STRATEGIC PLAN 2020 – 2024

Table of Contents

Executive Summary....3

I. Introduction....5

II. HT Mission(s) and Vision....6

III. Strategic Goals....9

Background and Rationale....9

Scientific Goals....11

Advanced Training....16

Openness and Collaboration....18

Institutional Relations....21

Operations and Administration....22

Financial Support....22

IV. Strategic Initiatives 2020–2024....24

Interdisciplinary Research....24

Research Support....29

Scientific Infrastructure and Facilities....29

Scientific Training....32

Technology Transfer and Industry Relations....37

Scientific Partnerships and Collaboration....38

V. Strategic Plan Implementation and KPIs....41

Building HT's Scientific and Organisational Structure....41

Progress Indicators....43

Evaluation of HT's Science....45

Executive Summary

Human Technopole's overarching mission is to promote and contribute to improving human health and wellbeing, including healthy ageing. It will pursue these aims by carrying out frontier research (a mix of fundamental and translational) in the life sciences, particularly focussing on developing novel approaches for personalised and preventive medicine. This strategic plan covers the first five years of HT implementation, during which it will grow to roughly one third of its final size. HT growth and diversification will continue after this period.

The HT operating model will represent a combination of creating an internationally competitive research institute and being a contributor to the Italian research community by the provision of user facilities and training, as well as by broad academic and translational collaboration.

HT strategic goals for 2020–2024 are:

1. Initiate biomedical and health research in specified areas and develop a solid research pipeline for the future
2. Build scientific infrastructure and services that are made available to the external scientific community
3. Establish processes and systems for the development of scientific talent, including training programmes
4. Lay the foundation for technology transfer and innovation
5. Establish transparent operational processes that support accountability
6. Initiate programmes that open HT to the external community and facilitate collaboration with that community

Biomedical research will include the following therapeutic areas:

- Cancer and cardiovascular disease, and their intermediate phenotypes;
- Neurodevelopmental and neurodegenerative disorders, such as autism and intellectual disabilities;
- Rare and orphan diseases;
- Respiratory diseases,

The first key strategic initiatives to be pursued by HT research teams will be:

- Understanding of genetic diversity and disease predisposition in Italy - a full genomic characterisation of the "Moli-sani" study, carried out by the Mediterrenean Neurological Institute – Neuromed IRCCS.
- High-throughput brain organoid longitudinal profiling for neurodevelopmental disease deconvolution of the cohorts centered around the IRCCS Associazione Oasi Maria Santissima in Troina, Sicily
- Machine learning-based analyses of the Italian Health Card System data

HT will develop the necessary technologies and infrastructure to enable the above initiatives and lay the foundation for future HT activities. The focus will be on functional and population genomics, cell biology, structural biology and human biomedicine.

Implementation of the Strategic Plan will gather pace as the team is hired and onboarded. By the end of the period covered in the plan, HT will have reached close to one third of its final size. The final HT steady state will support roughly 1000 scientists who will contribute to the HT vision and who will be supported by a comprehensive system of development programmes and trainings.

Core funding for Human Technopole's infrastructure and activities originates from public funds awarded by the Italian Government. Additional funding will be raised through competitive grants from various sources (e.g. the European Commission) and technology transfer through a commercial HT subsidiary.

I. Introduction

This document is the result of a major strategic and scientific planning exercise to develop a blueprint for the diverse activities scheduled for the first five-year period of Human Technopole development (2020–2024). It has been developed by the HT Directorate with input from the newly, and still incompletely, recruited scientific leadership as well as representatives of all parts of HT's organisational structure including the Governance Boards and Scientific Advisory Board and provides a comprehensive overview of Human Technopole's currently planned activities. As described below, these represent an ambitious mix of internal research, collaborative interactions with the community and the provision of both training and facility access to external researchers.

In developing these plans, close consideration was given to the existing biomedical and health research landscape in Italy as well as internationally. At the national level in particular, a comprehensive view of the current status and needs of the research community was achieved through extensive consultation and discussions with a variety of stakeholders, including Universities, scientific societies, individual research hospitals and institutions, and potential industry partners as well as existing networks of these institutions and societies that took place during 2019. The resulting plan aims to propose activities that will be maximally useful, complementary to or synergistic with ongoing efforts outside HT.

This Strategic Plan for 2020-2024 represents the first implementation phase of the Human Technopole (HT) and aims to present a realistic and concrete development plan based on available funds, the projected availability of space over time and initial researcher recruitment.

The activities outlined in this document form the basis for cost projections, that are all consistent with the multi-annual financial plan for HT. Due to the current early stage of development of Human Technopole, however, all the forecasts laid out in this Strategic Plan are indicative. They will have to be updated over time as recruitment progresses, depending on the detailed scientific plans of the scientists hired, and on the ongoing growth of available space for research and facilities. Moreover, as for any biomedical research institute, plans may need to be adapted rapidly in response to changes in the biomedical research landscape.

Note that we have produced five Supporting Documents that discuss parts of this Strategic Plan in much more detail, designed for experts interested in specific aspects of HT. These are; 1 Research Plans, 2 Scientific Infrastructure and Facilities, 3 Operations and Administration, 4 Financial Plan, 5 Campus Development Plans, 6 Risks to the HT Project. These documents will be published separately and made available to interested readers upon request.

II. HT Mission(s) and Vision

Human Technopole's overarching mission is to **promote and contribute to improving human health and wellbeing, including healthy ageing**. It will pursue these aims by carrying out frontier research in the **life sciences**, particularly focussing on **developing novel approaches for personalised and preventive medicine.** In order to achieve these goals we will put a strong initial emphasis on **Genomics and Computation**, two fields that are particularly well-placed to make use of and benefit from the wealth of systematic information being produced by systematic genomic analysis of human populations. Our research centres will be organised around **broad areas of science with wide applicability to many problems, not narrowly focussed on a single biological or health problems**. This organisation will increase and maintain the flexibility of HT to engage in research in many problems, including unexpected and challenging new areas of health research, as they develop.

Envisioned as a large-scale national research infrastructure, HT will also **set up and operate scientific facilities and services to be made available to external scientists,** aimed at responding to the needs of the national and international life science research communities. It will enhance Italian and European scientific capacity in the life sciences by organising and offering **top-quality scientific training** programmes and events. It will strive, by promoting technology transfer and maintaining an active dialogue as well as direct interactions with industry, to foster the **translation of scientific discoveries into tangible applications** and innovations for the benefit of patients and of society at large.

Finally, an important element of Human Technopole's mission will be the dissemination of scientific activities and achievements widely, so as to **promote understanding of the importance of basic research and knowledge-based innovation for advancing society, reinforcing the message that science is a public good**. HT plans to pursue all these activities in an open, collaborative way, working with partners whenever possible to promote life science research and innovation as broadly as possible. The combination of these activities, plus the plan to provide fixed-term contracts (see below) makes Human Technopole a very unusual organisation internationally, and will enable HT to make a unique contribution to the national research ecosystem.

Once fully developed, Human Technopole **will employ around 1,000 scientists** in diverse fields, including **biology, bioinformatics, chemistry, engineering, physics, mathematics, health science and computational and data science**. Scientific excellence will be the guiding principle for all HT activities. The vision is that of an internationally competitive research institute, applying the highest standards in biomedical research. HT staff will be recruited through international, open calls and stringent, strictly meritocratic selection procedures carried out by internal as well as external experts in the relevant fields. The aim is to attract top scientific talents and provide them with an optimal environment to pursue their research

interests. Most scientists will be offered **fixed-term contracts**. This will contribute to maintaining a dynamic, constantly changing, scientific environment and allow for the ongoing renewal of HT's expertise and scientific profile. At the same time, it will generate a pool of highly trained researchers that, after their time at HT, will flow into and enrich the national scientific community, exerting a long-term beneficial cascade effect on the country's research system.

Different models for biomedical institutes exist at the European and international level, ranging from top-level research centres where scientists are offered world-class facilities and opportunities (but, as a rule, after a certain number of years Principal Investigators must leave and establish themselves in national Universities or research centres), to national or intergovernmental research infrastructures, where cutting-edge instrumentation and expertise are made available to the life science community. **Human Technopole will represent a mix of both these models, combining an internationally competitive research institute with the wish to serve the wider community by providing access to technological platforms** and by offering top-level training opportunities, and through research collaborations and coordination in specific areas. The prime example of such an organisation in the Life Sciences is the European Molecular Biology Laboratory, an intergovernmental organisation with over 45 years of history of which Italy is a member, but there are also several others that function similarly in national systems such as the Crick institute in London, UK, in Life Sciences, or DESY, in Hamburg, Germany, that is mainly focussed on materials science and physics. Thanks to the European infrastructure projects organised under the ESFRI process (the European Strategy Forum on Research Infrastructures) more and more national organisations are moving toward this mixed model. Note however that it will be crucial to achieve the correct balance between research and "service" activities, to ensure the healthy development and optimal functioning of HT, as well as to maximise its impact on Italian and European research.

As described in more detail below, the **vision for Human Technopole's research is based on a mix of fundamental and translational research**. HT will host extensive core expertise in **basic research in areas relevant for the understanding of human biology and physiology**. **Translational and more medically oriented research**, on the other hand, will be conducted largely **in collaboration with external organisations, including clinical research and industry partners**.

The development and use of, as well as provision of access to, **cutting-edge research infrastructures, instruments and methods is also a cornerstone of Human Technopole's strategic vision**. Technology-driven research groups focused on developing innovative methods and tools for life science research will complement biology-driven research groups whose aim is to address important open questions in human biology and biomedicine. This setup has the important purpose of ensuring that HT infrastructure and facilities, including those made available to external scientists, are constantly pushed by the research questions

of in-house researchers whose work depends on those technologies, and therefore remain at the forefront of developments in the field.

This aspect of the HT vision stems from the notion that state-of-the-art research infrastructures are essential in all areas of research. In particle physics, CERN is a major example. Synchrotron facilities exist at both the national and European scales and host several thousands of visitors who come to carry out experiments that would be impossible at their home institution.

Data resources are a more recent form of research infrastructure that have become indispensable. The biomolecular data resources of the European Molecular Biology Laboratory, located at the European Bioinformatics Institute, were consulted over 60 million times daily in 2019, to give just one example. More distributed research infrastructures, that provide access to equipment that, while less expensive than the examples cited above still cost more, and require more technical expertise, than most individual research institutes can afford, also play a critical role, particularly in the life sciences. Alongside research infrastructures, there is wide consensus that a healthy national research environment also depends on a network of centres of research excellence that are funded in such a way as to allow longer-term, ambitious projects to be followed. Well-known examples of such networks are the Max Planck institutes in Germany or the UK Medical Research Council research units, the Cancer Research UK institutes in the United Kingdom or the Howard Hughes Medical Institute Investigator Program in the USA.

In line with the importance of such centres of excellence and of research infrastructures for scientific capacity building, Human Technopole is envisioned to enrich and contribute to advancing the national system, acting as a reference point for the Italian academic life science community through its combined missions. At the same time, Human Technopole's aim to achieve high standards (both in research and at the organisational and management level), in addition to providing a model for other similar centres, will make it an ideal partner for excellent European and international institutes and collaborative initiatives. By forging scientific connections with relevant international partners and networks, HT will gain visibility for and help raise the profile of Italian biomedical research.

III. Strategic Goals

1. Background and Rationale

Improved health and wellbeing is the ultimate goal of research in the biomedical sciences. This is especially important today, when societies are aging rapidly as a result of increased life expectancy, declining fertility rates and rapid social and economic development. Many people live longer, but not all live well or in good health, and major efforts are needed to prevent and manage diseases so that people of all ages can enjoy better quality of life and be productive members of society.

Health, aging, and quality of life are affected in a complex way by a combination of *intrinsic* factors, primarily related to each individual's genetics, and *extrinsic* factors, such as lifestyle and environment. Traditional disease classification and approaches, symptom-based and organ-centered, are no longer considered sufficient, due to recognition of the complexity of disease and the effect of shared biological mechanisms. Against this background, a new approach to health research is developing. It is based on causative pathways that include genes, environment and lifestyle, and increasingly translates into treatments according to disease etiology.

Major technological advances over the last decade and the advent of high-throughput methods, in particular, have paved the way for the global, systematic interrogation of the human genome (the complete DNA sequence of an individual) as well as other aspects of human biology. These include the epigenome (modifications to the genome that often occur in response to the environment and alter gene expression and function), the transcriptome (all the RNAs transcribed from the genome), the proteome (all the proteins made from RNAs) and the metabolome (all the metabolites present in a cell, organ, tissue or organism). In parallel, digital technologies and advanced computational analysis generate comprehensive datasets that cover a multitude of information types on many individuals and the methods required for their analysis. As a result, we are witnessing an era in biomedical research in which important biological questions directly related to human health can – at least in part – be tackled by directly studying human subjects as well as, where necessary, still using model organisms and other simpler systems.

Integrating and harnessing information from these massive amounts of biological data has boosted possibilities for scientists to develop stratified approaches and ultimately improved, more targeted, strategies to fight or prevent disease in a "personalised" or "stratified" approach to health – where information on the genetic makeup of individuals or of their diseased tissue is used to select the most appropriate interventions. A number of such personalised treatments are already in use in areas such as cancer, cystic fibrosis, inherited forms of blindness, etc. The development of these treatments depends not only on knowing the specific DNA or protein sequence of the "disease gene" in the patient, but also a deep

understanding of how a genetic change in that gene or protein can give rise to a disease state. It is widely believed that stratified or personalised approaches will change the way many illnesses are treated, to the extent that many countries, including prominently the United Kingdom, Finland, Iceland and the USA are undertaking very large-scale genomic sequencing studies as part of the analysis of cohorts of individuals whose health and wellbeing status are monitored over many years.

On the other hand, and in parallel, other types of large-scale data from heterogeneous sources, for example clinical or socioeconomic data, can be exploited in a similar way to develop novel strategies for public health or to improve the management of healthcare systems, also maximising people's health and wellbeing. Clearly, the current context of health-related research, as described above, calls for a holistic and multi-scale approach and for the further development of novel disciplines. In view of the current, unprecedented opportunities for health research, building an Italian centre for human biology at the scale envisioned for Human Technopole appears extremely timely. Because of the common requirement for the analysis of "Big Data", the use of these methods goes hand in hand with investment in computational methods, including statistics, bioinformatics, modelling and machine learning/artificial intelligence. HT will therefore also promote major initiatives in computation focussed on biomedicine.

The next five years should see the completion of the building infrastructure envisaged for Human Technopole and the setting up and consolidation of HT's initial lines of research, as well as service and other scientific activities. The plans for HT's development over this period, however, are heavily influenced by the limited availability of space, particularly of buildings suitable to host "wet lab" experimental research activities. Against this background, the HT leadership had to take a series of strategic decisions about the institute's initial priority activities and research areas.

Hence, the current **plans for HT's scientific development**, as described in this document, reflect the need to initially focus on a relatively limited number of areas in order to achieve critical mass in those, in a phase during which HT's growth potential is limited by external factors, particularly the availability of physical space.

Despite these limitations, HT deliberately chose to establish **Research Centres that are broadly based, in disciplines or fields applicable to many different topic areas in the context of human health and disease.** The rationale behind this strategic decision (as opposed to defining narrow or strictly objective/disease-based research programmes) was on the one hand to enhance possibilities to recruit outstanding research leaders, independent of the specific field of application of their work, and on the other to maximise opportunities for interdisciplinary collaboration within and beyond HT, capable of being applied to a wide variety of biological and health problems.

2. Scientific Goals

The cornerstone of HT's strategy to contribute to human health is a **comprehensive and interdisciplinary approach to the study of human biology**, aimed at understanding the basic mechanisms that regulate physiology and disease – to help tackle some of the most relevant challenges to human health. Collectively, HT's research work will advance our understanding of and help **develop novel therapeutic strategies (including advanced therapy medicinal products, ATMPs) for various disease groups**. Prominent examples of these, based on a number of projects that are kicking off, are chronic and degenerative diseases. For example,

i) cancer and cardiovascular disease, and their intermediate phenotypes;

ii) neurodevelopmental and neurodegenerative disorders, such as autism and intellectual disabilities;

iii) rare and orphan diseases, such as primary ciliary dyskinesia;

iv) respiratory diseases, such as cystic fibrosis.

Some of the disease areas above, most prominently cancer, neuropsychiatric disorders and cardiovascular diseases, are among the leading causes of death globally and represent some of the largest unmet treatment needs in contemporary medicine, while also constituting a major burden for healthcare systems in terms of their social costs. It is also important to say what HT is not. **HT is not a hospital and will not treat patients**. It will therefore be essential for HT to develop medical translation by carrying out research that enables us to collaborate with clinical research centres, a direction we are already taking, as can be seen in Supporting Document 1 ("Research Plans").

Five broad, complementary and highly relevant areas for biomedical and health-related research have been selected to form the basis for HT's research strategy in 2020–2024.

As explained above, **Genomics** is an essential component of modern biomedicine. In general, research in this area aims to uncover the mechanisms regulating gene expression and how heritable genetic information gives rise to differences between individuals that are relevant to health and wellbeing. Genomics research at Human Technopole will constitute a particularly large endeavour, composed of two complementary research programmes: one in **Functional Genomics** and the other in **Population and Medical Genomics**.

The former will focus on developing new methods in genomics and using these to investigate the significance of genomic changes at the individual level and their role in health, whereas the aim of the latter will be to understand the genetic structure of the wider population so as to pinpoint the genetic causes of specific defects – in particular by **investigating cohorts from different parts of Italy**. The Southern European, and particularly the Italian, population is known to have an unusual genetic composition, with distinctive genetic traits. These populations are however not well-characterised due to the relative delay in establishing large-scale genomics initiatives that cover them. A major goal of this work at HT will be to help **characterise Italy's genetic variation and unique environment to enhance our understanding**

of the genetic causes of various diseases in the population, unleashing additional potential for both research and clinical purposes. Both of these areas are large and important and we envisage having two senior researchers, each leading in one of the domains.

Neurobiology is another area of focus for Human Technopole – in view of the major public health burden that neurological disorders represent, but also as a research area where significant benefits deriving from the integration of genomics, disease modelling and other cutting-edge methods remain to be reaped. The application of novel -omics (including single-cell omics) technologies, in particular, to the study of neurobiology is intended to both complement and synergise with excellent ongoing research activities and programmes in this area, both at the Italian national and at the European level.

HT's research in neurobiology will combine **computational and experimental approaches** using different systems to investigate the structure-function and the development of the nervous system – with particular attention to the mechanisms underlying neuropsychiatric and neurodegenerative disorders.

Indeed, the development of novel treatments, for neurological as well as other disorders, depends not only on identifying genetic changes that give rise to disease states, but also, crucially, on understanding the molecular mechanisms involved. This type of small-scale mechanistic study relies on the combination of more tractable experimental systems, such as cellular models (e.g. standard human tissue culture cell lines), model organisms (e.g. yeast, fruit fly, mouse, etc.) and more complex *in vitro* systems, like organoids, to understand aspects of human neurobiology at the molecular level. In these experimental systems new techniques can be developed, refined and proven cost-effectively. Model systems, unlike humans, allow for more extensive experimental perturbation, and are often where new biological principles and mechanisms are revealed. Once techniques have been pioneered and proven in these systems and mechanisms are understood, these can be transferred to suitable human experimental systems to test whether similar mechanisms are at work. In turn, hypotheses generated from increasingly available human data such as genome sequences, which are often initially based on correlation, can be transferred back into experimental model systems for validation and mechanistic dissection.

In the area of molecular-scale mechanistic studies, a strong emphasis in **HT's initial strategy has been placed on Structural Biology**, which focusses on the elucidation of the **three-dimensional structure of macromolecules**. Research in this area provides detailed insight into the functioning of molecules, as well as frequently representing a crucial first step in the design of novel drugs. Structural Biology research at HT will investigate the structure of molecules and molecular complexes involved in human disease conditions. In addition to the relevance of such studies for uncovering disease mechanisms, the strategic focus on Structural

Biology is also and in large part motivated by the possibility for Human Technopole to provide access – by **setting up a one-of-a-kind cryo-electron microscopy user facility** – to a crucial recent technology that has revolutionised Structural Biology research elsewhere, but that is not broadly available to scientists in Italy because of its cost and technical complexity.

Research in all the areas described above generates huge amounts of data and must therefore integrate closely with research in **Computational Biology**, absolutely essential for any aspect of modern life science research. Computational biologists at HT will use statistical, computational and bioinformatics approaches to develop solutions for the analysis, management and integration of large-scale data in support of all areas of HT research.

In the area of Computational Biology, as well as of Genomics, **HT also plans to develop and/or host and manage software tools and data resources that will be accessible to the wider biomedical community**. The goal is both to provide a service to the community and, if it can be organised with the many stakeholders who will need to be involved, to **link the publicly accessible international biomolecular data resources to the more restricted national medical informatic data**.

Finally, statistical and 'big data' methods similar to those applied to molecular information to study aspects of human biology can be used to analyse different types of large-scale data, for example on treatment effectiveness, economic and social behavior, to investigate and solve problems related to Public Health and Healthcare Systems. Integrating big data from a variety of sources to develop tools in support of the medical system, particularly in the areas of precision medicine, health management and health economics, constitutes the major focus for HT research in the Centre for Analysis, Decisions and Society (CADS). This represents a novel and highly interesting area of research, though quite different in nature from HT's other research directions and goals, all united by a strong focus on human biology at the molecular scale. A major goal for this type of research at HT is to transfer this knowledge by **providing analysis and advice to different stakeholders, but in particular policymakers** – as the **design and implementation of models to evaluate the socio-economic impact on the national health system** of various aspects of precision medicine can be important tools to help design policy to optimise efforts in the areas above.

As previously stated, HT's efforts over the period covered by this Strategic Plan will largely be focused on s**etting up and consolidating scientific activities in the initially selected areas. Thereafter, additional research lines will be established**. The specific areas of biomedicine that these will focus on will partially depend on the development of the life science research landscape, which evolves quickly over time, as well as on the complementarity and potential for synergistic interactions with existing HT research groups or on new priority areas that are identified within the national landscape.

Potential **areas for HT's future development**, that are highly relevant and that would be ideal additions to further strengthen HT's science and maximise its potential to have an impact on human health can already be identified. Such research areas are, for example, **Cell Biology and Metabolism**.

Cell Biology, the study of cell structure, organisation and function, represents the natural missing link to bridge scales between the understanding of structures and mechanisms at the molecular level (provided e.g. by Structural Biology) and the information provided by large-scale (gen)omic level studies that operate at the level of organisms. The integration of these different disciplines or scales is what will enable scientists at Human Technopole to gain an in-depth and holistic understanding of the mechanisms that regulate human health and of their deregulation in disease. Many diseases are only manifested by defects that occur at the level of specific types of cells or collections of cells in tissues and organs. **A Research Centre for Cell Biology would represent a very broad research area, like Genomics or Structural Biology, that would complement and add to the possibilities of other Centres in HT**.

With a view to maximising synergies with the rest of the planned work at HT, the **Centre for Metabolism is instead intended to focus on areas related to human, and human microbiome, metabolism and the resulting individual response to the intake of food, pharmaceuticals, and microbes**. This is an emerging and extremely promising aspect of human biomedicine that will fit well with other planned research at HT, at the same time both making optimal use of genomics and other high-throughput technologies, and of computational biology infrastructure and expertise. Importantly, it would also open fields for collaboration with research in agri-food and nutrition located outside HT.

Human Technopole's research in all the areas above will be supported by state-of-the-art **scientific infrastructures and facilities**, essential to remain competitive in today's international research environment, that will cater for in-house and external users. A comprehensive framework will also support HT's scientists and collaborators in specific aspects of **research management, including activities related to grants management, technology transfer, research ethics and regulatory aspects of modern biomedical research.**

Taken together, the plans illustrated above will equip HT extremely well to study a vast range of human diseases and to tackle some of today's major health challenges. Collectively, the **goal of HT's research work is to enable the evaluation of risk and protective factors that influence disease development, the identification of novel targets and biomarkers, the development of novel therapies together with collaborators and the mechanistic understanding of various disease groups, including cancer, neurodevelopmental disorders, and cardiovascular diseases.**

In addressing such major health challenges, **HT's objectives** – both in terms of its overall scope and of specific topics that it will address – **overlap with selected European Commission (EC) mission areas**, i.e. the overarching societal challenges that have been recently identified and announced as an integral part of the Horizon Europe framework programme beginning in 2021. We will pay close attention to the EC missions and priorities, and we expect that specific research lines and projects at **HT will be able to tap into schemes dedicated to specific missions for example in the 'cancer' and potentially, depending on its further definition, 'soil health and food' areas, in particular.**

It is important to note, however, that while societal and research funding priorities at the European level change regularly (currently in cycles of seven years), it is important that HT, like any biomedical research institute, is able to develop and maintain stable research directions that are driven by an independent, long-term strategy in order to make an impact in selected focus areas.

Over time, HT's general emphasis on research relevant to human health will remain, though its scope in terms of **disease areas is likely to expand** as the volume of HT activities and number of research groups grow over time. Independent of specific projects or conditions investigated, however, HT's approach to human biology, with its mix of experimental and computational science and collaborative approach, constitutes an exceptional toolkit that can be applied to a wide range of problems and diseases. This means that HT will be agile, with the ability to **turn its skills to health problems as they arise either through recruitment or unforeseen events**. An illustrative and very current example of this is provided by HT's collaborative efforts in the **study of COVID-19**.

While HT's research does not have a strategic or long-term focus on virology, immunology, epidemiology or infectious diseases, in response to the recent and ongoing emergency situation caused by the spread of the Sars-CoV2 coronavirus, HT scientists have set up a number of projects and collaborations with major research and clinical institutions in Italy and abroad, particularly on the genetic and (single-cell) transcriptomic analysis of virus response and population stratification to study COVID-19 epidemiology and dynamics.

This work is paramount to uncover the mechanism and evolution of the Sars-CoV2 infection, as well as to identify potential associations with infection susceptibility and disease severity – ultimately aimed at identifying novel biomarkers, predicting disease course and repurposing existing drugs to steer the host response to the virus in a patient-specific manner. This work is being pursued in a manner that is consistent and integrated with the efforts of a number of international COVID-19-related initiatives in which our scientists are involved – for example in the context of the European LifeTime FET Flagship initiative and the COVID-19 Host Genetic Initiative – to ensure that results can be shared, integrated and analysed so as to yield the most meaningful and valuable information to everyone combatting the pandemic. These efforts undertaken by our scientists illustrate extremely well HT's collaborative culture, and

how its broad-based research approach, expertise and methods can be leveraged to contribute to a variety of human health related problems.

3. Advanced Training

An important goal for Human Technopole, and also a way to extend the reach of its activities beyond the institute to the outside community, will be the provision of advanced scientific training to young scientists. Over time, HT will increasingly engage in training activities in a broad range of areas relevant for biomedical and life science research, aimed at enhancing scientific capacity and benefiting the surrounding research community. **Training at Human Technopole will be both inward-and outward-facing**, with HT's dynamic and multidisciplinary environment providing an ideal context for the development of talented young scientists. The overarching and inspiring theme for the external training activities at HT will be to create a centre of excellence for training promising researchers in the biomedical sciences and enable broad access to HT's expertise, methods and resources.

Internal Training

In-house doctoral and postdoctoral fellows, as well as young Group Leaders who, for the first time, independently lead research groups or service teams, will benefit from mentoring programmes and career development activities, as well as from top-level scientific training. Interdisciplinary research will be especially encouraged, for example through **joint PhD or postdoc projects shared between research groups of different HT Research Centres or between HT groups**. We will also initially set up some **collaborative joint postdoctoral projects with external (academic or industry) partners**.

High standards of mentoring and guidance will be implemented to support doctoral and postdoctoral fellows on their paths to both research-based and non-research-based leadership positions. Special attention will also be given to the training of HT's early-stage researchers in research-related topics, for example **research ethics and bioethics**, in part with a view to preparing young scientists for clinical settings in the context of **translational research involving patient samples and disease data**. Internal training activities at HT will focus mainly on doctoral and postdoctoral fellows, but also a number of **undergraduate project students and early career visiting researchers** are expected to work at HT in future.

In the area of PhD training, Human Technopole is committed to providing high quality international-level training to its doctoral students. At least initially, this will mainly be achieved through participation in and/or implementation of **PhD Programmes in collaboration with national and international academic institutions**. HT has already joined existing doctoral programmes in selected fields of research, in collaboration with partner Universities in Italy. Further initiatives are planned in this area to enable an increasing number of excellent young graduates to carry out their doctoral research at HT in the coming years.

External Training

As part of its mission, HT will engage in organising and hosting scientific training activities and events aimed at scientists from outside HT, i.e. from Universities and other research institutes, as a service to the national and international community. In this context, **HT leadership has already been engaging in conversations with a variety of stakeholders in Italy**, including Universities, scientific societies, and individual research hospitals and institutions, to identify areas of particular need. Training events will include **symposia, workshops, and both theoretical and practical courses** at the forefront of scientific and technological development in **specific areas or technologies related to HT science and highly relevant for modern biomedical research** – with topics tailored as much as possible to fill gaps in available training, particularly for young scientists in Italy.

HT's training offer is expected to benefit scientists employed in **academic institutions, as well as in life science industries and in healthcare**. Overall, HT's external training activities will aim to create a world-class forum for sharing, discussing and learning about cutting-edge biomedical science and technology. The plans for training are described in more detail later in the document.

General Staff Training

Alongside specialised scientific training, HT will provide a variety of additional training opportunities to its staff by organising courses in "**soft skills**" as well as in **technical topics** of more general interest (e.g. IT courses and others), aimed at improving professional profiles and promoting the constant personal and professional development of staff. Available to all HT employees, such courses will provide scientists and non-scientists alike with the opportunity to learn and develop transferable skills relevant to their work at Human Technopole as well as to their careers beyond HT, and are intended to complement and synergise with scientific training (e.g. activities and courses developed specifically for PhD students and postdocs).

In addition to vocational training in areas relevant for HT, the training offer will include a broad range of courses and workshops designed to develop for example **personal, communication, project management, and computing skills**. In this framework, courses will also be offered in the area of **management and leadership development**, particularly for new research group leaders and/or administrative staff who move into managerial positions.

Finally, language courses will be available in line with HT's international nature – including basic courses to support the integration of international employees in the Italian environment, as well as advanced language training for specific HT work purposes. In general, the courses organised will aim to be flexible and tailored to the needs and requests of HT staff.

The envisioned scheme for such general training of employees will be designed and managed by the Human Resources department according to the organisation's needs. A structured and

detailed programme for these activities has not yet been planned, however these have already started on a small scale in 2019 and will expand, with the support of a dedicated staff member, over the period covered by this Strategic Plan. Access to external vocational training, if compatible with HT's budget and requirements of its staff, will also be offered. Further development opportunities will be provided to HT staff through dedicated national training Funds (e.g. "Fondimpresa" and "Fondirigenti").

4. Openness and Collaboration

In addition to its drive towards cutting-edge research and a strong commitment to improve the quality of human life, a spirit of inclusiveness, openness and collaboration lies at the heart of Human Technopole. These features of HT's culture will translate into intense collaboration within the institute, as well as permeate and characterise the interactions of HT and its scientists with the external scientific community (as already became evident in the response of HT researchers to Sars-CoV2). HT's role is that of a national hub and centre of reference for aspects of life science research. As such, it will actively engage and work together with partners of various sorts, both public and private actors in the fields of health and health-related research, to advance the Italian and European research and innovation ecosystem.

In the research domain, this will be done by establishing collaborations with national Universities and institutes as well as by setting up research infrastructures and user facilities that can be made accessible to public and private research organisations. Particularly in the former area, identifying partners that carry out work in areas complementary to Human Technopole and that offer opportunities for synergies is paramount. To this aim, connecting to the national and international scientific community is a crucial part of HT's external relations activities. It serves to build critical mass, exchange perspectives and expertise, and highlight complementarities and synergies.

HT has already taken important steps in this direction, by proactively **engaging with many representatives of the biomedical research community across Italy to identify potential areas of cooperation and foster synergies**. These meetings have largely served to introduce Human Technopole and the plans for its development, as well as to learn about the research, training and clinical activities carried out within the national biomedical science community. Much of the information derived from such consultations has been used to inform HT management and strategy decisions, for example on the organisation of HT research infrastructures and on the design and directions of HT research and training programmes. **Our goal is to avoid duplication of effort and promote initiatives of common interest whenever possible**.

While establishing connections with national institutions and networks, an important scientific goal and one of the expectations for Human Technopole is also to stimulate contacts with international research. It is therefore crucial for HT **to build links with European** and **other international initiatives, networks and infrastructures in the areas most relevant to its science**. In this context, productive discussions have already started with selected **biomedical Research Infrastructures of the ESFRI (European Strategy Forum on Research**

Infrastructures) Roadmap and with large European and international research consortia, as well as with individual potential research partners globally.

In view of its strong focus on human biology and health, HT naturally aims to develop strong relationships and collaborations with **clinical centres**, so as to **work closely with clinicians and practicing healthcare professionals** to enable the rapid translation of research findings to patients. In this context, significant effort has already gone into discussing with potential clinical partners – including but not limited to representatives of the major Italian research hospitals (**IRCCS – "Istituti di Ricovero e Cura a Carattere Scientifico**") – to ensure that HT's research, skills, databases and infrastructure can be effectively channeled to strengthen Italian clinical research and healthcare capabilities.

Such collaborations will enable clinical partners to be supported in specific aspects of their projects by the expertise and infrastructure available at HT, while they will give HT scientists an opportunity to test and further develop their research ideas and plans in a "real-world" setting. **A major area in which such fruitful discussions will be taken forward is that of population and medical genomics, but also pharmacogenomics and computational integration/analysis will be among the first joint HT-IRCCS projects.**

An equally important component in achieving Human Technopole's strategic goals is represented by building strong collaborative **links with industry**, working together with corporate partners to promote innovation and the development of products and applications that benefit society. HT will work towards fostering a collaborative network between its Research Centres and Facilities and industrial partners, to identify opportunities for synergies. By partnering with industry, and therefore identifying potential applications early in the research and development process, collaborative efforts will be aimed at maximising opportunities for research findings to lead to new drugs and healthcare products as well as innovative methods and technologies for life science research.

HT's strategy to collaborate with industry foresees a large array of possible interactions, ranging from project-based research collaborations, over joint training programmes, through to long-term strategic partnerships in specific areas of research and development. These various types of collaboration are envisioned with both national and international partners, from SMEs to large multinational companies. **In the national arena, interactions are being fostered with individual companies as well as through events and meetings with representative bodies such as Confindustria, Farmindustria (and related organisations) as well as the national clusters (e.g. Alisei and CLAN for life sciences and agri-food, respectively**).

Joint public-private ventures, for example in the areas of medical genomics and computation, are becoming more and more common internationally as a means for publicly funded research

to complement the needs of biotechnology, pharmaceutical and agri-food companies in pre-competitive research areas. While it is not possible to speculate at this point which specific partners or research areas these would involve at HT, such **public-private partnerships** certainly appear to be an obvious way in which HT's skills and expertise could be leveraged to stimulate industrial and technological development. The location on the MIND campus should help to promote such interactions as we expect innovative companies to be among the first to locate to the site. It should also facilitate the creation of space in which discoveries from research can take the initial steps to translation, either through the creation of start-up companies or through joint development with partners from industry.

Finally, HT's openness will be expressed through **activities involving its non-scientific stakeholders and the general public – including young children, students, teachers, and citizens from all walks of life.** By engaging in different communication, educational and outreach activities HT will play an active role in communicating science effectively, promoting an understanding among the public of the importance of scientific research and knowledge-based innovation, and stimulating a constant and productive discourse between science and society. This dialogue will involve not only the dissemination of scientific concepts, but will equally, if not more importantly, promote in-depth discussions on the role and responsibility of scientists, including the many important ethical issues related to modern scientific research.

Ultimately, HT's goal is to play an **active role in communicating science** effectively and making the work of our institute, as well as of science more broadly, heard and understood not just by scientists but also by regular citizens.

Towards achieving these goals, HT's communications strategy will be aimed at building, consolidating and maintaining Human Technopole's visibility and reputation by promoting events and initiatives that establish a positive relationship between the institute and its main stakeholders. Overall, communications activities will support HT's strategic development by raising its profile while creating reasonable expectations.

HT's work in this area will take advantage of a number of different tools – to be used selectively depending on the specific target audience among HT's varied stakeholder groups. These tools include national print, radio, TV and digital media, including selected scientific media, social media, and the organisation and participation in seminars, conferences and events – as a further way to raise awareness of HT's mission and work, by engaging in public dialogue. **In fact, Human Technopole's overarching mission is to contribute to the promotion of human health and wellbeing, and a key stakeholder therefore is the general public, everyday citizens who stand to benefit from HT's work in the long term.**

Available **space at Human Technopole will be used to host public events, seminars and conferences** to further Human Technopole's reach and engage with the local community as well as with visitors who travel to HT for such events. **Education and outreach activities (i.e.**

aimed at non-scientists) will be designed and organised in collaboration with academic and scientific dissemination and communications partners wherever possible, and will include HT's participation in relevant existing initiatives, **like the European Researchers' Night**, the "Festival delle Scienze", etc. Initial contacts with some of these potential partners have been initiated to explore and plan joint initiatives and HT scientists and leadership have already participated in such events. Particular attention will be given to engaging with younger generations through schools and existing science education programmes, to raise awareness of and promote careers in life sciences or biomedical research.

In all the areas described above, from scientific over clinical and industry relations through to interactions with the general public, Human Technopole will partner and work together with other organisations, both nationally and internationally.

5. Institutional Relations

As a Foundation established by the Italian Government, HT will maintain close relations with all the Republican institutions, including the Presidency of the Republic, the Presidency of the Council of Ministers, the three Founding Ministries of HT (i.e. Ministry of Economy and Finance; Ministry of Health; and Ministry of Universities and Research), and the Parliament with its relevant standing committees. In view of their supervisory and control function over HT, all of these are regularly updated on aspects of its administrative and financial management – on an annual basis, as well as through *ad hoc* reports and meetings.

In line with HT's mission to benefit the national biomedical research system at large, the Founding Ministries are also kept abreast of HT's activities and achievements, including the development of its scientific strategy, laboratory and facility planning, and recruitment of senior staff. One of HT's goals in this context is also to be involved – through relations with the relevant Ministries – in research initiatives of national interest coordinated by the Italian Government. To this end, preliminary, intense discussions have taken place with the three Ministries.

Notably, the **Ministry of Health** serves as the coordinator of the network of the Italian research hospitals (Istituti di Ricovero e Cura a Carattere Scientifico – IRCCSs), which – given the complementarity of their translational research and clinical activities – are natural partners for HT. Initiatives of national interest, for which there is a strong need in the health research community and which HT could contribute to, that have been explored in these settings include for example the **creation of a dedicated data infrastructure enabling remote access to both human bioinformatics and medical genomics data, as well as the digitisation and harmonisation of medical records and clinical data**. Against this background, we have also started to engage with regional health authorities, that are key players in healthcare and in the health data management system.

As well as interacting with a number of scientific stakeholders at the national level as described above, HT has obtained input from other research institutions, Universities and scientific societies including the Accademia dei Lincei, the premier Italian Academy, and the steering Board of FISV, the Federation of Italian Life Science Societies, aimed at raising our awareness of some of the needs of the national research community that HT may help ameliorate, as well as other requirements – for example in the area of sustained and stable research project funding for University researchers – where we can work together with others to try to achieve improvements. Human Technopole, in its role as a national centre of reference, will continue to promote a dialogue with Government institutions and contribute to the ongoing discussion on these topics.

6. Other Areas of HT Activity: Operations and Administration

The implementation of Human Technopole's scientific activities will go hand-in-hand with the expansion and consolidation of HT's administrative teams and activities, aimed at providing efficient and flexible services and creating an optimal working environment for HT scientists. A detailed overview of the goals and planned activities in the different areas of HT Operations and Administration, as well as the detailed plans for the development of Human Technopole's campus over the period 2020–2024 can be found in Supporting Document 3 ("Operations and Administration") and Supporting Document 5 ("Campus Development Plans"), respectively.

7. Financial Support of HT's Science

Core funding for Human Technopole's infrastructure and activities originates from public funds awarded by the Italian Government. It is expected, however, that as the institute grows and develops, and scientists transfer their research activities to HT, we will be able to attract increasing amounts of **additional funding through competitive grants from various sources**. It is hard to predict how much external funding Human Technopole might eventually raise. **Other similarly structured research institutes internationally raise up to 20-30% of their funding externally**. But that percentage is highly dependent both on the amount of internal funding used to support other activities, e.g. external users of facilities, and on the specifics of the national funding model in the country where the institute is located.

Given the HT structure and the Italian research funding landscape **we do not intend to apply for competitive funds from the Italian Ministries who fund research**. Rather, **international funding organisations and agencies are expected to represent the main sources of external funding for Human Technopole's research**. These will include the European Commission, through its Framework Programmes and other funding schemes such as the European Research Council and other individual awards, the National Institutes of Health (NIH), which fund some activities outside of the US, private foundations and non-profit organisations (i.e. charities). Looking to the future, additional funds are expected to contribute to HT's overall

budget, originating from **patent licencing and IP-related revenues** (e.g. royalties) as well as from joint programmes with industry.

IV. Strategic Initiatives 2020–2024

This chapter presents an overview of major strategic initiatives planned in HT's areas of activity over the period of this Strategic Plan. It should be noted, however, that these can naturally only provide a **partial view of planned actions** in these areas, based on the current early stage of development of Human Technopole (ca. **30 staff in total as this was written**) and on the relatively limited number (i.e. **seven) of research leaders** that have thus far been appointed. It is also necessary to take into account that for the Research Centres for which we have not yet recruited a Head of Centre, the description is of necessity less broad, as one of the tasks of the Heads of Research Centre is to contribute to strategy development in their Centre.

The plans for the first phase of HT development include setting up the following five Research Centres:

- Centre for Genomics
- Centre for Neurogenomics
- Centre for Computational Biology
- Centre for Structural Biology
- Centre for Analysis, Decisions and Society

The rationale for starting HT with these Centres is described above and in detail in Supporting Document 1 ("Research Plans").

By the end of 2024, Human Technopole is envisioned to host roughly 30 -35 research groups and 500 or more staff. This will be achieved by expansion of these **five Research Centres** to enable them to achieve **critical mass, rather than by the addition of new major research themes**. As new research groups are added however, the focus of each Research Centre will expand to enable increasing overlap between their interests and to promote more collaborative projects between Centres. The first examples of these are described below.

1. Interdisciplinary Research

HT's science will be interdisciplinary, including biologists, bioinformaticians, chemists, engineers, physicists, mathematicians, computer scientists, and scientists with medical backgrounds. The benefits of the breadth of available expertise, however, can only be reaped if scientists work together across disciplines to leverage synergies between their diverse skillsets. Internally, Human Technopole will promote and nurture interdisciplinary collaboration, for example through:

- the co-appointment of selected Group Leaders to more than one Research Centre

- interdisciplinary joint PhD and/or postdoc projects across Centres and
- potentially by funding jointly supervised postdoctoral or predoctoral fellows.

HT's Research will operate in a barrier-free setting and be characterised by a collegial management style, fostering an inclusive and open culture, with broad collaboration between different teams, sharing of laboratories and facilities, and collaboration across Centres. Whenever appropriate, **scientific activities will be managed using a "matrix system"**, where scientists become involved in multiple projects involving collaboration between different teams. This flexibility is essential, in particular in activities where technology development, data production and data analysis are coordinated for large-scale projects (e.g. in the area of genomics).

Close attention will be given to supporting the scientific development of PhD students, postdocs and young PIs to help develop the next generation of leading biomedical scientists. More generally, mentoring and fostering the development of scientists at all levels – established Group Leaders, starting Group Leaders, postdocs and students alike – will be a priority. Formal training in laboratory management will be provided for Group Leaders, and mentoring schemes (including complementary mentorship by external scientific leaders) will be encouraged. Seminar series, sharing of research reports, retreats, and journal clubs will all be used as instruments to strengthen scientific interactions, with particular emphasis on stimulating interactions between "wet" and "dry" scientists both within and across Centres.

A few strategic projects and initiatives to be pursued across different HT Centres and/or research teams are already planned and illustrated below by way of example. The first two are mainly aimed at generating new data in areas of general interest whereas the others include development of new tools for research that can be broadly applied beyond these specific projects.

1) Genomics initiatives aimed at enhancing understanding of genetic diversity and disease predisposition in Italy

As an exemplar project in this area we will carry out a **full genomic characterisation of the "Moli-sani" study, carried out by the Mediterranean Neurological Institute – Neuromed IRCCS. Moli-sani is a cohort study aiming to evaluate risk/protective factors (e.g. environmental, genetics, biomolecular) linked to chronic-degenerative disease** – with particular regard to cancer, cardiovascular disease and their intermediate phenotypes including hypertension, diabetes, dyslipidemia, obesity and metabolic syndrome. Between 2005 and 2010, the **study recruited over 24,000 people** aged ≥35 years living in the Molise region. The Moli-sani study participants underwent intense **phenotypic screening, and biological samples were collected and stored in a dedicated biobank.** This study will be spearheaded by Population and Medical Genomics scientists at HT, working closely with colleagues in the Functional Genomics programme to exploit the large biomaterials collection to systematically explore the function of individual alleles. The study will be instrumental in

establishing connections with HT other Research Centres and workflows that could be subsequently applied to other studies. Collaborations with CADS and the Computational Biology Centre are envisaged for epidemiological analyses and unsupervised data mining based on artificial intelligence approaches to maximally exploit the phenotypic depth of the data. Interaction with the Centre for Neurogenomics is foreseen for analyses related to cognitive phenotypes. In general, analyses will be coordinated with networks of national and international collaborators, for instance as part of global disease consortia or the International Common Disease Alliance (ICDA).

2) High-throughput brain organoid longitudinal profiling for neurodevelopmental disease deconvolution

Italy hosts one of the best-characterised **longitudinal cohorts in the world for neurodevelopmental disorders, centered around the IRCCS Associazione Oasi Maria Santissima in Troina, Sicily.** The cohort, which is integrated within the leading global consortia on the relevant disorders, has recruited well over **1500 patients with Autism Spectrum Disorder / Intellectual Disability**, who have been deeply phenotyped according to the highest standards. Genotyping and copy number variation analysis for ASD gene panels have been performed on over 1200 patients, who are currently undergoing exome sequencing. This Neurogenomics Centre-wide research line at HT will pursue the **reprogramming of iPSC lines and the longitudinal brain organoid characterisation for the entire cohort at single-cell transcriptomic / chromatin accessibility paired resolution, integrated with image-based phenotyping**.

This approach represents a large step forward in the ability to reconfigure neuropsychiatric phenotypes in terms of single-cell resolved neurodevelopment and represents a unique opportunity to add value to a world-class clinical cohort by **turning it into an unprecedented reference dataset of organoid-based disease analysis.** The functional examination of the top-scoring developmental pathway alterations *in vivo* will take advantage of innovative transgenic and xenografting approaches in ferrets (see below), thus enabling long-term studies that can reveal the consequences of such mutations on neuronal function and animal behaviour. The project obviously calls for strong synergies with groups active in other areas of HT science, including Genomics, Computational Biology, Structural Biology (to explore the role of cytoskeletal disruptions in cellular process generation and cilium dysfunction in neurodevelopmental phenotypes), and potentially CADS. Many collaborative possibilities outside HT are also envisaged.

3) Machine learning based mining of the Italian Health Card System (HCS) Data

A highly strategic and interesting project is being developed in collaboration between the Centre for Computational Biology and CADS. **The goal of the study is to access and analyse**

citizens' health data contained in the Health Insurance Card system, which contains registry data and medical expenses data at the individual-citizen resolution, ranging from pharmacy purchases to surgical interventions and medical examinations. If such data is compatible with high-level data analyses and computational methods, data-mining frameworks can be implemented to analyse data and identify statistical associations between the underlying variables, which would in turn allow to study disease co-morbidities and pharmaco-epidemiological trends, and to develop models of disease occurrence and of treatment outcomes. Moreover, HCS data can be used to build predictive models of future health status and events both at the individual- and at population- levels. Finally, if HCS data is coupled with genomics data, retrospective large-scale analyses can be performed, linking individual genomes to exposomes and clinico-pathological history. This could ultimately lead to building a national artificial-intelligence system which will assist medical doctors in taking clinical decisions, thus tailoring personalised therapeutic interventions onto individual patients.

Obviously, a critical aspect to this study (as well as of many other planned and potential projects in CADS' area of focus) is the possibility to access databases and information held by both national and regional authorities in Italy. HT leadership has initiated discussions with the relevant national Ministries in Rome and health authorities in the Lombardy region. Once appointed, taking these discussions to a successful conclusion will be a first task for the Head of CADS, jointly with the HT Director.

4) Development of key genomics and single-cell technologies

Major efforts will be devoted by the Genomics Centre to developing technologies to analyse genome and transcriptome structure and regulation. These will be aimed at mapping all the regulatory elements in the 3D space of cells, the interactomes that control their genes, as well as their epigenomes. They will enable the measurement and elucidation of DNA-DNA and DNA-proteome interactions in 3D, as well as of RNA-protein, RNA-DNA and RNA-DNA-protein interactions, so as to identify functional interactions that regulate biological activity. These technologies will be amenable to high-throughput approaches and thereby scalable to the genome level, to provide data that may help interpret genome variants, through the development and implementation of the latest technologies for the interpretation of human genetic variation (e.g. in genome-wide CRISPR screens). Technology development in the area of single-cell genomics will focus on methods enabling multi-omics measurements of many thousands of cells per experiment, with the additional aim to analyse cellular activity in living tissues via multiple temporal measurements, mapping cells and their dynamic interactions in 3D. Examples include technologies for measuring cell transcriptome, epigenome and cell-to-cell interactions within the 3D organisation of a tissue.

5) Development of bioinformatic tools and databases, while promoting an "open science" culture

In addition to technologies for data generation, Human Technopole will focus on developing state-of-the-art pipelines for data storage, restoration, curation and analysis. While these efforts will contribute to the integration and management of data produced at HT, we will also engage in the development of the infrastructure and methods required to make such tools and data widely available to the research community. Software engineers will focus on developing prototypic applications into robust and reusable computational modules to be shared with the bioinformatics community at large. The development of tools for bioinformatic analysis will go hand in hand with the creation and operation of databases, to facilitate broad usage of the data produced within HT. Particularly in the area of Genomics, developing tools for the analysis, visualisation and sharing of data from large-scale projects is key to boost the potential for strong interactions between biologists, geneticists, bioinformaticians and clinicians.

Genomic data produced at Human Technopole should be available to the community and primary data released whenever possible, while respecting the restrictions on individuals' data dictated by privacy and ethical issues. Similarly, **HT's partners in genomic initiatives agree that the results of the collaborative studies are published, deposited in public data repositories and/or shared with international collaborative projects**.

HT's efforts in its different areas of research will **aim to promote data distribution, reuse and reanalysis, in agreement with international "open science" standards and according to FAIR (Findable, Accessible, Interoperable and Reusable) principles**.

The activities above will largely be carried out by scientists in HT's Genomics and Computational Biology Centres but will be supported by computational researchers located in some of the other Centres working closely together. They will encompass many research lines at HT – in the areas of computational genomics, quantitative bio-image analysis, and others.

6) Pioneering the use of the ferret as a disease model for human neuropsychiatric disorders (NPD)

The ferret brain is an optimal model for human NPDs as, unlike the mouse, its brain recapitulates major features of human brain development that are affected by the disorders, i.e. neocortical size and folding. Transgenic ferrets will be generated using CRISPR/Cas9-mediated genome editing methods in pre-implantation embryos, and transplantation of human cerebral organoids (xenografts) will be established in the ferret. Both these approaches have been successfully tested in rodents. They will *de facto* transform this neurodevelopmental model into a genetically tractable platform for mechanistic studies, as well as enable the study of the long-term consequences of perturbations *in vivo*, complementing similar efforts in *in vitro* systems (e.g. cerebral organoids).

7) Cancer functional genomics and translational bioinformatics

Several planned projects across HT Research Centres and in collaboration with external partners will focus on **oncology and cancer (computational) genomics, exploiting data derived from *in vitro* functional genetic screens**. By leveraging deep learning computational methods and previously constructed large-scale pathway/signalling maps, this research will strive to produce computable models of pathways and biological networks driving cancer initiation and progression and will aim at implementing a programme to elucidate the systems biology of cancer dependencies and vulnerabilities. Pharmacogenomics approaches, on the other hand, will be exploited to:

(i) investigate how aggregating patient genomics and clinicopathologic data history might be predictive of responses to existing/future therapies and might forecast drug resistance emergence, as well as to

(ii) bridge cancer patient data with publicly available datasets from the multidimensional pharmacogenomic characterisation of large panels of pre-clinical cancer models.

2. Research Support

In order to guarantee that the research programmes and scientific services at Human Technopole remain cutting-edge, and to support the work of researchers in specific areas, "traditional" administrative functions will be complemented by crucial *ad hoc* research support functions, such as scientific project management, grants services, and ethics and regulatory support for projects involving human samples and/or data, and animal experimentation when it is required.

A more detailed description of planned activities in these areas and the relevant timelines is provided at the end of Supporting Document 1 ("Research Plans")

3. Scientific Infrastructure and Services

Research at HT will be supported by state-of-the-art scientific infrastructures and Facilities, that are essential to enable breakthrough discoveries in modern biomedical research. In addition to serving the needs of HT scientists, most of these Facilities and services will be set up on a sufficiently large scale to enable them to be made available to the outside scientific community, including public and private research organisations, on a meritocratic and competitive basis. HT's plans in the area of user-accessible scientific services are aimed as much as possible at addressing the needs of the research community, by providing access to equipment and technologies that are not readily available and that, in particular, scientists working in Italy have limited access to.

A detailed strategy and rules for accessing HT's different facilities and services are yet to be defined. They will be developed by HT Management before the relevant facilities begin their

operation together with the HT Heads of Research Centre and Facility managers, once these have been appointed. Priority in developing HT's user access strategy will be given to ensuring transparent and time-effective utilisation of the infrastructures by both internal and external researchers. **Scientists from Italian public research entities will have access to Human Technopole's research Facilities and services at the same costs as in-house HT scientists, and HT will provide some funding to support access to its services for users who would otherwise be unable to obtain access**. In order to broaden and further facilitate access for researchers as well as position HT's Facilities internationally, these will participate in European and other dedicated initiatives and programmes (e.g. iNEXT, Instruct, Euro-BioImaging, etc.) wherever possible.

In setting up its Facilities, Human Technopole is investing in innovative technologies, aiming to offer cutting-edge equipment and expertise. An important aspect of this is the need to recruit highly trained professionals (e.g. senior technical staff), who understand the technologies on offer and will support researchers with their experiments as well as promote the dissemination of crucial resources, methods and expertise in specific areas of technology relevant to HT's science. HT Facilities will also play an active role in training, directed at both 'biological users' and at more specialised technical staff from other national and international institutions.

At the operational level, each Facility will be managed by a Head of Facility, who will coordinate and supervise a small team of adequately trained and dedicated technical staff. Intense collaboration with HT's different Research Centres will be at the core of the Facilities' operational model. Having groups of scientists from different Centres and fields of research pursuing certain methods and techniques will allow the exploitation of equipment and technologies for a diverse range of applications, thereby pushing their development to address new experimental needs. In this context, strong collaborative links with research partners (i.e. Universities, research institutes, etc.) as well as with industry developers and suppliers of the relevant technologies will be key.

A collegial approach and the integration of different technologies will be driving principles for the HT Facilities. Regular discussions between facility staff and scientific stakeholders will be aimed at assessing and, if necessary, adjusting or expanding service activities. The integration of technologies and skills from traditionally distinct areas of research to develop new applications and experimental workflows, so crucial for the development of innovative methods, will be promoted by the close interaction among staff of the different Facilities. Formal instruments, such as user committees, or other, more technically oriented committees, may be implemented if they become necessary to fulfil these aims. Like HT's research activities, the Facilities will be subject to regular, four-yearly, external review.

The following main research Facilities will initially be set up:

- Data Centre
- Genomics Facility
- Cryo-EM Facility
- Light Microscopy Imaging Facility
- Image Analysis Facility
- Automated Stem Cell and Organoid Facility

Scientific activities at Human Technopole will require significant data storage and computing power to manage, store and analyse the huge amounts of heterogeneous data (omics, clinical, imaging, etc.) generated and used by its researchers. A large-scale **Data Centre** and a powerful computing infrastructure are therefore key assets to realise HT's plans, and the institute will be served by a high-performance, ultra-broadband network connection, in collaboration with existing national consortia and supercomputing infrastructures.

The **Genomics Facility** will develop, set up and implement essential omics technologies required by the HT Research Centres. It will be a large-scale DNA/RNA sequencing infrastructure, with the capacity to provide high-throughput next-generation sequencing, e.g. for population studies planned by HT researchers, as well as to support other large-scale or nationwide screening initiatives that HT will promote.

The **Cryo-Electron Microscopy Facility** represents a particularly ambitious and strategic initiative within HT's scientific infrastructure. It will provide a comprehensive platform for high-resolution molecular structure determination, including single particle analysis, cryo-focused ion-beam milling and cryo-electron tomography.

The **Light Microscopy Imaging Facility** will respond to the diversified demand of HT scientists by providing access and expertise in a broad array of light microscopy techniques and applications. These will range from more 'basic' setups such as widefield and confocal applications, to the most advanced and innovative techniques, such as super resolution, correlative light and electron microscopy and high content screening applications.

The **Image Analysis Facility** will further support internal and external scientists managing imaging-intensive projects by providing access to innovative software solutions and expertise in image restoration, downstream processing, smart microscopy or real-time image analysis, big data management and big data visualisation.

The **Automated Stem Cell and Organoid Facility** constitutes a particularly innovative endeavour and is aimed at streamlining, via dedicated automation pipelines, the key rate-limiting steps in disease modelling based on human cells and tissues, i.e. cell reprogramming, genome editing and longitudinal organoid culture.

In addition to such large instrumentation and centralised facilities, additional technological platforms and Core Facilities are planned, including fluorescence activated cell sorting (FACS) service, Protein expression and purification, crystallisation and biophysics, Proteomics, Metabolomics, Animal Research Facility and Transgenic Facility. The current planning foresees these as being set up on a relatively small scale, at least initially.

Aspects of these additional platforms and services may also be set up as joint facilities (also accessible to external users) in collaboration with external organisations that host related facilities and/or have expertise in selected technologies. In this context, it is worth mentioning a collaborative initiative that will lead to the development of a **comprehensive infrastructure and workflow for cross-linking coupled mass-spectrometry (currently lacking in the Italian proteomics ecosystem), to be jointly operated by HT and the European Institute of Oncology (IEO) in Milan**.

A detailed description of HT's planned research infrastructure and facilities can be found in Supporting Document 2 ("Scientific Facilities and Services").

Provision of crucial bioinformatics and biomedical data resources.

Maintaining data resources that will be accessible to the wider research community is a cornerstone of Human Technopole's strategy for scientific services. In addition to developing new tools and data resources for the community, HT will also achieve this goal by **hosting and collaboratively managing national bioinformatics resources that were developed and maintained outside HT to date**. A representative example of this is provided by our **cooperation with the University of Rome Tor Vergata for the continued maintenance and development of two data resources: the Molecular INTeraction (MINT) and the SIGnalling Network Open Resource (SIGNOR).** These two databases, aimed at capturing literature information about physical and functional molecular interactions respectively, are fundamental resources for the International bioinformatics community. MINT, in particular, has become increasingly important and is the only Italian data resource to be included among the ELIXIR[1] "Core Data Resources".

4. Scientific Training

PhD Training

Since 2018, HT has been part of the **joint PhD programme in Data Analytics and Decision Sciences (DADS) with Politecnico di Milano**, which stems from the cooperation among three of its departments – Electronics, Information and Bioengineering (DEIB), Management,

[1] ELIXIR is one of the European Strategy Forum for Research Infrastructures projects and is an independent intergovernmental organization with twenty-one European member states

Economics and Industrial Engineering (DIG) and Mathematics (DMAT) – and HT/PoliMi's collaborative Centre for Analysis, Decisions and Society (CADS). The aspect of this three-year programme that involves CADS will aim at training highly qualified data analysts and data managers enabling them to carry out research relevant to the health system and healthcare at Universities, clinical research centres, hospitals, health authorities, international institutions, financial institutions, technology companies, regulatory authorities and other public bodies. Courses, particularly in the first PhD year, are aimed at building the broad competence and strong interdisciplinary set of skills required for modern data analytics, in addition to focusing on the specific doctoral research project. DADS students are required to spend at least one semester in a research institution abroad, taking advantage of (and contributing to) the network of both Politecnico's and HT's international collaborations. Human Technopole has thus far supported seven DADS fellowships, in the academic years 2018-2019 and 2019-2020, and plans to support up to four more in 2020-2021. In this first phase, students have carried out their research with supervisors located at Politecnico but the programme will increasingly involve HT Group Leaders as CADS and Computational Biology at HT develop.

In 2019, Human Technopole joined the four-year **PhD Programme in Systems Medicine of the European School of Molecular Medicine (SEMM)**, as one of its host institutions. A collaborative venture among several Italian life science research institutes, the Statale University of Milan and the Federico II University of Naples, SEMM is a private foundation aimed at promoting training that integrates basic, translational and clinical research in emerging sectors of biomedicine. In this context, SEMM's PhD Programme in Systems Medicine offers curricula in Molecular Oncology, Human Genetics, Computational Biology and Medical Humanities, and comprehensive training courses – mostly carried out by the faculty of SEMM host institutions – in areas relevant and tailored to these different sectors of biomedicine. HT has thus far supported two fellowships for the academic year 2019-2020, funding students who currently carry out their doctoral work at the institution of origin of the relevant HT Group Leader, and who will transfer to HT during the first half of 2021, as HT premises are made ready to host their research activities. Six more HT PhD students are planned in the SEMM programme from 2020-2021.

Additional opportunities for joint PhD training with Italian Universities and research organisations are also being actively explored. Fruitful discussions are ongoing with the University of Naples Federico II for **doctoral programmes specifically in the areas of computational and quantitative biology**. Furthermore, we have started discussions with CNR (National Research Council), which has been tasked by the Ministry for University and Research (MUR) to develop and coordinate a **national PhD programme in Artificial Intelligence**, together with the University of Pisa and other Italian academic institutions. The programme, co-funded by MUR and scheduled to start in 2021-2022, foresees five doctoral courses in different areas of application of AI, including "Health and Life Sciences". Following a call that is expected to open in September 2020, Human Technopole will apply to join the

initiative as a partner. HT's participation is considered of great strategic value, both in terms of attracting excellent young computational scientists to the institute and in terms of contributing with its expertise to help shape activities in the AI field at the national level.

The next major step that is planned in the area of PhD training, to be initiated by the end of 2020 and concluded by the end of 2021, is for HT to join the **Open University's Affiliated Research Centre (ARC) Programme**, guaranteeing high standards and international best practices in doctoral training, as well as the benefits of a network of excellent research organisations. In general, all of HT's PhD training activities will encourage collaboration and periods to be spent abroad by the students (to be supported by a dedicated increase in the fellowship amount for the relevant period) as well as participation in scientific conferences and workshops.

Within the period covered by this Strategic Plan and as HT's faculty and scientific administration activities grow, HT will also explore and aim to set up additional joint programmes with other national and international partners, as well as begin to **design and explore possibilities to set up an HT PhD programme**, if that can be done compatibly with Italian regulations for the awarding of PhD degrees.

Courses and Conferences for External Scientists

As illustrated above, Human Technopole aims to organise and offer scientific training events as a means to enhance scientific capacity and benefit the surrounding research community. Although the timeline for their implementation will vary, a number of courses and workshops are being organised in several important areas. Members of the HT faculty and Heads of the HT Facilities, as well as external invited speakers/teachers, will lead the training. Courses to be organised from 2021 included **computational courses, for example in the areas of image analysis, computer programming, computational analysis of omics data**, and potentially modules (to be hosted at HT for scientists working in Italy) of off-site training courses offered by international training providers (e.g. by EMBL-EBI in the use of bioinformatic data resources). Due to the recent coronavirus outbreak and consequent travel limitations, however, the opportunity and feasibility of organising in-person training courses at Human Technopole in the near future had to be reassessed, and our efforts will focus only on the organisation of courses that can be delivered online for the rest of 2020. Other **courses, entailing both theoretical and hands-on sessions in areas of "wet lab" research – for example working with organoids, advanced genome editing courses or the use of Cryo-EM methods** – would in any case be implemented gradually from the second half of 2021 once the necessary laboratories, equipment and expertise are in place. Once HT is embedded in these networks, its training activities will be coordinated with European research infrastructures, for example ELIXIR and Euro-BioImaging, in the areas of bioinformatics/data management and of biological and medical imaging, respectively. Industry partners will also be important components of our planned training events, and we have already engaged in several discussions with industry partners who are willing to work together with us to this end.

A number of conferences are also envisioned, including a symposium on Cryo-EM to inaugurate HT's Facility in 2021, neuroscience conferences, meetings organised by large initiatives or international research consortia (e.g. Human Cell Atlas, LifeTime, and others), as well as dedicated conferences to explore synergies in specific fields with potential national collaborators (e.g. research institutes, Universities, scientific societies, IRCCSs, etc.).

Finally, we plan to offer training for external scientists in research-related topics, for example in the areas of entrepreneurship and technology transfer. Specifically, the first implementation of these will be the organisation of a course focussed on entrepreneurship for academic life scientists, aimed at promoting an entrepreneurial mindset in the academic world and helping scientists identify and pursue potential commercial opportunities arising from their work. The course is being designed in collaboration with an external partner expert in innovation, entrepreneurship and management, and will be offered to talented young PIs working at academic institutions throughout Italy. We expect to be able to advertise the first edition of the course by the end of 2020, for it to take place in the first half of 2021.

Depending on the outcome of their first editions, some of these events – both courses/workshops and symposia/conferences – could be repeated in updated formats on a regular basis so as to become reference events for scientists the relevant fields.

Scientific Visitor Programme

The design and implementation of a scientific visitor programme is a further initiative that HT will develop to ensure that its expertise, infrastructure and methods are shared with the external community. The vision underlying this programme is to **encourage mobility and the dissemination of expertise and methods developed in-house, by enabling external scientists to spend time at HT either for research collaborations, to learn methods in use at HT, or to use HT infrastructure and facilities.** While the programme will be open to scientific visitors from both national and international research institutions, it is expected that scientists from institutions in Italy will constitute a major proportion of the visitors.

The programme will be open to scientific visitors with different backgrounds and at different stages in their careers (i.e. group leaders, PhD students, postdocs, technologists, etc.) from other academic and research institutions, who will be hosted at Human Technopole for periods from a few days or weeks up to a maximum of one year. Longer stays could involve secondment of visitors from their host institution to Human Technopole. Scientific visitors to Human Technopole will include, for example, researchers interested in collaborating with HT scientists on specific projects in different areas of research, as well as scientists from different fields of life science research who wish to apply specific, cutting-edge technologies available at Human Technopole to their own projects and/or gain expertise in the relevant methods.

Participants will be evaluated and selected through a competitive process (i.e. based on individual merit and the quality of the proposed research projects) carried out by dedicated

expert committees that will be composed mainly of external scientists. In addition to providing logistic and administrative support to visitors, **HT intends to make visitor fellowships available to successful applicants**, which are aimed at contributing to reasonable research and accommodation costs for the period of the visit (with varying amounts awarded depending on the type of project, duration of the visit and other funding available to the visitor).

HT's scientific visitor programme will begin (with initially up to perhaps ten visitors) in 2021 – with the start of experimental labs and facility operation at HT – and will expand in subsequent years, alongside the growth in scientific expertise and research and service capacities at HT.

HT Early Career Fellows Programme

Until Human Technopole builds up its laboratory infrastructure its internal growth will be limited. During this period, with a view to enriching the national life science research community and increasing Italy's research performance, a scheme will be implemented to **support the development of outstanding junior PIs (Principal Investigators) who wish to carry out their independent research in Italy, to be hosted at different Italian academic institutions.** These research centres and Universities will act as Host Institutions for the fellows. The Early Career Fellowship Programme will be characterised by **stringent selection procedures in line with HT principles and will be organised in coordination with the Ministry for Universities and Research.** Candidates will apply with a detailed five-year project proposal for research work in line with the scientific mission of Human Technopole – and ideally with direct relevance to the focus areas of one or more of the first five HT Research Centres. They will also have identified a University or research centre that is prepared to host them. Research proposals will be evaluated by dedicated international committees composed of a mix of HT and external scientists. Following this stringent selection procedure, the HT Early Career Fellowships will provide dedicated funding to cover the salary of the Fellow, their junior laboratory staff and/or other research costs for a period of five years.

Similar successful programmes have already been in operation, for example the Career Development Award Program of the Giovanni Armenise-Harvard Foundation and the "Rita Levi Montalcini" Programme of the Ministry for Universities and Research (MUR), and are seen with great enthusiasm by the Italian community. They have served as general models that have inspired the plans for the HT Early Career Fellowships. **The scheme is also intended to further foster collaborative relationships between HT and the Italian research system**, both by creating specific opportunities for scientific exchange between the Early Career Fellows and HT Group Leaders and through fostering institutional links with the host institutes.

The programme will extend over the five-year period of this Strategic Plan. It is foreseen for an **overall budget of up to 20 million euros** to be dedicated to it. The first call for proposals will be opened by the end of 2020 for Fellows who should start their activity in 2021.

5. Technology Transfer and Industry Relations

The life sciences sector, including medical technologies, biotechnology and pharmaceuticals, is extremely productive and an area of major interest for innovation. Contributing to economic and social progress by transferring its research results into applications, therapies and products is a major goal of Human Technopole, and a further way for HT to fulfil its mission.

As our research activities grow, technology transfer activities will be set up in a structured way to help translate HT scientists' discoveries and inventions into tangible applications and marketable products. New technologies and methods that could emerge from HT's work broadly cover the span of the life sciences, including therapeutic and diagnostic strategies, enabling technologies, molecular tools and assays, instruments and devices as well as software applications and databases, to be developed in close connection with industrial partners in the pharmaceutical, biotech, engineering and IT fields.

A **technology transfer unit will be created that will act as HT's knowledge transfer arm and be responsible for the protection, utilisation and commercialisation of HT research, managing HT intellectual property through patents, licensing and the creation of spin-off firms**. A likely model that HT will apply in setting up such activities is that of **a commercial subsidiary, which would operate independently** of but in close collaboration with HT. The success of such an entity, however, depends on HT's ability to generate intellectual property and thus will be pursued as HT development progresses, after research and development activities have become active and consolidated on HT premises. The timeline currently envisioned is that Human Technopole's in-house technology transfer activities will begin in 2021.

Beyond setting up its own technology transfer activities, and in line with HT's commitment to the wider academic community, we are exploring potential ways in which Human Technopole could contribute to enhancing technology transfer opportunities for Italian researchers more broadly. Successful technology transfer requires a broad range of IP and business skills and expertise, coupled with research experience, in order to be able to understand the underlying science as well as understand, attract the interest of and negotiate with commercial partners to develop optimised commercialisation strategies for individual products and technologies.

Promoting an entrepreneurial mindset in the academic world is paramount. In this context, one avenue already described is entrepreneurship courses. Technology transfer professionals with adequate competence and skillset are also in short supply, particularly in Italian Universities and research institutions. In view of this, a further avenue for HT to engage in future would be to organise and provide systematic, high-level professional training for a new generation of technology transfer professionals with a focus on exploiting biomedical research and development results.

In addition to training courses, HT will be involved as much as possible in the organisation of other events and initiatives around the exploitation of research results for academic institutions, and in this context, we have started to engage with partners. For example, HT recently partnered with the 2020 edition of the BioinItaly/Startup Initiative, promoted by the biotech industry association Assobiotec and the accelerator Intesa San Paolo Innovation Center, with a focus on the development of biotechnology and healthcare startups. In the meantime, we continue to have discussions with relevant players at Universities and other public and private non-profit organisations active in this sector to explore the national technology transfer scene and identify additional ways in which HT could benefit the wider academic community. **While it is not envisioned for Human Technopole to directly set up and manage start-up accelerators or incubators over the period of this Strategic Plan**, initiatives in this area are being developed as part of the MIND site (Supporting Document 5 "Campus Development Plans") that HT will closely collaborate with and where possible take advantage of to create nearby "innovation spaces".

Human Technopole's relations with industry, however, will go beyond those directed at promoting technology transfer. Over the last year, the HT leadership has engaged in many interactions with potential corporate partners in a variety of areas, including biotech, pharmaceuticals, instrumentation and IT, talking with companies active in the fields of genomics, data analytics, biomedical imaging and multiple others. Different models have been discussed with each of these, depending on complementarity with HT's science and opportunities for specific collaborative initiatives. These range from the implementation of joint postdoctoral projects or programmes, over joint training initiatives (i.e. the organisation of courses and workshops) to R&D collaborations for the co-development of novel instruments, tools (e.g. algorithms and software) and applications – with such activities being sponsored or co-sponsored by the relevant corporate counterparts. Opportunities are also being explored to set up more formal, longer-term partnerships with selected firms, combining the provision of instruments and services with co-development endeavours and access to new technologies, for example to be made available for testing by HT researchers as well as external users through HT's Core Facilities. In future, joint HT-industry laboratories are also a possibility, though concrete plans for these are not yet in development.

6. Scientific Partnerships and Collaborations

HT's first institutional collaboration, with **Politecnico di Milano**, dates back to February 2018 – before the HT Foundation was formally established or any HT staff were employed – and led to the creation of the joint Centre for Analysis, Decisions and Society (CADS).

In 2019, a framework agreement was signed between HT and the **Statale University of Milan**, which lays the foundations for future scientific collaboration, to be established through e.g. joint research projects, training programmes, outreach and public engagement activities and/or exchange of staff. HT has recently concluded similar strategic partnership agreements with the **University of Naples Federico II** and with the **University of Torino**. We are currently discussing similar agreements with few other potential partners, and we will continue to

actively promote broad scientific collaboration agreements with academic institutions in Italy as well as abroad.

In line with HT's intention to engage with all relevant stakeholders, regular discussions have taken place and framework agreements for scientific collaboration similar to those made with academic partners were signed with **Alisei and CLAN, national "clusters" established by the Ministry for Universities and Research, to promote interactions between industry and academia** to enhance research and innovation capacities nationally in the fields of life science and agri-food and nutrition, respectively.

Interactions with the surrounding research community have been increasingly intensifying and diversifying over late 2019 and 2020, following the announcement of the first members of the HT scientific leadership, i.e. HT's first Heads of Research Centre and Group Leaders. Their appointment has triggered an intense wave of initiatives and meetings with various players in the biomedical science community, who are eager to collaborate with HT on the basis of complementary expertise and/or common research objectives. Concrete collaborations have kicked off with both academic and clinical partners, including the **European Institute of Oncology** and **University of Milan** and the **ASST FBF Sacco Hospital** in Milan, the **University of Padova** and the **Institute of Pediatric Research Citta' della Speranza – IRP** in Padova, the **IRCCS Neuromed** in Molise, and the **IRCCS Associazione Oasi Maria Santissima** in Sicily. Collaborative endeavours are also at an advanced stage of discussion with the **Istituto di Candiolo FPO IRCCS in Turin and the Ospedale Pediatrico Bambino Gesù in Rome** (outlined in Supporting Document 1 "Research Plans").

Already formalised collaborations (e.g. with the University of Rome Tor Vergata) as well as emerging ones (e.g. with the University of Naples) related to the management of biomedical databases and bioinformatics resources are also worth mentioning. Other potential collaborations, lying at the forefront of scientific and technical development in areas such as biomedical imaging technologies and neuroscience, are being explored but are not yet finalised.

As discussed above, it is also important for Human Technopole to **build links with European and international institutes and collaborative initiatives, including by coordinating Italian efforts and/or participating in large-scale international collaborative research endeavours and consortia**. Three of these, in which HT is already involved, are illustrated here by way of example. The participation in all of these initiatives is strategic for HT and as such will be cross-cutting, involving scientists from different Centres and Core Facilities who will work together across disciplines and research topics.

1. Human Technopole is joining the **European LifeTime FET Flagship initiative** as an associate partner. The LifeTime consortium, which brings together over 120 leading scientists from over 90 research institutes in 15 countries, aims to improve health and patient care by tracking and understanding human diseases at single cell resolution, with a particular focus on single-cell multiomics, organoids and machine learning.

2. The **Human Cell Atlas** represents a global effort combining expertise in biology, medicine, genomics, technology development and computation to build a comprehensive collection of cellular reference maps, characterising each of the thousands of cell types in the human body. A systematic study of the molecular mechanisms underlying the production, function and combined activity of different cell types in health and disease would be an incredibly valuable resource for the global research community.

3. The **Cancer Dependency Map** is a partnership begun between the Broad Institute (USA) and the Wellcome Sanger Institute (UK) that pools expertise, data and computational tools to systematically identify genetic and pharmacologic cancer dependencies and the biomarkers that predict them. Initial discussions with selected consortium partners have been very positive and are expected to result in HT joining the initiative, in an effort to dynamically characterise the genetic dependencies of glioblastoma, in particular.

HT will join collaborative endeavours in the area of research infrastructures and services in addition to research-oriented collaborations. In this context, relevant **ESFRI consortia for shared European research infrastructures**, such as ELIXIR (for data resources), Euro-BioImaging (for biomedical imaging) and BBMRI (for bio-banking), are of great strategic importance. Italy is a member of all three European projects, so a first step will be to connect with the Italian nodes of these infrastructures to learn about their activities, explore potential synergies and discuss what HT can contribute based on current needs. HT has already engaged in discussions with, and aims to join, **ELIXIR-IT (i.e. the Italian node of ELIXIR)** to contribute with its expertise and Facilities – together with the many other partners that make up the node – to the development and consolidation of a strong national bioinformatics infrastructure for Italian research. Once HT's imaging related Facilities (for Light Microscopy Imaging, Cryo-EM and Image Analysis) are successfully set up, we will initiate discussions with **Euro-BioImaging**, with a view to becoming a node for user access to selected applications and services.

V. Strategic Plan Implementation and Key Performance Indicators

This last section provides an outlook of the progress in Human Technopole's development to be expected over the period 2020–2024, based on the plans set out in this document. As mentioned above, it is important to note that these, especially in terms of scientific activities, are largely based on the current size and staff recruited to Human Technopole, whose growth over the next five years will lead to a significant expansion of activities and the likely development of new initiatives in many areas.

1. Building HT's scientific and organisational structure

The recruitment of the first core of HT scientific leadership started in 2019 and has led so far to the appointment of seven research leaders, who are expected to gradually transfer their research activities to Human Technopole over the end of 2020 and first half of 2021 as suitable space becomes available or is constructed. The researchers who were selected through this first round of scientific recruitments are (in alphabetical order):

- Piero Carninci – Geneticist; Deputy Director of the Center for Integrative Medical Sciences, Leader of the Laboratory for Transcriptome Technology, and Leader of the Laboratory for Single Cell Technologies at RIKEN (Tokyo, Japan); HT will take advantage of his expertise to build the Centre for Genomics where he will be Head of Functional Genomics.
- Francesco Iorio – Computer scientist; Principal Staff Scientist at the Wellcome Sanger Institute (Hinxton, UK); will be a Group Leader in the HT Centre for Computational Biology.
- Florian Jug – Computer scientist; Group Leader at the Center for Systems Biology Dresden of the Max Planck Institute of Cell Biology and Genetics (Dresden, Germany); will be a Group Leader in the HT Centre for Computational Biology and will lead the Image Analysis Core Facility.
- Nereo Kalebic – Molecular neurobiologist; postdoc at the Max Planck Institute of Cell Biology and Genetics (Dresden, Germany); will be a Group Leader in the HT Centre for Neurogenomics.
- Gaia Pigino – Structural cell biologist; Group Leader at the Max Planck Institute of Cell Biology and Genetics (Dresden, Germany); will be the Associate Head of the Centre for Structural Biology with the special responsibility to contribute to building up Cell Biology expertise and activity at HT.
- Giuseppe Testa – MD; Professor of Molecular Biology at the University of Milano and Group Leader at the European Oncology Institute (IEO) (Milan, Italy); will be the Head of the HT Centre for Neurogenomics.

- Alessandro Vannini – Structural Biologist; Deputy Head of the Structural Biology Division at the Institute for Cancer Research (London, UK); will be the Head of the HT Centre for Structural Biology.

The seven founding HT Group Leaders clearly represent a mix of established, senior scientists, recruited to lead HT's Research Centres and Programmes, and of more junior investigators who join Human Technopole as independent Group Leaders – in the areas of Genomics, Neurogenomics, Computational Biology and Structural Biology. While the first recruitment rounds in all of these areas included searches for senior investigators, in cases where no suitable senior candidate could be identified but outstanding Group Leader candidates were available, it was decided to recruit these as Group Leaders to be able to kick-start activities in the relevant areas.

Searches for the Heads of HT Research Centres and Programmes that were not identified in the first recruitment round were repeated in 2020. As a result, discussions are currently ongoing with candidates for the positions of Head of Population and Medical Genomics, Head of Computational Biology and Head of CADS. If these discussions are concluded positively with all three candidates, the appointment the HT senior scientific leadership for the period covered by this plan will be completed in Autumn 2020. A second round of calls for Group Leaders in all five of HT's Research Centre areas was recently launched that will identify additional PIs to start at HT over the course of 2021. It is envisioned that, including the founding investigators, each Research Centre will be composed of 5-6 independent groups at the end of the Strategic Plan period. In line with the larger size and programme-based structure envisioned for the Centre for Genomics, up to 8-10 independent groups will be recruited to it over the same period. As previously discussed, the overall growth and the number of research groups to be active at HT until 2024 also largely results from the limited availability of physical space – until the main HT research building (South Building, Supporting Document 5, "Campus Development Plans") can be constructed and ready for occupation.

All HT scientific staff is recruited through international, open calls and stringent, strictly meritocratic selection procedures carried out by internal as well as external experts in the relevant fields. Based on the strategy set out for the institute, most Group Leaders will be hired on fixed-term contracts for five years, renewable once (i.e. 5+5-year terms). After their time at HT, Principal Investigators (PIs) will be well equipped to access high-level job opportunities at national Universities, research hospitals and research centres. Flexibility, in terms of the timing of their relocation, will be guaranteed at the end of their term at Human Technopole to ensure that researchers can adequately plan the next step in their careers and move on to suitable, truly competitive positions. We will also encourage HT researchers to accept joint appointments in order to help them prepare for a move to another institution and will allow them to expend significant time and effort preparing their future position and laboratory in the final years of their contract.

Recruitment in the area of scientific facilities and services is also progressing rapidly and has already led to the identification of a Head of the Cryo-EM Facility. Searches for leaders of the other main HT Facilities are either ongoing or will be launched by the end of 2020, to ideally have the managers start at HT in early 2021. In terms of the higher-level, strategic oversight of these, in the initial phase of setting up and operation of HT's services, Facilities will largely be associated to Research Centres in the areas most closely related to or that make most use of their service. As the Facilities' activities grow and mature, an alternative model that sees a Head of Core Facilities taking responsibility for all of the Core Facilities will be adopted.

An overview of HT's scientific management structure, along with the state of the relevant recruitments is presented in Figure 1.

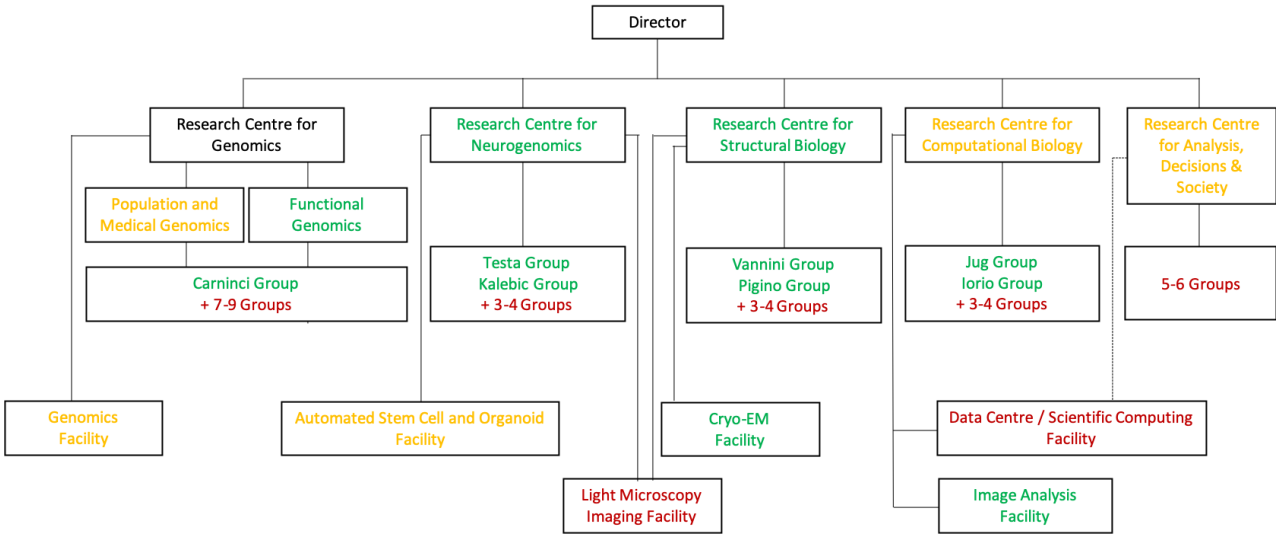

Figure 1. Planned management structure of HT Research Centres and Facilities and current state of recruitments. (green: leaders recruited; yellow: recruitment ongoing; red: not recruited)

In parallel to the scientists that will make up HT's Research Centres and Facilities, we also envision rapid growth of Human Technopole's overall structure and personnel over the period 2020-2024, including in the areas of Operations/Administration and other support functions. An overview of functions envisioned in HT's future organisation is shown in Figure 3, Annex 3 ("Operations and Administration"). **Of the roughly 80% scientific personnel that will make up HT staff, it is currently envisaged that roughly 70-75% will be dedicated to research and roughly 25-30% to service and scientific/technical support activities**.

2. Progress Indicators

A comprehensive update of the HT institutional strategy, resulting in the production of a detailed Strategic Plan, will be repeated every five years. This first document, in particular, lays out the plans for the first stage of Human Technopole build-up and the launch of its initial core activities. If all aspects of the current plan are carried out successfully, HT will be an

institute of significant size by the end of 2024. While the seven founding HT Group Leaders are identified at this point, it is envisioned that around thirty research groups will be active in the different HT Research Centres by the end of this period. Although it is too early to make reliable predictions, the first outcomes of HT's planned activities will be evident, both in terms of research outputs (e.g. publications, grants, etc.) and in terms of benefits to the surrounding biomedical communities (e.g. in the form of access to infrastructures, training, etc.). Many of HT's future activities, however, naturally depend on HT's evolution and on the research lines to be pursued by future recruits, hence it is difficult to set comprehensive milestones or targets for 2020–2024. We have however identified a number of indicative milestones, not intended to be interpreted rigidly, related to HT's mission areas and currently planned initiatives that can be used to monitor progress, which are presented in Figure 2.

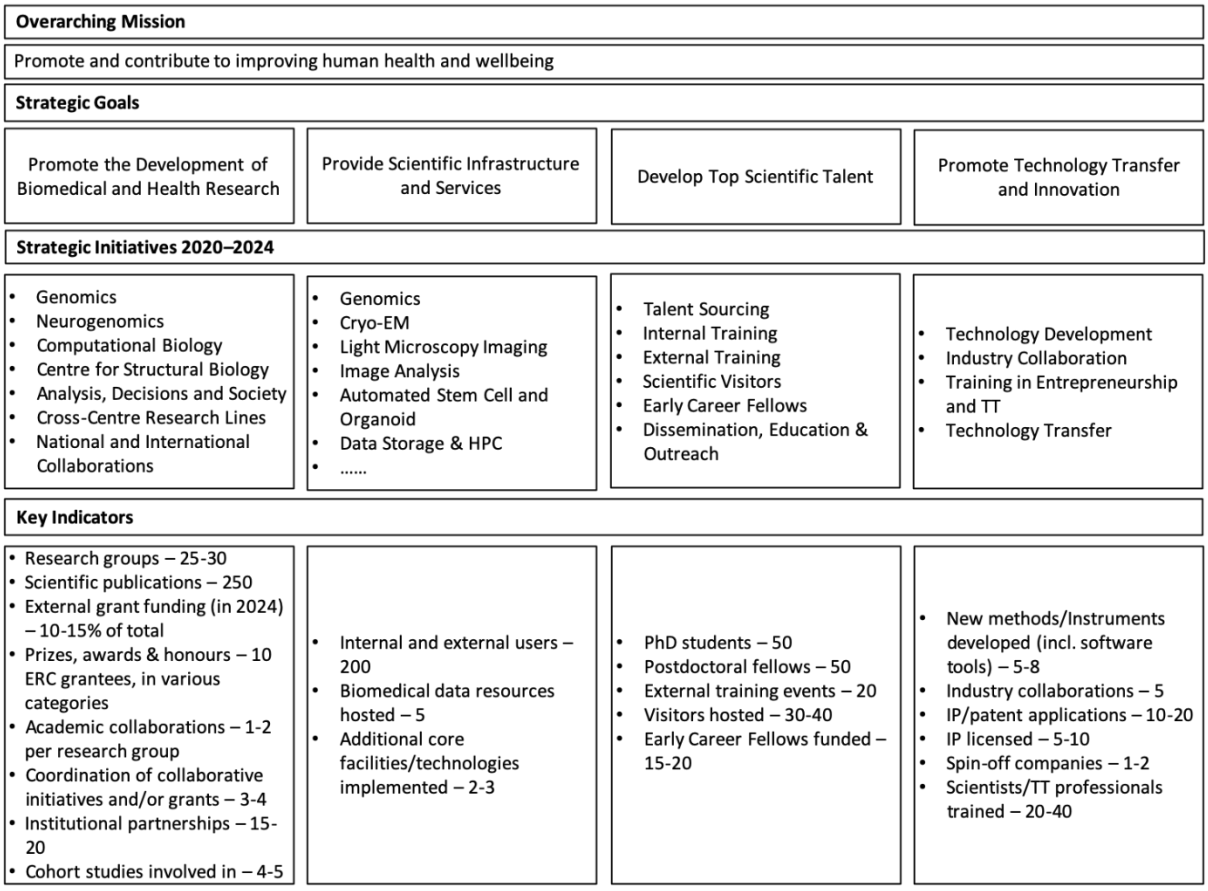

Figure 2. Strategic initiatives, progress indicators and indicative milestones related to HT mission areas and currently planned activities. The figures related to key indicators are to be intended as cumulative numbers by the end of 2024, unless indicated otherwise. **Note that, at this early stage in HT's development, these numbers can only be treated as indicative and should not be interpreted rigidly.**

3. Evaluation of HT's scientific activities

HT's activities and plans will be subject to stringent quality control – aimed at monitoring and assessing the institute's activities as well as their relationship to HT's multiannual research programmes – with the ultimate goal of ensuring scientific excellence, in line with best international practice and standards. As laid out in the HT by-laws, the evaluation of HT research activities will involve the Scientific Committee, which acts as the advisory body of Human Technopole, and the first core of which is represented by HT's Scientific Advisory Board (SAB). The SAB is composed of distinguished, internationally renowned scientists in a range of disciplines and fields of research relevant to HT's science and mission and gives advice with regard to all aspects of the development and implementation of the HT scientific strategy, as well as on proposals and initiatives from Management and how they fit into the realisation of HT's scientific programme.

The first task for the SAB is to provide an evaluation of this Strategic Plan. SAB will evaluate the proposed plans in all of areas of HT activity, as well as of its strategic position and value to the Italian, European and international research landscape.

SAB and later the Scientific Committee will also be involved in reviews of HT's research centres and facilities, that will take place every four years and will involve external expert panels covering the range of expertise required by the review. The reviews will cover the scientific performance of the parts of HT under review and, where relevant to scientific performance, aspects of scientific support and administrative development of HT. This reflects the best practice mechanism for the evaluation of top-level international biomedical research institutes and research scientists. The first evaluation of HT's scientific activities will be in 2024 by which time the initial phase of HT growth will have taken place and the researchers recruited early in the life of HT will have had time to establish their activities at HT. While all of HT will be reviewed simultaneously in 2024 it is envisioned that future growth of HT will necessitate separating the review of individual or pairs of Research Centres into different years due to the sheer size of the review panels required for a comprehensive review.

Following site visits, review panels will produce a comprehensive report that summarises the review process and incorporates the evaluations of the committee and their scientific or organisational recommendations. Having discussed the conclusions and outcomes of the review with the HT scientific leadership, the Director will formulate a written response to the report, to be sent to the members of the review panel and, together with the report, to the SAB, the Management Committee (Comitato di Gestione) and Supervisory Board (Consiglio di Sorveglianza). The Supervisory Board will receive the opinion of the SAB on the review and response and will take any action it deems necessary on the basis of the review and the SAB report.

Alongside the overall evaluation of research and service activities carried out by the different HT Research Centres and associated Facilities, these four-yearly reviews will also monitor and evaluate the performance of individual Group Leaders and Managers within the Centres and Facilities. Many different factors will be considered in making these assessments, including quality and innovation of research, productivity (quality and volume of scientific output, e.g. publications), mentoring and training record (including support to the career development of

junior group members), ability to raise external funding (i.e. grants) and scientific impact (e.g. awards, honours, IP, etc.). The Director will carefully consider the evaluation and recommendations of the review panels and will plan a response, including possibly through the expansion, contraction and/or redirection of specific research or service activities or of individual research lines. These plans will be part of the review response described above

In terms of the content of the evaluations, the review panels will be expected to provide their opinion in the form of a narrative evaluation of each Research Centre and individual under review that will be distributed to the HT leadership and governance as well as to the individual under review as well as her/his Head of Research Centre. This will be complemented by a summary rating of overall performance, to cater to the need for a more readily accessible and succinct evaluation for non-experts that will be confidential, only being shared with the HT Director and governance bodies. Experience in other institutions has shown that the confidentiality of such summary analyses is important in ensure the independence of review committees in reaching their conclusions. HT intends to adopt a system for scientific evaluation in which Category 1 corresponds to the top 5-10% internationally in a specific field of research (or provision of a specific technology), Category 2 the top 10-20%, Category 3 the top 20-30%, and Category 4 to average international performance. HT scientific activities and staff, being highly selected and provided with generous conditions, will be generally expected to rank in the first two categories. In the event of poor performance by an individual or Research Centre, the HT Director will consider consequences for contract renewal and Research Centre restructuring which will then be discussed with the SAB and Management Committee before implementation.