Muscle Regeneration and RNA

Subjects: Cell Biology

Contributor: Monica Ballarino

In skeletal muscle, regeneration is driven by a reservoir of resident progenitors, called satellite cells, able to efficiently replenish damaged muscle [44]. These cells are not present in the adult cardiac muscle, although a regenerative response, mediated by the proliferation of pre-existing cardiomyocytes, occurs in mice during the first week of life [45,46,47]. Temporal and tissue-specific nuances in the process of regeneration may underlie the participation of still unknown protagonists, whose ability to fine-tune myogenic expression becomes critical in both physiological and pathological conditions. The peculiar properties of RNA, along with its tissue specificity, satisfy the requirements for its integration in regenerative networks and will surely pave the way for future applications in medicine.

noncoding RNAs (ncRNAs) long noncoding RNA miRNA circRNA modRNA RNA therapeutics myogenesis skeletal muscle regeneration cardiac regeneration clinical trials

1. Introduction

The existence of distinct roles for RNA was initially suggested by the discovery of messenger (mRNA) [1][2], ribosomal (rRNA) [3][4], and transfer (tRNA) [5] RNAs. Later on, several classes of relatively small non-coding (nc)RNAs were also identified, such as the small nuclear (snRNA) [6][7], small nucleolar (snoRNA) [8][9], micro (miRNA) [10], piwi-interacting (piRNA) [11], and small interfering (siRNA) [12][13] RNAs. Among them, miRNAs have attracted considerable attention because of their participation in almost every aspect of physiological [14][15] and pathological [16][17][18][19][20] processes.

In the last years, research on RNA was fostered by the emergence of the Next-Generation Sequencing (NGS) technologies, which offered the chance to deepen the analysis of multiple (cell and tissue) transcriptomic landscapes [21][22][23][24][25]. As reported in the latest Ensembl release [26], in humans, this yielded a number of ncRNAs significantly higher than the coding ones (23,982 versus 20,442) and mainly represented (~16,896) by long non-coding RNAs (lncRNA). LncRNA constitute the most recent and heterogeneous class of ncRNAs acting at transcriptional as well as at post-transcriptional levels through a variety of mechanisms [27][28][29]. A distinctive class of lncRNAs is constituted by the circular (circ)RNAs, whose covalently closed structure is key to their exceptional stability in the cellular environment [30][31]. As such, they have evolved conserved roles in multiple physiological processes and their involvement in pathology has deserved increasing consideration from the scientific community [32][33][34].

2. Applications of Small and Long RNAs as Therapeutic Tools for Muscle Regeneration

2.1. Small Non-Coding RNAs

2.1.1. microRNA (miRNA)

For therapeutic purposes, researchers can use small ncRNA-based drugs functioning as miRNA "mimics" (**Figure 1**A) or "inhibitors" (antagomiR) (**Figure 1**B). While "mimics" are designed to imitate [35], "antagomiRs" instead counteract endogenous miRNA activities [36]. These types of drugs have been applied to several diseases, such as blood cancer (antagomiR-155, Cobomarsen) [37], Alport's nephropathy syndrome (antagomiR-21, Lademirsen) [38], and malignant pleural mesothelioma (mimic_miR-16, TargomiRs) [39] and also represent a prevailing revolution in the field of muscle regeneration, as demonstrated by their use in animal models (i.e., mice, rats, and pigs) [40].

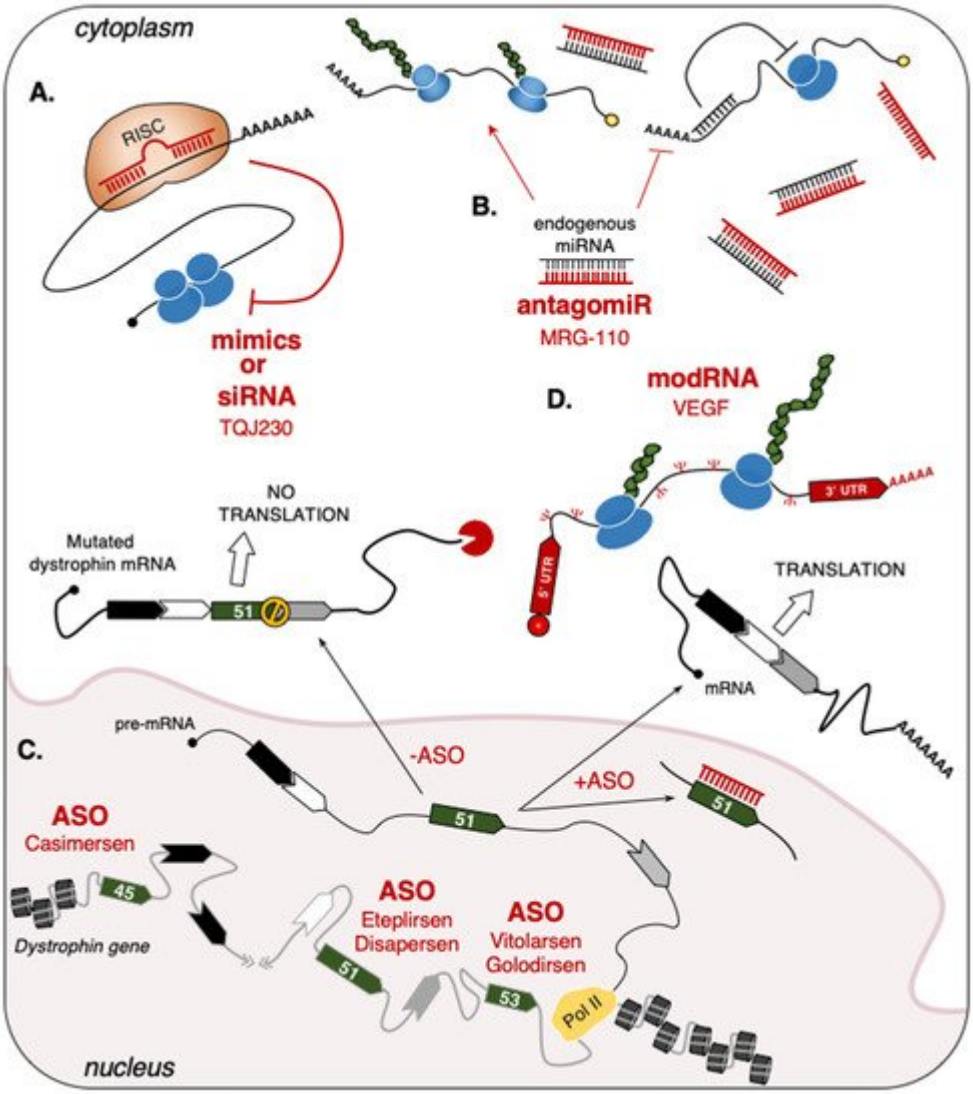

Figure 1. RNA-based drugs in muscular and cardiovascular pathologies. (**A**) "Mimics" and siRNAs act by targeting specific mRNAs to inhibit their translation. Examples include the TQJ230 siRNAs, which specifically recognize and

induce the degradation of ApoA mRNA in patients with pre-existing cardiovascular diseases [41]; (**B**) "AntagomiRs" act by sponging endogenous miRNAs, thus preventing their translational repression. MRG-110 was used to block miR-92a activity on pro-angiogenic genes to induce wound healing [42]; (**C**) ASO can be used to modify the splicing of precursor mRNAs (pre-mRNA). The exon-skipping strategy applied to dystrophin exon 51 is shown as an example. In DMD patients (-ASO), genetic mutations lead to the formation of a premature stop codon (STOP symbol) in the mature transcript that causes the lack of protein translation. The use of ASO base-pairing with dystrophin exon 51 (+ASO) promotes its exclusion from the mature mRNA and leads to the translation of a shorter (but functional) protein. For each targeted exon, the ASO approved by the FDA (Food and Drug Administration) are indicated [43][44][45][46][47]; (**D**) VEGF modRNA used in MI patients [48]. The uridine into pseudouridine substitution is represented by the greek Ψ symbol (red). Grey line: DNA; black line: RNA; red line: Therapeutic RNA.

In cardiac muscle, one of the challenges being tackled by researchers using these drugs was to re-establish heart functionality upon myocardial infarction (MI). In particular, different strategies have attempted to revert the necrotic death caused by MI-dependent hypoxia, either by increasing the proliferation of cardiomyocytes or by developing new blood vessels [49]. An example is represented by miR-199-a, a highly conserved miRNA shown to stimulate cardiac regeneration by promoting cell-cycle re-entry of adult rat cardiomyocytes [50]. Similarly, intramyocardial AAV6-injection of miR-199-a mimics in pigs, which underwent infarction by coronary artery occlusion, was found to stimulate cardiomyocytes proliferation [51]. The treatment also ameliorated the overall cardiac conditions by reducing the MI size and fibrosis and by improving the contractile functions. However, the inability to control the number of immature cardiomyocytes led to adverse effects, as 70% of the treated pigs died 7–8 weeks after injection [51]. Another example is miR-325-3p, of which administration in MI mice reduced the myocardiac damage through the repression of the necroptotic factor RIPK3 (Receptor Interacting Protein Kinase 3) [52][53].

In skeletal muscle, regeneration follows a very different path in respect to the heart due to the presence of satellite cells, the most representative muscle stem cells. Historically, satellite cells' specification and self-renewal were ascribed to the activity of the paired-box Pax7 transcription factor [54][55][56]. The fact that, in mice, the regulation of Pax7 levels by miR-1/miR-206 influences the commitment of satellite cells from self-renewal to differentiation [56] paved the road for the use of miRNA-based drugs for the treatment of skeletal muscle diseases. In mice, miR-127 regulates the translation of S1PR3 (Sphingosine 1 Phosphate Receptor 3), a protein involved in the maintenance of satellite cells quiescence [57]. Mice engineered to overexpress miR-127 and subjected to skeletal muscle injury by cardiotoxin show increased satellite cells' differentiation and accelerated regeneration. Interestingly, miR-127 overexpression also produced a beneficial effect in murine dystrophic muscles [58], which suggested potential applications for the treatment of muscular dystrophies. In the same year, Li and colleagues demonstrated the efficacy of miR-29b-based drugs in atrophy. In rodents, miR-29b is upregulated in multiple types of skeletal muscle atrophy models, which parallels with decreased levels of its direct targets, such as IGF-1 (Insulin-like growth factor 1) and PI3K (p85a) (Phosphatidylinositol 3-Kinase 85 KDa Regulatory Subunit Alpha), both involved in the mTOR signaling pathway [59][60]. MiR-29b inhibition through intramuscular antagomiRs injection was sufficient to attenuate atrophy and to increase the gastrocnemius-weight/body-weight ratio and myofibers diameter [61].

2.1.2. Single-Stranded Antisense Oligonucleotides (ASO)

ASO provided good performances in the treatment of several muscle pathologies [62]. They can be divided into two main categories: The DNA-based ASO, which induces target degradation through the recruitment of RNase H1 [63] and the RNA-based ASO, which alters mRNA processing [64] or translation [65][66] by a base-pairing block. In 2016 and 2017, respectively, the FDA (Food and Drug Administration) and EMA (European Medicine Agency) agencies approved Spinraza [67], the first RNA-based ASO found to be effective in the treatment of the spinal muscular atrophy (SMA) [68] (**Table 1**). In 2016, the FDA also approved Eteplirsen-ASO [69] for use in patients affected by Duchenne Muscular Dystrophy (DMD). This pathology is caused by several types of mutations of the dystrophin gene, which lead to the formation of premature stop-codons in dystrophin mRNA with the consequent loss of protein expression. Over the years, the use of ASO-based drugs able to convert the out-of-frame mutation to in-frame deletions to produce a shorter, but functional, dystrophin protein has been steadily increasing [70]. To date, the exons targeted by this strategy are represented by exon-51 (Eteplirsen, Drisapersen), exon-53 (Vitolarsen, Golodirsen), and exon-45 (Casimersen) (**Figure 1**C and **Table 1**) [43][44][45][46][47]. In particular, Eteplirsen is a 30-nucleotide phosphorodiamidate ASO that induces the skipping of dystrophin exon-51 by impeding the recognition of its splicing sites, thus preventing the formation of a premature stop codon [69]. Even though Eteplirsen was proven to be successful, the treatment can only be applied to ~14% of all DMD patients that present this specific type of mutation [71].

Table 1. RNA-based drugs and biomarkers for cardiac and skeletal pathologies.

Drug	RNA Type	Target	Disease/Condition	Company	Phase	Reference
MRG-110	Anti-miR	miR-92a	Wound Healing	miRagen (Viridian)	Phase I	NCT03603431
Spinraza (Nusinersen)	ASO	SMN2	SMA	Ionis	FDA/EMA approved	NDA:209531 EMEA/H/C/004312
Eteplirsen (Exondys 51)	ASO	Dystrophin	DMD	Sarepta Inotersen	FDA approved	NDA:206488
Drisapersen (Kyndrisa)	ASO	Dystrophin	DMD	BioMarin	Phase III	NCT02636686
Vitolarsen (Viltepso)	ASO	Dystrophin	DMD	Nippon Shinyaku	FDA approved	NDA:212154
Golodirsen (Vyondis 53)	ASO	Dystrophin	DMD	Sarepta Therapeutics	FDA approved	NDA:211970
Casimersen (Amondys 45)	ASO	Dystrophin	DMD	Sarepta Therapeutics	FDA approved	NDA:213026
TQJ230	siRNA	Apo(a)	Cardiovascular Disease, Elevated Lp(a)	Novartis	Phase III	NCT04023552

Drug	RNA Type	Target	Disease/Condition	Company	Phase	Reference
AZD8601	mRNA	VEGF	Ischemic Heart Disease	Moderna, Astrazeneca	Phase II	NCT03370887
HEARTBiT	miR	Biomarker	Heart Transplant Rejection			NCT03575910
CRUCIAL	Circulating RNAs	Biomarker	Acute Heart Failure	[72][73][74]		NCT03345446

at model
. (DM1).
nduction
defects, and cognitive impairments [75]. It is caused by the abnormal expansion of CTG repeats in the 3′UTR of *DMPK* (dystrophia myotonica protein kinase) transcripts [76] that induces their nuclear retention [77] and sequestration of several RNA-binding proteins, which functional alteration leads to splicing errors [78]. Subcutaneous injection of ASO against DMPK in different DM1 mouse models has yielded positive results in reducing splicing errors, myotonia, and cardiac defects while increasing both skeletal muscle strength [79][80] and the number of satellite cells [81], thus facilitating the regeneration process.

2.1.3. Short-Interfering RNA (siRNA)

Other strategies that employ small RNAs are based on the use of small interfering RNAs (siRNAs), which exploit RISC to base-pair and degrade target mRNAs, thus impeding the production of the corresponding protein [82]. Along the years, the efficacy of these molecules has been tested in clinical trials for muscular as well as non-muscular diseases, ranging from polyneuropathy (Patisiran) [83] and chronic hepatitis B viral infection (1JNJ-3989) [84] to different types of cancer, such as pancreatic cancer (siG12D-LODER) [85] and hepatocellular carcinoma (TKM-080301) [86]. In cardiac muscle, these agents are currently being tested in patients with pre-existing cardiovascular diseases. For instance, the administration of TQJ230 siRNAs is shown to inhibit the production of the Apolipoprotein-a (ApoA) and reduce the inflammatory activity of circulating monocytes (**Figure 1**A and **Table 1**) [41][87].

2.2. Long-Sized RNAs

2.2.1. Protein-Coding RNAs

mRNA is the ideal instrument for treatments that require the expression of specific proteins. Over the years, this opportunity has inspired researchers to find new strategies for increasing its stability and minimizing immunogenicity through the modification of specific nucleosides. This culminated with the production of modRNAs, synthetic and chemically modified mRNAs originally applied in phase I and II clinical trials (https://clinicaltrials.gov accessed on 10 September 2021) to prevent virus infections, such as Coronavirus (NCT04470427), Zika virus (mRNA-1893, NCT04064905; NCT04917861), and Cytomegalovirus (mRNA-1647, NCT04232280), or in the treatment of solid tumors [88]. In cardiac muscle, modRNAs represent a chance for future MI treatments. As for miRNAs, modRNA-based recipes are thought to stimulate cardiomyocytes' proliferation and increase the blood flow to the wounded area. For example, VEGF-A (Vascular Endothelial Growth Factor-A) is part of a large family of paracrine factors regulating angiogenesis, endothelial cells' proliferation, and endothelial precursor cells'

differentiation [89]. First tested in cardiac-injured mice [90][91], pigs and monkeys [92], the direct delivery of VEGF-A modRNAs through epicardial injection yielded encouraging results in terms of survival, by increasing the density of capillaries surrounding the heart and by reducing apoptotic and scarred areas (**Figure 1**D and **Table 1**).

2.2.2. Non-Coding RNAs

Cytoplasmic ncRNAs

The functional participation of lncRNAs in muscle regeneration makes them promising targets for clinical applications. In particular, their ability to act as competing endogenous RNAs (ceRNA) attracted the scientific community and currently represents the most exploited way to dose the relative abundance of miRNAs and their targets in vivo (**Figure 2**A) [93][94][95]. Starting from 2011, several lncRNAs were shown to act in the cytoplasm of muscle cells as miRNA sponges [96]. One of the first studies led to the identification of linc-MD1, a lncRNA that governs the timing of skeletal muscle differentiation by sponging miR-133 and miR-135 [97]. Upon induction of myoblasts' differentiation, linc-MD1 starts to be transcribed and inhibits miR-133 and miR-135 activities on their respective targets, MAML1 (Mastermind like transcriptional coactivator 1) and MEF2C (Myocyte enhancer factor 2C). Both proteins are important factors for the transcriptional regulation of pro-differentiating genes [98], thus the ncRNA-mediated regulation of their expression is essential for the correct induction of the latest stages of myogenesis.

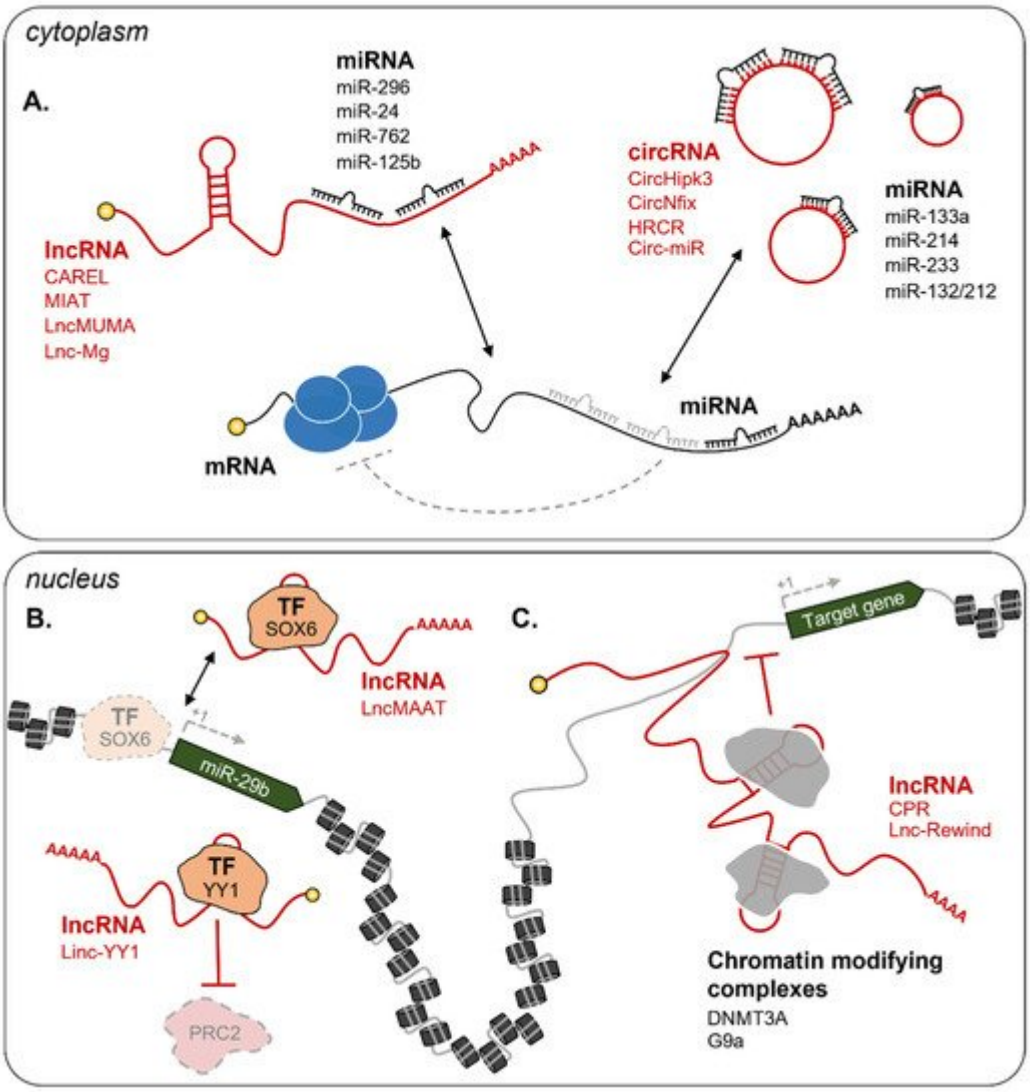

Figure 2. Examples of lncRNA circuitries in muscle regeneration. (**A**) In the cytoplasm, lncRNAs and circRNAs can act as competing endogenous RNAs (ceRNA) to interfere with miRNA binding to their targets. Examples include CAREL/mir-296 [99], MIAT/miR-24 [100], LncMUMA/miR-762 [101], Lnc-Mg/miR-125b [102], CircHipk3/miR-133a [103], CircNfix/miR-214 [104], HRCR/miR-233 [105], and Circ-miR/miR-132/212 [106]. In the nucleus, lncRNAs can influence gene expression at the epigenetic level through several mechanisms [96]. Examples in the figure include (**B**) lncRNA decoys: LncMAAT impedes SOX6 binding on the promoter of miR-29b to repress its transcription [107], Linc-YY1 binds YY1 and blocks its interaction with the PRC2 complex [108]; (**C**) lncRNA guides: CPR [109] and Lnc-Rewind [110] respectively interact with the DNMT3A and G9a repressive complexes and guide them on specific promoters. Dashed grey lines represent the loss of interaction and regulation. TF = Transcription Factor. See text for further details.

Nuclear ncRNAs

The ability to act as sponges is mostly executed by cytoplasmic RNAs. Nuclear and chromatin enriched lncRNAs act as epigenetic rheostats of myogenesis through a variety of mechanisms [111][96]. Among the most recent examples, LncMAAT (Muscle-Atrophy-Associated Transcript) is a lncRNA that inhibits miR-29b transcription by

impeding the binding of the transcription factor SOX6 to its promoter (**Figure 3**B). LncMAAT overexpression has been proposed as a possible strategy to treat muscle atrophy due to the significant attenuation of the pathological phenotypes (i.e. decreased weight of gastrocnemius muscles and grip strength and increased apoptosis) observed in AngII-induced atrophy mice [107]. Another example of a nuclear regulator is CPR (cardiomyocyte proliferation regulator), a lncRNA acting as a guide for the inhibitory DNMT3A (DNA methyltransferase 3 alpha) factor on the promoter of MCM3 (Minichromosome Maintenance Complex Component 3), whose expression is essential for genome replication and cell cycle progression (**Figure 2**C) [109][112]. In CPR knock-out mice, cardiomyocytes appear smaller than wild-type ones, although they are equipped with higher renewal capability. Indeed, upon MI, these mice show a higher percentage of proliferating cardiomyocytes accompanied by a clear improvement in cardiac functions, as compared to control animals [109]. Contrarily, the lncRNA Linc-YY1 acts as a decoy for YY1 (Yin-Yang 1) by blocking its interaction with the PRC2 complex, leading to the deregulation of several pro-differentiation genes (**Figure 2**B) [113]. Depletion of Linc-YY1 by siRNAs in satellite cells caused a significant decrease of MyoG and Pax7 positive cells. This result was also mirrored in vivo in cardiotoxin-induced mice in addition to a reduced number of newly formed myofibers [108]. A further example is Lnc-Rewind (Repressor of wnt induction), a chromatin-associated lncRNA previously identified by transcriptomic analysis [114] and recently shown to act as an epigenetic regulator of satellite cells proliferation and expansion [110]. Mechanistically, Lnc-Rewind directly interacts with the methyltransferase G9a to mediate the repression of its neighboring gene, Wnt7b, the expression of which is important for satellite cells' differentiation (**Figure 2**C).

3. RNA as a Diagnostic Molecule for Muscle Diseases

Together with clinical treatment, the possibility to identify a pathological condition quickly and precociously is extremely important to prevent the worst outcomes. For this reason, studies aimed at the identification of specific RNA biomarkers for different diseases have been steadily growing in the latest years. Both coding and ncRNAs have been found in nearly all peripheral bodily fluids [115][116] and could help fill the void of reliable biomarkers.

In muscular diseases, the measurement of circulating biomarkers can lead to extremely rapid, non-invasive, and easy-to-perform diagnostic paths, which overcome the need for surgical biopsies. An increasing number of studies have demonstrated the validity of using circulating miRNAs as biomarkers for muscular disorders, such as DMD and DM1. For instance, the expression of miR-1, miR-206, and miR-133 myo-miRs was found to be high in the serum of DMD patients and strongly correlated to disease severity [117][118]. However, as their expression decline with age [119], probably due to the progressive loss of skeletal muscle mass, it is extremely hard to use them as markers in patients. Indeed, it is difficult to discriminate whether their levels are reduced during the pathology due to treatment or age. Another miRNA, miR-483-5p, has been added as a potential biomarker for DMD. Even though it has a lower predictive power in respect to myo-miRs, miR-483-5p expression levels are unchanged with age, thus offering an advantage in monitoring the progress of treated patients [120]. Together with myo-miRs, the pool that includes miR-27b, miR-140-3p, miR-454 and miR-574 can significantly discriminate DM1 patients from healthy controls if analyzed in combination or alone [121]. Their abundance in plasma correlates well with skeletal muscle strength and the levels of creatine kinase, which confirm the potential of miRNAs as biomarkers.

4. Conclusions and Perspectives

RNA shows incredible potential for both diagnosis and treatment of a vast number of diseases, including muscular and cardiovascular pathologies. The use of RNA-based drugs has several advantages, mainly (i) the quick and easy method of design, (ii) the high specificity in target recognition, mostly achieved by base-pairing, (iii) the possibility to target specific cell types or tissues, and (iv) their functional versatility. The usefulness and reliability of small ncRNAs-based drugs (i.e., miRNA, ASO, and siRNA) have already been recognized by the competent FDA and EMA institutions, which have given approval for their use in SMA and DMD. Long RNAs also represent appealing candidates for the development of innovative approaches. Chemical modifications to improve mRNA stability and prevent its immunogenicity have also allowed researchers to pursue their use for the treatment of several conditions. As of now, clinical trials that are being conducted to test the effect of modRNAs expression are still in Phase I or II; however, they already show promising results for future use in human patients. Among the non-coding species, lncRNA-based drugs could be exploited to directly target the nucleus, thus influencing the early stages of gene expression, such as gene transcription, epigenetic regulation, and RNA processing. Despite several studies demonstrating the feasibility of using these molecules for therapeutic purposes in animal models, their application in human patients is still far from being tested. Nevertheless, it is undeniable their potential to revolutionize, in the future, the approaches to therapeutic treatments.

References

1. Brenner, S.; Jacob, F.; Meselson, M. An Unstable Intermediate Carrying Information from Genes to Ribosomes for Protein Synthesis. Nature 1961, 190, 576–581.
2. Jacob, F.; Monod, J. Genetic regulatory mechanisms in the synthesis of proteins. J. Mol. Biol. 1961, 3, 318–356.
3. Scherrer, K.; Darnell, J.E. Sedimentation characteristics of rapidly labelled RNA from HeLa cells. Biochem. Biophys. Res. Commun. 1962, 7, 486–490.
4. Scherrer, K.; Latham, H.; Darnell, J.E. Demonstration of an unstable RNA and of a precursor to ribosomal RNA in HeLa cells. Proc. Natl. Acad. Sci. 1963, 49, 240–248.
5. Hoagland, M.B.; Stephenson, M.L.; Scott, J.F.; Hecht, L.I.; Zamecnik, P.C. A Soluble Ribonucleic Acid Intermediate in Protein Synthesis. J. Biol. Chem. 1958, 231, 241–257.
6. Weinberg, R.A.; Penman, S. Small molecular weight monodisperse nuclear RNA. J. Mol. Biol. 1968, 38, 289–304.
7. Wassarman, D.; Steitz, J. Interactions of small nuclear RNA’s with precursor messenger RNA during in vitro splicing. Science 1992, 257, 1918–1925.

8. Reddy, R.; Busch, H. Small Nuclear RNAs: RNA Sequences, Structure, and Modifications. In Structure and Function of Major and Minor Small Nuclear Ribonucleoprotein Particles; Springer: Berlin/Heidelberg, Germany, 1988; pp. 1–37.
9. Bachellerie, J.P.; Cavaillé, J.; Hüttenhofer, A. The expanding snoRNA world. Biochimie 2002, 84, 775–790.
10. Lee, R.C.; Feinbaum, R.L.; Ambros, V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell 1993, 75, 843–854.
11. Cox, D.N.; Chao, A.; Baker, J.; Chang, L.; Qiao, D.; Lin, H. A novel class of evolutionarily conserved genes defined by piwi are essential for stem cell self-renewal. Genes Dev. 1998, 12, 3715–3727.
12. Fire, A.; Xu, S.; Montgomery, M.K.; Kostas, S.A.; Driver, S.E.; Mello, C.C. Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans. Nature 1998, 391, 806–811.
13. Hamilton, A.J.; Baulcombe, D.C. A Species of Small Antisense RNA in Posttranscriptional Gene Silencing in Plants. Science 1999, 286, 950–952.
14. Li, M.; Li, J.; Ding, X.; He, M.; Cheng, S.-Y. microRNA and Cancer. AAPS J. 2010, 12, 309–317.
15. O'Brien, J.; Hayder, H.; Zayed, Y.; Peng, C. Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation. Front. Endocrinol. 2018, 9, 402.
16. Fatica, A.; Rosa, A.; Ballarino, M.; Marchis, M.L.D.; Rasmussen, K.D.; Bozzoni, I. Role of microRNAs in myeloid differentiation. Biochem. Soc. Trans. 2008, 36, 1201–1205.
17. Deiuliis, J.A. MicroRNAs as regulators of metabolic disease: Pathophysiologic significance and emerging role as biomarkers and therapeutics. Int. J. Obes. 2016, 40, 88–101.
18. Abdul-Muneer, P.M. MicroRNA in the Pathophysiology of CNS Injury: Implication in Neuroregenerative Medicine. CNS Neurosci. Ther. 2016, 22, 543–545.
19. De Benedittis, G.; Ciccacci, C.; Latini, A.; Novelli, L.; Novelli, G.; Borgiani, P. Emerging Role of microRNAs and Long Non-Coding RNAs in Sjögren's Syndrome. Genes 2021, 12, 903.
20. He, X.; Kuang, G.; Wu, Y.; Ou, C. Emerging roles of exosomal miRNAs in diabetes mellitus. Clin. Transl. Med. 2021, 11, e468.
21. Carninci, P.; Kasukawa, T.; Katayama, S.; Gough, J.; Frith, M.C.; Maeda, N.; Oyama, R.; Ravasi, T.; Lenhard, B.; Wells, C.; et al. The Transcriptional Landscape of the Mammalian Genome. Science 2005, 309, 1559–1563.
22. Mattick, J.S. The central role of RNA in human development and cognition. FEBS Lett. 2011, 585, 1600–1616.

23. Nagano, T.; Fraser, P. No-Nonsense Functions for Long Noncoding RNAs. Cell 2011, 145, 178–181.
24. Harrow, J.; Frankish, A.; Gonzalez, J.M.; Tapanari, E.; Diekhans, M.; Kokocinski, F.; Aken, B.L.; Barrell, D.; Zadissa, A.; Searle, S.; et al. GENCODE: The reference human genome annotation for The ENCODE Project. Genome Res. 2012, 22, 1760–1774.
25. Abugessaisa, I.; Noguchi, S.; Hasegawa, A.; Harshbarger, J.; Kondo, A.; Lizio, M.; Severin, J.; Carninci, P.; Kawaji, H.; Kasukawa, T. FANTOM5 CAGE profiles of human and mouse reprocessed for GRCh38 and GRCm38 genome assemblies. Sci. Data 2017, 4, 170107.
26. Howe, K.L.; Achuthan, P.; Allen, J.; Allen, J.; Alvarez-Jarreta, J.; Amode, M.R.; Armean, I.M.; Azov, A.G.; Bennett, R.; Bhai, J.; et al. Ensembl 2021. Nucleic Acids Res. 2021, 49, D884–D891.
27. Fatica, A.; Bozzoni, I. Long non-coding RNAs: New players in cell differentiation and development. Nat. Rev. Genet. 2013, 15, 7–21.
28. Yao, R.-W.; Wang, Y.; Chen, L.-L. Cellular functions of long noncoding RNAs. Nat. Cell Biol. 2019, 21, 542–551.
29. Rinn, J.L.; Chang, H.Y. Long Noncoding RNAs: Molecular Modalities to Organismal Functions. Annu. Rev. Biochem. 2020, 89, 283–308.
30. Chen, L.-L. The biogenesis and emerging roles of circular RNAs. Nat. Rev. Mol. Cell Biol. 2016, 17, 205–211.
31. Kristensen, L.S.; Andersen, M.S.; Stagsted, L.V.W.; Ebbesen, K.K.; Hansen, T.B.; Kjems, J. The biogenesis, biology and characterization of circular RNAs. Nat. Rev. Genet. 2019, 20, 675–691.
32. Braicu, C.; Zimta, A.-A.; Gulei, D.; Olariu, A.; Berindan-Neagoe, I. Comprehensive analysis of circular RNAs in pathological states: Biogenesis, cellular regulation, and therapeutic relevance. Cell. Mol. Life Sci. 2019, 76, 1559–1577.
33. Patop, I.L.; Wüst, S.; Kadener, S. Past, present, and future of circRNAs. EMBO J. 2019, 38, e100836.
34. Xie, R.; Zhang, Y.; Zhang, J.; Li, J.; Zhou, X. The Role of Circular RNAs in Immune-Related Diseases. Front. Immunol. 2020, 11, 545.
35. Goldgraben, M.A.; Russell, R.; Rueda, O.M.; Caldas, C.; Git, A. Double-stranded microRNA mimics can induce length- and passenger strand–dependent effects in a cell type–specific manner. RNA 2016, 22, 193–203.
36. Tang, L.; Chen, H.Y.; Hao, N.B.; Tang, B.; Guo, H.; Yong, X.; Dong, H.; Yang, S.M. microRNA inhibitors: Natural and artificial sequestration of microRNA. Cancer Lett. 2017, 407, 139–147.

37. Seto, A.G.; Beatty, X.; Lynch, J.M.; Hermreck, M.; Tetzlaff, M.; Duvic, M.; Jackson, A.L. Cobomarsen, an oligonucleotide inhibitor of miR-155, co-ordinately regulates multiple survival pathways to reduce cellular proliferation and survival in cutaneous T-cell lymphoma. Br. J. Haematol. 2018, 183, 428–444.

38. Weinstock, B.A.; Feldman, D.L.; Fornoni, A.; Gross, O.; Kashtan, C.E.; Lagas, S.; Lennon, R.; Miner, J.H.; Rheault, M.N.; Simon, J.F.; et al. Clinical trial recommendations for potential Alport syndrome therapies. Kidney Int. 2020, 97, 1109–1116.

39. van Zandwijk, N.; Pavlakis, N.; Kao, S.C.; Linton, A.; Boyer, M.J.; Clarke, S.; Huynh, Y.; Chrzanowska, A.; Fulham, M.J.; Bailey, D.L.; et al. Safety and activity of microRNA-loaded minicells in patients with recurrent malignant pleural mesothelioma: A first-in-man, phase 1, open-label, dose-escalation study. Lancet Oncol. 2017, 18, 1386–1396.

40. Huang, C.-K.; Kafert-Kasting, S.; Thum, T. Preclinical and Clinical Development of Noncoding RNA Therapeutics for Cardiovascular Disease. Circ. Res. 2020, 126, 663–678.

41. Tsimikas, S.; Karwatowska-Prokopczuk, E.; Gouni-Berthold, I.; Tardif, J.-C.; Baum, S.J.; Steinhagen-Thiessen, E.; Shapiro, M.D.; Stroes, E.S.; Moriarty, P.M.; Nordestgaard, B.G.; et al. Lipoprotein(a) Reduction in Persons with Cardiovascular Disease. N. Engl. J. Med. 2020, 382, 244–255.

42. Gallant-Behm, C.L.; Piper, J.; Dickinson, B.A.; Dalby, C.M.; Pestano, L.A.; Jackson, A.L. A synthetic microRNA-92a inhibitor (MRG-110) accelerates angiogenesis and wound healing in diabetic and nondiabetic wounds. Wound Repair Regen. 2018, 26, 311–323.

43. Cirak, S.; Arechavala-Gomeza, V.; Guglieri, M.; Feng, L.; Torelli, S.; Anthony, K.; Abbs, S.; Garralda, M.E.; Bourke, J.; Wells, D.J.; et al. Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: An open-label, phase 2, dose-escalation study. Lancet 2011, 378, 595–605.

44. Voit, T.; Topaloglu, H.; Straub, V.; Muntoni, F.; Deconinck, N.; Campion, G.; De Kimpe, S.J.; Eagle, M.; Guglieri, M.; Hood, S.; et al. Safety and efficacy of drisapersen for the treatment of Duchenne muscular dystrophy (DEMAND II): An exploratory, randomised, placebo-controlled phase 2 study. Lancet Neurol. 2014, 13, 987–996.

45. Clemens, P.R.; Rao, V.K.; Connolly, A.M.; Harper, A.D.; Mah, J.K.; Smith, E.C.; McDonald, C.M.; Zaidman, C.M.; Morgenroth, L.P.; Osaki, H.; et al. Safety, Tolerability, and Efficacy of Viltolarsen in Boys With Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping: A Phase 2 Randomized Clinical Trial. JAMA Neurol. 2020, 77, 982–991.

46. Frank, D.E.; Schnell, F.J.; Akana, C.; El-Husayni, S.H.; Desjardins, C.A.; Morgan, J.; Charleston, J.S.; Sardone, V.; Domingos, J.; Dickson, G.; et al. Increased dystrophin production with golodirsen in patients with Duchenne muscular dystrophy. Neurology 2020, 94, e2270–e2282.

47. Shirley, M. Casimersen: First Approval. Drugs 2021, 81, 875–879.
48. Gan, L.-M.; Lagerström-Fermér, M.; Carlsson, L.G.; Arfvidsson, C.; Egnell, A.-C.; Rudvik, A.; Kjaer, M.; Collén, A.; Thompson, J.D.; Joyal, J.; et al. Intradermal delivery of modified mRNA encoding VEGF-A in patients with type 2 diabetes. Nat. Commun. 2019, 10, 871.
49. Kaur, K.; Zangi, L. Modified mRNA as a Therapeutic Tool for the Heart. Cardiovasc. Drugs Ther. 2020, 34, 871–880.
50. Eulalio, A.; Mano, M.; Ferro, M.D.; Zentilin, L.; Sinagra, G.; Zacchigna, S.; Giacca, M. Functional screening identifies miRNAs inducing cardiac regeneration. Nature 2012, 492, 376–381.
51. Gabisonia, K.; Prosdocimo, G.; Aquaro, G.D.; Carlucci, L.; Zentilin, L.; Secco, I.; Ali, H.; Braga, L.; Gorgodze, N.; Bernini, F.; et al. MicroRNA therapy stimulates uncontrolled cardiac repair after myocardial infarction in pigs. Nature 2019, 569, 418–422.
52. He, S.; Wang, L.; Miao, L.; Wang, T.; Du, F.; Zhao, L.; Wang, X. Receptor Interacting Protein Kinase-3 Determines Cellular Necrotic Response to TNF-α. Cell 2009, 137, 1100–1111.
53. Zhang, D.-Y.; Wang, B.-J.; Ma, M.; Yu, K.; Zhang, Q.; Zhang, X.-W. MicroRNA-325-3p protects the heart after myocardial infarction by inhibiting RIPK3 and programmed necrosis in mice. BMC Mol. Biol. 2019, 20, 17.
54. Seale, P.; Sabourin, L.A.; Girgis-Gabardo, A.; Mansouri, A.; Gruss, P.; Rudnicki, M.A. Pax7 Is Required for the Specification of Myogenic Satellite Cells. Cell 2000, 102, 777–786.
55. von Maltzahn, J.; Jones, A.E.; Parks, R.J.; Rudnicki, M.A. Pax7 is critical for the normal function of satellite cells in adult skeletal muscle. Proc. Natl. Acad. Sci. USA 2013, 110, 16474–16479.
56. Chen, J.-F.; Tao, Y.; Li, J.; Deng, Z.; Yan, Z.; Xiao, X.; Wang, D.-Z. microRNA-1 and microRNA-206 regulate skeletal muscle satellite cell proliferation and differentiation by repressing Pax7. J. Cell Biol. 2010, 190, 867–879.
57. Fortier, M.; Figeac, N.; White, R.B.; Knopp, P.; Zammit, P.S. Sphingosine-1-phosphate receptor 3 influences cell cycle progression in muscle satellite cells. Dev. Biol. 2013, 382, 504–516.
58. Zhai, L.; Wu, R.; Han, W.; Zhang, Y.; Zhu, D. miR-127 enhances myogenic cell differentiation by targeting S1PR3. Cell Death Dis. 2017, 8, e2707.
59. Barclay, R.D.; Burd, N.A.; Tyler, C.; Tillin, N.A.; Mackenzie, R.W. The Role of the IGF-1 Signaling Cascade in Muscle Protein Synthesis and Anabolic Resistance in Aging Skeletal Muscle. Front. Nutr. 2019, 6, 146.
60. Schiaffino, S.; Mammucari, C. Regulation of skeletal muscle growth by the IGF1-Akt/PKB pathway: Insights from genetic models. Skelet. Muscle 2011, 1, 4.

61. Li, J.; Chan, M.C.; Yu, Y.; Bei, Y.; Chen, P.; Zhou, Q.; Cheng, L.; Chen, L.; Ziegler, O.; Rowe, G.C.; et al. miR-29b contributes to multiple types of muscle atrophy. Nat. Commun. 2017, 8, 15201.
62. Stephenson, M.L.; Zamecnik, P.C. Inhibition of Rous sarcoma viral RNA translation by a specific oligodeoxyribonucleotide. Proc. Natl. Acad. Sci. USA 1978, 75, 285–288.
63. Wu, H.; Lima, W.F.; Zhang, H.; Fan, A.; Sun, H.; Crooke, S.T. Determination of the Role of the Human RNase H1 in the Pharmacology of DNA-like Antisense Drugs. J. Biol. Chem. 2004, 279, 17181–17189.
64. Dulla, K.; Aguila, M.; Lane, A.; Jovanovic, K.; Parfitt, D.A.; Schulkens, I.; Chan, H.L.; Schmidt, I.; Beumer, W.; Vorthoren, L.; et al. Splice-Modulating Oligonucleotide QR-110 Restores CEP290 mRNA and Function in Human c.2991+1655A>G LCA10 Models. Mol. Ther.-Nucleic Acids 2018, 12, 730–740.
65. Baker, B.F.; Lot, S.S.; Condon, T.P.; Cheng-Flournoy, S.; Lesnik, E.A.; Sasmor, H.M.; Bennett, C.F. 2′-O-(2-Methoxy)ethyl-modified Anti-intercellular Adhesion Molecule 1 (ICAM-1) Oligonucleotides Selectively Increase the ICAM-1 mRNA Level and Inhibit Formation of the ICAM-1 Translation Initiation Complex in Human Umbilical Vein Endothelial Cells. J. Biol. Chem. 1997, 272, 11994–12000.
66. Liang, X.; Shen, W.; Sun, H.; Migawa, M.T.; Vickers, T.A.; Crooke, S.T. Translation efficiency of mRNAs is increased by antisense oligonucleotides targeting upstream open reading frames. Nat. Biotechnol. 2016, 34, 875–880.
67. Glascock, J.; Lenz, M.; Hobby, K.; Jarecki, J. Cure SMA and our patient community celebrate the first approved drug for SMA. Gene Ther. 2017, 24, 498–500.
68. Hua, Y.; Vickers, T.A.; Baker, B.F.; Bennett, C.F.; Krainer, A.R. Enhancement of SMN2 Exon 7 Inclusion by Antisense Oligonucleotides Targeting the Exon. PLOS Biol. 2007, 5, e73.
69. Lim, K.R.Q.; Maruyama, R.; Yokota, T. Eteplirsen in the treatment of Duchenne muscular dystrophy. Drug Des. Devel. Ther. 2017, 11, 533–545.
70. Himič, V.; Davies, K.E. Evaluating the potential of novel genetic approaches for the treatment of Duchenne muscular dystrophy. Eur. J. Hum. Genet. 2021, 29, 1369–1376.
71. Bladen, C.L.; Salgado, D.; Monges, S.; Foncuberta, M.E.; Kekou, K.; Kosma, K.; Dawkins, H.; Lamont, L.; Roy, A.J.; Chamova, T.; et al. The TREAT-NMD DMD Global Database: Analysis of More than 7,000 Duchenne Muscular Dystrophy Mutations. Hum. Mutat. 2015, 36, 395–402.
72. Tasfaout, H.; Cowling, B.S.; Laporte, J. Centronuclear myopathies under attack: A plethora of therapeutic targets. J. Neuromuscul. Dis. 2018, 5, 387–406.
73. Buono, S.; Ross, J.A.; Tasfaout, H.; Levy, Y.; Kretz, C.; Tayefeh, L.; Matson, J.; Guo, S.; Kessler, P.; Monia, B.P.; et al. Reducing dynamin 2 (DNM2) rescues DNM2-related dominant

centronuclear myopathy. Proc. Natl. Acad. Sci. USA 2018, 115, 11066–11071.

74. Muñoz, X.M.; Kretz, C.; Silva-Rojas, R.; Ochala, J.; Menuet, A.; Romero, N.B.; Cowling, B.S.; Laporte, J. Physiological impact and disease reversion for the severe form of centronuclear myopathy linked to dynamin. JCI Insight 2020, 5, e137899.
75. Day, J.W.; Ranum, L.P.W. RNA pathogenesis of the myotonic dystrophies. Neuromuscul. Disord. 2005, 15, 5–16.
76. Mahadevan, M.; Tsilfidis, C.; Sabourin, L.; Shutler, G.; Amemiya, C.; Jansen, G.; Neville, C.; Narang, M.; Barceló, J.; O'Hoy, K.; et al. Myotonic dystrophy mutation: An unstable CTG repeat in the 3′ untranslated region of the gene. Science 1992, 255, 1253–1255.
77. Taneja, K.L.; McCurrach, M.; Schalling, M.; Housman, D.; Singer, R.H. Foci of trinucleotide repeat transcripts in nuclei of myotonic dystrophy cells and tissues. J. Cell Biol. 1995, 128, 995–1002.
78. Echeverria, G.V.; Cooper, T.A. RNA-binding proteins in microsatellite expansion disorders: Mediators of RNA toxicity. Brain Res. 2012, 1462, 100.
79. Jauvin, D.; Chrétien, J.; Pandey, S.K.; Martineau, L.; Revillod, L.; Bassez, G.; Lachon, A.; McLeod, A.R.; Gourdon, G.; Wheeler, T.M.; et al. Targeting DMPK with Antisense Oligonucleotide Improves Muscle Strength in Myotonic Dystrophy Type 1 Mice. Mol. Ther. Nucleic Acids 2017, 7, 465.
80. Yadava, R.S.; Yu, Q.; Mandal, M.; Rigo, F.; Bennett, C.F.; Mahadevan, M.S. Systemic therapy in an RNA toxicity mouse model with an antisense oligonucleotide therapy targeting a non-CUG sequence within the DMPK 3′UTR RNA. Hum. Mol. Genet. 2020, 29, 1440–1453.
81. Yadava, R.S.; Mandal, M.; Giese, J.M.; Rigo, F.; Bennett, C.F.; Mahadevan, M.S. Modeling muscle regeneration in RNA toxicity mice. Hum. Mol. Genet. 2021, 30, 1111–1130.
82. Pratt, A.J.; MacRae, I.J. The RNA-induced Silencing Complex: A Versatile Gene-silencing Machine. J. Biol. Chem. 2009, 284, 17897–17901.
83. Solomon, S.D.; McMurray, J.J.V.; Anand, I.S.; Ge, J.; Lam, C.S.P.; Maggioni, A.P.; Martinez, F.; Packer, M.; Pfeffer, M.A.; Pieske, B.; et al. Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. N. Engl. J. Med. 2019, 381, 1609–1620.
84. Wooddell, C.I.; Gehring, A.J.; Yuen, M.-F.; Given, B.D. RNA Interference Therapy for Chronic Hepatitis B Predicts the Importance of Addressing Viral Integration When Developing Novel Cure Strategies. Viruses 2021, 13, 581.
85. Golan, T.; Khvalevsky, E.Z.; Hubert, A.; Gabai, R.M.; Hen, N.; Segal, A.; Domb, A.; Harari, G.; David, E.B.; Raskin, S.; et al. RNAi therapy targeting KRAS in combination with chemotherapy for locally advanced pancreatic cancer patients. Oncotarget 2015, 6, 24560–24570.

86. El Dika, I.; Lim, H.Y.; Yong, W.P.; Lin, C.-C.; Yoon, J.-H.; Modiano, M.; Freilich, B.; Choi, H.J.; Chao, T.-Y.; Kelley, R.K.; et al. An Open-Label, Multicenter, Phase I, Dose Escalation Study with Phase II Expansion Cohort to Determine the Safety, Pharmacokinetics, and Preliminary Antitumor Activity of Intravenous TKM-080301 in Subjects with Advanced Hepatocellular Carcinoma. Oncologist 2019, 24, 747-e218.

87. Stiekema, L.C.A.; Prange, K.H.M.; Hoogeveen, R.M.; Verweij, S.L.; Kroon, J.; Schnitzler, J.G.; Dzobo, K.E.; Cupido, A.J.; Tsimikas, S.; Stroes, E.S.G.; et al. Potent lipoprotein(a) lowering following apolipoprotein(a) antisense treatment reduces the pro-inflammatory activation of circulating monocytes in patients with elevated lipoprotein(a). Eur. Heart J. 2020, 41, 2262–2271.

88. Dammes, N.; Peer, D. Paving the Road for RNA Therapeutics. Trends Pharmacol. Sci. 2020, 41, 755–775.

89. Apte, R.S.; Chen, D.S.; Ferrara, N. VEGF in Signaling and Disease: Beyond Discovery and Development. Cell 2019, 176, 1248–1264.

90. Zangi, L.; Lui, K.O.; von Gise, A.; Ma, Q.; Ebina, W.; Ptaszek, L.M.; Später, D.; Xu, H.; Tabebordbar, M.; Gorbatov, R.; et al. Modified mRNA directs the fate of heart progenitor cells and induces vascular regeneration after myocardial infarction. Nat. Biotechnol. 2013, 31, 898–907.

91. Lui, K.O.; Zangi, L.; Silva, E.A.; Bu, L.; Sahara, M.; Li, R.A.; Mooney, D.J.; Chien, K.R. Driving vascular endothelial cell fate of human multipotent Isl1 + heart progenitors with VEGF modified mRNA. Cell Res. 2013, 23, 1172–1186.

92. Carlsson, L.; Clarke, J.C.; Yen, C.; Gregoire, F.; Albery, T.; Billger, M.; Egnell, A.-C.; Gan, L.-M.; Jennbacken, K.; Johansson, E.; et al. Biocompatible, Purified VEGF-A mRNA Improves Cardiac Function after Intracardiac Injection 1 Week Post-myocardial Infarction in Swine. Mol. Ther.-Methods Clin. Dev. 2018, 9, 330–346.

93. Salmena, L.; Poliseno, L.; Tay, Y.; Kats, L.; Pandolfi, P.P. A ceRNA Hypothesis: The Rosetta Stone of a Hidden RNA Language? Cell 2011, 146, 353–358.

94. Song, C.; Zhang, J.; Qi, H.; Feng, C.; Chen, Y.; Cao, Y.; Ba, L.; Ai, B.; Wang, Q.; Huang, W.; et al. The global view of mRNA-related ceRNA cross-talks across cardiovascular diseases. Sci. Rep. 2017, 7, 10185.

95. Ala, U. Competing Endogenous RNAs, Non-Coding RNAs and Diseases: An Intertwined Story. Cells 2020, 9, 1574.

96. Ballarino, M.; Morlando, M.; Fatica, A.; Bozzoni, I. Non-coding RNAs in muscle differentiation and musculoskeletal disease. J. Clin. Invest. 2016, 126, 2021–2030.

97. Cesana, M.; Cacchiarelli, D.; Legnini, I.; Santini, T.; Sthandier, O.; Chinappi, M.; Tramontano, A.; Bozzoni, I. A Long Noncoding RNA Controls Muscle Differentiation by Functioning as a Competing Endogenous RNA. Cell 2011, 147, 358–369.

98. Shen, H.; McElhinny, A.S.; Cao, Y.; Gao, P.; Liu, J.; Bronson, R.; Griffin, J.D.; Wu, L. The Notch coactivator, MAML1, functions as a novel coactivator for MEF2C-mediated transcription and is required for normal myogenesis. Genes Dev. 2006, 20, 675.
99. Cai, B.; Ma, W.; Ding, F.; Zhang, L.; Huang, Q.; Wang, X.; Hua, B.; Xu, J.; Li, J.; Bi, C.; et al. The Long Noncoding RNA CAREL Controls Cardiac Regeneration. J. Am. Coll. Cardiol. 2018, 72, 534–550.
100. Qu, X.; Du, Y.; Shu, Y.; Gao, M.; Sun, F.; Luo, S.; Yang, T.; Zhan, L.; Yuan, Y.; Chu, W.; et al. MIAT Is a Pro-fibrotic Long Non-coding RNA Governing Cardiac Fibrosis in Post-infarct Myocardium. Sci. Rep. 2017, 7, 42657.
101. Zhang, Z.-K.; Li, J.; Guan, D.; Liang, C.; Zhuo, Z.; Liu, J.; Lu, A.; Zhang, G.; Zhang, B.-T. Long Noncoding RNA lncMUMA Reverses Established Skeletal Muscle Atrophy following Mechanical Unloading. Mol. Ther. 2018, 26, 2669–2680.
102. Zhu, M.; Liu, J.; Xiao, J.; Yang, L.; Cai, M.; Shen, H.; Chen, X.; Ma, Y.; Hu, S.; Wang, Z.; et al. Lnc-mg is a long non-coding RNA that promotes myogenesis. Nat. Commun. 2017, 8, 14718.
103. Si, X.; Zheng, H.; Wei, G.; Li, M.; Li, W.; Wang, H.; Guo, H.; Sun, J.; Li, C.; Zhong, S.; et al. circRNA Hipk3 Induces Cardiac Regeneration after Myocardial Infarction in Mice by Binding to Notch1 and miR-133a. Mol. Ther.-Nucleic Acids 2020, 21, 636–655.
104. Huang, S.; Li, X.; Zheng, H.; Si, X.; Li, B.; Wei, G.; Li, C.; Chen, Y.; Chen, Y.; Liao, W.; et al. Loss of Super-Enhancer-Regulated circRNA Nfix Induces Cardiac Regeneration After Myocardial Infarction in Adult Mice. Circulation 2019, 139, 2857–2876.
105. Wang, K.; Long, B.; Liu, F.; Wang, J.-X.; Liu, C.-Y.; Zhao, B.; Zhou, L.-Y.; Sun, T.; Wang, M.; Yu, T.; et al. A circular RNA protects the heart from pathological hypertrophy and heart failure by targeting miR-223. Eur. Heart J. 2016, 37, 2602–2611.
106. Lavenniah, A.; Luu, T.D.A.; Li, Y.P.; Lim, T.B.; Jiang, J.; Ackers-Johnson, M.; Foo, R.S.-Y. Engineered Circular RNA Sponges Act as miRNA Inhibitors to Attenuate Pressure Overload-Induced Cardiac Hypertrophy. Mol. Ther. 2020, 28, 1506–1517.
107. Li, J.; Yang, T.; Tang, H.; Sha, Z.; Chen, R.; Chen, L.; Yu, Y.; Rowe, G.C.; Das, S.; Xiao, J. Inhibition of lncRNA MAAT Controls Multiple Types of Muscle Atrophy by cis- and trans-Regulatory Actions. Mol. Ther. 2021, 29, 1102–1119.
108. Zhou, L.; Sun, K.; Zhao, Y.; Zhang, S.; Wang, X.; Li, Y.; Lu, L.; Chen, X.; Chen, F.; Bao, X.; et al. Linc-YY1 promotes myogenic differentiation and muscle regeneration through an interaction with the transcription factor YY1. Nat. Commun. 2015, 6, 10026.
109. Ponnusamy, M.; Liu, F.; Zhang, Y.-H.; Li, R.-B.; Zhai, M.; Liu, F.; Zhou, L.-Y.; Liu, C.-Y.; Yan, K.-W.; Dong, Y.-H.; et al. Long Noncoding RNA CPR (Cardiomyocyte Proliferation Regulator) Regulates Cardiomyocyte Proliferation and Cardiac Repair. Circulation 2019, 139, 2668–2684.

110. Cipriano, A.; Macino, M.; Buonaiuto, G.; Santini, T.; Biferali, B.; Peruzzi, G.; Colantoni, A.; Mozzetta, C.; Ballarino, M. Epigenetic regulation of wnt7b expression by the cis-acting long noncoding rna lnc-rewind in muscle stem cells. Elife 2021, 10, e54782.

111. Mercer, T.R.; Mattick, J.S. Structure and function of long noncoding RNAs in epigenetic regulation. Nat. Struct. Mol. Biol. 2013, 20, 300–307.

112. Alvarez, S.; Díaz, M.; Flach, J.; Rodriguez-Acebes, S.; López-Contreras, A.J.; Martínez, D.; Cañamero, M.; Fernández-Capetillo, O.; Isern, J.; Passegué, E.; et al. Replication stress caused by low MCM expression limits fetal erythropoiesis and hematopoietic stem cell functionality. Nat. Commun. 2015, 6, 8548.

113. Wang, H.; Hertlein, E.; Bakkar, N.; Sun, H.; Acharyya, S.; Wang, J.; Carathers, M.; Davuluri, R.; Guttridge, D.C. NF-κB Regulation of YY1 Inhibits Skeletal Myogenesis through Transcriptional Silencing of Myofibrillar Genes. Mol. Cell. Biol. 2007, 27, 4374–4387.

114. Ballarino, M.; Cazzella, V.; D'Andrea, D.; Grassi, L.; Bisceglie, L.; Cipriano, A.; Santini, T.; Pinnarò, C.; Morlando, M.; Tramontano, A.; et al. Novel Long Noncoding RNAs (lncRNAs) in Myogenesis: A miR-31 Overlapping lncRNA Transcript Controls Myoblast Differentiation. Mol. Cell. Biol. 2015, 35, 728–736.

115. Tzimagiorgis, G.; Michailidou, E.Z.; Kritis, A.; Markopoulos, A.K.; Kouidou, S. Recovering circulating extracellular or cell-free RNA from bodily fluids. Cancer Epidemiol. 2011, 35, 580–589.

116. El-Mogy, M.; Lam, B.; Haj-Ahmad, T.A.; McGowan, S.; Yu, D.; Nosal, L.; Rghei, N.; Roberts, P.; Haj-Ahmad, Y. Diversity and signature of small RNA in different bodily fluids using next generation sequencing. BMC Genomics 2018, 19, 408.

117. Cacchiarelli, D.; Legnini, I.; Martone, J.; Cazzella, V.; D'Amico, A.; Bertini, E.; Bozzoni, I. miRNAs as serum biomarkers for Duchenne muscular dystrophy. EMBO Mol. Med. 2011, 3, 258–265.

118. Zaharieva, I.T.; Calissano, M.; Scoto, M.; Preston, M.; Cirak, S.; Feng, L.; Collins, J.; Kole, R.; Guglieri, M.; Straub, V.; et al. Dystromirs as Serum Biomarkers for Monitoring the Disease Severity in Duchenne Muscular Dystrophy. PLoS One 2013, 8, e80263.

119. Coenen-Stass, A.M.L.; Betts, C.A.; Lee, Y.F.; Mäger, I.; Turunen, M.P.; EL Andaloussi, S.; Morgan, J.E.; Wood, M.J.A.; Roberts, T.C. Selective release of muscle-specific, extracellular microRNAs during myogenic differentiation. Hum. Mol. Genet. 2016, 25, 3960–3974.

120. Coenen-Stass, A.M.L.; Sork, H.; Gatto, S.; Godfrey, C.; Bhomra, A.; Krjutškov, K.; Hart, J.R.; Westholm, J.O.; O'Donovan, L.; Roos, A.; et al. Comprehensive RNA-Sequencing Analysis in Serum and Muscle Reveals Novel Small RNA Signatures with Biomarker Potential for DMD. Mol. Ther.-Nucleic Acids 2018, 13, 1–15.

121. Perfetti, A.; Greco, S.; Cardani, R.; Fossati, B.; Cuomo, G.; Valaperta, R.; Ambrogi, F.; Cortese, A.; Botta, A.; Mignarri, A.; et al. Validation of plasma microRNAs as biomarkers for myotonic

dystrophy type 1. Sci. Rep. 2016, 6, 38174.