Micro-RNAs as Biomarkers for Myocardial Damage Following Cardiac Surgery in Children

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- **Successful treatment of disease depends on <u>early detection</u> and <u>appropriate therapy</u>**

- **The presence of certain disease states can be identified by monitoring the expression levels of biomarkers (DNA, RNA, proteins)**

- **Biomarkers are an extremely important tool in areas like oncology, virology inflammation and heart disease**

Congenital Heart Disease (CHD) – some facts:

- **Incidence of congenital heart disease: 8/1000 births**
- **50% of children with CHD will be operated for the repair of the defect during their first years of life**
- **Post-operative myocardial complications are a major cause for morbidity and mortality**

Post-operative myocardial injury

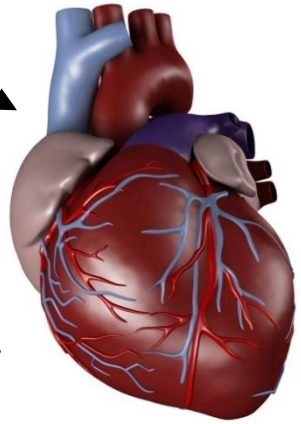
Direct surgical trauma

Hypothermia

Cardiopulmonary bypass (CPB)

Aortic cross clamp (ACC)

Ischemia-reperfusion injury



Myocardial dysfunction

Low cardiac output syndrome

End- organ failure & complications

Can we predict which of the children will suffer from post-operative complications?

The Need

- Serum biomarkers for early and accurate detection of heart damage following pediatric cardiac surgery

- The present biomarkers for detecting heart failure are insufficient as they suffer from lack of specificity (Troponin, CPK)

- Additional biomarkers with increased predictive performances are needed for more precise and earlier prediction of complications after pediatric cardiac surgery

Objective

Development of a diagnostic tool that will improve medical management and outcome following cardiac injury

<u>Adequate Biomarker should be:</u>

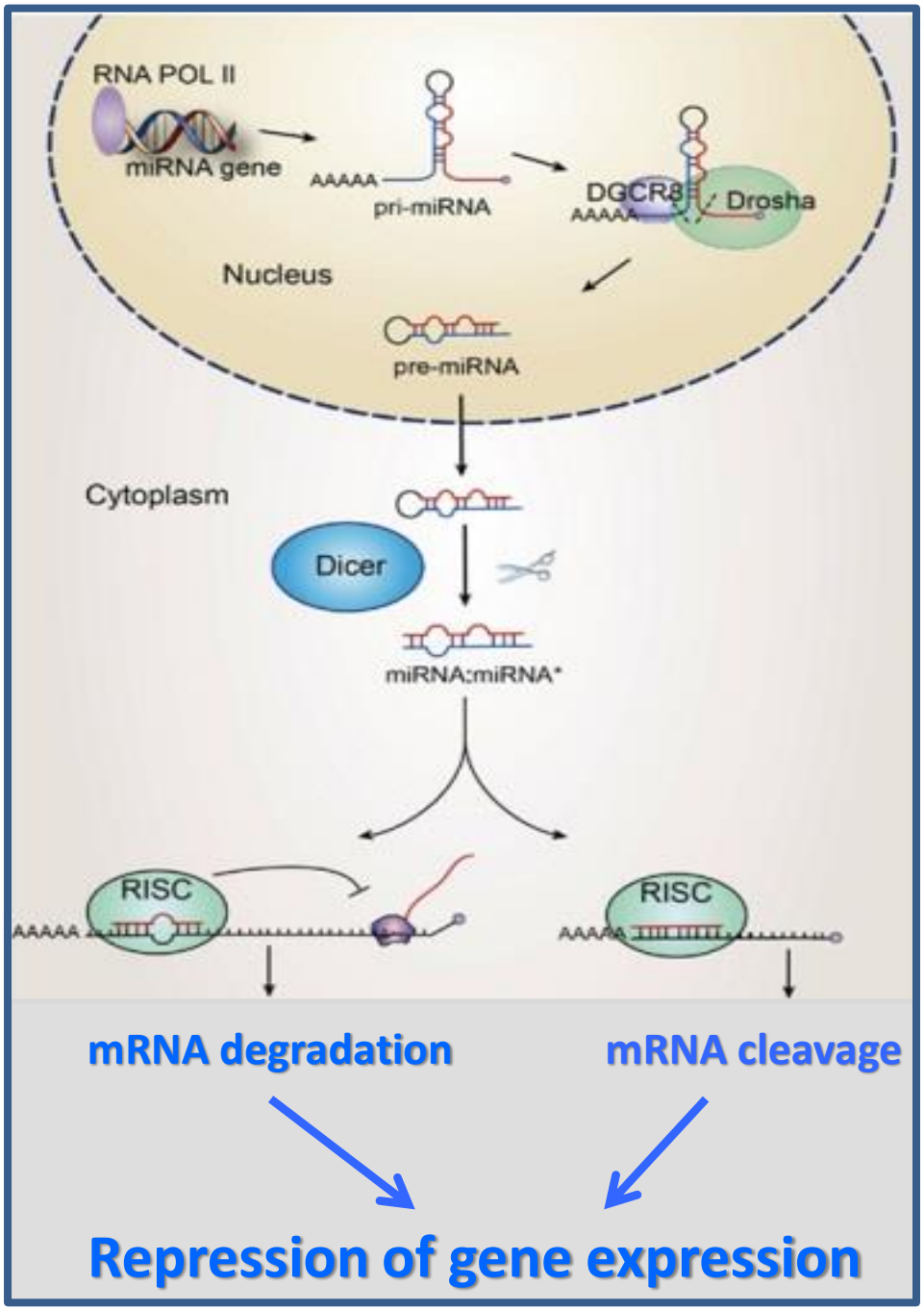
- **Stable**
  - **Rapid release kinetics**
    - **Specific to the organ we would like to monitor**
      - **Detectable in a small sample of plasma**

Micro-RNAs (miRNAs)

- Short non-coding RNAs (~22 nt)
- Encoded by the DNA
- Transcribed by RNA Pol II
- Processed in the nucleus
- Exported to the cytoplasm
- Processed by Dicer
- Repress gene expression by:

  mRNA degradation

  mRNA cleavage



miRNAs

- Involved in all biological processes
- Tissue-specific expression pattern
- Released from cells upon damage
- Few may play a role in cell communication
- High biostability when excreted into plasma

Emerged as plasma biomarkers for many pathological states (cancer, diabetes, viral infections)

Overview of our Study

- Samples were obtained from 79 pediatric patients with CHD, pre-operatively (0), 6, 12 and 24 hours after the operation
- miRNAs were extracted from plasma samples
- The relative amount of the miRNAs in plasma was measured by QRT-PCR
- Demographic and medical information regarding the patients was collected and processed
- The miRNAs of interest: miR-208a, miR-208b, miR-499

Table of demographic parameters

Age (y) (median)	0.57
Weight (Kg) (median)	6
Sex - male	44 (56%)
Non Elective/ Elective	29/50
Mortality	4

Types of operations

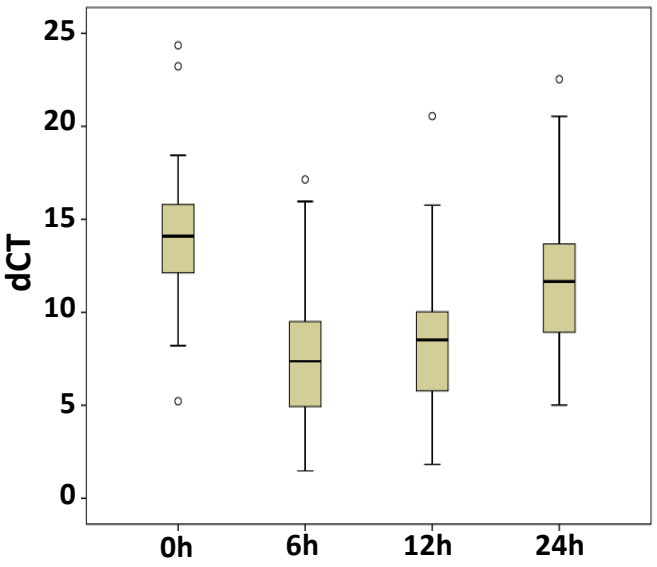
VSD/ASD	17
AV CANAL	4
TGA	13
TOF	9
COA+arch repair	7
BT shunt	5
Norwood	5
Glenn	5
Fontan	6
RV to PA conduit	8
Total	79

Surgical characteristics

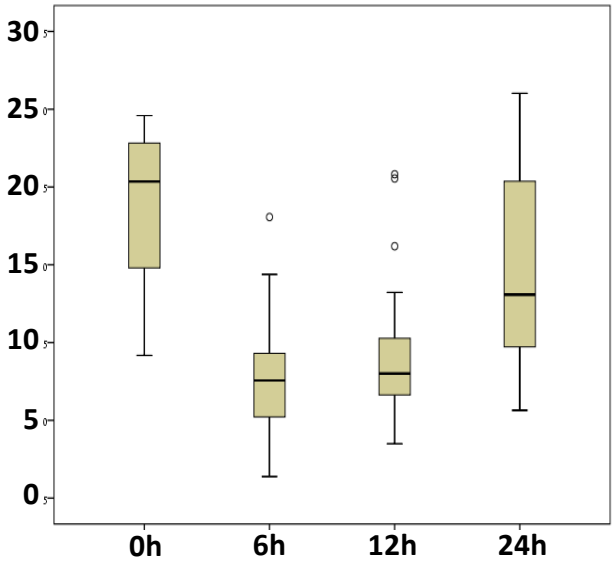
Hospitalization length (days) (median)	8
Non-invasive ventilation (days) (median)	1.16
Invasive ventilation (days) (median)	0.91
Children requiring reintubation	16
No. of children on ECMO	3
Max. Inotropic score (median)	14.9
Inotropic support (days) (median)	2
CardioPulmonary Bypass (CPB) time (min.) (mean)	62
Aortic Cross Clamping (ACC) time (min.) (median)	30
Complications (cardiac and infection)	22

The amount of miRNA 208a, 208b and 499 pre- and post-operation

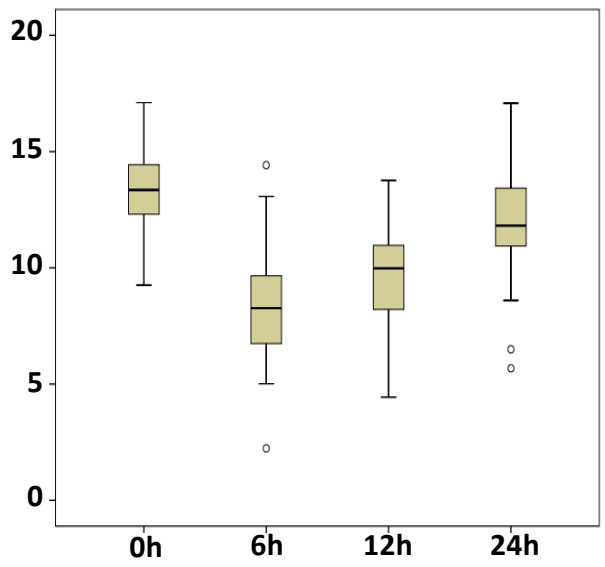
miR-208a



miR-208b



miR-499



p<0.01

The amount of miRNAs 208a, 208b, 499 correlates with myocardial damage

- **The amount each of the three miRNAs post-op (6h, 12h, 24h) correlates with Troponin and Lactate levels**

- **The amount of the three miRNAs post-op (6h, 12h, 24h) correlates with CPB time and ACC length**

p<0.01

The amount of the post-op miRNAs in the plasma is predictive of the patients outcome

- **The amount of miR208a at 6h and 12h post-op correlates with complications suffered by the patients**
- **The amount of the three miRNAs at 12h correlates with the length of hospitalization**
- **The amount of the three miRNAs at 6h correlates with the number of days they will be ventilated invasively**
- **The amount of miRNAs208a and 208b at 6h correlates with the levels of Creatinine**

(All correlations are at least $p<0.05$)

Conclusions

- Circulating miRNAs-208a, -208b, and -499 are detectable in the plasma of children undergoing cardiac surgery
- The amount of these miRNAs rises sharply 6h after the operation and then declines
- The amount of miRNAs-208a, -208b, and -499 is correlative to myocardial damage

Quantifying miRNAs 208a, 208b and 499 can predict the patient's outcome as early as 6h after the operation

And therefore are useful as biomarkers for the postoperative course

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Thank-you

Dr. Tomer Ziv-Baran

Pediatric Cardiac Intensive Care Unit

Thank-you!

Good luck!!!