccm.202008-3087ED on August 26, 2020