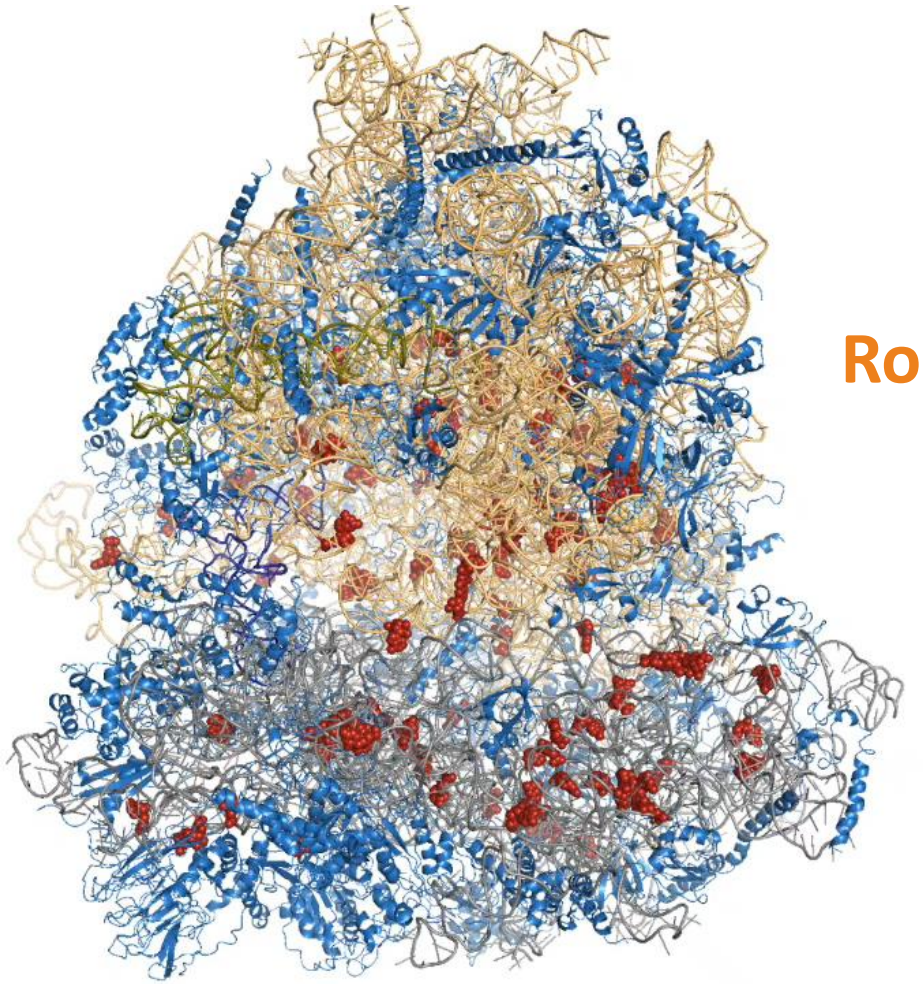


Programme PAIR Sein 2014-2018
Early stage of breast cancer

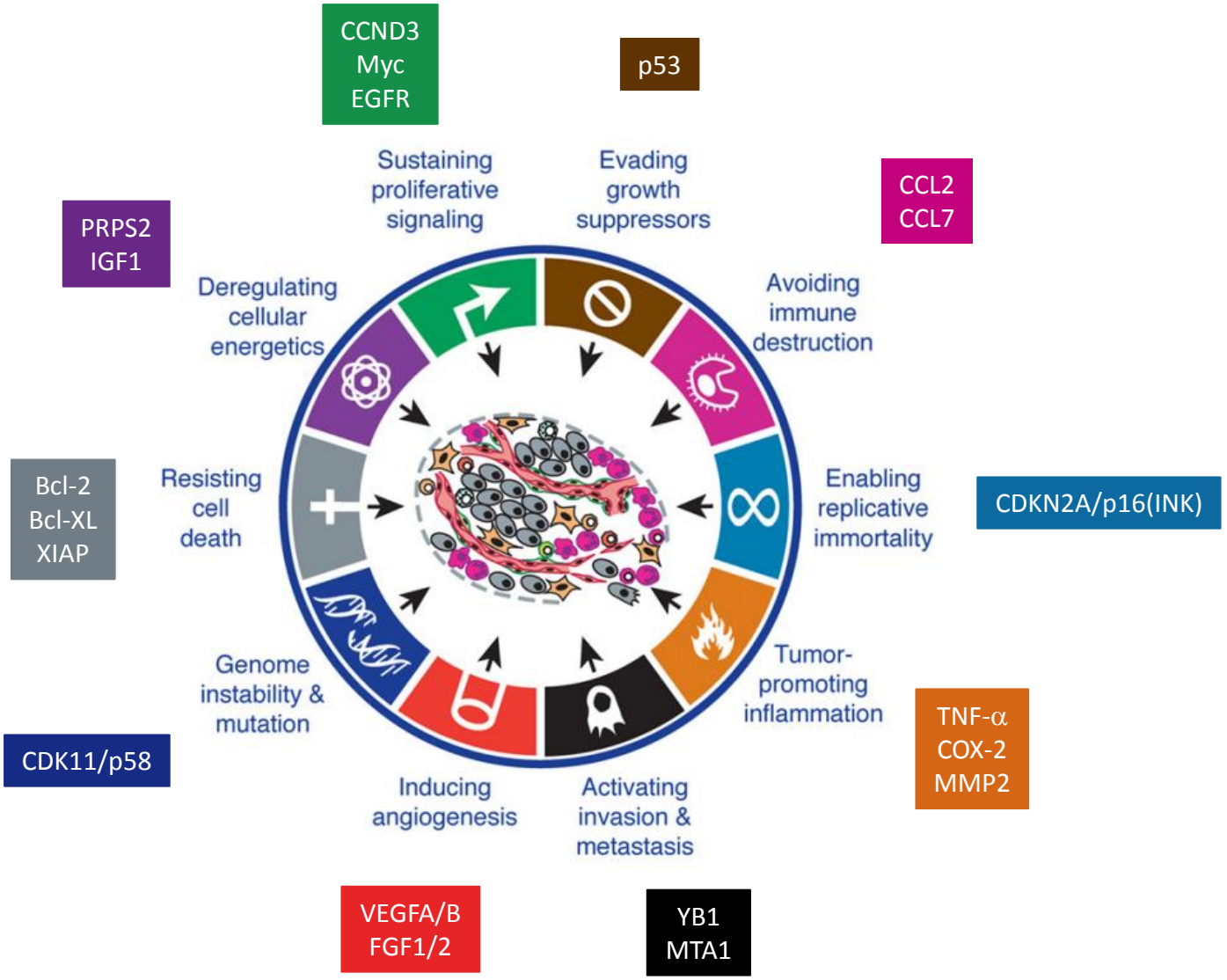
- RiboTEM -

Role of ribosome alterations in epithelial-to-mesenchymal transition in breast cancer

Jean-Jacques DIAZ

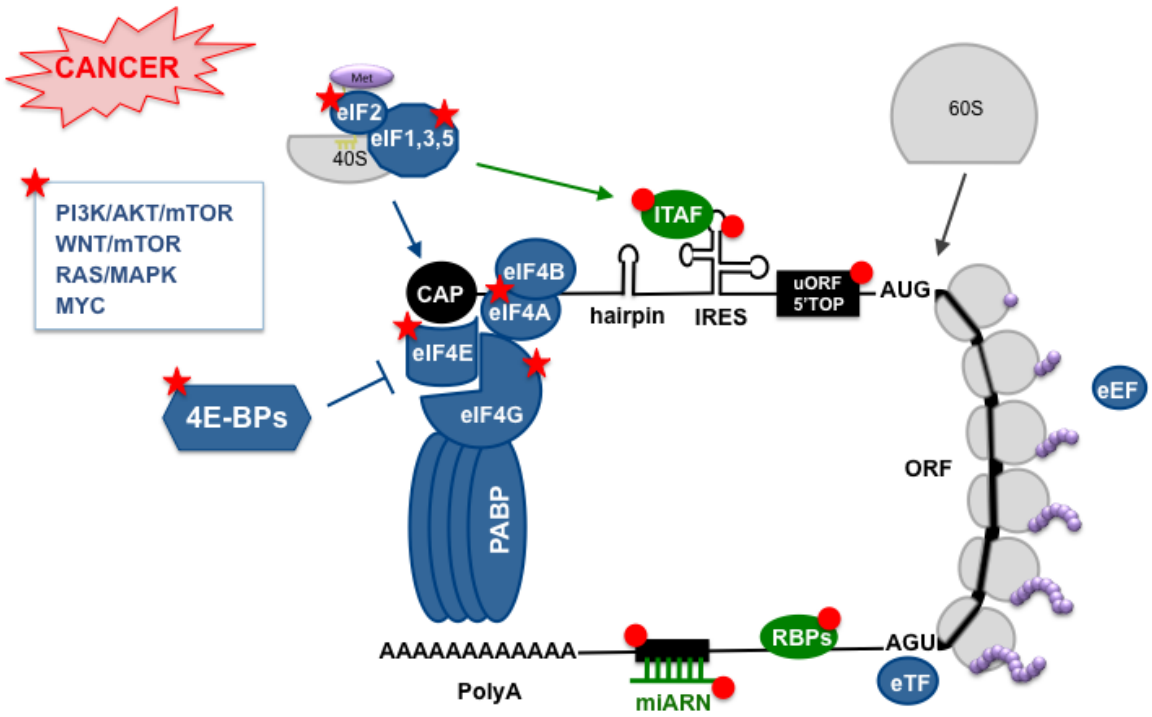
« Nuclear Domains & Pathologies » Team
Cancer Research Center of Lyon (CRCL)

Translation contributes to the hallmarks of cancer

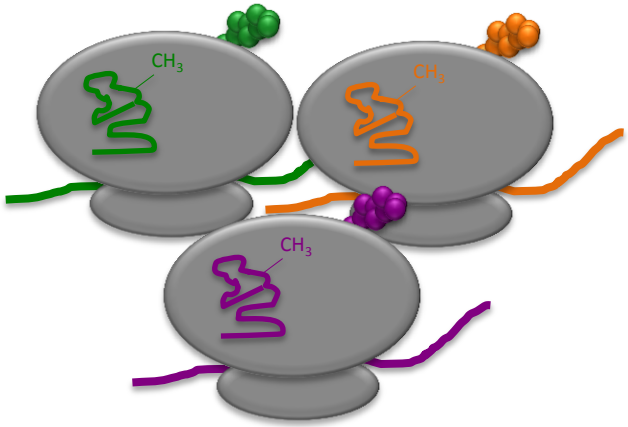


Adapted from Hanahan & Weinberg, Cell 2011
Truitt & Ruggero, Nat Rev Cancer 2016

Dysregulation of translation in cancer



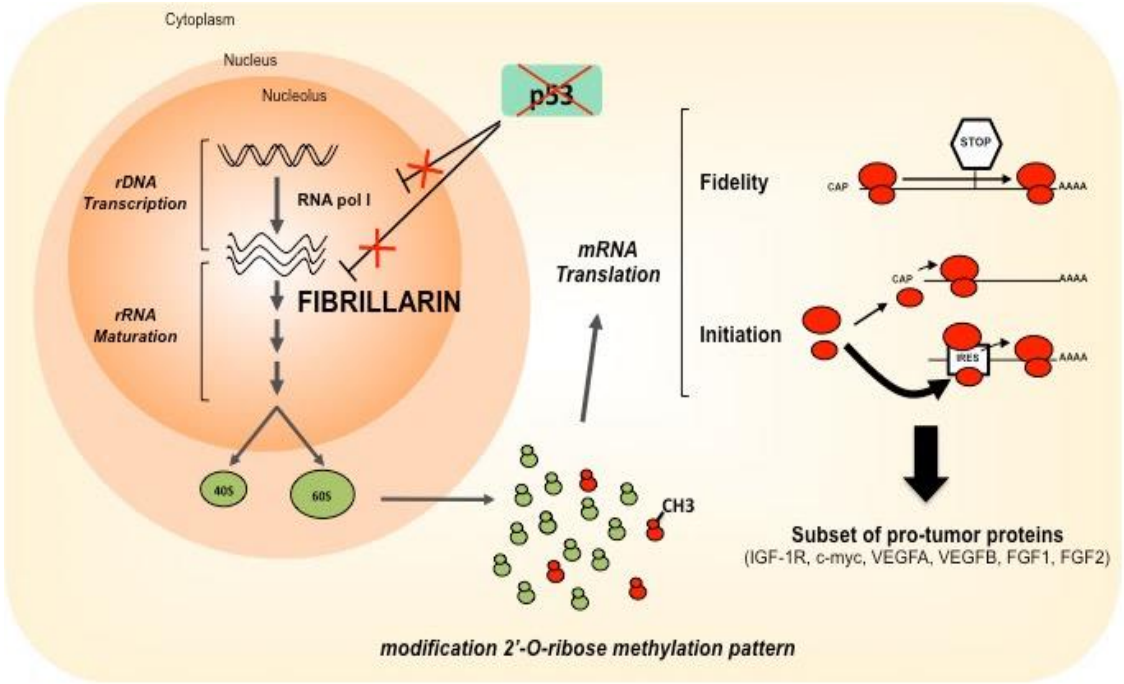
Marcel et al, Oncogene 2015
Truitt & Ruggero, Nat Rev Cancer 2016
Tahmasebi et al, Nat Rev Mol Cell Biol 2018
Marcel et al, Cancers 2018



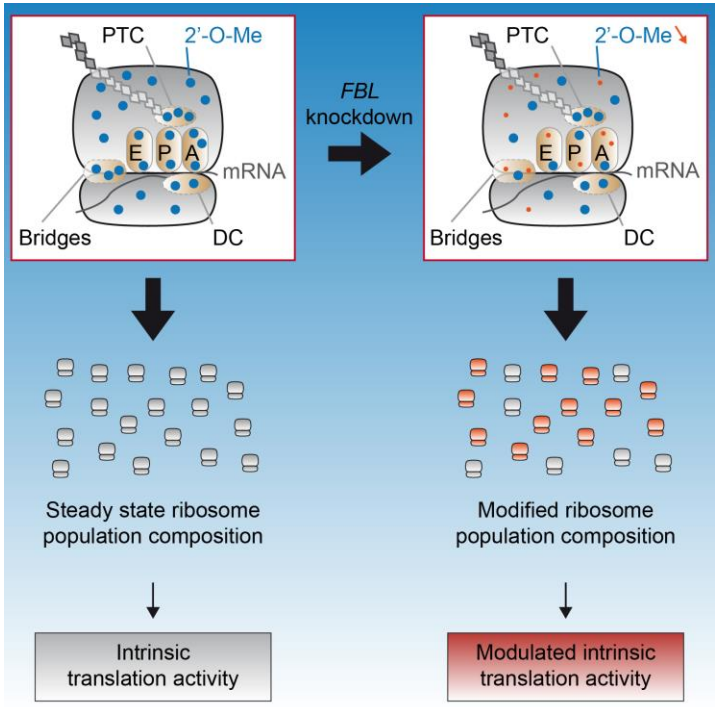
Specific mRNA translation

Xue & Barna, Nat Rev Mol Cell Biol 2012
Shi & Barna, Annu Rev Cell Dev Biol 2015
Genuth & Barna, Nat Rev Genetics 2018
Dalla Venezia et al, IJMS 2019

rRNA methylation modulates translation



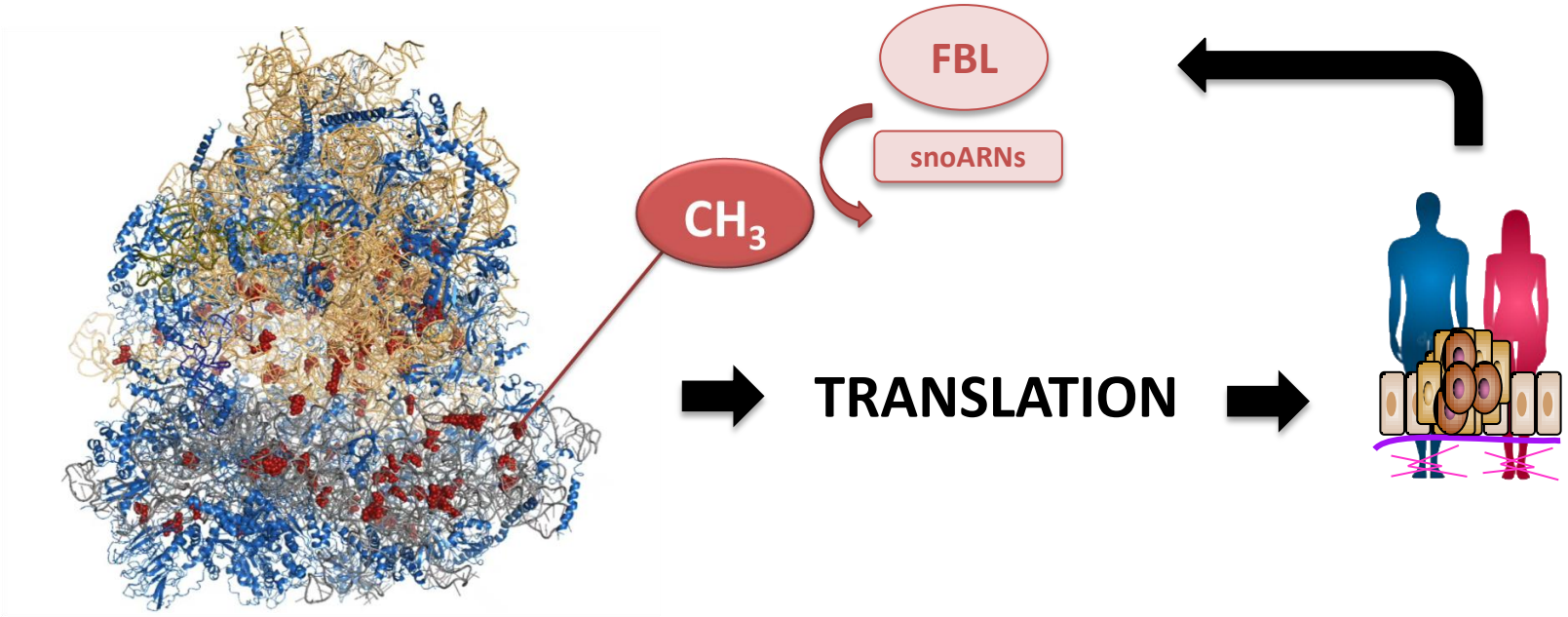
Marcel et al, Cancer Cell 2013



Erales et al, PNAS 2017

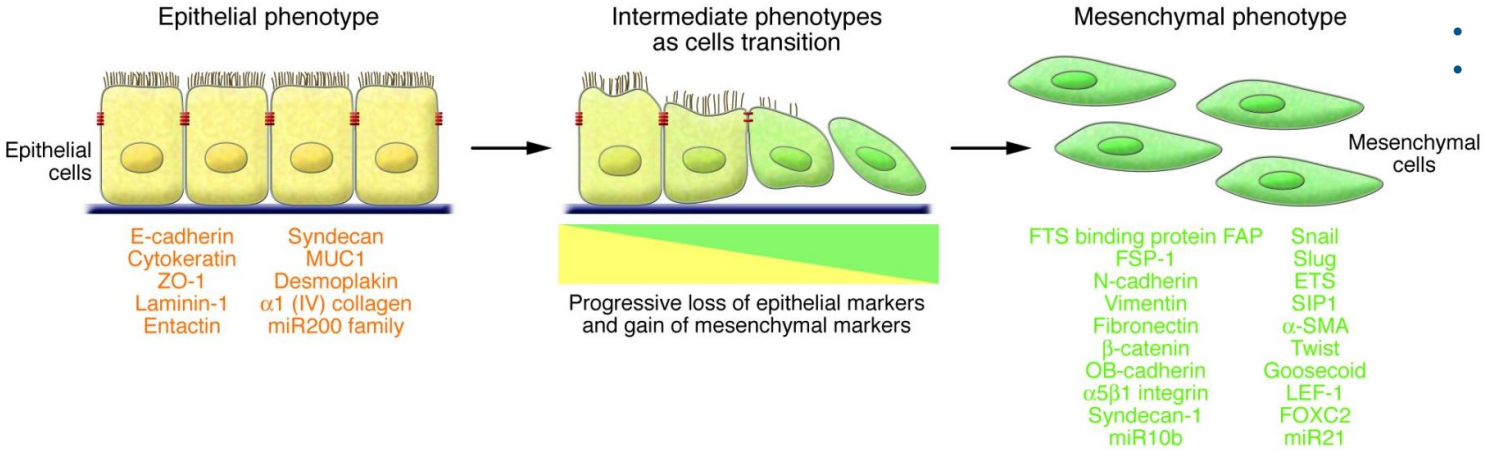
Belin et al, Plos ONE 2009
Marcel et al, Oncotarget 2013
Marcel et al, Med Sci 2014
Marcel et al, Mol Cell Biol 2015
Marcel et al, Oncogene 2015
Thérizols et al, Book « Epigenetic Cancer Therapy » 2015
Marcel et al, Cancers 2018
Monaco et al, Biomolecules 2018
Catez et al, Bioch Pharmacol 2019
Dalla Venezia et al, IJMS 2019
Wei et al, Mol Cell 2019

Objectives and hypotheses of PAIR Sein program

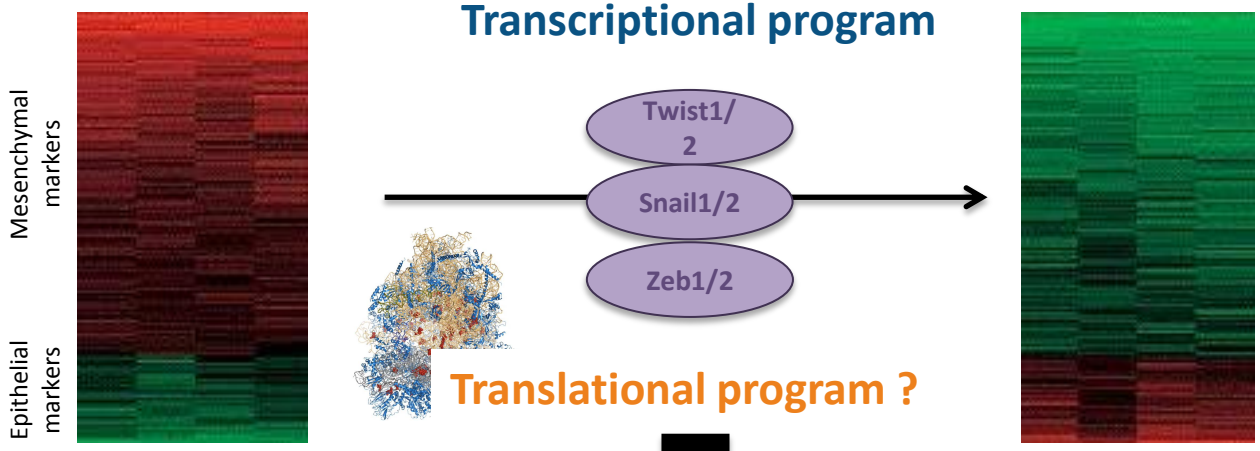


- ✓ Role of ribosome alterations in early stage of mammary tumorigenesis ?
- ✓ Use of ribosome alterations as biomarkers of prognosis at early diagnosis ?

Part 1 | Alterations of ribosome composition and translation in EMT



- **Tumor initiation**
- **Invasion and migration**



Integrated genome-wide approaches

Partners

A. Puisieux

CRCL Centre de Recherche en Cancérologie de Lyon

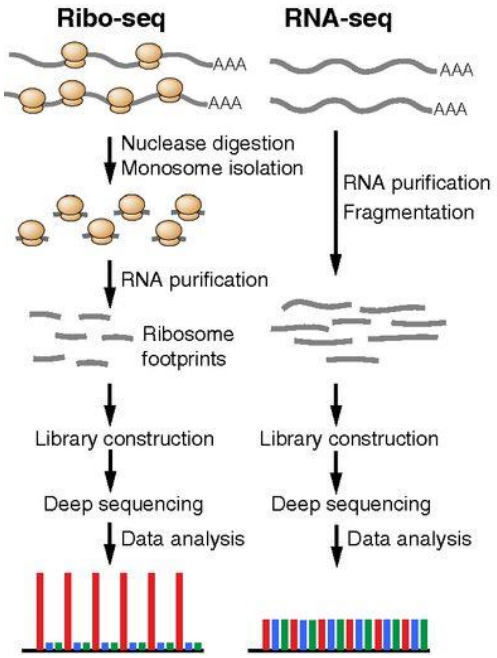
O. Namy

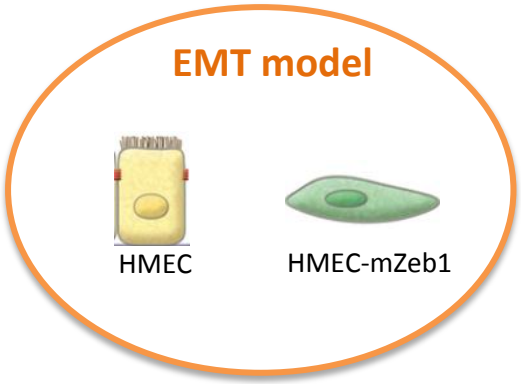
I2BC

Kalluri & Weinberg, JCI 2009
Puisieux et al, Nat Cell Biol 2014

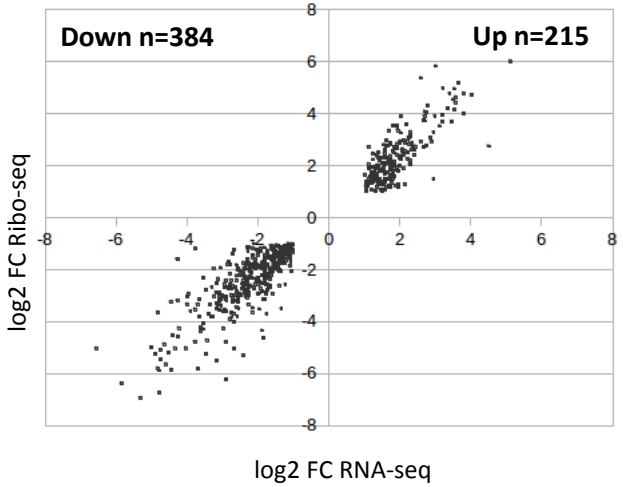
Part 1 | A translational reprogramming occurs in EMT

Ribosome Profiling

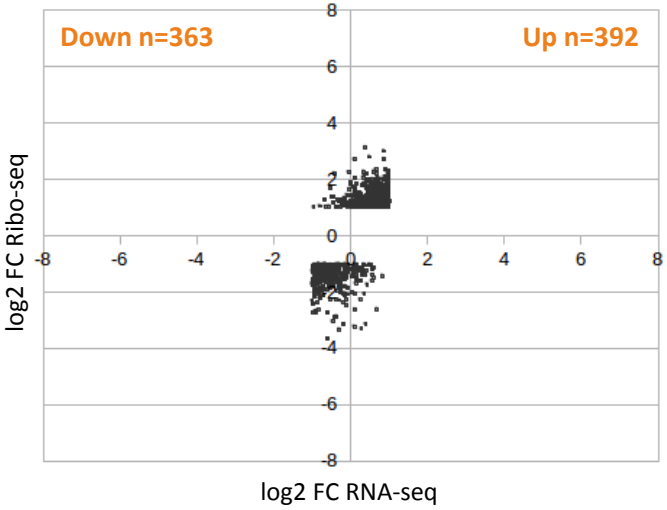




Coordinated change in mRNA levels and translation



Change in translation without change in mRNA levels



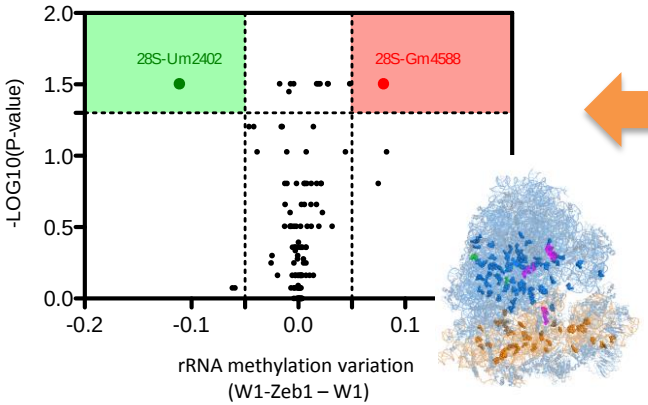
- **Transcription n=599 genes**
- **Translation n=755 genes**

Polly Yingshan Hsu et al. PNAS 2016

Planchard et al, NAR 2018

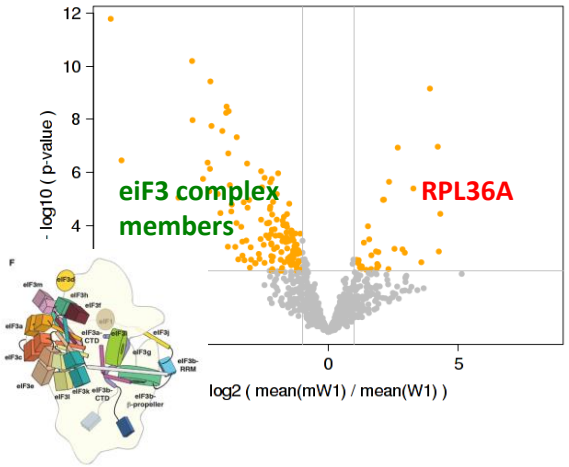
Part 1 | The composition of the translational machinery is changed in EMT

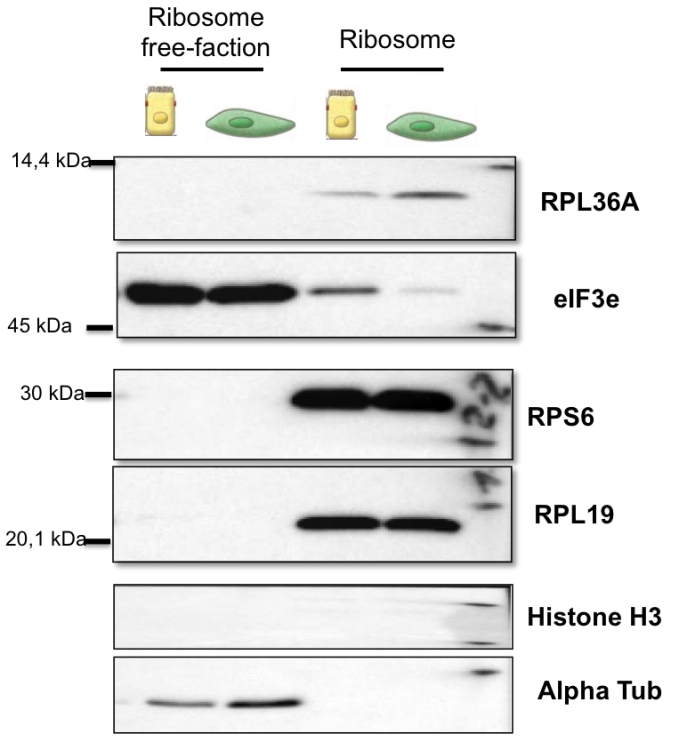
rRNA methylation profiling
(RiboMETH-seq)



EMT model

RiboProteome





Y. Couté

Y. Motorin

A. Viari, J. Kielbassa

Part 2 | Prognostic values of ribosome biogenesis factors in breast cancer diagnosed at early stages

Series 1 : 216 total RNA
(Collab: Jean Christophe Bourdon, Dundee)

Test series

Series 2 : 40 total RNA
(Collab: Gilles Clapisson, Lyon)

Series 6 : 434 tissues (TMA)
(Collab: Isabelle Treilleux, Lyon)

Series 3 : 11 total RNA from healthy donors mastectomy
(Collab: Thierry Dubois, Paris)

Series 4 : 661 total RNA
(The Cancer Genome Atlas)

Validation series

Series 5 : 196 total RNA
(Collab: Fabrice André, Paris)

Series 7 : 1987 tissues (TMA)
(Collab: Fabrice André, Paris)

Partners

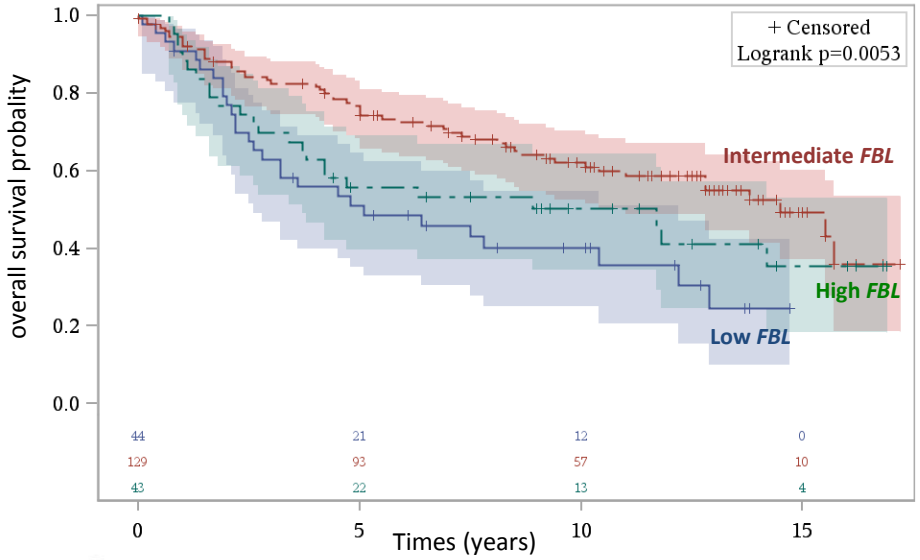
I.Treilleux
D. Pérol

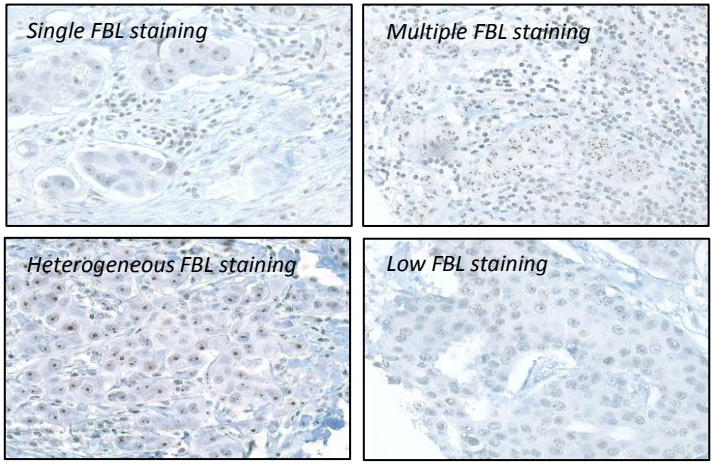
F. André

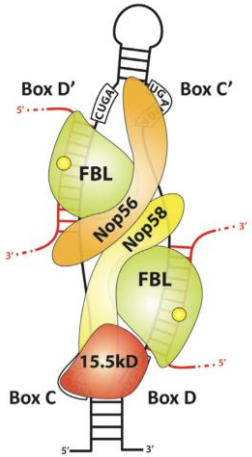
Characteristics of the series

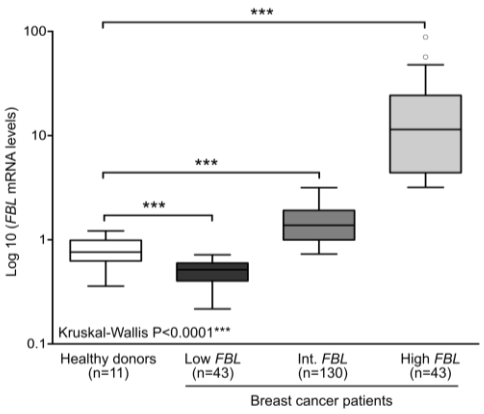
- Women
- No medical history
- Invasive tumors
- No distant metastasis at diagnosis

Part 2 | FBL and NCL are independent markers of poor prognosis in early breast cancer









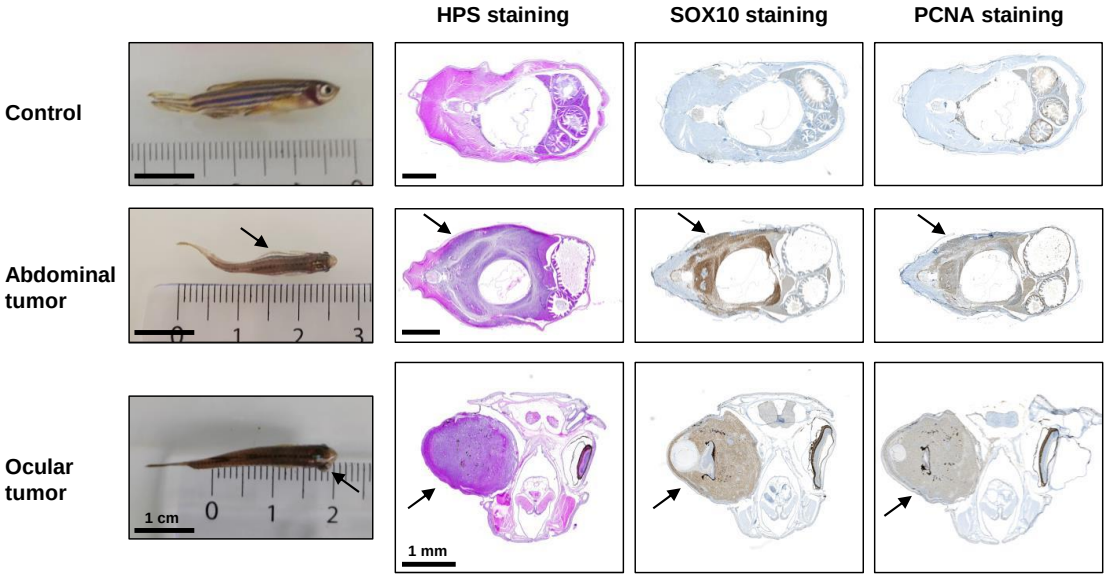
Variables		HR		P-value
FBL	intermediate	1.00		
	low	1.83	[1.13 – 2.96]	0.0215*
	high	1.69	[1.02 – 2.80]	
Size	small (< 30mm)	1.00		< 0.0001***
	large (≥ 30mm)	2.27	[1.08 – 2.46]	
Lymph node	no	1.00		0.0201*
	yes	1.63	[1;52 – 3.40]	

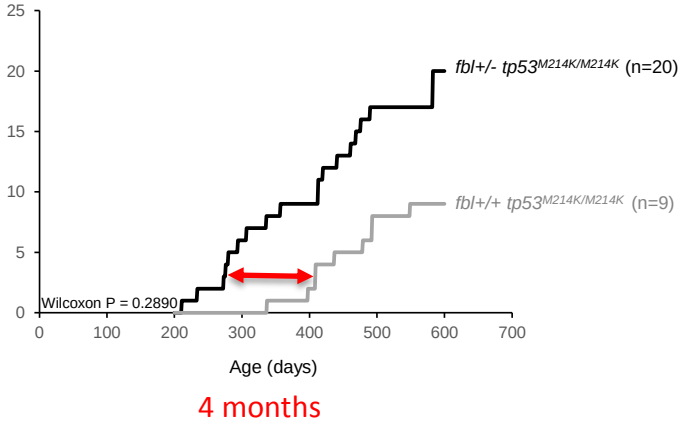
Nguyen Van Long et al, Cancers 2018
Nguyen Van Long et al, submitted

Part 2 | Decreased expression of *FBL* contributes to spontaneous tumorigenesis *in vivo*

Cohort of 124 zebrafishes

Spontaneous model of tumorigenesis (tp53M214K/M214K) X fbl+/-

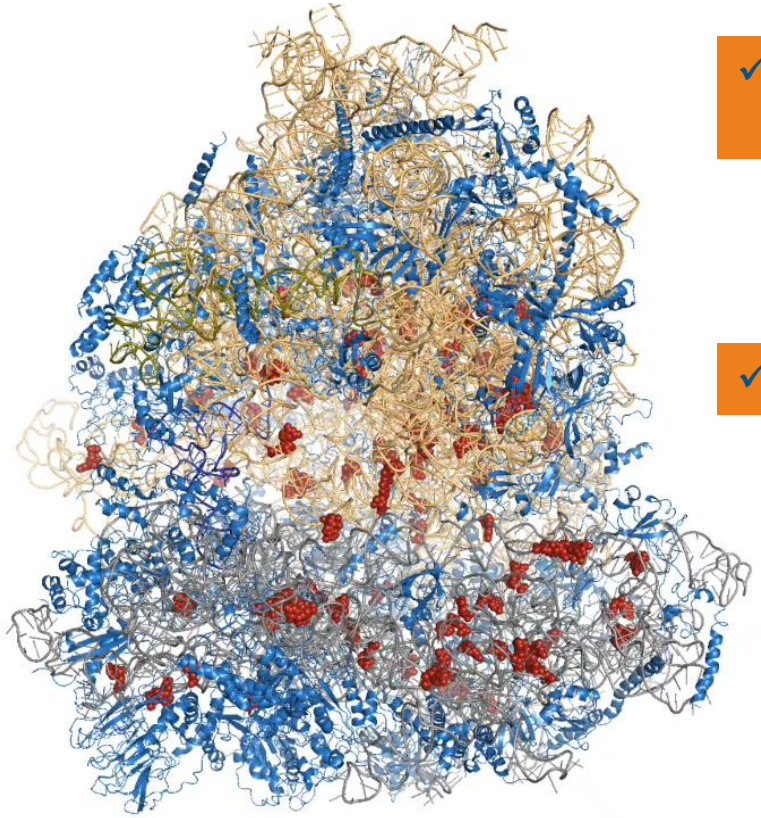




4 months

Nguyen Van Long et al, submitted

Conclusions



✓Basic research: **novel ribosome-associated concepts in early breast cancer tumorigenesis**

- **Translational reprogramming** and **alterations of ribosome composition** in EMT
- **Reduction of ribosome biogenesis** contributes in mammary tumorigenesis

✓Translational/clinical research: **ribosome as biomarker**

- FBL and NCL are **pronostic markers**

Perspectives

- Role of **ribosome in EMT** (ARC, LNCC)
- Alterations and role of **rRNA methylation in breast cancer** (MARACAS: ARC 2017, PLBio 2019; ACTIMETH: ANR 2019)
- Use of **rRNA methylation as biomarker of EMT** (EMT-Concept: PRT-K 2017)

DEBRIEFING | RiboTEM program

Opportunities

- Initiate a **long-term research program** on ribosome and EMT
- Set aside **strong collaborations with clinicians**
- Build **consortium of about 10 national and international teams** on ribosome/translation in breast cancer

PAIR Sein
2014-2018

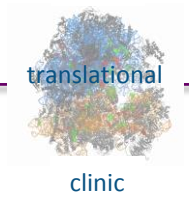
FONDATION ARC POUR LA RECHERCHE SUR LE CANCER
Reconnue d'utilité publique

LA LIGUE CONTRE LE CANCER

INSTITUT NATIONAL DU CANCER

Difficulties

- **Pursue the program as an integrated one** (basic and translational research) due to the lack of equivalent funding
  - ➢ Separation of research into different sub-projects



Valorization

- 9 publications
- 1 bioinformatic tool (Ribosome Profiling)
- ≈20 invited presentations

PNAS
Proceedings of the National Academy of Sciences of the United States of America

RibGalaxy

Perspectives

- Role of **ribosome in EMT** (ARC, LNCC)
- Alterations and role of **rRNA methylation in breast cancer** (MARACAS: ARC 2017, PLBio 2019; ACTIMETH: ANR 2019)
- Use of **rRNA methylation as biomarker of EMT** (EMT-Concept: PRT-K 2017)

Acknowledgements

"Nuclear domains & Pathologies" Team

Jean-Jacques DIAZ
Virginie MARCEL
Flora NGUYEN VAN LONG
Hermes PARAQINDES
Nathalie PION
Déborah MONCHIET
Valentin SIMIONI
Marjorie MARTIN
Agathe DOLBEAU
Paul ROLLET
Akari SAKU
Xinrui DONG

Philippe BOUVET
Frédéric CATEZ
Nicole DALLA VENEZZIA
Hélène DELAGE
Hichem MERTANI
Fabien MONGELARD
Karine MONIER
Jean-Christophe SAURIN
Anne VINCENT
Mounira CHABALI
Elizabeht GOMEZ CRUZ
Piero LO MONACO
Anthéa HULEUX
Angéline GAUCHEROT

Collaborators

CRCL/Curie
(Lyon, France)
Alain Puisieux
Anne-Pierre Morel

CLB – UBET
(Lyon, France)
David Pérol
Sylvie Chabot
Isabelle Treilleux
Audrey Lardy-Cleaud

CLB – Bioinformatics
G.Thomas platform
(Lyon, France)
Alain Viari
Janice Kielbassa

Université de Lorraine
(Nancy, France)
Iouri Motorine
Virginie Marchand

CLB – Translational research
(Lyon, France)
Pierre Saintigny
Sandra Ortiz-Cuaran
Marie-Alexandra Albaret

IGDR
(Rennes, France)
Reynald Gillet
Sophie Chat

Université Paris XI
(Paris, France)
Olivier Namy
Laure Bidou
Agnès Baudin-Baulieu

IGR
(Villejuif, France)
Fabrice André
Ibrahim Bouakka

University of Dundee
(Scotland, UK)
JC Bourdon
Susan Bray
Alastair Thompson

EDyP – INSERM/CEA/UGA
(Grenoble, France)
Yohan Couté
Annie Adrait