Le sfide computazionali per la terapia genica e i farmaci a RNA

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Italiadomani PIANO NAZIONALE DI RIPRESA E RESILIENZA

RNA &GENETHERAPY CENTRO NAZIONALE DI RICERCA

RNA drugs: lessons from COVID-19

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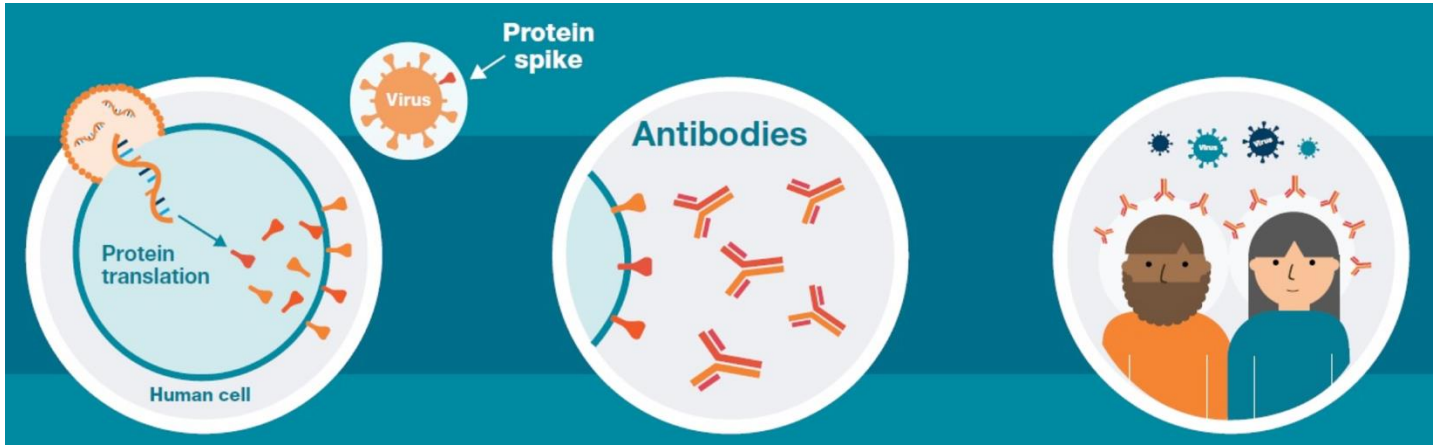
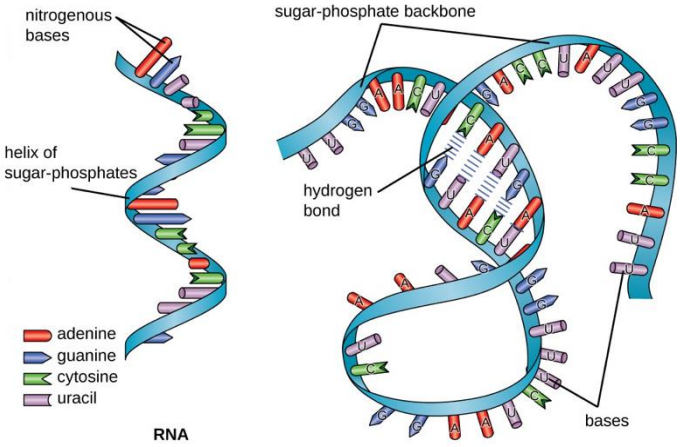


Adapted from the UK Health Security Agency

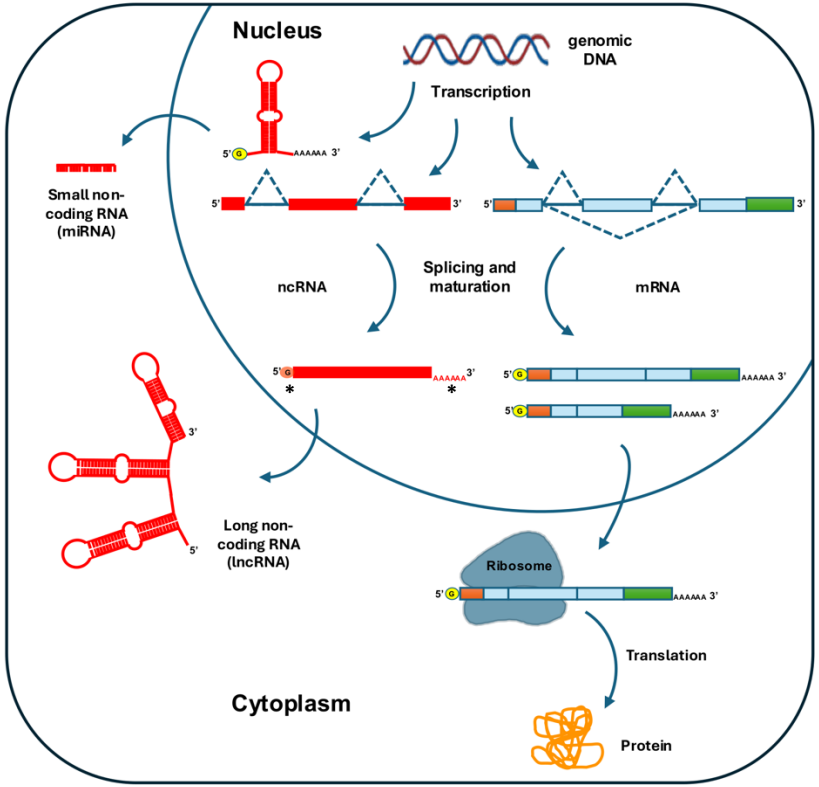
The emergence of the COVID-19 pandemic in 2019 presented an urgent need for an effective vaccine. The traditional vaccine development process typically takes years, but mRNA technology enabled an accelerated response. With the genomic sequence of SARS-CoV-2 made available, researchers swiftly designed mRNA vaccines encoding the spike protein of the virus to trigger an immune response.

RNA: not only a messenger

RNA is a flexible and versatile molecule in the cell ecosystem. RNAs play crucial roles in the flux of genetic information and regulation of gene expression, making them attractive therapeutic targets. However, RNA molecules are inherently labile and susceptible to degradation by ubiquitous ribonuclease.



https://courses.lumenlearning.com/suny-microbiology/



* Cap and polyA may not be always present in ncRNAs

E. Picardi 2025, *In Press*

RNA drugs: a revolution in modern medicine

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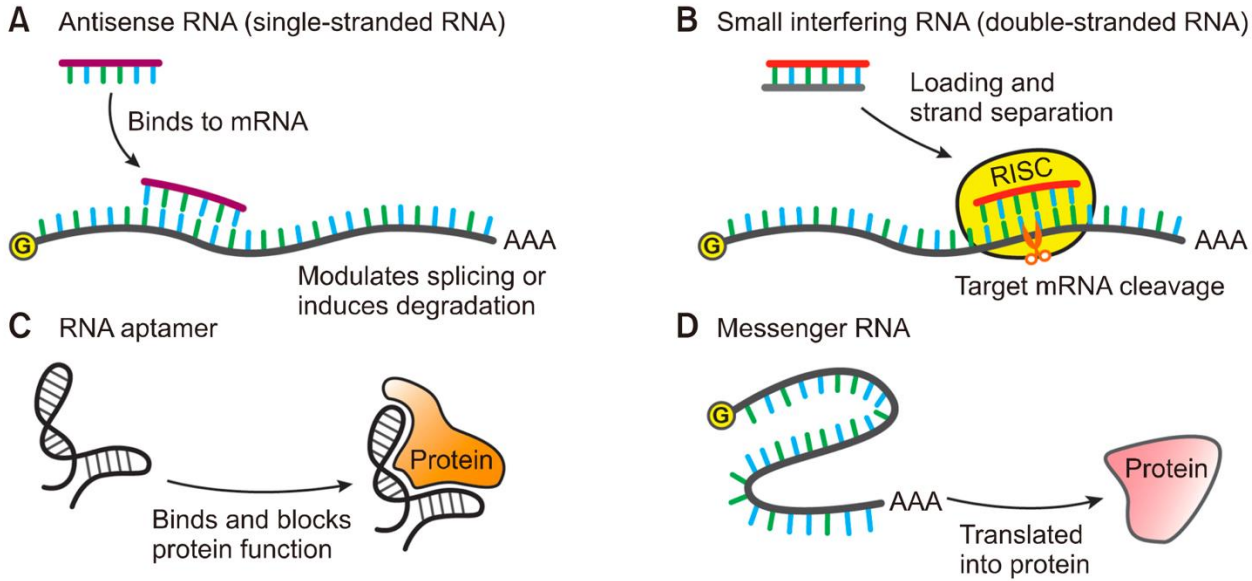
RNA-based therapeutics have emerged as a revolutionary field in drug development, because of the RNA ability to target almost any genetic component within the cell. RNA-based therapeutics harness the power of RNA molecules to modulate gene expression, leading to tailored interventions.



Kim, Chonnam Med J. 2020

RNA drugs: main advantages

RNA-based drugs are known to exhibit a wide variety of advantageous traits, making them ideal candidates for the development of various novel therapeutic strategies. Some of the major advantages of these technologies are shown here.

RNA and Gene Therapy National Research Center

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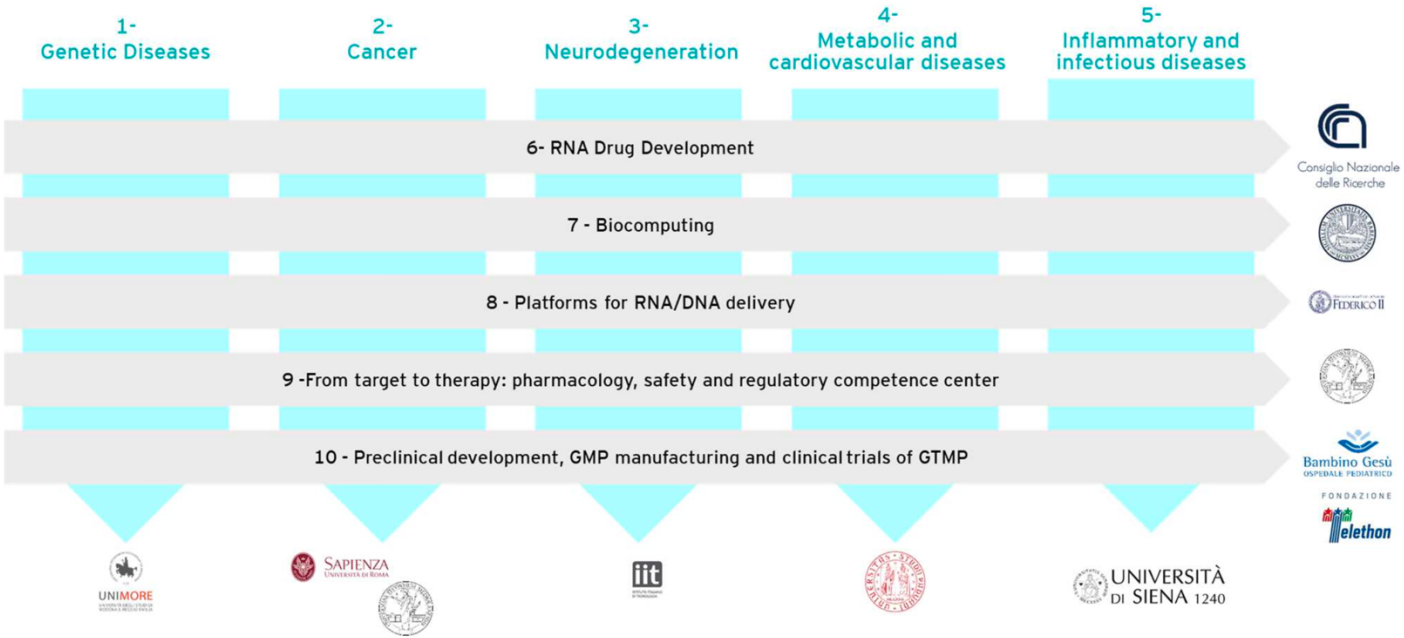
The National Center for Gene Therapy and Drugs based on RNA Technology aims to 1) identify the most promising candidate targets for RNA-based drugs in five major areas of human diseases ("Vertical Spokes"), and 2) build and disseminate the technological know-how necessary for designing, delivering and producing RNA drugs ("Horizontal Spokes").



The genomic revolution: Omics Sciences

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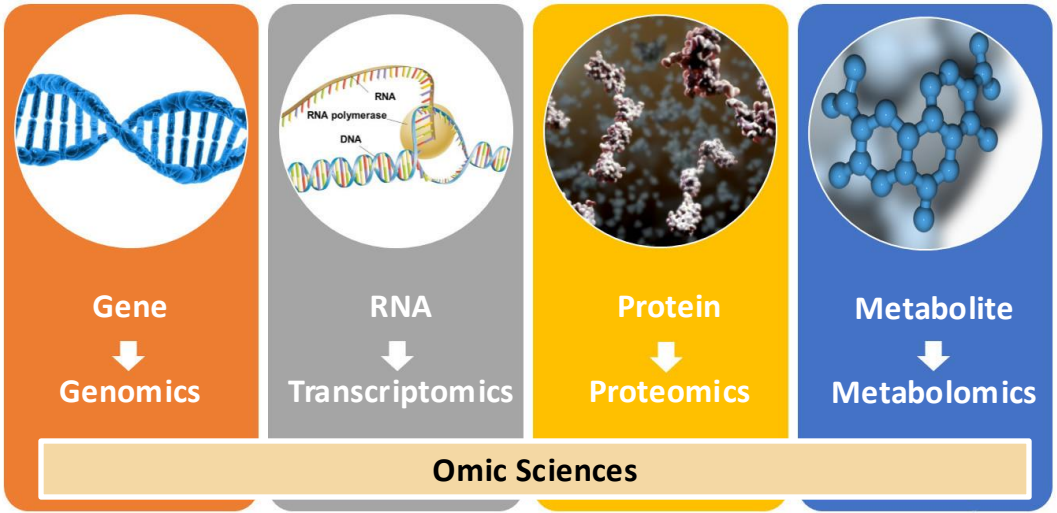
Technological advancements in molecular technologies for the study of main biological macromolecules such as nucleic acids (DNA and RNA) and proteins have led to Omics Sciences and the advent of the era of Big Biological Data.



Many more Omics Sciences have been established so far … (miRNomics, metagenomics, epitranscriptomics and so on)

Omics Data Production

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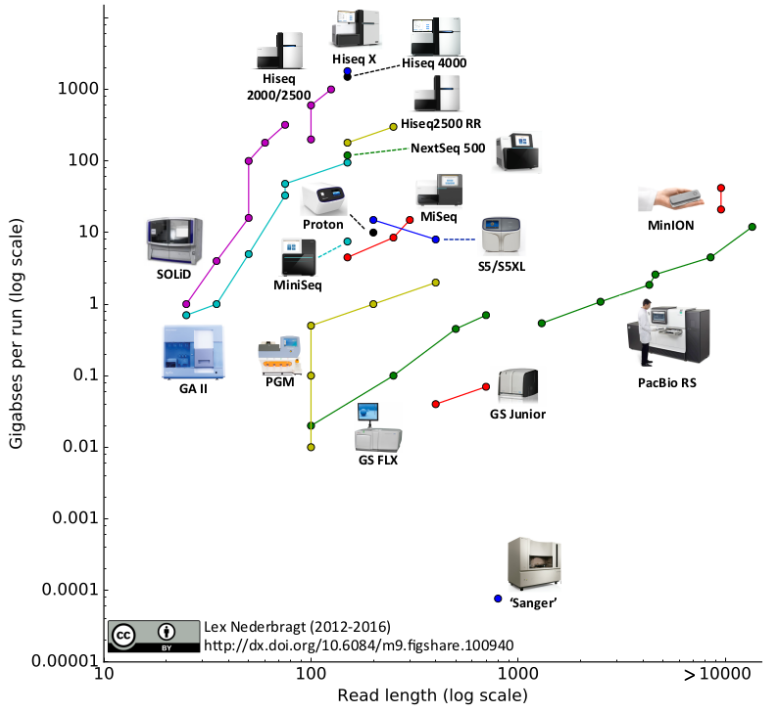
New sequencing technologies have speeded up the birth of Omics Sciences … leading to different challenges!

Omics Data Production

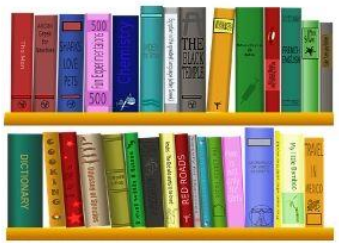


https://www.genome.gov/

One of the latest NGS sequencers (Illumina NovaSeq X Plus) can generate up to **52 x 10^9** strings and approximately **16 Tera Bases**:

16 TB = 16000 GB

16000 GB / 3 GB = 5334 Human genomes



It's also equivalent to 130 genomes from 130 different individuals, each one read 40 times on average!

Omics Data and RNA Bionformatics

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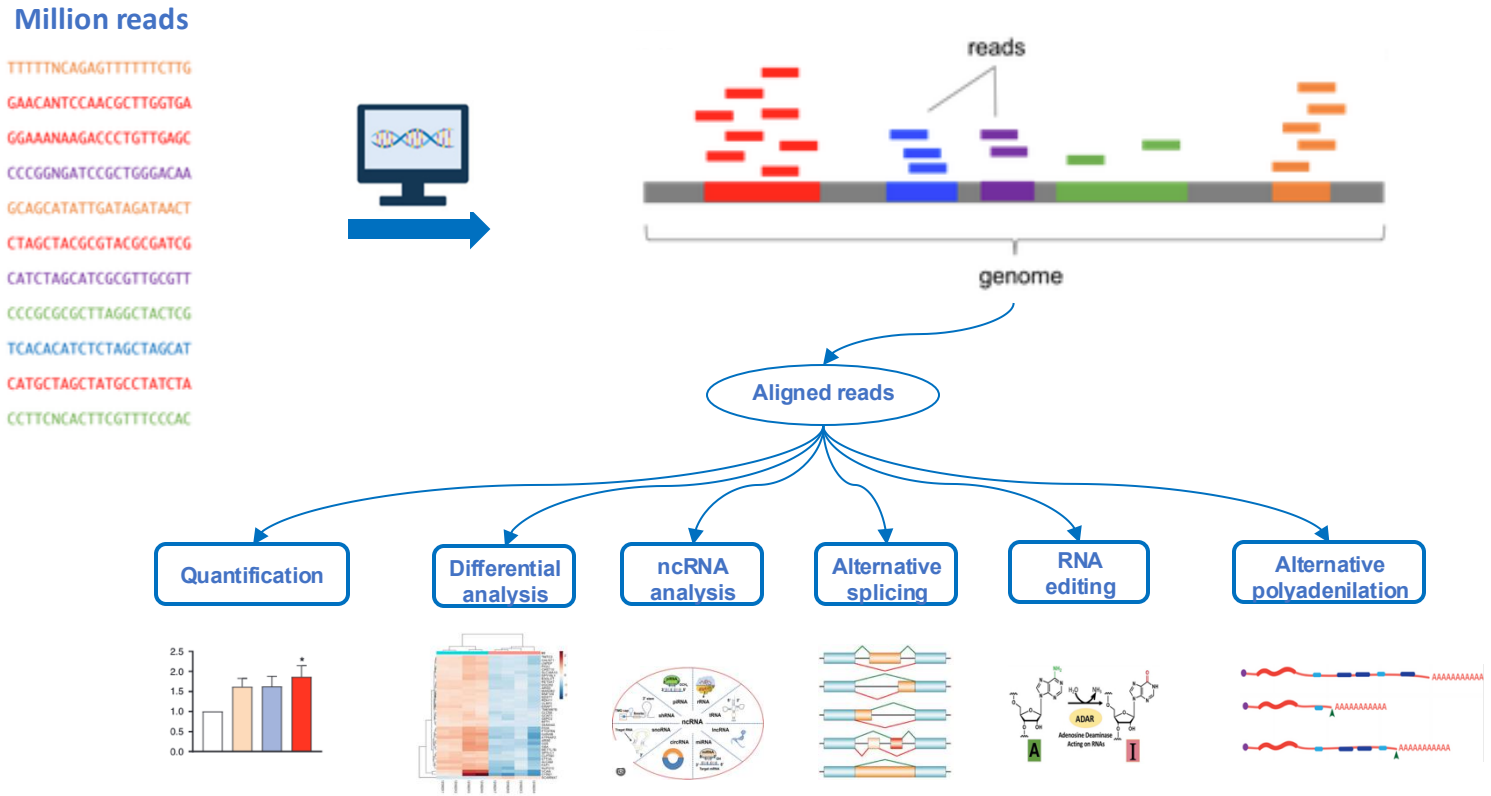

Omic Data and RNA Bionformatics

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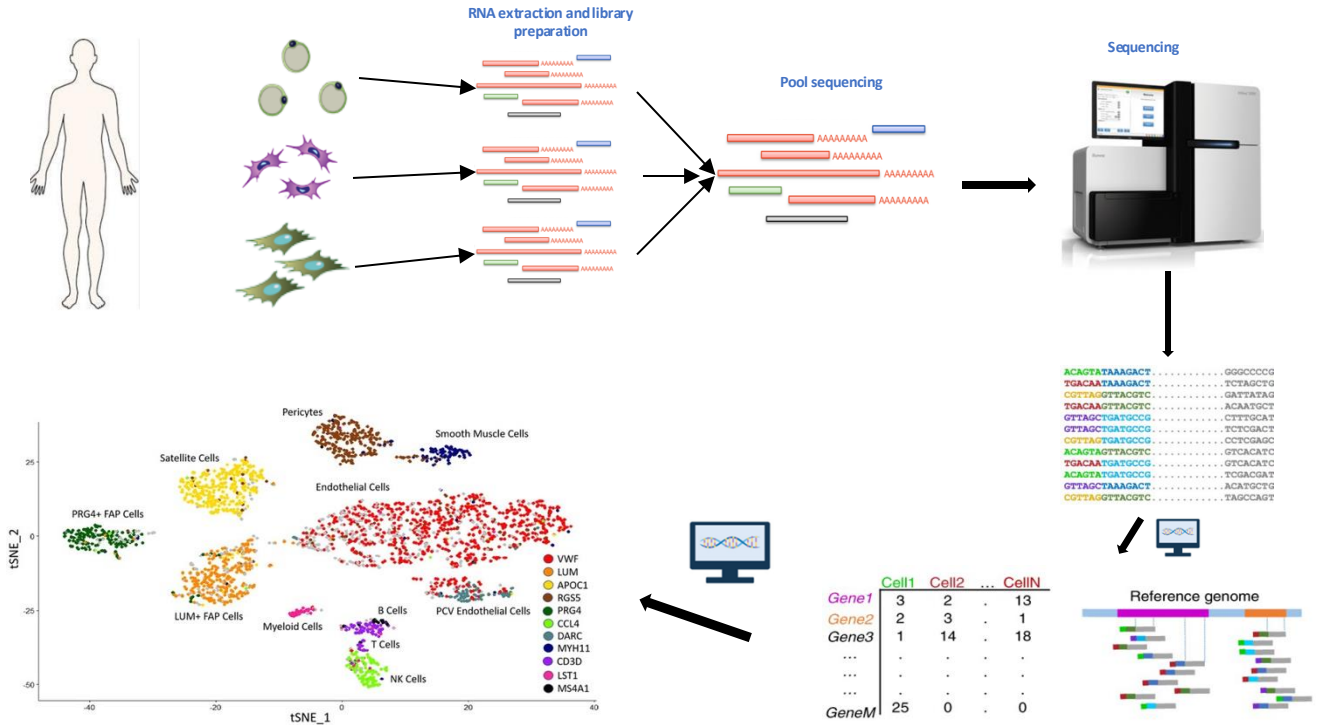
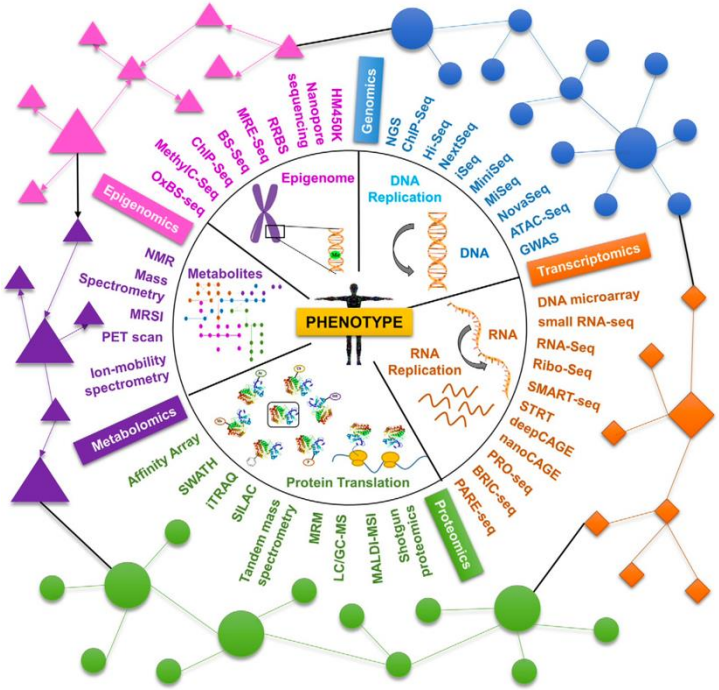
Novel technologies allow now the analysis of RNA at the single cell level with a high impact in biomedicine.



Spoke 7 - Biocomputing



A Biocomputing (Spoke 7) Flagship was established for empowering integrative omics data production and computational analysis.

The Biocomputing Spoke Flagship was integrated in Omics and Compute platforms the Italian Node of ELIXIR, the European Research Infrastructure for Life Science Data through the provision of advanced equipment of omics data production and ICT empowerment for high performance computing and storage.

The Biocomputing Spoke is coordinated by UNIBA (Prof. Graziano Pesole) and involves researchers from other 6 Italian Institutions.

Biocomputing: Empowering Omics

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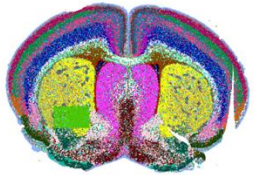
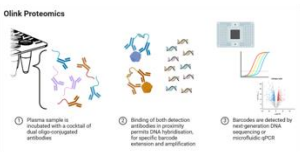
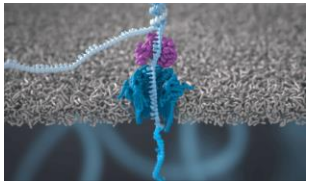
The Omics platform of the Biocomputing Spoke Flagship, already equipped with the most advanced platforms for high-throughput sequencing was empowered by instruments for integrative omics data generation.

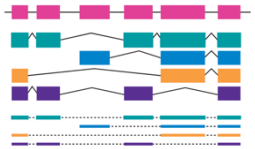


Xenium Platform (10X Genomics) for Spatial Transcriptomics

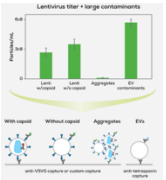


Olink Explore HT (Novogene) for NGS-based proteomics





PacBio VEGA for long genome and transcriptome reads



Leprechaun (Unchained Labs) for lentivirus and exosome characterization

Biocomputing: Empowering Computing

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The Compute platform of the Biocomputing Spoke Flagship, was empowered for both HPC/HTP computing and storage (>10,000 CPU; >50 GPU; >15 PB storage; >20 PB Tape storage). A bioinformatic environment was established with tools and data, also on-demand following a partnership survey.
The Biocomputing Spoke Flagship may provide:

Virtual Machines: 20 CPUs Intel(R) Xeon(R) Gold 6238R CPU @ 2.20GHz, 200 GB RAM, 600 Gb scratch storage, 2 TB (Shared Datastore for all VMs for reference datasets and tools), 30 TB (Data Analysis Storage), Interconnecting network 25/40 Gbps VMs-storage

Data Biorepository relying on the Dell EMC Isilon technology with >5PB capacity, GDPR compliance and geographic redundancy.

Recas DataCenter at UNIBA

Biocomputing: Main Activities and Goals – WP1

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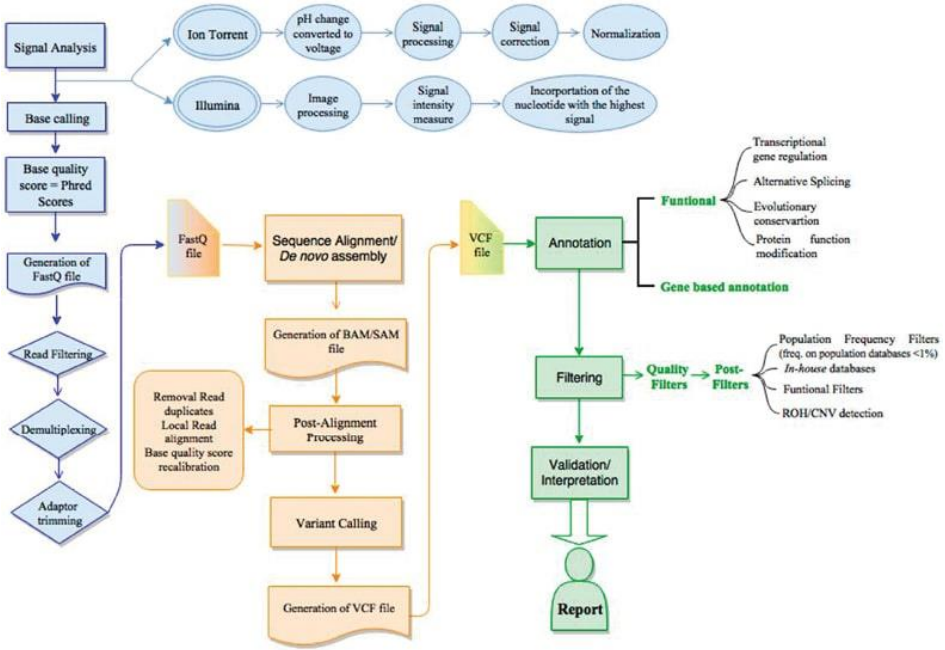
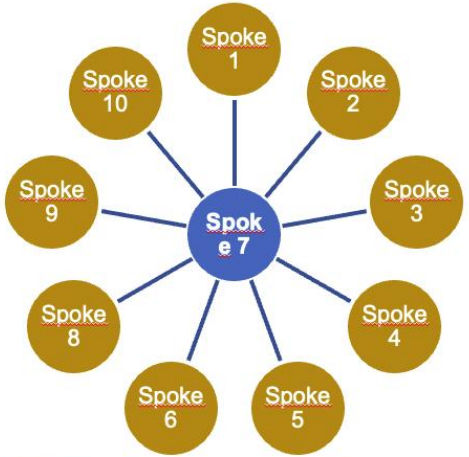
Setup and development of the bioinformatics environment for omics data analysis (UNIBA, UNIMI).





Biocomputing: Main Activities and Goals – WP2

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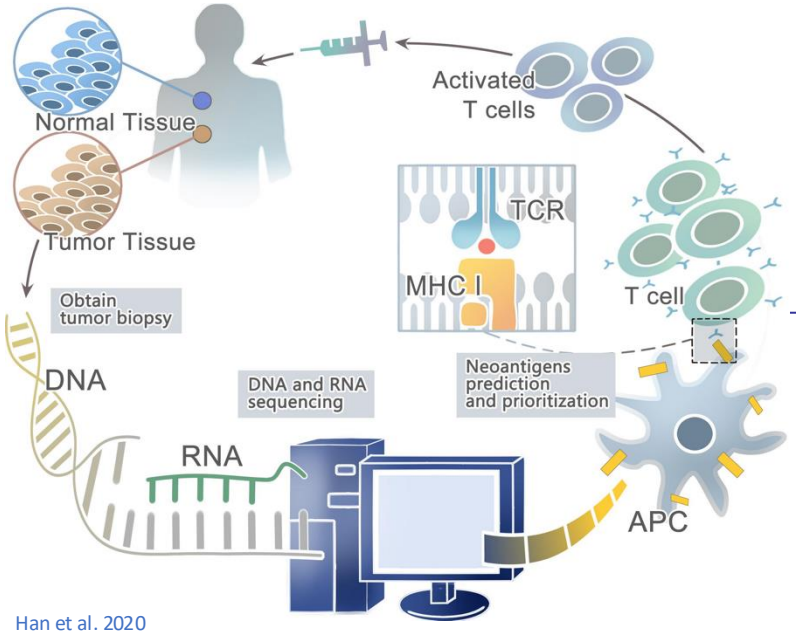
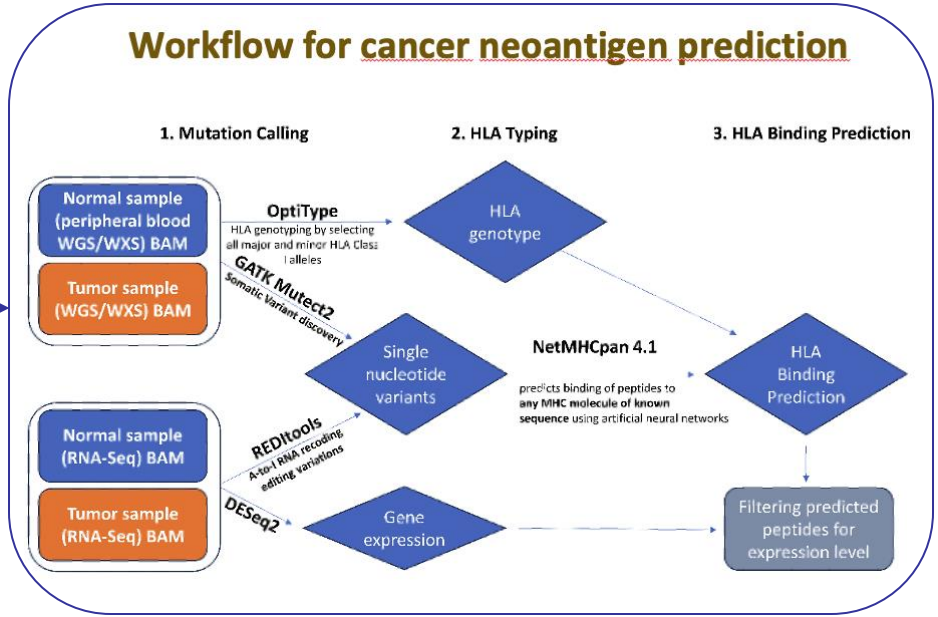
Bioinformatics for the identification of neo-antigens for mRNA vaccinology (UNIBA, UNINA)





Han et al. 2020

Biocomputing: Main Activities and Goals – WP2

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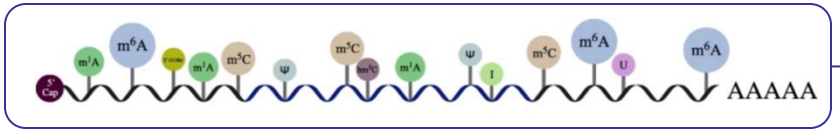
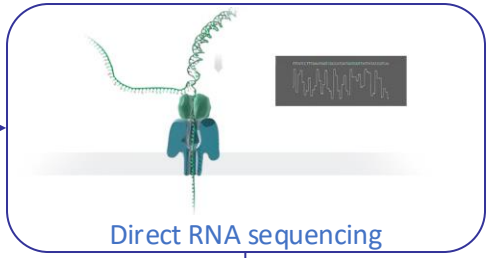
Bioinformatics for profiling RNA modifications

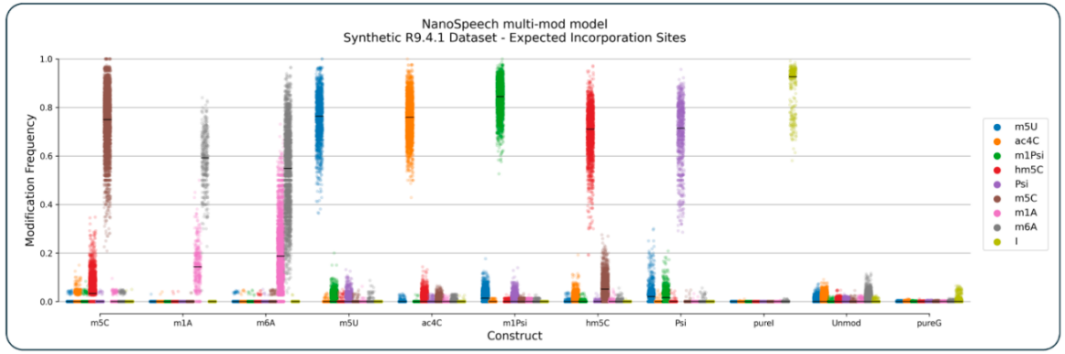




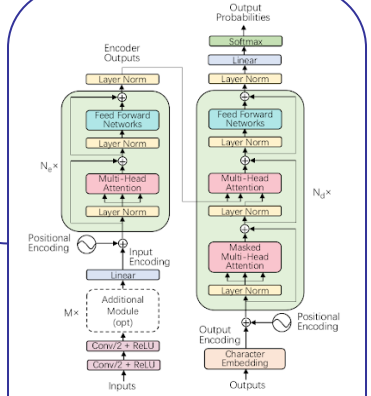
Direct RNA sequencing

```
target      ctatggcgtgacccctagcctaaaccatgcgcccatgtcagcgctcttgtgtggg--- 56
pred        -tatggcgtgacccctagcctaaaccatgcgcccatgtcagcgctcttgtgtgggcaa 58
             ************************************************************
```

Direct Basecalling



Fonzino et al., in revision



Transformer model for
Speech to text translation

Biocomputing: Main Activities and Goals – WP3

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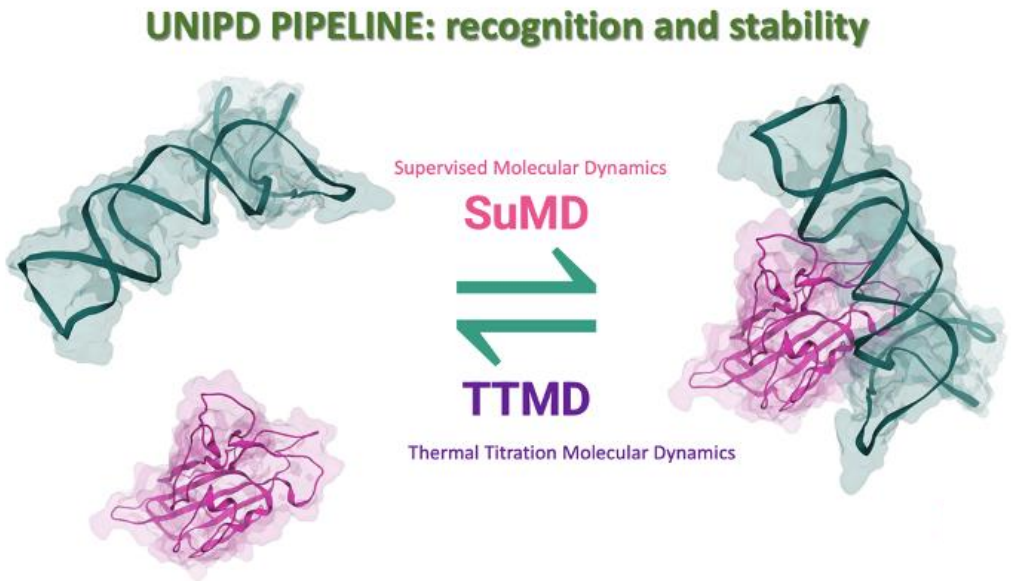
Design and development of RNA drugs in different therapeutic areas (CNR, UNIPD, IIT)



Biocomputing: Main Activities and Goals – WP4

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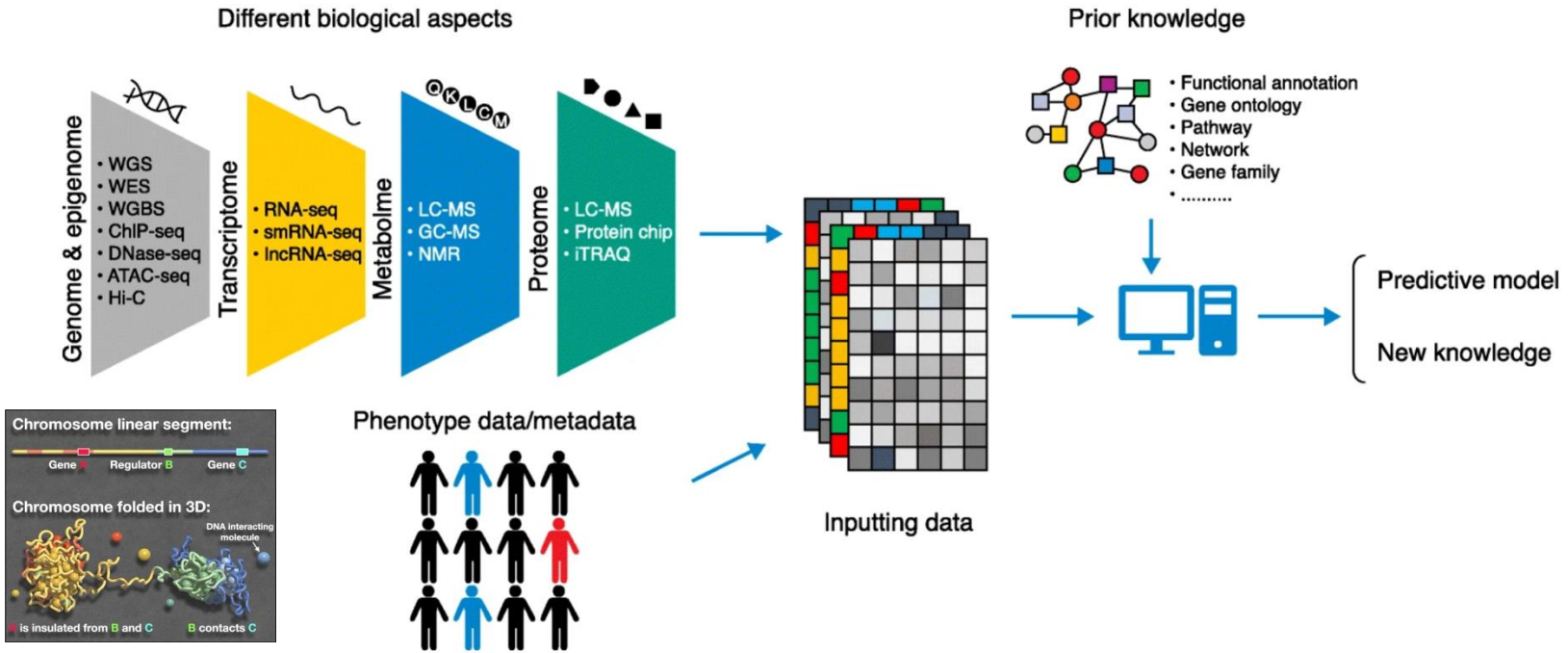
Computational Systems Biology and integrative data analysis (UNINA, UNIMI, UNIROMA2)



In conclusion …

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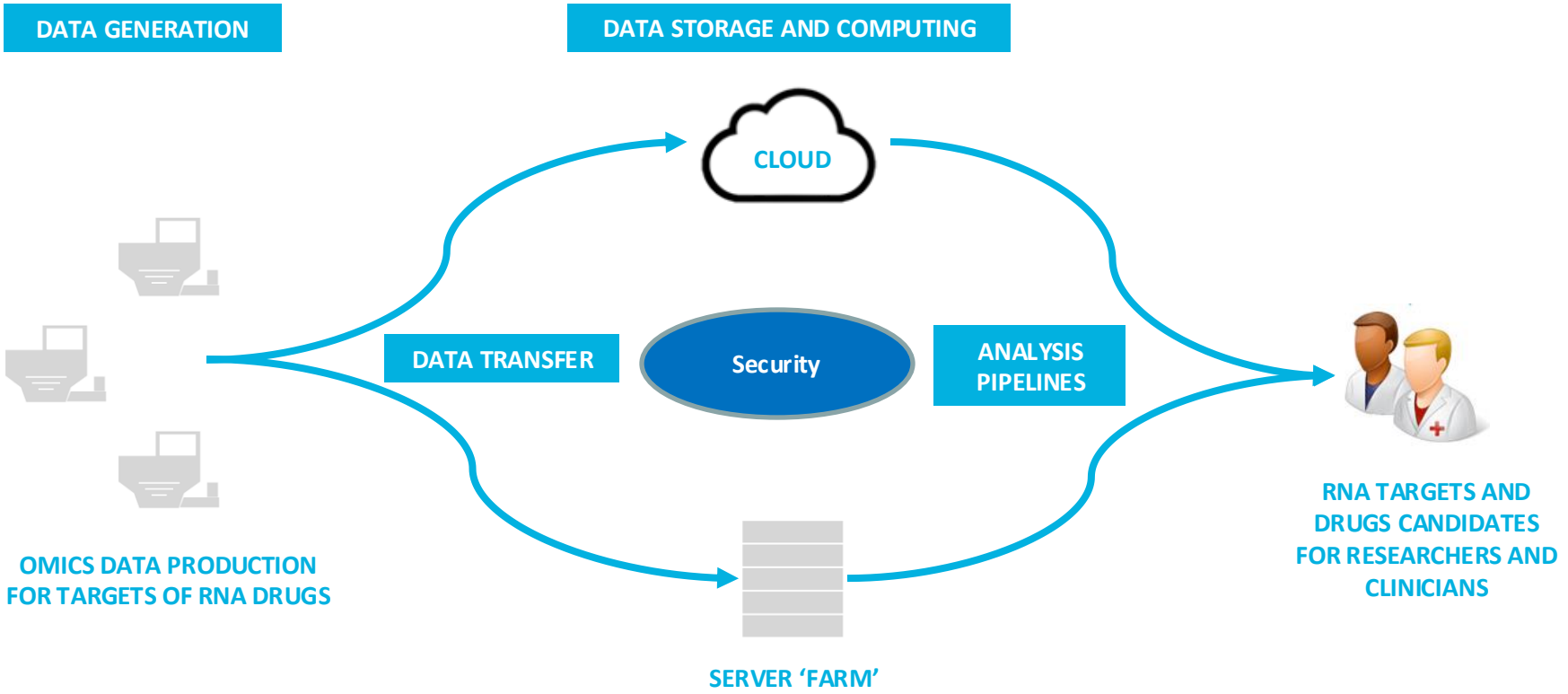

Thank you!

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The Bioinformatics and Comparative Genomics team at UNIBA and IBIOM-CNR

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Consolidation of the Italian Infrastructure for Omics Data and Bioinformatics

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