2. Huang L, Li X, Gu X, Zhang H, Ren L, Guo L, *et al.* Health outcomes in people 2 years after surviving hospitalisation with COVID-19: a longitudinal cohort study. *Lancet Respir Med* 2022;10:863–876.
3. Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, *et al.* 1-Year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. *Lancet* 2021;398:747–758.
4. Latronico N, Peli E, Calza S, Rodella F, Novelli MP, Cella A, *et al.*; LOTO Investigators. Physical, cognitive and mental health outcomes in 1-year survivors of COVID-19-associated ARDS. *Thorax* 2022;77:300–303.
5. Maestre-Muñiz MM, Arias Á, Mata-Vázquez E, Martín-Toledano M, López-Larramona G, Ruiz-Chicote AM, *et al.* Long-term outcomes of patients with coronavirus disease 2019 at one year after hospital discharge. *J Clin Med* 2021;10:2945.
6. Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, *et al.*; Canadian Critical Care Trials Group. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003;348:683–693.
7. Needham DM, Wozniak AW, Hough CL, Morris PE, Dinglas VD, Jackson JC, *et al.*; National Institutes of Health NHLBI ARDS Network. Risk factors for physical impairment after acute lung injury in a national, multicenter study. *Am J Respir Crit Care Med* 2014;189:1214–1224.
8. Chommeloux J, Valentin S, Winiszewski H, Adda M, Pineton de Chambrun M, Moyon Q, *et al.* One-year mental and physical health assessment in survivors after ECMO for COVID-19-related ARDS. *Am J Respir Crit Care Med* 2023;207:150–159.
9. Schmidt M, Zogheib E, Rozé H, Repesse X, Lebreton G, Luyt CE, *et al.* The PRESERVE mortality risk score and analysis of long-term outcomes after extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *Intensive Care Med* 2013;39:1704–1713.
10. Griffiths J, Gager M, Alder N, Fawcett D, Waldmann C, Quinlan J. A self-report-based study of the incidence and associations of sexual dysfunction in survivors of intensive care treatment. *Intensive Care Med* 2006;32:445–451.
11. Jackson JC, Pandharipande PP, Girard TD, Brummel NE, Thompson JL, Hughes CG, *et al.*; Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors (BRAIN-ICU) Study Investigators. Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. *Lancet Respir Med* 2014;2:369–379.
12. Hopkins RO, Weaver LK, Pope D, Orme JF, Bigler ED, Larson-LOHR V. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1999;160:50–56.
13. Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, *et al.*; BRAIN-ICU Study Investigators. Long-term cognitive impairment after critical illness. *N Engl J Med* 2013;369:1306–1316.
14. Girard TD, Thompson JL, Pandharipande PP, Brummel NE, Jackson JC, Patel MB, *et al.* Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study. *Lancet Respir Med* 2018;6:213–222.
15. Pun BT, Badenes R, Heras La Calle G, Orun OM, Chen W, Raman R, *et al.*; COVID-19 Intensive Care International Study Group. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. *Lancet Respir Med* 2021;9:239–250.
16. Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. *JAMA Neurol* 2020; 77:1018–1027.
17. Kannapadi NV, Jami M, Premraj L, Etchill EW, Giuliano K, Bush EL, *et al.* Neurological complications in COVID-19 patients with ECMO support: a systematic review and meta-analysis. *Heart Lung Circ* 2022;31:292–298.
18. Vink EE, Azoulay E, Caplan A, Kompanje EJO, Bakker J. Time-limited trial of intensive care treatment: an overview of current literature. *Intensive Care Med* 2018;44:1369–1377.
19. Schou A, Mølgaard J, Andersen LW, Holm S, Sørensen M. Ethics in extracorporeal life support: a narrative review. *Crit Care* 2021;25:256.
20. Barbaro RP, MacLaren G, Boonstra PS, Combes A, Agerstrand C, Annich G, *et al.*; Extracorporeal Life Support Organization. Extracorporeal membrane oxygenation for COVID-19: evolving outcomes from the international Extracorporeal Life Support Organization Registry. *Lancet* 2021;398:1230–1238.
21. Herridge MS, Chu LM, Matte A, Tomlinson G, Chan L, Thomas C, *et al.*; RECOVER Program Investigators (Phase 1: Towards RECOVER); Canadian Critical Care Trials Group. The RECOVER program: disability risk groups and 1-year outcome after 7 or more days of mechanical ventilation. *Am J Respir Crit Care Med* 2016;194:831–844.
22. Tramm R, Ilic D, Sheldrake J, Pellegrino V, Hodgson C. Recovery, risks, and adverse health outcomes in year 1 after extracorporeal membrane oxygenation. *Am J Crit Care* 2017;26:311–319.
23. Unroe M, Kahn JM, Carson SS, Govert JA, Martinu T, Sathy SJ, *et al.* One-year trajectories of care and resource utilization for recipients of prolonged mechanical ventilation: a cohort study. *Ann Intern Med* 2010;153:167–175.
24. Azoulay E, Resche-Rigon M, Megarbane B, Reuter D, Labbé V, Cariou A, *et al.* Association of COVID-19 acute respiratory distress syndrome with symptoms of posttraumatic stress disorder in family members after ICU discharge. *JAMA* 2022;327:1042–1050.
25. Gayat E, Cariou A, Deye N, Vieillard-Baron A, Jaber S, Damoisel C, *et al.* Determinants of long-term outcome in ICU survivors: results from the FROG-ICU study. *Crit Care* 2018;22:8.

Fibroblast Activating Protein: Skimming the Surface of Molecular Imaging to Assess Fibrotic Disease Activity

Noninvasive studies to assist with the diagnosis of pulmonary fibrosis and individual prognostication represent a "holy grail" for idiopathic pulmonary fibrosis (IPF) and other interstitial lung diseases (ILDs). Multiple studies have investigated the ability of physiologic measurements, molecular profiling, circulating cellular markers (i.e., monocytes), and imaging biomarkers to predict disease progression. However, there remains no clinically used disease activity marker for single–time point assessment to assist with treatment decisions. In this issue of the *Journal*, Yang and colleagues (pp. 160–172) evaluate "fibroblast activating protein" (FAP) as a molecular marker of disease activity with the potential to be leveraged for prognostic purposes (1).

FAP is a transmembrane serine protease that was initially found to be expressed by cancer-associated stromal cells and subsequently

Supported by NIH grant K23HL150331 (S.B.M.) and NIH grant R01HL141195 (J.C.H.).

Originally Published in Press as DOI: 10.1164/rccm.202208-1638ED on September 8, 2022

shown to be expressed on other cell types, including macrophages (2). While associated with fibrosis, FAP has been shown to have antifibrotic actions linked to its role in the proteolytic degradation and processing of collagen. Indeed, FAP-deficient mice have increased collagen accumulation in lungs after radiation- or bleomycin-induced injury (3). However, FAP is also reported to enhance α_2-antiplasmin function, which would be expected to stabilize fibrinogen and fibronectin and contribute to lung fibrosis (4, 5).

FAP expression is increased by the profibrotic cytokine TGF-β (transforming growth factor-β), and expression is increased in murine models of lung fibrosis. Within the lungs of patients with IPF, FAP was upregulated within fibroblastic foci, but not in the adjacent alveolar epithelium or in normal lung tissues (6). However, increased expression may not be detrimental; a recent study showed that depletion of FAP^+ cells or genetic deletion of FAP exacerbated fibrosis in a murine model of repetitive bleomycin injury and had no impact on fibrosis induced by adenoviral overexpression of TGF-β (7). Regardless of its role in pathogenesis, recent studies have used FAP to direct delivery of approved and emerging antifibrotic drugs, supporting its potential as an indicator of active wound repair and fibrosis (8, 9).

Here Yang and colleagues (1) evaluate FAP expression using human lung fibroblasts, a murine model of pulmonary fibrosis, single-cell sequencing, and a radiolabeled FAP inhibitor administered to patients with ILD. This study has several major findings. Fibroblast expression of FAP is induced by TGF-β. Similar findings have been shown in fibroblasts from several sources and disease states (2, 6). *In vivo*, increased FAP expression was detected 1 week after bleomycin-induced lung injury. FAP expression was increased in fibrotic human lung tissue, with half of explanted IPF samples and almost all of silicosis lung tissue samples showing elevations, demonstrating that increased FAP expression is not specific for IPF. Single-cell transcriptomic analysis indicated that FAP was highly expressed in mesenchymal cells and that there was moderate correlation with other mesenchymal cell markers associated with fibrosis (α-SMA [α-smooth muscle actin], fibronectin, and collagen I).

In a small group of healthy volunteers and a larger group of subjects with ILD (IPF and non-IPF), ^{68}Ga-FAPI-04 positron emission technology (PET) uptake was increased in the lungs of subjects with ILD compared with healthy volunteers. Differences in total standardized uptake value (SUVtotal) but not mean standardized uptake value were seen between the IPF and non-IPF ILD groups, with the IPF group having a higher SUVtotal. As SUVtotal, a measurement defined by the authors, captures the extent of probe uptake above a threshold, this finding hints at underlying biologic heterogeneity among ILD subtypes. SUVtotal correlated moderately with subsequent changes in FVC and $D_{L_{CO}}$; however, the follow-up times for pulmonary function testing were nonuniform, ranging from 4 to 24 months.

A major strength of this study lies in the application of molecular imaging to establish a link between FAP expression as a biologic indicator of fibroblast activation and a noninvasive indicator of disease activity. PET probes targeting type I collagen, CCR2 (C-C chemokine receptor 2), αvβ6 integrin, and CXCR4 (C-X-C motif chemokine receptor 4) have been recently applied to patients with IPF to detect disease or to assess treatment effects (10–13). ^{68}Ga-FAPI-04 PET/computed tomography has been performed in systemic sclerosis–associated ILD, and the degree of probe uptake was associated with disease progression (14). This study by Yang and colleagues (1) illustrates several important applications of molecular imaging to ILD. First, it can be used to obtain molecular information otherwise not available and thus advance our understanding of molecular heterogeneity within individuals and ILD subtypes. Second, imaging of molecular pathways involved in fibrogenesis could provide a window into disease activity at a single time point. This study also highlights important considerations in using molecular imaging. PET biomarkers that incorporate both magnitude of uptake and amount of lung involved may better predict disease progression for diffuse lung diseases compared with traditional PET measurements such as mean standardized uptake value.

Several important gaps remain in establishing FAP as a reliable marker of disease activity. This study does not definitively link FAP expression with profibrotic fibroblast activity. Indeed, although FAP correlated with ACTA2 (actin alpha 2, smooth muscle), COL1A1 (collagen type I alpha 1 chain), and FN1 (fibronectin 1) in single-cell analysis, transcriptional expression does not always reflect protein concentration. Given its role in collagen turnover, FAP may have a functional role in controlling the wound-repair response to prevent the excessive collagen accumulation that characterizes fibrosis. Thus, studies will need to determine the ability of molecular imaging for FAP to distinguish between physiologic and fibrotic repair. More definitive studies are needed to determine if ^{68}Ga-FAPI-04 PET can reliably predict disease progression in ILD and whether FAP activity can predict responsiveness to antifibrotic therapies. Although the premise of differentiating "active" from "stable" disease by noninvasive FAP assessment as a decision tool to guide pharmacotherapy is appealing, fibrosis progression is not linear and for some individuals may occur in a stepwise manner. In the liver, FAP expression in hepatic stellate cells correlates with fibrosis severity (15), and circulating FAP is increased in patients with increased liver stiffness, supporting a potential role for FAP in the risk stratification of patients for liver fibrosis (16). In the lung, one modality may not provide the sensitivity and specificity needed for risk prediction or guidance of therapy in an individual patient. Nevertheless, the combination of accessible serum or genetic markers with physiologic measurements and molecular imaging may improve our ability to risk stratify individuals with ILD. ■

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

Jeffrey C. Horowitz, M.D.
Division of Pulmonary, Critical Care and Sleep Medicine
The Ohio State University
Columbus, Ohio

ORCID IDs: 0000-0002-5724-6808 (S.B.M.); 0000-0002-1505-2837 (J.C.H.).

References

1. Yang P, Fang Q, Fu Z, Li J, Lai Y, Chen X, *et al.* Comprehensive analysis of fibroblast activation protein (FAP) expression in interstitial lung diseases (ILDs). *Am J Respir Crit Care Med* 2023;207:160–172.
2. Fitzgerald AA, Weiner LM. The role of fibroblast activation protein in health and malignancy. *Cancer Metast Rev* 2020;39:783–803.
3. Fan M-H, Zhu Q, Li H-H, Ra H-J, Majumdar S, Gulick DL, *et al.* Fibroblast activation protein (FAP) accelerates collagen degradation and clearance from lungs in mice. *J Biol Chem* 2016;291:8070–8089.
4. Horowitz JC, Rogers DS, Simon RH, Sisson TH, Thannickal VJ. Plasminogen activation–induced pericellular fibronectin proteolysis promotes fibroblast apoptosis. *Am J Respir Cell Mol Biol* 2008;38: 78–87.
5. Tucker TA, Idell S. The contribution of the urokinase plasminogen activator and the urokinase receptor to pleural and parenchymal lung injury and repair: a narrative review. *Int J Mol Sci* 2021;22:1437.
6. Acharya PS, Zukas A, Chandan V, Katzenstein A-LA, Puré E. Fibroblast activation protein: a serine protease expressed at the remodeling interface in idiopathic pulmonary fibrosis. *Hum Pathol* 2006;37: 352–360.
7. Kimura T, Monslow J, Klampatsa A, Leibowitz M, Sun J, Liousia M, *et al.* Loss of cells expressing fibroblast activation protein has variable effects in models of TGF-β and chronic bleomycin-induced fibrosis. *Am J Physiol Lung Cell Mol Physiol* 2019;317:L271–L282.
8. Fang Q, Liu S, Cui J, Zhao R, Han Q, Hou P, *et al.* Mesoporous polydopamine loaded pirfenidone target to fibroblast activation protein for pulmonary fibrosis therapy. *Front Bioeng Biotechnol* 2022;10:920766.
9. Hettiarachchi SU, Li Y-H, Roy J, Zhang F, Puchulu-Campanella E, Lindeman SD, *et al.* Targeted inhibition of PI3 kinase/mTOR specifically in fibrotic lung fibroblasts suppresses pulmonary fibrosis in experimental models. *Sci Transl Med* 2020;12:eaay3724.
10. 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.
11. 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* 2021;203: 78–89.
12. Kimura RH, Wang L, Shen B, Huo L, Tummers W, Filipp FV, *et al.* Evaluation of integrin αvβ6 cystine knot PET tracers to detect cancer and idiopathic pulmonary fibrosis. *Nat Commun* 2019;10:4673.
13. Derlin T, Jaeger B, Jonigk D, Apel RM, Freise J, Shin H-O, *et al.* Clinical molecular imaging of pulmonary CXCR4 expression to predict outcome of pirfenidone treatment in idiopathic pulmonary fibrosis. *Chest* 2021; 159:1094–1106.
14. Bergmann C, Distler JHW, Treutlein C, Tascilar K, Müller A-T, Atzinger A, *et al.* ^{68}Ga-FAPI-04 PET-CT for molecular assessment of fibroblast activation and risk evaluation in systemic sclerosis-associated interstitial lung disease: a single-centre, pilot study. *Lancet Rheumatol* 2021;3:e185–e194.
15. Levy M, McCaughan G, Marinos G, Gorrell M. Intrahepatic expression of the hepatic stellate cell marker fibroblast activation protein correlates with the degree of fibrosis in hepatitis C virus infection. *Liver* 2002;22: 93–101.
16. Williams KH, de Ribeiro AJV, Prakoso E, Veillard AS, Shackel NA, Bu Y, *et al.* Lower serum fibroblast activation protein shows promise in the exclusion of clinically significant liver fibrosis due to non-alcoholic fatty liver disease in diabetes and obesity. *Diabetes Res Clin Pract* 2015; 108:466–472.

Too Little, Too Late: Adult Lung Disease Cannot Be Prevented by Interventions in Adult Life

Ask a layperson what images heart disease conjures up, and they will probably talk about a relatively young adult suddenly clutching their chest and being rushed off to hospital, defibrillators, intensive care units, and interventions and maybe surgery. The sentiment will be "there but for the Grace of God go I". Ask the same layperson about lung disease, and it will be an old person coughing and maybe on oxygen, the author of their own misfortunes because of current or previous smoking. This is a totally unfair caricature, but without doubt, the perception exists and accounts in part for the disparities in charity funding for heart and lung disease.

However, it is becoming increasingly clear that many adults with lung disease are actually the victims of early life adverse events, long before they had any control over their own fate. The prime example is chronic obstructive pulmonary disease (COPD). Failure to reach a normal plateau of spirometry at age 20–25 years carries a 26% risk of COPD (1), and peak attained spirometry is largely determined by antenatal and early preschool exposures (reviewed in [2]). If early lung growth is normal, the risk of COPD reduces to 6%, which relates to an accelerated decline in spirometry (1). There are likely many reasons for an accelerated decline in lung function, and no consistent single cause is reported from the big COPD cohorts recruited in adult life, but early adverse exposures such as maternal smoking in pregnancy and severe respiratory infections are implicated in three large studies (3–5). Adult smoking is a factor, but not one that is consistently reported (6). Asthma in the third and fourth decades of life can be traced back to antenatal adverse exposures (7). Women with so-called late onset asthma in fact had airway disease by six years of age, which they had forgotten (8), reminding us how inaccurate retrospective recall of childhood respiratory disease actually is (9). Early adverse life events also increase the risk of occupational asthma (10); in a study of 13,499 occupational cleaners who were administered the Respiratory Health in Europe (RHINE) III questionnaire, the risk of self-reported wheeze, adult-onset asthma and COPD were greatest in those with early life disadvantage, including maternal smoking and severe respiratory tract infection before five years of age.

In this issue of the *Journal*, He and colleagues (pp. 173–182) add to these concerning studies by relating lung cancer risk to early adverse life events (11). They included nearly 400,000 participants from the UK Biobank study in their analysis, in whom nearly 2,000 lung cancers were recorded. These volunteers were recruited to the Biobank at age

Originally Published in Press as DOI: 10.1164/rccm.202208-1537ED on August 16, 2022