

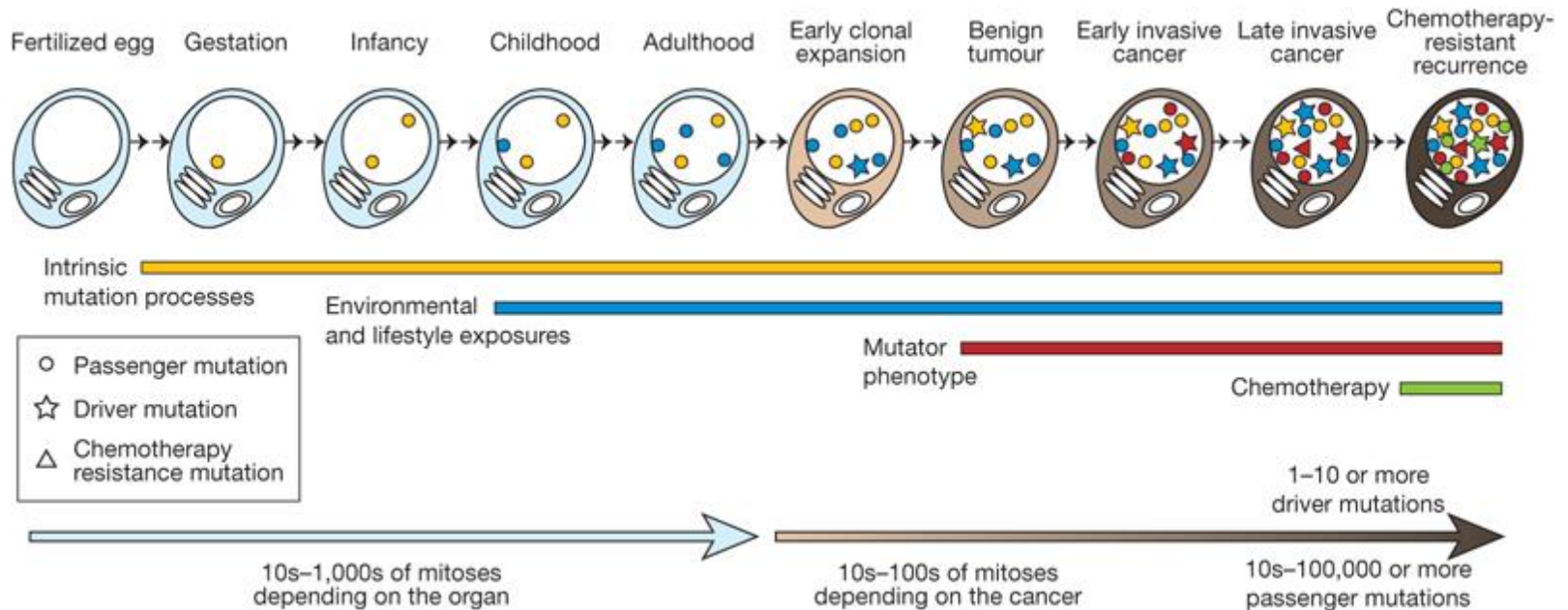
Multi-omics data integration in cancer research

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Integrated CANcer GENomics (ICAGEN) team
CRCI2NA, Nantes



Understanding the molecular history of cancer cells



Study #1: Integrating genomic and clinical data to understand
mutational processes

Risk factors for hepatocellular carcinoma (HCC)



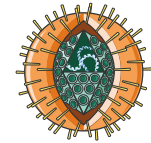
United States

NASH associated
with diabetes
and/or obesity



France

>50% alcohol



Japan/Egypt

HCV



Rare
Hemochromatosis

Age-normalized incidence for
100,000 people

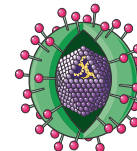


Source: GLOBOCAN 2012

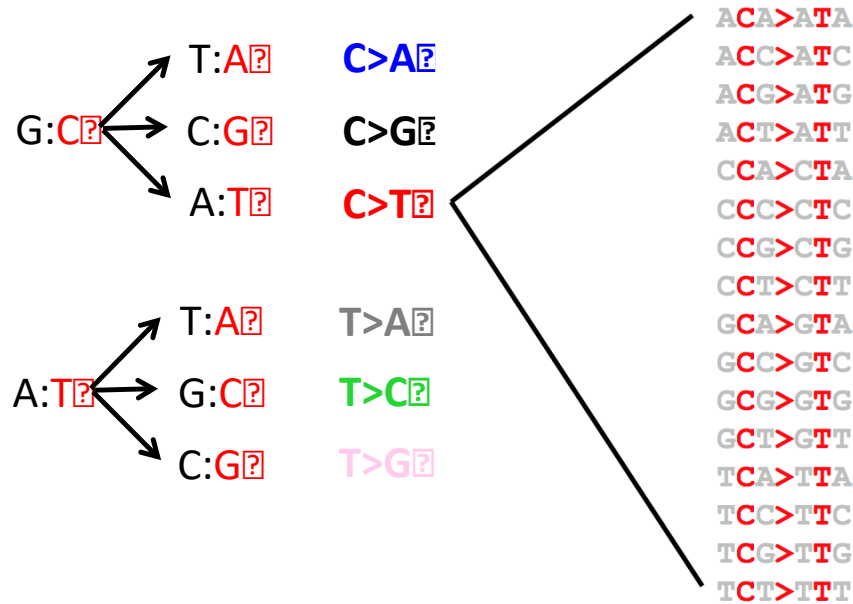
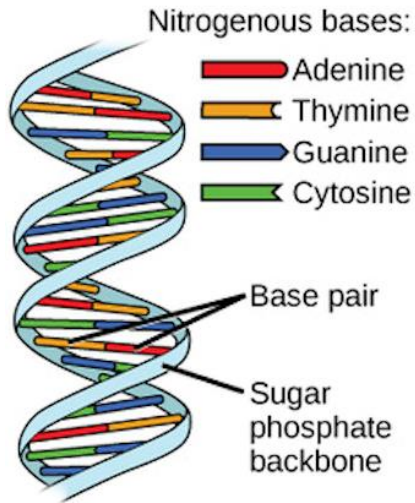
China/sub-Saharan Africa

HBV

Aflatoxin B1

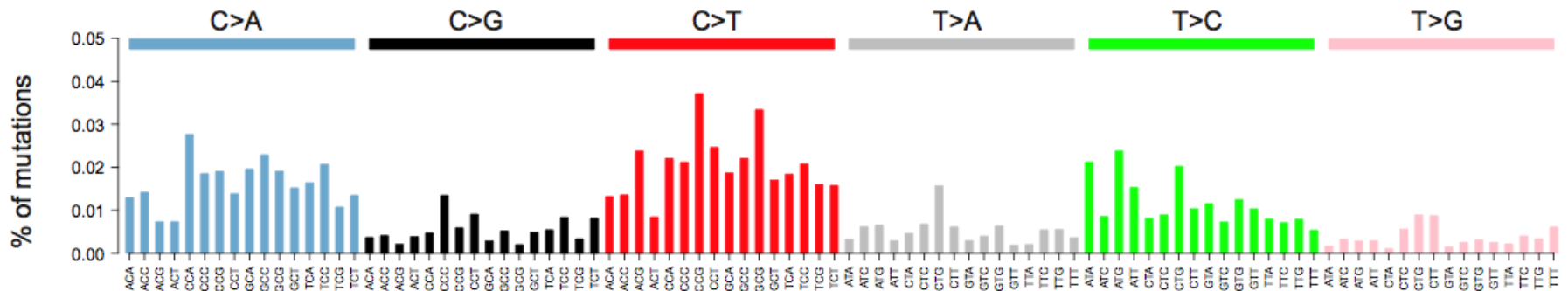


Mutational signatures

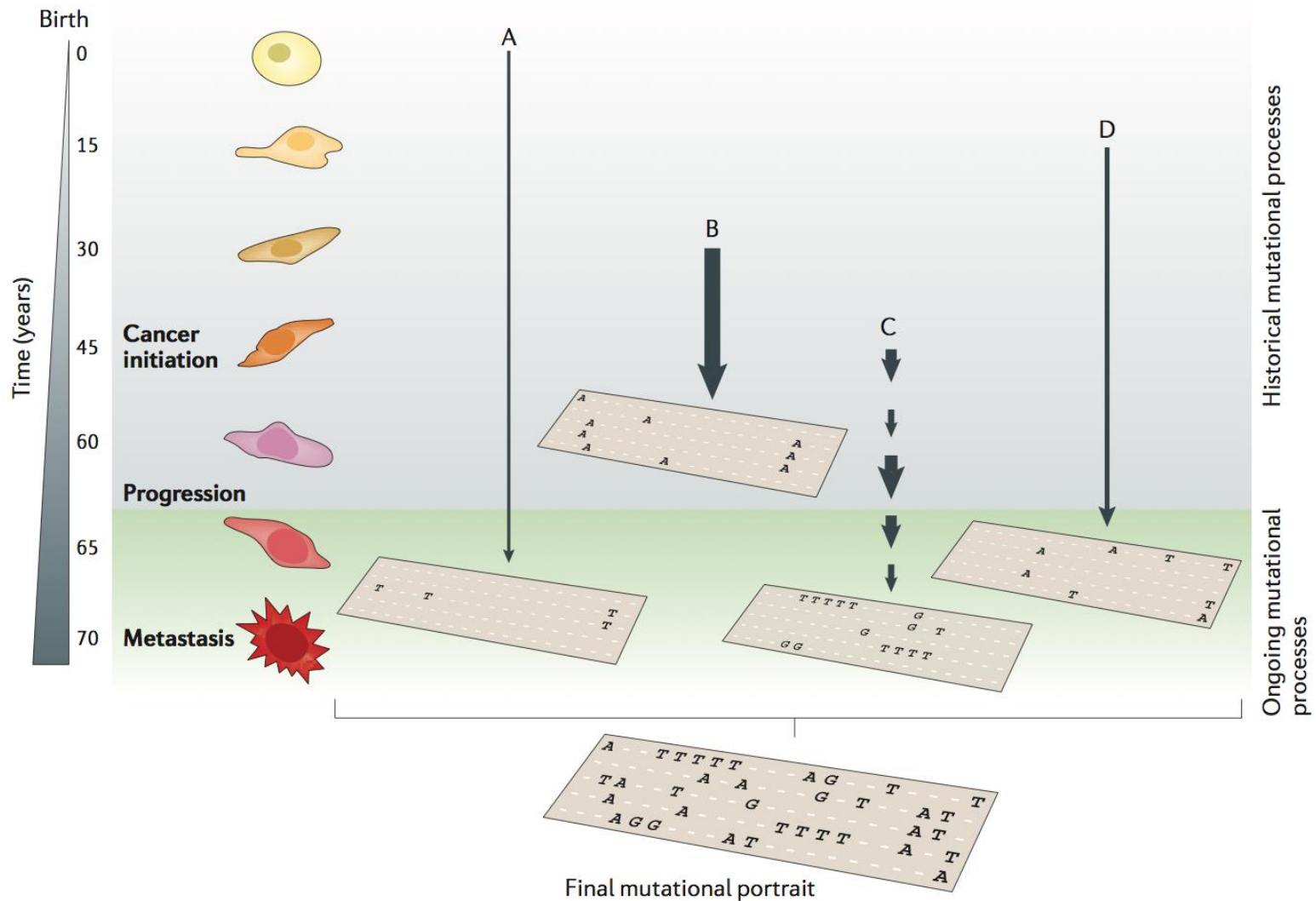


6 substitution types x 16 trinucleotide contexts = **96 categories**

Mutational profile of an average HCC genome (~10,000 somatic mutations)

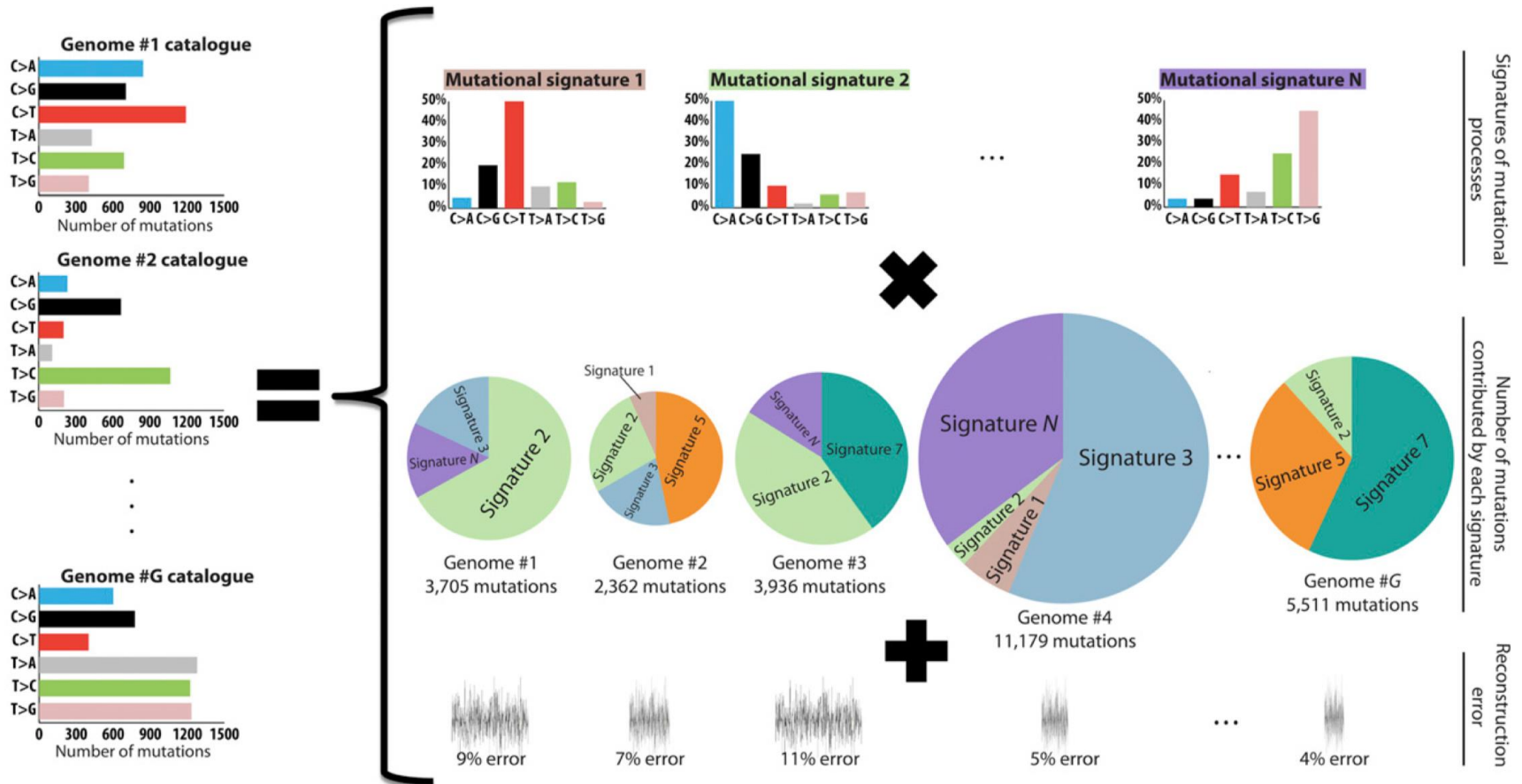


The mutational spectrum of a tumor reflects the accumulation of several mutational processes

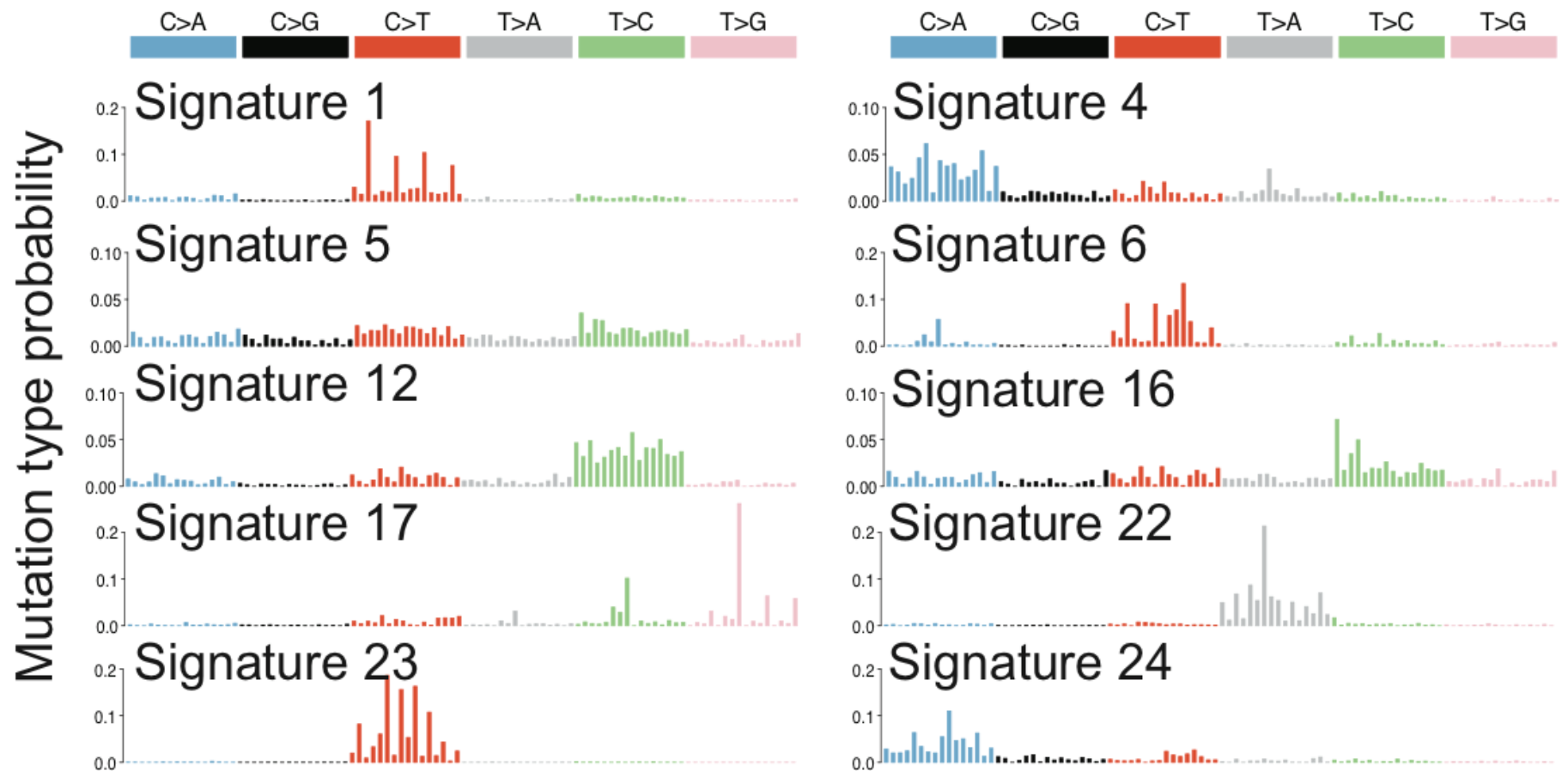


Extracting mutational signatures from NGS data

- NMF (non-negative matrix factorization) can disentangle mutational signatures and their contribution to each tumor genome:



10 mutational signatures identified in liver cancers



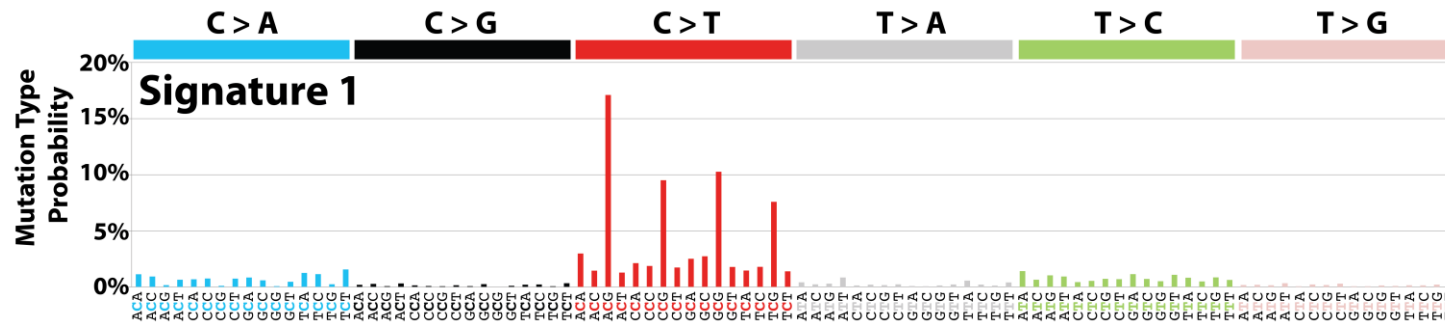
Alexandrov *et al.*, Nature 2013

Schulze*, Imbeaud*, Letouzé* *et al.*, Nature Genetics 2015

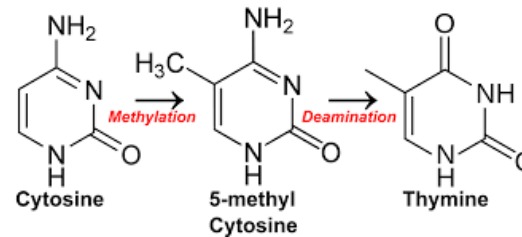
Poon *et al.*, STM 2013

Fujimoto, Furuta, Totoki, Tsunoda, Kato *et al.*, Nature Genetics 2016

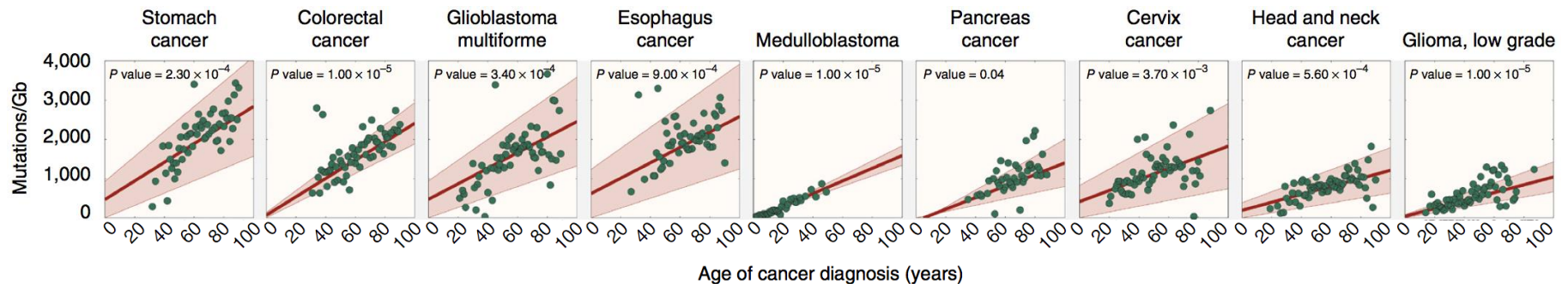
Clock-like mutational signature



- **C>T mutations at CpG sites**

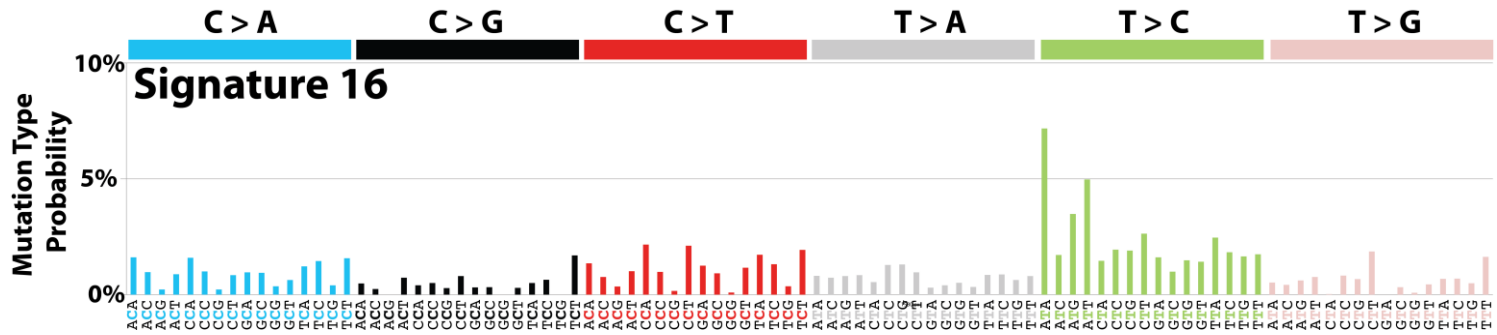


- **Ubiquitous** and correlated with age

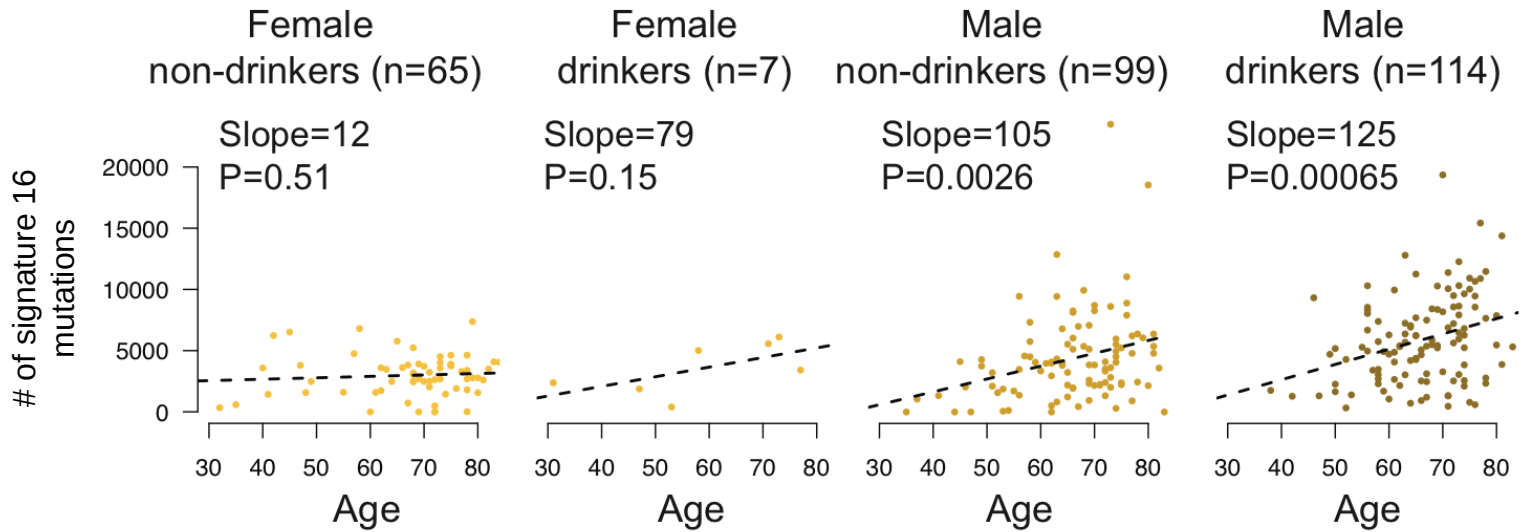


Alexandrov *et al.*, Nat Genet, 2017

Alcohol-related signature



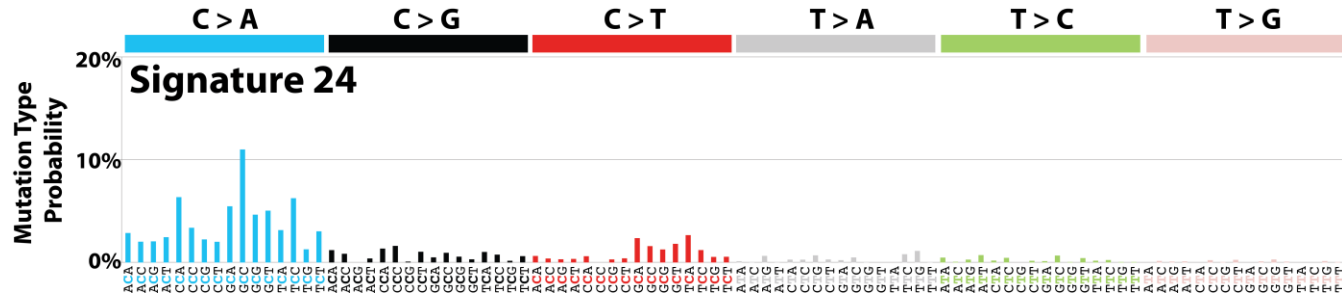
- Signature 16 is significantly associated with age, **gender**, **alcohol** and **tobacco**:



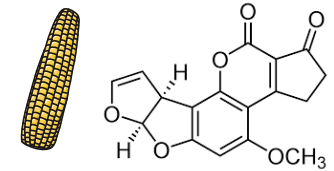
Signature 16 may be due to a product of **liver metabolism**, which production is increased in males, smokers and drinkers.

Aflatoxin B1-related signature

Signature 24

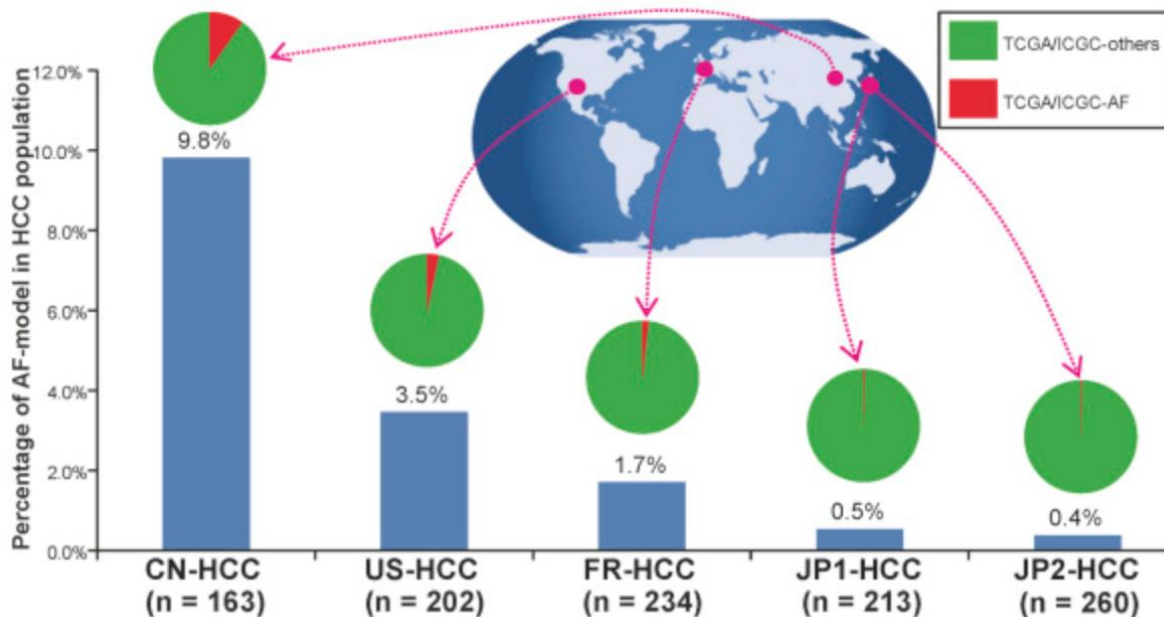


 **Aflatoxin B1**



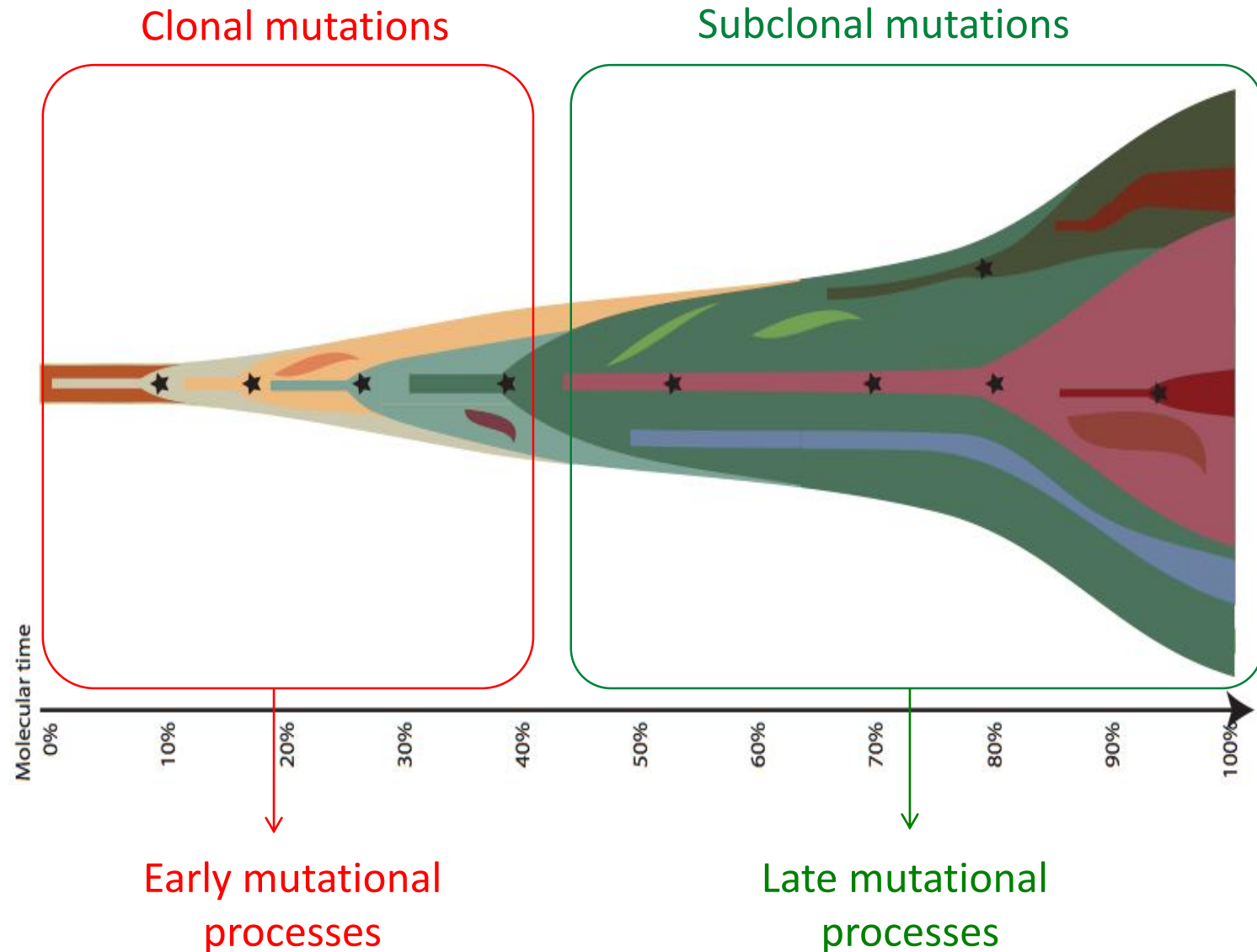
- Only detected in African patients exposed to aflatoxin B1.

Schulze*, Imbeaud*, Letouzé* *et al.*, Nat Genet 2015

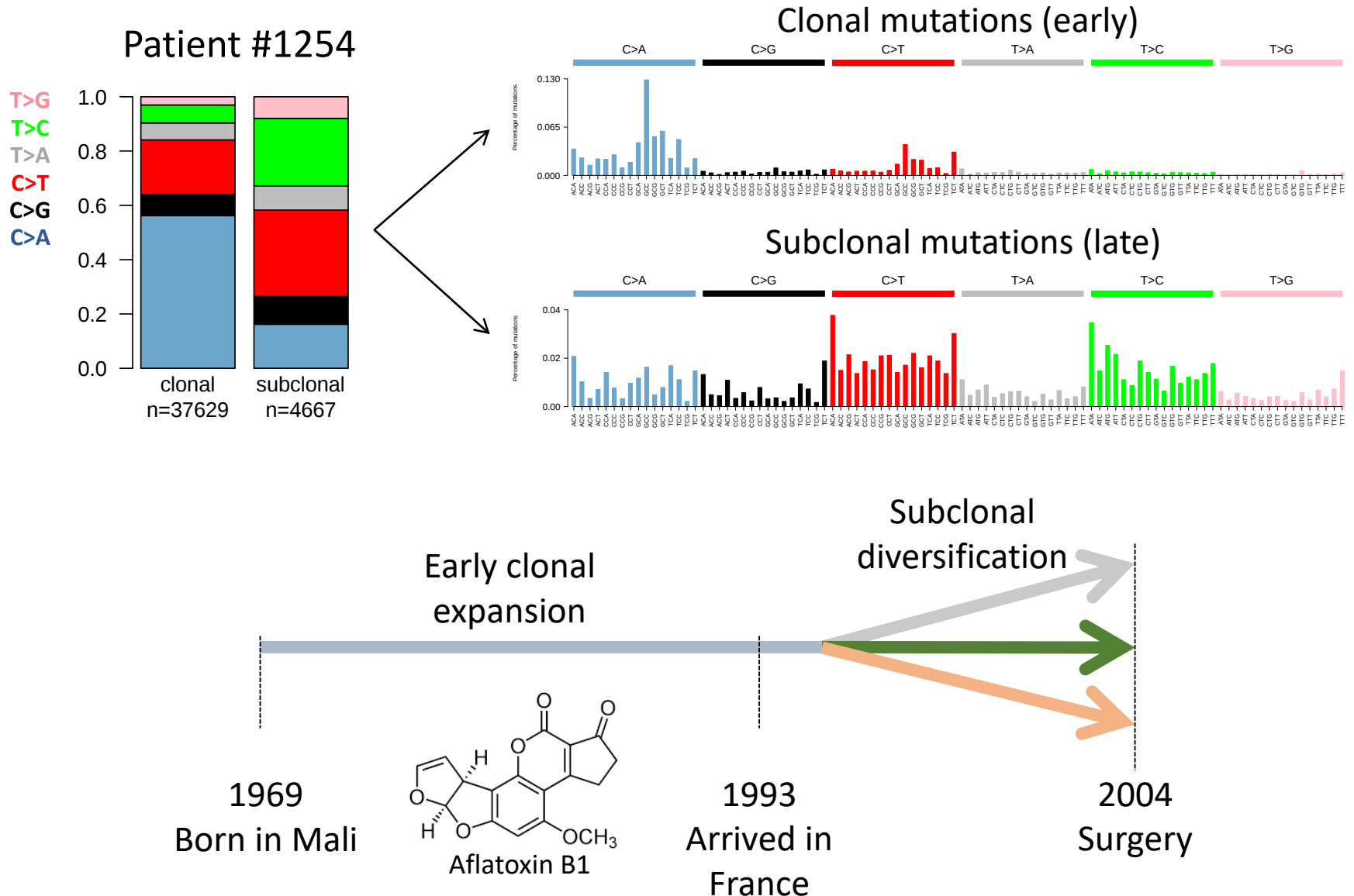


Zhang, He, Zang, Wu, Zhao, Lu
et al., Gastroenterology 2017

How do mutational processes evolve during tumor evolution?

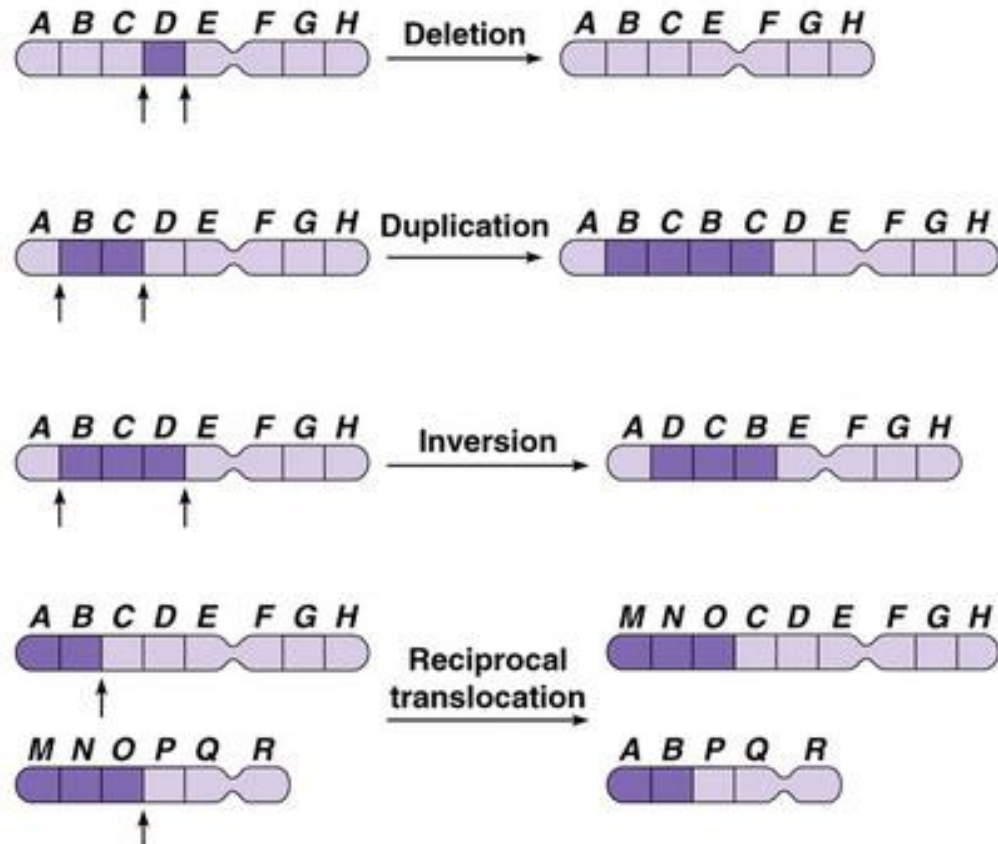


Mutational signature evolution in an African migrant



Study #2: Multi-omics data integration identifies a new
subtype of liver cancer

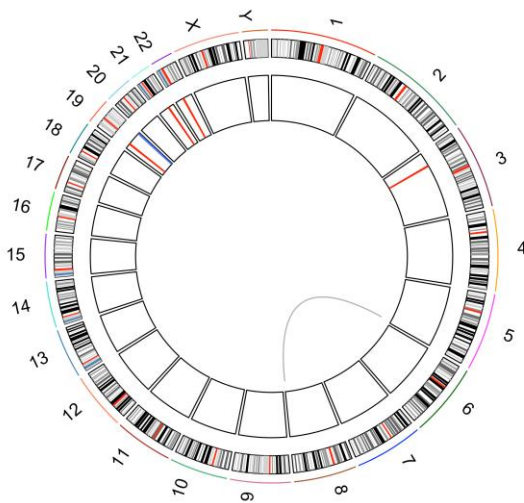
Categories of structural rearrangements



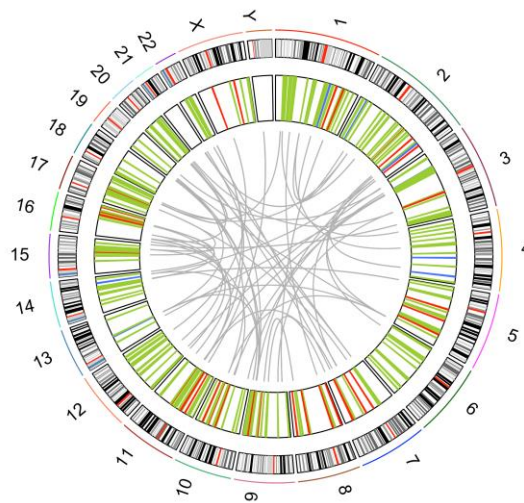
Structural rearrangements in liver cancers

- HCC display heterogeneous patterns of structural rearrangements:

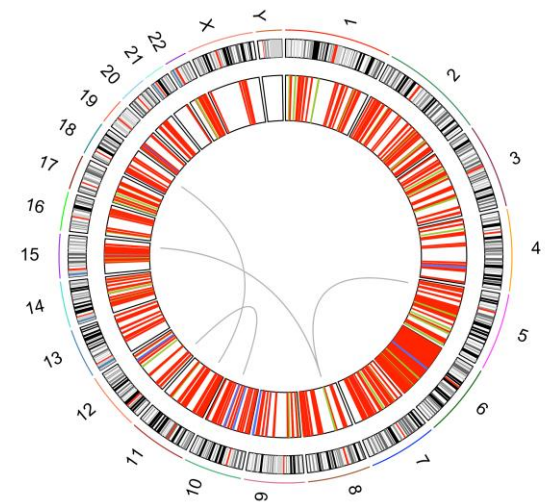
CHC892T



CHC2449T



CHC218T



Deletion

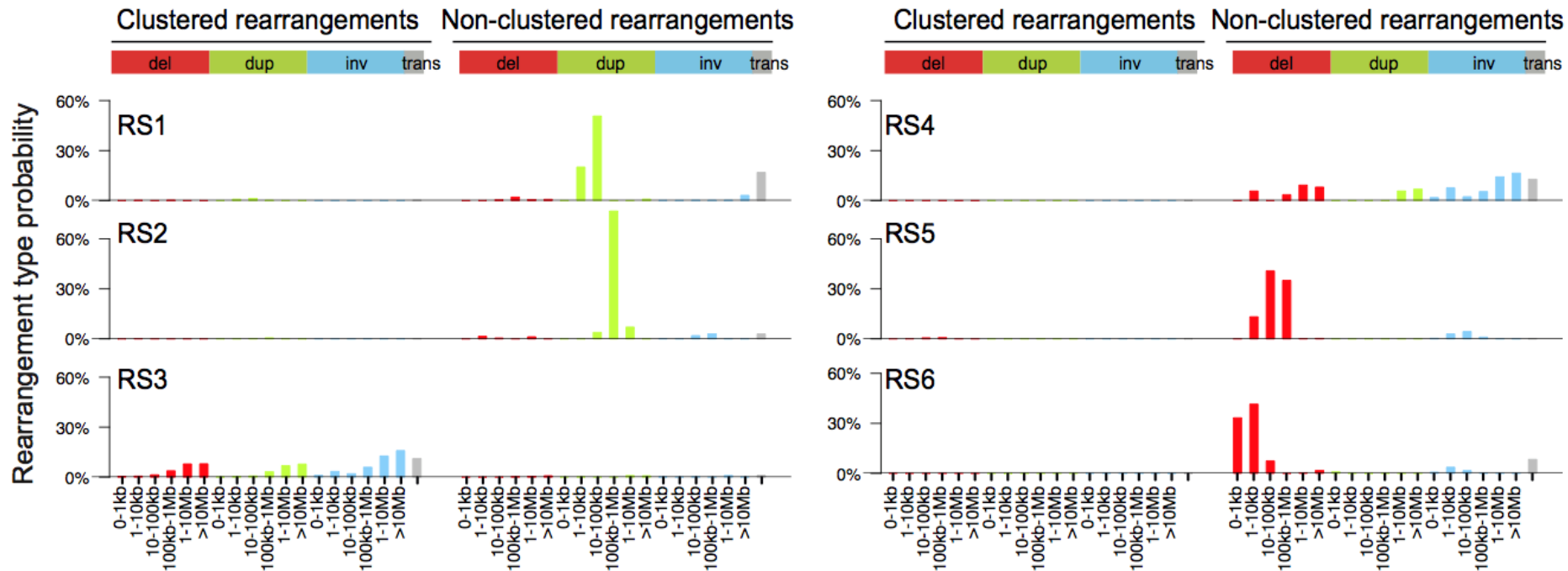
Tandem duplication

Inversion

Interchromosomal translocation

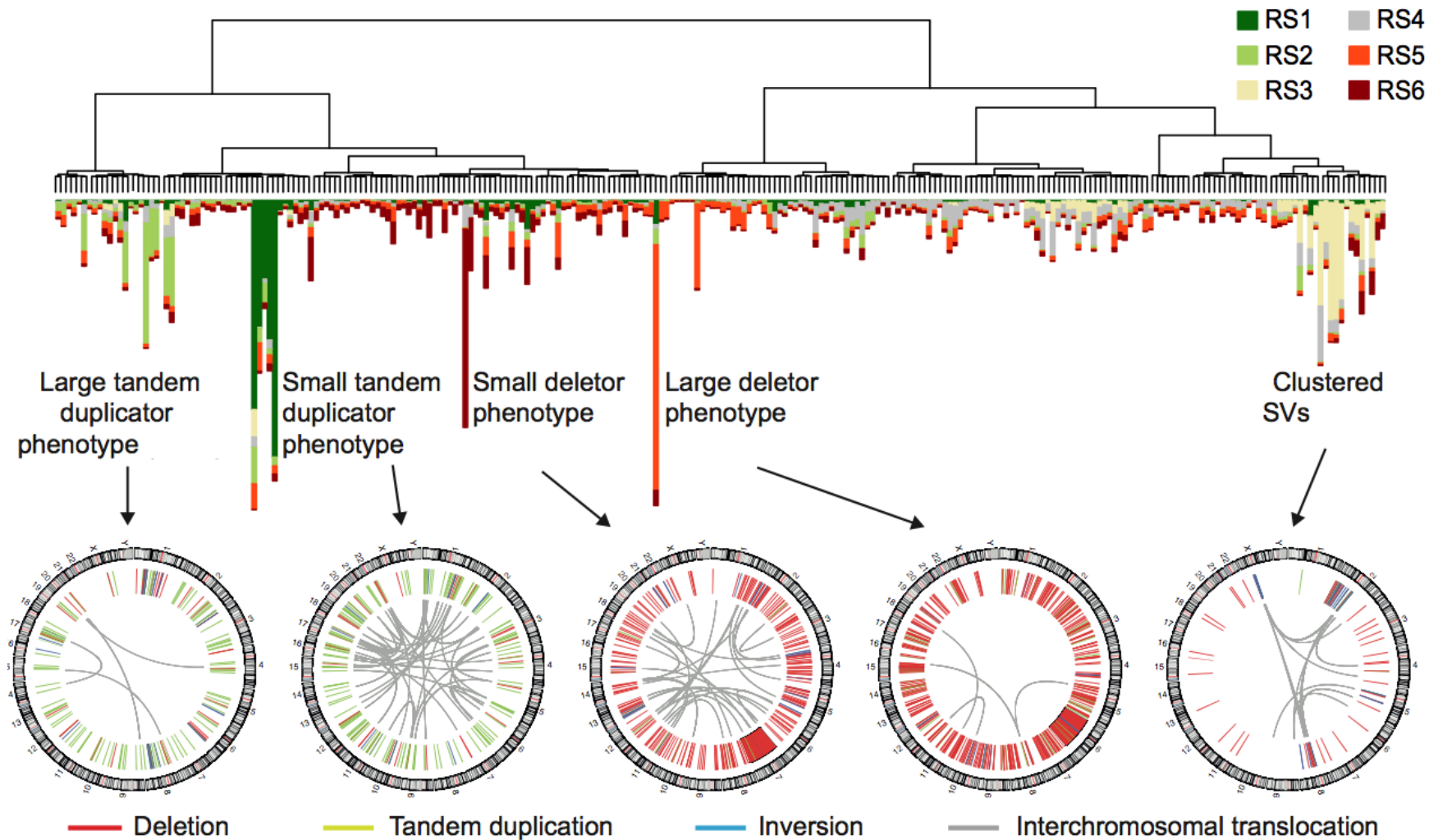
Structural rearrangement signatures in HCC

- NMF reveals **6 rearrangement signatures** operative in HCC:



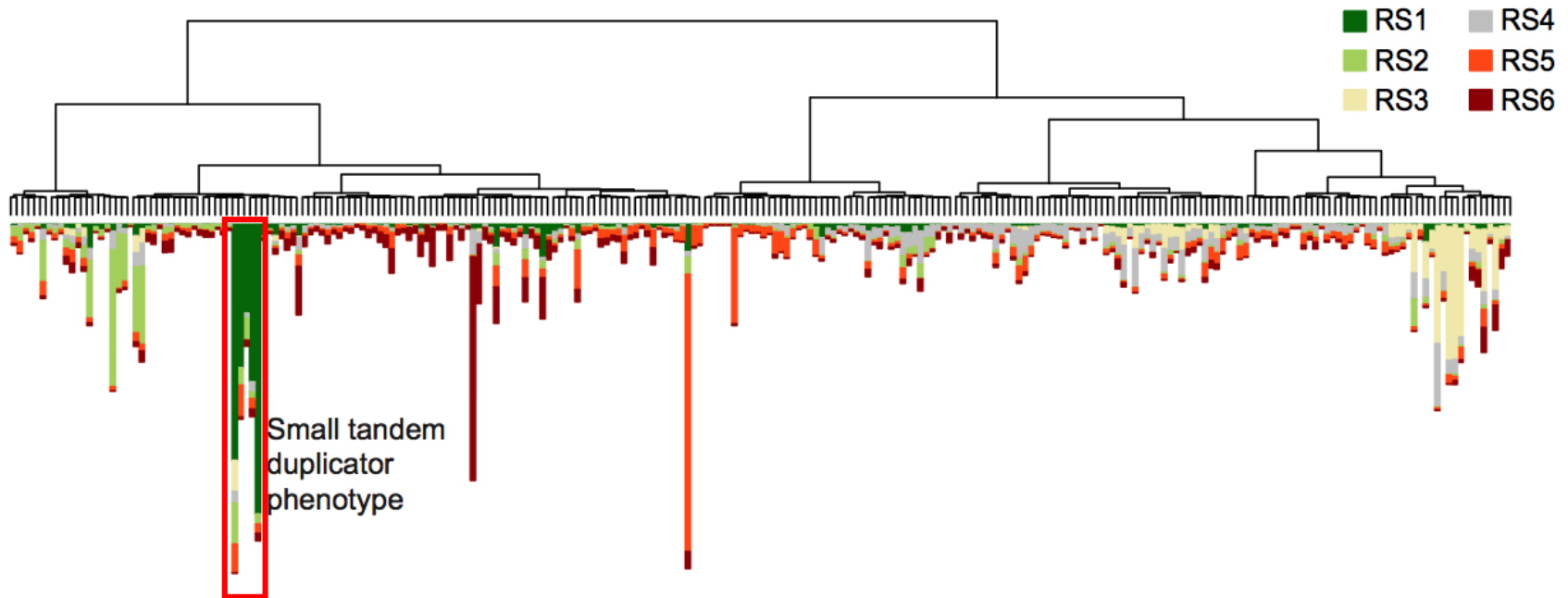
Extreme structural rearrangement phenotypes

- These signatures reveal rare phenotypes of highly rearranged tumors:

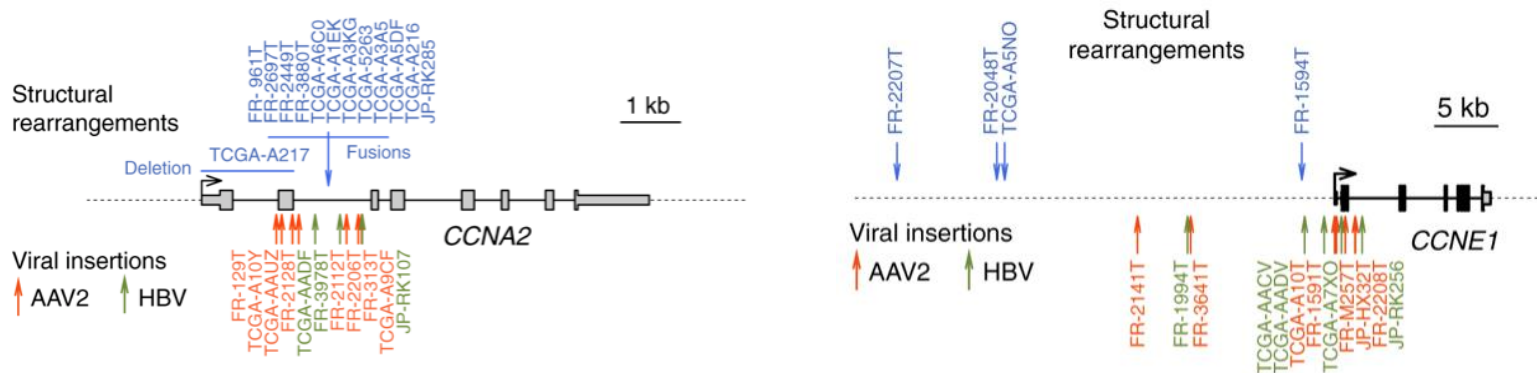


Extreme structural rearrangement phenotypes

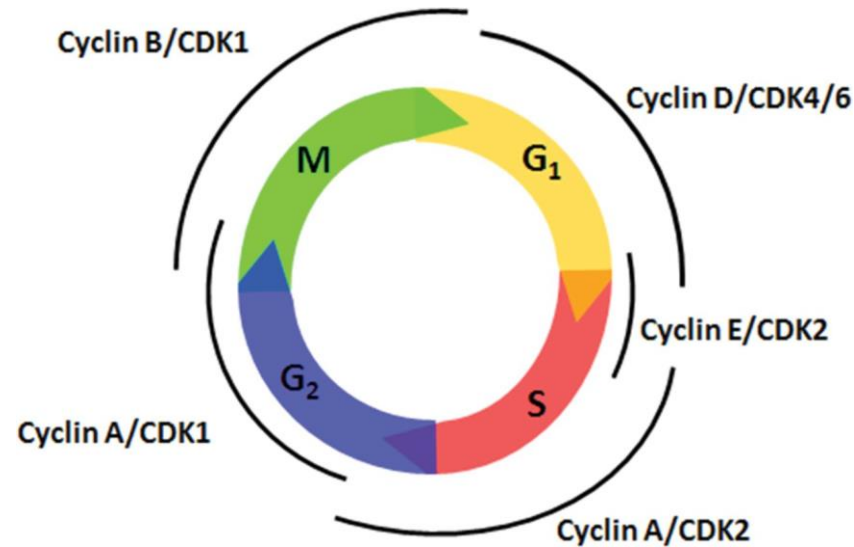
- These signatures reveal rare phenotypes of highly rearranged tumors:



Associated with *CCNA2*/*E1* activation



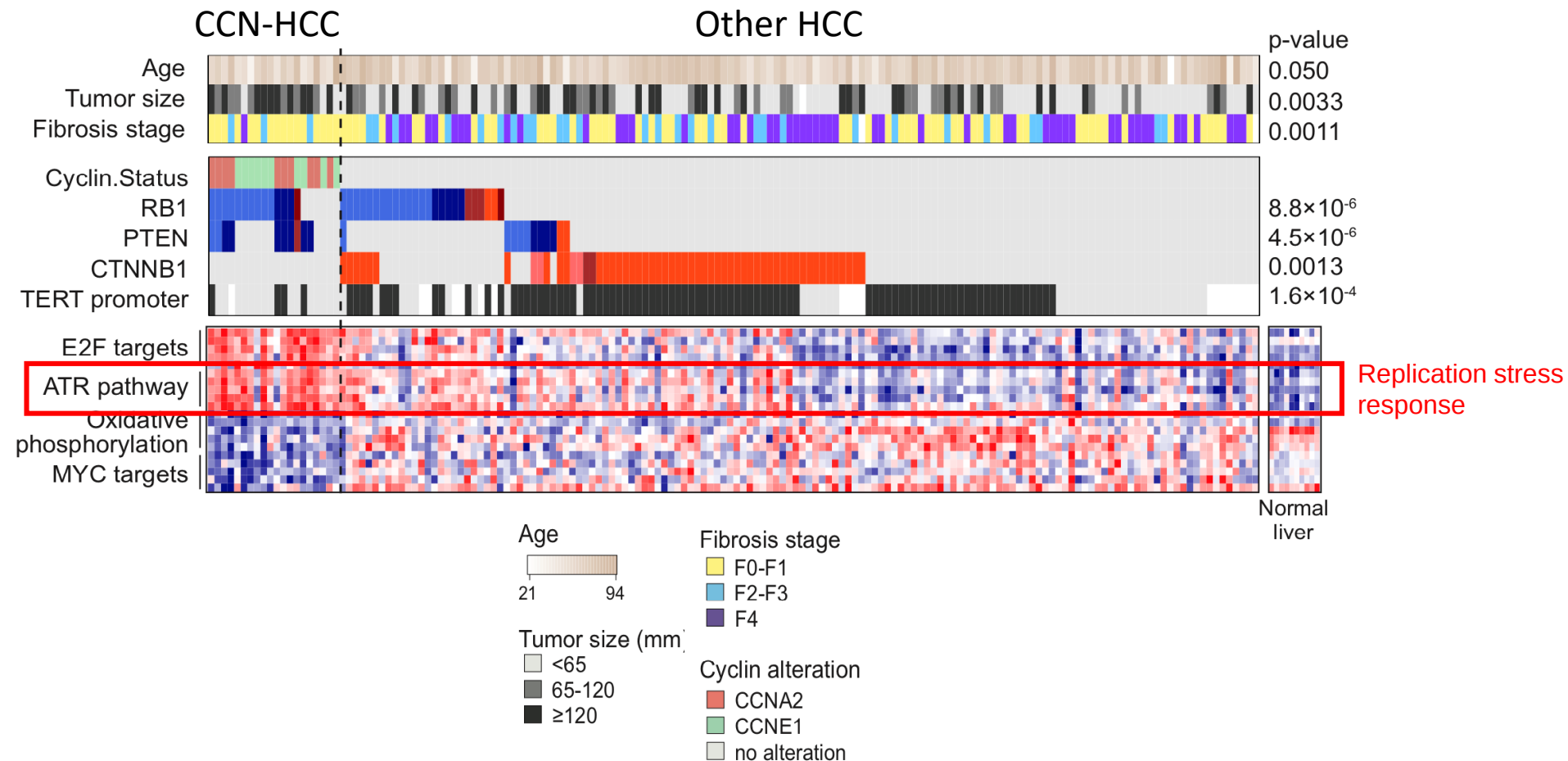
Cyclin activation leads to DNA replication stress



Hypothesis:

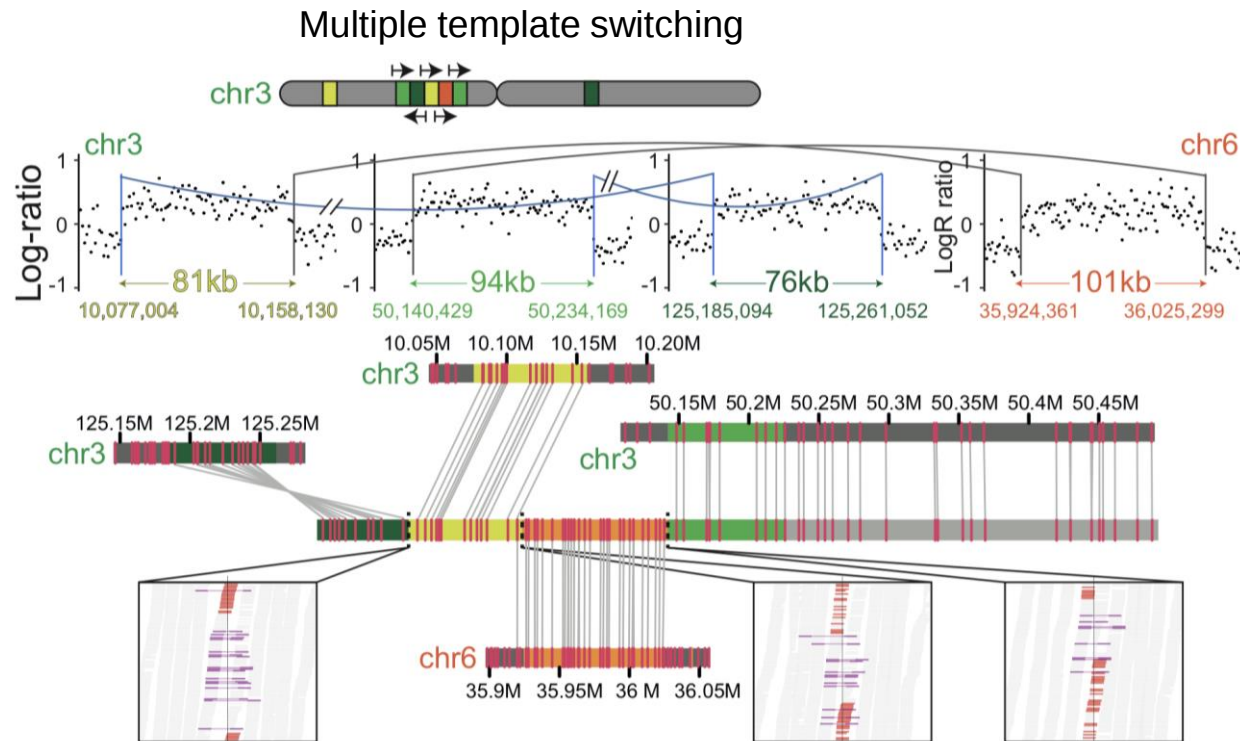
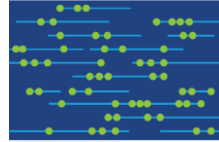
Cyclin A2/E1 activation → Premature S phase entry → Replication stress → Signature RS1

Cyclin A2/E1 activation defines a homogenous HCC subclass (CCN-HCC)

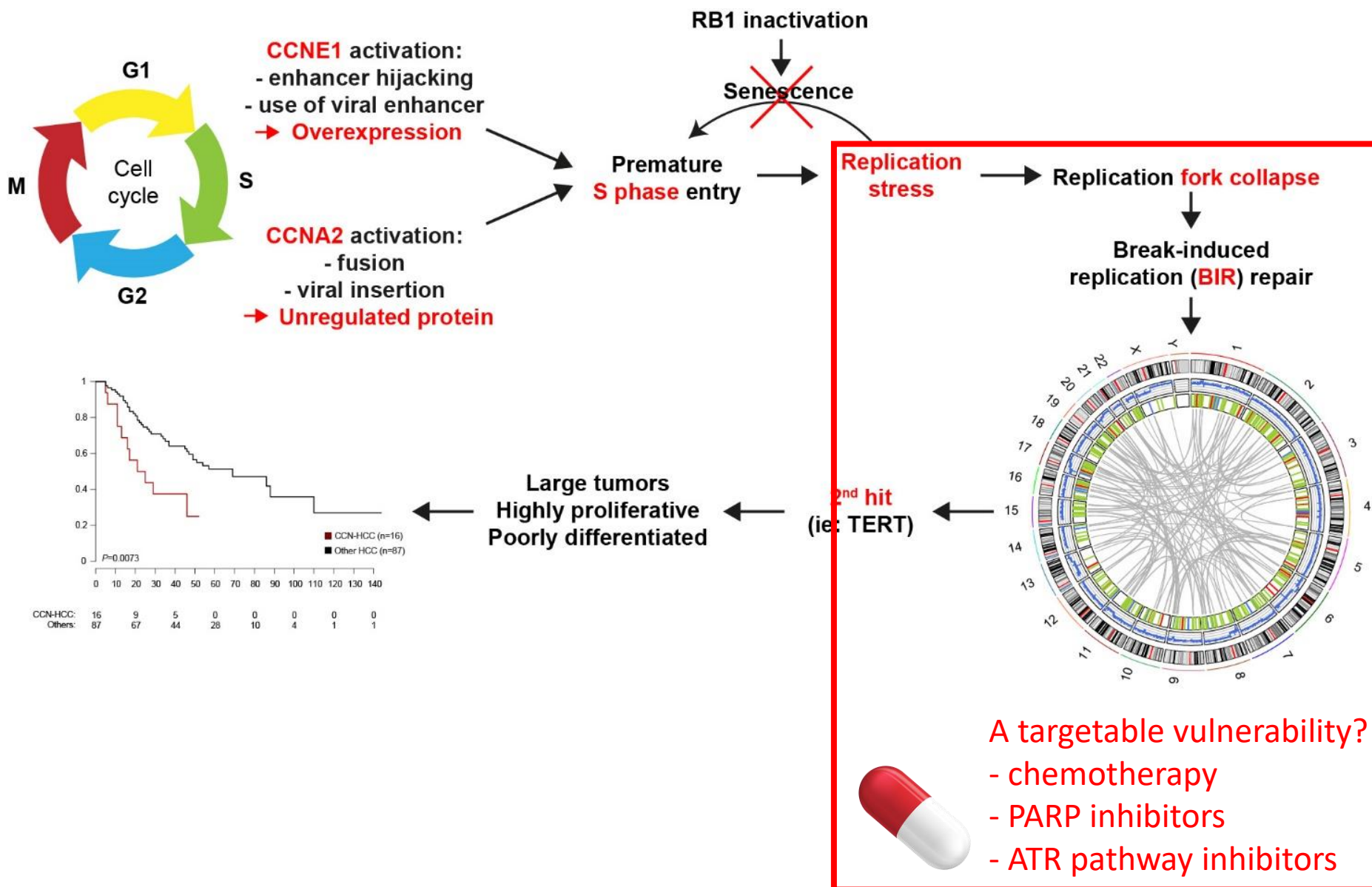


Complex rearrangements result from multiple template switching events

Long molecule optical mapping

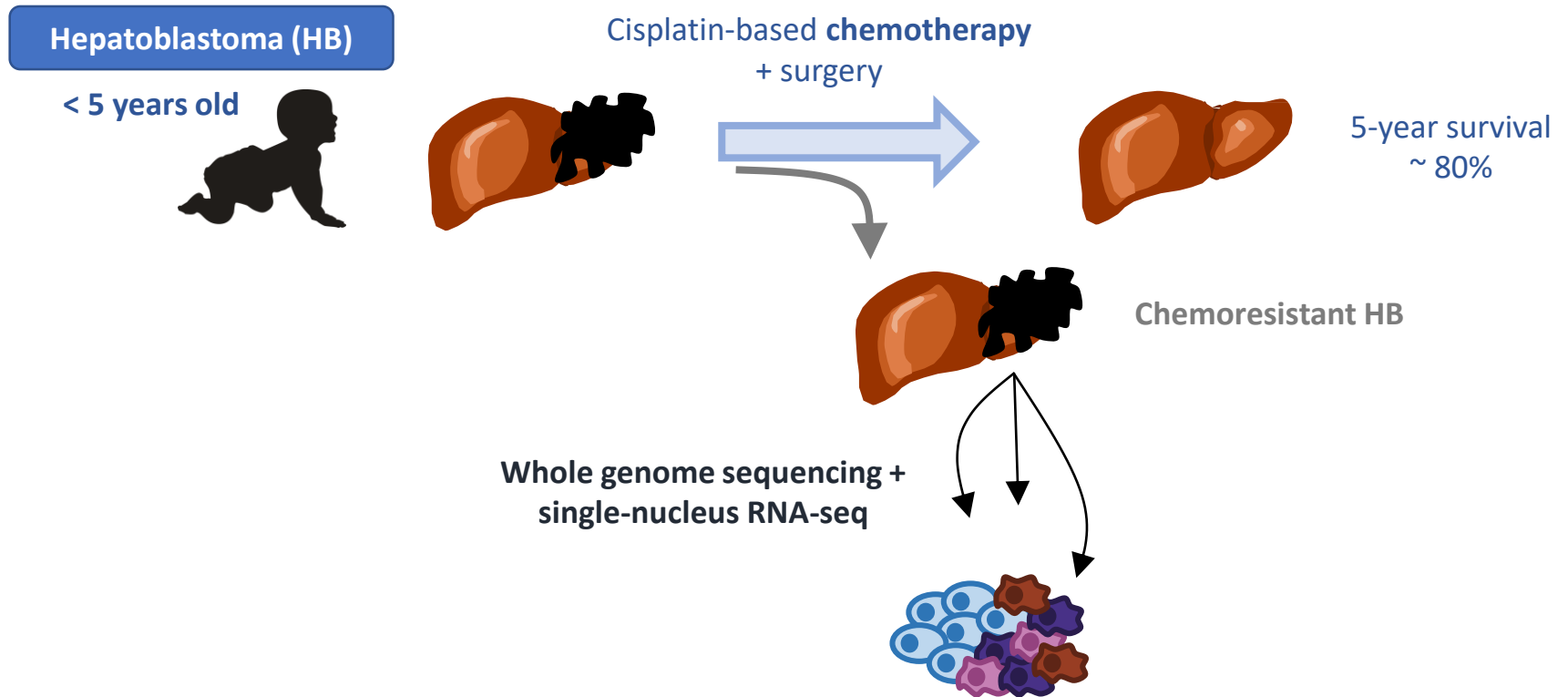


Wrap-up: The natural history of CCN-HCC



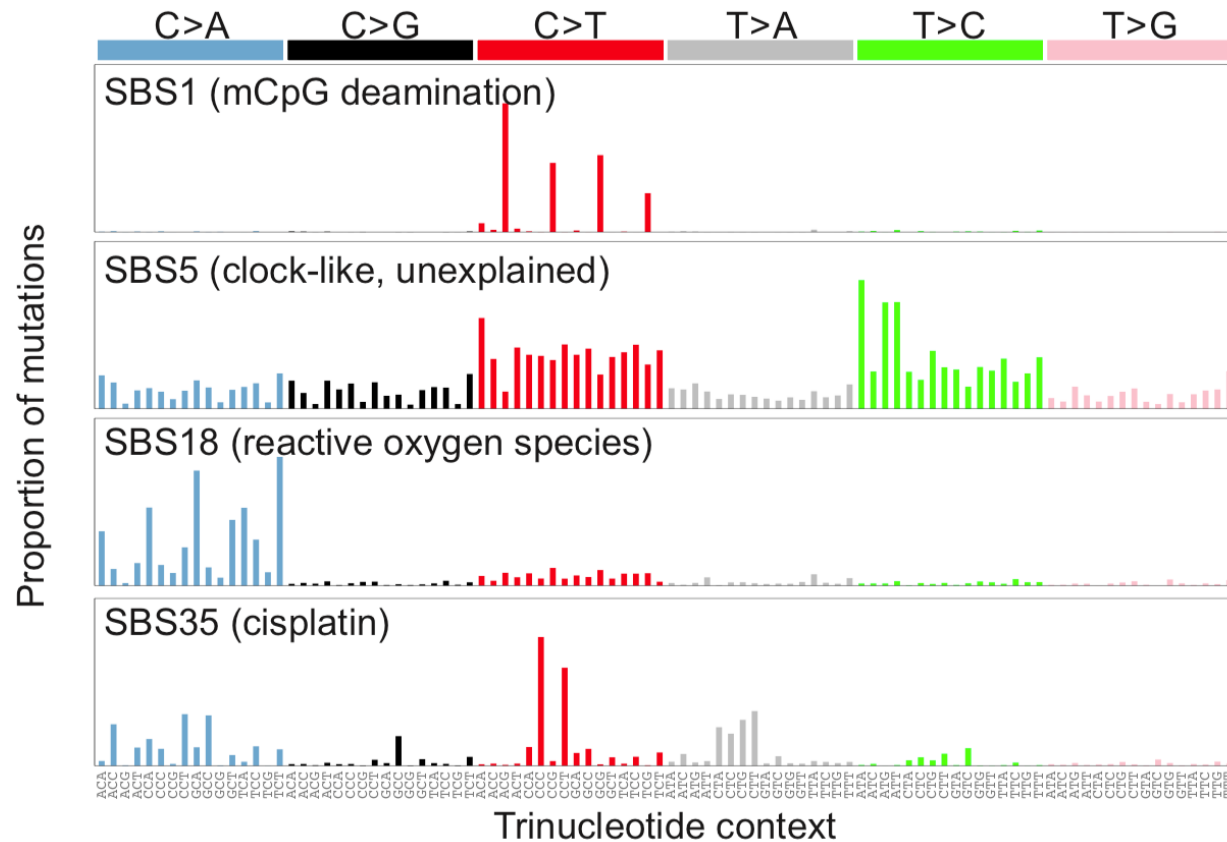
Study #3: Multi-omics data integration highlights chemoresistant cells in hepatoblastoma

Integrated genomic analysis of hepatoblastoma

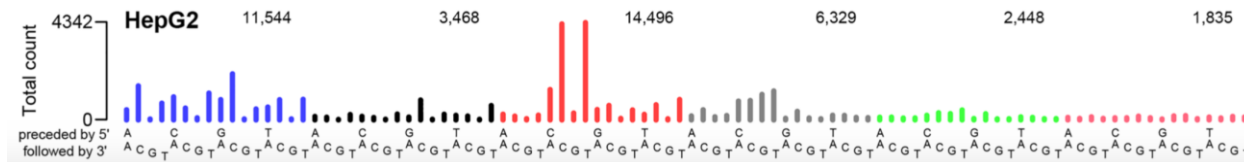


Mutational signature of cisplatin-induced mutations

4 mutational signatures identified in hepatoblastoma



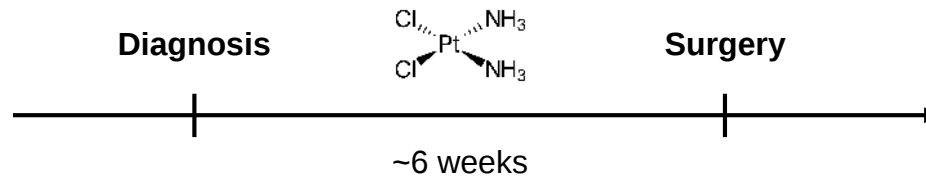
Cisplatin-exposed cell line (Boot et al. 2018)



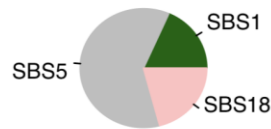
Cisplatin signature is subclonal in primary tumors

Treatment protocol

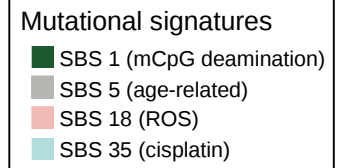
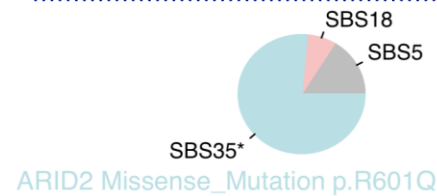
4 cisplatin cycles



CLONAL



SUBCLONAL

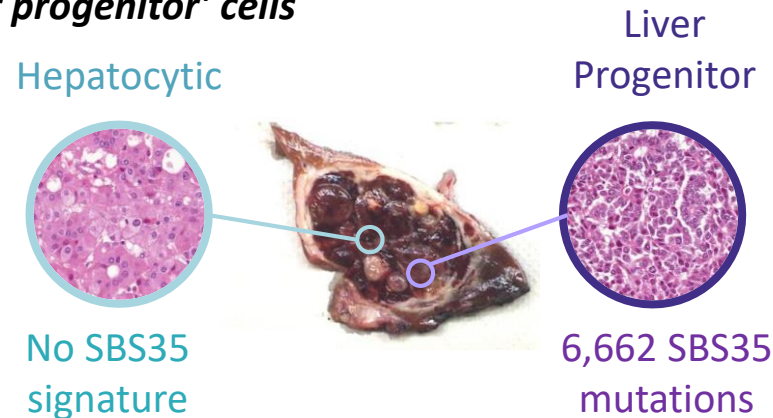


438 mutations

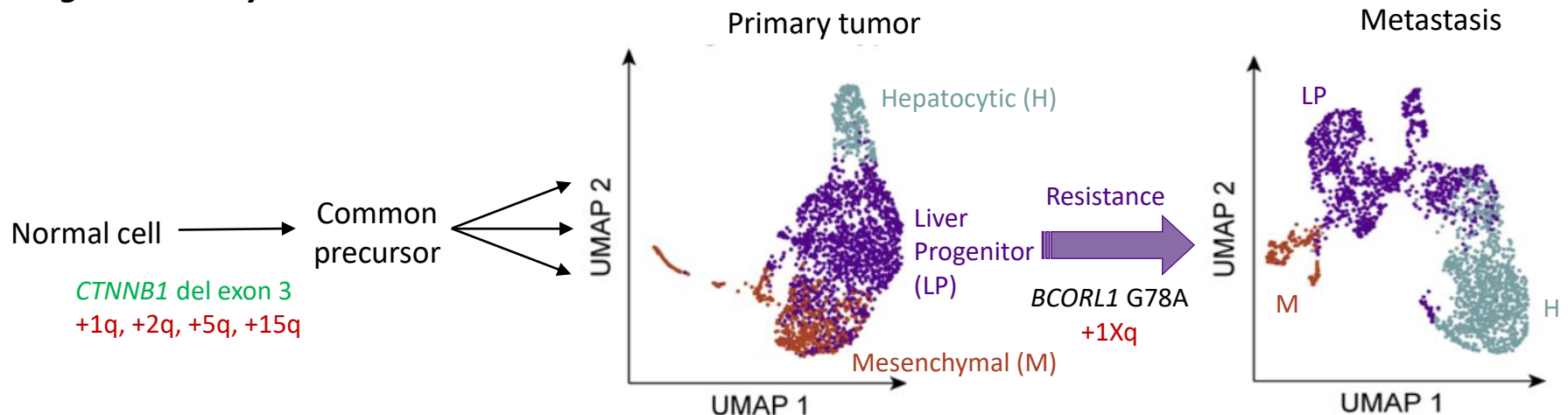
15121 mutations

'Liver progenitor' cells resist to chemotherapy and give rise to metastases

Cisplatin signature is specific of 'liver progenitor' cells

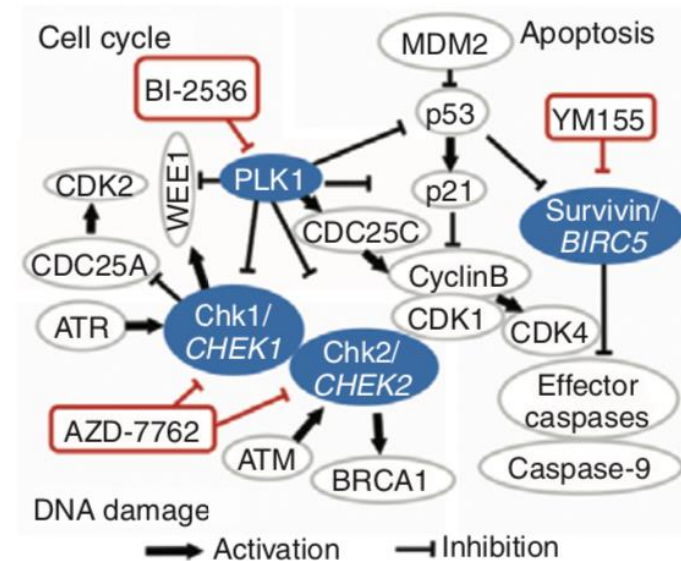


Single-cell analysis

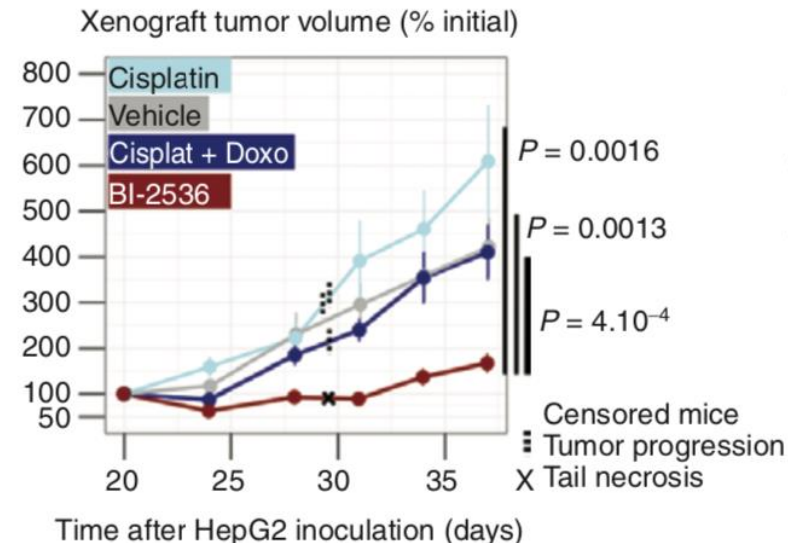
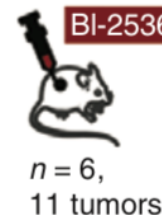


Identification of targetable genes in chemoresistant cells

Genes overexpressed in liver progenitor cells



PLK1 inhibitor is highly efficient against chemoresistant hepatoblastoma



Équipe FunGeST – Centre de Recherche des Cordeliers, Paris



Jessica Zucman-Rossi

Quentin Bayard

Théo Hirsch

Jill Pilet

Guillaume Morcrette

Amélie Roehrig

Sandra Rebouissou

Stefano Caruso

Sandrine Imbeaud

Raphaël Teboul

Pierre Morel-Ribeiro

Gabrielle Couchy

Barkha Gupta

Samantha Schaeffer

Michalina Grabias

Jean-Charles Nault

Rozenn Riou

Elvire Desjonqueres

Long Pan

Manon Cavaignac

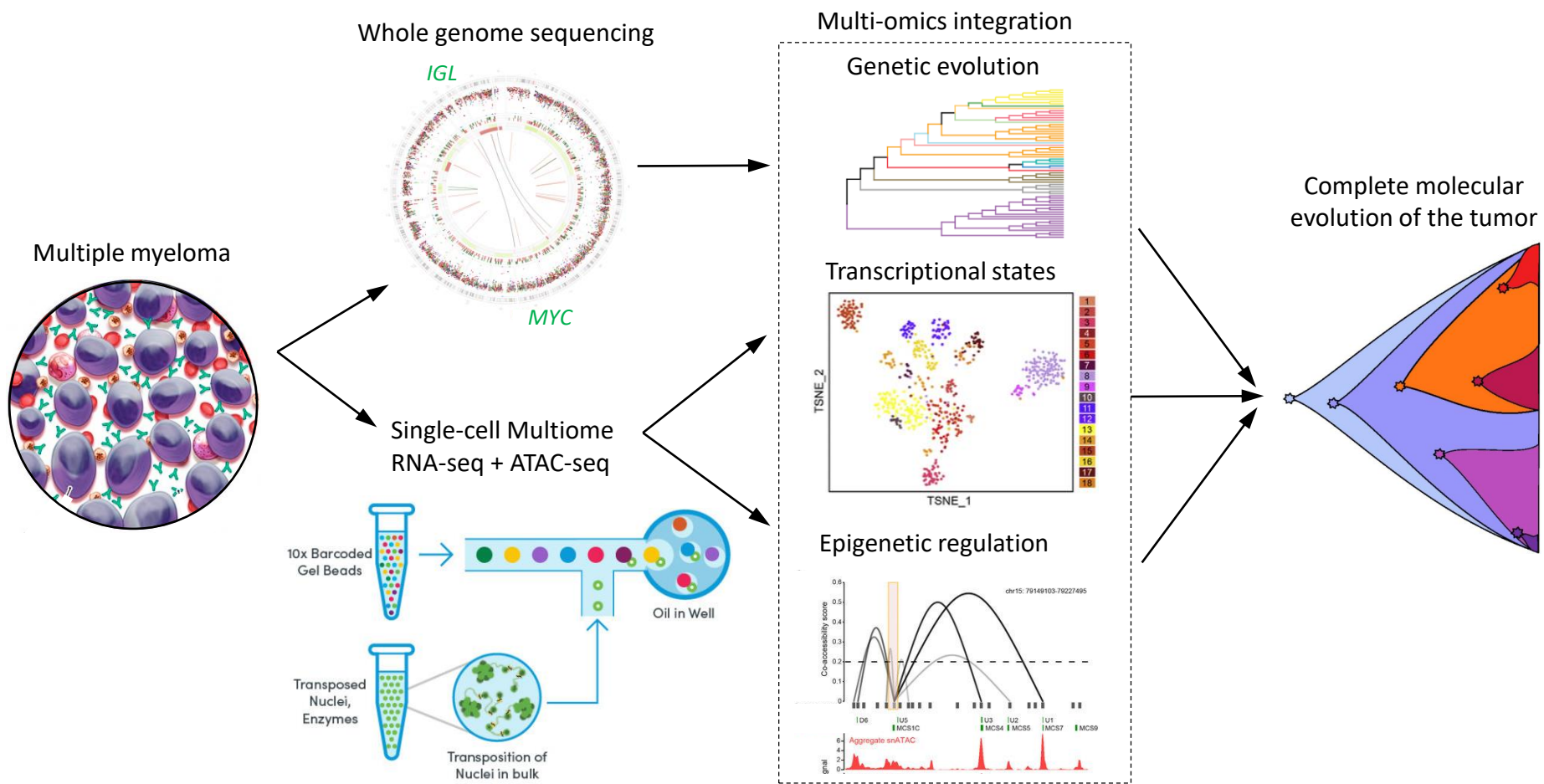
Hélène Péré

Eric Trepo

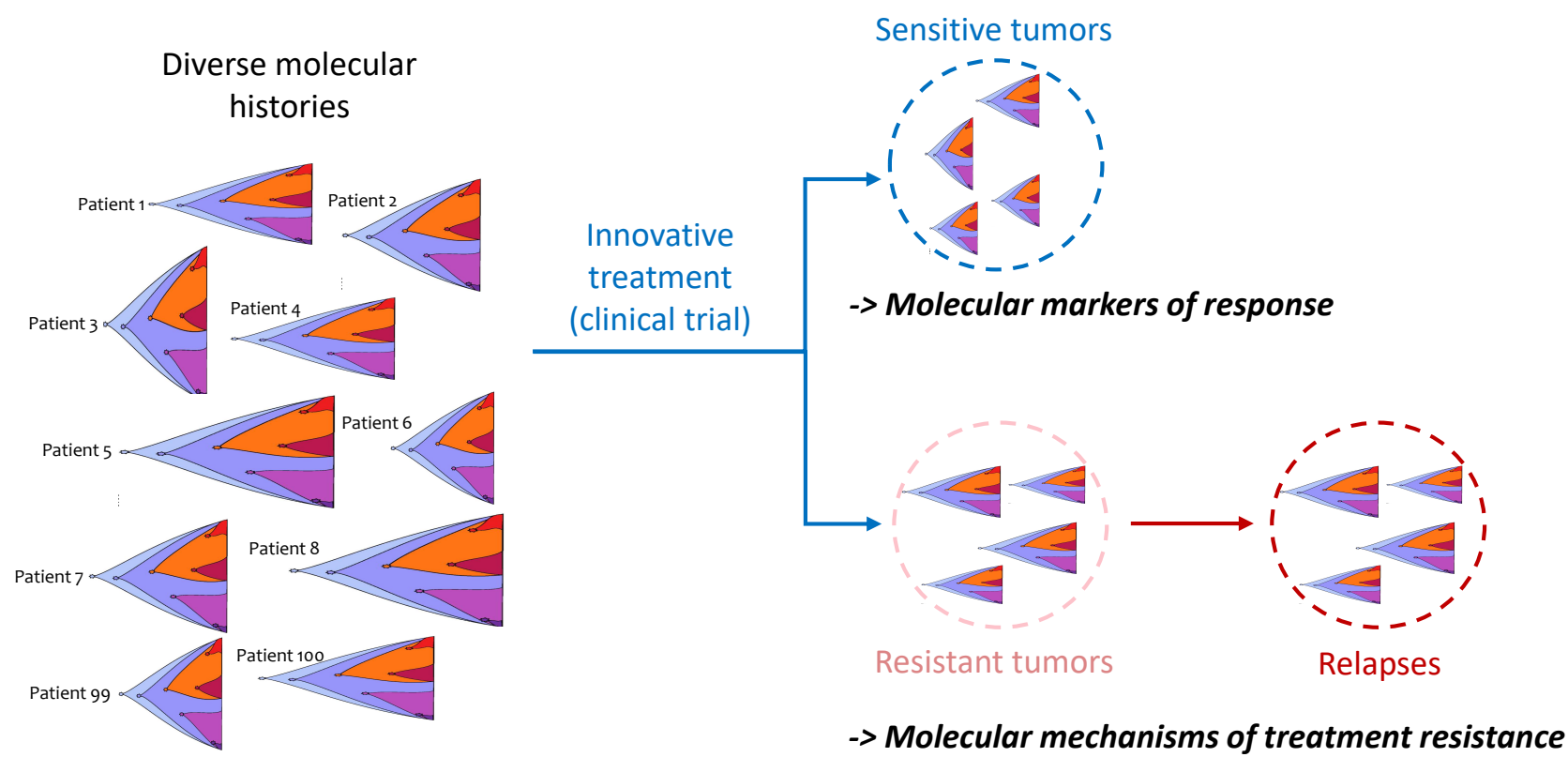
**All the former lab
members and the
clinicians/technicians...**



Genetic evolution and molecular plasticity in multiple myeloma



Genetic evolution and molecular plasticity in multiple myeloma



ICAGEN (Integrated CANcer GENomics team) – CIRCI2NA, Nantes



Co-direction: Stéphane Minvielle & Eric Letouzé

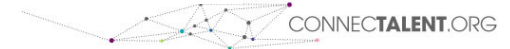
Florence Magrangeas (researcher)
Jennifer Derrien (engineer)
Victor Gaborit (engineer)
Catherine Guérin-Charbonnel (engineer)
Jonathan Cruard (PhD student)
Anthony Ozier-Lafontaine (PhD student)

Elise Douillard (technician)
Magali Devic (technician)
Antoine Frigout (Masters student)
Sarah Gastineau (Masters student)
Loïc Campion (physician)

Collaborators

- Philippe Moreau (CHU Nantes)
- Cyrille Touzeau (CHU Nantes)
- Bertrand Michel (LMJL)
- Carl Herrmann (Heidelberg Univ)

Funding





CRCI²NA

ICAGEN (Integrate



Co-direction: Stéphane

Florence Magrangeas (I
Jennifer Derrien (engin
Victor Gaborit (enginee
Catherine Guérin-Charl
Jonathan Cruard (PhD s
Anthony Ozier-Lafontai

Engineer / post-doc positions available!

**Translational single-cell multi-omics in
multiple myeloma**

Integrated Cancer Genomics (ICAGEN) team
Centre de recherche en cancérologie, Nantes



CRCI²NA



ators

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antes - Angers



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