2020 UPDATE: Division of Rheumatology and Immunology



THE OHIO STATE UNIVERSITY COLLEGE OF MEDICINE • THE OHIO STATE UNIVERSITY WEXNER MEDICAL CENTER





<u>Welcome</u>

Dear Friends and Colleagues,

Looking back on 2019, I can't help but think about how far we've come — not just last year, but in the last decade.

Over the past 10 years, the medical community has witnessed major advances in the field of rheumatology and immunology, particularly in the area of drug development. And here at The Ohio State University, we've also made remarkable contributions to patient care. Since 2010, our division members have launched multidisciplinary clinics and novel studies. They've obtained dozens of grants and trained two dozen fellows.

But it's not time to rest on our laurels; too many people still count on us to provide care for life-altering rheumatic diseases. That's why at Ohio State, 2019 was a year of intentional growth for our division:

- We welcomed five new clinical and research faculty: Bryan Coniglio, MD; Beatriz Hanaoka, MD; Judith Lin, MD; Jisna Paul, MBBS; and Song Guo Zheng, MD, PhD. This was the largest recruitment we've ever had during a calendar year, increasing the size of our clinical and research team to 18 faculty members.
- Dr. Zheng joined our team as the Ronald L. Whisler Endowed Chair in Rheumatology and Immunology. He's relocated his renowned research lab, including several active National Institutes of Health grants, from Penn State University.
- We established another endowed professorship and have begun recruiting some of the best and brightest minds in the field.
- We opened a new outpatient clinic site in Gahanna, a suburb on the east side of Columbus. Patients now have access to rheumatology care at seven locations.

My colleagues and I also expanded our research efforts, which you can read more about in this report. During 2019, we started or completed many pivotal projects and published or presented many key findings. For example:

• Alexa Meara, MD, MS, published an important article in Proceedings that examines an understudied aspect of medicine: that a patient's ability to understand numbers impacts their health outcomes.





Judith Lin. MD



Bryan Coniglio, MD

Jisna Paul, MBBS

- Members of our faculty gave 20 presentations at the American College of Rheumatology annual conference in Atlanta. The Jarjour laboratory, alongside my colleague Noah Weisleder, PhD, from Ohio State's Department of Physiology and Cell Biology, was honored to have an oral presentation by Kevin McElhanon regarding our collaboration in myositis. We recently showed that autoantibodies against TRIM72, a critical protein involved in sarcolemmal membrane repair, is elevated in patients with idiopathic inflammatory myopathies.
- New faculty member Beatriz Hanaoka, MD, transferred exciting research from her previous position at the University of Alabama at Birmingham. She's conducting a K23-funded study to explore whether insulin resistance contributes to skeletal muscle dysfunction in people with rheumatoid arthritis.
- New NIH funding for Dr. Zheng and me will allow for the expansion for the research program in the division.
- Hareth Madhoun, DO, led a two-day, intensive CME ultrasound workshop featuring national experts in musculoskeletal ultrasound that included more than 10 hours of hands-on training in small groups, and learning ultrasound-guided injections on cadavers. Look for our next workshop in early 2021 at ccme.osu.edu.

For many people, growth means change — and change can be difficult. But among our outstanding faculty, growth means progress — and progress can improve outcomes and transform lives.

Thank you for allowing me to share our 2019 achievements. I encourage you to send me your comments or questions by emailing me at Wael.Jarjour@osumc.edu.



Wael Jarjour, MD, FACP

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Wael Jarjour, MD, FACP

Martha Morehouse Chair in Arthritis and Immunology Research Director, Division of Rheumatology and Immunology Department of Internal Medicine The Ohio State University College of Medicine The Ohio State University Wexner Medical Center

Unique Research Examines Link Between Math Skills and Medical Outcomes

New research suggests having — or lacking — certain numeracy skills can help predict chronic disease outcomes. The study, conducted by rheumatologists and psychologists at The Ohio State University, assessed "objective numeracy" (math skills) and "numeric confidence" (having confidence in one's own math abilities) among patients with systemic lupus erythematosus.

Their results found that lupus patients who are good with numbers and feel confident in their math abilities had less disease activity. This finding may help researchers develop more effective patient engagement strategies.

Math Struggles May Correlate With Health Struggles

Previous research has shown that around one-third of American adults are innumerate, meaning they have a hard time understanding or performing basic math. And for people with chronic diseases that affect multiple organs, innumeracy can significantly impact disease management.

"Rheumatic diseases like lupus have a level of complexity that's different from many other medical conditions," says rheumatologist and co-principal investigator Alexa Meara, MD, MS. "To keep their lupus under control, patients face complicated tests and treatments that often require math skills. They may need to take different doses of multiple medications at specific times of day, understand the results of lab tests or precisely taper down steroids."

But being good at math may not be enough to guarantee better health outcomes. The study results, published in *Proceedings of the National Academy of Sciences of the United States of America* in September 2019, showed that success in managing a complex disease also requires numeric confidence.

Mismatched Skills Predictive of Poorer Outcomes

The two-year study was designed with the help of co-principal investigator Ellen Peters, PhD, an internationally renowned decision scientist who studies how to improve decision making by increasing numeracy. Dr. Peters, a former professor of psychology at Ohio State, is now director of the University of Oregon's Media Center for Science and Technology.

More than 90 patients from Ohio State's Lupus, Vasculitis and Glomerulonephritis Registry participated in the numeracy study. They took tests that measured their objective math skills and filled out questionnaires that measured how confident and self-assured they felt using numbers.

"As we predicted, patients whose lupus is well-controlled were more likely to have strong objective math skills and high subjective confidence," says Dr. Meara. "Perhaps more importantly, 'mismatched' skills were tied to worse outcomes. Patients with low math skills and high confidence — meaning



Alexa Meara, MD

they thought they were good at math but scored poorly on the test — were most likely to need further lupus treatments compared to the other participants."

Specifically, their findings showed that:

- Among the most numerate patients, those who were also highly confident had only a 7% chance of having harmful disease activity
- Patients with good math skills but little confidence, which may indicate a willingness to give up easily, were 31% more likely to have disease activity
- Patients with low math skills but high confidence were 44% more likely to have disease activity
- The low-confidence/low-skill group do better than the discordant group of high-confidence/low-skill

Improving Outcomes by Removing Obstacles

The team plans to continue their numeracy research among patients with a different autoimmune disease: vasculitis. If their results are consistent — meaning increased disease flares correlate with mismatched numeracy scores — it may provide momentum for clinicians to create targeted interventions.

"An eventual next step may be finding practical ways to identify this subset of high-risk, chronic disease patients," says Dr. Meara.

In the meantime, she adds, their results serve as a reminder for physicians to identify barriers that make it hard for patients to understand and follow their treatment plans.

"If our patients don't adhere to their medication regimen or make recommended lifestyle changes, we shouldn't assume they're not engaged," she says. "Instead, we should aim to meet them where they're at, in a nonjudgmental way, and help them overcome those barriers to the best of their abilities."

On the Cover: TOP: Rheumatology Experts BACK LEFT TO RIGHT: Kevin Hackshaw, MD, Beatriz Hanaoka, MD, Clark Anderson, MD, Ali Ajam, MBBS, Ronald Whisler, MD, Bryan Coniglio, MD, and Hareth Madhoun, DO; MIDDLE LEFT TO RIGHT: Latha P. Ganesan, PhD, Beatrice Kenol, MD, Jisna Paul, MBBS, Song Guo Zheng, MD, PhD, Stacy Ardoin, MD, and Sheryl Mascarenhas, MD; FRONT LEFT TO RIGHT: Wael Jarjour, MD, Alexa Meara, MD, Zhanna Mikulik, MD, Crystal Losambe, APRN-CNP, and Judith Lin, MD; BOTTOM PICTURE ROW: Beatrice Kenol, MD, Latha P. Ganesan, PhD, William Willis, PhD

Patient Care

Ohio State Expanding Access to Multispecialty Autoimmune Disease Care

Two multidisciplinary clinics launching in 2020 will give people with inflammatory eye diseases and myositis access to convenient, "one-stop" care.

The new Ohio State clinics will let patients see multiple specialists in a shared space on the same day. They will also make it easier for patients to participate in promising research opportunities, including clinical trials and registries.

An Efficient and Effective Model of Care

When the inflammatory eye disease and myositis clinics open later this year, they'll join five other multispecialty programs run by clinicians in The Ohio State University Wexner Medical Center's Division of Rheumatology and Immunology.

"All of our clinics are modeled after our lupus clinic, which was essentially a pilot program when it launched in 2010," says rheumatologist Sheryl Mascarenhas, MD, assistant professor and the division's general rheumatology clinic director. "What started as a group of four rheumatologists and nephrologists has evolved into a nationally renowned program with nine attending physicians, robust clinical trial recruitment and a registry that has enrolled more than 500 patients with lupus, vasculitis and glomerulonephritis." Building off the success of the lupus clinic, the division created dedicated clinics for people with vasculitis, scleroderma and psoriatic arthritis. A fifth clinic managed by Dr. Mascarenhas offers diagnostic and therapeutic musculoskeletal ultrasound procedures.

Following a Familiar Framework

The forthcoming inflammatory eye disease clinic, slated to open this summer, will be a collaboration between Ohio State's rheumatologists and ophthalmologists. Together they'll manage primary autoimmune diseases of the eye and also take care of patients whose autoimmune disorders cause eye complications such as uveitis.

The new myositis clinic will be a collaboration between Ohio State's rheumatologists and neurologists. It will benefit patients who often need to see multiple specialists to confirm their diagnosis or manage disease progression.

Dr. Mascarenhas adds, "Just like our existing clinics, the new inflammatory eye disease and myositis clinics can be a resource for physicians and patients across the country."

<u>Research</u>

Research on Treg Cell Subsets May Lead to New Therapies for Autoimmune Diseases

Song Guo Zheng, MD, PhD, a

renowned scientist responsible for

to regulatory T cells (Tregs), has joined The Ohio State University as

groundbreaking discoveries related

the Ronald L. Whisler Endowed Chair

in Rheumatology and Immunology.

helping lead Ohio State's influential

rheumatology and immunology

In his new role, Dr. Zheng is

research program.



Song Guo Zheng, MD, PhD

A History of Firsts

Dr. Zheng's current research builds off several of his previous achievements.

Other scientists have studied how naturally occurring regulatory T cells (nTregs) suppress inflammation and

regulate immune system activity. However, Dr. Zheng and his colleagues were the first to discover that a cytokine called transforming growth factor beta (TGF- β) can induce naïve T cells to turn into Treg cells.

Since then, one of Dr. Zheng's primary goals has been understanding the differences between these induced Tregs (iTregs) and nTregs — including their stability under inflammatory conditions. One of his studies in mouse models showed that nTregs prevented autoimmune diseases from occurring but was less effective at slowing the progression of existing disease.

"We found that nTregs are not stable," says Dr. Zheng. "Because of their plasticity, they convert to different pathogenic cells with diminished functionality under inflammatory conditions, specifically Th1 and Th17 effector cells."

Their next monumental discovery was two-fold: Not only do Treg cells induced with TGF- β and interleukin-2 remain stable

and functional in inflammatory conditions, but nTregs can be stabilized when primed with a type of vitamin A called all-trans retinoic acid (ATRA) — even in the presence of inflammation.

These findings, which are now patented, suggest that Treg cells that had been modified or equipped have gained an enhanced functional ability and may help keep the immune system under control once stabilized.

"All-trans retinoic acid, also known as tretinoin, has been used to treat other medical conditions for decades," says Dr. Zheng. "Unlike current medications for autoimmune diseases, which often cause severe side effects, ATRA is generally well-tolerated."

Results of another study in his group, published in *Cell Reports* (February 2019), showed that high-salt diets do not impact the development, differentiation and functional activities of TGF- β induced Tregs. However, excess salt does adversely affect stability and function of nTreg cells.

"This is further evidence that iTreg cells may have different biological features than nTreg cells," explains Dr. Zheng. "Induced Tregs may have greater potential for clinical utility in patients whose autoimmune disease is impacted by diet, environment and other factors."

The Next Phase of Research

Dr. Zheng joined Ohio State in February 2019. He is the principal investigator on the following National Institutes of Health-funded studies:

• GCM2 distinguishes induced Treg from natural Treg subset. An NIH STAR award-funded investigation of GCM2, a marker that may distinguish different Treg populations.

- Therapeutic immunoregulation mediated by TGF-betainduced iTregs in autoimmune arthritis. An R01-funded study to test whether iTreg cells maintain their phenotype and function in the presence of inflamed synovial tissues, and whether a molecule called DBC1 helps regulate Treg stability.
- Mesenchymal stem cells derived from human gingiva (GMSC) inhibit bone erosion in autoimmune arthritis. An R-61 funded study to assess whether gingival mesenchymal stem cells can directly inhibit the formation of osteoclasts and activities of inflamed synovial tissues — mechanisms that may help protect against bone erosion and cartilage damage in rheumatoid arthritis.

Dr. Zheng is part of a research collaboration with the University of Utah that received a \$2.7 million R01 grant in April 2019. He and principal investigator Mingnan Chen, PhD, along with other members of Dr. Chen's lab, aim to develop a precision immune cell-ablation therapy for autoimmune diseases. This therapy may be more effective than current treatments for its ability to broadly cover pathogenic cells and may also eliminate the immunodeficiency associated with current therapies.

Dr. Zheng is also site principal investigator on an R01 grant led by Xiao Chen, MD, PhD, an immunologist from the University of Wisconsin. They're studying how ATRA controls graft-versus-host disease and underlying molecular mechanisms.

"All of my research is connectable," says Dr. Zheng. "It started with a single discovery that, more than 20 years later, has led to additional findings that may influence how we care for millions of people with autoimmune disorders. It's my hope that regulatory T cell therapy will one day replace or at least reduce the immunosuppressive drugs currently used to treat these debilitating conditions."

Promising Study Explores Whether Insulin Resistance Impacts Skeletal Muscle Dysfunction in RA



Beatriz Hanaoka, MD

An ongoing study examining whether insulin resistance contributes to muscle weakness and physical impairment may lead to new interventions for people with rheumatoid arthritis (RA).

Principal investigator Beatriz Hanaoka, MD, a rheumatologist at The Ohio State University Wexner Medical Center, is leading a clinical

trial to determine whether treatment with the insulin-sensitizer drug pioglitazone improves skeletal muscle function. Her findings could help people with RA become more active, which is a key to maintaining functional independence.

RA Linked With Muscle Weakness, Insulin Resistance

Previous research has established that the systemic inflammation associated with RA affects the muscles as well as the joints. Nearly two-thirds of RA patients suffer from loss of skeletal muscle mass, which causes weakness and subsequent disability — but scientists aren't sure why.

"Even when their disease is well-controlled, RA patients often have abnormalities in body composition such as lower muscle mass and excess abdominal fat," says Dr. Hanaoka, whose research is funded by a five-year, K23 award from the National Institute of Arthritis and Musculoskeletal and Skin Diseases. "Current RA treatments help preserve joint function but can't reverse muscle dysfunction, which means many patients still have poor mobility."

Research has also shown that low skeletal muscle density is often accompanied by lipid accumulation, which reduces insulin sensitivity and muscle strength. To that end, Dr. Hanaoka suggests that increased lipid content in skeletal muscle contributes to insulin resistance — a common problem in people with RA — which may impair skeletal muscle homeostasis and function.

She also proposes that pioglitazone, a drug used to treat type 2 diabetes, will decrease this lipotoxicity — potentially improving muscle function by restoring the anabolic effects of insulin and calming inflammation.

Getting to the Root Cause of Impairment

To test her hypothesis, Dr. Hanaoka is enrolling patients in a double-blind, placebo-controlled trial comparing RA patients with insulin resistance to non-RA controls. After measuring participants' physical function, body composition, disease activity and skeletal muscle strength, she and her team will evaluate the effects of pioglitazone versus a placebo. They aim to confirm whether the experimental group has improved muscle function after receiving treatment for insulin resistance.

Dr. Hanaoka says they've recruited half of their target enrollment of 110 patients, and early results are promising.

"So far we've seen that the patients with RA are significantly insulinresistant compared to the non-RA controls," she explains. "We're also seeing that inflammation is associated with higher energy expenditure, which is typical in RA patients who have muscle wasting, and that higher protein consumption may diminish that."

Following completion of the study, which just entered its fourth year, Dr. Hanaoka says they may be one step closer to finding an important new application for an existing drug.

"If our results show that insulin resistance is an underlying but treatable cause of skeletal muscle dysfunction, it could be a gamechanger," she says. "Ultimately, we may be able to provide novel targets to prevent or manage a devastating complication of RA."

Researchers Combine Nanobiotechnology, Neutrophils and Nucleic Acid to Combat Lupus

Scientists at The Ohio State University are the first to test whether a novel biochip technology can transform neutrophils into microscopic vehicles that deliver therapeutic agents throughout the body.

The study is funded by a two-year, R21 grant from the National Institutes of Health. It focuses on transfection — the process of artificially introducing foreign nucleic acid into a cell — and may pave the way for new, personalized treatments for lupus.

Overcoming the Limitations of Transfection

Nucleic acids such as microRNA (miRNA) have broad therapeutic potential for a variety of diseases, says Wael Jarjour, MD, director of Ohio State's Division of Rheumatology and Immunology and principal investigator on the study.

He and his team have created a patent-pending cocktail of antimiRNAs and small interfering RNAs (siRNAs) that can significantly suppress the inflammatory response in mouse models of lupus. However, figuring out how to deliver these and other therapeutic agents into living cells has been challenging — until now.

"Some delivery techniques including viral vectors, micro-injections and electroporation can inject biomolecules into live cells, but the doses are imprecise," says Dr. Jarjour. "And during the transfection process, many of the cells don't survive."

But a new, patented technology created by Ohio State faculty emeritus L. James Lee, PhD, co-principal investigator, is the first to transfect cells with precise doses of nucleic acid — and virtually no cell mortality.

Game-Changing Gene Therapy

Dr. Lee, who is the Helen C. Kurtz Chair Emeritus in the Department of Chemical and Biomolecular Engineering, says he has spent the last 20 years working on alternative methods of nucleic acid delivery that don't rely on viral infection.

"Historically, the most efficient way to deliver nucleic acid was through a virus," Dr. Lee explains. "Researchers modify a virus by replacing its genes with therapeutic nucleic acid, then reintroducing the virus into the body. But viruses are hard to control; they can mutate in the body, posing safety concerns." Several years ago, Dr. Lee's lab created a nanosized device called nanochannel electroporation (NEP). It consists of two microchannels connected by a nanochannel. A living cell is positioned in one microchannel and the transfection agent is placed in the other.

A pulse transmitted between the microchannels produces an intense electric field over a tiny area on the cell membrane, allowing a precise amount of transfection agent to be driven through the nanochannel, the cell membrane and into the cell cytoplasm — without affecting cell viability.

"This is the first system that can transfect cells precisely without using a needle," says Dr. Lee. "Dose control is achieved by adjusting the duration and number of pulses."

Although Dr. Lee has used his device in cancer research, this collaboration with Dr. Jarjour is his first venture into inflammatory diseases.

The Novelty of Neutrophils

Not only are neutrophils the most abundant type of immune cells, they're known to target and penetrate inflamed and infected tissue.

"For systemic inflammatory diseases like lupus, neutrophils are ideal carriers of biological drugs," says Dr. Jarjour. "After being pre-loaded with therapeutic agents, they should travel to the site of inflammation. And because they're relatively short-lived, they should release their cargo upon death."

Dr. Lee notes that because neutrophils don't last long, they were once nearly impossible to transfect.

"If you take neutrophils outside of circulation, they usually die within 24 hours," he says. "And when you try to get nucleic acid inside them, they often die even faster. The beauty of NEP is that we can deliver the nucleic acid quickly, within one minute. And because our system doesn't harm the neutrophils, they have time to reach the inflammatory site once they're injected into an animal body."

A High-Tech Therapy With High Potential

In this study, Drs. Jarjour and Lee aim to transfect neutrophils with precise doses of anti-miRNAs and siRNAs using the NEP system. They'll inject the engineered neutrophils into lupus mice to assess

whether the cells deliver the therapeutic nucleic acid — and whether that cargo downregulates the inflammatory response that causes tissue damage.

"Because our cocktail reduces pro-inflammatory gene expression and increases anti-inflammatory expression, we anticipate a robust suppression of the inflammatory response and improved outcomes," says Dr. Jarjour. "Bringing together experts in immunology, autoimmunity, nucleic acid delivery and nanobiotechnology may seem like an uncommon collaboration, but together we have the potential to develop safe, effective therapies for a debilitating disease."

Novel Research May Lead to Targeted Gout Treatment

Researchers at The Ohio State University were the first to study the role of caspase-11 in gout. They have published their significant — and surprising — findings in *Frontiers in Immunology* (Nov. 2019).

The team discovered that caspase-11 not only releases cytokines in the presence of inflammation, it also affects the ability of innate immune cells to then migrate to the site of the infection or other insult. Their results may pave the way for a targeted new treatment for gout and other inflammatory conditions.

Caspases More Complex Than Previously Thought

Since 1993, scientists have understood that caspases, a family of protease enzymes, are responsible for programmed cell death. But that's not their only function, says Amal Amer, MD, PhD, full professor in the Department of Microbial Infection and Immunity at The Ohio State University College of Medicine.

"Caspases have been studied almost exclusively in the context of death signaling," explains Dr. Amer, the study's principal investigator. "However, when our lab has examined them under physiological conditions, it's become increasingly evident that they don't exist solely to trigger cell death. If that was their only role, there wouldn't need to be 12 different kinds of caspases."

The Role of Caspase-11 in Gout

Innate immune responses by macrophages, neutrophils and other cells are the primary drivers of tissue destruction and inflammation in gout, which occurs when monosodium urate crystals (MSU) build up inside the joints. Gout is also characterized by excessive production of a cytokine called interleukin-1 beta (IL1- β); when IL1- β is released during a gout flare, it sends signals to inflammatory cells to come to the site of the crystals.

Previous studies have suggested that in some medical conditions, including asthma, caspase-11 plays a role in releasing IL1- β from cells. However, IL1- β can be released without the cell dying — meaning in those circumstances, caspase-11 is not causing apoptosis.

"We wanted to determine why so much inflammation occurs in gout and define the pathway that leads to it," says Dr. Amer. "If we could find out how IL1- β gets out of the

,cell and target that molecule or the downstream effector molecules, we could potentially stop the release of IL1- β in the first place."

In 2015, another group of scientists identified a previously unknown protein called gasdermin D. It operates downstream of caspase-11 and is responsible for making the hole in the cell membrane that allows the release of IL1- β .

A Key Discovery

Using animal models and in vitro cells, Dr. Amer and her colleagues — including Wael Jarjour, MD, director of Ohio State's Division of Rheumatology and Immunology — compared immune responses in an acute model of gout with and without caspase-11.

Compared to their wild-type controls, caspase-11 knockout mice exhibited fewer signs of joint inflammation, including swelling and tissue damage, after they were injected with MSU crystals. This confirmed the team's assumption that in response to urate crystal build-up, caspase-11 plays an important role in the release of IL1- β .

However, they were surprised to learn that the presence or absence of caspase-11 also impacts the ability of innate immune cells to migrate.

> "Caspase-11 didn't affect the ability of macrophages and neutrophils to move, but it did impact their ability to move in the right direction," notes Dr. Amer. "Without caspase-11 the cells were haphazardly moving around in circles. But the cells that received caspase-11 knew where they were going. This demonstrates that caspase-11 helps promote the chronic inflammation associated with gout."

> > Dr. Amer says that an interesting next step would be to investigate whether caspase-11 functions like a compass or GPS. In other words, does it tell innate immune cells where they need to go and if so, how?

"In the meantime, our current evidence suggests that the caspase-11 pathway including its effectors can be used as pharmacological targets," she adds.

"These results help lay the groundwork for new drugs to treat gout and other inflammatory conditions associated with an abundance of $IL1-\beta$."



Wael Jarjour, MD, and Amal Amer, MD, PhD



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Rheumatology Fellowship Program

BACK LEFT TO RIGHT: Fahad Khan, MD, Jacob Seymour, DO, Roshan Patel, MD, Veronica Mruk, MD, and Ryan Mathew, MD; FRONT LEFT TO RIGHT: Yue Ding, MD, Hareth Madhoun, DO, Assistant Director, Kevin Hackshaw, MD, Program Director, Sheryl Mascarenhas, MD, Associate Director, and Lydia Cortes-Betancourt, MD

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A selection of journal articles from the impressive list of publications authored or co-authored by our faculty:

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