tied to their clinical productivity) and thereby decrease adoption? Will the added data collection be actionable in terms of clinical management [13], or merely potentially valuable in the future? Who should order and interpret a novel assay – a consulting sub-specialist (perhaps board-certified in Laboratory Medicine or Clinical Genetics) or the treating clinician, who may be best positioned to interpret results in the context of the patient’s presentation and pre-test probability, perhaps aided by machine learning or artificial intelligence?

Early multi-stakeholder collaborative partnerships can directly consider the financial models that sustain the innovation (assuming it is adopted at scale) and related decisions about initial use cases (including which research questions, disease indications, or reimbursement models). Uncertain reimbursement is frequently cited as a systemic barrier to the use of genetic testing, for instance [14]. Given the broader shifts occurring in healthcare reimbursement, it is possible that certain clinical innovations (such as a novel phenotype that improves risk stratification) would engender better stakeholder financial alignment under a value-based (as opposed to a fee-for-service) reimbursement model.

Finally, healthcare services are increasingly delivered away from hospitals and clinics and in some cases, marketed directly to consumers (in a reverse of the shift from the early 20th century). Future innovations should evaluate how their adoption might enable, or benefit from, these trends in healthcare delivery. Digital platforms may be particularly useful in this context, as they can facilitate both data acquisition and clinical care in the home, and in a more continuous and less obtrusive manner.

Concluding Remarks
The SARS-CoV-2 pandemic has highlighted the myriad connections between scientific discovery, healthcare delivery, the healthcare industry, and society at large. In this interconnected environment, widespread adoption of a scientifically-validated technology requires understanding stakeholder perspectives and their conceptions of the technology’s value. Efforts to efficiently incorporate novel genomic or phenotypic insights into a learning health system (and ultimately to change clinical practice) would benefit from a more systematic, holistic assessment of the ecosystem into which these innovations must take root.

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References
1. Council, N.R (2011) Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease. The National Academies Press
2. Tamburier, E. et al. (2020) Therapies for rare diseases: therapeutic modalities, progress and challenges ahead. Nat. Rev. Drug Discov. 19, 93–111
3. Abul-Husn, N.S. and Kenny, E.E. (2019) Personalized medicine and the power of electronic health records. Cell 177, 59–69
4. Huckvale, K. et al. (2019) Toward clinical digital phenotyping: a timely opportunity to consider purpose, quality, and safety. npj Digit. Med. 2, 88
5. Sherman, R.E. et al. (2016) Real-world evidence - what is it and what can it tell us? N. Engl. J. Med. 375, 2203-2207
6. Manolio, T.A. et al. (2019) Opportunities, resources, and techniques for implementing genomics in clinical care. Lancet 394, 511–520
7. Morris, Z.S. et al. (2011) The answer is 17 years, what is the question: understanding time lags in translational research. J. R. Soc. Med. 104, 510–520
8. Howell, J.D. (1989) Technology in the Hospital: Transforming Patient Care in the Early Twentieth Century; Johns Hopkins University Press
9. Howell, J.D. (1989) Machines and medicine: technology transforms the American hospital. In The American General Hospital: Communities and Social Contexts (Long, D.E. and Golden, J., eds), pp. 109–134, Cornell University Press
10. Institute of Medicine (1998) Telemedicine: A Guide to Assessing Telecommunications in Health Care, The National Academies Press
11. Mehrotra, A. et al. (2020) Telemedicine: What Should the Post-Pandemic Regulatory and Payment Landscape Look Like?, Commonwealth Fund

12. Ginesburg, G.S. and Philips, K.A. (2018) Precision medicine: from science to value. Health Aff. (Millwood) 37, 694–701
13. Aron, Z. et al. (2020, 406–416) Moving genomics to routine care: an initial pilot in acute cardiovascular disease. Circ. Genom. Precis. Med. 13, 406–416
14. Zehrov, A.M. et al. (2019) Qualitative study of system-level factors related to genomic implementation. Genet. Med. 21, 1534–1540

Forum
CGRP Receptor Antagonism in COVID-19: Potential Cardiopulmonary Adverse Effects
Tom Skaria,1 Thomas Wälchli,2,3,4,5,6 and Johannes Vogel1,*

Recently, the US FDA has authorized a drug repurposing trial with calcitonin gene-related peptide (CGRP) receptor antagonists to reduce lung inflammation in coronavirus 2019 (COVID-19). However, the well-established cardiopulmonary protective effects of CGRP raise concerns about the safety of antagonizing CGRP in COVID-19. Awareness regarding potential cardiopulmonary adverse effects may enable their early detection and prevent illness from worsening.

Antagonizing Vasodilatory and Nociceptive Signaling via CGRP Antagonists for Migraine Prophylaxis
In migraine, CGRP release by trigeminal nerves is increased and causes dural and pial meningeal vessel dilation. Moreover, CGRP enhances the central relay of pain
signals from the trigeminal nerves to the caudal trigeminal nucleus (Table 1). Therefore, antagonizing the vasodilatory and nociceptive signaling activated by the neurotransmitter CGRP is a very potent therapeutic concept. Small molecule receptor antagonists (gepants) or monoclonal antibodies directed against the CGRP receptor, and the ligand CGRP, have recently been approved as migraine prophylaxis. However, all clinical trials evaluating the efficiency of anti-CGRP therapy were conducted in migraineurs without any pre-existing cardiovascular diseases such as systemic hypertension or stroke. This has raised concerns about the potential adverse effects of long term anti-CGRP therapy in hypertension and stroke because inhibition of endogenous CGRP worsens ischemic stroke and causes heart failure in systemic hypertension in preclinical models [1,2]. Accordingly, pharmacotherapy by a systemically administered long-lasting cCGRP-analog reduced elevated systemic blood pressure and consequently improved cardiac function in murine models of hypertension and heart failure [3]. In humans, cCGRP administration delays the onset of myocardial ischemia upon exercise in patients with stable angina pectoris and enhances cardiac function in patients with congestive heart failure (Table 1) (cf. discussions in [1,3]).

### Repurposing CGRP Receptor Antagonists for COVID-19 Treatment
Apart from the clinical use of CGRP antagonists in migraine prophylaxis, most recently, the FDA has provided authorization for initiating a Phase II, randomized trial of a small molecule CGRP receptor antagonist, originally advancing to Phase III development for acute treatment of migraine, to reduce severe lung inflammation, impending oxygen desaturation, acute respiratory distress syndrome, need for supplemental oxygenation, artificial ventilation, or death in hospitalized COVID-19 patients.

### Rationale against the Repurposing of CGRP Receptor Antagonists
However, several arguments speak against the use of small molecule CGRP receptor antagonists to treat COVID-19 patients. Conflicting results exist for the role of CGRP in enhancing IL-6 production, explained by a concentration-dependent stimulation or no effect of endogenous CGRP and modulation of cAMP bioavailability by the presence of additional pharmacological agents [7–9]. Further, CGRP expression is decreased in airway responsiveness during persistent allergic and RSV airway inflammation, suggesting that endogenous CGRP does not induce airway hyper-responsiveness; rather, it can even have beneficial effects [10]. Moreover, CGRP suppresses type 2 cytokine synthesis and type 2 innate lymphoid cell proliferation (Table 1) [11]. It is particularly important to further stress that the hypothesis that CGRP release is enhanced in COVID-19 and that its release

### Table 1. Calcitonin Gene-Related Peptide (CGRP) in Related Diseases

| Effect              | Mechanism                                | Disease                                      | Refs                        |
|---------------------|------------------------------------------|----------------------------------------------|-----------------------------|
| Pathological        | Dural and pial vessel dilation           | Migraine                                    | i                           |
|                     | Central sensitization                     | Migraine                                    |                             |
| Protective          | Suppression of elevated systemic blood pressure | Systemic arterial hypertension              | [3]                         |
|                     | Suppression of myocardial fibrosis       | Systemic arterial hypertension               | [1]                         |
|                     | Inotropy                                  | Heart failure                               | Discussion in [1,3]         |
|                     | Suppression of elevated pulmonary arterial pressure | Pulmonary hypertension                      | [13,14]                     |
|                     | Suppression of right ventricular remodeling | Pulmonary hypertension                      |                             |
|                     | Prevention of airway hyper-responsiveness | Lung inflammation in allergy and respiratory virus infection | [10], discussion in [10]   |
| Conflicting         | Inflammatory cytokine production         | Local and systemic inflammation             | [7–9,11], discussion in [7] |

Table 1. Calcitonin Gene-Related Peptide (CGRP) in Related Diseases

- **Effect**: Pathological, Protective, Conflicting
- **Mechanism**: Dural and pial vessel dilation, Central sensitization, Suppression of elevated systemic blood pressure, Suppression of myocardial fibrosis, Inotropy, Suppression of elevated pulmonary arterial pressure, Suppression of right ventricular remodeling, Prevention of airway hyper-responsiveness, Inflammatory cytokine production
- **Disease**: Migraine, Systemic arterial hypertension, Pulmonary hypertension
- **Refs**: [3], [1], [13,14], [10], [7–9,11]
is stimulated by upregulation of transient receptor potential channels is not yet supported by direct evidence. A non-peer reviewed paper suggests that circulating CGRP concentrations are actually decreased in COVID-19 patients, negatively affecting disease outcome. These findings suggest restoring CGRP levels as a therapeutic approach [12].

A critical factor, still completely ignored, which may predict a life-threatening adverse effect of this effort is the consistent preclinical finding that endogenous CGRP is protective in pulmonary hypertension (PH) by suppressing pulmonary artery remodeling, elevation of total pulmonary resistance, and, thus, right ventricular (RV) remodeling in chronic hypoxia (Table 1) [13,14]. Increasing evidences indicate PH and resulting RV impairment in hospitalized COVID-19 patients, including even those with nonadvanced disease [15]. Moreover, preliminary survey results show that the incidence of COVID-19 infection is 2.1 cases per 1000 patients and 30% of PH patients infected with COVID-19 had to be hospitalized [16]. A crucial role for endogenous CGRP and its receptors in attenuating hypoxia-induced PH becomes evident from previous studies, which showed that infusion of CGRP neutralizing antibody, CGRP receptor antagonist, or antisense oligodeoxynucleotides targeting CGRP and the CGRP receptor component RAMP1 mRNA in lungs exacerbates pulmonary artery pressure and RV hypertrophy in chronic hypoxic rats [13,14]. Additionally, circulating CGRP concentrations are reduced in pulmonary hypertensive patients and rats with hypoxia-induced PH, in correlation with the rise in pulmonary artery pressure. Reduced CGRP concentration may permit unopposed action of vasoconstrictors such as endothelin-1. Although cells attempt to simultaneously upregulate CGRP receptor expression and thus increase CGRP binding to counteract the effects of decreased peptide bioavailability, this adaptive mechanism is not effective in restoring the dilatory potential of CGRP in pulmonary vasculature [14]. Rather, increasing endogenous CGRP concentrations by infusion of CGRP analogs and gene therapy (intratracheal administration of adenoviral vector encoding CGRP) are capable of inducing pulmonary vasodilation, reducing elevated total pulmonary resistance, and preventing PH and RV remodeling in chronic hypoxic rats. Furthermore, CGRP protects also against pulmonary vasoconstriction induced by endothelin-1, angiotensin II, and the nitric oxide synthase inhibitor Nω-nitro-L-arginine methyl ester [13]. In addition, the well-established positive inotropic effect of CGRP [3] alone may enhance pulmonary hemodynamics by regulating RV function.

Concluding Remarks

What do these studies tell us about the potential cardiopulmonary risks associated with the use of CGRP receptor antagonists in COVID-19 patients? In COVID-19 patients with PH, CGRP receptor antagonist therapy may exacerbate: (i) existing PH and RV remodeling, thus accelerating the transition to RV heart failure; and (ii) vasoconstriction that may further amplify intravascular coagulopathy and lung infarcts. Moreover, it generates the question whether there exists a correlation between circulating CGRP concentrations and PH, which may predict such adverse effects? If yes, those who have been receiving CGRP antagonists for migraine prophylaxis may have increased risk of developing cardiopulmonary complications upon COVID-19 infection and therefore require a specific clinical assessment program to detect earlier signs of such complications and termination of anti-CGRP therapy. Currently, subjects with chronic diseases are considered to be much more susceptible to fatal complications of COVID-19. Migraineurs receiving CGRP antagonists should also be considered in this category if cardiopulmonary adverse effects of CGRP antagonists become evident in COVID-19 patients. We suggest that considering these adverse effects, predicted on the basis of consistent preclinical findings and provided in this report, may further improve design of the proposed clinical trial to detect these adverse effects with adequate statistical power.

In conclusion, endogenous CGRP protects against pulmonary vascular remodeling and hypertension and subsequent right heart failure in preclinical models of chronic hypoxia. Therefore, CGRP receptor antagonism may be associated with cardiopulmonary adverse effects, including exacerbation of hypoxia-preceded PH and RV dysfunction in COVID-19 patients. Appropriate safety considerations should be made to enable their early detection during the investigational CGRP receptor antagonist therapy in COVID-19 patients.

Resources

1 https://clinicaltrials.gov/ct2/show/NCT02066415
2 https://clinicaltrials.gov/ct2/show/NCT04346615

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References

1. Skaria, T. et al. (2019) Blood pressure normalization-independent cardioprotective effects of endogenous, physical activity-induced alpha calcitonin gene-related peptide (alphaCGRP) in chronically hypertensive mice. Circ. Res. 125, 1124–1140
2. Mulder, I.A. et al. (2020) Anti-migraine calcitonin gene-related peptide receptor antagonists worsen cerebral ischaemic outcome in mice. Ann. Neurol. 88, 771–784
3. Aubdool, A.A. et al. (2017) A novel alpha-calcitonin gene-related peptide analogue protects against end-organ damage in experimental hypertension, cardiac hypertrophy, and heart failure. Circulation 136, 367–383
4. Robertson, C.E. (2020) Could CGRP antagonists be helpful in the fight against COVID-19? Headache 60, 1450–1452
5. Lange, M. et al. (2009) Role of calcitonin gene-related peptide (CGRP) in ovine burn and smoke inhalation injury. J. Appl. Physiol. (1985) 107, 176–184
6. Aoki-Nagase, T. et al. (2007) Calcitonin gene-related peptide mediates acid-induced lung injury in mice. Respiratory 12, 807–813
7. Ma, W. et al. (2010) Lipopolysaccharide induces calcitonin gene-related peptide in the RAW264.7 macrophage cell line. Immunology 130, 399–409
8. Milei, I. and Vignery, A. (1997) The neuropeptide calcitonin gene-related peptide inhibits TNF-alpha but poorly induces IL-6 production by fetal rat osteoblasts. Cytokine 9, 999–1007
9. Romero-Reyes, M. et al. (2015) A potent and selective calcitonin gene-related peptide (CGRP) receptor antagonist, MK-8825, inhibits responses to neuroceptive trigeminal activation: role of CGRP in orofacial pain. Exp. Neurol. 271, 95–103
10. Dakharma, A. et al. (2005) Alteration of airway neuropeptide expression and development of airway hyperresponsiveness following respiratory syncytial virus infection. Am. J. Physiol. Lung Cell. Mol. Physiol. 288, L761–L770
11. Wahlapp, A. et al. (2019) Calcitonin gene-related peptide negatively regulates alarmin-driven type 2 innate lymphoid cell responses. Immunity 51, 709–723
12. Ochoa-Callejero, L. et al. (2020) Circulating levels of calcitonin gene-related peptide (CGRP) are lower in COVID-19 patients. medRxiv. Published online October 2, 2020. https://doi.org/10.1101/2020.10.01.20205088
13. Champion, H.C. et al. (2000) In vivo gene transfer of prepro-calcitonin gene-related peptide to the lung attenuates chronic hypoxia-induced pulmonary hypertension in the mouse. Circulation 101, 923–930
14. Qing, X. and Keith, I.M. (2003) Targeted blocking of gene expression for CGRP receptors elevates pulmonary artery pressure in hypoxic rats. Am. J. Physiol. Lung Cell. Mol. Physiol. 285, L86–L96
15. Creel-Bulou, C. et al. (2020) Acute cor pulmonale in critically ill patients with Covid-19. New Engl. J. Med. 382, e70
16. Lee, J.D. et al. (2020) A survey-based estimate of COVID-19 incidence and outcomes among patients with PAH or CTEPH and impact on the process of care. Ann. Am. Thorac. Soc. Published online July 29, 2020. https://doi.org/10.1513/AnnalsATS.202005-521OC