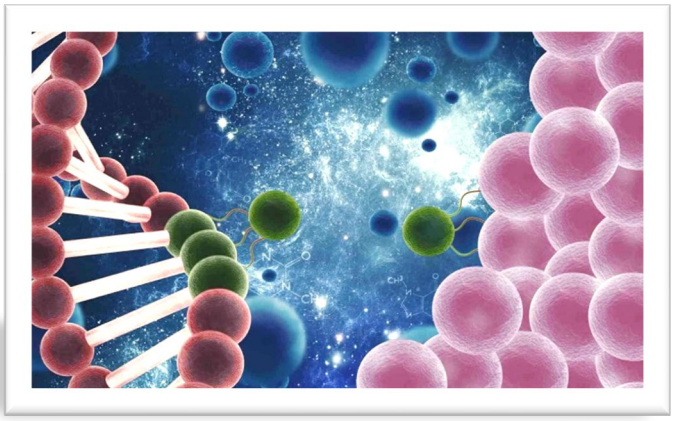
What are you waiting for? The science of **REGENERATION IS READY FOR YOU**. Let us guide you to **ANSWERS** and **SOLUTIONS.**

*"Regenerative medicine is a rapidly evolving multidisciplinary, translational research enterprise whose explicit purpose is to advance technologies for the **repair and replacement of damaged cells, tissues, and organs**. Scientific progress in the field has been steady and expectations for its robust clinical application continue to rise."* [1]



Check the date: we knew this 10 years ago....

Get the Science Right --- Recapturing Peak Youth Is Actually Possible

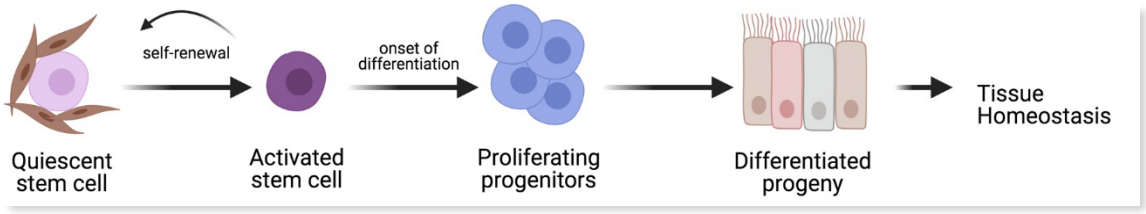


Figure 1 [2]

RESPONSIVE REGENERATION

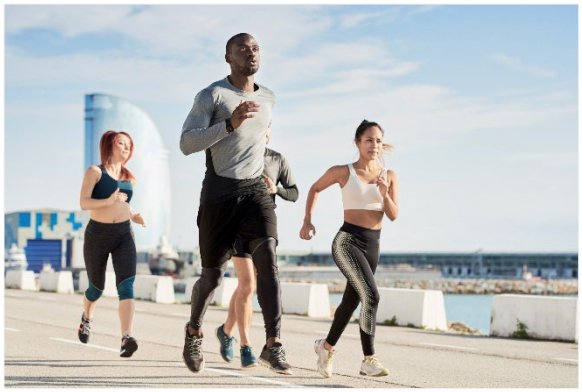
You may be needlessly living with chronic pain and debilitation

Talk to your Clinician

PROACTIVE REGENERATION

Don't wait to experience deterioration or subpar performance

Visit Asciere.com for more information



*"Adult ('tissue') stem cells [can] maintain tissue homeostasis and facilitate repair.... Therefore, considerable effort is being invested in **restoring stem cell function to counter degenerative diseases and age-related tissue dysfunction**."* [3]

*"As our understanding [of the different roles of miRNA] continues to expand, so does the therapeutic potential of **modulating specific miRNAs to change the course of the aging process and associated diseases**."* [4]

Synopsis of Regenerative Science

Regenerative science theory has historically focused on living stem cells. Because this necessarily restricted product sourcing based on DNA, blood type, and other factors, the process for acquiring serviceable stem cells for regenerative therapy was complex and often painful (e.g. bone marrow extraction).

As an educational and disease-state awareness platform, Asciere embraces progressive theories in this science that consistently demonstrate the regenerative capacity of stem cells is not derived from their mere existence. Rather, stem cells have regenerative capacity because they naturally produce and express proteins from mRNA in response to physiological activity and development. It is these expressions or **regenerative messages** from the stem cells that truly promote natural healing and growth.

While it is true that everyone experiences natural attrition in their stem cell count as they age, traditional "stem-cell therapies" that attempt to replace or supplement stem cell counts have produced mixed results. In fact, there is compelling research which contends that a significant number of the stem cells from these procedures actually fail to establish themselves within a person's biome and they are ultimately rejected by the body altogether, producing little or no effect.

This raises a threshold question that requires a thoughtful answer. Should regenerative science focus solely on stem cells or the **regenerative messages** they produce?

There is no binary answer to a complex question like this. However, advancements in understanding this science have begun shifting focus from stem cells (themselves) over to the regenerative messages they produce. To wit, sophisticated laboratories can subject stem cells to normal biological stressors so they naturally express proteins, mRNA and miRNA. Moreover, importantly, it is then possible to isolate these expressions – **regenerative messages** – so that what is collected has no residual DNA or idiosyncratic biomarkers of any kind. In other words, this evolution in the science results in a synthesis of naturally regenerative material that can be safely applied to practically anyone.

Products Associated with Protocols

Note: Asciere does not manufacture any products that are associated with the protocol guidance it has gathered. Instead, Asciere closely monitors developments in the science and uses that knowledge to maintain a dynamic set of criteria for evaluating manufacturers' products.

Asciere Educational Video Content

Manufacturing and Diagnostic Benchmarks

- Safe and responsible manufacturers source gestational tissue from regulated donor services by caesarian in selected hospitals, demographics, ages, genetics, and multi-variate testing. All donor services should be led by Certified Tissue Bank Specialists (CTBS), following FDA, HIPAA, and American Association of Tissue Bank (AATB) standards.

- Donor serology should be conducted by a third-party FDA licensed, CLIA accredited lab tested for Genetics, HIV, HTLV, Hepatitis B, Hepatitis C, Syphilis, CMV, Zika, EBV, Hepatitis E, HHV6, HHV7, HHV8, HSV1, HTLV1, HTLV2, BKV, and Norovirus. These criteria exceed all testing and quarantine requirements for donor and tissue down to endotoxin levels safe for intrathecal administration.

- These sourcing and serology procedures ensure all products can be certified by third parties for release and homologous use in patients. Moreover, the absence of DNA removes the risk of adverse reactions, off-target effects, and contraindications.

- Third-party diagnostics are essential to validate that products manufactured using this methodology have efficacy levels consistent with what occurs naturally in early youth (i.e. > 300 expressions). This closes the loop from sourcing through to production to ensure that application will not only be safe but also optimally effective.

Note: Cell Factors are NOT regulated class controlled - 1.) HCT/Ps. 21 C.F.R. § 1271.3; 2.) 351 or 3.) 361. See 21 C.F.R.§ 201.128 (drugs and biologics); see also 21 C.F.R. § 801.4 (medical devices) under FDA - Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products Minimal Manipulation and Homologous Use. Approved manufacturers must act under ISO 10993 standards and be FDA registered for human tissue products (HCT/P) in compliance with the requirements of Section 361 of the PHS Act and 21 CFR §1271.10 and core CGTP specified in 21 CFR §1271.180.

Clinical Services Associated with Protocols

Note: Asciere does not provide clinical services for any protocol guidance it has gathered. Instead, Asciere closely monitors clinical best practices for applying these protocols. As a support option, Asciere can arrange Concierge Clinical Services from third-party clinicians that meet or exceed essential application benchmarks as outlined below.

Clinical Application Benchmarks

- As noted in all Asciere's guidance, all applications should be administered by a Licensed Physician.

- If/as applicable, clinical services should include pre- and post-application imaging of organs, tissue, or joints (et al) to assess indications accurately and monitor progress incisively. Please note that imaging services typically increase overall costs.

- For indications that require injections (in addition to validating licensure), it is prudent to confirm clinicians have particularized training for each specific application. For example, the American Arthritis Foundation offers training and certification to clinicians for joint injections which are intended to elevate the standard of care and create additional peace of mind.

- It is worth inquiring whether one's chosen clinician has the capacity to conduct pre- and post-testing of cell vitality at application sites to validate that individual biological responses align with expectations. Please note that cell vitality testing typically increases overall costs.

Next-Level Research and Commentary

Transcription (mRNA) and translation do not occur in a vacuum. They are highly regulated by chromatin remodeling, histone modifications, methylation and regulatory RNAs (LnRNAS and miRNAs), and post-transcriptional and translational modifications. Multiple biological functions overlap and act synergistically to produce effects. Compared to placebo (control), secretome components induce gene expressions > 1.5X up and down to establish effect.

True Potential

The science demonstrates that complete regenerative messaging remodels to youthful stasis, including but not limited to:

- Joints
- Auto-immunity
- Mutations
- Hormones
- Cognition
- Muscle
- Neurological
- Cardiovascular
- Pulmonary
- Organs

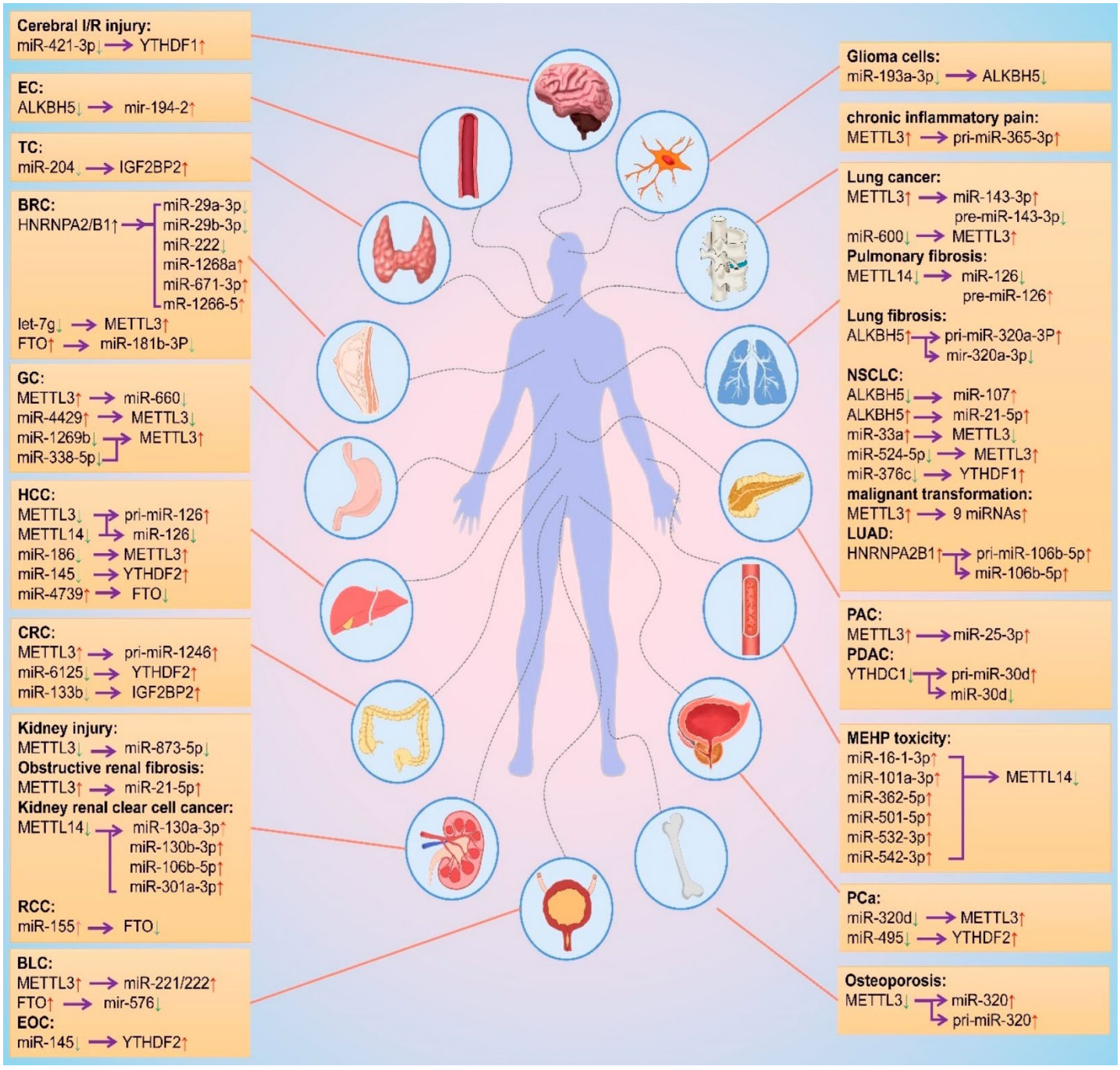
RNA from monocytes, macrophages, neutrophils, epithelial, mesenchymal, adipocytes, progenitors and multiple stem cell lineages promotes up and down regulation for:

- Immunomodulatory
- Pro-inflammatory
- Anti-inflammatory
- All tissue balance
- Proteolytic enzymes and proteolytic enzyme inhibitors
- Cytokines
- Angiogenesis
- Proliferation of fibroblasts, osteoblasts, tenocytes
- Vascular smooth muscle cells
- Degradation of gelatin and denatured collagen including I, II and V

Moreover, this provides a conductive scaffold for cell migration and proliferation during tissue repair and remodeling near the sites of application along with removal of dead tissues following inflammation.

See Figure 1 on the following page.

Figure 1 – **"Mutual Regulation between m^{6}A Modifications and miRNAs.** The red and green arrows represent the level rise and fall, respectively. The purple arrows point to the regulated object. EC: esophageal cancer; TC: thyroid cancer; BRC: breast cancer; GC: gastric cancer; HCC: hepatocellular carcinoma; CRC: colorectal cancer; RCC: Renal cell carcinoma; BLC: bladder cancer; EOC: epithelial ovarian cancer; NSCLC: non-small cell lung cancer; LUAD: lung adenocarcinoma; PAC: pancreatic cancer; PDAC: Pancreatic ductal adenocarcinoma; PCa: prostate cancer." [5]



Scientific Details

Ideal products are commonly constituted as follows:

- Biocompatible and/or bioinert components - water (98.24 wt.%)
- Soluble salts of sodium chloride (0.64 wt.%)
- Potassium phosphates (0.02 wt.%)
- Salts of uric acid (0.01 wt.%), glucose (0.02 wt.%)
- Soluble proteins (~ 10^3 µg/mL) representing approximately 0.54 wt.% of product mass.

Standard unit osmolarity is 290-305 mOsm/kg with a pH of 7.0-7.2 and is considered isobaric.

Reconstitution from dry weight to isobaric is also possible for specific applications (IV, CSF, IA, IM, SQ).

Medium per application may include normal saline, RPMI, DMEM.

As noted above, constitution and concentration should be validated through third-party diagnostics.

See Table 1 on the following page.

- Functions and responses outlined in Table 1 are typically experienced only when applied under a complete milieu over a prescribed period of time.
- **X** signifies no assays or amounts too low for an effect.

Table 1 – miRNA Constitution and Concentration Comparative Matrix

miRNA	Symbol	Gene Summary Regulation	National Library of Medicine Ref	Ideal Product	Wharton's Jelly	Amnion	PRP	Bone Marrow	~ ng/ml	~ µg/ml
miR-5011-5p	**AR**	Hormones	https://pubchem.ncbi.nlm.nih.gov/gene/367	☑	✗	✗	✗	✗	25-100+	1-100³
miR-4531	**BMP-2**	Bone, cartilage	https://pubchem.ncbi.nlm.nih.gov/gene/650	☑	☑	✗	✗	✗	25-100+	1-100³
miR-6867-5p	**BMP-4**	Heart	https://pubchem.ncbi.nlm.nih.gov/gene/652	☑	✗	✗	✗	✗	25-100+	1-100³
miR-6867-5p	**BMP-5**	Metabolism	https://pubchem.ncbi.nlm.nih.gov/gene/653	☑	✗	✗	✗	✗	25-100+	1-100³
miR-1185-2-3p	**BMP-7**	Bone, cartilage and muscle	https://pubchem.ncbi.nlm.nih.gov/gene/655	☑	☑	✗	✗	☑	25-100+	1-100³
miR-302e	**GDF-11**	Nervous, organ systems, aging	https://pubchem.ncbi.nlm.nih.gov/gene/10220	☑	✗	✗	✗	✗	25-100+	1-100³
miR-499b-5p	**GDF-15**	Inflammation, cell repair, growth, oxid stress	https://pubchem.ncbi.nlm.nih.gov/gene/9518	☑	☑	☑	✗	✗	25-100+	1-100³
miR-32-3p	**NTF-3**	Central nervous system	https://pubchem.ncbi.nlm.nih.gov/gene/4908	☑	✗	✗	✗	✗	25-100+	1-100³
miR-8070	**NTF-4**	Peripheral nervous system	https://pubchem.ncbi.nlm.nih.gov/gene/4909	☑	☑	✗	✗	✗	25-100+	1-100³
miR-3942-3p	**TGFa**	Gastrointestinal	https://pubchem.ncbi.nlm.nih.gov/gene/7039	☑	✗	✗	✗	✗	25-100+	1-100³
miR-663a	**TGF-ß1**	Growth regulation	https://pubchem.ncbi.nlm.nih.gov/gene/7040	☑	✗	✗	✗	✗	25-100+	1-100³
miR-6783-5p	**TGF-ß3**	Inflammation and immune system	https://pubchem.ncbi.nlm.nih.gov/gene/7043	☑	☑	☑	☑	☑	25-100+	1-100³
miR-643	**PIGF**	Growth	https://pubchem.ncbi.nlm.nih.gov/gene/5228	☑	☑	✗	✗	✗	25-100+	1-100³
miR-1277-5p	**VEGFA**	Vasculature, inflammation regulation	https://pubchem.ncbi.nlm.nih.gov/gene/7422	☑	✗	✗	✗	✗	25-100+	1-100³
miR-410-3p	**VEGF R2**	Endothelial modulation	https://pubchem.ncbi.nlm.nih.gov/gene/3791	☑	✗	✗	✗	✗	25-100+	1-100³
miR-16-5p	**VEGF R3**	Vasculature, organ systems	https://pubchem.ncbi.nlm.nih.gov/gene/2324	☑	☑	✗	✗	✗	25-100+	1-100³
miR-5692a	**IL-1RA**	Auto-immune	https://pubchem.ncbi.nlm.nih.gov/gene/3552	☑	☑	✗	✗	✗	25-100+	1-100³
miR-11181-5p	**IL-6**	Auto-immune B cells	https://pubchem.ncbi.nlm.nih.gov/gene/3569	☑	✗	✗	✗	✗	25-100+	1-100³
miR-379-3p	**IL-10**	Immunoregulator intestinal tract	https://pubchem.ncbi.nlm.nih.gov/gene/3586	☑	✗	✗	✗	✗	25-100+	1-100³
miR-545-5p	**IL-12**	Inflammation and macrophage modulation	https://pubchem.ncbi.nlm.nih.gov/gene/3593	☑	☑	✗	✗	✗	25-100+	1-100³
miR-5692a	**TNF-RI**	Tumor suppressor	https://pubchem.ncbi.nlm.nih.gov/protein/Q15628	☑	✗	✗	✗	✗	25-100+	1-100³
miR-4263	**TNF-RII**	Apoptosis	https://pubchem.ncbi.nlm.nih.gov/gene/7133	☑	✗	☑	☑	☑	25-100+	1-100³

Table 1 – miRNA Constitution and Concentration Comparative Matrix *continued*

miRNA	Symbol	Gene Summary Regulation	National Library of Medicine Ref	Ideal Product	Wharton's Jelly	Amnion	PRP	Bone Marrow	~ ng/ml	~ µg/ml
miR-6835-3p	**PDGF-A**	Platelet and vasculature growth	https://pubchem.ncbi.nlm.nih.gov/gene/5154	☑	☑	✗	✗	☑	25-100+	1-100³
miR-6867-5p	**PDGF-B**	Modulates soft and hard tissues	https://pubchem.ncbi.nlm.nih.gov/gene/5155	☑	☑	✗	✗	✗	25-100+	1-100³
miR-1293	**TIMP-1**	Cell health, cytokine activity	https://pubchem.ncbi.nlm.nih.gov/gene/7076	☑	✗	✗	✗	✗	25-100+	1-100³
miR-544a	**TIMP-2**	Cartilage and extracellular matrix	https://pubchem.ncbi.nlm.nih.gov/gene/7077	☑	☑	☑	☑	☑	25-100+	1-100³
miR-4714-3p	**HGF**	Liver	https://pubchem.ncbi.nlm.nih.gov/gene/3082	☑	☑	✗	✗	✗	25-100+	1-100³
miR-6832-3p	**GDNF**	Nerve survival	https://pubchem.ncbi.nlm.nih.gov/gene/2668	☑	✗	✗	✗	✗	25-100+	1-100³
miR-3121-3p	**BDNF**	Central nervous system	https://pubchem.ncbi.nlm.nih.gov/gene/627	☑	✗	✗	✗	✗	25-100+	1-100³
miR-5692a	**FGF-4**	Soft tissue repair	https://pubchem.ncbi.nlm.nih.gov/gene/2249	☑	✗	✗	✗	✗	25-100+	1-100³
miR-126-5p	**FGF-7**	Collagen and connective tissue	https://pubchem.ncbi.nlm.nih.gov/gene/2252	☑	☑	☑	☑	✗	25-100+	1-100³
miR-190a-3p	**IGFBP-1**	IGF binding protein	https://pubchem.ncbi.nlm.nih.gov/gene/3484	☑	☑	✗	✗	✗	25-100+	1-100³
miR-3667-3p	**IGFBP-2**	T-cell	https://pubchem.ncbi.nlm.nih.gov/gene/3485	☑	✗	✗	✗	✗	25-100+	1-100³
miR-374a-5p	**IGFBP-3**	Smooth muscle	https://pubchem.ncbi.nlm.nih.gov/gene/3486	☑	✗	✗	✗	✗	25-100+	1-100³
miR-4271	**IGFBP-4**	B-cell pancreas	https://pubchem.ncbi.nlm.nih.gov/gene/3487	☑	✗	✗	✗	✗	25-100+	1-100³
miR-1226-5p	**IGFBP-6**	Anti-tumorigenic	https://pubchem.ncbi.nlm.nih.gov/gene/3489	☑	✗	✗	✗	✗	25-100+	1-100³
miR-1297	**PTEN**	Tumor suppressor	https://pubchem.ncbi.nlm.nih.gov/gene/5728	☑	✗	✗	✗	✗	25-100+	1-100³
miR-3121-3p	**CSF3**	Bone marrow and stem cells	https://pubchem.ncbi.nlm.nih.gov/gene/1440	☑	✗	✗	✗	☑	25-100+	1-100³
miR-4795-3p	**CCR1**	White blood cells	https://pubchem.ncbi.nlm.nih.gov/gene/1230	☑	☑	✗	✗	☑	25-100+	1-100³
miR-3671	**MIGA1**	Mitochondria	https://pubchem.ncbi.nlm.nih.gov/gene/374986	☑	☑	✗	✗	✗	25-100+	1-100³
miR-6825-5p	**NGFR**	Nerve growth	https://pubchem.ncbi.nlm.nih.gov/gene/4804	☑	✗	✗	✗	✗	25-100+	1-100³
miR-141-5p	**EGFR**	Skin collagen	https://pubchem.ncbi.nlm.nih.gov/gene/1956	☑	☑	☑	☑	☑	25-100+	1-100³
miR-374a-5p	**GH**	Multi-tissue growth and metabolism	https://pubchem.ncbi.nlm.nih.gov/gene/2688	☑	✗	✗	✗	✗	25-100+	1-100³
miR-6867-5p	**IGF-1**	Cell growth	https://pubchem.ncbi.nlm.nih.gov/compound/16131429	☑	✗	✗	✗	✗	25-100+	1-100³

Direct Citations

[1] Christ GJ, Saul JM, Furth ME, Andersson KE. The pharmacology of regenerative medicine. *Pharmacol Rev.* 2013 Jul 1;65(3):1091-133. doi: 10.1124/pr.112.007393. PMID: 23818131; PMCID: PMC3698935.

[2] Rando TA, Jones DL. Regeneration, Rejuvenation, and Replacement: Turning Back the Clock on Tissue Aging. *Cold Spring Harb Perspect Biol*. 2021 Sep 1;13(9):a040907. doi: 10.1101/cshperspect.a040907. PMID: 34187808; PMCID: PMC8411956.

[3] Ibid.

[4] Kinser HE, Pincus Z. MicroRNAs as modulators of longevity and the aging process. *Hum Genet*. 2020 Mar;139(3):291-308. doi: 10.1007/s00439-019-02046-0. Epub 2019 Jul 11. PMID: 31297598; PMCID: PMC6954352.

[5] Mei, Z.; Mou, Y.; Zhang, N.; Liu, X.; He, Z.; Gu, S. Emerging Mutual Regulatory Roles between m^{6}A Modification and microRNAs. *Int. J. Mol. Sci.* 2023, *24*, 773.

Other References

https://www.sciencedirect.com/science/article/pii/S000294401500259X

https://academic.oup.com/stcltm/article/3/8/969/6388222

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3881095/

https://www.sciencedirect.com/science/article/pii/S0014579311003589

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6954352/

https://stemcellres.biomedcentral.com/articles/10.1186/s13287-017-0551-0/tables/1

https://www.frontiersin.org/articles/10.3389/fgene.2012.00191/full

https://www.mdpi.com/2079-7737/9/12/486

https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/antagomir