Alix VENTURES

Market Deep Dive Report

Precision Immunology

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Contents

1. Summary

Big data generation and computational processing have enabled the beginnings of a shift in medicine from a “one-size-fits-all” approach to patient stratification for targeted treatment. In many cases, the recognized patient subpopulations span multiple indications and so enable the utilization of the precision therapeutics with vastly improved safety and efficacy given biomarker-driven selection. While significant achievements using “-omics" data have been made in precision oncology, immune-mediated diseases (IMDs) are only now just beginning to benefit from a data-driven approach. Despite IMDs wide range of etiologies – from autoimmune to autoinflammatory to anticoagulatory conditions – therapeutics agents and regimens have yet to account for heterogeneous pathogeneses in treatment, instead being painted with the same broad brush approach and resulting in widely differentiated patient outcomes. The application of precision medicine to immunology is a game-changing opportunity that will drive breakthrough clinical & lucrative commercial outcomes.

Market leaders in this new field of precision immunology should develop easily-adaptable platform approaches that employ patient data to identify immune-specific subpopulations and advance guided-therapies to ensure patients receive personalized treatment with improved efficacy and performance. We believe that broadening immune analysis from mechanistic biology to immune states through the analysis of large, proprietary patient datasets will increase throughput while both deeper and broader immune biology understanding advances. Combining this analysis with the development of companion diagnostics for guided therapies will improve treatment efficacy/performance. Together, the approach creates an attractive investment opportunity with high potential to advance precision immunology.

2. Market Overview

The emerging precision immunology market is positioned at the intersection of precision in vitro diagnostics (IVD) and immunology.

At an estimated value of over $80B in 2020, the global IVD market is predicted to thrive at a CAGR of 4.5% and reach a value of $120B by 2030. Top players include: Abbott, Bio-Rad, Becton, Dickinson and Company, Roche, Siemens, QIAGEN, and Thermo Fisher. Clinical chemistry and immunoassays dominate the revenue share; molecular diagnostics and point-of-care-testing continue to grow at the highest rates; and tissue diagnostics and hemostasis will experience moderate growth followed by rest of the technology segments. The top-10 companies serving the IVD industry together accounted for 65.2% of the global revenue in 2020, while the top-20 companies together made up 78.8% of the global proceeds. The North American region, primarily with contributions from the US, leads the market, maintaining its stronghold on the IVD industry. APAC, primarily driven by Japan, China, and India, along with

the other growing economies will experience the highest growth rate, while Europe will continue to grow at a slower pace.

Meanwhile, the global immunology market is currently valued at $87B and is expected to grow to $160B in 2028 at a CAGR of 8.1%. The immunology space has been home to many of the pharmaceutical industry's most successful drugs, with 7 current blockbusters that are second in number only to oncology's 9 blockbusters. Humira is worth special mention as the world's best-selling pharmaceutical since 2012, with sales topping $20B in 2021. Despite the number of blockbusters, the immunology market still has a lot of room for growth. This rapid expansion is being driven by a global and continuously increasing patient incidence, and is supported by new mechanism biologics, novel oral agents, biosimilars, and precision diagnostics and treatments.

While precision immunology was born out of the need to generate new targets for immunotherapy in cancer, its applications extend to battling broader immune-mediated diseases (IMDs) and viral and bacterial infections. Based on disease indication, the IMD landscape can be split between critical and chronics IMDs. Among critical IMDs, sepsis, acute respiratory distress syndrome (ARDS), prophylaxis of organ rejection, DIC, lymphopenia, and cytokinemia are prominent. Chronic conditions – also commonly known as autoimmune disorders – occur when the immune system overreacts or attacks its own component parts by accident, triggering inflammatory responses. Autoimmune conditions can be classified into rheumatoid arthritis (RA), psoriatic arthritis, plaque psoriasis, ankylosing spondylitis, inflammatory bowel disease (ulcerative colitis, Crohn's), and other inflammatory illnesses. Such conditions are both highly prevalent and typically long-term in nature, giving rise to the $87B market.

Today, of the over 30 million patients diagnosed with moderate-to-severe forms of chronic immune diseases alone, only 5 million receive advanced therapies and only 2 million experience adequate responses. A key barrier to the development of novel therapies and treatment paradigms for IMDs has been the complexity and heterogeneity of these IMDs, which consist of different disease states with distinct unmet medical need and biology. It is clear that advances in scientific understanding of disease pathophysiology are needed to identify biomarkers for mechanistic and immune state-driven patient stratification so that we can both repurpose existing therapeutics to new clinical paths and develop new medicines with mechanisms of action tailored to differentiated patient populations.

On the basis of drug class, the market is segregated into monoclonal antibodies (mAb), fusion proteins, immunosuppressants, and polyclonal antibodies (pAb), among others. Based on drug class, monoclonal antibodies (mAb) held a global immunology market share of about 64.5% in 2020 and are expected to dominate in the coming years. This dominance is attributable to the increasing number of approvals for mAb by the government bodies to treat chronic ailments globally. Moreover, on the basis of the distribution channel, the market is trifurcated into hospital pharmacies, retail pharmacies, and online pharmacies.

Lastly, based on region, North America stood at $46B in 2020 and is likely to hold the highest position in the market for the next ten years. This is due to the increasing prevalence of chronic ailments and the higher diagnosis rate of the patients that will boost the adoption of advanced immunology drugs in the region. The European market is also expected to experience considerable growth backed by the increasing prevalence of chronic disorders, such as rheumatoid arthritis, that propels the demand for effective immunology therapies and drugs. For instance, according to the British Society for Immunology, around 400,000 people in the U.K. suffered from rheumatoid arthritis in 2018.

2.1 Pitchbook Market Statistics

Immunology is one of the most active sectors for investors, with an overall funding of $97B in 1,400+ companies by 2020. It is also interesting to note that around half of the funding was raised in just 3 years, from 2018-2020.

JLABS, Orbimed, NIH, MPM Capital and RA Capital Management are amongst the most active investors in this sector, by number of investments.

- **Quick stats**
  - No. Companies: 793
  - No. Deals: 1,848
  - No. Investors: 1,683
  - No. Exits: 432
  - Largest deal: $80.27B

- **Deal Count - Last 3 Years:**
  - VC
    - 2021: 101
    - 2020: 80
    - 2019: 69
  - **Corp/Strategic M&A**
    - 2021: 22
    - 2020: 14
    - 2019: 17
  - **IPO/Liquidity**
    - 2021: 13
    - 2020: 4
    - 2019: 10

- **Capital Invested - Last 3 Years**
  - **VC**
    - Last 3 years total: $10.12B
    - Annual Total
      - 2021: $4.42B
      - 2020: $2.92B
      - 2019: $2.78B
  - **Corp/Strategic M&A**
    - Last 3 years total: $154.06B
    - Annual Total
      - 2021: $7.91B
      - 2020: $5.15B
      - 2019: $141B
  - **IPO/Liquidity**
    - Last 3 years total: $4.46B
    - Annual Total
      - 2021: $1.60B
      - 2020: $1.16B
      - 2019: $1.70B

- **Most Active VCs by Deal Count:**
    - OribiMed - 27
    - HBM Healthcare Investments - 22
    - Horizon 2020 - 18
    - RA Capital Management - 18
    - SV Health Investors - 15
    - Boehringer Ingelheim Venture Fund - 14
    - Alexandria Venture Investments - 13
    - HBM Partners - 13
    - MPM Capital - 13

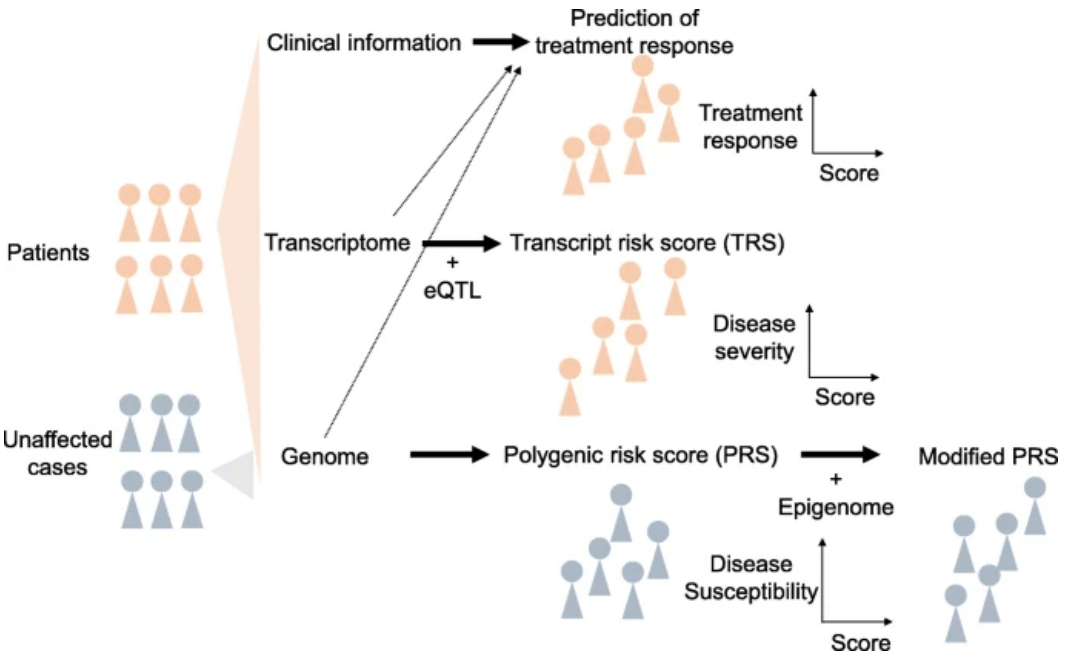
3. Technology Overview

3.1 Layman's Synopsis

Precision immunology seeks to analyze large amounts of patient data to discover biological insights that can help define smaller patient groups with similar likelihoods of response to specific treatments. By developing an understanding of the biomarkers that distinguish these patient populations, we are able to create diagnostics to identify the patient groups and either select or develop drugs to most effectively treat patients. This includes the repurposing of existing therapies to targeted patient subpopulations (near-term) & the development of novel therapies for individualized treatment (mid- to long-term).

3.2 Current Techniques and Platforms

A growing number of drugs, from small molecule compounds to biologics, have been approved for IMDs so far. Clinically, prediction of the treatment response before administering therapy to reduce the risk of side effects and the economic burden has gained great interest. To drive this change, big data generation and computational processing have enabled the beginnings of a shift in medicine from a "one-size-fits-all" approach to patient stratification for targeted treatment. In many cases, the recognized patient subpopulations span multiple indications and so enable the utilization of the precision therapeutics with vastly improved safety and efficacy given biomarker-driven selection. While significant achievements using "-omics" data have been made in precision oncology, immune-mediated diseases (IMDs) are only just beginning to benefit from a data-driven approach. Despite IMDs wide range of etiologies – from autoimmune to autoinflammatory conditions – therapeutics agents and regimens have yet to account for heterogeneous pathogeneses in treatment, resulting in widely differentiated patient outcomes. The application of precision medicine to immunology is a game-changing opportunity that will drive breakthrough clinical & lucrative commercial outcomes.



Although still in its infancy, there have been numerous efforts to apply omics data in clinical practice using various approaches (Fig. 1). **Fig. 1. Present strategies for stratification of disease-affected and unaffected cases.** How clinical information, transcriptome, and genome data can be used for predicting clinical outcomes or disease susceptibility.

- **Genomic Data –** Application of genomic data for precision medicine, especially for disease prevention, has gained wide interest. In particular, the polygenic risk score (PRS) has been applied to a variety of diseases, and some of the results have been promising. PRS is calculated by summing the effects of all common variants on disease onset to estimate the overall risk of developing a particular disease. It is especially useful for polygenic traits, in which small effects of numerous common variants contribute to disease onset. Generally, a larger sample size in genome-wide association studies (GWAS) is necessary for better prediction of the PRS, although the explained genetic variance of each trait also has an influence.

- **Transcriptomic Data –** In contrast to genomic data, transcriptomic data reflect the variance acquired from environmental factors as well as from genetics. For instance, exposure to inflammation, cellular activation, or cellular composition can be reflected in transcriptomic data [27]. In some reports, transcriptomic data proved useful for patient stratification.

- **Expression Quantitative Trait Loci (eQTL) Data –** eQTL analysis is used to identify the association between genetic variants and gene expression. The datasets are quite useful for estimating the effects of disease-associated variants. Generally, the majority of non-coding disease-associated genetic variants are assumed to modulate the

expression of genes that play roles in disease pathogenesis. Thus, it is reasonable to integrate GWAS results with eQTL data and estimate gene-level associations with diseases to reduce the multiple testing burden and facilitate biological interpretation. This approach, referred to as transcriptome-wide association studies (TWAS), has garnered great interest.

Therapies commonly used in the clinic today are corticosteroids, antimalarial drugs, or other systemically acting immunosuppressants that are associated with substantial side effects. So, in addition to precision diagnostics approaches informing treatment for more traditional biologics and small molecule drugs, new modalities are being explored to combat IMDs, including: Cell & Gene Therapy

3.3 Late Stage Privates & Publics

The market is highly competitive with many potential players such as AbbVie, Johnson & Johnson, Roche, Amgen, Pfizer, Novartis, Astellas, Bristol-Myers Squibb Company, and Merck. Companies such as Sanofi, J&J, AbbVie, Novartis, and Pfizer have selected immunology as a key area of investment, with J&J and Sanofi worthy of particular mention.

- **Johnson & Johnson** – and its Janssen Pharmaceutical Companies plan to launch or file for regulatory approval of more than 10 new products with "blockbuster potential" by the end of 2021. With a growing core business of differentiated medicines and a strong line-up of innovative products expected to launch or file over the next five years, Johnson and Johnson are leading the industry in the traditional, one-size-fits-all approach.

- **Sanofi** – by contrast, declared its intent to create a world leading precision immunology franchise on January 11th 2022. Their current approach focuses on the development of precision therapeutics based on highly detailed mechanistic and cellular hypotheses. Using single-cell genomics, genetics, and proteomics, Sanofi R&D teams are creating molecular profiles of both disease models and patients participating in clinical studies. This enables them to track the activity of genes and proteins in different cell types and observe how they change depending on the conditions and treatments at various times. The application of AI-advanced analytics to this combination of bioinformatics, disease biology, and real-world data about patient health will reveal immune / patient patterns. This approach is empowering Sanofi to discover targets for new, more precise therapeutics, and to reposition medicines already approved for use. It is also helping identify biomarkers to guide patient stratification in clinical studies. Furthermore, Sanofi plans to increase their investment into immunology startups, leading among pharmaceutical VCs with 10 deals to date.

4. Historical Context, Key Trends, & Future Development

4.1 History

Since the approval of Humira in 2002, a growing number of therapeutics - from small molecule compounds to biologics - have been approved for use in immune-mediated diseases (IMDs). However the treatment response varies considerably from patient to patient; often, less than 30% of patients show an adequate response to first-line drugs – assuming there is an approved therapeutic available. Patients across numerous indications may also suffer a loss of treatment efficacy over time (e.g. antiTNFs), often without therapeutic alternatives.

4.2 Present-Day Status

With such significant differentiation in patient response, there is considerable interest in prediction of the treatment response before therapeutic administration to increase efficacy / performance, and reduce the risk of side effects and economic burden. This burgeoning field is known as precision immunology. Early approaches have focused on oncology, with advances such as T cell receptor technologies and checkpoint inhibitors demonstrating considerable success. Despite these significantly improved outcomes, there has been little progress or even adaptation of precision medicine to the over 80 critical and chronic IMDs that make-up a rapidly growing immunology market.

The delay in progress comes, in part, because of the unique feature of immune cells to shift between multiple active states, rendering immunology a special layer of complexity and further increasing difficulties when stratifying patient groups by the traditional reductionist biomarker approach, and when understanding multimorbidity relationships across patient subpopulations. Thus the key advantage of precision immunology goes beyond identification of disease specific biomarkers for therapy, it leads to deeper understanding of the immune system in health and disease. To overcome these challenges requires contextualizing immune states through the aggregation of adequately powered patient cohorts and refined clinical data to achieve actionable multi-omics and EHR integration.

Today, pharmaceutical companies are capitalizing on previous commercial successes and continuing with a one-size-fits-all approach, while most startups are advancing precision approaches to treatment and diagnostics based on mechanistic biology.

4.3 Near-Term Predictions

With the exponential growth of the market, we will see increasing investment in the development of therapies across modalities, and of data / diagnostic platforms for patient stratification. Most drug development programs will be driven by mechanistic biology, with mixed success anticipated given the incredible complexity of immune biology. To bridge this gap in scientific understanding, we will also see continued exploration of immune biology, integrated with systems biology and big data / analytics approaches.

As an alternative approach, we expect a few select players will recognize the importance of advancing precision immunology treatments and the considerable challenges associated with doing so through mechanistic biology and, instead, advance immune state stratification to serve as a transition step between the one-size-fits-all approach and truly individualized treatments. These companies will be able to identify patient subsets as high responders to the plethora of emerging treatment options that are generating such mixed performance outcomes.

4.4 Mid- to Long-Term Predictions

In the mid-term, pharmaceutical companies will begin to adopt the immune state stratification approach and larger and larger patient datasets will be aggregated. With these data, patient subgroups will be analyzed and, we expect, found to respond to guided-therapies across indications. Throughout this stepwise development of precision immunology, our understanding of immune biology will continue to grow. With this advanced knowledge of cellular and mechanistic biology, we will be able to develop truly individualized immunology treatment options.

5. Opportunities

As the field of precision immunology takes off, there will be opportunities on three fronts: patient data-driven stratification via understanding of immune states (near-term), guided-therapies (near- to mid-term), and considerably advanced understanding of immune biology for the development of truly individualized and guided therapeutics (long-term).

5.1 Startups to Watch

Today, immunotherapy has over 1,600 startups receiving greater than $97B in funding to develop precision diagnostics, antibodies, vaccines, cytokines, and small molecules for the treatment of various diseases. Despite this large number of immune-focused startups, a majority of startups focus specifically in the immuno-oncology space. For those startups targeting critical and chronic IMDs, they focus either on developing precision diagnostics to recognize mechanistic biology or patient disease states (such as ImmuneID and Inflammatix), or on development of more targeted therapeutic assets based on an initial and often mechanistic biological hypothesis. When a company creates a platform that uses patient information to

identify patient subpopulations and define biomarkers for immune states, and employs that knowledge to progress guided-therapies, we expect them to advance far superior outcomes.

Endpoint Health

- Early-stage precision medicine company that has developed a novel approach to address urgent needs in immune-driven critical and chronic illnesses by developing therapeutics and companion diagnostics to enable personalized treatment and dramatically improve patient outcomes.

- Technology:
    - AI-powered patient stratification platform fueled by proprietary real-world evidence datasets. The discovery of immune states from combined omics and EHR datasets can be utilized to identify key biomarkers of differentiation and enable companion diagnostic development for rapid patient stratification.
    - Differential responses are generated from therapies with pharmacology related to innovate versus adaptive immune function. These responses enable targeted therapeutic selection for in-licensing / partnership.
- Special Notes:
    - Founding team are serial entrepreneurs who founded Geneweave, a precision diagnostics platform for critical care that had a $425M outcome to Roche in 2015. They reunited as co-founders to launch Endpoint Health in 2018. Their background in bacterial diagnostics at Geneweave provides industry expertise and credibility in their lead indication, sepsis.
    - The company's platform allows them to generate patient stratification profiles and rapid companion diagnostics that pair with in-licensed therapeutics assets to follow new clinical paths. These capabilities will allow Endpoint Health to build partnerships with pharmaceutical companies to rapidly advance previously de-risked therapeutic assets with patient subpopulations that have been defined as high responders, thus creating the potential for repeated blockbuster assets and for corresponding non-dilutive funding for development, manufacturing, and commercialization.

Girihlet

- Girihlet is attempting to understand the interactions of our diet and the environment via microbiome analysis, and of our genome
- Technology:
    - HLA mapping of T-cell variable beta receptor regions (TCR-Vbeta repertoire)
    - Developer of a novel patented technology intended to purify and sequence mitochondrial DNA
- Special Notes:

- Offers a cell sequencing assay that helps to measure the immune system by creating an immune map database to predict and measure a person's health status, enabling researchers to have a significant impact in the clinic and assist in advance basic research.
- The human leukocyte antigen (HLA) system encodes cell surface molecules specialized to present antigenic peptides on T-cells. By understanding individual patient's T-cell receptors, they then aim to modify TCRs for treatment. While this approach presents an interesting value proposition, the current technology stack will present a challenge for Girihlet to accumulate enough data to build accurate computational models for personalized treatment given our current understanding of immune biology.

5.2 Emerging Technologies & Applications

In predicting disease susceptibility, disease severity, and treatment response, multi-omics data is beginning to play an important role in clinical practice. So far, some attempts at patient stratification have been performed using genomic, epigenomic, transcriptomic, and clinical data; however, most of those studies were based on information from a single level. Combination of multi-level information will improve the prediction of these outcomes. Construction of large-scale patient cohorts with high-quality clinical data (e.g., treatment response, clinical prognosis, and genomic, transcriptomic, and epigenomic data, preferably from diseased tissues) and refined analytic approaches to handle these data would contribute to a better understanding of IMD biology and accelerate precision medicine in IMD patients.

In overcoming the limitations of single level information, systems biology approaches have an increased potential to be able to identify clinical biomarkers and enable precision medicine and personalized interventions and in the treatment and prevention of disease in other vulnerable populations.

One systems biology approach includes the comprehensive study of T cells. The peculiarity of T cells is their ability to recognize an infinite range of self and foreign antigens. This ability is achieved through the expression of a very heterogeneous population of surface antigen receptors, the T Cell Receptors (TCRs). TCRs are cell specific and represent a sort of "molecular tag" of T cells and have been widely studied to monitor the dynamics of T cells in terms of clonality and diversity in several contexts including lymphoid malignancies, infectious diseases, autoimmune diseases, and tumor immunology.

The vast majority of human T cells express TCRs composed of α (alpha) and β (beta) chains while a small subset expresses TCR composed of γ (gamma) and δ (delta) chains. The genes encoding alpha (TCRA) and beta (TCRAB) chains are composed of multiple non-contiguous gene segments which include variable (V), diversity (D), and joining (J) segments for TCRB gene and variable (V) and joining (J) for TCRA gene (2) (Figure 1A). The enormous diversity of T cell repertoires is generated by random combinations of germ line gene segments (combinatorial diversity) and by random addition or deletion at the junction site of the segments that have been joined (junctional diversity).

T cell repertoire is therefore dynamic and directly reflects the diversity of immune responses: antigen presentation to a naïve T cell in fact, in association to co-stimulatory signals, drives a rapid clonal expansion of cells carrying identical TCRs to generate a population of "effector cells." After antigen clearance, a reduced number of these cells remain in the blood as "memory cells." Thus, the characterization of the TCR repertoire has always been of great scientific interest because it accurately describes T cell dynamics in a wide range of diseases, including malignancies, autoimmune disorders, and infectious diseases.

Within the field of TCR mapping, numerous approaches have been developed. Among the more promising is the study of Vbeta clones.

- **TCR-Vbeta repertoire mapping –** Beta chain has always been the main target in all the TCR repertoire studies due to its higher diversity related to a larger combinatorial potential compared to alpha chain. Moreover, the beta chain represents a "unique label" for T cells. Initially, next-generation sequencing allowed for high-throughput sequencing of alpha and beta chains of TCRs and so enabled investigations into the TCR repertoire. Single-cell based approaches then brought the analysis to a higher level of complexity and now provide the opportunity to sequence paired alpha and beta chains. And today, novel approaches are being developed through the integration of TCR tracking and mRNA single cell sequencing to associate antigen specificity to transcriptional dynamics and to understand the molecular mechanisms of T cell plasticity.

In addition to TCR analysis, the study of immunopeptidomics also presents a powerful way to identify novel targets.

- **Immunopeptidomics –** is the study of naturally presented ligands of the Human Leukocyte Antigen (HLA) molecules. HLA molecules are expressed on all nucleated cells in the body and present antigens in the form of peptides, lipids or other small molecules to the immune system. This mode of antigen presentation lends itself to broad immunosurveillance by T-lymphocytes (T-cells) which can recognize the HLA molecules and the antigenic peptide presented to elicit an appropriate immune response. The HLA complexes loaded with disease-specific peptides thus convey the state of cellular health to the immune system making them attractive targets for precision immunology.

In addition to precision diagnostics approaches informing treatment, new modalities are being explored to combat IMDs, cell therapy, gene therapy, RNA therapy, and reverse vaccination among them.

Cell Therapy

- Could be a powerful approach to induce immune tolerance and restore immune homeostasis with a deeper understanding of immune tolerance mechanisms and the development of new techniques.
- Most immunoregulatory cells exhibit issues regarding survivability, stability, plasticity, and homing capacity. Cells for tolerogenic treatment can be derived from an autologous or allogeneic source. Further, the fact that autologous cells might contain gene-related defects, resulting in less effective tolerogenic therapy, cannot be ignored. Whereas, the short survival period of allogeneic cells, because of rejection, might lead to poor treatment efficacy, the prolonged persistence of allogeneic cells will raise safety concerns. After infusion, the avoidance of the transformation of immunoregulatory cells into effector cells is essential for the long-term efficacy of tolerogenic therapy. In particular, if the regulatory cells used for targeted cell therapy (e.g., CAR-Treg) are

unstable and transform into inflammatory cells, they might exert an adverse effect on the disease. For treatment with Tregs, the memory Tregs induce a stronger inflammatory response than naïve Tregs. Therefore, not only the choice between autologous or allogeneic cells, as well as the cell type, needs to be considered, but also the stable subpopulation of cells for treatment should be considered.

- Genetically modified immune cell therapy technology, such as CAR-Treg, could present a breakthrough for the treatment of ADs. Genetic modification can compensate for genetic defects to a certain extent and has advantages for therapeutic cell targeting, chemotaxis, and enhancement. Similarly, the safety of gene therapy should be carefully considered, including genetically modifying vectors, the recombination of internal and exogenous genes, the controllability of gene expression, and even ethical issues.

    - T Regulatory Cells (Tregs)*:* Tregs are important regulatory cells that maintain peripheral immune tolerance. While previous results have been lacking, proponents expect that a new class of genetically engineered Treg cell transplants, which a number of companies hope to test soon in clinical trials, will prove much more effective. The idea is that each person's Treg cells will be tailored to help them better guard against rogue T effector (Teff) cells. However, whether Treg cells can effectively function under conditions of established systemic inflammation or reverse severe autoimmunity and prevent its relapse has been a subject of intense debate. A large body of work has shown that inflammatory mediators can either inhibit the suppressive function of Treg cells or render pro-inflammatory effector cells refractory to suppression. This raises questions about the potential for therapeutic use of Treg cells in treating autoimmune diseases. Previous studies attempting to address this question, in both clinical and experimental settings, mostly generated negative or inconclusive results, because the adoptive transfer models they relied on have intrinsic issues such as failure to engraft or home to the appropriate tissue.
    - To develop the next generation of engineering Tregs, biotechnology companies — many of them start-ups — are leveraging two rapidly advancing technologies: chimeric antigen receptor (CAR) T-cell manipulation, which provides T cells with receptor proteins matched to specific cell targets; and CRISPR–Cas9 genome-editing tools.
        - *CAR-Tregs:* In recent years, studies of Tregs engineered with chimeric antigen receptors (CAR-Tregs) have made great progress in optimizing anti-inflammatory and immune-tolerogenic responses in preclinical studies. These CAR-Tregs display the hallmarks of cell therapy, including being target-specific, long-lasting, chemotaxic, and highly efficient for broad application in the treatment of ADs, graft-versus-host diseases, and transplant rejection. We believe that CAR-Tregs will be a key modality in the development of anti-inflammatory and tolerogenic therapies.
            - *Startups to Watch: QuellTX, TxCell, Kyverna, Sangamo Therapeutics, GentiBio*

    - Mesenchymal stromal cells (MSCs): widely distributed in various connective tissues, MSCs have multi-directional differentiation potential and strong immune regulation and tissue repair functions. Therefore, MSCs naturally play a role in modulating ADs, organ transplantation, and graft-versus-host disease (GVHD). MSC-related clinical trials include the treatment of diabetes, RA, Behcet's disease, organ transplantation, systemic lupus erythematosus, and others. MSC sources currently used for clinical trials include

bone marrow, perinatal tissue, dental pulp, and adipose tissue. Differences associated with tissue source, such as donor-related variability, cell culture system, passage number, and reagent formulation, might be important factors for the biological characteristics of MSC. These characteristics mainly include the homing ability of MSCs, viability in vivo, and immunosuppressive ability, which exert important influences on the therapeutic effect of tolerability. Intravenous injection is one of the most commonly used infusion methods for MSCs, which can play a systemic regulatory role. Whether MSCs can home to the site of inflammation is an important factor influencing their therapeutic effect, as these cells require interactions between tissue-specific chemokines and the corresponding receptors. The majority of MSC-based trials for ADs are still in early phases I or II. Some have promising results and no reported toxicity to date, but phase III studies will be needed to confirm their efficacy.

- **Gene Therapy: Reverse Vaccination –** uses exposure to teach the immune system to ignore foreign substances. The novel treatment pairs essential proteins and enzymes with lysophosphatidylserine (Lyso-PS), a fatty acid that helps the immune system tolerate foreign substances, reducing adverse reactions to the drugs. The approach could be applied to a broad range of drug therapies, autoimmune disorders and allergies.

- **RNA Therapy –** Researchers from the Stephan lab in the Fred Hutch Clinical Research Division developed in vitro transcribed mRNA to rationally reprogram myeloid cells as a strategy to treat autoimmune disease. Tested preclinically in Systemic Lupus Erythematosus, the engineered nanoparticles transcribing mRNA encoded for glucocorticoid-induced leucine zipper (GILZ). The researchers postulated that GILZ, a master regulator of inflammation that is expressed at low levels in auto-immune disease, would generate anti-inflammatory actions within the target host if expressed at higher levels. The specificity of these nanoparticles in targeting inflammatory immune cells was confirmed and treatment with the nanoparticles greatly increased the lifespan of the experimental mice.

    - *In April 2019, Sanofi acquired the Fred Hutch spin-out company Tidal Therapeutics, which was launched to commercialize this technology to treat autoimmune disease, for $460M.*

5.3 Industry Challenges

As described above, immunology has mirrored the broader pharmaceutical industry in benefiting from next generation sequencing and the rise of omics / computational analysis. Today, the primary challenge to precision immunology comes from our preliminary understanding of the complexity of immune biology.

To overcome this challenge, techniques such as immunopeptidomics are being developed to further our understanding of cellular and mechanistic immune biology, and patient data are being aggregated within and across indications, spanning omics, EHR, and more. While these data present a significant opportunity for learning, integrating data obtained from multiple sources and processed with multiple software types will present its own challenges. Building

standardized data generation and analysis workflows will thus be essential to streamline biological discovery.

6. Conclusions

6.1 Overall Summary

The precision immunology market is beginning to emerge as a clinically and commercially impactful field. Investment to elucidate the complexity of cellular and mechanistic biology is rapidly accelerating, and understanding the role of higher level immune states in patient stratification is driving early success. With novel tools for aggregating and analyzing patient data to discover subpopulations and compare the phenotypes to the heterogeneity in drug responses, immunology is poised to follow oncology in the improvement of diagnostics and treatments.

New market leaders should be able to provide full or significant patient segmentation analyses and rely on easily-adaptable workflows to tailor them across indications. We believe that the combination of broadening of assaying and omic capabilities, increased data aggregation across multiple sources, and enhanced analytics throughput will enable the identification of high responding patient cohorts and strengthen diagnostics and drug discovery. Together, these advances underlie the attractive investment opportunities in precision immunology. Below we summarise the particular strengths and weaknesses underlying our investment theses.

6.2 Vertical Strengths

- **Rapidly Growing Market:** Precision immunology is a rapidly growing market with huge potential that we expect to continue driving growth for several decades. This rapid expansion is being driven by a global and continuously increasing patient incidence, and is supported by new mechanism biologics, novel oral agents, biosimilars, and precision diagnostics and treatments.

- **Market Expansion Due to Enhanced Patient Outcomes:** Market economics will significantly expand to support enhanced patient outcomes coming from guided-therapies for high responding patient populations.

- **Early Partnership Opportunities:** Upfront repurposing of the large volume of therapeutics being developed to new, more precise clinical paths through collaborations with pharmaceutical companies able to pay upfront and then using the earnings to verticalize into a full stack drug discovery platform minimize risk while increasing opportunity.

6.3 Vertical Weaknesses

- **Provider Fragmentation = Limited Clinical Support:** While there are a considerable number of patients who may benefit from precision immunology treatments, there are few hospitals that focus on IMDs in such a way as to advance clinical trials rapidly, and currently few precision diagnostics integrated to support patient recruitment & the collection of longitudinal patient data.

- **Market Fragmentation = Slow Data Aggregation:** Data will be a key driver enabling the advance of precision immunology. Today, there exists no centralized data repository or methodology to ease the aggregation and analysis of the incoming volumes of data.

6.5 Opportunity Cost of Capital

Immunology is the second largest profit segment within the pharmaceutical industry, with 7 blockbuster drugs currently on the market - a number second only to oncology's 9 blockbusters. Precision immunology is the highest potential segment within the immunology market for the mid- to long-term, with immunology poised to follow oncology towards precision medicine. Finally, few companies have the requisite combination of expertise and experience to develop platforms at this early stage, ensuring that selection of the correct entrants will provide a significant return on capital.

6.6 Investment Theses

- **Requisite & Representative Patient Data:** We are interested in teams that have established proprietary data sets & a pipeline of exclusive partnerships that provide access to high quality & longitudinal patient data. Thus serving as the foundation for novel patient biomarker identification.

- **Hyper-Targeted Patient Stratification:** Software platforms that can stratify high responding patient subpopulations through the identification of novel biological insights. These biomarkers will then serve as the foundation for the diagnostic development & targeted therapeutics.

- **Companion Diagnostics:** Once patient subpopulations have been identified, diagnostic assays to match patients to subpopulations are essential to ensure reliable & repeatable clinical outcomes. The utilization of companion diagnostics will also serve as a superior go to market strategy to drive therapeutic adoption once commercialized.

- **New Clinical Path (Repurposing):** The identification of novel biomarkers enables the identification of new modes of treatment & development of therapeutics. We are

excited by approaches that minimize therapeutic development risk through the repurposing of assets to new clinical paths. In combination with companion diagnostics for patient stratification, this approach becomes even more attractive because companies can rapidly progress known assets with proven safety profiles into patient subpopulations that have been identified as high responders therefore dramatically increasing overall drug performance. If companies can also leverage investment from early partnerships to expand use of their platform across the precision immunology market this will allow for a less dilutive equity path.

- **Continuous Feedback Loop:** Platforms that generate real-world evidence regarding which patients are / are not responding to treatments will enable continuous learning & further improve patient stratification. This strategy has the potential to serve as incredibly powerful tools for therapeutic progression, ensure future proofing of a company's technology, & enable an enduring long-term advantage.

7. References & Further Reading

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- **Emerging therapeutic options**
  - **RNA therapy**
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  - **Cell, Gene, & RNA therapy**
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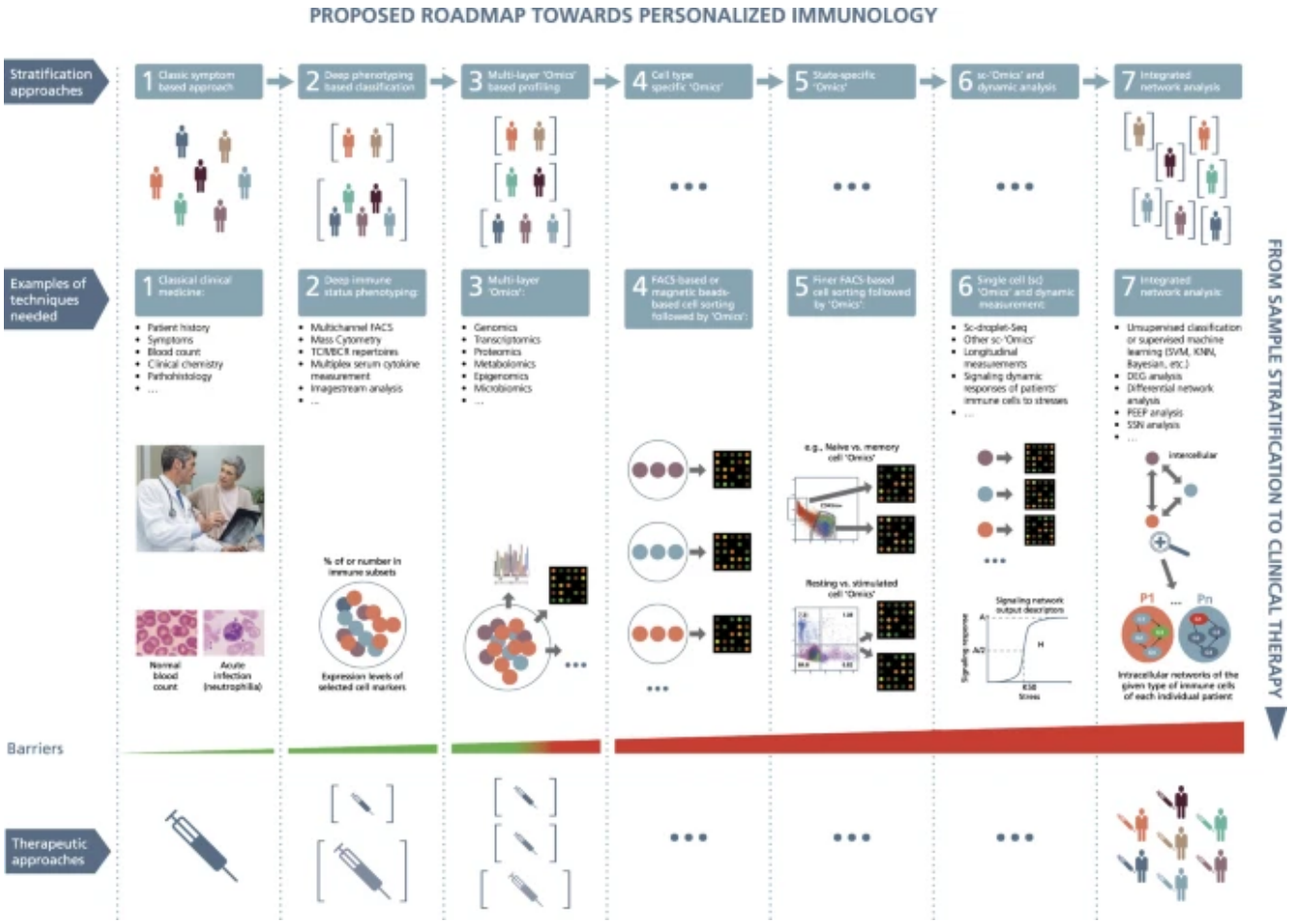
8. Appendix



A roadmap proposed towards personalized immunology. There exist both horizontal and vertical roadmaps towards personalized immunology. Vertically, to translate sample stratification to clinical therapies, we need to utilize the state-of-the-art "Omics" analysis and network integration approaches to stratify patients into subgroups and then implement personalized therapeutic approaches to treat individual patients, which needs to overcome various types of barriers at different steps. Horizontally, we might need to go through at least 7 steps to enable personalized immunotherapies, 1) classic symptom-based approach, 2) deep phenotyping approach, 3) multi-layer "Omics"-based profiling, 4) cell type-specific "Omics", 5) state-specific "Omics", 6) single-cell (sc) "Omics" and dynamic response analysis of immune cells, 7) integrated network analysis. FACS, fluorescence activated cell sorting; TCR/BCR, T cell

receptor/B-cell receptor; DEG, differential expression gene; PEEP, personalized expression perturbation profile; SSN, sample-specific network; SVM, support vector machine; KNN, K-nearest neighbors; under the first layer (the so-called stratification layer), different colors of patients indicate individual patients with different cellular and/or molecular profiles while brackets represent patient subgroups; under the second layer (the so-called technique layers), different small circles with distinct colors indicate different immune cells while big circles represent patient (sub)groups; under the technique layers, the snapshot of microarray representing either microarray-based or RNA-seq-based transcriptome analysis; under the third layer (the so-called therapeutic layer), the syringes with different colors or tonalities indicate different therapeutic approaches; P1,..., Pn at step 7 designate different patients; G1, G2, G3, G4 represent different genes, the arrows between them representing regulatory relationships. Three images in the second layer of step 1 are used with permissions from Fotolia.com

Approaches to Further Precision Immunological Treatments:

- **Cell Therapy –** Could be a powerful approach to induce immune tolerance and restore immune homeostasis with a deeper understanding of immune tolerance mechanisms and the development of new techniques. To date, there are three primary approaches:

    - Hematopoietic Stem Cell Transplantation (HSCT) for Immune Reconstitution: There are two purposes for using HSCT: one is to eliminate autoreactive immune cells, and the other is to rebuild the self-tolerant immune system. Several clinical trials showed that autologous HSCT was superior to conventional treatments for the treatment of severe ADs, including multiple sclerosis and systemic sclerosis, and induces long-term disease remission without immunosuppressive drugs. However, some patients still experienced AD recurrence after transplantation and so HSCT is still a high-risk treatment, with the occurrence of transplant failure, recurrence of disease, infection, and other complications that might decrease the survival rate of patients. Therefore, HSCT is only considered suitable for patients with serious disease and risk of death. It should be noted that incomplete eradication of autoreactive memory cells or the infusion of unpurified lymphocytes could cause disease recurrence.

    - Adoptive Immunotherapy to Eliminate Autoreactive Immune Cells:
      Autoimmunity is characterized by the presence of autoantibodies and autoreactive T cells directed against normal components of an individual.

        - *T-cell vaccination (TCV) therapy:* is a type of autologous, personalized cell-based therapy in which attenuated autoreactive T cells are administered as immunogenic agents and targeted T-cells are deleted or inactivated. Moreover, TCV has shown safety and effectiveness in various clinical trials, mostly for patients with MS but also for RA, SLE, and ALS. TCV has been somewhat ignored in the past due to standard pharmaceutical avoidance of cell-based and individualized treatments. Nonetheless, cell therapy appears to be coming of age, and TCV has been granted fast-track status by the FDA for the treatment of some types of multiple sclerosis.

        - *CAAR for B cell targeting:* B cell/plasma cells have been recognized as an important target for the treatment of some ADs. While CAR-T targeting B-lineage antigens can also lead to normal B cells being killed, thus significantly impairing the body's ability to fight disease, the chimeric autoantibody receptor (CAAR) has

been constructed based on autoantigens and is capable of binding to the BCR of autoreactive B lymphocytes and therefore has the ability to specifically eliminate autoantigen-reactive B cells. However, there are multiple autoantigens that are attacked by the immune system and individual differences in ADs. Therefore, not only the coverage of disease-associated antigens but also the molecular weight and spatial epitope of each antigen should be considered in the design and construction of effective CAARs to treat such diseases.

- Rebuilding Autoimmune Tolerance Using Various Immunoregulatory Cells: Antigen-presenting cells (APCs), including dendritic cells (DCs) and monocytes/macrophages, play an important role in the regulation of innate and acquired immunity, as well as bidirectional regulation in both antigen-specific immunity and immune tolerance.

  - *Regulatory T (Treg) Cells:* Tregs are important regulatory cells that maintain peripheral immune tolerance. Clinical trials of therapies using regulatory T (Treg) cells, in which a person's own Treg cells are removed, expanded and re-administered, began in 2004. But the results have been less than dazzling. Dozens of small trials, to facilitate organ transplants as well to treat as autoimmune conditions, have demonstrated that although the procedure is safe, it is, in general, not that effective.

  - *Tolerogenic DCs (tolDCs):* a heterogeneous pool of dendritic cells with immunosuppressive properties. In autoimmunity, DCs tend to produce pro-inflammatory cytokines and lead to the activation of autologous antigen-reactive T cells. The DC-induced immune response or immunotolerance is determined by the maturation state of DCs, and both immature DCs (iDCs) and semi-mature DCs have been shown to be tolerogenic. TolDCs modulate adaptive immune responses and restore tolerance through different mechanisms that involve anergy, the generation of regulatory lymphocyte populations, or the deletion of potentially harmful inflammatory T cell subsets. Thus, in as yet undetermined subsets of patients, autologous tolDCs induce antigen-specific immune tolerance in various IMDs.

  - *Regulatory Macrophages (Mregs) and Transplant Acceptance-Inducing Cells:* Transplant acceptance-inducing cells (TAICs) are primarily considered a class of immunoregulatory macrophages. These TAICs are a type of immunoregulatory macrophage with the capacity to specifically dampen allogeneic rejection responses to a degree, with donor-derived TAICs allowing safe minimization of conventional immunosuppressive therapy (i.e. inducing allogeneic tolerance during organ transplantation).

- **Gene Therapy –** Although mostly used to treat monogenic diseases, gene-transfer mediated by AAV can also be exploited to deliver immunotherapeutics, such as monoclonal antibodies. The coding sequence of properly characterized protective/neutralizing antibodies against a pathogen of interest can be delivered via rAAV, thus aiming to prevent or treat infectious diseases and confer long-lasting immunity. This strategy passively bypasses the immune system as no immune response to an immunogen is required. As demonstrated during the COVID-19 pandemic, AAVs

can become game changers in our fight against transmissible diseases, including HIV, dengue, influenza and others. Antigens can also be delivered in AAV vectors with the aim of conferring protection to a disease in the recipient with a vectored vaccination regimen.

- **RNA Therapy –** RNA therapies can be sorted into one of three broad categories: those that target nucleic acids (either DNA or RNA), those that target proteins, and those that encode proteins. Hybrid approaches that combine several RNA-based mechanisms into a single package are also emerging. Within precision immunology, there are multiple RNA therapy approaches and several dozen in the pre-clinical through clinical pipeline.