Latest drug developments in the field of Internal medicine: Cardiology, Heart failure, Diabetes, and Inflammation

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Abstract:

Internal medicine is a field of medicine where doctors use their clinical judgment and scientific knowledge to identify and treat a wide range of illnesses and health issues in adults. The greatest cause of early death and disability in people is cardiovascular disease (CVD), and its prevalence is rising around the globe. Due to their significant impact on the rising cost of healthcare, CVDs also place a significant socioeconomic burden on the general populace. Due to its rising incidence worldwide and the tight association between persistent hyperglycemic states and obesity, liver disease, and several cardiovascular problems, type 2

diabetes mellitus (T2DM) continues to be a significant medical issue. Inflammation, however, can cause cancer, neurological diseases, and autoimmune or autoinflammatory disorders if left untreated. Aspirin and other nonsteroidal anti-inflammatories are only a few of the safe and efficient anti-inflammatory medications that are now on the market, and there are many more that are being developed. This review offers a comprehensive analysis of internal medicine, especially in the fields of cardiology, heart failure, diabetes, and inflammation.

Keywords: Internal medicine, cardiology, heart failure, diabetes, and inflammation.

Drug development in the field of Internal medicine:

Internists are medical professionals who focus on identifying, diagnosing, and treating a wide range of diseases and other adult-specific health problems. They are professionals in the treatment of both simple and complex, acute and chronic illnesses, as well as the promotion of health and the prevention of disease. In addition to general medical education, internal medicine residents also spend time rotating through several outpatient and inpatient specialist clinics. Trainees in internal medicine obtain experience through working in such fields as Rheumatology, infectious illnesses, endocrinology, Critical care medicine, Cardiovascular diseases, Pulmonary diseases Gastroenterology, Nephrology, Haematology, and Oncology, dermatology, ophthalmology, dermatology, neurology, and gynecology, Palliative medicine, non-surgical orthopedics, and otorhinolaryngology, Geriatrics, sleep medicine, and rehabilitation medicine.

The study, diagnosis, and treatment of illnesses that affect the internal organs, including heart disease, hypertension, diabetes, obesity, and lung disease, is known as internal medicine. Internal medicine professionals frequently treat patients with multisystem, chronic, and complex illnesses. Inside medicine, Numerous disorders are identified, managed, and treated by doctors. These include cancer, infections, and ailments affecting the digestive, respiratory, and circulatory systems, as well as the heart, blood, kidneys, and joints.

Depending on the ailment, general health, and wellness objectives of the patient, internal medicine doctors carry out or prescribe tests, procedures, and surgeries. These include non-invasive coronary artery calcium testing and the OralID® cancer screening tool. "Coronary artery calcium score testing helps us determine the atherosclerotic load in asymptomatic patients at increased risk for heart disease, and Calcium scoring can help us to

identify at-risk patients and treat them more aggressively." Additionally, internists are at the forefront of oropharyngeal cancer screening due to the increase in head and neck cancer incidence. The Centres for Disease Control and Prevention (CDC) advises annual screenings for all persons 18 and older.

Ultrasound, computed tomography, and magnetic resonance imaging (MRI) are used by internal medicine and many other medical specialties to direct invasive treatments. To access parts of the body that are difficult to access, flexible fiberoptic equipment may be employed (1).

Drug development in the field of Cardiology & Heart failure:

Greater than all malignancies combined, heart disease is the leading cause of death in the world. This is even though cardiovascular mortality has significantly decreased in the industrialized world since the middle of the 20th century, (2) mostly due to a decline in ischemic heart disease. (3, 4) Multiple factors contribute to this trend, including a decrease in tobacco use, dietary changes, treatment of hypertension, improvements in fast coronary revascularization, and the introduction of HMG-CoA reductase inhibitors and P2Y12 ADP receptor antagonists. (5) However, there has been an increase in the global burden of cardiovascular diseases (CVD) (6) and a stalling of progress in the United States due to the adoption of the Western diet and lifestyle in the developing world as well as the rise in the prevalence of cardiometabolic disorders and obesity. (7,8)

Although drug therapy is a major form of treatment for cardiovascular disease, there haven't been many new drugs authorized for use. However, the quantity of new agents does not mean that there aren't any new concepts in the sector. The present assessment focuses on the newest, most promising approaches to resolving each of the major cardiovascular disorders with medicine and determines the most promising of the agents under study.

The lack of new drugs and the end of patent protection for major statins, angiotensin receptor blockers (ARBs), and antiplatelet drugs by 2012 have had a major adverse effect on the market for cardiovascular drugs. (9) Prasugrel and dronedarone are two agents that came out of the current pipeline and were sold in 2009. An ADP receptor blocker called prasugrel competes with clopidogrel to keep the arteries open after percutaneous coronary intervention (PCI). Similar to amiodarone, dronedarone is a medication used to treat atrial fibrillation (AF). The two major categories of drugs in the 2010 pipeline are antidyslipidemic

medications and antiplatelet/antithrombotic therapies. The most effective antiplatelet/antithrombotic medications in 2010 are ticagrelor, rivaroxaban, and dabigatran. The most effective antidyslipidemic medications are darapladib, a certraid, and fenofibricacid. (10, 11)

Acute myocardial ischemia, often known as acute coronary syndrome (ACS), is a broad term for disorders that result in chest pain from inadequate blood supply to the heart muscle. Heart attacks and unstable angina are also included in ACS and are major causes of mortality and morbidity, resulting in 2.5 million hospital admissions yearly. Antiplatelet drugs and antithrombotics, often known as coagulation inhibitors, are the two main treatment paradigms being investigated for ACS. (12)

Drug therapy methods for treating angina have not proven successful in developing new treatments. Myocardial hypoxemia, which results from an imbalance in oxygen supply against demand, is what causes angina. Over the past ten years, supply-side models for the treatment of fixed stenotic lesions, thrombus, and coronary artery vasospasm have been addressed. Demand-side models are similarly concerned with oxygen consumption that is controlled by heart rate, inotropy, afterload, and preload. Beta-blockers, Ca2+ channel blockers, and nitrates are now mature pharmacological groups with conceptually few unique techniques that have been used to address increased oxygen demand. The vascular endothelium's malfunction or illness, which impacts both oxygen demand and supply, has drawn the most attention. Nitric oxide (NO) and prostacyclin, which widen coronary arteries and prevent clot formation, are produced by the healthy vascular endothelium as a protective mechanism. Vasoconstriction, platelet aggregation, and clot formation result from an inefficient vascular endothelium's inability to produce enough NO and prostacyclin. (13)

The models emphasize the ability of NO, at low concentrations, to prevent tissues from suffering from ischemia, but at sustained levels, NO causes tissue damage and vascular collapse. Nitrates, the NO synthase transcription enhancer AVE9488, Ca2+ channel blockers, particularly diltiazem, and the heart metabolic modulator ranolazine are among the treatments under investigation.

Gene therapy and models that target atherosclerosis and restenosis have become the main focuses of treatment for coronary artery disease. Statins are used with extended-release niacin formulations in atherosclerosis models. The goal of the extended-release niacin is to reduce flushing, while the statin is typically simvastatin, a generic medicine that is added to a

combination product to enable the extension of the brand's patent. Niaspan plus simvastatin, extended-release niacin and statins, and extended-release niacin and simvastatin are a few examples.

Another strategy being investigated to stop coronary artery disease is gene therapy. Hypoxia-inducible factor-1-alpha, which is being developed by BioCardia, USA, is currently of interest. By expressing genes that code for proteins involved in angiogenesis, energy metabolism, erythropoiesis, cell proliferation, vascular remodeling, and vasomotor responses, hypoxia-inducible factor-1-alpha maintains oxygen homeostasis. (14)

As the population ages, arrhythmia (AF), the most prevalent symptomatic tachyarrhythmia, is projected to increase. In 2050, there are expected to be 5.6 million people living in the AF, up from 2.1 million in 1995. Several approaches have been used in drug treatment models for AF, including rate control, rhythm control, medicines that change the atrial substrate, anticoagulation, and ablation. Only rhythm control studies—which resulted in dronedarone, a drug comparable to amiodarone—have so far led to an approved substance.

Heart rate, resting membrane potential, action potential form, and duration are all regulated by K+ channels in the heart. The two types of these channels are voltage-gated and ligand-gated, respectively. Voltage-gated channel blockers or combinations of voltage- and ligand-gated channel blockers have been used in research to target K+ channels for atrial-specific arrhythmias. (15)

Alternative model channel blockers, including mixed Na+/K+ blockers, stretch-activated ion channel blockers, and Na+ current blockers, have also undergone preliminary studies. These drugs are comparable to amiodarone and azimilide. Along with gap junction modifiers like rotigaptide, there are also early versions of receptor antagonists like ryanodine receptor-stabilizing protein and piboserod. One drug intended to lessen the toxicity profile of amiodarone while still producing multichannel blocking properties is dronedarone. The most used rhythm control drug, amiodarone, has several toxicities and dose-limiting adverse effects. (15)

Current research on myocardial infarction treatment uses a variety of strategies. The study of myocardial infarction as an inflammatory model has garnered considerable interest. These models include inhibitors of complement, intracellular electrolytes, and enzymes, as well as anticoagulants and antithrombotics. The approval process for anticoagulants and

antithrombotics is the most advanced; they include thrombolytics to compete with tissue plasminogen activators and alternatives to unfractionated heparins, such as enoxaparin.

There are more strategies for combating the inflammatory cascade that is being researched and developed. DG051 is a small molecule leukotriene A4 hydrolase inhibitor, poly(ADP ribose) polymerase inhibitor and KAI-9803 is an isozyme-selective delta protein kinase inhibitor. AMR001 is an autologous bone marrow-derived, CD34-enriched cell product for the treatment of damaged heart muscle following acute myocardial infarction. Mesenchymal stem cell treatment and pexelizumab, an anti-C5 antibody fragment being tested in coronary artery bypass graft surgery to reduce inflammation, are still in the early stages of development. Diuretics, renin/aldosterone inhibitors to enhance renal function and generate vasodilation, inhibitors of progressive myocardial remodeling, activation of cardiac myosin, myocardial rescue, and myoblast transplantation are some of the approaches used to study congestive heart failure. A selective antidiuretic hormone receptor antagonist called lixivaptan is the most recent antidiuretic hormone receptor antagonist to garner attention. With tolvaptan, a vasopressin V2 receptor antagonist, vasopressin remains a target of interest. (16)

Enzyme inhibitors including AVE8134, which binds to DNA and controls gene expression, AVE3085, an endothelial NO synthase transcription enhancer, and daglutril, an endothelin-converting enzyme inhibitor, were used in the early stages of the development of pharmaceutical therapy for heart failure. Animal models are being used to study these medicines, but significant human testing is still necessary. (17, 18)

A recent HF compendium highlighted several translational successes, including the promising future of SGLT2 inhibitors for heart failure with reduced ejection fraction (HFrEF) (19) or heart failure with preserved ejection fraction (HFpEF), (20) and tafamidis for transthyretin (TTR) cardiac amyloidosis. (21) Surprisingly, only one of the therapeutic philosophies covered in several HF compendia was translated into a new treatment for HF patients. The systems-level analysis of cell networks and pathways implicated in the pathogenesis of HF in humans, which may one day lead to the discovery of novel therapeutic approaches, is still in its infancy. (22) Therefore, even though fibrosis is essential for the development of HF and cardiac remodeling, it is yet unknown whether medicines created specifically to target fibrosis will be effective in treating HF. (23) To create rational therapy

solutions for HF, biobanking attempts to find biomarkers and molecular signatures of disease progression before progression to end-stage heart disease will be helpful. (24)

Tafamidis symbolizes a victory of mechanism-based rational medication design for TTR amyloid cardiomyopathy. TTR amyloid fibrils are progressively deposited in TTR amyloid cardiomyopathy. While several destabilizing TTR variations can result in cardiomyopathy or polyneuropathy, the wild-type TTR protein is susceptible to aggregation in older people, which can cause heart illness. Tafamidis was created by Kelly and colleagues as a victory of structure-based chemical biology. Tafamidis binds to TTR and stops amyloidogenesis and pathogenic TTR aggregation. (25)

Tafamidis is marketed as an "orphan" treatment with a very high price tag, but given that the V142I variation, which is present in 3.5% of African Americans, is linked to higher incident heart failure rates and a shorter overall survival rate, it may ultimately show to be effective for a wider population. (26)

New treatment insights could be gained via a complete understanding of the molecular and mechanistic underpinnings of the pathogenesis of uncommon inherited dilated cardiomyopathies. Future treatments for heart failure caused by mutations in RBM20, LMNA, and BAG3 may, for instance, use particular tactics that regulate RNA metabolism, (27) mechanosensing, (28) and proteostasis, (29) respectively.

The Tafamidis tale also emphasizes the ability of human genetics to clarify workable therapeutic approaches because certain TTR mutations that destabilize TTR structures were known to be associated with either familial amyloid neuropathy or amyloid cardiomyopathy. The pharmaceutical and biotech industries are investing in genomics to better target selection and lower the chance of failure due to lack of efficacy (30) or negative effects (31) as a result of the high costs and risks associated with producing new molecular entities (NMEs).

Human genetics has had a significant impact on the development of cardiovascular drugs. A compelling "failsafe rationale" for the development of antibodies and small interfering RNAs (siRNAs) against PCSK9, or even gene editing, for the treatment of hypercholesterolemia and prevention of atherosclerosis, was provided by the discovery of PCSK9 (proprotein convertase subtilisin/kexin type 9) loss-of-function mutations, which confer lifelong protection against atherosclerosis and coronary heart disease (CHD) without discernible deficit. (32)

Since HF is a diverse syndrome with numerous separate pathologies and, in contrast to lipidomics, lacks a single unifying biomarker that is causally connected with HF, applying human genetics to discover therapeutic targets for HF is significantly more difficult. Phenome-wide association studies (PheWAS) and even larger clinical-genetic datasets may help discover new therapy possibilities. (33)

Although small molecules have dominated the therapeutic landscape for hundreds of years, the advent of antibody therapeutic agents with precise target engagement has dramatically accelerated drug development. A key disadvantage of therapeutic antibodies is that they only target extracellular proteins. In contrast, siRNA and antisense mRNA can selectively modulate their targets, regardless of localization. In recent years, gene therapies have regained momentum, especially for rare genetic diseases. A promising new approach for gene delivery and the targeted destruction of profibrotic-activated fibroblasts has been made possible by the astounding success of modified mRNA and lipid nanoparticles (LNP) for COVID-19 vaccines (34). Verve Therapeutics recently made the audacious decision to permanently delete the PCSK9 gene in vivo using the newest genomic editing technology (35). These new techniques have the potential to revolutionize the therapeutic development of human genetics-validated therapeutic targets and promote the creation of several "niche" therapeutics for certain disease subtypes, especially in conjunction with advancements in organ-targeted LNPs (36).

Drug development in the field of Diabetes and other diseases:

The groundbreaking research by Banting, and later Best, Macleod, and Collip, which eventually led to the discovery of insulin as a treatment for diabetes, occurred one hundred years ago this year (37). Since then, diabetic patients' clinical prognosis and life expectancy have significantly improved. According to Kharroubi and Darwish (38), the prevalence of progressive metabolic disease, which is brought on by hereditary and environmental causes, is nevertheless rising at worrisome rates. It is predicted that 784 million persons would have either type 1 or type 2 diabetes mellitus by 2045. (39).

Diabetes mellitus type 1 is an autoimmune condition. When genes are important, the immune system accidentally targets pancreatic cells., which reduces the ability to produce insulin. In contrast, the interaction of genetic and behavioral variables are significant risk factors for developing type 2 diabetes mellitus (T2DM), in which insensitive and damaged pancreatic -cells result in high blood glucose levels (hyperglycemia). (40, 41) About 90% of

all instances of diabetes are T2DM, the most prevalent kind. This is partly because of the radical lifestyle shifts that have occurred over the past 30 years, during which time processed foods and foods high in calories have been more widely available and it has become simpler to remain productive while inactive. Micro and macrovascular problems brought on by hyperglycemia frequently result in patient mortality. While macrovascular consequences involve large arteries and vessels and cause cardiovascular illnesses, stroke, and peripheral artery disease, microvascular problems impact small arteries and veins and cause neuropathy, nephropathy, and retinopathy. (42)

Since the FDA authorized human insulin (Humulin) in 1982, 59 different antihyperglycemic medications have been approved. The list of authorized medications includes 23 original pharmacological combinations of two or more antihyperglycemic medicines as well as 36 novel molecular entities (NMEs) as monotherapies. Most recently approved NMEs that are monotherapies target proven molecular pathways that have been verified by other approved antihyperglycemic drugs. For instance, sodium-glucose cotransporter type 2 (SGLT2), which was .licensed in 2014, is the most recent molecular target. However, approvals of combination therapies that target various routes for the treatment of diabetes mellitus have also been rising. Between 2015 and 2020, 375 clinical trials involving around 100 antihyperglycemic drugs are registered. (43)

With at least 14 different analogues and combination regimens, different forms of insulin make up a sizeable fraction of FDA-approved medications for the treatment of diabetes. The insulin lispro, aspart, and glulisine are examples of rapid-acting insulin analogues that provide the bolus insulin level needed at mealtimes (prandial insulin). Combinations of insulin and glucagon-like peptide-1 (GLP1) receptor agonists have also been approved, in addition to insulin plus insulin combo regimens. Additionally, adjuvant medications or basal insulin therapy combinations are also administered. (44)

Glucose-dependent and glucagon-like peptide (GLP) Incretins or peptides generated from the gut are known as insulinotropic polypeptides (GIP). A series of naturally occurring metabolic hormones known as incretins promotes a drop in blood glucose levels. The pancreatic beta cells begin producing and secreting insulin in response to GLP-1. The new class of injectable medications for the treatment of type 2 diabetes is GLP-1 agonists or analogues. (45)

Despite being a crucial finding for the management of diabetes, insulin is rarely employed as a first-line therapy. When individuals develop insulin tolerance and the dose of insulin provided needs to be raised, there is a risk of developing severe hypoglycemia, cancer, and cardiovascular problems. (46)

For the treatment of type 2 DM, several oral non-insulin-based treatments have been developed namely insulin secretagogues, biguanides, insulin sensitizers, alpha-glucosidase inhibitors, incretin mimetics, amylin antagonists, and SGLT2 inhibitors. (47) Sulfonylureas (SU) were the only licensed insulin rivals until metformin was approved, and they were widely employed to treat T2DM. There are just three SU medications that can be obtained by prescription at this time (glimepiride, glipizide, and glyburide). Glyburide/metformin and glipizide/metformin are two SU and metformin combo regimens that are now on the market and have received FDA approval. (48) The sole FDA-approved antihyperglycemic medication in this pharmacological class, biguanide metformin has dramatically improved T2DM therapy since its approval in 1995. (49)

Acarbose, the first alpha-glucosidase inhibitor (AGI), and miglitol, the second AGI, were both approved by the FDA as antihyperglycemic medications in 1995 and 1996, respectively. There are just two AGIs authorized for sale in the United States, though voglibose was given the go-ahead by the Japanese Pharmaceuticals and Medical Devices Agency. (50) There are now two TZDs on the market, rosiglitazone, and pioglitazone, both of which received FDA approval in 1999. (51)

The first incretin-dependent T2DM medications were authorized in 2005 and 2006, and since then, both single therapy and combo regimens have gained popularity. Exenatide, liraglutide, dulaglutide, albiglutide, lixisenatide, and semaglutide are six injectable GLP1 receptor agonists that have received approval. They differ in how long they stay in the bloodstream and how well they can treat hyperglycemia. Currently, the FDA has approved four DPP4 inhibitors: sitagliptin, saxagliptin, linagliptin, and alogliptin. But at least seven other DPP4 inhibitors are registered in phase III and IV trials and have received permission from different regulatory bodies. 10 DPP4 inhibitors are also being developed clinically, including two more phase III medicines, one in phase II studies, and 10 further DPP4 inhibitors. (52) The FDA has approved two meglitinides: nateglinide in 2009 and repaglinide in 2013. There aren't any meglitinides in clinical studies right now. (53)

The newer medication classes utilized for T2DM nowadays are Alpha-glucosidase inhibitors, Amylin agonists, Incretin mimetics (GLP – 1 Agonists and DPP – IV inhibitors), and SGLT2 antagonists/ inhibitors. The two main enzymes involved in the metabolism of carbohydrates are alpha-amylase and alpha-glucosidase. Oral anti-diabetic medications called alpha-glucosidase inhibitors (AGIs) are typically used to treat T2DM. (54) The only medication in this class of amylin analogues that is currently on the market is pramlintide acetate, which is taken via subcutaneous injection. (55)

The goal of monotherapy for the treatment of T2DM is to lower hemoglobin (HbA1c) that has been glycosylated by up to 0.5 to 1.5%. When the value is less than 7%, further control of postprandial glucose level is more important for improving HbA1c. (56) Combination therapy is advised to the patient to establish glycemic control and so postpone the decline of beta cells when monotherapy is unable to manage the glycemic parameters in the treated individuals. Drug combinations in combination therapy can be two or three. Sometimes insulin therapy is paired with the use of oral hypoglycemics. (57)

Conventional drug delivery methods have some drawbacks, such as poor efficacy brought on by insufficient or inappropriate dosage, diminished potency or altered effects brought on by drug metabolism, and a lack of target specificity. Due to their advantages in decreased dose frequency, improved bioavailability, prevention from degradation in acidic stomach environments, focused therapeutic efficacy with a decrease in associated side effects, and other advantages, Novel Drug Delivery Systems (NDDS) are one of the rising fields in recent years. Although many NDDSs are being investigated for the treatment of various disorders, few have been reported for the treatment of T2DM. These can be grouped into: Two types of particle systems microparticulate and nanoparticulate systems. Niosomes and Liposomes in the Vesicular System and Other i) Transdermal drug delivery system ii) Self nano-emulsifying drug delivery system. (58-60)

SGLT2 inhibitors are the most recent and promising therapeutic class. Canagliflozin and dapagliflozin, the first SGLT2 inhibitors, were approved in 2013. Subsequent monotherapy drugs empagliflozin and ertugliflozin were approved in 2014 and 2017, respectively. SGLT2 inhibitors are also popular in regimens that combine metformin, DPP4 inhibitors, and combinations of all three plus TZD medications. (61) SGLT2 inhibitors, such as Canagliflozin, Dapagliflozin, Empagliflozin, Ipragliflozin, Luseogliflozin, and

Tofogliflozin, are prescribed either alone or in conjunction with metformin, sulfonylurea, thiazolidinediones, or insulin. (62)

Along with a steady rise in the variety of approved oral combinations, the proportion of combinations that are approved over monotherapies has also increased. The majority of approved anti-diabetic medication regimens consist of combinations. There are 23 different antihyperglycemic medication combinations available right now. In 2019, a triple combination treatment containing metformin, saxagliptin, and dapagliflozin received approval. In 2020, metformin, linagliptin, and empagliflozin received approval for another triple combination. (63) More than 40% of the drugs found in clinical trials target either multiple targets or unique therapeutic compounds. The most common classes of new targets are receptors and enzymes, followed by transporters and ion channels.

Glucose protein-coupled receptor 119 (GPR119), which is expressed in enteroendocrine cells and pancreatic beta-cells, is essential for maintaining glucose homeostasis. Phase I trials for the second-generation GPR119 agonist DA-1241 are now underway, and it is hoped that these trials will result in significant glucose-lowering effects and improved safety profiles for diabetic patients. (64) Tirzepatide, a dual agonist, is now being tested in clinical studies (Phase III). (65) Thyroid hormone receptors (THR) are frequently targeted in the therapy of metabolic illnesses, but research has indicated that they are also promising targets in the management of diabetes. (66)

Currently, phase II clinical studies for at least one promising drug (IONIS DGAT2Rx) from the selective Diacylglycerol acyltransferase (DGAT) inhibitors category are complete. It is not a traditional hyperglycemic medication because it is a hepatoprotectant, but it indirectly impacts glycemia by improving insulin sensitivity and preserving islet -cells. (67) The kallikrein-kinin system might offer an intriguing strategy for treating diabetes. (68) Another component of glucose homeostasis is the enzyme fructose-1,6-bisphosphatase-1 (FBP1), which is involved in gluconeogenesis. (69) Inhibiting Methionine Aminopeptidase 2 (MetAP2) is a promising treatment option for diabetes and obesity, according to recent studies. (70) Angiopoietin-related protein 3 (ANGPTL3) is a different protein that plays a role in angiogenesis, which in turn contributes to cancer, but it also plays a crucial role in glucose metabolism. (71)

Because it starts gluconeogenesis, glucokinase is an essential enzyme that helps to maintain healthy glucose homeostasis and has a glucostatic impact on the blood. Many

Glucokinase activators (GKAs) have started clinical trials (such as Piragliatin, ARRY-403, AZD1656, and PSN010), but many have since stopped showing clinical progress. However, the introduction of numerous next-generation GKAs, including TTP399, a hepatoselective drug, and dorzagliatin, a novel, dual-acting agent that targets both pancreatic and hepatic glucokinases, has sparked renewed interest (72) TTP339 and SY004, two further novel GKAs, are in phase II studies, while Dorzaliatin is presently undergoing phase III trials. Several direct AMP-activated protein kinase (AMPK) activators have been developed recently, and phase II studies on PXL770 and PBI-4050 have just been finished. (73) Phase II clinical trials for the fructokinase inhibitor PF-06835919 are presently underway. (74)Tolimidone (MLR-1023) is now in phase II with patients receiving metformin treatment and has completed phase II in patients with uncontrolled T2DM. (75)

The second generation of insulin sensitizers, MSDC-0602K, is anticipated to be less likely to cause side effects than the first-generation substances. Phase III clinical studies are anticipated to begin in 2022. (76)

Drug development in the field of Inflammation:

Around the world, the prevalence, morbidity, and mortality rates of infectious and inflammatory illnesses are high. (77) The physiological process of inflammation involves a variety of distinct chemicals and cellular reactions. From the standpoint of drug research, the mediators that come through the two routes are of special interest. The first group of mediators involved in the inflammatory process, leukotrienes (LTs), are crucial to the entire inflammatory process. The second group is more varied and takes effect once the COXs that turn arachidonic acid into prostaglandin are active. Due to their powerful vasodilator effects, PGE2 and PGI2 increase blood flow in inflammatory regions. The suppression of vascular endothelium and platelet aggregation is caused by prostacyclin (PGI2). Prostacyclin E2 and Prostacyclin I2's vasodilation effects help preserve the gastric mucosa by increasing mucus secretion and reducing the amount of acid and pepsin in the stomach. (78)

When used in adequate doses, nonsteroidal anti-inflammatory medicines (NSAIDs) are a class of prescription medications that help lessen discomfort, inflammation, blood clotting, and fever. NSAIDs work by inhibiting COX-1 and COX-2 enzymes either non-selectively or selectively. (79)

The discovery and validation of new drug targets will continue to rely heavily on computational methods in therapeutic development, which will speed up the procedure. Our efforts to comprehend how cells function better are spearheaded by the science of bioinformatics. Novel compounds were chosen based on their overall high selectivity for COX-2, capacity to pass drug-likeness and ADME analyses, potent anti-inflammatory action, lack of gastrointestinal side effects, and safety when evaluated in human cell culture. (80-81)

To create medicines with safe profiles, research is still being done on how to selectively inhibit COX-2 to provide anti-inflammatory activity with the fewest possible side effects. Shady Burayk et al., demonstrated the effectiveness and safety profile of two novel benzimidazole piperidine and phenoxy pyridine derivatives in achieving this objective, which would be regarded as a significant advancement in the field of inflammatory therapy. Virtual screening, in vitro COX-1 and COX-2 inhibition, in vivo carrageenan-induced rat paw edema experiment, cytotoxicity against Raw264.7 cells, and histological analysis of rat paw and stomach were all used to evaluate the compounds. Two new compounds, compound 1 ([(2-{[3-(4-methyl-1H-benzimidazol-2-yl) piperidin-1- yl]carbonyl}phenyl)amino]acetic acid) and compound 2 (ethyl 1-(5-cyano-2-hydroxyphenyl)-4-oxo5-phenoxy-1,4-dihydropyridine-3-carboxylate) showed high selectivity against COX-2, favorable drug-likeness and ADME descriptors, a lack of cytotoxicity, relived paw edema, and inflammation without noticeable side effects on the stomach. These two substances represent potential novel NSAIDs. (78)

The onset of atherosclerotic plaque and the spread of inflammation is supported by the integrity of the endothelium, which is a rare condition brought on by acute and uncontrolled inflammatory responses (such as the cytokine storm brought on by SARS-CoV-2 infection). More frequently, however, the vascular tree is the initial target of slowly progressing inflammatory processes. Due to this endothelial dysfunction, NO production is decreased, vascular tone regulation is disturbed, and platelet aggregation is enhanced. Atherosclerotic lesions experience macrophage infiltration as a result of this protracted subclinical inflammation. Therefore, numerous attempts should be made to identify practical means of preventing inflammation in vascular endothelium.

The therapeutic and nutraceutical approaches serve as practical instruments for treating, reducing, or avoiding various stages of vascular inflammation. The nutraceutical method may offer a potential preventive strategy to maintain the integrity of the endothelium

tissue, whereas the pharmaceutical approach should be used in advanced phases characterized by clinical symptoms of vascular disease. (82)

Salicylate-containing plant extracts have been used to treat pain, inflammation, and fever for as long as there have been records of human history. Felix Hoffman acetylated salicylic acid and produced aspirin one hundred fifty years ago. The cyclooxygenase (COX) enzymes COX-1 and COX-2, which are involved in the production of prostaglandins and thromboxanes, are inhibited by aspirin. The primary therapeutic function of aspirin is its capacity to inhibit the synthesis of prostaglandins and thromboxanes. Nonsteroidal anti-inflammatory medicines (NSAIDS), which target COX-2 and subsequently the manufacture of prostaglandins, particularly PGE2, come in second to aspirin. artificial variations in natural cortisol (also known as glucocorticoids) are frequently used to treat a variety of inflammatory illnesses, and despite their negative side effects, they continue to be a staple for lowering inflammation. To cure the short-term effects of chronic inflammatory disorders as well as the long-term symptoms of acute inflammation, pharmaceutical chemists must yet produce more potent and less hazardous treatments.

Proinflammatory cytokines such as tumor necrosis factor (TNF)-, interleukin (IL)-1, and vascular endothelial growth factor (VEGF) play key roles in the dynamic process of inflammation. (83)

In general, resolvins are part of the anti-inflammatory repertoire that coexists alongside inflammation. Synthetic versions of RvE1 are currently in clinical trials for treating eye disorders and other local inflammatory conditions. In animal models of sterile inflammation, RvE1 decreases the amount of infiltrating neutrophils and macrophages as well as lowering expression of the genes encoding TNF-α, IL-1β, and VEGF (84) The anti-inflammatory effects of omega-3 fatty acids include reduction of IL-1β and TNF-α production (85) and the mechanism of action of omega-3 fatty acids may entail enhancing the production of resolvins of the D and E series.

Glucocorticoids are used routinely on a chronic basis to treat most autoimmune disorders. Short-term glucocorticoid medication is utilized in gout, and intra-articular injections of glucocorticoids are routinely used to treat painful osteoarthritic joints and tendonitis Although there are various methods by which glucocorticoids suppress inflammation, a major one may be to reduce expression of cytokine-induced genes.

Methotrexate, cyclosporine, tacrolimus, and rapamycin are a few orally active, disease-modifying medications used to treat autoimmune illnesses that also have anti-inflammatory qualities. In vivo, methotrexate reduces the synthesis of chemokines and TNF-. The anti-inflammatory profile of methotrexate may also be influenced by its antiangiogenic activities. Cyclosporine, tacrolimus, and rapamycin are immunosuppressive drugs, which are used broadly in many clinical scenarios from preventing allograft rejection to treating psoriasis and managing vasculitis. (86)

Statins have been utilised to stop degenerative processes, control immune cell activation, and reduce inflammation. Some doctors recommend statin medication for unapproved conditions due to their widespread use and lengthy track record of safety. (87)

Sepsis continues to be a major cause of death despite numerous randomized, placebo-controlled trials of anti-inflammatory drugs and anti-cytokine therapy. Activated protein C (aPC) is the only medication that has been found to lower sepsis-related mortality. By suppressing the transcription factors NF-B (88) and p38 MAPK, (89) reducing endothelial cell death, and preventing leukocyte adherence and chemotaxis, aPC prevents the generation of the proinflammatory cytokines IL-1 and TNF-. Antithrombin and low molecular weight heparins have anti-inflammatory properties, mostly through lowering cytokine production and thrombin-induced endothelial activation.

The nuclear receptor superfamily includes the peroxisome proliferator-activator receptors (PPARs). PPAR, PPAR/, and PPAR are three distinct gene products with highly similar DNA-binding domains. Functionally, retinoic acid receptors and PPARs combine to generate heterodimers. The expression of various proinflammatory cytokines, the majority of chemokines, and cell adhesion molecules are decreased by PPAR agonists, which makes them anti-inflammatory drugs even though this interaction has downstream implications on the control of glucose metabolism. (90)

Natural products, particularly secondary metabolites derived from medicinal plants, are a valuable source of novel chemical compounds that can be exploited in pharmacological research, particularly for the treatment of infectious and inflammatory illnesses.

Betulinic acid, a pentacyclic triterpene of the lupane type that is frequently isolated from Betula species, was discussed in a review by Oliveira-Costa and colleagues (OliveiraCosta et al.). This compound has anti-inflammatory properties. In many models of

inflammation, betulinic acid was discovered to affect the production of major inflammatory mediators both in vitro and in vivo, which is likely because it inhibits the nuclear factor kappa-B (NF-B) and mitogen-activated protein kinase (MAPK) pathways.

In RAW264.7 macrophages and zebrafish embryos treated with lipopolysaccharide (LPS), Kuang et al. looked into the sesterterpenoid fusaproliferin and its analogues' anti-inflammatory properties. Nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) expression of inflammatory enzymes were both shown to be downregulated in response to the sesterterpenoid's action, which was also linked to the inhibition of nitric oxide (NO), reactive oxygen species (ROS), and cytokine production.

The NLRP3 inflammasome is an intracellular multiprotein complex with key roles in inflammation and host defense. Four articles examined the impact of natural products on this complex. NLRP3 inhibitor piperlongumine, an alkaloid isolated from Piper longum L., works by preventing the inflammasome from coming together. (-)-Epicatechin, a flavonoid with antioxidant and anti-inflammatory properties, dramatically reduced the inflammatory response in acute gouty arthritis caused by MSU.

A total of 99 substances, predominantly flavonoids, were found in QWZK. These compounds showed protective properties against LPS-induced ALI, probably by preventing the activation of the NLRP3 inflammasome and the TLR4/NF-kB signaling pathway. Inflammation is typically treated with the Chinese medicinal herb Tetrastigma hemsleyanum Diels et Gilg (Vitaceae), also known as Sanyeqing. It was shown that Guchangzhixie's anti-inflammatory effects come from reducing inflammatory mediator production and macrophage polarisation, which promotes mucosal repair.

Conclusion:

One review could not possibly cover all the notable recent developments in internal medicine, but those about the treatment of cardiovascular diseases, diabetes, and inflammation symptoms have attracted particular attention. The future of the internal medicine field is being shaped as old positions fade and new ones emerge. Hospitals and healthcare organizations will continue to adopt new technology to deliver patient-centered care in a smarter, quicker, and more economical manner. Failure to do so puts providers in danger of fading into obscurity.

REFERENCES:

1. By Sridhar Nadamuni, Debra Fulghum Bruce, Ph.D. (Editor), Medically Reviewed by Robert Jasmer, MD, Last Updated: May. 25, 2021
2. Centers for Disease Control and Prevention (CDC) (1999). A decline in deaths from heart disease and stroke--United States, 1900-1999. MMWR. Morb. Mortal. Wkly. Rep. 48, 649–656.
3. Mensah, G. A., Wei, G. S., Sorlie, P. D., Fine, L. J., Rosenberg, Y., Kaufmann, P. G., et al. (2017). The decline in cardiovascular mortality: Possible causes and implications. Circ. Res. 120, 366–380.
4. Nowbar, A. N., Gitto, M., Howard, J. P., Francis, D. P., and Al-Lamee, R. (2019). Mortality from ischemic heart disease. Circ. Cardiovasc. Qual. Outcomes 12, e005375.
5. Arnett, D. K., Blumenthal, R. S., Albert, M. A., Buroker, A. B., Goldberger, Z. D., Hahn, E. J., et al. (2019). 2019 ACC/AHA guideline on the primary prevention of Cardiovascular Disease: A report of the American college of cardiology/American heart association Task Force on Clinical practice guidelines. J. Am. Coll. Cardiol. 74, e177–e232.
6. Roth, G. A., Mensah, G. A., Johnson, C. O., Addolorato, G., Ammirati, E., Baddour, L. M., et al. (2020). Global burden of cardiovascular diseases and risk factors, 1990-2019: Update from the GBD 2019 study. J. Am. Coll. Cardiol. 76, 2982–3021.
7. Sinatra, J. A., and Huston, S. L. (2020). Stall in heart disease death rates, evidence from Maine, 1999-2017. Prev. Chronic Dis. 17, E86.
8. Charles, C. Hong. (2022). The grand challenge of discovering new cardiovascular drugs. Front. Drug. Discov. 2:1027401.
9. Sipahi, I., Debanne, SM., Rowland, D. Y. (2010). Angiotensin-receptor blockade and risk of cancer: Meta-analysis of randomized controlled trials. Lancet Oncol. 11, 627-36.
10. Jones, P. H., Bays, H. E., Davidson, M. H. (2008). Evaluation of a new formulation of fenofibric acid, ABT-335, co-administered with statins: Study design and rationale of phase III clinical programme. Clin Drug Investig. 28, 625-34.
11. Bui, Q.T., Wilensky, R. L. (2010). Darapladib. Expert Opin Investig Drugs. 19, 161-8.
12. Wiviott, S. D., Braunwald, E., McCabe, C. H. (2007). TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 357, 2001-15.

13. Kush, D., Hu, D. Y., Ye, P. (2009). Flushing profile of extended-release niacin/laropiprant at the initiation of therapy in Asian lipid clinic patients. Cardiology. 114, 192-8.
14. Shah, S., Ceska, R., Gil-Extremera, B. (2010). Efficacy and safety of extended-release niacin/laropiprant plus statin vs. doubling the dose of statin in patients with primary hypercholesterolemia or mixed dyslipidemia. Int J Clin Pract. 64, 727-38.
15. Davy, J. M., Herold, M., Hoglund, C. (2008). ERATO Study Investigators. Dronedarone for the control of ventricular rate in permanent atrial fibrillation: The Efficacy and safety of dRonedArone for the control of ventricular rate during atrial fibrillation (ERATO) study. Am Heart J. 156:527.e1-9.
16. Kiesman, W. F., Elzein, E., Zablocki, J. (2009). A1 adenosine receptor antagonists, agonists, and allosteric enhancers. Handb Exp Pharmacol. 193, 25-58.
17. Torre-Amione, G., Bourge, R. C., Colucci, W. S. (2007). A study to assess the effects of a broad-spectrum immune modulatory therapy on mortality and morbidity in patients with chronic heart failure: The ACCLAIM trial rationale and design. Can J Cardiol. 23, 369-76.
18. Stern, C. S., Lebowitz, J. (2010). Latest drug developments in the field of cardiovascular disease. Int J Angiol19(3):e100-e105.
19. McMurray, J. J. V., Solomon, S. D., Inzucchi, S. E., Kober, L., Kosiborod, M. N., Martinez, F. A., et al. (2019). Dapagliflozin in patients with heart failure and reduced ejection fraction. N. Engl. J. Med. 381, 1995–2008.
20. Nassif, M. E., Windsor, S. L., Borlaug, B. A., Kitzman, D. W., Shah, S. J., Tang, F., et al. (2021). The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: A multicenter randomized trial. Nat. Med. 27, 1954–1960.
21. Maurer, M. S., Schwartz, J. H., Gundapaneni, B., Elliott, P. M., Merlini, G., Waddington-Cruz, M., et al. (2018). Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N. Engl. J. Med. 379, 1007–1016.
22. Mann, D. L. (2021). Heart failure 2021: A compendium of translational success. Circ. Res. 128, 1419–1420.
23. Sweeney, M., Corden, B., and Cook, S. A. (2020). Targeting cardiac fibrosis in heart failure with preserved ejection fraction: Mirage or miracle? EMBO Mol. Med. 12, e10865.

24. Hahn, V. S., Knutsdottir, H., Luo, X., Bedi, K., Margulies, K. B., Haldar, S. M., et al. (2021). Myocardial gene expression signatures in human heart failure with preserved ejection fraction. Circulation 143, 120–134.
25. Bulawa, C. E., Connelly, S., Devit, M., Wang, L., Weigel, C., Fleming, J. A., et al. (2012). Tafamidis, a potent and selective transthyretin kinetic stabilizer that inhibits the amyloid cascade. Proc. Natl. Acad. Sci. U. S. A. 109, 9629–9634.
26. Chandrashekar, P., Alhuneafat, L., Mannello, M., Al-Rashdan, L., Kim, M. M., Dungu, J., et al. (2021). Prevalence and outcomes of p.Val142Ile TTR amyloidosis cardiomyopathy: A systematic review. Circ. Genom. Precis. Med. 14, e003356.
27. Schneider, J. W., Oommen, S., Qureshi, M. Y., Goetsch, S. C., Pease, D. R., Sundsbak, R. S., et al. (2020). Dysregulated ribonucleoprotein granules promote cardiomyopathy in RBM20 gene-edited pigs. Nat. Med. 26, 1788–1800.
28. Chai, R. J., Werner, H., Li, P. Y., Lee, Y. L., Nyein, K. T., Solovei, I., et al. (2021). Disrupting the LINC complex by AAV-mediated gene transduction prevents the progression of Lamin-induced cardiomyopathy. Nat. Commun. 12, 4722.
29. Martin, T. G., Myers, V. D., Dubey, P., Dubey, S., Perez, E., Moravec, C. S., et al. (2021). Cardiomyocyte contractile impairment in heart failure results from reduced BAG3-mediated sarcomeric protein turnover. Nat. Commun. 12, 2942.
30. Cook, D., Brown, D., Alexander, R., March, R., Morgan, P., Satterthwaite, G., et al. (2014). Lessons learned from the fate of AstraZeneca's drug pipeline: A five-dimensional framework. Nat. Rev. Drug Discov. 13, 419–431.
31. Nguyen, A. H., Marsh, P., Schmiess-Heine, L., Burke, P. J., Lee, A., Lee, J., et al. (2019). Cardiac tissue engineering: State-of-the-art methods and outlook. J. Biol. Eng. 13, 57.
32. King, E. A., Wade Davis, J., and Degner, J. F. (2019). Are drug targets with genetic support twice as likely to be approved? Revised estimates of the impact of genetic support for drug mechanisms on the probability of drug approval. PLoS Genet. 15, e1008489.
33. Challa, A. P., Lavieri, R. R., Lewis, J. T., Zaleski, N. M., Shirey-Rice, J. K., Harris, P. A., et al. (2019). Systematically prioritizing candidates in genome-based drug repurposing. Assay. Drug Dev. Technol. 17, 352–363.
34. Rurik, J. G., Tombacz, I., Yadegari, A., Mendez Fernandez, P. O., Shewale, S. V., Li, L., et al. (2022). CAR T cells are produced in vivo to treat cardiac injury. Science 375, 91–96.

35. Musunuru, K. (2022). Moving toward genome-editing therapies for cardiovascular diseases. J. Clin. Invest. 132, e148555.
36. Cheng, Q., Wei, T., Farbiak, L., Johnson, L. T., Dilliard, S. A., and Siegwart, D. J. (2020). Selective organ targeting (SORT) nanoparticles for tissue-specific mRNA delivery and CRISPR–Cas gene editing. Nat. Nanotechnol. 15, 313–320.
37. Quianzon, C. C., and Cheikh, I. E. (2012). History of Current Non-insulin Medications for Diabetes Mellitus. J. Community Hosp. Intern. Med. Perspect. 2 (2).
38. Kharroubi, A. T., and Darwish, H. M. (2015). Diabetes Mellitus: The Epidemic of the Century. World J. Diabetes 6 (6), 850–867.
39. International Diabetes Federation (2021). IDF Diabetes Atlas. 10th edn. Brussels, Belgium. Available at: https://www.diabetesatlas.org (Accessed December 2, 2021)
40. R. DeFronzo. (2009). From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus, Diabetes 58, 773–795.
41. Ndisang, J. F., Vannacci, A., and Rastogi, S. (2017). Insulin Resistance, Type 1 and Type 2 Diabetes, and Related Complications 2017. J. Diabetes Res. 2017, 1478294.
42. Chawla, A., Chawla, R., and Jaggi, S. (2016). Microvascular and Macrovascular Complications in Diabetes Mellitus: Distinct or Continuum? Indian J. Endocrinol. Metab. 20 (4), 546–551.
43. Dahlén, A. D., Dashi, G., Maslov, I., Attwood, M. M., Jonsson, J., Trukhan, V., and Schiöth, H. B. (2022) Trends in Antidiabetic Drug Discovery: FDA Approved Drugs, New Drugs in Clinical Trials and Global Sales. Front. Pharmacol. 12:807548.
44. Chaudhury, A., Duvoor, C., Reddy Dendi, V. S., Kraleti, S., Chada, A., Ravilla, R., et al. (2017). Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management. Front. Endocrinol. (Lausanne) 8, 6.
45. Holst, J. (2019). Which to choose, an oral or an injectable glucagon-like peptide-1 receptor agonist? Lancet 394, 4–6.
46. Lebovitz, H. E. (2011). Insulin: Potential Negative Consequences of Early Routine Use in Patients with Type 2 Diabetes. Diabetes Care 34 Suppl 2 (Suppl. 2), S225–S230.
47. Seino, S., Sugawara, K., Yokoi, N., Takahashi, H. (2017). β-Cell signalling and insulin secretagogues: A path for improved diabetes therapy, Diabetes. Obes. Metab. 19, 22–29.
48. Glimepiride (2021). Glimepiride/metformin - Laboratorios Silanes - AdisInsight. Available at: https://adisinsight.springer.com/drugs/800045426.

49. Wang, Y., An, H., Liu, T., Qin, C., Sesaki, H., Guo, S., et al. (2019). Metformin Improves Mitochondrial Respiratory Activity through Activation of AMPK. Cell Rep 29 (6), 1511–e5.
50. Oki, T., Matsui, T., and Osajima, Y. (1999). Inhibitory Effect of Alpha-Glucosidase Inhibitors Varies According to its Origin. J. Agric. Food Chem. 47 (2), 550–553.
51. Lebovitz, H. E. (2019). Thiazolidinediones: the Forgotten Diabetes Medications. Curr. Diab Rep. 19 (12), 151.
52. Yamamoto-Honda, R., Takahashi, Y., Mori, Y., Yamashita, S., Yoshida, Y., Kawazu, S., et al. (2018). Changes in Antidiabetic Drug Prescription and Glycemic Control Trends in Elderly Patients with Type 2 Diabetes Mellitus from 2005- 2013: An Analysis of the National Center Diabetes Database (NCDD-03). Intern. Med. 57 (9), 1229–1240.
53. O'Brien, M. J., Karam, S. L., Wallia, A., Kang, R. H., Cooper, A. J., Lancki, N., et al. (2018). Association of Second-Line Antidiabetic Medications with Cardiovascular Events Among Insured Adults with Type 2 Diabetes. JAMA Netw. Open 1 (8), e186125.
54. H. Rang, M. Dale, J. Ritter, P. Moore, Pharmacology, ninth ed., 2003, pp. 408–419. Churchill Livingstone, Edinburg.
55. Hoogwerf, B. (2008) Pramlintide, the synthetic analogue of amylin: physiology, pathophysiology, and effects on glycemic control, body weight, and selected biomarkers of vascular risk, Vasc. Health. Risk. Manag. 4, 355–362.
56. Monnier, L., Lapinski, H., Colette, C. (2003) Contributions of Fasting and Postprandial Plasma Glucose Increments to the Overall Diurnal Hyperglycemia of Type 2 Diabetic Patients: Variations with increasing levels of HbA1c, Diabetes. Care. 26, 881–885.
57. Cahn, A., Cefalu, W. (2016). Clinical Considerations for Use of Initial Combination Therapy in Type 2 Diabetes, Diabetes. Care. 39, S137–S145.
58. Rai, V., Mishra, N., Agrawal, A., Jain, S., Yadav, N. (2016). Novel drug delivery system: an immense hope for diabetics, Drug. Deliv. 23, 2371–2390.
59. DiSanto, R., Subramanian, V., Gu, Z. (2015). Recent advances in nanotechnology for diabetes treatment, Wiley. Interdiscip. Rev. Nanomed. Nanobiotechnol. 7, 548–564.
60. Santwana, P., Amit Kumar, N., Anindita, B. (2020). Type II diabetes mellitus: a review on recent drug-based therapeutics. Biomedicine & Pharmacotherapy. 110708.

61. Brown, E., Wilding, J. P. H., Barber, T. M., Alam, U., and Cuthbertson, D. J. (2019). Weight Loss Variability with SGLT2 Inhibitors and GLP-1 Receptor Agonists in Type 2 Diabetes Mellitus and Obesity: Mechanistic Possibilities. Obes. Rev. 20 (6), 816–828.
62. Tentolouris, A., Vlachakis, P., Tzeravini, E., Eleftheriadou, I., Tentolouris, N. (2019). SGLT2 Inhibitors: A Review of Their Antidiabetic and Cardioprotective Effects, Int. J. Environ. Res. Public. Health. 16, 2965–2991.
63. Ramzan, S., Timmins, P., Hasan, S. S., and Babar, Z. U. (2019). Trends in Global Prescribing of Antidiabetic Medicines in Primary Care: A Systematic Review of Literature between 2000-2018. Prim. Care Diabetes 13 (5), 409–421.
64. Ritter, K., Buning, C., Halland, N., Pöverlein, C., and Schwink, L. (2016). G ProteinCoupled Receptor 119 (GPR119) Agonists for the Treatment of Diabetes: Recent Progress and Prevailing Challenges. J. Med. Chem. 59 (8), 3579–3592.
65. Mathiesen, D. S., Bagger, J. I., Bergmann, N. C., Lund, A., Christensen, M. B., Vilsbøll, T., et al. (2019). The Effects of Dual GLP-1/GIP Receptor Agonism on Glucagon Secretion-A Review. Int. J. Mol. Sci. 20 (17).
66. Saponaro, F., Sestito, S., Runfola, M., Rapposelli, S., and Chiellini, G. (2020). Selective Thyroid Hormone Receptor-Beta (TRβ) Agonists: New Perspectives for the Treatment of Metabolic and Neurodegenerative Disorders. Front. Med. (Lausanne) 7 (7), 331.
67. Hong, D. J., Jung, S. H., Kim, J., Jung, D., Ahn, Y. G., Suh, K. H., et al. (2020). Synthesis and Biological Evaluation of Novel Thienopyrimidine Derivatives as Diacylglycerol Acyltransferase 1 (DGAT-1) Inhibitors. J. Enzyme Inhib. Med. Chem. 35 (1), 227–234.
68. Lau, J., Rousseau, J., Kwon, D., Bénard, F., and Lin, K. S. (2020). A Systematic Review of Molecular Imaging Agents Targeting Bradykinin B1 and B2 Receptors. Pharmaceuticals (Basel) 13 (8).
69. Zhao, W., Yang, S., Chen, J., Zhao, J., and Dong, J. (2018). Forced Overexpression of FBP1 Inhibits Proliferation and Metastasis in Cholangiocarcinoma Cells via Wnt/β-Catenin Pathway. Life Sci. 210, 224–234.
70. Wentworth, J. M., and Colman, P. G.Zafgen Study Group (2020). The Methionine Aminopeptidase 2 Inhibitor ZGN-1061 Improves Glucose Control and Weight in Overweight and Obese Individuals with Type 2 Diabetes: A Randomized, Placebo-Controlled Trial. Diabetes Obes. Metab. 22 (7), 1215–1219.

71. Ahmad, Z., Banerjee, P., Hamon, S., Chan, K. C., Bouzelmat, A., Sasiela, W. J., et al. (2019). Inhibition of Angiopoietin-like Protein 3 with a Monoclonal Antibody Reduces Triglycerides in Hypertriglyceridemia. Circulation 140 (6), 470–486.
72. Toulis, K. A., Nirantharakumar, K., Pourzitaki, C., Barnett, A. H., and Tahrani, A. A. (2020). Glucokinase Activators for Type 2 Diabetes: Challenges and Future Developments. Drugs 80 (5), 467–475.
73. Steinberg, G. R., and Carling, D. (2019). AMP-activated Protein Kinase: the Current Landscape for Drug Development. Nat. Rev. Drug Discov. 18 (7), 527–551.
74. Khitan, Z., and Kim, D. H. (2013). Fructose: a Key Factor in the Development of Metabolic Syndrome and Hypertension. J. Nutr. Metab. 2013, 682673.
75. Ochman, A. R., Lipinski, C. A., Handler, J. A., Reaume, A. G., and Saporito, M. S. (2012). The Lyn Kinase Activator MLR-1023 Is a Novel Insulin Receptor Potentiator that Elicits a Rapid-Onset and Durable Improvement in Glucose Homeostasis in Animal Models of Type 2 Diabetes. J. Pharmacol. Exp. Ther. 342 (1), 23–32.
76. Harrison, S. A., Alkhouri, N., Davison, B. A., Sanyal, A., Edwards, C., Colca, J. R. (2020). Insulin Sensitizer MSDC-0602K in Non-alcoholic Steatohepatitis: A Randomized, Double-Blind, Placebo-Controlled Phase IIb Study. J. Hepatol. 72 (4), 613–626.
77. Vos, T., Lim, S., Abbafati, C., Abbas, K., Abbasi, M., Abbasifard, M. (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: A systematic analysis for the global burden of disease study 2019. Lancet 396, 1204–1222.
78. Shady, B., Kentaro, O., and Mahmoud, (2022). K. Drug Discovery of New Anti-Inflammatory Compounds by Targeting Cyclooxygenases. Pharmaceuticals. 15, 282.
79. Groesch, S., Niederberger, E., Geisslinger, (2017). G. Investigational drugs targeting the prostaglandin E2 signaling pathway for the treatment of inflammatory pain. Expert Opin. Investig. Drugs. 26, 51–61.
80. Kandeel, M., Al-Nazawi, M. (2020). Virtual screening and repurposing of FDA approved drugs against COVID-19 main protease. Life Sci. 251, 117627.
81. Kandeel, M., Yamamoto, M., Park, B.K., Al-Taher, A., Watanabe, A., Gohda, J., Kawaguchi, Y., Oh-Hashi, K., Kwon, H.-J., Inoue, J. (2021). Discovery of New Potent anti-MERS CoV Fusion Inhibitors. Front. Pharmacol. 12, 1241.

82. Alma, M., Valentina, C., Vincenzo, C. (2020). Recent efforts in drug discovery on vascular inflammation and consequent atherosclerosis. Expert Opinion on Drug Discovery.
83. Charles, A., Dinarello. (2010). Anti-inflammatory Agents: Present and Future. Cell. 140(6), 935–950.
84. Jin, Y., Arita, M., Zhang, Q., Saban, D. R., Chauhan, S. K., Chiang, N., Serhan, C. N., Dana, R. (2009). Anti-angiogenesis effect of the novel anti-inflammatory and pro-resolving lipid mediators. Invest. Ophthalmol. Vis. Sci. 50, 4743–4752
85. Endres, S., Ghorbani, R., Kelley, V. E., Georgilis, K., Lonnemann, G., van der Meer, J. W., Cannon, J. G., Rogers, T.S., Klempner, M.S., Weber, P. C. (1989). The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. N. Engl. J. Med. 320, 265–271.
86. Sampaio, E. P., Sarno, E. N., Galilly, R., Cohn, Z. A., Kaplan, G. (1991). Thalidomide selectively inhibits tumor necrosis factor-alpha production by stimulated human monocytes. J. Exp. Med. 173, 699– 703
87. Hilgendorff, A., Muth, H., Parviz, B., Staubitz, A., Haberbosch, W., Tillmanns, H., Holschermann, H. (2003). Statins differ in their ability to block NF-kappaB activation in human blood monocytes. Int. J. Clin. Pharmacol. Ther. 41, 397–401.
88. Esmon, C. T. (2006). Inflammation and the activated protein C anticoagulant pathway. Semin. Thromb. Hemost. 32, 49–60
89. Nold, M. F., Nold-Petry, C. A., Fischer, D., Richter, B., Blaheta, R., Pfeilschifter, J., Muhl, H., Schranz, D., Veldman, A. (2007). Activated protein C down-regulates p38 mitogen-activated protein kinase and improves clinical parameters in an in-vivo model of septic shock. Thromb. Haemost. 98, 1118–1126.
90. Dasu, M. R., Park, S., Devaraj, S., Jialal, I. (2009). Pioglitazone inhibits Toll-like receptor expression and activity in human monocytes and db/db mice. Endocrinology. 150, 3457–3464