Hogan Lovells

Immunoglobulin Therapies in the U.S.: How they are used

Roundtable report

Executive Summary

On September 9, 2021, a panel of experts convened to discuss the use of immunoglobulin (Ig) therapies, detail the therapeutic benefits of Ig therapies for various disease states, offer practitioner insights on the impact of the COVID-19 global pandemic on patient treatment, and discuss how policies can play a role in optimal patient treatment with Ig therapies.[1] The following key takeaways emerged from the discussion:

- Ig is used to treat immune deficiencies and other conditions that involve the immune system.
- The majority of Ig therapy use (approximately 65%) is as treatment for U.S. Food and Drug Administration (FDA) approved indications and the rest is as treatment for other conditions that are supported by scientific or practice-based evidence.
- Use of Ig therapies has increased as a result of patients on therapy living longer, improved diagnosis rates, wider use in oncology-related secondary immunodeficiencies, and expanding scientific knowledge of Ig benefits for patients.
- Access challenges can result in patients missing or delaying Ig treatment, which can have severe and immediate consequences on patient health.
- Switching patients between Ig therapies is not simple as some patients do not tolerate certain products but do tolerate others.
- Ig therapies provide significant benefits to patient health, outcomes, and quality of life, and for many patients, it is the only treatment option.
- Clinicians recognize that Ig availability is dependent on plasma donations from healthy volunteers and believe that increasing plasma collection is a safer and more promising approach to address access challenges than restricting Ig use.

Roundtable Summary

Dr. Maik Klasen presented information on Ig therapies and their use in a variety of clinical indications, which has been studied by Adivo Associates for more than 20 years.[2] Following the presentation, Stuart Langbein moderated a discussion on access to and use of Ig therapies and took questions from a live audience. Joining Dr. Klasen on the panel were leading experts in the U.S. who use Ig to treat patients: Antoine Azar, M.D., Syed S. Mustafa, M.D., Christina Price, M.D., and Gil Wolfe, M.D., FAAN. A summary of Dr. Klasen's presentation and highlights from the roundtable discussion follows; the event agenda and speaker biographies can be found in the Appendix.

Overview of Ig Therapies and Trends in Use – Dr. Klasen

Plasma is the liquid portion of blood that contains proteins such as Ig, also termed antibodies, which can be 'fractioned off' to make Ig therapies. There are two main purposes for which Ig therapies are used: to replace Ig in patients who have too little or none, and to regulate an overactive immune system in patients with autoimmune diseases.

Primary immunodeficiencies are a group of disorders that affect the immune system. In many of these conditions, the body does not make enough or the right type of antibodies that are required to fight the infections and regulate other essential functions. Secondary immunodeficiencies occur when patients with certain diseases (e.g., cancers, certain autoimmune diseases) receive treatments that destroy the part of the immune system responsible for making antibodies against infections. Patients with both primary and secondary immunodeficiencies rely on Ig therapies to replace missing antibodies, often for long periods or the duration of their lives.

1. This panel was commissioned by the Plasma Protein Therapeutics Association.
2. Adivo Associates uses an audit platform that includes volume, price, and indication data from hospitals, integrated delivery networks, specialty pharmacies, and infusion clinics – as well as electronic medical records – to project overall IG market estimates that are checked against external sources including PPTA, insurance claims, patient registries, and others.

In patients with autoimmune diseases, the body makes autoantibodies (antibodies against itself). Rather than fighting infections, the body recognizes its own tissue as foreign and makes autoantibodies to attack and destroy it. The body keeps a constant level of antibodies, so when autoimmune patients are given high doses of Ig therapy, it signals the immune system to purge antibodies, which gets rid of the harmful autoantibodies.

Ig therapies are available in two forms: intravenous Ig (IVIG), meaning infused into the veins of a patient, and subcutaneous Ig (SCIG), meaning it is injected under the skin, either manually or by a pump.

Current Use of Ig in the U.S

Approximately 275,000 patients are treated each year in the U.S. with IVIG and SCIG therapies. In 2020, roughly 110 million grams of Ig were used to treat patients. These patients have conditions in more than eight medical specialties and receive treatment for hundreds of indications. Figure 1 presents the estimated breakdown of Ig volume by condition category.

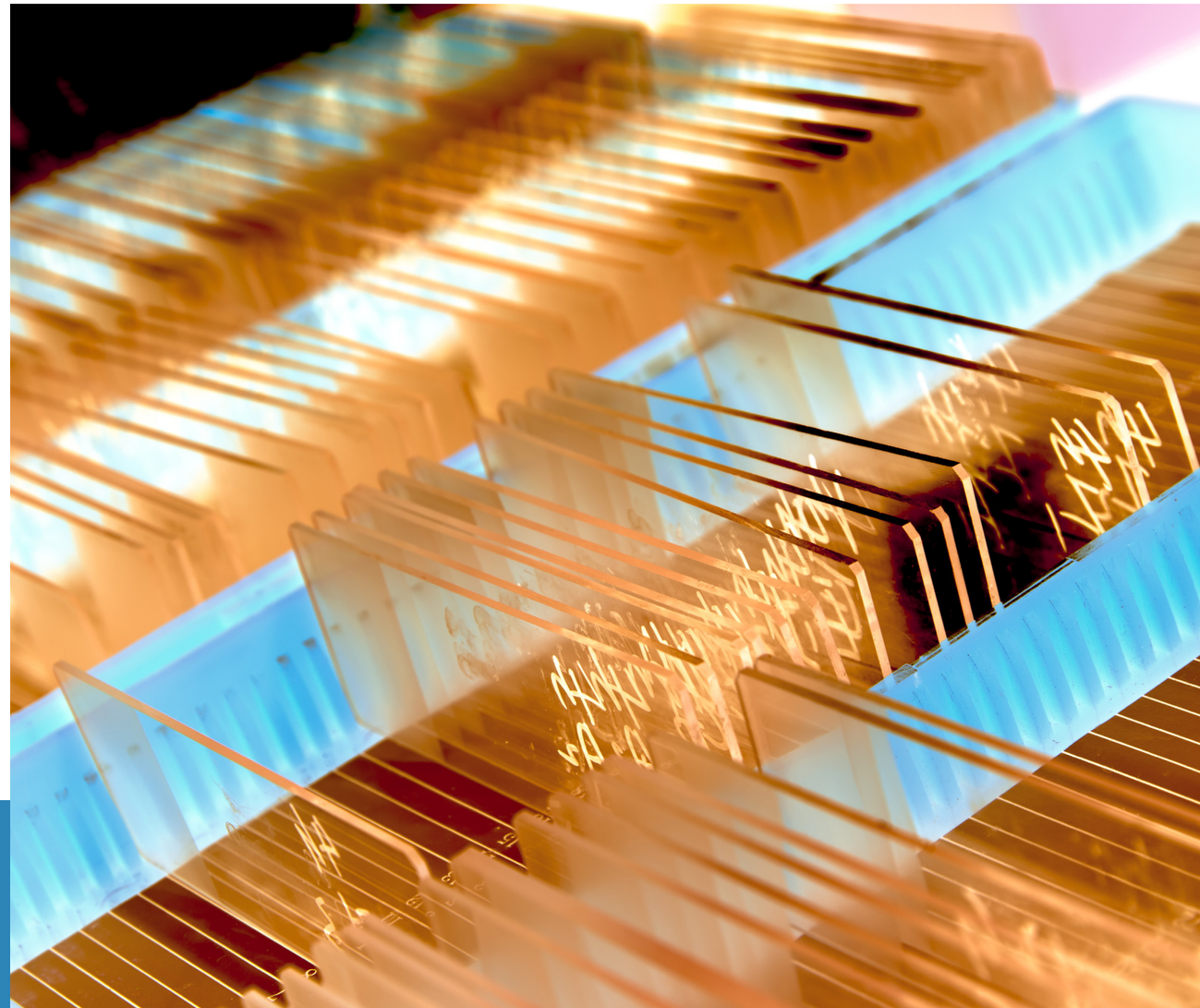
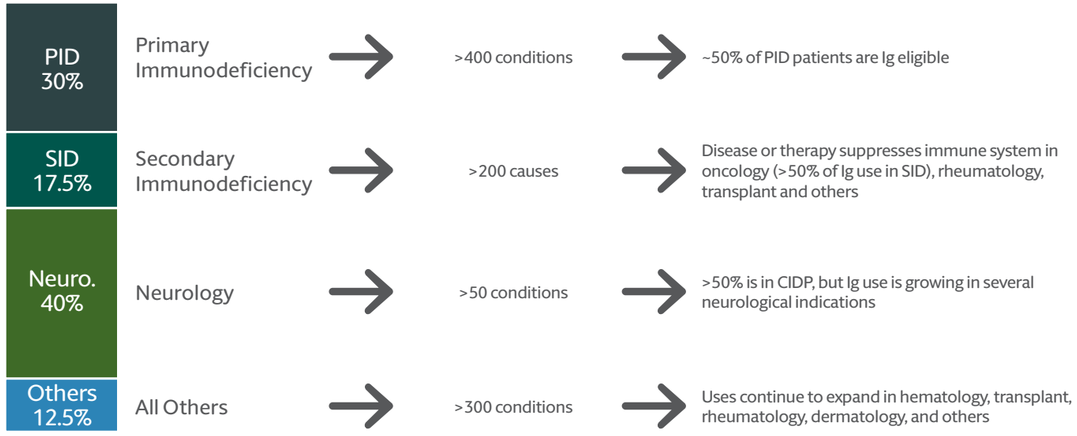


Figure 1: Conditions treated with IVIG and SCIG



(Adivo Associates, 2021)

Approximately 65% of all Ig use in the U.S. is prescribed to treat conditions for which the therapy was approved by the FDA. The remaining 35% of Ig is prescribed to treat conditions where it is medically acceptable according to existing treatment guidelines and evidence-based, real-world use. More than 70% of medically acceptable Ig use is in conditions for which manufacturers are currently performing large clinical trials in pursuit of FDA approval for relevant indications to the Ig labels. Figure 2 summarizes the categories of Ig use by indication. For many of these life-threatening conditions, Ig therapies are the only effective treatment.

Figure 2: Ig usage by indication versus medically acceptable, evidence-based use

~65% On-Label Use

Immunology
- PID

Hematology
- Immune Thrombocytopenic Purpura

Neurology
- CIDP (Brand dependent)
- Multifocal Motor Neuropathy (Brand dependent)

~35% Medically Acceptable Use

~25% Active Development*

Oncology
- SID

Neurology
- Myasthenia Gravis
- PANS/PANDAS

Rheumatology
- Dermatomyositis**
- Systemic sclerosis

~10% No Active Development

Neurology
- Guillain-Barré Syndrome
- Stiff-Person Syndrome
- Autoimmune encephalitis
- Multiple Sclerosis

Transplant
- Antibody mediated rejection
- Desensitization protocols

Hematology
- Aplastic anemia

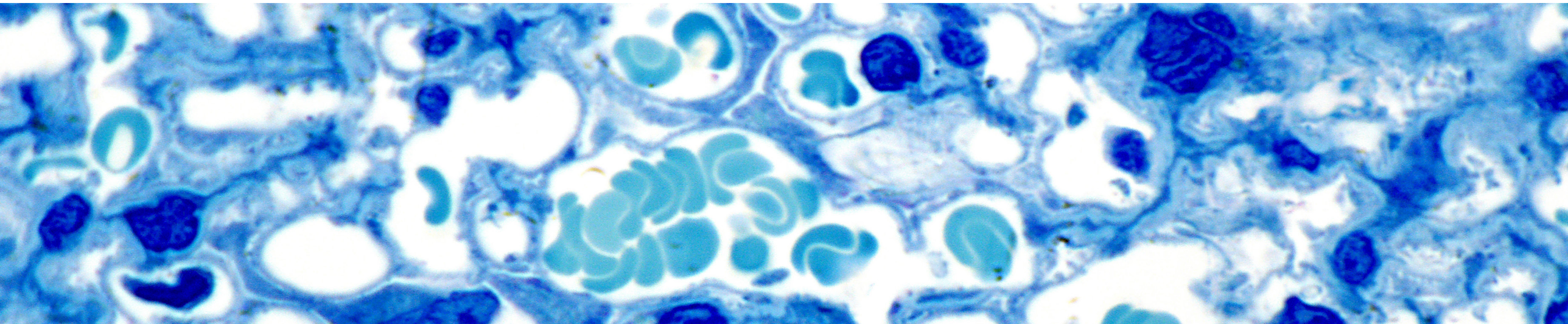
Dermatology
- Toxic epidermal necrolysis
- Pemphigoid diseases

Many Others

*Ig manufacturers currently performing large clinical performing large clinical trials seeking to add indications to their product labels
**First Ig product approved in July 2021

(Adivo Associates, 2021)

The clinicians stated that they take a conservative approach to initiate Ig therapy for patients, making sure treatment practices are in line with current guidelines and/or evidence-based scientific knowledge. Dr. Mustafa noted that when prescribing Ig for conditions beyond the labeled indications, “we do not prescribe this stuff unless we believe it is really scientifically indicated.” There is good scientific evidence supporting Ig use in conditions like secondary immunodeficiencies, Guillain-Barré Syndrome and Myasthenia Gravis. The panelists view Ig therapies as a critical tool for clinicians from various branches of medicine as they work to manage patients’ chronic conditions and complications of the immune system.



Increases in Ig Use

From 2015 to 2020, the volume of Ig used in the United States nearly doubled, growing from approximately 67 million grams to approximately 110 million grams. This increase represents a compound annual growth rate of approximately 10% per year. The volume growth in SCIG outpaced that of IVIG during these five years, and growth by indication ranged from 4 to 12%.

Several factors contribute to the steady growth in Ig consumption. Panelists attributed the growth to the following reasons:

- An increase in the number of patients diagnosed with conditions requiring Ig therapies, and early initiation of treatment.
- Clinicians acknowledge that timely and optimized Ig treatment plays a leading role in extending lifespan and improving patients' quality of life: as diagnosis rates have improved, so too have rates at which the clinicians are prescribing Ig therapies to treat these conditions.
- An increase in the number of discovered immunodeficiencies. Advances in disease identification, including genetic testing, have led to a significant increase in the number of primary immunodeficiency disorders, with currently more than 400 unique disorders identified.
- The increased use of SCIG in the home setting for patients with primary immunodeficiencies.
- Patients experience longer lifespans due to improved treatment options, including Ig, which in turn contributes to increased consumption of Ig over time.

Dr. Azar also pointed to the real-world, clinical experience that supports the benefits of Ig therapies in other conditions. This evidence-based prescribing may also contribute to the increased Ig use for rare conditions.

All Panelists agreed that Ig therapy use is likely to continue to grow. They pointed again to increasing awareness of conditions that can be treated with Ig therapies. Dr. Wolfe noted that in the neurology field, Ig is commonly tried in the growing number of immune-mediated encephalitis cases, which will drive further use in the future. Panelists especially emphasized that as other treatments are developed, such as therapies for hematologic, oncologic, autoimmune or inflammatory conditions that weaken the immune system, more Ig therapies will be required to treat the increasing number of persons diagnosed with secondary immunodeficiency.

The growing use of Ig therapies reflects its benefits for patient health, outcomes, and quality of life.

> IVIG is critical for our managing of several different immune-mediated neuromuscular conditions...They help us eliminate or reduce the need of things like corticosteroids, which we all know have terrible adverse events. Both in the [clinical] trials and in regular practice...you will see improvements based on Ig therapy introduction.
>
> Dr. Gil Wolfe

> Somebody in the immune deficiency arena who's constantly sick, off work, off school, in a vicious cycle of illness after illness... [with a variety of] infections that require hospitalizations, so Ig therapy for these patients leads to a tremendous improvement in their quality of life. There's a lot of data on this: many patients can go back to having a normal life as long as they receive regular treatment so it's a huge change.
>
> Dr. Antoine Azar

Current Trends in Access to Ig Therapies – Moderated Panel

Access Challenges in the Ig Market

Dr. Klasen indicated that the U.S. is generally in a good position for the overall clinical need for Ig to be met within the country. Other Panelists did not dispute this general statement, but Dr. Price noted, and panelists agreed, that their institutions "never have enough" Ig, even before the pandemic.

Panelists shared that at times they were put in a position to lower doses or delay treatments, which can have profound consequences for patients. For patients with immunodeficiencies, missing or experiencing a delay in just one treatment can result in hospitalization for a severe infection such as pneumonia or sepsis. On the neurology side, patients experience increasing weakness, motor disability, and falls. It was mentioned that some patients do not tolerate certain products but do tolerate another, so moving from one product to another is not a simple thing to do.

> All immunoglobulin products may not be interchangeable, so if a patient is doing well on one product and tolerating it well, it doesn't mean that you can always immediately switch to something else that's more available. – Dr. Antoine Azar

COVID-19 Effect on the Ig Market

As clinical need has continued to increase, the availability of Ig in the U.S. has so far roughly kept pace to stay in balance. There is concern, though, that as clinical need grows, factors influencing the availability of plasma to manufacture therapies (i.e., pandemic-related decreases in collections) could cause patients who rely on Ig therapy to experience difficulties with access not only to their Ig product but any Ig therapy. The Panelists emphasized the need to increase plasma collection so that patients receiving Ig would not be left without the important therapies for which there are no alternatives.

The Panelists indicated that they had so far been very fortunate that their patients have not experienced significant access challenges exacerbated by COVID-19. However, they noted that there were, at times, challenges to having patients receive Ig treatments. While many patients can use SCIG in the home, IVIG typically is given in the office setting, which became more problematic during the pandemic.

Insurance Coverage for Ig Therapies Limiting Access

Insurance coverage was a key topic of discussion. Panelists noted that there are significant concerns about whether the Ig therapy prescribed will be covered by patients' insurance plans and that it is a never-ending challenge. There was agreement that clinicians must be diligent, only prescribing Ig therapy to patients with conditions that can truly be improved by the treatment. While insurance coverage should not be a barrier to optimal patient care, they acknowledged that for some it is.

The Panelists discussed that there are additional barriers by insurance companies for certain brands or dosages of Ig that diminish the physician's ability to optimally pair the individual patient with the most appropriate therapy. One such challenge with insurance coverage is when intravenous formulations are covered but not subcutaneous, or vice versa.

> Haphazard coverage really boxes [clinicians] into choices that may not be optimal for patient care. – Dr. Syed Mustafa

This limitation is especially important given that Ig therapies are not readily interchangeable. It is critical that insurance coverage not only recognize the general benefit of Ig therapies but acknowledge the need for giving patients the most appropriate Ig therapy so that patients can achieve the best health outcomes.

Conclusion

Overall, the Panelists emphasized the significant role Ig therapies play in extending and improving the lives of patients with immune deficiencies, autoimmune diseases, immune-mediated neurological conditions, and other conditions. The Panelists each discussed how improved awareness of the conditions as well as the effectiveness of Ig therapies has led to increased clinical need that requires a concurrent increase in Ig. Finally, Panelists noted that it is imperative that:

1. the regulatory environment be improved to promote increased plasma collection,
2. insurance companies should work to limit the delay and restriction of Ig therapy when prescribed by subspecialists in the field, e.g. immunologists and neurologists as opposed to general practitioners, and
3. insurance coverage be extended to the evidence-based uses even if not yet labeled as an FDA approved indication because there are often no alternatives to the Ig therapies, which are necessary to optimal patient care.

Appendix

Agenda

Immunoglobulin Roundtable Agenda

Thursday, September 9, 2021
1:00pm – 2:30pm EDT

Agenda

1:00pm – 1:10pm Welcome, Introduction of Panelists, Roundtable Overview

Stuart Langbein, JD | Partner, Hogan Lovells

- Background on PPTA and PPTs and the diseases they treat
- Factors that influence patient access to PPTs
- Purpose of the roundtable

1:10pm – 1:30pm Presentation: Immunoglobulin Use in the United States

Maik Klasen, PhD | Managing Director, Adivo Associates

1:30pm – 2:10pm Moderated Discussion: Physician Perspectives

Stuart Langbein, JD | Partner, Hogan Lovells (moderator)

Antoine Azar, MD | Clinical Director, Division of Allergy and Clinical Immunology and Assistant Professor of Medicine – Johns Hopkins University School of Medicine

Christina Price, MD | Assistant Professor of Medicine and Pediatrics; VA Medical Center Section Chief, Allergy and Clinical Immunology – Yale School of Medicine

Syed S. Mustafa, MD | Clinical Associate Professor, University of Rochester Medical Center

Gil Wolfe, MD, FAAN | Professor and Chair, Department of Neurology – University at Buffalo Jacobs School of Medicine & Biomedical Sciences

2:10pm – 2:25pm Live Q&A Session

Moderated by Stuart Langbein, JD | Audience members may ask questions of Drs. Azar, Price, Klasen, Mustafa, and Wolfe.

2:25pm – 2:30pm Concluding Remarks

Speaker Biographies

Antoine Azar, MD

Dr. Azar is Clinical Director for the Division of Allergy and Clinical Immunology, and Director for the Adult Primary Immunodeficiency Center of Excellence at the Johns Hopkins University. He did his residency and fellowship training at the University of Iowa where he remained on faculty until he moved to Johns Hopkins University and established the Adult Primary Immunodeficiency Center of Excellence.

Dr. Azar has been involved in multiple areas of clinical and translational research. Along with collaborators in Pulmonary medicine, he has spearheaded the evaluation of COPD exacerbations and its association with antibody deficiency syndromes. He has served on the Primary Immunodeficiency Committee at the AAAAI for the past several years and is currently a member of the AAAAI workgroup on Secondary Hypogammaglobulinemia.

Dr. Azar has been honored by being designated as Scholar of the Center of Innovative Medicine (CIM) at Johns Hopkins, has been featured in the New York Times Magazine, the Hopkins Medicine Magazine, and “Top Doctors” in the Baltimore Magazine, and nominated for the Johns Hopkins Best Consultant Physician Award.

Maik Klasen, PhD

Maik is one of the founding Managing Directors of Adivo Associates. Maik started his career as an Immunologist and Geneticist at UCSF before entering the Biotech world via three California-based companies that were later divested. He continues to serve on the board of directors a BioPharma company in California and joined Renovate Biosciences’ management team to follow a dual path as an entrepreneur and strategy consultant; roles that constantly expose him to new technologies and the impact they might have on transforming standards of care. Maik’s continuous to focus on rare diseases with an auto-immune background as well as rare genetic disorders where he accumulated over 20 years of scientific and business experience.

Prior to founding Adivo, Maik was responsible for Frost & Sullivan’s Global Healthcare and Life Science Consulting Practice where he managed global consulting engagements with top 500 pharmaceutical, biotechnology, medical device, IVD/MDx and Healthcare IT companies.

Maik’s entrepreneurial approach and his ability to analyze both business and scientific issues allow him to converse with a broad range of audiences on many levels which is highly valued by his peers. Maik holds a magna cum laude Ph.D. in Immunogenetics in collaboration with the University of California, San Francisco and the Ludwig-Maximillians University in Munich, and a summa cum laude Masters in Molecular Biology from the University of Hannover, Germany.

Syed S. Mustafa, MD

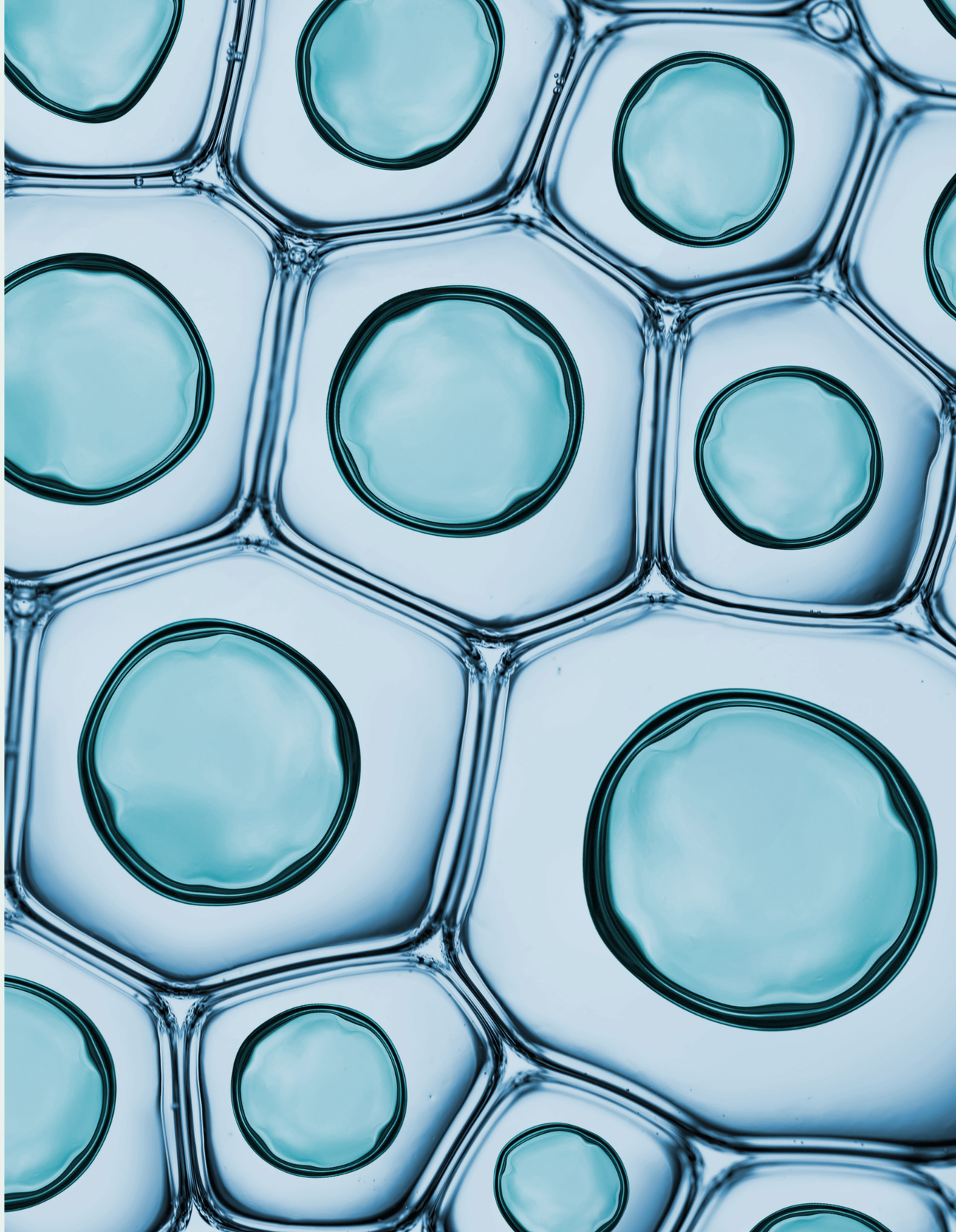
Dr. S Shahzad Mustafa pursued his undergraduate studies at the Johns Hopkins University and attended medical school at SUNY Buffalo. He then completed his internal medicine training at the University of Colorado and stayed in Denver to complete his fellowship training in allergy and clinical immunology at the University of Colorado, National Jewish Health, and Children's Hospital of Denver. Dr. Mustafa is the chief of allergy, immunology, and rheumatology at Rochester Regional Health, where he sees both pediatric and adult patients. Dr. Mustafa is also on faculty at the University of Rochester, where he is Clinical Associate Professor of Medicine, and the clerkship director for the medical student elective in allergy/clinical immunology. In addition to teaching and seeing patients, Dr. Mustafa is also a lead investigator on multiple clinical research projects, with a special interest in secondary immunodeficiency due to malignancy and chemotherapeutics.

Christina Price, MD

Christina Price, MD is a board-certified allergist and clinical immunologist who treats a wide range of conditions. She is an Assistant Professor of Medicine and Pediatrics and Clinical Chief of Rheumatology, Allergy and Immunology at the Yale School of Medicine, as well as Section Chief in Allergy and Clinical Immunology at the West Haven, Connecticut Veterans Affairs Medical Center. Dr. Price has a particular expertise in patients with immune deficiency and immune dysregulation. Patients with autoimmune disease who require immune suppression are managed with their specialists in a team approach. She has collaborated with Smilow Cancer Center to provide immunology services to patients receiving immunotherapy and leads the immunotoxicity conference and Smilow Immunology Clinic. She received her medical degree from St Louis University School of Medicine.

Gil Wolfe, MD, FAAN

Gil I. Wolfe, MD, is Professor and Chairman of the Dept. of Neurology at University at Buffalo Jacobs School of Medicine and Biomedical Sciences, SUNY, where he holds the Irvin and Rosemary Smith Chair. He attended medical school at University of Texas Southwestern Medical School and trained as a neurology resident and neuromuscular/electromyography fellow at the University of Pennsylvania Medical Center. He is board certified in neurology, neuromuscular medicine and in clinical neurophysiology. His clinical activity and academic investigation focus on neuromuscular disorders, particularly on myasthenia gravis and peripheral neuropathies. He has authored or co-authored over 145 papers and 25 chapters on neuromuscular disorders. He is a Fellow of the American Neurological Association and American Academy of Neurology. He has been named a University at Buffalo Distinguished Professor, and in 2018 was awarded the Chancellor's Award for Excellence in Scholarship and Creative Activities by the State University of New York.



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