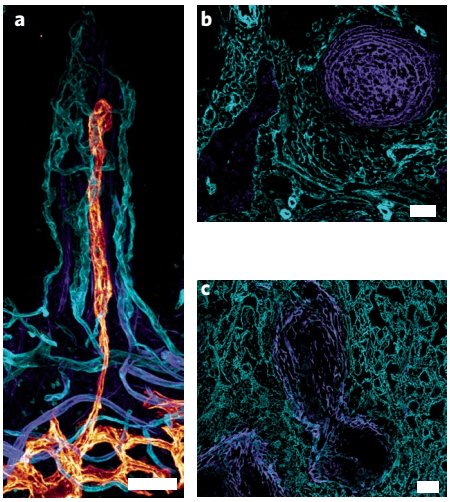

Fig. 2 | Modern imaging techniques in lymphatic research. A comprehensive map of the human lymphatic system requires advanced clinical and optical imaging approaches. **a**, Confocal image (200 µm projection) of human jejunum prepared by clearing-enhanced 3D (Ce3D) imaging[6] and labeled with antibodies directed against lymphatic endothelial cell marker LYVE-1 (orange, lacteal), blood endothelial cell marker CD34 (cyan, endothelial), and vimentin (purple, mesenchymal). **b**, Iterative bleaching extends multiplexity (IBEX) image of human lymph node labeled with antibodies directed against CD21 (purple, follicular dendritic cells) and α-SMA (cyan, fibroblastic reticular cells). **c**, IBEX image of human spleen labeled with antibodies directed against CD49a (cyan, red pulp stromal cells) and α-SMA (purple, white pulp stromal cells). All scale bars, 50 µm. Original data for **b** and **c** were published in ref. [7]. Confocal images provided by Andrea J. Radtke. Clinical imaging approaches not shown.

appropriated research funds. These data are available at RePORT.

An effort to create public categories related to 'Lymphatic Research' and 'Lymphedema' was initiated by the NIH National Heart, Lung, and Blood Institute in 2020 and completed in 2021. This trans-NIH effort leveraged 'category sessions' that involved subject matter experts across the NIH who gathered to discuss broad scientific category parameters encompassing all lymphatic research and gained consensus on areas of inclusion through iterative refinement of the fingerprint. These new categories are expected to be released in early 2022. Going forward, the categories will be maintained by the NIH Division of Scientific Categorization and Analysis annually with review, validation and input from Institute and Center experts to ensure the most accurate project listings are updated with emerging areas of science.

Modern, multidisciplinary approaches are needed to augment the limited amount of scientific research and published literature on the human lymphatic system. A comprehensive atlas across scales, including gross anatomy, cellular and molecular levels, will empower basic research and clinical management of lymphatic diseases. This is an urgent public health need, as hundreds of millions of people are affected each year with lymphedema and related conditions worldwide. We hope that these NIH-funded initiatives distinguish the twenty-first century of lymphatic research as an era of overflowing optimism for patients, clinicians, and researchers. ❐

Andrea J. Radtke[1]✉, Jessica M. Lukacs[2], Nancy E. Praskievicz[2], Selen C. Muratoglu[3], Ilsa I. Rovira[3] and Zorina S. Galis[3]✉

[1]*Lymphocyte Biology Section and Center for Advanced Tissue Imaging, Laboratory of Immune System Biology, NIAID, NIH, Bethesda, MD, USA.* [2]*Division of Scientific Categorization and Analysis, Office of Research Reporting and Analysis, Office of Extramural Research, Office of the Director, National Institutes of Health, Bethesda, MD, USA.* [3]*Division of Cardiovascular Sciences, National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, MD, USA.*

✉*e-mail: andrea.radtke@nih.gov; zorina.galis@nih.gov*

Published online: 9 June 2022
https://doi.org/10.1038/s41591-022-01865-5

References

1. Natale, G. et al. *J. Anat.* **231**, 417–429 (2017).
2. Oliver, G. et al. *Cell* **182**, 270–296 (2020).
3. Sappey, M. P. C. (Adrien Delahaye, 1874).
4. Stouthandel, M. E. J. et al. *Anat. Rec.* **302**, 1681–1695 (2019).
5. Grant, S. M. et al. *J. Cell Sci.* **133**, jcs241828 (2020).
6. Germain, R. N. et al. *Immunol. Rev.* **306**, 8–24 (2022).
7. Radtke, A. J. et al. *Nat. Protoc.* **17**, 378–401 (2022).
8. Takeda, A. et al. *Immunity* **51**, 561–572.e565 (2019).
9. Börner, K. et al. *Nat. Cell Biol.* **23**, 1117–1128 (2021).
10. Rockson, S. G. *Circ. Res.* **128**, 2003–2016 (2021).

Acknowledgements

This work was supported by the Intramural Research Program of the NIH, NIAID and NCI, and the Extramural Programs at NIH and NHLBI. We are very appreciative of insights and resources provided by R. N. Germain and image provided by C. Chu. We are grateful for domain expertise from our colleagues: D. Singhal, M. Amore, K. Börner, E. Chaikof, M. Detmar, M. Hollmén, J. Iliff, M. Itkin, T. Makinen, G. Oliver, T. Padera, E. Quardokus, H. Suami and G. Weber. We are indebted to D. M. Sullivan and A. Yarmosh who conceived and executed Fig. 1. The confocal and IBEX images in Fig. 2 were obtained experimentally by A. J. Radtke and C. Chu (human jejunum).

Author contributions

A.J.R., J.M.L., N.E.P., S.C.M., I.I.R. and Z.S.G. conceived and wrote the manuscript.

Competing interests

All the authors are government employees. The authors do not have any financial conflict of interests. The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Institutes of Health or any of its Institutes; or the US Department of Health and Human Services.

Check for updates

Myths about diversity in clinical trials reduce return on investment for industry

To the Editor — Misconceptions in drug development often begin at the earliest stages. People enrolled in clinical trials are in general not representative of the population with medical need[1], but the problem is particularly pernicious in early, first-in-human phase 1 studies. This is, in part, a result of stricter eligibility criteria in early studies, and is also due to clustering of phase 1 trial centers in urban locations that are less accessible to patients in rural or underserved areas. Efforts to enhance or mandate enrollment of a diverse population in phase 1 trials are often deferred, in the belief and expectation that later phase 2 and 3 studies can address this need. Yet limiting access to new therapies while they are being tested in phase 1 trials fails to promote inclusive research and is also ethically concerning. In an interview study of 100 adult patients with solid tumors, a significant majority believed that access to investigational new drugs is a fundamental right and yet is also too difficult, citing frequent ineligibility and time-consuming enrollment as barriers to entering these early-phase studies[2].

Table 1 | Dispelling DEI myths within industry creates benefits

Factor	When DEI myths are prevalent	When DEI myths are dispelled
Site recruitment strategy	DEI agnostic	DEI motivated
Commitment and resources to implement inclusive research	Lacking	Committed
Patient advocacy groups	Limited collaboration	Active collaboration
Clinical trial population	Non-diverse and non-representative	Diverse and representative
Study validity	Reduced	Improved
Market opportunity	Restricted	Widened

Phase 1 studies provide key safety data, can detect preliminary signals of efficacy and, in an era of expedited programs, may even enable accelerated approval of new drugs. The benefits of recruiting patients to a phase 1 trial cannot be reconciled with the longstanding belief in industry that clinical trial participants from under-represented populations need to be included only in the later stages of drug development. The recent accelerated US Food and Drug Administration (FDA) approval of the antibody–drug conjugate sacituzumab govitecan (Trodelvy; Gilead) highlights the dilemma facing drug developers and regulators. Although Black women have mortality rates for triple-negative breast cancer that are 41% higher than those of non-Hispanic white women, FDA approval was based on a study of 108 patients in which only 7% were Black[3]. Ultimately, a subgroup analysis of the confirmatory phase 3 study revealed an equal clinical benefit for Black patients, but it would have been much better to address efficacy in this patient group at an earlier stage, to determine the true impact of the approval of this medication.

As researchers in industry, we have been concerned to observe the lack of diversity in phase 1 clinical trials of perhaps the most significant development of recent times, vaccines for COVID-19. Forty of the 45 patients in the Moderna mRNA vaccine phase 1 study were white[4]; similarly, the Oxford COVID Vaccine Trial Group reported that the first-in-human study of their adenovirus-based vaccine consisted of "fairly young and healthy volunteers, the majority of whom were white"[5]. There is no doubt that these initial studies were remarkable in their innovation and speed, and later studies explicitly enrolled more diverse populations. But, beyond the moral and scientific imperatives, lack of inclusivity in the earliest phases of drug development can meaningfully impact and impair public trust, particularly among under-represented populations. If a drug is not tested in a representative sample at an early stage, this could lead to hesitancy to take the treatment; indeed, under-represented, minority populations in both the UK and USA saw reduced uptake of the COVID-19 vaccines.

As drugs that we have developed move from early development into later-stage studies, we have personally encountered unsubstantiated fear that diversity may lead to heterogeneous and difficult-to-interpret results. Yet we argue that, to truly understand how medicines work in the real world, clinical trials must be purposefully designed to reflect the populations who will use them. Inclusive research can reveal potential variations in outcomes in subgroups, as well as yielding opportunities to identify unique or specific responses, as observed in a study of the epidermal growth factor receptor (EGFR) inhibitor erlotinib (Tarceva; Genentech, Roche) in non-small-cell lung cancer (NSCLC)[6]. Both women and people of Asian descent had higher response rates than the overall trial population, a difference that was ultimately attributed to the L858R EGFR mutation, which is common in women of Asian descent. The enrollment of a diverse population in this study illuminated a predictive pharmacogenetic marker and uncovered an efficacy signal that has brought benefit to a myriad of patients.

Another myth to bust is that enrolling heterogeneous populations automatically equates to heterogeneity in outcomes. For example, the Surveillance, Epidemiology, and End Results databases indicate that Black patients with colorectal cancer in the real world have a 32% higher mortality risk than white people. Yet recent analysis suggests that this arises from unequal access to care: notably, Black and white patients with colorectal cancer had similar outcomes in a well-controlled clinical trial in which patients received similar healthcare[7]. Artificial intelligence provides similar evidence that a broader, more inclusive patient population will not alter trial outcomes. Trial Pathfinder used the Flatiron Health database to simulate recent large phase 3 studies in NSCLC[8]. When eligibility criteria were either fully relaxed or broadened with a data-driven approach, the number of eligible patients was drastically increased without affecting overall survival hazard ratios.

The specter of financial pragmatism looms large in industry, and we are frequently asked whether delays to recruit diverse participants will incur additional costs. Our first-hand evidence suggests that this is not the case. For example, in two similar studies examining the role of tocilizumab in COVID-19 pneumonia, speed of enrollment in the Empacta[9] study (16% white) was comparable to that for Covacta[10] (58% white). On the contrary, inclusive research will be a valuable ally to financial budgets. Implementing a diverse recruitment strategy in early development can improve the accuracy of key stop/go decisions, halting costlier pivotal studies on ineffective treatments and leading to longer-term savings. Enrollment of patients from historically under-represented groups will also afford an opportunity to make greater use of community hospitals. As these sites have reduced overhead costs and require fewer resources, this is a cost-effective strategy.

Embracing inclusion and increasing diversity at all stages of clinical trials can create a virtuous loop with tangible return on investment: inclusive trials with diverse patient populations make it easier to attract subjects from a broader pool; the patients enrolled may be more willing to stay in the study and become more engaged; and this, in turn, will increase the scientific and financial robustness of the study. Partnership between industry, clinical research sites, patient advocates and under-represented and excluded communities will be key to achieving these goals (Table 1).

To quote James Baldwin, "Not everything that is faced can be changed, but nothing can be changed until it is faced." The commitment to facing our misconceptions within biotech is central to delivering the change needed to deliver diverse, equitable and inclusive research. ❐

Mohammed Suhail Chaudhry[1]✉, Jessica Spahn[2], Shilpen Patel[3], Charles S. Fuchs[2,4], Jennifer Lauchle[1], Nikheel Kolatkar[5], Nicole Richie[6], Quita Highsmith[7], Meghan McKenzie[7] and Ruma Bhagat[8]

[1]Oncology Early Clinical Development, Genentech, South San Francisco, CA, USA. [2]Oncology and Hematology Product Development, Genentech, South San Francisco, CA, USA. [3]Health Equity and Inclusive Research, US Medical Affairs, Genentech,

South San Francisco, USA. [4]*Yale University, Yale Cancer Center, New Haven, CT, USA.* [5]*Scientific Operations and Evidence Generation, US Medical Affairs, Genentech, South San Francisco, CA, USA.* [6]*Health Equity & Population Science, Genentech, South San Francisco, CA, USA.* [7]*Chief Diversity Office, Genentech, South San Francisco, CA, USA.* [8]*Global Health Equity Strategy, Portfolio and Product Development, Genentech, South San Francisco, CA, USA.*
✉*e-mail: chaudhry.suhail@gene.com*

Published online: 6 June 2022
https://doi.org/10.1038/s41591-022-01858-4

References

1. US Food and Drug Administration (FDA). Enhancing the Diversity of Clinical Trial Populations Eligibility Criteria, Enrollment Practices, and Trial Designs for Industry; https://www.fda.gov/media/127712/download (2019).
2. Pentz, R. D. et al. *IRB* **29**(4), 1–6 (2007).
3. FDA. Drug Trial Snapshot: TRODELVY; https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trial-snapshot-trodelvy (2020).
4. Jackson, L. A. et al. *N. Engl. J. Med.* **383**, 1920–1931 (2020).
5. Folegatti, P. M. et al. *Lancet* **396**, 467–478 (2020).
6. Shepherd, F. A. et al. *N. Engl. J. Med.* **353**, 123–132 (2005).
7. Lee, S. et al. *JNCI Cancer Spectr.* **5**, pkab034 (2021).
8. Liu, R. et al. *Nature* **592**, 629–633 (2021).
9. Salama, C. et al. *N. Engl. J. Med.* **384**, 20–30 (2021).
10. Rosas, I. O. & Hunter, S. et al. *N. Engl. J. Med.* **384**, 1503–1516 (2021).

Author contributions

M.S.C., J.S., S.P. and R.B. conceptualized the manuscript. All authors drafted the manuscript. M.S.C. edited the manuscript.

Competing interests

C.S.F. reports consulting roles for Amylin Pharmaceuticals, Astra-Zeneca, Bain Capital, CytomX Therapeutics, Daiichi-Sankyo, Eli Lilly, Entrinsic Health, Evolveimmune Therapeutics, Genentech, Merck and Taiho, served as a Director for CytomX Therapeutics, owns unexercised stock options for CytomX and Entrinsic Health, is a co-founder of Evolveimmune Therapeutics and has equity in this private company, and has provided expert testimony for Amylin Pharmaceuticals and Eli Lilly. All authors are employees of Roche Genentech and hold stock in Roche Genentech.