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First in Class MicroRNA Therapy Regenerates Heart Tissue to Treat Heart Failure

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A Resurgence of Interest in CV investment

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BioPharmaDive Oct 8, 2020:

Two big deals for heart drugs in less than a year might give the impression that more could soon follow.

But what Bristol Myers Squibb did this Monday with its $13 billion bid for MyoKardia, and what Novartis did last November with its $10 billion buy of The Medicines Co., was in an already shallow pool of biotechs that work on cardiovascular drugs. With relatively few left to pick from, industry followers expect some time to pass before they see a steady stream of M&A.

"There's a scarcity of assets in cardiology," said Salim Syed, an analyst at Mizuho Securities USA

Venture firms mostly steered clear of cardiovascular research over the last decade, opting instead to put their money into biotechs focused on cancer, the brain or the immune system. And yet, recent takeouts may be able to drum up more interest in heart drugs, as the right assets can clearly fetch a high price and a significant return for investors.

A Pre-Seed Biotech Company with a Seasoned Scientific and Technical Management Team

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Edward E. Morrisey, Ph.D. (Scientific co-founder)

- Inventor of miRNA-302 technology - International leader in pulmonary & cardiovascular development and regenerative biology
- Professor - University of Pennsylvania
- Scientific Director - Penn Inst for Regenerative Medicine (IRM)

Jason Burdick, PhD (Formulation Technology)

- Professor of Bioengineering - UPenn School of Engineering
- Expert in gel formulations for cardiac delivery

Funding: $200,000 invested by founder

Awarded $273,000 SBIR grant for initial porcine PK/PD studies

Seeking $1.8 M seed funding to pig model POC / clinical development decision

A Significant Unmet Need, with 3M US Patients Living with Heart Failure after a Heart Attack

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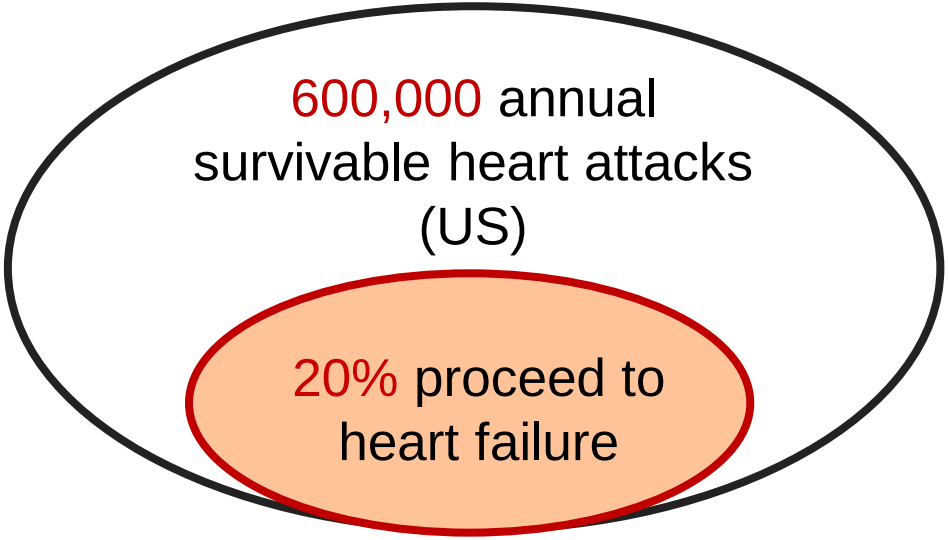

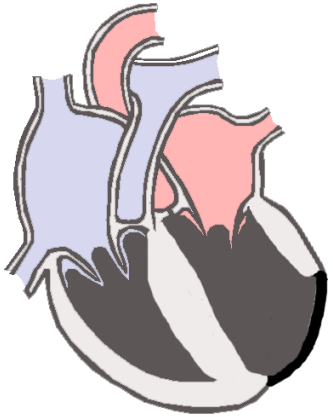

- >3 million US people suffer from heart failure after a heart attack
- HF represents an annual economic burden of >$30 billion (US)

PRO-302 Has the Potential to Prevent Heart Failure by Regenerating Heart Tissue

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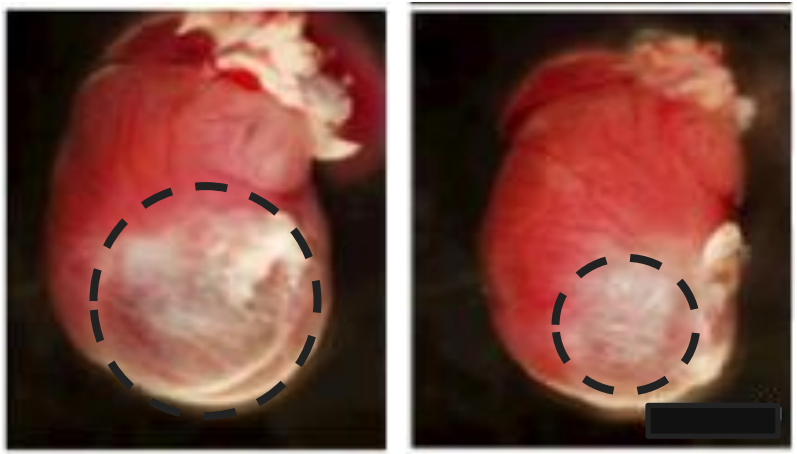
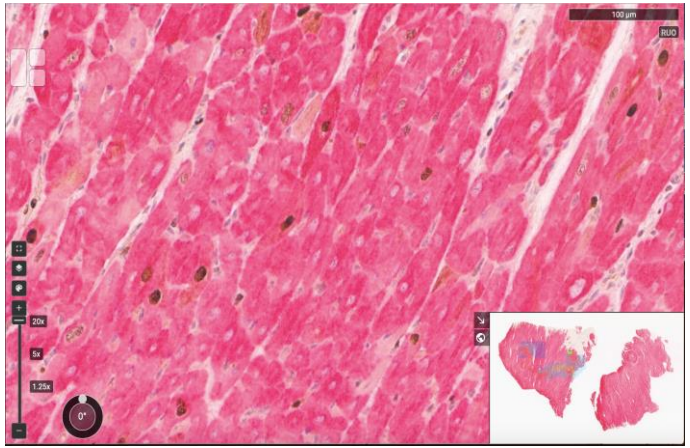
Mouse heart after heart attack treated with PRO-302 shows a reduced area of damaged tissue



untreated treated

Pig heart treated with PRO-302 show cardiomyocyte proliferation (indicated by brown spots)



Infarct on day 0, PRO-302 injection into infarct border zone on day 7, sample/IHC on day 18

Functional Recovery

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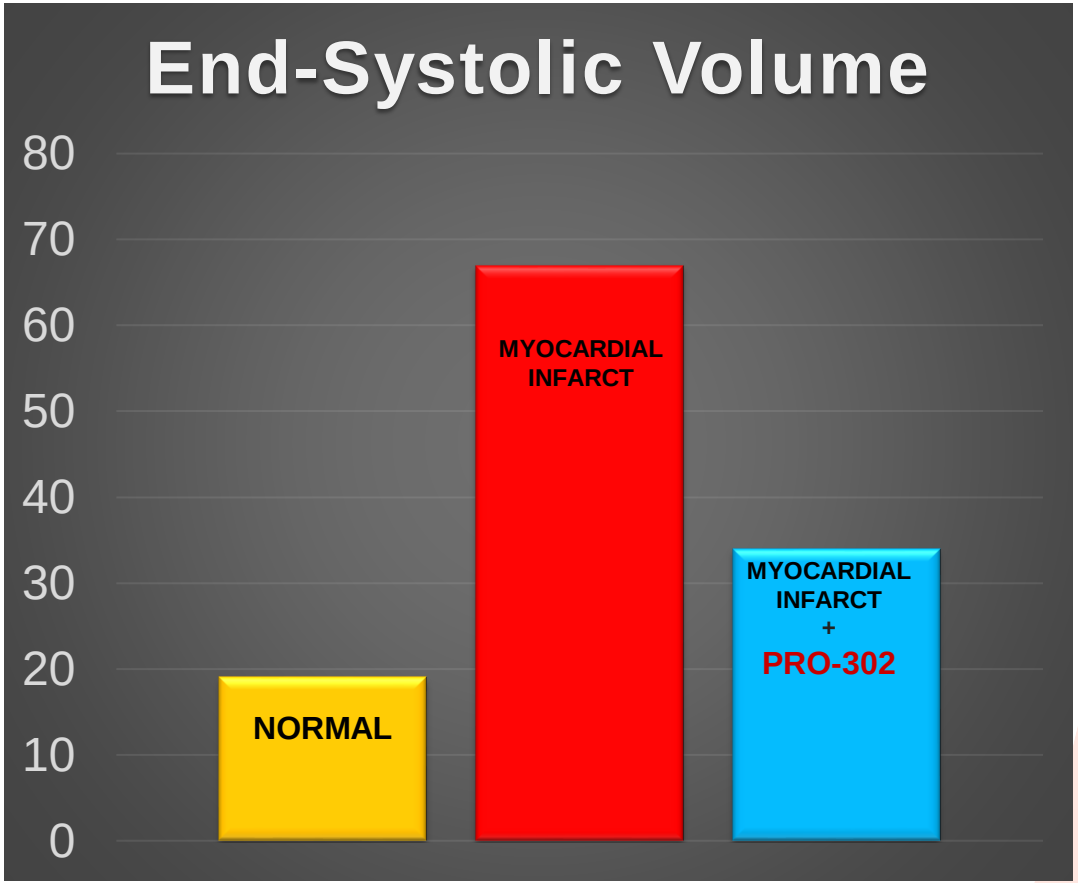
Recovery of cardiac function in mice (week 4 after infarct)



For details, see
Wang et al., Nat Biomed Eng. 2017; 1:983-992.

Nobel Prize-Winning RNA Technology is Used to Transiently Deliver a miRNA Involved in Proliferation to the Heart

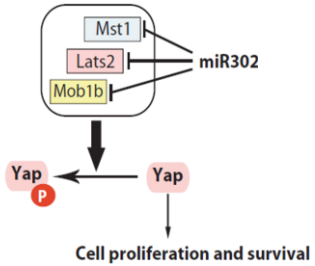
Over the last two years, small RNA-based molecules have produced successful medicines in a variety of diseases, including a cardiovascular indication

Aug 10, 2018 **Alnylam Announces First-Ever FDA Approval of an RNAi Therapeutic, ONPATTRO™ (patisiran) for the Treatment of the Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis in Adults.**

Nov 20, 2019 **FDA approves givosiran (GIVLAARI, Alnylam) for adults with acute hepatic porphyria.**

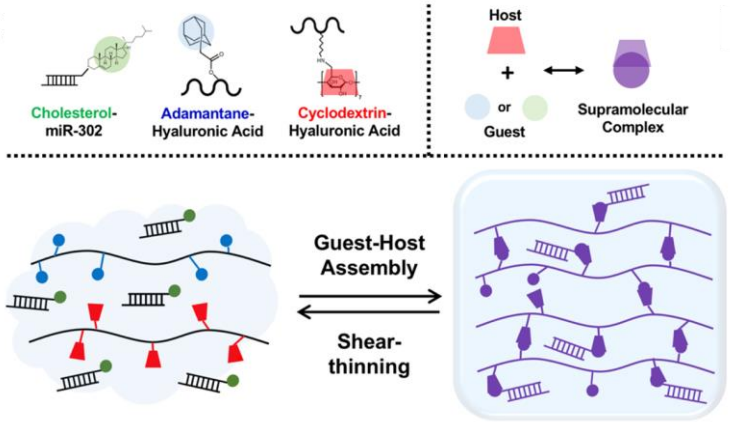
Jan 06, 2020 **Novartis successfully completes acquisition of The Medicines Company, adding a potentially first-in-class, investigational cholesterol-lowering therapy inclisiran. The New Drug Application (NDA) for inclisiran was submitted to the FDA in December 2019 and inclisiran is now recommended for approval by EMA's CHMP.**

Prolifagen's miR-302 potently activates proliferation of adult cardiomyocytes by impacting the Hippo pathway



A Patented Hydrogel Formulation Ensures a 7 Day Transient Local Delivery

PRO-302 is composed of miR-302 and a shear-thinning hydrogel



Schematic illustration of hyaluronic acid (HA) modified with β-cyclodextrin (CD-HA, red) and adamantane (Ad-HA, blue) with the assembly (self-healing, purple) and disassembly (shear-thinning) of the guest–host complex. Encapsulation and delivery of Cholesterol-labeled microRNA (green) upon *in vivo* delivery.

Local hydrogel delivery to the border zone of myocardial infarct directs targeted, transient cardiomyocyte proliferation, while limiting systemic dissemination

PRO-302 is a first in class approach with few other promising mechanisms in development

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	Prolifagen miR-302	Gene therapy	Stem cells	Angiogenesis -focused approaches	Bio materials	Reperfusion injury prevention
Transient regeneration mechanism – safety	✓	✗	✗	✓	NA	NA
Timing: Opportunity for intervention outside of emergency situation	✓	✓	✓	✓	✓	✗
Single molecular entity (vs. gene therapy or exogenous cells)	✓	✗	✗	✓	NA	✓
Direct regeneration of *functional cardiac muscle*	✓	✓	✓	✗	✗	NA

See attached word document for more info

Prolifagen is planning for a porcine efficacy study and IND enabling studies

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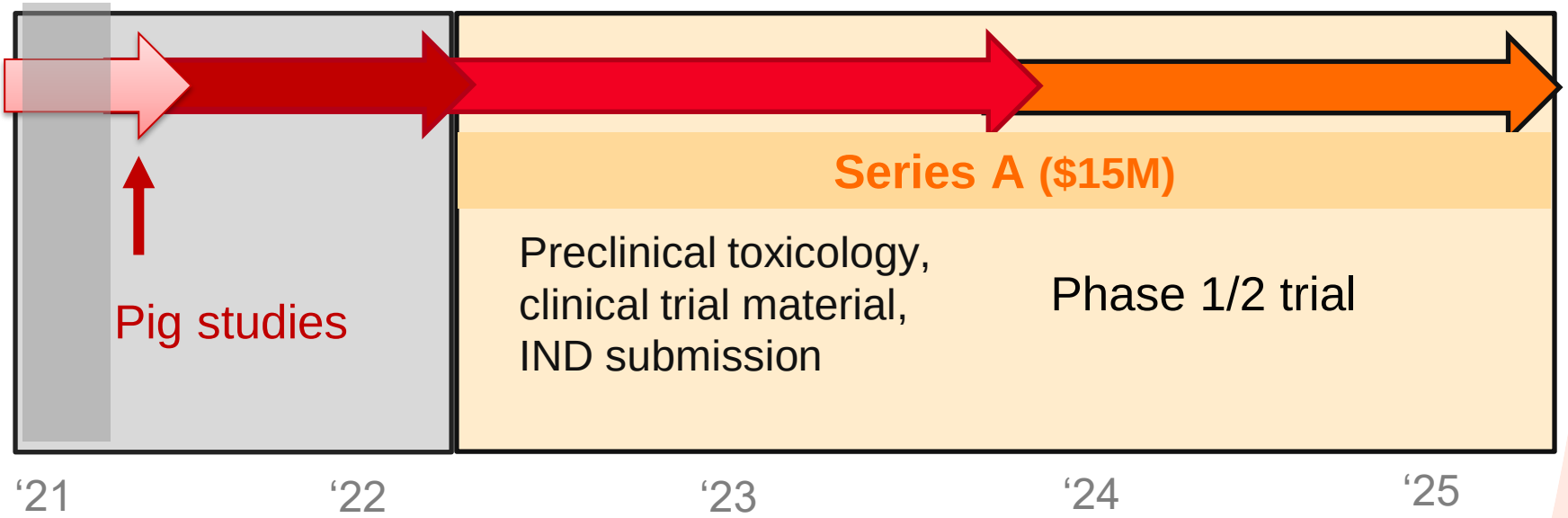
SBIR **Seed ($1.8M)**

Exit: BI, AZ, Novartis, Eli Lilly, CSL-Behring, Bayer, Servier, … **EXIT**



Intellectual Property:
Exclusive licenses from University of Pennsylvania

- Patent 9,115,345 (PCT filed 3/25/2011)
  "MicroRNA induction of pluripotential stem cells and uses thereof"

- "MicroRNA induction of cardiac regeneration"
  - US Patent 10/590,419 issued March 2020.
  - European Patent 3143123

- Patent application filed 04/02/2018; PCT/US2018/25652
  "Compositions and methods for cardiac regeneration"

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Summary

- Breakthrough technology - Single synthetic molecule / single time point of administration/ maximize local effect, minimize systemic dissemination
- HF prevention after MI: large target population / high medical need
- Powerful functional impact in mouse cardiac model / potent activation of cardiomyocyte proliferation in pigs
- $1.8M to clinical effect in pigs / clinical development decision
  - + $ 2.8M to IND
  - + $ 12.2M to clinical phase 1/2 results

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Appendix

Publications

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Tian Y, Liu Y, Wang T, Zhou N, Kong J, Chen L, Snitow F, Morley M, Li D, Petrenko N, Zhou S, Lu M, Gao E, Koch WJ, Stewart KM, Morrisey EE.

A microRNA-Hippo pathway that promotes cardiomyocyte proliferation and cardiac regeneration in mice.

Science Translational Medicine 2015: Vol. 7, Issue 279, p. 279

See also:

- Ge Tao, Jun Wang and James F. Martin Small RNA: From development to regeneration *Science Translational Medicine* 18 Mar 2015: Vol. 7, Issue 279
- Giacca M. RNA mimics as therapeutics for cardiac regeneration: a paradigm shift. *Mol Ther*. 2015 Jun;23(6):984-6

Wang LL, Liu Y, Chung JJ, Wang T, Gaffey AC, Lu M, Cavanaugh CA, Zhou S, Kanade R, Atluri P[3], Morrisey EE, Burdick JA.

Local and sustained miRNA delivery from an injectable hydrogel promotes cardiomyocyte proliferation and functional regeneration after ischemic injury.

Nat Biomed Eng. 2017; 1:983-992.

See also:

- Irene Fernandez-Ruiz A hydrogel–miRNA complex stimulates heart recovery *Nature Reviews Cardiology* Published online 14 Dec 2017; doi:10.1038/nrcardio.2017.210

miR302-367 Promotes Cardiomyocyte Proliferation through Regulation of Hippo Pathway Kinases

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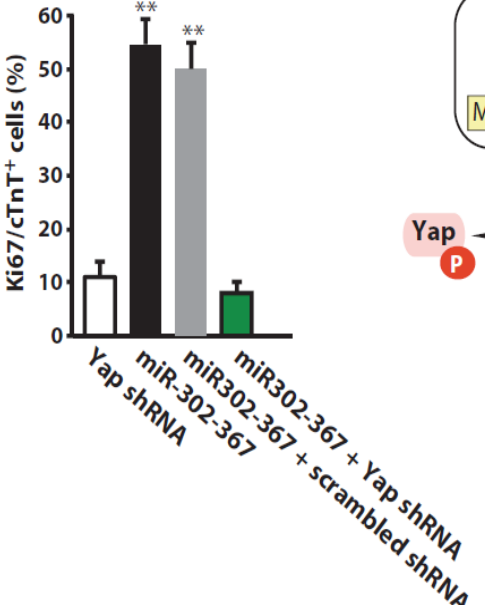

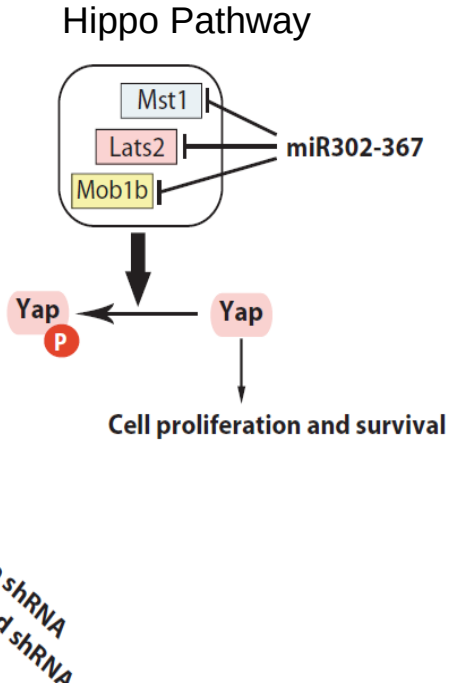

Supporting external literature;

Hippo Pathway Deficiency Reverses Systolic Heart Failure Post-Infarction. Leach JP, Heallen T, Zhang M, Rahmani M, Morikawa Y, Hill MC, Segura A, Willerson JT, Martin JF, *Nature. 2017; 550(7675): 260–264.*

YAP Partially Reprograms Chromatin Accessibility to Directly Induce Adult Cardiogenesis In Vivo. Monroe TO, Hill MC, Morikawa Y, Leach JP, Heallen T, Cao S, Krijger PHL, de Laat W, Wehrens XHT, Rodney GG, Martin JF, *Dev Cell. 2019; 48(6):765-779.e7.*

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Preliminary Clinical/Regulatory Strategy

- Porcine efficacy studies
- Preclinical toxicology; clinical lot - CMC
- Phase 1/2 in 30-60 MI patients (1-2 weeks after AMI)
  - Safety and preliminary efficacy
  - 6 months study with additional safety follow-up
- Phase 2 trial (12 months, 300 patients) to clinical POC
- *Note: FDA recently revised its strict 'outcomes study' based requirements for phase 3 CV studies and is prepared to consider objective surrogate end-points (June 2019).*

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Commercial

Incidence:

- >400,000 new patients per year in US/EU

Pricing and reimbursement:

- MiR-302 will treat the *underlying cause* of post-MI heart failure (rather than disease symptoms) *in one administration*
- Strong arguments for treatment reimbursement
  - Cost of avoided hospitalizations, heart transplants and death

Prolifagen Technology vs. Stem Cells

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- Most cardiac regeneration efforts have been focused on the transfer of exogenously produced stem cells
  ⇒ Poor efficacy due to complexity and **poor implantation** of cells

- Prolifagen's solution
  - MiRNA302, administered transiently to the target tissue, induces **resident** cardiomyocytes to proliferate, then to differentiate into functional cells

FAQs

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- Why will this have a better chance of success than current stem cell efforts?
  - Administration of a single molecular entity induces in situ de-differentiation and re-population with new functional cells without need for implantation of exogenously administered cells (a major limitation in stem cells approaches)
- Administration of RNA molecules for therapeutic purposes has been difficult, due to rapid degradation and difficulty to reach target tissues
  - Local administration of microRNA302 in our formulation at a single time point leads to RNA release for several days and is sufficient to provide the required growth impetus to resident cells in damaged tissue – the lack of persistence of the microRNA favors differentiation to functional adult non-proliferating cells after this initial proliferation phase. A single administration is required.
- The microRNA induces reversion of adult cells to proliferating stem cells – will this approach be oncogenic?
  - The maintenance of the 'proliferative state' requires the *continuous* presence of microRNA302. The lack of persistence of the RNA is a plus in our approach as cells differentiate to adult, functional and non-proliferative cells after the microRNA has decayed.