Sanguine

Bridging Translational and Precision Medicine with the Prospective Collection of Human Biospecimens

By Geoffrey Feld, PhD[1,2] & Gerald Lee[1]

1. Sanguine Biosciences, 2. Geocyte LLC

Background

Translational precision medicine is an emerging discipline that integrates the patient experience into drug development through a biomarker and patient-centric approach.

While patient engagement is a critical component of translational precision medicine, in practice patients themselves are underutilized in the therapy development process.

Insight

Using prospectively collected human biospecimens in biomarker studies represents an approach that engages patients with prespecified inclusion criteria and integrates their journey to help address the translation gap.

Key evidence

Prospectively collected human biospecimens have been used to:

- Validate early-stage discovery and preclinical biomarkers to build confidence for clinical trials
- Facilitate flexible trial design measuring analytical and digital biomarkers that capture the patient journey in a clinically meaningful quantitative panel
- Benchmark critical biomarkers in a patient population for direct comparison to preclinical and clinical assay results

Conclusions

Prospectively collected human biospecimens support precision medicine initiatives by incorporating patient engagement in translational study design, providing access to specific and recallable patient populations, and capturing their individual journeys through biomarkers and annotated records.

PRECISION MEDICINE uses state-of-the-art scientific tools for the immediate benefit of patients who are both the benefactors of treatments tailored to their individual biology and the linchpin for the efficient and accelerated delivery of these therapies. Approaches designed to ensure that early-stage research translates into clinical applications rely on procuring human biospecimens, including blood, stool, and tissue. Successful drug and diagnostics development ultimately depends on deploying relevant human specimens to address the translation gap that emerges between laboratory models and real-world patients.[1]

Translational precision medicine aims to address this gap, combining early development based on mechanisms and biomarkers with patient-centric late drug development approaches.[1,2] Access to the most relevant patients and their corresponding data accelerates translational research and improves its accuracy toward disease-specific treatment development. In this sense, patient centricity forms the cornerstone of translational and precision medicine.* As such, quantitation of the patient experience may be construed as the goal of identifying clinically relevant, outcome-linked biomarkers.

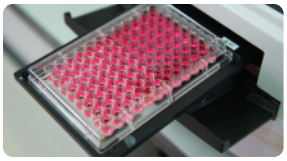
Both analytical and digital biomarkers represent objective indicators of the patient profile, disease status, and drug selection, all of which drive clinical trial design.[1] For example, screening individuals following specific inclusion and exclusion criteria, either phenotypic or genotypic, enables a more directed biomarker discovery approach. Decentralized prospective biospecimen collection also encourages elucidating longitudinal biomarkers reporting on disease progression or therapeutic efficacy through multiple sampling over a defined timeline.

Overall, the intrinsic value of any given biomarker centers on its association with phenotypic data and medical outcomes. Accordingly, Sanguine Biosciences elevates patient centricity as the focal point of its prospective biospecimen collection model. By leveraging its direct-to-patient approach, Sanguine can collect. the annotated patient data essential for biomarker utility in precision medicine, such as medical records, patient-reported outcome (PRO) documentation, patient/caretaker questionnaires, wearable device data, and demographics.

Patient engagement via direct-to-patient biospecimen collection

A growing body of evidence shows that engaging patients early in drug development provides the most value and impact.[1,3] In practice, a literature review of investigator-initiated engagement from 2011 to 2021 demonstrates the waning and limited integration of the patient voice into research programs. Of the 69 cited examples, 56 involved patients only after development goals had already been set.[4] Clearly, patient engagement represents a potentially powerful but underutilized translational precision medicine principle for improving the chances of therapy success.

One way to engage patients is to use



Discovery

- Disease taxonomy & target discovery
- Target validation
- Mechanism of action

Preclinical

- Lead candidate selection
- Safety & efficacy biomarkers
- Pharmacology biomarkers

Translation Gap

Clinical

- Diagnostic development
- Drug response & prognostic biomarkers
- Patient stratification

Cell & Gene Therapy Manufacturing

- Process development
- Rare cell isolation

Prospective Human Biospecimens

Biomarker discovery & validation | Patient engagement | Flexible Trial Design | Study benchmarking

Onsite collection programs for healthy cohorts

- Establishing clinical best practices
- Screening for specific activity
- Evaluating biomarker validity

Figure 1: Utility of prospective human biospecimens in addressing the translation gap across the therapy development pipeline.

prospectively collected, patient-derived biospecimens in translational research. Sanguine has built a network of more than 70,000 research-ready individuals across the US to facilitate patient participation in medical research and accelerate the therapy development process.[5,6]

Patient-facing coordinators speak directly with individuals and represent them in study design accordingly. Technology and partnership-driven recruitment initiatives leverage social media and patient advocacy group outreach to educate specific communities about relevant therapeutic research. In addition, in-home specimen collections by professional phlebotomists promote patient participation not limited to an individual's geography or mobility. Together, this framework transforms passively surveyed individuals into willing partners actively invested in advancing therapeutics across diverse disease conditions. This model enables biomarker studies that are longitudinal and multidimensional (e.g., multiple specimens collected in tandem or wearable devices) and ensures specimens include annotations, such as PRO documentation. In this paper, we present examples that range from rare to low-prevalence diseases to showcase the power of collecting and retaining valuable samples.

Sponsors contract with Sanguine to develop a prospective study design for their therapy program.[6] Patient recruitment, consent, and data retrieval requirements, such as inclusion and exclusion criteria, are established from study conception.[7] Specimen collection, processing, and storage requirements, including preanalytical sample isolation procedures, are additionally dictated before study commencement. Such specifications and customizations enable prospective studies to mirror proposed clinical trial parameters, control variability, and safeguard sample integrity compared to retrospectively collected biobank specimens.[8,9] Including healthy matched-control donors in a study design provides context on individual patient responses, particularly for longitudinal studies.

In effect, specimens collected under these circumstances resemble highly desirable clinical samples, which are prospectively collected yet avoid the logistical, regulatory, and handling considerations prohibiting the latter's utility.[10] Furthermore, in-home prospective studies can complement clinical site programs in a hybrid approach, fueling comprehensive biomarker discovery integral to translational precision medicine.

Integrating translational processes across the drug development spectrum transforms a one-way pipeline into a bidirectional flow of information, whereby research and clinical results together can inform an individual's response to treatment.[1,11] The precision medicine approach of using biomarker profiles, molecular biology, and patient-centric principles is actively applied to conditions beyond oncology, including autoimmune and infectious diseases.[12,13] We describe several published use cases demonstrating how Sanguine-led prospective studies provide a research and development tool for identifying, confirming, bridging, and expanding the pool of relevant biomarkers that mitigate the translation gap **(Figure 1)**.

Translation of early-stage biomarkers: developing and testing hypotheses with biospecimens

Minimally invasive, patient-derived specimens – such as peripheral blood, stool, urine, and skin tapes – serve as a conduit for validating the translatability of biomarkers discovered and refined in early-stage drug development. Prospective collection of these valuable samples ensures specimen annotation and alignment with subsequent clinical study design and objectives.

SARS-CoV-2/COVID-19

Screening individuals for genetic traits corresponding to disease or treatment outcomes can reveal new therapeutic strategies. In screening the class I human leukocyte antigen (HLA) immunopeptidome in a SARS-CoV-2 viral infection cell model, researchers discovered several novel candidate peptides presented early in infection that elicited early and sustained T-cell responses against COVID-19.[14] To test whether

a similar immunogenic response occurred in affected patients, the team engaged Sanguine to obtain peripheral blood mononuclear cells (PBMCs) isolated from convalescent COVID-19 donors expressing specific class I HLA alleles. Disrupted access to clinical sites at the height of the pandemic necessitated in-home, prospective blood collection from previously infected individuals. Robust cytotoxic T-cell responses were observed for several novel HLA peptides, including stronger signals than spike and other canonical SARS-CoV-2 proteins, strongly supporting their presentation in affected patients. Thus, human specimens can help confirm whether discoveries in model systems will translate into new vaccine candidates and immune monitoring biomarkers in patients.

Evaluating Sulf-2 in autoimmune conditions

While therapeutic modalities addressing a biological mechanism are often translatable to humans, their performance in the context of specific human disease states warrants investigation. The cancer drug target Sulf-2 is believed to regulate several inflammatory pathways, including TNFα, but its role in various autoimmune conditions is unknown.

A multi-institute team designed a prospective study with Sanguine to interrogate Sulf-2 in sera from patients with either rheumatoid arthritis (RA) or multiple sclerosis (MS) and healthy-matched controls. In this early-stage study, Sulf-2 levels were significantly higher among the RA cohort than MS or healthy controls, suggesting Sulf-2 inhibition may represent a viable therapeutic strategy for RA autoimmunity.[15] Subsequent experiments in patient-derived synovial tissue and mouse models demonstrated a unique role of Sulf-2 in TNFα-mediated activation of RA synoviocytes, green-lighting further preclinical investigations.

Evaluating checkpoint inhibitors for viral infections

Screening noteworthy therapeutic targets for novel mechanisms of action can yield improved treatment options for patients and valuable intellectual property for developers. Checkpoint inhibitors that block the receptor PD-1 from binding its ligand PD-L1 are successful cancer immunotherapies, revolutionizing the standard of care for several cancer types involving tumor-directed immune suppression. A team from Arbutus Biopharma discovered a small molecule capable of inhibiting PD-1/PD-L1, likely through dimerization and subsequent receptor internalization rather than blocking the interaction.[16] While the compound demonstrated robust *in vitro* PD-1/PD-L1 inhibition and anti-tumor activity in a mouse model, it was unclear whether the drug stimulated an immune response in humans. Given that PD-1 immune tolerance is implicated in chronic viral infections, a therapeutic focus of Arbutus, a prospective study was undertaken with Sanguine involving PBMCs from patients with chronic hepatitis B virus or cytomegalovirus infection. The novel compound showed similar T cell, B cell, and IFNγ responses as the canonical antibody inhibitors in these specimens, suggesting the drug acts through an immunostimulatory mechanism in humans and could represent an avenue for treating chronic viral infections.

Building confidence for human studies with minimally invasive patient-derived biospecimens

Precision medicine is rewriting the playbook on commonly held clinical principles by identifying patient characteristics that predict response to targeted therapy. For example, the FDA published new draft guidance recommending extensive pharmacokinetic analysis in phase I trials of targeted cancer therapies to determine optimal dosing in subsequent trials rather than relying on the traditionally accepted maximum tolerated dose.[17] Indeed, leveraging preclinical data can inform dose optimization strategies, predicting whether specific treatments should be evaluated at lower doses.[18]

Oncology studies increasingly integrate patient-derived biospecimens, such as tumor organoids and xenografts, into the discovery and preclinical development stages to increase the likelihood of individual response to therapy.[19] Such samples require invasive biopsy, limiting their utility broadly across populations and disease conditions. Prospectively collected, minimally invasive biospecimens provide an accessible and patient-driven validation that preclinical pharmacology and underlying biology signals also occur in the context of a specific patient population.

B cell depletion is an approved and actively researched therapy arena for recurring and relapsing MS. Bruton's tyrosine kinase (BTK) inhibitors have emerged as an attractive therapeutic avenue, given their non-cytotoxic, non-depletive ability to attenuate B cell and myeloid cell activation and effector functions.[20] A novel reversible BTK inhibitor showed promising selectivity and potency in discovery and preclinical models, but its performance in a human disease context was unclear. Biogen scientists engaged Sanguine to investigate inhibitor pharmaco-dynamic performance in prospectively collected whole blood from patients with MS and healthy matched controls with specific inclusion and exclusion criteria. The compound similarly attenuated B cell activation in the human donor samples, recapitulating the preclinical observations. Early indications from the resulting phase I trial revealed that such activity was dose-dependent.[21] Thus, measuring pharmacological biomarkers in prospective whole blood from patients with the disease condition justified the translatability of the underlying biological mechanism, paving the way for a first-in-human evaluation.

Describing the patient experience in biomarkers: Sickle cell disease

While identifying biomarkers that chronicle disease natural history and treatment response constitutes a primary goal of translational precision medicine, much of the patient experience occurs outside the clinical setting. Flexible trial design (defined here as decentralized, direct-to-participant, and hybrid clinical trials) features the dual patient-centric goals of reducing the burden of participation while increasing the collection of real-world evidence and biomarkers.[22] Prospective biospecimen collection enables the at-home recording of analytical and digital biomarkers from predefined patient populations longitudinally, extending the patient experience beyond the clinic (**Figure 2**).

Sickle cell disease (SCD) is commonly associated with unpredictable and debilitating severe pain episodes called vaso-occlusive crises (VOCs). While VOC frequency and severity correlate with SCD morbidity and mortality, the VOC clinical endpoint relies exclusively on the patient visiting a medical facility for treatment, grossly underreporting the patient experience. To capture the natural history of SCD-associated VOCs, investigators partnered with Sanguine to implement the Evaluation of Longitudinal Pain Study in Sickle Cell Disease (ELIPSIS). This minimally invasive, prospective study cataloged the patient experience through continuously measured actigraphy, daily electronic patient-reported outcomes (ePROs), and longitudinal exploratory and established clinical assays to identify meaningful blood and digital biomarkers for future treatment investigations.[23] Since VOCs often occur and are managed in-home, reported VOCs triggered a series of mobile phlebotomy collections, which were included alongside blood samples taken at medical facilities.

ELIPSIS demonstrated the feasibility of prospectively collecting diverse and longitudinal biomarker streams associated with VOCs that may represent new endpoints in SCD clinical trials.[23] Longitudinal blood collections associated with VOCs reported outside a medical facility enabled the identification of flow-based adhesion assay biomarkers predictive of a patient's risk for experiencing a VOC.[24] The resulting standardized clinical test correlated strongly with SCD severity, VOC onset, and treatment status, indicating assay utility for patient stratification in clinically

evaluating SCD therapies.[25] Reports from ELIPSIS suggest that the patient experience can be captured through biomarkers outside a clinical setting and could be broadly applied to other disease conditions.

Expanding the reach of clinical trials

The tools for achieving flexible trials have evolved into common practice, precipitated by disruptions to site-based specimen and data collection during the COVID-19 pandemic.[26] By taking advantage of virtual tools and in-home visitation, trial sponsors can engage a voluminous and diverse patient population more efficiently, inclusively, and cost-effectively, regardless of participant geography or mobility.[22,26] Sanguine's nationwide network of patients and professional phlebotomists ensure that in-home, prospective studies are conducted reliably and compliantly according to predetermined protocols, especially when access to clinical sites is limited or burdensome.

Benchmarking biomarkers: COVID-19 vaccine and diagnostic development

A well-characterized human sample containing relevant biomarkers is often necessary to benchmark measurements and connect data streams from preclinical and myriad decentralized clinical sites.[27] In evaluating multiple COVID-19 vaccine candidates, developers coordinated with Sanguine to prospectively collect convalescent sera in-home from unimmunized symptomatic and asymptomatic patients. Vaccine-induced humoral and neutralizing antibody responses could be subsequently benchmarked against individuals who had recovered from COVID-19.

Ranging from 18 to 83 years of age, individuals in the Pfizer/ BioNTech vaccine cohort donated blood in their homes at least 14 days post-diagnosis and were asymptomatic at the time of collection.[28] In preclinical results involving immunized rhesus macaques, the two lead mRNA formulations elicited tighter IgG binding to the spike protein receptor binding domain (RBD) and neutralizing antibodies against SARS-CoV-2, compared to the unimmunized convalescent cohort.[29]

In subsequent clinical trials, the immune responses of immunized individuals were consistently compared to the at-home collected convalescent sera cohort. The two lead Pfizer/ BioNTech vaccine candidates demonstrated robust and durable immunogenicity in the phase I/II trial after the second vaccine dose, compared to the COVID-19 recovered cohort.[28,30,31]

A similar benchmarking strategy was utilized in an approved virus-like particle (VLP) vaccine derived from plants. Compared to the antibody responses of recovered individuals, the VLP candidate demonstrated long-term durability six months after immunization in a phase I trial, immunogenicity in older individuals and those with comorbidities, and cross-reactivity with variants of concern.[32–34] Thus, benchmarking can effectively be applied broadly to connect data streams from various studies.

The lead Pfizer/BioNTech mRNA candidate was selected based on its favorable safety profile in the phase I trial despite both formulations showing similar immunogenicity profiles.[35] Both vaccine candidates generated equivalent or superior neutralizing antibody titers and IgG binding compared to the convalescent sera cohort among older and younger immunized individuals, demonstrating broad utility in the population. One could envision a scenario whereby the selection of the lead candidate depended on immunogenicity differences among candidates compared to recovered individuals rather than the safety profiles.

Robust, standardized, and validated assays that provide accurate and precise readouts across different treatments, trials, and geographies enable the accelerated global development of vaccines and other therapies. During the pandemic, Sanguine provided safe and reliable mobile, in-home biospecimen collections that supported the development of such unified assays.

The performance of two immunogenicity assays quantifying either SARS-CoV-2 neutralizing antibodies or IgG antibodies against spike, nucleocapsid, and RBD proteins was evaluated against pooled convalescent sera from COVID-19 recovered individuals. The resulting validated assays represent simple and standardized tools for the clinical evaluation of new vaccines and antivirals.[36] Prospective collection of these critical benchmarking samples thus circumvented the need for clinical site access to develop clinically meaningful diagnostic assays.

On-demand healthy biospecimens support all stages of development

Mobile phlebotomy and regulatory expertise enable companies and research institutions to establish programs managed by Sanguine whereby healthy employees with no underlying conditions can donate specimens anonymously onsite. Requesting scientists prospectively design studies addressing research questions across the therapy development pipeline. Given these specimens can be utilized within minutes of collection, they represent a unique tool for replicating clinical and real-world conditions and identifying avenues for optimization. For example, post-collection delays in processing PBMCs from whole blood are inevitable in clinical trials, yet the negative impact on cell viability and underlying biology is not well documented. In utilizing specimens from their onsite program, researchers established a time course ranging from two to 48 hours to analyze the consequences of processing delay, providing valuable feedback on their clinical trial practices.[37]

Blood specimens from a pool of healthy onsite program participants can be screened for specific assay activity. A nonclinical study compared the four interleukin (IL)-23 monoclonal antibody inhibitors approved for psoriasis in the US. In designing an *in vitro* potency assay, investigators identified specific whole blood specimens from onsite program donors demonstrating a high response to IL-23 stimulation, facilitating the evaluation.[38]

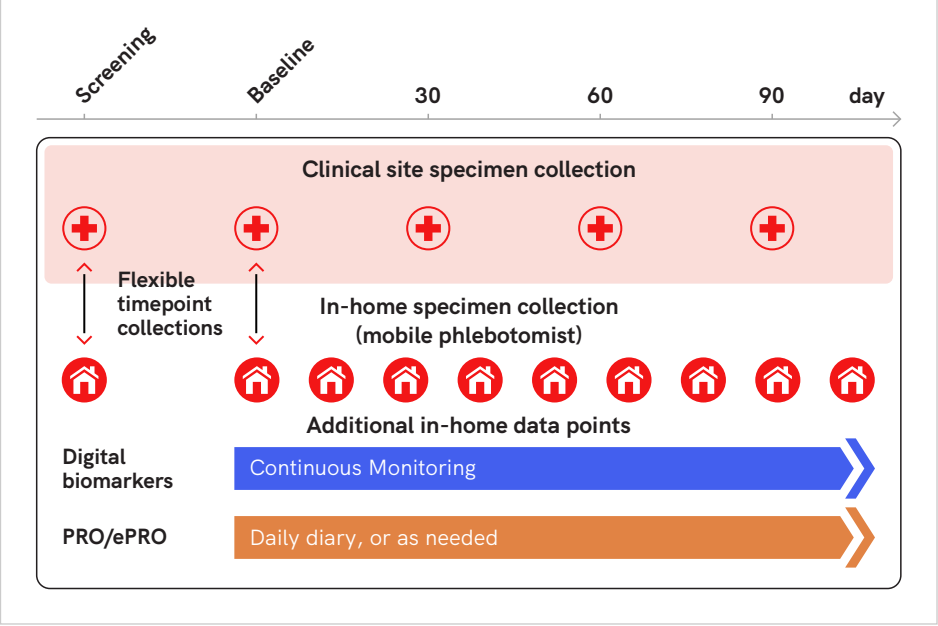


Figure 2: Generic representation of a flexible trial design. Concept inspired by Pittman et al.[20]

On-demand healthy specimens can further be used to evaluate mechanisms of action or biomarker validity. In healthy human PBMCs collected in a Sanguine-managed onsite program, researchers found that adalimumab uniquely induces a macrophage wound healing response phenotype among several anti-TNFα therapies.[39] This mechanism supports why adalimumab is the sole anti- TNFα therapy indicated for hidradenitis suppurativa and its possible therapeutic application in other chronic wound conditions.

Leukopaks: high-volume immune cell specimens for cell & gene therapy

The rise of cell and gene therapies to treat genetic, oncology, and autoimmune diseases has created a new demand for human blood biospecimens in translative research.[40,41] Given that these therapies (whether autologous or allogeneic) are produced from living cells, the manufacturing process requires optimization, quality control, and scale-up for viable worldwide clinical trials and product distribution.[42,43] Prospectively collected leukapheresis products provide researchers with typically billions of PBMCs from a single donor that replicate the final therapy product and prove useful for assay validation, process development, and rare cell isolation (e.g., CD34+ hematopoietic stem cells). Researchers specify the donor characteristics and disease conditions to be recruited from Sanguine's patient network and stipulate whether the leukapheresis product should be delivered fresh, cryopreserved, or further processed into PBMCs or specific lymphocytes, depending on needs. Concurrently, patient donors directly participate in expediting potentially life-changing treatments for their disease while receiving compensation.

Summary

Patient-centric biomarkers that capture the individual's experience, link to outcomes, and translate science into practice are the cornerstone of precision medicine. Sanguine has built a unique infrastructure for the prospective, in-home collection of biospecimens, building relationships with patients and patient advocacy groups nationwide to increase their participation in the translational and clinical research process. A strong commitment to patient engagement facilitates precision medicine goals through specimen annotation and participant recallability in longitudinal studies. Researchers can prospectively design analytical and digital biomarker studies that engage patients in a manner complementary to the clinic while maintaining double-blind anonymity. Such an approach ensures that patients actively impact their future care through inclusion in research initiatives addressing the translation gap.

Geoffrey Feld, PhD

Geoff is the founder and principal consultant of Geocyte, offering broad and market-tailored science and medical communication services to the life sciences. He partners with industry leaders and nonprofits to educate and persuade expert and information-consuming audiences through strong science-based narratives, peer-reviewed publications, and messaging. Geoff earned his Ph.D. in biophysical chemistry from the University of California, Berkeley. He has demonstrated postdoctoral and professional expertise in the structural biology of infectious diseases, metabolism, -omics technologies, and microbiome impact on human and animal health.

Gerald Lee

Gerald is co-founder and chief product officer of Sanguine Biosciences, leading operations and product development for preclinical research and laboratory services over the last decade. He is a patient advocate and offers expertise in decentralized research, laboratory services, patient engagement, and specimen biobanks. Gerald earned his B.S. in molecular, cellular, and developmental biology from the University of California, Los Angeles, followed by more than three years at Stanford University in the department of hematology-oncology, where he studied the immune response from patients diagnosed with chronic myeloid leukemia and breast cancer and helped build the department's oncology biobank.

References

1. Hartl, D. et al. Translational precision medicine: an industry perspective. J Transl Med 19, 245 (2021).
2. Director's Corner | National Center for Advancing Translational Sciences. https://ncats.nih.gov/director.
3. Fox, G. et al. Patient engagement in preclinical laboratory research: A scoping review. EBioMedicine 70, (2021).
4. Zvonareva, O., Cravet, C. & Richards, D. P. Practices of patient engagement in drug development: a systematic scoping review. Res Involv Engagem 8, (2022).
5. Participate in Research Studies | Sanguine Bio. https://sanguinebio. com/patients/.
6. Seydel, C. Complex Research Calls for Sophisticated Biobanking Tools. Genetic Engineering & Biotechnology News 39, S10–S12 (2019).
7. Specimen Procurement & Data Collection | Sanguine Bio. https://sanguinebio.com/researchers/patient-biospecimens-and-data-collection/.
8. Ellervik, C. & Vaught, J. Preanalytical variables affecting the integrity of human biospecimens in biobanking. Clin Chem 61, 914–934 (2015).
9. Whitcomb, D. C. Primer on Precision Medicine for Complex Chronic Disorders. Clin Transl Gastroenterol 10, (2019).
10. Durant, T. J. S., Gong, G., Price, N. & Schulz, W. Bridging the collaboration gap: Real-time identification of clinical specimens for biomedical research. J Pathol Inform 11, (2020).
11. Austin, C. P. Translating translation. Nature Reviews Drug Discovery 2018 17:7 17, 455–456 (2018).
12. Demerle, K., Angus, D. C. & Seymour, C. W. Precision Medicine for COVID-19: Phenotype Anarchy or Promise Realized? JAMA 325, 2041–2042 (2021).
13. Chasset, F., Dayer, J. M. & Chizzolini, C. Type I Interferons in Systemic Autoimmune Diseases: Distinguishing Between Afferent and Efferent Functions for Precision Medicine and Individualized Treatment. Front Pharmacol 12, 583 (2021).
14. Weingarten-Gabbay, S. et al. Profiling SARS-CoV-2 HLA-I peptidome reveals T cell epitopes from out-of-frame ORFs. Cell 184, 3962-3980. e17 (2021).
15. Siegel, R. J. et al. Extracellular sulfatase-2 is overexpressed in rheumatoid arthritis and mediates the TNF- -induced inflammatory activation of synovial fibroblasts. Cell Mol Immunol 19, 1185–1195 (2022).
16. Park, J. J. et al. Checkpoint inhibition through small molecule-induced internalization of programmed death-ligand 1. Nat Commun 12, (2021).
17. U.S. Department of Health and Human Services & Food and Drug Administration. Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases Guidance for Industry: DRAFT GUIDANCE. https://www.fda.gov/ BiologicBloodVaccines/GuidanceComplianceRegulatoryInformation/ Guidances/default.htm.
18. Goldstein, M. J., Peters, M., Weber, B. L. & Davis, C. B. Optimizing the Therapeutic Window of Targeted Drugs in Oncology: Potency Guided First in Human Studies. Clin Transl Sci 14, 536–543 (2021).
19. Pauli, C. et al. Personalized in vitro and in vivo cancer models to guide precision medicine. Cancer Discov 7, 462–477 (2017).
20. Contentti, E. C. & Correale, J. Current Perspectives: Evidence to Date on BTK Inhibitors in the Management of Multiple Sclerosis. Drug Des Devel Ther 16, 3473–3490 (2022).
21. Bame, E. et al. Next-generation Bruton's tyrosine kinase inhibitor BIIB091 selectively and potently inhibits B cell and Fc receptor signaling and downstream functions in B cells and myeloid cells. Clin Transl Immunology 10, (2021).
22. van Norman, G. A. Decentralized Clinical Trials: The Future of Medical Product Development? Basic to Translational Science 6, 384–387 (2021).
23. Pittman, D. D. et al. Evaluation of Longitudinal Pain Study in Sickle Cell Disease (ELIPSIS) by patient-reported outcomes, actigraphy, and biomarkers. Blood 137, 2010–2020 (2021).
24. Hines, P. C. et al. Flow adhesion of whole blood to P-selectin: a prognostic biomarker for vaso-occlusive crisis in sickle cell disease. Br J Haematol 194, 1074–1082 (2021).
25. White, J. et al. Longitudinal assessment of adhesion to vascular cell adhesion molecule-1 at steady state and during vaso-occlusive crises in sickle cell disease. Br J Haematol 196, 1052–1058 (2022).
26. Anderson, M. How the COVID-19 pandemic is changing clinical trial conduct and driving innovation in bioanalysis. Bioanalysis 13, 1195–1203 (2021).
27. Folegatti, P. M. et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. The Lancet 396, 467–478 (2020).
28. Sahin, U. et al. COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. Nature 586, 594–599 (2020).
29. Vogel, A. B. et al. BNT162b vaccines protect rhesus macaques from SARS-CoV-2. Nature 592, 283–289 (2021).
30. Sahin, U. et al. BNT162b2 vaccine induces neutralizing antibodies and poly-specific T cells in humans. Nature 595, 572–577 (2021).
31. Mulligan, M. J. et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature 586, 589–593 (2020).
32. Charland, N. et al. Safety and immunogenicity of an AS03-adjuvanted plant-based SARS-CoV-2 vaccine in Adults with and without Comorbidities. NPJ Vaccines 7, 1–13 (2022).
33. Gobeil, P. et al. Durability and cross-reactivity of immune responses induced by a plant-based virus-like particle vaccine for COVID-19. Nat Commun 13, 1–10 (2022).
34. Ward, B. J. et al. Phase 1 randomized trial of a plant-derived virus-like particle vaccine for COVID-19. Nat Med 27, 1071–1078 (2021).
35. Walsh, E. E. et al. Safety and Immunogenicity of Two RNA-Based COVID-19 Vaccine Candidates. New England Journal of Medicine 383, 2439–2450 (2020).
36. Bonhomme, M. E. et al. Robust validation and performance comparison of immunogenicity assays assessing IgG and neutralizing antibodies to SARS-CoV-2. PLoS One 17, e0262922 (2022).
37. Yi, P-C, et al. Impact of delayed PBMC processing on functional and genomic assays. J Immunol Methods, 519, 113514 (2023).
38. Zhou, L. et al. A non-clinical comparative study of IL-23 antibodies in psoriasis. MAbs 13, 1964420 (2021).
39. Cao, Y. et al. Adalimumab Induces a Wound Healing Profile in Patients with Hidradenitis Suppurativa by Regulating Macrophage Differentiation and Matrix Metalloproteinase Expression. Journal of Investigative Dermatology 141, 2730-2740.e9 (2021).
40. Finck, A. v., Blanchard, T., Roselle, C. P., Golinelli, G. & June, C. H. Engineered cellular immunotherapies in cancer and beyond. Nat Med 28, 678–689 (2022).
41. Mackensen, A. et al. Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus. Nat Med 28, 2124–2132 (2022).
42. Frangoul, H. et al. CRISPR-Cas9 Gene Editing for Sickle Cell Disease and -Thalassemia. New England Journal of Medicine 384, 252–260 (2021).
43. Tyagarajan, S., Schmitt, D., Acker, C. & Rutjens, E. Autologous cryopreserved leukapheresis cellular material for chimeric antigen receptor–T cell manufacture. Cytotherapy 21, 1198–1205 (2019).

* What Is Patient-Centered Care? NEJM Catalyst (2017). https://catalyst. nejm.org/doi/full/10.1056/CAT.17.0559