



LUXEMBOURG
INSTITUTE
OF HEALTH

Recherche translationnelle sur les biomarqueurs de l'arrêt cardiaque

RNAs as prognostic biomarkers after cardiac arrest

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Journée de la Recherche Médicale
et Translationnelle – JRMT

16/10/2024

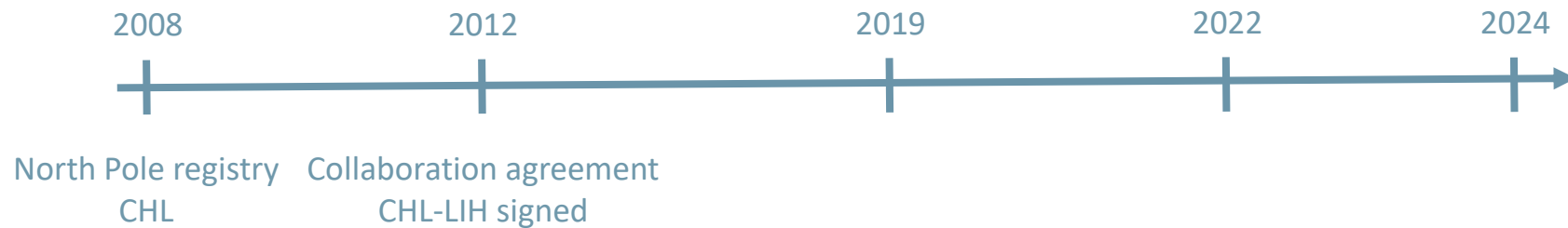


Aim of the collaboration between CHL and LIH

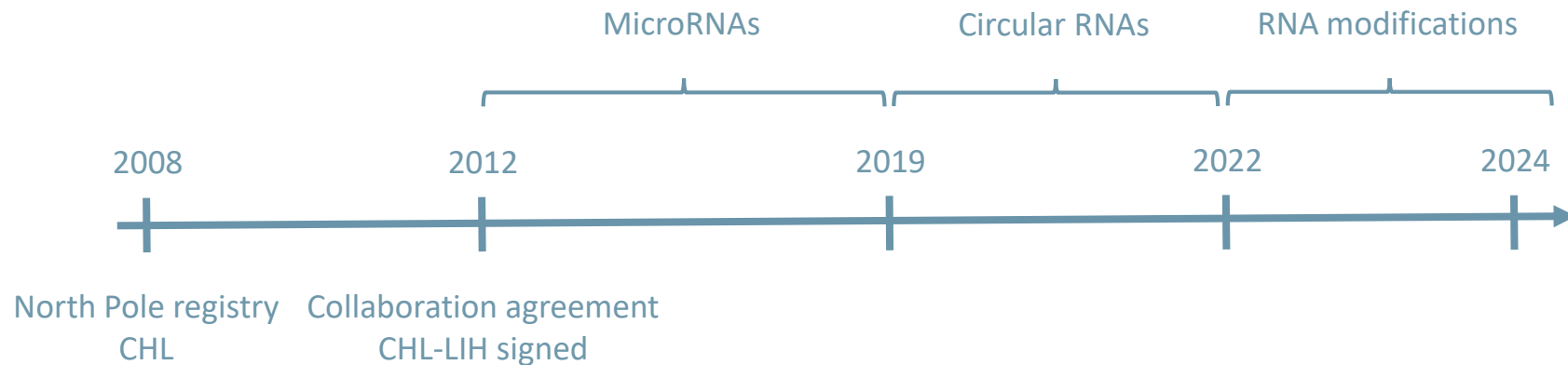
- Define RNA biomarkers of neurological outcome and survival after cardiac arrest



A long lasting collaboration between CHL and LIH

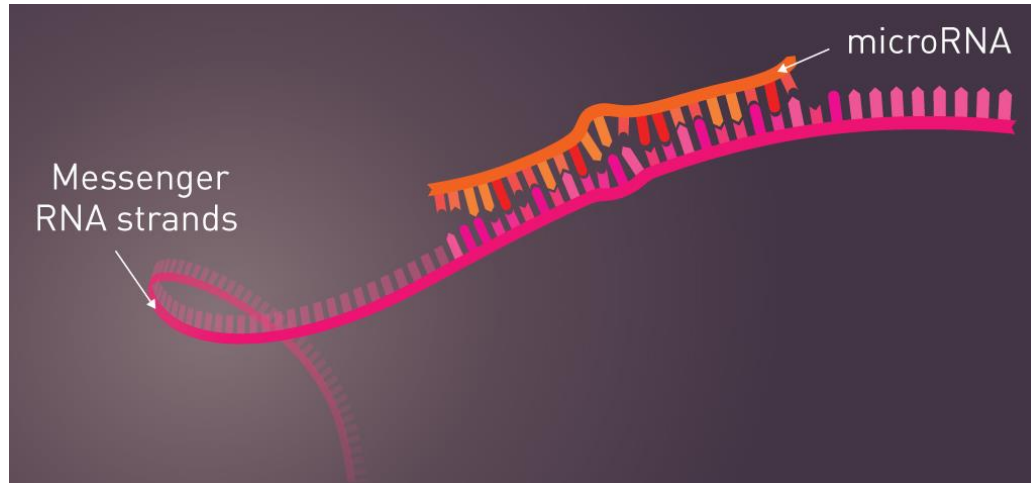


A long lasting collaboration between CHL and LIH

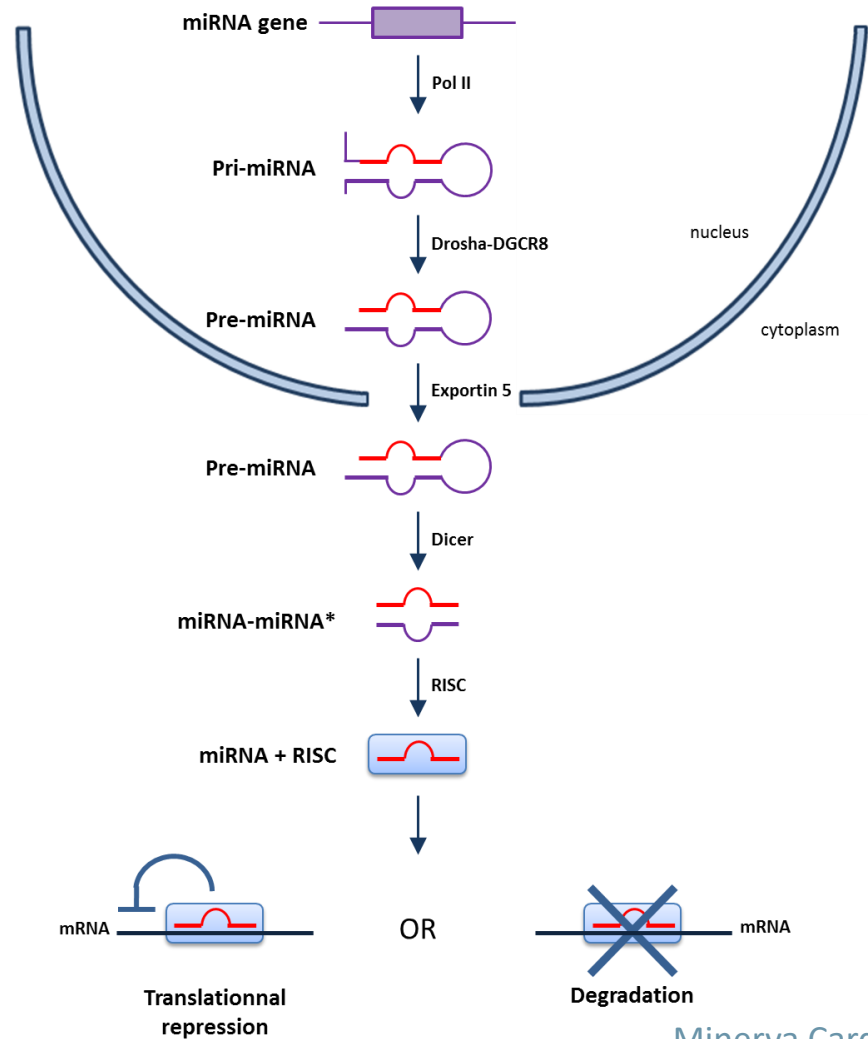


MicroRNAs

Definition: microRNAs (miRNAs) are 20-22 nucleotides-long small RNA molecules able to regulate gene expression



MicroRNAs biogenesis and regulation of gene expression





Can microRNAs predict outcome after cardiac arrest ?



Can microRNAs predict outcome after cardiac arrest ?

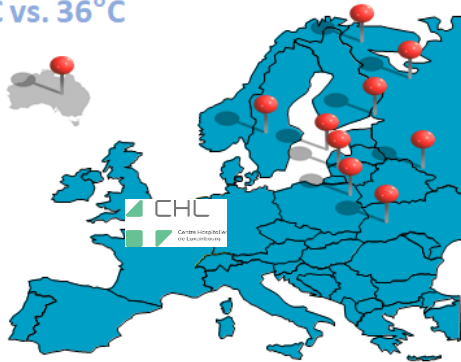
TTM-trial

2010-2013

Patients randomised: **950**

Cardiac causes

33°C vs. 36°C



NCT01020916

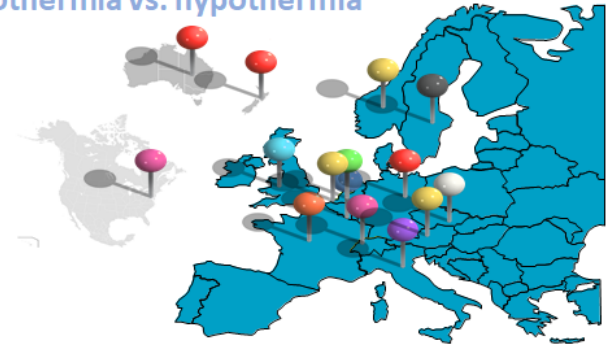
TTM2-trial

2017-2020

Patients randomised: **1900**

Cardiac causes

Normothermia vs. hypothermia



NCT02908308



Integrated Biobank of Luxembourg



N Engl J Med 2013

N Engl J Med 2021

MicroRNA-124-3p predicts neurological outcome and survival after cardiac arrest

Original Investigation

June 2016

FREE

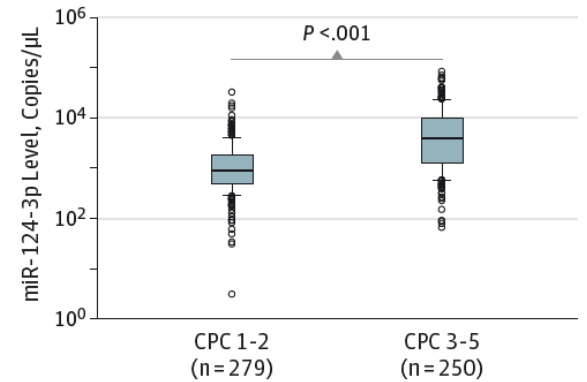
Association of Circulating MicroRNA-124-3p Levels With Outcomes After Out-of-Hospital Cardiac Arrest A Substudy of a Randomized Clinical Trial

Yvan Devaux, PhD¹; Josef Dankiewicz, MD²; Antonio Salgado-Somoza, PhD¹; Pascal Stammet, MD³; Olivier Collignon, PhD⁴; Patrik Gilje, MD²; Olof Gidlöf, PhD²; Lu Zhang, MSc¹; Mélanie Vausort, MSc¹; Christian Hassager, MD, DMSc⁵; Matthew P. Wise, MD, DPhil⁶; Michael Kuiper, MD, PhD⁷; Hans Friberg, MD, PhD⁸; Tobias Cronberg, MD, PhD⁹; David Erlinge, MD, PhD²; Niklas Nielsen, MD, PhD¹⁰; for Target Temperature Management After Cardiac Arrest Trial Investigators

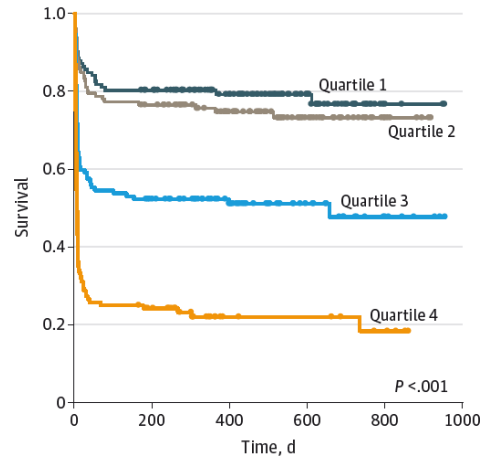
> [Author Affiliations](#) | [Article Information](#)

JAMA Cardiol. 2016;1(3):305-313. doi:10.1001/jamacardio.2016.0480

B Outcome for all patients



D Prognostic value



FNR CORE CA-miRs project (grant # C14/BM/8225223)

MiR-124-3p and miR-122-5p show incremental prognostic value

Theranostics 2017; 7(10):2555-2564. doi:10.7150/thno.19851 [This issue](#) [Cite](#)

PDF



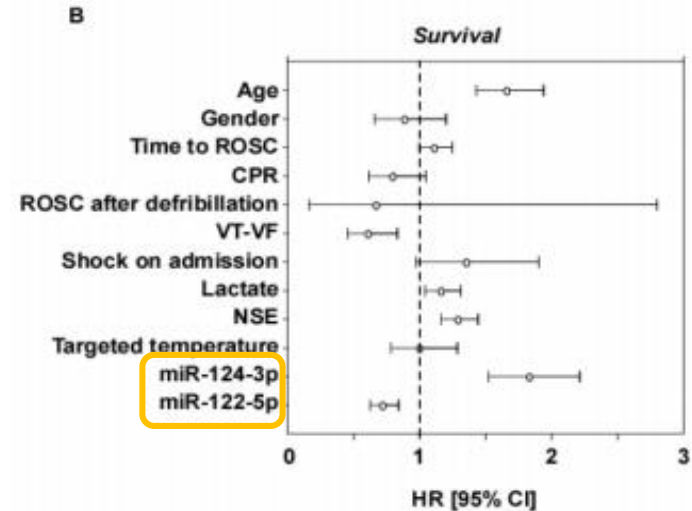
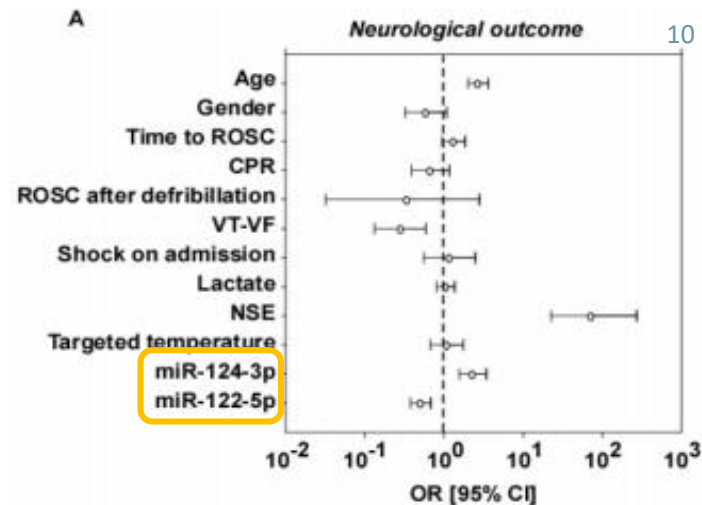
Research Paper

Incremental Value of Circulating MiR-122-5p to Predict Outcome after Out of Hospital Cardiac Arrest

Yvan Devaux¹, Antonio Salgado-Somoza⁴, Josef Dankiewicz², Adeline Boileau¹, Pascal Stammet³, Anna Schritz⁴, Lu Zhang⁴, Mélanie Vausort⁴, Patrik Gilje², David Erlinge², Christian Hassager³, Matthew P. Wise⁶, Michael Kuiper⁷, Hans Friberg⁸, Niklas Nielsen⁹, the TTM-trial investigators On behalf of the Cardiolinc™ network

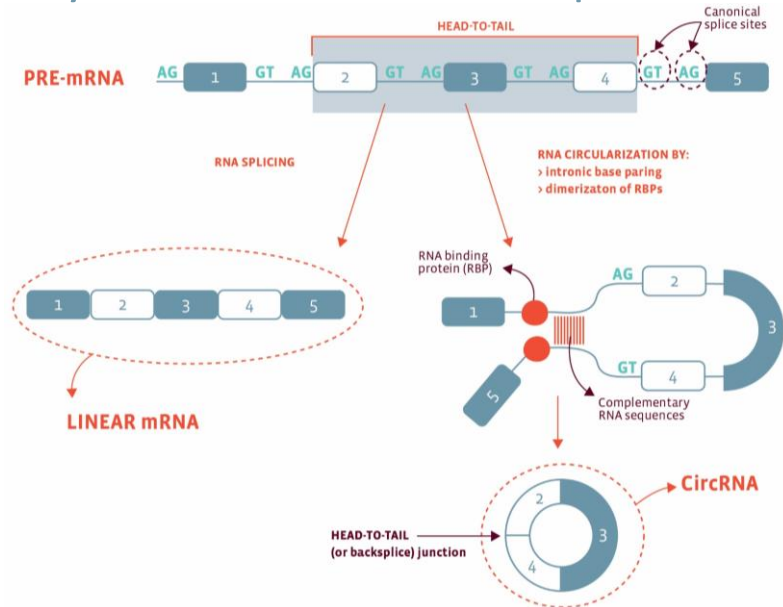
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Circular RNAs

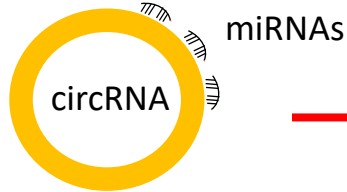
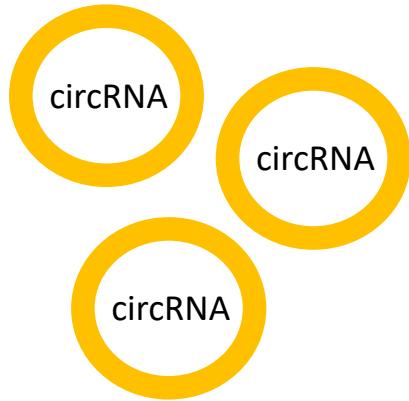
Definition: circular RNAs (circRNAs) are single-stranded RNA molecules forming a covalently closed continuous loop



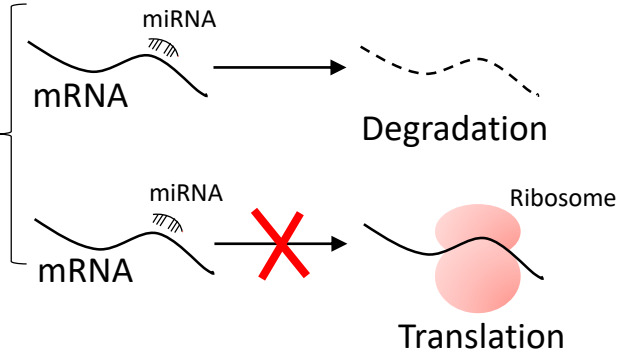
Mode of action



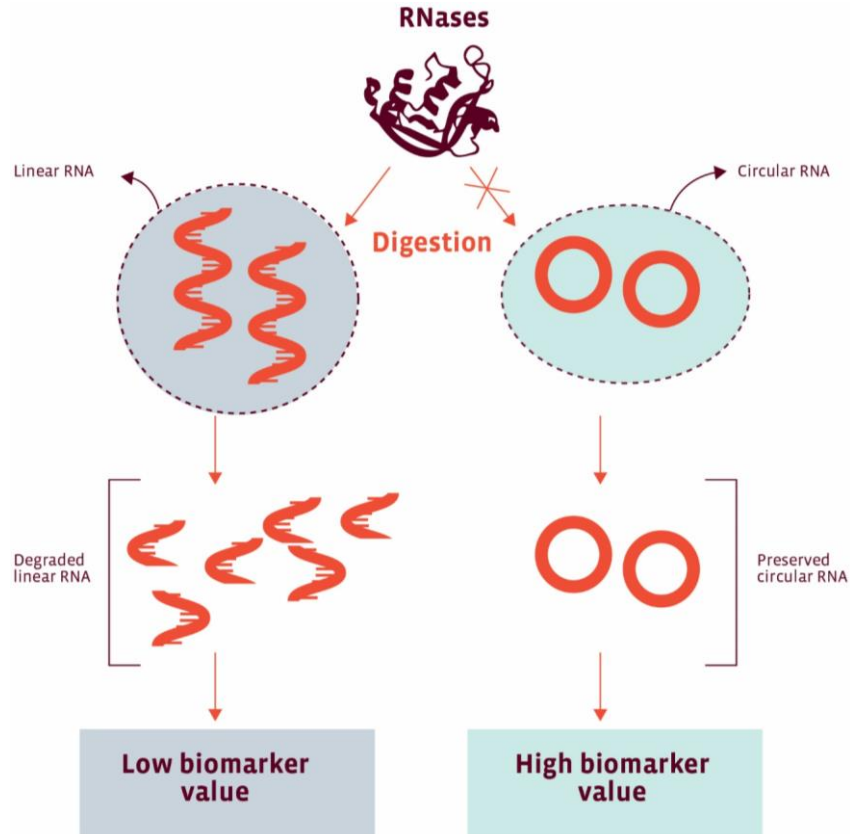
Transcription regulators



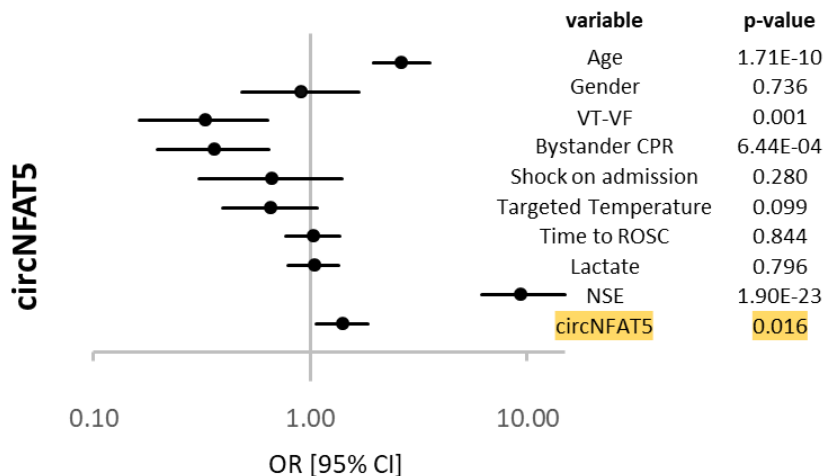
miRNA sponges



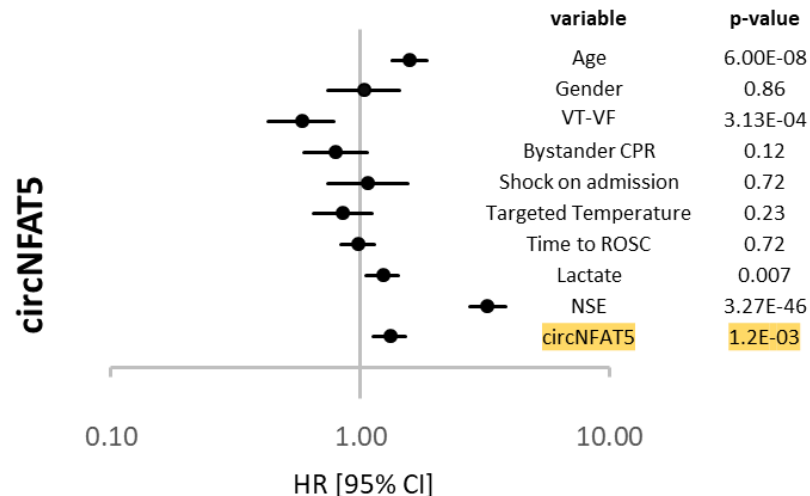
Circular RNAs as biomarkers



CircNFAT5 predicts neurological outcome and survival after cardiac arrest



Neurological outcome

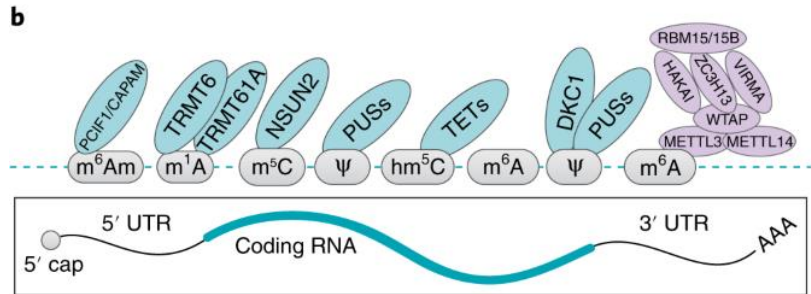
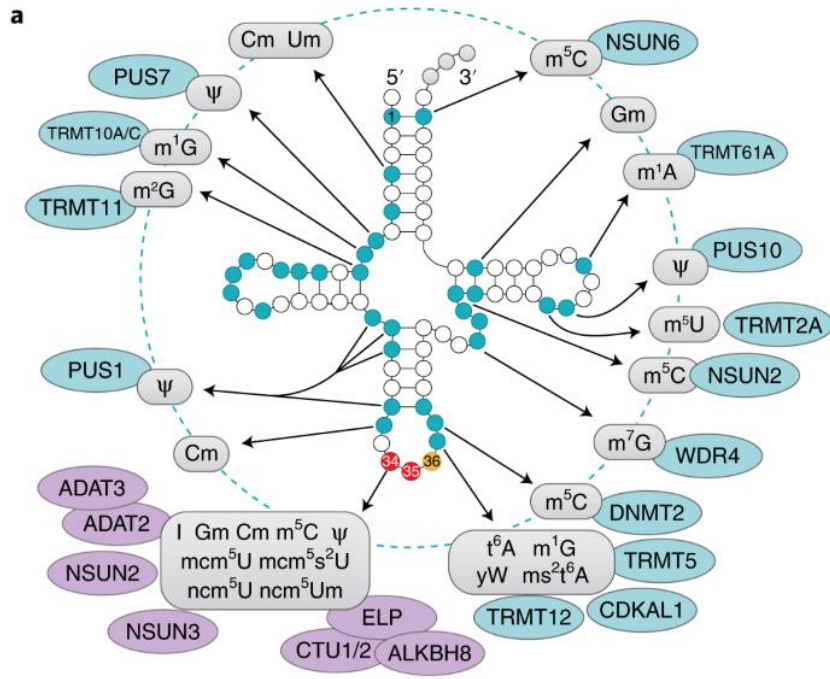


Survival



TTM-trial; n=542

RNA modifications

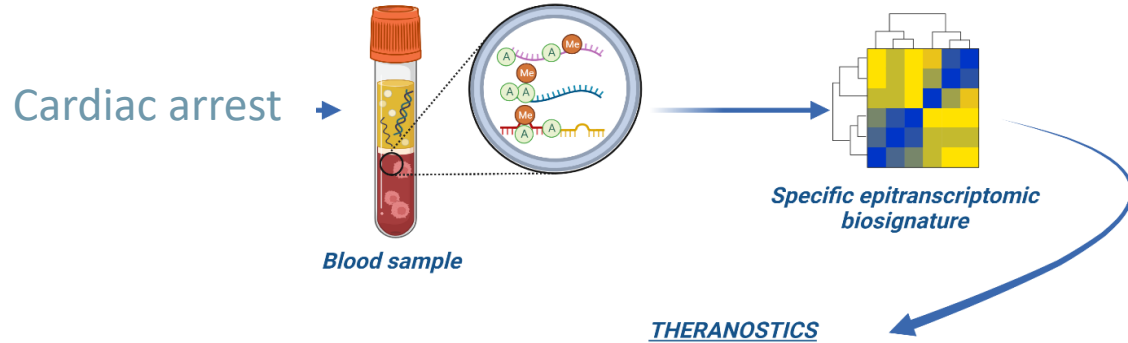




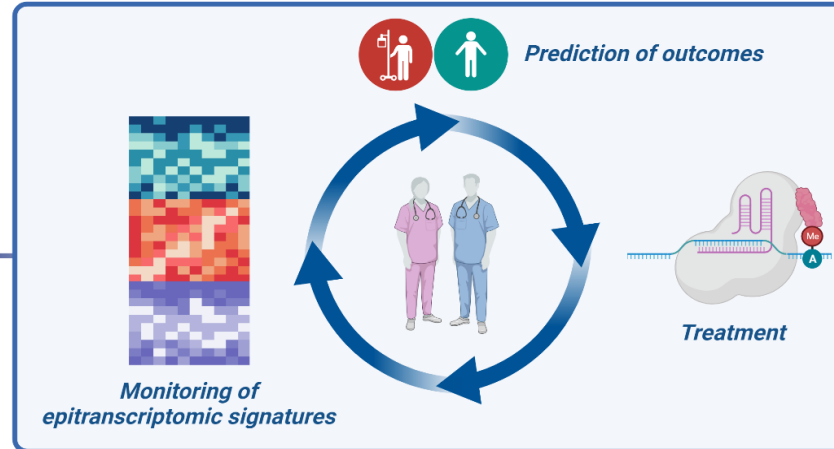
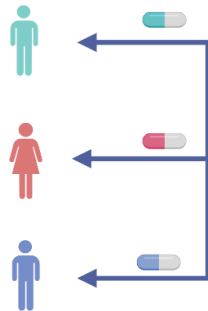
Can m6A predict outcome after cardiac arrest ?



The YMCA project



Personalized healthcare for improved outcomes



Background

Sudden cardiac arrest (SCA) is the 3rd leading cause of death in Europe.

It is the **sudden loss of heart function**, occurring when the heart's electrical system malfunctions, **causing the heart to stop beating effectively**. Blood stop flowing to the brain, lungs and other vital organs.

Patients can die within minutes (80%). Among survivors, **cardiac and neurological impairments are common**. They can be categorized into those with:

- **Good neurological outcomes (Cerebral Performance Category CPC 1-2)** ~10%
- **Poor neurological outcomes (CPC 3-5)** ~10%

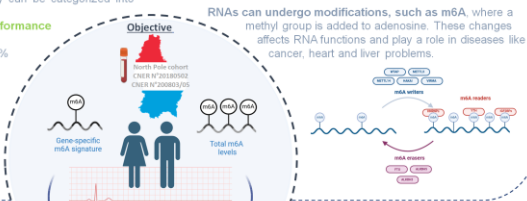
Currently, **prognostic tools and biomarkers** to predict neurological outcome after cardiac arrest remain **limited**.

Recently, RNAs molecules are gaining significant attention due to their diagnostic, therapeutic and prognostic potential.

They present different benefits:

- **Reflect real-time changes in physiological and disease states**
- **Stable**
- **Non-invasive method** (blood, urine, saliva testing)
- **Low costs**
- **Sensitive and Specific**
- **In line with personalized medicine**, optimizing efficacy and reducing side effects.

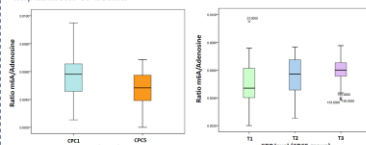
RNAs can undergo modifications, such as m6A, where a methyl group is added to adenosine. These changes affects RNA functions and play a role in diseases like cancer, heart and liver problems.



Global m6A profiling

Comprehensive view of RNA methylation patterns by **Liquid Chromatography coupled to mass spectrometry (LC-MS)**.

Quantification of total m6A to compare m6A content between patients **with** and **without** post SCA neurological impairment or death.



- **Hypomethylation** is associated to renal impairment
- **Hypermethylation** is associated to the increase of inflammation (C-reactive protein level).
- **Hypomethylation** is associated to liver enzymes (Aspartate aminotransferase and Alanine aminotransferase) in patients dying from poor neurological outcomes after cardiac arrest.

Direct RNA sequencing

From Oxford Nanopore Technologies company – Sequencing method using a tiny hole, called nanopore, to read RNA molecules one letter at a time.

Only direct RNA sequencing method available to detect m6A RNA modification, allowing real-time data acquisition, and long reads sequencing

Identification of SCA-specific m6A biosignature

Comparison between: blood samples of 25 **SCA patients developing neurological impairment** and 25 age- and sex-matched patients **not developing neurological impairment post-SCA** → m6A profiles on coding and non-coding RNAs → Is there a link to prognosis ?

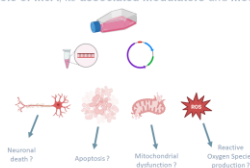
So far, **Differential expression analysis** revealed that **22 genes** are differentially expressed at the gene, transcript, full length transcript level and have difference in the m6A sites between CPC5 vs CPC1 group.



According to the **KEGG pathways analysis** : they could be involved in the transport across the blood brain barrier, inflammatory response, glucose starvation, erythrocyte development...

Perspectives: Functional characterization

What is the role of m6A, its associated modulators and modified RNAs?



Conclusion

Clinical Impact : m6A (hypo- or hypermethylation) is linked to poor outcomes after cardiac arrest.
 → But we still need to study if it can be a biomarker or at least if it can improve the biomarker potential of current markers to predict poor outcomes.
 → Can it help to stratify patients ?

Scientific impact: We have identified differentially expressed genes and transcripts involved in the poor outcome of patients.
 → We will better understand their roles and potentially find therapeutic targets.



Take home messages

- RNAs hold promise to aid in outcome prognostication after cardiac arrest
- More research is needed to identify specific RNAs for clinical application
- The collaboration between CHL and LIH has been/is instrumental





Acknowledgements

Collaborators

- ❑ Department of Intensive Care Medicine, CHL
 - Prof Pascal Stammet and all colleagues who contributed to patient recruitment and project management
- ❑ Helsingborg Hospital, Lund University
 - Prof Niklas Nielsen and colleagues
- ❑ TTM recruiting centers
- ❑ IBBL
- ❑ Cardiovascular Research Unit, LIH
 - Francesca Stefanizzi, Victoria Stopa, Mélanie Vausort, Andrew Lumley, Christelle Nicolas

All patients who contributed biological samples and clinical data

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- Ministère de l'Éducation Supérieure et de la Recherche
- Fondation Cœur Daniel Wagner (YMCA project)





Thank you

