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Review

Innate immunity in cardiovascular diseases – Identification of novel molecular players and targets

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Abstract:

During the past few years unexpected developments have driven studies in the field of clinical immunology. One driver of immense impact was the outbreak of a pandemic caused by the novel virus SARS-CoV-2. Excellent recent reviews address diverse aspects of immunological research into cardiovascular diseases. Here, we specifically focus on selected studies taking advantage of advanced state-of-the-art molecular genetic methods ranging from genome-wide epi/transcriptome mapping and variant scanning to optogenetics and chemogenetics. First, we discuss emerging clinical relevance of advanced diagnostics for cardiovascular diseases - including those associated with COVID-19 - with a focus on the role of inflammation in cardiomyopathies and arrhythmias. Second, we consider newly identified immunological interactions at organ and systems level which affect cardiovascular pathogenesis. Thus, studies into immune influences arising from the intestinal system are moving towards therapeutic exploitation. Further, powerful new research tools have enabled novel insight into brain – immune system interactions at unprecedented resolution. This latter line of investigation emphasizes the strength of influence of emotional stress - acting through defined brain regions - upon viral and cardiovascular disorders. Several challenges need to be overcome before the full impact of these far-reaching new findings will hit the clinical arena. 200 words

Keywords: Immunology; innate immunity; immunogenetics; noncoding genome; tRNA biology; evolutionary genetics (list 3-10 specific to the article yet reasonably common within the subject discipline)

1. Introduction

Multiple excellent reviews have addressed diverse important aspects of immunological research into cardiovascular diseases during the past few years. In this review we specifically focus on preclinical and clinical studies which have provided unexpected insights by taking advantage of recent state-of-the-art molecular genetic and virological technologies ranging from clinical genome-wide transcriptome mapping and variant scanning to optogenetics and chemogenetics. Due to the intense worldwide efforts in these fields during the past years the present review cannot be comprehensive, but instead tries to convey an up-to-date perspective on promising developments which may shape research at the crossroads of cardiology – immunology - neurology. Whereas advanced

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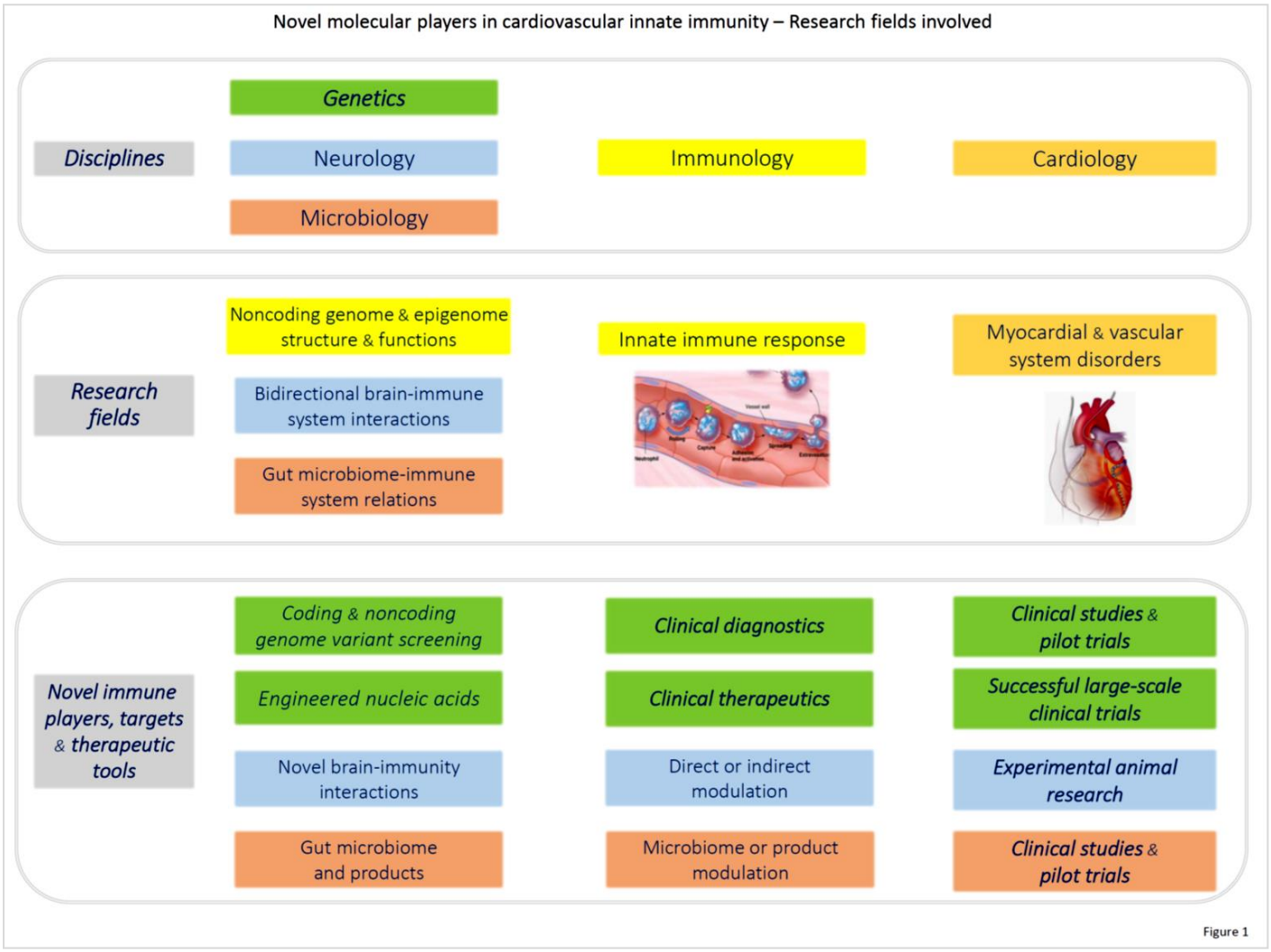
technologies are often confined to applications in basic research, we focus here on those with already proven or upcoming use in the clinical arena.

Figure 1 | At the crossroads cardiology – immunology - neurology



2. Molecular immunogenetics of cardiovascular diseases

While molecular genetic methods have been extensively employed in cardiovascular research since decades, only the rather recent advent of comprehensive and still affordable mutation/variant scanning tools ready for day-to-day clinical practice have significantly enhanced their clincal impact. As with all other topics discussed in this review, availability of practice-ready analytical tools is not simply a gradual step forward, but *the* critical threshold before widespread relevance for clinical medicine may be achieved. This degree of technological evolution may well take decades, as highlighted in recent reviews *[1, 2]* covering therapeutics based on noncoding RNAs and related nucleic acids. Once achieved, however, this defines the quantum leap from a "promising" to a "revolutionary" medical development.

2.1. Novel insights into the role of inflammation in human cardiomyopathies

Despite multiple obstacles to unequivocal detection of myocardial inflammation, it has been long known that myocardial inflammation [3-12] occurs in association with multiple types of 'genetic' [13-18] and 'non-genetic' [19, 20] cardiomyopathies. The possible therapeutic potential of immunomodulation has been addressed in this context [21-23], but this issue remains unsolved so far. Recent clinical studies employing highly advanced but clinical practice-ready genetic diagnostics [4, 24, 25] [26] have revealed significant

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direct impact of myocardial inflammation upon the induction of life-threatening arrhythmias. These studies investigated patients with well-defined genetic anomalies identified by large-scale mutation scanning. A missense variant E1295K of the sodium channel gene SCN5A was associated with recurrent ventricular fibrillation and myocardial inflammation [25]. Another study found familial recurrent myocarditis to be triggered by exercise in patients with a truncating variant of the desmoplakin gene [24]. This work illustrates the potential of advanced genetics in combination with state-of-the-art clinical myocardial diagnostics not only to improve clinical practice, but also to reveal unexpected pathogenetic processes. A third paper [4] investigating acute myocarditis associated with desmosomal gene variants (DGVs) found strong adverse impact of DGV-associated inflammation upon ventricular arrhythmogenesis and survival.

Anomalous immune activation and macrophages are involved in cardiomyopathies, but until recently were not investigated in the context of ion-channel disorders. SCN5A encodes a sodium channel α-subunit responsible for action potential initiation and conduction of electrical stimuli through the heart. SCN5A was initially assumed to be exclusively expressed in the myocardium, but recently a SCN5A splice variant was found to activate antiviral innate immune signaling. Pioneering work revealed that SCN5A modulates myelin degradation by macrophages in multiple sclerosis (MS) and that overexpression of the macrophage SCN5A variant in mice protects against murine autoimmune encephalomyelitis, an experimental MS model. Endosome-associated SCN5A variants thus emerged as novel innate immune sensors, indicating that patients so far classified as ‘pure‘ myocardial ion-channel disease cases may carry independent ‘immunologic‘ risk through hitherto-neglected anomalous function of their mutant ion channels.

Unfortunately, there are multiple obstacles to unequivocal clinical recognition of myocardial inflammation as a precipitating factor for life-threatening arrhythmias or the development of terminal heart failure. Even in narrowly focused patient cohorts for whom genetic predisposition is suspected e.g. by family history or direct detection of pathogenic variants [4, 24, 25], recognition of myocardial inflammation requires in-depth diagnostic work-up (cardiac MRI, EMB, PET-CT) which may be unfeasible in many cases. Many of these patients may carry ICDs, often preventing reliable cardiac MRI diagnostics, and diagnostic accuracy of EMB may be limited by sampling error. Even *post mortem* examination would be unable to detect transient bouts of inflammation during the sometimes decades-long course of cardiomyopathies, unless inflammation persists until the time of death. It is most likely that only a minor fraction of all inflammation-triggered arrhythmic events or critical heart failure progression will be clinically detected, generating a blind spot regarding the potential value of anti-inflammatory treatments in these contexts. It is important to note that therapeutic potential of immunosuppression does not rely on the presence of *genetic* SCN5A variants, because inflammation *per se* may cause dysfunction of genetically normal SCN5A channels. Thus, a rather large number of patients might possibly benefit from immunmodulation as observed in first index cases [4, 24, 25].

It appears recommendable to further evaluate the hypothesis of independent immunologic risk in major cohorts of patients carrying SCN5A or desmosomal gene variants. Conduction of such studies is challenging indeed and requires multicentric cooperation between experienced centers, but given the often young age of affected patients and possible life-saving impact the effort appears warranted. For further in-depth discussion regarding design and key problems of immunomodulating treatment trials in human cardiomyopathies we may refer the reader to a recent review [27].

2.2. Common gene variants affecting antiviral response and myocardial disease

To illustrate that not only rare genetics variants, but also rather common genetic polymorphisms may significantly influence the immune response and associated cardiovascular diseases, we briefly discuss here a number of studies into the forkhead transcription factor Foxo3 [28, 29]. Foxo3 is involved in cell cycle regulation, apoptosis, oxidative stress, angiogenesis, and immunity. The immune-modulatory function of Foxo3 in adaptive immune responses has been elucidated to some extent. Foxo3 contributes to maintenance of

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T cell tolerance and quiescence and the differentiation of regulatory T cells is regulated by the transcription factor. Moreover, Foxo3 maintains neutrophil vitality in models of neutrophil inflammation and plays an important role in cardiac hypertrophy, cardiomyocyte survival, cell differentiation and remodelling, and provokes resistance to oxidative stress in cardiac fibroblasts.

Remarkably, single nucleotide polymorphisms (SNPs) of the *FOXO3* gene are associated with longevity, and low prevalence of cardiovascular diseases in diverse populations. These impressive initial studies have triggered a broad spectrum of research into translational aspects of Foxo3. Regarding the immune response, a human SNP in *FOXO3* is associated with increased risk for malaria, but a milder course in patients with autoimmune disease. Further, combined experimental and clinical work revealed that Foxo3 negatively regulates natural killer (NK) cell function and viral clearance in myocarditis [30]. Virus-triggered myocarditis is associated with high mortality and an important cause for the need for heart transplantation. It is not well understood how the immune system recognizes and controls coxsackievirus B3 (CVB3) infections [31, 32], but murine studies suggest that NK cells play a critical role in viral clearance and host survival. Consistent with this, a paper by Loebel et al. [30] found an association of the FOXO3 SNP rs12212067 with human NK cell function and clinical outcome in patients with virus-positive inflammatory cardiomyopathy, corroborating evidence from animal studies.

2.3. Novel immune players from the human non-coding genome

Similar to the above considered evolution of molecular genetic diagnostics, decades passed from the discovery that about 99% of the human genome do not encode proteins, but instead generate a broad spectrum of non-coding RNAs (ncRNAs) many of whom are involved in the immune response [33-62], until finally successful clinical exploitation of ncRNAs and of novel drugs developed using them as blueprints was achieved [1, 2]. Across the entire spectrum of medical disciplines it has been ascertained that the non-coding genome plays a key role in genetic programming and gene regulation during development as well as in health and disease.

Within the cardiovascular field, multiple early experimental studies [63-72] showed that certain ncRNAs (miRNAs) are regulators of cardiovascular pathogenesis in animal models. This of course immediately suggested they might have potential to improve diagnostics and could possibly even be developed into novel therapeutics. The road to in-depth understanding of the molecular workings of at least a few of the numerous ncRNA classes, and beyond that the development of highly sophisticated bioengineered nucleic acid drugs [63, 73-83] which are critically required to render them safe and efficacious for clinical applications, took two decades counting from early experimental work to the first clinically successful trials. Particularly advanced is the development of RNA interference (RNAi) drugs which use recently discovered pathways of endogenous short interfering RNAs and are becoming versatile tools for efficient silencing of protein expression. Pioneering clinical studies include RNAi drugs targeting liver synthesis of PCSK9 resulting in highly significant lowering of LDL cholesterol or targeting liver transthyretin (TTR) synthesis for treatment of cardiac TTR amyloidosis. Further novel drugs mimicking actions of endogenous ncRNAs may arise from exploitation of molecular interactions not accessible to conventional pharmacology. For a more in-depth coverage of the enormously challenging bioengineering, safety and regulatory hurdles to be overcome towards clinical therapy during the past decades we may refer the reader to comprehensive recent reviews [1, 2, 84].

Whereas a series of ground-breaking clinical trials [78, 82, 83, 85-105, 106] has provided definite evidence of therapeutic potential of RNA interference and antisense drugs for cardiovascular disorders, the inclusion of ncRNA profiling into the clinical diagnostic process and prognosis assessment is less conclusive so far. Still, it may significantly contribute to optimize patient care in selected complex or otherwise equivocal cases. Thus, rapid diagnosis of life-threatening idiopathic giant cell myocarditis and cardiac sarcoidosis is significantly improved by myocardial gene expression profiling [107]. In another

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disease with highly variable clinical course and outcome, human enterovirus cardiomyopathy, differential cardiac microRNA profiling helps to predict the clinical course and the need for antiviral therapy [108]. As another example, circulating exosomal microRNAs predict functional recovery after interventional repair of severe mitral regurgitation [109]. Of course it needs to be emphasized that the definitive establishment of predictive or differential diagnostic expression profiles requires confirmation by several independent clinical studies. This has been rarely achieved so far [1, 2], but the available evidence does suggest significant clinical potential for selected clinical settings [1, 2, 110-113].

2.4. Continuously emerging new levels of complexity of the human genome

The more recent history of human genetics is characterized by several revolutionary discoveries [1, 2]. After the very important sequencing of the entire genome of humans (and meanwhile of a vast number of other species) it became apparent that 99% of the ascertained sequence does not encode proteins. This already suggested that this huge noncoding fraction plays truly critical and so far only very incompletely understood roles for the proper functioning and environmental adaptations of individuals, but for evolution itself through advanced species. Furthermore, prenatal influences as well as environmental factors are known to alter the genome through epigenetic mechanisms or imprinting. An individual's genome is on the one hand rather fixed at DNA level (except somatic mutations/recombinations), but it's functional status may still be significantly and durably altered by the environment via epigenetics. One may safely assume these complexities of evolutionary advanced genomes convey a distinct survival benefit, otherwise they would not have become commonplace in higher species. In the following we consider further data suggesting that certain genomic regions give rise to multiple immunomodulatory transcripts interacting with each other in a way reminiscent of integrated electronic circuits to generate an optimized responses to complex inputs. All hitherto known functional levels of the genome – from DNA editing [82, 98, 99] to epigenome-targeting "epi-drugs" [100, 114-120] – have already been investigated with regard to possible therapeutic potential.

To illustrate the multi-level functional integration of major strands of the human genome, we invoke the evolutionary conserved *NEAT1-MALAT1* cluster encountering high interest in both cardiovascular medicine and oncology. In the cardiovascular field, suppression of lncRNA NEAT1 was observed in circulating immune cells of post-myocardial infarction (MI) patients. Mice lacking the lncRNAs *NEAT1 or MALAT1* displayed immune disturbances affecting monocyte-macrophage as well as T cell differentiation and rendering the immune system highly vulnerable to stress stimuli, thereby promoting the development of atherosclerosis. Uncontrolled inflammation is also a key driver of multiple other diseases. The human *NEAT1-MALAT1* gene cluster generates large noncoding transcripts remaining nuclear, while tRNA-like transcripts (mascRNA, menRNA), enzymatically generated from these precursors, translocate to the cytosol. *NEAT1*$^{-/-}$ *and MALAT1*$^{-/-}$ mice display massive atherosclerosis and vascular inflammation [121-124]. A recent study found that these tRNA-like molecules are critical components of innate immunity. They appear as prototypes of a new class of noncoding RNAs distinct from others (miRNAs, siRNAs) by biosynthetic pathway and intracellular kinetics. CRISPR-generated human ΔmascRNA and ΔmenRNA monocytes/macrophages display defective innate immune sensing, loss of cytokine control, imbalance of growth/angiogenic factor expression impacting upon angiogenesis, and altered cell-cell interaction systems. Antiviral response, foam cell formation/oxLDL uptake, and M1/M2 polarization are defective in ΔmascRNA and ΔmenRNA macrophages, defining the tRNA-like molecules' first described biological functions [125].. This study revealed that menRNA and mascRNA represent novel components of innate immunity arising from the noncoding genome. Their *NEAT1-MALAT1* region of origin appears as archetype of a functionally highly integrated RNA processing system [125].

Two other recent studies illustrate the power of state-of-the-art genetics to reveal fundamentally new insights into immune system evolution [126] and large-scale human

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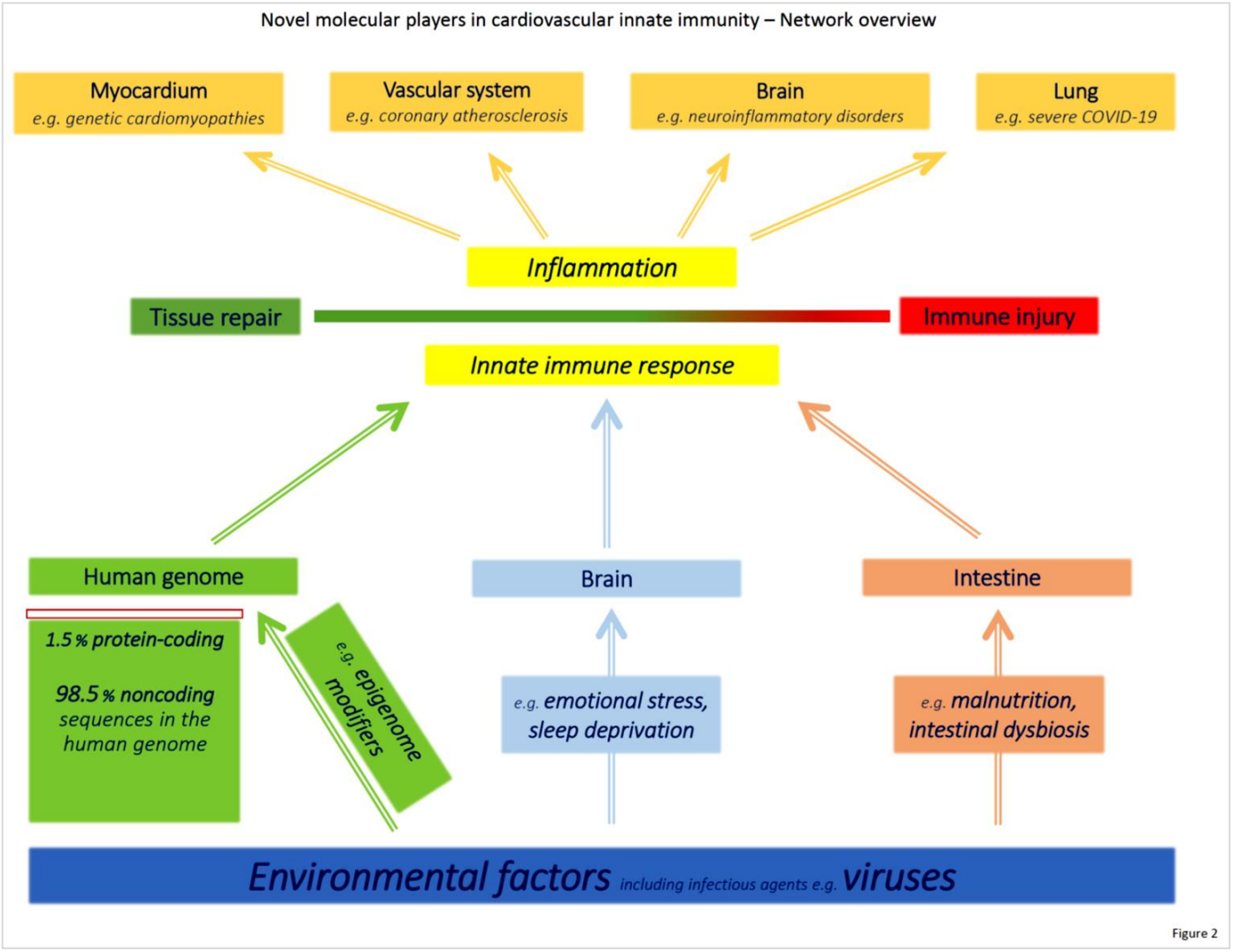
evolution in general [127]. Thus, a protective HLA extended haplotype was found to outweigh the major COVID-19 risk factor inherited from Neanderthals in the Sardinian population [126]. Another large study [128] conducted multilocus genotyping of SARS-CoV-2 genomes sampled globally and found evidence the majority of SARS-CoV-2 infections in 2020 and 2021 caused by genetically distinct variants that likely adapted to local populations. For further information on novel insights into genome structure and function we may refer the reader to a series of recent landmark papers and websites [129-145].

Beyond the developments as reviewed in section 2.3, a further level of complexity - *i.e.* the human epigenome and its life-time dynamics in health and cardiovascular disease [84, 146-155] – emerged as holding promise for possible therapeutic exploitation [114-120, 156, 157]. At the present time, however, the impact of epigenetic drugs upon clinical medicine is still limited as compared to the nucleic acid drugs discussed above.

Figure 2 | New levels of complexity of the human genome



3. Current expansion of virological research in the cardiovascular field

3.1 Impact of viral infections upon the cardiovascular system

Infection of the myocardium with cardiotropic viruses is one of the main causes of myocarditis and acute and chronic inflammatory cardiomyopathy (DCMi). However, viral myocarditis and subsequent dilated cardiomyopathy is still a challenging disease to diagnose and to treat and is therefore a significant public health issue globally [158]. Advances in clinical phenotyping and thorough molecular genetic analysis of intramyocardial viruses and their activation status have incrementally improved our understanding

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of molecular pathogenesis and pathophysiology of viral infections of the heart muscle. To date, several cardiotropic viruses have been implicated as causes of myocarditis and DCMi. These include, among others, classical cardiotropic enteroviruses (Coxsackieviruses B) [31, 159], the most commonly detected parvovirus B19 [160], human herpes virus 6 [161, 162], and hepatitis C virus (HCV) [163, 164]. Entirely unwelcome newcomer is the respiratory virus which has triggered the worst pandemic since a century, SARS-CoV-2, whose involvement and impact in viral cardiovascular disease is under scrutiny [165-170] . Despite extensive research into the pathomechanisms of viral infections of the cardiovascular system, our knowledge regarding their treatment and management is still incomplete. Recent reviews aimed to explore and summarize the current knowledge and available evidence on viral infections of the heart, focused on pathophysiology, diagnostics, clinical relevance and cardiovascular consequences, and current and novel treatment strategies [158].

Prophylaxis and vaccination: Whereas conventional antiviral vaccine development methods have proven efficient against SARS-CoV-2, the most recent virus inducing the COVID 19 pandemic, novel RNA-based vaccines have yielded exceptionally good results against this pathogen. The revolutionary method successfully used to develop the BioNTecVC and ModernaVC vaccine was never before employed at scale, and indeed the RNA modification/stabilization/purification methods as well as the associated nanoparticle delivery tools are of recent origin. Importantly, as emphasized by the authors of the landmark paper reporting the results of the BioNTecVC vaccine trial, development of the vaccination RNA sequence started immediately after publication of the novel virus genome sequence, which was derived soon after the recognition of COVID-19 as a new disease entity. Speed of development and adaptability to entirely new or variant viruses, which unfortunately are most likely to emerge in the future, bring significant advantages lasting beyond the current pandemic.

Need for highly versatile antiviral tools: The current pandemic, originating from transmission of a mutated animal virus to men, has heightened concerns and awareness that amongst the vast number of animal viruses others may cross the species barrier to humans. Therefore, foresighted expansion of our antiviral arsenal appears warranted. Fortunately, novel therapeutic approaches as reviewed in section 2.3 offer high versatility enabling rapid adaption to essentially any coding or non-coding, viral or host cell, molecular target [171-179]. Further, their large-scale production will follow similar (*i.e.* RNA, DNA, and XNA) synthetic pathways, enabling massive up-scaling of therapeutics production if required.

Advanced molecular virological tools: While several human-pathogenic cardiotropic viruses are identified, there is good reason to believe that traditional molecular virological tools (*e.g.* PCR, RT-PCR) will fail to recognize novel viruses with any of those currently in focus. Thus, the etiology of giant cell myocarditis (GCM), most fulminant and life-threatening of the inflammatory cardiomyopathies, is unknown. GCM presents with extensive myocardial inflammation that is only responding to high-dose immunosuppression. GCM has been associated with other autoimmune diseases, suggesting a relevant autoimmune component in its pathogenesis. However, the phenomenon of giant cells has been observed during viral infections such as herpes, suggesting a contribution of viral pathogens. In a recent paper, a study of plasma, peripheral blood mononuclear cells, endomyocardial biopsies (EMBs), and cardiac tissue samples from explanted heart of patients with GCM and other subtypes of myocarditis, *Virome Capture Sequencing for Vertebrate Viruses (VirCapSeq-VERT)* was employed, a novel method that simultaneously screens for all known vertebrate viruses with sensitivity similar to real-time PCR [180, 181]. The entire field of basic and clinical virology took great advantage from broad application of novel technologies and large – sometimes global - research consortia [182-184]. Within the cardiovascular field, extended use of these novel, more comprehensive virological tools may well lead to important insights into the pathogenesis of long-known but still etiologically enigmatic human diseases (cardiac sarcoidosis, eosinophilic cardiomyopathy, GCM and others.)

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3.2 *The human genetic architecture of SARS-CoV-2*

The current COVID-19 pandemic, caused by infection with SARS-CoV-2, resulted in enormous health and economic burden worldwide [185-188]. One of the most remarkable features of SARS-CoV-2 infections is the extremely high variability of clinical sequelae, ranging from asymptomatic patients to life-threatening pneumonia and acute respiratory distress syndrome [158, 165-168, 189-196]. Since the rise of the COVID-19 pandemic, there has been an urgent need to identify pathophysiological characteristics leading to a severe clinical course in patients infected with SARS-CoV-2 [158].

Although established host factors correlate with disease severity (*e.g.* increasing age, male sex, higher body-mass index), these risk factors alone do not explain all of the variability in disease severity observed across individuals. Genetic factors contributing to COVID-19 susceptibility and severity may provide new biological insights into disease pathogenesis and identify mechanistic targets for therapeutic development or drug repurposing, as treating the disease remains a highly important goal despite the recent development of vaccines. A large number of genome-wide association studies (GWAS) addressing the contribution of common genetic variation to COVID-19 in different populations worldwide have provided support for the involvement of several genomic loci associated with COVID-19 severity and susceptibility [128, 179, 189-192, 197-224]. The global COVID-19 Host Genetics Initiative (COVID-19 HGI) (https://www.covid19hg.org/) [225] recently reported the results of meta-analyses of 46 studies from 19 countries for host genetic effects [192]. Smaller studies analyzed e.g. the association between COVID-19 severity and HLAs in 435 individuals from Germany (n = 135), Spain (n = 133), Switzerland (n = 20) and the United States (n = 147). This study described a biologically plausible potential association of HLA-C*04:01 with severe clinical course of COVID-19, as HLA-C*04:01 has fewer predicted binding sites for relevant SARS-CoV-2 peptides compared to other HLA alleles.

For an excellent overview and discussion of invoked loci and their clinical implications we refer the reader to van der Made *et al.* [197] who provide comprehensive tables with significant large-scale genome-wide associations in patients with severe or critical COVID-19. Importantly, they also review and discuss the reported outcomes of SARS-CoV-2 infection in patients with known inborn errors of immunity (IEI). One recent study [198] important for the assessment of GWAS emphasizes the impact of COVID-19 phenotype definitions, and revealed distinct patterns of genetic association and protective effects upon their replication analysis of 12 previously reported COVID-19 genetic associations. From a clinical practice perspective, GWAS have not identified a single gene locus with overwhelming impact upon disease course suggesting population-wide screening for high-risk individuals. On the other hand, for severely affected patients genetic screening for IEI as suggested by van der Made *et al.* [197] may reveal individual clinical insights with possible therapeutic use.

Another type of contribution of large-scale molecular genetic analyses to better understand the variable clinical expression of SARS-CoV-2 infections, and the global dynamics of virus evolution, has been published by Chan *et al.* [128]. They have described the contrasting epidemiology and population genetics of COVID-19 infections defined by multilocus genotyping of the SARS-CoV-2 genomes. Their analysis of 22,164 SARS-CoV-2 genomes sampled worldwide suggests that the majority of SARS-CoV-2 infections in 2020 and 2021 were caused by genetically distinct variants that likely adapted to local populations.

3.3 *Cardiovascular immunobiology of COVID-19 and long COVID syndromes*

With regard to cardiovascular medicine, it is desirable to know specific genetic risk factors for the development of myocarditis during COVID-19 or upon vaccination [112, 165-170, 226-232], or for development of long COVID syndromes [191, 233-239]. Fortunately, SARS-CoV-2 is rather rarely causing severe myocarditis or cardiomyopathies [165-170]. The observed effects are rather induced by secondary immune phenomena than by

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the virus itself. In individuals developing this condition, however, the molecular virological and immunological tools outlined in section 3.1 should be employed to characterize the myocardial disease, since this may enable individualized measures beyond standard heart failure and antiarrhythmic therapy.

4. Novel immune pathomechanisms at organ and systemic level

The individual response of the innate immune system to environmental (*e.g.* viral or other microbial infections) as well as to endogenous stimuli (*e.g.* tissue injury of any kind) is partially determined by genetic factors, but subject to modulation by non-genetic factors (*e.g.* stress of various types). While this has been well known for decades *[240-242]*, recent research employing novel research tools *[243-253]* has uncovered interactions between brain and immune system at unprecedented resolution. Similiarly, advanced molecular genetic methods *[182, 254-259]* contributed to elucidate mechanistic pathways linking the GIT microbiome to the systemic innate immune response with its impact upon cardiovascular *[260, 261]* and neurological diseases *[262, 263]*. Below we try to assess the clinical translational status of these research fields, focusing on therapeutic modulation of stress-induced disturbed brain - immune system interactions (section 4.1), and of the GIT microbiome and its products (section 4.2).

4.1 Brain - immune system interactions

The adverse effect of psychological stress upon various human diseases has been well known since decades *[240-242]* and several stress-induced brain – immune system interactions have been elucidated at cellular and molecular level *[241, 264]*. It is also obvious that stress reduction is highly desirable with regard to cardiovascular diseases *[265-268]*, although often difficult to achieve in everyday life or the clinical setting. Any new avenue arising from recent neuroimmune research would be most welcome, of course. Clinically, neuromodulation strategies have been evaluated to reduce inflammation and lung complications of COVID-19 patients *[269]*, and cardiovascular sequelae in posttraumatic stress disorders *[270]*. In experimental animal models other approaches have been addressed: brain control of humoral immune responses by behavioural modulation *[271]*; modulation of the gut microbiome regulating psychological stress-induced inflammation *[272, 273]*; IL-17A blockade or depletion of Th17 cell-inducing gut microbiota to reduce stress-induced vaso-occlusive episodes (VOEs) of sickle cell disease as a vascular disease model *[272]*.

Folk wisdom has long suggested that emotional stress takes a toll on health. The field of psychoneuroimmunology is now providing novel mechanistic insight into the pathways through which psychological stress and negative emotions are translated into physiological changes [242]. Neuroimmunology in general is one of the fastest-growing fields in the life sciences aiming to stepwise elucidate the highly complex interactions between nervous system and immune system at the molecular and cellular level [243, 274-276] [277]. It is long known that acute and short-term stress induce rapid and significant redistributions of immune cells among different body regions. The underlying mechanisms are under close scrutiny, as stress-induced leukocyte redistribution appears to be of fundamental importance for survival. It appears critical to direct suitable immune cells to defined target organs in response to diverse external or internal challenges, thus significantly enhancing speed and efficacy of the immune response [241].

Despite this secured general knowledge, the details of the mechanistic pathways linking stress networks in the brain to peripheral leukocytes remain poorly understood. A recent experimental study has, for the first time, demonstrated that distinct brain regions shape leukocyte distribution and function throughout the body upon different types of acute stress in mice. Employing optogenetics and chemogenetics this work revealed that motor circuits induce rapid neutrophil mobilization from the bone marrow to peripheral tissues via skeletal-muscle-derived neutrophil-attracting chemokines. Conversely, the paraventricular hypothalamus controlled monocyte and lymphocyte egress from

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secondary lymphoid organs and blood to the bone marrow through direct, cell-intrinsic glucocorticoid signaling. These stress-induced, counter-directional, population-wide leukocyte shifts were associated with altered disease susceptibility. On the one hand, acute stress changed innate immunity by reprogramming neutrophils and directing their recruitment to sites of injury. On the other hand, corticotropin-releasing hormone neuron-mediated immune cell shifts protectede against the acquisition of autoimmunity, but impaired immunity against SARS-CoV-2 and influenza infection. These data identified distinct brain regions differentially and rapidly tailoring the immune cell landscape during psychological stress, thereby calibrating the ability of the immune system to respond to physical threats [243].

A recent study in mice and humans [277] revealed that sleep exerts lasting effects on hematopoietic stem cell function and diversity. In mice, sleep fragmentation altered the hematopoietic stem and progenitor cells (HSPCs) epigenome, priming cells for exaggerated inflammatory bursts. In humans, sleep restriction altered the HSPC epigenome and activated hematopoiesis. This work provides, for the first time, mechanistic insight into the prolonged effects of sleep disruption, another well-known stress-factor.

A third neuro-immune study investigated whether brain activities may directly control adaptive immune responses in lymphoid organs [271]. It was found that splenic denervation in mice specifically compromised plasma cell formation during a T cell-dependent, but not T cell-independent, immune response. Neurons in the central nucleus of the amygdala (CeA) and the paraventricular nucleus (PVN) expressing corticotropin-releasing hormone (CRH) connected to the splenic nerve. Ablation or pharmacogenetic inhibition of these neurons reduced plasma cell formation, while pharmacogenetic activation of these neurons increased plasma cell abundance. A behaviour regimen, with mice made to stand on an elevated platform, led to activation of CeA and PVN CRH neurons and increased plasma cell formation. In immunized mice, the elevated platform regimen induces an increase in antigen-specific IgG antibodies. By identifying a specific brain-spleen neural connection autonomically enhancing humoral responses, and by demonstrating immune stimulation by behaviour modification, this experimental study revealed brain control of adaptive immunity, suggesting possible enhancement of immunocompetency by behavioural intervention.

Another study, employing retrograde tracing and chemical as well as surgical and chemogenetic manipulations, identified a sympathetic aorticorenal circuit that modulates ILC2s in gonadal fat and connects to higher-order brain areas, including the paraventricular nucleus of the hypothalamus [278]. Similar to the other work, these results identify a neuro-mesenchymal unit translating signals from long-range neuronal circuitry into adipose-resident ILC2 function, thereby modulating host metabolism and obesity.

4.2 Immune impact and therapeutic perspectives of the intestinal microbiome

The gastrointestinal tract (GIT) hosts a pool of immune cells representing 70% of the entire immune system, and the largest population of macrophages in the human body [279]. Through its local immune system, the GIT detects and responds to the local microbiome [263], but also impacts upon remote immune processes [280-295]. During the past years multiple experimental studies have revealed that the microbiome and local immune system of the GIT may modulate distant inflammation within the cardiovascular system and brain [242, 245, 262, 263, 272, 274, 278, 279, 296-302]. However, whereas experimental models incriminate disturbed gut microbiota in a number of diseases (CNS disorders, atherosclerosis), data from human studies are sparse [17, 298, 299, 303, 304]. A theoretical basis for the use of microbiota-directed therapies in these disorders has been developed, but support from stringent clinical trials is missing and clinical confirmation is not yet received.

Regarding the cardiovascular system, a recent combined experimental and clinical study identified a novel regulatory circuit that links the gut microbiota metabolite propionic acid (PA), a short-chain fatty acid, with the gut immune system to control intestinal cholesterol homeostasis. The mechanism involves PA-mediated increase in regulatory T-

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cell numbers and IL-10 levels in the intestinal microenvironment, subsequently suppressing the expression of NPC1L1, a major intestinal cholesterol transporter. In a proof-of-concept clinical study, it was demonstrated that oral supplementation of PA over the course of 8 weeks significantly reduced LDL and non-HDL cholesterol levels in hypercholesterolaemic subjects. The data suggest PA supplementation may improve cholesterol homeostasis and contribute to cardiovascular health. Another translational perspective is modulation of the gut microbiome by dietary approaches, or by prebiotics to sustainably increase the intestinal abundance of PA producing species as an "intrinsic" concept of atheroprotection [260, 261]. An experimental study in mice found that a subset of integrin β7+ gut intraepithelial T lymphocytes within the small intestine enterocyte layer modulates systemic metabolism in a manner advantageous when food is scarce, but detrimental upon consumption of high fat and sugar diets [305]. This metabolic checkpoint might be therapeutically addressed by modulation of the GIT microbiome, *e.g.* through dietary approaches or prebiotics.

Critical impact of GIT microbiota upon the host immune system had previously been discovered in mice. Murine studies are paramount for the elucidation of basic biological phenomena, but have several limitations. These include conflicting results caused by divergent microbiota, and limited translational research value. Rosshart *et al.* [306] transferred C57BL/6 embryos into wild-type mice thus creating "wildlings." These had natural microbiota and pathogens at all body sites while retaining the well-defined and tractable genetics of the parent inbred strain. The bacterial microbiome, mycobiome, and virome [254] [182, 255-259] of "wildlings" affected their immune landscape in multiple organs. Their gut microbiota outcompeted lab strain microbiota and proved resilient to environmental challenge. "Wildlings", but not the lab mice, phenocopied human immune responses in two preclinical investigations. This landmark study demonstrated that a combined natural microbiota- and pathogen-based model holds promise to enhance the reproducibility of experimental biomedical research and to improve translational success of immunological studies.

Regarding the brain, a series of important experimental studies uncovered hitherto unsuspected bidirectional relationships between gut and brain, challenging the classical view of the central nervous system as an immune-privileged site. These studies identified new specialized immune cell subtypes located to distinct anatomical sites: skull and vertebral bone marrow are myeloid cell reservoirs for meninges and CNS parenchyma [307]; the meninges contain diverse immune cells populations: macrophages, T cells, B cells [308], plasma cells producing IgA essential for defense of the central nervous system [309], and gut-licensed NK cells driving anti-inflammatory astrocytes [310]. Furthermore, host GIT microbiota constantly control maturation and function of microglia in the CNS [311-315]. They are also capable to reversibly modulate behavioral and physiological anomalies associated with neuroinflammation [306, 316-318].

5. Clinical perspectives of recent studies into novel immune mechanisms

5.1 Recognition of high genetic risk for severe COVID-19 or cardiovascular involvement

One of the most vexing feature of SARS-CoV-2 infections [319] is the extraordinary variability of clinical consequences, ranging from asymptomatic to pneumonia and acute respiratory distress syndrome. Of course, variable clinical course is common in diverse viral diseases, but rarely to such an extent as observed with SARS-CoV-2. Established host factors such as high age or body-mass index or concomitant diseases correlate with disease severity, but do not explain all of the variability observed across individuals. These observations have driven most extensive research into genetic factors contributing to COVID-19 susceptibility and severity [158, 165-168, 189-196], and the goal to identify otherwise healthy individuals at high genetic risk will persist despite any progress for prophylaxis or treatment options so far. Knowledge of particularly high individual risk would require and possibly enable tailor-made approaches towards these individuals.

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From the clinical perspective, none of the molecular genetic risk factors identified so far (chapter 3.2) has entered day-to-day outpatient or clinical practice.

Fortunately, SARS-CoV-2 is rather rarely causing severe myocarditis or cardiomyopathies [165-170]. In individuals developing these conditions, however, application of the entire molecular virological and immunological repertoire to characterize the myocardial disease process needs to be applied and may enable dedicated therapeutic measures beyond standard heart failure and antiarrhythmic therapy.

5.2 Inflammation as therapeutic target in life-threatening arrhythmias and heart failure

Anomalous immune activation and macrophages are involved in multiple types of cardiomyopathies. From a clinical perspective, there are multiple obstacles to unequivocal detection of myocardial inflammation as a precipitating factor for life-threatening arrhythmias or cardiac remodeling and failure. Even in narrowly focused patient cohorts for whom genetic predisposition is suspected—such as by detection of pathogenic variants—this requires significant additional diagnostic work-up (cardiac MRI, EMB, PET-CT), which may not be feasible in all cases. It is highly likely that only a small fraction of all inflammation-triggered arrhythmic events or progressive heart failure will be clinically detected, generating a blind spot regarding the potential of anti-inflammatory treatments in this context. Notably, anti-arrhythmic potential of immunosuppression does not rely on genetic SCN5A variants because inflammation *per se* may cause dysfunction of normal SCN5A channels, generating a broader clinical incentive to follow this line of research. In view of possible therapeutic relevance, it appears recommendable to further evaluate the hypothesis of independent immunologic risk in major SCN5A variant-carrier cohorts [25]. For further in-depth discussion of recent approaches towards the potential of immunomodulating therapies in human cardiomyopathies we may refer the reader to a recent review covering the field from classical inflammatory cardiomyopathies to immune-checkpoint inhibitor-associated and SARS-CoV-2-associated myocardial inflammation [27].

5.3 Remaining clinical challenges in gastrointestinal microbiome and neuroimmune stress research

The novel immune pathomechanisms at organ and systemic level discussed in section 4 have certainly opened new avenues for clinical research. Experimental studies have documented significant impact of the gut microbiome and gut-brain-axis upon remote inflammation in cardiovascular system and brain. The rationale for the use of microbiota-directed therapies in these disorders is obvious, a clinical pilot trial was recently published [261], but final support from stringent clinical trials is not yet available. Within the field of psychoneuroimmunology, recent landmark experimental studies employing advanced genetic and neurosurgical methods have provided novel mechanistic insights into adverse immune impact resulting from different types of stress. Remarkable is their elucidation of differential impact arising from defined brain areas and neuroimmune pathways. Translational evaluation of possible relevance and clinical evaluation in cardiovascular medicine is awaited.

Figure 3 | Clinical translational status of the research fields

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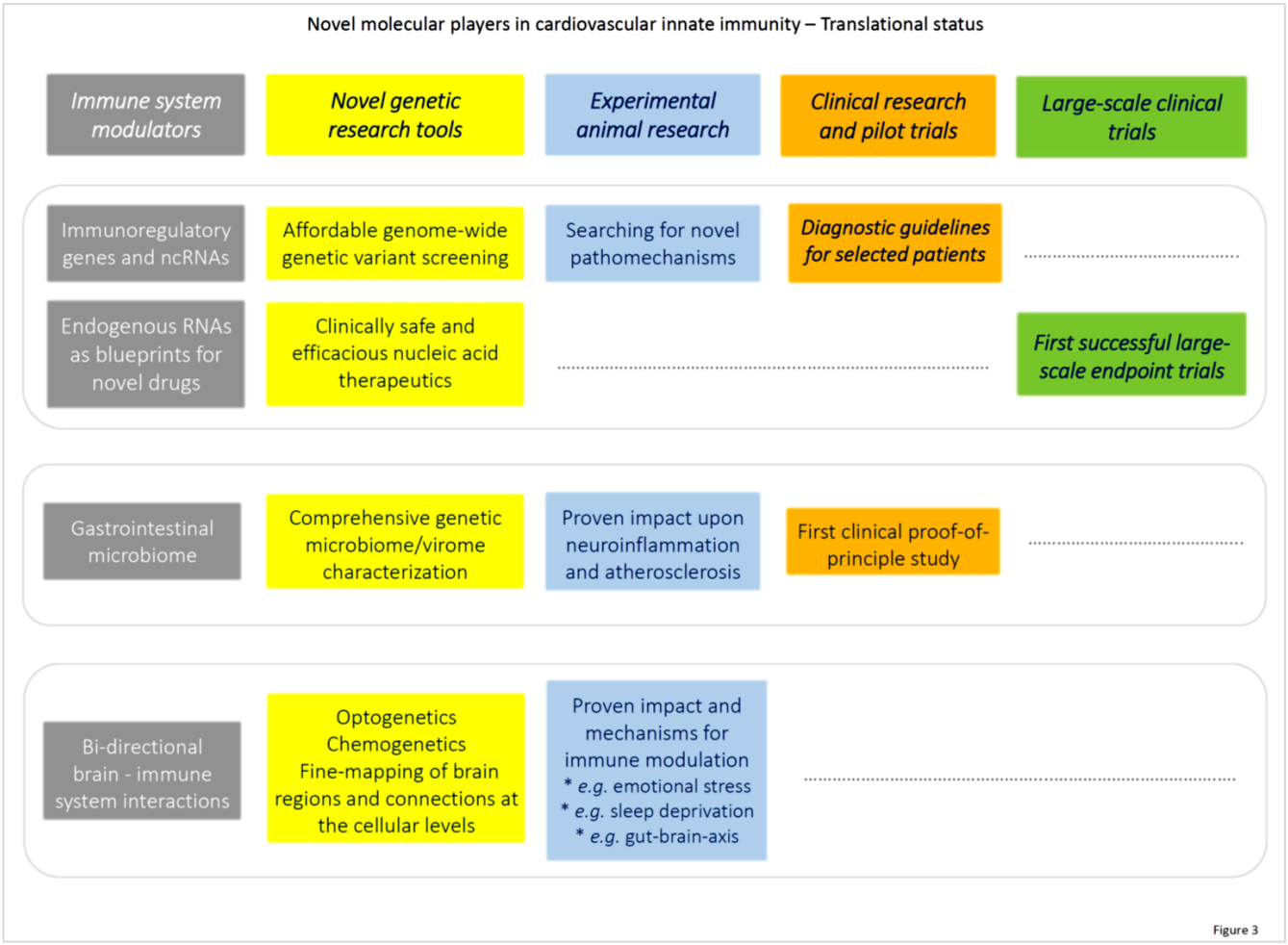

Figure 3

6. Clinical perspectives

While multiple excellent recent reviews have addressed diverse important aspects of immunological research into cardiovascular disorders, we have deliberately focused on selected studies characterized by their use of particularly advanced methodology in pre-clinical or clinical settings. Due to the immense worldwide efforts in the field during the past years the present review cannot be comprehensive, but instead tries to convey an up-to-date perspective on promising developments which may shape research at the cross-roads of cardiology – immunology - neurology. During the next few years extensive use of the new research tools should lead to a deeper understanding of the processes at these crossroads, long recognized, but still facr from being fully exploited in clinical medicine. Although several challenges need to be overcome before the full impact of these far-reaching new findings will hit the clinical arena, the above reviewed studies already exemplify an overarching aspect *i.e.* its interdisciplinary character of work to come.

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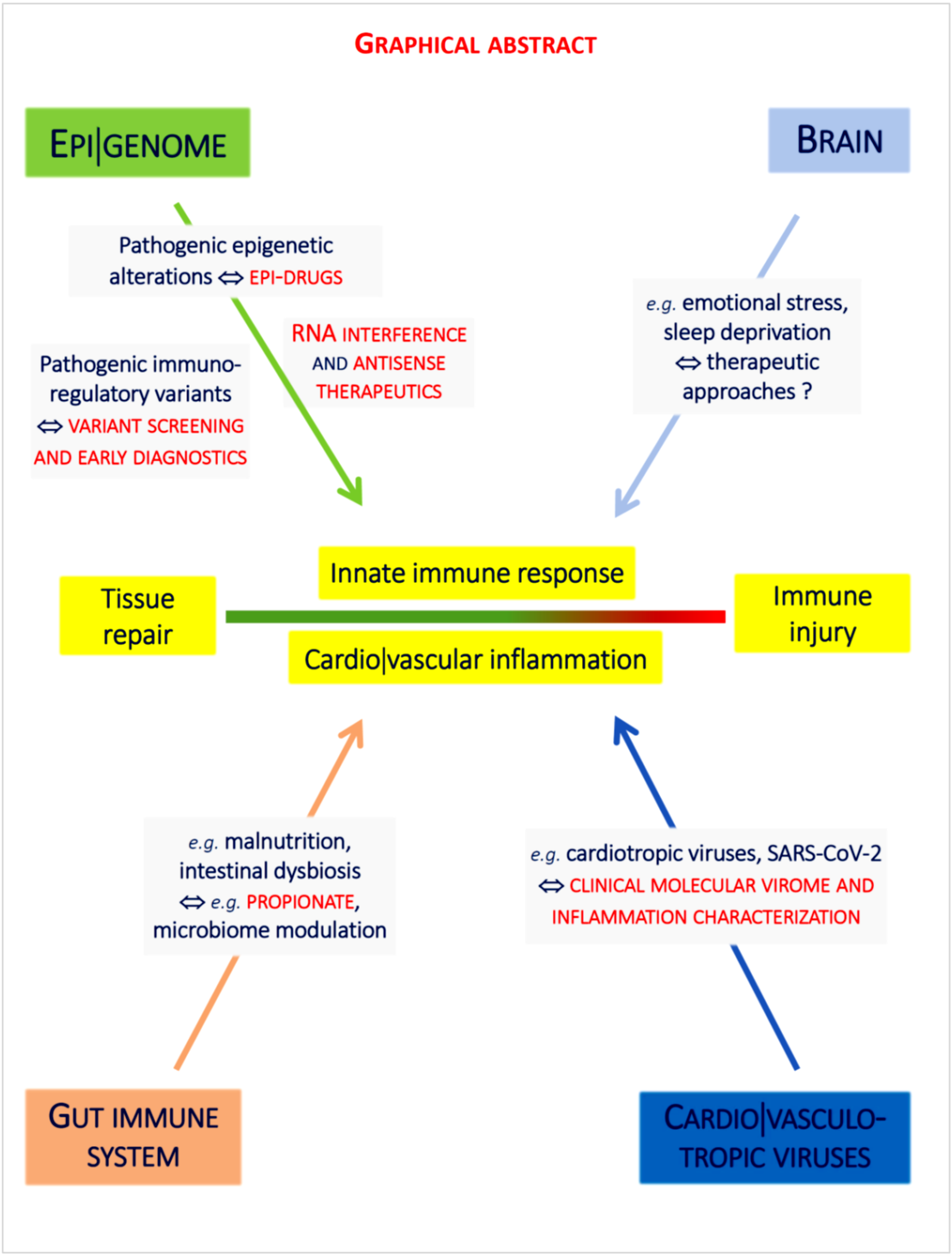
GRAPHICAL ABSTRACT



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