

# Genetic interactions of the hepatitis C virus ARF protein with cell proliferation pathways in HCV-positive hepatocellular carcinoma

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## Overview

Hepatocellular carcinoma (HCC) is the second cancer with the highest mortality rate worldwide. The replication of hepatitis viruses B and C (HBV and HCV, respectively) in hepatocytes represent the main etiology of HCC, with the predominance of HCV. HCV is a positive-strand RNA virus that encodes 10 proteins in a unique open read frame (ORF). The viral genes *CORE*, *NS3*, *NS5A*, and *NS5B* are known as oncogenes. In 1998, a new virus ORF was discovered and named ARFp (alternative reading frame protein). However, 20 years after its discovery, little is known about the biological role of ARFp.

## HCV genome

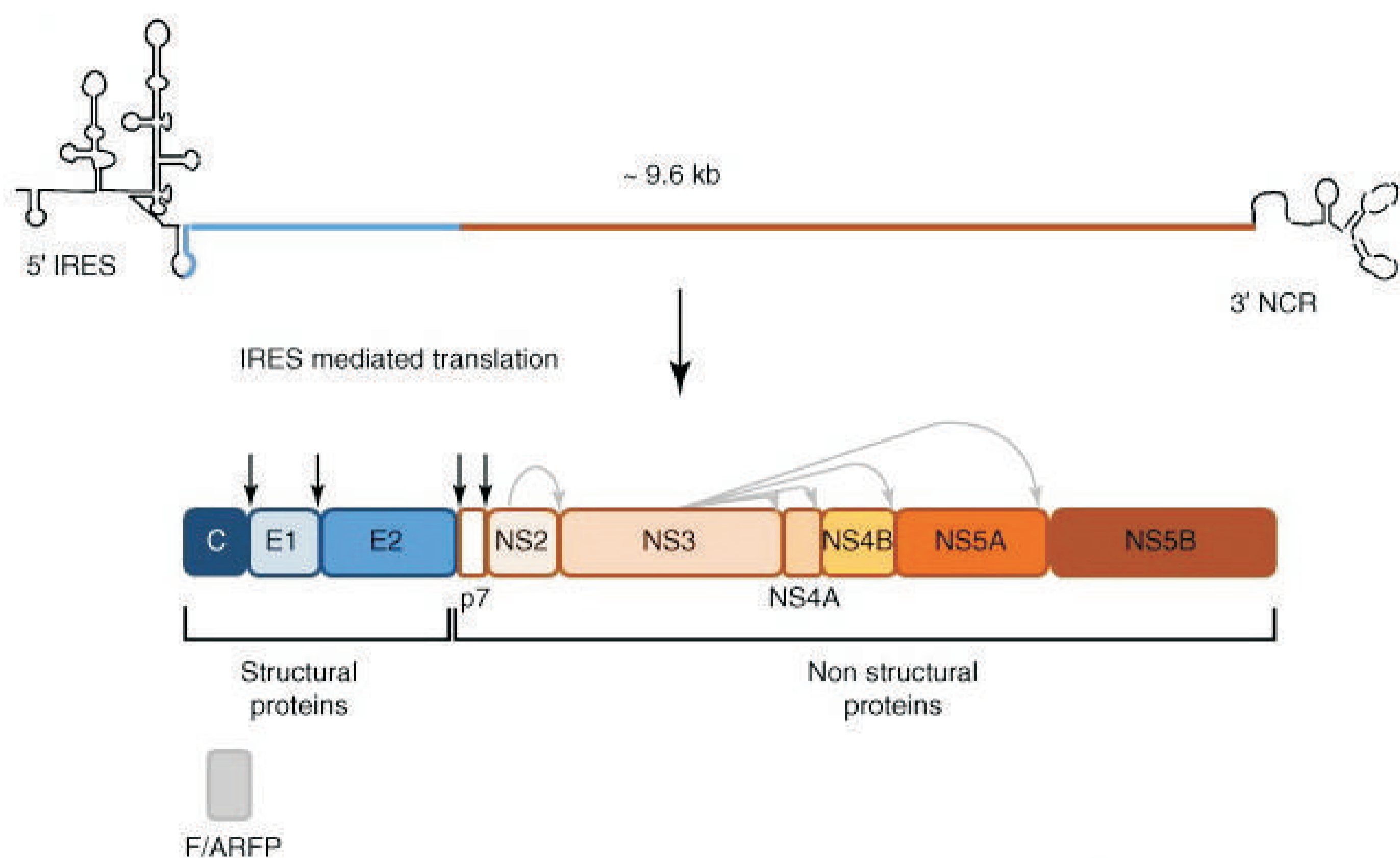


Figure 1. HPV genome. Source: Georgel et al. (2010)[1].

## ARF-P and Hallmarks

Recently, the cyclin D1/pRb pathway has been implicated as modulated by ARFp, thus assigning a role of this protein in carcinogenesis [2]. The study that described such role used cell lineages of hepatocytes and the results observed in the cultures infected by the ARFp was the increase in cellular proliferation and expression of genes related with proliferation as cyclin D1 (*CCND1*), *VAV1*, *C-FOS*, and *C-JUN*.

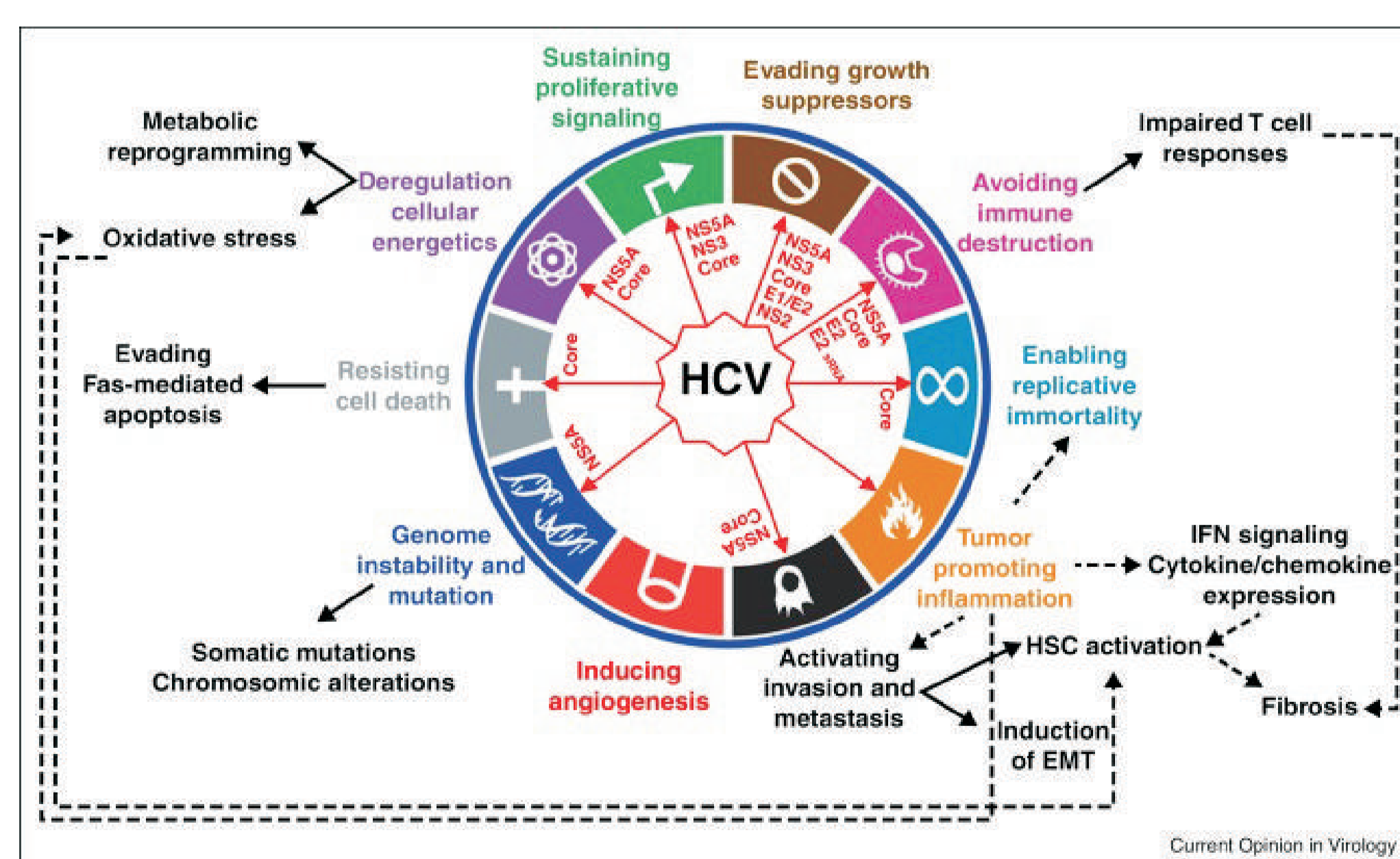


Figure 2. Source: Bardiera et al. (2016)[3].

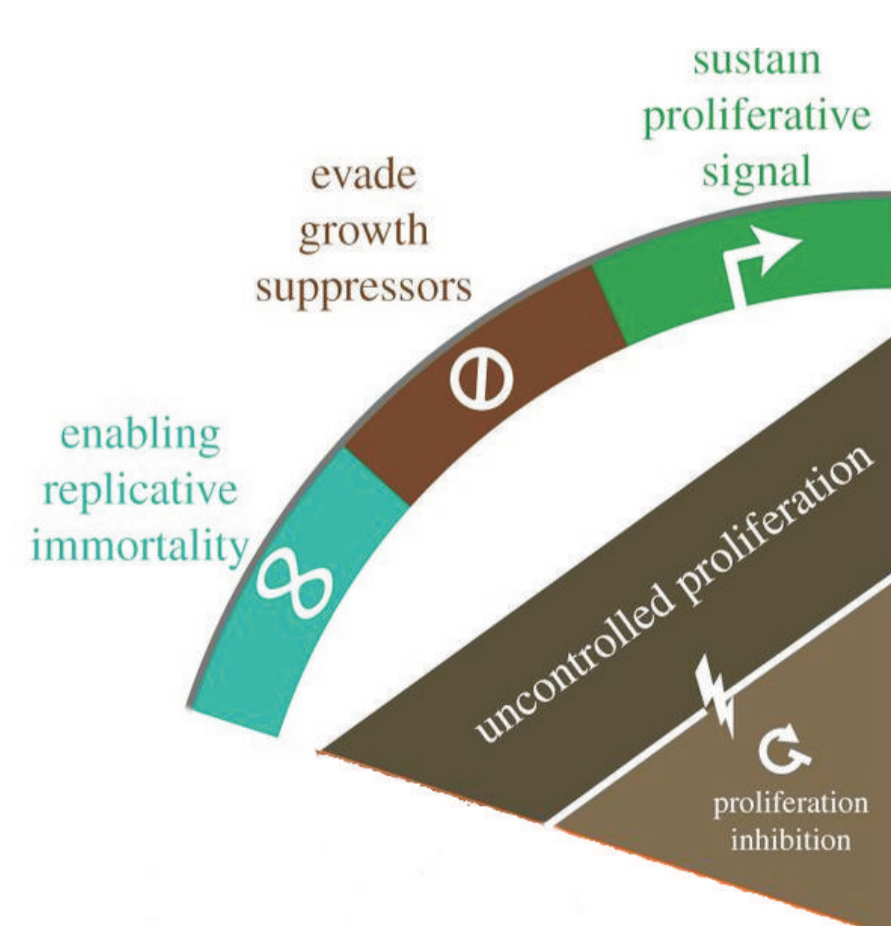


Figure 3. Modified from: Aktipis et al. (2015)[4].

## Hypotesis

Based on this study, some hypotheses were formulated, including:

- Could this study be replicated in clinical biopsy samples?
- Are there other genes modulated by ARFp in pathways that promote cell proliferation?
- What were those genes?

## Methods

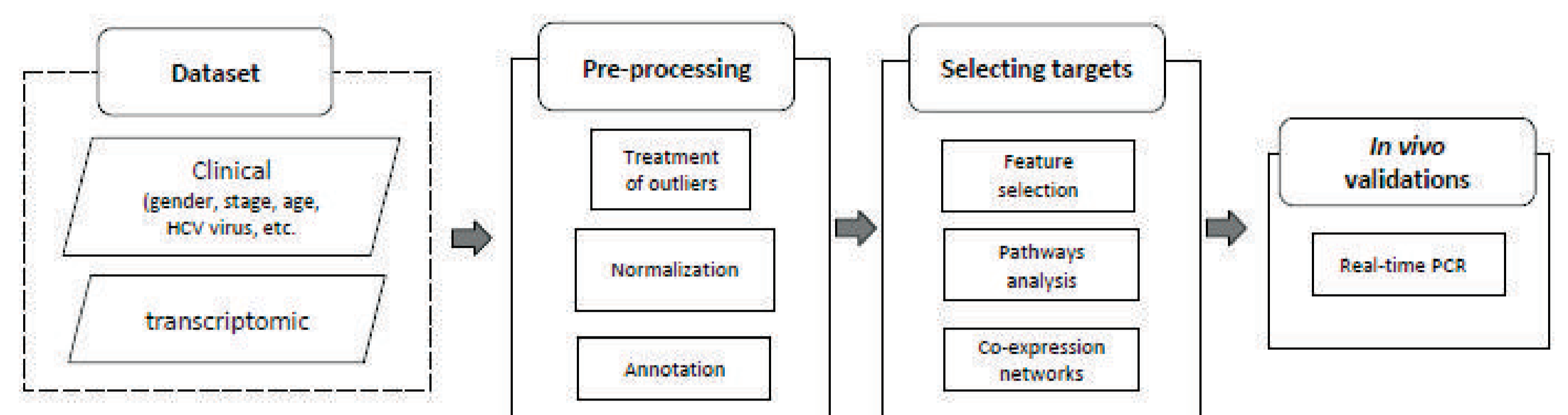


Figure 4. Flowchart representing the main steps of the project.

## Preliminary results

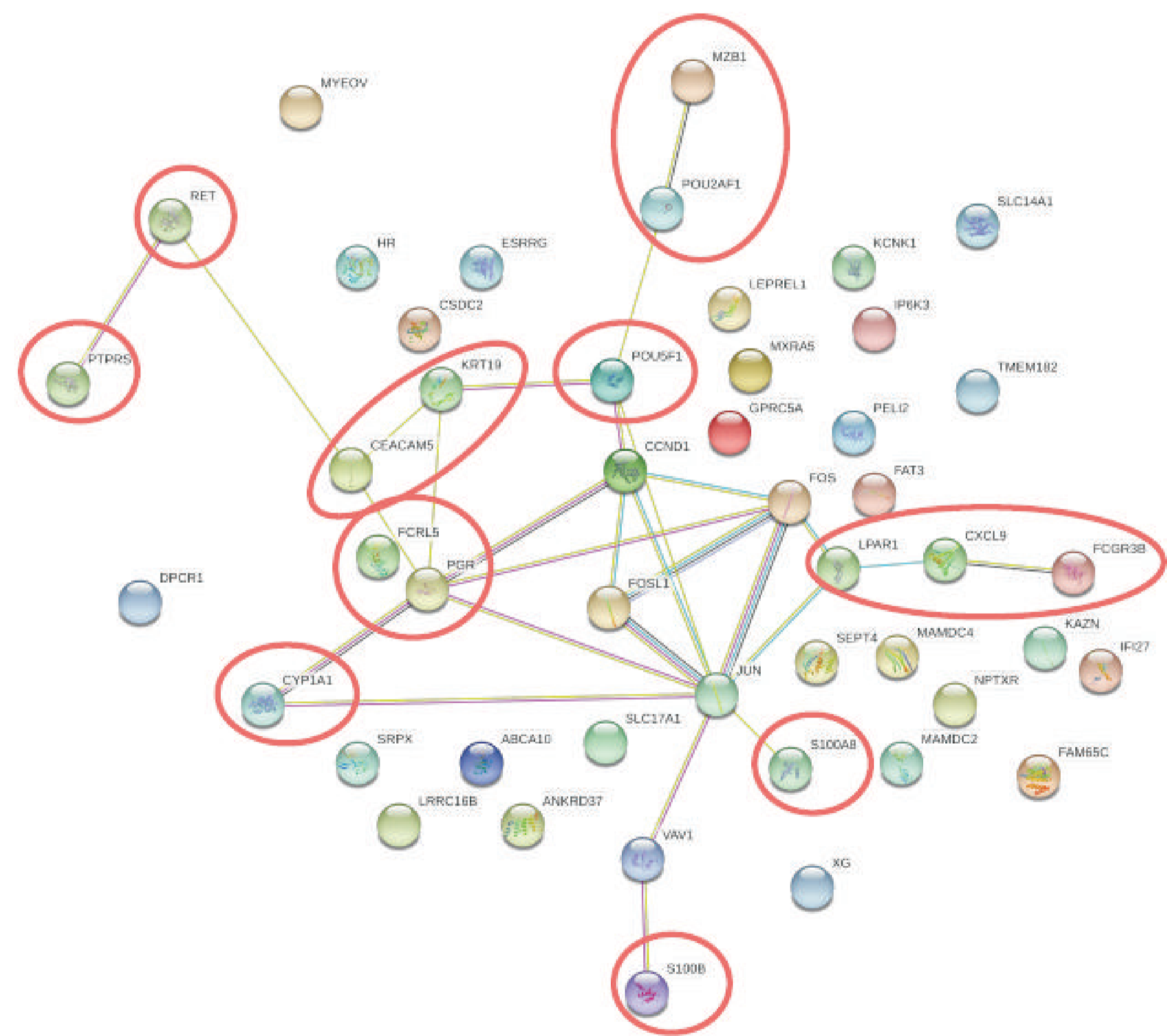


Figure 5. Preliminary results showing genes co-expressed with targets as *CCND1*, *FOS* and *JUN*.

## References

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- [4] C. Athena Aktipis, A. M. Boddy, G. Jansen, U. Hibner, M. E. Hochberg, C. C. Maley, and G. S. Wilkinson, "Cancer across the tree of life: Cooperation and cheating in multicellularity," *Philosophical Transactions of the Royal Society B: Biological Sciences*, vol. 370, no. 1673, 2015.

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Projeto Gráfico: Setor de Edição e Informação Técnico-Científica / INCA